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Phytotherapy

a textbook for pharmacy students

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Reviewed by:

Dr. Sándor Gonda

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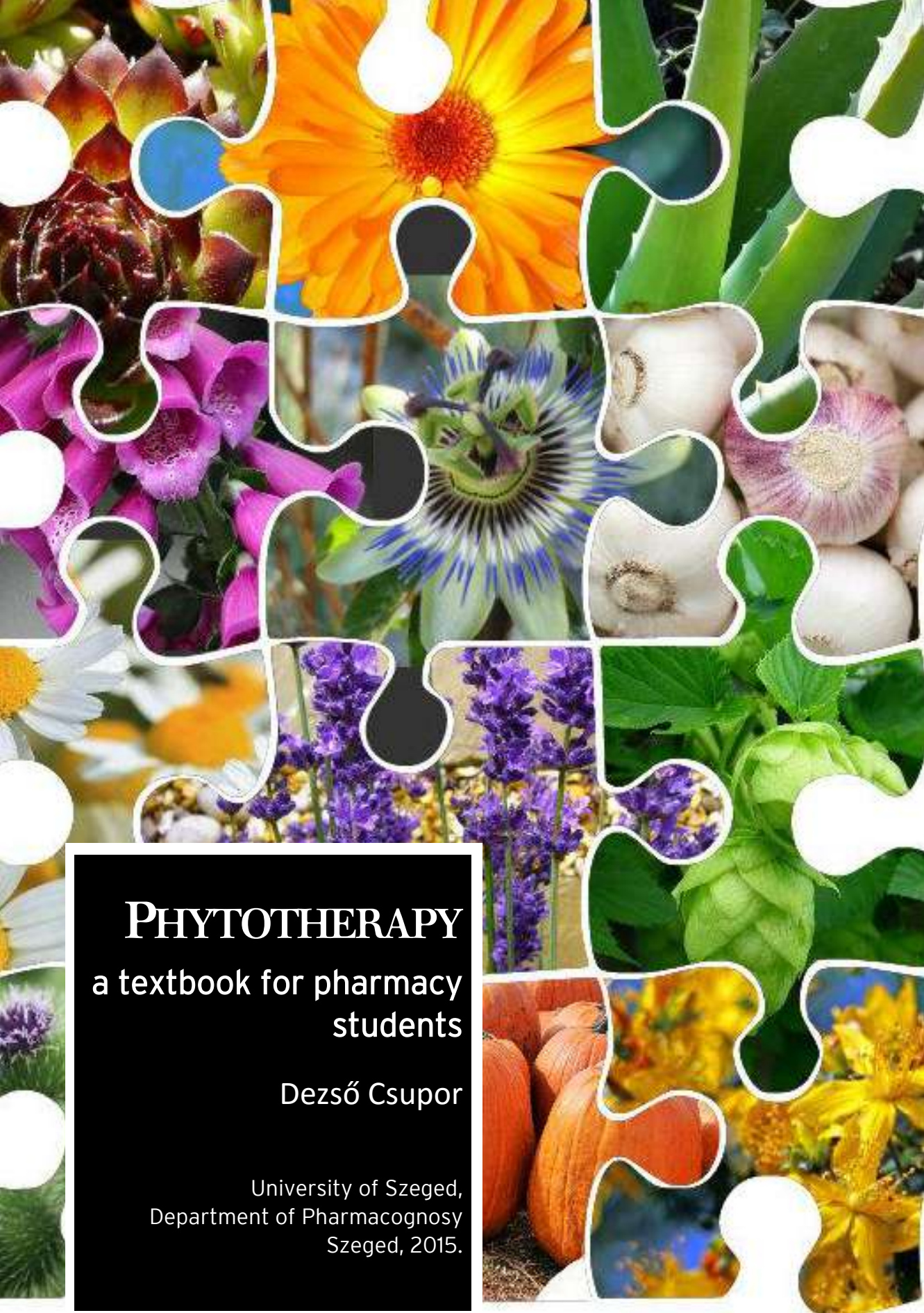

PHYTOTHERAPY

a textbook for pharmacy students

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Table of contents

1. Introduction

The application of medicinal plant-based products has recently been increasing rapidly. The "green wave" started in the 1970s and has been steadily accelerating during the past ten years. In parallel with the growing demand, the marketing of these products is undergoing diversification. Although the number of herbal medicines that are applied in evidence-based medicine is rising, a much steeper increase may be seen in the category of food supplements. Since the legal regulations relating to these categories are basically different, the processed products may differ greatly in quality and efficacy.

The application of medicinal plants in modern therapy requires competence in both phytochemistry and phytopharmacology. The wide and varied spectrum of plant-based products necessitates special expertise. Thanks to their studies in botany, chemistry, pharmacognosy, physiology and pharmacology, pharmacists have the basic knowledge required for phytotherapy. The curriculum of this subject provides knowledge for pharmacists to be able to meet the needs and demands of patients to receive effective and safe phytomedicines as part of their therapy. The major task of a pharmacist is to help patients choose appropriate products for the relief of their already diagnosed diseases and to serve as a reliable source for information concerning the application of these products. The pharmacist must have all the skills to provide advice ensuring safe use and is responsible for avoiding unnecessary adverse effects and interactions with other medicines.

The goal of this textbook is to summarize the current knowledge in the field of modern phytotherapy so that it can serve as a basis and guideline of phytotherapeutic counseling in the pharmacy. The therapeutic indications of the medicinal plants are in line with the monographs published by the European Medicines Agency (up-to-date monographs are available on the webpage of EMA).

Szeged, 23/09/2015

2. From plants to medicines

The most traditional way in which medicinal plants are applied in therapy is in the form of infusions or decoctions. These are water extracts that provide a safer way of application than eating the raw (ground) plant material: heating helps to destroy pathogens (at least partly), the risk of infection by a medicinal plant is therefore decreased. Medicinal teas have nowadays lost their importance, and considering some of the drawbacks (the preparation is time-consuming and water is not the best extracting solvent for several active components of medicinal plants), this is easy to understand.

Modern phytotherapeutic preparations are usually prepared from plant extracts. And in contrast with synthetics, it is typical that a product contains a combination of several extracts. The reason for preparing combination products has a long tradition, going back to ancient times, but in many cases there is a rationale behind the compositions. In the case of functional gastrointestinal problems, for example, it is wise to apply plants with different mechanisms of actions so as to provide relief for the different components of the syndrome. However, there is no general basis for the commonplace saying that combination products are useful since each of the components strengthens the effect of the others. Just the opposite may be true: in some cases antagonistic effects may occur (e.g. the absorption of certain components may be inhibited).

The use of herbal extracts in phytotherapeutics has several advantages. First, extraction ensures that post mortem enzymatic processes do not alter the composition of the product, and the microbiological stability of extracts is greater than that of dry plant materials. Secondly, if concentrated extracts are prepared it is possible to administer quite large doses of plant material in a convenient way (e.g. 1 capsule instead of 50 g of dry leaf). The measure of concentration is characterized by the drug-extract ratio (DER). The DER indicates how many grams of plant material are

used for the production of 1 g of extract. For example, if the DER is 5:1, 1 g of extract is prepared from 5 g of plant material (the measure of "concentration" is 5-fold). In certain cases, the DER is given as a range, e.g. 5-10:1. The reason for this is that the compositions of herbal raw materials harvested in different places and at different times may vary greatly and the amount of extract that can be gained from a specific amount may vary accordingly. If the DER reflects the ratio of the plant material and the extracting solvent, it is called the "DER genuine". If the DER is not specified as "genuine", the ratio may reflect the weights of the starting plant material and the final extract; the latter may contain added solvent or some other excipient, or the weight of the final extract may have been decreased by partial evaporation of the extracting solvent. Depending on the extent of evaporation, the native liquid extracts may even result in semisolid or solid (dry) extracts.

The extracting solvent is of determinating importance in the quality (and quantitative composition) of the extract. If the active components of a plant are lipophilic, apolar solvents should be preferred in order to gain an extract rich in active constituents. In contrast, in the case of hydrophilic compounds, polar extracting solvents should be used. In modern preparations, the extraction circumstances (besides the extracting solvent, the method, time, temperature, etc. of extraction) are optimized for cost-efficient production. For example, the majority of milk thistle preparations contain extracts prepared with ethyl acetate since this solvent is ideal for the extraction of the pharmacologically active flavonolignans. An extract prepared with a solvent with a very different polarity (even if the DERs are similar) would contain a much lower amount of flavonolignans and would therefore be of inferior quality.

It is clear that the characterization of products only in terms of their DER may result in quite large differences in efficacy, since the levels of the active components may also vary greatly. The intention is therefore to provide final products with a unified content of active component. This is a major step forward. If the active component (the secondary metabolite of a plant that is responsible for the pharmacologic effect) is known, it is more important to keep its level constant in the final product than to adhere to a very specific DER. The aim of producing extracts/final products with uniform active component content is standardization. Standardized herbal substances are adjusted within an acceptable tolerance to a given content of constituents with known therapeutic activity; standardization is achieved by adding excipients for adjustment to the herbal substance or by blending batches of the herbal substance. If the active components are not known, herbal substances may be quantified. Quantified herbal substances are adjusted to a defined range of constituents (active markers); adjustments are made by blending batches of herbal substances used in the manufacturing process. Standardization or quantification of extracts is especially useful when efficacy is reviwed on the basis of different clinical studies. Most clinical studies of *Ginkgo biloba* have been conducted with the standardized preparation EGb

761® (24% flavone glycosides (primarily quercetin, kaempferol and isorhamnetin) and 6% terpene lactones (2.8-3.4% ginkgolides A, B and C, and 2.6-3.2% bilobalide)). These studies may serve as the basis of meta-analyses and the aggregation of the positive results furnishes reliable confirmation of the efficacy of this plant. However, the assessment of efficacy is more problematic if only studies involving several different extracts are to be compared.

When the active components are known, the extracts can be enriched in them (in another word, refined). Refining extracts may have the aim of removing constituents with undesirable effects (toxic ones or having side-effects) or of increasing the content of active constituents (standardized extracts and quantified extracts). Refined extracts no longer have the total spectrum of constituents present in the original extract. Purification leads from native total extracts through refined extracts in the direction of pure isolated constituents. The latter do not come under the scope of phytotherapy, and they will therefore not be discussed here. Removing the herbal matrix (which contains both pharmacologically active and inert compounds) may result in a modification of the pharmacological effect. According to a reflection paper published by the Committee on Herbal Medicinal Products (HMPC, the committee at the European Medicines Agency that is responsible for preparing the Agency's opinions on herbal medicines), refined extracts may be grouped as follows:

- Isolated constituent (e.g. morphine), for which a characteristic impurity profile may be established and the purity has to be proven within the usual margins of acceptance for chemical substances.
- Mixtures of purified constituents obtained by specific processing methods (e.g. precipitation of sennosides as calcium salts). Concomitant constituents have been removed or are present at insignificant levels.
- Mixtures of chemically defined substances with related chemical structures extracted from herbal material. These may be difficult to separate (e.g. an alkaloid fraction not containing *N*-oxides or quaternary alkaloids, or a saponin fraction containing only monodesmoside saponins). Concomitant constituents have been removed or are present at insignificant levels.
- Chemically defined compounds extracted from herbal material and partially purified, e.g. 85%, but where the remaining part is represented by concomitant constituents.
- Isolated class of constituents (e.g. total alkaloids, or the total saponin fraction) in which the natural variability is maintained and identification of the main constituents in the mixture is possible.
- Standardized extracts adjusted to a specified content of constituents with known therapeutic activities (e.g. sennosides). Natural concomitants are present.

- Quantified extracts with a specified content of constituents regarded as active markers (e.g. quantified *Hypericum* extracts). Natural concomitants are present.
- Purified extracts that are neither standardized nor quantified, for which the pattern of active constituents has to be determined.

Herbal substances whose constituents with known therapeutic activity or active markers are unknown (these are the "other herbal substances" in the terminology of HMPC) are essentially defined by their production process and their specifications.

The precise description of a herbal preparation requires the name of the herbal substance and the definition of the herbal preparation, including the physical state, the ratio of the herbal substance to the genuine herbal preparation (the DER genuine, also named the native DER) and extraction solvent(s), if appropriate. The name of the herbal substance is the scientific Latin name of the plant species according to the binomial system (genus, species, variety and author) with the name of the plant part. If possible, extracts should be standardized or quantified (in these cases, the quantities of active components or markers should be declared). Without these essential data, phytotherapeutic preparations cannot be characterized properly. The availability of all the data (which is required for all medicines) makes it possible to compare different products. Unfortunately, in the case of food supplements, these essential data are very often scanty and the efficacy of the products therefore cannot be assessed.

Verification questions

1. What is DER?
2. What is the difference between standardized and quantified extracts?
3. What are the factors influencing the efficiency of extraction of herbal compounds from raw material?

3. Phytotherapy around the world

In European countries which have a long tradition of the application of medicinal plants in therapy (especially Germany, Austria, Switzerland and France), the pharmaceutical industry has steadily maintained its interest in medicinal plants, and phytotherapy is therefore regarded as part of modern medicine. Hundreds of preparations based on medicinal plants are marketed as registered medicines in these countries. The majority of these products are prepared from plant extracts or purified, fortified plant extracts. The active components and the mechanisms of action have been elucidated in several cases and several clinical trials have been carried out to confirm efficacy. In the second half of the 20th century, public interest for products of natural origin increased in developed countries. This interest explains why herbal products are continuing to gain ground at present. In the USA and Europe, a large proportion (30-80%) of the adult population use alternative (= not synthetic) preparations as part of their self-medication. Phytotherapeutic products used phytotherapy is amongst the most frequently used ones.

However, even in the era of the modern pharmaceutical industry, the majority of the population of the world has no access to synthetic medicines. Nearly 4 billion people living in the developing countries have at best limited access to medical care, or they cannot reach or afford modern medicines. For them, local traditional medicine is the main source of healing, though there has recently been a rapid rise on the sale of fake medicines. Traditional medicines are usually based on medicinal plants (or are rarely of animal or fungal origin). In Asia (and especially in China), traditional medicine is part of the official medicine and is taught at university level. In fact, the main source of plant-based products (and raw materials) is Asia: the agricultural cultivation of medicinal plants is rapidly increasing, the processing methods are being modernized, and the volume of raw materials and finished products for export is rising. In terms of commercial turnover, five of the ten medicinal plants ranking highest (soy, garlic, *Ginseng*, *Ginkgo* and *Cimicifuga*) are cultivated to a significant extent in Asia. Nearly 80% of the medicinal plant export aimed at the United States originates from China or from India, and the tendency may be similar in Europe.

The World Health Organization (WHO) has recognized that the developing countries may be supplied with appropriate medicinal products only through the development of locally available resources. In order to achieve this goal, the WHO

launched its Traditional Medicine Strategy in the 1980s. This initiative resulted in the appearance of new medicinal plants on the European market and an increasing number of these have gained acceptance in the European Pharmacopoeia. The scientific analysis of Asian medicinal plants is very intense and the body of knowledge supporting their rational application is increasing. Several traditional medicinal plants originating outside Europe have become part of European phytotherapy, and the influence of Asian traditional medicinal systems in Europe has intensified. However, in parallel with this, the range of traditional applications is becoming progressively narrower.

The food industry in the developed countries has targeted the positive consumer attitude towards plant-based products. Products referred to as "functional food", "fortified food" or "health food" have emerged to satisfy these demands. The most popular product category is the food supplements (also known as dietary supplements, although the former term is used in legislation). As compared with medicines, the legal background of these categories is lacking or defective. In food supplements some decades ago, the main components were vitamins and minerals. Nowadays, as a consequence of the gaps in the legal background, the most popular components stem from medicinal plants, and many products are practically identical to registered herbal medicines. In order to resolve the contradictions between the supplementation of the usual diet with vitamins and minerals and the application of other, non-food ingredients in food supplements, first the American, and later the European Union legislators introduced the possibility for the use of what they termed "other substances with nutritional or physiological effects". As a result of this liberalization, the number of possible ingredients and products abruptly increased and several thousand new products have subsequently been introduced on the market. The vast majority of herbal components has been borrowed from the materia medica of traditional or evidence-based medicine. Although many of these components have confirmed efficacy in certain diseases, this cannot be mentioned when they are applied in food supplements, because "*the labeling, presentation and advertising must not attribute to food supplements the property of preventing, treating or curing a human disease, or refer to such properties*". The main problem in the case of food supplements is that the doses of plant-derived ingredients and the quality of the finished products (at least in the European Union) are practically uncontrolled, which results in this product category being extremely diverse.

The characteristics of the marketed medicinal plant products and the regulatory practices in certain countries (leaders in tradition, research, industry or legislation) will be briefly presented below, with special respect to their influence in Europe.

3.1 China

Thousand year-old methods and preparations remain in use today in China. Traditional Chinese Medicine (TCM) provides numerous examples of how to preserve and modernize traditional medicinal plant application and provide a worldwide market for their tradition-based preparations.

The collective manufacturing value of Chinese medicinal plant processing companies in 2005 was approximately 14 billion USD, and the value is constantly increasing. Around 6000 plant species are used in medicine in China. A great proportion of them are to be found in the Pharmacopoeia of the People's Republic of China: 1967 medicinal plant drugs were official in the 8th edition issued in 2005 (this accounts for more than 60% of all pharmacopoeial monographs).

China is a good example of how different experts in healthcare (pharmacists and medical doctors of TCM and western medicine) can co-operate. China has long integrated the concept and methods of traditional medicine into its own healthcare system. The majority of Chinese hospitals have a ward for traditional medicine, and 30-50% of the country's drug consumption is in the form of traditional preparations. TCM products are produced in pharmaceutical factories, or pharmacists may prepare them according to a doctor's prescription (and the requirements of the Pharmacopoeia). Certain preparations are administered in a processed form (the aim of processing is usually to decrease the toxicity of the final product). If the knowledge required to prepare TCM remedies in a proper way is not available, there is a danger of toxicity or the loss of efficacy.

In China, the China Food and Drug Administration (CFDA registers and controls medicines. Herbal (and animal) TCM drugs are considered to have equal status to that of Western pharmaceutical drugs.

The current TCM is a healing concept and by no means represents a closed and rigid system. This allows the "modernization" of TCM preparations in accordance with recent scientific results and even the development of new products with novel therapeutic indications. In this sense it is a system that is undergoing continuous transformation and development. Food supplements and related products also occur in China. They are supervised by the CFDA in cooperation with other supervisory bodies.

3.2 North America

In the USA, the Food and Drug Administration (FDA) classifies all products into basically three product categories: medicines, foods and cosmetics. For medicinal plant-based products, the same level of documentation as applied to any other pharmaceutical drug of synthetic or natural origin is needed to gain registration as a

medicine (evidence based on traditional applications is disregarded). As a result, herbal preparations have practically not been marketed as medicines, but only as groups of food products with special functions (food supplements, fortified food, etc.). The Dietary Supplement, Health and Education Act of 1994 in the USA accepted that food supplements may be suitable for the prevention of chronic disorders and for the alleviation of their symptoms. The application of medicinal plants and "other substances with physiological effects" in food supplements was allowed and "health claims" were applied instead of therapeutic indications. In the USA, several important (European) medicinal plants are marketed only as food supplements. The US regulations have indirectly contributed to the fact that medicinal plant-based preparations are practically not used within the frame of the institutional therapy, but only within the category of complementary and alternative medicines.

The increasing demand for products manufactured from medicinal plants, together with the emerging quality problems of certain food supplements have led to various corrective measures. "United States Pharmacopoeia (USP) dietary supplement herbal monographs" have been elaborated by the Pharmacopeial Commission of the United States of America to improve the quality of products. As a result of the growing number of quality problems with products of Chinese origin, a Chinese-American medicinal plant and product quality controling center will be established in Shanghai, with the aim of controlling the quality of products exported to the USA.

In Canada, the popularity of alternative and complementary preparations and methods is high: approximately 70% of the adult population use such preparations, and the proportion of herbal products is also significant. The Natural Health Products Regulations, which has powers over all product categories containing ingredients of natural origin, defines all the substances of natural origin that may be used in products of natural origin. It also regulates all activities related to these products, including marketing and the labeling of products. A positive feature of the Canadian domestic regulation is that (similarly as in the USA) the supervision of all medicinal plant-containing products is the responsibility of one joint authority, but the legal background is more pragmatic and more flexible.

3.3 Europe

Since the beginning of the 20th century, Germany has occupied a leading position in the establishment of the principles and practice of rational phytotherapy. Several important medicinal plants (e.g., *Valeriana, Echinacea, Silybum, Cimicifuga, Vitex, Aesculus, Hedera* and *Ginkgo*) were developed to medicines by German researchers, and these modern preparations occurred first on the German market in the 1950s. As concerns traditional herbal medicine, the Bundesgesundheitsamt (BGA) started a requalification procedure for the several thousand products with the help of the E-

Kommission. It was the task of the E-Kommission to evaluate medicinal plants and, depending upon the scientific evidence, to publish positive or negative monographs. These monographs served as the scientific background for registration for decades. Following the German model, the European Scientific Cooperative on Phytotherapy (ESCOP) was founded on the basis of European collaboration in 1989 in order to prepare monographs to facilitate the registration of herbal medicines with established therapeutic effects. However, the EU regulations overwrote this practice of registration and founded new product categories which resulted in total rearrangement (the original intention was described as the unification of the European market).

Europe is the birthplace not only of modern phytotherapy, but of several other healing concepts (e.g. anthroposophy and homeopathy) which usually make use of plant products, but these lie outside modern (phyto)therapy and are therefore not discussed here. Phytotherapy is based on the application of pharmacologically active substances and the aim of the therapy is to act on pharmacological targets (e.g. enzymes and receptors). In modern phytotherapy the confirmation of efficacy and safety is required by clinical studies. Although the evidences are missing in case of several traditional medicinal plants, the direction of progress is to gain scientific data on the active components, their mechanisms of action and the clinical applicability of the herbal products. This is the basis of the development and quality control of modern phytotherapeutics, which is quite different from those of other medicinal systems applying plant-based products. However, there are transitions from and to phytotherapy to and from other methods: the effects of certain essential oils applied by aromatherapy are confirmed sufficiently to be considered to be the part of modern therapy and there are some plants that fall out from phytotherapy for toxicological reasons (e.g. certain pyrrolizidine alkaloid-containing plants) or for the lack of efficacy.

3.3.1 Herbal medicines

In the EU, medicinal products (including those of herbal origin) are registered and controlled by the European Medicines Agency (EMA), though national agencies also exist in parallel. In order to unify the marketing, registration and control policy of these products, the EU created new regulations and according to these goals the Committee on Herbal Medicinal Products (HMPC) was formed as part of the EMA to deal with questions and problems related to medicinal

plant products. The HMPC was established in 2004, and Directive 2004/24/EC came into force at the same time, with the objective of harmonizing European regulatory practices. The basic principle of this directive was to integrate the countless categories of products used with healing purposes throughout the EU. The two categories established by this directive into which all already existing products were to be requalified were the traditional herbal medicines and herbal medicines.

The most important consequence of this directive was the appearance of a new product category: ***traditional herbal medicinal products***. These can be used without medical diagnosis and supervision, and are not restricted by prescriptions; they can be applied orally, externally or by inhalation, and have been used in medicine for at least 30 years (not necessarily as licensed pharmaceutical druglike products), from which at least 15 years could be verified within the European Economic Area (EEA). These products are therefore authorized for marketing within the frame of a "simplified registration procedure". This simplified registration procedure is intended for herbal medicinal products with a long tradition, which do not fulfil the requirements for marketing authorization, and in particular those requirements whereby an applicant can demonstrate by detailed references to published scientific literature that the constituent or the constituents of the medicinal products has or have a well-established medicinal use with recognized efficacy and level of safety ("well-established use"). The simplified procedure allows the registration of herbal medicinal products without requiring particulars and documents on tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the Community. With regard to the manufacturing of these products and their quality, applications for registration of traditional herbal medicinal products have to fulfil the same requirements as applications for a marketing authorization.

The varied traditional use of medicinal plants in Europe made it necessary to establish an integrated "register" that *integrates traditional use* within the EU. According to Directive 2001/83/EC, this register is created in the form of community herbal monographs accepted by the HMPC. These monographs summarize the indications, posology, undesirable effects and contraindications for each herbal drug on the basis of documented traditional use. The drawback (quite apart from the advantages) of preparing such monographs is that products registered on this basis cannot necessarily be considered effective according to the principles of evidence-based medicine (since the efficacy of traditional herbal medicinal products is not confirmed clinically, but is only plausible on the basis of data coming from traditional applications). Unfortunately, the monographs reflect only traditional applications and there is no possibility to utilize preclinical or (weak) clinical data to expand the indications. Moreover, the majority of the monographs can be used only for the licensing of monocomponent products.

Non-traditional ***herbal medicines*** are registered according to requirements identical with those applying to all other (synthetic) medicines. Although the risk and financial expenditure are the same as in the case of synthetic drugs, as a consequence of legal (the patenting of plant-based products does not necessarily mean full protection for the patent holder) and financial considerations (the achievable profit is usually higher in the case of a new chemical entity, especially if it has superior efficacy to the already existing medicines) the large pharmaceutical companies do not develop medicines based on herbal extracts. For the same reasons, the number of clinical trials with plants is considerably lower than that for synthetics. This situation is also reflected at the regulatory level: the HMPC monographs record not merely the traditional uses, but additionally the well-established uses of plants. A product can be classified under well-established medicinal use provisions if well-established use is demonstrated with the provision of scientific literature (clinical trials) establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least 10 years, with recognized efficacy and an acceptable level of safety. In this case the 15/30-year-long presence on the market should not be applied as a requirement. HMPC monographs on the well-established uses of plants facilitate the registration of herbal remedies with clinically proved efficacy by release of the applicant from the completion of expensive clinical trials.

The main advantage of these monographs may be that they make registration easier and uniform, but they are legally binding to the national authorities in the process of registration only if they are part of the Community List. This is a list of plants that have been proven harmless during therapeutic application and whose preclinical safety has also been confirmed. Unfortunately, due to the lack of data, this list is rather short and the majority of the HMPC monographs therefore do not warrant a unified registration practice within the EU.

3.3.2 Food supplements

Directive 2002/46/EC regulating the category of food supplements was created in order to harmonize the legislation of the European Union. The previous chaotic relations were replaced by a liberally regulated market where the guaranteeing of the free competition on the market and the free flow of products were at least as important as professional viewpoints and consumer protection. The significant change was introduced that food supplementation from this point means not only the

consumption of vitamins and minerals, but also certain non-food ingredients, among them various medicinal plants that have never been regarded as food. The reason is simple: according to this new regulation, besides vitamins and minerals, food supplements may contain "nutrients or other substances with a nutritional or physiological effect". Considering the strict regulation of herbal medicines, it is not surprising that there is a shift from that category to food supplements. Within some years, the number of food supplements within the EU has reached several ten thousand within the EU. It is not rare that former herbal medicines appear on the market as food supplements with practically unchanged composition. However, quality guarantees for food supplements are much weaker. There is no obligation to apply GMP or similar quality assurance systems during processing, and before entering the market there is no authorization procedure (and no quality control from the authorities). Although there are initiatives to improve and ensure the quality of products, these are voluntary and do not rule out the presence of low-quality products on the market. In certain countries (e.g. Belgium, the Czech Republic and Italy), negative or positive lists have been created to limit the range of possible ingredients to the safe components.

Improper regulation results in certain possible negative consequences for customers. Since there is no legal guarantee (or governmental responsibility) as concerns the safety of these products, it is the manufacturer who bears all responsibility for safety and efficacy. Depending on the level of the sense of responsibility, the quality of food supplements ranges from products of GMP quality to adulterated preparations (without an active component or containing synthetics in order to increase the efficacy). A further source of problems is that, whereas Directive 2002/46/EC on food supplements provides for the setting of maximum and minimum contents of vitamins and minerals in these products, the doses of herbal components are completely unregulated (possibly varying from almost zero to above the therapeutic dose). In pursuance of the provisions of law, it is forbidden to attribute healing properties to food supplements, but unfortunately this rule is ignored by certain distributors from time to time. This is partly understandable, since the same quantity of the same plant will not lose its effect just because it is marketed in a different product category. For food supplements, so-called "health claims" should be used instead of therapeutic indications. These claims refer to the effect of the ingredient in a "softer" way than therapeutic indications of medicines.

3.3.3 Medical devices

The core of the legal framework of medical devices is Directive 93/42/EEC. According to this Directive, *"a medical device means any instrument, apparatus, appliance, software, material or other article (...) intended (...) to be used for human beings for*

the purpose of: (...) the diagnosis, prevention, monitoring, treatment or alleviation of disease, (...) and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means". This opens a wide door for various products that are quite different from the original idea of medical devices. As a result (since there is no restriction), more and more products of medicinal plant origin have appeared within this category. These medicinal plant-containing products are generally external preparations (e.g. creams), but the number of orally applied products is increasing. The reason why a (herbal) product is put on the market as a medical device may be the fact that these products do not need to be authorized; only a simple registration (without the need for clinical trials) is necessary. These products can be marketed with more concrete recommendations than the health claims of food supplements, and this may be one of the driving forces to explain why this category is preferred to food supplements.

Verification questions

1. What does the acronym TCM stand for?
2. What does the acronym FDA stand for?
3. What are the "health claims"?
4. What are the differences of the registrations of traditional herbal medicinal products and non-traditional herbal medicines in the European Union?
5. What is the reason of the possibility of quality problems with food supplements in the European Union?

4. Central nervous system

Anxiety, a depressed mood and sleeping disorders may be part of the normal life, but if these symptoms become permanent and affect the quality of life, psychotherapy and/or pharmacotherapy is indispensable. These symptoms are often regarded as civilization diseases, since the increased level of stress and decreased physical activity may play a role in their development. Some of these diseases (e.g. depression) were first described and defined in the 20th century. The availability of more sophisticated diagnostic methods and criteria have led to an increase in the number of patients by revealing the disease in previously undiagnozed patients.

Although the number and variety of synthetic antidepressants, antianxiety drugs and sleeping pills are rather high, there is a demand for more effective medicines with fewer side-effects. The most important undesirable effects of sleeping pills and antianxiety drugs are dependence and increasing tolerance. Antidepressants may have a wide range of side-effects, including obesity and a deterioration in the quality of life. Herbal remedies usually have fewer undesirable effects, although their efficacy is inferior to that ofsynthetics. However, in well-defined stages of the above-mentioned states, phytotherapeutics may be harmless equal alternatives to synthetic medicines and in efficacy.

4.1 Anxiety, sleeping disorders

The symptoms of anxiety include uneasiness, nervous tension and apprehension, and a sleeping disorder may also occur. Patients may additionally experience physical symptoms, e.g. gastrointestinal disturbances, headache or excessive perspiration. All stressful and traumatic life events are normally accompanied by anxiety, but if the symptoms become exaggerated, treatment is needed. For an assessment of severity of the anxiety, the Generalized Anxiety Disorder Assessment (GAD 7) questionnaire may be used. This is a self-administered patient questionnaire which can be used even in pharmacies. The questions to be answered are the following:

Over the last 2 weeks, how often have you been bothered by the following problems?

1. Feeling nervous, anxious or on edge
2. Not being able to stop or control worrying
3. Worrying too much about different things
4. Trouble relaxing
5. Being so restless that it is hard to sit still
6. Becoming easily annoyed or irritable
7. Feeling afraid as if something awful might happen

The GAD-7 score is calculated by assigning scores of 0, 1, 2 or 3 to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively, and adding together the scores for the seven questions. Scores of 5, 10 and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively. Mild anxiety may be treated with phytotherapeutics. In more severe cases, a medical doctor should be consulted

Insomnia may also be a consequence of normal life events, but the most common causes are related to an inadequate lifestyle (the lack of physical activity, obesity, or alcohol or caffeine consumption) or psychiatric diseases. The primary goal is the elimination of identified causes of insomnia (in cases of secondary insomnia), though in some cases, and especially in primary insomnia, pharmacotherapy (including phytotherapy) is inevitable.

The diagnostic critera for primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders IV. are as follows:

- The predominant complaint is difficulty in initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or an impairment in social, occupational or other important areas of functioning.
- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder or a parasomnia.
- The disturbance does not occur exclusively during the course of a mental disorder such as a major depressive disorder, generalized anxiety disorder, a delirium.
- The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse or a medication) or a general medical condition.

Medicines used in the treatment of anxiety and insomnia usually act by enhancing the effects of GABA (gamma-aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system. The mechanisms of action involve direct action on the GABA receptor, increasing the affinity of the receptor for GABA or increasing the concentration of GABA in the synaptic cleft by decreasing its breakdown or increasing its synthesis. In the pathophysiology of anxiety, a further neurotransmitter, 5-HT (serotonin), may also play a role. Excessive activation of the serotonergic system results in anxiety, whereas its inhibition decreases the symptoms. Similarly to synthetic drugs, herbal medicines act through the above-mentioned mechanisms. However the mechanism of action in certain plants has not been fully elucidated so far.

Although hypnotics and antianxiety drugs represent two distinct groups in the case of modern synthetics, in plants these two effects overlap, and primarily the applied dose determines the effect. Synthetic medicines are effective in more severe cases, while herbal remedies are effective in mild or moderate insomnia or anxiety. One further difference is the onset of the effect. Herbal hypnotics are more effective if applied for a long time, in contrast with the straight-acting synthetics. Since dependence and tolerance have not been described so far in the case of plants and they have fewer side-effects, phytotherapeutics may be realistic and favorable alternatives of synthetic medicines in the long-term treatment of less severe cases.

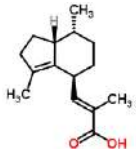
4.1.1 Valerian

The roots of *Valeriana officinalis* have been applied for the treatment of central nervous system disorders since ancient times. This species is native to Europe, but in other parts of the world further *Valeriana* species are applied for similar purposes (e.g. *V. wallichii* in Asia). In the therapy, the dried and very odorous roots are applied, primarily as an extract in coated tablets or capsules to achieve the appropriate compliance of the patients. However, some patients use valerian as a tea; since it is a root, a decoction should be prepared. Valerian is often used in combination with hops or lemon balm.

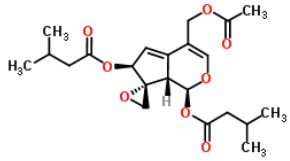
- **Chemical composition and mechanism of action**

The odour of the roots is linked to its volatile oil content. The volatile oil of valerian consist of monoterpenes and sesquiterpenes. One characteristic component is the sesquiterpene valerenic acid. Valerenic acid allosterically modulates GABA-A receptors and induces anxiolytic activity.

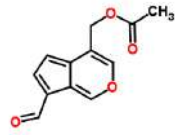
The monoterpene valepotriates may have an important role in the effect. These compounds are rather unstable (even at room temperature, but low pH and high temperature increase their degradation). Their metabolites (and presumed active forms) are baldrinal and its derivatives. In the course of the degradation of valeoptriates, isovaleric acid is among the compounds formed (it is not present in the fresh roots), and ispartly responsible for the distinct unpleasant odor of the herbal drug. Valerian roots also contain lignans.



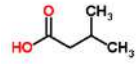
valerenic acid



valtrate (a valepotriate)



baldrinal



izovaleric acid

Although the mechanism of action has not been elucidated in detail so far, much is known of the effects of valerian extracts on the central nervous system (CNS). Valerian extracts have affinity for the GABA receptors, and increase the synthesis and release of GABAand inhibit the decrease of its level in the synaptic cleft. An effect through adenosine receptors is also presumed (agonists of these receptors have a relaxing effect, whereas antagonists such as caffeine have the opposite effect). Some flavonoids of the plant are ligands for the benzodiazepine binding site of the GABA receptor. However, these activities are not definitely linked to the individual compounds of the plant. In the therapy, therefore mostly extracts are used. The most widely applied extracts are prepared with ethanol/water. In traditional medicine, dry extracts prepared with water, expressed juice from the fresh roots and a valerian root essential oil are also applied.

- ## Efficacy and indications

In clinical trials, valerian root improved sleep (as confirmed by EEG) rather than exerting a general sedating effect. Sleep EEG changes were more pronounced after several days of treatment. Efficacy has been studied in non-organic insomnia and nervous tension. Randomized, double-blind clinical studies have confirmed that aqueous-ethanolic extracts of valerian root have a clinical effect in sleep disturbances, as assessed by means of subjective ratings and psychometric scales. In a comparative study, valerian was as effective as oxazepam for the treatment of insomnia. Placebo-controlled studies have confirmed the efficacy of the plant in sleep disorders. The qualitative dichotomous results of a meta-analysis based on 18 randomized controlled studies suggested that valerian is effective for a subjective improvement of insomnia. Although the antianxiety effect of valerian was also studied, the amount and quality of the available data are quite limited.

In a placebo-controlled study, valerian led to a reduction of hot flush frequencies 4 and 8 weeks after the treatment. In a double-blind, randomized, placebo-controlled trial, the severity of menstrual pain was significantly reduced by valerian and the total scores of the systemic manifestations associated with dysmenorrhea also decreased.

The EMA has published monographs relating to the well-established and the traditional uses of valerian root. As a well-established medicine (must be prepared by extraction with 40-70% ethanol, valerian can be used

- for the relief of mild nervous tension and sleep disorders.

Traditional herbal medicinal products may be applied

- for the relief of mild symptoms of mental stress and to aid sleep.

In well-established use a single dose is equivalent to 2 to 3 g of the herbal substance. In the treatment of anxiety, the maximal dose is 4 times daily. It can be administered to adolescents over 12 years of age, adults and the elderly.

Valerian root is not appropriate for the acute treatment of mild nervous tension or sleep disorders. To achieve an optimal treatment effect, administration for 2-4 weeks is recommended.

- **Side effects, interactions & contraindications**

With the exceptions of hypersensitivity, lactation and pregnancy, no contraindications are known. Gastrointestinal symptoms (e.g. nausea or abdominal cramps) may occur. Clinically relevant drug interactions have not been observed. Valerian may increase the effect of sedatives. In contrast with benzodiazepines, valerian root does not reduce the level of vigilance during the morning after it has been taken to relieve insomnia. An overdosage results in benign and reversible symptoms.

4.1.2 Hop

The dried female inflorescence (strobiles) of *Humulus lupulus* L. is widely used in the food industry for its bitter taste. In comparison with this application, its phytotherapeutic use is almost negligible. This climbing perennial herb is grown primarily for use in the beer industry.

The medicinal application of the hop is documented in folk tradition. Apart from the conventional modes of administration (tea), the hop has also been used in hop pillows, which have been claimed to have a sedative, sleep-inducing effect.

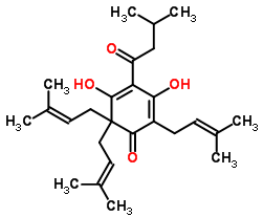
Nowadays, the hop is usually used as an extract in combination products

(especially with valerian). Hop tea is less popular because of its taste.

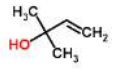
- **Chemical composition and mechanism of action**

The bitter taste of the hop stems from its prenylated phloroglucinols (also known as alpha-acids or humulones and beta-acids or lupulones. The essential oil content of the inflorescence makes the taste more complex. Flavonoids, including special prenylated ones and chalcones (xanthohumol and its derivatives) are characteristic of the genus.

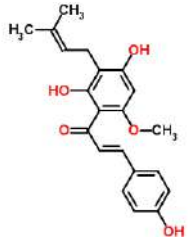
The most important component from the aspect of bioactivity is 2-methyl-3-buten-2-ol. Although only traces of this compound are to be found in freshly harvested hops, its amount increases during storage because of the decomposition of phloroglucinols. The hop contains isovaleric acid in low concentration.



lupulone



2-methyl-3-buten-2-ol



xanthohumol

The mode of action of this plant is not fully understood. Isovaleric acid may contribute to the action, but 2-methyl-3-buten-2-ol is of greater importance. The sedative effect of hop extracts has been confirmed in multiple animal experiments. With pure phloroglucinols, this effect cannot be achieved. However, following the administration of 2-methyl-3-buten-2-ol, the bioactivity of the plant extract can be reproduced. Processed products contain significant amounts of this compound, and it may also be generated *in vivo* by metabolism of the bitter acids. A hop extract may also have an agonistic effect on melatonin receptors (this has been confirmed indirectly), which may contribute to the clinical effect. The compounds responsible for this activity are not known.

The spasmolytic effect of the hop has been demonstrated preclinically. Currently the most intensively studied aspect of its bioactivity is its estrogenic activity. The discovery of this effect emerged from the experience that menstrual disturbances are common among female hop pickers. This has been linked to the potential estrogenic activity of hop strobiles. The agonist effect of a hop extract on estrogen receptors has been confirmed and the most active componenst has been identified as 8-prenylnaringenin, a flavonoid in this plant, which has been claimed to have the strongest activity among the phytoestrogens. Xanthohumol derivatives (and primarily isoxanthohumol) can be transformed to 8-prenylnaringenin in the liver. Since 8-

prenylnaringenin may be absorbed through the skin, the effect observed in female hop pickers has a rational explanation.

- **Efficacy and indications**

No clinical studies are available in which the hop featured as single component. There have been some controlled, double-blind clinical studies on patients with non-organic sleep disorders in which a fixed combination of hops and valerian was applied. Although these ended with positive results, they cannot serve as confirmation of the clinical efficacy of hops.

According to the EMA, hops can be used as a traditional herbal medicinal product in the form of tea, dry herbal substance, liquid or dry extracts (prepared with a mixture of water and ethanol or methanol). The approved indication is

- relief of mild symptoms of mental stress and to aid sleep.

- **Side-effects, interactions & contraindications**

The possibility of the use during pregnancy and lactation and in children under 12 years of age has not been established due to the lack of adequate data. No contraindications (except for hypersensitivity) and special side-effects are known. In therapeutic doses, an estrogenic effect of hops is negligible and has not been recorded so far.

4.1.3 Lavender

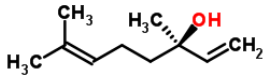
In phytotherapy, lavender flowers and essential oil are used. Lavender flower consists of the dried flowers of *Lavandula angustifolia* Miller (*L. officinalis* Chaix). The essential oil is obtained by steam distillation from the flowering tops of *L. angustifolia*. This species is often confused with other lavender species, e.g. *L. x intermedia* Emeric. (lavandin) and *L. latifolia* Medik. (spiklavender). However, in the European Pharmacopoeia only the drugs of *L angustifolia* are official. Lavender species are indigenous to the Mediterranean region, but are cultivated extensively because of their industrial importance. Lavender oil is required in large quantities by the cosmetic industry (however, it should be noted that many lavender-scented products contain synthetic linalool rather than the essential oil of the plant).

The essential oil of lavender has been used in therapy (maily as a sedative) since the Middle Ages, following the development of steam distillation for similar purposes as today. The traditional indications of lavender include the relief of gastrointestinal complaints and musculoskeletal disorders (in the latter case, it has been applied

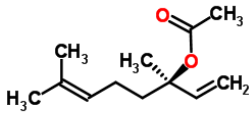
externally). However, cutaneous application may also target restlessness and sleeping or digestive problems.

- **Chemical composition and mechanism of action**

The lavender flower contains a noteworthy amount (1-3%) of essential oil. The main components of the oil are monoterpenes alcohols and their derivatives (60-65%), with the major constituents linalool and linalyl acetate.



linalool



linalyl acetate

In preclinical studies, lavender extracts and oil proved to exert a spasmolytic effect; this is related to their application in the treatment of gastrointestinal symptoms. The antimicrobial effect of the oil has been demonstrated against several strains. Sedative (a prolongation of the sleeping time and a decrease in locomotor activity) effects of various extracts and oils has been demonstrated in animals. Linalool derivatives reach a pharmacologically active concentration in the blood plasma even after inhalation. These compounds act by increasing the effect of GABA.

- **Efficacy and indications**

Although experiments have been carried out with herbal extracts, in human therapy and studies only the oil has been applied. The anxiolytic activity of lavender oil has been studied in certain conditions (anxiety and depression). Lavender oil has been administered orally or as aromatherapy. Lavender oil positively influences anxiety and stress-related restlessness. However, in consequence of the variability in the applied dose and the examined effect and the low quality of some products, the EMA has granted only a monograph for the traditional application of this plant (its application with specific indications was not considered to be well-established).

Lavender essential oil may be marketed as traditional herbal medicinal products for

- relief of mild symptoms of mental stress and exhaustion and to aid sleep.

Its oral daily dose is 20-80 mg, though it can also be applied as a bath additive (with a proposed dose of 1-3 g).

- **Side-effects, interactions & contraindications**

Its use in children under 12 years of age is not recommended. Safety during pregnancy and lactation has not been established. A full bath is contraindicated in cases of open wounds, large skin injuries, acute skin diseases and when a warm bath may be dangerous (circulatory diseases). No cases of an overdosage, no adverse effects and

no drug interactions have been reported. The only known contraindication is hypersensitivity to the oil.

4.1.4 Lemon balm

In phytotherapy, the dried leaves of *Melissa officinalis* L. are used. Lemon balm has a long tradition of medicinal use in Europe, especially in the form of herbal tea or alcoholic extracts, for the relief of mild stress, sleeping disorders and mild gastrointestinal complaints (e.g. bloating and flatulence). Lemon balm was the most important component of the medieval "panacea", Aqua carmelitarum. The spirit called Melissengeist, a poular home remedy in German-speaking countries was the first registered traditional herbal medicine in the European Union.

- **Chemical composition and mechanism of action**

The leaves contain a notable amount (~5%) of phenylpropanoids, including hydroxycinnamic acid derivatives such as caffeic and chlorogenic acids and in particular rosmarinic acid. The essential oil content is low; lemon balm oil is therefore expensive and is often substituted in cosmetics by lemongrass (*Cymbopogon* sp.) oil.

In *in vitro* experiments, lemon balm extracts proved to inhibit GABA transaminase activity, resulting in elevated GABA levels. A GABA-increasing effect has been confirmed in animal studies too. The sedative and antianxiety effects of extracts have also been documented preclinically. Although the essential oil does not seem to have a role in the effects on the central nervous system, its confirmed spasmolytic activity may be crucial in the relief of gastrointestinal problems.

The effects on cognitive functions may be explained by the fact that lemon balm has acetylcholine receptor activity in the central nervous system and had the ability to inhibit acetylcholinesterase enzyme.

A specific preparation of *M. officinalis*, consisting of a highly purified, dry aqueous extract (70:1) of the leaves, is used for the treatment of herpes infections. This extract is standardized with respect to its antiviral activity. Although the exact mechanism of action and active components are not known, this extract has a preclinically (and also clinically) confirmed antiherpes effect.

- **Efficacy and indications**

An improvement of the cognitive functions has been confirmed in clinical studies in healthy volunteers. In a population of Alzheimer patients, similar effects have been observed.

An open study on volunteers suffering from mild to moderate anxiety disorders and sleep disturbances resulted in improvements in the anxiety symptoms and insomnia.

According to the EMA, lemon balm tea and preparations containing a dried herbal substance as ethanolic liquid or dry ethanolic or water extracts may be applied as traditional herbal medicinal products

- for the relief of mild symptoms of mental stress and to aid sleep for adolescents over 12 years of age, adults and the elderly.

The dose as herbal tea is 1.5-4.5 g of the comminuted herbal substance as a herbal infusion, 1-3 times daily.The posology of the powdered herbal substance is 0.19-0.55 g, 2-3 times daily.

- **Side-effects, interactions & contraindications**

Its use in children under 12 years of age has not been established due to the lack of adequate data. Although there are no data concerning the safety in lactating and pregnant women, lemon balm is also applied in this population, as tea or food. No contraindications except hypersensitivity, and no undesirable effects are known. There have been no reports on the consequences of anoverdosage.

Preclinical data indicate that lemon balm may inhibit the activity of the thyroid stimulating hormone, but the clinical relevance of this finding is not known.

4.1.5 Passion flower

Passion flower medicines contain the aerial parts (including the stems, leaves, flowers and fruit) of *Passiflora incarnata* L., a perennial climbing plant native to the Americas. Native Americans have used it for several medicinal purposes. In Europe, it has been used traditionally for the relief of mild symptoms of mental stress and to aid sleep.

Several species of the genus are cultivated outside America (including Europe) for their beautiful flowers and delicious fruit. The fruit of *P. incarnata* is also edible and known as maypop. However, passion fruit or maracuja (*P. edulis*) and sweet granadilla (*P. ligularis*) are more widely used for this purpose.

Chemical composition and mechanism of action

Flavonoids, mainly the *C*-glycosides of apigenin and luteolin, are characteristic of this species. It contains essential oil only in traces. The plant contains beta-carboline alkaloids (e.g. harman and harmol), but these are undetectable and therefore pose no threat in the finished products.

In vitro studies indicate that *P incarnata* extracts have affinity for the $GABA_A$ receptors and inhibit GABA uptake to the neurons. Anxiolytic and sedative effects, including the reduction of spontaneous locomotor activity and a prolongation of the sleeping time has been confirmed in animals. The available data suggest that the effects on the central nervous system may be mediated via modulation of the GABA system, but the doses employed in animal experiments are rather high relative to the human therapeutic dose.

Efficacy and indications

There are only limited data to support the well-established use of passion flower.

In a multicentric, double-blind study, passion flower was compared with mexazolam in the treatment of neurotic symptoms. After 4 weeks, passiflora showed a significant effect on 4 features (including anxiety, tenseness and irritation) among the major neurotic symptoms, while mexazolam did so on 8 items. The effect of a passion flower extract was compared with that of oxazepam in patients with general anxiety. After 4 weeks, the score on the Hamilton anxiety rating scale was the same in both groups. In a Cochrane review (published in 2009) of the use of *Passiflora incarnata* for the treatment of anxiety disorder, the aforementioned two studies with a total of 198 participants were analyzed. The authors concluded that the relevant randomized clinical trials examining the effectiveness of passiflora for the treatment of anxiety were too few to permit any conclusions to be drawn.

In a double-blind, placebo-controlled study, the effects of *Passiflora incarnata* tea on the quality of sleep were investigated. The treatment improved the sleep-onset latency and the sleep efficiency, but not the total sleeping time or the nocturnal awakenings.

In a small study, the effects of a passion flower extract were compared with those of placebo and diazepam. Diazepam and, to a lesser degree, the placebo and the passion flower extract, all decreased mental alertness, though the effect of the passion flower extract could not be detected by EEG.

In a study, passion flower has proved to effectively decrease the symptoms of opiate withdrawal. The combination of passion flower and clonidine was superior to clonidine alone with respect to psychological symptoms. A randomized study revealed that oral premedication with *Passiflora incarnata* reduced preoperative anxiety without inducing sedation or influencing the psychomotor functions.

Data from randomized clinical trials of the effectiveness of passiflora for anxiety are too few and too weak to allow any conclusions concerning the efficacy. As a traditional herbal medicinal product, passionflower may be used

- for relief of mild symptoms of mental stress and to aid sleep.

The dose as herbal tea is 1-2 g of the comminuted herbal substance as herbal infusion, 1-4 times daily or as powdered herbal substance: 0.5-2 g, 1-4 times daily as powdered herbal substance 0.5-2 g, 1-4 times daily. Herbal extracts with similar posology may also be applied.

- **Side-effects, interactions & contraindications**

The use in children under 12 years of age is not recommended. Safety during pregnancy and lactation has not been established. No drug interactions, no contraindications (except hypersensitivity) and no special undesirable effects are known. No case of overdosage has been reported.

4.1.6 Oat

Avena sativa L. (oat) has been used for centuries for various medicinal purposes, most frequently for the relief of cutaneous problems and as a sedative. The herb is harvested before flowering for medicinal purposes and administered as a herbal tea or some other liquid extracts or as the juice expressed from the fresh herb as sedative. The dried grain (fruits) has been used externally as a bath preparation, as a colloidal extract of oat flour or as oatmeal in liquid paraffin.

- **Chemical composition and mechanism of action**

Oat fruits are rich in proteins and sugars (including beta-glucans). Grains of oats contain the highest lipid fraction among all feeding crops of the Poaceae family. It contains an indole alkaloid, gramine in low amount, saponins and flavonoids.

Oat herb contains noteworthy amounts of sugars (including beta-glucans), saponins, flavonoids and in traces the cyanogenic glycoside (the concentration of the latter decreases during the development of the plant).

Alcoholic extracts of *Avena sativa* herb, made with different ethanol concentrations, were tested *in vitro* for MAO-B inhibition, and significant activity was observed.

In an animal experiment, a special extract enhanced stress coping, the speed of learning and alertness, and a positive effect on social behavior was also observed.

A polyphenol from the fruit inhibited vascular smooth muscle cells and enhanced nitric oxide (NO) production *in vitro*. After local treatment of a skin surface subjected to triggered inflammation, an oat fruit extract decreased vasodilation and edema. An extract decreased the expression of COX-2 and phospholipase *in vitro*. Inhibition of interleukin production was also observed. The substance P-mediated stimulation of NO synthesis was blocked by an *Avena* flour preparation. *Avena* flour preparations have also proved effective in an experimental wound healing model.

The beta-glucan of oat decreased cholesterol level in an animal experiment.

- **Efficacy and indications**

The effects of oatmeal for the skin care of children were assessed in a 3-month study. Physicians found the treatment effective in the majority of the cases. In a double blind study, experimental skin irritation was relieved by the application of an oat-based product. The corticoid-sparing effect of a cutaneous oat extract was evaluated in children with atopic dermatitis during 6 weeks. There was a decrease of 42% of topical corticoid use in the intervention group (in the control group: 7.5%)

In an 11-week randomized, controlled trial, the consumption of an oat-containing cereal preparation resulted in a significant reduction of the LDL-cholesterol level relative to those who consumed corn cereal. In a further 4-week trial, the HDL cholesterol level increased significantly in those who were taking an oat bran supplement. Some studies have suggested that oat meal consumption may have a beneficial effect on blood pressure, though the results are not conclusive.

The evidence available from traditional use indicates that dried fruits comminuted to oat flour, or colloidal oatmeal may be used as a traditional herbal medicinal product for the

- symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in the healing of minor wounds.

For a bath of 150 to 200 litres 60 g of oat flour should be used. Colloidal extracts of flour are used in concentrations up to 20–30%, mixed with a vehicle. Liquid paraffin containing 5% oatmeal may also be applied

The results of traditional application demonstrate that oat herb may be used as traditional herbal medicinal products for the relief of

- mild symptoms of mental stress and to aid sleep.

The single dose of the comminuted herbal substance as an infusion is 3 g. Other aqueous or ethanolic extracts and the juice expressed from the fresh herb (10 ml) may also be used 3-4 times daily.

- **Side-effects, interactions & contraindications**

Following cutaneous application, skin reactions may occur in atopic patients and in patients with contact dermatitis. When it is used internally, caution is advised for patients with celiac disease because data on the protein content are not available.

4.1.7 Motherwort

Leonurus cardiaca L. is a medicinal plant that has long traditions in European folk medicine and also forms part of contemporary medicine. Aerial parts of the plant have been used for different cardiovascular symptoms (palpitation, cardiac pain and further cardiac complaints) since the 1600s.

According to the definition of the European Pharmacopoeia, Leonuri cardiacae herba is the whole or cut, dried flowering parts of *Leonurus cardiaca*, with a total flavonoid content of not less than 0.2%.

- **Chemical composition and mechanism of action**

Characteristic constituents are labdane-type diterpenes (about 0.4%, e.g. leocardin, leosibiricin). The herb may contain up to 1.5% of the alkaloid stachydrine and approximately 1% of the phenylethanoid lavandulifolioside. Old studies reported the presence of cardiac glycosides, but more recent investigations did not confirm this.

