1

Introduction

2

Phytochemistry

- **Branch of pharmacognosy**, deal with **chemical** & **biological** characters, in order to obtain the **medicament**, by **natural** or semisynthetic pathways.

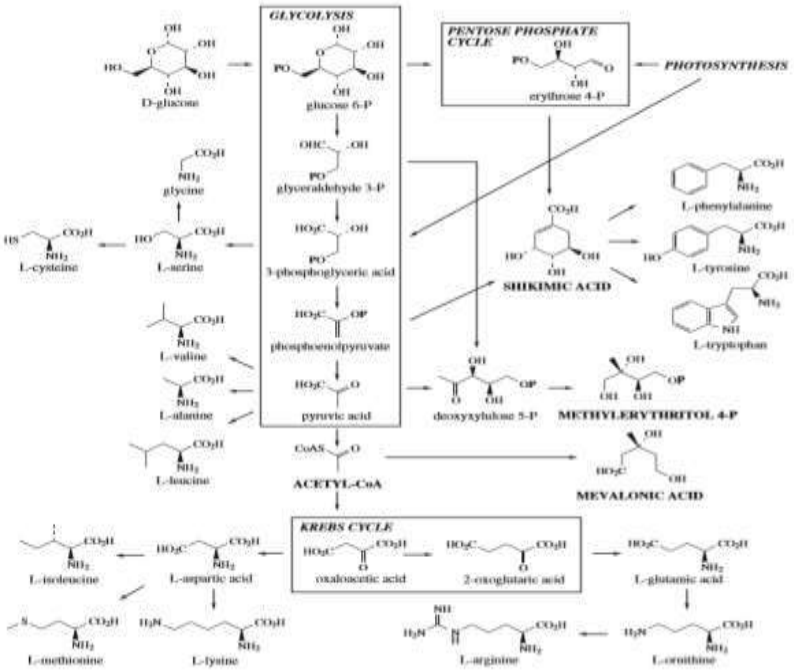
3

The Building Blocks

- All organisms **need to transform** and **interconvert** a vast number of **organic compounds** to enable them **to live, grow, and reproduce**.
- They **need to provide** themselves with **energy in the form of ATP**, **and a supply of building blocks to construct their own tissues.**
- Building blocks **based on amino acids** are frequently employed in natural product synthesis.
- **The building blocks for secondary metabolites are derived from primary metabolism**

4

Secondary Metabolism: The Building Blocks & Construction Mechanisms



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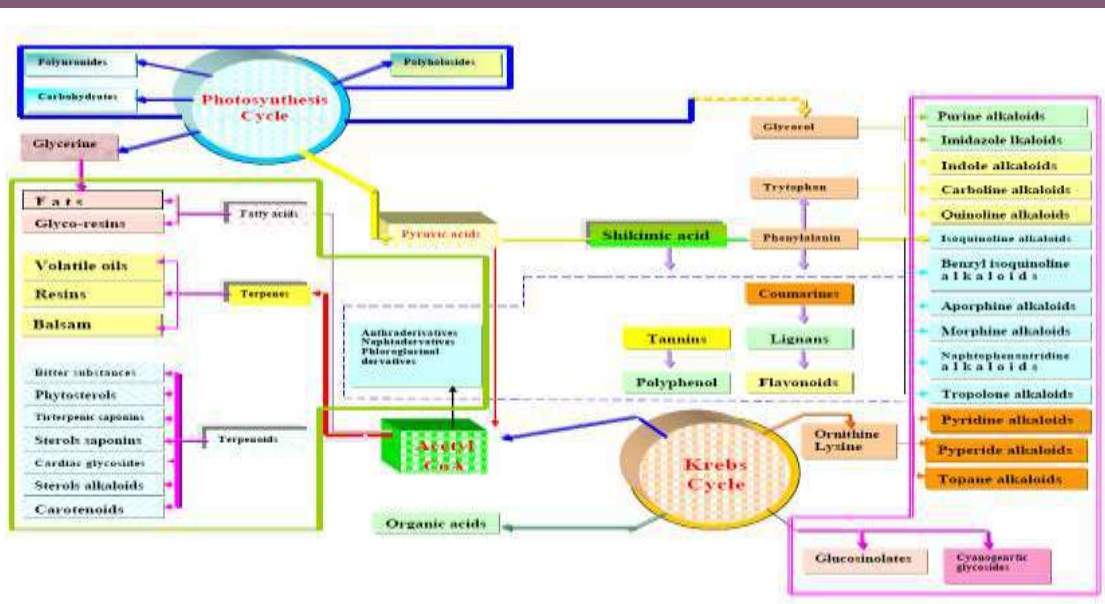

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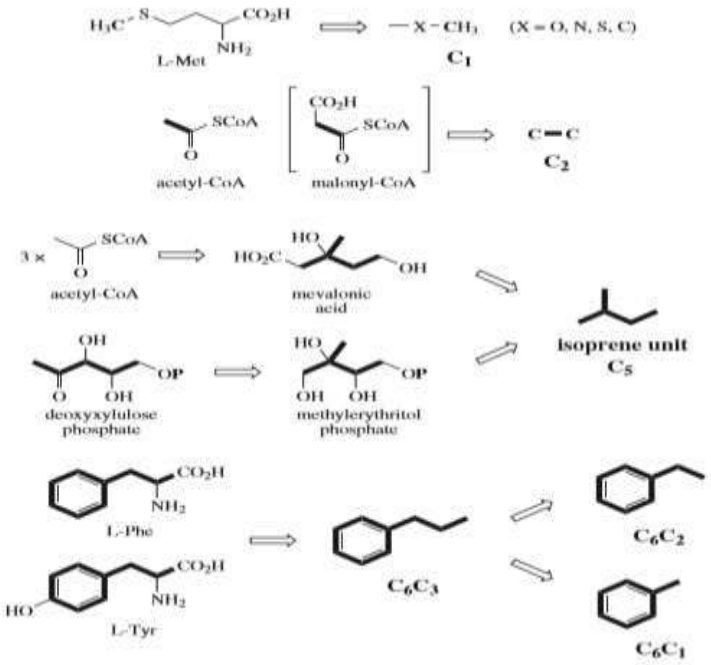
The structural features of these building blocks



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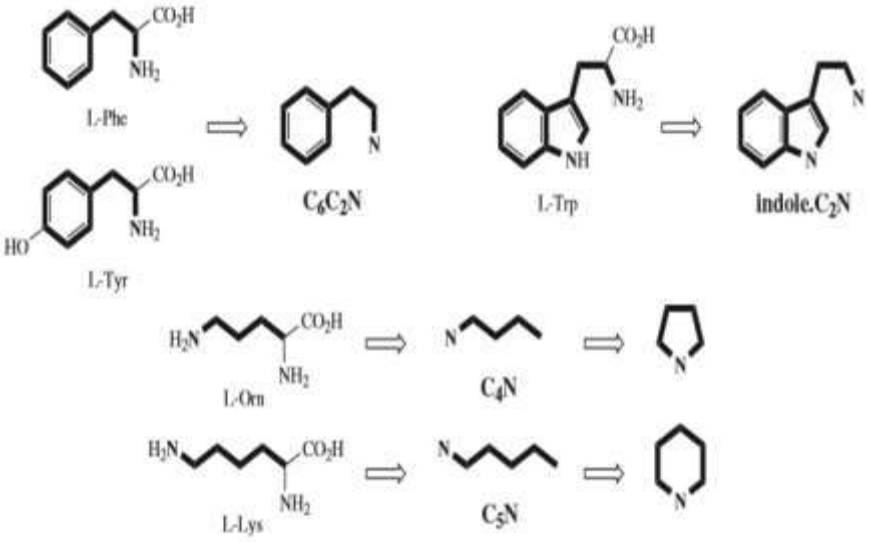
The structural features of these building blocks



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The structural features of these building blocks

C1: The simplest of the building blocks is composed of a single carbon atom, usually in the form of a **methyl group,** and most frequently it is **attached to oxygen or nitrogen**, but **occasionally** to **carbon or sulfur**. It **is derived from the S-methyl of l-methionine.**

C2: A two-carbon unit may be **supplied by acetyl-CoA**.

C5: The branched-chain **C5 'isoprene'** unit is a feature of compounds formed from mevalonate or methylerythritol phosphate.

C6-C3: This refers to a **phenylpropyl unit** and is obtained from the carbon skeleton of either **L-phenylalanine or L-tyrosine**, two of the shikimate-derived aromatic amino acids.

9

The structural features of these building blocks

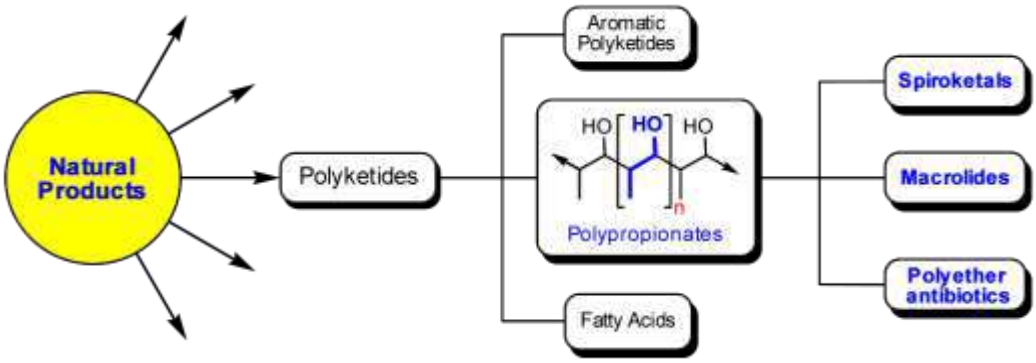
C6-C2N: Again, this building block is formed from either **L-phenylalanine or L-tyrosine**, with l-tyrosine being by far the more **common precursor**.

indole.C2N: The third of the aromatic amino acids is **L-tryptophan.**

C4N: The C4N unit is usually found as a **heterocyclic pyrrolidine system** and is produced from the non-protein amino acid **L-ornithine**.

C5N: This is produced in exactly the same way as the C4N unit but using **L-lysine** as precursor.

10



THE ACETATE PATHWAY: FATTY ACIDS AND POLYKETIDES

11

Polyketide

- Polyketides are bioactive natural products isolated from **diverse microorganisms.**
- Polyketides are a large class of structurally diverse, acetate derived natural products that **exhibit a wide range of bioactivities**.
- The **biosynthesis of polyketides from acyl-CoA thioesters** is catalyzed by polyketide synthase (PKS), a multi-enzyme complex that is highly homologous to fatty acid synthase (FAS).
- Many polyketides are clinically important, with **antimicrobial**, **anticancer** and **immunosuppressive properties**.
- Moreover, they are important in the producing organisms, facilitating competition for **substrates and communication between organisms**.

12

Fatty Acids

- **Fatty acid**, important component of lipids in plants, animals, and microorganisms.
- Generally, a fatty acid consists of a straight chain of an even number of carbon atoms, with hydrogen atoms along the length of the chain and at one end of the chain and a carboxyl group (—COOH) at the other end.
- **Fatty acids** are the **building blocks of the fat in our bodies** and in the food we eat.
- During digestion, the body breaks down fats into **fatty acids**, which can then be absorbed into the blood.
- **Fatty acid** molecules are usually joined together in groups of three, forming a molecule called a **triglyceride**.
- A few fatty acids have branched chains; others contain ring structures (e.g., **prostaglandins**).

13

What are fatty acids used for?

- **Fatty acids** serve as:
  1. Anti-inflammatory agents
  2. Antioxidants
  3. Enhance the immune system
  4. Fat Burner
- **Fatty acids** that are **not used up as energy are converted into triglycerides.**

14

Examples of Fatty Acids

- **Examples** would be fats, oils, cholesterols, and steroids.
- **Fatty acids** are in fact carboxylic **acids** with long aliphatic chain, which can be **saturated** (containing only C-C single bonds) such as palmitic **acid**, stearic **acid** etc. or **unsaturated** (containing multiple bonds between carbon atoms). Or **trans fats**.
- Omega-3 fatty acids are a family of important fats that you must obtain from your diet.
- The three most important types are **ALA** (alpha-linolenic acid "omega 3"), **DHA** (docosahexaenoic acid), and **EPA** (eicosapentaenoic acid).
- ALA is mainly found in plants, while DHA and EPA occur mostly in animal foods and algae.
- LA or Linoleic (Omega 6) (Corn oïl, soya oïl, canola oïl)

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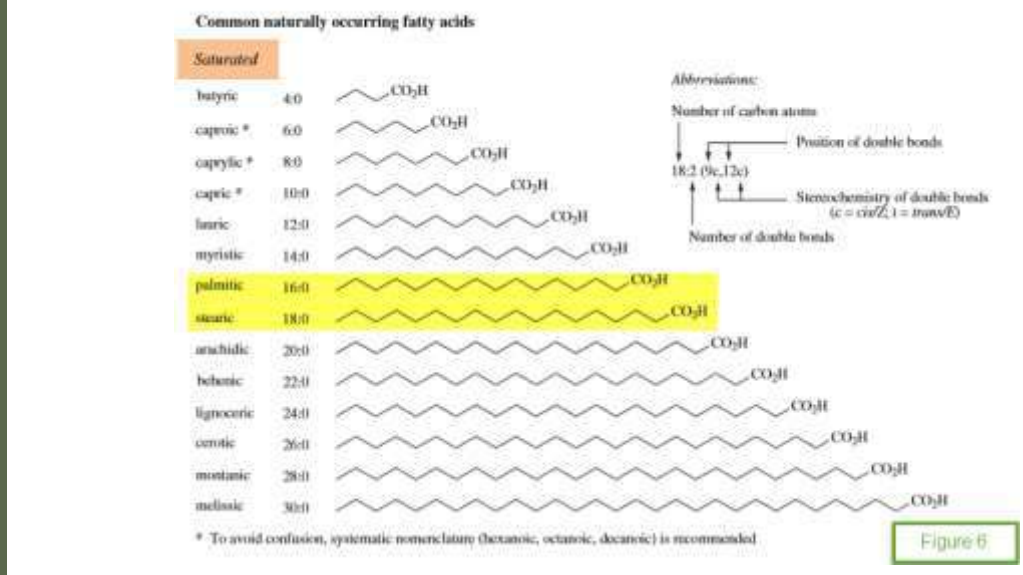

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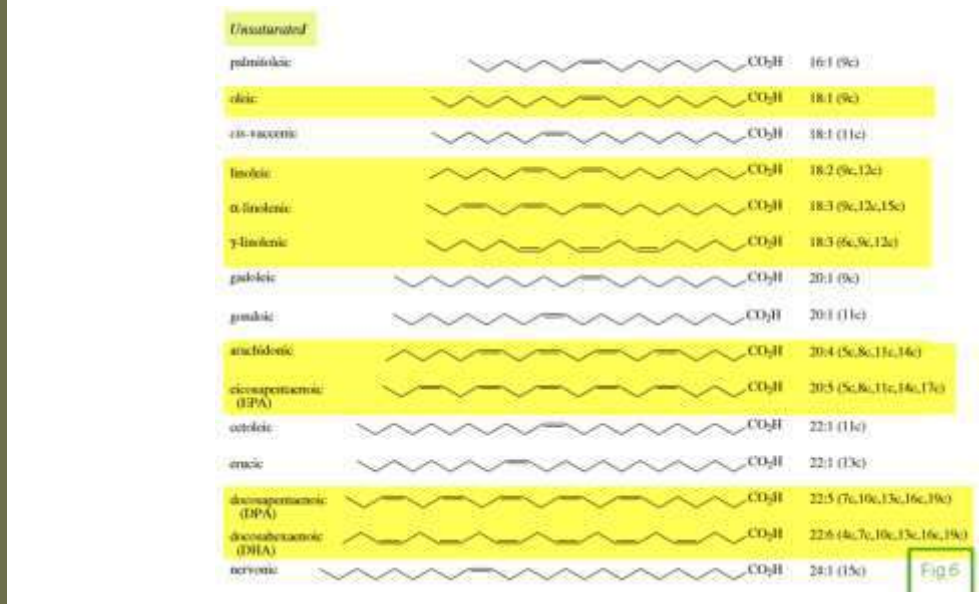


17

Omega 3

- Omega−3 fatty acids, also called Omega-3 oils, ω−3 fatty acids or n−3 fatty acids, are polyunsaturated fatty acids characterized by the presence of a double bond three atoms away from the terminal methyl group in their chemical structure

18

Omega 3 Benefits

- An added benefit to fish: **Omega-3** fatty acids, which can improve cardiovascular health and lower triglycerides and may increase dopamine production and reduce the risk for depression all pluses for the **libido** and orgasm potential.
- Increase IQ
- Antihypertensive
- Reduce blood sugar level
- Skin disorder

19

Symptoms of omega 3 Deficiency:

- Low IQ (Decrease Learning)
- Retina disorder
- Heart Problems
- Blood Pressure
- Inflammation process
- Decrease Mood: Depression, Anxiety
- Decrease Sperm Count
- Dry scaly skin

20

Omega 3 Side effects

- Risk of hemorrhagic stroke
- Diarrhea
- Acid reflux
- Insomnia
- Low blood pressure
- Nausea

21

Linoleic acid (AA) (Omega 6)

- Gamma Linoleic Acid (GLA) – Great for inflammation, skin health and allergies
- Arachidonic Acid (AA)– building block of prostaglandins, a body chemical that is involved in inflammation that helps heal the body in areas of injury and infection.

22

The omega-6 to omega-3 ratio

- The recommended ratio of omega-6 to omega-3 fatty acids in the diet is **4:1 or less**.
- However, the diet has a ratio between 10:1 and **50:1**

23

Omega 9

- Omega-9 fatty acids are a family of **unsaturated fatty acids** which have in common a final carbon–carbon double bond in the omega−9 position; that is, the **ninth bond from the methyl end of the fatty acid**.

24

Benefits of omega 9

- Because **omega-9 fatty acids** have been shown to increase HDL **cholesterol** and decrease LDL **cholesterol**, they help eliminate plaque build- up in the arteries, which causes heart attack and stroke.

25

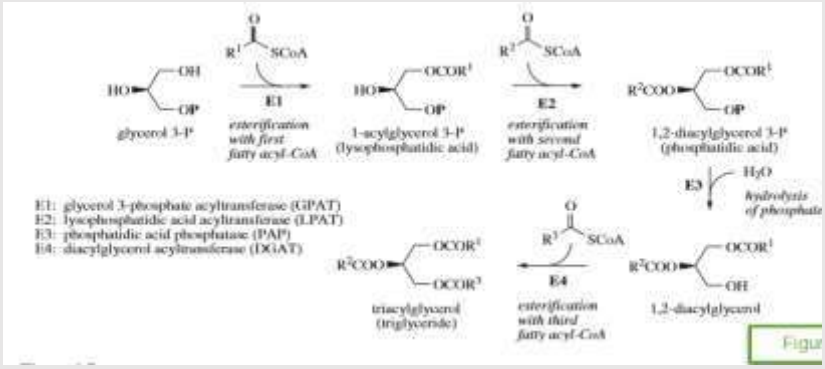
Foods High in Omega-9 Fats

- The body can make **Omega 9** itself out of the unsaturated fats we eat,
  - **Olive oil**: 83g.
  - **Cashew oil**: 73g.
  - **Almond oil**: 70g.
  - **Avocado oil**: 60g.
  - **Peanut oil**: 47g.
  - **Almonds nut**: 30g.
  - **Cashews nut**: 24g.
  - **Walnuts nut**: 9g.

26

FATTY ACID SYNTHASE: SATURATED FATTY ACIDS

- Triglycerides are produced predominantly from glycerol 3-phosphate by esterification with fatty acyl-CoA residues, the phosphate being removed prior to the last esterification.



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28

29

UNCOMMON FATTY ACIDS

- Ricinoleic acid: 12-hydroxy derivative of oleic acid and is the major fatty acid found in castor oil, expressed from seeds of the castor oil plant (*Ricinus communis*; Euphorbiaceae).

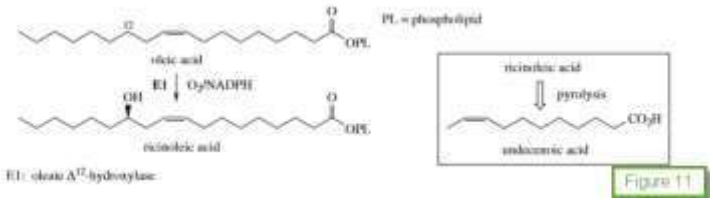
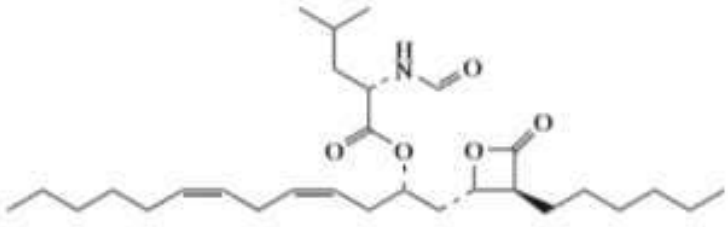


Figure 11

30

UNCOMMON FATTY ACIDS

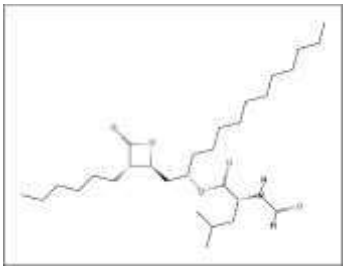
- **Lipstatin**: found in *Streptomyces toxytricini*, has ability to inhibit pancreatic lipase; the key enzyme for intestinal fat digestion.
- It has since been developed into an anti-obesity drug.
- **Lipstatin** is formed from the two fatty acids **tetradeca-5,8-dienoic acid** *(originate from linoleic acid derived from sunflower oil)* and **octanoic acid**;



31

UNCOMMON FATTY ACIDS

- Tetrahydrolipstatin (**orlistat**): obtained by catalytic hydrogenation of lipstatin,
- Orlistat **reduces the absorption of dietary fat** and is used **in conjunction** with a low-fat calorie-reduced diet to reduce body mass in obese patients.
- **Absorption of fat-soluble vitamins, especially vitamin D,** is also inhibited, and vitamin supplements are usually co-administered.

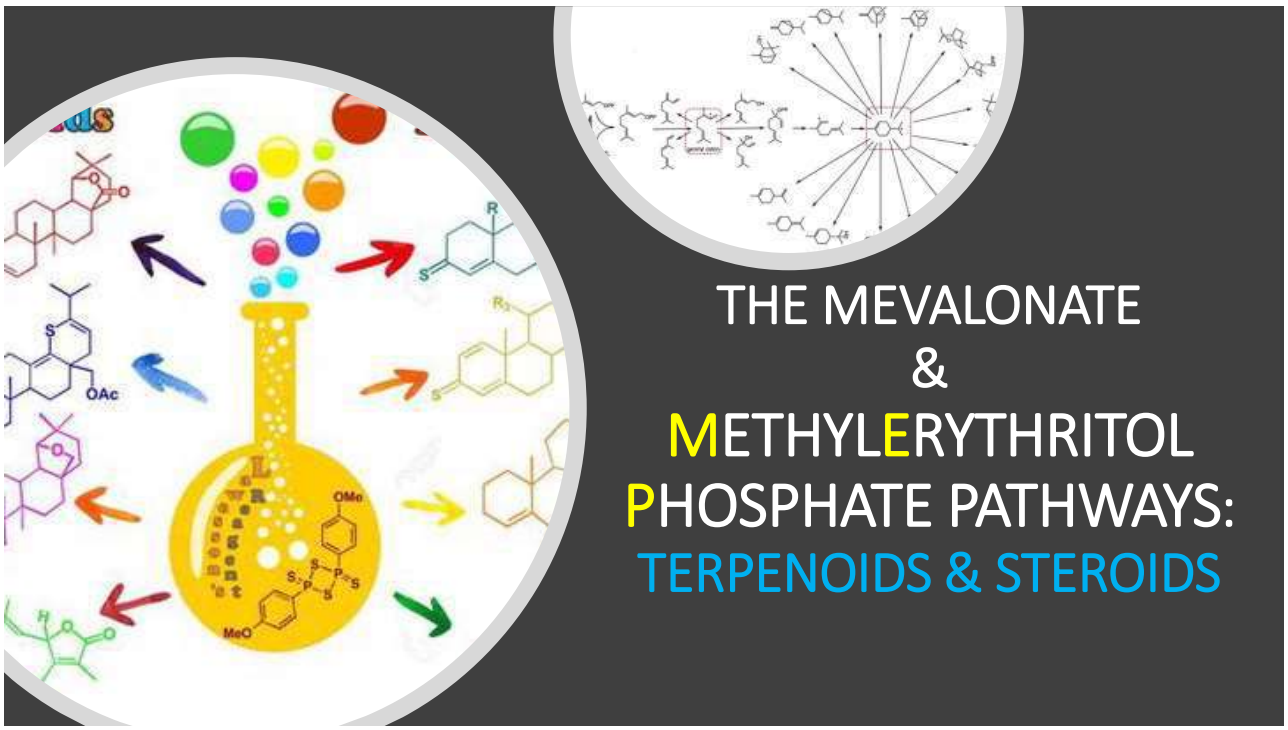


32

PROSTAGLANDINS

- The prostaglandins are a group of **modified C20 fatty acids** first **isolated from human semen** and initially assumed to be **secreted by the prostate gland.**
- PGE1 and PGF1α were initially isolated from sheep seminal plasma, but these compounds and PGD2, PGE 2, and PGF 2α are widely distributed.
- The prostaglandins display a wide range of pharmacological activities, including **contraction and relaxation of smooth muscle** of the uterus, the cardiovascular system, the intestinal tract, and of bronchial tissue.
- They also **inhibit gastric acid secretion**, **control blood pressure and suppress blood platelet aggregation**, as well as acting as mediators of inflammation, fever, and allergy.

