Cardiovascular System

phytomedicines play a significant role :

- in the treatment of mild forms of **heart failure (فشل قلبي)** and **coronary insufficiency (قصور تاجي)**
- in the prevention and treatment of **atherosclerosis (تصلب عصيدي)** and its **sequelae**
- and in the symptomatic treatment of **chronic venous insufficiency** (قصور وريدي مزمن)

Hawthorn

(heart failure فشل قلبي and coronary insufficiency قصور تاجي)

- **garlic**

(atherosclerosis تصلب عصيدي)

- **ginkgo**

(arterial occlusive disease انسداد الشرايين)

- **horse chestnut**

(chronic venous insufficiency قصور وريدي مزمن).

Heart Failure and Coronary Insufficiency

The classic remedies used to treat myocardial insufficiency are the **cardiac glycosides** derived from purple and Grecian foxglove (***Digitalis* species**)

- These compounds are colorless, bitter-tasting substances that cause local irritation.

- Their chemical compositions are known, and they can be synthetically produced

- for economic reasons the 14 pure glycosides or their precursors are still obtained by extraction from *digitalis* **leaf**.

Because the cardiac glycosides are specific, identifiable chemical compounds that have a narrow therapeutic dose range , **they are not considered phytotherapeutic agents** and are outside the realm of herbal medicine.

- Galenic preparations made from *Digitalis* leaves are obsolete in modern pharmacotherapy

- **Lanatoside A**

↓ - Acetyl

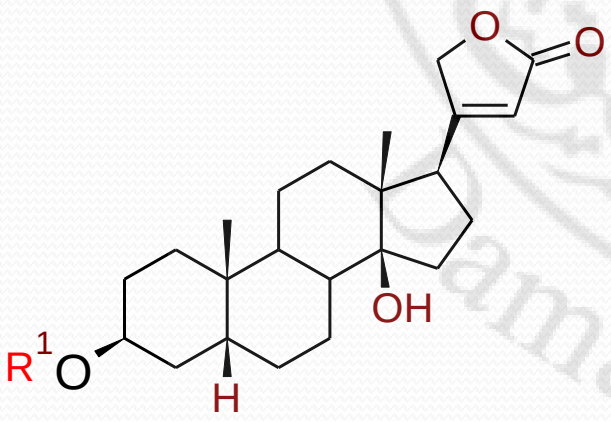
Purpurea A

↓ - Glu

Digitoxin

↓ - 3 digitoxose

Digitoxigenine



- **Lanatoside C**

↓ - Acetyl

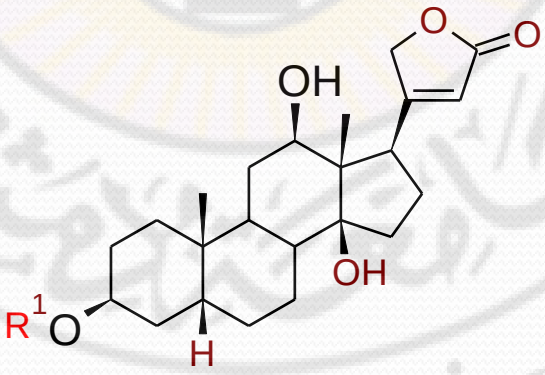
Purpurea C

↓ - Glu

Digoxin

↓ - 3 digitoxose

Digoxigenine



- **Lanatoside B**

↓ - Acetyl

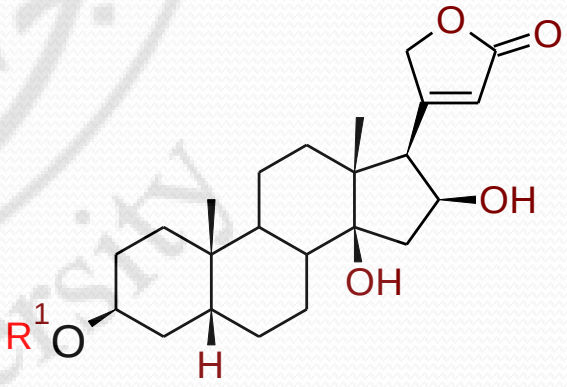
Purpurea B

↓ - Glu

Gitoxin

↓ - 3 digitoxose

Gitoxigenine



Herbs Containing Digitaloids

- **Digitaloids** are cardioactive glycosides that exert a digoxin-like action but are not derived from *Digitals* species.
- The digitaloids include, most notably, convallatoxin, cymarin, oleandrin, G- and K-strophanthin, and proscillaridin.
- The principal sources of digitaloids are false hellebore, lily-of-the-valley, squill bulbs, and oleander leaves.