A purified water extract (free from furanic diterpenes) of *L. cardiacae* herba was investigated in the isolated rabbit heart *in vitro*, and was found to exert Ca^{2+}-antagonistic and class III-like antiarrhythmic effects (the left ventricular pressure was decreased and QTc was prolonged). In voltage clamp experiments, the purified extract exerted a Ca^{2+}-antagonistic activity and reduced the repolarizing current, whereas the Na^{+} current was not affected. Proarrhythmogenic activity was not observed. Stachydrine applied i.v. was reported to reduce the systolic heart rate in an animal experiment.

Anti-inflammatory, antimicrobial and antioxidant effects of *Leonurus* extracts have been confirmed in *in vitro* studies. Weak sedative activity was observed in several animal experiments.

- **Efficacy and indications**

Only one clinical study is available with this species. Fifty patients with arterial hypertension with symptoms of anxiety and sleep disorders were treated for 28 days with 1200 mg of an extract from *L. cardiaca*. A significant decrease in blood pressure was observed relative to the baseline. The symptom scores of anxiety and sleep also improved significantly.

On the basis of its folk medicinal use and the available preclinical data, motherwort may be used as a traditional herbal medicinal product

- to relieve the symptoms of nervous tension, or
- to relieve symptoms of nervous cardiac complaints such as palpitations, after serious conditions have been excluded by a physician.

The daily dose of the comminuted herbal substance for tea preparation is 3-10 g, and as powdered herbal substance is at most 450 mg. A tincture or liquid extracts may also be applied.

- **Side effects, interactions & contraindications**

In cases of hypersensitivity and during pregnancy, the use of motherwort is contraindicated. Its use in children and adolescents under 18 years of age has not been established due to the lack of adequate data.

4.2 Depression

Depression is an emotional disorder, characterized by sadness, a feeling of helplessness, a loss of interest or pleasure, poor concentration, and feelings of guilt or low self-worth. It may be accompanied by disturbed sleep or an altered appetite and a feeling of tiredness. Depression may impair a person's ability to function at work and in social functioning. Severe depression poses a severe risk of suicide. Depression often starts at a young age. Stress and tragic life events can provoke the development of the disease. In females, the prevalence of depression (20%) is almost double that in males. Depression may be permanent or recurrent. In all stages of the disease, psychotherapy is a useful tool in the treatment. Mild to moderate depression can be treated with phytotherapeutic preparations, but in more severe cases synthetics are needed. For the assessment of severity, self-reported questionnaires are available on the Internet. One of the most widely applied ones is the Patient Health Questionnaire-9 (PHQ-9). The sum of scores of the answers to the following questions gives information on the severity (not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3).

Over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or of hurting yourself in some way

A PHQ-9 total score of 5-9 suggests minimal symptoms, 10-14 minor depression, dysthymia or mild major depression, 15-19 moderately severe major depression, and 20+ severe major depression. In all cases of suspected depression, the patient should be asked to consult a doctor, and in all cases of major depression, only treatment proposed by a doctor should be applied.

The etiology of depression is not fully understood. Apart from provoking life events (stress and traumatic experiences), it is widely accepted that the underlying cause is the dysregulation of certain neurotransmitters. The original assumption that depression results from a functional deficit of noradrenaline and serotonine (5-HT) has been refined and today it is accepted that the dysregulation of further

neurotransmitters (GABA and dopamine) and some neuropeptides (endogenous opioids) also have a role. Pharmacological treatment usually aims at inhibition of the reuptake of serotonine or noradrenaline [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs)] or the breakdown of noradrenaline, serotonin and dopamine [monoamine oxidase inhibitors (MAOIs)]. The fact that the efficacy of antidepressants lags behind the desired level underlines the assumption that the disease is a consequence of the dysregulation of several compounds in the central nervous system.

The modern phytotherapy of depression is limited to a single plant, *Hypericum perforatum*. Although some other plants, primarily with anxiolytic and sedative effects, have also been used in folk medicine for this purpose, it must be made clear that depression as a disease was defined only in the 20th century, and it is therefore not possible to identify antidepressant herbs from the foregoing tradition.

4.2.1 St. John's wort

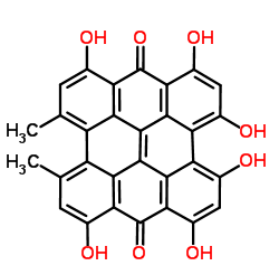
The dried flowering tops of *Hypericum perforatum* L., harvested during flowering, have been used for different central nervous system indications for centuries. It has also been used to 'strengthen the nerves', which may refer to its application in states similar to depression in order to restore the emotional balance.

This yellow-flowered perennial weed is indigenous to Europe. The common name St. John's wort indicates that its flowers were gathered traditionally on St. John's day (24th of June).

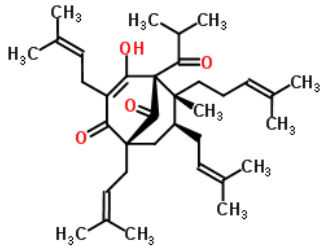
- **Chemical composition and mechanism of action**

The characteristic compounds of *Hypericum* are phloroglucinol derivates (mainly hyperforin, 0.2-4%), naphthodianthrones (0.06-0.4%; hypericin and its derivatives), flavonoids (2-4%; mainly glycosides, quercetin and also biflavones, e.g. amentoflavone). The *Hypericum* extracts used in industry have a hypericin content of 0.16-0.32%, and a hyperforin content in the range 1.5-6%. The total flavonoid content is 6-8%. The most widely studied (and chemically well-defined extracts) are WS 5570, LI 160 and Ze 117. WS 5570 and LI 160 are very similar in composition. In Ze 117, the hyperforin content is less (below 0.2%). Medicines with well-established indications should be quantified with respect to hypericin, and the amounts of hyperforin and total flavonoids must be declared. In the case of traditional herbal medicinal products, the

amounts of hyperforin and hypericin should be specified and the daily intake of hyperforin must be below 1 mg.



hypericin



hyperforin

Although several preclinical studies involving different *Hypericum* extracts and pure constituents have been publishd, the mechanisms of action are still under discussion. The confirmed bioactivities relating to the clinical effect include inhibition of the reuptake of serotonin (5-HT), noradrenaline and dopamine, the upregulation of dopaminergic receptors and postsynaptic 5-HT_1 and 5-HT_2 receptors and the downregulation of beta-adrenergic receptors. The extract also has an effect on GABA receptors (increasing the affinity; however, this is related to amentoflavone, a flavonoid present in the plant only in traces).

The effect of *Hypericum* was originally explained by its inhibitory effect on MAO. Indeed, the flavonoids of this plant inhibit MAO and catechol-*O*-methyltransferase (COMT), but the concentration needed to achieve this effect could not be expected to be achieved in the course of application in human therapeutic dosages.

Hypericin inhibits the dopamine beta-hydroxylase, and increases the level of serotonin in the brain after 2 months of treatment in a comparable manner to imipramine. Hyperforin inhibits neurotransmitter (serotonin, dopamine, noradrenaline, GABA and glutamate) reuptake in a concentration lower that what could be achieved through the therapeutic application of the plant. This effect may be a result of the enhancement of the intraneuronal Na^+ level and the inhibition of P-type Ca^{2+} channels. The role of flavonoids in increasing the bioavailability of hyperforin and hypericin has been demonstrated.

The anxiolytic and antidepressant effects of various extracts have been confirmed in animal experiments (the latter primarily using forced swimming tests).

- **Efficacy and indications**

The extract LI 160 has been assessed in several randomized, double-blind, placebo-controlled trials lasting for 4-12 weeks on patients with mild to moderate major depression. LI 160 proved significantly more effective than placebo, and superior (or

not inferior) to fluoxetine and sertraline, as confirmed by the reduction in the Hamilton Depression Scale score. In some studies, efficacy could not be confirmed. The responder rate (where analyzed) was higher than in the placebo group.

WS 5570 was also found to be effective in mild to moderate depression and was also studied in patients with moderate to severe depression and in these groups proved equally as effective as paroxetine. In one study, it exhibited a beneficial effect in preventing a relapse after recovery from acute depression.

In studies with a similar design to the previous ones, Ze 117 was therapeutically equivalent to imipramine and fluoxetine in patients with mild to moderate depression and significantly superior to placebo

There have been several sporadic studies with different *Hypericum* extracts, and these usually confirmed the efficacy of St. John's wort in mild to moderate depression. In the most recent (2009) Cochrane meta-analysis that assessed the overall efficacy of St. John's wort in major depression, 29 trials involving 5489 patients (including 18 comparisons with placebo and 17 comparisons with synthetics) were analyzed. In nine larger trials, the combined response rate ratio (RR) for *Hypericum* extracts as compared with placebo was 1.28; in 9 smaller trials, it was 1.87. relative to tri- or tetracyclic antidepressants and SSRIs, respectively, the RRs were 1.02 and 1.00 (this means that the plant products were similarly as effective as standard treatment with synthetics). The frequency of side-effects, however, was lower among the patients who received phytotherapeutic treatment.

Data published on the efficacy of *Hypericum* in the treatment of premenstrual syndrome and menopause indicate its favorable effect in decreasing the psychological and psychosomatic symptoms.

In the EMA monograph for well-established use, three dry extracts are to be found. The dry extract with DER 3-7:1 [extraction solvent methanol (80% v/v)] is identical with WS 5570, and the dry extract with DER 3-6:1 [extraction solvent ethanol (80 v/v)] is equivalent to LI 160. Additionally, a dry extract (DER 2.5-8:1, extraction solvent ethanol (50-68% v/v) is also included. The first two of these extracts can be registered as herbal medicinal products for the

- treatment of mild to moderate depressive episodes,

and the third for the

- short-term treatment of symptoms in mild depressive disorders.

The daily doses range between 600 and 1800 mg. The mechanisms of action (changes in neurotransmitter levels) suggest that, similarly to synthetics, the onset of the effect can be expected within 4 weeks of treatment.

For traditional use, expressed juice, dry herbal material and several liquid and dry extracts are listed in the EMA monograph. Their indication is the

- relief of temporary mental exhaustion

(in view of the antidepressant effect, although the EU regulations do not allow such an indication for traditional herbal medicinal products). With regard to their confirmed traditional application, some extracts can be used for the symptomatic relief of mild gastrointestinal discomfort.

- **Side-effects, interactions & contraindications**

In comparison with synthetic antidepressants, the safety profile of St John's wort is more favorable and it is better tolerated.

On the basis of the reported photosensitizing effect of hypericin, numerous publications have analyzed (and confirmed experimentally) the potential phototoxicity of *Hypericum* extracts. The extracts are less phototoxic than pure hypericin. After the therapeutic administration of *Hypericum*, the skin level of total hypericin was two orders of magnitudes lower than the estimated phototoxic level. From clinical experience, *H. perforatum* can be considered safe when administered in the therapeutic dosage. After the oral application of 1800 mg daily for 2 weeks, the skin sensitivity to UVA was increased, but no signs of phototoxicity were observed.

Hypericum participates in clinically important interactions with conventional drugs. These are a result of induction of the enzymes CYP3A4, CYP2C9 and CYP2C19 and permeability glycoprotein (Pgp), and they lead to loss of the therapeutic effect. The extent of induction of CYP3A depends on the hyperforin content of the product. The activity of CYP3A returns to the basal level by 1 week after the termination of St. John's wort administration. Hypericin is claimed to be responsible for Pgp induction,. In the event of the concomitant administration of drugs that increase the serotonin level, serotonin syndrome may develop. The most important interactions are summarized below.

Most significant drug interactions of St. John's wort

Mechanism:

1. CYP induction
2. Induction of permeability glycoprotein
3. Increase of serotonin activity

Medicine	Mechanism	Sequel
HIV protease inhibitors	1, 2	Decreased antiviral efficacy
HIV reverse transcriptase inhibitors	1	
Coumarin-type oral anticoagulants	1	Decreased anticoagulant effect
Cyclosporine, tacrolimus	1, 2	Rejection of a transplanted organ
Oral anticoncipients	1	Breakthrough bleeding, unwanted pregnancy
Antiepileptics	1	Epileptic seizure
Digoxin	2	Heart failure, arrhythmia
Theophylline	1	Asthmatic attack
Triptans	3	Serotonin syndrome
SSRIs	3	

As adverse effects, mild gastrointestinal disorders, allergic skin reactions, fatigue and restlessness may occur. During the treatment, intense UV exposure should be avoided, since mild photosensitivity may occur in sensitive patients. In the absence of sufficient clinical data, administration to children, or during pregnancy and lactation is not recommended. There is no known absolute contraindication except hypersensitivity to St. John's wort.

Verification questions

1. List four plants with anxiolytic effect (English and Latin names)!
2. What are the main elements of the mechanism of action of valerian?
3. What is the active component of hop?
4. What is the mode of action of lavender?
5. What are the therapeutic applications of lemon balm?
6. Which of the plants used with CNS indications are known also as ornamental plants?
7. Which part of oat is used to relieve mental stress?
8. What are the therapeutic indications of motherwort?
9. What are the clinically important drug interacions of St. John's wort?
10. What is the mode of action of *Hypericum preforatum*?

5. Gastrointestinal system

The treatment of different diseases of the digestive tract and alleviation of the related symptoms is a very wide area and has the longest tradition in phytotherapy. The majority of the applied plants originate from folk medicine, though some of them have been investigated studied in modern clinical studies too. One further characteristic of this area is that there is an overlap of the therapeutically used species and spices. The spices not only provide a pleasant taste for dishes but also possess medicinal properties: they increase the appetite, relieve gastrointestinal spasms, etc. Moreover, some food plants have therapeutic effects (e.g. the plum in obstipation, and the dandelion in bile problems).

Diseases of the digestive system may be based on underlying organic pathologies, but more generally they are functional disturbances. This means that no organic irregularity or disorder can be detected despite the obvious symptoms. The armamentarium of the plants used in therapy covers a wide range of symptoms and it is not uncommon that a single plant has multiple targets. This in line with the nature of (functional) digestive disorders, i.e. a phytotherapeutic agent, particularly if it contains several constituents, relieves the symptoms by a variety of mechanisms of action.

5.1 Functional gastrointestinal disturbances

Depending on the nature of the symptoms, functional gastrointestinal disorders can be categorized as functional dyspepsia or functional bowel disorders. In the former case, stomach problems predominate; in the latter case, symptoms originating from the bowel are more characteristic. However, there is an overlap between these states and also between the patients: functional dyspepsia affects 10% of the population, whilst the prevalence of functional bowel disorders is about 10%, and approximately 30% of the patients suffer from both diseases. There is likewise an overlap between the applied plants. The recommended medicinal plants range from bitters to cholagogues and spasmolytics.

The most recent Rome Criteria (available at http://www.romecriteria.org/) diagnostic lists the criteria of functional gastrointestinal disorders as follows:

Functional dyspepsia

One or more of the following:

- bothersome postprandial fullness
- early satiation

- epigastric pain
- epigastric burning

and no evidence of any structural disease (including on upper endoscopy) that is likely to explain the symptoms (criteria fulfilled for the last 3 months with symptom onset at least 3 months prior to diagnosis). Subcategories of this disease are postprandial distress syndrome and epigastric pain syndrome.

In these patients, insufficient bile, pancreatic or gastric juice may be detected, but these, together with gastric *Helicobacter pylori* infection, accompany rather than cause the syndrome. Since functional dyspepsia is often related to psychic factors (depression and anxiety), in phytotherapy plants targeting these diseases may be used. The fundamentals of the therapy rely on the application of plants that improve the digestion (by increasing the appetite, or gastric juice or bile production), protecting the gastric mucosa and relieving gastrointestinal spasms.

Functional bowel disorders are grouped as irritable bowel syndrome, functional bloating, unspecified functional bowel disorder, functional diarrhea or functional constipation, depending on the leading symptoms. The diagnostic criteria are the following (criteria fulfilled for the last 3 months with symptom onset at least 3 months prior to diagnosis):

Irritable bowel syndrome

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following:

- An improvement on defecation
- Onset associated with a change in frequency of the stools
- Onset associated with a change in form (appearance) of the stools

Functional bloating

- A recurrent feeling of bloating or visible distension at least 3 days/month in the last 3 months AND
- Insufficient criteria for a diagnosis of functional dyspepsia, irritable bowel syndrome, or other functional gastrointestinal disorder

Functional constipation

The diagnostic criteria must include two or more of the following:

- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- A sensation of incomplete evacuation for at least 25% of defecations
- A sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week

- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome

Functional diarrhea

- Loose (mushy) or watery stools without pain occurring in at least 75% of stools

Unspecified functional bowel disorder

- Bowel symptoms not attributable to an organic etiology that do not meet criteria for the previously defined categories

It is clear that functional bowel disorders display a very diverse clinical picture, ranging from diarrhea to obstipation. The core of these symptoms is the disturbed motility of the bowels. Besided plants with specific gastrointestinal effects, phytotherapeutics containing anxiolytic herbs may also be used in the therapy.

Carminatives

Bloating, a feeling of fullness and flatulence are common symptoms in functional dyspepsia and functional bowel disorders. The (usually unidentified) causes of bloating may range from insufficient biliary and pancreatic secretion to gastrointestinal inflammatory states. Overeating or consumption of the foods containing digestive enzyme-blocking components (e.g. beans or soy) also results in bloating. The direct cause of the symptoms is excessive gas formation, which may result in gastrointestinal discomfort for the patient.

In the treatment of bloating, spasmolytics are usually applied as synthetic medicines. As concerns phytotherapeutics, the first-choice drugs contain carminatives. Their name is derived from the Latin word *carminare* (to cleanse). These are taken to relieve the symptoms of bloating and flatulence, primarily because of their spasmolytic activities. However, in contrast with synthetics, they also promote digestion by enhancing the appetite and increasing the production of digestive juices.

The majority of carminative plants are well-known spices rich in essential oils and their activity is linked partly to the presence ofthe oil. However, the preparations that arefound to be effective (empirically or experimentally) usually contain both the oils and the water-soluble components. In the cases of some plants, the activity can be attributed mainly to the oil (e.g. peppermint), but in some cases the alcoholic or water extract is more effective.

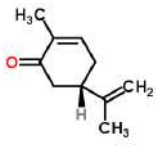
From the range of carminatives, caraway has the most pronounced effect, and this, coupled with the distinct taste of this plant, makes it suitable for application for adults. For children, the most appropriate choices are fennel or aniseed.

5.1.1 Caraway

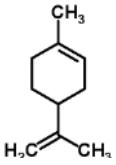
Caraway (*Carum carvi* L.) is the most widely applied and one of the most effective carminatives. The species is included in the plant family Apiaceae. For medicinal purposes, its fruit (the whole, dry mericarp) and its essential oil (obtained by steam distillation) are applied. Caraway is one of the earliest cultivated herbs worldwide. Its medicinal application (in the treatment of gastrointestinal symptoms, primarily bloating and flatulence) has been widespread from Europe to Asia and North America.

- **Chemical composition and mechanism of action**

Caraway fruit contains 3-7% of essential oil with the major components carvone (50-65%) and limonene. It contains 10-20% fixed oil, 20% protein and about 15% carbohydrates and in lower quantities phenolic acids, mainly caffeic acid.



S-(+)-carvone



limonene

The enantiomer *S*-(+)-carvone is present in caraway, whereas *R*-(–)-carvone is a constituent of spearmint oil. In gingergrass oil, a mixture of these two enantiomers is found.

Alcoholic caraway fruit extracts have proved to exert a spasmolytic effect in various gastrointestinal models. In *in vivo* models of colitis and gastric mucosal injuries in rats, certain extracts and the essential oil were effective.

Antimicrobial activity has been reported for ethanolic extracts and the essential oil. An aqueous caraway fruit extract and the essential oil have been shown to decrease the blood glucose and plasma lipid levels in animal experiments.

There have been reports on studies of the effectson intestinal smooth muscle cells in guinea pigs.

- **Efficacy and indications**

The effects of caraway extracts and essential oil on gastrointestinal symptoms have not been investigated in detail. The application of this plant in medicine largely relies on its traditional use.

The effects on the motility of the gallbladder and on the orocecal transit time of 50 mg of caraway oil have been studied in healthy volunteers. Caraway oil inhibited gallbladder emptying, but did not prolong the orocecal transit time. The same dose reduced the contraction amplitude in the duodenum and reduced the contraction amplitude and the duration of contractions in the gastric corpus during certain phases of the migrating motor complex.

On the basis of its traditional application, the EMA (draft) monograph indicates that caraway-containing products (including caraway essential oil) may be applied for the

- symptomatic relief of digestive disorders such as bloating and flatulence. The most traditional way of application is drinking tea prepared from the drug.

According to the EMA monograph, 0.5-2 g of the herbal substance or comminuted herbal substance should be extracted with 150 ml of boiling water as a herbal infusion 1-3 times daily. In the case of the essential oil, 0.15-0.3 ml divided into up to 3 doses should be used daily.

Essential oil-containing (2%) semi-solid preparations can be used cutaneously on the abdominal area for the same purpose.

- **Side-effects, interactions & contraindications**

Contraindications are limited to hypersensitivity to the active substance, to other plants of the Apiaceae (Umbelliferae) family (fennel, anise, celery, coriander and dill), to mugwort or to birch. Administration to patients with liver disease, cholangitis, achlorhydria, gallstones or any other biliary disorder is not recommended. Safety during pregnancy and lactation has not been established.

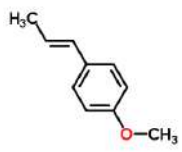
5.1.2 Fennel

Bitter and sweet fennels, belonging in the Apiaceae family, are used in both traditional and official medicine (sweet fennel is more widely applied). The fruit is administered after crushing, as a tea or as solid or liquid extracts. The essential oil obtained by steam distillation from the ripe fruits is also used. Bitter fennel usually grows spontaneously, whereas sweet fennel is cultivated for its edible foliaceous sheets. In the European Pharmacopoeia, both species (*Foeniculum vulgare* Miller sp. *vulgare* var. *vulgare* and *Foeniculum vulgare* Miller sp. *vulgare* var. *dulce* (Miller) Thellung) can be found.

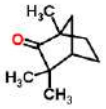
Fennel fruit has been reported to be useful in the treatment of dyspeptic complaints and of catarrh of the upper respiratory tract, and to relieve painful menstruation and symptoms of the female climacteric in traditional medicine.

- **Chemical composition and mechanism of action**

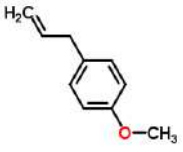
Fennel usually contains >2% essential oil (in bitter fennel the essential oil content is higher). The oils are based on monoterpenoids: bitter fennel oil contains not less than 60% trans-anethole and 15% fenchone and not more than 6%% estragole, whereas in sweet fennel fruits the oil contains not less than 80% trans-anethole and not more than 7.5% fenchone and 10% estragole.



trans-anethole



fenchon



estragole

Fennel fruits contain water-soluble glycosides of monoterpenoids, aromatic compounds, proteins, fixed oil, phytosterols and traces of furanocoumarins.

The application of fennel largely relies on the spasmolytic, secretolytic and antibacterial activity of the essential oil.

Alcoholic fennel fruit extracts and the essential oil have been found to exert a relaxing effect on *in vitro* precontracted smooth muscles from different animal organs by antagonizing certain spasmogenic compounds. Aqueous extracts increased gastric acid secretion in rats.

Mucociliary transport was increased after the administration of aqueous fennel extract to animals, whereas fenchone (but not anethole) had a secretolytic effect after its application by inhalation. Fennel fruit extracts and oil exhibited *in vitro* inhibitory activities against the growth of a wide spectrum of pathogenic bacteria and fungi.

Fennel essential oil exerted a hypoglycemic effect in mices with alloxan-induced diabetes.

Oral administration of fennel extracts to male and female rats caused dose-dependent estrogenic effects. *In vitro* and *in vivo* studies revealed the estrogenic activity of trans-anethole.

- **Efficacy and indications**

In adults, no studies have been carried out to confirm the efficacy in gastrointestinal disorders.

However, in children there is some clinical evidence of the efficacy. A randomized, placebo-controlled study on infants (2 to 12 weeks of age) suggested that the oral administration of a 0.1% fennel seed oil emulsion was significantly superior to placebo

in decreasing the intensity of infantile colic. Similar results were achieved on the application of a product containing fennel, camomile and lemon balm extracts.

In a small study, the efficacy of fennel essential oil against primary dysmenorrhea was demonstrated in terms of pain reduction.

In a double-blind placebo-controlled study, women affected by idiopathic hirsutism were treated for 12 weeks with creams containing 0-2%, ethanolic fennel extracts. A significant reduction in facial hair growth was observed.

Although the efficacy of fennel has not been demonstrated appropriately in clinical studies, the traditional use of the plant indicates that bitter fennel may be applied

- for the symptomatic treatment of mild, spasmodic gastrointestinal complaints including bloating and flatulence
- for the symptomatic treatment of the minor spasms associated with menstrual periods and
- as an expectorant in cough associated with a cold.

The daily dose is 3 x 1.5-2.5 g freshly comminuted fruits as tea.

The essential oil of bitter fennel is indicated as an expectorant in the cough associated with a cold. The daily dose is 0.2 ml.

Side-effects, interactions & contraindications

Fennel oil extracts were found to be mutagenic *in vitro.* Several studies have shown the carcinogenic effects of estragole in mice. According to the EMA, the genotoxic risk related to estragole is not considered to be relevant for adults due to the small amount present in fennel oil, but the risk cannot be assessed with high doses or prolonged use or in young children. According to the EMA recommendation 'Public statement on the use of herbal medicinal products containing estragole', "the exposure of estragole to sensitive groups such young children, pregnant and breastfeeding women should be minimized." Therefore, in contrast with the common practice in several countries in Europe, the EMA does not recommend the application of fennel for these patient populations. Fennel oil is contraindicated for pregnant and breastfeeding women and those under 18. The oil should not be taken for more than two weeks.

Fennel is contraindicated in the event of hypersensitivity to the active substance and its preparations or to Apiaceae (aniseed, caraway, celery, coriander and dill) or to anethole.

5.1.3 Anise

Pimpinella anisum L. belongs in the Apiaceae family. The medicinally applied plant part is the fruit. Aniseed has been used in traditional medicine to treat dyspeptic complaints, as a mild expectorant, as a galactogogue and to relieve menstrual pain. This herbaceous plant is native to the Mediterranean region, probably originating from the Near East, but today it is cultivated in many countries in Europe.

- **Chemical composition and mechanism of action**

Aniseed is characterized by a content of essential oil (anise oil) not lower than 2%, with the main constituent trans-anethole (80-95%). In contrast with fennel, anise oil does not contain a marked amount of fenchone and contains much smaller amounts of estragole. The quality of anise oil depends upon the presence of oxidized forms of anethole (such as anisaldehyde, anisalketone and anisic acid, which are present only in oils of inferior quality).

Other constituents include flavonol glycosides, phenolic acids, proteins and fatty oil. It contains furocoumarins in traces (mainly bergaptene) and hydroxycoumarins (mainly umbelliferone).

The medicinal use of aniseed is based on the preclinically confirmed antispasmodic, secretolytic and antibacterial effects of its essential oil.

Alcoholic aniseed extracts and essential oil proved to exert a relaxing effect *in vitro* on precontracted smooth muscles by antagonizing contraction-inducing agents.

The velocity of mucociliary transport was increased by the application of an aniseed infusion. Anise oil induced a pronounced increase in the respiratory tract fluid in guinea pigs during the first 2 hours after intragastric administration. A similar effect was achieved by inhalation.

Anise oil and different extracts exhibited *in vitro* inhibitory activities against a wide spectrum of pathogenic bacteria and fungi.

The main component of the essential oil, trans-anethole, demonstrated estrogenic effects in animal experiments.

- **Efficacy and indications**

The medicinal use of anise is not supported by clinical evidence. However, on the basis of the long-standing traditional use of the plant, its application as a traditional medicinal plant appears acceptable. Clinical trials have been carried out with combination products containing anise to confirm expectorant, antiasthmatic and

laxative effects. However, from these no definite conclusions can be drawn as regards the efficacy of anise.

On the basis of its use in traditional medicine, aniseed and anise essential oil can be marketed as traditional herbal medicinal products

- for the symptomatic treatment of mild, spasmodic gastrointestinal complaints and
- as an expectorant in the cough associated with a cold.

It can be applied as a tea, with a single dose of 1-3.5 g of the whole or freshly comminuted aniseed. The dose of anise oil is 3 x 0.05-0.2 ml.

Side-effects, interactions & contraindications

The contraindications include hypersensitivity to the active substance or to Apiaceae (caraway, celery, coriander, dill and fennel) or to anethole.

Since its safety during pregnancy and lactation and in children under 12 has not been established, and anethole was found to be weakly mutagenic, its *in vitro* application is not recommended. However, anise is widely used without any signs of danger. Although estragole is not abundant in the oil, its use is contraindicated in children and adolescents under 18 years of age because of the lack of data and the presence of estragole.

The estrogenic effect of aniseed has not beenconfirmed in humans on the basis of the epidemiological data relating to the common therapeutic use of aniseed.

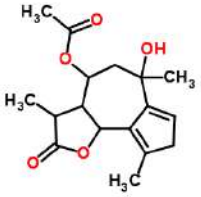
Although anethol epoxide, a metabolite of trans-anethole, was reported to be hepatotoxic in animal experiments, the metabolism in humans is different, and this compound therefore poses no real threat in the course of therapeutic application.

5.1.4 Yarrow

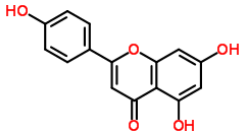
Achillea millefolium L. s.l. (sensu lato = in the broad sense) is a morphologically, and chemically polymorphic aggregate. The species of this genus are native to the northern hemisphere. In traditional medicine, the aboveground parts (or inflorescences) are frequently applied to relieve mild cramp-like, gastrointestinal complaints, respiratory catarrh and a loss of appetite. The name *Achillea* may come from the Greek hero Achilles, who allegedly treated his wounds with the herb. The ancient name Herba Militaris refers to its use as a vulnerary drug on battle wounds. Externally, yarrow may be applied to treat inflammatory inflammation (dermatitis), pruritus or insect bites.

- **Chemical composition and mechanism of action**

Yarrow contains 3-4% tannins and 0.5-1.5% volatile oil. Guaianolide-type sesquiterpene lactones (achillicin, achillin) and flavonoids (e.g. apigenin, luteolin) and phenolic constituents are secondary metabolites of pharmacological importance.



achillicin



apigenin

A water extract of yarrow *in vitro* inhibited the activities of different proteases and lipoxygenase, and the biosynthesis of prostaglandin. These activities may be related to the anti-inflammatory effect of yarrow tea. Analgesic and anti-inflammatory effects of the water and alcoholic extracts have been confirmed in *in vivo* studies.

Flavonoid-rich and alcoholic extracts of the plant displayed spasmolytic activity on isolated animal smooth muscle. An extract rich in dicaffeoylquinic acids (these are water-soluble) significantly increased the bile flow, due to its choleretic effect. Yarrow had a gastroprotective effect in animal experiments.

Yarrow extract has exhibited antioxidant activities in several assays. Different extracts exerted *in vitro* antiproliferative effect on cancer cell lines. Flavonoids and sesquiterpenoids were identified as active constituents.

Yarrow was found to be have an estrogenic effect *in vitro*, but the compounds identified as active (apigenin and luteolin) displyed only low-level activity.

Various extracts of the plant were active against a series of pathogenic microorganisms *in vitro*.

- **Efficacy and indications**

The clinical efficacy of yarrow has not been studied in modern trials with monocomponent products (only some studies of multicomponent preparations are available). Its usefulness against mild, spasmodic gastrointestinal complaints is supported by the inflammatory, antispasmodic and choleretic activity of the plant. Its spasmolytic activity is related to its efficacy in minor spasms associated with the menstrual periods. The antiphlogistic and antimicrobial effects of yarrow are useful for topical application.

In view of its long-standing use, yarrow may be used as a traditional herbal medicinal product for

- a temporary loss of appetite,
- the symptomatic treatment of mild, spasmodic gastrointestinal complaints,
- the symptomatic treatment of minor spasms associated with menstrual periods, and
- the treatment of small superficial wounds.

For these purposes, a herbal tea (prepared from 2-4 g of dried herb 3-4 times daily or from 2 x 1.5-2 g of the flowers) or different liquid extracts may be applied. To improve the appetite, tea is consumed 30 minutes before meals.

- **Side-effects, interactions & contraindications**

Hypersensitivity to the active substance and to other plants of the Asteraceae family contraidicates the application of yarrow. Very rarely, hypersensitivity reactions appear with a rash, the formation of vesicles and pruritus after internal use. Contact allergy is more common.

With regard to its traditional application as an abortifacient, emmenagogue and contraceptive, and for stimulating uterine contractions, large doses are contraindicated in pregnancy.

Although its safety during pregnancy and lactation and in children has not been established, there have been no reports on the dangers of yarrow when used therapeutically.

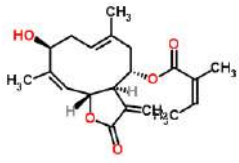
5.1.5 Roman camomile

Chamaemelum nobile (L.) All. (syn. *Anthemis nobilis* L), the Roman camomile, is a perennial herb of the Asteraceae family. It is native to South-West Europe, but the plant is present throughout Europe, North Africa and South-West Asia. According to the definition of the European Pharmacopoeia, Chamomillae romanae flos consists of the dried flowers of the cultivated double-flowered variety of *Chamaemelum nobile* and it contains not less than 7 ml/kg of essential oil.

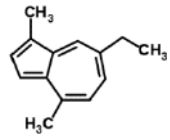
Roman camomile has been known as a medicinal plant since the Middle Ages. The European cultivation of the plant started in England in the 16th century. The double variety of the flower, which now serves as the main commercial herbal substance, was certainly known in the 18th century. The flowers have been applied both internally (primarily to treat dyspeptic complaints) and externally (skin problems).

- **Chemical composition and mechanism of action**

Roman camomile flowers contain 0.6-2.4% volatile oil with a very complex composition. Low molecular weight esters are present in noteworthy quantity, with the main constituents isobutyl angelate (25-35%), isoamyl isobutyrate (10-25%), 2-methylbutyl angelate (10-20%) and isoamyl tigliate (10-20%). The oil contains about 4% monoterpenes such as alpha- and beta-pinen, beta-myrcene, limonene, gamma-terpinene, and 2% sesquiterpene derivatives, including alpha- and beta-caryophyllene, chamazulene, bisabolane and bisabolene. Sesquiterpene lactones of the germacranolide type are also present (~0.5%, nobilin and its derivatives). The flowers contain 0.5% flavonoids, mainly as glycosides and polysaccharides.



nobilin



chamazulene

As a result of their similar chemical compositions, especially as concerns their azulenes, German and Roman camomile are thought to possess similar pharmacological activities. The anti-inflammatory and antiedema effects of the polysaccharides have been confirmed in animal experiments. Antioxidant and antimicrobial activities have been demonstrated *in vitro*. The spasmolytic effect has not been studied.

- **Efficacy and indications**

The efficacy of Roman camomile has not been confirmed by human studies. On the basis of its traditional application, therefore, the plant may be used as a traditional herbal medicinal product for the treatment of

- mild, spasmodic gastrointestinal complaints, including bloating and flatulence.

The posology is 1-4 g of the herbal substance as a herbal infusion 3 times daily between meals (or liquid extracts with a similar dosage).

Interestingly, the external application of Roman camomile is not accepted by the EMA – because of the lack of convincing confirmation of the traditional applications.

- **Side-effects, interactions & contraindications**

The only contraindication is hypersensitivity to the active substance and to other plants of the Asteraceae family.

5.1.6 Cinnamon

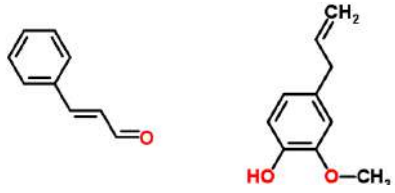
The term cinnamon may refer to the bark of two plants: *Cinnamomum verum* J. S. Presl. (=*Cinnamomum zeylanicum* Nees) and *Cinnamomum aromaticum* Nees (synonym: *Cinnamomum cassia Blume*). Although these are chemically similar and both are widely used as spices, only the former (and its essential oil) is official in the European Pharmacopoeia. On the European market, therefore this is the predominant raw material. Cinnamon consists of the dried bark, freed from the outer cork and the underlying parenchyma, of the shoots grown on cut stock of *Cinnamomum zeylanicum* and it should contain not less than 12 ml/kg of essential oil. Ceylon cinnamon bark oil is obtained by steam distillation of the bark of the shoots of *C. zeylanicum*.

Cinnamon has been used as a spice for thousands of years worldwide. The Portuguese found cinnamon trees growing in Sri Lanka (Ceylon) and brought its bark as spice to Europe. Since that time, Sri Lanka has been the most important supplier of

cinnamon. Although Ceylon cinnamon is preferred by the pharmaceutical industry and as a spice, Chinese (cassia) cinnamon can also be found in several (food) products, including dietary supplements. Further, rarely applied species are *C. burmmanii* (Burma cinnamon) and *C. loureirii* (Saigon cinnamon). In folk medicine in Europe, cinnamon has been used as a stomachic, and to counter diarrhea, dyspepsia, bloating and hyperacidity.

- **Chemical composition and mechanism of action**

Cinnamon bark contains 0.5-2.5% essential oil, with the main constituents cinnamaldehyde (60-75%), eugenol (1-10%) and cinnamyl acetate (1-5%). The bark contains several bioactive nonvolatile components, e.g. oligopolymeric procyanidins, cinnamic acid and polysaccharides. The main differences between the essential oils of Ceylon and cassia cinnamon ar the lack of eugenol and the presence of coumarin in the latter.



cinnamaldehyde **eugenol**

The effects on the gastrointestinal system have been studied in part in preclinical settings. In an animal model of flatulence, the efficacy of cinnamon oil was confirmed. Papaverine-like spasmolytic effects of cinnamon oil and cinnamaldehyde on isolated smooth muscles have been observed. Cinnamaldehyde is an inhibitor of stomach peristalsis and also stimulates bile secretion *in vivo*. The oil (and its constituent eugenol) exerted anti-inflammatory activity by blocking the enzyme cyclo-oxygenase.

Cinamon oil has pronounced antimicrobial activities (on both bacteria and fungi), although this has no consequence as concerns its therapeutic applications.

- **Efficacy and indications**

Interestingly, *C. zeylanicum* has not been studied in clinical trials. However, several studies have been conducted with *C. cassia*, but with a different endpoint from gastrointestinal application. The most widespread contemporary use of cinnamon is the application as antidiabetic treatment. For this purpose, food supplements are used. There is no medicinal product with this indication on the market.

Although there have been numerous studies indicating blood glucose level-lowering effect of *C. cassia*, these results are rather inconclusive, primarily due to the heterogeneity of the studies and the use of nonquantified extracts. In a clinical study on patients with type 2 diabetes, treatment with capsules containing *Cinnamomum cassia* 1.3 or 6 g daily for 40 days, complementing the antidiabetic medication,

significant reductions of fasting serum glucose (20-30%), triglyceride (20-30%) and LDL cholesterol (7-27%) levels were observed relative to the placebo group. In a 4-month trial with a similar patient group, the water extract of 3 g cinnamon daily resulted in a significant reduction of the fasting plasma glucose level (10%) as compared with the placebo group, thoug the HbA_{1c} level was not influenced.

The therapeutic application of cinnamon and its essential oil relies on the empirical knowledge gained from traditional use. Thus, according to the monographs of the European Medicines Agency, cinnamon may be applied as a traditional herbal medicinal product for

- symptomatic treatment of mild, spasmodic gastrointestinal complaints, including bloating and flatulence, or
- symptomatic treatment of mild diarrhea.

The dose as a tea is 0.5-1 g of comminuted herbal substance as an infusion, up to 4 times daily. The dosage of the liquid extract and tinctures is about 2-4 ml daily.

For similar reasons, cinnamon oil may also be used as traditional herbal medicinal products for

- the symptomatic treatment of mild, spasmodic gastrointestinal complaints, including bloating and flatulence.

The dose of cinnamon oil is 50 to 200 mg daily, in 2 to 3 doses. In order to avoid local irritation, the use of the undiluted oil is not recommended.

Side-effects, interactions & contraindications

Cinnamaldehyde is an irritating and sensitizing component that may be the cause of dermatitis, but such an adverse reaction does not develop following oral application. In the case of hypersensitivity to cinnamon or to Peru balsam, the use of cinnamon-containing products is contraindicated. The oil may cause local irritation of the oral mucosa.

In view of the fact that the safety of the therapeutic application of cinnamon (i.e. the application of higher doses than those used as a spice) and cinnamon oil during pregnancy and lactation has not been established, their use during pregnancy and lactation is not recommended.

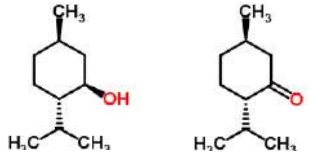
5.1.7 Peppermint

Peppermint is a perennial plant native to Europe, which has been used as a spice and in the medicine since the antiquity; it was one of the first cultivated medicinal plants. *Mentha* x *piperita* L. (Lamiaceae) is a hybrid of spearmint (*Mentha spicata* L.) and water mint (*Mentha aquatica* L.). The leaves and the essential oil obtained from the fresh leaves are of medicinal importance.

In folk medicine, it has been used for a wide variety of diseases. Nowadays, it is used primarily to relieve gastrointestinal disorders and externally for dermatological ailments.

- **Chemical composition and mechanism of action**

Peppermint leaves contain 1-4% essential oil. The main active components of the oil are menthol (30-55%) and menthone (15-30%). Further components are menthyl acetate (2-10%), cineole (5-15%), menthofuran (1-10%) and pulegone (up to 4%). It contains flavonoids, with the main component eriocitrin, and phenolic acids.



Leaf extracts, peppermint oil and menthol exert antispasmodic effects on isolated animal smooth muscles *in vitro*. This activity could be reproduced with the flavonoid fraction of the leaf extract, but the flavonoid-free essential oil was also effective. Peppermint reduces the tone of the esophageal sphincter. Peppermint oil inhibits potential-dependent Ca^{2+} currents, with a similar effect to those of Ca^{2+} channel antagonist medicines. This finding was reinforced by experiments in which menthol and peppermint oil inhibited nitrendipine binding to smooth muscle preparations.

Peppermint extracts and peppermint oil exert a choleretic effect in dogs.

Vaporized menthol increases the soluble mucus content in the bronchi and decreases the viscosity of the respiratory tract fluid. This may be a result of the stimulation of mucus-secreting cells in the respiratory tract. The nasal airway resistance did not decrease after the inhalation of peppermint oil, but the sensation of nasal airway dilation was enhanced. The possible explanation of this phenomenon may

be that menthol presumably acts upon trigeminal sensory nerve endings within the nose.

Extracts of the leaves and the oil possess antioxidant and antimicrobial effects against some bacteria.

- **Efficacy and indications**

The efficacy of peppermint leaf as a monocomponent preparation has not been studied. On the basis of its long-standing application, it can be used as a traditional herbal medicinal product

- for the symptomatic relief of digestive disorders such as dyspepsia and flatulence.

Its daily dose is 4.5-9 g as a herbal tea, or 6-9 ml as atincture. For children, only herbal tea may be used (prepared from 3-5 g daily).

The efficacy of peppermint oil has been assessed in several clinical trials. In double blind,-crossover studies of irritable bowel syndrome, the effect of 0.2-1.2 ml of peppermint oil daily was compared with that of placebo. The patients felt significantly better and experienced less disease-related symptoms while taking peppermint oil capsules. Some other trials did not confirm the efficacy in this indication. Altogether, 8 of 12 placebo-controlled studies have indicated statistically significant effects in favor of peppermint oil.

Topical intraluminal administration of peppermint oil during endoscopy and colonoscopy, resulted in a superior antispasmodic effect to that of placebo in several studies.

The effect of a locally applied peppermint oil preparation (10% in ethanol) on tension-type headache as compared with acetaminophen and placebo was examined in a randomized, placebo-controlled double-blind crossover study. Relative to the placebo, the peppermint preparation significantly reduced the headache intensity after only 15 minutes. There was no significant difference between the efficacy of 1 g of acetaminophen and the peppermint oil solution.

The clinical evidences reveals that peppermint oil can be used as a well-established medicine with the following indications:

- symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome,
- symptomatic relief of mild tension-type headache (external use).

For oral use, the daily dose is 0.6-1.2 ml. To relieve headache, a solution containing 10% of the essential oil should be rubbed onto the skin of the forehead and temples every 15 minutes.

In the lack of clinical data, the oil can be used as a traditional herbal medicinal product with the following indications:

- relief of symptoms in coughs and colds (external use)

- symptomatic relief of localized muscle pain (external use)
- symptomatic relief of localized pruritic conditions in intact skin (external use)
- relief of symptoms in coughs and colds (inhalation)
- relief of symptoms in coughs and colds (oromucosal use).

Externally, preparations containing 2-20% of the essential oil can be used. For inhalation, 2-4 drops are applied up to three times daily, and for oromucosal use 2-3 drops, 3-4 times per day.

Side effects, interactions & contraindications

The use of peppermint is contraindicated in cases of hypersensitivity to peppermint leaf or menthol. Peppermint preparations should not be used below the age of 4 years.

In the event of gastro-esophageal reflux, peppermint leaf preparations should be avoided because heartburn may increase (due to the relaxing effect on the esophageal sphincter). Patients with gallstones and any other biliary disorders should be cautious in using peppermint leaf preparations.

Hypersensitivity reactions such as skin rash, contact dermatitis and eye irritation have been reported. During inhalation, apnea, and broncho- and laryngoconstriction have been reported in hypersensitive patients. On oromucosal use, contact sensitivity can occur in patients presenting with intra-oral symptoms in association with burning mouth syndrome, recurrent oral ulceration or a lichenoid reaction.

Allergic reactions to menthol have been reported. Following cutaneous use, hypersensitivity reactions such as skin rash, contact dermatitis and eye irritation may occur.

The safety during pregnancy and lactation has not been established.

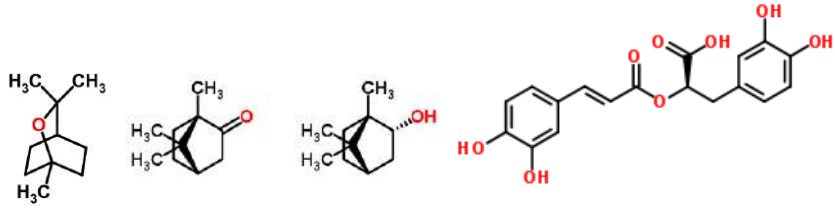
5.1.8 Rosemary

Rosmarinus officinalis L. (Labiatae), native to the Mediterranean region, has been an important medicinal plant and spice since anicent times. Its essential oil has been used since the Middle Ages for its scent and for medicinal purposes.

- **Chemical composition and mechanism of action**

Rosemary leaves contain 0.5-2.5% of volatile oil, predominantly mono-terpenes. There are three chemotypes, based on the composition of the oil: the eucalyptol type (Italy and North Africa), the camphor-borneol type (Spain) and the alpha-pinene-verbenone type (France). It contains considerable amounts of polyphenols (flavonoids), triterpenoids (oleanolic, betulinic and ursolic acids) and caffeic acid derivatives (rosmarinic acid). Its phenolic diterpenes, such as carnosol and carnosic acid, have very strong antioxidant effects.

The spasmolytic effects of the extracts and the essential oil have been determined on isolated animal smooth muscles. Antioxidant, antimicrobial, hepato- and chemopreventive activities have been confirmed for various extracts and phenolic diterpenes. Rosmarinic acid has proved effective in reducing both gingival inflammation and plaque accumulation in monkeys.



In an animal experiment, rosemary extracts exerted choleretic, diuretic and hepatoprotective activity. In a further study, a choleretic effect was confirmed for the essential oil. Additional data on a diuretic effect were gained from a study, where

urinary excretion of Na^+, K^+ and Cl^- was observed after the oral application of a *Rosmarinus* extract.

- **Efficacy and indications**

As a result of on the long-standing use, rosemary leaf may be used as a traditional herbal medicinal product

- for the symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract, and
- as an adjuvant in the relief of minor muscular and articular pain and in minor peripheral circulatory disorders (as a bath additive).

For the former indication, rosemary leaf can be sonsumed as a tea with a daily dose: of 2-6 g, or as a liquid extract with different posologies (up to 60 ml daily). When it is used as a bath additive, 1 liter of a decoction of the herbal substance should be added to the bath water, or 50 g of herbal substance for a full bath.

Rosemary oil can be used as a traditional herbal medicinal product

- for the symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract (oral use), and
- as an adjuvant in the relief of minor muscular and articular pain and in minor peripheral circulatory disorders (cutaneous use).

For of oral use, the dose is 2 drops daily; for cutaneous use, 6-10% essential oil in semi-solid and liquid dosage forms is applied, 2-3 times daily, while: 10-27 mg/l is used as a bath additive.

- **Side effects, interactions & contraindications**

In cases of oral use, hypersensitivity to rosemary, obstruction of the bile duct, cholangitis, liver disease and gallstones are contraindications of the application.

Full baths are contraindicated in cases of large skin injuries, open wounds, acute skin diseases, high fever, severe infections, severe circulatory disturbances and cardiac failure. In the case of the essential oil, contact with the eyes should be avoided. A semi-solid form should not be applied near the mucous membranes.

Hypersensitivity (contact dermatitis) has been reported during the use of rosemary.

Its use in children under 12 years of age is not recommended due to the lack of adequate data and because medical advice should be sought. Safety during pregnancy and lactation has not been established.

5.1.9 Sage

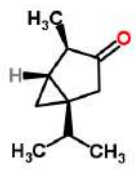
Salvia officinalis L. is a perennial subshrub native to the Mediterranean region, the leaves and oil of which have been traditionally applied in medicine and as a spice. The leaves are official in the European Pharmacopoeia under the name Salviae folium, which consists of the whole or cut dried leaves of *Salvia officinalis*. The whole or cut

leaves should contain at least 15 or 10 ml/kg of essential oil, respectively. Sage tincture (with an essential oil content of 0.1%) has a separate monograph in the European Pharmacopoeia.

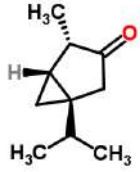
Sage leaf has been used since antiquity for various diseases, e.g. to treat wounds, as a gargle to treat sore throat, for digestive disorders, to enhance memory function, and for hyperhydrosis.

- **Chemical composition and mechanism of action**

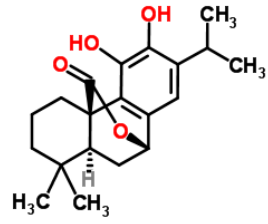
Sage leaf contains up to 3% of essential oil, characterized by monoterpenoids. The principal components of the essential oil, in addition to alpha- and beta-thujone (up to 90%), are cineol (5-15%) and camphor (5-20%). In addition, the leaves contain caffeic acid derivatives, with rosmarinic acid as main component (3%), phenolic diterpenes (carnosol, carnosoic acid and rosmanol) and about 1% flavonoids.



alpha-thujone



beta-thujone



carnosol

Sage oil has strong antimicrobial activity, attributed principally to thujone. *In vitro* studies have indicated inhibitory activity against Gram-positive (*Bacillus subtilis*) and Gram-negative (*Escherichia coli, Shigella sonnei* and *Salmonella* sp.) bacteria and against a range of fungi (*Candida* sp.). In the liquid extracts, the triterpene oleanolic and ursolic acids also play a part in the efficacy.

Sage extracts exert a spasmolytic effect on smooth muscles, which can be attributed to the non-volatile components (partly to flavonoids). Oleanolic, ursolic and rosmarinic acids exerted anti-inflammatory activity in *in vitro* experiments.

In vitro, sage extracts have cholinesterase- and butyrylcholinesterase-inhibitory properties.

The marked antioxidant effect of sage extracts is due to the caffeic acid derivatives, primarily rosmarinic acid.

- **Efficacy and indications**

The excessive sweating induced by pilocarpine was inhibited by a sage preparation in an open study. Some old studies also support this effect. Interestingly, in one study people who sweated little experienced a more excessive perspiration, whereas those who perspired excessively experienced reduced perspiration and a diuretic effect.

The effects on cognitive performance were studied in healthy volunteers and patients with dementia in some new studies. In a double-blind, placebo-controlled study on healthy young volunteers, improvements of the cognitive performance and mood were observed after the application of a single dose of a sage preparation. In a further randomized, placebo-controlled, double-blind study, the acute effects of a sage extract on the cognitive performance in older adults were investigated. As compared with the placebo, the use of the sage preparation was associated with a significant enhancement of the memory performance. In a randomized, double-blind, placebo-controlled study, patients with mild to moderate dementia were treated for 16 weeks with a sage product or placebo. At the end of the study, the Clinical Dementia Rating and the Alzheimer`s Disease Assessment Scale scores were improved in the treated group. These observations may be linked to the acetylcholinesterase-inhibitory effect of *Salvia*.

The efficacy and tolerability of a sage product (spray) against placebo were assessed in the treatment of patients with acute pharyngitis. The spray moderately decreased the pain intensity.

Although the efficacy has not been confirmed convincingly in clinical trials In any of the indications, the long-standing use of sage is the basis of its application as a traditional herbal medicinal product

- for the symptomatic treatment of mild dyspeptic complaints such as heartburn and bloating,
- for relief of excessive sweating,
- for the symptomatic treatment of inflammations in the mouth or the throat, and
- for relief of minor skin inflammations.

For these indications, 1-2 g of comminuted herbal substance should be used for a tea preparation and applied three times daily. Several different dry and liquid extracts (ethanol-water) with different posologies may also be used.

Sage preparations should not be taken for more than 1 week (for cutaneous use: 2 weeks).

Side effects, interactions & contraindications

Thujone (especially alpha-thujone) is neurotoxic and induces a convulsant effect through modulation of the gamma-aminobutyric acid (GABA) type A receptor. The use of chemotypes low in thujone should therefore be preferred in order to minimize the exposure to thujone (the intake of thujone should not exceed 5.0 mg/day). However, during the preparation of a tea, less than 20% of the thujone content is extracted. The effects of medicinal products acting via the GABA receptor (e.g. barbiturates or benzodiazepines) may be influenced, and concomitant use with such medicinal products is therefore not recommended

Its use in children and adolescents under 18 years of age is not recommended because the data are not sufficient.

Liver and biliary diseases

The liver, as an exocrine gland secretes bile, which is essential for normal lipid digestion. In case of insufficient bile secretion or gallbladder emptying, dyspeptic symptoms develop. However, liver impairment results in more serious consequences, since this organ has a key role in protein synthesis and metabolism of several endogenous and exogenous compounds, including nutrients. The most common liver diseases are cirrhosis and hepatitis. Hepatitis, which is characterized by the inflammation of the liver and consequent functional lesion, is usually caused by toxins (e.g. alcohol, medicine abuse) or viruses (hepatitis A, B and C). Cirrhosis is a chronic state characterized by the fibrosis and necrosis of the liver.

The therapy of liver diseases aims at the protection of liver cells. Unfortunately, there are no herbal remedies to eliminate the virus and it is not possible to achieve complete remission in case of chronic liver diseases, but the improvement of liver functions and life expectancies and the support of life quality may be viable goals of the treatment.

Cholagogues are plants that improve the flow of the bile into the intestinal system. The two large groups of these plants are the cholekinetics (which promote the emptying of the gallbladder) and the choleretics (which improve the production of bile in the liver). A lack of bile may result in the imperfect digestion of fats and oils, and this may cause subjective symptoms. According to current knowledge, plants classified as cholagogues are effective not only in cases of confirmed bile deficiency, but also in other forms of dyspepsia. Clinical and empirical data indicate that these herbs may be used effectively in dyspepsia characterized by pain (or a pressure sensation) in the upper abdomen.