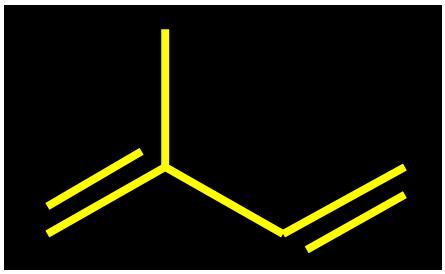
33



34

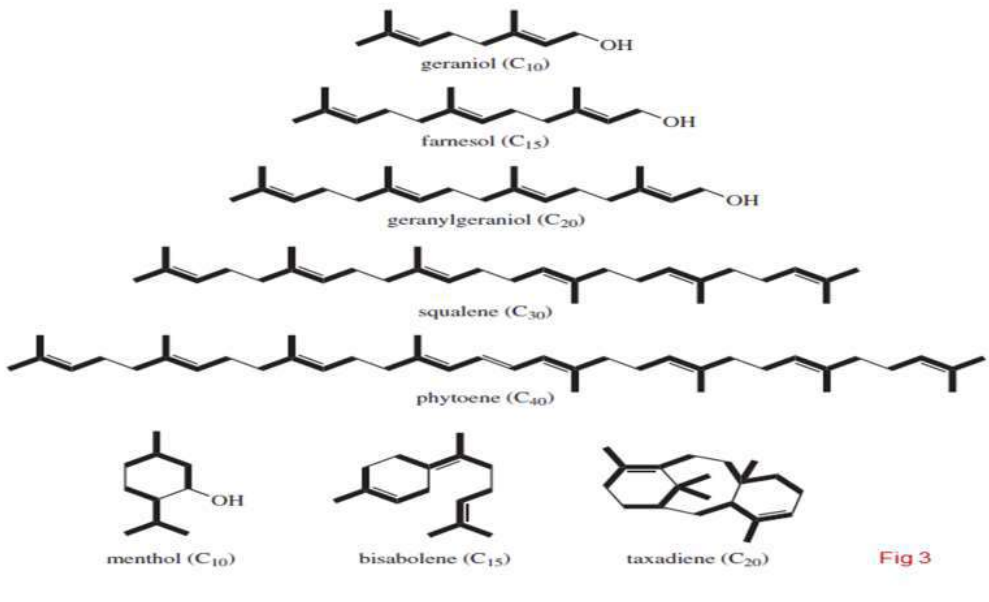
Terpenoids

- Terpenoids form a large and structurally diverse family of natural products derived from C5 **isoprene units** (Isoprene (2-methyl-1,3-butadiene) joined in a head-to-tail fashion.
- Typical structures contain carbon skeletons represented by (C5)*n*, and are classified as **hemiterpenes** (C5), **monoterpenes**(C10), **sesquiterpenes** (C15), **diterpenes** (C20), **sesterterpenes**(C25), **triterpenes**(C30), and **tetraterpenes** (C40)



Isoprene
(2-methyl-1,3-butadiene)

35



36

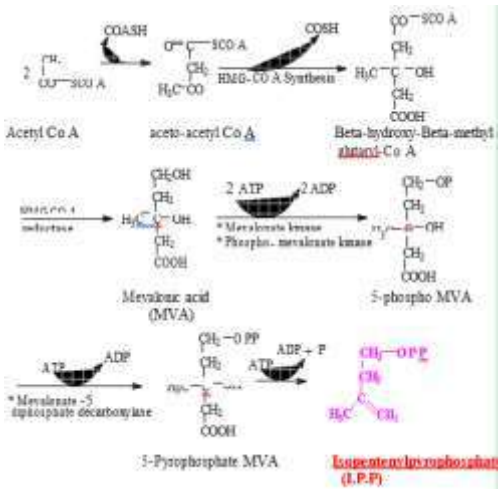
Terpenoids

The biochemically active isoprene units were subsequently identified as the **di**phosphate (**pyro**phosphate) esters **dimethylallyldiphosphate** (**DMAPP**) and **isopentenyl-diphosphate** (**IPP**)

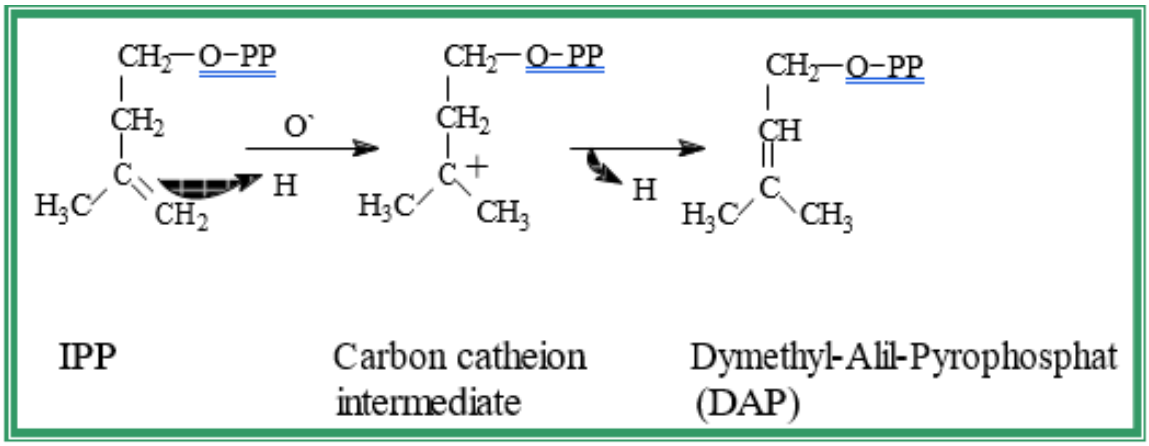
37

Formation of isopentenyl-diphosphate (IPP)

38


COASH
COSH
HMG-CO A Synthesis
Acetyl Co A
aceto-acetyl Co A
Beta-hydroxy-Beta-methyl
2 ATP
2 ADP
Mevalonic acid
(MVA)
5-phospho MVA
ATP
ADP
ADP + P
5-Pyrophosphate MVA

39


O`
H
H
IPP
Carbon catheion
intermediate
Dymethyl-Alil-Pyrophosphat
(DAP)

40

MONOTERPENES (C10)

41

Monoterpenes (C_{10})

1. Cation mechanisms:

- **Loss of Proton**
- **Quenching with water**
- **Repeated Cyclization**
- **Wagner–Meerwein Rearrangements**

2. DMAPP and IPP yield geranyldiphosphate, by loss of proton.

42

Monoterpene Formation

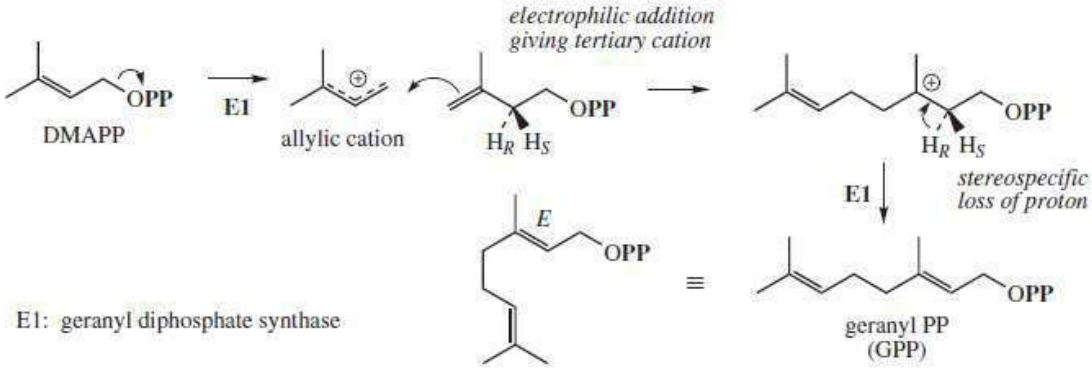


Fig 6

43

Monoterpenes
(C_{10})

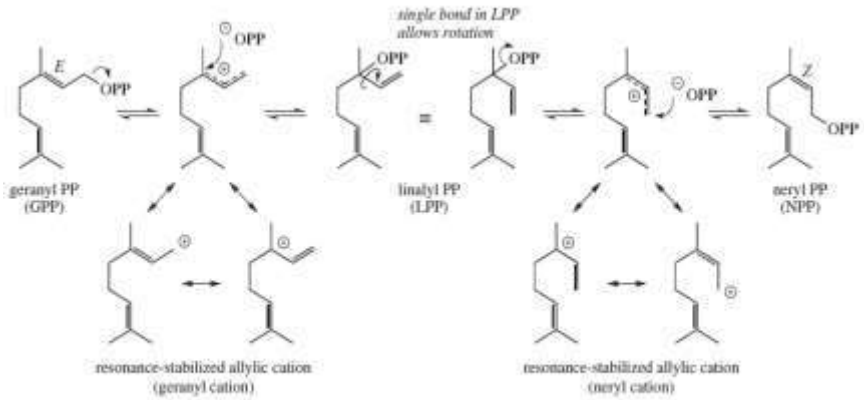


Fig 7

3. Linalyl PP and neryl PP are isomers of GPP
4. formed from GPP by ionization to the allylic cation

44

5. These three compounds (GPP, LPP, NPP), by relatively modest changes, can give rise to a range of linear monoterpenes found as components of volatile oils used in flavoring and perfumery.

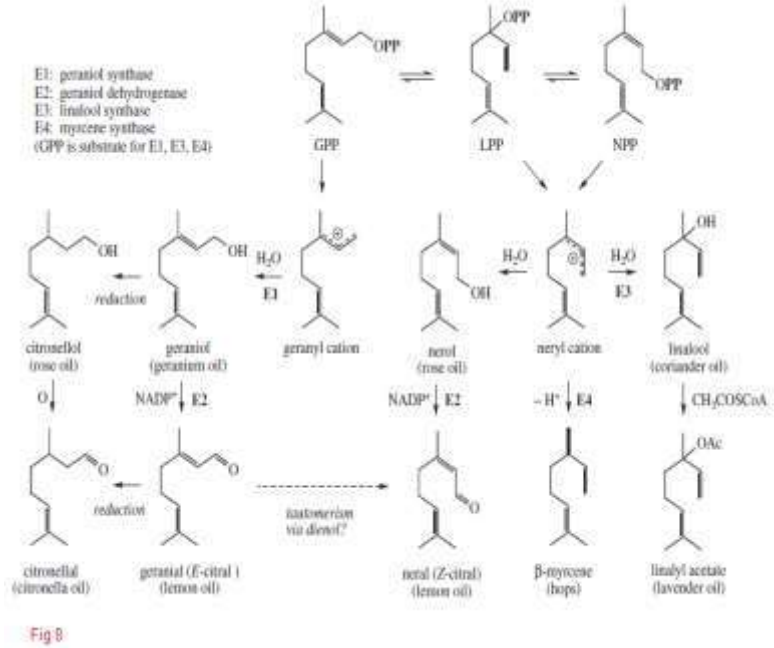
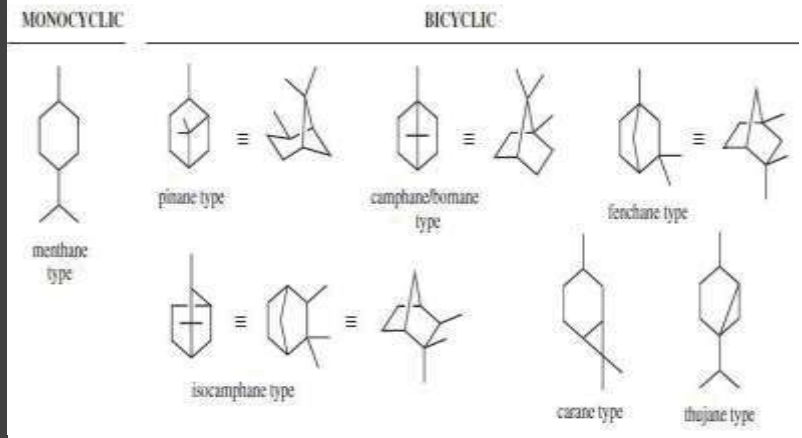


Fig 8

45

6. Majority of monoterpenoid structures arising from the head-to-tail coupling of two C5 GPP units, and may be

- **Acyclic**
- **Monocyclic**
- **Bi & tricyclic**
- **Irregular monoterpenes**
- **Iridoids**



46

7. The newly generated menthyl cation could be:

- quenched by attack of water, in which case the alcohol **α-terpineol** would be formed
- or it could lose a proton to give **limonene**

8. α-terpineol by loss of proton and influence of 1,8 cineole synthase lead to cineol.

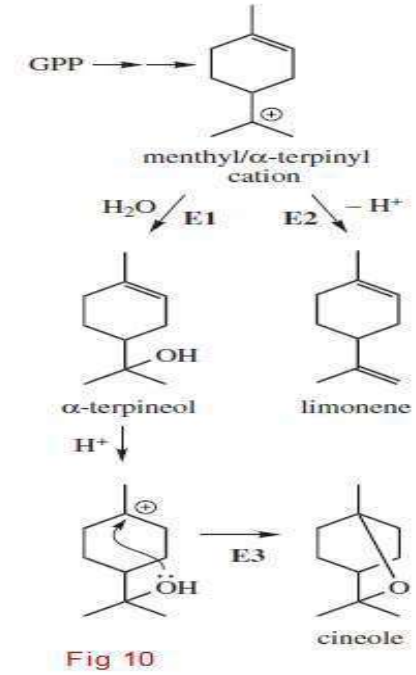


Fig 10

47

9. Alternatively, folding the cationic side-chain towards the double bond (via the surface characteristics of the enzyme) would allow a **repeat of the cyclization** mechanism and **produce bicyclic pinyl and bornyl cations**.

10. α-pinene and β-pinene arise **by loss of different protons** from the pinyl cation

11. Borneol could potentially result from **quenching** of the bornyl cation with water

12. Oxidation of Borneol lead to Camphor

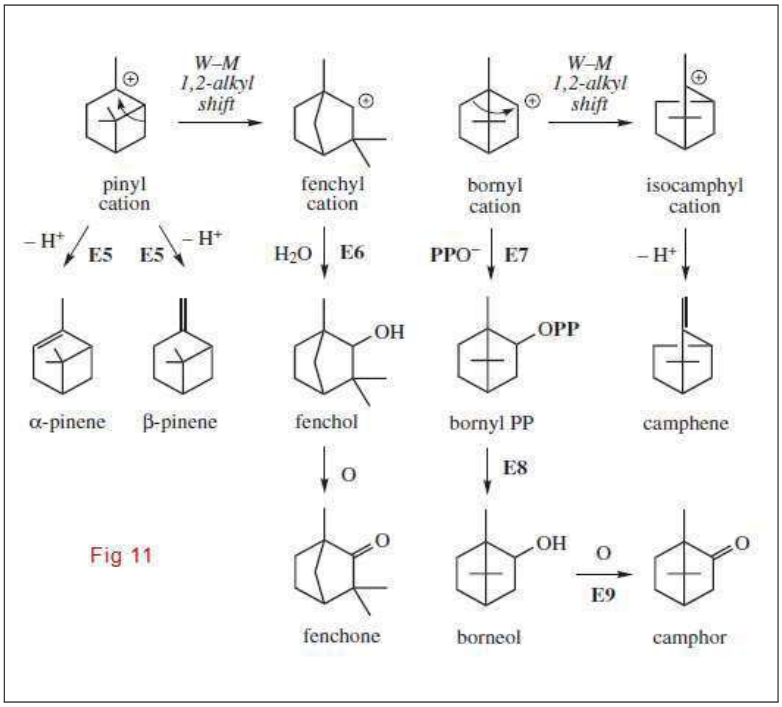
15. **Wagner–Meerwein Rearrangements** of Pinyl cation (carbon atoms or hydride migrate to achieve stability for the cation via tertiary against secondary character) to produce Fenchyl cation.

16. **Wagner–Meerwein Rearrangements** of Bornyl cation to produce isocamphyl cation

17. Fenchyl cation by **quenching with water** lead to fenchol which by oxidation lead to fenchone.

18. Isocamphyl cation by **loss of proton** lead to camphene.

48



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19. Menthyl α terpinyle cation through **W-M rearrangement (1-3 shift)** lead to phellandryl cation.

20. Phellandryl cation by **loss of proton** lead to α-Phellandrene

21. Phellandryl cation by **loss of proton** & influence of β-phellandrene synthase lead to β-phellandrene.

22. Menthyl α terpinyle cation through **W-M rearrangement (1-2 shift)** leads to terpinen cation-4yl & thujyl cation.

23. Terpinen cation-4yl through **loss of proton** lead to α terpinene.

24. Thujyl cation through **loss of proton** lead to sabinene which by oxidation & reduction lead to thujone.

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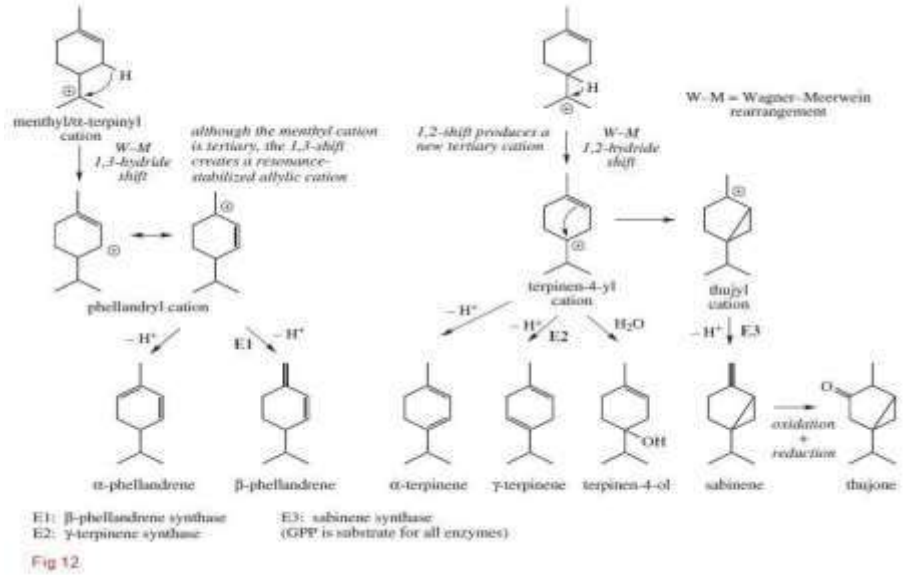


Fig 12

51

- Most monoterpenes are **optically active.**
- Peppermint (*Mentha piperita*; Labiatae/Lamiaceae) typically produces (−)-**menthol**, with smaller amounts of the stereoisomers (+)-**neomenthol**, (+)-**isomenthol**, and (+)-**neoisomenthol**, covering four of the possible eight stereoisomers
- Oils from various *Mentha* species also contain significant amounts of ketones, e.g. (−)-menthone
- **Limonene is a precursor of carvone** ***(from Caraway)*****.**

52

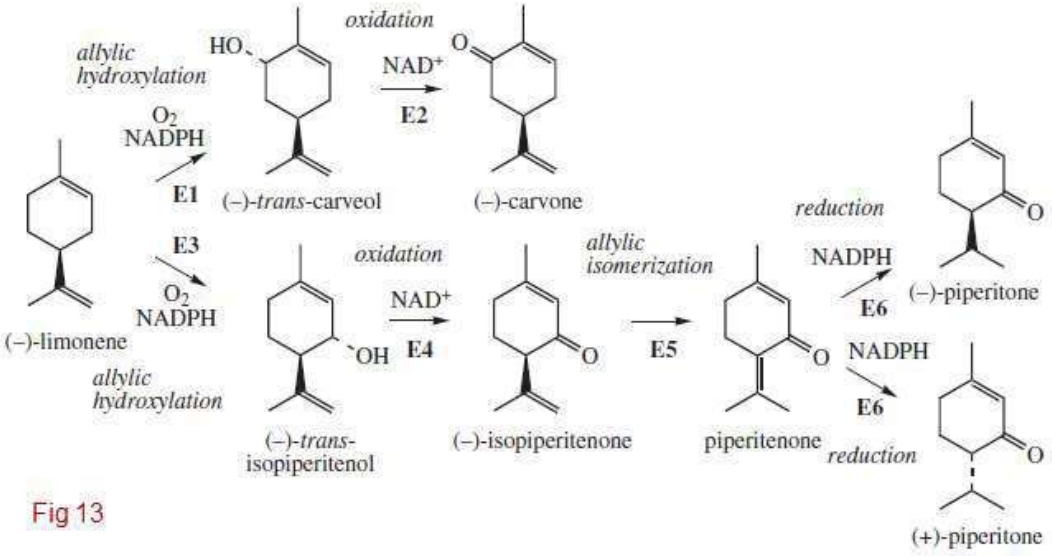


Fig 13

53

IRREGULAR MONOTERPENES

- A number of natural monoterpene structures contain carbon skeletons which, although obviously derived from two isoprene C5 units, do **not seem to fit the regular head-to-tail coupling mechanism**. Allowing for possible rearrangements, the two isoprene units appear to have coupled in another manner.

regular monoterpene skeleton

irregular monoterpene skeletons

Fig 14

54

IRREGULAR MONOTERPENES

- DMAPP and IPP are utilized in their biosynthesis, GPP and neryl PP do not appear to be involved.

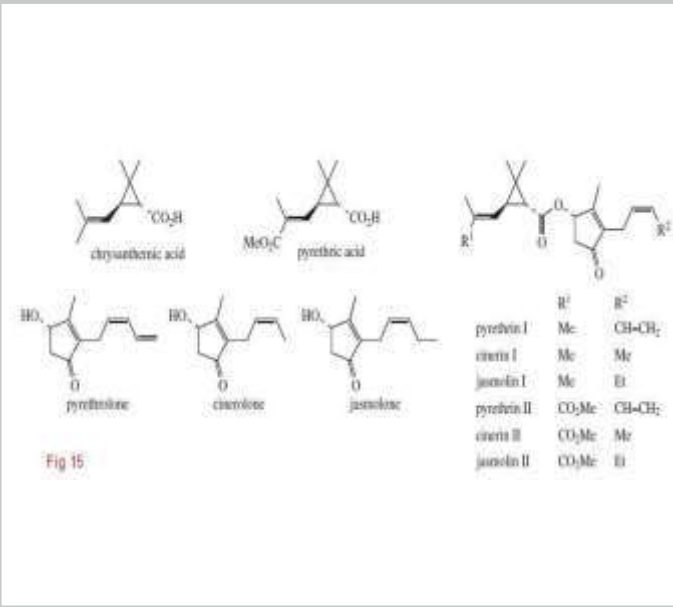


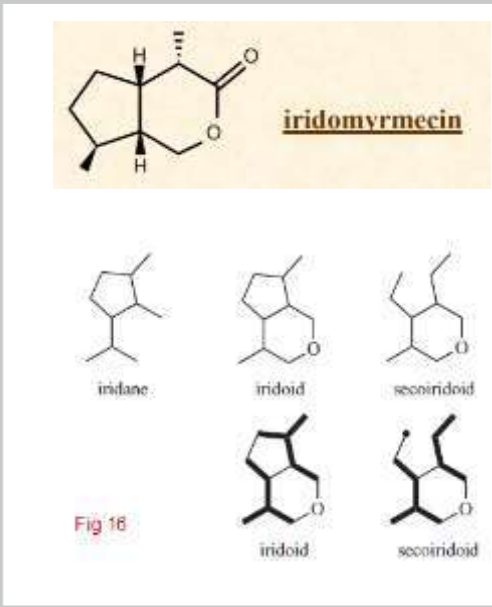
Fig 15

55

56

Iridoids

- Iridoids $(C_5H_8)_2$ are a class of secondary metabolites found in a wide variety of plants and in some animals. They are monoterpenes biosynthesized from isoprene.
- **Chemically**, the iridoids usually consist of a **cyclopentane ring** fused to a **six-membered oxygen heterocycle**.



57

Classification:

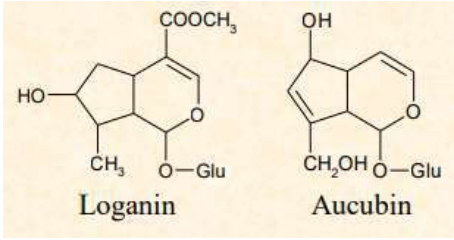
- Iridoids Classify in 4 groups:
  - Cyclopentan types
  - Seco-iridoids
  - Iridoids of plants from family Valerianaceae
  - Iridoids-alkaloids

58

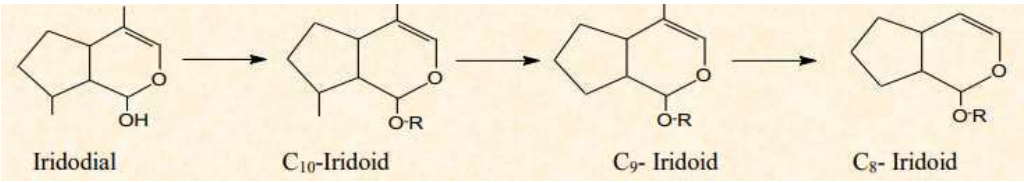
Classification

Cyclopentan types:

- According to number of C atom in skeleton of aglycon they could be divided on 4 types: C_8 , C_9 , C_{10} and C_{14}.



Loganin Aucubin



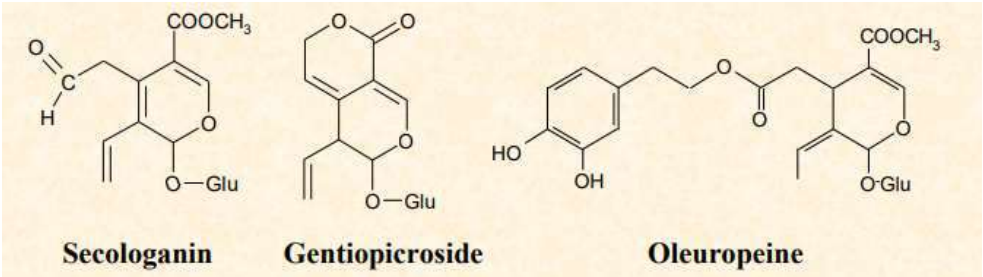
Iridodial C_{10}-Iridoid C_9- Iridoid C_8- Iridoid

59

Classification

Seco-iridoids:

- Cleavage of a bond in the cyclopentane ring gives rise to secoiridoids.



Secologanin Gentiopicroside Oleuropeine

60

Monoterpene Containing Drugs

61

Essential Oils

62

Factors that affect the Ingredients in an Essential oil

- **Which part of the plant used**
- **Growing season**
- **Altitude**
- **Soil Conditions**
- **Fertilizer (chemical or organic)**
- **Geographical Location**
- **Harvesting Methods**
- **Distillation process (low heat vs high heat)**

63

Essential Oils Benefits

The benefits of essential oils have been recognised for thousands of years.

Their use is described in the Bible & Quran.

They were used in massaging services and in healing the sick.

Used in perfumes, cosmetic products, cleaning products and as flavorings in foods.

64

Essential Oil Benefits

- **Balance Hormones** (estrogen, progesterone, cortisol, thyroid and testosterone levels) **such as sage, geranium and thyme.**
- **Boost Immunity & Fight Infections, such as** oregano, myrrh, ginger, lemon, eucalyptus, peppermint and cinnamon.
- **Support Digestion, such as ginger oil**
- **Boost Energy Levels, such as** peppermint oil increased brain oxygen concentration.
- **Improve Brain Function,** neuroprotective effects and can help to improve cognitive performance, such as peppermint oil.

65

Essential Oil Benefits

- **Reduce Emotional Stress & Anxiety** include lavender, Roman chamomile, bergamot, orange, and rose oil.
- **Alleviate Aches and Pains,** include lavender, peppermint, eucalyptus, chamomile, rosemary, thyme, turmeric, ginger and myrrh.
- **Boost Skin and Hair Health,** include lavender, Roman chamomile, tea tree, geranium, myrrh, rosemary and sage.
- **Reduce Toxicity,** include lemon, grapefruit, parsley, fennel, lemongrass, peppermint and ginger.
- **Relieve Headaches and Migraines, such as** lavender.
- **Promote Restful Sleep such as** lavender oil.