Digitaloids

- There are no qualitative differences between the digitaloids and the classic cardiac glycosides digoxin and digitoxin in terms of their pharmacologic mechanism of action and cardiac efficacy
- Digitaloids and digitalis glycosides differ in their pharmacokinetics. however, particularly in their rates of absorption and clearance.
- treatment with digitaloid herbs carries a higher overall risk than treatment with isolated cardiac glycosides
- Another difficulty is that digitaloid extracts do not meet phytotherapeutic requirements for a broad therapeutic range. Thus, physicians who have no personal experience with these products should use them only with great caution

Digitaloids

All these compounds are:

- positively inotropic
- negatively chronotropic
- negatively dromotropic

Inotropic: Affecting the force of muscle contraction. An inotropic heart drug is one that affects the force with which the heart muscle contracts.
Chronotropic : affecting the rate of rhythmic movements, such as the heartbeat.
dromotropic : affecting conductivity of a nerve fiber. Relating to or influencing the conductivity of nerve fibers or cardiac muscle fibers.

Table 3.3. Pharmacokinetic parameters of digitaloid glycosides compared with digitoxin and digoxin (after Loew, 1997).

	Digitalis spp. (Digitoxin)	Digitalis lanata (Digoxin)	Adonis	Convallaria	Oleander	Squill
Number of glycosides considered	1	1	ca. 27	ca. 40	ca. 25	ca. 30
Principal glycoside	Digitoxin	Digoxin	Cymarin	Convallatoxin	Oleandrin	Proscillaridin A
Absorption (%)	95–100	60–80	15–37	10	65–86	20–30
Half-life t 1/2 (h)	ca. 200	ca. 40	13–23	–	–	23–49
Daily activity loss (%)	7–10	20–25	28–39	40–50	41	30–50
Duration of action (d)	10–21	4–8	2.8	–	2.65	2–3
Protein binding (%)	90–97	20	–	16	50	85
Excretion	Renal, biliary	Mainly renal	Mainly renal	Renal, biliary	Renal, biliary	Mainly renal

ادونيس الربيعي False hellebore

- **L** : ***Adonis vernalis***
- **F** : **Ranunculaceae**
- **U P** : **The whole plant,**

(particular the root)

Use : mild heart failure, especially when accompanied by nervous symptoms

Lily of the Valley
لؤلؤة الوادي

L : *Convallaria majalis*

F: Liliaceae

U P: aerial parts gathered during the flowering period

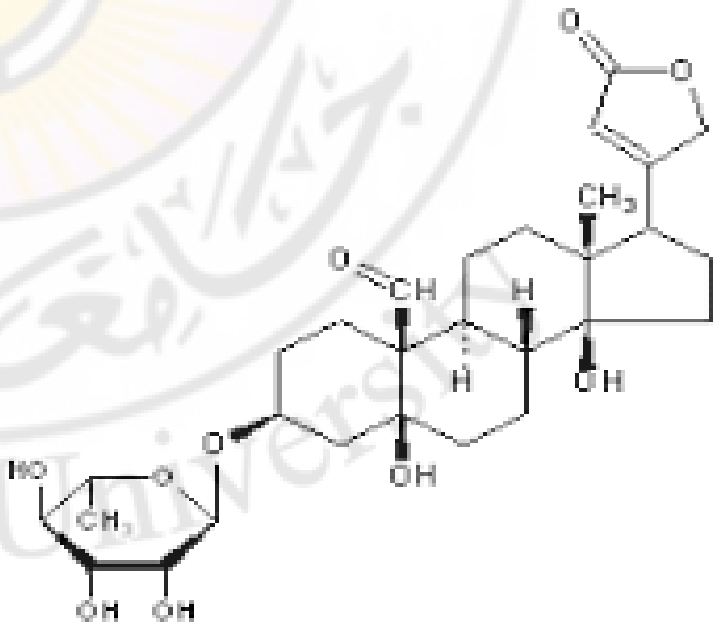
Contents:

convallatoxin +convallatoxol.

convallatoxin gives on hydrolysis convallatoxigenine + rhamnose

- The standardized powdered drug has a **0.2–0.3%** content of cardio – active glycosides, which number more than 30

- Convallatoxin has
  - an absorption rate of about 10%
  - and 24 h clearance rate of about 50%.
  - The maintenance dose is **0.2–0.3 mg** intravenously and **2–3 mg** orally