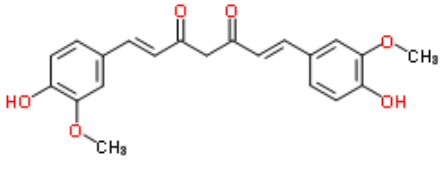
5.1.10 Turmeric

In medicine and as a spice, two turmeric species are used: *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich), also known as Javanese turmeric, and *Curcuma longa* L. (*C. domestica* Valeton), also known as turmeric. According to the definitions of the European Pharmacopoeia, the product Curcumae xanthorrhizae rhizoma consists of the sliced dried rhizome of *Curcuma xanthorrhiza* and should contain a minimum of 1% of dicinnamoyl methane derivatives, expressed as curcumin, whereas Curcumae longae rhizoma consists of the scalded and dried rhizomes of *Curcuma longa*. The minimal dicinnamoyl methane derivative content of the latter is 2%.

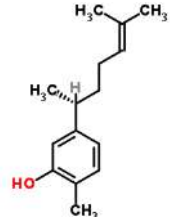
In Asia, the use of turmeric has a long tradition as a colorant, spice and medicine. Turmeric has a wide range of indications, including gastrointestinal symptoms, but it is also applied topically. In Ayurvedic medicine, turmeric is also used as an anti-inflammatory drug in arthritis. *Curcuma longa* is used mainly as a spice (e.g. in curry), while *C. xanthorrhiza* is used more frequently as a medicinal plant.

- **Chemical composition and mechanism of action**

The most characteristic components of *Curcuma* are the yellow curcuminoids (1-5%), which are present as a mixture of dicinnamoyl methane derivatives such as curcumin as the main component. It also contains volatile oil (3-10%), composed mainly of sesquiterpenes (e.g. xanthorrizol).



curcumin



xanthorrizol

The presence of xanthorrhizol and the absence of bisdesmethoxycurcumin are species-specific characteristics of *Curcuma xanthorrhiza*, which allow the identification of the herbal products.

Oral administration of turmeric essential oils to rats caused a persistent increase in bile secretion, the essential oil of *Curcuma xanthorrhiza* proving slightly more active

than that of *Curcuma longa*. The effect of curcumin (in the same dose) was weaker than that of the essential oils. Subsequent analyses resulted in the camphor found in the oil being regarded as the key for the cholagogic effect. In a further animal experiment, the application of curcumin or bisdesmethoxycurcumin increased the bile flow significantly. A single oral dose of 20 mg of curcumin stimulated contraction of the human gall-bladder, reflecting the cholekinetic effect of the compound.

Orally administered turmeric extracts inhibited gastric juice secretion and ulcer formation comparable to the effects of ranitidine. This effect may be mediated through H_2 receptors.

Various turmeric extracts (and also pure curcumin and xantorrhizol) have been shown to have marked antioxidant, antiphlogistic, hepatoprotective and chemopreventive effects. Curcuminoids inhibit the enzymes.

Wound healing activity for locally applied turmeric has been documented. This may be linked to its antiphlogistic and its elastase, hyaluronidase and collagenase-inhibiting properties.

- **Efficacy and indications**

For *C. xanthorrhiza*, no clinical studies are available. *C. longa* has been investigated more thoroughly, the majority of the studies focusing on its gastrointestinal effect. Nevertheless, *Curcuma* products (typically food supplements) are nowadays most widely used in the treatment of articular pains and cancer. The former indication is under clinical investigation and has roots in traditional Indian medicine, while the latter is based primarily on preclinical and epidemiologic data. It should be noted that the confirmed chemopreventive effect of *Curcuma* extracts does not imply efficacy in the treatment of malignant tumors.

In a study with patients with irritable bowel syndrome, half of the patients received 72 mg of turmeric (*C. longa*) extract, and the others the double dose. Relative to the baseline, the intake of turmeric resulted in a significant reduction in the prevalence of this syndrome, though the efficacy was similar within the two groups.

In a randomized, double-blind, placebo-controlled multicenter study patients with dyspeptic complaints were treated daily for 7 days with 2 g of turmeric (*C. longa*), a herbal combination or placebo. At the end of the study, 87% of the patients in the turmeric group, 83% in the herbal extract mixture group and 53% in the placebo group reported a notable improvement. The difference between turmeric and placebo was significant and clinically relevant.

The effect of turmeric on peptic ulcers was examined in an uncontrolled trial in which, after taking 600 mg of turmeric/day for 12 weeks, 19 of the 25 patients had no ulcers.

The available data are not sufficient to support a well-established use indication for Javanese turmeric. On the basis of the bibliographic and pharmacological data, the use of Curcumae xanthorrhizae rhizoma is considered plausible with the indication

- symptomatic treatment of digestive disturbances, such as a feeling of fullness, slow digestion and flatulence.

As a herbal tea, the single dose is 1 g of comminuted herbal substance in 100 ml of boiling water (3 times daily). The following dry extracts are also in use: DER 20-50:1, extraction solvent ethanol (daily dose 24-39 mg), and DER 9-12:1, extraction solvent acetone (daily dose 100-200 mg).

Similarly, in the case of Curcumae longae rhizoma, a traditional use monograph has been prepared with the indication of

- increasing the bile flow for the relief of symptoms of indigestion (such as a sensation of fullness, flatulence, and slow digestion).

For this purpose, the daily dose of the herbal substance (either as powdered rhizome or as tea) is 1.5-3 g. Tinctures may be used in a dose of 1.5-3 ml (1:10) or 10 ml (1:5) daily. The daily doses of the different dry extracts range from 80 to 400 mg.

Side-effects, interactions & contraindications

Curcumin and turmerone inhibit arachidonic acid-induced platelet aggregation with IC_{50} values similar to that ofacetylsalicylic acid. Curcumin is a potent inhibitor of certain cytochrome P450 enzymes, and in therapeutic doses the development of interactions is not probable.

Because of itse possible stimulation of bile secretion, *Curcuma xanthorrhiza* is not recommended in cases of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases. Mild gastrointestinal symptoms such as dry mouth, flatulence and gastric irritation may occur.

The safety of itstherapeutic application (which may involve the use of higher doses than as a spice) during pregnancy and lactation has not been established.

5.1.11 Artichoke

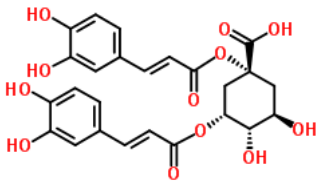
Artichoke is a perennial plant originating from the Mediterranean region. The plant (*Cynara scolymus*) has a long tradition of medicinal and food applications. In medicine, its leaves are used, but as a food the buds are consumed. Artichoke leaves have been used as a diuretic and choleretic plant since ancient times.

However, the taxon *Cynara scolymus* covers phenotypically different species. As a result of a recent botanical taxonomic revision of the genus *Cynara*, leafy cardoon (*Cynara cardunculus* L.) and globe artichoke (*Cynara scolymus* L.) are defined as two cultivars of a new subspecies *Cynara cardunculus* L. subsp. *flavescens* Wiklund.

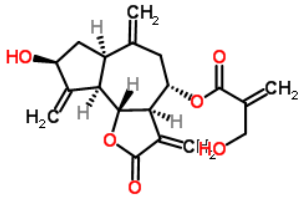
However, the European Pharmacopoeia does not distinguish these two taxa, and the monograph on Cynarae folium refers to both. Pharmacopoeial grade artichoke leaf consists of the dried basal leaves of *Cynara scolymus* L. containing a minimum of 0.8% chlorogenic acid.

- **Chemical composition and mechanism of action**

The bitter taste of artichoke leaves is primarily due to the cynarin content. This constituent can be found in highest concentration in the leaves. Cynarin belongs among the phenolic acids, which constitute up to 2% of the dry weight. Further important members of this chemical group are chlorogenic acid and caffeic acid. Artichoke contains bitter sesquiterpene lactones with cynaropicrin as the predominant constituent, and a low amount of flavonoids.



cynarin



cynaropicrin

Artichoke leaf extracts inhibited the biosynthesis of cholesterol in rat hepatocytes. Luteolin and its glycoside, cynaroside, are mainly responsible for this activity. The administration of artichoke to rats fed on an atherogenic diet proved to lower the serum cholesterol level and to prevent the formation of atherosclerotic plaques. A similar effect was reported for pure cynarin.

In vitro, artichoke increased the secretion of biliary substances in cultured hepatocytes and in the isolated liver, different extracts dose-dependently enhanced the bile flow. The choleretic activity is linked to mono- and dicaffeoylquinic acids. A dose-dependent increase in bile flow was registered following a single intravenous administration of cynarin. Chlorogenic acid administered orally to rats had a significant choleretic effect and also stimulated peristalsis. The increase in bile flow reached 70% and the effect lasted for 4 hours.

An extract of the plant exerted spasmolytic activity on isolated smooth muscles. Artichoke has strong antioxidant, cytoprotective and hepatoprotective activities.

- **Efficacy and indications**

In one double-blind placebo-controlled cross-over clinical trial on 20 male volunteers with acute or chronic metabolic disorders, the choleretic effect of a single dose of an

artichoke product was investigated. The bile secretion was 127% higher at 30 minutes after administration, 150% after 60 minutes (the maximum effect) and 94% after 90 minutes (compared to the placebo group).

In a multicentric open study with patients with dyspeptic complaints, 960-1920 mg of artichoke extract daily resulted in a significant decrease of the digestive complaints within 6 weeks of treatment. As compared with the initial values, the subjective score reduction was approximately 66% for meteorism, 76% for abdominal pain, 82% for nausea and 88% for emesis. In a subgroup of 302 patients, the total cholesterol level decreased by 11.5% and thet of triglycerides by 12.5%. In a subgroup analysis, there was a significant fall in the incidence of irritable bowel syndrome after treatment. A significant shift in self-reported usual bowel pattern away from "alternating constipation/diarrhea" toward "normal" was also observed.

In a double-blind, randomized placebo-controlled trial with patients with functional dyspepsia, the overall symptom improvement over the 6 weeks of treatment was significantly greater with artichoke leaf extract than with the placebo.

Blood lipid and cholesterol-lowering effects of artichoke have been reported in a series of trials. In a randomized double-blind, placebo-controlled study, the lipid-lowering effects of an artichoke leaf extract were investigated in healthy volunteers over 12 weeks. The cholesterol level was not significantly different after treatment with the extract as compared with placebo, but significant efficacy in triglyceride level reduction was confirmed. In a study involving healthy elderly subjects, decreases in cholesterol and triglyceride levels were observed after the administration of 0.45-0.9 g of artichoke extract daily for 6 weeks. In a comparative study, the efficacy of the artichoke extract was compared with that of cynarin. The effects on the total lipid and triglyceride levels were similarly favorable in both cases.

In a multicentric, randomized, placebo-controlled, double-blind, 6-week study, the effect of 1.8 g of artichoke leaf dry extract was investigated in patients with hyperlipoproteinemia. In the verum group, the reductions of total cholesterol (18.5%) and the LDL-cholesterol (23%) were significantly superior to those in the placebo group (9% and 6%, respectively).

On the basis on the traditional application of the plant, the European Medicines Agency granted a traditional use monograph for artichoke with the indication of the

- symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence.

The posology is 6 g of the comminuted herbal substance as a herbal infusion daily or 600-2400 mg of dry or soft extract daily.

- **Side-effects, interactions & contraindications**

The use of the plant is contraindicated in cases of hypersensitivity to artichoke or to plants of the Asteraceae family, obstruction of the bile ducts, cholangitis, gallstones and any other biliary diseases or hepatitis.

As adverse effects, slight diarrhea with abdominal spasms, epigastric complaints such as nausea, and heartburn have been reported.

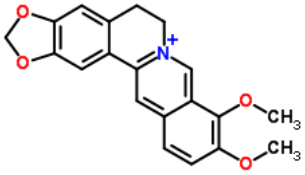
5.1.12 Greater celandine

Chelidonium majus (Papaveracecae) is a ruderal plant widely distributed throughout the world. The European Pharmacopoeia defines Chelidonii herba as the dried, whole or cut aerial parts of *Chelidonium majus* L. collected during flowering, with a minimum 0.6% content of total alkaloids.

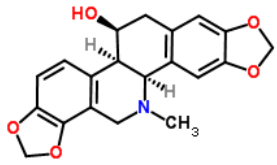
Greater celandine has been used in folk medicine since the Middle Ages for bile and liver disorders. Its fresh, yellow latex has been utilized in the treatment of various dermatological problems, and especially warts.

- **Chemical composition and mechanism of action**

Celandine contains 0.1-1% benzylisoquinoline alkaloids belonging in the protoberberine (berberine, coptisine and stylopine), benzophenanthridine (chelerythrine, chelidonine and sanguinarine) or protopine subgroups. The plant is rich in plant acids.



berberine



chelidonine

The antiviral activity of the plant and its constituents (which may be related to its efficacy against viral warts) has been observed in multiple preclinical studies. Total alkaloid extracts have proved active against multiple viruses (influenza, herpes

simplex virus, polio virus and adenoviruses) *in vitro*. Protoberberine and benzophenanthridine alkaloids inhibited the reverse transcriptase activity of different viruses. Certain alkaloids exerted antiproliferative effects on tumor cell lines.

An ethanolic extract of celandine induced a choleretic effect in an animal experiment. Liquid extracts of the herb exerted a spasmolytic effect on the animal ileum *in vitro*. Alkaloids were found (at least partly) to be responsible for this effect. On the isolated stomach, the extract of the plant had prokinetic activity.

- **Efficacy and indications**

In a randomized, double-blind, placebo-controlled trial, the efficacy of tablets containing *C. majus* extract was evaluated as concerns the alleviation of functional epigastric complaints. After 6 weeks, the reduction in symptom score was significantly greater in the *C. majus* group. There have been several studies with a positive outcome relating to patients with diseases of the bile ducts, gallstone complaints, or abdominal discomfort, with a product called Panchelidon®, though the exact composition (e.g. what kind of celandine extract it contains) was not published.

The European Medicines Agency has concluded that, in the case of oral application, the evidence of clinical efficacy is lacking for monotherapy and a well-established use indication was therefore not supported. As a traditional herbal medicinal product, the benefit-risk assessment of orally applied preparations is negative (see below). As concerns cutaneous use, the European Medicines Agency decided that the indication was not sufficiently supported by the available data. Nevertheless, in combination products, celandine is available in several countries of the EU, and products for cutaneous use are also available.

- **Side-effects, interactions & contraindications**

The fresh plant and its latex are toxic in large doses (when taken orally), but drying of the plant reduces the toxicity considerably. Long-term application may result in hepatotoxicity (cholestasis and hepatitis). In the Vigisearch database of WHO, there are more than 100 reported adverse drug reactions affecting the hepatobiliary system, and the benefit/risk ratio of the consumption of products containing appreciable amounts of celandine extract is therefore unfavorable.

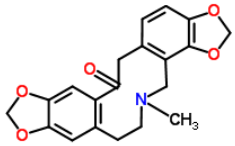
5.1.13 Fumitory

According to the European Pharmacopoeia, Fumariae herba is the whole or fragmented dried aerial parts of *Fumaria officinalis* with a minimum of 0.40% alkaloid content.

Fumitory has been known since ancient times, used as a digestive and diuretic.

- **Chemical composition and mechanism of action**

The pharmacologically most active constituents of fumitory are the alkaloids (0.2-1%). The main types of the alkaloids are the isoquinoline alkaloids (protopine and allocryptopine), which are quantitatively the most important group, and protoberberines, benzophenanthridines, etc. It also contains flavonoids and caffeic acid derivatives. Nowadays, it is applied typically for bile-related symptoms. Externally, it is also used to treat eczema and various dermatological problems.



protopine

Fumitory has amphocholeretic activity, which means that it has no effect on normal choleresis, but it modifies the bile flow when it is experimentally increased or decreased. This effect has been confirmed in animal experiments, similarly to the inhibition of gall bladder calculus formation. The extract of the plant has an antispasmodic effect on smooth muscles.

- **Efficacy and indications**

One double-blind placebo-controlled clinical trial was performed on patients with different biliary disorders (1.5 g of extract daily) for 28 days. The safety and tolerability were proven, and for all 30 patients the results were positive, especially in case of fullness and flatulence

In a clinical trial involving patients with biliary disorders, treatment with 1.5 g offumitory extract daily decreased the symptoms. In another clinical trial, the same dose was used for one year in a group of patients with biliary disorders. The majority of the patients claimed a favorable result. Some other smaller, open, uncontrolled studies were also in favor of the efficacy of fumitory. One study found fumitory to be ineffective in irritable bowel syndrome.

In the lack of conclusive clinical evidence, fumitory may be used as a traditional herbal medicinal product

- to increase bile flow for the relief of symptoms of indigestion (such as a sensation of fullness, flatulence and slow digestion).

The daily dose is 2-4 g as a tea and 1.1 g as powdered herbal substance. Dry extracts may be used in daily doses of about 1 g, and liquid extracts with doses of 1-4 ml.

- **Side-effects, interactions & contraindications**

Bile ducts obstruction, cholangitis, gallstones, any other biliary diseases, hepatitis, and hypersensitivity are contraindications of its application. Safety during pregnancy and lactation has not been established.

5.1.14 Dandelion

Taraxacum officinale Weber is one of the most widely spread medicinal plants in Europe. Although its importance in modern therapy is not outstanding, it has been applied throughout Europe for several indications, ranging from the treatment of diabetes to urinary tract infections, lung diseases and jaundice. The leaves and the dried whole or comminuted aerial parts, collected in spring, and roots and rhizome of *Taraxacum officinale* are all used in official medicine and are official in the European Pharmacopoeia (Taraxaci officinalis herba cum radice and Taraxaci officinalis radix).

- **Chemical composition and mechanism of action**

The root of the plant is rich in inulin, the amount of which is highest in the autumn (up to 40%). The sesquiterpenes in the roots belong in the eudesmanolides and guaianolides. It contains sterols, such as taraxasterol and its derivatives, and a wide variety of phenolic acids. The leaves contain appreciable amounts of phenolic acids and flavonoids, and their potassium salt content is markedly high (up to 4%).

The diuretic action of dandelion herb has been observed in animal experiments. The efficacy of aqueous extracts obtained from dandelion leaves was more pronounced than that of those from the root extracts. Its saluretic effect may be due to the high potassium salt content of the plant.

The choleretic effect of the leaves has been confirmed in different animal species.

The extracts of leaves and roots proved to possess anti-inflammatory activity in different experimental settings. The extract of the plant inhibited ADP-induced human platelet aggregation *in vitro*.

In animal experiments, the extracts of the plant exerted a glucose level-lowering effect. This may be a result of the inulin content and the moderate alpha-amylase and alpha-glucosidase-inhibitory activities.

- **Efficacy and indications**

The efficacy of the herbs and roots has not been studied clinically. Therefore, in view of the long-standing use, the European Medicines Agency published a monograph for traditional herbal medicinal products

- for the relief of symptoms related to mild digestive disorders (such as a feeling of abdominal fullness, flatulence, and slow digestion) and a temporary loss of appetite, and
- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

With this indication, the comminuted dried root with herb should be used, 3-4 g as a decoction or 4-10 g as an infusion, up to 3 times daily. Several dry and liquid extracts are also included in the monograph. For the first indication, expressed juice from the fresh flowering herb with root may also be applied (10 ml, 3 times daily).

For the leaves, the European Medicines Agency considered only the use as a diuretic acceptable. The daily dose of the leaves is 4-10 g as an infusion, 3 times daily. The expressed juice from the fresh leaves can be used in a dose of 10-20 ml daily.

- **Side effects, interactions & contraindications**

In cases of of bile duct obstructions, cholangitis, liver diseases, gallstones, active peptic ulcer and any other biliary disease, or hypersensitivity to the plant or other species of the Asteraceae family, its use is contraindicated.

Its use in patients with renal failure or heart failure should be avoided because of the possible risks due to hyperkalemia. If it is used as a diuretic, an adequate fluid intake is required to ensure an increased amount of urine.

Its use in children under 12 years of age and during pregnancy and lactation has not been established due to lack of adequate data.

Epigastric pain and hyperacidity may occur as adverse effects.

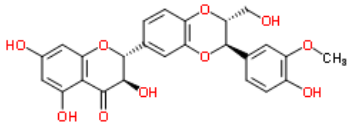
5.1.15 Milk thistle

According to the definition of the European Pharmacopoeia, Silybi mariani fructus is the mature fruit, devoid of the pappus, of *Silybum marianum* L. Gartner (Asteraceae), with a minimal silymarin content of 1.5%, expressed as silibinin. A dry, refined and quantified material is also official.

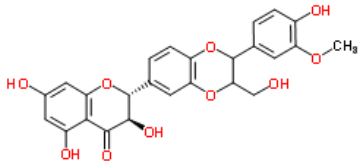
The traditional use of milk thistle goes back to ancient times, when it was used for different liver (e.g. jaundice and hepatitis) and gallbladder problems (digestive symptoms).

Chemical composition and mechanism of action

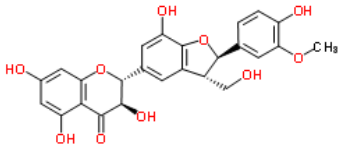
From a therapeutic point of view, the most important secondary metabolites of milk thistle are the flavonolignans (1.5-3%, with silibinin and isosilibinin, silicristin and silidianin as main constituents). The fruit contains flavonols (taxifolin, quercetin and kaempferol) and flavones (apigenin and chrysoeriol) and phytosterols. Its fatty oil content is 20-30%, with linoleic and oleic acid as main components.



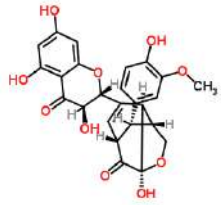
silibinin



isosilibinin



silicristin



silidianin

The pharmacological effects of milk thistle are linked to its flavonolignans. In several studies, mixtures of these compounds (silymarin) or some pure flavonolignan constituents have been investigated.

The hepatoprotective effect depends in part on the protein synthesis-increasing action of flavonolignans in the hepatocytes. Silybin activates DNA-dependent RNA polymerase 1, this enzyme increasing the rate of synthesis of ribosomal RNAs and consequently protein biosynthesis.

The antifibrotic effect of silymarin may be explained by the inhibition of the activation of hepatic starry cells (which transform to myofibroblasts). This activity is related to the inhibition of the NF-κB activation. In a further *in vitro* experiment, silybin prevented the transformation of fat-storing liver cells into myofibroblasts. In animal

experiments, milk thistle extract prevented the development of hepatic fibrosis, and it decreased collagen accumulation in different experimental models.

The antioxidant effect of silymarin and its constituents has been studied in several experiments. Flavonolignans possess strong antioxidant activity and exert scavenging activity against different radicals. This was confirmed in several *in vitro* and *in vivo* studies. Silymarin administration led to a higher total glutathione content and improved the redox state of the liver. The effects of several hepatotoxins are neutralized by the marked antioxidant action of flavonolignans.

Milk thistle extract attenuated the liver injury caused by alcohol in animal experiments (as reflected in the liver enzyme activities).

The efficacy in viral hepatitis may be due to the inhibition of the RNA-polymerase-dependent hepatitis C viruses. Moreover, silymarin inhibits the entrance of the virus into the host cell, probably as a result of its effects on the cell membrane.

The antitoxic effects of flavonolignans are due to their influence on (hepatocyte) cell membranes. Silybinin changes the physical properties of the liver cell membrane by decreasing the turnover rate of phospholipids, hence changes membrane permeability, which prevents the uptake of mushroom (*Amanita phalloides*) toxins into liver cells.

- **Efficacy and indications**

The efficacy of silymarin (i.e. a standardized milk thistle extract (DER 36-44:1)) has been studied in a number of trials. Many of these involved several hundreds of patients with alcoholic liver disease. Most of them showed improvements in clinical symptoms, but with no changes in the laboratory parameters. In a 6-month study on patients with alcoholic cirrhosis, the subjects were randomized to receive milk thistle treatment or placebo. Significant increases in biochemical markers of the endogenous antioxidant defense and liver protection were found. In a 6-month study including patients with alcoholic liver disease, biochemical markers such as AST and ALT were normalized, and GGT and procollagen III levels were decreased in the silymarin-treated patients. Further studies were conducted with similar outcomes. In a 4-week study, the symptoms relating to biliary retention (e.g. dark urine and jaundice) improved significantly as a result of the intervention. In another study, patients diagnosed with hepatic cirrhosis were randomly assigned to receive silymarin or placebo for 4 years. By the end of the study, the proportion of survivors in the treated group was consistenly above that in the placebo group.

Several studies have been conducted on patients with viral hepatitis (acute or chronic, hepatitis A, B or C). In earlier studies, a positive tendency was found in the biochemical parameters, but an antiviral effect was not observed. Some recent studies in which larger doses were applied suggested the possible antiviral effect of silymarin.

The majority of the well-designed trials were carried out with a dry extract (DER 36-44:1, extraction solvent: ethyl acetate, standardized to contain 40-65% of silymarin). For this extract, a well-established indication was accepted as follows:

- supportive treatment of alcoholic liver disease.

The dose is 173-186.7 mg of extract standardized to a content of 108.2 mg of silymarin, calculated as silibinin, 3 times daily. The average duration of use is 2 months.

For other extracts and preparations, clinical efficacy has not been confirmed conclusively, and they can therefore be applied as traditional herbal medicinal products

- for the symptomatic relief of digestive disorders with a sensation of fullness, bloating and flatulence.

For this purpose, the tea prepared from the fruits (6-15 g daily), the dry plant material (up to 1800 mg daily) or its different dry or liquid extracts prepared with ethyl acetate, ethanol or acetone may be used.

Side effects, interactions & contraindications

The only contraindication is hypersensitivity to this or other plants of the Asteraceae family. Its use is not recommended in children and adolescents below 18 years of age, or for pregnant or lactating women, due to the lack of data on safety and efficacy.

Mild gastrointestinal symptoms such as dry mouth, nausea, gastric irritation and diarrhea, headache and allergic reactions (urticaria, skin rash, pruritus, anaphylaxis, asthma) may occur.

5.2 Loss of appetite

The loss of appetite may be a result of different diseases (ranging from simple gastrointestinal disorders to infections and tumors) or the side-effect of certain medications (e.g. antibiotics or chemotherapeutics). It is very frequently related to stress or a symptom of a psychic disease (anorexia nervosa). Since the appetite is directly linked to the sensation of the taste of the meal, decreased taste reflexes (which is common in the elderly) may lead to a loss of appetite. Similarly, a lack of digestive enzymes may also lead to a lack of appetite. The appetite may be improved through the stimulation of taste sensors and the improvement of digestion.

The most traditional herbal remedies for the treatment of a lack of appetite are based on bitter plants. The sensation of the bitter taste in the mouth stimulates (within 30 minutes) salivary, gastric and biliary secretion, at least in conditions where the reflex secretion of gastric juice is inhibited in the cephalic phase. Gastrin secretion is induced, and this hormone stimulates hydrochloric acid secretion in the stomach. It is not clear, whether this effect occurs in healthy people. The efficacy of bitters relies in part on the placebo effect, as confirmed by a study in which bitters improved the appetite in patients with gastric achylia (in whom gastric acid secretion cannot be induced).

The efficacy of bitter herbs is proportional to the intensity of their taste. This is characterized by the bitterness value (i.e. the level of dilution of their extracts which is still bitter). However, overdosed bitters reduce gastric secretions, presumably through their direct effect on the gastric mucosa. Some bitter plants may induce headache in susceptible patients. In high doses, bitter herbs cause nausea and vomiting. As a consequence of their stimulant effect on gastrc acid secretion, bitters are contraindicated for those suffering from gastric or duodenal ulcer.

5.2.1 Wormwood

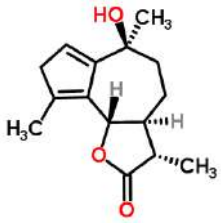
Artemisia absinthium L. (Asteraceae) is native to temperate regions of Europe, Asia and Africa. According to the definition of European Pharmacopoeia, the medicinally applied herb consists of the basal leaves or slightly leafy, flowering tops, or mixtures of these dried, whole or cut organs of *Artemisia absinthium*, and has a bitterness value of at least 10,000.

Wormwood has a very long tradition of medicinal application, primarily because of its bitter taste. It has been used for centuries to improve the digestion and appetite. However, in the food (liquor) industry, wormwood is usually marketed as non-bitter products: absinthe, a popular spirit prepared from the distillate of the plant, which is void of the non-volatile bitter substances. Absinthe was very popular in the late 19th century, but in the first early decades of the 20th century it was banned almost everywhere in the world as a result of its toxic effects. Toxicity is related to the thujone content of the products. Since 1988 absinthe has been on the market in the European Union with a maximum thujone level of 10 mg/kg; this limit is considered to provide safe consumption, at least from the aspect of the toxicity of thujone.

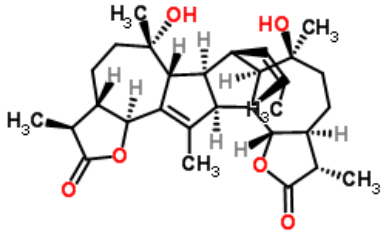
- **Chemical composition and mechanism of action**

Wormwood herb contains up to 1.5% essential oil with alpha-thujone, (*Z*)-epoxyocimene, transsabinyl and chrysanthenyl acetate as main components. The composition of the oil depends on the origin of the sample, and seasonal variation also plays a role. Some plants are regarded to be of pure chemotype (these contain one main component), whereas others are mixed (with more than one major component). In the pure chemotype, alpha-thujone ispredominant in plants growing below 1000 m. In Central and Eastern Europe, mixed chemotypes are typical.

Further, and from the point of view of medicinal application more important compounds are the bitter constituents (0.15-0.4%). Chemically, these are sesquiterpene lactones, with artabsin, absinthin and matricin as main constituents.



artabsin



absinthin

In an animal experiment, purified fractions of an extract proved to have antiulcer effects on acetylsalicylic acid-induced ulcers in rats. Some fractions significantly decreased the volume of gastric juice, and ulcer formation was also inhibited. This observation is in contradiction with the known gastric acid secretion-promoting effect of bitter herbs. One explanation may be that the purified extracts were void of bitter components. In a further trial, orally administered absinthin increased the amount of gastric juice. In a subsequent study, a crude extract exerted a bile secretion-increasing effect in dogs.

Wormwood extracts have exhibited antimicrobial activities on different strains (including *Plasmodium* sp.). Studies with the essential oils suggest that these activities are at least partly related to the volatile components. Antioxidant activity has been confirmed *in vitro*. In animal experiments, *Artemisia absinthium* displayed an antipyretic effect.

Alpha-thujone, a major component of the essential oils of some chemotypes, has no importance as regards medicinal applications, but it is a determinant of the toxicological profile of the plant. The mechanism of alpha-thujone neurotoxicity relies on the modulation of the GABA-gated Cl^- channel. The symptoms of acute intoxication are epileptiform convulsions. After prolonged application, the possibility of mortality is increased, with indications of neurotoxicity (tremor and seizures). On the basis of animal experiments, the Council of Europe allocated a temporary maximum daily intake (TMDI) of 10 μg/kg for thujone. In therapy, chemotypes with low thujone content should be preferred.

- **Efficacy and indications**

In a placebo-controlled study, a dry ethanolic preparation and a powder of *A. absinthium* were administered as aqueous solutions to healthy test persons via a duodenal tube. Duodenal and alpha-amylase secretion were increased by both treatments as compared with placebo. In a double-blind, randomized clinical study on healthy persons, extract administered via a duodenal tube increased the volume of biliary secretion, and the amounts of trypsin, alpha-amylase and lipase.

In a clinical study, a dry extract was administered via a duodenal tube to patients with hepatic disorders. After the preparation had been administered, the duodenal secretion was measured for 100 min. The treatment stimulated the secretion of lipase and alpha-amylase.

In a randomized, placebo-controlled double-blind trial, patients with Crohn's disease treated with steroids received 1500 mg ofwormwood daily or placebo as adjuvant treatment. The efficacy was evaluated with the help of a Crohn's Disease Activity Index (CDAI) questionnaire, an Inflammatory Bowel Disease Questionnaire (IBDQ), the 21-item Hamilton Depression Scale (HAMD) and an 8-item Visual Analogue Scale (VA-Scale). At the end of week 10, the trial medication was discontinued. The concomitant medications were maintained at the same dose levels until the end of the observation period, i.e. the end of week 20. At week 10, 65% of the patients in the verum group were almost free of CD symptoms and there was no need to restart the steroid treatment in the follow-up weeks. Certain patients from this group tolerated the reduction in the steroids. The VA and HAMD iscores mproved significantly in the treated patients as compared with the placebo group.

The clinical evidence is not sufficient to allow the well-established use of this plant. Wormwood herb may therefore be used as traditional herbal medicinal products for the following indications, exclusively based upon long-standing use:

- a temporary loss of appetite and
- mild dyspeptic/gastrointestinal disorders.

The daily dose is 2-3 g of the comminuted herbal substance as a herbal tea or tincture or 10 ml of expressed juice. In the case of a loss of appetite, it is to be taken 30 minutes before meals, but in the latter indication after meals. With this dose, a daily intake of 3 mg/person of thujone is considered acceptable for a maximum duration of use of 2 weeks.

- **Side-effects, interactions & contraindications**

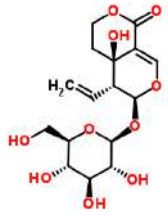
The contraindications of the treatment are hypersensitivity to the plant and to other plants of the Asteraceae family, obstruction of the bile duct, cholangitis or liver disease. Patients with gallstones and any other biliary disorders should use wormwood only after consulting a medical doctor. Use should be avoided during pregnancy and lactation and for children and adolescents.

5.2.2 Centaury

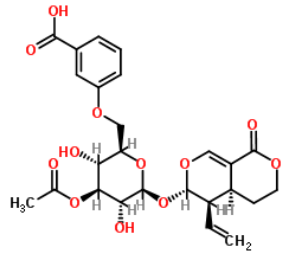
Centaurium erythraea has been used for centuries in Europe, mainly for the relief of digestive complaints and a lack of appetite. In ancient times, its herb was also used for the treatment of fever, malaria, diabetes and snakebites, and as a "blood purifier", tonic and sedative. According to the definition of European Pharmacopoeia, Centaurii herba consists of the whole or fragmented dried flowering aerial parts of *Centaurium erythraea* Rafn s. l., including *C. majus* (H. et L.) Zeltner and *C. suffruticosum* (Griseb.) Ronn. (syn.: *Erythraea centaurium* Persoon; *C. umbellatum* Gilibert; *C. minus* Gars.)

- **Chemical composition and mechanism of action**

The bitter components of *Centaurium* are secoiridoid glucosides, with the main constituent swertiamarin. The most bitter compound is centapricin with a bitterness value of 4,000,000. Further bitter secoiridoids are gentiopicrin, sweroside, centauroside, dihydrocornin and their derivatives. Further characteristic constituents are the secoiridoid alkaloids (e.g. gentianine and gentianidin).



swertiamarin



centapicrin

Although the mechanism of action has not been studied in detail, the knowledge on bitter substances suggests that the bitter constituents stimulate the gustatory nerves in the mouth and thereby increase the secretion of gastric juice and bile and consequently enhance the appetite and promote digestion. Moderate antiphlogistic and antipyretic activities have been confirmed in animal experiments. The antibacterial and antimalarial effects of certain secoiridoids (the latter for gentiopicrin) have also been reported.

- **Efficacy and indications**

No clinical trials have been carried out with *Centaurium*. On the basis of its long-standing application, the preparations of this plant may be marketed as a traditional herbal medicinal product used in

  - mild dyspeptic/gastrointestinal disorders, and/or a temporary loss of appetite.

The daily dose of *Centaurium* is 1-4 g, up to 4 times (comminuted herbal substance for tea preparation) or 0.25-2 g powdered herbal substance, up to 3 times, or liquid or soft extracts with similar posologies.

- **Side-effects, interactions & contraindications**

If high doses are administered, stomach disturbances and nausea may occur. Due to the stimulation of gastric juice secretion, products containing Centaurii herba must not be used in cases of peptic ulcer. It is contraindicated in the event of hypersensitivity to the active substance. In the absence of sufficient data, its use during pregnancy and lactation is not recommended.

5.2.3 Fenugreek

Trigonella foenum-graecum L. (Fabaceae) is a plant that has long been applied in the medicine and as a food/spice. Its seeds are official in the European Pharmacopoeia.

The plant originated from India and North Africa. Its applications were first documented in ancient Egypt. Later, it was used in the folk medicine of Asia, Africa and Europe, with different therapeutic indications, ranging from gynecological problems and the stimulation of lactation to digestive problems. Its contemporary uses extend from external use (dermatological problems) to its application in cases of an elevated blood glucose level or hyperlipidemia.

- **Chemical composition and mechanism of action**

Fenugreek seeds contain 30-45% of galactomannan-type polysaccharides, saponins (about 1%), protoalkaloids, including trigonelline, sterols and flavonoids.

The majority of the preclinical trials focused on the blood glucose-lowering effect of fenugreek seeds. Fenugreek seeds and water and ethanol extracts exerted a hypoglycemic effect in normal and in diabetic rats and other animal species. It is supposed that fenugreek polysaccharides decrease the intestinal glucose absorption. Some studies indicated the potential stimulation of pancreatic insulin secretion. Inhibition of intestinal glycosidases may also play a role. More recent studies concluded that fenugreek increases the translocation of glucose transporter GLUT4 to the cell surface. However, what is quite clear from the available data is that the whole seeds and polar extracts are active, while the apolar extracts are void of hypoglycemic activity.

The hypolipidemic effect of fenugreek has also been thoroughly investigated. In animals with normal lipid levels, the contents of total cholesterol, VLDL and LDL were decreased. The impact on HDL levels is contradictory. This activity may be related to the polysaccharides and saponins of the seeds.

Efficacy and indications

In contrast with the huge amount of preclinical data, the body of evidence from clinical trials is insufficient. In one 6-week double-blind randomized placebo-controlled trial, the effects of a fenugreek seed extract on the eating behavior of overweight subjects were studied. The fasting serum insulin and plasma glucose levels decreased significantly in subjects treated with a fenugreek seed extract as compared with the placebo group, whereas no effect was observed on the plasma lipid profile. The daily fat consumption decreased significantly in those who consumed the fenugreek seed extract.

In a further study, patients with noninsulin-dependent diabetes mellitus with uncontrolled blood glucose levels were involved. The patients were asked to continue to consume a prescribed diet and in addition 25 g of fenugreek seed powder daily. Glucose tolerance tests and the reduction of the glycated hemoglobin level revealed the significant efficacy in comparison with the control group.

In a clinical trial study, type 2 diabetic patients were given 10 g/day fenugreek seeds for 8 weeks. The triglyceride and VLDL levels decreased significantly in the treated group.

In a placebo-controlled trial with newly diagnosed patients with type 2 diabetes, the adjunct use of fenugreek seeds improved the glycemic control and decreased the insulin resistance and there was also a favorable effect on hypertriglyceridemia.

The antidiabetic and antihyperglycemic effects of fenugreek were not demonstrated sufficiently in these trials. This plant is therefore not in use in well-established medicine, but, thanks to its traditional applications, the European Medicines Agency has published a monograph classifying it as traditional herbal medicinal product with the indications of a

- temporary loss of appetite and for the
- symptomatic treatment of minor inflammations of the skin.

Internally, it can be used as a tea (1 to 6 g daily in divided doses) or as dry (water-ethanol) extracts. Externally, the infusion prepared from 50 g/250 ml of water should be used in a cataplasm.

Side effects, interactions & contraindications

Its use in children and adolescents under 18 years of age and during pregnancy and lactation has not been established due to the lack of adequate data.

On oral use, close of glycemic control monitoring should be considered in patients with diabetes mellitus due to the possible hypoglycemic effect of fenugreek. Gastrointestinal disorders (flatulence and diarrhea) and dizziness may also occur.

In cases of cutaneous use, allergic reactions have been reported (facial angioedema and wheezing).

5.3 Diarrhea

Diarrhea may have a number causes. The most common factors are pathogenic bacteria or viruses, toxins of non-microbial origin (including some medicines) or improper diet. A direct cause of diarrhea may be increased secretion and the decreased absorption of water in the gastrointestinal system, increased motility and increased osmotic pressure or a combination of the above factors.

Frequent defecation or the passage of a (semi)liquid stool is a common disease, usually related to infections. Uncomplicated acute diarrhea usually lasts only for some days and is tipycally self-limiting. Chronic diarrhea persists much longer (even for weeks) and may have more severe underlying causes (bowel diseases or endocrinological causes).

Independently from the cause, herbal antidiarrheal preparations may be effective through their antibacterial or antiviral effects, by inhibiting the absorption of toxins and water and by decreasing secretion to the gut.

The majority of antidiarrheal plants act by virtue of their tannin content. Most tannins are catechin derivatives that are resistant to acid hydrolysis. Gallotannins are hydrolyzed in the intestine and therefore have no astringent effects in the colon. By coagulating proteins, tannins have an antibacterial effect and form a protective layer on the mucosal membrane of the gut, thereby inhibiting secretion. Tannins are water-soluble, and their optimal application is therefore in the form of teas. In high doses or when applied for a long time, tannins may cause gastrointestinal disturbances by inhibiting digestive enzymes and decreasing the bioavailability of several medicines and ions.

Pectin-containing plants also have a beneficial effect in diarrhea. Pectins are polysaccharides rich in galacturonic acid; they are resistant to digestive enzymes and are fermented by the bacterial flora of the colon to form short-chain fatty acids. These compounds decrease motility and increase water absorption in the colon. Pectin-containing plants are food plants rather than typical medicinal plants. Typical examples are banana, carrot and apple. Their antidiarheal effect is inferior to that of tannin-containing plants, but they may also be applied in the treatment of small children. Since pectins are hydrolyzed into soluble sugars during ripening, unripe pectin-containing fruits are more effective.

5.3.1 Tea

The fresh leaves of *Camellia sinensis* (L.) Kuntze (Theaceae), also known as *Thea sinensis* L., are an important industrial raw material for the food industry, but they are additionally applied for medicinal purposes. Tea is the most consumed beverage in the world after water. The tea initially imported into Europe in the 17th century was green tea. In therapy, only green tea is used. Green tea is prepared by processing the fresh leaves of *C. sinensis* to prevent the enzymatic oxidation of catechins. The enzymes are inactivated by heat. Other types of tea (e.g. black, puerh) undergo a fermentation process which decreases their catechin content.

In ancient times, tea was consumed as a health-promoting drink in Asia. This may be related to the fact that boiling the water to prepare tea reduces the risk of infectious diseases. In folk medicine in different parts of the world, tea has been used for the treatment of a wide variety of diseases. The present application of tea in health protection and therapy is versatile. Due to its high catechin content, green tea is used in the treatment of diarrhea. Green tea is popular for its presumed effect in decreasing the incidence of certain chronic diseases (cardiovascular and cancer). For this purpose, extracts enriched in a special catechin, epigallocatechin-3-*O*-gallate (EGCG) are used. Although tea is well known for its stimulating effect, due to caffeine, special decaffeinated extracts of green tea have recently been marketed for their relaxing effects.

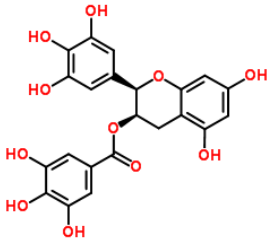
Green tea leaf leaf is not included in the European Pharmacopoeia. According to the definition of the French Pharmacopoeia, Camelliae sinensis non fermentatum folium consists of whole or cut young, unfermented, rapidly hot-dried leaves of *Camellia sinensis* (L.) Kuntze and its cultivated varieties with a caffeine content of not less than 2.0% .

- **Chemical composition and mechanism of action**

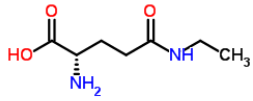
Tea leaves contain methylxanthines, with caffeine as the major compound (2.5-4.0%), theophylline (0.02-0.04%) and theobromine (0.15-0.2%), and different classes of flavonoids, including flavanols (10-25%, (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-O-gallate (ECG), and (-)-epigallocatechin-3-O-gallate (EGCG)), flavonols (eg. quercetin, kaempferol and their glycosides) and flavones (e.g. apigenin, and luteolin as *C*-glucuronides) L-Theanine (3%, 5-*N*-ethylglutamine) is the most

important of the amino acids of the plant. Tea leaves also contain saponins, phenolic acids and tannins.

caffeine



EGCG



theanine

A cup of tea contains approximately 60 mg of caffeine (a cup of coffee contains about 100 mg) and the amount of this methylxanthine is independent of the mode of processing (black, green or other types). However, the theanine and polyphenol concentration is the highest in green tea.

Although no experimental data are available, the antidiarrheal effect of tea is directly linked to the polyphenol content of the drink. When applied in diarrhea, therefore green tea should be preferred.

The mild stimulant effect of green tea can be interpreted on the basis of its caffeine content. The oral administration of green tea increased locomotor activity in rats. It was confirmed that this activity can be attributed to the caffeine content of the tea. In a mouse model of chronic fatigue syndrome, green tea was effective in reversing the increase in immobility time.

Tea extracts have a beneficial influence on the glucose metabolism. A tea extract enriched and standardized to catechins improved the glucose tolerance and insulin sensitivity in rats. After 12 weeks of green tea supplementation, the green tea group had lower fasting plasma levels of glucose, insulin and triglyceride than the control rats. The insulin-stimulated glucose uptake of the adipocytes was significantly increased in the green tea group. In a rodent model of type 2 diabetes mellitus, green tea extracts reduced the glucose levels of food-deprived mice, and the glucose-stimulated insulin secretion was enhanced.

The potential effect of green tea on body weight was linked to its caffeine content. However, recent studies have pointed to the role of other secondary metabolites of tea too. In a study on mice involving an experimental model of obesity, the intake of decaffeinated green tea for 6 weeks significantly slowed the rate of weight gain, as compared with the control group. In a further experiment, treatment induced a significant reduction in white adipose tissue weight as compared with high-fat-fed control mice. In mice fed a high-fat diet, EGCG treatment for 16 weeks reduced the body weight gain and body fat percentage. In one experiment, EGCG significantly reduced food intake in rats. EGCG treatment attenuated the insulin resistance and

decreased the plasma cholesterol level. In a furtherstudy, EGCG, but not other catechins (EC, EGC and ECG) caused a body weight loss in rats. However, in other investigations green tea had no effect on body weight, and some experiments suggest the primary role of caffeine in weight reduction.

Green tea exerted an antimicrobial effect against a series of bacteria, including *Streptococcus mutans*. This may be the explanation of the experimentally conformed anti-caries effect of tea (and EGCG).

Different tea extracts and the catechins of tea exerted antioxidant effects in *in vitro* models. Inhibition of tumorigenesis in the lung, prostate and digestive tract by tea and its constituents (primarily EGCG) has been consistently demonstrated in different animal models.

- **Efficacy and indications**

The stimulatory activity of green tea is due to its caffeine content. Although there have been no modern clinical with (green) tea to confirm this effect, the available data on caffeineindicate that tea extracts containing a significant amount of caffeine (100-200 mg) may be used to enhance attention and alertness in modern phytotherapy.

Recently, tea extracts enriched in theanine have been applied with the opposite goal: to achieve relaxation without affecting the cognitive performance. After ingestion of a soft drink containing a green tea extract rich in theanine, a higher level of mental performance and an improvement of attention were observed by EEG. The effect of a theanine-containing green tea extract has been studied in a randomized, double-blind, placebo-controlled trial. A preparation containing 120 mg of theanine improved memory and attention in subjects with a mild cognitive impairment. The brain theta waves, an indicator of cognitive alertness, were increased significantly.

In a randomized, double-blind, placebo-controlled study, healthy adult participants received either 250 mg of caffeine, 200 mg of theanine, both or neither. Caffeine increased the self-rated alertness and blood pressure. Theanine antagonized the action of caffeine on blood pressure but did not significantly affect alertness and mood. Another study investigated the effect of a combination of 97 mg of L-theanine and 40 mg of caffeine as compared with placebo treatment on the cognitive performance, alertness, blood pressure and heart rate in a sample of young adults. Cognitive performance and self-reported mood, blood pressure and heart rate were measured before and after L-theanine and caffeine administration. The treatment significantly improved accuracy during task switching and self-reported alertness and reduced self-reported tiredness.

The efficacy of different green tea extracts as a slimming agent has been analyzed in several studies. In a 12-week double-blind study, 690 mg of catechins/day decreased the body weight, the BMI, the waist circumference significantly as compared with placebo. A green tea beverage (625 mg of total catechins and 39 mg of caffeine/day) reduced abdominal fat, but had only a marginal effect on body weight versus a control

beverage (39 mg of caffeine) (-2.2 vs. -1.0 kg) after a 12-week treatment. In 2009, a meta-analysis including 11 trials concluded that catechins or an EGCG-caffeine mixture had a small positive effect on weight loss and weight maintenance, the effect on the body weight loss proving larger for Asian participants (-1.51 kg) than for Caucasian participants (-0.82 kg).

The cardiovascular protective effect of green tea is supported by epidemiological data from the Far East. In a prospective cohort study, the effect of green tea consumption on 8,552 Japanese citizens for a period of 12 years was analyzed, and a significant reduction in risk of death from cardiovascular mortality was reported among men (RR=0.58) and women (RR=0.82) who consumed more than ten cups a day (1500 ml) of green tea, as compared with those who consumed 3 cups/day (450 ml). In the prospective Rotterdam Study conducted on more than 3,000 adults (55 years or older), an investigation of aortic atherosclerosis revealed that daily tea consumption is inversely associated with the development of severe aortic atherosclerosis. The odds ratios decreased from 0.54 (for drinking 125 to 250 ml of tea) to 0.31 (for drinking more than 500 ml/day). In the Ohsaki National Health Insurance Cohort Study, a population-based, prospective cohort study, 40,530 Japanese adults aged 40 to 79 years were followed up for up to 11 years. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. In those who drank at least 5 cups daily, the RR was 0.77-0.88 in comparison with those who drank less than 1 cup (RR = 1.00). The strongest inverse association was observed for stroke mortality.

The role of green tea in the prevention of further chronic diseases has also been studied. In a retrospective cohort study including 17,413 persons with a 5-year follow-up, the consumption of green tea and coffee was inversely associated with the risk of diabetes 2. Although several studies have focused on the efficacy of green tea in cancer prevention, the insufficient and conflicting evidence does not allow the establishment of clear associations.

Although the antidiarrheal activity of green tea is common knowledge, no human studies are available to confirm it. The basis of the effect is the noteworthy polyphenol content of the herbal drug. For this purpose, unfermented green leaves are the most appropriate.

According to the assessment report of the EMA, the efficacy of (green) tea has not been confirmed in any of the above-mentioned indications to grant a well-established use monograph. However, on the basis of the traditional application, green tea may be used as a traditional herbal medicinal product

- for the relief of fatigue and the sensation of weakness.

For this purpose, herbal tea prepared as an infusion from 1.8–2.2 g of whole or comminuted herbal substance, 3–5 times daily, or powdered herbal substance in a single dose of 390 mg, 3-5 times daily, may be applied.

When tea is prepared, the caffeine is almost completely dissolved in the water after 3 min, whereas the tannin content increases when the tea is left to brew., In the case of diarrhea, therefore green tea should be extracted longer than when a drink is prepared for its pleasant taste.

- **Side-effects, interactions & contraindications**

The absorption of alkaline drugs may be delayed because of their chemical binding with the polyphenols of tea.

Pregnant women should limit their caffeine intake to less than 200 mg of caffeine per day (this is equivalent to approximately 10 g of tea leaves; at this level, no risk of miscarriage or preterm birth was detected). It is not recommended before bedtime since it may cause sleep disturbances. The consumption of tea products containing >300 mg can lead to restlessness, elevated reflex excitability and tremor.

5.3.2 Agrimony

Agrimony (*Agrimonia eupatoria* L, Rosaceae) was a popular medicinal plant in ancient times, applied for a plethora of medicinal indications, including diarrhea and inflammation of the throat and mouth. The medicinally applied part is the flowering herb.

- **Chemical composition and mechanism of action**

Agrimony contains 3-10% tannins, consisting mainly of proanthocyanidins (condensed tannins). Triterpenoids, sterols and flavonoids have no role in the antidiarrheal effect, which relies on the appreciable tannin content of the above-ground parts.

Agrimony exhibits anti-inflammatory (elastase-inhibiting) and antibacterial activity against some bacteria *in vitro*.

In animal experiments, aqueous extracts exerted antihyperglycemic, insulin-releasing and insulin-like activities.

- **Efficacy and indications**

The efficacy of agrimony is not backed by clinical studies, but may be considered plausible on the basis of its tannin content, its long-standing use and experience. Agrimony may therefore be used in traditional herbal medicinal products

- for the symptomatic treatment of mild diarrhea
- as a gargle for the symptomatic relief of minor inflammations of the mouth and throat, and
- for the relief of minor skin inflammation and small, superficial wounds.

The dose in diarrhea or as gargle is 1.5–4 g of the comminuted herbal substance as a tea 2-4x daily. In the case of external application, 3-10 g of the comminuted herbal substance is extracted with 250 ml of water and applied as an impregnated dressing to the affected areas of the skin or as a bath additive.

- **Side-effects, interactions & contraindications**

In cases of diarrhea, agrimony should not be used for longer than 3 days if it is not effective. As a gargle or for topical treatment, the duration of use is at most 7 days. In the event of hypersensitivity, application is contraindicated. Although drug interactions have not been documented, tannins may decrease the bioavailability of concomitantly taken medicines.

5.3.3 Tormentil

Potentilla erecta (L.) Raeusch (syn. *Potentilla tormentilla, Tormentilla erecta*) is a perennial plant (Rosaceae) native to Europe. According to the European Pharmacopoeia, Tormentillae rhizoma consists of the dried rhizome, freed from the roots of *Potentilla erecta*. It contains not less than 7% of tannins, expressed as pyrogallol.

Tormentil rhizome has been used internally in European folk medicine to treat diarrhea, and externally for wounds, burns, and inflammation of the skin and oral mucosa.

- **Chemical composition and mechanism of action**

Tormentil rhizome contains 15-20% of tannins (the majority catechin-type condensed tannins), with hydrolizable ellagitannins in smaller amounts), flavonoids, triterpene saponins and phenol carboxylic acids.

The therapeutic efficacy of tormentil depends on its tannin content. These polyphenols coagulate proteins, thereby forming a protective layer on the skin and mucosa, inhibiting the absorption of toxins and exerting an antimicrobial effect. However, not all these effects have been confirmed specifically for tormentil.

Aqueous tormentil extracts exert antimicrobial and antiviral effects on various bacteria (*Shigella* sp., *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli* and *Streptococcus faecalis*) and herpes virus.

- **Efficacy and indications**

In an open-label study, the safety and clinical efficacy of an ethanolic dry extract (2.4 g/day) were studied in patients with active ulcerous colitis. The colitis activity index was reduced statistically significantly, from a mean of 8 to 4, and additionally the stool frequency, bloody stools and C-reactive protein levels decreased.

In a study, involving children with rotavirus diarrhea, treatment with a tormentil tincture was applied until discontinuation of the diarrhea or at most for 5 days. In the treated group, the duration of the diarrhea was 3 days, while in the placebo group it was 5 days.

In the lack of appropriate clinical evidence, tormentil rhizome may be used as a traditional herbal medicinal product

- for the symptomatic treatment of mild diarrhea or
- for the symptomatic treatment of minor inflammations of the oral mucosa.

As an infusion, the maximal daily dose is 12 g; as a decoction it is 6 g. Internally, tinctures or liquid extracts may be used in a daily dose of 3-12 ml, while the dose of the dry extract is 1.2 g daily. For rinsing, a liquid extract or a tea may be used.