66

Argan Oil (*Argania spinosa L.*)

- **Skin infections, bug bites and skin rashes**
- **Boost cell production while promoting healthy skin and hair.**
- **Nighttime Moisturizer**
- **Skin Toner**
- **Exfoliant** ***(to remove dead cells from the surface of the skin)***
- **Acne Remedy**
- **Stretch Mark Remedy**
- **Razor Bumps and Burn Treatment**
- **Foot Treatment**

67

Almond oil - *Prunus dulcis* (*Amygdalus communis L.*)

- **Regulates Cholesterol**
- **Reduces Risk of Heart Disease**
- **Protects Against Diabetes**
- **Promotes Healthy Weight**
- **Natural laxative**
- **Keeps Your Colon and Rectum Healthy**
- **Treats Earaches**
- **Dark circles under your eyes**

68

Jojoba wax/oil (*Simmondsia chinensis*)

- Moisturizes Skin
- Eczema & acne treatment
- Antiaging
- stimulates collagen synthesis
- Promotes Hair Health
- Contains Vitamin E
- Contains Vitamin B Complex
- Fights Fungi and Infections

69

Lavender Essential Oil

- Calming, stress relieving, sleep promoter.
- Stops the itch and burn of insect bites.
- Soothes burns and sunburns
- As a flavor boost

70

Clove Oil

- **For toothache and dental abscess**
- **Potent anti-fungal**.
- **For cold sores (**Clove oil has anti-viral properties, especially against herpes simplex),
- **For arthritic pain**
- **Help kills bacteria in the kitchen & around the home**

71

Grapefruit Essential Oil

- **In your drinking water**
- **Eases a hangover**. Grapefruit oil's natural ability to stimulate the gall bladder and liver helps to detox
- **Banish anxiety**.
- **Helps to overcome sugar cravings**.

72

Orange Essential Oil

- Cold and flu prevention
- Helps heal mouth ulcers.
- Wound disinfectant.
- Foot callus softener/remover.
- Skin anti-aging.

73

Lemon Essential Oil

- In your cooking or drinking water.
- For spot-free dishes
- Foot callus softener/remover (Not for face!!)
- For oily hair.

74

Geranium Rose Essential Oil

- **For premenstrual tension and cramps**
- **For hemorrhoids**
- **For liver detoxing.**
- **Skin healing and regeneration**

75

Peppermint Essential Oil

- **Cool a hot flash**
- **As a driving aid (**ts ability to wake up the nervous system and keep your brain alert is unmatched).
- **For aching muscles and joints**.
- **For allergy relief.**
- **As a digestive aid**

76

Oregano Oil

- As an infection fighter
- As an anti-aging antioxidant
- Ease a sore throat.
- For athlete's foot and fungal infections
- Eliminates intestinal worms.

77

Rosemary Oil

- Anti-cancer, anti-proliferative
- Improves circulation, varicose veins.
- Improves brain health.
- For healthy scalp and beautiful hair.
- Counteract the effects of stress.

78

Eucalyptus Essential Oil

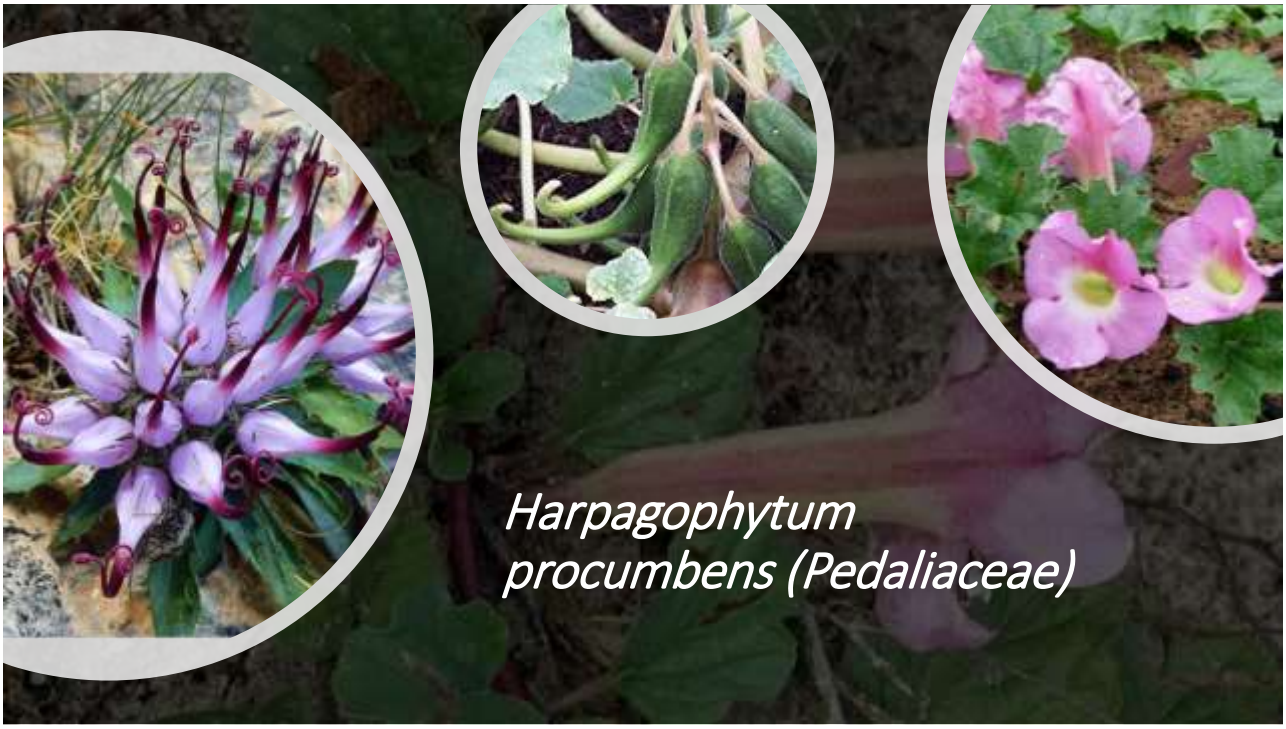
- **Strong insect repellent.**
- **Fever reducer.**
- **Improves blood flow to brain**
- **Assists upper respiratory infections and eases asthma attacks.**

79

Tea Tree Oil (*Aka melaleuca*)

- **For eczema and psoriasis.**
- **Tea tree oil's potent antibacterial properties**
- **Prevents razor burn (after shaving).**
- **Natural insecticide, bug repellent, and bite reliever.**
- **For Acne**

80

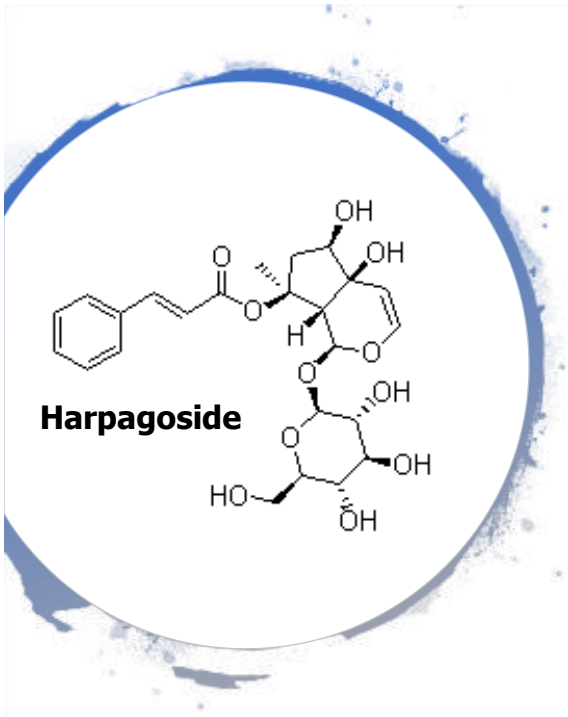


81

Harpagophytum procumbens

- **Common Name: Devil's Claw**
- **Family: Pedaliaceae**
- Devil's claw is a prostrate, sprawling plant with a stout, perennial rootstock that has a group of secondary storage tubers arising from it.
- The plant has very spiny fruits that lay on the ground and can cause serious damage to the feet.
- Devil's claw has long been a traditional medicine of the people in southern Africa as anti-inflammatory agent.

82



Chemical Characters

- **L-iridoide monoterpenes:** including **harpagoside** (extremely bitter), harpagide, procumbide
- **Phenylethanol derivatives:** including acteoside (verbascoside); isoacteoside
- **Oligosaccharides:** stachyose
- Harpagoquinones(traces)

83

Biological Characters

- **Part used:** The roots and tubers of the plant.
- **Effect:** Devil's Claw stimulates gastric juice secretion and is **choleretic**.
- Anti-inflammatory, analgesic effect has been shown in animal experiments.
- **Indication:**
  - Dyspeptic complaints
  - Hardening of the arteries" (**atherosclerosis**),
  - **arthritis**, gout, muscle **pain** (myalgia), **back pain**, **fibromyalgia**, tendonitis,
  - chest **pain**, gastrointestinal (GI) upset or heart burn, **fever**, and migraine headache.

84

Precaution & Side Effects

- **Allergic reaction**: rash; difficult breathing; swelling of your face, lips, tongue, or throat.
- Diarrhea, stomach pain;
- Nausea, vomiting, loss of appetite;
- Changes in menstrual periods;
- Headache, ringing in your ears; or.
- Altered sense of taste.
- Loss of taste.
- It can also cause allergic skin reactions, and
- Changes in blood pressure.

85

Contraindication

- Allergic reaction
- Pregnancy

86

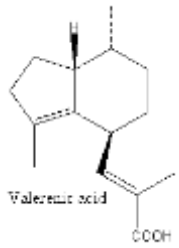
Valeriana officinalis (Valerianaceae)

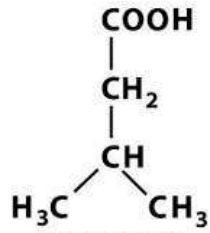
- The flowers are fragrant and the rhizome smells strongly when dried.
- The odor is not present in the fresh plant.
- Hydrolysis of components in the root form **isovaleric acid** which is responsible for the offensive smell.

87

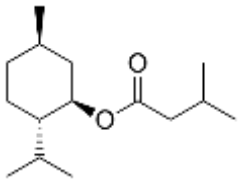
Phytochemicals

- **Iridoids**: valepotriates (**valeriana-epoxy-triacylates**,
- **Iridoid monoterpenes**, (0.5-2.0%) chief components (50-80%). isovalerate (up to 46%).
- **Volatile oil** (0.2-1.0%): chief components (-)-bornyl isovalerenate and **isovalereic acid** (both aroma-carriers).
- **Sesquiterpenes**: valerenic acid (0.1-0.9%)
- **Pyridine alkaloids**
- **Caffeic acid derivatives**

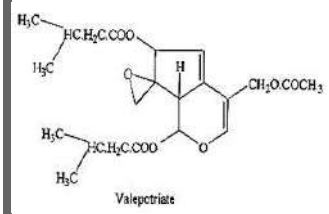




Isovaleric Acid
(3-Methylbutanoic acid)



Menthyl isovalerate

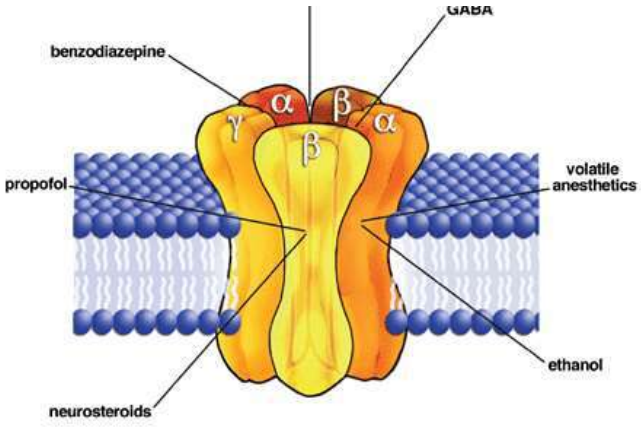


Valepctriate

88

Mechanism of Action

- Gamma-aminobutyric acid, or GABA, is a neurotransmitter that sends chemical messages **through the brain** and the **nervous system**, and is involved in **regulating communication between brain cells.**
- The role of GABA is to **inhibit or reduce the activity of the neurons or nerve cells.**
- GABA plays an important role in **behavior, cognition**, and the **body's response to stress**.
- GABA helps to **control fear and anxiety** when neurons become overexcited.



89

Biological Activity

- **Effect:**
  - Tranquilizer – Sedative – or Hypnotic???
  - increase of GABA at the synaptic cleft via inhibition of re-uptake and an increase in secretion of the neurotransmitter.
  - The increase of available GABA is one factor that may be responsible for the tranquilizer/sedative properties of Valerian root.
- **Indication**
  - Nervousness and insomnia
- **Mode of Administration**

90

Olea europaea L.
(Oleaceae)

91

Olea europaea L.
(Oleaceae)

- **Part used:** Leaves & Fruits
- **Traditional Medicine:**
  - Since **Ayurveda** believes all disease begins in the digestive tract, food is your first ... You'll learn your body type, and whether **Olives** is a good fit as digestive aid.
  - **In Chinese Medicine olives** are used to quench thirst, heal a sore throat, treat laryngitis, alleviate a whooping cough, and combat dysentery.
  - In **Islamic Medicine**: Mention in Quran 7 times & In Sunna

92

PHYTOCHEMICALS:

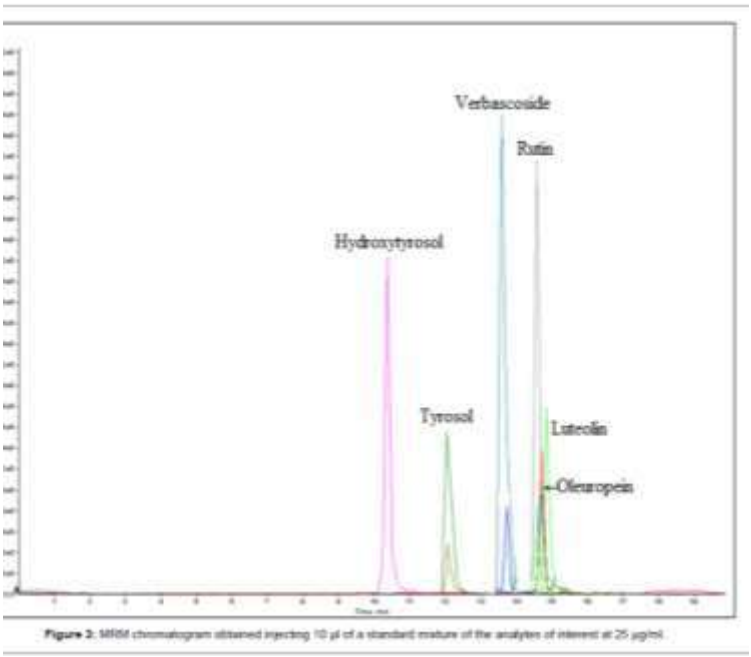
OLIVE LEAVES

- **Iridoid monoterpenes:**
  - **oleoropine** (6-9%), additionally 6-O-oleoropinesaccharose, ligstroside, oleoroside.
- **Triterpenes**:
  - **oleanolic acid, maslinic acid**
- **Flavonoids**: luteolin-7-O-glucoside, apigenine-7-O-glucoside
- **Hydroxytyrosol**

OLIVE OILS

- **Chief fatty acids:**
  - **oleic acid** (56-83%), **palmitic acid** (8-20%), **linoleic acid** (4-20%)
- **Steroids:**
  - β-sitosterol, delta7-stigmasterol, delta5-avenasterol, campesterol, stigmasterol
- **Tocopherols** (0.02%)

93



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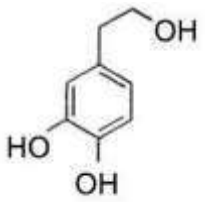
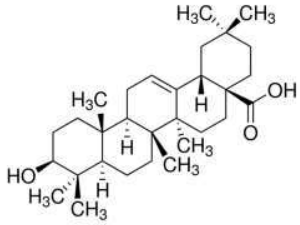
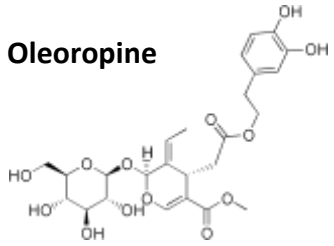


Hydroxytyrosol

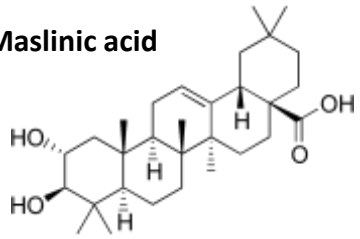
Oleanolic acid



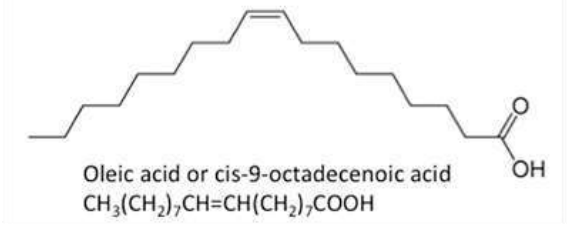
Oleoropine



Maslinic acid

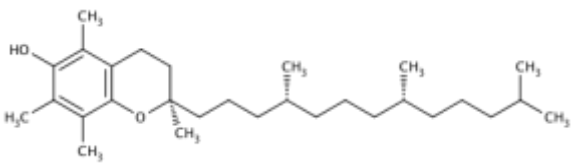


95

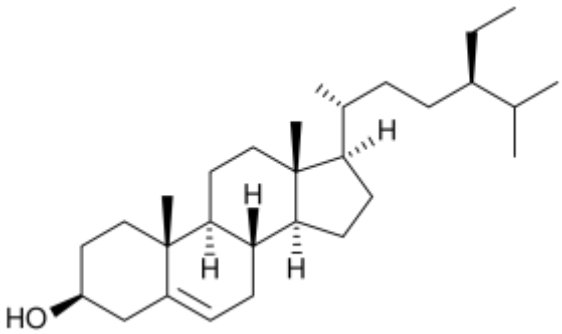


Oleic acid or cis-9-octadecenoic acid

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$

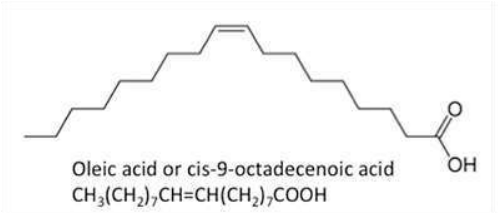


Tocopherols

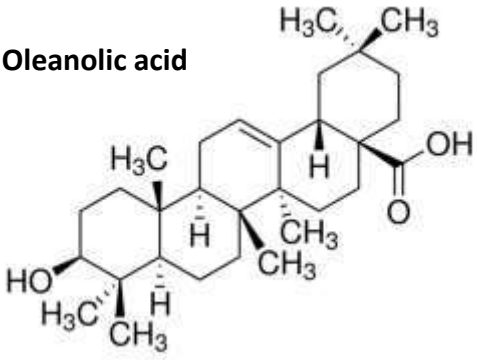


β-sitosterol

96



Oleanolic acid



قال تعالى: اللَّهُ نُورُ السَّمَاوَاتِ وَالْأَرْضِ مَثَلُ نُورِهِ كَمِشْكَاةٍ فِيهَا مِصْبَاحٌ الْمِصْبَاحُ فِي زُجَاجَةٍ الزُّجَاجَةُ كَأَنَّهَا كَوْكَبٌ دُرِّيٌّ يُوقَدُ مِن **شَجَرَةٍ مُّبَارَكَةٍ زَيْتُونِةٍ لَّا شَرْقِيَّةٍ وَلَا غَرْبِيَّةٍ** يَكَادُ **زَيْتُهَا يُضِيءُ** وَلَوْ لَمْ تَمْسَسْهُ نَارٌ نُّورٌ عَلَى نُورٍ يَهْدِي اللَّهُ لِنُورِهِ مَن يَشَاء وَيَضْرِبُ اللَّهُ الْأَمْثَالَ لِلنَّاسِ وَاللَّهُ بِكُلِّ شَيْءٍ عَلِيمٌ.

97

Effect of Olive

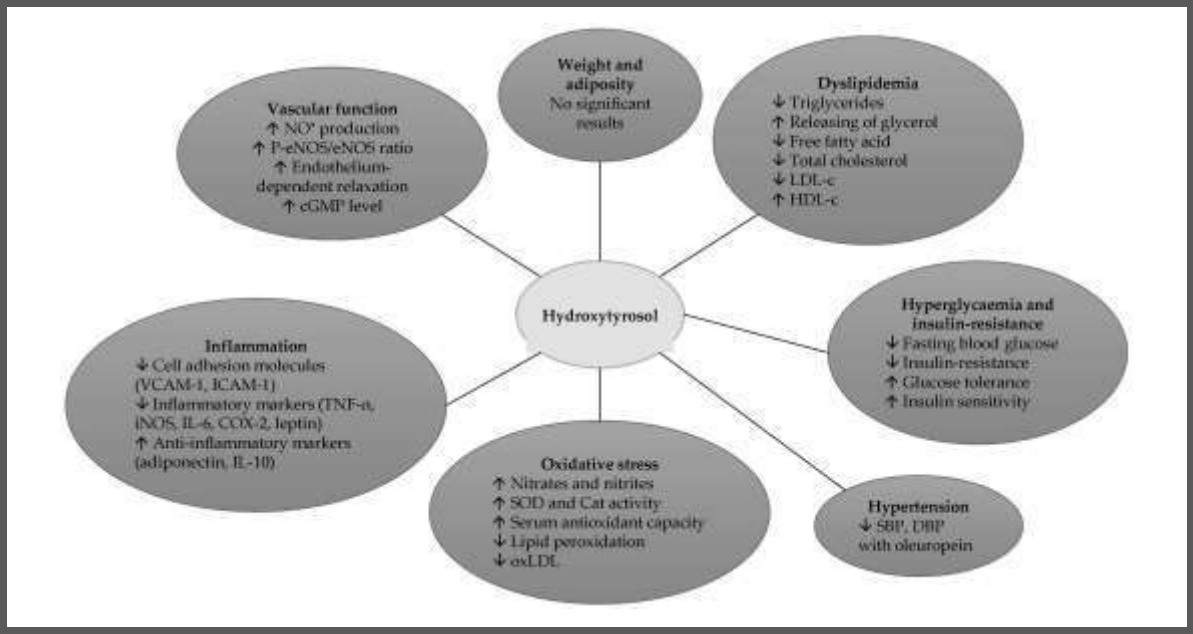
OLIVE LEAVES Extract

- Anti-inflammatory agent
- Neuroprotective
- Antihypertensive
- Spasmolytic effects on the smooth muscle of the intestine
- Fights harmful microbes and boosts the immune system. ... As a natural antimicrobial (NOT kill the beneficial bacteria).
- Reduce cholesterol
- Improved insulin sensitivity
- Oleuropein has also shown protective capabilities against breast cancer

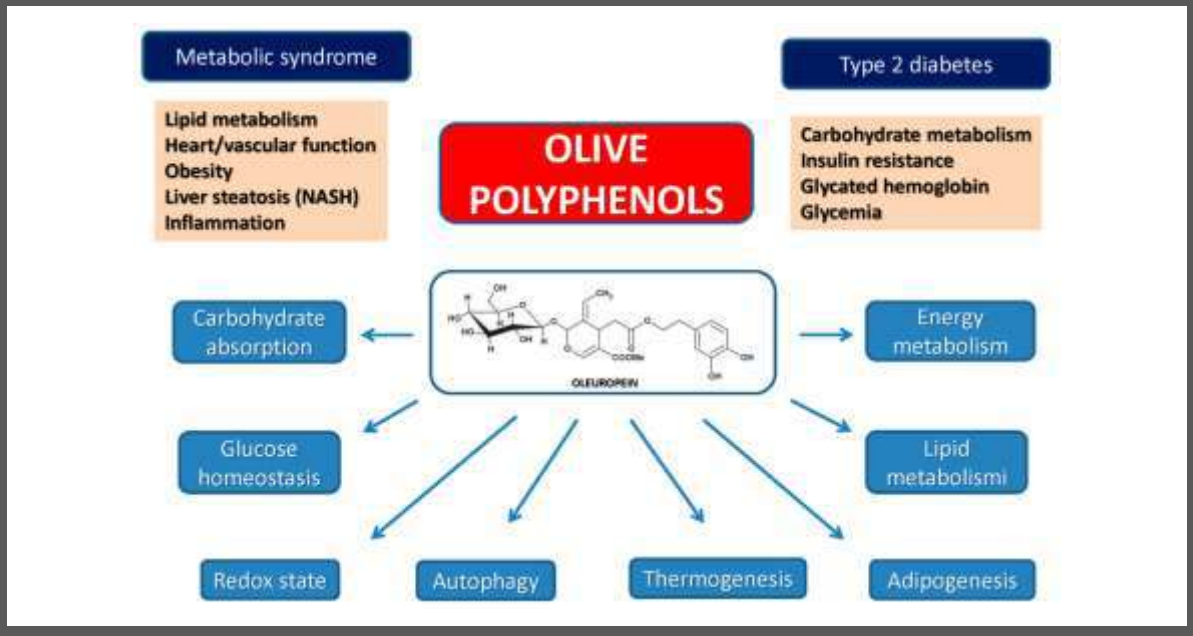
OLIVE OIL

- Anti-inflammatory agent
- Boost immune system
- Fat burner
- Antioxidant
- prevent heart attack and stroke
- constipation,
- high cholesterol, high blood pressure, blood vessel problems associated with diabetes,
- pain associated ear infections, arthritis, and gallbladder disease.
- Olive oil is also used to treat jaundice,
- It is also used to destroy the bacteria that causes some ulcers, helicobacter pylori.

98


Hydroxytyrosol
Weight and adiposity
No significant results
Vascular function
↑ NO• production
↑ P-eNOS/eNOS ratio
↑ Endothelium-dependent relaxation
↑ cGMP level
Dyslipidemia
↓ Triglycerides
↑ Releasing of glycerol
↓ Free fatty acid
↓ Total cholesterol
↓ LDL-c
↑ HDL-c
Hyperglycaemia and insulin-resistance
↓ Fasting blood glucose
↓ Insulin-resistance
↑ Glucose tolerance
↑ Insulin sensitivity
Inflammation
↓ Cell adhesion molecules (VCAM-1, ICAM-1)
↓ Inflammatory markers (TNF-α, iNOS, IL-6, COX-2, leptin)
↑ Anti-inflammatory markers (adiponectin, IL-10)
Oxidative stress
↑ Nitrates and nitrites
↑ SOD and Cat activity
↑ Serum antioxidant capacity
↓ Lipid peroxidation
↓ oxLDL
Hypertension
↓ SBP, DBP with oleuropein

99


Metabolic syndrome
Lipid metabolism
Heart/vascular function
Obesity
Liver steatosis (NASH)
Inflammation
Type 2 diabetes
Carbohydrate metabolism
Insulin resistance
Glycated hemoglobin
Glycemia
OLIVE POLYPHENOLS
OLEUROPEIN
Carbohydrate absorption
Energy metabolism
Glucose homeostasis
Lipid metabolismi
Redox state
Autophagy
Thermogenesis
Adipogenesis

100

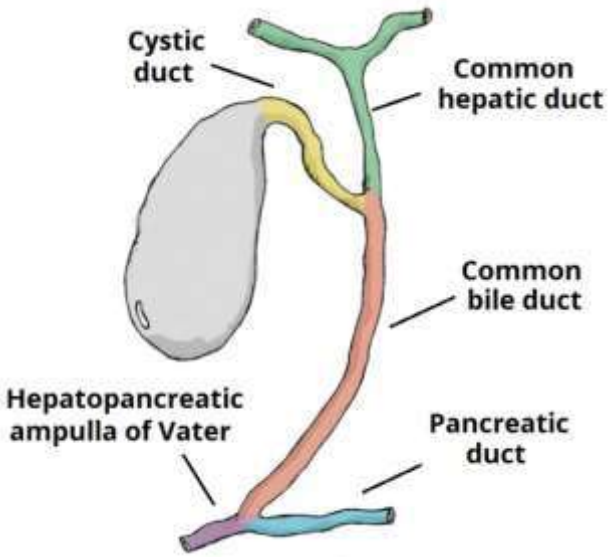
Side Effects

- Olive oil is **LIKELY SAFE** when taken as 14% of total daily calories.