الدفلة Oleander

L : *Nerium oleander*

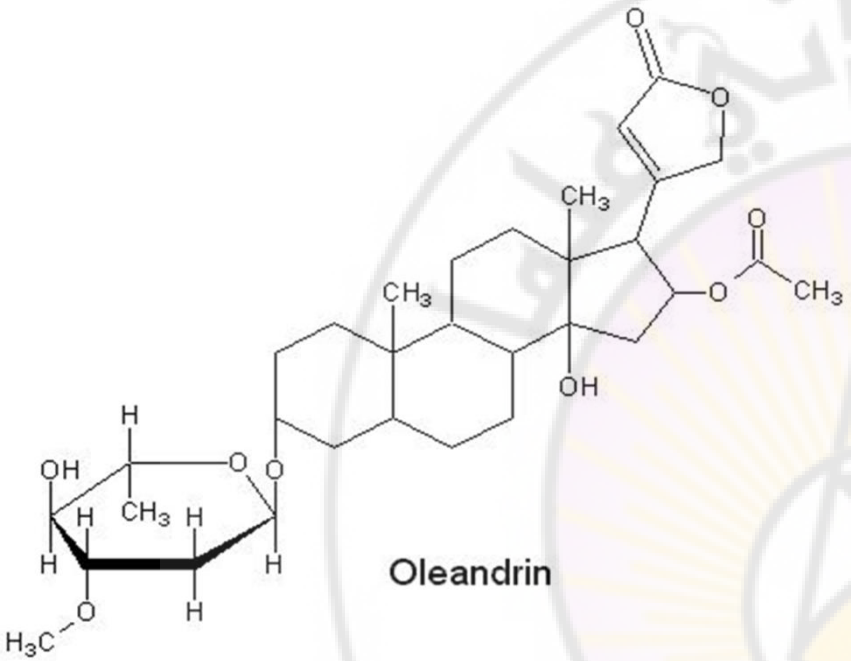
F: Apocynaceae

U P: Leaf

Contents:

Oleandrin
(aglycone is closely related to the gitoxin)

Uses: الاستعمال



it is considered particularly useful in cases of

- mild myocardial insufficiency
- and where digitalis intolerance exists.

Oleander ingestion causes many cases of poisoning.