- **Side effects, interactions & contraindications**

On its internal application, the absorption of concomitantly administered medicines may be delayed. For this reason, tormentil preparations should be taken 1 hour or more before or after the intake of other medicinal products. Safety during pregnancy and lactation has not been established.

In cases of oral use, mild gastrointestinal complaints such as nausea and vomiting may occur.

5.3.4 Oak

Oak species (Fagacae), have traditionally been applied in European folk medicine. In the Middle Ages, they were used as tanning material in leather processing. The medicinally applied bark is harvested in spring. Oak bark hs been applied topically to treat wounds and burns, and orally in diarrhea.

In the European Pharmacopoeia, Quercus cortex is described as the cut and dried bark of young branches and the lateral shoots of *Quercus robur*, *Quercus petraea* and/or *Quercus pubescens*, with a minimal amount of 3% of tannins.

- **Chemical composition and mechanism of action**

Oak bark contains 10-20% of tannins, both hydrolyzable and condensed ones. The latter are easily oxidized into phlobaphens, which have no tanning properties.

The biological activities of oak bark are largely due to its tannins. These polyphenolic compounds precipitate proteins, thereby forming a protective layer on the skin or mucous membranes; in the gut, they inhibit the absorption of toxins, decrease water secretion and exert an antimicrobial effect. These are general characteristics of tannins, some of which have also been studied with oak extracts and constituents.

The astringency of oak bark is mainly due to its oligomeric proanthocyanidins (condensed tannins), since hydrolyzable tannins have only a limited ability to form complexes with proteins.

In experimental models, different oak bark extracts exhibited gastroprotective action. *In vitro* antibacterial (*Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Psedomonas aeruginosa* and *Proteus mirabilis*), antifungal

(*Candida albicans*) and antiviral (herpes, influenza and HIV) effects of oak extracts and pure tannins have been demonstrated in a series of studies

- **Efficacy and indications**

Although no clinical data support its efficacy, on the basis of the traditional use and the preclinical data, oak bark can be used as a traditional herbal medicinal product for the

- symptomatic treatment of mild diarrhea,
- symptomatic treatment of minor inflammation of the oral mucosa or skin, and
- symptomatic relief of itching and burning associated with hemorrhoids, after serious conditions have been excluded by a physician.

For the first indication, daily 9 g of bark can be used as a tea, or 3 g of dry drug or 560 mg of dry extract (prepared with 50% ethanol). For the second indication, bark as a decoction for oromucosal use at 20 g/l is applied. For the latter two indications, a decoction of 5 g/l comminuted herbal substance is added to the bath.

For the first indication, it is not to be used for more than 3 days, whereas in the other two cases the maximal duration of use is 1 week.

- **Side effects, interactions & contraindications**

Open wounds, large dermal and mucosal injuries and infection of the skin and mucosa are contraindications of its application as a bath.

The intestinal absorption of concomitantly administered medicines may be delayed, and it should be therefore taken 1 hour or more before or after the intake of other medicines. Safety during pregnancy and lactation has not been established.

Allergic reactions may develop.

5.3.5 Raspberry

Rubi idaei folium consists of the dried chopped leaves of *Rubus idaeus* L. (Rosaceae). In traditional medicine, raspberry leaf has been recommended for the treatment of various gynecological disorders (menstruation and parturition problems), gastro-intestinal symptoms (diarrhea), or inflammation of the skin or the mucosa. More recently, raspberry leaf tea has been very popular among pregnant women to stimulate and facilitate labor and shorten its duration.

Chemical composition and mechanism of action

Raspberry leaves contain noteworthy amounts of polyphenols, mainly hydrolyzable gallo- and ellagitannins (2.5-7%), flavonoids (up to 1%; kaempferol, quercetin and their glycosides) and phenolic acids.

In an animal experiment, raspberry leaf water extracts were tested on uterine strips from both non-pregnant and pregnant rats. Little or no effect was seen in the uteri from the non-pregnant rats, whereas a more regular rhythm and less frequent contractions were observed in the pregnant uteri. A further study revealed that aqueous extracts of raspberry leaf could trigger contractions of uterine strips both from pregnant and from non-pregnant rats, while the ethanol extract had no effect on contractility. In older studies, both relaxing and contracting effects were described in different animals. Extracts prepared with organic solvents had smooth muscle-relaxing effects.

Efficacy and indications

The clinical data on raspberry leaf focus on its contemporary use during pregnancy. A double-blind, randomized, placebo-controlled study was continued from 32 weeks of gestation until the beginning of labor. Tablets containing 2.4 g raspberry leaf daily had no significant effect on the length of pregnancy, the medical augmentation of labor, the need for pain relief during labor, or the times of the three stages of labor.

In accord with the long-standing application in folk medicine and the evident effect of polyphenols, raspberry leaf may be used as a traditional herbal medicinal product for the

- symptomatic relief of the minor spasms associated with menstrual periods,
- symptomatic treatment of mild inflammation in the mouth or throat, and
- symptomatic treatment of mild diarrhea.

For the first of these indication the maximal dose of a water extract (DER 4:1) is 904 mg. For the other two indications, herbal infusions may be used, prepared as 1.5-8 g of the comminuted herbal substance in 150 ml of boiling water, 3 times daily. In cases of mild inflammation in the mouth or throat, it should be used as a gargle.

Side effects, interactions & contraindications

Safety during pregnancy and lactation has not been established. In the event of hypersensitivity to raspberry leaf, its application is contraindicated.

5.4 Obstipation

Obstipation is a common complaint in 1-5% of the population and 20–80% of the elderly. Functional constipation is the most common type without any specific etiology. Obstipation may be a result of organic causes, or it can be induced by an improper diet or by medicines (chemotherapeutic agents that act on the autonomic nervous system, such as paclitaxel, vinca alkaloids, oxaliplatins; opioids, sedatives, hypnotics, anxiolytics; anticholinergic preparations such as spasmolytics, antiparkinsonism agents and antidepressants; antacids, diuretics, phenothiazines, and iron and calcium supplementation. In order to exclude severe diseases, the organic cause must be determined by a medical doctor, especially if the condition arises suddenly. According to the recommendations of National Cancer Institute, the following questions may provide a useful assessment guide:

1. What is normal for the patient (frequency, amount and timing)?
2. When was the last bowel movement? What was the amount, consistency and color? Was blood passed with it?
3. Has the patient been having any abdominal discomfort, cramping, nausea or vomiting, pain, excessive gas, or rectal fullness?
4. Does the patient regularly use laxatives or enemas? What does the patient usually do to relieve constipation? Does it usually work?
5. What type of diet does the patient follow? How much and what type of fluids are taken on a regular basis?
6. What medication (dose and frequency) is the patient taking?
7. Is this symptom a recent change?
8. How many times a day is flatus passed?

The most common reasons for obstipation are dietary habits (a diet poor in fibre and insufficient water consumption), and lack of physical activity. In some cases, the intestinal motility is disturbed (e.g. in those who are suffering from irritable bowel disease), and this is the major reason for obstipation in the elderly.

Obstipation is characterized by straining heavily to produce stools, in some cases accompanied by a feeling of incomplete defecation, and abdominal cramps. Obstipation may increase the risk of hemorrhoids and chronic constipation may be related to an increased risk of colon cancer.

The treatment of obstipation should start with dietary (an increase of fibre and water intake) and lifestyle changes. If this is insufficient, bulking agents such as phytotherapeutics should be used. Osmotic laxatives may also be applied. Stimulant anthranoid-containing laxatives are agents of second choice, and should be used only occasionally.

Bulk-forming laxatives

The safest laxatives belong in the group of bulk-forming agents. These products are especially rich in fibers and may be regarded as supplementation of a fiber-deficient diet. Bulking agents are enzymatically indigestible carbohydrates, though they may be completely or partially broken down by the bacteria in the colon. Fibers are swollen by water and soften and increase the volume of fecal material and soften the stool. Moreover, bulk-forming agents stimulate the intestinal activity by causing distension of the bowel. Hence, these compounds act primarily through physical effects, without being absorbed from the gastrointestinal system. As a result, the transit time in the colon is shortened and the straining during defecation is relieved. The efficacy of bulking agents furtherrelies on their effect on the intestinal flora. These products provide the bacterial flora with a proper substrate for proliferation, and the bacterial mass and consequently the stool weight are therefore increased. This component of the clinical effect is plausible only on long-term treatment (in clinical trials, these kinds of products are especially effective after several weeks of treatment). The colonic bacteria break these materials down (at least partly), resulting in the formation of short-chain fatty acids. These may have a protective effect on the mucosa, but more importantly act as osmotic laxatives in the colon.

Bulk-forming laxatives are not absorbed, and therefore have no systemic effects. They are a safe way of treating the obstipation of pregnant women and also in the case of long-term treatment. The most common side-effect is flatulence and a feeling of fullness. Bulk-forming agents may decrease the absorption of concomitantly taken drugs.

5.4.1 Linseed

Linseed, a herbal material official in the European Pharmacopoeia, consists of the dried, ripe seeds of *Linum usitatissimum* L. with a minimal swelling index of 4.

Linseed has been applied in folk medicine for several hundred years, typically as a laxative and expectorant, or externally to treat skin problems, but also for other indications for which it is considered today to be ineffective (e.g. venereal diseases). One of the most interesting indications was its use to remove foreign material from the eye; a seed was moistened

with water and placed under the eyelid, the material in the eye adhered to the seed and could be removed.

- **Chemical composition and mechanism of action**

The seeds contain 3-6% of mucilage, 3-8% of alimentary fibers, 20-30% of protein and 30-45% of fatty oil, and is rich in polyunsaturated fatty acids, e.g. linoleic acid, and lignans. Its cyanogenic glycoside content is 0.1-1.5%,

The laxative effect of linseed is attributed to the swelling of polysaccharides in the intestines, to form a softer stool and exert pressure on the gut wall. It should be noted that broken seeds have an inferior laxative efficacy since the increase of the volume may already start in the stomach. An animal experiment confirmed that the oral application of linseed increased the water content of the feces.

Animal experiments have demonstrated that the consumption of linseed lowers cholesterol levels. This may be related to the unsaturated fatty acid content of the oils and to the fibers, which inhibit the absorption of cholesterol. Some studies have indicated that lignans may also play a role in this effect.

Linseed extracts exert estrogenic effect in different *in vitro* models. The antioxidant effect is due to the lignan and unsaturated fatty oil content.

- **Efficacy and indications**

In a randomized trial, patients with constipation-predominant irritable bowel syndrome received 6-24 g/day of either linseed or psyllium for 3 months. In the linseed group, the constipation and abdominal symptoms were decreased significantly, whereas in the psyllium group the reduction was not statistically significant.

In a non-controlled study, patients suffering mainly from constipation were treated with 10 g of bruised linseed three times a day for 4-6 weeks. The majoriy of the patients experienced relief of their symptoms.

A cholesterol-lowering effect has been observed in several clinical trials. This may be due in part to the composition of linseed oil, and in part to its polysaccharides and lignans. The hypothesis that the alpha-linolenic acid content of linseed oil may have a cardioprotective effect was investigated in a dietary intervention study. Subjects were randomly assigned to one or other of three diets enriched with either linseed oil, sunflower oil or fish oil for 12 weeks. The total plasma cholesterol level decreased by 12.3% in the linseed group (this was the most extensive change within the 3 treated groups). In an 8-week, randomized, double-blind, placebo-controlled study with 55 hypercholesterolemic patients, a linseed extract with a lignan content of 300-600 mg/day significantly decreased the total cholesterol LDL-C and glucose concentrations.

Although estrogenic effects have been observed preclinically, such effects (primarily in postmenopausal women) have not been observed in clinical trials in terms of menopausal symptom alleviation.

The well-established use of linseed as a laxative is based on general evidence from some open clinical trials, and a well-established use monograph was therefore granted by the Euroepan Medicines Agency with the following indication:

- treatment of habitual constipation or in conditions in which easy defecation with soft stool is desirable.

The daily dose is 20-45 g daily.

The traditional use as a demulcent preparation is supported by general evidence from more than 30 years in Europe, and the plausibility is supported by both empirical knowledge and limited clinical evidence. Linseed may therefore be used as a traditional herbal medicinal product with the indication of a

- demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort.

The daily dose is 15-30 g.

It should be consumed with a sufficient water intake and at least 1/2-1 hour before or after the intake of other medicines. The effect starts 12-24 hours later. It should not be taken immediately prior to bedtime.

Side effects, interactions & contraindications

Although 100 g of linseed may contain cyanogenic glycosides equivalent to 30 mg of hydrogen cyanide (the lethal dose of which is about 50-100 mg), linseed consumption is not dangerous from this aspect. The reason is that linseed contains cyanide in glycosidic form and its release is catalyzed by the enzyme linamarase (present in the seeds). This enzyme is inactivated by the gastric acid and the (low) amount of cyanide released is transformed to the harmless thyocyanate by the rhodanase enzymes.

Linseed should not be used by patients with a sudden change in bowel habit that has persisted for more than 2 weeks, with undiagnosed rectal bleeding or with a failure to defecate following the use of a laxative. Linseed should likewise not be used by patients with abnormal constrictions in the gastrointestinal tract, with diseases of the esophagus or cardia or with an existing intestinal blockage (ileus), orparalysis (ileus) of the intestine or megacolon. It should not be taken by patients who have difficulty in swallowing or any throat problems.

The long-term use of linseed may have an estrogenic effect, and its use is therefore not recommended in women with hormonally dependent tumors.

In order to decrease the risk of gastrointestinal obstruction (ileus), linseed should be used together with medicinal products known to inhibit peristaltic movement (e.g. opioids or loperamide) only under medical supervision.

As an adverse effect, meteorism is common. Reactions of hypersensitivity including anaphylaxis-like reactions may occur very rarely.

5.4.2 Isphagula and Psyllium

Both in folk medicine and in modern phytotherapy several, *Plantago* species are used for their polysaccharide-rich seeds. The most important representatives of these are known under the names isphagula and psyllium.

Isphagula is the common name of the plant *Plantago ovata*, a species widely applied in traditional medicine in Europe, Asia and America, externally as an emollient, and internally as a demulcent, a diuretic and for different digestive problems. Both the seeds and the separated husk are used. According to the definition of European Pharmacopoeia, Ispaghula seeds are the whole, dried, ripe seeds of *Plantago ovata* Forssk. (syn. *Plantago ispaghula* Roxb.). Ispaghula husk (also part of the European Pharmacopoeia) consists of the episperm and collapsed adjacent layers removed from the seeds of *Plantago ovata*.

Psyllium is used similarly to isphagula in folk medicine, and also in official medicine. According to the European Pharmacopoeia, Psyllium seeds are of the ripe, whole, dry seeds of *Plantago afra* L. (*Plantago psyllium* L.) or *Plantago indica* L. (*Plantago arenaria* Waldstein and Kitaibel)

- **Chemical composition and mechanism of action**

From a chemical aspect, isphagula is more valuable than psyllium due to its higher polysaccharide content. Ispaghula seeds contain 20–30% of arabinoxylan-type polysaccharides, which are located in the epidermis of the husks, and the husk is therefore richer in mucilage. The ispaghula husk consists of 85% water-soluble fiber. The seeds also contain high amounts of protein and oil. The minimal swelling index of the seeds is 9. The husk is capable of absorbing up to 40 times its own weight of liquid. Psyllium seeds contain approximately 10% of mucilaginous polysaccharides.

Plantago polysaccharides are not digested by enzymes, but to varying degrees they are fermented by bacteria in the colon, resulting in gas production.

In an investigation of the effects of a 4-week supplementation with *Plantago ovata* seeds, husk and wheat bran in rats, the seeds increased the fecal weight and water content significantly. The husk was the most effective. The total fecal bile acid excretion was stimulated and the beta-glucuronidase activity was reduced by both *Plantago ovata* preparations.

The influence of psyllium preparations (psyllium seeds and husk relative to cellulose and pectin) on plasma lipids was studied in cholesterol-fed rats. Cellulose had no effect on the serum lipids. Psyllium seeds decreased the total serum cholesterol equally to pectin, but also increased the high-density-lipoprotein cholesterol level. Feeding with psyllium husk normalized the liver lipids and the liver size. This effect may be a result of the inhibition of absorption. Through the same mechanism, psyllium may also influence the blood glucose level, but this was not confrmed experimentally.

Efficacy and indications

The majority of clinical trials have been carried out with isphagula. However, in view of the chemical similarity, similar effects may be attributed to psyllium, though with inferior efficacy as well, since its polysaccharide content is lower.

The clinical efficacy of *Plantago* seeds in constipation is confirmed by long-standing experience and several clinical trials involving hundreds of patients. The studies were predominantly carried out with isphagula husk. In short-term trials, a response to treatment in the form of at least one daily bowel evacuation was achieved in more than 50% on the first day, and in 90% on the third day. The fecal consistency also improved.

Since isphagula can absorb a high amount of water, it can theoretically also be useful in diarrhea. In a study with hospital inpatients with diarrhea, a good response was noted in 20% of the cases and an adequate response in 10%. The average daily frequency of bowel movements diminished significantly and the stool consistency changed from liquid or semi-liquid to soft but formed, or solid.

A combination product containing ispaghula seeds and husk was studied in a randomized placebo-controlled study of patients with irritable bowel syndrome (diarrhea-predominant IBS (type I), constipation-predominant IBS (type II) or IBS with the alternate occurrence of diarrhea and constipation (type III)). After 30 days of treatment, 90% of the patients in the verum group reported a symptomatic improvement and their need for antispasmodic medication dropped by more than 50%. In the placebo group, 33% of the patients displayed a symptomatic improvement, but their antispasmodic intake remained just as high as before the trial. In a further placebo-controlled trial, patients with irritable bowel syndrome were randomized. The rate of response (more than two weeks of adequate relief per month) was significantly higher with psyllium than with placebo during the first and the second month of treatment, but not during the third month.

The LDL cholesterol-lowering effect of isphagula husk was observed in randomized, double-blind, placebo-controlled studies. A significant increase in bile acid synthesis was also noted in some patients. A meta-analysis involving 21 clinical trials determined that, after the consumption of psyllium for 20 weeks, the serum total cholesterol level was reduced from the baseline level by nearly 10%, and the LDL concentration by nearly 7%.

The convincing results indicate that isphagula and psyllium seeds can be used in well-established therapy

- for the treatment of habitual constipation and
- in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures or hemorrhoids.

For adults, the daily dose is 8-40 g/25-40 g of herbal substance, while for children from 6 to 12 years of age it is 4-25 g/12-25 g (isphagula/psyllium). A sufficient amount of liquid should always be taken (at least 30 ml of water per 1 g of herbal substance). Isphagula husk has well-established use indications for

- the treatment of habitual constipation,
- in conditions in which easy defecation with soft stools is desirable, e.g. in cases of painful defecation after rectal or anal surgery, anal fissures or hemorrhoids
- for patients to whom an increased daily fibre intake may be advisable e.g. as an adjuvant in constipation-predominant irritable bowel syndrome, or as an adjuvant to the diet in hypercholesterolemia.

For the first two of these indications, the daily dose for adults is 7–11 g, and that for children 6-12 years of age is 3–8 g. For the third indication, the daily dose for adults is 7-20 g.

- **Side effects, interactions & contraindications**

These materials should be taken during the day at least 1/2 to 1 hour before or after the intake of other medicines, and not immediately prior to bed-time. The enteral absorption of concomitantly administered medicines may be delayed. The effect starts 12-24 hours later.

The use of isphagula is contraindicated in cases of hypersensitivity, undiagnosed rectal bleeding, a failure to defecate following the use of a laxative, abnormal constrictions in the gastrointestinal tract, diseases of the esophagus and cardia, a potential or existing intestinal blockage (ileus), paralysis of the intestine or megacolon, and difficulties in swallowing or throat problems.

Flatulence may occur when the product is used, but it generally disappears in the course of the treatment. Abdominal distension and the risk of intestinal or esophageal obstruction and fecal impaction may occur, particularly if the material is swallowed with insufficient fluid.

Use is not recommended in children below 6 years of age because there are insufficient data on efficacy. The use of ispaghula seeds may be considered during pregnancy and lactation, if necessary, and if a change of nutrition is not successful.

Stimulant laxatives

Stimulant laxatives have adirect effect on the intestinal mucosa and relieve obstipation by increasing the water content of the fecal matter and the intensity of bowel peristalsis. Although the application of *Ricinus communis* oil has along tradition, primarily anthranoid-containing plants are nowadays applied as stimulant laxatives. Since the active components are known, there are products on the market containing

pure anthranoids rather than dry herbal material or a crude extract. These products (especially medicines) are standardized to their active components.

The main components of the mechanisms of action of anthranoids are

- inhibition of the Na^+-K^+-ATPase in the bowel epithelium, resultsing in decreased water and Na^+ absorption, and
- the increase of cyclic AMP (cAMP) in the enterocytes, which results in the increased secretion of Na^+ and water
- stimulation of the synthesis of certain autacoids and neurotransmitters (NO and 5-HT), resulting in increased intestinal motility, a shortened transit time and decreased water and electrolyte absorption

In contrast with the pharmacodynamics, the pharmacokinetics of anthranoid-containing herbs and pure compounds (except sennosides) is only poorly understood. The term "anthranoid" covers a wide range of chemically related compounds, which differ in their degree of oxidation. The aglycones are pharmacologically active, but plants contain predominantly gylcosides. The glycosides are pharmacologically inert, they are not absorbed in the intestine and they enter the colon unchanged. Anthranoid glycosides are metabolized by the bacteria of the colon. Only a small proportion of the aglycones is absorbed, the majority is excreted with the feces. The absorbed anthranoids are conjugated and excreted in the urine, changing its color to orange or red. Anthranoids may enter the breast milk, and since the pharmacokinetic profile of anthranoid-containing plants has not been studied in detail, they are contraindicated for nursing mothers for precautionary reasons. Reliable data are available only for sennosides. After the repeated application of 20 mg of sennosides (this is their therapeutic dose), sennosides have been detected in low concentration in the blood plasm, however, as concerns their presence in the breast milk, no data are available.

The most common side-effect of anthranoids is spastic abdominal pain. Since anthranoids, and especially the active components of aloe, increase the blood flow of the uterus, it has been speculated that they may increase the risk of miscarriage. Although there are no human data to support this, avoidance of use of anthranoids during pregnancy is usually proposed. The most severe problem with the application of anthranoids is abuse. Long-term application may lead to water and electrolyte loss and hypokalemia. Hypokalemia may result in the worsening of obstipation and some patients therefore increase the dose to a toxic level. A benign consequence of long-term application is pseudomelanosis coli, reversible pigmentation of the intestinal mucosa. This is a result of the accumulation of a brown metabolite (presumably lipofuscin) of anthranoids in the macrophages; it disappears 6–12 months after the discontinuation of laxative administration.

Anthraquinone-containing plants may be applied for the short-term treatment of atonic constipation and before surgery or endoscopy of the gastrointestinal tract. In

cases of spastic constipation and bowel obstruction, their application is contraindicated.

5.4.3 Senna

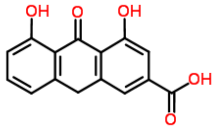
Cassia species have been used for medicinal purposes for centuries. Their application was introduced into European medicine by the Arabs in the 9th century. In folk medicine in different parts of the world, they are used as an expectorant, an antidysenteric, a carminative agent, and for the treatment of venereal diseases, skin diseases, wounds, dyspepsia and fever. However, the most important indication in Europe for centuries has been obstipation. In modern times, they are used as a "blood purifier" and to remove toxins from different organs. Although such a purification was considered to be the first step in the treatment of certain diseases in ancient times, the use of laxatives for this purpose is totally obsolete.

For medicinal purposes, *Cassia* leaves and fruits are applied. Senna leaves consist of the dried leaflets of *Cassia senna* L. (*Cassia acutifolia* Delile), known as Alexandrian or Khartoum senna, or *Cassia angustifolia* Vahl, known as Tinnevelly senna, or a mixture of the two species. The herbal substance contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B.

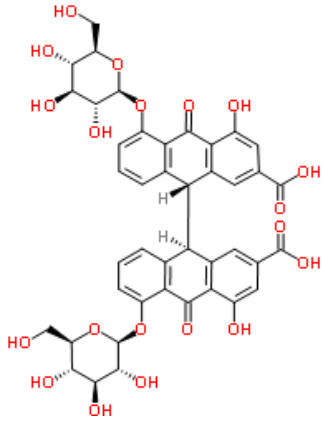
- Chemical composition and mechanism of action

The active constituents of senna are the anthranoids that are present in the leaves of the herbal substance as dianthrones (75–80%) and as anthrones (20–25%). The proportion of anthranoids of the emodin type is higher in the leaves than in the fruits. Senna leaves contains small quantities of (toxic) aglycones, the amount of which increases during storage. Preparations prepared through the use of heat (e.g. teas) contain aglycones in higher amounts, whereas cold extracts do not contain these constituents. The amount of aglycones should be limited in the finished products.

Anthranoid glycosides are not absorbed from the intestinal tract. Neither the acidic milieu of the stomach nor alpha-glycosidase enzyme in the small intestine is able to hydrolyze the beta-*O*-glycosidic substituents of sennosides. However, the beta-glycosidase of the bacteria of the colon is able to hydrolyze glycosides, resulting in the formation of anthrones (rhein-9-anthrone is the most important metabolite). As regards the time of transport to the colon and metabolization into active compounds, *Senna* extracts act within 8-12 hours



rhein-9-anthrone



sennoside

The laxative effect is based onthe increased colonic motility (leading to reduced fluid absorption), the inhibition of absorption and stimulation of the secretion of water and electrolytes.

- Efficacy and indications

The clinical efficacy of senna has been evaluated in clinical trials in the treatment of obstipation and for bowel cleansing before medical interventions. In several studies, *Cassia* has been combined with bulk-forming agents (usually *Plantago*). The efficacy in chronic constipation was confirmed in randomised, double-blind trials. The frequency of loose stools was greater as a result of the treatment.

The bowel-cleansing efficacy was tested with a senna fruit dry extract preparations with a single dose corresponding to 150 mg of sennoside in patients referred for colonoscopy. Although the treatment was assessed as effective, more recent studies do not unequivocally confirm that bowel cleansing with high doses of anthranoids is superior to other preparations (e.g. sodium phosphate or polyethylene glycol lavage). The combination of different prducts seems to offer the most favorable benefit-risk ratio.

On the basis of the available experimental and clinical data, the EMA granted a well-established use monograph to senna. Preparations containing standardized herbal substances or extracts may be indicated for

- short-term use in cases of occasional constipation.

For adolescents, adults and the elderly the daily dose should contain 15–30 mg of hydroxyanthracene derivatives, calculated as sennoside B (to be taken once daily at night). Normally, it is sufficient to take this medicinal product up to two to three times a week. The maximum daily dose of hydroxyanthracene glycosides is 30 mg. The correct individual dose is the smallest amount required to produce a comfortable soft-formed motion. Senna leaves should only be used intermittently and if other actions,

such as behavioural modification, dietary changes and the use of bulk-forming agents, have failed.

- **Side-effects, interactions & contraindications**

The effects of *Senna* anthranoids on breast-fed babies have been studied with post-partum women to whom 15 mg sennosides was administered daily. 0.007% of the sennoside intake (calculated as rhein) was excreted in the breast milk, and none of the breast-fed infants had an abnormal stool consistency. Although no human data are available, animal experiments demonstrated that the placental passage of rhein is very low. Although there is no unequivocal evidence of the carcinogenic activity of senna anthranoids in animals, metabolic activation leads to the formation of the genotoxic metabolite 2-hydroxyemodin. However, there are no reports of undesirable or damaging effects during pregnancy, or on the fetus when used at the recommended dosage. As a consequence of experimental data indicating a genotoxic risk of certain anthranoids, its use is to be avoided during pregnancy (especially in the first trimester). It is not recommended for use in children under 12 years of age.

In theory, anthranoids may increase hyperemia in the pelvic region, and stimulation of uterine muscles is also presumed. However, no such effect has been recorded in humans and there have been no reports of undesirable effects during pregnancy or on the fetus.

It is contraindicated in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease and ulcerative colitis), abdominal pain of unknown origin, or a severe dehydration state with both water and electrolyte depletion. The chronic use of senna leaves may lead to hypokalemia, which may increase the activity of *Digitalis* glycosides and result in interaction with antiarrhythmic agents, medicines inducing a QT-prolongation and drugs inducing hypokalemia (e.g. diuretics and adrenocorticosteroids).

Long-term use (for at least 4 months) of anthranoid-containing products leads to the development of pseudomelanosis coli (brown pigmentation of the gut wall). This reversible condition is demonstrated by the accumulation of lipofuscin-storing macrophages (lipofuscin is a breakdown product of anthranoids).

Certain studies suggest that there is a statistically significant association between the occurrence of colorectal carcinoma and laxative use, but it is disputed whether it is the obstipation itself or the chronic use of laxatives that is the real risk factor. Animal studies have not revealed any evidence of carcinogenicity.

Yellow or red-brown discoloration of the urine by metabolites may occur during the treatment; it is not clinically significant.

5.4.4 Aloe

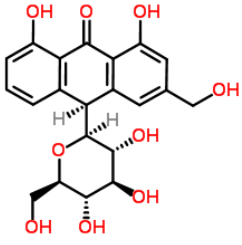
Aloe species are succulent plants that grow in tropical regions. For cosmetic purposes, the gel gained from the mucilaginous tissue (parenchymatous cells) in the center of the leaf is applied. This gel is transparent and tasteless. For this purpose, the species *Aloe barbadensis* Mill. (synonym: *Aloe vera* L.) is cultivated extensively, especially in the USA. The pericyclic cells and the adjacent parenchyma cells of the leaves produce a yellow, bitter latex (or sap/juice). Though very different in appearance and composition, the juice and the gel are often confused.

The juice can be applied as a laxative. In modern medicine, two products are widely used (both included in the European Pharmacopoeia). Barbados aloe consists of the concentrated and dried juice of the leaves of *Aloe barbadensis* Miller. It contains not less than 28% of hydroxyanthracene derivatives, expressed as barbaloin. Cape aloe consists of the concentrated and dried juice of the leaves of various species of *Aloe*, mainly *Aloe ferox* Miller and its hybrids. It contains not less than 18% of hydroxyanthracene derivatives, expressed as barbaloin.

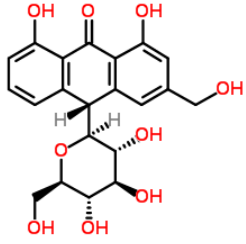
Aloe juice is obtained by cutting the leaf transversely near the base and collecting the light-colored juice. The juice is thickened over a fire to obtain a vitreous mass (this is called aloe lucida). Aloe hepatica, a lusterless product, is prepared by slow evaporation (usually under the sun). Both aloe products have a blackish color.

- **Chemical composition and mechanism of action**

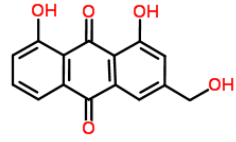
The active constituents of Barbados and Cape aloe are anthrone-10-*C*-glycosides (aloin A and aloin B), named barbaloin, and some other anthranoid derivatives. Both drugs contain aglycones (aloe emodin and chrysophanol) in small quantities.



aloin A



aloin B



aloe emodin

The anthranoid-glycosides of aloe are not absorbed in the upper gut. The intestinal flora is able to break down *O*-glycosides fully, but *C*-glycosides (the major constituents of aloe) only to a certain extent. The anaerobic bacteria *Eubacterium* sp. are able to metabolize barbaloin to aloe-emodin, but this strain is not present in human feces. In a human pharmacokinetic study on healthy volunteers, aloe-emodin (aloe-emodin-9-anthrone is the main active of aloe) was detected in very low concentration (<2 ng/ml) in the plasma after oral administration of aloe (equivalent to 16.4 mg of hydroxyanthracene derivates) for 7 days. Aloe-emodin is quickly oxidized to rhein. The absorbed aglycone is conjugated with glucuronide in the liver and excreted via the urine and the bile. With regard to the time of transport to the colon and the metabolism to active compounds, aloe acts within 6 to 12 hours after oral administration.

The mechanism of action of aloe includes a direct effect on the motility, leading to a reduced transit time, inhibition of the absorption of water, Na^+ and Cl^-, and an increase of the secretion of water and electrolytes into the lumen. The increase in volume of the intestine content increases the intraluminal pressure, which also facilitates peristalsis. Aloe-emodin-9-anthrone inhibits Na^+/K^+-ATPase and the Cl^- channels and increases the paracellular permeability of the colonic mucosa, and it therefore increases the water content of the intestine. Possible mediators of the laxative effects are NO (an enteric inhibitory neurotransmitter), platelet-activating factor (which stimulates the anion secretion of the colon mucosa cells) and the prostaglandins. Anthranoids of aloe increase the production of these transmitters.

- **Efficacy and indications**

The medicinal use of aloe is regarded as well-established for the short-term treatment of occasional constipation. Interestingly, there have been no clinical studies of aloe monopreparations for this specified indication. The only available study was carried out on patients with chronic constipation, in which a multicomponent product composed of celandine, aloe and psyllium was used. The postulated laxative effect of aloe is On the basis of pharmacological data gained with anthranoids and clinical experience.

For adolescents over 12 years of age and adults, the daily dose should contain 10–30 mg of anthranoid derivatives, calculated as barbaloin, to be taken once daily at night (if necessary, 2-3 times weekly). Use for more than 1-2 weeks requires medical supervision.

- **Side-effects, interactions & contraindications**

Porolonged use or an overdosage may lead to hypokalemia which may enhance the effects of cardiac glycosides and interfere with the antiarrhythmic agents, inducing a QT-prolongation. This may be triggered by the concomitant application of medicines that induce hypokalemia (corticosteroids, certain diuretics and liquorice).

Anthranoids may induce hyperemia in the pelvic region through the neuromuscular stimulation of the uterine muscles, which may lead to miscarriage or

preterm birth. Although this has not been supported by human data, for safety reasons anthranoid-containing medicines are contraindicated for pregnant women. Moreover, aloe-emodin is able to induce mutagenic effects *in vitro*. Its use during lactation is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Because of the lack of safety data, it is contraindicated for children under 12.

Aloe is contraindicated in cases of intestinal obstruction and stenosis, inflammatory colon diseases, abdominal pain of unknown origin, and a severe dehydration state with water and electrolyte depletion.

The long-term administration of anthranoid-containing products leads to the development of pseudomelanosis coli (pigmentation of the colonic mucosa) and in anatomic changes in the colon, characterized by the loss of haustral folds. The data on the possible carcinogenic risk of long-term anthranoid use are contradictory. Some studies have reported that the use of anthranoid-containing laxatives is associated with an increased risk of colorectal cancer, but obstipation itself and an improper diet may also contribute.

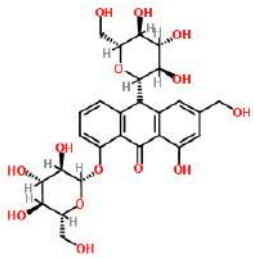
Aloe preparations may lead to colicky abdominal pain, especially in patients with an irritable colon. A yellow-to-brown discoloration of the urine may occur during the treatment (this is a result of the excretion of anthranoid metabolites in the urine and it poses no health risk).

5.4.5 Cascara

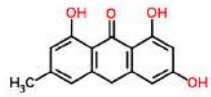
Rhamni purshianae cortex (European Pharmacopeia) consists of the dried, whole or fragmented bark of *Rhamnus purshianus* D.C. (*Frangula purshiana* (D.C.) A. Gray ex J.C. Cooper). It contains not less than 8.0% of hydroxyanthracene glycosides of which not less than 60% consists of cascarosides.

- **Chemical composition and mechanism of action**

The pharmacologically active contituents of the bark are the anthranoids. The major components are the cascarosides, which are anthrone-*C*- and -*O*-glycosides. The total hydroxyanthracene complex of the dried bark consists of 60-70% of cascarosides and 10–30% of aloins. During (heat) drying, the monoanthrones and their *O*-glycosides, which cause undesirable emetic effects, are oxidized to dianthrone- and anthraquinone-*O*-glycosides. Emodin-9-anthrone and chrysophanol anthrone are the most important metabolites of genuine anthranoids, which are produced by the intestinal bacteria.



cascaroside A



emodin-9-anthrone

The mode of action of anthranoids is based on increasing the colonic motility, thereby reducing the transit time and fluid. The absorption of water and electrolytes ($Na^+$and Cl^-) is decreased, whereas the leakiness of the tight junctions and secretion of water and electrolytes into the lumen are augmented.

Cascara *ex vivo* significantly increases Ca^{2+}-dependent constitutive NO synthase activity in the rat colon, and this may also be involved in the laxative effect.

Efficacy and indications

The efficacies of 15 mg of glucofrangulin, 5 mg of bisacodyl and 0.1 g of a water-soluble glucoside extract from cascara were compared in a randomized double-blind crossover trial. Within a period of 3 weeks, patients with chronic constipation were treated consecutively for 5 days with each laxative. Glucofrangulin was shown to be most effective in cases of severe constipation; in moderate cases, the effectiveness of the three test preparations did not differ significantly. The amount, consistency and color of the feces did not show any considerable differences. Several further studies, with a positive outcome were carried out with combination products.

With regard to the well-established efficacy of anthranoids and the clinical data on cascara, this plant may be applied within the frame of well-established use therapy with the following indication:

- short-term use in cases of occasional constipation.

The daily dose should contain 10-30 mg of hydroxyanthracene derivatives, calculated as cascaroside A, to be taken once daily at night. Normally, it is sufficient to take it 2 or 3 times a week.

Side effects, interactions & contraindications

The use of cascara is contraindicated in cases of hypersensitivity, intestinal obstruction, stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease or ulcerative colitis), abdominal pain of unknown origin, or a severe dehydration state with water and electrolyte depletion.

Hypokalemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, medicinal products which induce reversion to a sinus rhythm (e.g. quinidine) and medicinal products inducing a QT prolongation. Concomitant use with other medicinal products

that induce hypokalemia (e.g. diuretics, corticosteroids or liquorice root) may enhance an electrolyte imbalance.

Long-term use should be avoided. If stimulant laxatives such as cascara are taken for longer periods, this may lead to an impaired function of the intestines and a dependence on laxatives. Cascara preparations should be used only if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk-forming agents.

Cascara may produce abdominal pain and spasms and the passage of liquid stools, in particular in patients with an irritable colon. Chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Yellow or reddish-brown (pH-dependent) discoloration of the urine by metabolites, which is not clinically significant, may occur during the treatment.

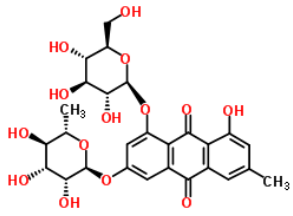
There have been no reports of undesirable or damaging effects during pregnancy or on the fetus when used at the recommended dosage. However, as a consequence of experimental data indicative of a genotoxic risk of several anthranoids, use is not recommended during pregnancy. Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in the breast milk.

5.4.6 Frangula

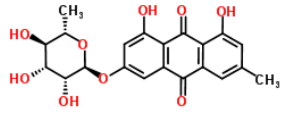
According to the European Pharmacopoeia, Frangulae cortex consists of the dried, whole or fragmented bark of the stems and branches of *Rhamnus frangula* L. (*Frangula alnus* Miller) and should contain not less than 7.0% of glucofrangulins.

- **Chemical composition and mechanism of action**

The pharmacologically active constituents of *Frangula* bark are emodin-di-(glucofrangulins) and monoglycosides (frangulins). It also contains small amounts of aglycones (emodin and emodin-9-anthrone).



glucofrangulin



frangulin

The glucofrangulins are present in the fresh bark in reduced form, and in the stored bark in oxidized form. The reduced forms are presumed to be responsible for the

gastrointestinal side-effects seen in the stomach after oral administration. Emodin-9-anthrone, the most important metabolite, is produced by the bacteria of the large intestine.

The mode of action of the anthranoids is based on increasing the colonic motility, thereby reducing the transit time and fluid. The absorption of water and electrolytes ($Na^+$and Cl^-) is decreased, whereas the leakiness of the tight junctions and the secretion of water and electrolytes into the lumen are augmented.

The administration of a methanolic extract of *Frangula* bark to mice resulted in a dose-dependent decrease of the intestinal transit time.

Efficacy and indications

Although there is no convincing clinical evidence of the efficacy of *Frangula* monopreparations, the results gained with combination products and the knowledge on the mechanisms of action of anthranoids permit the application of this plant within the frame of well-established use therapy with the following indication:

- short-term use in cases of occasional constipation.

The daily dose should contain 10-30 mg of hydroxyanthracene derivatives, calculated as glucofrangulin A, to be taken once daily at night. Normally, it is sufficient to take it 2 or 3 times a week.

Side effects, interactions & contraindications

The use of *Frangula* is contraindicated in cases of hypersensitivity, intestinal obstructions, stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease or ulcerative colitis), abdominal pain of unknown origin, or a severe dehydration state with water and electrolyte depletion.

Hypokalemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, medicinal products which induce reversion to a sinus rhythm (e.g. quinidine) and medicinal products inducing a QT prolongation. Concomitant use with other medicinal products inducing hypokalemia (e.g. diuretics, corticosteroids or liquorice root) may enhance an electrolyte imbalance.

Long-term use should be avoided. If stimulant laxatives such as *Frangula* are taken for longer periods, this may lead to an impaired function of the intestines and a dependence on laxatives. It should be used only if a therapeutic effect cannot be achieved through a change of diet or the administration of bulk-forming agents.

Frangula may produce abdominal pain and spasm and the passage of liquid stools, in particular in patients with an irritable colon. Chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. Yellow or reddish-brown (pH-dependent) discoloration of the urine by metabolites, which is not clinically significant, may occur during the treatment.

There are no reports of undesirable or damaging effects during pregnancy or on the fetus when used at the recommended dosage. However, as a consequence of experimental data indicative of a genotoxic risk of several anthranoids, use is not recommended during pregnancy. Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in the breast milk.

5.4.7 Rhubarb

According to the definition of the European Pharmacopoeia, Rhei radix consists of the whole or cut, dried underground parts of *Rheum palmatum* L. or of *Rheum officinale* Baillon, or of hybrids of these two species, or of a mixture, with a hydroxyanthracene derivative content not less than 2.2%.

- **Chemical composition and mechanism of action**

Rhubarb roots contain 3-12% of hydroxyanthracene derivatives, mainly comprising anthraquinone mono- and diglycosides (55-80%), and dianthrone glycosides (sennosides, 10-20%); aglycones and anthrone glycosides are present in only small amounts. Rhubarb also contains a noteworthy amount (5%) of gallotannins. There are contradictory reports on the stilbene content of the roots. Rhei radix meeting the criteria of the European Pharmacopoeia should be free of these substances.

The mode of action of the anthranoids is based on increasing the colonic motility, thereby reducing the transit time and fluid. The absorption of water and electrolytes ($Na^+$and Cl^-) is decreased, whereas the leakiness of the tight junctions and the secretion of water and electrolytes into the lumen are augmented. Tannins may counteract the laxative effect of the anthraquinones, and rhubarb is therefore considered to be a milder laxative than other anthraquinone-containing plants.

- **Efficacy and indications**

Although there are no convincing clinical findings concerning *Rheum* monopreparations, in view of the results gained with combination products and the knowledge on the mechanisms of action of anthranoids, this plant may be applied within the frame of well-established use therapy with the following indication:

- short-term use in cases of occasional constipation.

The daily dose should contain 10-30 mg of hydroxyanthracene derivatives, calculated as rhein, to be taken once daily at night. It is normally sufficient to take it 2 or 3 times a week.

Side effects, interactions & contraindications

The use of *Rheum* is contraindicated in cases of hypersensitivity, intestinal obstruction and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease or ulcerative colitis), abdominal pain of unknown origin, or a severe dehydration state with water and electrolyte depletion.

Hypokalemia (resulting from long-term laxative abuse) potentiates the action of cardiac glycosides and interacts with antiarrhythmic medicinal products, medicinal products which induce reversion to a sinus rhythm (e.g. quinidine) and with medicinal products inducing a QT prolongation. Concomitant use with other medicinal products inducing hypokalemia (e.g. diuretics, corticosteroids or liquorice root) may enhance an electrolyte imbalance.

Long-term use should be avoided. If stimulant laxatives such as rhubarb are taken for longer period of treatment, this may lead to an impaired function of the intestines and dependence on laxatives. Rhubarb preparations should be used only if a therapeutic effect cannot be achieved through a change of diet or the administration of bulk-forming agents.

Rheum may produce abdominal pain and spasm and the passage of liquid stools, in particular in patients with an irritable colon. Chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation. A yellow or reddish-brown (pH-dependent) discoloration of the urine by metabolites, which is not clinically significant, may occur during the treatment.

There have been no reports of undesirable or damaging effects during pregnancy or on the fetus when used at the recommended dosage. However, as a consequence of experimental data indicating a genotoxic risk of several anthranoids, use is not recommended during pregnancy. Use during breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in the breast milk.

6. Nausea

6.1.1 Ginger

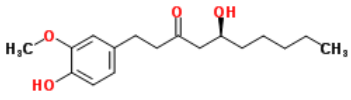
Zingiber officinale Roscoe (Zingiberaceae) is a very popular spice and medicinal plant in Asia. The plant originates from South-east Asia, but its rhizome is applied worldwide due to its taste or medicinal value. Several varieties of ginger are cultivated; in European phytotherapy, the West Indian type (Jamaica ginger) and Indian types (Bengal-ginger) are applied.

Zingiberis rhizoma consists of the whole or cut rhizome of *Zingiber officinale*, with the cork removed, either completely or from the wide, flat surfaces only, with at least 1.5% of essential oil content according to the European Pharmacopoeia.

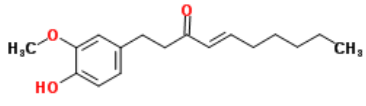
Ginger has been an important plant in Chinese and Indian traditional medicinal systems to treat digestive problems, including nausea, and articular pain. In Europe, it has been in use for at least 2000 years, primarily to relieve gastrointestinal symptoms.

- **Chemical composition and mechanism of action**

Ginger roots contain 1-4% of volatile oil, the majority of which comprises sesquiterpenoids (e.g. alpha-zingiberene, zingiberol, beta-bisabolene and alpha-farnesene). The most characteristic compouds are the pungent principles, i.e. the gingerols (5-7.5%), with the major component 6-gingerol. This group of compounds consists of homologous molecules with different chain lengths (e.g. 8-gingerol and 10-gingerol). During processing, the gingerols are partially converted to shogaols which may further metabolized to paradols.



6-gingerol



6-shogaol

In animal experiments, ginger reversed an experimentally induced delay in gastric emptying, but had no effect on normal peristalsis. In nausea induced by chemotherapeutics, a ginger extract and 6-gingerol had antiemetic effects. Both a ginger extract and also 6-, 8- and 10-gingerol inhibited serotonin-induced contractions of the isolated animal ileum *in vitro*, probably by exerting an antagonistic effect on 5-HT_3 receptors. Vanilloid receptors may also be involved in the effect of ginger, since the rat ileum smooth muscle activity provoked by electrical stimulation was inhibited by ginger, and this effect was influenced by vanilloid receptor antagonists. In human studies, powdered ginger modified the gastric muscular contractions and increased gastric emptying.

Ginger has anti-inflammatory and analgesic activities, partly through the inhibition of NF-kappa-B expression and COX-2 and 5-LOX. *In vitro*, ginger inhibited the formation of thromboxane B_2 and platelet aggregation.

The extracts of the plant demonstrated *in vitro* antibacterial properties against both Gram-positive and Gram-negative human pathogenic bacteria (e.g. *Escherichia coli, Pseudomonas, Staphylococcus* and *Proteus* sp.).

- **Efficacy and indications**

The efficacy in preventing nausea or vomiting of different etiologies has been studied extensively. One of the most typical indications is the treatment of motion sickness; the efficacy of ginger in this special indication has been studied in 8 randomized studies. Some studies involved healthy volunteers with experimentally induced motion sickness (e.g. rotating chair), while other studies examined the efficacy during traveling. In 5 of the available 8 studies, ginger was nore effective than placebo in preventing motion sickness.

The most recent systematic review and a meta-analysis of the efficacy of ginger in postoperative nausea and vomiting included 5 randomized and placebo-controlled trials. The patients underwent gynecological surgery, laparoscopy or laparotomy. The administered dose corresponded to at least 1 g of crude ginger, which was administered 1 hour before anesthesia induction. The meta-analysis found that ginger was significantly better than placebo for the prevention of postoperative nausea and vomiting and vomiting alone. When ginger was administered, the relative risk was 0.65 for postoperative nausea and vomiting and 0.62 post-operative vomiting.

The use in the prevention of pregnancy-related nausea is another major focus of clinical research. In a systematic review, 6 double-blind randomized studies were analyzed in which ginger was used for the treatment of 675 women with pregnancy-induced nausea and vomiting (morning sickness and hyperemesis gravidarum). In 4 of the 6 randomized trials, ginger was superior to placebo; the remaining 2 trials demonstrated that ginger was as effective as the reference treatment (vitamin B_6) in relieving nausea and vomiting. In the literature, altogether 10 randomized studies are available which were performed during the first trimester of pregnancy. As

comparator, placebo, vitamin B_6 or dimenhydrinate was used. The dose of ginger was 1-1.5 g, and the duration of studies varied from 3 days to 3 weeks.

The efficacy of ginger in chemotherapy-induced nausea is insufficient. The only study with a positive outcome demonstrated the non-inferiority to metoclopramide; further studies did not confirm efficacy.

Some studies assessed the efficacy of ginger in osteoarthritis. Although the results were positive, the design (a short treatment period, and high drop-out rates) do not allow the confirmation of efficacy in this indication.

The European Medicines Agency has published two monograph for ginger. Well-established use was declared with the indication of

- the prevention of nausea and vomiting in motion sickness.

The dose of powdered ginger rhizome is 1-2 g 1 hour before the start of travel. Use in children and adolescents under 18 years of age is not recommended

The traditional application of ginger was the basis of 2 other indications for traditional herbal medicinal products:

- the symptomatic relief of motion sickness, and
- the symptomatic treatment of mild, spasmodic gastrointestinal complaints, including bloating and flatulence.

For the former indication, 750 mg of powdered rhizome should be taken 30 min before traveling (for children between 6 and 12 years: 250-500 mg). Use in children under 6 years of age is not recommended.

For the latter indication, the dose of the dried rhizomes is 3x180 mg. Use in children and adolescents under 18 years of age is not recommended.

Side effects, interactions & contraindications

The use of ginger is contraindicated in cases of hypersensitivity to the plant. A moderate number of data on pregnant women indicate no malformative or feto/neonatal toxicity of ginger root. As a precautionary measure, it is preferable to avoid the its during pregnancy. In the absence of sufficient data, use during lactation is not recommended.

Minor gastrointestinal complaints, and particularly stomach upset, eructation, dyspepsia and nausea, have been reported as adverse reactions.

Verification questions

1. List the main types of laxative plants!
2. Which medicinal plants can be used in the treatment of irritable bowel syndrome?

3. What is the mechanism of action of milk thistle?
4. List 3 cholagogue medicinal plants!
5. Which of the plants have both choleretic and cholekinetic effects?
6. Which plants can be used to improve appetite?
7. What are the contraindications of wormwood?
8. Which medicinal plants can be used to relieve the flatulence of children?
9. What is the basis of the antidiarrheal effect of tannin-containing plants?
10. Which type of laxatives can be used in case of chronic obstipation?
11. What are the differences in the modes of action of stimulant laxatives and bulk-forming agents?
12. List 4 stimulant laxatives!
13. What is the mode of action of ginger?

7. Cardiovascular system

In the 50 years, the global average of life expectancy at birth has increased with more than 20 years. With industrial development, in developed countries the major causes of disabilities death have shifted from a predominance of infectious diseases to chronic diseases such as cancer and cardiovascular diseases. The treatment of the latter is challenging, and the medication is based on synthetics, herbal prepatrations have major role in prevention and therapy.

7.1 Chronic venous insufficiency

Chronic venous insufficiency is a very common problem, afflicting about 20% of the population. The frequency of the disease increases with age, resulting in a deterioration of the quality of life, due to the symptoms relating to varicose veins and more serious consequences such as leg ulcer. Varicose veins develop as a result of the destruction of proteoglycans in the elastic tissue of the vein wall. This leads to dilation of the vessels and edema formation.

Apart from surgical treatment, chronic venous insufficiency cannot be cured, but the symptoms may be relieved and the process of vessel wall destruction may be slowed down.

Szent-Györgyi in the lab (source: wikipedia)

The pharmacotherapy of chronic venous insufficiency is usually based on the local or systemic application of natural or semisynthetic flavonoids. These compounds were first applied by the Nobel laureate of Szeged, ALBERT SZENT-GYÖRGYI, who discovered that the efficacy of vitamin C in vascular purpura may be enhanced if the substance contains flavonoids (the original observation was made with an impure vitamin C prepared from *Citrus* fruits). Since then, several clinical studies have confirmed the efficacy of flavonoids in vasoprotection. However, despite their beneficial effects, these compounds are not essential, and hence they are not vitamins (SZENT-GYÖRGYI proposed the name vitamin P, i.e. permeability vitamin, for flavonoids).

The aim of the treatment is to increase the capillary resistance and venous tone and relieve the symptoms. This can be achieved by the application of flavonoids (in many cases "bioflavonoids" are applied, i.e. a flavonoid-rich fraction gained from different plants). However, other secondary metabolites than flavonoids can also be

useful in venous insufficiency. Some triterpene saponins also have a beneficial effect on vessel walls. Nevertheless, their mechanism of action is party different, involving the inhibition of certain enzymes that are responsible for the breakdown of the vein wall structure. Flavonoid-containing plants are usually applied as industrial sources for bioflavonoids. The only plant of phytotherapeutic importance is bilberry. Among the saponin-containing plants, horse chestnut, butcher's broom and hydrocotile are the most significant. Because of the similar pathophysiological background, these herbs can also be used in the treatment of hemorrhoids.

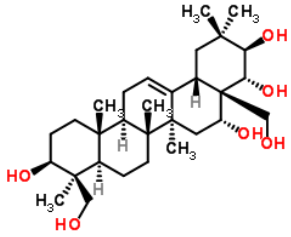
7.1.1 Horse chestnut

Aesculus hippocastanum (Hippocastanaceae), a tree indigenous to Asia, was introduced to Europe by the Turkish invaders in the 16th century. Horse chestnut was an important medicinal plant in the treatment of human and animals (especially horses). Today it is an ornamental tree that is cultivated worldwide. In the Middle Ages, different plant parts were applied. From the 19th century, the seeds gained primary importance in medicine. Seed extracts were already used therapeutically in the early 1800s and there are several reports on their successful application in hemorrhoids. The active constituents of the extracts were (correctly) identified as saponins.

Traditionally, horse-chestnut extracts have been used locally to treat contusions and edema, orally in the prevention and reatment of various peripheral vascular disorders.

- **Chemical composition and mechanism of action**

Horse chestnut seeds contain 3-10% saponins (more than 30 different compounds) based on the aglycones protoaescigenin and barringtogenol C. This saponin mixture is called aescin. Three fractions of aescinhave been described: crypto-, alpha- and beta-aescin. Cryptoaescin and beta-aescin differ in the positions of acetyl groups, while alpha-aescin is a mixture of the other two. Beta-aescin has, but cryptoaescin lacks hemolytic activity.



protoaescigenin

The seeds contain flavonoids, essential oil and sterols, but for medicinal purposes purified beta-aescin is usually applied.

Different experimentally induced edemas have been inhibited by the application of beta-aescin in animals. Different extracts and beta-aescin contracted isolated veins and exhibited antiedematous activity after oral administration. Aescin inhibited the enzyme hyaluronidase *in vitro*.