101

CONTRAINDICATIONS

- **Biliary colic,** gallbladder attack or **gallstone** attack, is when a **colic** can even be found **in patients** post-cholecystectomy.

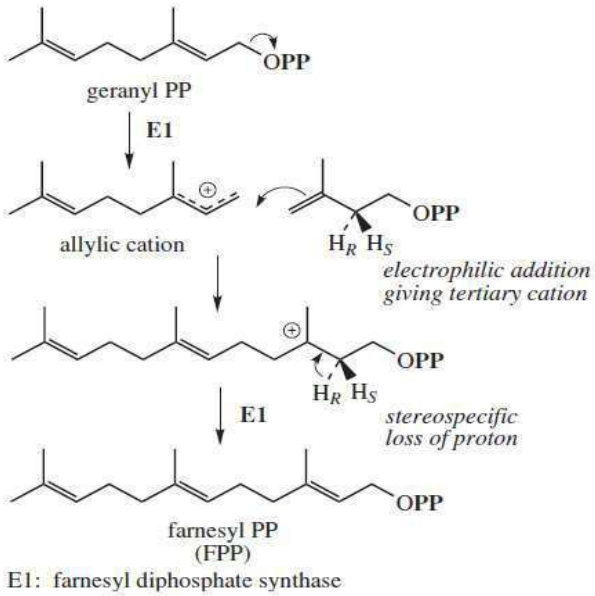


102

SESQUITERPENES (C_{15})

103

Biosynthesis

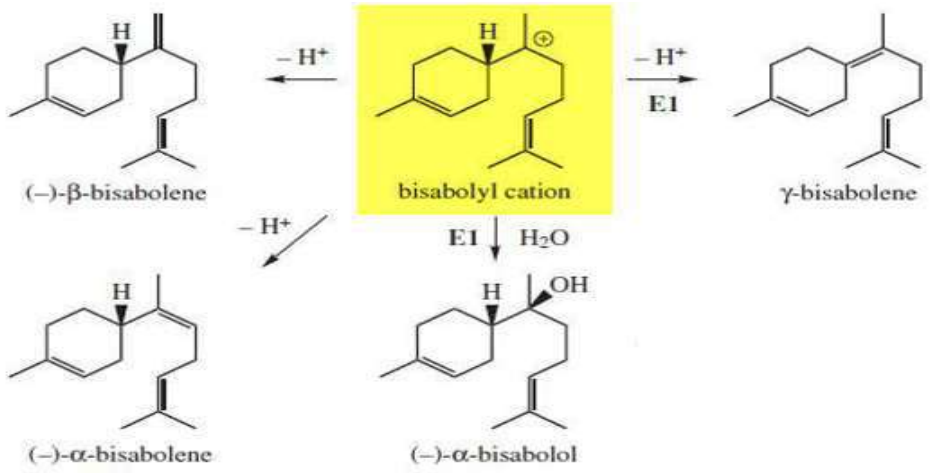


E1: farnesyl diphosphate synthase

Fig 23

104

Chemistry of sesquiterpene



105

Sesquiterpene Containing Drugs

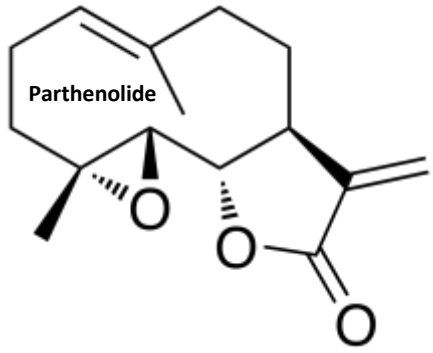
106

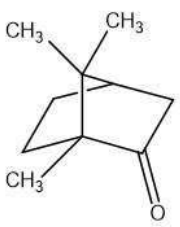
Tanacetum parthenium
(Asteraceae/Compositae)
= Feverfew=

107

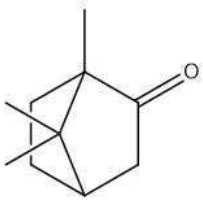
Phytochemicals

- **Sesquiterpene lactones:** Parthenolide as active ingredient
- **Monoterpene:** Camphor responsible of the odor





Camphor

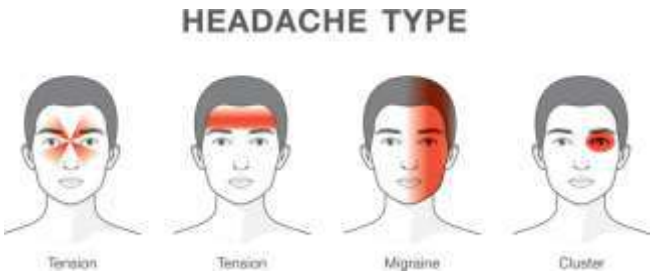


camphor

108

Pharmacological Properties

- Prophylactic treatment for migraine
- Inhibit blood platelet aggregation
- Release of 5-hydroxytryptamine (5-HT, serotonin) from platelets
- Release of histamine from mast cells
- Production of prostaglandins, thromboxanes, and leukotrienes



109

Chamomile and Matricaria

- *Chamaemelum* ***nobile*** (formerly ***Anthemis nobilis***) (Compositae/Asteraceae) and
- *German chamomile* ***Matricaria chamomilla*** (***Chamomilla recutica***) (Compositae/Asteraceae).

110

Chemistry of Chamomile

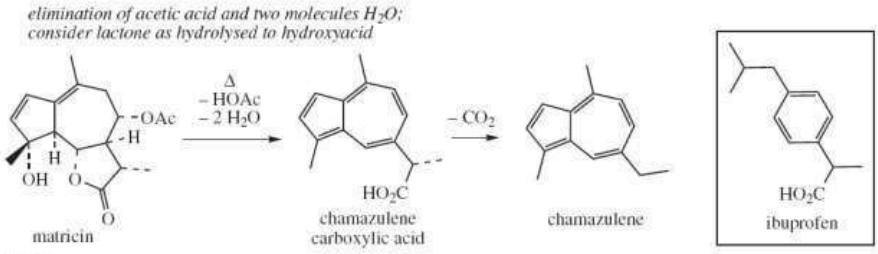


Fig 27

- Sesquiterpenes:
  - **α-bisabolol** (10–25%), bisabolol oxides A and B (10–25%)
  - **Chamazulene** (0–15%) (Chamazulene is a thermal decomposition product from matricin, is responsible for the **dark blue coloration of the oil).**

111

Pharmacological Properties

- Aid digestion
- Curb flatulence
- Mouthwashes, shampoos, and many pharmaceutical preparations
- Antiseptic and anti-inflammatory properties
- Volatile oil

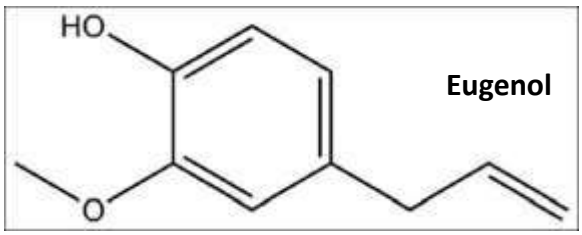
112

Syzygium aromaticum;
(Myrtaceae)
Clove

113

PHYTOCHEMICALS

- **Volatile oil** (15-21%): chief components eugenol (70-90%), eugenyl acetate (aceteugenol, up to17%), beta-caryophyllene(5-12%).
- **Triterpenes**: oleanolic acid (1%), crataegolic acid (maslicacid, 0.15%).
- **Steroids**: sterols, including beta-sitosterol.
- **Flavonoids**: including astragalin, isoquercitrin, hyperoside, quercetin-3,4'-di-0-glycoside
- **Tannins** (10%): ellagitannins, including eugenin.



Eugenol

114

Chemistry of Clove

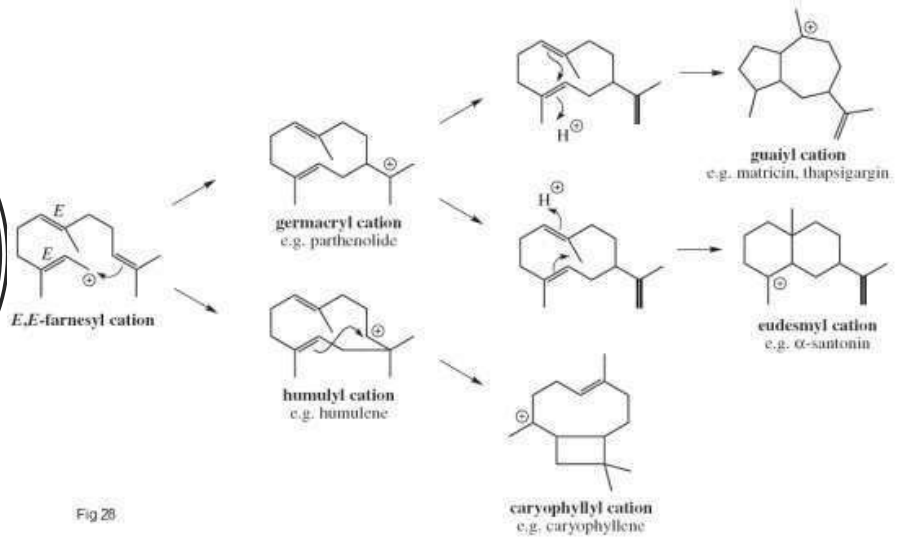
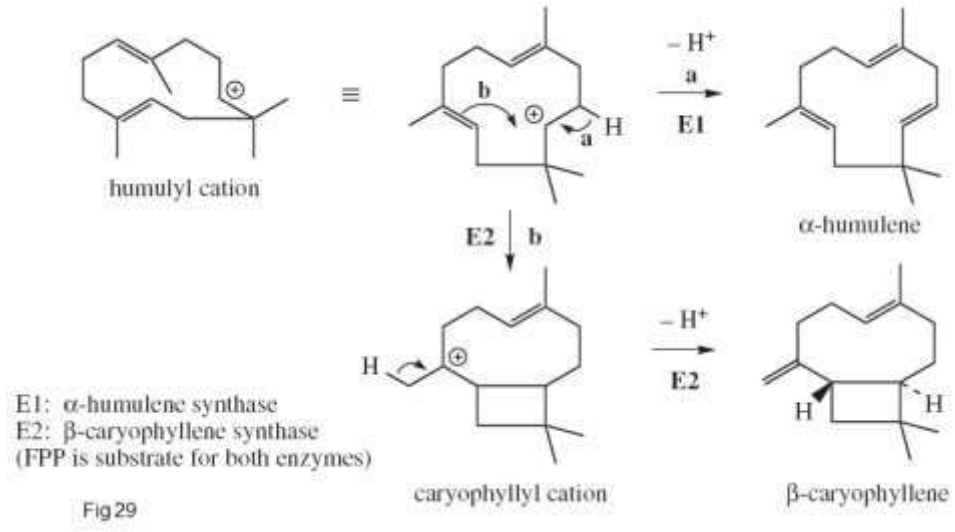


Fig 28

115



E1: α-humulene synthase
E2: β-caryophyllene synthase
(FPP is substrate for both enzymes)

Fig 29

116

Biological Activity

117

Effect

- Antiseptic,
- Antibacterial,
- Antifungal,
- Antiviral,
- Spasmolytic and
- Local anesthetic.

118

Artemisia absinthium Artemisia annua

(Compositae/ Asteraceae)

119

Chemistry of Artemisia

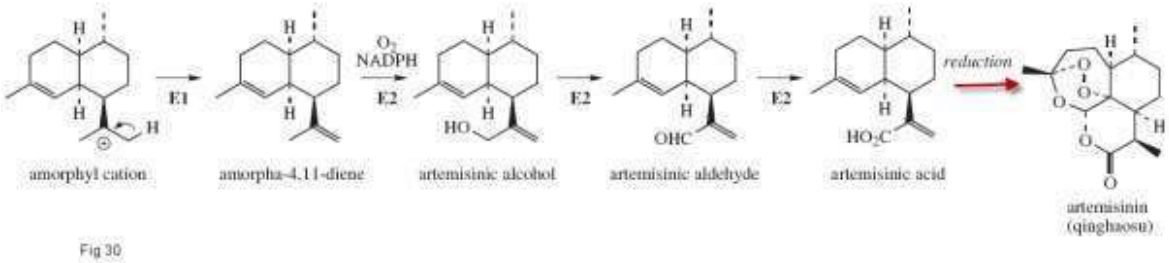


Fig 30

Sesquiterpene lactone: **Artemisinin, Artemisinin Artemisinic acid**

120

Biological Activity

- **Artemisia annua** is an herb traditionally **used in** Chinese medicine to treat fever, inflammation, and malaria.
- **Artemisia** has been shown to be effective in the treatment of malaria.
- Artemisia **used for** various digestion problems such as loss of appetite, upset stomach, gall bladder disease, and intestinal spasms.
- **Absinthe** is regulated by the Food and Drug Administration and, until recently, was completely **banned in the U.S.** and most of Europe. The reason for this is that **absinthe** contains **thujone blamed as hallucinogenic effect.**

121

Gossypium species

122

Gossypium species

- **Species:** G. hirsutum, G. herbaceum, G. arboreum, G. barbadense;
- **Family:** Malvaceae
- The active **ingredient** is (-) gossypol & (+) gossypol
- **Effect:** contraceptive, altering sperm maturation, spermatozoid motility, and inactivation of sperm enzymes necessary for fertilization due to present of (-) gossypol.
- **Toxic** effect due to (+) gossypol

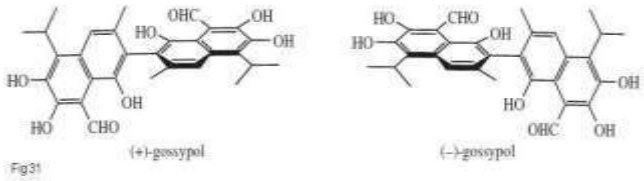


Fig31

123

124

Biosynthesis

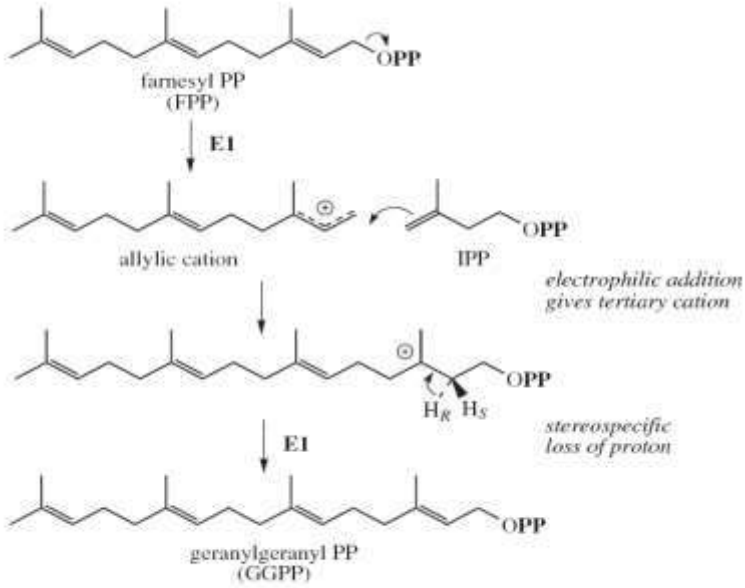


Fig 32

E1: geranylgeranyl diphosphate synthase

125

Chemistry of Diterpen

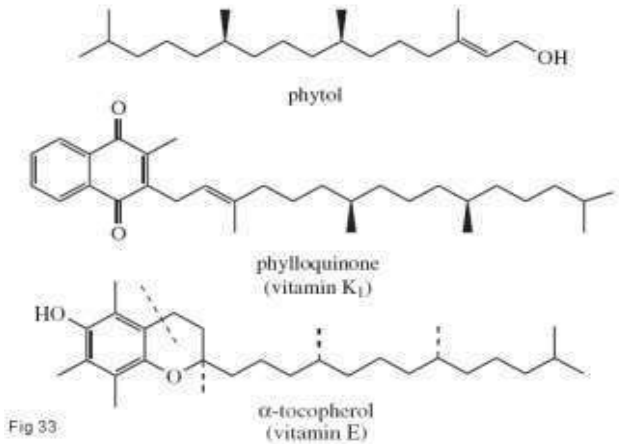
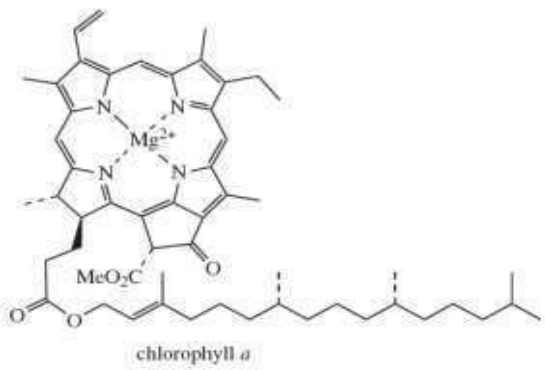


Fig 33



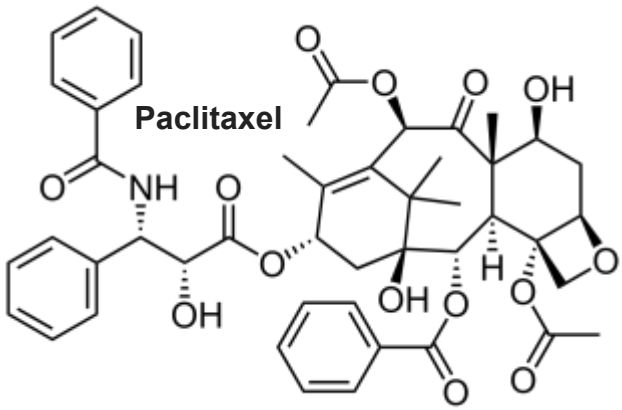
126

Diterpenes Containing Drugs

127

Taxus baccata; Taxaceae

- **Cyclization reactions of GGPP mediated by carbocation formation, plus the potential for Wagner–Meerweinre arrangements, will allow many structural variants of diterpenoids to be produced.**
- **The toxic principle „taxine" has been shown to be a mixture of at least 11 compounds based on the taxadiene skeleton.**



128

Action

Taxol prevents the compaction and straining of the microtubule, inactivating it and eventually killing the cell.

This kills dividing cells, in particular cancer cells, which are known for rapid proliferation.

Taxol usually causes complete**hair loss**, including head,

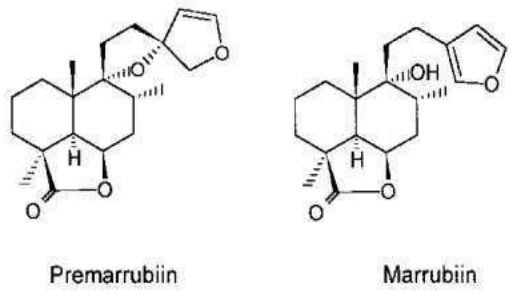
129

Marrubium vulgare (Labiatae/ Lamiaceae)

130

Phytochemicals

- **Diterpene bitter principles**: chief components marrubiin (0.1-1.0%), premarrubiin (0.1%).
- **Caffeic acid derivatives:** including among others chlorogenic acid, cryptochlorogenic acid
- **Flavonoids:** including among others chrysoeriol, vicenin II, lactoyl flavones, for example luteolin-7-lactate, apigenin-7-lactate
- **Volatile oil** (traces): including among others camphene, p-cymene, fenchene



Premarrubiin Marrubiin

Fig 35

131

EFFECTS

- Anti-inflammatory agent
- The bitter ingredients act as a gastric juice stimulant;
- Marrubinic acid acts as a choleretic.
- The main active principles, essential oil, diterpene-amaroids, tannins and flavonoids indicate that the drug would probably stimulate gastric juice secretion.

132

INDICATIONS AND USAGE

Dyspeptic complaints

Loss of appetite

133

PRECAUTIONS AND ADVERSE REACTIONS

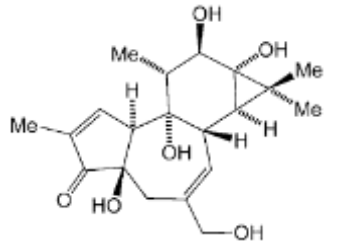
General: No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages.

Pregnancy: Not to be used during pregnancy.

134

Euphorbia spp

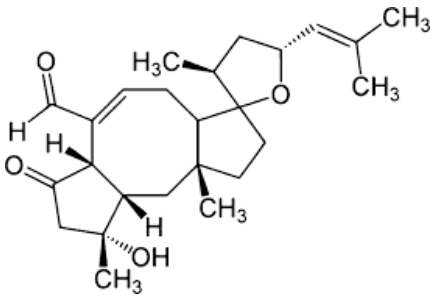
- The latex of some plants in the genus *Euphorbia* (Euphorbiaceae).
- All succulent Euphorbiaceae contain a **poisonous** sap which exudes from the tiniest injuries or sometimes even when only touching the **plant**.
- Most of the biological effects are due to diterpene esters, **phorbol,** which activate protein kinase C, an important and widely distributed enzyme responsible for phosphorylating many biochemical entities.
- The permanent activation of protein kinase C is thought to lead to the uncontrolled cancerous growth.



135

Sesterterpenes (C_{25})

- The origins of **ophiobolene** and **ophiobolin A** from cyclization of **geranyl farnesyl PP** (**GFPP**) in the plant pathogen *Helminthosporium maydis.*
- GFPP arises by a continuation of the chain extension process, adding a further IPP unit to GGPP.
- Ophiobolin A shows a broad spectrum of biological activity against bacteria, fungi, and nematodes.
- The most common type of marine sesterterpenoid is exemplified by **sclarin**



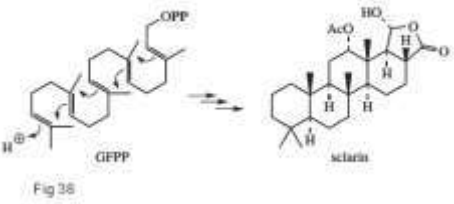


Fig 38

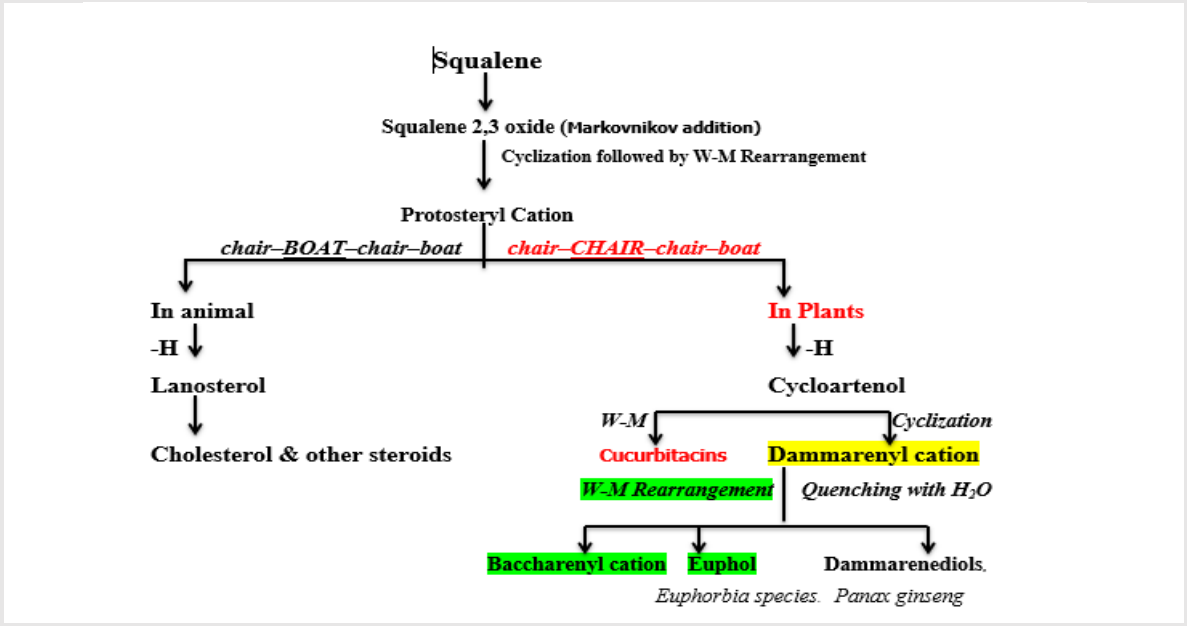
136


GOOD LUCK
FOR
MIDTERM EXAM

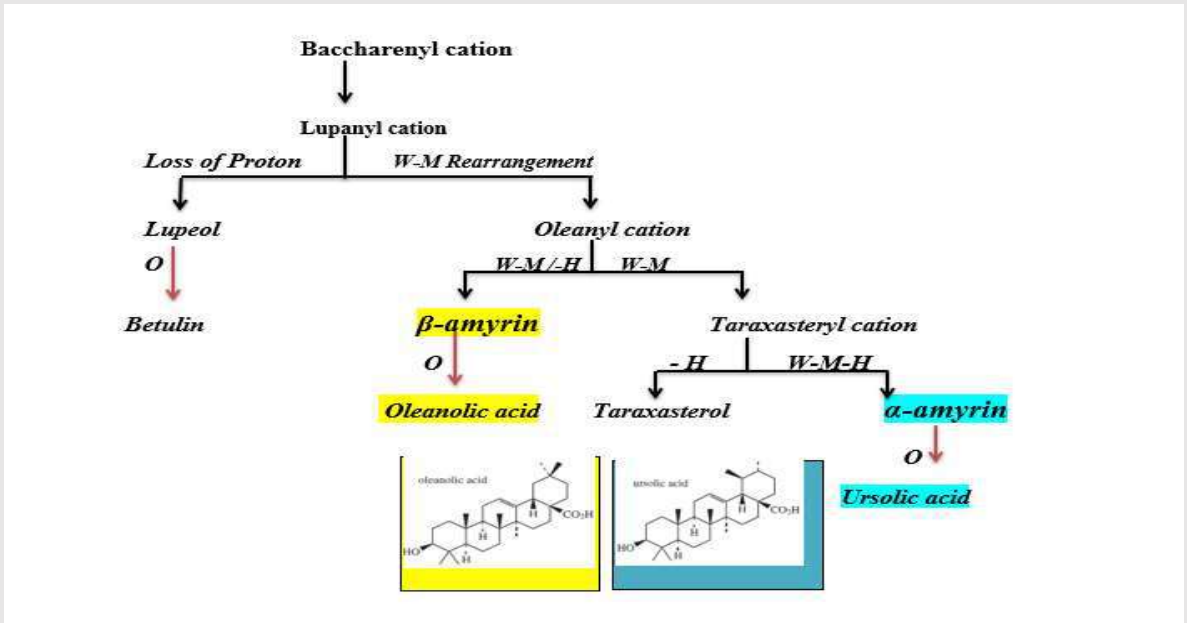
137


ADVANCED
RESEARCH
SQUALENE
SHARK LIVER OIL
500 mg
100 Softgels
Dietary Supplement

138


Squalene
Squalene 2,3 oxide (Markovnikov addition)
Cyclization followed by W-M Rearrangement
Protosteryl Cation
chair–BOAT–chair–boat
chair–CHAIR–chair–boat
In animal
-H
Lanosterol
Cholesterol & other steroids
In Plants
-H
Cycloartenol
W-M
Cyclization
Cucurbitacins
Dammarenyl cation
W-M Rearrangement
Quenching with H2O
Baccharenyl cation
Euphol
Dammarenediols.
Euphorbia species. Panax ginseng