العنصل Squill

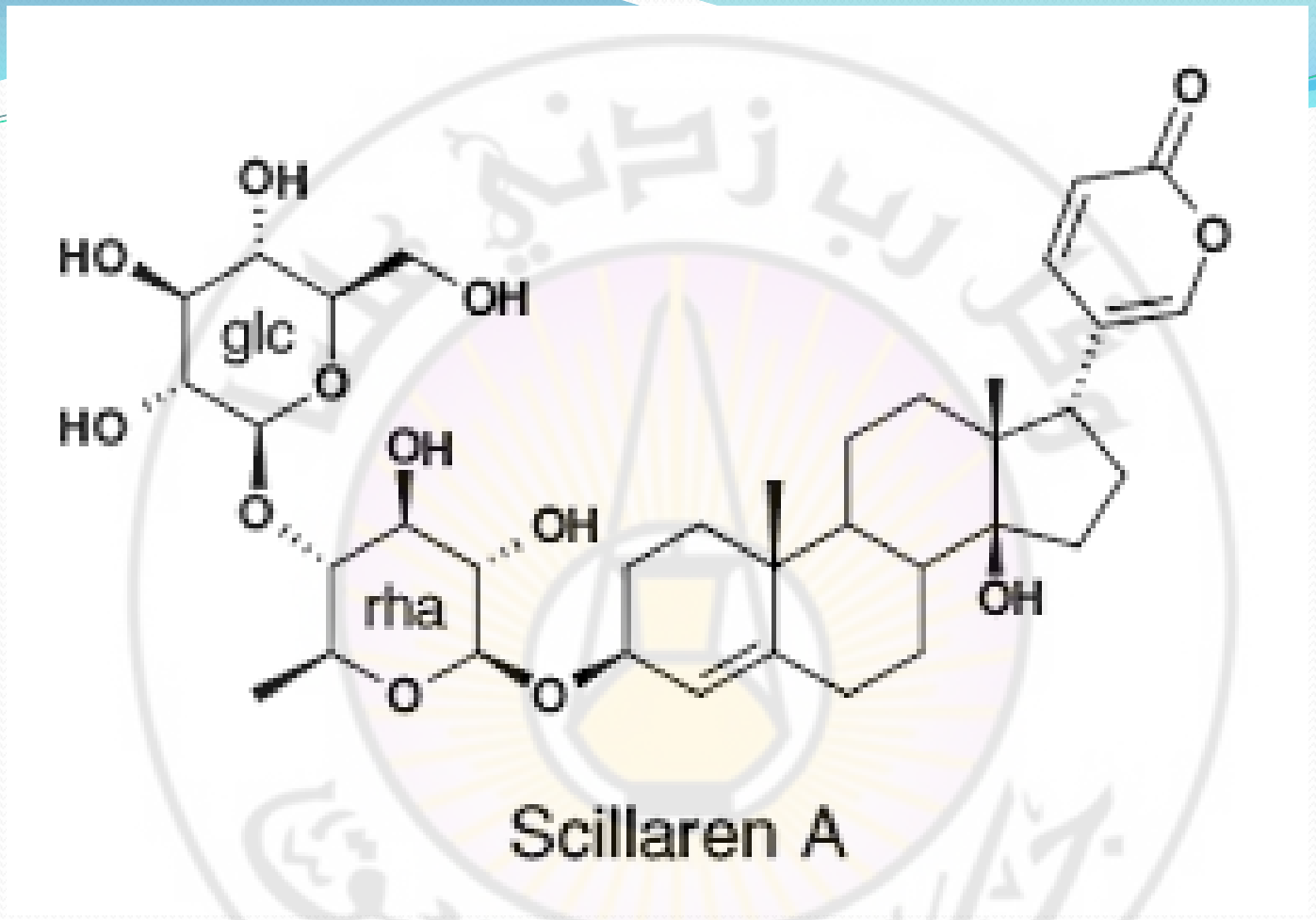
L : *Urginea maritima*

F: Asparagaceae

U P: the squill bulb
(after the flowering season)

Contents:

0.1% ▪ 2.4% total **bufadienolides**,
▪15 glycosides The principal glycosides are scillaren A and proscillaridin



Scillaren A

The gastrointestinal absorption rate is about 15% for scillaren and 20-30% for proscillaridin. The half-life of proscillaridin is approximately 24h.

The daily dose ranges from **0.1 to 0.5 g** of the standardized **squill powder**

Hawthorn الزعرور

Latin name: *Crataegus monogyna*
Crataegus oxyacantha

Family: Rosaceae

Used part: fruits, Leaves and flowers

- Only the white-blooming hawthorn is used therapeutically
- The red-blooming hawthorn has no medicinal uses.

Therapeutic efficacy has been most reliably documented for hawthorn **leaves** and **flowers**

- The German Pharmacopeia describes the crude drug as consisting of the **dried tops** of the flowering shrub.

The dried herb has a faint, distinctive odor and a slightly bitter or astringent taste.

- A fixed combination of hawthorn flowers, leaves, and fruits has also been recognized as having therapeutic efficacy.
- By themselves, the dried berry-like fruits (haws) have a sweet mealy or mucilaginous taste.

Constituents

The main constituents that have been isolated from hawthorn are :

.Flavonoids (0.1-1% in fruits, 1-2% in leaves and flowers)

- Flavonol (e.g. kaempferol, quercetin)
- flavone derivatives (e.g. apigenin, luteolin),
- Rutin, hyperoside, vitexin glycosides, orientin glycosides.

The **fruits** contain relatively more **hyperoside** and the **leaves** relatively more **vitexin-2-rhamnoside**.

.Tannins

.Other constituents **triterpene acids** (0.5%-1.4% in fruits), **organic acids** (2%-6%), **sterols , amino and purine derivatives**

The key constituents for testing pharmaceutical quality are

- the **flavonoids**, calculated as **hyperoside**.
- and the **oligomeric procyanidins**, calculated as **epicatechin**.

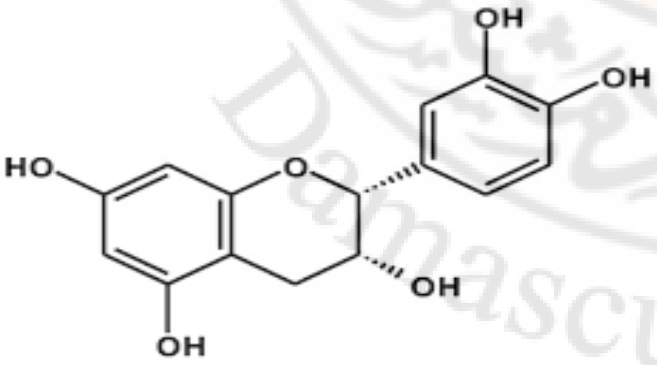
➢ the **flowers** contain higher levels of **flavonoids**, the **leaves** containing the highest levels of **oligomeric procyanidins** (OPCs)

❑ Recommended daily dose is **160-900 mg** hawthorn extract with a designated content of