- **Efficacy and indications**

The effect of a special extract (DER 5:1, 50% ethanol), standardized to 50 mg aescin/capsule (240-290 mg extract/capsule) on transcapillary filtration has been assessed by measuring capillary filtration coefficients in clinical studies. The capillary filtration coefficient proved to be decreased significantly as compared with placebo. The inhibitory effect on edema formation may improve the edema-related symptoms in venous diseases. Plethysmographic studies confirmed that the extract dose-dependently increased the venous tone in healthy volunteers.

In a study on patients with varicose veins, oral administration of the extract decreased the activity of three hydrolases (beta-N-acetylglucosaminidase, beta-glucuronidase and arylsulfatase) that catalyze the breakdown of the proteoglycans of the capillary walls.

Several clinical studies have assessed the efficacy of horse chestnut in relieving the symptoms of chronic venous insufficiency. In the majority of the studies, the above-mentioned special extract was applied (the daily dose of beta-aescin was 100-150 mg), and the studies lasted for 2-16 weeks and were usually placebo-controlled and double-blind. The endpoints were symptoms related to the chronic venous insufficiency (leg pain, edema and pruritus) and objective measures such as leg volume and circumference. The effects on the subjective symptoms and edema were found to be reduced significantly by the active treatment relative to placebo.

On the basis of the clinical evidence, extracts standardized to 100 mg aescin may be applied orally as well-established medicines

- for the treatment of chronic venous insufficiency (characterized by swollen legs, varicose veins, a feeling of heaviness, pain, tiredness, itching, tension and cramps in the calves).

At least 4 weeks of treatment may be needed to achieve a beneficial effect.

In view of the traditional application of horse chestnut seeds, some extracts may be applied topically as traditional herbal medicinal products

- to relieve symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances, or
- for the relief of signs of bruises, such as local edema and hematoma.

For this purpose, a dry extract (ethanol 25-50% v/v) in a strength corresponding to ca 1% aescin in an ointment/gel base, or a tincture (1:5; extraction solvent: 50% ethanol v/v), 20% in an ointment/gel base, may be applied 1-3 times daily.

Side-effects, interactions & contraindications

In clinical trials, no treatment-related adverse events have been recorded. The frequency of aspecific, mild side-effects (nausea, headache, gastrointestinal disorders and pruritus) was the same as in the placebo group. Absolute contraindication of the treatment is limited to hypersensitivity to the active substance.

Saponins may have an irritative effect in the stomach, resulting in nausea. However, high tolerance has been demonstrated for controlled-release dosage forms.

Although the hemolytic activity of saponins led to the suggestion that aescin might increase the effect of anti-coagulants, this was not confirmed by theclinical data.

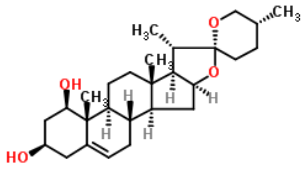
Oral application is not intended for those under 18; for topical application, the age limit is 12 years. If there is inflammation of the skin, thrombophlebitis or subcutaneous induration, severe pain, ulcers, sudden swelling of one or both legs, or a cardiac or renal insufficiency, the products may be applied only after a medical doctor has been consulted. Topical application should be avoided on broken skin, around the eyes or on the mucous membranes. In the absence of sufficient data, use during pregnancy and lactation is not recommended.

7.1.2 Butcher's broom

Ruscus aculeatus L. (Liliaceae) is an evergreen shrub native to Europe. Its English name originates from the use of the stems by butchers to clean their cutting boards (it was thought that the plant had antiseptic effects). In folk medicine, both the stems and the rhizomes have been used. It was applied for several purposes, including diuretic and menstrual disorders and venous problems. The rhizome of the plant is official in the European Pharmacopoeia; it should contain not less than 1.0% of total sapogenins expressed as ruscogenins.

Chemical composition and mechanism of action

The rhizome contains appreciable amounts of steroid saponins (main components: ruscogenin and neoruscogenin). The aboveground parts also contain these compounds, but in lower concentrations.



ruscogenin

In *in vitro* studies, *Ruscus* extracts proved to constrict both animal and human veins. This effect was mediated by the activation of postjunctional alpha$_1$- and alpha$_2$-adrenoreceptors, and stimulation of the release of norepinephrine from adrenergic nerve endings. The venoconstricting property was confirmed in *in vivo* animal models. Oral administration was also effective and the involvement of the alpha-adrenergic system was confirmed (it could be antagonized by the alpha-adrenergic antagonist phentolamine.

A *Ruscus* extract exerted contractile effects both *in vitro* and *in vivo* on lymphatic vessels, suggesting that it improves the function of the lymphatic pumping system. Moreover, a *Ruscus* extract had protective effects against experimentally induced edema *in vitro* and inhibited the microvascular permeability induced by histamine *in vivo.*

Efficacy and indications

The majority of the clinical studies were carried out with a combination product containing flavonoids apart from *Ruscus* extract. To date there has been one good-quality clinical trial with *Ruscus* to confirm its clinical efficacy.

A multicenter double-blind, randomized, placebo-controlled clinical study has been performed to assess the efficacy and safety of a *Ruscus* extract. The study enrolled women with a chronic venous insufficiency; the treatment phase lasted for 12 weeks. The primary variable of the study was the change in foot and lower leg volume. The leg volume decreased significantly in the treated group, but increased in the placebo group. The overall efficacy of the *Ruscus* extract was usually evaluated by the investigator as very good or good, whereas that of the placebo was more frequently assessed as moderate or poor.

In a human study, the application of a single dose of a *Ruscus* extract led to significant decreases in the venous capacity and the venous outflow of the feet, and the tissue volume was also decreased as compared with that for the placebo.

Although clinical studies do not provide firm evidence of efficacy, the long-standing use and preclinical results indicate that butcher's broom can be used as atraditional herbal medicinal product

- to relieve symptoms of discomfort and heaviness of the legs related to minor venous circulatory disturbances, and
- for symptomatic relief of itching and burning associated with hemorrhoids.

The daily dose of the dry root is 1050 mg, while the dry extracts (prepared with water or ethanol) can be used in a daily dose up to 600 mg.

- **Side effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. Nausea, gastrointestinal complaints, diarrhea and lymphocytic colitis may occur during the application of *Ruscus*.

7.2 Cardiac insufficiency

Chronic cardiac insufficiency, or congestive heart failure (CHF) is one of the most common causes of death in the elderly population. The reduction of the pump function results in an insufficient oxygen supply to the organs, including the heart, leading to a wide range of symptoms (edema, cyanosis, tachycardia, hypertension and arrhythmia). According to the classification of the New York Heart Association (NYHA), heart failure may be grouped as follows:

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective assessment

A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

In the history of phytotherapy, a myocardial insufficiency was usually treated with cardiac glycoside-containing plants. In Europe, the most widely applied species applied for the treatment of chronic cardiac failure belonged in the genus *Digitalis*. In acute cases, the quick-acting glycosides of *Strophanthus* seeds were used. More recently, pure digitaloids have been used instead of the extracts of the plants since the narrow therapeutic range of the compounds may result in intoxications. Although cardiac glycosides can be synthetized, for economic reasons they are still obtained by extraction from herbal raw material. However, because of their unfavorable pharmacological properties (a narrow therapeutic range and arrhythmogenic potential), the importance of cardiac glycosides in therapy is decreasing.

The cornerstone of the efficacy of cardiac glycosides is the inhibition of Na^+-K^+-ATPase, which results in an increased intracellular Ca^{2+} level and an improvement of the heart muscle contraction (a positive inotrope effect). For this purpose, beta-adrenoreceptor agonists and ACE-inhibitors are used most widely in modern therapy. From among the "classical" phytomedicines, only one plant, hawthorn, is of noteworthy importance in the treatment of a cardiac insufficiency. However, hawthorn has the major limitation that it is clinically effective only in mild and moderate cases.

7.2.1 Hawthorn

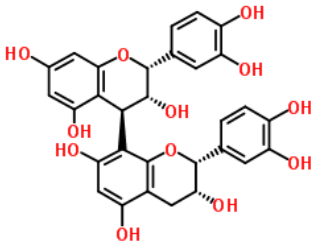
Crataegus spp. are thorny shrubs or small trees native to the northern hemisphere. In the European Pharmacopoeia, whole or cut, dried flower-bearing branches of *Crataegus monogyna* Jacq. (Lindm.), *C. laevigata* (Poir.) DC. (syn. *C. oxyacanthoides* Thuill.; *C. oxyacantha* auct.) or their hybrids or, more rarely, other European *Crataegus* species, including

C. pentagyna Waldst. et Kit. ex Willd., *C. nigra* Waldst. et Kit. and *C. azarolus* L., are official as Crataegi folium cum flore. The dry and the quantified liquid extract produced from hawthorn leaves with flowers are also part of the European Pharmacopoeia. The latter contains 0.8-3% of flavonoids, expressed as hyperoside.

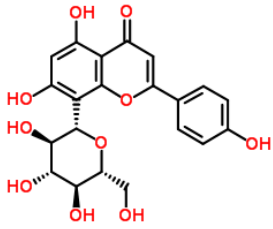
Crataegus species have been used as cardiotonics in folk medicine since ancient times. In the Middle Ages, several therapeutic indications were documented, ranging from the treatiment of jaundice to use as a constipating agent. Hawthorn became one of the most important plants for the treatment of cardiovascular diseases in the second half of the 19th century, when an Irish doctor named Green used the plant (as part of a secret mixture) for the very successful treatment of different heart diseases. After his death, the main components of the remedy was revealed and since then, *Crataegus* is an essential part of the phytotherapy of cardiac insufficiency.

- **Chemical composition and mechanism of action**

The plant material contains proanthocyanidins as key constituents (1-3%). These are flavan derivatives, based mainly on (+)-catechin and (-)-epicatechin, flavonoids, including flavones and flavonoles, mainly as glycosides, e.g. vitexin, hyperoside (0.1% in the fruits and 1% in the aerial parts), triterpenes and aromatic amines.



procyanidin B_2



vitexin

The most important effect of hawthorn as concerns its efficacy is the positive inotropic activity. *Ex vivo* have studies confirmed that *Crataegus* extracts significantly increase the force of contraction of the human myocardium. The extract of the plant inhibits Na^+-K^+ adenosine triphosphatase, which indirectly hampers the Na^+-Ca^{2+} antiport leading to an increased intracellular Ca^{2+} level. The catecholamine-like activity upon the adenylyl cyclase leads to an increase of the cAMP level, which activates protein kinase A and finally leads to the increased contractility of the cardiomyocytes. Phosphodiesterase-inhibitory activity may also play a part in increasing the contractility.

Hawthorn improves the coronary blood flow, presumably through the endothelial nitric oxide (NO) synthesis-enhancing properties of the extract. In an animal

experiment, treatment with a *Crataegus* extract dose-dependently lowered the pathologically increased blood pressure, but had no effect in normal control animals.

Crataegus extracts prolonged pacemaker repolarization, indicating anthyarrhytmic class III–like activity.

In an animal experiment, following the application of oral doses of 100 mg/kg for 12 weeks (this is markedly higher than the human therapeutic dose), the levels of serum cholesterol and triglycerides decreased significantly as compared with the control values. In a further experiment, i.v. administration of different *Crataegus* extracts resulted in a decrease of the blood pressure.

- **Efficacy and indications**

The efficacy of *Crataegus* has been demonstrated in several clinical trials. Although the quality of the applied extracts was very diverse, the overall picture waas positive since the majority of the studies indicated effectiveness relative to placebo. In a recent meta-analysis (2011), clinical data from 10 trials conducted with one of the most widely studied *Crataegus* dry extracts (4-6.6:1, ethanol 45% m/m) were pooled. The results showed that the physiological outcome parameters (the maximal workload (MWL), the left ventricular ejection fraction (LVEF), and the exercise tolerability) improved more in the active treatment group than in the placebo subjects. The typical symptoms such as reduced exercise tolerance, exertional dyspnea, weakness, fatigue and palpitations improved more following active treatment and in patients with more severe symptoms.

In the following, some of the clinical trials conducted with hawthorn will be presented in more detail,

In a randomized, double-blind placebo-controlled clinical study (24 months), *Crataegus* (900 mg extract) was assessed as an add-on treatment in congestive heart failure (NYHA II-III) patients with an impaired left ventricular ejection fraction (LVEF < 35%). The primary endpoint was the number of days between the baseline and the first cardiac event. In the subgroup with LVEF < 25%, the extract significantly reduced sudden cardiac death (39.7% at month 24), whereas the trend for the combined endpoint did not reach statistical significance.

In another study, it was investigated whether long-term therapy with *Crataegus* is efficacious as add-on therapy to pre-existing diuretic treatment in patients with heart failure in a more advanced stage of the disease (NYHA class III), whether the effects are dose-dependent, and whether the treatment is safe and well tolerated. Patients were randomized to treatment with 1800 mg of *Crataegus* extract, 900 mg of *Crataegus* extract, or placebo for 16 weeks. In the 1800 mg extract group, the maximal tolerated workload showed a statistically significant increase in comparison with the other two groups. Typical heart failure symptoms as rated by the patients were reduced to a greater extent by the extract (both doses) than by the placebo.

The efficacy of a *Crataegus* extract was assessed at a dosage of 600 mg per day in a randomized, placebo-controlled and double-blind clinical trial involving patients with NYHA stage II heart failure (8 weeks). Efficacy was measured by bicycle ergometry. The exercise tolerance during use of the hawthorn preparation improved significantly in comparison with the placebo group.

The effectiveness of an extract (900 mg, 8 weeks) was compared with the ACE inhibitor captopril in a multicenter, double-blind study involving NYHA stage II heart failure patients. The exercise tolerance increased statistically significantly during the treatment period in both treatment groups. The incidence and severity of the symptoms also decreased by around 50% in both groups. None of the target parameters indicated any significant difference between the *Crataegus* preparation and the reference drug.

Although the majority of the studies confirmed the efficacy of *Crataegus*, the primary endpoint of these trials does not meet contemporary requirements. In these trials, the examined endpoints are considered to be of secondary importance according to the current guideline of the European Society of Cardiology (2012). In order to demonstrate efficacy, according to the European Society of Cardiology, the goals of treatment should be to relieve the symptoms and signs (e.g. edema), to prevent hospital admission and to improve survival. Since the efficacy of hawthorn has not been confirmed as concerns these criteria, the European Medicines Agency has granted a traditional-use monograph to the plant, with the following indications:

- traditional herbal medicinal product used to relieve symptoms of temporary nervous cardiac complaints (e.g. palpitations, perceived extra heart beat due to mild anxiety) after serious conditions have been excluded by a medical doctor, and
- traditional herbal medicinal product for the relief of mild symptoms of mental stress and to aid sleep.

Interestingly, the latter indication is not supported by any preclinical or clinical data, though the documented traditional application is an appropriate basis for such indication.

There are several extracts (apart from the dry plant material) that can be used in therapy: dry extract (DER 4-7:1, extraction solvent aqueous methanol or ethanol), liquid extract (DER 1:1-2, extraction solvent aqueous ethanol), expressed juice, etc. Typical daily doses are 0.25-1 g of the dry extracts, 1.5-5 g for the liquid extracts.

Side-effects, interactions & contraindications

With regard to its effect on the Na^+-K^+ pump and phosphodiesterase inhibitory activity, it may be presumed that hawthorn may potentiate the effect of digitalis glycosides, beta-blockers and other antihypertensives, but in human studies no such interactions have been recorded.

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, its use during pregnancy and lactation is not recommended.

Verification questions

1. What is the difference between the action of cardioactive glycosides and hawthorn?
2. What are the indications and advantages of application of hawthorn?
3. List three plants that can be used int he treatment of chronic venous insufficiency!
4. What is the mode of action of horse chestnut?

8. Urinary tract

As concerns the treatment of the large variety of the diseases of the urinary tract, effective phytotherapeutics are available only for benign prostatic hyperplasia (BPH) and urinary tract infections. Herbal diuretics may also be applied in the cases of urinary stones and renal gravel, but these indications are more contradictory than the treatment of infections and BPH.

8.1 Infections of the urinary tract

Urinary tract infections (UTI) are among the most common bacterial infections. The majority of infections are caused by intestinal bacteria, and primarily by *Escherichia coli*.

The incidence of urinary tract infections is significantly higher in women of reproductive age than in men. Incidence of UTIs men is increases with age. In women aged 15–39 years, the mean annual incidence is 15%, and with advancing age the frequency decreases. The frequency in men older than 60 years approaches that in women, in consequence of the development of prostatic hypertrophy accompanied by incomplete bladder emptying, which is a factor predisposing to urinary infections.

In modern therapy, urinary tract infections are usually treated with antibiotics, albeit in mild cases the drawbacks of the application of this class of medicines outweigh the benefits. In the majority of the cases, cystitis may be treated effectively with herbal remedies, including plants with a diuretic or a direct or indirect antibacterial effect.

In European folk medicine, several plants have been applied for their presumed diuretic effects. Besides their application in urinary infections (and renal gravels), these plants are popular as components of slimming teas and, more recently, for their "detoxifying" effects. "Detoxication" is simply a misconception based on the hypothesis that diuresis results in the increased removal of toxins. The rationale of using these plants to facilitate weight reduction relies on the temporary slight reduction in the water content of the body. This effect is therefore very limited. Very interestingly, for the majority of these plants, a diuretic effect has never been proven. Apart from the aquaretic effect (which is a result of increased water consumption), there is no real clinical evidence for the effect. It is known that diuretic plants increase the volume of urine without inhibiting the resorption of Na^+ and Cl^-, and therefore, in contrast with to synthetic diuretics, they are not useful for the treatment of edema or hypertension.

Although certain secondary metabolites are linked to the diuretic action (essential oil, flavonoids, saponins and mineral salts), the exact mechanism of action is usually

unknown and even preclinical data are scarce. Nevertheless, the experience from traditional application indicates that the list of diuretic plants is quite long. If there is a diuretic effect (at least as concerns an increased water intake), the therapeutic application of these plants can be regarded as rational since the increased diuresis facilitates the removal of ascending bacteria, crystallization nuclei and renal gravel.

There are some plants with more specific effects in urinary tract infections. Recently the most popular of these, cranberry, has an indirect effect by inhibiting bacterial colonization on the urinary mucosa. Bearberry is applied for its strong antibacterial action, whereas *Petasites* may be useful in urolithiasis because of its spasmolytic activity.

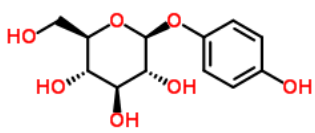
8.1.1 Bearberry

Bearberry (*Arctostaphylos uva-ursi* (L.) Spreng., Ericaceae) is a small shrub growing in the mountains of the northern hemisphere, with red globular, edible berries. Bearberry leaves have been in medicinal use since the Middle Ages in North Europe and by the North American Indians. In Central Europe bearberry has been used on a larger scale only in the past 300 years. Its medicinal applications have ranged from the treatment of venereal diseases to ailments of the urinary tract.

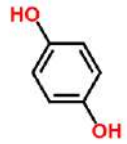
According to the European Pharmacopoeia, bearberry leaf (Uvae ursi folium) consists of whole or cut, dried leaves of *Arctostaphylos uva-ursi* containing not less than 7% of anhydrous arbutin.

- **Chemical composition and mechanism of action**

The pharmacologically active components of bearberry are the hydroquinone derivatives: 5-15% arbutin (hydroquinone-*O*-beta-D-glucoside), up to 5% methyl arbutin (*O*-methyl hydroquinone-*O*-beta-D-glucoside), and traces of galloyl derivatives of arbutin and free hydroquinone. The leaves contain 10-20% gallotannins and about 1% flavonoids.



arbutin



hydroquinone

Different extracts of bearberry leaves were found to exert *in vitro* antibacterial effects against several pathogens, including *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli.* Water extracts increased the hydrophobicity of *E. coli, Helicobacter pylori* and *Acinetobacter baumanii* strains *in vitro*.

It is debated whether arbutin itself or its metabolites are responsible for the antibacterial effect in the urinary tract. Arbutin is hydrolyzed by the intestinal flora to form the aglycone, hydroquinone, which is partly converted to hydroquinone conjugates of glucuronic acid and sulfuric acid. It is supposed that these, together with arbutin, are transformed in the urinary bladder to hydroquinone, the active form. It has been suggested that arbutin could be hydrolyzed directly to hydroquinone in the urinary tract by the beta-glucosidase activity of pathogenic bacteria causing the infection, or the hydrolysis could be triggered by the alkaline pH of the urine. However, the hydroquinone level of the plasma does not increase significantly after treatment with the drug. The antibacterial action reaches a maximum 3–4 hours after oral administration. Only a very low ratio (0.6%) of free hydroquinone is eliminated with the urine; the marority is excreted as conjugates with the feces.

Oral administration of an extract containing 800 mg of arbutin to healthy volunteers demonstrated strong antibacterial activity against *Staphylococcus aureus* and *E. coli* in alkaline urine. In a further study in humans, urine samples collected after the administration of 0.1 or 1 g of arbutin with or without the additional use of acetazolamide were tested on the antibacterial activity against 74 strains of bacteria. An antimicrobial effect was observed even after administration of 0.1 g of arbutin. The efficacy was more pronounced in alkaline urine. The antimicrobial activity of arbutin was found to be dependent on the beta-glucosidase activity of the infective bacterial organism. In *Streptococcus faecalis, Klebsiella* and *Enterobacter* strains, this activity is high, whereas in *E. coli* it is low. It is supposed therefore that, in cases of infection by a beta-glucosidase-active bacterium, the pH of the urine is not crucial, but in the case of E. *coli* the alkalinity of the urine is crucial.

In an animal experiment, an aqueous extract of bearberry leaves was administered intraperitoneally to rats. The urine volume of the rats treated with the herbal extract was significantly higher than that of the non treated controls and comparable to that

in animals receiving hydrochlorothiazide treatment. The bearberry treatment did not increase the excretion of Na^+ and K^+.

In preclinical studies, the antiviral and anti-inflammatory effects of bearberry extracts and the antitussive effects of arbutin have been reported.

Efficacy and indications

In a dose-response study in healthy volunteers, an antibacterial effect has been observed after the administration of 0.1 or 1 g of arbutin. The lower dose resulted in a less pronounced antibacterial effect. However, independently of the dose, the (alkaline) pH value of the urine was the most important factor determining the antibacterial activity.

No clinical trials that have assessed the effects of bearberry leaf extract as a single substance are available. Efficacy may be assessed on the basis of the results of extensive pharmacological studies of the plant material and its constituents and on empirical knowledge. Three controlled clinical trials with bearberry leaf extract in combination with other herbal extracts (typically diuretics) have been published on urinary tract infected patients. These studies revealed the efficacy of the analyzed products in terms of the treatment of urinary tract infections and in the prophylaxis of recurrent cystitis.

Since no confirmation of efficacy has not been carried out with clinical trials, the EMA has granted a traditional use monograph with the indication of the

- treatment of symptoms of mild recurrent lower urinary tract infections such as a burning sensation during urination and/or frequent urination in women, after serious conditions have been excluded by a medical doctor.

The dose is 1.5-4 g of the comminuted herbal substance as a herbal infusion or macerate, 2 to 4 times daily, corresponding to the maximum daily dose of 8 g of herbal preparations, with a single dose corresponding to 100-210 mg of hydroquinone derivatives, 2 to 4 times daily. The macerate preparation should be preferred since extracts prepared with hot water contain higher amounts of tannin and therefore their taste is more unpleasant.

Side-effects, interactions & contraindications

The use of bearberry may cause nausea, stomach ache and vomiting due to stomach irritation from the high tannin content.

The long-term use of higher doses of bearberry leaf may lead to hepatotoxicity and other adverse effects (including hemolytic anemia, steatosis and de-pigmentation of the hair), but these are not supported by human data.

For safety reasons, its use in pregnant and lactating women, children and adolescents is not recommended. It should not be used for more than one week.

Bearberry may cause a greenish-brown discoloration of the urine.

8.1.2 Couch grass

Couch grass is a widely distributed weed throughout the northern hemisphere, with long-standing traditional medicinal application. The utilized herbal substance is the dried rhizomes and short pieces of stem of *Agropyron repens* (L.) P. Beauv. (Poaceae).

- **Chemical composition and mechanism of action**

Couch grass rhizome contains polysaccharides, fructose, sugar alcohols (mannitol and inositol) and flavonoids.

In animal experiments, a water extract of couch grass exhibited diuretic effect in comparison with water. A moderate anti-inflammatory activity was described in animal experiments.

Oral application of the aqueous extract decreased the blood glucose and cholesterol levels of normal and diabetic rats.

- **Efficacy and indications**

Couch grass rhizome has been traditionally used as a diuretic throughout Europe since ancient times. However, no clinical trials have been carried out to confirm the presumed effect.

In an open clinical trial involving patients with micturition disorders, a 20% ethanol fluid extract of couch grass was administered for 1 month. The complaints of urge incontinence, dysuria and nocturia were significantly reduced. Laboratory markers of inflammation also improved.

On the basis of the long-standing use, couch grass may be applied as a traditional herbal medicinal product

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The daily dose as a herbal tea is 10-20 g. Couch grass may also be applied as liquid extract and tincture. Traditionally it is used over a period of from 2 up to 4 weeks.

- **Side-effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. In the event of hypersensitivity and in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease), the application of couch grass is contraindicated.

8.1.3 Burdock

Arctium lappa L. (burdock) is a biennial member of the Asteraceae native to Europe, Northern Asia and North America. In folk medicine, the leaves and the fruits are applied, but the medicinally most important plant part is the root. Infusions of the leaves are used to treat stomach ulcer and gastritis, as a gargle and for skin diseases. Alcoholic extracts are applied in cosmetics to promote hair growth. The roots from this or related species are collected in the autumn of the first year or in the spring of

the second year. The main indications of burdock roots are the promotion of urinary and digestive elimination functions. In some countries, and especially in Japan, cultivated burdock is eaten as a vegetable.

The herbal teas called "Essiac" and "Essiac plus" contain burdock as the main constituent, together with *Rheum palmatum* L., *Rumex acetosella* L. and *Ulmus rubra* L. and additionally *Nasturtium officinale* L., *Cnicus benedictus* L., *Trifolium pratense* L. and *Laminaria digitata* (Huds.) Lamour in the latter product. These teas are promoted as anticancer remedies, but clinical evidence as to efficacy is missing.

Chemical composition and mechanism of action

Burdock root contains essential oil, sesquiterpenes, pyrazines, polyacetylenes, lignans and a considerable amount of sterols.

In an *in vitro* study, arctiin, a major lignan of the plant, inhibited the growth of several types of cancer cells. This activity may be related to the downregulation of cyclin D1 protein.

Some lignans inhibit the NO production of the macrophages, thereby exerting anti-inflammatory activity. Arctiin significantly reduces the release of inflammatory mediators *in vitro*.

Root extracts exhibited hypoglycemic activity in animal experiments. Because of their inulin content, the roots have aprebiotic effect.

Efficacy and indications

The therapeutic application of burdock relies solely on its traditional use. Neither preclinical nor clinical studies confirm the rationale of its application.

"Essiac" tea was studied in a retrospective cohort study with women with breast cancer. Although it appeared to be safe, there was no benefit from its application, and the health-related quality of life did not improve.

In view of he traditional use in different parts of Europe, burdock roots may be used as traditional herbal medicinal products

- to increase the amount of urine in order to achieve flushing of the urinary tract, as an adjuvant in minor urinary tract complaints,
- in the event of a temporary loss of appetite
- in the treatment of seborrheic skin conditions.

The dose of the products usually corresponds to 2-6 g of roots.

Side-effects, interactions & contraindications

In cases of hypersensitivity to the active substance or to plants of the Asteraceae family, the use of burdock root is contraindicated. In the absence of sufficient data, its use during pregnancy and lactation is not recommended.

8.1.4 Birch

The therapeutic use of *Betula* (birch) species goes back to ancient times. In the Middle Ages, birch leaf juice was used as a blood purifier, a diuretic and for gout and rheumatism. In contemporary folk medicine, birch leaves are used as a diuretic for urinary tract infections and for kidney gravel or rheumatic disorders. Externally, it is also employed as an astringent in mouthwashes.

According to the definition of the European Pharmacopoeia, birch leaves are whole or fragmented dried leaves of *Betula pendula* Roth and/or *Betula pubescens* Ehrh. or hybrids of both species. They contain no less than 1.5% of flavonoids, expressed as hyperoside.

Chemical composition and mechanism of action

Birch leaves contain 1.5-3.5% of flavonol glycosides, predominantly as quercetin glycosides (e.g. hyperoside) and other flavonoid glycosides. Flavonoid aglycones on the surfaces of the leaves may constitute up to 10% of the dry weight of the leaves. The leaves contain polymeric procyanidins and other phenolics. The ratio of potassium and sodium salts in the leaves is extremely high, at 200:1.

After the oral administration of a birch leaf tea to different animal species, the urine volume increased dose-dependently up to about 40% and the Cl^- excretion also increased. The water extracts exhibited more pronounced effects than the alcoholic extracts. The available results point to the possible role of flavonoids in the diuretic effect (and probably the high potassium-sodium ratio too). An ethanolic extract decreased the adhesion of uropathogenic *E. coli* on human bladder cells. Animal experiments have indicated that a minimum of 50 mg of flavonoids per day (2-3 g of drug as a tea several times in the course of a day) is necessary to increase the amount of the urine with birch leaf.

Efficacy and indications

In a randomized, double-blind, placebo-controlled pilot study, patients with infections of the lower urinary tract were treated with 4 cups of birch leaf tea or placebo tea daily for 20 days. The microbial counts in the urine of the birch leaf tea group decreased by 39%, as compared with 18% in the placebo group.

In a non-interventional study, patients were classified into four groups: 73% suffered from urinary tract infections, 14% from irritable bladder, 9% from urinary

stones and 3% from miscellaneous complaints. 56% of the patients in the first group also received antibiotic therapy. All the patients received a dry aqueous extract of birch leaf for 2-4 weeks. At the end of the study the symptoms had disappeared in 78% of the patients in the first group, and in 65% in the second and in the third group.

On the basis of the traditional application, birch leaves may be the basis of traditional herbal medicinal products

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The dose of the comminuted herbal substance as herbal tea is 2-3 g up to 4 times daily. Powdered herbal substance with a single dose of 650 mg, 2 times daily, may also be used, as can several dry and liquid extracts.

- **Side-effects, interactions & contraindications**

The use of birch leaves may result in the development of non-serious adverse events, such as mild skin and gastrointestinal system disorders. Hypersensitivity to the active substance or to birch pollen and conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease) are contraindications of the therapeutic application.

8.1.5 Horse-tail

Equisetum arvense L. is widely distributed throughout the temperate zones of the northern hemisphere. According to the European Pharmacopoeia, Equiseti herba is the whole or cut, dried, sterile aerial parts of *Equisetum arvense*. The herb has been used primarily in the treatment of diseases of the urinary organs (and some other indications, eg. gout, menstrual disorders and tuberculosis) since ancient times.

- **Chemical composition and mechanism of action**

Equisti herba contains about 5-10% silicic acid (or silicates), flavonoids (0.5-1%), and caffeic acid derivates. In older books it is claimed that it contains a saponin complex called "equisetonin", but this was a mixture of sugars and flavonoids.

The extract of the plant has a pronounced antioxidant effect, but was inactive in antimicrobial experiments. It was reported to exert a hepatoprotective effect *in vitro*.

The diuretic effect of *E. arvense* was tested in older *in vivo* studies, and in the mahority of the cases it was found to be effective in increasing the urine volume. The mechanism of action is not known.

- **Efficacy and indications**

The efficacy of horse-tail has not been confirmed. Nevertheless, its use is well documented and it may be used as a traditional herbal medicinal product

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Its daily dose is 6-9 g as a herbal tea or liquid/dry extracts or expressed juice with various posologies.

- **Side-effects, interactions & contraindications**

It is contraindicated in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal diseases) and in cases of hypersensitivity. Mild gastrointestinal complaints and allergic reactions (e.g. a rash) may occur.

8.1.6 Juniper

Common juniper, or *Juniperus communis* L. (Cupressaceae), is a traditionally applied medicinal plant and spice. For culinary and medicinal purposes, the berry is used. The essential oil of the fruits is also used for therapeutic purposes and in the cosmetics industry as well.

According to the definition of the European Pharmacopoeia, Juniperi pseudo-fructus is the dried ripe cone berry of *Juniperus communis*.

The plant is native to the mountain areas of Europe, with four distinct subspecies (ssp. *alpina*; ssp. *communis*; ssp. *hemisphaerica* and ssp. *nana*).

Historically, juniper berries have been applied as a diuretic since ancient times. Further applications with roots in folk medicine are the uses in dyspepsia, and muscle and articular pain (externally).

- **Chemical composition and mechanism of action**

The berries contain 0.5-3.5% of essential oil. Predominant constituents of the oil are the monoterpenes, with the main constituent alpha-pinene (about 20%). Further secondary metabolites are diterpenic acids, flavonoids, tannins. The fruit contains noteworthy amounts of invert sugar.

The diuretic effect of juniper has been confirmed in animal experiments. Usually berry extracts have been studied, but the essential oil has also been used. The diuretic activity relies on the increased excretion of both water and ions (Cl^-). It should be noted that diuretic activity was not observed in all the studies, and in animal experiments relatively high doses were applied. The possible therapeutic consequences of the diuretic effect were not studied.

In one study, a juniper extract displayed antidiabetic activity in animals with experimentally induced diabetes. Interestingly, the effects on gastrointestinal symptoms have not been studied.

- **Efficacy and indications**

The efficacy of juniper has not been studied in any indication. In view of the traditional use, juniper berry and its essential oil may be used as a traditional herbal medicinal product

- to increase the amount of urine so asto achieve flushing of the urinary tract as an adjuvant in minor urinary tract complaints, or
- for the symptomatic relief of digestive disorders such as dyspepsia and flatulence.

For the former indication treatment should start on day 1 with 5 cone berries(well chewed), the number then being increased by 1 cone berry every day up to 15 cone berries, the number then being decreased 1 per day less to 5 cone berries; the duration of the therapy is therefore 21 days, the maximum daily dose being 15 cone berries. The dosages of herbal preparations for both indications are 2 g of the crushed or comminuted herbal material as herbal tea, 2-3 times daily, 6-12 ml of liquid extract or 3-6 ml of tincture daily. The dose of essential oil for these purposes is 60-100 mg.

The essential oil may also be used as a traditional herbal medicinal product

- as an adjuvant in the relief of minor muscular and articular pain.

In this indication, the essential oil can be used as a bath additive 3-4 times weekly (1-1.5 g of juniper oil in a full bath for 10-20 minutes).

- **Side effects, interactions & contraindications**

Overdosing with the essential oil can lead to renal damage (albuminuria and hematuria). Rarely, symptoms of central stimulation, such as convulsions, and metrorrhagia and abortion occur too. In the event of prolonged use, the urine has a violet smell.

Its use is contraindicated in severe renal diseases, including infectious interstitial nephritis, pyelitis and pyelonephritis. In conditions where a reduced fluid intake is recommended (e.g. severe cardiac diseases), its use as a diuretic should be avoided.

The possibility of its use in children and adolescents under 18 years of age and during pregnancy and lactation has not been established due to the lack of adequate data. Allergic skin reactions may occur.

8.1.7 Lovage

Lovage has a long tradition of medicinal use. Its application as spice and medicinal plant has been documented since ancient times. Of the very diverse therapeutic applications (e.g. skin problems and digestive dirorders), its application in urinary tract problems is the most important today. The roots of *Levisticum officinale* Koch are official in the European Pharmacopoeia.

- **Chemical composition and mechanism of action**

Lovage root contains about 0.5-1% of volatile oil, 70% of which are alkylphthalides, with *Z*-ligustilide as the major constituent. Phthalide dimers (levistolides) are also present. Sotolone has been identified as the constituent responsible for the intense curry-like odor. The root contains furanocoumarins (e.g. bergapten, umbelliferone and psoralen) and polyacetylenes (falcarindiol).

Lovage essential oil exerts significant antibacterial activity against both Gram-positive and Gram-negative bacteria (including *Escherichia coli*) *in vitro*. Polyacetylenes of the plant have antifungal activity.

Certain animal experiments with Levistici radix infusions revealed a slight increase of the urine volume and the concentration of Cl^- ions, but this was not confirmed by more recent studies.

Ligustilide and other phthalides possess a spasmolytic effect *in vitro*, presumably by inhibiting the voltage-dependent Ca^{2+} channels.

- **Efficacy and indications**

In the lack of clinical data, lovage roots may be applied as traditional herbal medicinal products

  - to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The average daily dose as an infusion is 4-6 g. It should not to be used for more than 2-4 weeks.

- **Side effects, interactions & contraindications**

In cases of hypersensitivity to the plant and to other plants of the Apiaceae, the applicacion of lovage roots is contraindicated. Safety during pregnancy and lactation has not been established.

8.1.8 Spiny restharrow

Ononis spinosa L. is a perennial, spiny subshrub native throughout Europe, Asia and northern Africa. According to the European Pharmacopoeia, Ononidis radix is defined as the whole or cut, dried root of *Ononis spinosa*.

The roots have been widely used since ancient times as a diuretic and to remove urinary stones. In folk medicine, the most frequent uses are for the treatment of the lower urinary tract disorders.

- **Chemical composition and mechanism of action**

Restharrow roots contain saponins, phenolic acids, and a small amount of essential oil (up to 0.2%). Isoflavones (although in low concentration), e.g. formononetin, genistein and biochanin A, are characteristic secondary metabolites of the plant.

The diuretic effect, confirmed in animal experiments, is presumed to be linked to the saponins of the plant. The diuretic effect is accompanied by saluretic activity. In an animal study, genistein, exhibited a diuretic action comparable to that offurosemide.

Restharrow extracts exert antimicrobial effects on some bacteria.

- **Efficacy and indications**

In the lack of clinical data, spiny retharrow roots may be used as a traditional herbal medicinal product

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The maximum daily dose as a herbal tea is 12 g.

- **Side effects, interactions & contraindications**

In cases of hypersensitivity to the plant and in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease), the use of restharrow is contraindicated. Safety during pregnancy and lactation has not been established.

8.1.9 Java tea

Orthosiphon stamineus Benth. (syn. *O. spicatus* Bak., *O. aristatus* Miq.) (Lamiaceae), which is native to tropical regions of Asia and Australia, has been used as a medicinal plant by local residents for centuries.

In Java, it was traditionally used to cure hypertension, kidney disorders, gout and diabetes. In Europe, its medicinal use started in the 19th century.

- **Chemical composition and mechanism of action**

Java tea contains a considerable amount of potassium salts (3%), and small amounts of essential oil (up to 0.05%) diterpenes (orthosiphols A-E 0.2%), flavonoids (e.g. sinensetin and isosinensetin) and organic acids.

The diuretic activities of various extracts (aqueous or hydro-ethanolic) have been evaluated *in vivo* in animals (typically rats). In several studies, the extract was found to enhance ion excretion (Na^+, K^+ and Cl^-), but the hypothesis that this was due to the high K^+ content was not confirmed by the results with K^+-aspartate.

The hypouricemic activity of Java tea and its effect on the growth of oxalate crystals were studied in animal experiments. The uric acid concentration was decreased statistically significantly in rats treated with a Java tea extract. In a further study, both the extract and sodium citrate inhibited the growth of calcium oxalate crystals.

The plant exerts anti-inflammatory and antibacterial effects on certain species.

- **Efficacy and indications**

In a placebo, controlled, double-blind study, no influence was observed on the 12- or 24-hour urine volume or the excretion of Na^+ and K^+ after the administration of 600 ml of an aqueous decoction of Java tea daily to 40 healthy young volunteers. In a further study on 6 healthy volunteers, the alkalinity of the urine increased without a diuretic effect.

Although convincing clinical evidence is missing, Java tea may be used as a traditional herbal medicinal product

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary tract complaints.

The herbal substance may be used for the preparation of tea in a daily dose of 6-12 g. Different dry or liquid extracts may also be used.

- **Side effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. It is not to be used in cases of hypersensitivity to Java tea.

8.1.10 Goldenrod

Solidaginis virgaureae herba is the dried, flowering parts of *Solidago virgaurea* L. According to the European Pharmacopoeia, it should contain 0.5-1.5% of flavonoids, expressed as hyperforin. *S. virgaurea* has been used for the treatment of different diseases (including the urinary tract) in Europe since medieval times. Two invasive species from North America (*S. gigantea* and *S. canadensis*) have also recently been used with the same medicinal purpose as *S virgaurea*.

- **Chemical composition and mechanism of action**

European goldenrod contains flavonoids (up to 1.5%, with quercetin, kaempferol and their derivatives as main glycosides), triterpene saponins (at most 2%), phenolic acids, the phenol glycosides leiocarposide and virgaureoside A, polyphenols and a small amount of essential oil.

Anti-inflammatory activities of crude extracts, saponins and leiocarposide from *Solidago virgaurea* has been observed in animal experiments. For the latter compound, analgesic activity has also been demonstrated.

Leiocarposide and the flavonoids of goldenrod proved to exert a diuretic effect in animal experiments. The saluretic effect seems to be contradictory. In experimentally induced renal calculi, the administration of leiocarposide significantly decreased the growth of the calculi.

The extract of this plant exhibited antimicrobial activity agains the uropathogens *Candida* sp., *Pseudomonas aeruginosa, Escherichia coli, Proteus* sp., *Staphylococcus aureus* and *Staphylococcus epidermidis in vitro*, and also a spasmolytic effect.

- **Efficacy and indications**

The clinical efficacy of European goldenrod was assessed in certain clinical trials. In an open postmarketing study with placebo control in healthy subjects, a significant increase of the urine volume (27%) was observed. In a further postmarketing study involving patients with different urinary tract diseases (irritable bladder, urinary tract infections or renal gravel), the efficacy of an extract from *Solidago virgaurea* was assessed after an average treatment of 4 weeks. In almost 80% of the patients, a significant overall improvement of the symptoms was observed. In an open multicenter postmarketing study, an extract of the plant was tested in patients with symptoms of urinary tract inflammation. After the course of treatment (which lasted up to 1 year), a significant clinical improvement was observed in 65% of the patients.

The design of these studies does not allow firm conclusions as concerns efficacy. European goldenrod may therefore be used as traditional herbal medicinal products

- to increase the amount of urine, as an adjuvant in the treatment of minor urinary complaints.

The daily dose of the comminuted herbal substance as a tea is 3-5 g, 2-4 times daily. Liquid extracts prepared with ethanol-water can be applied in a dose of 1.5-6 ml daily, and the dry extract in a dose of 1050-1350 mg daily.

- **Side effects, interactions & contraindications**

Its use is not recommended in children under the 12 years of age because of the lack of available experience. Hypersensitivity reactions or gastrointestinal disorders may occur. In the event of hypersensitivity, the use of goldenrod is contraindicated.

8.2 Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is the enlargement of the prostate, which results in a wide variety of symptoms. The ratio of affected men increases with age: at the age of 50, about half of the male population have symptoms related to BPH, and with every 10 life years this increases by 10%.

As the prostate enlarges, it can narrow the urethra and this leads to obstructive symptoms. Further, the bladder wall becomes thicker, and the bladder may weaken and lose its ability to empty completely, resulting in irritative symptoms.

BPH is a multifactorial disease. With aging, the plasma level of testosterone decreases, and the testosterone/estrogen ratio therefore decreases, resulting in increased estrogen activity, and this may facilitate the hyperplasia of the prostate cells. Another theory focuses on dihydrotestosterone (DHT), a male hormone that plays a role in prostate development and growth. In older men, the activity of the enzyme 5-alpha-reductase (this converts testosterone to DHT) is increased, leading to a decreased testosterone/DHT ratio. DHT may promote prostate cell growth, resulting in BPH. Some symptoms may occur due to a change in adrenoreceptor densities (e.g. an increased ratio of $alpha_1$ receptors has a major role in irritative symptoms).

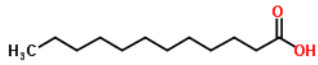
Pharmacotherapy focuses mainly on the above-mentioned targets, and the most widely applied medicinal plants also act through these enzymes and receptors.

8.2.1 Saw palmetto

Serenoa repens (W. Bartram) Small (syn. *Sabal serrulata* (Mich.) Nutall ex Schult and *Serenoa serrulata* Hook) is a small palm, growing to a maximum height of 2–3 m, native to the southern part of the USA. The dried ripe fruit of *Serenoa repens*, containing a minimum of 11% of total fatty acids, can be found in the European Pharmacopoeia under the name Sabalis serrulatae fructus. In the folk medicine of Native Americans, it was used as anaphrodisiac and to improve fertility. Although these applications may be seen in the case of food supplements, the modern medicinal application is different: the plant is specifically used to relieve the symptoms of benign prostatic hyperplasia (BPH).

- **Chemical composition and mechanism of action**

The fruit contains a high amount (40-80%) of fatty acids (main components: caproic acid, caprylic acid, capric acid, lauric acid, myristic acid and oleic acid), sterols, flavonoids and carbohydrates.



lauric acid

Lipophilic extracts (and free fatty acids) of the plant inhibit the enzyme 5-alpha-reductase, thereby decreasing the level of dihydrotestosterone (DHT). This has been confirmed in several experiments. Aromatase-inhibitory activity was also observed, which leads to a decrease of the estrogen/testosterone ratio (aromatase catalyzes the conversion of androgens into estrogens). The metabolism of testosterone by inhibiting 17-beta-hydroxysteroid dehydrogenase further increases the ratio of testosterone compared to DHT and estradiol. The DHT-lowering effect has been observed in human studies too.

Lauric acid and oleic acid bind noncompetitively to alpha-1-adrenergic, muscarinic and 1,4-DHP Ca^{2+} channel receptors, and can thereby be regarded as inhibitors. Different extracts exert weak inhibitory activity on androgen receptors. A human study revealed that the extract of *Serenoa repens* competes with DHT at the level of the androgenic receptors.

An ethanolic extract inhibited the epidermal growth factor (EGF) and the lipopolysaccharide-induced proliferation of prostatic epithelial cells *in vitro*.

Lipophilic extracts display anti-inflammatory activities, partly through inhibition of the enzymes COX and 5-LOX.

Efficacy and indications

The efficacy of *Serenoa* in the treatment of BPH has been studied in several trials involving several thousands of participants, with durations of 3-72 weeks. Many of these studies were sufficiently well designed to serve as the basis of the confirmation of the well-established use of certain products. In studies with different lipophilic extracts, *Serenoa repens* has been reported to be superior to placebo and equivalent to finasteride (with fewer adverse effects) in the alleviation of lower urinary tract symptoms due to BPH.

A meta-analyses critically evaluated 17 studies, including 13 randomized, double-blind trials (with several hundreds of patients) carried out with a hexane extract. In seven studies, IPSS (International Prostate Symptom Score) was used as the outcome. The treatment with *Serenoa* improved the IPSS, the peak urinary flow and nocturia relative to placebo. This hexane extract has been found to be equivalent to finasteride in improving the symptoms in a 26-week study on BPH patients (IPSS > 13). A study with a similar design confirmed the equivalence with tamsulosine in BPH patients (IPSS > 10). The efficacy has further been supported by a series of open-label studies.

For one soft extract (extraction solvent hexane: DER 7-11:1, containing 97% of free fatty acids), the clinical evidence was sufficient to grant a well-established use monograph with the indication of

- symptomatic treatment of benign prostatic hyperplasia.

For an ethanolic extract, the body of less convincing evidence resulted in the preparation of a traditional use monograph with the following indication:

- relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a physician.

In both cases the daily dose is 320 mg of extract. Long-term use is possible.

- **Side effects, interactions & contraindications**

In cases of hypersensitivity to *Serenoa* or hepatic disease, the application of the plant is contraindicated.

Gastrointestinal disorders (nausea or abdominal pain), a skin rash and edema may occur. Cases of acute hepatitis have been reported very rarely. In some cases, reversible gynecomastia has been observed.

A few cases of suspected interactions with warfarin and increased INR-values (INR is the acronym of international normalized ratio, which is the ratio of a patient's prothrombin time to a normal sample) have been reported.

8.2.2 Pumpkin

Cucurbita pepo L., belonging in the Cucurbitaceae, is indigenous to Central and North America. In medicine, its whole, dried, ripe seeds are used either in a ground form or as extracts or as the fatty oil obtained from the plant material. These have been used for centuries as a diuretic and anthelminthic and, from the 20th century, to relieve difficulties associated with BPH.

There are no published monographs in the European Pharmacopoeia for pumpkin seed. For medicinal purposes typically the variety *C. pepo* L. convar. *citrullina* I. Greb. var. *styriaca* I. Greb. is used, because of the thin testa of the seeds (this makes oil pressing easier than in the case of other varieties). The fatty oil is pressed from the comminuted seeds which are roasted before processing.

- **Chemical composition and mechanism of action**

Pumpkin seeds contain approximately 50% fatty oil (with linoleic and oleic acid as the main fatty acid components), 30-50% proteins and 5-10% carbohydrates. Further,

pharmacologically important constituents are delta-7-sterols (avenasterol and spinasterol) and delta-5-sterols (sitosterol and stigmasterol). Its tocopherol content is noteworthy, carotenoids (lutein and beta-carotene) and chlorophyll are responsible for the color, and the squalene content is usually regarded as a marker in quality analysis.

In *in vitro* studies with animal cell lines, a pumpkin seed extract inhibited the enzymes aromatase and 5-alpha-reductase. Pumpkin seeds alleviated the signs of experimentally induced BPH and the size of the prostate in rats. In an animal experiment, a pumpkin seed extract significantly increased the bladder volume and decreased the urination frequency as compared with an inactive control.

The oil has hepatoprotecttive and antihyperlipidemic effects (the latter due to the high ratio of unsaturated fatty acids). The anti-inflammatory and antioxidant activities of different extracts and the oil have been demonstrated in several experiments. The seeds have confirmed nematicidal effects, as a result of the amino acid cucurbitine (which is not present in the oil).

- **Efficacy and indications**

There have been several studies with different alcoholic pumpkin seeds. Although these usually confirm clinical efficacy, the validity of the results is weakened by their design (open studies). The efficacy is demonstrated by decreasing the I-PSS (International Prostate Symptom Score), with an improvement of the quality of life, or objective measures such as the urinary flow.

The pumpkin was the first medicinal plant that gained popularity in the treatment of BPH in Hungary and was the basis of the first registered herbal product with this indication. Four studies carried out in Hungary (to support the registration of the product containing pumpkin seed oil, 1.8 g daily) described the reduction of symptoms of painful and frequent urination, dysuria, nocturia and increase of urinary flow in a majority of the patients.

The anthelminthic effect of (whole) pumpkin seed has been confirmed in multible human studies against different parasites.

Since the efficacy has not been confirmed convincingly, pumpkin seed may be used as a traditional herbal medicinal product

- for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia or related to an overactive bladder, after serious conditions have been excluded by a medical doctor.

For this purpose, comminuted, ripe and dried seeds (5-15 g daily), fatty oil (3-4 g), soft extract (DER 15-25:1, extracting solvent 92% ethanol, 1 g daily) or a dry extract (15-30:1, extraction solvent 60% ethanol, 0.3 g daily) may be used.

- **Side-effects, interactions & contraindications**

Mild gastrointestinal complaints may occur. No contraindication is known except an allergy to pumpkin seed.

8.2.3 Nettle

Nettle is a versatile medicinal plant. Different plant parts have been applied with a wide range of application. In folk medicine, nettle herb and leaves are of the highest importance, but the use of the roots and seeds also has traditions in some regions (e.g. Russia). The above-ground parts have been used primarily to treat urinary tract problems (but also as an antitussive, styptic or antirheumatic agent), while the roots have been applied as a tonic, and in gastrointestinal diseases, and skin and respiratory disorders. Nettle root was first used in urinary tract disorders in the 1950s, with a quite specific indication (benign prostatic hyperplasia). In official medicine, the leaves of *Urtica dioica* L., *Urtica urens* L., their hybrids or their mixtures are used (these have a European Pharmacopoeia monograph as well).

- **Chemical composition and mechanism of action**

Nettle roots contain approximately 1% of polysaccharides, lectins (up to 0.5%, the Urtica dioica agglutinins, UDA), lignans, sterols, with beta-sitosterol as the main component (up to 1%) and hydroxy fatty acids.

Nettle leaves contain flavonoids (up to 2%, derivatives of quercetin, kaempferol and isohamnetin), silica (up to 4%), beta-sitosterol, coumarins, caffeic acid derivatives, and in the stinging hairs formic acid, serotonin and leukotrienes. The K^+/Na^+ ratio is remarkably high (about 60:1).

The majority of preclinical studies with nettle roots have focused on its effects on the prostate. In contrast with several other plants used in BPH, nettle extracts did not affect the 5-alpha-reductase activity, and inhibited DHT binding to the androgen receptors in the prostate only very moderately. However, nettle root extracts inhibited the binding of DHT to sexual hormone binding globulin (SHBG), the levels of which decreased significantly in human studies too. Different extracts of the roots statistically significantly inhibited the proliferation of cultured BPH-tissue cells. Lectins may have crucial role in this effect. Histological examinations of tissue samples from patients receiving nettle root therapy revealed that the biological activity in the cells had decreased.

Lipophilic nettle root extracts inhibited aromatase *in vitro*; the inhibition of aromatase gene expression may be involved in this effect. The documented anti-inflammatory activity of the root extracts may also have a role in the clinical efficacy.

One of the most marked bioactivities of nettle leaves and herbs is the anti-inflammatory effect (this was demonstrated in a series of *in vitro* and *in vivo* studies). The key component of this is the inhibition of NF-kappa B activation. In *in vitro* studies, *Urtica dioica* exerted antiplatelet action in which mainly flavonoids were implicated.

Nettle leaves exhibited a blood glucose-lowering effect in animal experiments. Increases in the insulin content of the blood sera were also observed in normal and diabetic rats. In an *in vitro* study, nettle increased the insulin secretion of pancreatic cells. The diuretic effect of the leaves has been confirmed in animal experiments.

- **Efficacy and indications**

Clinical examinations of nettle roots have been carried out to elucidate its efficacy in benign prostatic hyperplasia. In a double-blind, placebo-controlled study involving patients with BPH (stage I), after 6-8 weeks of treatment, statistically significant differences were found in the average urinary flow rate (1.3 ml/s versus 0.2 ml/s) and in the residual urine volume decrease (40% versus 8%) in favor of the active treatment.

BPH patients (stages I-II) enrolled in a double-blind, controlled study were treated for 9 weeks. Significant increases in micturition volume and highly significant decreases in serum levels of SHBG were observed. The maximum urinary flow improved by 9% in the treated group, but decreased to the same extent in the placebo group.

In a randomized, double-blind, placebo-controlled study on BPH II patients, decreases in micturition frequency and SHBG level were observed in the verum group after 6 months. The subjective symptoms score improved significantly in the verum group, whereas there was no change in the placebo group.

In a randomized, double-blind, placebo controlled study, involving a 1-year treatment of patients, the IPSS decreased statistically significantly relative to the placebo.

In a 6-month, double-blind, placebo controlled, randomized trial a significant improvement was documented in the nettle group as compared with the placebo group in the IPSS score, maximum urinary flow rate and postvoid residual urine volume.

Further open studies have been reported. The major weaknesses of the trials performed so far are the short duration (in many cases only some weeks) and the fact that the prostate size-decreasing effect was not confirmed. A monograph allowing the use nettle root as a traditional herbal medicinal product was therefore granted by the European Medicines Agency with the indication of the

- relief of lower urinary tract symptoms related to benign prostatic hyperplasia after serious conditions have been excluded by a physician.

It can be used as a herbal tea (1.5 g of the comminuted herbal substance as a decoction 3-4 times daily) or as different dry or liquid extracts prepared with mixtures of water and methanol/ethanol. Long-term use is possible.