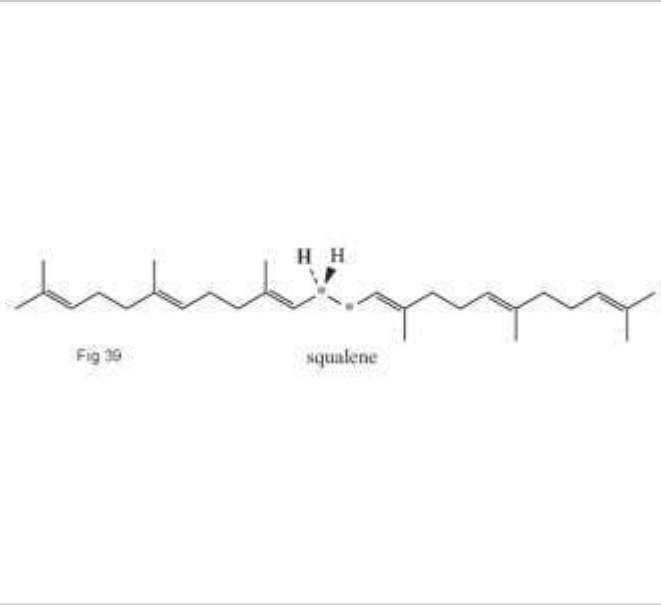
139


Baccharenyl cation
Lupanyl cation
Loss of Proton
W-M Rearrangement
Lupeol
O
Betulin
Oleanyl cation
W-M/-H
W-M
β-amyrin
O
Oleanolic acid
Taraxasteryl cation
- H
W-M-H
Taraxasterol
α-amyrin
O
Ursolic acid

140

TRITERPENES (C_{30})

- Triterpenes are not formed by an extension of the now familiar process of adding IPP to the growing chain. Instead, two molecules of FPP are joined tail-to-tail to yield **squalene**



141

Chemistry of Triterpenes

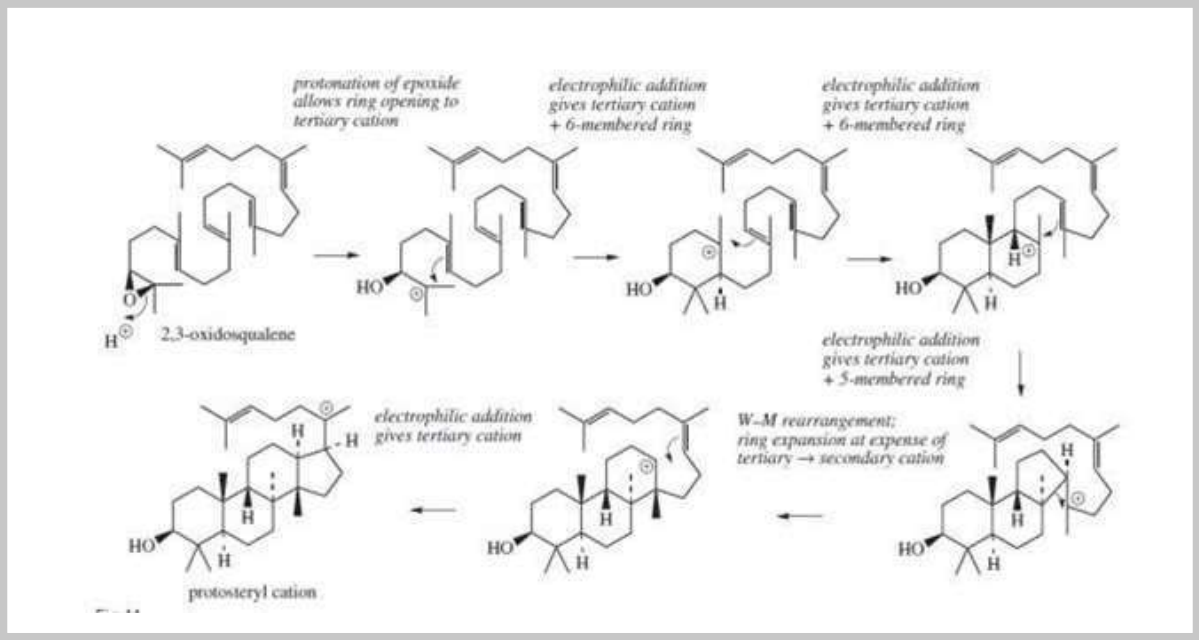
Cyclization of squalene is via the **intermediate 2,3-oxidosqualene** (squalene-2,3-oxide); **catalyzed by squalene epoxidase.**

Protonation of the epoxide group will allow opening of this ring and generation of the preferred tertiary carbocation, suitably placed to allow electrophilic addition to a double bond, formation of a six-membered ring, and production of a new tertiary carbocation.

This process continues twice more, generating the **ideal tertiary carbocation** after each ring formation, though the third ring formed is consequently a five-membered one, (**Markovnikov addition**).

A further electrophilic addition generates the tertiary **protosteryl cation**

142



143

Chemistry of triterpenes

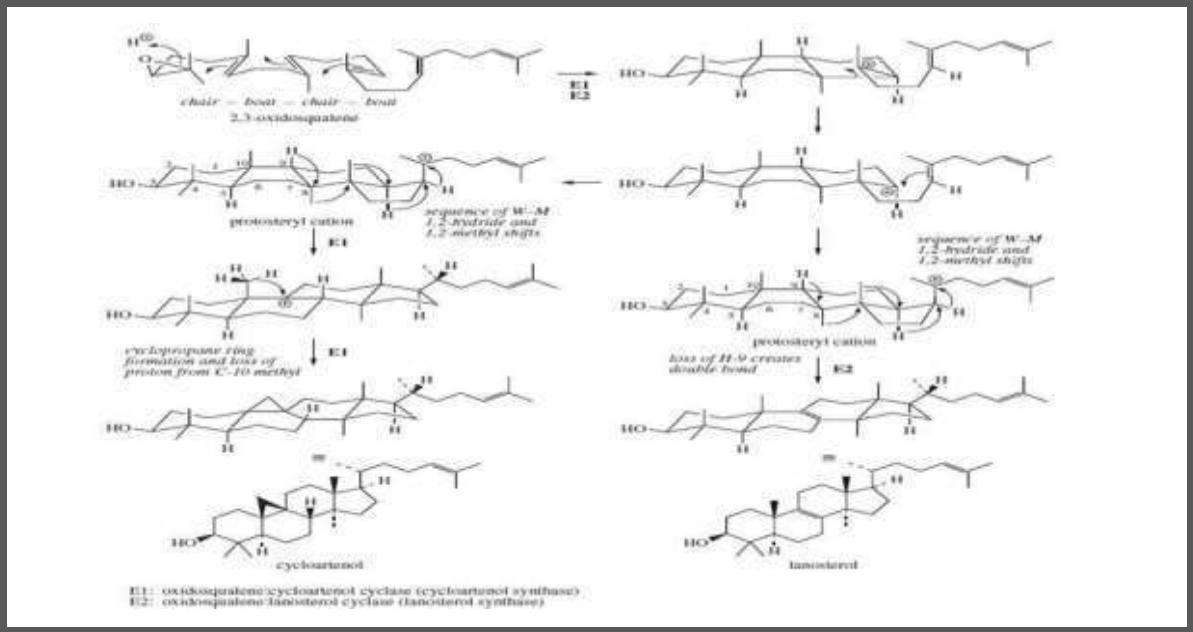
The stereochemistry in this cation are controlled by the type of folding achieved on the enzyme surface, and this probably also limits the extent of the cyclization process.

If the folded oxido-squalene approximates to a ***chair–BOAT–chair–boat*** conformation the transient **protosteryl cation** will be produced with these conformational characteristics.

This cation then suffers a series of **Wagner–Meerwein 1,2-shifts**, first migrating a hydride and generating a new cation, migrating the next hydride, then a methyl and so on until **a proton is lost forming** a double bond and thus creating **lanosterol.**

Lanosterol is a typical animal triterpenoid, and **the precursor for cholesterol and other sterols in animals and fungi**.

144

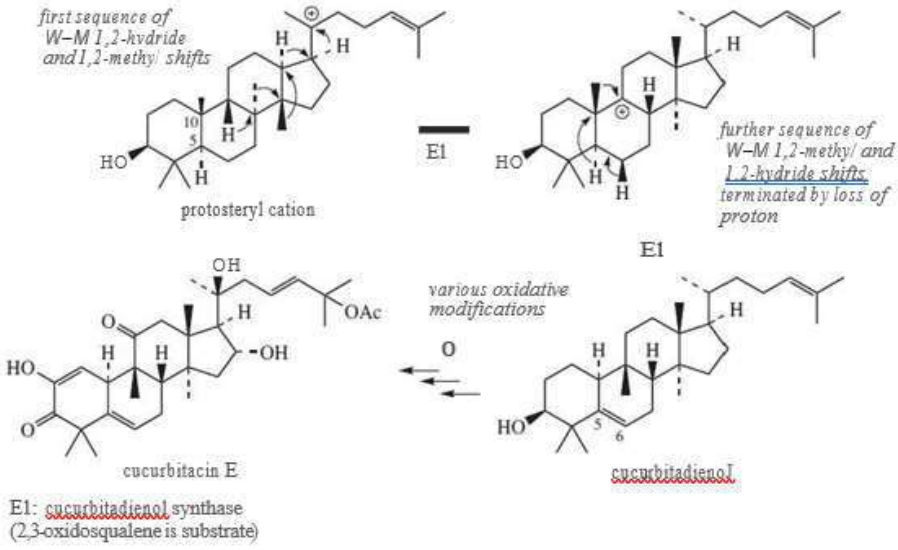


145

Chemistry of triterpenes

- **In plants**, its **intermediate role is taken by cycloartenol**, which contains a cyclopropane ring, generated by inclusion of carbon from the methyl at C-10.
- For many plant steroids, this cyclopropane ring has then to be reopened.
- An additional feature of the protosteryl cation, also disposed to Wagner–Meerwein rearrangements, lead to cucurbitacins, a group of highly oxygenated triterpenes encountered in the Cucurbitaceae, the cucumber/melon/marrow family.

146



147

Chemistry of triterpenes

- If the folded oxido-squalene approximates to a ***chair–CHAIR– chair–boat*** conformation by binding to another type of cyclase enzyme, then an identical carbocation mechanism results.
- However, the transient **dammarenyl cation** formed has different stereochemical features to the protosteryl cation.
- The dammarenyl cation typically undergoes further carbocation-promoted cyclization, without any major changes to the ring system already formed.
- Occasionally, the migrations do occur: **euphol** from *Euphorbia* species (Euphorbiaceae) is a stereoisomer of lanosterol.

148

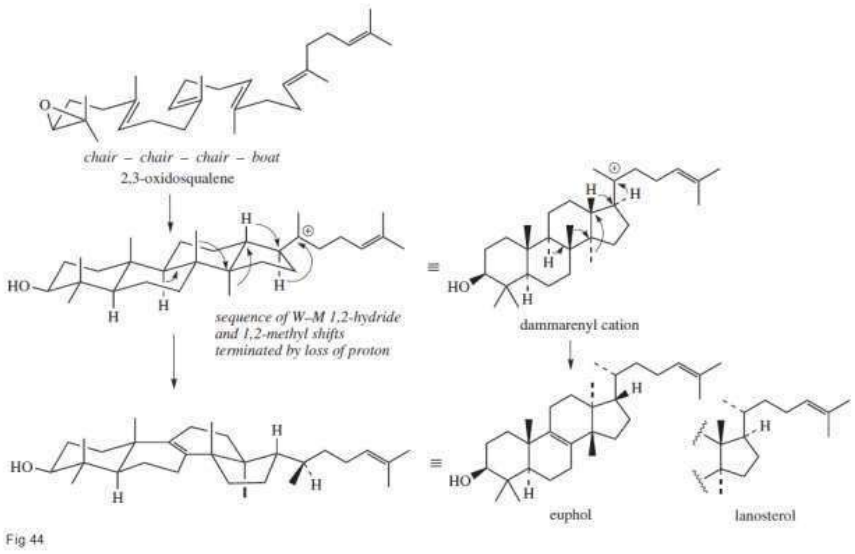


Fig 44

149

Chemistry of triterpenes

- If the Wagner–Meerwein rearrangements do not take place, then the dammarenyl cation could be quenched with water, giving the epimeric **dammarenediols**, as found in Dammar resin from *Balanocarpus heimii* (Dipterocarpaceae) and **ginseng** (*Panax ginseng*; Araliaceae).

150

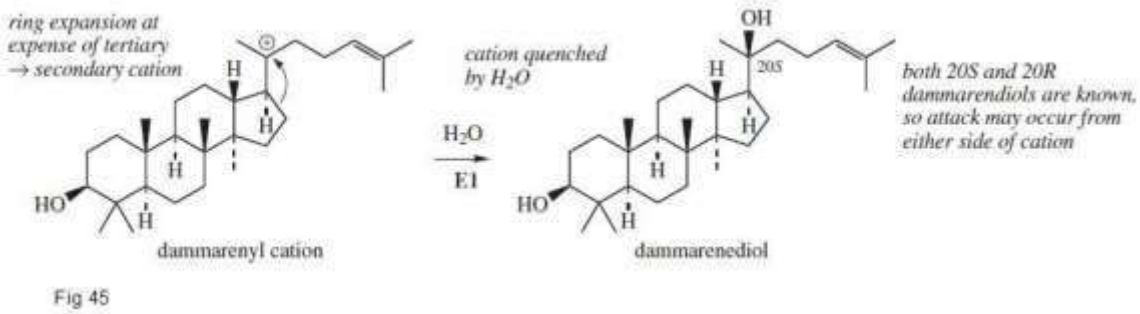


Fig 45

151

Chemistry of triterpenes

Alternatively, the alkyl migration shown gives the baccharenyl cation, relieving some ring strain by creating a six-membered ring, despite sacrificing a tertiary carbocation for a secondary one.

A pentacyclic ring system can now be formed by cyclizations onto the double bond, giving a new five-membered ring and the tertiary lupenyl cation gives **lupeol**, found in lupin (*Lupinus luteus*; Leguminosae/Fabaceae).

152

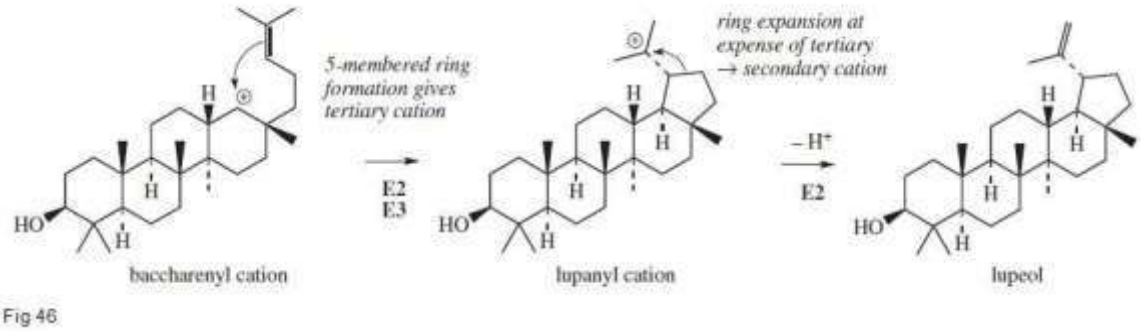


Fig 46

153

Chemistry of triterpenes

Ring expansion in the lupanyl cation by bond migration gives the oleanyl system, and labelling studies have demonstrated this ion is discharged by hydride migrations and loss of a proton, giving the widely distributed **β-amyrin**.

Formation of the isomeric **α-amyrin** involves first the migration of a methyl in the **oleanyl cation,** then discharge of the new taraxasteryl cation by three hydride migrations and loss of a proton.

Loss of a proton from the non-migrated methyl in the taraxasteryl cation is an alternative way of achieving a neutral molecule, and yields **taraxasterol** found in dandelion (*Taraxacum officinale*; Compositae/Asteraceae),

154

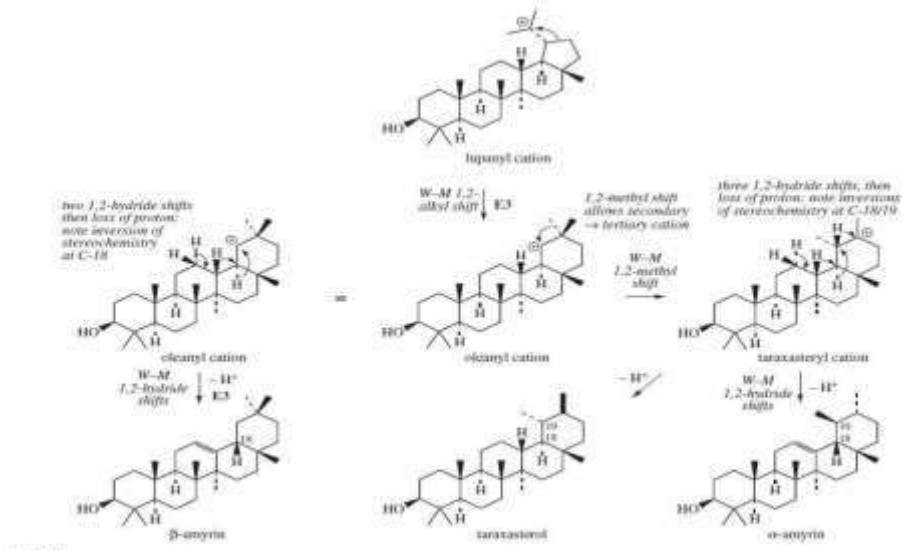


Fig 47

155

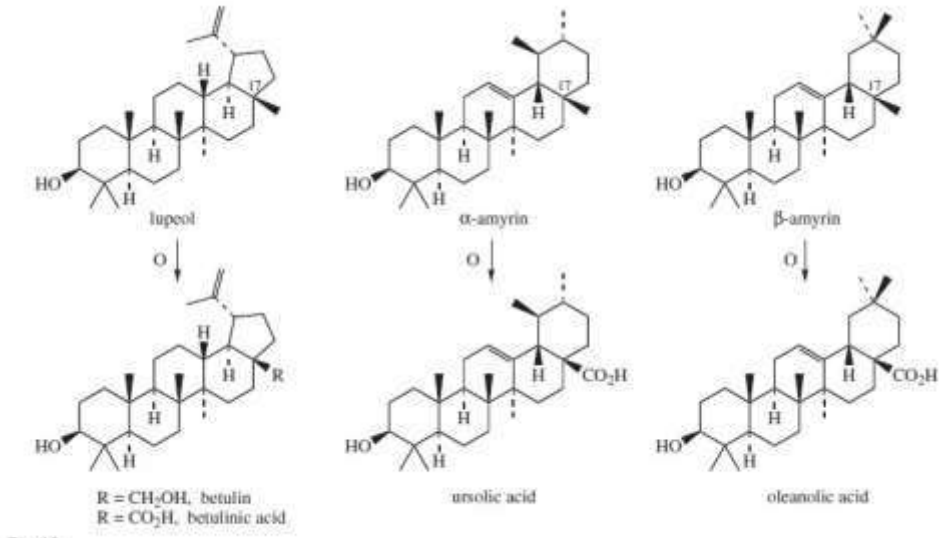


Fig 48

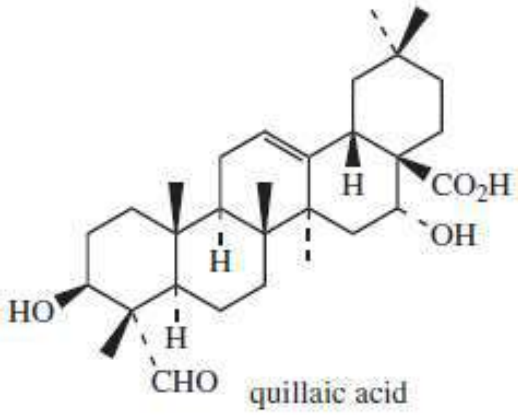
156

Chemistry of triterpenes

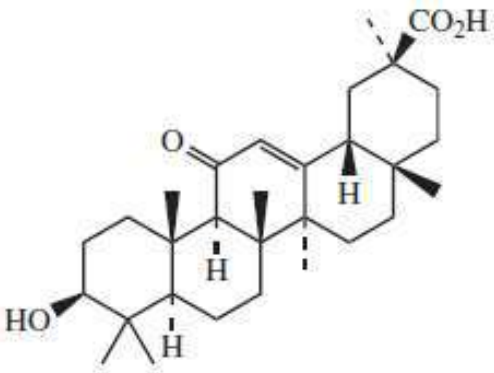
Olives (*Olea europaea*; Oleaceae) contain large quantities of **oleanolic acid**, in which the C-17 methyl of β-amyrin has been oxidized to a carboxylic acid.

Oxidative transformations at other methyl groups and/or ring carbon atoms are required to produce triterpenoids such as **glycyrrhetic acid** and **quillaic acid**

157



quillaic acid



glycyrrhetic acid

Fig 49

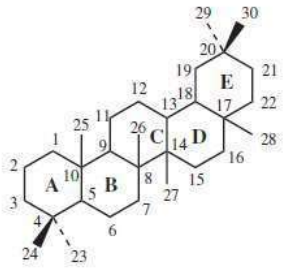
158

Triterpenoid Saponins

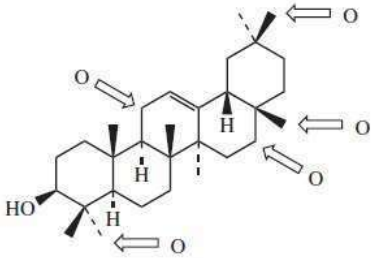
159

Triterpenoid Saponins

- The **pentacyclic triterpenoid** skeletons exemplified by lupeol, α- amyrin, and β- amyrin are frequently met in the form of triterpenoid saponin structures.



pentacyclic triterpenoid skeleton



potential sites for oxidation (β-amyrin type)

Fig 50

160

Saponins characters

- Saponins are glycosides
- Produce a persist frothing in aqueous solution
- These materials also cause haemolysis,
- Highly toxic when injected into the bloodstream.
- Harmless when taken orally.

161

Saponins Containing Drugs

162

Glycyrrhiza glabra

- **Liquorice** (licorice; glycyrrhiza) is the dried unpeeled rhizome and root of the perennial herb, *Glycyrrhiza glabra* (Leguminosae/Fabaceae)
.

163

Phytochemicals

- **Glycyrrhizin**, a mixture of the potassium and calcium salts of glycyrrhizic (=glycyrrhizinic) acid
- The bright yellow color of liquorice root is provided by flavonoids (**liquiritigenin** and **isoliquiritigenin**)
- **Glucose** and **sucrose** are also present.

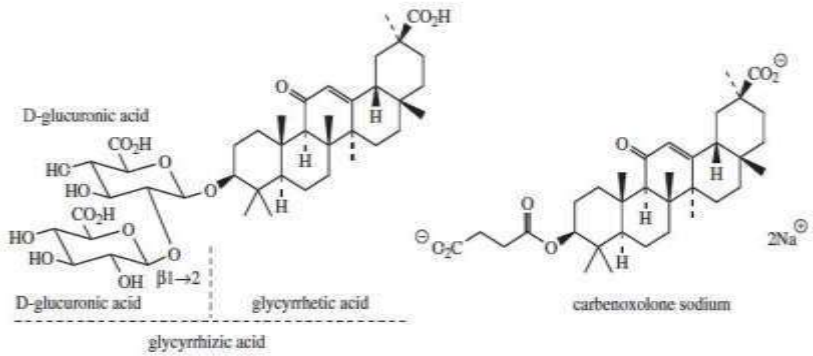


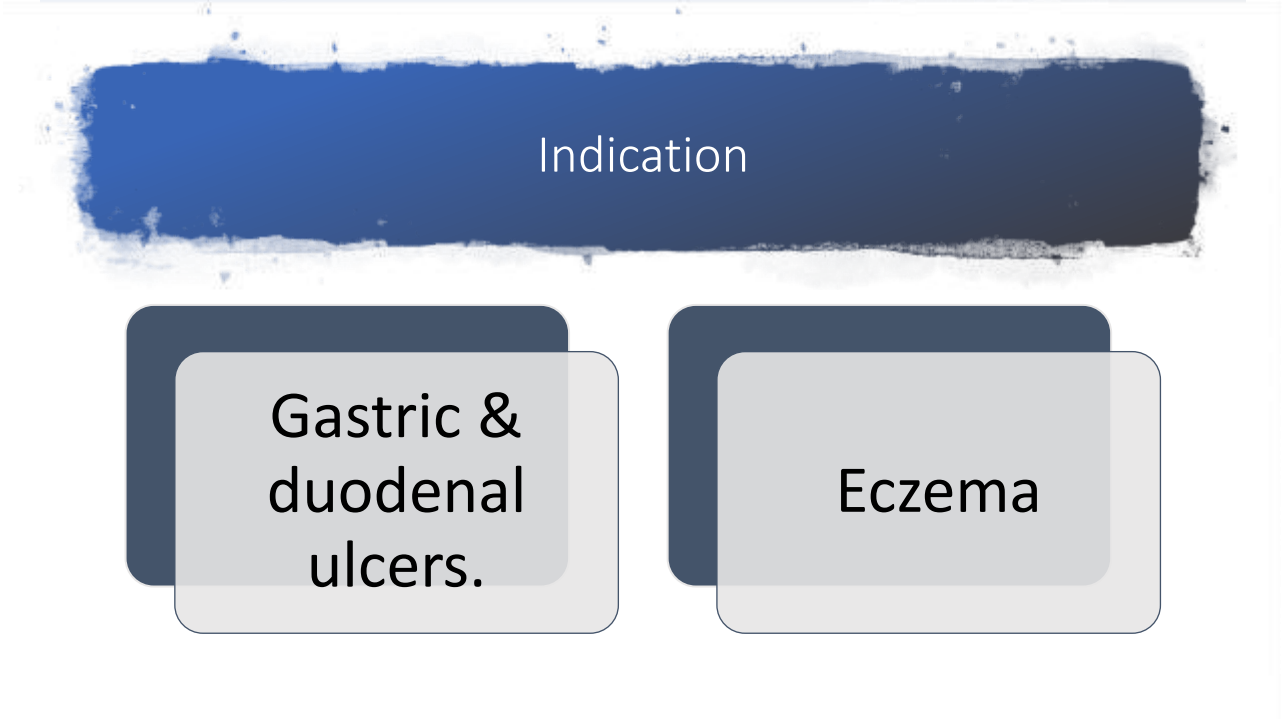
Fig 51

164

Biological Properties of **Liquorice**

- 50–150 times as sweet as sucrose
- in pharmacy to mask the taste of bitter drugs.
- demulcent and mild expectorant properties
- corticosteroid-like activity
- mild anti-inflammatory and mineralocorticoid activities.
- These have been exploited in the treatment of rheumatoid arthritis, Addison's disease (chronic **adrenocortical insufficiency**), and various inflammatory conditions.
- inhibit enzymes that catalyse the conversion of prostaglandins and glucocorticoids into inactive metabolites.
- People with eczema improved with application of ointment with pure glycyrrhetinic acid, which was as effective as hydrocortisone.