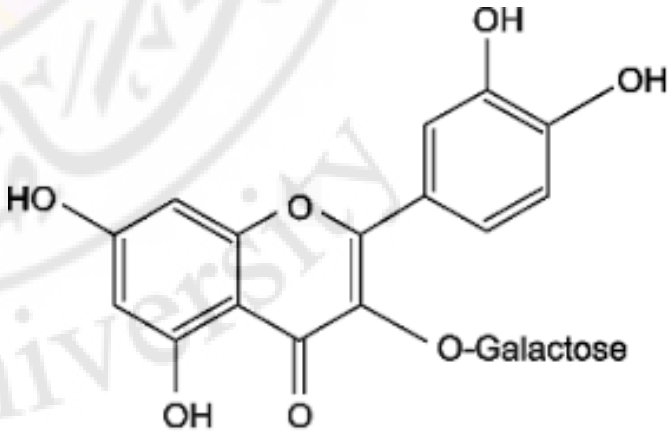
flavonoids (4-30 mg)

oligomeric procyanidins (30-160 mg).

❑ Hawthorn preparations should be taken **orally** and should be continued for **at least 6 weeks**.



(-)-epicatechin



cardiovascular effects

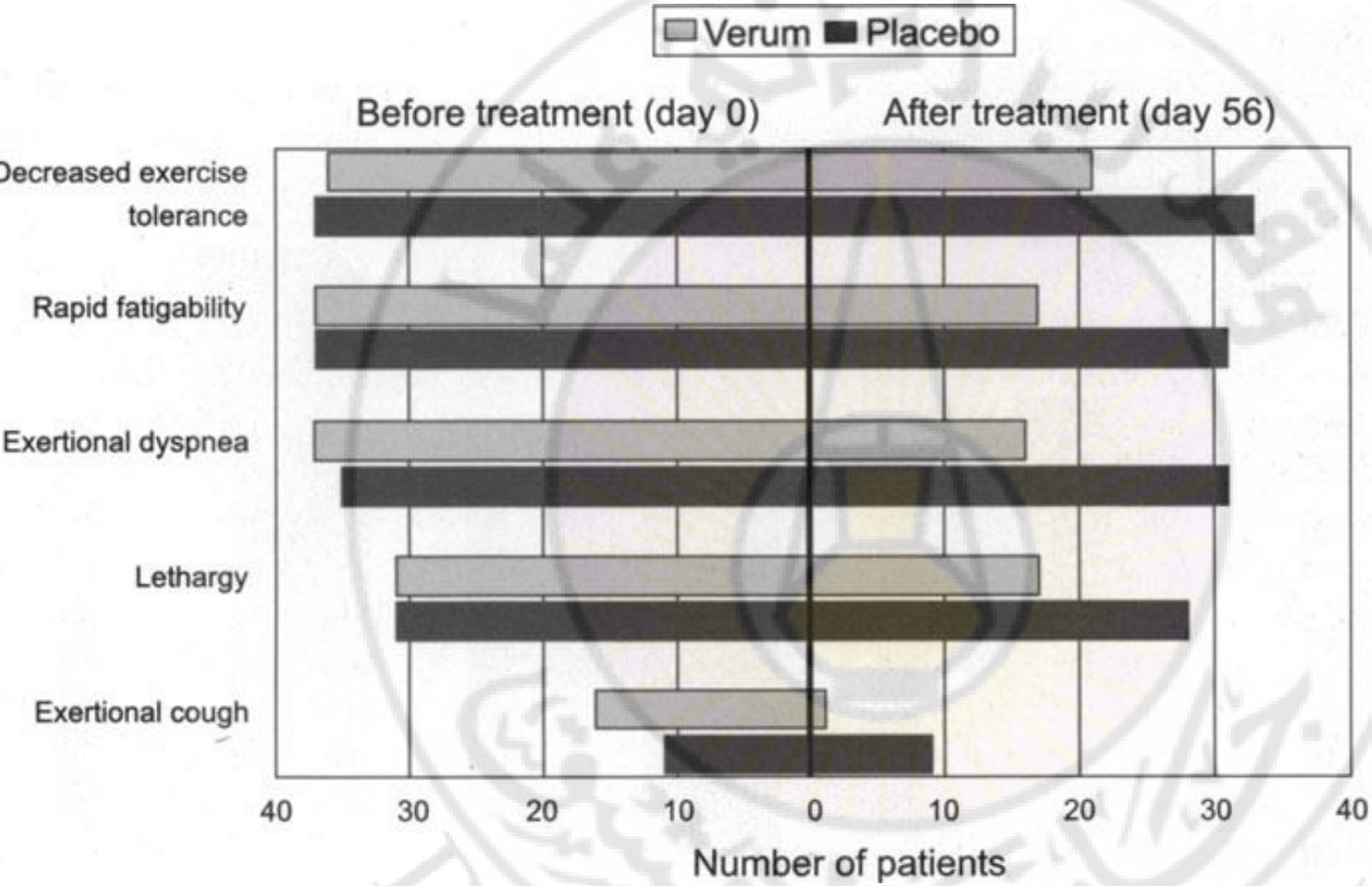
- Increase amplitude of myocardial contractions
- Increase in coronary blood flow
- Decrease in heart rate
- Antiarrhythmic effects
- Reductions in the duration of fibrillations and the occurrence of tachycardi
- Cardio protective effect
- Hawthorn extract is positively inotropic but appears to stabilize the heart rhythm (unique effect because antiarrhythmic agents are generally negatively inotropic)