In the cases of nettle leaves and herb, clinical trials have focused on its effects on articular pain. Several open, uncontrolled studies have been carried out with a positive outcome. In one controlled trial, it was found that nettle significantly increased the efficacy of the NSAID diclofencac. A randomized controlled double-blind crossover study was conducted in patients with osteoarthritic pain at the base of the thumb or index finger. The patients applied stinging nettle leaf daily for one week to the painful area. After treatment for one week with nettle sting, the pain reduction was significantly greater than with placebo (it must be noted that in this case blinding was incomplete).

Although the clinical efficacy has not been confirmed sufficiently, the documented long-standing use permits the application of nettle leaves and herb as a traditional herbal medicinal product

- for the relief of minor articular pain or
- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

It may be used as a herbal tea (2-4 g, 3-6 times daily) or as different liquid or dry extracts (prepared with water or water-ethanol). It is not to be used for more than 2-4 weeks.

- **Side effects, interactions & contraindications**

Gastrointestinal complaints such as nausea, heartburn, a feeling of fullness, flatulence, diarrhea or allergic reactions, i.e. pruritus, rash or urticaria may occur. Its use is contraindicated in cases of hypersensitivity to the plant.

The above-ground parts should not be used in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease). Its use in children under 12 years of age and during pregnancy and lactation has not been established due to the lack of adequate data.

Verification questions

1. What is the rational application of diuretic plants?
2. List 5 diuretic plants!
3. What is the mechanism of action of bearberry?
4. What is the indication and side effects of *Arctostaphylos uva-ursi*?

5. What is the difference between the mode of action of synthetic and herbal diuretics?
6. What are the most important plants and their modes of action in the treatment of benign prostatic hyperplasia?
7. What are the the therapeutic indications of different parts of nettle?

9. Gynecological disorders

The treatment of different gynecological disorders has long been at the focus of herbal medicine. For centuries, the prevention of pregnancy and abortion have been among the main fields of application. A further important use was to promote the menstrual flow, since it was thought that menstruation was important to preserve health, and irregular or insufficient beeding was regarded as a sign of illness (the plants used were called emmenagogues).

Nowadays, in the age of modern anticoncipients, the use of phytotherapy has shifted to the therapy of premenstrual syndrome (PMS), menstrual irregularities and menopausal problems. In these cases, phytotherapeutic agents may be regarded as first-choice medicines, since the available modern medicines (usually hormones or synthetics) may have unfavorable side-effect profile to be a safe alternative for long-term treatment.

In folk medicine, a plethora of medicinal plants are applied for gynecological purposes. However, the majority of them rely purely on tradition, without any confirmation of efficacy. Two medicinal plants stand out from the list due to the body of evidence that supports their rational application in therapy. These are chaste tree (used for PMS) and black cohosh (used principally for menopausal complaints). Apart from these, phytoestrogen-containing plants are of significant importance in modern phytotherapy.

9.1 Menstruation-related disorders

In folk medicine, several plants have been applied to treat menstrual irregularities. The improvement of bleeding was earlier an important goal (since it was thought that regular menstruation helped to preserve health), whereas nowadays painful and heavy bleeding are symptoms that need to be treated in several patients. Irregular menstruation (frequently coupled with fertility problems) is also a frequent topic in modern therapy. For these problems (apart from some kinds of menstrual irregularities) there are no real evidence-based herbal therapeutic options.

The most common problem related to menstruation is premenstrual syndrome, in which case phytotherapy is one of the first-choice therapeutic modalities. The majority of women experience a variety of physical and psychic symptoms that usually start some days before the menstruation and subside with the start of the bleeding.

According to the Mayo Clinic, the most common emotional and behavioral symptoms are the following:

- Tension or anxiety
- Depressed mood
- Crying spells
- Mood swings and irritability or anger
- Appetite changes and food cravings
- Trouble falling asleep (insomnia)
- Social withdrawal
- Poor concentration

The physical signs and symptoms include:

- Joint or muscle pain
- Headache
- Fatigue
- Weight gain related to fluid retention
- Abdominal bloating
- Breast tenderness
- Acne flare-ups
- Constipation or diarrhea

The most common physical symptoms are related to water retention and some form ofhormonal imbalance (breast swwelling and pain or edema of the ankles, face and hands). Digestive and behavioral symptoms are also common features of the syndrome. A special form of PMS is called premenstrual dysphoric disorder (PMDD). This disabling syndrome involves depression, mood swings, anger, anxiety, irritability, tension and concentration problems.

The symptoms involving breast discomfort are related to a latent hyperprolactinemia. The phytotherapeutic measures to be applied depend on the clinical picture. Focused therapy of PMS is the application of chaste tree (this plant has a direct effect on the prolactin level and, apart from PMS, is also useful in certain menstrual irregularities), but other plants may also be applied to overcome gastrointestinal and behavioral symptoms.

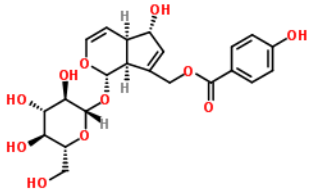
9.1.1 Chaste tree

Vitex agnus-castus L. (Verbenaceae) is a shrub native to the Mediterranean region, the fruits of which have been used as a spice and for medicinal purposes since ancient times. The Latin name agnus castus means chaste lamb, which may refer to the libido-reducing effect of the seeds. For this presumed effect, chasteberry was used by monks as a spice and this is the origin of the English name monk's pepper.

Agni casti fructus is official in the European Pharmacopoeia. The use of chasteberry in gynecological disorders started in the 20th century after the discovery of the hormone-like properties of the plant. Nowadays, it is also used in modern phytotherapy and homeopathy. It should be noted, that the therapeutic indications of the plant in allopathy and homeopathy are practically the same; moreover, the quantities of the herbal extracts in homeopathic and allopathic medicines also overlap.

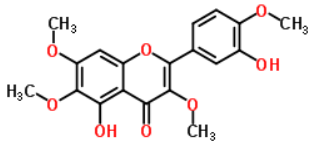
- **Chemical composition and mechanism of action**

The characteristic compounds in chasteberry fruits are iridoid glycosides (1%, with agnuside, agnucastosides and aucubin as the main constituents), diterpenes (less than 0.5%, vitexilactone and rotundifuran), methoxylated flavonoids (casticin and penduletin), flavonoid *O*- or *C*-glycosides (orientin and vitexin).



agnuside

rotundifuran



casticin

The clinical efficacy of chasteberry is attributed to its effects on prolactin secretion and on dopamine receptors. The extracts of the fruits exerted dopaminergic (D_2) receptor-binding activity in animal brain samples, and inhibited the binding of the D-receptor ligand spiroperidole. Certain diterpenes (e.g. rotundifuran) also exerted such effects. *Vitex agnus-castus* extracts (and some diterpenes) inhibited prolactin release

via interaction with D_2-receptors in lactotrophic cells. The prolactin level-increasing effect was observed in some human studies too.

In vitro studies confirmed the effect of μ-type opiate receptors and indicated the beta-endorphin-like action of chasteberry. Oral administration of the plant extract resulted in an increase of the beta-endorphin level in female rats. In some studies, chasteberry extract exhibited binding affinity to estrogen receptors (preferentially to the beta-subtype).

- **Efficacy and indications**

Most of the clinical trials were carried out to study the efficacy in premenstrual syndrome (PMS). In one randomized, double-blind, placebo-controlled study, women with PMS were treated with chastebery extract or placebo. The primary endpoint was the decrease of the PMS score based on the self-assessment of 6 different symptoms (irritability, mood changes, tension, headache, breast fullness, and other premenstrual symptoms such as bloating and mastalgia) by the end of the 3-month treatment period. Statistical analysis showed a significant superiority over placebo in the PMS score and the key individual symptom scores. The responder rates were 52% for chasteberry and 24% for placebo. Some other studies have also confirmed efficacy in this indication.

In a randomized, placebo-controlled, double-blind study, the efficacy of chasteberry in the treatment of luteal phase defects due to latent hyperprolactinemia was investigated. After three months of treatment, the extent of prolactin release was reduced and the length of the luteal phases was normalized in the *Vitex* group but not in the placebo group. According to some older studies, *Vitex* was effective in the normalization of different menstrual irregularities (polymenorrhea, oligomenorrhea, and menorrhagia).

One special extract (DER 6-12:1, extraction solvent: ethanol 60% m/m), which was the subject of the majority of the clinical trials, was accepted for well-established use by the European Medicines Agency with the indication of

- the treatment of premenstrual syndrome.

The daily dose is 20 mg of extract (equivalent to 180 mg of the herbal substance). To achieve an optimal treatment effect, continued use over three months is recommended.

A traditional-use monograph has been published for traditional herbal medicinal products for which the clinical efficacy has not been confirmed, with the indication of

- the relief of minor symptoms in the days before menstruation (premenstrual syndrome).

For this purpose, 800 mg of powdered herbal substance or liquid (water/ethanol) extracts corresponding to 28-52 mg of plant material should be used daily.

- **Side effects, interactions & contraindications**

In cases of estrogen-sensitive cancer or a history of a pituitary disorder, the use of chasteberry is not recommended. In cases of prolactin-secreting tumors of the pituitary gland the intake of *Vitex agnus-castus* fructus can mask the symptoms of the tumor. Patients who are using dopamine agonists, dopamine antagonists, estrogens or antiestrogens should consult their doctor before using *Vitex agnus-castus*.

During the use of chasteberry, allergic reactions, headache, dizziness, gastrointestinal disorders (such as nausea and abdominal pain), acne or menstrual disorders may occur.

Its use in children and adolescents under 18 years of age has not been established due to the lack of adequate data. It is not recommended during pregnancy or lactation.

9.1.2 Shepherd's purse

Capsella bursa-pastoris (Brassicaceae) is a cosmopolitan weed that grows up to 40 cm and is indigenous to Europe, Asia and Africa. The Latin and other common names are derived from the purse-shape of the plant's seed pods. Although applied widely in folk medicine, shepherd's purse is not an important plant of official medicine and has no monograph in the European Pharmaopoeia. The dry above-ground parts are usually applied in the medicine.

In European folk medicine, *Capsella* has been used as a diuretic and to treat diarrhea. Its extract has served as a substitute for ergot of rye to stop various forms of bleeding. In one theory, its hemostatic action may be attributed to fungi growing on the plant. *Capsella* has been used to treat dysmenorrhea, menorrhagia and metrorrhagia.

- **Chemical composition and mechanism of action**

Capsella herbs contain flavonoids (eg. quercetin, kaempferol and luteolin), amino acids, peptides, amines (e.g. choline and acetylcholine), phenolic acids, saponins and small amount of essential oil. Some studies have reported the presence of cardenolides and sinigrin in *Capsella bursa-pastoris*, but quantitative data are lacking

- **Efficacy and indications**

Different extracts of the plant have been reported to exert an anti-inflammatory and capillary permeability-reducing effect in animals. Certain extracts exerted contractile activity on uterus and intestinal smooth muscles. Diuretic and CNS-depressant activities have also been observed.

No clinical trials have been carried out with shepherd's purse. On the basis of its folk medicinal applications, the plant may be used in traditional herbal medicinal products to

- reduce heavy menstrual bleeding in women with regular menstrual cycles, after serious conditions have been excluded.

Administration should be started 3-5 days before the menstruation and should be continued during menstrual bleeding. The dose of the comminuted herbal substance is 1-5 g for the preparation of herbal tea, 2-4 times daily.

- **Side-effects, interactions & contraindications**

No special adverse effects are known (except hypersensitivity). Since its safety during pregnancy and lactation has not been established, the use in these cases is not recommended.

9.2 Menopause-related symptoms

The menopause is defined as a 12-month menstruation-free period which marks the end of the menstrual cycles. The menopause is a natural biological process, and is a result of the change in hormone production in the organisms of women. Physiologically, it usually occurs in the 40s or 50s. As the menopause approaches, the menstrual periods become irregular and bleeding occurs more and more rarely.

The root cause of menopause is the decreased estrogen and progesterone production of the ovaries. Although it is a natural phenomenon, the decreased estrogen level and the consequently increased LH and FSH levels trigger a variety of long- and short-term symptoms and changes in the body, respectively. In the postmenopausal periods, the main reason for health complaints is the permanently low estrogen level in the blood plasma.

In the period of menopause, the following symptoms occur most frequently:

- Hot flushes
- Vaginal dryness, sexual problems, and a decreased libido
- Night sweats and sleeping problems
- Mood changes and depression
- Weight gain

Hot flushes, the most common symptoms that affect at least 70% of women, are frequently related to the periodic LH pulses. However, in some cases, hot flushes are not accompanied by an increased LH level and, conversely, LH pulses do not necessarily induce hot flushes. It was discovered recently that hot flushes are related to an increased level of a noradrenaline metabolite, 3-methoxy-4-hydroxyphenylglycol. Both of the above-mentioned theories are supported by clinical observations. The role of the noradrenaline metabolite is emphasized by the facts that 1) clonidine, an alpha$_2$-adrenergic agonist that reduces the brain noradrenaline level, significantly reduces the frequency of hot flushes, and 2) yohimbine, an alpha$_2$-adrenergic antagonist, provokes hot flushes. The role of LH in the development of hot flashes is underscored by clinical experiments on the only effective herbal remedy, *Actea racemosa*.

9.2.1 Black cohosh

Actea racemosa (syn. *Cimicifuga racemosa* (L.) Nutt.) is a perennial plant (Ranunculaceae) native to North America. Amerindians have used its underground parts for various medicinal purposes, including gynecologic disorders, but in modern medicine its application is confined to the treatment of menopausal symptoms. In contrast with the great industrial importance of the plant, no European Pharmacopoeia has been published on its rhizome so far.

- **Chemical composition and mechanism of action**

The major groups of secondary metabolites of the root and rhizome are cycloartenal-type triterpenes (e.g. actein and cimifugosid), phenolics, flavonoids and quinolizidine alkaloids (cytisine). There are controversial reports on the occurrence of the phytoestrogen isoflavone formononetin. Although this compound may be present in traces in the plant, it is not detectable in the commercial products.

The manner of action of *Actea* is disputed in the literature. The initial conception, that the efficacy is linked to the phytoestrogen formononetin, is confuted by the lack of this isoflavone in the medicinal products. It has been suggested that black cohosh should be regardad as a phyto-SERM-containing plant (SERM = selective estrogen receptor modulators). Although its effects resemble those of SERMs (e.g. tamoxifen), the constituents responsible for these are not known.

A methanolic extract of the plant demonstrated *in vitro* binding to eestrogen receptors. In low concentration, the extract did not display a proliferative effect on an estrogen receptor-negative breast cancer cell line, but in higher concentration it inhibited its proliferation. A hydroethanolic extract did not stimulate (and according to other data, even inhibited) cell proliferation in the estrogen receptor alpha-positive (ER^+) human breast cancer cell line T-47D, whereas similar extracts exert a proliferative effect on ER^+ MCF-7 cells. Treatment with an ethanolic extract did not affect the weight of the uteri of mice.

According to an animal experiment, *Actea* exerted estrogenic effects in the bone and fat tissue, but not in the uterus of ovariectomized rats, reflecting a SERM-like effect. The extract of the plant did not promote mammary tumor growth or metastatic potential of the primary tumour.

- **Efficacy and indications**

The efficacy of *Actea* has been assessed in clinical studies on >6000 patients through use of the Kupperman Index (KI) or the Menopause Rating Scale (MRS). In a double-blind, randomized, placebo-controlled multicenter study (12 weeks) of postmenopausal patients, the menopausal symptoms were assessed with the MRS. The aim of that study was to examine whether *Actea* tablets (containing a hydroalcoholic extract, equivalent to 40 mg of the herbal substance) improve the menopausal complaints in comparison with a standard hormone replacement therapy (CE) and placebo. The

results indicated a significant advantage of *Actea* and CE vs. placebo in the MRS as regards the subscores of sexual desire, sexual activity and satisfaction, urination complaints, a feeling of dryness in the vagina and rheumatic-like pains. In patients treated with the herbal product, the serum levels of alkaline phosphatase were increased, indicating increased osteoblast activity.

In a multicenter, randomized, placebo-controlled double-blind study with menopausal women, in those who had a Kupperman Index of 20, a significant superiority over placebo was demonstrated following treatment with a hydorethanolic *Actea* extract corresponding to 40 mg of herbal drug daily.

In a double-blind, randomized, placebo-controlled 3-month of postmenopausal women, the efficacy of an isopropanolic extract with a daily dose corresponding to 40 mg of plant material daily was measured as the decrease in the MRS score. Three subscores (hot flushes, atrophy and psyche) improved significantly in the treated group. With this extract, several open studies were also conducted, which indicated efficacy of the treatment.

With the above-mentioned extracts, studies were also carried out to assess the effect on menopausal symptoms in patients with breast cancer. Overall, *Actea* seems to have a positive effect on hot flashes in this population, without any severe side-effect (and also in comparison with SERM treatment).

In the clinical trials, the efficacy of the following extracts was confirmed conclusively:

- Dry extract (DER 5-10:1), extraction solvent ethanol 58% (v/v)
- Dry extract (DER 4.5-8.5:1), extraction solvent ethanol 60% (v/v)
- Dry extract (DER 6-11:1), extraction solvent propan-2-ol 40% (v/v).

These dry extracts, in a daily dose corresponding to 40 mg of the herbal substance, may be used as well-established treatment

- for the relief of menopausal complaints such as hot flushes and profuse sweating.

Although there are no signs of the danger of persitent use, for safety reasons it should not be taken for more than 6 months without medical advice.

Side-effects, interactions & contraindications

Liver toxicity has been reported following the use of certain *Actea* containing products (these were not identical with the clinically studied extracts). Out of 44 partially poorly documented cases, four indicated coherence between liver damage and the intake of *Actea*; a cause-effect relationship was not revealed. However, special attention should be paid to the signs of liver toxicity (loss of appetite, tiredness, jaundice, nausea and dark urine) in the event of the therapeutic application of this plant.

Actea preparations should not be taken together with estrogens unless advised by a doctor. Patients who have been treated or who are undergoing treatment for breast

cancer or other hormone-dependent tumors should not use preparations without medical advice.

Verification questions

1. What is the therapeutic indication of chasteberry?
2. What is the mode of action of chasteberry?
3. What are the components of premenstrual syndrome?
4. What are the clinical effects of the application of black cohosh?

10. Respiratory system

Infectious diseases of the respiratory tract are the most common infectious diseases in the western world. The upper (pharynx, larynx and paranasal sinuses) and the lower respiratory tract (trachea and bronchi) may be affected. The pathogens responsible for upper respiratory tract infections are viruses (rhinoviruses, but excluding influenza viruses); bacteria are only very rarely the primary cause. Although the common cold requires no special treatment, phytotherapy may be useful in relieving the symptoms and, perhaps more importantly, in making antibiotic treatment unnecessary. Unfortunately, in practice simple viral infections are often treated with antibiotics, since both patients and medical doctors are interested in the wish to achieve quick recovery. However, the overuse of antibiotics is a great financial burden and also the main reason for the rapidly spreading antibiotic resistance. Differential diagnosis is important, since in contrast with the common belief, herbal remedies are not able to cure bacterial infections. Although there are several plant extracts and essential oils that have antibacterial effects *in vitro*, their pharmacokinetic characteristics (poor systemic bioavailability) make them inappropriate for clinical use. Similarly, plants are not effective against influenza (an infection caused by the influenza viruses). In this section, plants will be presented that have effects on infections of the respiratory systems.

10.1 Dry cough

A cough is a result of irritation of the respiratory mucosa. If the mucosa is dry and irritated as a result of an infection, the receptors of the larynx and pharynx are stimulated. This stimulation may be inhibited by the use of polysaccharide-containing plants. Since direct contact is indispensable for the clinical effect, these plants are typically applied as teas. The mucilage that is formed during the tea preparation acts as a protective layer against irritants on the pharyngeal mucosa. Recent studies indicate that polysaccharides may have a local immunomodulatory effect and this can also contribute to the clinical effect. Moreover, a study on marshmallow confirmed that the effect is not limited to the pharynx, but through a vagal reflex also involves the tracheobronchial mucosa. Mucilaginous herbs are safe even on prolonged use. Their use is not associated with any known adverse effect, but polysaccharides may affect the absorption of concomitantly taken medicines.

10.1.1 Marshmallow

Marshmallow (*Althaea officinalis* L., Malvaceae) has been used in traditional European medicine since ancient times for the local treatment of wounds, burns and injuries and internally to treat cough and several other symptoms. Both its roots and its leaves have been applied. In the European Pharmacopoeia, both are included. Marshmallow root consists of peeled or unpeeled, whole or cut, dried roots of *Althaea officinalis*. It has a swelling index of at least 10, determined on the powdered herbal substance.

- **Chemical composition and mechanism of action**

The root contains 5-10% polysaccharides, mainly acid arabinanogalactans, galacturonic rhamnans, arabans and glucans, with the predominant neutral mucilage component (1→6)-alpha-D-glucan. It also contains pectins, saccharose, starch, phenolic acids and flavonoids.

The mucilage of marshmallow root forms a layer on the mucosa and protects it from irritation. In *in vitro* studies, polysaccharides exhibited moderate adhesion to the epithelial tissue. The antitussive effect may be related to the inhibition of the mucociliary activity of the esophageal epithelium. In an animal study of marshmallow extracts, the antitussive activity was found to be inferior to that of codeine, but more pronounced than those of the non-narcotic drugs prenoxdiazine and dropropizine.

Various extracts of marshmallow roots exert an *in vitro* antimicrobial effect against several pathogens, including *Pseudomonas aeruginosa, Proteus vulgaris* and *Staphylococcus aureus*. Following local application, marshmallow extract exhibited antiphlogistic activity, whereas no systemic effect was observed after oral administration. A flavonoid of the plant, hypolaetin 8-glucoside, exerted anti-inflammatory, analgesic and anti-ulcer activity in rats.

In an animal experiment, intraperitoneally applied marshmallow polysaccharide resulted in a significant reduction of the blood glucose level.

- **Efficacy and indications**

In a double-blind placebo-controlled clinical trial involving patients with a dry cough associated with ACE inhibitors, a liquid marshmallow extract significantly decreased the cough frequency after 4 weeks in comparison with placebo.

In a post-marketing surveillance study of children (0-12 years) with a dry irritating cough, the efficacy and tolerability of a marshmallow root syrup was examined. The

cough frequency and intensity were reduced significantly after three days of treatment and the treatment was very well tolerated. In a retrospective observational study of similar patients and the same product, the efficacy was assessed as "very good" or "good" in >90% of the cases and no adverse effects were recorded.

Although the clinical efficacy has not been confirmed, in view of the traditional application of marshmallow roots, the EMA has granted a traditional use monograph with the following indications:

- symptomatic treatment of oral or pharyngeal irritation and an associated dry cough, and
- symptomatic relief of mild gastrointestinal discomfort.

In the case of the former indication, the single dose is 0.5–3 g for the macerate preparation, several times daily up to a maximal daily dose of 15 g (for children aged 6-12 years: at most 3 times daily; for children aged 3-6 years: a single dose of 0.5–1 g for macerate preparation, 3 times daily). In the event of the gastrointestinal indications, the dose is 3–5 g for macerate preparation, 3 times daily. Other preparations with similar posologies may also be applied.

The macerate should be prepared with water with a temperature of at most 40 °C by steeping for at least 30 minutes. (The use of too hot water may lead to the extraction of starch.)

- **Side-effects, interactions & contraindications**

Since the absorption of concomitantly administered medicines may be decreased, marshmallow should not be taken less than 1 hour before or after the intake of other medicines. Although the safety during pregnancy and lactation has not been established (and its application is therefore not recommended by the EMA), there are no data concerning the risk of the application of marshmallow roots.

10.1.2 Iceland moss

Cetraria islandica grows in arctic and subarctic areas, in northern and eastern Europe, Siberia and North America. According to the European Pharmacopoeia, iceland moss (Lichen islandicus) consists of the whole or cut, dried thallus of *Cetraria islandica* (L.) Acharius s.l. (Parmeliaceae). The swelling value of the dry drug is at least 4.5.

In the Middle Ages, *Cetraria islandica* was popular for the treatment of pulmonary and digestive ailments. In arctic and subarctic areas, lichens were also used as emergency food in famines. In that case it was pretreated with alkaline wood ash to remove the bitter lichen acids. The contemporary application is similar: to treat irritation or inflammation of the oral and pharyngeal mucosa and the associated dry cough, bronchitis and a loss of appetite and externally to treat wounds.

Chemical composition and mechanism of action

The pharmaceutically most important connstituents of iceland moss are the polysaccharides (25-50%). These are lichenans (or lichenins, a hot water-soluble, linear beta-D-glucan), isolichenan (or isolichenin, a cold water-soluble, linear alpha-D-glucan), and further polysaccharides with various structures and solubility. Other characteristic constituents are the lichen acids.

The efficacy in relieving dry cough may be related to the theory that the mucilage covers the mucosa and protects it from local irritation. To support this, a preclinical study described bioadhesive effects of polysaccharides isolated from *Lichen islandicus* on isolated animal buccal membranes. Moreover, different extracts of *Lichen* exerted antimicrobial effects against a number of pathogenic bacteria. Water extracts and purified polysaccahrides stimulated granulocytic phagocytosis *in vitro* and this immunomodulating effect was confirmed in animal experiments. The antiphlogistic activity of *Lichen* has been observed preclinically.

Although there have been no studies to support the efficacy against a loss of appetite, because of the bitter taste of the lichen acids, this effect seems plausible.

Efficacy and indications

In an open study, patients with laryngitis, pharyngitis or bronchial catarrh were treated with pastilles containing an aqueous extract of Iceland moss. The results were assessed as significantly positive in 86% of the cases, whereas no significant effect was observed following adjuvant treatment in more severe bronchial ailments. The efficacy against loss of appetite has not been studied.

With regard to the traditional application and the plausibility relating to the constituents of *L. islandicus*, it can be applied as a traditional herbal medicinal product as a

- demulcent for the symptomatic treatment of oral or pharyngeal irritation and the associated dry cough, and
- to treat a temporary loss of appetite.

To enhance theappetite, it may be used as a herbal tea prepared from 1–2 g of the comminuted herbal substance as an infusion or decoction 3 times daily, or as liquid extracts with similar posology. For oromucosal use, soft extracts in various dosages are used.

Side-effects, interactions & contraindications

The absorption of concomitantly administered medicines may be delayed, and the Iceland moss should therefore not be taken within 1 hour before or after the intake of other medicinal products. In the event of hypersensitivity, the application of *Lichen* is contraindicated.

10.2 Productive cough

In cases of respiratory tract infections, the bronchial mucus resulting from the inflammation of the mucosa, can be transformed into an exudate which triggers a cough as a reflex to remove the irritant. In such cases, expectorants may be useful, since they reduce the viscosity of the mucus and facilitate its removal by coughing. Herbal expectorants can be divided into two major groups:

- **Directly acting expectorants** These are typically essential oils or essential oil-containing plants. The effect is based on the stimulation of the serous glandular cells and the ciliar activity of the epithelium. Essential oils may be applied directly (by inhalation). However, after oral or transdermal application, they are excreted in the bronchi and act similarly to inhaled oils, but in a delayed and prolonged manner.
- **Reflex expectorants** These expectorants contain saponins that irritate the gastrointestinal mucosa to induce a reflex stimulation of respiratory secretion, resulting in an increased production of mucus with lower viscosity.

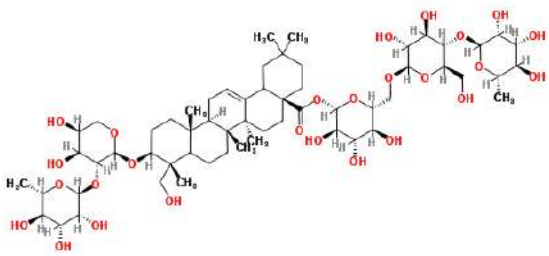
10.2.1 Ivy

According to the European Pharmacopoeia, Hederae folium is the whole or cut, dried leaves of *Hedera helix* L., collected in spring, with a minimum hederacoside content of 3.0%.

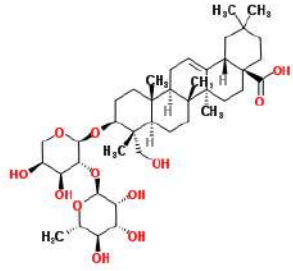
Ivy leaves and berries have been applied in medicine since antiquity but their indications (e.g. jaundice and dysentery) differed from its contemporary use. Today, only the leaves are applied and only in the treatment of respiratory diseases.

- **Chemical composition and mechanism of action**

Ivy leaves contain 2.5-6% triterpene saponins, based on the aglycones hederagenin, oleanolic acid and bayogenin. The majority of the saponins are bisdesmosides, with the main compound hederacoside C (hederasaponin C). Monodesmosides (such as alpha-hederin) are present in smaller amounts. Bisdesmosides may be cleaved to monodesmosides during drying or processing. Further secondary metabolites are caffeic acid derivatives, flavonoids, coumarins and polyacetylenes (e.g. falcarinol).



hederacoside C



alpha-hederin

The expectorant effect of ivy is more complex (or more precisely described) than those of other saponin-containing plants. Apart from the reflex expectorant effect through irritation of the gastric mucosa, other activities also play a part. *Hedera* treatment increased the density of beta-adrenoreceptors *in vitro* and alpha-hederin inhibited the terbutaline-stimulated internalization of the $beta_2$-adrenoreceptors in the alveolar cells. The bronchodilating activity of the extract was observed in *in vivo* studies. Moreover, the stimulation of $beta_2$-adrenoreceptors leads to increased surfactant production.

Ivy leaf extracts and their saponins exerted spasmolytic activities on isolated animal smooth muscles. Flavonoids and caffeic acid derivatives with less pronounced activity may also contribute to the effect. Extracts of the plant and its saponins exerted anti-inflammatory effects in animal experiments and were active against several bacteria and viruses *in vitro*.

- ## Efficacy and indications

The efficacy of ivy leaf was analysed in several clinical trials. In a controlled study, children (7 months-15 years) suffering from acute inflammatory diseases of the respiratory tract were treated either with ivy dry extract or with ambroxol for 7-14 days. After 7 days of treatment, the velocity parameters of external respiration were normalized in nearly all of the children with obstructive diseases, while in the ambroxol group normalization could not be documented; further, a fast decrease of crepitation only was seen in the group treated with ivy.

In an open and controlled study, children (2-10 years) with acute bronchitis were treated either with ivy dry extract or with acetylcysteine for 7-10 days. After 5 days of the treatment, the improvements of the parameters relating to the upper and middle airway functions (e.g. FVC and FEV_1) were significantly greater in the ivy group. After

10 days, 15% of the *Hedera* group and 29% of the acetylcysteine group had cough and a liquid (non-viscous) sputum.

In a randomized, controlled, double-blind comparative study of adult patients with mild to moderate, simple or obstructive chronic bronchitis, treatment corresponding to 0.25-0.42 g of herbal substance daily was compared with ambroxol. Improvements in spirometric and auscultation parameters were observed in both groups, with no significant differences between the groups.

In a randomized, double-blind, placebo-controlled crossover comparative study children aged 4-12 years, with bronchial asthma were treated for 3 days, with a dry extract from ivy leaves (equivalent to 218 mg of herbal substance) or with placebo. In the active group, a statistically significant reduction of the airway resistance was demonstrated in comparison with the placebo therapy.

The efficacy of ivy leaf has been examined in several non-controlled clinical studies in the treatment of children and adults with various respiratory diseases, all accompanied by coughing. The typical endpoint of these studies was a reduction of the cough frequency. The design of these studies and the (in some cases) small patient number did not allow conclusions concerning efficacy, but the results tended to confirm the findings of controlled trials. Moreover, studies with several thousands of participants have confirmed the good tolerability of the treatment.

The available clinical evidence supports the efficacy of certain extracts in well-stablished therapy

- as an expectorant in cases of productive cough.

The daily doses of these extracts are as follows:

- Dry extract (DER 4-8:1, extraction solvent ethanol 24-30%): adults: 45-105 mg; 6-12 years: 33-70 mg; 2-5 years: 24-36 mg.
- Dry extract (DER 6-7:1, extraction solvent ethanol 40%); adults: 42-54 mg; 6-12 years: 15-40 mg; 2-5 years: 17-27 mg.
- Dry extract (DER 3-6:1, extraction solvent ethanol 60%); adults: 66 mg; 6-12 years: 50 mg; 34 mg.
- Liquid extract (DER 1:1, extraction solvent ethanol 70%); adults 300 mg; 6-12 years: 225 mg.

Use in children under 2 years of age is contraindicated because of the risk of the aggravation of respiratory symptoms.

For one preparation (soft extract (DER 2.2-2.9:1), extraction solvent: ethanol 50% - propylene glycol (98:2), traditional use has been documented, and this can therefore be used as a traditional herbal medicinal product

- as an expectorant in cough associated with colds.

Its maximal daily dose for adults, for children aged 5-12 years and for 4-years-old children is 120 mg, 80 mg and 60 mg, respectively. The use in children between 2 and 4 years of age is not recommended.

- **Side effects, interactions & contraindications**

It has been documented in numerous case reports that fresh ivy leaves may cause contact dermatitis, presumably due to their falcarinol content. In cases of oral use, no such risk has been documented. Allergic reactions (urticaria, skin rash and dyspnea) and gastrointestinal reactions (nausea, vomiting and diarrhea) have been observed in clinical studies. An overdose can provoke nausea, vomiting, diarrhea and agitation. In patients with gastritis or gastric ulcer, the symptoms may be aggravated.

Concomitant use with antitussives is not recommended. Safety during pregnancy and lactation has not been established. It is contraindicated in cases of hypersensitivity to ivy or to plants of the Araliaceae family.

10.2.2 Thyme

There are several thyme species native to Europe, and many of them have been applied in traditional medicine during the ages. In current official medicine, two species, *vulgaris* L. and *Thymus zygis* L. are applied.

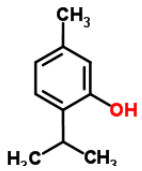
The whole leaves and flowers are separated from the previously dried stems of *Thymus vulgaris* or *Thymus zygis* or a mixture of both species. The minimum content of essential oil is 1.2% with a minimum 40% of thymol + carvacrol. Thyme essential oil is defined as the essential oil obtained by steam distillation from the fresh flowering aerial parts of *Thymus vulgaris, T. zygis* or a mixture of both species

Thyme species have a long tradition of use in Europe, primarily in the treatment of respiratory diseases. The anti-infective effect of the herbal extracts and essential oils of these species is well known. Thyme oil is one of the essential oils with the longest documented therapeutic use, going back to the Middle Ages.

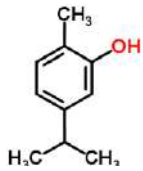
- **Chemical composition and mechanism of action**

Thyme leaves contain a noteworthy amount (2-2.5%) of essential oil. Although there are several chemotypes, only those with thymol as predominant compound are acceptable for the European Pharmacopoeia. The main components of the oil are thymol, carvacrol, *p*-cymene, gamma-terpinene and terpinen-4-ol. According to the

definition of the Pharmacopoeia, the thymol content should be 36-55%. The leaves also contain triterpenes, flavonoids (apigenin, luteolin and their derivatives) and caffeic acid derivatives.



thymol



carvacrol

The efficacy of thyme largely relies on its antimicrobial effect. This is primarily due to the essential oil content of the plant. The essential oil exerts strong antibacterial (on both Gram-positive and Gram-negative pathogens), antiviral and antifungal effects on several strains (e.g. methicillin-resistant *Staphyloccus aureus, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Candida albicans, Trichophyton* sp. and *Herpes simplex*). Even the vapor of the oil is highly effective against respiratory tract pathogens. The activity is mainly attributed to thymol and carvacrol.

A liquid extract of the plant alleviated experimentally induced contraction of the rat trachea. This may be related to the agononistic effect of the beta-2-adrenoreceptors. The essential oil (and thymol and carvacrol) was also effective. Flavonoids additionally play a role in this effect, presumably through inhibition of the availability of Ca^{2+} for muscle contraction.

In animal experiments, thyme extracts improved the ciliary transport in the respiratory tract.

- **Efficacy and indications**

In a randomized, double-blind study, patients with a productive cough in uncomplicated respiratory infections were treated with a thyme syrup or a bromhexine preparation for 5 days. No significant difference was observed between the two interventions in the self-reported alleviation of the complaints. In an open study, children aged 2 months to 14 years with bronchial catarrh or bronchitis were treated daily with a thyme syrup for 7-14 days. As compared with the start of the study, an improvement of the coughing was reported in 94% of the patients.

Although these studies are not convincing from the point of view of clinical efficacy, the long-standing use of thyme permits the application of the plant material, certain extracts and the essential oil as traditional herbal medicinal products

- in the productive cough associated with a cold.

There are several liquid or soft extracts (extracted with water, ethanol, glycerol, ammonia) preparations with varying posologies. The herbal tea should be prepared

from 1-2 g of the comminuted herbal substance and consumed 3-4 times daily. Certain preparations can be applied from the age of 4, but the usual lower age limit is 12 years.

For the essential oil, the dose for oral use is 4-5 drops, 3-5 times daily.

The essential oil may also be applied cutaneously or as a bath additive as a traditional herbal medicinal product

- for the relief of symptoms in coughs and colds.

As cutaneous use, the essential oil in liquid or semi-solid dosage forms in concentrations up to 10% should be applied to the chest and the back up to 3 times daily. As a bath additive 0.007–0.025 g/l should be used.

- **Side effects, interactions & contraindications**

In the event of hypersensitivity to thyme or other plants of the Lamiaceae, use of the plant is contraindicated. Safety during pregnancy and lactation has not been established.Oral use of the oil in children and adolescents under 18 years of age is not recommended.

Full baths are contraindicated in cases of open wounds, large skin injuries, acute skin diseases, high fever, severe infections, severe circulatory disturbances and a cardiac insufficiency.

During the use of thyme preparations, gastric disorders may occur. Thyme oil should not be applied to the face, and particularly the nasal area of babies and infants under the age of two years because of the risk of a laryngospasm.

10.2.3 Eucalyptus

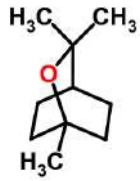
The leaf and the essential oil obtained from the leaves of *Eucalyptus globulus* Labill. are widely applied in official medicine and can also be found in the European Pharmacopoeia. Eucalyptus leaves are the whole or cut dried leaves of older branches of *Eucalyptus globulus* Labill. with a minimal essential oil content of 20 ml/kg.

The eucalyptus tree is indigenous to Australia, but it is cultivated in many parts of the world, including the Mediterranean region. For essential oil production, other species are also available, such as *Eucalyptus polybractea* R.T. Baker and *Eucalyptus smithii* R.T. Baker. The 1,8-cineole content of the Pharmacopeia-grade oil should not be less than 70%.

In folk medicine, the use of *Eucalyptus* leaves has focused on the relief of symptoms affecting the respiratory and gastrointestinal systems. The first users were the Australian aboriginals. In official medicine, its use started in the 19th century.

Chemical composition and mechanism of action

The leaves contain 1-3.5% volatile oil, with 1,8-cineole (eucalyptol) as the major constituent (50-95% of the oil). The herbal substance also contain tannins, flavonoids and phloroglucinol derivatives.



eucalyptol

Eucalyptus globulus leaf extracts, essential oil and cineole exert antiviral (against influenza virus) and high inhibitory activity on bacterial (including *Staphylococcus* and *Streptococcus* strains), and fungal growth *in vitro*.

Oral administration of the oil augmented the output of respiratory tract fluid in guinea pigs. On synthetic and pulmonary surfactant layers, *Eucalyptus* oil exhibits surfactant-like effects, which may support its expectorant activity.

In an *in vitro* experiment, extracts of *Eucalyptus globulus* leaves inhibited (experimentally induced) histamine release activity from rat leukemia cells. Plant extracts, oil and cineole displayed anti-inflammatory activities in different experimental models.

Efficacy and indications

The antitussive effects of *Eucalyptus* oil as a "chest rub" were studied in healthy subjects with induced cough in a single-blind cross-over study. The *Eucalyptus* oil formulation resulted in a statistical decrease in the cough count as compared with the baseline.

A double-blind placebo-controlled study on patients with COPD (chronic obstructive pulmonary disease) was carried out for 8 weeks. Standard therapy (beta$_2$-sympathomimetics, glucocorticosteroids and methylxanthines) was supplemented with 600 mg of 1,8-cineole or placebo. The objective lung function parameters (airway resistance) were statistically significantly reduced in comparison to the placebo group.

The effects of 1,8-cineole (600 mg daily for 6 months as concomitant therapy) were assessed in comparison with placebo in a double-blind, placebo-controlled study of COPD patients. 1,8-Cineole reduced both the exacerbations and the dyspnea, and significantly improved the lung function (e.g. forced expiratory volume and vital capacity) in comparison with the placebo.

In order to compare the effects of oral therapy with 1,8-cineole (600 mg/day) and ambroxol (90 mg/day), a randomized double-blind, cross-over trial with patients with COPD was performed. The lung function parameters and symptom score indicated

better improvements in response to therapy with 1,8-cineole, but the findings failed to reach the level of statistical significance in comparison with ambroxol.

The efficacy and safety of cineole were compared with those of placebo in patients with acute rhinosinusitis in a 1-week study. After 7 days, the differences between the two groups regarding the symptoms of the disease were statistically significant. In a further study, 150 patients with acute rhinosinusitis were treated with cineole or a herbal combination product (Gentianae radix, Primulae flos, Ramicis herba, Sambuci flos and Verbenae herba). Both treated groups exhibited an improvement in all relevant characteristics for rhinosinusitis within 7 days. The symptom scores (such as headache and nasal obstruction) were significantly lower in the case of treatment with cineole than in response to the treatment with the herbal combination product.

On the basis of its traditional use, Eucalypti folium and essential oil may be used as a traditional herbal medicinal product

- for the relief of the cough associated with a cold.

A herbal tea may be prepared from 4.5-12 g of the comminuted leaves daily. The infusion may also be used for inhalation.The tincture of the leaves should be used in a daily dose of 2.5-10 g.

In the event of oral use, the daily dose of the oil is 200-1000 mg. For inhalation, 3-8 drops should be used. As bath additive, 1.5-6 g essential oil/100 l ofwater may be applied. The essential oil can also be used cutaneously as an ointment containing 10% oil. Alternatively, some drops may be rubbed into the skin.

The essential oil may also be used as a traditional herbal medicinal product

- for the symptomatic relief of localized muscle pain.

With this indication, the single doses of liquid dosage forms are a few drops on the affected areas, 2 or 3 times daily. Semi-solid dosage forms containing 10% *Eucalyptus* oil may also be applied.

- **Side-effects, interactions & contraindications**

In children under 30 months of age (due to the risk of laryngospasm), in children with a history of seizures and in cases of hypersensitivity, the use is contraindicated.

Eucalyptus oil should not be applied on broken or irritated skin. It should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract. In the absence of sufficient data, its use during pregnancy and lactation is not recommended.

10.2.4 Licorice/liquorice

In different parts of the world various species of the genus *Glycyrrhiza* are applied for medicinal purposes. In Europe, the use of *G. glabra* has the longest tradition. In the current edition of the European Pharmacopoeia, other species are also official: liquorice root consists of the dried, unpeeled or peeled, whole or cut roots and stolons

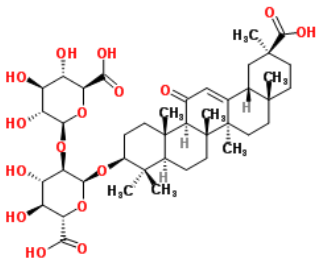
of *Glycyrrhiza glabra* L and/or of *Glycyrrhiza inflata* Bat. and/or *Glycyrrhiza uralensis* Fisch.and should contain at least 4% 18-beta-glycyrrhizic acid.

In the Pharmacopoeia, dry and liquid extracts are also listed. Liquiritiae extractum fluidum ethanolicum normatum contains 3-5% of 18-beta-glycyrrhizic acid. Liquorice dry extract for flavoring purposes (Liquiritiae extractum siccum ad saporandum) is produced from the cut liquorice root by a suitable procedure using water, and contains: 5-7% of 18-beta-glycyrrhizic acid.

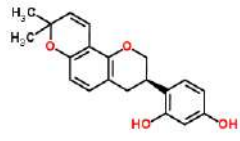
Glycyrrhiza glabra is a perennial herb native to Asia and the Mediterranean region. *G. uralensis, G. inflata* and *G. glabra* are used in Traditional Chinese Medicine, and their monographs can be found in the Chinese Pharmacopoeia. The roots have been applied in Europe since ancient times for a number of medicinal purposes. From the list of applications, its uses in gastrointestinal symptoms and for diseases of the respiratory tract are considered to be part of modern phytotherapy. Thanks to its efficacy against gastric ulcers, glycyrrhizin has been the subject of successful drug development: carbenexolone sodium, an anti peptic ulcer drug, is a succinate derivative of 18-beta-glycyrrhetinic acid. The application of glycyrrhizin in the treatment of viral hepatitis infection has recently been studied extensively.

- **Chemical composition and mechanism of action**

The word liquorice originates from the Greek *glykyrrhiza*, which means "sweet root". Indeed, licorice is sweet due to its glycyrrhizin content. Liquorice root contains triterpenoid saponins (5–20%, predominantly glycyrrhizin, which is a mixture of potassium and calcium salts of 18-beta-glycyrrhizic acid), which is about 50 times sweeter than sugar. The aglycone of glycyrrhizic acid, called glycyrrhetic acid can be found in traces in the roots. The roots contain a variety of flavonoids, with flavanones and chalcones as the main groups of these compounds. Isoflavones, such as glabridin, are also present. The coumarin content is low. Stilbene derivatives are among the characteristic components of the plant.



glycyrrhizic acid



glabridin

Glycyrrhizin is the pharmacologically most important metabolite of liquorice. Because of the structural similarity to the corticosteroid hormones, it was earlier hypothesized

that liquorice may have mineralocorticoid and glucocorticoid effects. However, it emerged that the affinities of glycyrrhizin and 18-glycyrrhetinic acid for the corticoid receptors are at least 3000 times less than those of the endogenous hormones. However, 18-beta-glycyrrhetinic acid is a competitive inhibitor of the enzyme 11beta-hydroxysteroid dehydrogenase. This leads to higher cortisol plasma levels, which, through mineralocorticoid receptors promotes the reabsorption of Na^+ (an indirect mineralocorticoid effect). Studies involving healthy subjects fed with liquorice confirmed that the corticosteroid-like effects were associated with a change in the cortisol metabolism.

Liquorice inhibits the enzyme 15-hydroxyprostaglandin dehydrogenase, which converts prostaglandins E_2 and F_{2alfa} to inactive metabolites. Thus, liquorice increases the local concentrations of the above-mentioned prostaglandins, which promote mucous secretion and cell proliferation in the stomach, and therefore has an antiulcer effect. The gastroprotective effect was observed after the application of glycyrrhizic acid-free extracts, and it was found that the flavonoids are also responsible for this effect. Moreover, glabridin has anti-*Helicobacter pylori* activity *in vitro*, which may also contribute to the antiulcer effect (without affecting acid production and ingestion).

Liquorice extracts and glycyrrhizin inhibit the growth of several viruses, including HIV, influenza, SARS, hepatitis and cytomegalovirus, possibly through the inhibition of binding to the cell membrane, replication mechanisms or the induction of interferon production in T-cells. Antimicrobial activities against several pathogenic bacteria and fungi (e.g. *Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium* and *Staphylococcus aureus*) have been demonstrated *in vitro*.

Hepatoprotection against experimentally induced injury (alcohol or CCl_4) has been demonstrated in animals. The anti-inflammatory effects of liquorice extracts have been confirmed *in vitro*.

Interestingly, the expectorant effect has not been studied in detailed animal experiments. The phytochemistry of the plant (the presence of saponins) has led to the assumption that *Glycyrrhiza* exerts its expectorant effect via a reflex mechanism through the gastric mucosa. Further, it is presumed that mucilage present in the drug, or secretion produced as a result of the treatment, covers the pharyngeal surface, thereby relieving a dry cough.

- **Efficacy and indications**

A randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of an extract of *Glycyrrhiza glabra* in patients with functional dyspepsia. The patients received either placebo or the extract (150 mg daily) for 30 days. Efficacy was evaluated in terms of the change in the severity of the symptoms and on overall assessment of efficacy in comparison with placebo. The extract led to a significant decrease in total symptom scores, and an improvement in the global assessment of efficacy.

Several studies have been performed to investigate the effect of deglycyrrhizinated liquorice in gastric ulcer. As a result of the negative outcome studies or the poor experimental design, the available studies did not confirm the presumed effect.

In two studies, the antihyperlipidemic and antiatherogenic (protection of the LDL from oxidation) activity of liquorice was observed, but these studies comprised only low numbers of participants.

In a placebo-controlled study, liquorice bioadhesive hydrogel patches were effective in relieving pain and reducing the healing time of recurrent aphthous ulcer.

Although the results of clinical trials are not convincing, the traditional applications of liquorice justify its use as a traditional herbal medicinal product

- as an expectorant in the cough associated with a cold, or
- for the relief of digestive symptoms, including a burning sensation and dyspepsia.

The dose is 2-8 g daily as a tea, or in the case of the former indication, 3.6-6 g of soft extract (DER 3:1, extraction solvent water) and, in the case of the latter indication, at most 160 mg of soft extract (DER 1:0.4-0.5, water) daily. Liquorice should not be used for more than 4 weeks.

- **Side-effects, interactions & contraindications**

The data of clinical studies suggest that the short-term (not more than 4 weeks) use of liquorice is safe. Chronic use or overdosage can cause hypokalemia, hypertension, arrhythmia and encephalopathy. It is not recommended to be used in patients with hypertension, kidney diseases, liver or cardiovascular disorders or hypokalemia, as they are more sensitive to the adverse effects of liquorice. Concomitant use with diuretics, cardiac glycosides, corticosteroids, stimulant laxatives or other medications which may aggravate an electrolyte imbalance is not recommended.

Safety during pregnancy and lactation has not been established, but animal studies revealed that 18-beta-glycyrrhetinic acid crosses the placenta, and in high doses exhibited an embryotoxic effect. According to one study, heavy glycyrrhizin exposure was associated with preterm delivery.

10.2.5 White horehound

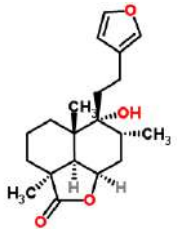
Marrubium vulgare L. (Lamiaceae) is a plant native to Europe and North Africa. According to the definition of the European Pharmacopoeia, Marrubii herba is the whole or fragmented dried flowering aerial plants of *Marrubium vulgare* L. with a minimum marrubiin content of 0.7%.

In the Mediterranean region, it has been used to treat coughs for centuries, whilst in German-speaking territories it was utilized primarily as a bitter to improve the

digestion. Outside Europe it was used for similar indications, but in some parts of North Africa it was also applied as a hypotensive, hypoglycemic and cardiotonic herb.

- **Chemical composition and mechanism of action**

White horehound contains labdane-type diterpenes with the bitter-tasting marrubiin (0.12-1%) as main component. The essential oil content is low (<0.05%). Tannins (up to 7%), flavonoids and hydroxycinnamic acid-derivates are present in noteworthy quatities.



marrubiin

Its effect in dyspeptic complaints and a loss of appetite are based on the increase of gastric and biliary secretion by its bitter components. Expectorant action may be induced by the stimulation of bronchial secretion by marrubiin.

Marrubium extracts exerted spasmolytic effect on smooth muscle preparations *in vitro*. The herbal extract and one diterpene, marubenol, have been reported to possess vasorelaxant activity, which may a result of the inhibition of L-type voltage-dependent Ca^{2+} channels in smooth muscle cells. Moderate analgesic and antiphlogistic effects have also been observed.

In a model of ethanol-induced ulcers in mice, both white horehound extract and pure marrubiin exhibited a gastroprotective effect.

Marrubium extracts exert antihyperlycemic effects in different animal models of diabetes.

- **Efficacy and indications**

No clinical data are available to support the use of *Marrubium* as a well-established medicinal plant. However, as a result of its folk medicinal use, it may be used as a traditional herbal medicinal product

- as an expectorant in coughs associated with colds
- for the symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence, and
- for a temporary loss of appetite.

The daily dose as a herbal tea is 3-6 g, and as a powdered herbal substance is 675-1350 mg. 30-60 ml of expressed juice and up to 12 ml of liquid extract may also be used. In cases of gastrointestinal symptoms, it should be taken 1/2 hour before a meal.

- **Side effects, interactions & contraindications**

In the event of hypersensitivity to the plant and to other species of the Lamiaceae family, and in cases of obstruction of the bile duct, cholangitis, liver disease or ileus, the use of *Marrubium* is contraindicated.

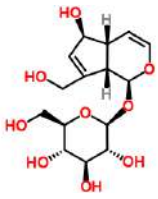
10.2.6 Ribwort plantain

Plantago lanceolata is a common perennial weed abundant in Europe and Asia. According to the definition of the European Pharmacopoeia, Plantaginis lanceolatae folium is the whole or fragmented, dried leaf and scape of *Plantago lanceolata* L.s.l.

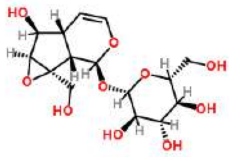
Plantaginis lanceolatae folium has long been applied throughout Europe for the treatment of complaints associated with colds, or for the treatment of inflammations of the mouth and throat. In the past, it was also used externally to treat dermatological symptoms and diseases. Today, the most typical preparations are syrups.

- **Chemical composition and mechanism of action**

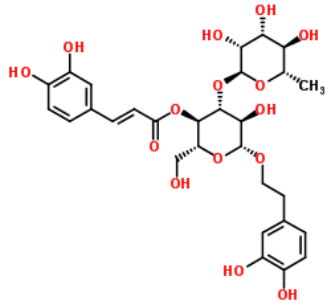
Plantain leaves contain about 2-3% of iridoid glycosides (main components: aucubin and catalpol). The iridoid content is much lower in older leaves and, since these components are thermally unstable, drying above room temperature considerably decreases their quantity. Moreover, if fermentation occurs during drying, aucubin is converted to biologically less valuable brown polymers. The plant contains phenylethanoids (acteoside, plantamajoside), flavonoids, with apigenin and luteolin as major components, tannin, organic acids and about 5% of polysaccharide.



aucubin



catalpol



acteoside

Its use in respiratory disorders can be explained in part by its polysaccharide content, which has confirmed adhesive effects on the mucus membranes, covering the mucosa, forming a protective layer and decreasing local irritations, thereby relieving dry cough.

Aqueous extracts exert an antimicrobial effect on several species, including some responsible for respiratory diseases (e.g. *Staphylococcus aureus, Streptococcus hemolyticus, Proteus vulgaris, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*).

Plantain extracts and the phenylethanoids acteoside and plantamajoside as well as the iridoidglycosides catalpol and aucubin have demonstrated anti-inflammatory effects in different experimental models. Their activities may be explained by inhibition of NO production and the enzyme COX-2. Aqueous extracts promote the epithelizing healing of wounds. The experimentally observed spasmolytic activity can be attributed to the iridoids and phenylethanoids in the plant.

- **Efficacy and indications**

The only available clinical trial is a prospective, multicenter study of a cough syrup (100 ml of syrup containing 20 g of fluid extract, DER 1:1, extraction solvent ethanol) involving patients with unspecific acute respiratory diseases. After 3-14 days of treatment, the intensity and frequency of coughing were reduced by 67% and 66%, respectively. The level of thoracal pain decreased by 80%, and the irritative cough and dyspnea by 69%. The overall Global efficacy was assessed as good or excellent in 88% of the patients by the physicians.

As controlled clinical trials with extracts from *Plantago lanceolata* have not been performed, a well-established use monograph cannot be granted. Plantain can be administered as a traditional herbal medicinal product

- as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and the associated dry cough.