165



166

Side effects

- Loss of potassium and increase in sodium levels,
- Water retention

167

Contraindication

- Hypertension
- Pregnancy

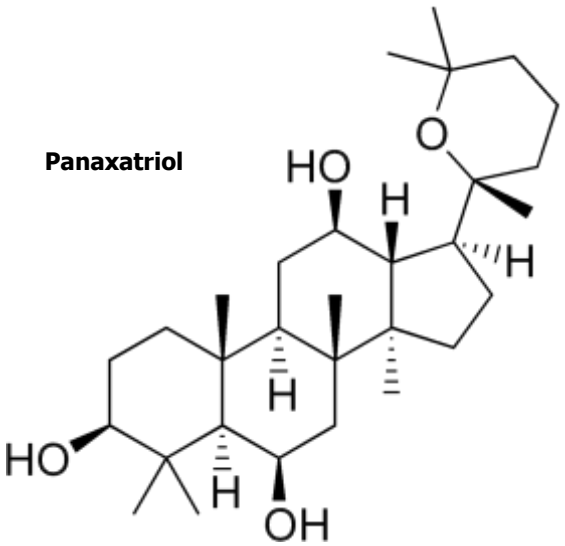
168

Panax ginseng

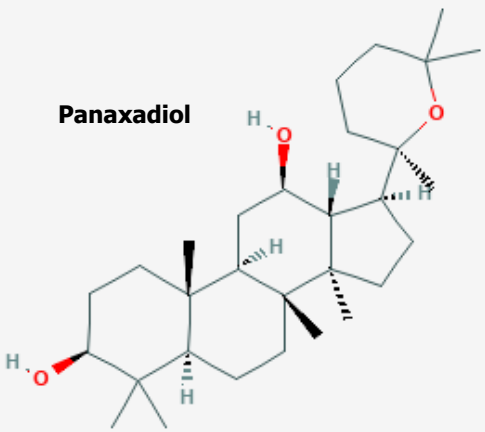
- The roots of the herbaceous plants *Panax ginseng* (Araliaceae) from China, Korea and Russia, and related *Panax* species

169

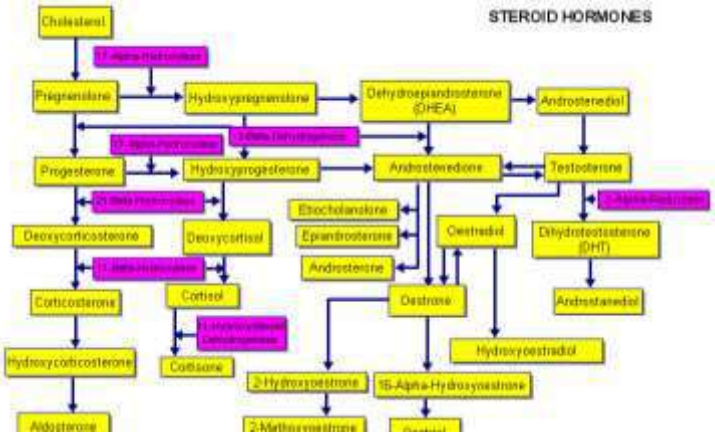
Panaxatriol



Panaxadiol



170



Adaptogens

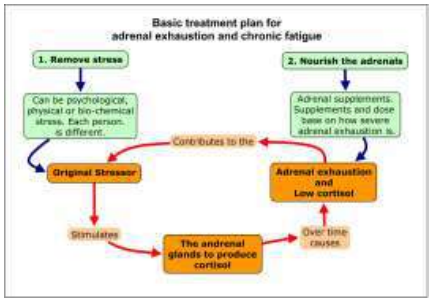
- Adaptogens or adaptogenic substances are used in herbal medicine for:

1. **claimed stabilization of physiological processes** and
2. promotion of homeostasis.

171

How do adaptogens work?

- Adaptogens work at a molecular level by **regulating a stable balance in the hypothalamic, pituitary, and adrenal glands.** These are involved in the stress response.
- **They work by "hacking" the stress response in the body.**
- Typically, when our bodies are stressed, we go through three stages of stress:
  - Alarm phase
  - Phase of resistance
  - Phase of exhaustion



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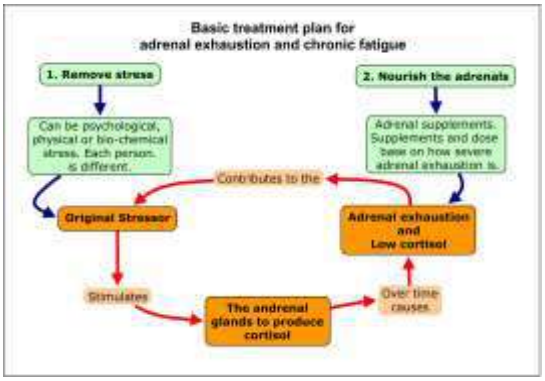

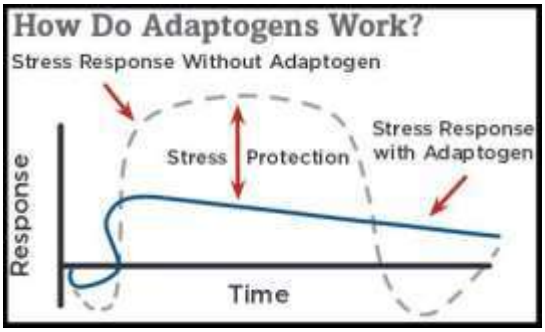

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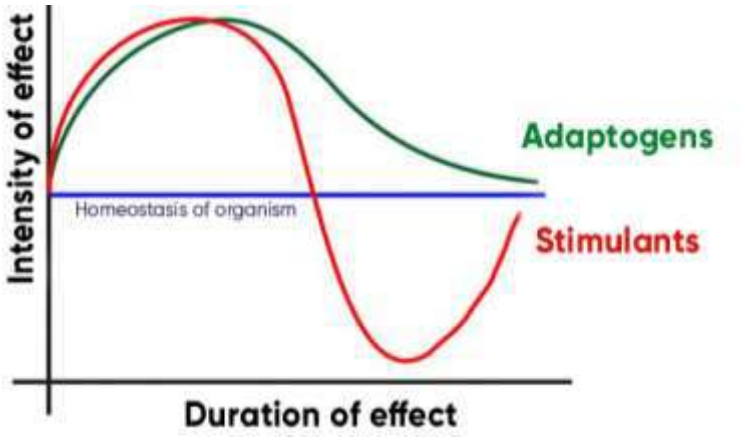


Adaptogenic Effect

- Neuroprotective elements
- Anti-fatigue properties
- Antidepressive effects
- Stimulant for central nervous system

174

Indication

- Adaptogen to stress
- Depression
- Anxiety
- General fatigue
- Chronic Fatigue Syndrome (CFS),
- Multiple sclerosis
- Boosting the immune system, and
- cystic fibrosis.
- Boost energy,
- Lower blood sugar and cholesterol levels,
- Promote relaxation and manage sexual dysfunction in men.

175

Aesculus hippocastanum

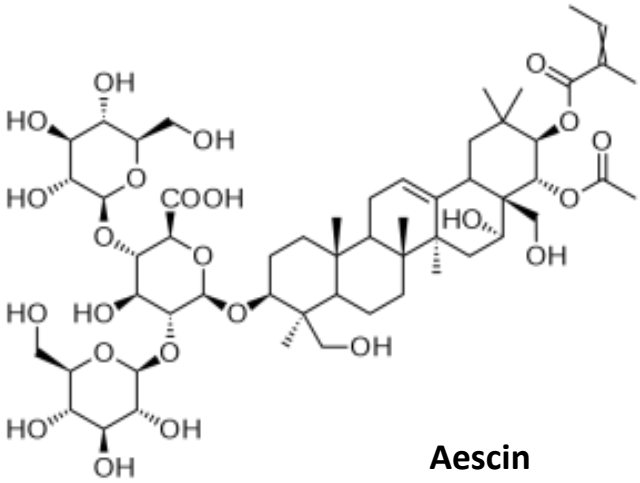
- Horse Chestnut
- Hippocastanaceae

- **Traditional use**:
  - as a cough remedy and to reduce fevers.
  - treat skin ulcers and skin cancer
  - **varicose veins and hemorrhoids**

176

Active constituents

- The seed cotyledons are very rich in starch (40-50%) and other sugars, and contain lipids (6-8%), flavonol glycosides and saponins.
- Extracts of the seeds are the source of a saponin known as **aescin**

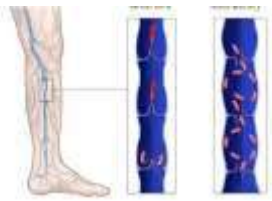


Aescin

177

Pharmacological Properties

- Aescin promotes normal tone in the walls of the veins
- promoting return of blood to the heart
- chronic venous insufficiency and varicose veins
- anti-inflammatory properties
- to reduce edema



178

179

STEROIDS

180

Steroids

- The steroids are modified triterpenoids containing the tetracyclic ring system of lanosterol but lacking the three methyl groups at **C_4 and C_{14}.**

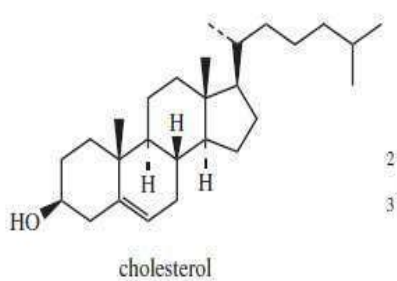


Fig 54

181

Steroids - chemistry

- **Natural steroids**: A/B ring fusion being *trans* or *cis*, or having unsaturation, either 4 or 5.
- **Oestrogens**:
  - ring A can even be aromatic
  - no bridgehead substituent at C-10 and,
  - the normal C-10 methyl (C-19) must be lost
- **From nature to semisynthetic**: *trans* B/C fusion, though *cis* forms
- **Cardioactive glycosides**: The C/D fusion is also usually *trans.*

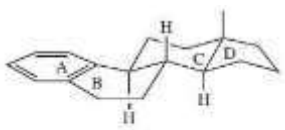


Fig 57

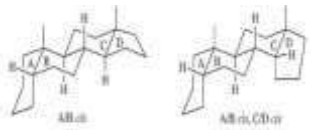


Fig 58

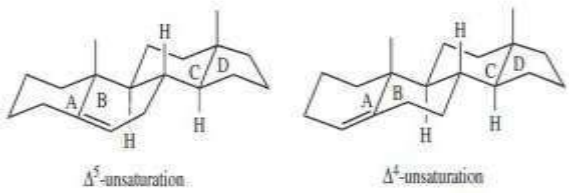


Fig 56

182

Cholesterol

- In animals, the triterpenoid alcohol **lanosterol** (C_{30}) is converted into **cholesterol** (C_{27}) a process that, as well as the loss of three methyl groups, requires reduction of the side- chain double bond, and generation of a 5,6-double bond in place of the 8,9 double bond.
- The methyl at C_{14} is usually the one **lost first**, and this is removed as formic acid.
- The reaction is **catalysed by a cytochrome P-450 monooxygenase** which achieves two oxidation reactions to give the 14α-formyl derivative, Loss of the C_4 methyl groups occurs sequentially, usually after removal of the 14α-methyl.

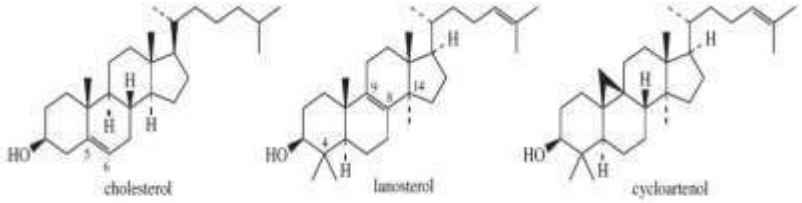


Fig 59

183

Biological Properties

- **Cell membrane synthesis** – Cholesterol is a raw material for cell membrane, helps to regulate membrane fluidity over the range of physiological temperatures.
- **Maintains membrane fluidity**, microdomain structure, and permeability.
- **Increase brain activity**
- **Antioxidant**
- **Anti-inflammatory**
- **Make vitamin D**
- **Precursor for Adrenal hormones "cortisol" & sex hormones**- Sex-steroids (Sex hormones like Estrogen, Progesterone and Testosterone etc.).
- **Help the bile to extract ADEKs vitamins**.

184

Phytosterols

- **Phytosterols**, **(C_{24})** or plant sterols, are a family of molecules related to cholesterol.
- **Plant sterols or phytosterols have the same basic function in plants as cholesterol in animals**
- They are found **in the cell membranes of plants**, where they play important roles, just like cholesterol in humans.
- The most common **phytosterols in the human diet** are campesterol, sitosterol and stigmasterol.
- **Phytosterols** - "Heart-**Healthy**" Nutrients

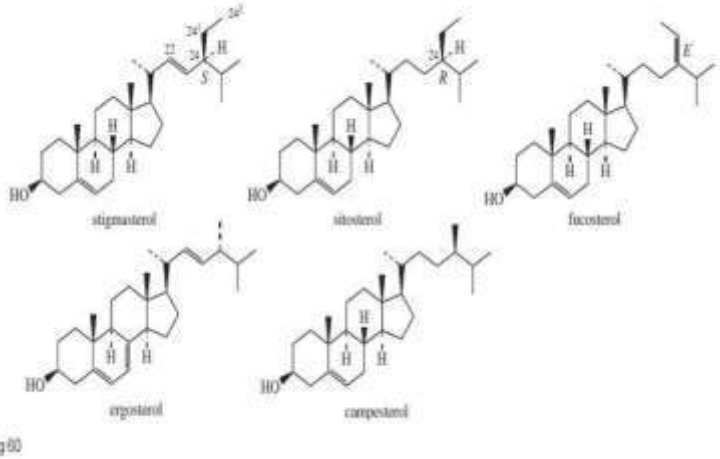


Fig 60

185

Vitamin D

Vitamin D is a group of fat-soluble seco-steroids **controlled by parathyroid** hormone and **activated** by **liver** and **kidney,** the most important compounds in this group are vitamin D_3 and vitamin D_2.

Vitamin D3 (**colecalciferol**, cholecalciferol) is a sterol metabolite formed photochemically in animals from 7-dehydrocholesterol by the sun's irradiation of the skin.

Vitamin D2 (**ergocalciferol**) is formed from ergosterol in the same way and is found naturally in plants and yeasts.

186

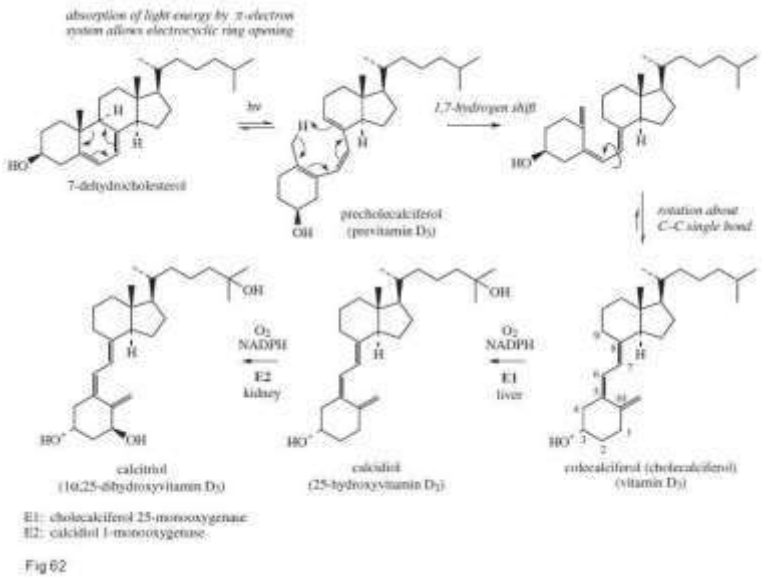


Fig 62

187

Causes of vitamin D deficiency

- Absence of gallbladder
- Bile disorder
- Cortisol (stress block vitamin D)
- Winter season
- Clothes

188

Vitamin D functions

- Increase absorption of calcium, Mg, phosphate, iron and zinc
- Lower blood pressure
- Enhance the immune system
- Prevent asthma
- Turn off asthma symptoms
- Prevent depression
- Reduce bone pain

189

Vitamin D sources

- **Sunlight**
- **Fatty fish**, like **tuna**, **mackerel**, and **salmon**.
- **Beef liver**.
- **Cheese**.
- **Egg yolks**.
- **Almond milk**
- **Mushrooms**
- **Fortification**
- **Cod Liver oil**

190

Vitamin D and vitamin K_2 relationship

- Vitamins D and K are both fat-soluble vitamins and play a central role in calcium metabolism.
- Vitamin D promotes the production of vitamin K-dependent proteins, which require vitamin K for carboxylation in order to function properly.
- vitamin K2 may be the **missing link** between **diet and several chronic diseases.**
- **It's believed that vitamin K2 may play a critical role in dental health.**

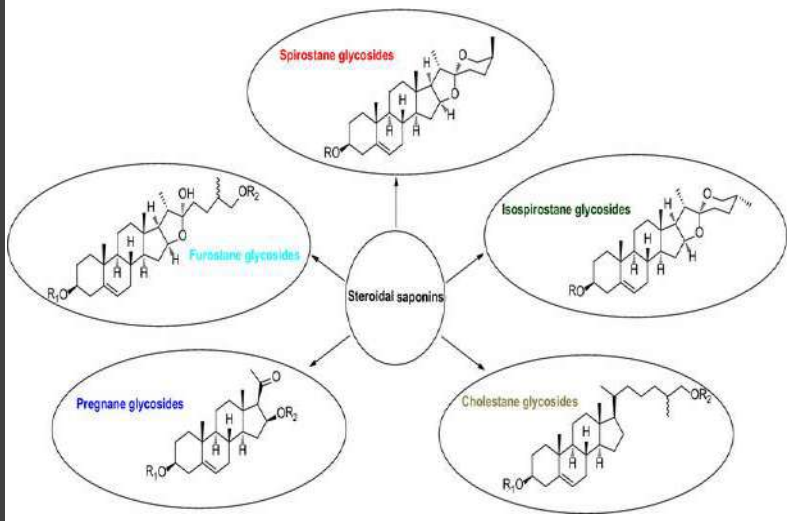
191

Steroidal Saponins

192

Steroidal saponins

- Steroidal saponins have similar biological properties to the triterpenoid saponins, e.g.
- **They are found in many monocot families, especially the Dioscoreaceae (e.g. *Dioscorea*), the Agavaceae (e.g. *Yucca*).**
- Their sapogenins are C_{27} sterols in which the side-chain of cholesterol



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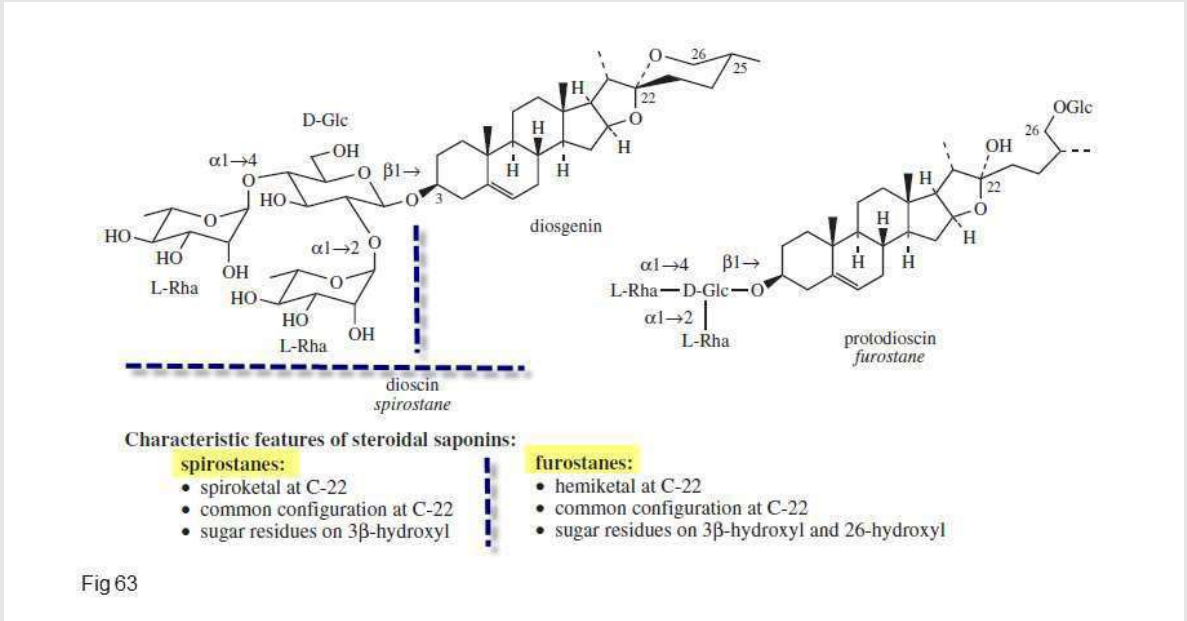


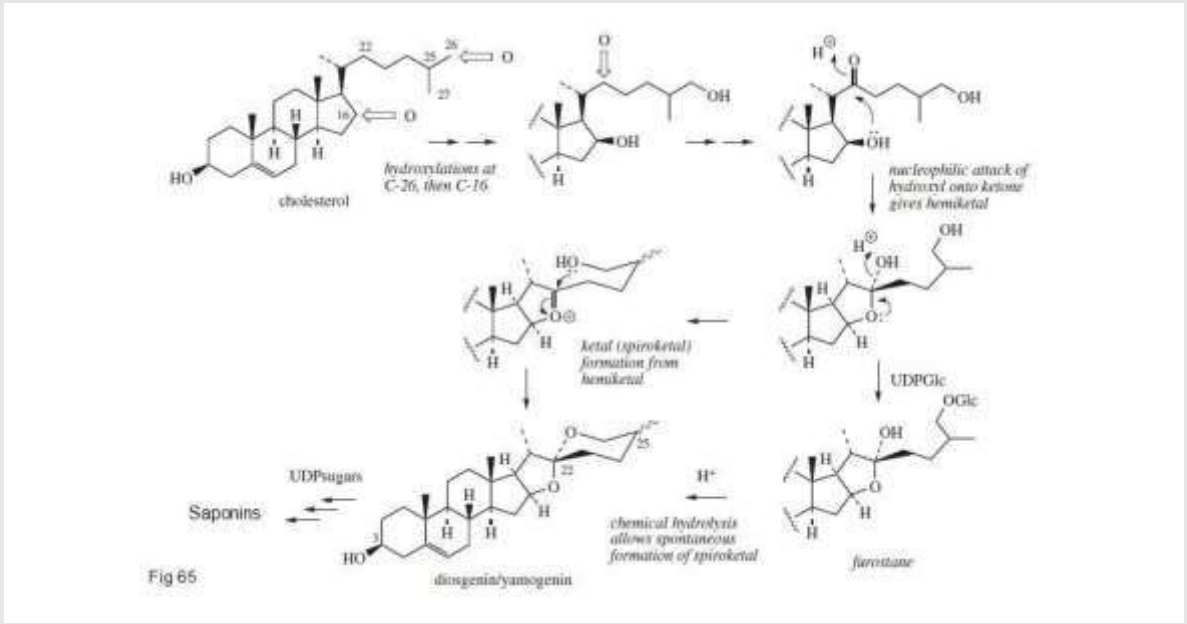
Characteristic features of steroidal saponins:

spirostanes:
- spiroketal at C-22
- common configuration at C-22
- sugar residues on 3β-hydroxyl

furostanes:
- hemiketal at C-22
- common configuration at C-22
- sugar residues on 3β-hydroxyl and 26-hydroxyl

Fig 63

194



195

Dioscorea spp

196

Diosgenin (Wild yam)

- Wild yam is a natural alterative to estrogen therapy.
- it used for estrogen replacement therapy, vaginal dryness in older women, PMS (premenstrual syndrome), menstrual cramps, weak bones (**osteoporosis**)
- **However, large amounts of wild yam can lead to side effects, including:**
  - nausea.
  - vomiting.
  - headaches.
  - digestive issues.

197

Trigonella foenum-graecum (Leguminosae): Fenugreek

198

Trigonella foenum-graecum (Leguminosae): Fenugreek

- **Fenugreek seeds contain 6–10% lipids, 44–59% carbohydrates, and 20–30% protein.**
- **one tablespoon of whole seeds contains 35 calories and several nutrients:**
  - **Fiber: 3 grams.**
  - **Protein: 3 grams.**
  - **Carbs: 6 grams.**
  - **Fat: 1 gram.**
  - **Iron: 20% of your daily requirements.**
  - **Manganese: 7% of your daily requirements.**
  - **Magnesium: 5% of your daily requirements.**
- **Fenugreek soluble fiber along with other glucose, cholesterol, and triglyceride lowering compounds.**
- **It would be a significant contribution to the daily management and stabilization of blood glucose and lipid levels for non-insulin-dependent diabetics.**

199

Trigonella foenum-graecum (Leguminosae): Fenugreek

- **Fenugreek** is rich in galactomannan, which is a healthy polysaccharide that triggers **fat** breakdown and sugar metabolism in the body.
- **Testosterone**-boosting supplement **is fenugreek**
- **Fenugreek** also increases insulin release, which can help increase muscle mass after weight training.
- Soothe **upset stomach** and digestive problems.
- Reduce menstrual cramps.
- Produce menstruation
- Prevent **Hair** Fall: have high protein and nicotinic acid content, which are known to be **beneficial** against **hair** fall and dandruff.

200

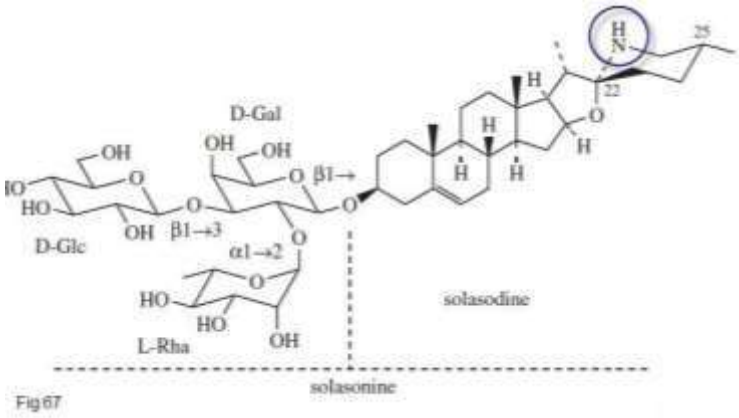
Vitex agnus-castus

201

Vitex agnus-castus

- **Vitex agnus-castus** is commonly taken by mouth for conditions related to the menstrual cycle such as premenstrual syndrome and a more severe form called premenstrual dysphoric disorder.
- **Vitex** supports your pituitary gland to produce progesterone and luteinizing **hormone** – both of which are necessary for your body to ovulate, for regular menstrual cycles, and for you to avoid symptoms of **hormonal** imbalance like PMS.
- Low doses of **Vitex** have resulted in decreased **estrogen** levels and **increased** progesterone and prolactin levels—possibly caused by an inhibition of the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), higher doses of Vitex, FSH and LH levels did not change.