toxicity

- Acute toxicity studies were performed in mice and rats using a **water-and ethanol** hawthorn **extract** (45% v/v, herb-to-extract ratio 5:1)

➢ No deaths resulted from oral or intraperitoneal doses up to 3000 mg/kg body weight.

- Intraperitoneal doses higher than 3000 mg/kg produced toxic symptoms consisting of **sedation**, **dyspnea**, and **tremor**
- The water-and-ethanol extract has been shown to be **non mutagenic** in various tests



the graph shows that significantly more patients became free of complaints while on treatment with the hawthorn extract

Fig.: Frequency of key symptoms before and after treatment with 600 mg/day hawthorn extract. At 56 days, patients on the drug showed significantly greater symptom reductions than patients on the placebo

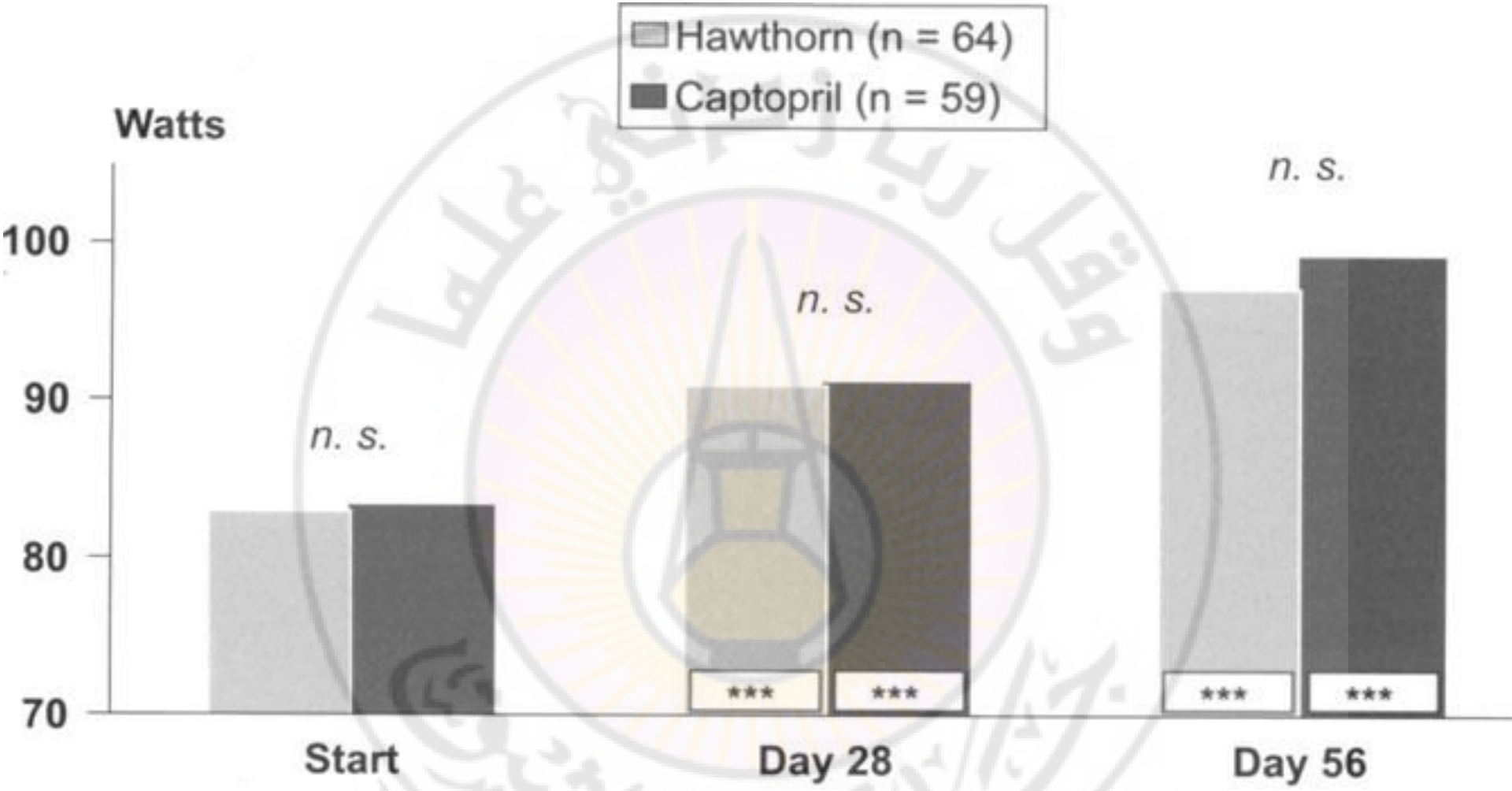


Fig.:. Mean values of exercise tolerance in patients with cardiac failure. **Double-blind** comparison of **900 mg/day hawthorn** extract with **37.5 mg/day captopril.**
Both groups showed a highly significant increase in exercise tolerance during the course of treatment (···=p<0,001), with no statistically significant differences

Risks and Contraindications

There are **no** known **risks**, **contraindications**, or **drug-drug interactions**.

As a possible adverse reactions :

- gastrointestinal complaints
- Palpitations
- vertigo
- Headache
- flushing

The analysis showed that a fall in blood pressure during hawthorn treatment occurred in initially hypertensive patients **but not in** patients who were **normotensive or hypotensive** at the start of therapy.

- It was also found that a decrease in heart rate occurred only in tachycardiac patients and **not in** patients with initially **normal or bradycardiac rates**