For this purpose, several dry, liquid or soft extracts, expressed juice or syrups can be used. The daily dose as a tea is 6-9 g.

- **Side effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. Oral use in children under 3 years of age is not recommended.

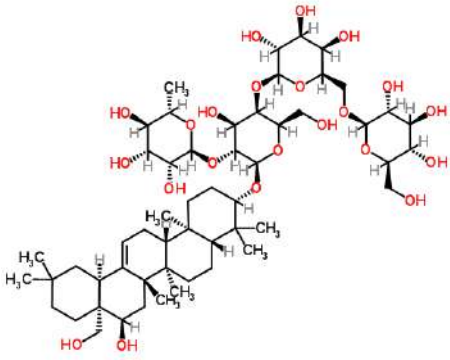
10.2.7 Primula

Primulae radix consists of the whole or cut, dried rhizome and root of *Primula veris* L. or *Primula elatior* (L.) Hill as described in the European Pharmacopoeia. Although having traditions in folk medicine, the widespread use of *Primula* roots started only during World War I as a substitute for Senegae radix. *Primula* flowers are also used in therapy, but, less extensively.

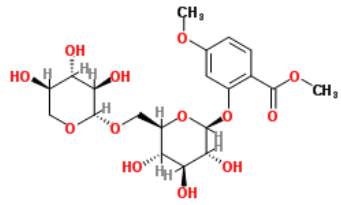
- **Chemical composition and mechanism of action**

Primula roots contain 3-10% of triterpene saponins (e.g. primulasaponin and primacrosaponin). The methoxysalicylic acid derivative phenolic glycosides primverin and primulaverin occur in both species, and are responsible for the odor of the roots when metabolized to aglycones during drying. The roots do not contain quinoid compounds such as asprimin, which are responsible for the contact allergenic effect of aerial parts of *Primula* species.

The therapeutic use of *Primula* depends largely on its saponin content. Saponins irritate the gastric mucosa, leading to a reflex increase in less viscous bronchial secretion. Irritation of the mucous membranes in the throat is also involved in this effect. Moreover, the saponins reduce the surface tension of the mucus and ease its removal by coughing. In an animal experiment, *Primula* saponins improved the ciliary activity, and in a further experiment *Primula* flower extracts increased the production of bronchial secretion.



primulasaponin



primverin

Extracts and saponins of *Primula* species exert *in vitro* antibacterial activities on pathogens such as *Staphylococcus aureus* and *Escherichia coli*. Apolar extracts exhibit anti-inflammatory activity through the inhibition of cyclooxygenase-1 and -2 enzymes.

- **Efficacy and indications**

The clinical efficacy of monocomponent preparations has not been studied. Although several clinical trials have been performed with combinations of *Primula* root and thyme, these cannot contribute to the evidence of the clinical of *Primula* root. Therefore, *Primula* roots as a traditional herbal medicinal products can be used

- as an expectorant in coughs associated with colds.

The daily doses of liquid extracts is tipically 1.5-3 g, while the dry extract should be used in a daily dose of 0.3-0.6 g. Extracts are usually prepared with mixtures of ethanol and water.

- **Side effects, interactions & contraindications**

Its use in children under 12 years of age is not recommended (there are some exceptions; for certain extracts, the age limit is 4 years). In the absence of sufficient data, its use is not recommended during pregnancy and lactation.

Gastrointestinal irritation may occur.

10.3 Plants with immunomodulant or aspecific effect

One possibly strategy to prevent or overcome respiratory infections is stimulation of the immune system. Several herbs have ben claimed to have such an effect, but their activity is quite different from that of vaccines since herbal metabolites have no antigenic relationship to pathogens. Their effect is non-specific and relies on the stimulation of cellular immunity. The term immunomodulant is a better expression to characterize the mechanism of action of these plants. Since their effect cannot be predicted in special cases (e.g. immunosuppression, autoimmune diseases and certain chronic diseases such as tuberculosis), these plants must be applied very carefully.

Certain plants relieve several symptoms of common cold. One of these, *Peargonium* has clinically confirmed efficacy, others, such as elder are used solely based on tradition.

10.3.1 Echinacea

The most widely used herbal immunomodulants are *Echinacea* species. In European phytotherapy, three species are used: *Echinacea angustifolia* DC (narrow-leaf coneflower), *Echinacea pallida* (Nutt.) Nutt. (pale coneflower), and *Echinacea purpurea* (L.) Moench. (purple coneflower). The confusion with the taxonomy and the differentiation of the species means that early research (before the 1990s) reported to have been carried out on *Echinacea angustifolia* in Europe was probably in fact conducted on *Echinacea pallida.*

The above-mentioned three species have monographs in the European Pharmacopoeia. The roots of all three species are official, together with the flowering aerial parts of *Echinacea purpurea.*

Echinaceae angustifoliae radix consists of the whole or cut, dried underground parts of *Echinacea angustifolia*, with an echinacoside content of not less than 0.5%. Echinaceae pallidae radix consists of the whole or cut, dried underground parts of *Echinacea pallida*, containing not less than 0.2% echinacoside.

Echinaceae purpureae radix consists of the whole or cut, dried underground parts of *Echinacea purpurea*, which contains at least 0.5% of caftaric acid + cichoric acid.

Echinaceae purpureae herba is the dried, whole or cut flowering aerial parts of *Echinacea purpurea*, with a minimum 0.1% content of caftaric acid + cichoric acid.

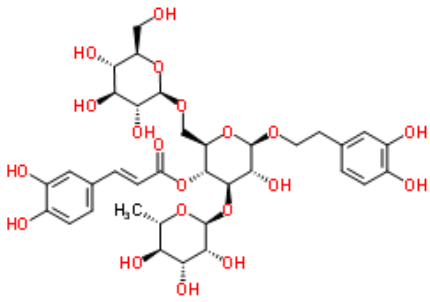
Interestingly, the fresh herbal drug that is used as raw material in the production of several allopathic products (to prepare expressed juice), is described only in the German Homeopathic Pharmacopoeia.

Many and varied *Echinacea* species were used for medicinal purposes first by American Indians, *Echinacea angustifolia,* one of the most popular herbal remedies in North America some hundred years ago, was widely applied as an antidote for snakebite and other venomous bites and stings and poisonous conditions. *Echinacea purpurea* was less frequently used, primarily externally. The career of this plant in Europe began in homeopathy in the late 19th century. Due to the growing demand, cultivation of this species started in the first half of the 20th century in Germany. In homeopathy, the expressed juice of the herb is used, and interestingly many of the preclinical and clinical studies have been carried out with this homeopathic raw material.

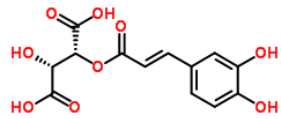
- **Chemical composition and mechanism of action**

Alkamides (up to 0.7% in *E. angustifolia* and *E. purpurea* roots) are characteristic compounds of coneflowers, whereas they can be found only in traces in *E. pallida*. Chemically, these compounds are usually isobutylamides or 2-methylbutylamides of unsaturated fatty acids.

Caffeic acid derivatives are also present (1.0-1.5% in *E. angustifolia* and *E. pallida*, with about double the amount in *E. purpurea*), with the main component echinacoside (0.5-1.5%) in *E. angustifolia* and *E. pallida*, and caftaric acid and cichoric acid in *E. purpurea*. These are caffeic acid glycosides, or caffeic acid esters of quinic acid (e.g. chlorogenic acid).



echinacoside



caftaric acid

From the point of view of immunomodulating activity, polysaccharides and glycoproteins are also of interest.

The roots contain the saturated pyrrolizidine-type alkaloids tussilagine and isotussilagine (since these have a 1,2-saturated necine structure, they are not hepatotoxic).

Polysaccharides (heteroglycans) of *Echinacea purpurea* and *E. angustifolia* were found to stimulate the activity of mouse macrophages *in vitro* and increase interleukin-1 secretion. In a further experiment, ethanolic extract of *E. angustifolia* root enhanced phagocytosis *in vitro*. A significant increase in phagocytosis was demonstrated in mice after the oral administration of *E. angustifolia* root extracts. Polysaccharides of the herb and root of *Echinacea purpurea* strongly activated macrophages *in vitro*.

An *in vivo* study was conducted to examine the immunomodulatory effects of *Echinacea angustifolia* preparations in rats. The phagocytic activity of alveolar macrophages increased in response to increasing oral doses. Among the components, alkylamides significantly increased the phagocytic activity of alveolar macrophages. A 90% ethanolic extract of pale coneflower root enhanced the phagocytosis of human granulocytes. *Echinacea purpurea* expressed juice induced a significant increase in the percentage of phagocytosing granulocytes *in vitro*. The phagocytosis of macrophages from mice and rats was significantly stimulated after the i.p. or oral application of *Echinacea purpurea* expressed juice. A purified alkamide fraction of *E. purpurea* administered orally to rats enhanced the phagocytic activity and phagocytic index of lung alveolar macrophages.

In a human study, healthy volunteers took an ethanolic extract of purple coneflower root or placebo daily for 5 days. By day 5, a significant increase in phagocytosis of 120% was observed in the verum group, as compared with 20% in the placebo group. The effect was transient, and the phagocytotic activity returned to normal within 6 days.

Alcoholic extracts of *Echinacea angustifolia, Echinacea pallida,* and *Echinacea purpurea*, were investigated for immunomodulating properties in mice. The three herb extracts induced similar changes in the percentages of the immune cell populations and their biological functions. The herbal extracts significantly increased IFN-alpha production, but inhibited the release of TNF-gamma and IL-1-beta. Only the mice treated with *Echinacea angustifolia* and *Echinacea pallida* demonstrated a significantly higher production of IL-4 and IL-10. In a further experiment, polysaccharides and glycoproteins from pale coneflower root significantly increased the concentration of the cytokine IL-1 in the serum of mice after i.v. administration.

Echinacea purpurea was evaluated for its capacity to stimulate the cellular immune function of peripheral blood mononuclear cells. The extract of the roots significantly

enhanced the natural killer (NK) function. Polysaccharides of *E. purpurea* enhanced the cytotoxic action of macrophages toward tumor cells.

Certain alkamides were confirmed to have *in vitro* anti-inflammatory activity. Extracts of the three widely applied species inhibited 5-lipoxygenase. The antiphlogistic effect was confirmed after both local and oral administration. Ethanol extracts of *Echinacea angustifolia, Echinacea pallida, Echinacea simulata,* and *Echinacea sanguinea* significantly inhibited PGE_2 production in LPS-stimulated mouse macrophages. Certain alkamides of *Echinacea angustifolia* inhibited COX-2-dependent PGE_2 formation in an animal experiment.

An animal study revealed that chronic administration of *E. purpurea* root extract extended the lifespan of mice. Moreover, the number of NK cells, acting as the first line of defense against developing neoplasms, was significantly elevated.

Different extracts of *Echinacea* species and certain pure compounds (eg. echinacoside) exerted antimicrobial activities against several bacteria. *E. purpurea* herb was active against several viruses, including rhinoviruses and influenzaviruses.

The healing surgical of skin wounds on guinea pigs was accelerated by an *Echinacea purpurea* herb-containing ointment.

According to recent results, alkamides act on the cannabinoid (CB) receptors. The alkylamides dodeca-2*E*,4*E*,8*Z*,10*Z*-tetraenoic acid isobutylamide and dodeca-2*E*,4*E*-dienoic acid isobutylamide bind to the CB_2 receptor more strongly than the endogenous cannabinoids.

- **Efficacy and indications**

In the following, the clinical evidence based on studies with monocomponent preparations is presented. Although there have been several clinical trials with combinations, they are not suitable for an assessment of the efficacy of *Echinacea* species.

No clinical trials with a positive outcome support the efficacy of *Echinacea angustifolia*. One human study indicated increased phagocytosis after the oral consumption of a narrow-leaved coneflower root extract, but without any clinical endpoint. In a double-blind, placebo-controlled study to investigate the efficacy of *Echinacea angustifolia* extracts in the prevention of upper respiratory tract infections, no superiority was detected over placebo. A further study indicated that extracts of *Echinacea angustifolia* root do not have clinically significant effects on rhinoviral infection or on the illness that results from it.

The efficacy of *Echinacea pallida* root preparations in the treatment of the cold was assessed in two randomized, placebo controlled, double-blind studies. In one, patients with influenza-like infections of the upper respiratory tract were treated for 8-20 days either with a hydroalcoholic liquid extract of pale coneflower root at a daily dose corresponding to 900 mg of dried root or with placebo. Significant improvements in major symptoms, i.e. weakness, pain in the arms and legs, and headache, and in the

overall symptom score were observed in the verum group as compared with the placebo group. The duration of the illness was significantly shorter in the verum patients in those with putative bacterial infections; 9.8 days as compared with 13.0 days in the placebo group; and in those with putative viral infections, 9.1 days as compared with 12.9 days in the placebo group. A double-blind randomized placebo-controlled trial with the same treatment was performed to evaluate the use of *Echinaceae pallida* roots in influenza-like upper respiratory symptoms in 160 patients. The length of the illness and the overall symptom scores uniformly demonstrated a significant superiority over the placebo.

For *E. purpurea*, only a few cinical trials are available. In one study, extracts of the herb and roots of *Echinacea purpurea* or placebo were administered to volunteers at the onset of their cold for a period of 7 days. The decrease in the total daily symptomatic score was more pronounced in the *Echinacea* group than in the placebo group, associated with a significant increase in the number of circulating total white blood cells, monocytes, neutrophils and NK cells. In a randomized, double-blind, placebo-controlled study, the efficacy and safety of different doses and preparations of *Echinacea purpurea* were assessed in the treatment of the common cold. The primary endpoint was the relative reduction of the complaint index defined by 12 symptoms during the common cold according to the doctor's record. The quantified preparations were significantly more effective than the placebo. In a double-blind, placebo-controlled study, patients with influenza, randomized into three groups, were given a tincture of purple coneflower root at daily dosages corresponding to 450 mg or 900 mg of dried root, or placebo. After 3-4 days and 8-10 days, the 900 mg dose resulted in a highly significant reduction in the symptom score at both time points as compared with the lower dose and placebo.

Because of the lack of proper clinical evidence, but based on the traditional use, according to the opinion of European Medicines Agency, the above-mentioned *Echinacea* species roots may be used as traditional herbal medicinal products

- for the supportive treatment of the common cold. The therapy should start at the first signs of the common cold.

For *E. angustifolia* roots, the therapeutic daily dose is 3 g of the comminuted herbal substance as a decoction or infusion, 1.5 g of the powdered herbal substance, or 0.75-6 ml of the liquid extract or tincture.

In the case of *E. pallida roots*, the daily dose is about 100 mg of dry (50% ethanolic) extract or 125 drops of tincture daily.

For *E. purpurea* roots, the maximal daily dose is 360 mg of a dry extract (extraction solvent ethanol 45%).

The efficacy of the aerial parts of *E. purpurea* has been studied thoroughly, and apart from the numerous non-randomized, non-controlled or open trials, there are

publications on well-designed human studies. A randomized double-blind placebo-controlled trial was initiated with 120 patients with initial symptoms of acute, uncomplicated upper respiratory tract infection. Treatment with either *Echinacea purpurea* expressed juice (20 drops every 2 h for the first day and thereafter 20 drops three times daily) or placebo lasted for up to 10 days. The time until improvement was significantly shorter in the *Echinacea* group than in the placebo group. In the sub-group of patients with the fully expressed disease, the median time needed for improvement was 4 days (*Echinacea* group) or 8 days (placebo group). The average time until the termination of treatment due to improvement was 6 days (*Echinacea* group) or 10 days (placebo group). In a further double–blind placebo-controlled trial with *Echinacea purpurea* pressed juice (10 ml/day for 10 days) administered at the first signs of a cold, the median duration of the illness was 6 days in the verum group as compared with 9 days in the placebo group.

The clinical trials confirmed the efficacy of a well-described expressed juice (DER 1.5-2.5:1). On the basis of this evidence, the European Medicines Agency granted a well-established use monograph for this product with the following indication:

- short-term prevention and treatment of the common cold.

The daily dose is 6-9 ml expressed juice (or the corresponding dry expressed juice). For prevention and treatment, it should not be used for more than 10 days. For treatment, therapy has to be started at the first signs of the common cold.

For expressed juices different from that mentioned above, a traditional use monograph was published with the following indication in case of topical application:

- treatment of small superficial wounds.

For this purpose, ointments containing 10-20% juice may be used.

Side-effects, interactions & contraindications

In rare cases, hypersensitivity reactions, e.g. skin reactions, may occur. In the event of hypersensitivity to coneflowers and other plants of the *Asteraceae* family, the use of these plants is contraindicated. There is a possible risk of anaphylactic reactions in atopic patients.

The use of coneflowers is not recommended in cases of progressive systemic diseases such as tuberculosis, diseases of the white blood cells, collagenoses, multiple sclerosis, AIDS, HIV infections and other immune diseases. Extracts of *Echinacea purpurea* and its alkamides inhibited CYP isoenzymes experimentally, but the clinical relevance of this interaction has not been observed.

For *E. pallida* and *E. angustifolia*, safety during pregnancy and lactation has not been established. In the case of E. purpureae herba, data from exposed pregnant women indicate no adverse effects on pregnancy or on the fetus.

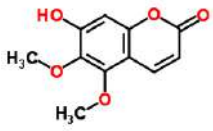
10.3.2 Pelargonium

Pelargonium species (Geraniaceae) indigenous to South Africa have a long tradition of use in the local folk medicine. Infusions of the roots of *Pelargonium sidoides* DC and *Pelargonium reniforme* Curt. have been used to treat coughs, chest problems including tuberculosis, and gastrointestinal disorders such as diarrhea and dysentery. The drug was introduced to Europe in the 19th century for the treatment of tuberculosis. Marketing and scientific analysis of its applicability for the treatment of bronchitis and symptoms of the common cold started in the 1970s.

The use of both of the above-mentioned species is accepted by the European Pharmacopoeia monograph, which describes *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt. in one monograph without defining specific parameters for differentiation. The tannin content, expressed as pyrogallol, should be at least 2%.

- **Chemical composition and mechanism of action**

The most characteristic compounds in *Pelargonium* roots are the polyhydroxylated coumarins (e.g. umckalin and artelin). Apart from the widely distributed disubstituted scopoletin, all the coumarins possess tri- or tetra-substituted oxygenated skeletons. Other secondary metabolites include phenolic acids, flavonoids and oligomeric and polymeric proanthocyanidins.



umckalin

An *in vitro* antimicrobial analysis of the effects *Pelargonium* coumarins on 8 microorganisms responsible for numerous respiratory tract infections, including Gram-positive (*Staphylococcus aureus, Streptococcus pneumoniae* and *beta-hemolytic Streptococcus*) and Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa and Haemophilus influenzae*) revealed moderate activity. Certain extracts exerted pronounced activities on respiratory pathogens. The antimicobacterial efficacy cannot be confirmed convincingly. Antiviral activity against herpes simplex virus types 1 and 2 was demonstrated in a cell culture experiment.

The immunomodulatory effect of the extracts may be related to the macrophage activating activity. *In vitro, Pelargonium* exract increased the release of NO and the production of IL-1, IL-12, and TNF-alpha, thereby reducing the survival rate of intracellular parasites. An increase of the IFN-beta production was also observed.

Efficacy and indications

Five quite uniform, randomized, double-blind, placebo-controlled studies have evaluated the efficacy of a special *Pelargonium* extracts in comparison with placebo, in several hundreds of patients with acute bronchitis. Following enrolment, control examinations were performed on days 3-5 and day 7. The primary outcome criterion was a change in Bronchitis Severity Scores (BSS) on day 7. The BSSs are the most important features of acute bronchitis, i.e. cough, sputum, rales/rhonchi, chest pain during coughing and dyspnea. In each study, the decrease in BSS was significantly higher in patients treated with *Pelargonium* than in patients treated with placebo. A meta-analysis of these treatments revealed a significant decrease in the BSS score as compared with placebo. In one study, remission by day 4 occurred in 69% of the patients under receiving substance treatment, in comparison with 33% of the patients receiving placebo. Treatment shortened the duration of working inability by nearly 2 days. In a further study, complete recovery by day 7 was observed by the physician in 45% of the actively treated patients relative to 6% of the patients on placebo. Certain open studies with a positive outcome have confirmed the efficacy.

The efficacy of *Pelargonium* as compared with placebo was examined in adult patients with the common cold in a double-blind, placebo-controlled study. The primary outcome criterion was the sum of the symptom intensity differences (SSID) of the cold intensity score (CIS) from day 1 to 5 according to a five-point verbal rating scale. From baseline to day 5, the mean SSID improved by 14.6 points in the actively treated group, as compared with 7.6 points in the placebo group. After 10 days, 63.5% versus 11.8% were clinically cured. The main duration of the inability to work was significantly lower in the *Pelargonium*-treated patients (6.9 days) than in the placebo group (8.2 days)

The effectiveness in rhinosinusitis was also assessed in a randomized, double-blind, placebo-controlled trial; treatment was applied for 3 weeks. The mean decrease in Sinusitis Severity Score was 5.5 points in the *Pelargonium* group and 2.5 points in the placebo group. A multicenter, prospective, open study investigated the efficacy and change in symptoms in patients with acute sinusitis. The primary outcome criterion was the sum of the objective and subjective symptoms of the sinusitis score. The mean total symptom score was 15 points at baseline; at the final examination on day 28, it was 2.5 points.

Although there is are appreciable clinical data tha support the efficacy of *Pelargonium*, for methodological reasons the European Medicines Agency has not granted a well-established use monograph for *Pelargonium*. With regard to its its documented long-standing use, one liquid extract (DER 1:8-10, extraction solvent ethanol 11% (m/m)) and one dry extract (DER 4-25:1, extraction solvent ethanol 11% (m/m)) can be used as traditional herbal medicinal products

- for symptomatic treatment of the common cold.

For adolescents over the age of 12 years and adults, the daily dose of the liquid extract is 1.19-1.25 ml, 3 times daily, while that of the dry extract is 60 mg. For children between 6 and 12 years, 0.79-0.83 ml of liquid extract 3 times daily or 40 mg of dry extract should be used.

- **Side effects, interactions & contraindications**

Its use in children under 6 years of age has not been established due to the lack of adequate data. Hepatotoxicity and hepatitis cases have been reported in association with the administration of some *Pelargonium* products, though these were not identical with the clinically studied ones.

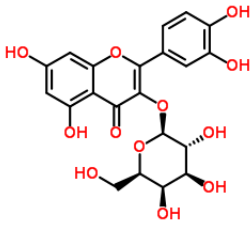
Mild gastrointestinal complaints (diarrhoea, epigastric discomfort, nausea or vomiting and dysphagia), mild nasal and gingival bleeding and allergic reactions have been reported during the use of *Pelargonium*. Coumarins of the plant do not possess the structural characteristics needed for anticoagulant activity (a hydroxy group at position 4 and a non-polar functionality at position 3). In a focused animal experiment, the anticoagulant action of warfarin was not influenced after concomitant use with *Pelargonium*.

10.3.3 Elder

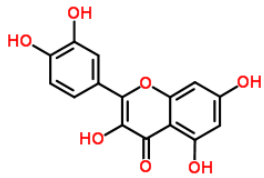
Elder flowers and berries have been used in traditional medicine and food since ancient times. Against the common cold, both plant parts have been used, but the application of the flowers is more widespread and better documented. Sambuci flos (European Pharmacopoeia) consists of the dried flowers of *Sambucus nigra* L. which contain not less than 0.8% of flavonoids.

- **Chemical composition and mechanism of action**

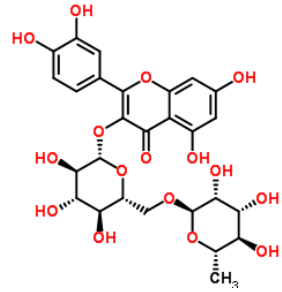
The flowers contain up to 3% of flavonoids (e.g. isoquercitrin, quercetin, rutin and hyperoside) about 3% of caffeic acid derivatives, triterpenes and a small amount of mucilage.



hyperoside



quercetin



rutin

Elder flower extracts exert antimicrobial effects against certain pathogens (e.g. *Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) *in vitro*, this presumably being related to its caffeic acid derivatives. The herbal drug also has a mild anti-inflammatory effect (observed both *in vitro* and in animal experiments). Some animal experiments have revealed the diuretic effect of the plant. For its diaphoretic effect, no firm confirmation can be found in the literature.

- **Efficacy and indications**

Although there are no data to support its clinical efficacy, as a result of the long-standing use elder flower can be applied as a traditional herbal medicinal product

- for the relief of the early symptoms of the common cold.

The herbal substance may be used for the preparation of a tea (2-5 g 3 times daily); liquid extracts prepared with 25% ethanol (DER 1:1: 3x3-5 ml, DER 1:5: 3x10-25 ml) can also be applied.

- **Side effects, interactions & contraindications**

Its use is not recommended in children under 12 years of age, and during pregnancy and lactation due to the lack of adequate data.

10.3.4 Lime tree

The lime or linden tree is native throughout Europe and is cultivated in Asia and North America. The flowers of several species are used in folk medicine, most typically as a tea. According to the European Pharmacopoeia, Tiliae flos consists of the whole dried inflorescence of *Tilia cordata* Miller, *Tilia platyphyllos* Scop., *Tilia* x *vulgaris* Heyne or a mixture of these.

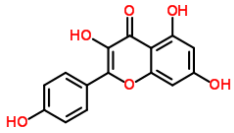
Lime flowers have been used as a diaphoretic since the Middle Ages, and were most frequently used in the treatment of diseases of the respiratory tract and for some other indications (e.g. as tranquilizer or in cases of digestive symptoms)

Chemical composition and mechanism of action

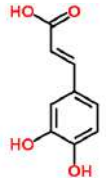
Lime flowers contain flavonoids (kaempferol, quercetin and their glycosides), caffeic acid derivatives, mucilage polysaccharides (3%), tannin, and a low amount of essential oil and, according to some reports, saponins.

Water extracts of *Tilia platyphyllos* and *Tilia vulgaris* exhibited spasmolytic activity *in vitro*. This activity may be related to the flavonoids of the plant.

The presumed diaphoretic activity is thought to be connected with the caffeic acid derivatives.



kaempferol



caffeic acid

In an animal experiment, lime flower extract displayed a clear anxiolytic effect. The mechanism of action has not been elucidated, but the role of benzodiazepine receptors is assumed.

The extract of lime flowers exerted antifungal action in one experiment on several strains.

Efficacy and indications

The diaphoretic action of lime flowers was investigated in an open clinical trial in patients with uncomplicated respiratory catarrhal disease. Fifteen patients with catarrhal disease inhaled the steam vapor of linden tea, whilea control group of 15 patients inhaled vapor from colored water. All patients experienced a certain subjective relief. It was also suggested that the inhalation of a preparation of Tiliae flos had a diaphoretic effect, but this was not documented convincingly.

As a result of on the traditional application of lime flowers, the European Medicines Agency accepted the use of *Tilia*-based traditional herbal medicinal products for

- the relief of symptoms of common cold, and
- relief of mild symptoms of mental stress.

Lime flower can be consumed as a tea (1.5 g of the comminuted herbal substance as a herbal infusion 2–4 times daily) or as liquid extracts prepared with ethanol-water mixtures.

With the former indication, use in children under 4 years of age is not recommended due to the lack of adequate data. For the latter indication, the age limit is 12 years.

- **Side effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. The use of lime flowers is contraindicted in cases of hypersensitivity.

Verification questions

1. What is the therapeutic indication of Iceland moss?
2. What are the pharmacologically active compounds of marshmallow?
3. What are the components of mechanism of action of ivy?
4. What are the active components of thyme?
5. What may be the side-effects of licorice?
6. What is the most frequent side-effects of saponin-containing plants?
7. What is the clinically confirmed effect of Pelargonium?

11. Adaptogens

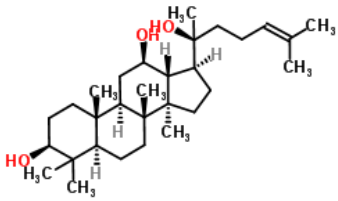
Recurring physical and psychical stress within manageable limits is part of normal life. However, if stress is above the level of tolerance or if it is permanent, it may lead to the exhaustion and damage of the organism. Gastric ulcer, irritable bowel syndrome and anxiety are typical consequences of excessive stress. Stress tolerance, which has remarkable interindividual differences, is decreasing with age. However, resistance to stress may be improved by adaptogens. The group of adaptogens consists of drugs only of herbal origin. Adaptogens have multiple physiological activities and their overall effect is the adaptation to stress, the normalization of physiologic functions affected by stress. This effect is non-specific, i.e., independent from the nature of the stress and results in the prolongation of adaptation phase and prevention of exhaustion.

11.1.1 Ginseng

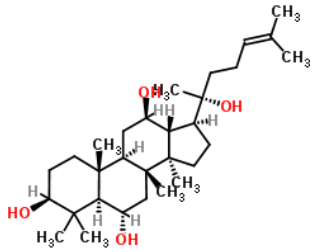
Panax ginseng L. is one of the most popular medicinal plants worldwide. The roots of the plants are widely used in Traditional Chinese Medicine. Its versatile application may be related to the man-like shape of the root. In traditional medicine, ginseng is used for its restorative qualities, to promote physical endurance, vitality and longevity. For these general purposes low doses are taken long-term, but it is also used for more specific medicinal. In the Eurpoean Pharmacopoeia, the roots (Ginseng radix) and the dry extract of the roots (Ginseng extractum siccum) are official.

- **Chemical composition and mechanism of action**

The pharmacologically most important constituents are ginsenosides, which chemically are saponins, however, certain non-saponin components, primarily polysaccharides are also considered as active constituents with favourable effects. Ginsenosides are based on dammarane-type (protopanaxadiol and protopanaxatriol) or oleanolic acid-type skeletons.



protopanaxadiol



protopanaxatriol

The pharmacology of the ginseng has been studied very extensively, and although the antistress (improvement of resistance to physical and metal stress) effect seems to be conclusive, there are many contradictory results in the literature. Individual ginsenosides, contrary to the fact that they are chemically very similar, may have opposite effects. Certain ginsenosides exhibited CNS-depressant effect in animal experiments, others had CNS-stimulant activity. However, this is fully in line with the normalizing effect of adaptogens.

Ginseng has corticosteroid-like action presumably by increasing adrenal steroidogenesis through acting on the pituitary gland (the endocrine effect was observed in intact animals but not in hypophysectomised ones). Increased physical endurance, which may be related to this effect, was described in several animal experiments after the administration of ginseng.

The hypotensive, antiarrhytmic and positive inotropic effect of ginseng extracts and certain individual ginsenosides has been confirmed experimentally. *Panax ginseng* reduced serum cholesterol and triglycerides, and increased high-density lipoprotein levels of animals. It also had antiplatelet effect, presumably by inhibiting thromboxane formation.

Ginseng has hypoglycaemic activity as demonstated in several preclinical trials. Ginsenosides promoted insulin release in pancreas *in vitro*, what is more, the number of insulin receptors was also increased after the administration of ginseng in animal experiments. Hypoglycaemic effect was demonstrated in healthy animals and also after experimental induction of diabetes. Apart from ginsenosides, polysaccharides have also role in this activity.

Antioxidant, antiproliferative and antiviral activities of different ginseng extracts have been demonstrated in *in vitro* studies.

- **Efficacy and indications**

Clinical trials with ginseng usually assess different components of the adaptogenic effect. Although there are quite several human studies, the number of good-quality trials is low (small number of patients, short duration and improperly defined

endpoints). One further drawback of the studies is that the studies products are different commercial products with variable dosages and chemical composition, which makes difficult to draw general conclusions on efficacy.

Interestingly the available clinical data do not support the improvement of physical performance in healthy adults (although there are several trials available, these had usually negative outcomes). In case of cognitive performance, clinical trials supporting efficacy were performed with healthy volunteers, therefore no conclusion can be drawn for therapeutic application. In a double-blind, placebo-controlled study involving healthy individuals, modulation of cerebroelectrical activity was confirmed using EEG. In a double-blind, placebo-controlled study, significant improvement of cognitive performance was observed in those who were taking ginseng. In a further study with similar design, administration of root extract led to significant improvements in speed of memory and attention. Efficacy was also confirmed with combination products (ginseng with caffeine-containing plants or *Ginkgo*).

The hypoglycemic effect of ginseng was not demonstrated in two single-blind, placebo-controlled, crossover studies after the administration of 500 mg dry ginseng root. However, the 200-400 mg ginseng extract reduced blood glucose concentrations in healthy subjects.

The chronic use of ginseng may have effect on life quality and expectancy. A case-control study with ~2000 case–control pairs, regular ginseng consumers had a lower risk of cancer, compared with non-users (odds ratio 0.50). In a cohort study involving more than 4000 people, 55% of the participants with cancer used ginseng previously, whereas 70% of individuals without cancer were taking ginseng. The relative risk of cancer in ginseng users was 0.40. A systematic review of 9 trials reported improvement in at least one quality-of-life measure, but this paper has many weaknesses in design, therefore its conclusions cannot be considered as a firm confirmation of the general effect of ginseng on life quality of healthy or ill subjects.

The European Medicines Agency has not published a monograph on ginseng so far. The usual dose of ginseng roots is 0.5-1 g daily, however in China larger doses (up to 9 g) are used in processed form. The standardized extract G115 has been applied at doses of 100–400 mg daily in clinical studies.

- **Side-effects, interactions & contraindications**

In clinical trials, frequency and character (mostly gastrointestinalof adverse events were similar to those reported for the placebo groups. Consumption of large doses of ginseng together with caffeine-containing drugs was reported to cause "ginseng abuse syndrome", characterized by diarrhea, hypertension and anxiety. However, other authors dispute the existence of this syndrome. Nevertheless, overdosage may lead to nausea, vomiting, cardiovascular symptoms (palpitation).

Based on preclinical and clinical data, ginseng should be used with caution in patients with diabetes and cardiovascular diseases. Although it could be assumed that

ginseng may interfere with oral anticoagulants, clinical data do not support this assumption. The safety of ginseng during pregnancy, breastfeeding and in children has not been established.

11.1.2 Rhodiola

The dried roots and rhizomes of *Rhodiola rosea* L. (Crassulaceae), a plant native throughout the mountains of Europe, Asia and North America, have been used in traditional medicine for centuries. Its name (roseroot, and the Latin name) refers to the rose-like odor of the roots.

- **Chemical composition and mechanism of action**

Its characteristic constituents are phenylalkanoids (the phenylethanoid salidroside, and the phenylpropenoid rosin, rosarian and rosavin) and phenylpropanes (tyrosol). The essential oil content is very low (0.05%). It contains some specific flavonoids (e.g. rhodalidin, rhodionin and rhodiolgidin), phenolic acids and flavonolignans.

Stress-protective effects of *Rhodiola* have been observed in different animal experimental settings (restraint stress, noise stress and chronic mild stress). In further studies, it demonstrated antidepressant-like, anxiolytic-like and stimulating effects, and morphine dependence and signs of nicotine withdrawal could be reduced. According to some results, it has a normalizing effect on the 5-HT level of the central nervous system. *Rhodiola* has an anti-fatigue effect, as confirmed in animal experiments (e.g. it significantly improved exhaustive swimming-induced fatigue).

In diabetic mice, *Rhodiola* decreased blood glucose and glutathione levels. This might be linked to its inhibitory activities on alpha-amylase and alpha-glucosidase.

Neuro-, cardio- and hepatoprotective, antioxidant and anti-inflammatory effects of different extracts and some pure compounds have been confirmed. Salidroside has perspective antiproliferative effects on cancer cells (it induces a cell-cycle arrest and apoptosis).

- **Efficacy and indications**

The improvement of physical and mental performance has been studied in several studies. In a randomized, double-blind, placebo-controlled study, the plant was tested in the treatment of individuals with stress-related fatigue. Significant effects of the extract in comparison with the placebo were observed on symptoms of fatigue and attention, and the treatment decreased the cortisol response to awakening stress. In a further study, the effect of repeated low-dose treatment with a *Rhodiola* extract on fatigue during night duty was investigated among healthy young physicians. A statistically significant improvement in mental fatigue was observed in the treated group after 2 weeks of treatment as compared with placebo.

The adaptogenic (stimulating and normalizing effect) of a *Rhodiola rosea* extract was examined in students during a stressful examination period in a double-blind,

randomized and placebo-controlled study. Significant improvements were seen in physical fitness, mental fatigue and neuromotoric tests in the verum group.

The objective of a randomized double-blind placebo-controlled study was to assess the efficacy and safety of a *Rhodiola* extract in patients with a mild/moderate depression. In actively treated patients, depression, together with insomnia, emotional instability and somatization improved significantly, while the placebo group did not show such improvements.

Although because of methodological problems the clinical evidence is not totally convincing, on the basis of the traditional application *Rhodiola* may be used as a traditional herbal medicinal product

- for the temporary relief of symptoms of stress, such as fatigue and a sensation of weakness.

The daily dose of the roots is 144–400 mg.

Side effects, interactions & contraindications

Use in children, adolescents under 18 years of age and during pregnancy and lactation has not been established due to the lack of adequate data.

Verification questions

1. What is the point of the adaptogenic effect?
2. How can ginseng influence blood glucose level?
3. What may be the long-term effect of ginseng use?
4. What is the indication of *Rhodiola*?

12. Inflammation, pain

Pain relief is one of the most ancient goals of phytotherapy. Besides several traditional and clinically effective plants, the plant kingdom is also the source of modern anti-inflammatory drugs, since the first non-steroidal anti-inflammatory drug (NSAID) was developed from a natural product, i.e. the salicylates of willow bark. In the event of more severe pain, the most widely applied drugs contain a natural alkaloid (morphine) or its derivatives. In some cases, e.g. in the treatment of migraine, phytotherapeutic preparations are able to provide targeted treatment, but some traditional preparations, such as rubefacients, have unspecific, though clinically significant effects.

12.1 Posttraumatic, muscle and articular pain

Mild injuries caused by different traumas (strains, sprains, bruises and contusions) can result in injuries of muscles, edema, hematoma and pain that limit the motion of the affected limb. In modern medicine, non-steroidal anti-inflammatory drugs (administered orally or topically) are the first-choice treatment. Edema and hematoma may be relieved by the local application of heparin.

The phytotherapy of posttraumatic states is based on the application of herbal preparations with anti-inflammatory activities. These are typically applied topically. The available possibilities also include herbal products with anti-edematous effects.

12.1.1 Arnica

Arnica is a genus comprising about 30 species, all native to the mountains of Europe. *Arnica montana* L., the most widely used species, is official in the European Pharmacopoeia. In the Middle Ages, arnica was used as a medical plant with numerous indications, such as muscular pain, phlebitis, gout and rheumatism. According to the definition of the Pharmacopoeia, Arnicae flos consists of the dried flower heads of *Arnica montana* with a sesquiterpene lactone content of at least 0.4%. Arnica tincture (also included in the European Pharmacopoeia) is defined as a tincture produced from *Arnica* flowers with a minimum content of 0.04% sesquiterpene lactones expressed as dihydrohelenalin tiglate. Previously, some national pharmacopoeias (e.g. the German) permitted the use of flowers of *A. chamissonis* to replace *A. montana* since the latter is protected and cannot be cultivated.

Chemical composition and mechanism of action

The biologically active constituents of *Arnica* flowers are pseudoguaionolide-type sesquiterpene lactones (0.3-1%), which can also be found as ester derivatives in the native plant material. The most important constituents are helenalin and 11,13-dihydrohelenanin and their derivatives. The essential oil and flavonoids have no major role in the anti-inflammatory effect.

helenalin

In an *in vitro* experiment, *Arnica* extracts inhibited activation of the transcription factors NF-κB and NF-AT and this effect correlated with their sesquiterpene lactone content. Helenalin and 11,13-dihydrohelenalin (the latter with less pronounced activity) inhibited the activation of NF-κB. A methanolic extract reduced the protein level of inducible NO synthase (iNOS) and COX-2 *in vitro*.

Certain sesquiterpene lactones may cause contact hypersensitivity. In an animal experiment, sesquiterpene lactones and tinctures from *Arnica* were only weak inducers of skin inflammation, and the extracts decreased experimentally induced eczema. In a subsequent experiment, contact hypersensitivity could not be induced, even if the tincture or sesquiterpene lactones were applied undiluted to the inflamed skin.

Efficacy and indications

Besides the experimental and empirical data, clinical studies also support the efficacy of *Arnica*.

In a randomized, double-blind, placebo-controlled study with participants with facial telangiectasia, the efficacy of topical *Arnica* gel on post-laser treatment bruises could not be demonstrated. Similarly, a pilot study with an *Arnica* compress to relieve acute soft-tissue pain did not confirm any superiority over placebo.

In a randomized, placebo-controlled study, patients with chronic venous insufficiency were treated for 3 weeks with an *Arnica* gel or placebo, and in addition all patients received hydrotherapy. The improvement in venous capacity was significant in both groups, but with a significantly better effect in the verum group.

In a small randomized controlled trial, experimentally inflicted bruises were treated topically (ointments containing 5% vitamin K, 1% vitamin K + 0.3% retinol, 20% *Arnica* or white petrolatum, respectively). The improvement associated with 20% *Arnica* was

greater than that with white petrolatum or that with the mixture of 1% vitamin K and 0.3% retinol, but was not greater than that with 5% vitamin K.

In a randomized, double-blind study, patients suffering from hand osteoarthritis were treated either with ibuprofen gel or with *Arnica* gel. There were no differences between the two groups as concerns the pain and hand function improvements. In an open study, *Arnica* gel was used for the treatment of osteoarthritis of the knee for 6 weeks. The treatment resulted in a significant reduction of the total score of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The levels of pain, stiffness and function also demonstrated a significant improvement.

Although the clinical data are not sufficient for a well-established EMA monograph, the traditional use and the empirical knowledge, justify its use as a traditional herbal medicinal product

- for the relief of bruises, sprains and localized muscular pain.

In practice, liquid extracts and semi-solid dosage forms containing 20-50% liquid extract may be used topically.

- **Side-effects, interactions & contraindications**

The most frequent adverse events related to the application of *Arnica* are allergic skin reactions such as itching, redness of the skin and eczema, and in some cases contact dermatitis may also occur. It should be noted that alcohol enhances penetration, and topically applied *Arnica* tincture therefore has much greater allergenicity than semisolid preparations.

Hypersensitivity to the active substance and to other plants of the Asteraceae family is a contraindication of the application. The preparation should not be used on broken skin.

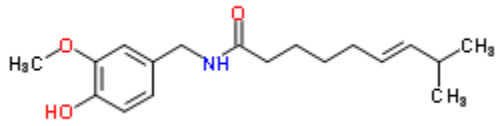
12.1.2 Capsicum

According to the definition in the European Pharmacopoeia, Capsici fructus is the dried ripe fruits of *Capsicum annuum* L. var. *minimum* (Miller) Heiser and small-fruited varieties of *Capsicum frutescens* L. with a minimum 0.4% of total capsaicinoids. The European Pharmacopoeia also contains Capsicum oleoresin, refined and standardised (Capsici oleoresina raffinata et normata, standardized to a content of 12.0-18.0% of total capsaicinoids), Capsicum soft extract, standardized (Capsici extractum spissum

normatum, standardized to a content of 2.0-2.4% of total capsaicinoids), and Capsicum tincture, standardized (Capsici tinctura normata, standardized to 0.020-0.060% of total capsaicinoids).

- **Chemical composition and mechanism of action**

The most characteristic compounds of *Capsicum* are capsaicinoids: 0.3–2%, containing capsaicin as main compound (60-80%), 20-30% dihydrocapsaicin and 1-10% nordihydrocapsaicin. The fruit contains appreciable amounts of ascorbic acid and carotenoids.



capsaicin

The analgesic activity of *Capsicum* extracts is related to their capsaicinoid content. Capsaicinoids act as agonists on the vanilloid receptors (these are transient receptor potential vanilloid (TRPV) channels) located primarily on the ends of substance P-containing axons. These neurons are also responsible for the perception of pain. TRPVs are sensitive to temperature and acidic milieu, and some subtypes (e.g. TRPV1) also to capsaicin. The excitation caused by capsaicinoids leads to excitation of the nociceptors (depolarization of the neurons) and consequently local burning and erythema. This initial phase is followed by a desensitization phase accompanied by a decrease in the pain. Previously (based on animal experiments), it was assumed that the antinociceptive effect is partly due to neuronal damage, but recent studies suggest that the topical application of capsaicin at low concentrations causes only a reversible impairment of the terminals of the C fibers in the skin without affecting the properties of the cell soma. The analgesic effects of *Capsicum* and capsaicin have been confirmed preclinically. In one study, the local application of a capsaicin-containing cream decreased the pain in a peripheral neuropathy (the treatment of neuropathic pain with conventional analgesics is problematic). It was recently was discovered that capsaicin blocks TNFalpha-induced NF-κB activation, which may also play a role in the chronic effect of capsaicin.

The effect of hot pepper on gastric acid secretion is empirical knowledge. This has also been confirmed in animal experiments. The application of chilli to rats resulted in a significant rise of hydrochloric acid production in the stomach, without increasing the peptic activity. In a further experiment, capsaicin increased the gastrointestinal transit time in rats; this was limited only to the stomach, the total gut transit time was unaffected. In a human experiment, the gastric emptying was slower, while the whole

gut transit was faster after chilli consumption, but there was no significant difference in orocecal transit time. The gastroprotective effect of capsaicin was reflected in a study where the administration of capsaicin to rats significantly enhanced the activities of the antioxidant enzymes (catalase, superoxide dismutase, glutathione reductase and glutathione-5-transferase) in the gastric and intestinal mucosa and had a positive effect on mucosal glycoproteins.

- **Efficacy and indications**

Clinical trials with *Capsicum* extract or capsaicin and with semi-solid dosage forms indicated efficacy in indications relating to muscular or articular pain. In a randomized double-blind study, patients with chronic soft tissue pain were treated with a cream containing either capsaicin or placebo. After 3 weeks of treatment, the median pain sum score had decreased by 49% (capsicum group) or 23% (placebo group). In a double-blind, randomized study, a *Capsicum* plaster was compared with a placebo for 3 weeks in patients with non-specific back pain. The rate of responders in the *Capsicum* group was 60%, against 42% in the placebo group. In a similar study, the compound pain subscore was reduced by 42% (*Capsicum*) or 31% (placebo) from the values on entry. The responder rate was 67% versus 49%. The efficacy of a capsaicin gel was compared with that of placebo in patients with knee osteoarthritis in a double-blind, randomized trial. The treatment was more effective than the placebo in terms of pain and stiffness reduction. In a double-blind randomized study, patients with osteoarthritis or rheumatoid arthritis received capsaicin or placebo for four weeks. A significantly greater relief of pain was reported by the capsaicin-treated patients than the placebo patients throughout the study; after four weeks of capsaicin treatment, rheumatoid arthritis and osteoarthritis patients demonstrated mean reductions in pain of 57% and 33%, respectively. An 8-week double-blind, parallel study compared the efficacy of topical capsaicin and oral amitriptyline in patients with painful diabetic neuropathy involving the feet. The topical capsaicin and oral amitriptyline produced equal and statistically significant improvements in pain over the course of the study. Further placebo-controlled studies confirmed the superiority of capsaicin over placebo in this disease. In a double-blind, vehicle-controlled study with patients with chronic postherpetic neuralgia, the efficacy of topically applied capsaicin cream was confirmed.

In another study, the effect of capsaicin (applied as 2.5 g chili pepper powder/day) on dyspeptic symptoms was analyzed. The 5-week study was performed on patients with functional dyspepsia and without gastro-esophageal reflux disease or irritable bowel syndrome. The overall symptom score and the epigastric pain, fullness and nausea scores of the treated group were significantly lower than those of the placebo group. However, a study on the postprandial gastrointestinal symptoms of patients with diarrhea-predominant irritable bowel syndrome (IBS-D) revealed that chilli ingestion produced more abdominal pain and burning in IBS-D patients than in healthy

volunteers, but was associated with similar oral burning symptoms. In a further study, hot pepper had no inhibitory effect on *Helicobacter pylori* in infected patients.

According to the (draft) monograph of the European Medicines Agency, the use of *Capsicum* is well-established

- for the relief of muscle pain such as lower back pain.

Capsicum extracts may be used in plasters and in semi-solid dosage forms. 1 medicated plaster should contain 171-552 mg of soft extract of Capsici fructus, corresponding to 4.8-11 mg of capsaicinoids. A maximum of 1 plaster per day should be applied to the affected area for at least 4 and up to 12 hours. There should be an interval of at least 12 hours before a new plaster is applied at the same application site. Different preparations of semi-solid dosage forms containing 50 mg of capsaicinoids/100 g should be applied 2-4 times daily.

The treatment should be continued until the relief of pain is achieved, but after 3 weeks of use a break of at least 2 weeks is required.

- **Side-effects, interactions & contraindications**

In cases of hypersensitivity to capsaicinoids or on broken skin or wounds, *Capsicum* preparations should not be applied. Their use is not recommended in children below 12 years of ag,e due to the lack of data on safety and efficacy. The preparations should not be applied near the eyes or to mucous membranes. Skin hypersensitivity and allergic reactions (e.g. urticaria, blisters or vesiculation at the application site) may occur.

Animal studies revealed shown reproductive toxicity after high subcutaneous doses of capsaicin. Capsaicin crosses the placenta and may pass into the breast milk. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use of capsaicin during pregnancy and lactation is not recommended.

12.1.3 Comfrey

Symphytum officinale L. (Boraginaceae) or common comfrey is a perennial plant native to Europe and Asia. In folk medicine, both its roots and its leaves have been reported to be used for medicinal purposes. In some countries, the leaves are consumed as vegetables.

Comfrey has been used as a poultice for blunt injuries, fractures and dermatological conditions since ancient times. In the Middle Ages, it was popular for healing broken bones. Until quite recently, it was also used internally in folk medicine for different diseases.

- **Chemical composition and mechanism of action**

Comfrey roots contain allantoin (0.75-2.5%), steroidal and triterpene saponins, caffeic acid derivatives and up to 0.4% of pyrrolizidine alkaloids (e.g. symphytine, lycopsamine

and lasiocarpine). The latter group of compounds have no role in the therapeutic effect, but possess hepatotoxic, carcinogenic and mutagenic activities.

Symphytum extracts possess anti-inflammatory activites, but not much is known of the active constituents. The lipophilic fractions inhibit COX-1 and COX-2 enzymes. A glycopeptide exhibited an antiphlogistic effect in an animal experiment, and rosmarinic acid also exerted such activity.

The wound-healing activity is linked to the allantoin content, though there are no confirmatory data to support this.

- **Efficacy and indications**

Four randomized, controlled studies and one open-observational study were performed with a special comfrey extract (with lowered pyrrolizidine alkaloid content). In a double-blind, multicenter, randomized, placebo-controlled study, efficacy was assessed in patients with unilateral acute ankle sprains. In the verum group, there was a significantly stronger alleviation of pain, the reduction of swelling was significantly more rapid and the joint mobility was significantly increased in the verum group as compared with the placebo group.

In patients suffering from osteoarthritis of the knee, efficacy was assessed in a randomized, double-blind, placebo-controlled clinical trial. The pain at rest and movement, the quality of life and the mobility of the knee improved significantly in the verum group relative to the placebo group.

In a double-blind, randomized clinical trial, patients with acute upper or low back pain were treated with verum or placebo ointment. There was a significant treatment difference in favor of comfrey extract as regards the pain intensity.

In a single-blind, randomized study, the efficacy of *Symphytum* was compared with that of diclofenac gel in the treatment of acute unilateral ankle sprain. After 7 days of treatment, the pain at rest and at movement had improved and the swelling had reduced significantly, without difference between the two groups.

These results cannot be used to prepare a well-established use monograph for comfrey, since the exact composition of the extract (i.e. the manner of pyrrolizidine alkaloid removal) is not known. Although the traditional use of comfrey is widespread in Europe, the long-standing use to meet legal criteria could be documented only in the case of one extract (a liquid extract prepared by extraction with ethanol 65% (v/v) followed by partial evaporation and adjustment to a DER 2:1). For this, a traditional-use monograph was published by the European Medicines Agency with the indication of

- symptomatic relief of minor sprains and bruises.

The semi-solid containing 10% of liquid extract should be applied 2 times daily. It is not to be used for more than 10 days. The pyrrolizidine alkaloid content in the daily dose should be limited to below 0.35 μg/day for adults.

- **Side effects, interactions & contraindications**

It should not be applied to broken or irritated skin. Contact with the eyes or mucous membranes should be avoided. Its use in children and adolescents under 18 years of age and in pregnant and lactating women has not been established due to the lack of adequate data. With regard to the hepatotoxic effects of pyrrolizidine alkaloids (and the fact that the rate of their absorption through human skin is not known), the application of comfrey in these sensitive patient groups should be avoided.

12.1.4 Ash

Fraxini folium is by definition the dried leaves of *Fraxinus excelsior* L. or *F. angustifolia* Vahl (syn. *F. oxyphylla* M. Bieb). or of hybrids of these two species, with a minimum of 2.5% of total hydroxycinnamic acid derivatives, expressed as chlorogenic acid.

Fraxinus is a genus of deciduous trees distributed in the northern hemisphere. As a result of certain beliefs, the ash tree was greatly respected in several parts of Europe. Since ancient times, the leaves and the bark have been used as a diuretic and in rheumatic remedies. In the last hundred years, the leaves have primarily been used against fever and rheumatism. The bark is still utilized in folk medicine, but is not part of official medicine.

- **Chemical composition and mechanism of action**

Ash leaves contain a marked amount of flavonoids (0.5-2%), with rutin as the main component. Phenolic acids (including chlorogenic acid) and secoiridoids are characteristic compounds. The leaves contain coumarins in traces and mannitol in a concentration of about 20%.

Extracts of the leaves of *Fraxinus excelsior* suppressed the growth of different fungi. In animal experiments, an aqueous extract of the leaves dd not display a diuretic effect, whereas the alcoholic extract significantly increased the urinary Na^+ concentration. Some secoiridoids of the plant have demonstrated anti-inflammatory activities preclinically.

- **Efficacy and indications**

The effectiveness of the traditional uses is not documented, and a monograph on a well-established use was therefore not granted by the European Medicines Agency. The accepted indications based on the traditional applications are for

  - the relief of minor articular pain and

- to increase the amount of urine so as to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

The daily dose is 10-30 g of the comminuted herbal substance as a tea.

- **Side-effects, interactions & contraindications**

In the event of hypersensitivity to the plant and in conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease), the use of ash leaves is contraindicated. Safety during pregnancy and lactation has not been established.

12.1.5 Devil's claw

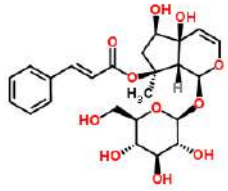
Harpagophytum species (Pedaliaceae) are native to the Kalahari desert and the Namibian steppe region. Their tuberous secondary roots are commonly called "devil's claw" because of their shape.

In folk medicine, *Harpagophytum procumbens* is most widely used. Nevertheless, in the European Pharmacopoeia the drug Harpagophyti radix may be derived from two species, *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne.

In African folk medicine, devil's claw has been widely used for various medicinal purposes. In Europe its application is narrower, focusing on its use in articular pain and in improving appetite. *Harpagophytum* appeared as a medicine on the European market in the 1970s for the treatment of arthrosis, but on the basis ofits bitter taste it was first used to treat gastrointestinal problems.