202

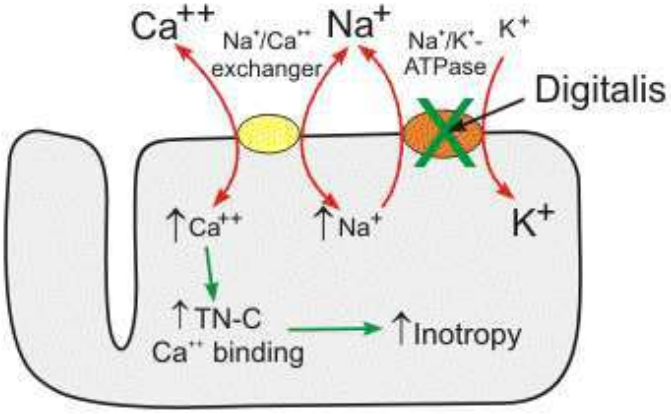


Steroidal Alkaloids

- Some steroidal alkaloids are **nitrogen** analogues of steroidal saponins and display similar properties, such as surface activity and hemolytic activity, but these compounds are **toxic when ingested**.

203

Cardioactive Glycosides



204

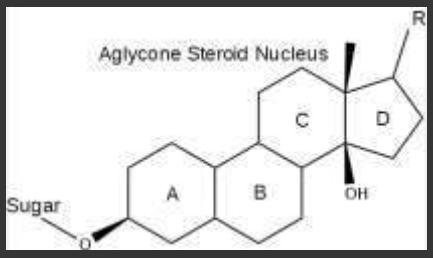
Cardioactive Glycosides

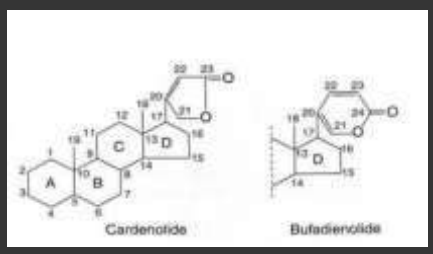
- These glycosides are found in the plant genera **Digitalis**, Scilla, and Strophanthus.
- Cardiac **glycosides** are a class of organic compounds that **increase the output force of the heart** and **decrease its rate of contractions** by acting on the cellular sodium-potassium ATPase pump.
- They are used in the treatment of heart diseases, e.g., congestive heart failure and arrhythmia.
- **Cardiac glycosides** are medicines for treating heart failure and certain irregular heartbeats.

205

Cardiac Glycosides Chemistry

- The general structure of a cardiac glycoside consists of a **steroid molecule attached to a sugar (glycoside) and an R group**.
- The steroid nucleus consists of five fused rings to which other **functional groups** such as **methyl**, **hydroxyl**, and **aldehyde** groups can be attached to influence the overall molecule's biological activity.
- In particular, the structure of the ring attached at the R end of the molecule allows it to be classified as either a **cardenolide** or **bufadienolide**.





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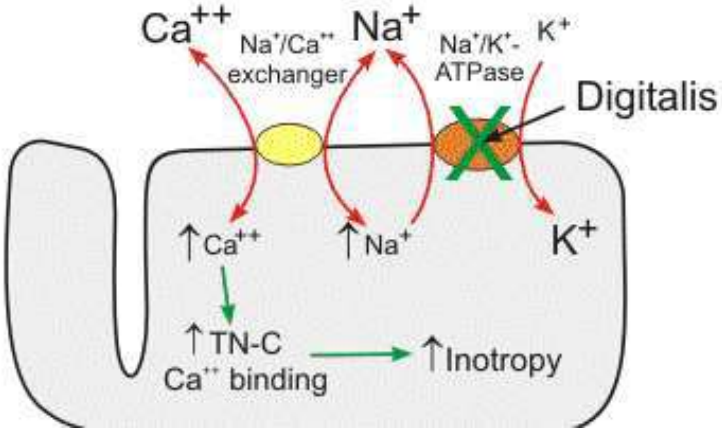
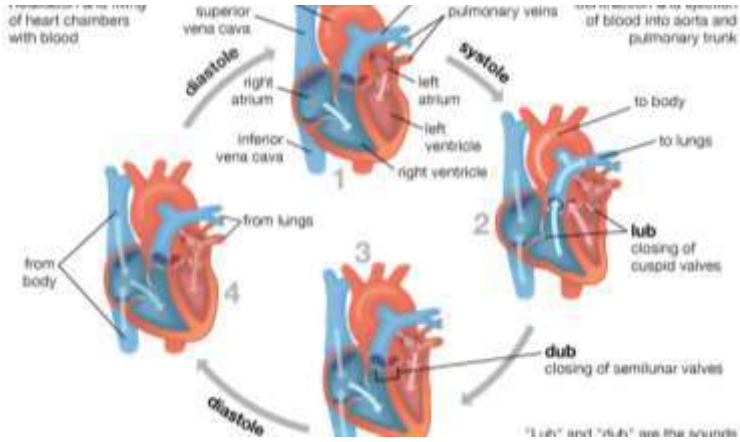


Mechanism of Action

- There are two important **ion transport mechanisms** we need to know:

1) **The Na^+ /K^+ ATPase**: is an **energy dependent transporter**. It removes $3Na^+$ from the cell in exchange for $2K^+$ from the extracellular space
2) **Na^+ /Ca^{2+} exchanger:** Moves 1 Ca^{2+} outward in exchange for 3 Na^+ which move inward into the cell.

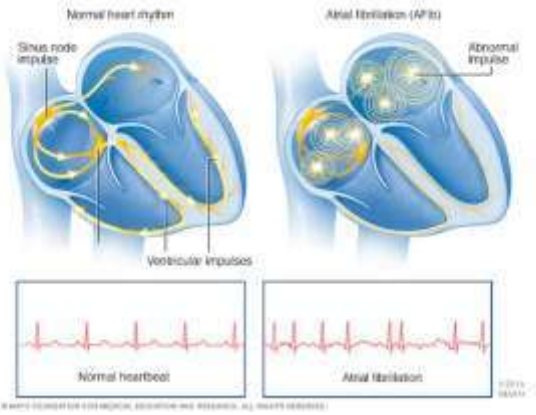
207



Effect on the Heart

- **contraction**
- The **rate and rhythm of the heart**:
  - **Reduce the rate** of conduction through the atrioventricular (AV) node (*by increasing vagal outflow)*
  - **Slow the heart rhythm**
- However they disturb cardiac rhythm through **blockade of AV conduction**.
- **Congestive heart failure**, occurs when **heart** muscle doesn't pump blood as well as it should.

208

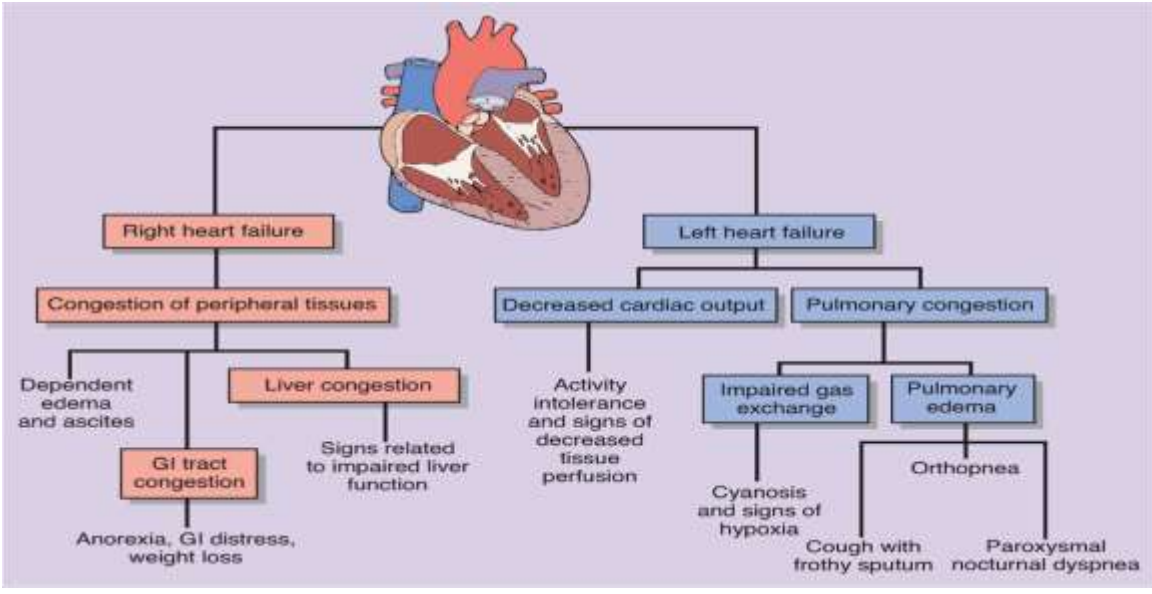


Effect on Heart Rate and Rhythm

- **Cardiac glycosides slows AV conduction** by:

1. increasing vagal activity via an action on the CNS:
   - **Benefits:** useful against rapid atrial fibrillation
   - **Disadvantages:** large doses disturb cardiac rhythm
2. Slow AV conduction that could progress to **AV block**

209



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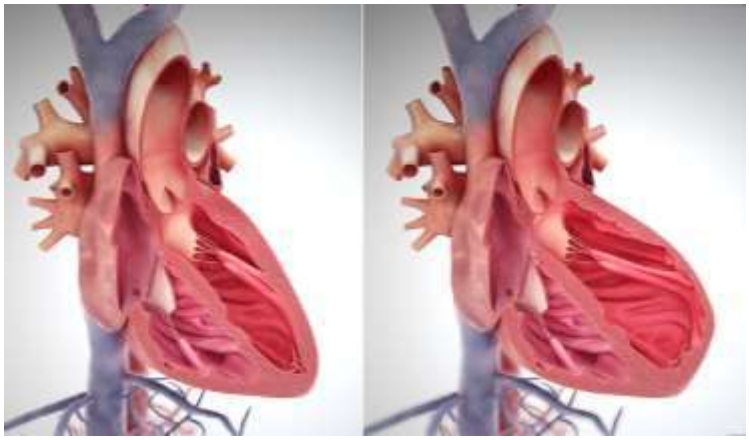
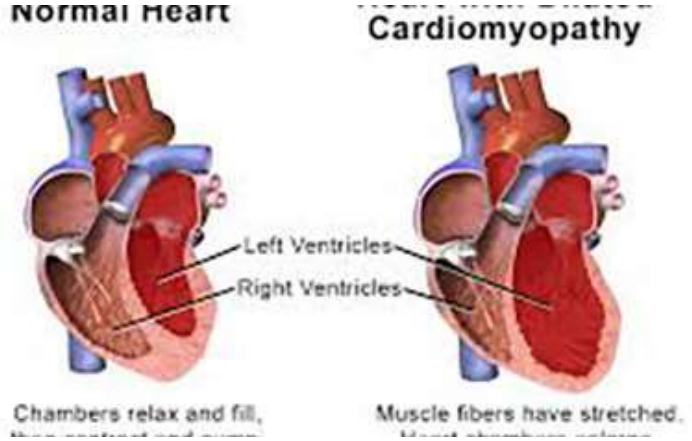


Pathophysiology of Heart Failure

- **Systolic dysfunction**, with reduced cardiac output and significantly reduced ejection fraction, is typical of acute failure, especially that resulting from myocardial infarction.
- **Diastolic dysfunction** often occurs as a result of hypertrophy and stiffening of the myocardium, and although cardiac output is reduced, ejection fraction may be normal.
- **Heart failure due to diastolic dysfunction does not usually respond optimally to positive inotropic drugs.**
- **CHF describes the inability or failure of the heart to supply the needs of organs and tissues for oxygen and nutrients**

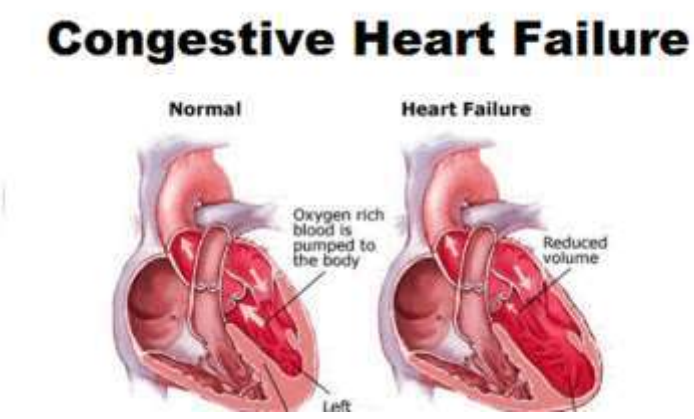
211



Pathophysiology of Heart Failure

- The primary signs and symptoms of all types of heart failure include:
  - **Tachycardia**,
  - **Decreased exercise tolerance,**
  - **Shortness of breath**, &
  - **Cardiomegaly**.

212



Uses of Cardiac Glycosides

- Treatment of **Congestive Heart Failure** (CHF)
- To slow ventricular rate in rapid persistent atrial fibrillation i.e. (Antidysrrhythmic agents)

213

Adverse Effects of Cardiac Glycosides

Narrow margin between effectiveness and toxicity.

- **A) Cardiac adverse effects**
  - Cardiac slowing and reduced rate of conduction through AV node
  - Increased force of contraction
  - Disturbances of cardiac rhythm especially block of AV conduction and increased ectopic pacemaker activity
- **B) Extracardiac adverse effects**
  - Nausea
  - Vomiting
  - Diarrhoea
  - Confusion
  - Visual disturbances (Photophobia, blurring of vision (color visual disturbances)

214

Cardiotonic glycosides Containing Drugs

215

Digitalis purpurea

Digitalis leaf consists of the dried leaf of the red foxglove *Digitalis purpurea* (Scrophulariaceae

It is potentially very toxic, but the leaf is unlikely to be ingested by humans

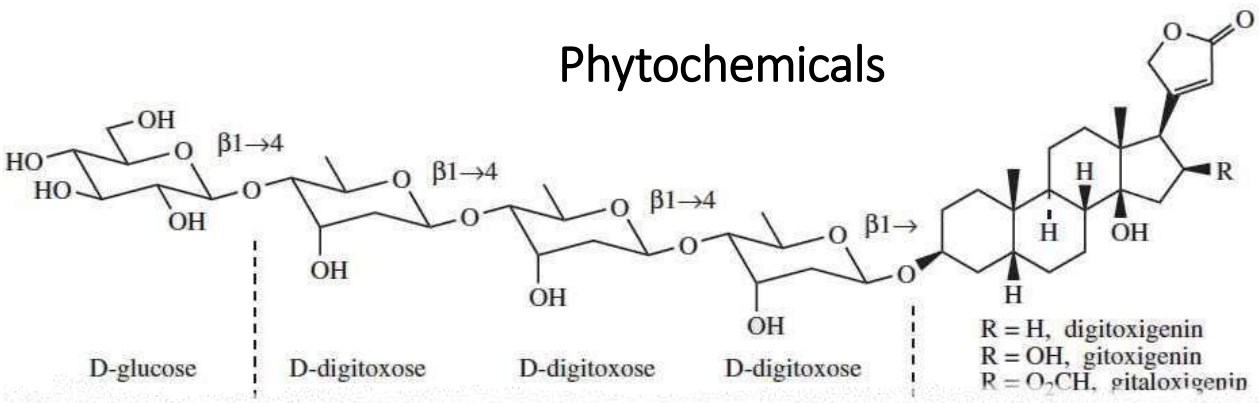
D. purpurea is cultivated for drug production, principally in Europe, the first year leaves being harvested then rapidly dried at 60◦C as soon as possible after collection.

This procedure is necessary to inactivate hydrolytic enzymes which would hydrolyse glycoside linkages in the cardioactive glycosides, giving rise to less active derivatives. Even so, some partial hydrolysis does occur.

Excess heat may also cause dehydration in the aglycone to **biologically inactive C14-anhydro compounds.**

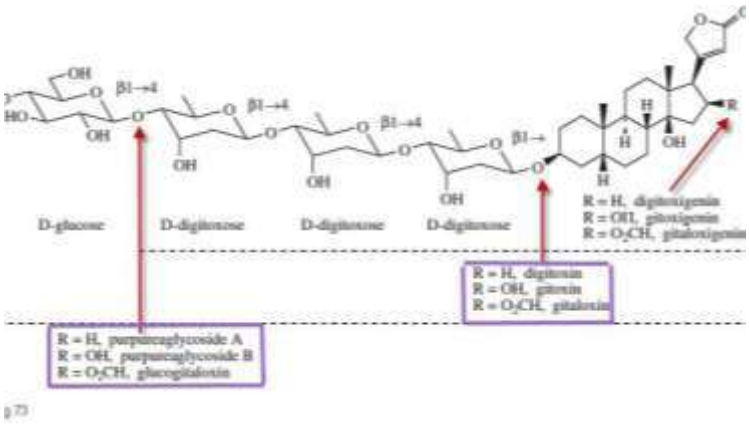
216

Phytochemicals



- The major components are based on the aglycones **digitoxigenin**, **gitoxigenin**, and **gitaloxigenin**, the latter being a format ester.

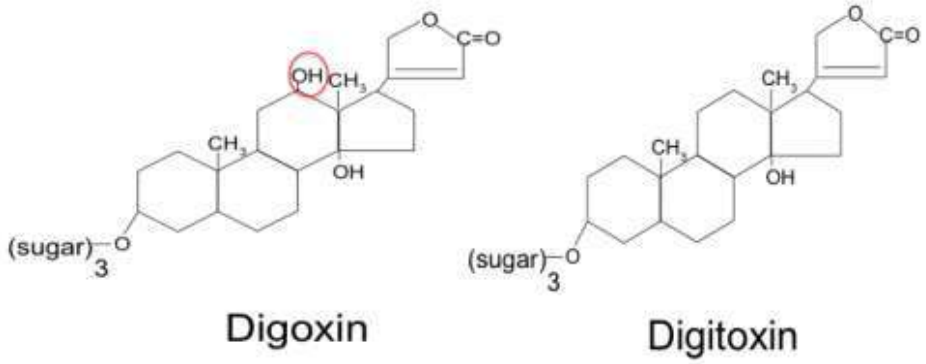
217



Phytochemicals

- Thus, the principal glycosides in the fresh leaves, namely **purpureaglycoside A** and **purpureaglycoside B,** are partially converted into **digitoxin** and gitoxin respectively, which normally predominate in the dried leaf.

218



Digitoxin

219

Biological Activity

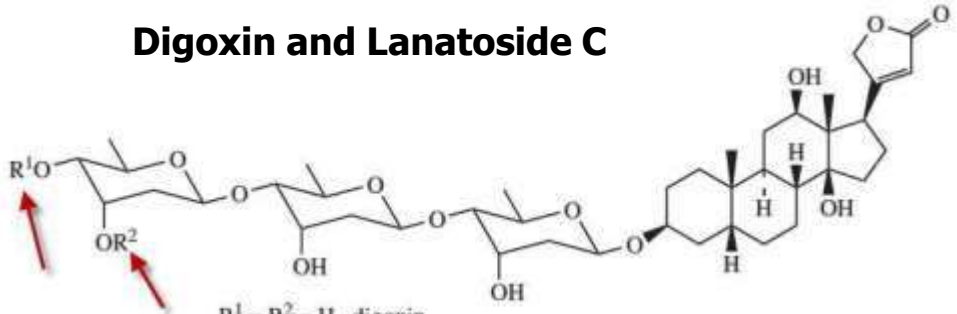
Slides 207-214

220

Digitalis Lanata (Scrophulariaceae)

221

Digoxin and Lanatoside C



$R^1 = R^2 = H$, digoxin

$R^1 = Glc$, $R^2 = Ac$, lanatoside C

Fig 74

Phytochemistry

222

Biological Activity

Slides 207-214

223

Strophanthus komb´e

- Strophanthus comprises the dried ripe seeds of *Strophanthus komb´e* (Apocynaceae), which are tall vines from equatorial Africa.
- *S. komb´e* has a history of use by African tribes as an arrow poison,
- The seeds contain 5–10% cardenolides, a mixture known as **K-strophanthin**.

224

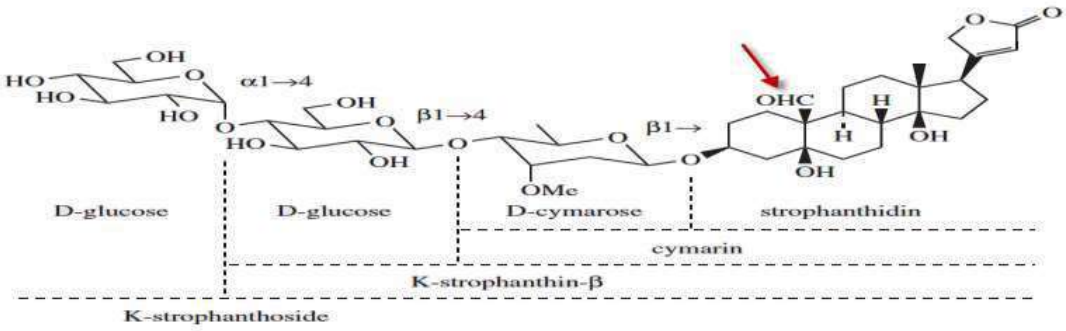
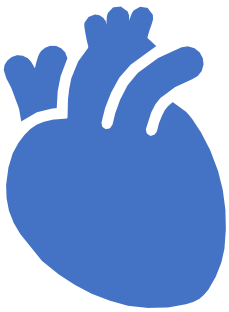


Fig 75

Phytochemicals

- **Cardioactive steroid glycosides (cardenolids, 4 to 8%): chief glycoside presumably k- strophanthoside.**

225



Indications

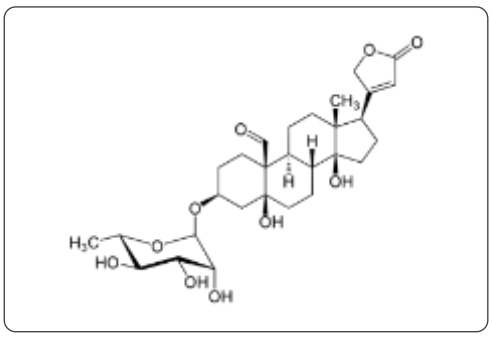
Emergency cardiac complaints & cardiac insufficiency.

226

Convallaria majalis (Liliaceae/Convallariaceae).

- In **folk medicine**, Lily-of-the-Valley was also used- for **weak contractions in labor**, **epilepsy**, **dropsy**, **strokes** and **leprosy**.
- Use for these applications is no longer common because of the drug's toxic effect.

227



- Cardioactive steroid glycosides (cardenolides): varying according to geographical source, chief **glycoside convallatoxin**

Phytochemistry

228

Effects

Convallaria glycosides are qualitatively similar to digitoxin and strophanthin.

The rest of digitalis

229

Indications

Arrhythmia

Cardiac insufficiency

Nervous heart complaints

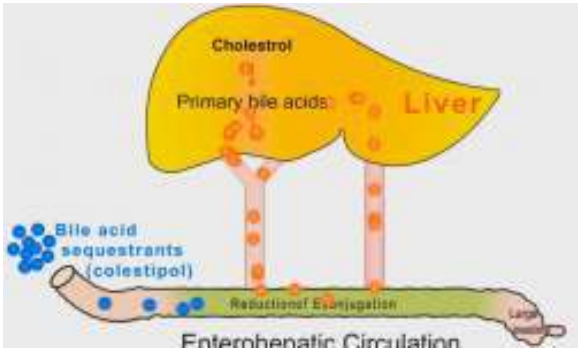
230

Drug Interactions

- Calcium supplements
- Quinidine
- Quinin
- Digoxin (Lanoxin)
- Medications for inflammation (Corticosteroids)
- Stimulant laxatives
- Diuretic drugs

231

Bile Acids



232

Bile Acids

1

The **bile acids** are C24 steroidal acids, e.g. **cholic acid,** which occur in salt form in bile, secreted into the gut to **emulsify fats and encourage digestion**.

2

The bile acids are **FORMED in the liver from cholesterol,** both cholic acid and chenodeoxycholic acid are formed in the liver, **STORED in the gall bladder**, and **RELEASED into the intestine**

233

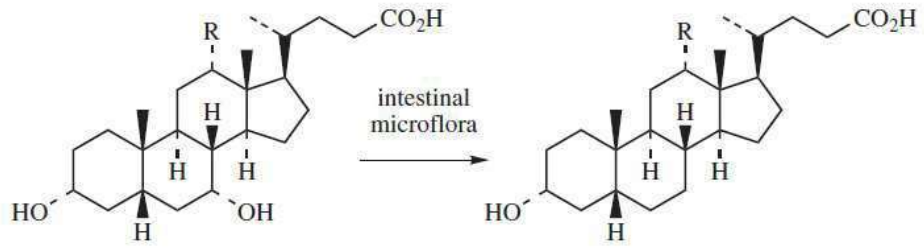


Fig 78

R = OH, cholic acid
R = H, chenodeoxycholic acid

R = OH, deoxycholic acid
R = H, lithocholic acid

Bile Acids

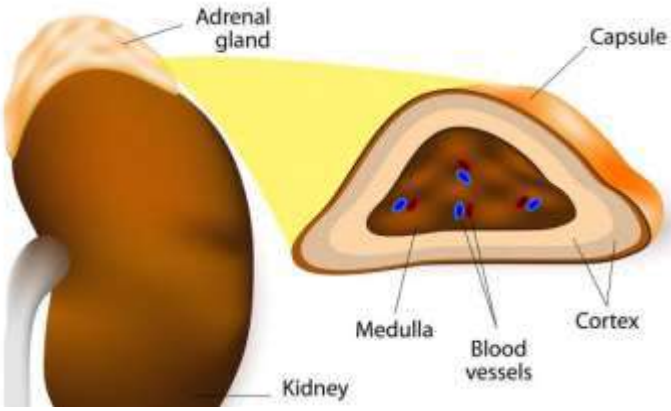
Mammalian bile also contains **deoxycholic acid** and **lithocholic acid**, which are termed **secondary bile acids**.

234

Bile Acids

- The **bile salts are then usually reabsorbed and stored in the gall bladder**, although
- they are also **excreted** to **eliminating excess cholesterol**.
- **Inability to remove cholesterol by bile acid synthesis and excretion may contribute to atherosclerosis and gallstone disease**; gallstones often contain more than 70% of cholesterol.

235



Adrenocortical Hormones/Corticosteroids

236

Adrenocortical Hormones/ Corticosteroids

A large number of steroid hormones have been isolated and characterized from the adrenal glands.

Corticosteroids are a class of drugs based on **hormones** formed in the adrenal gland or derived synthetically.

They are **created from cholesterol** and divided into two major groups: **glucocorticoids** and **mineralocorticoids**.

The secretion of these **hormones** increases during stress related to anxiety and severe injury.

237

Adrenocortical Hormones/ Corticosteroids

Five classes of steroid hormones are produced in the adrenal cortex: **glucocorticoids**, **mineralocorticoids**, **progestins**, **androgens**, and **estrogens**.

However, the amount of progestin, **androgen**, and estrogen produced by the adrenal is a minor fraction of the total amount of these steroids produced in the body.

Long periods of **high**-dose **corticosteroids** have severely decreased the body's natural **cortisol** production.

Corticosteroids work by **decreasing inflammation** and **reducing** the activity of the immune system.

238

Adrenocortical Hormones/ Corticosteroids

Glucocorticoids are concerned with the synthesis of carbohydrate from protein and the deposition of glycogen in the liver.

Mineralo-corticoids are concerned with the control of electrolyte balance, active compounds promoting the retention of Na+ and Cl−, and the excretion of K+.

Examples of natural glucocorticoids include **hydrocortisone** (**cortisol**) and **corticosterone**, whilst **aldosterone** and **deoxycorticosterone** (**cortexone**) type of mineralocorticoids.