Table 3.2. Comparison of the therapeutic risks of hawthorn extract and cardiac glycosides

Therapeutic risk	Crataegus	Digitalis
Therapeutic range	Very large	Very small
Dosage errors	No danger	High risk
Arrhythmogenic potential	None	Relatively large
Renal function impairment	Not a problem	Danger of intoxication
Diuretics, laxatives	Can be safely used	Require potassium monitoring
Tolerance to oxygen deficit	Increased	Reduced

Other Cardioactive Plant Drugs

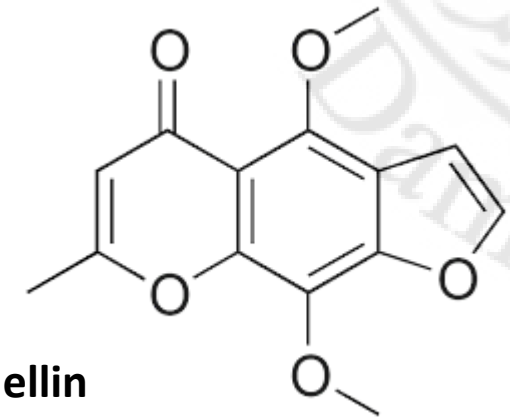
Extract from ***Ammi visnaga*** fruits (**Apiaceae**)and the their isolated compounds (khellin and visnagin) improve myocardial perfusion by increasing blood flow through the coronary vessels.

- These actions form the basis for the use of *visnaga* extract in relieving angina due to coronary heart disease.

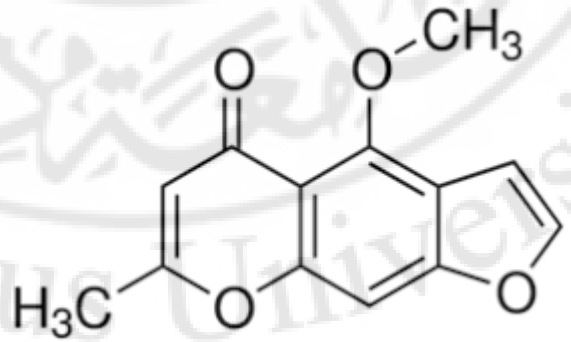
Reports of **adverse effects**

- isolated cases of pseudoallergic reactions,
- reversible cholestatic jaundice,
- elevated hepatic transaminase levels

prompted Commission E to withdraw its claim that *Ammi visnaga* extract was appropriate for the treatment of "mild angina pectoris."



khellin



Other Cardioactive Plant Drugs

Antiarrhythmic agents of plant origin include the drugs

- **Ajmaline** (alkaloid , the root of ***Rauwolfia*** **species**),
- **Quinidine** (alkaloid , the bark of ***Cinchona*** **species**)
- **Sparteine** (alkaloid , ***Cytisus scoparius***).

- The treatment risks associated with these compounds are similar to those of synthetic antiarrhythmic drugs.
- it is better to use the substances in pure, isolated form rather than in the form of herbal extract-based preparations.