- **Chemical composition and mechanism of action**

Iridoid glucosides (0.5–3%) are the pharmacologically most important secondary metabolites of *Harpagophytum* roots. The most important representatives of this group are harpagoside (the main iridoid), harpagide, procumbide, procumboside and their derivatives.



harpagoside

The *Harpagophytum procumbens* extract suppressed the expression of COX-2 and iNOS mRNAs *in vitro*, resulting in the inhibition of PGE_2 synthesis. The methanol extract of the plant inhibited TPA-induced COX-2 expression in mice by different

mechanisms. Further, human leukocyte elastase and the release of TNF-alpha from human monocytes was inhibited *in vitro*.

The aqueous extracts of *Harpagophytum procumbens* were found to have analgesic and anti-inflammatory activities in different animal models, but the isolated compounds (harpagoside and harpagogenin) were not or not very effective. Orally administered preparations proved inactive. This may be a result of the inactivation of the active components by the acidity of the stomach. Indeed, acid treatment of an extract abolished its anti-inflammatory activity previously reported after *i.p.* application.

- **Efficacy and indications**

In a randomized double-blind study involving patients with coxarthrosis, the successive reduction of an ibuprofen dose of 400 mg twice daily was investigated over a period of 20 weeks, during concomitant treatment with either *Harpagophytum* extract or placebo. An increase in pain score by a maximum of 20% in the period without ibuprofen (which was regarded as a clinically relevant response) was fulfilled by 70% of the patients in the *Harpagophytum* group, but by only 40% of patients in the placebo group.

A randomized, double-blind study compared an aqueous extract of *Harpagophytum* (containing 60 mg of harpagoside) and rofecoxib (12.5 mg per day) in the symptomatic treatment of chronic low back pain. The number of pain-free patients increased during the course of treatment in both groups. No statistically significant difference was observed between the two treatments.

In a 4-month, double-blind, randomized, multicentric trial trial, the efficacy of *Harpagophytum* (435 of g drug powder) was evaluated compared to diacerrhein (an NSAID) in patients with osteoarthritis of the knee or the hip. The primary efficacy endpoint was defined by the level of spontaneous pain. No differences were found between the treatments.

Several open studies have additionally been carried out, but those cannot be used to assess the efficacy of *Harpagophytum*.

The clinical data are not sufficient to serve as the basis of well-established use of the plant. Therefore, it might be used as traditional herbal medicinal products

- for the relief of minor articular pain or
- for the relief of mild digestive disorders such as bloating and flatulence and where there is a loss of appetite.

The posology as a tea in articular pain is 4.5 g daily, whereas the daily dose of the powdered herbal substance is 1.35 g. Several liquid (15 ml), dry (0.3-2.7 g) and semisolid (10 ml) extracts may also be used. For digestive disorders, the daily dose is 1.5 g as a tea or 10 ml of a soft extract.

The duration of use should be restricted to a maximum of 2 weeks in cases of digestive problems and 4 weeks in articular pain.

- **Side effects, interactions & contraindications**

Gastrointestinal disorders (diarrhea, nausea, vomiting and abdominal pain), central nervous system symptoms (headache and dizziness), allergic skin reactions may occur in the course of the application of devil's claw. In the event of hypersensitivity, its use is contraindicated.

Caution should be taken when *Harpagophytum* is administered to patients affected by cardiovascular disorders.

Use in children and adolescents under 18 years of age, in pregnancy and in lactation is not recommended because of the lack of available experience.

12.1.6 Willow

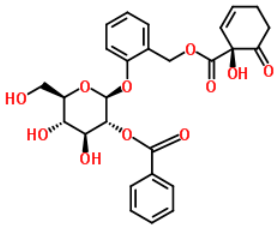
From among the several species of the *Salix* genus, native mainly to Europe and Asia, *Salix alba, S. nigra* and *S. purpurea* were earlier considered to be the most important medicinal plants, but other species have recently become more widely applied and acknowledged because of their higher salicylate content. According to the European Pharmacopoeia, Salicis cortex is the whole or fragmented dried bark of young branches or whole dried pieces of current-year twigs of various species of the genus *Salix*, including *S. purpurea* L., *S. daphnoides* Vill. and *S. fragilis* L. The drug should contain not less than 1.5% of total salicylic derivatives, expressed as salicin. A willow bark dry extract, also official in the European Pharmacopoeia, contains a minimum of 5% of total salicylic derivatives, expressed as salicin.

Willow bark has a long tradition as an antipyretic, and as an antiphlogistic since the 18th century. After the identification of its active constituent, salicin, and the synthesis of salicylic acid (and acetylsalicylic acid) based on this herbal metabolite, interest in willow bark has been lost.

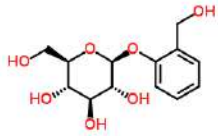
- **Chemical composition and mechanism of action**

The salicylate content of the above-mentioned species is variable (1-10%). Willow bark contains salicylates as glycosides. Major glycosides are salicortin and tremulacin.

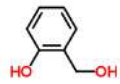
Salicin is the most active anti-inflammatory compound in willow. In wllow bark it can be found in the form of "prodrugs" (glycosides); these are hydrolyzed to salicin, which is further metabolized to saligenin (salicyl alcohol)enzymatically and by the flora of the lower intestines, and finally to salicylic acid after absorption.



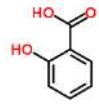
tremulacin



salicin



saligenin



salicylic acid

Salicin and tremulacin exerted antiphlogistic activity in different *in vitro* test systems, with a delayed onset of action in comparison with salicyl alcohol or acíetylsalicylic acid. A *Salix* extract inhibited prostaglandin synthesis *in vitro* and COX-1 and COX-2 enzymes. It was confirmed experimentally that polyphenols also contribute to the overall enzyme-inhibitory effect of willow bark.

Salicin (and willow bark extract) does not induce gastric lesions in rats since active (COX-inhibitory) metabolites are formed after passing through the stomach as intact glycosides. In contrast with acetylsalicylic acid, thrombocyte aggregation is less effectively inhibited by willow bark (an extract containing 240 mg of salicin as compared with 100 mg of acetylsalicylic acid). Pharmacokinetic studies indicate that, based on serum salicylate concentrations, 240 mg of salicin as an extract is bioequivalent to 50-85 mg of acetylsalicylic acid.

- **Efficacy and indications**

In a randomized, placebo-controlled double-blind clinical trial patients with osteoarthritis of the hip or knee were treated daily for 2 weeks with a willow bark extract containing 240 mg of salicin or placebo. A (borderline) significant superiority of willow bark over placebo with regard to pain relief was observed.

In a randomized, double-blind controlled clinical trial, willow bark extract was compared with diclofenac and placebo. An analysis of the data on patients with osteorathritis of the hip or knee indicated that the pain scores decreased for willow bark (though not significantly), but significantly for diclofenac. There have been several other open-label studies that have supported the efficacy of willow bark over placebo in different articular pain conditions.

From the clinical evidence, one dry extract (8-14:1, ethanol 70%, 15% total salicin) was considered by the European Medicines Agency to possess well-established use

- for the short-term treatment of low back pain.

The daily dose is 1572 mg of dry extract.

For further extracts and the comminuted herbal substance, the clinical evidence is insufficient, but their documented long-standing use and the plausibility of the effect

due to their salicin content, led to a traditional use monograph being granted with the indication of

- minor articular pain,
- fever associated with common cold, or
- headache.

The doses of the dry extracts are about 1.2 g, while those of the liquid extract and tincture are 9-24 ml. 1-3 g of comminuted herbal substance should be used for tea preparation, 3 or 4 times daily. The posology of the powdered herbal substance is 260-500 mg three times daily.

- **Side effects, interactions & contraindications**

In the event of chronic use, the duration should be restricted to a maximum of 4 weeks.

The use of willow bark is contraindicated in cases of hypersensitivity to salicylates or to other NSAIDs (e.g. a history of angioedema, bronchial spasm or chronic urticaria in response to salicylates or to other NSAIDs), asthma, active peptic ulcer disease and in the third trimester of pregnancy. It is contraindicated in children and adolescents under 18 years of age because of the risk of Reye's syndrome.

Willow bark may increase the effects of anticoagulants such as coumarin derivatives. Allergic reactions such as rash, pruritis, urticaria, asthma or exanthema, and gastrointestinal symptoms such as nausea, vomiting, abdominal pain, dyspepsia, heartburn or diarrhea, may occur.

Its use during the first and second trimesters of pregnancy and during lactation is not recommended.

12.1.7 Meadowsweet

Filipendula ulmaria (L.) Maxim. (syn.: *Spiraea ulmaria* (L.)) is one of the plants used in phytotherapy that has direct anti-inflammatory activity. It is official in the European Pharmacopoeia as Filipendulae ulmariae herba, which consists of the whole or cut, dried flowering tops of *Filipendula ulmaria*. The Pharmacopoeia requires a minimum of 1 ml/kg of steam-volatile substances in the plant material.

The medicinal use of the plant has been documented from the 16th century. Originally it was applied as a diuretic and antirheumatic, but its application has shifted toward use as an antiphlogistic.

- **Chemical composition and mechanism of action**

The plant material contains about 0.2% essential oil, with salicylates as the main components (mainly salicylaldehyde, up to 70%). However, the salicylates are mostly present in the form of glycosides (0.5%). The aerial parts contain flavonoids, and especially quercetin and kaempferol derivatives.

Most of the anti-inflammatory activity of the plant is related to its salicylate content, though flavonoids also contribute to the effect. The aqueous extract of the plant inhibits both prostaglandin biosynthesis and the platelet activation factor-induced release of elastase. Antipyretic activity has been documented in animal experiments.

A flavonoid-rich extract inhibits xanthine oxidase inhibitory activity *in vitro*. The effect on gastric ulcers is contradictory. This may be explained by the different salicylate/flavonoid contents of the extracts, the former being ulcerogenic, and the latter having ulcoprotective effects. Orally administered flavonoids, and also flower extracts from *Filipendula ulmaria* (rich in flavonoids), appear to have a protective effect against experimentally induced lesions of the rat stomach.

- **Efficacy and indications**

Although there have been no human studies to support the efficacy, the effectiveness of *Filipendula ulmaria* may be substantiated on the basis of its salicylate content and the empirical knowledge gained through its application. On this basis, meadowsweet may be used as a traditional herbal medicinal product

- for the relief of minor articular pain and
- for the supportive treatment of common cold.

As herbal tea, the daily dose is 2-18 g; as powdered herbal substance, it is 250-1500 mg. The daily dose of the tincture is 6-12 ml. Preparations are not to be used for more than 4 weeks.

The flowers may be used with the same indications, in a daily dose of 2.5-6 g, as an infusion.

- **Side-effects, interactions & contraindications**

In cases of hypersensitivity to salicylates, the use of meadowsweet is contraindicated. Its use in children and adolescents under 18 years of age has not been established due to the lack of adequate data. Safety during pregnancy and lactation has not been established.

12.2 Migraine, headache

Tension type headache is the most common type of headache, accounting up to 90% of the cases and as many as 80% of the population experience tension headache at least once during their lifetime. The exact underlying mechanisms is not known, but peripheral pain mechanisms are most likely involved. If tension headache is chronic, peripheral and central pain mechanism are also involved. The therapy of tension headache relies on the application of non-steroid anti-infammatory drugs. From plants, salicylate-containing grugs, e.g willow bark may be applied. Peppermint oil is a unique tool which allows topical, clinically confirmed therapy for headache.

Migraine is a neurological disease accompanied by severe headache. The therapy of migraine is complex, for pain management usually NSAIDs are applied. Preventive treatment includes the application of differend medicines; from phytotherapeutics, feverfew may be applied.

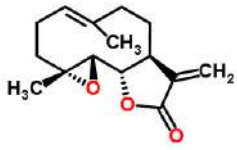
12.2.1 Feverfew

Tanacetum parthenium (L.) Schultz Bip. (Asteraceae) is indigenous to South-East Europe. Its traditionally used plant parts, the above-ground parts, are official in the European Pharmacopoeia. Tanaceti parthenii herba consists of the dried, whole or fragmented aerial parts of *Tanacetum parthenium*, and it contains no less than 0.2% of parthenolide.

In folk mediine it has been applied primarily to treat gynecological disorders and to reduce fever. Its contemporary use goes back to the 1970s; some patients reported that the plant was effective in preventing migraine attacks.

- **Chemical composition and mechanism of action**

Sesquiterpene alpha-methylenebutyrolactones are characteristic compounds of the plants. A major representative of this group is parthenolide, the concentration of which may reach 1%. Further major secondary metabolites are the flavonoids and the monoterpenes of the essential oil.



parthenolide

The exocyclic alpha-methylene group of parthenolide has an important role in its bioactivity. This moiety reacts with the sulfhydryl groups of proteins.

Parthenolide has anti-inflammatory activity. It inhibits the expression of COX-2 and proinflammatory cytokines and nitric oxide production by inducible nitric oxide synthase (iNOS) *in vitro*. The anti-inflammatory effects of different extracts have been demonstrated in animal experiments.

The extract of the plant inhibits blood platelet aggregation. The release of serotonin from platelets induced by various aggregating agents was inhibited.

Feverfew extracts and parthenolide inhibit smooth muscle contractility *in vitro*, and also inhibit the neuronal release of 5-HT, but in contrast with some anti-migraine medicines) without interfering with the 5-HT receptors. A feverfew extract inhibited stimulated histamine release *in vitro*.

- **Efficacy and indications**

Feverfew is applied in modern phytotherapy with the very specific indication of preventing migraine attacks. Some of its pharmacological effects overlap with those of certain anti-migraine medicines, e.g. the inhibition of blood platelet aggregation and 5-HT secretion similar to the effects of triptans.

A double-blind placebo controlled-trial involving patients who already ate fresh leaves of feverfew daily as prophylaxis against migraine was carried out. The patients were allocated randomly to receive either freeze-dried feverfew leaves or identical placebo capsules. The treatment with feverfew was associated with a reduction in the number and severity of the attacks and the frequency of vomiting in a two-month period, while the duration of the individual attacks was unaltered.

In a double-blind crossover trial on patients with migraine one group received placebo for 30 days, while the other continued taking feverfew. In the first crossover phase, there were further reductions in the migraine severity and the severity of nausea and vomiting in the feverfew group, and an increase in severity in the placebo group.

The efficacy of a supercritical extract of feverfew in migraine prevention was investigated in a randomized, double-blind, placebo-controlled study with migraine patients. After 16 weeks of treatment, the migraine frequency was significantly decreased in the feverfew group as compared with the placebo group.

In view of its preclinically confirmed effect and the clinical and empirical evidence, feverfew appears to be suitable for the prevention of migraine attacks. However, the European Medicines Agency did not find the body of evidence sufficiently convincing to grant a well-established use monograph for the plant. Therefore, on the basis of its long-standing use, the use of feverfew is accepted as a traditional herbal medicinal product

- for the prophylaxis of migraine headaches after serious conditions have been excluded by a physician.

The average daily dose of powdered feverfew leaf is 100 mg.

- **Side effects, interactions & contraindications**

Its use in children and adolescents under 18 years of age and during pregnancy and lactation is not recommended due to the lack of adequate data.

Gastrointestinal disturbances may occur as adverse effects. In cases of hypersensitivity to feverfew and other plants of the Asteraceae family, its use is not recommended.

Verification questions

1. What is the therapeutic indication of comfrey?
2. What are the pharmacologically active constituents of devil's claw?
3. What is the mode of action of *Capsicum*?
4. What are the active components of willow bark?
5. What is the clinical effect of feverfew?

13. Skin disorders

The skin is composed of two layers, the epidermis and the dermis. The epidermis consists of 5 layers, and only the deepest one, the germinative layer, is able to reproduce itself and form new cells. The connective tissue, containing sudoriferous and sebaceous glands, is part of the dermis. The integrity and physiological functioning of this very complex system may be affected on different levels. However, treatment is usually carried out cutaneously (though there are some instances of oral treatment too). In the treatment of inflammations, infections, traumas and different lesions, a series of medicinal plants containing different active components may be applied. In order to achieve a targeted therapy, the active constituents of the products must reach different layers of the dermis and/or epidermis; nevertheless, a systemic effect is usually undesirable. In the dermal application of medicinal plants, therefore much depends on the pharmaceutical form (cream, ointment, lotion, etc.) and the vehicles used.

13.1 Inflammatory skin disorders

Various skin disorders are caused by a superficial injury of the skin, followed by infection and inflammation. Inflammation may be a result of different causes, e.g. burns.

Eczema and atopic dermatitis involve chronic inflammation of the skin, accompanied by pruritus, erythema, exudation and crusting. In simple forms of inflammatory skin disorders, herbal products may ensure causal therapy, whereas in cases of eczema the goal of the treatment is the temporary relief of the symptoms.

In the treatment of inflammatory skin disorders, plants with different mechanisms of action may be applied. One cornerstone of the therapy is the application of plants with confirmed anti-inflammatory activity. This is usually achieved similarly to synthetic antiphlogistics (e.g. inhibition of the enzyme COX), but the the manner in which herbal extracts act is more complex. For example, camomile acts primarily by inhibiting COX through its azulenes, but the overall effect is a result of the activities of polysaccharides, flavonoids and bisabolol derivatives.

Herbal preparations with strong antimicrobial activities are indispensable constituents of preparations intended to be used for infectious diseases. These are usually essential oils with a broad antibacterial and antifungal spectrum.

A very special group of phytotherapeutics applied in inflammatory skin diseases are the astringents. These contain water-soluble polyphenolic substances which coagulate proteins, and thereby exert antimicrobial and anti-inflammatory action. Adstringents decrease exudation by coagulating the superficial injured tissue and

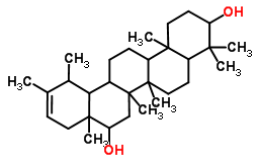
creating a protective layer, thereby promoting wound healing. These compounds possess mild local painkiller activity.

13.1.1 Marigold

Calendula officinalis L. has been used in the traditional medicine for centuries. Rarely, it has been applied internally, but due to the lack of safety and efficacy data only the cutaneous application is acceptable in modern therapy. The petals have been used in salads or as a replacement for saffron as a food colorant. The name marigold may derive from "Mary's Gold", referring to the use of the flowers in early Roman Catholic events in some countries. According to the European Pharmacopoeia, Calendulae flos is the whole or cut, dried, fully-opened flowers, which have been detached from the receptacle, of the cultivated, double-flowered varieties of *Calendula officinalis* L. The drug should contain not less than 0.4% of flavonoids, calculated as hyperoside.

- **Chemical composition and mechanism of action**

The pharmacologically most important constituents are the triterpene derivatives, including free and esterified triterpene mono-, di- and triols (2-10%; mainly faradiol derivatives) and triterpene saponins. The drug contains polysaccharides, carotenoids (5%, predominantly lutein and zeaxanthine), flavonoids and coumarins and essential oil (comprising mainly of sesquiterpenes).



faradiol

The anti-inflammatory effect of marigold has been reported in animal experiments. One of the most active substances is the triterpene diol faradiol, with a molar activity comparable to that of indomethacin. Faradiol esters and monools are less active. The essential oil, the flavonoids and different extracts of the plant inhibit the growth of several bacteria and fungi.

A water extract of the drug exerted an angiogenic effect *in vitro*, referring to the wound-healing activity of the plant. Dry 70% ethanolic and aqueous extracts of *Calendula* flower accelerated the healing of surgically inflicted skin wounds in rats.

- **Efficacy and indications**

In an observational study, patients with venous leg ulcers were treated with a *Calendula* extract-containing cream or placebo for 3 weeks. In the treated group, a significant acceleration of wound healing was observed.

In a randomized, controlled, open study patients with 2nd or 3rd degree burns were treated with either a *Calendula* ointment, a proteolytic ointment or a control (vaseline). A slightly significant difference in favor of the *Calendula* over the vaseline was observed.

In a phase III randomized single-blind trial, *Calendula* was compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. Patients who had been operated on for breast cancer and who were to receive postoperative radiation therapy were treated on the irradiated fields. The occurrence of acute dermatitis of grade 2 or higher was significantly lower following the use of *Calendula* in comparison with trolamine.

Based on the folk medicinal application of the plant, marigold may be used as traditional herbal medicinal products

- for the symptomatic treatment of minor inflammations of the skin (such as sunburn) and as an aid in the healing of minor wounds, and
- for the symptomatic treatment of minor inflammations in the mouth or the throat.

An infusion for cutaneous and oromucosal application should be prepared from 1-2 g of dry flowers. Externally, different liquid extracts may be applied. As a gargle or mouth wash marigold tincture should be applied in a 2% solution.

- **Side-effects, interactions & contraindications**

Hypersensitivity to plants of the Asteraceae (Compositae) family is a contraindication of the treatment. Skin sensitization may develop as an adverse effect in cases of cutaneous application.

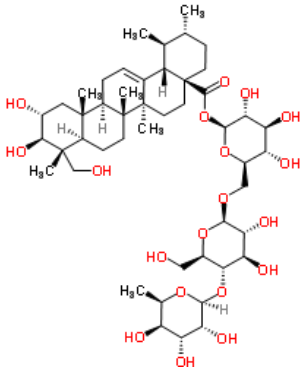
13.1.2 Centella

Centella asiatica (L.) Urban (syn. *Hydrocotyle asiatica* L.) is a perennial herb belonging in the plant family Apiaceae, growing in damp areas in Asian and African tropical countries. According to the European Pharmacopoeia, the herbal substance consists of the dried, fragmented aerial parts, containing a minimum of 6% of total triterpenoid derivatives, expressed as asiaticoside.

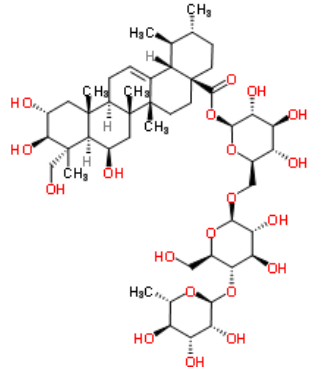
Centella asiatica has been applied in the ancient traditional Chinese and in Indian Ayurvedic medicine for about 3000 years, for very varied purposes. In Malaysia, this herb is commonly eaten fresh as a vegetable, and is also said to have beneficial effects in improving memory and in treating wounds. In Europe, different *Centella asiatica* products are used in medicine to treat wounds or as cosmetic preparations in the area of skin care. Medicinal products containing a special extract, Madecassol® (see below), are used orally to improve the symptoms of a chronic venous insufficiency.

- **Chemical composition and mechanism of action**

The therapeutically important components of *Centella* are the triterpenoid glycosides asiaticoside and madecassoside (= asiaticoside A) and their respective aglycones (asiatic acid and madecassic acid). The total amount of triterpenes varies in the interval 1-8%. *Centella asiatica* leaves are rich in carotenoids and flavonoids, and also contain polysaccharides.



asiaticoside



madecassoside

In the literature, experimental data can be found on the following special extracts: Madecassol® or Centellase® or Blastoestimulina®, TECA, TTFCA and TTF, all containing

40% of asiaticoside and 60% of the aglycones (asiatic acid and madecassic acid). These (practically identical) highly purified extracts, fractionated and enriched in triterpenic acid and triterpenic sugar ester fractions, have a long history of use in Europe for the therapy of wounds.

The pharmacological activities of *Centella asiatica* extracts have been investigated in several preclinical studies, including animal experiments. The medicinal effects are attributed primarily to the triterpene saponins. Topically applied preparations accelerate wound healing, stimulating epithelization and increasing the rate of wound contraction. This effect has also been observed in the case of oral administration. Madecassoside facilitated wound closure in a time-dependent manner after oral treatment. Asiaticoside increased tensile strength and collagen content and resulted in the better epithelization of experimental wounds. Asiaticoside has been shown to induce collagen synthesis in human dermal fibroblast cells. *Centella asiatica* promoted angiogenesis in an experimental model. The application of asiaticoside at doses as low as 10^{+8}-10^{+12}% facilitated burn wound repair. This might be due to the promotion of angiogenesis during skin wound repair as a result of the stimulation of VEGF (vascular endothelial growth factor) production.

In a human study, a special extract improved venous wall alterations in chronic venous hypertension, protecting the endothelium. Serum enzymes involved in the mucopolysaccharide metabolism (beta-glucuronidase, beta-*N*-acetylglucosaminidase and arylsulfatase) were reduced in patients with varicose veins, thereby causing a protecting effect on the connective tissue and the vascular wall.

The marked antioxidant and antimicrobial activities of different extracts have been observed in several studies. The antiphlogistic activity of the extracts may also play a role in the clinical efficacy.

In a study carried out on animals, the extent of radiation injury was reduced after the topical application of a *Centella* product. Aqueous extracts of *Centella asiatica* inhibited keratinocyte replication, which suggests the potential use of the plant extracts as a topical anti-psoriatic agent.

The effects of *Centella asiatica* and asiaticoside in the prevention of experimentally induced gastric lesions in animals were confirmed in a series of experiments.

The aqueous extract of the plant lrd to an improvement in the learning and memory of rats. An alcoholic extract dose-dependently increased the GABA level in rats, reflecting to the anxiolytic effect of the plant. The anxiolytic effect was confirmed in animal experiments (elevated plus-maze test and hole-board test involving rats). A more rapid functional recovery and increased axonal regeneration and neuronal dendritic growth stimulation were confirmed in animals.

Certain studies report the chemopreventive, antimutagenic and antiproliferative effects of different esxtracts.

Efficacy and indications

Six studies (2-8 weeks) were carried out to assess the efficacy of TTFCA in patients with a chronic venous insufficiency. The endpoints investigated were the filtration rate, PO_2, PCO_2, resting flux, permeability, edema, ankle swelling and subjective symptoms. These studies showed that TTFCA dose-dependently (60-180 mg/day) ameliorated the endpoints.

A multicenter, randomized, double-blind placebo-controlled study on patients (duration: 2 months) with venous insufficiency revealed that TECA was significantly more effective in reducing heaviness in the lower limbs and edema, and in the overall evaluation by the patient.

A placebo-controlled, 12-month-long study was designed to evaluate the efficacy of TTFCA in patients with atherosclerosis. TTFCA was used at a dose of 180 mg daily. No significant changes were observed in the controls, whereas a qualitative increase in plaque homogeneity was observed in the TTFCA group and the plaque size did not increase (in contrast with the control group).

Patients with diabetic microangiopathy were studied in a placebo-controlled study. The administration of 120 mg of TTFCA daily for 6 months significantly improved the microcirculatory parameters and decreased capillary permeability.

The effect of skin aging was studied with several cosmetic preparations. A randomized double-blind study was carried out on the photoaged skin of female volunteers to investigate the effects of topically applied 5% vitamin C and 0.1% madecassoside. The cream was applied twice daily for 6 months to the face, and to the assigned half of the neck and upper chest and one of the arms of each volunteer, whereas the other half of the neck and the other arm received the control cream. After the treatment, significant improvements of the clinical scores for deep and superficial wrinkles, suppleness, firmness and skin hydration were observed. Two-thirds of the subjects exhibited an improvement, and the reappearance of a normally structured elastic fiber network.

Prophylaxys with an antistria cream containing a *Centella asiatica* extract as active constituent was assessed in a double-blind trial in pregnant women. In the placebo group, 56% of the women presented striae, whereas in the treated group only 34% of the women developed striae in this pregnancy. The intensity of the striae was also lower in the treated group. In women with a history of striae during puberty, the active cream was preventive in 59% of the cases, whereas in the placebo group all the women developed striae.

Since the exact manner of preparing the above-mentioned, clinically carefully studied special extracts was not published, and the traditional application was not sufficiently documented, the European Medicines agency did not prepare a monograph for this plant. However, several *Centella* products are available on the

market on the basis oftheir clinically confirmed efficacy. The following are the most important applications:

- Cream containing 1% extract: for the treatment of moderate or benign problems in wound formation, such as atonic wounds, hypertrophic scars, keloids in the active phase, cutaneous ulcerations and cutaneous gangrene.
- Cutaneous powder containing 2% extract: for cutaneous ulcerations and wound healing agent (scars, keloid scars and burns).
- Ointment containing 1% extract: for the treatment of leg ulcers, decubitus scabs, gangrene, defective scars, fistulas, traumatic and surgical wounds, burns and cutaneous-mucosal injuries.

Pharmaceutical forms for oral use containing special extracts (typically 60-120 mg triterpenes daily) are authorized in different European countries

- for the treatment of atonic wounds, hypertrophic scars, keloids in the active phase, for the improvement of symptoms of venous stasis, and for the treatment of prevaricose syndromes and of complications of varicose veins (phlebitis, varicose ulcers and cutaneous dystrophy).

According to the ESCOP monograph, for internal use the adult dose is 0.6 g of dried drug as an infusion, tincture or extract, up to four times daily, and for external use semi-solid preparations containing 1% of extract or tincture.

The internal application of *Centella* has been less extensively studied. On the basis of the the traditional application of the plant, a randomized, placebo-controlled, double-blind study investigated the effect of *Centella asiatica* on the cognitive function of healthy elderly volunteers. The participants received the plant extract at various doses in the range 250-750 mg once daily for 2 months. The highest dose of the plant extract enhanced the working memory, and improvement of the self-rated mood was also reported.

- **Side-effects, interactions & contraindications**

In the event of oral administration of *Centella*, gastrointestinal complaints and nausea may occur, but the frequency is not higher than for placebo. If there is allergy to Apiaceae, the use of *Centella* is contraindicated. It should also be avoided during pregnancy, due to its reputed emmenagogue effect. A sensitizing effect of the triterpenes was confirmed in animal experiments; however, in the case of commercial products, such side-effects are not characteristic.

13.1.3 Witch hazel

Hamamelis virginiana L. (Hamamelidaceae) is a deciduous, tall shrub, or small tree, native to North America and also cultivated in Europe.

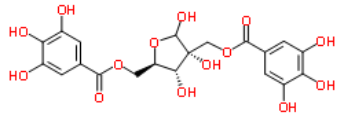
In North American folk medicine, different parts of the plants are applied. In the European Pharmacopoeia, two drugs are official. Hamamelidis folium consists of the

dried or fresh leaves of *Hamamelis virginiana* and it contains not less than 3% of tannins. Hamamelidis cortex consists of the dried bark from the stems, branches and twigs of *Hamamelis virginiana*, collected in spring, containing not less than 4.0% of tannins. Apart from these, the distillate of the leaves, bark and twigs is also used in the medicine (and especially in the cosmetics industry), under the name Hamamelidis aqua (Hamamelis water).

In the folk medicine of Native Americans, the aqueous infusion of the bark was used to treat diarrhea, wounds, inflammations, hemorrhages and hemorrhoids. Hamamelis water was the invention of a German medicinal doctor, *Hering*, who modified the production process and used distillation for the first time in the 19th century. His product was marketed under the name "hazaline".

- **Chemical composition and mechanism of action**

The pharmacologically most important components of witch hazel are the tannins. While the bark contains predominantly hydrolyzable tannins, the leaves contain mainly condensed tannins. The bark contains about 10% tannins. The main tannin component is hamamelitannin (2',5'-di-*O*-galloyl-D-hamamelose). Catechins and flavonoids are present in small amounts. The essential oil content is approximately 0.1%, with phenylpropanoids and sesquiterpenoids as the main constituents.



hamamelitannin

The leaves contain 3-10% of tannins (catechins, proanthocyanidins and gallotannins), flavonoid glycosides, phenolic acids and low amounts (<0.5%) of volatile oil, mostly as aliphatic alcohols.

The term *Hamamelis* distillate (Hamamelidis aqua) covers products prepared by different methods and with various compositions. These preparations are clear colorless liquids with a characteristic odor. Evaporation results in only a small amount of residue, typically not more than 0.025%. Since alcohol is used for distillation, Hamamelis waters may contain variable amount of ethanol.

On injured skin and mucous membranes, *Hamamelis* extracts precipitate proteins, form a protective layer on the injured surface, causes capillary vasoconstriction, and decrease vascular permeability, inflammation and exudation. *Hamamelis* leaf extracts have a vasoconstrictor effect, as confirmed by a human study in which local treatment produced a significant reduction in skin temperature. Anti-inflammatory effects of polyphenols of *Hamamelis* have been observed in preclinical studies. Proanthocyanidins of the plant strongly increased the keratinocyte proliferation,

reflecting the effects of these compounds. Since these effects are due to polyphenols, the polyphenol-free distillate does not have such action (apart from the moderate adstringent effect of the alcohol).

Interestingly, both extracts and water exert an antimicrobial effect, but the efficacy of the latter is more moderate.

- **Efficacy and indications**

The clinical effects of *Hamamelis* extracts have been relatively little studied. A randomized double-blind three-limb study with a duration of 21 days compared the efficacies of rectal ointments containing either a *Hamamelis* liquid extract, bismuth subgallate or a local anesthetic in the treatment of patients with hemorrhoidal symptoms. All these ointments were equally effective in improving the symptoms of the disease (pruritus, a burning sensation, bleeding and pain)

The effects of Hamamelis water were assessed in more detail. The anti-inflammatory efficacy of an aftersun lotion containing 10% *Hamamelis* distillate as compared with active component-free formulations was tested in healthy volunteers, with a modified UVB erythema test as inflammation model. The erythema suppression ranged from approximately 20% at 7 h to 27% at 48 h in the *Hamamelis* fields, while a suppression of 11-15% was recorded in the fields treated with the other lotions.

The anti-inflammatory activity of Hamamelis water was explored in healthy volunteers experimental irritation models. *Hamamelis* produced significant reductions in cutaneous blood flow and skin redness as compared with the vehicle.

In an open-label clinical study, the effect of Hamamelis water on skin aging was studied. After a period of 4 weeks of application, the anti-aging effect was significant and clinically relevant. Scaling and fissures were clearly reduced and symptoms such as tautness, roughness and itching were improved. Howeer, it is not possible to decide whether the effect is to be attributed to the ointment base or to the Hamamelis water.

A randomized, double-blind, placebo-controlled trial compared the efficacies of three creams containing either a *Hamamelis* distillate, or a 0.5% hydrocortisone cream or a drug-free vehicle for the symptomatic treatment of severe atopic eczema. All treatments significantly reduced the incidence of itching, scaling and erythema after 1 week of treatment. Hydrocortisone proved superior to the *Hamamelis* distillate, while the result for the cream containing the *Hamamelis* distillate did not differ from that for the vehicle.

On the basis of the available data on the phytochemistry and the traditional application of *Hamamelis*, efficacy is plausible and therefore acceptable for the traditional herbal medicinal product in the following indications

- relief of minor skin inflammation and dryness of the skin.
- the symptomatic relief of itching and burning associated with hemorrhoids

- as a mouthwash and gargle for the relief of minor inflammation of the mucous membranes of the oral cavity.

For these indications, the herbal tea, tincture, liquid or dry extract (also as suppositories for hemorrhoids) may be applied.

The indications of Hamamelis water as a traditional herbal medicinal product are for

- the relief of minor skin inflammation and dryness of the skin, and
- the temporary relief of eye discomfort due to dryness of the eye or to exposure to the wind or sun.

For ocular use, a diluted (1:10) distillate prepared from dried twigs (1:2; ethanol 14-15%), should be applied with a posology of 2 drops ineach eye, 3-6 times daily.

- **Side effects, interactions & contraindications**

Allergic contact dermatitis may occur in sensitive patients following dermal application. Conjunctivitis cases have been reported during ocular application.

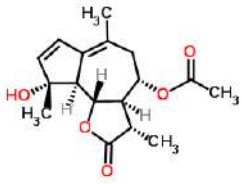
13.1.4 Camomile

Matricaria recutita L. (syn. *Chamomilla recutita* (L.) Rauschert) is one of the most popular medicinal plants. Its dried flowers and the essential oil are widely used. Both are official in the European Phamacopoeia. According to the pharmacopoeial definition, Matricariae flos is the dried capitula of the plant, its essential oil content is at least 4 ml/kg and it should contain at least 0.25% of apigenin-7-glucoside. Matricariae aetheroleum is the essential oil obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *Matricaria recutita*. There are 2 types of matricaria oil, one characterized by a high bisabolol oxide content, the other being rich in (−)-alpha-bisabolol. A liquid extract, Matricariae extractum fluidum, can also be found in European Pharmacopoeia, with a minimum content of 0.3% of essential oil. This extract is prepared with a mixture of water, ethanol and ammonia.

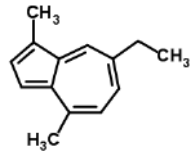
The most common applications of camomile extracts in folk medicine have been its cutaneous use for wound healing and its oral use for gastrointestinal complaints. The essential oil has typically been used externally.

Chemical composition and mechanism of action

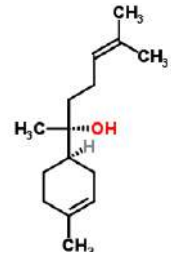
Camomile flowers contain 0.3-2% of essential oil. Sesquiterpene-lactone proazulenes such as matricin and matricarin are genuine metabolites of the plant, but they are converted to blue azulenes during steam distillation. (The same chemical reaction can be observed during the preparation of a tea: the initial blue color of a camomile tea is due to the appearance of azulenes in the tea.) The essential oil contains up to 20% of azulenes, with chamazulene as the main constituent, (-)-alpha-bisabolol (up to 50%) and bisabolol oxides A and B as characteristic compounds.



matricin



chamazulene



alpha-bisabolol

Camomile is rich in flavonoids (approximately 5%), with apigenin, quercetin and luteolin and their derivatives as the main components. It contains low amounts of coumarins (less than 0.1%), with representatives such as umbelliferone and herniarin. Its aqueous extract contains marked amounts of polysaccharides.

The anti-inflammatory activities of camomile extracts are a result of the effects of chemically different constituents. Flavonoids have a major role, apigenin having been most extensively studied. In *in vitro* experiments, it inhibited prostaglandin synthesis, the production of cyclooxygenase-2, tumor necrosis factor-alpha and NO. Azulenes are also important active components; chamazulene inhibits the synthesis of leukotriene B_4 *in vitro*. The anti-inflammatory activities of camomile extracts and certain pure compounds ((-)-alpha-bisabolol, bisabololoxides, apigenin) have been observed in several animal experiments involving different inflammation models. An antiphlogistic effect was confirmed after the local treatment of experimentally irritated human skin (chemical irritation or UV irradiation) with camomile extracts.

The wound healing ability of *Matricaria* extracts has been confirmed on experimentally inflicted wounds and burns in animals. In one study, a hydroalcoholic extract demonstrated a protective effect against ethanol-induced gastric mucosal lesions in rats. The essential oil exhibited antimicrobial activity against certain species of bacteria, fungi and viruses *in vitro*.

When the spasmolytic effects of different *Matricaria* extracts and compounds were examined in the isolated guinea pig ileum, alpha-bisabolol and apigenin proved to be the most active pure compounds. Antispasmodic effects have also been confirmed in animal experiments.

The sedative effect of extracts (and apigenin) has been observed in animals. In one experiment, an aqueous extract had benzodiazepine-like hypnotic activity, which could be antagonized by flumazenil, a benzodiazepine receptor antagonist. The active components are not known; certain studies have excluded the direct effect of apigenin on benzodiazepine receptors.

- **Efficacy and indications**

In a blind, placebo-controlled randomized trial, patients with moderate atopic dermatitis on both arms received treatment with a camomile extract (on one side) or placebo/hydrocortisone (on the other side). The camomile extract was found to be superior to hydrocortisone cream, but not better than placebo.

In a further trial, eczema patients were treated on the left side with a liquid camomile extract (2.7-5.5:1, extraction solvent: ethanol 95.4%) and on the right side with either a 0.25% hydrocortisone, 0.75% fluocortin butyl ester cream or a 5% bufexamac cream. The treatment with the camomile extract was as effective as hydrocortisone, better than fluocortin butyl ester and considerably better than bufexamac.

In another study, patients with ulcus cruris and 35 with decubital ulcers were treated with a liquid extract (1:4.0-4.5, extraction solvent: ethanol 38.5%). The treatment was successful (very good or good) in 60% of the decubital ulcers, and in 83% of the ulcus cruris cases.

In an open controlled study on children, the efficacy of an extract in the treatment of diaper dermatitis was investigated. Camomile cream was applied with every change of diapers for 2 weeks. Symptoms improved after 7 days and recovery was nearly complete after 14 days.

In a trial involving female patients with breast cancer after operation, the efficacy of a camomile extract in preventing skin irritation during irradiation was observed.

In an uncontrolled study, ambulant patients with unspecific gastrointestinal complaints were treated for 6 weeks with an ethanolic camomile extract. Pressure in the stomach improved in 84.5%; eructation in 77.5%, heartburn in 81.7%; loss of appetite in 61%; nausea in 88.7%; and vomiting in 77.8% of the cases.

In a randomized, double-blind, placebo-controlled clinical trial with a dose-escalating design patients with a generalized anxiety disorder were enrolled. After 4 weeks of treatment (maximal dose: 880 mg of an extract standardized to apigenin daily), the reduction of the HAM-A (Hamilton Anxiety Rating Scale) Score was significant in the treated group.

The versatile application of camomile flowers is reflected in the indications. Although the clinical efficacy has not been confirmed conclusively, the well-documented and widespread use indicate that camomile flowers (and the extracts) may be used as traditional herbal medicinal products for

- the symptomatic treatment of minor gastrointestinal complaints such as bloating and minor spasms (oral use),
- the relief of symptoms of the common cold (steam inhalation),
- the treatment of minor ulcers and inflammations of the mouth and throat,
- the adjuvant therapy of irritations of the skin and mucosa in the anal and genital region, after serious conditions have been excluded by a physician (oromucosal use), and
- the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles) (cutaneous use).

For the listed indications, several different extracts may be used.

Camomile essential oil may be applied in the therapy based on its traditional applications. Sufficient evidence to support its use as a traditional herbal medicinal product has been found for the

- adjuvant therapy of irritations of the skin and mucosa in the anal and genital region, after serious conditions have been excluded by a physician.

For this indication camomile essential oil can be used as a bath additive in a dose of 0.5-1 mg per liter.

- **Side effects, interactions & contraindications**

Hypersensitivity reactions, including severe allergic reaction (dyspnea, Quincke's disease, vascular collapse and anaphylactic shock) have been reported following mucosal contact with liquid camomile preparations. The use of camomile is contraindicated in cases of hypersensitivity to the plant and to other species of the Asteraceae family.

If applied to the breasts, the nipples should be cleaned before breast-feeding in order to prevent a sensitization of the child.

Full baths (with camomile essential oil or camomile tea) are contraindicated in the event of open wounds, large skin injuries, acute skin diseases, high fever, severe infections, severe circulatory disturbances and a cardiac insufficency.

13.1.5 Tea tree

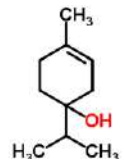
The name "tea tree" refers to several species of the genera *Leptospermum* and *Melaleuca* (Myrtaceae). The most widely applied species is *Melaleuca alternifolia*, which is also known as the Australian tea tree. In modern therapy, the essential oil of the leaves is used. The European Pharmacopoeia, which also lists tea tree oil as an official medicinal raw material, requires a minimum content of 30% of terpinen-4-ol and a maximum content of 15% of 1,8-cineole in the oil. This oil may be obtained by steam distillation from the foliage and terminal branchlets of *Melaleuca alternifolia* (Maiden and Betch) Cheel, *M. linariifolia* Smith, *M. dissitiflora* F. Mueller and/or other species of the *Melaleuca* genus.

The essential oils of other species of the genus are also applied in industry under the names of niaouli oil (from *Melaleuca quinquenervia*) and cajeput/cajuput oil (*Melaleuca cajuputi*).

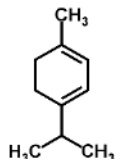
Tea tree oil has been used externally by Australian Aborigines as a traditional medicine to treat dermatological problems and cure bites. The value of the oil was recognized by the first European settlers, but its use in official European medicine started only in the 20th century, as a local antiseptic in surgery and dentistry, and in the treatment of dermatological diseases.

- **Chemical composition and mechanism of action**

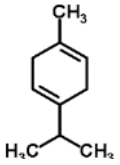
Tea tree oil contains cyclic monoterpenes as main constituents, about half of which are oxygenated. The major component of the oil is terpinen-4-ol, and with gamma-terpinene and alpha-terpinene in remarkable quantities.



terpinen-4-ol



alpha-terpinene



gamma-terpinene

The oil has a broad spectrum of antimicrobial activity *in vitro*, against *Escherichia coli, Streptococcus* spp., *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA).

Lactobacillus strains are more resistant to tea tree oil than organisms responsible for bacterial vaginosis. This difference allows the use of the oils in vaginal infections without causing an unfavorable effect on the vaginal flora.

Melaleuca oil has an inhibitory effect on *Herpes simplex* virus and on influenza virus replication at doses below the cytotoxic dose. It has broad antifungal effects, also proving active against *Candida albicans* and *Malessezia furfur*.

The antimicrobial activity of the oil is mainly attributed to terpinen-4-ol and 1,8-cineole.

- **Efficacy and indications**

A double-blind, randomized controlled trial demonstrated that 100% tea tree oil has comparable efficacy to that of clotrimazole in the treatment of onychomycosis.

A randomized, controlled, double-blind study confirmed the efficacy of 50% and 25% tea tree oil-containing external products versus placebo in the treatment of interdigital tinea pedis with the development of dermatitis. In a further study, a product with 10% oil concentration was ineffective.

A 90-day clinical study on patients with vaginitis caused by *Candida albicans* infection proved the efficacy of a vaginal capsule containing 0.2 g of tea tree oil (the infection was eliminated in 80% of the patients).

The efficacy of a shampoo containing 5% of tea tree oil as compared with placebo was investigated in a randomized, single-blind trial lasting for 4 weeks. The oil-containing shampoo led to a 41% improvement in the severity score, in comparison with 11% in the placebo group.

Two studies indicated that a *Melaleuca*-based oral solution was effective in AIDS patients with fluconazole-resistant oropharyngeal *Candida infections.*

The efficacy against acne vulgaris was demonstrated in a series of single or double-blind clinical trials. A gel containing 5% of tea tree oil was equally as effective as 5% benzoyl peroxide, and significantly more effective than placebo in the treatment of mild to moderate acne. Its efficacy in the treatment of furuncles was also confirmed. Clinical studies proved that tea tree oil positively influences wound healing (shortening the healing time and reduceing the risk of infection) due to its antimicrobial activity.

Although several studies have been carried out with tea tree oil, no herbal medicinal product used in clinical trials with a positive outcome has been authorized in Europe for a least 10 years, and the well-established medicinal use was therefore not supported by the European Medicines Agency. However, the results of clinical studies reinforce the plausibility of the traditional uses of tea tree oil, and it can therefore be used as a traditional herbal medicinal product for the

- treatment of small superficial wounds and insect bites.

The dosage is 0.03-0.07 ml of undiluted essential oil on the affected area, applied with using a cotton bud 1-3 times daily, or a liquid preparation containing 0.5% to 10% of essential oil on the affected area 1-3 times daily.

- treatment of small boils (furuncles and mild acne)

Oily liquid or semi-solid preparations containing 10% of essential oil are applied to the affected area 1-3 times daily, or 0.7-1 ml of essential oil stirred in 100 ml of lukewarm water is applied as an impregnated dressing to the affected areas of the skin.

- relief of itching and irritation in cases of mild athlete´s foot

Oily liquid or semi-solid preparations containing 10% of essential oil, are applied to the affected area 1-3 times daily. 0.17-0.33 ml of essential oil in an appropriate volume of warm water is used to cover the feet, which should be soaked for 5-10 minutes a day. Undiluted essential oil is applied to the affected area with a cotton bud 2-3 times daily.

- symptomatic treatment of minor inflammation of the oral mucosa.

0.17–0.33 ml of essential oil is mixed in 100 ml of water and applied as a rinse or gargle several times daily.

Side effects, interactions & contraindications

Tea tree oil was found to cause mild to moderate skin irritation in animal studies. However, the oxidized (sub-standard) oil has a greater potential to induce skin sensitization. The undiluted oil has been reported to cause skin irritation in about 5% of the treated subjects.

Adverse skin reactions, including pruritus, a burning sensation, irritation, itching, stinging, erythema, edema and contact dermatitis may occur during the application of the oil.

Use of the essential oil is contraindicated in cases of hypersensitivity to the essential oi or to colophony. It should not be used orally or as an inhalation or in the eyes or ears.

Its safety during pregnancy and lactation has not been established. In the absence of sufficient data, its use during pregnancy and lactation is not recommended.

13.1.6 Myrrh

In ancient times, myrrh was one of the most important and expensive goods, since it was difficult to obtain on a large scale and it was used for several purposes, from medicinal to sacral applications. Myrrh was obtained from several different species of the *Commiphora* genus. Nowadays, the most important source is *Commiphora myrrha* (Nees) Engler, which is a synonym of *Commiphora molmol* Engler. Other species that are also frequent sources of myrrh are *Commiphora abyssinica* (Berg) Engler and *Commiphora schimperi* (Berg) Engler. According to the definition of the European Pharmacopoeia, myrrh is a gum resin, hardened in the air, obtained by incision or produced by spontaneous exudation from the stem and branches of *Commiphora molmol* and/or other species of *Commiphora*.

At present, myrrh is typically marketed in combination products used as bitters for stomach problems (e.g. Schwebendbitters). Its tincture is used in phytotherapy for inflammations of the gingiva and the skin.

- **Chemical composition and mechanism of action**

The main components of myrrh are the volatile oil constituents (2-10%), resin and gum. The main constituents of the volatile oil are furano-sesquiterpenes. Important components of the alcohol-soluble resin (25-40%) are the diterpene commiphoric acids and their esters. The gum (30-60%) is water-soluble and consists of a mixture of proteoglycans.

Myrrh and its sesquiterpenes and diterpene acids demonstrate a potent antibacterial effect against several bacteria, including the most common wound pathogen *Staphylococcus aureus* and *Candida albicans*. Myrrh has been shown to stimulate phagocytosis *in vitro*. Sesquiterpene-rich extracts exhibited local anesthetic activity in animal experiments. Orally administered myrrh exerted analgesic, antipyretic and anti-inflammatory activities.

Oral administration of the sesquiterpene fractions resulted in a reduction of the blood glucose level (with a similar efficacy to that of metformin).

- **Efficacy and indications**

No clinical studies are available to support the efficacy related to the traditional application of myrrh. A commercial product based on myrrh was applied in several studies in Africa for the treatment of schistosomiasis, but with inconclusive results. Its use in the therapy of the zoonotic disease fascioliasis is supported by some promising clinical trials.

The use of myrrh has not received sufficient clinical confirmation, and it can therefore be used as traditional herbal medicinal products

- for the treatment of minor ulcers and inflammation in the mouth (stomatitis and gingivitis), or
- for the treatment of minor wounds and small boils (furuncles).

Oromucosally, 0.5-5 ml of tincture should be used in 150 ml of water for rinsing or gargling 3 times daily, or the undiluted tincture may be applied to the affected areas with a cotton bud 2-3 times daily. On cutaneous use, the wound or furuncle should be dabbed 2-3 times daily with the undiluted or diluted tincture in water.

- **Side-effects, interactions & contraindications**

Hypersensitivity to myrrh is a contraindication for the use of myrrh-containing products. Contact of the eyes with myrrh tincture should be avoided. Allergic skin reactions may occur.

13.1.7 Evening primrose

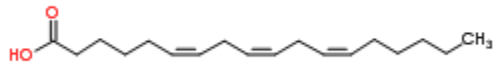
Oenothera species are native to North America, but their oil with its especially high gamma-linolenic acid content is used worldwide by the pharmaceutical industry. According to the definition of the European Pharmacopoeia, evening primrose oil is the fatty oil obtained from seeds of *Oenothera biennis* or *Oenothera lamarckiana* by extraction and/or expression. It contains at least 65% of linoleic acid, 7-15% of gamma-linolenic acid (gamma-linolenic acid) and a maximum of 0.5% of alpha-linolenic acid. Other substances are 5-12% oleic acid, 1-4% stearic acid, 4-10% palmitic acid and a maximum of 0.3% saturated fatty acids with chain length less than C_{16}.

Oenothera biennis was first used by North American Indians, primarily to treat dermatological problems. In the 1600s, it was introduced into Europe under the name 'king's cure-all', which made it popular with a wide range of indications. At the beginning of the 20th century, an unusual fatty acid was found in the seed oil, which

was named gamma-linolenic acid (GLA). The unique structure and biological effects made the oil of evening primrose very fashionable. Its medicinal uses were very widespread, but many of the claimed indications cannot be supported by clinical data.

Chemical composition and mechanism of action

Linoleic acid (LA) is an essential fatty acid. The rate-limiting factor in its metabolism is the enzyme delta-6-desaturase (D6D), which catalyzes its transformation into dihomo-gamma-linolenic acid (DGLA). In the next step, delta-5-desaturase catalyzes the formation of arachidonic acid. From DGLA and arachidonic acid, series 1 and 2 prostaglandins are metabolized, respectively, this step being catalyzed by cyclooxygenase (COX).



gamma-linolenic acid

The activity of the enzyme delta-6-desaturase is deficient in certain diseases and states (eczema, premenstrual syndrome and with aging) and this leads to a decrease in the DGLA metabolites. The decreased level of PGE_1 causes an increased IgE concentration, which triggers allergic-like reactions. The decrease in PGE_2 results in a reduction of T-suppressor lymphocytes, which finally also leads to IgE production. Moreover, an increased sensitivity as concerns prolactin in premenstrual syndrome might be caused by the disturbed fatty acid metabolism. Since evening primrose oil is a good source of gamma-linolenic acid, if the activity of delta-6-desaturase is insufficient, supplementation with the oil may normalize the level of prostaglandins that are usually produced predominantly from linoleic acid.

In an animal study, rabbits were fed on an atherogenic diet or an atherogenic diet with 15% *Oenothera* oil. In the primrose oil-treated group, the cholesterol level was reduced by 25% and the triglyceride value by 51%, while the HDL-cholesterol was raised by 64%. In a 60-day experiment with rabbits, the oil exhibited anticoagulant properties, related to its anti-inflammatory effect.

In an animal experiment, *Oenothera* oil exerted a significant anti-ulcer effect on various experimentally induced gastric lesions.

Efficacy and indications

In a randomized, double-blind, placebo-controlled trial over a period of 2 weeks, patients with mild or moderate atopic eczema received an *Oenothera* cream or placebo. The self-assessment scores from the patients indicated significant better results for the *Oenothera* cream; however, the physician's scores did not reveal any significant difference.

In a double-blind, randomized, placebo-controlled study involving adults with moderate to severe atopic dermatitis, orally applied *Oenothera* oil reduced the inflammation significantly relative to the placebo group. The DGLA concentration increased significantly, whereas the PGE_1 level in the plasma did not rise.

A randomized, double-blind, placebo-controlled cross-over study during 6 weeks on patients with atopic eczema compared orally applied *Oenothera* oil with placebo with the parallel use of a mild topical steroid preparation. The patients receiving evening primrose oil showed a modest but significant improvement on both the physician's and their own assessment.

There have been several further trials that have asessed the efficacy of evening primrose oil in eczema, but some of them had a negative outcome, while others were of insufficient quality to be used as confirmation of a clinical effect. In cases of rheumatoid arthritis, premenstrual syndrome and menopausal hot flashes, several clinical trials did not provide convincing evidence of efficacy.

The evidence of a well-established use in any of the indications is inadequate. Since traditional oral use is well documented, and the plausibility is supported by certain clinical studies, evening primrose oil can be used as a traditional herbal medicinal product

- for the symptomatic relief of itching in acute and chronic dry skin conditions.

The daily dose of the oil is 4-6 g

- **Side effects, interactions & contraindications**

Safety during pregnancy and lactation has not been established. Gastrointestinal effects, indigestion, nausea, softening of the stools, hypersensitive reactions such as exanthema and headache have been reported during the use of *Oenothera* oil.

Verification questions

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1. What are the active constituents of *Centella*?
2. What are the medicinally applied parts and products of withch hazel and what is their indications?
3. What is the basis of clinical efficacy of tea tree oil?
4. What is the mode of action of evening primrose?
5. What are the therapeutic indications of chamomile?

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