239

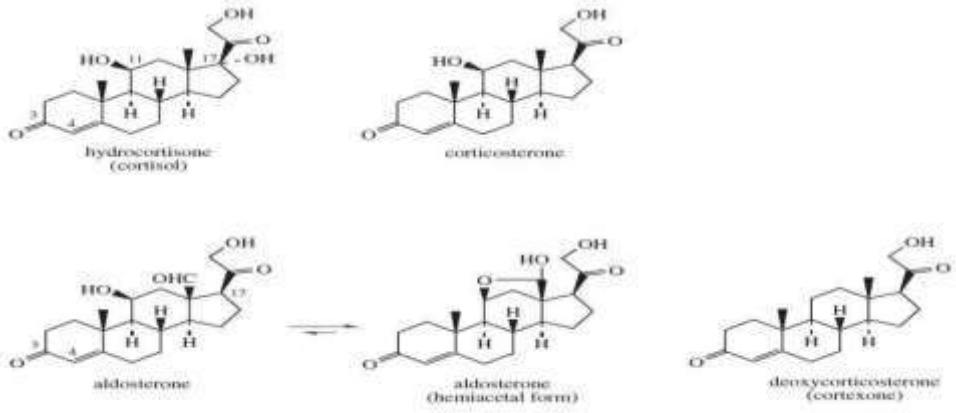


Fig 79

Adrenocortical Hormones/Corticosteroids

240

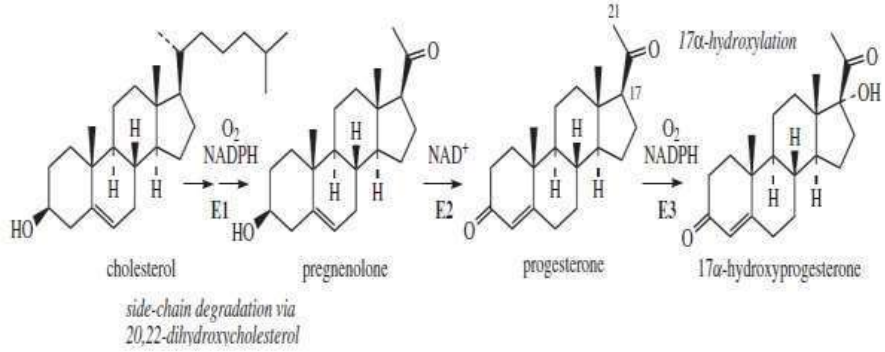


Fig 80

The corticosteroids are **produced from cholesterol** via **pregnenolone** and **progesterone**.

241

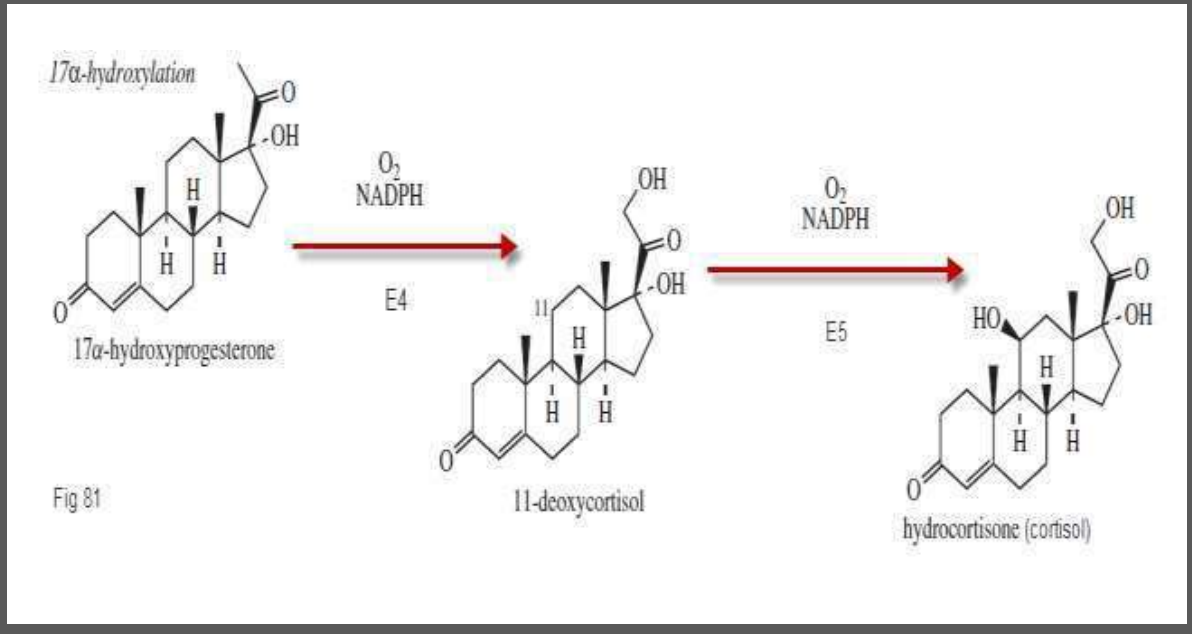


Fig 81

242

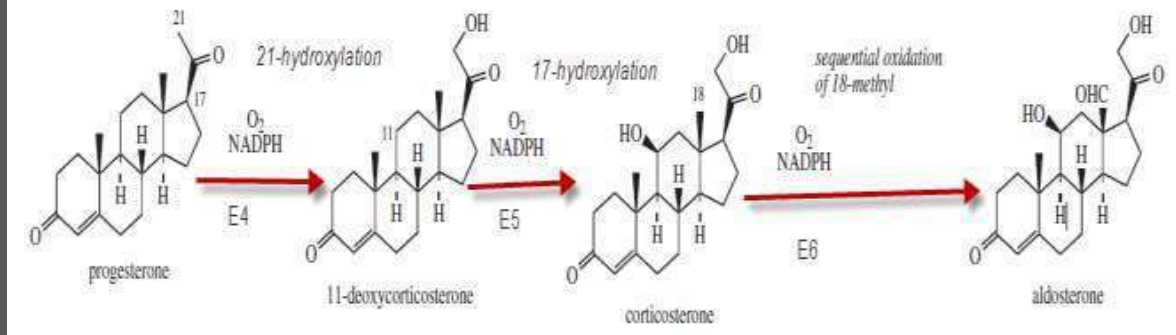
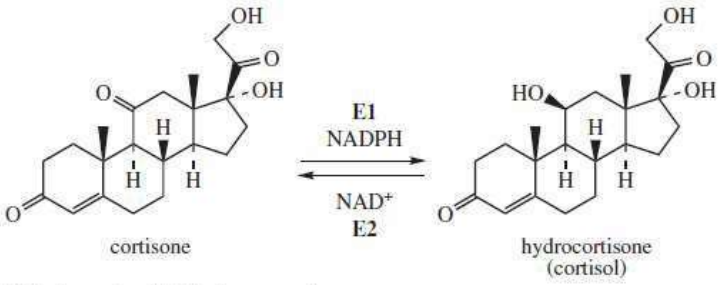


Fig 82

243

Note that:

- Cortisone itself was not the active agent; **it was reduced in the liver to hydrocortisone** as the active agent



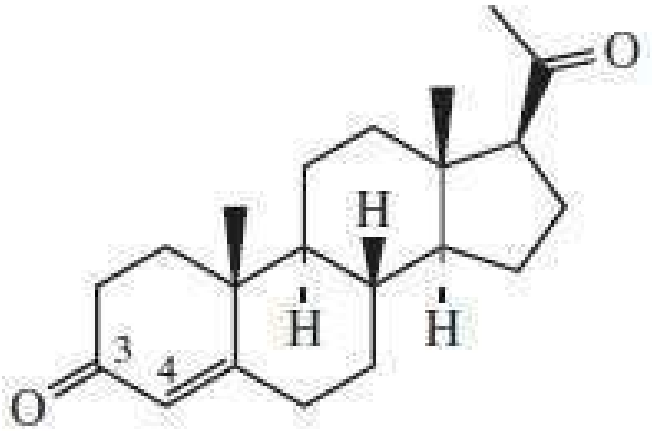
E1: 11β-hydroxysteroid dehydrogenase 1
E2: 11β-hydroxysteroid dehydrogenase 2

Fig 83

244

Progestogens

- A natural or synthetic steroid hormone, such as progesterone, that maintains pregnancy and prevents further ovulation during pregnancy.
- **Normal level in the middle of the menstrual cycle: 5 to 20 ng/mL**
- **Pregnant women in their first trimester: 11.2 to 90 ng/mL**



progesterone

245

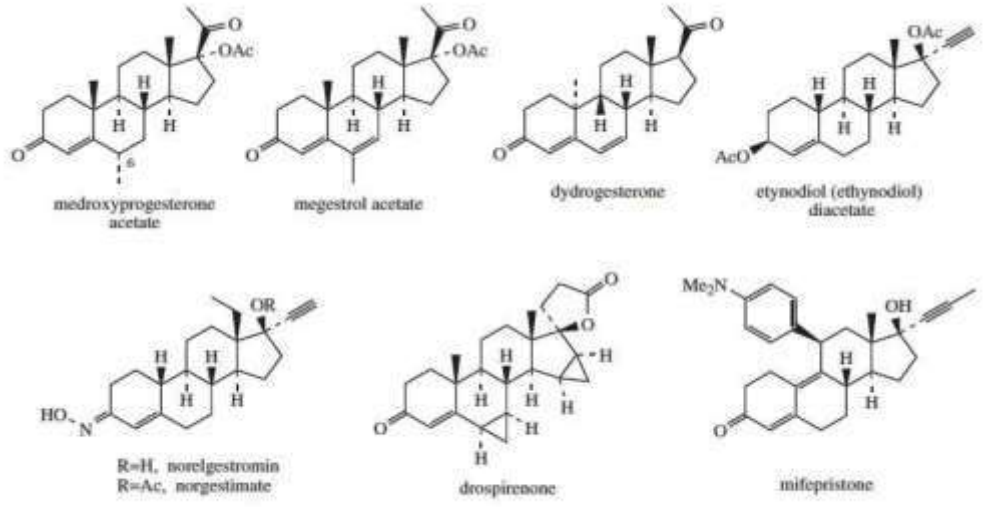


Fig 91

246

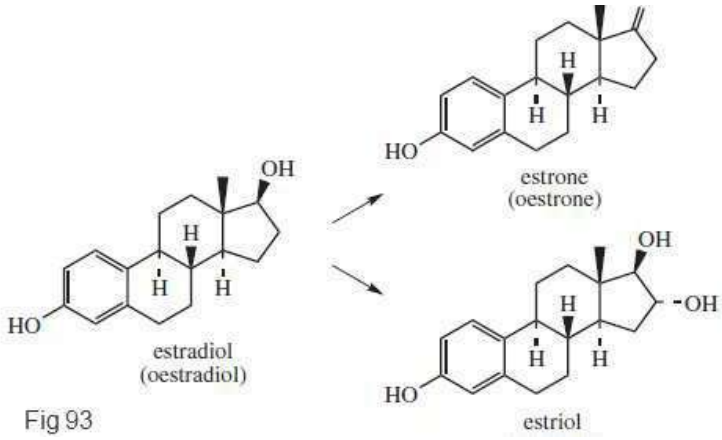


Fig 93

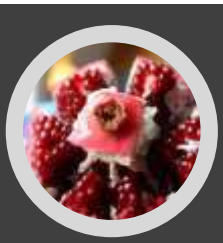
Oestrogens

- **Estrogens** are female sex hormones produced in the ovaries, and in the placenta during pregnancy.
- They are responsible for the **female sex characteristics** and, together with progesterone, **control the menstrual cycle**.
- Mid-follicular phase: 27-**123 pg/mL**

247

Phytoestrogen

- **Isoflavonoids**
- **Wild Yam**
- **Trigonella**
- **Anisi**
- **Fennel**
- **Pomegranate**

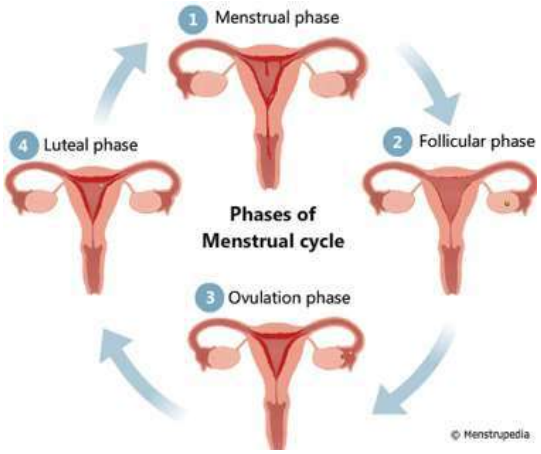




248

Menstruation

- The menstrual cycle is the **monthly** series of changes a woman's body goes through in preparation for the possibility of pregnancy.
- Each month, one of the ovaries releases an egg a process called **ovulation**. At the same time, hormonal changes prepare the uterus for pregnancy.
- **28 days** is an average number, it is common for women to experience **cycles** that last anywhere from 20 to **40 days**.
- **Cycles** longer than six weeks are considered unusual.
- Keep in mind that use of **certain types of contraception**, such as extended-cycle birth control pills and intrauterine devices (IUDs), **will alter your menstrual cycle**.



249

Dysmenorrhea

- Menstrual cycle irregularities can have many different causes, including:
  - **Pregnancy or breast-feeding**
  - **Eating disorders / Bulimia**
  - **Polycystic ovary syndrome (PCOS)**
  - **Premature ovarian failure.**
  - **Pelvic inflammatory disease (PID)**
  - **Uterine fibroids.**

250

Pregnancy

- During pregnancy, the corpus luteum continues to secrete progesterone for the first 3 months, after which the placenta becomes the supplier of both progesterone and oestrogen.
- Progesterone prevents further ovulation and relaxes the uterus to prevent the fertilized egg being dislodged.
- In the absence of pregnancy, a decline in progesterone levels results in shedding of the uterine endometrium and menstruation.
- To enhance the number of ovules (Clomiphene Citrate)
  - **Naturally: water-cinnamon-Ginger-Kale-berries-Avocado- Beans and lentils**
- To increase ovulation maturity (FSH/LH =Menotropin=), (FSH=urofollitropin)
  - **Naturally: DHEA, Co-Q-10, Selenium, Omega 3, probiotics, zinc**
- Fixation: Dehydrogesterone**,** progest
  - **Naturally: Healthy fats, D3, omega 3, meditation, sleep enough at night.**

251

Is the contraceptive pills safe?

- Oral contraceptives are medications that prevent pregnancy.
- Oral contraceptives are hormonal preparations that may contain combinations of the hormone's estrogen and progestin or progestin alone.
- **Birth control pills work** by emitting naturally-occurring hormones **estrogen and progestin to prevent pregnancy.**
- These hormones stop sperm from fertilizing an egg by stopping ovulation.

252

The biosynthetic pathway to estradiol and estrone

- The biosynthetic pathway to estradiol and estrone (Figure 94) proceeds **from cholesterol** via pregnenolone and bears a resemblance to the hydrocortisone pathway (Figure 80-82) in the early 17-hydroxylation step.

253

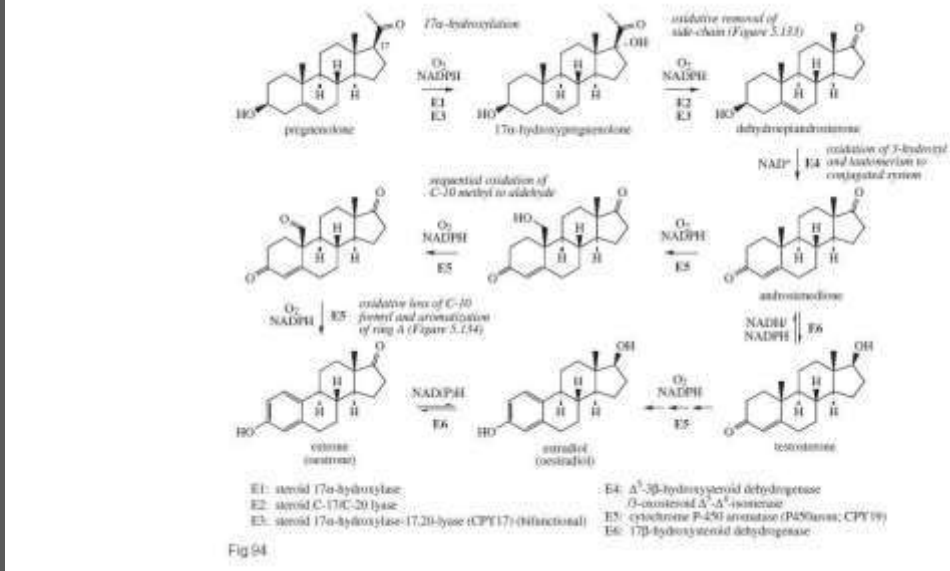


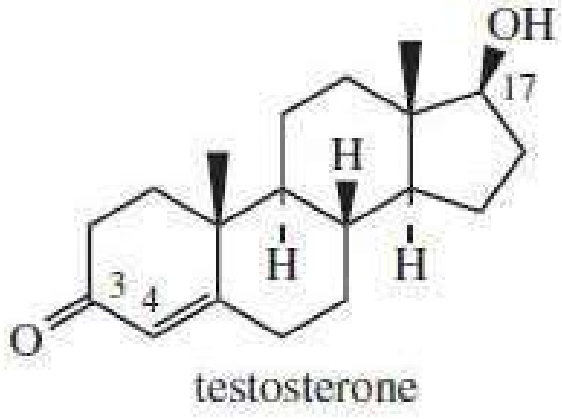
Fig 94

254

Hormone Replacement Therapy

- **Treatment with oestrogens** with the aim of alleviating menopausal symptoms or osteoporosis.
- Some signs for men that you could be a candidate for hormone replacement therapy include:
  - **Fatigue, exhaustion or low energy.**
  - **Difficulty achieving or sustaining an erection.**
  - **Lack of mental clarity and difficulty concentrating.**
  - **Loss of libido.**
  - **Weight gain.**
  - **Thinning hair.**
  - **Dryer skin.**
  - **Moodiness, anxiety or depression.**

255



testosterone

Fig 9.6

Androgens

- The primary male sex hormone, or **androgen**, is **testosterone.**
- **Androgens** are synthesized in the testes, the ovaries, and the adrenal glands.
- **Androgens** increase in both boys and girls during puberty.
- The **major androgen** in males is **testosterone**.

256

Androgens

This is secreted by the testes and is **responsible for development and maintenance of the male sex characteristics.**

Androgens also have a secondary physiological effect, an anabolic activity which stimulates growth of bone and muscle and promotes storage of protein.

Obese men with confirmed androgen deficiency

Testosterone is **not active orally**, since it is easily metabolized in the liver; it has to be implanted or injected in the form of esters.

257

Normal values

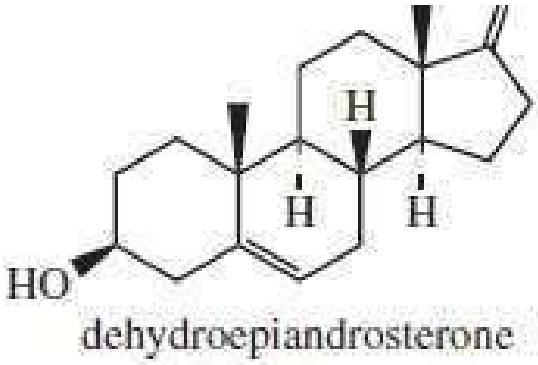
The normal range in males is about **270 to 1070 ng/dL** with an average level of **679 ng/dL**.

A normal male testosterone level peaks at about **age 20,** and then it slowly declines.

At **age of 70** testosterone levels are recognized as **less than 220 to 300 ng/dL.**

For **women** ages 19 and up, normal testosterone levels range from **8 to 60 ng/dL**

258



dehydroepiandrosterone (DHEA)

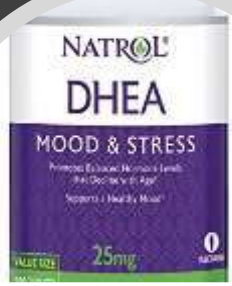
Dehydroepiandrosterone (DHEA)

- DHEA (**dehydroepiandrosterone**) is a hormone **produced by adrenal glands.**
- DHEA is a hormone that is **naturally made by the body.**
- DHEA works in the body to make other male and female sex hormones within the body.

259

Biological Activity of DHEA

- DHEA is a **precursor** of **androgens and oestrogens**; it is the most abundant steroid in the blood of young adult humans, levels peaking at about 20 years of age and then declining as the person ages.
- **DHEA is not a precursor** of glucocorticoids, mineralocorticoids, or of progestogens.
- **Symptoms of low DHEA**
  - **Not able to perform sexually or have no interest in sex,**
  - **Low energy and fatigue**
  - **Depression & Mood Swings**
  - **Weight Gain**
  - **Painful Joints**



260

Steroid hormone biosynthetic interrelationships

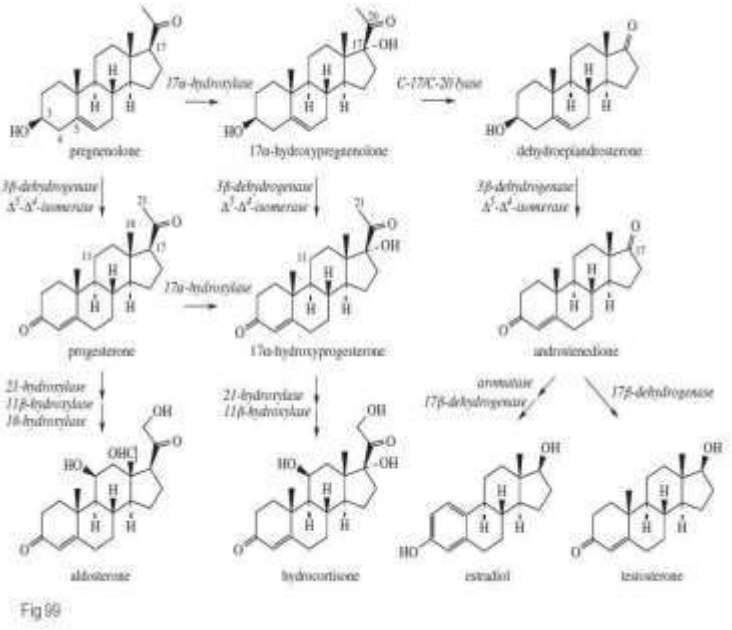


Fig 99

261

TETRATERPENES (C40)

262

TETRATERPENES (C40)

The tetraterpenes are represented by only one group of compounds, the **carotenoids**, though several hundred natural structural variants are known. These compounds play a role in photosynthesis, but they are also found in non-photosynthetic plant tissues, in fungi, and in bacteria.

Formation of the tetraterpene skeleton, e.g. **phytoene**, involves tail-to-tail coupling of two molecules of **geranylgeranyl diphosphate (GGPP)** in a sequence essentially analogous to that seen for squalene and Triterpenes "Lycopene".

263

Lycopene

- Lycopene is the characteristic carotenoid pigment in ripe tomato fruit (*Lycopersicon esculente*; Solanaceae).
- Lycopene is a bright red carotene and carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons, and papayas, **but it is not in strawberries or cherries**.

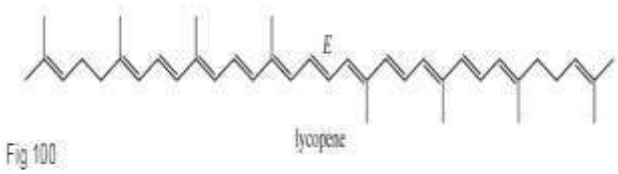
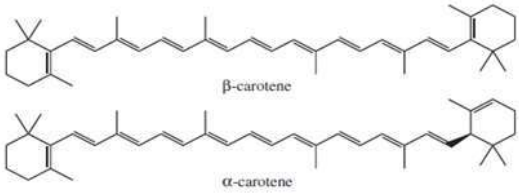


Fig 100 lycopene

264

β-carotene

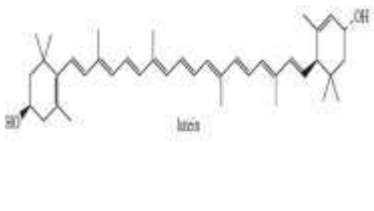


The orange color of carrots (*Daucus carota*; Umbelliferae/Apiaceae) is caused by β-carotene

265

Lutein (*the eye vitamin*)

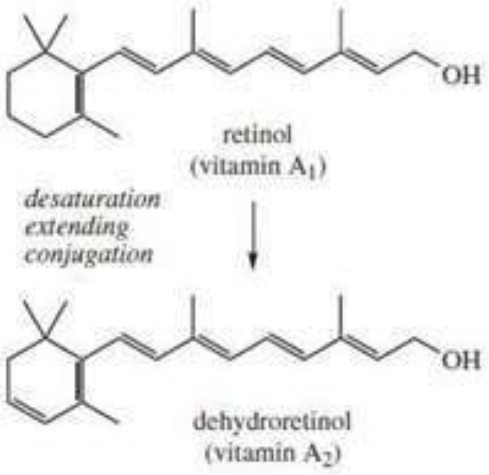
- **Lutein** is a xanthophyll and one of 600 known naturally occurring **carotenoids**.
- **Lutein is synthesized only by plants** and like other xanthophylls is found in high quantities in green leafy vegetables such as spinach, kale and yellow carrots.
- **Foods rich in lutein** include broccoli, spinach, kale, corn, orange pepper, kiwi fruit, grapes, orange juice, zucchini, and squash.
- Lutein is absorbed best when it is taken with a high-fat meal.



266

Vitamin A

- The A group of vitamins are important metabolites of carotenoids.
- **Vitamin A1 (retinol)** effectively has a diterpene structure, but it is **derived in mammals by oxidative metabolism of a tetraterpenoid, mainly β-carotene**, taken in the diet.



267

Vitamin A

- **Vitamin A1 (retinol)** and **vitamin A2** (dehydroretinol) are fat-soluble vitamins found only in animal products, particularly eggs, dairy products, and animal livers and kidneys.
- Vitamin A2 has about 40% of the activity of vitamin A1.
- Carotenoid precursors (provitamins) are widely distributed in plants, and after ingestion, these are subsequently transformed into vitamin A in the liver. Green vegetables and plant sources rich in carotenoids, such as carrots, help to provide adequate levels.

268

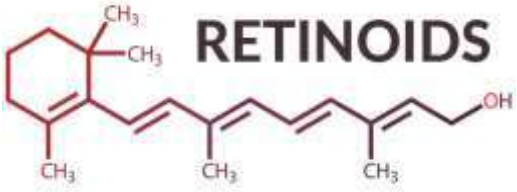
Vitamin A Deficiency

- Night blindness
- Drying and degenerative disease of the cornea.
- Dry skin
- Infertility
- Delayed growth
- Throat and chest infections
- Poor wound healing

269

Retinoids (vitamin A & analogues)

- The retinoids are a class of chemical compounds that are vitamers of vitamin A or are chemically related to it.
- Retinoids have found use in medicine where they regulate epithelial cell growth.
- Retinoids for Acne.
- Retinoids stimulate the production of new **skin** cells.
- Retinoids also help to fade dark spots resulting from photo-aging, hyperpigmentation, hormonal changes, and blemish scars.



270


Hevea brasiliensis
(Euphorbiaceae) (Rubber)
Higher Terpenoids
(C_{40}–C_{50})

271


Thank
You

272