Motherwort ذنب الأسد القلبى

Extracts from ***Leonurus cardiaca*** (**Lamiaceae**) are recommended for the treatment of nervous heart conditions

- according to European Pharmacopoeia (7th edition), it should contain a minimum of 0.2% flavonoids expressed as **hyperoside**
- an average daily dose : **4.5 g** of the crude drug.
- The dried aerial parts of motherwort occur as ingredients in "cardiovascular teas",

and its extract is an ingredient of several combination products (e.g., Oxacant).

Hypotension and Hypertension

- Hypotension and hypertension are not considered primary indications for phythotherapy

- Nevertheless, some herbal medications are suitable for short-term use in the symptomatic treatment of orthostatic complaints associated with low blood pressure

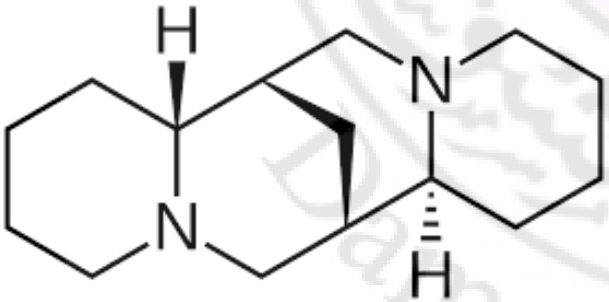
- and for longer-term use as a supportive therapy in patients with high blood pressure.

Phythotherapy of Hypotension

- **Hypotension** ordinarily refers to blood pressure **less** than 90 mm Hg systolic and 60 mm Hg diastolic.
- Low blood pressure has no pathologic significance in itself and is even beneficial in inhibiting atherosclerotic disease.
- Hypotension requires treatment only if it is associated with orthostatic symptoms such as dizziness, grogginess, headache, and fatigue.

- Physical therapy and dietary measures (increased fluid and salt intake) are the mainstays of treatment,
- medications are used only temporarily in a supportive role.
- **Dihydroergotamine** (a hydrogenation product of the alkaloid ergotamine), is believed to increase the tonus of capacitance vessels by the **stimulation of α-adrenergic receptors**, resulting a rise in blood pressure.
- Dihydroergotamine is a modified pure plant constituent and, as such, is not considered a phytotherapeutic agent.

- Extracts from the broom shrub (*Cytisus scoparius,* Fabaceae) can no longer be recommended for antihypotensive therapy.
- the main alkaloid constituent of broom, **sparteine**, has shown a narrow range of therapeutic utility.
- Also, sparteine is poorly metabolized in a significant percentage of the population who have a congenital enzyme defect, delaying the excretion of this compound by a factor of 1000 so that even low doses can pose a significant health risk.



➢Preparations made from

- **caffeine**-containing herbs
- certain **aromatic herbs** containing volatile oils

are classified as **(herbal anti hypotensives**)

Caffeine-Containing Herbs and Beverages

- Caffeine and caffeine-containing beverages are agents with unpredictable anti hypotensive effects.
- It is a common experience, however, for people with low blood pressure to feel better after drinking their morning coffee or tea.
- Caffeine and other methyl xanthines act directly on the pressor centers of the circulatory system; they also exert mild positive inotropic and chronotropic effects on the heart.
- Their duration of action is approximately 1-3 h.

- A morning **coffee** infusion is prepared with **5-8 g** of roasted coffee per cup (150 mL).
- Roasted coffee has a caffeine content of about **1-2%** so a total of about **100 mg** of caffeine is ingested in **one cup** of coffee.

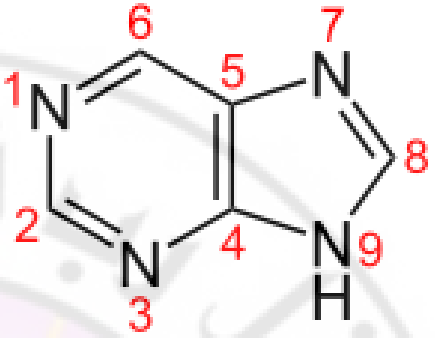
- Dried **tea** leaves contain **2-5%** caffeine. But given the smaller amount of herb that is used, and the method of extraction (infusion) so **one cup** of black tea contains only about **30-50 mg** of caffeine.

- Other caffeine-containing herbs are **guarana seeds**, **cola seeds**, **mate leaves**, and **cocoa beans**.

- Extracts from **guarana** and **cola seeds** are sold over the counter in the form of chewable tablets or drink mixtures.

- Due to the unpredictable risks, especially to children and adolescents (**lethal caffeine dose between 3 and 10 g)**, efforts are being made to restrict the over-the-counter availability of guarana products.

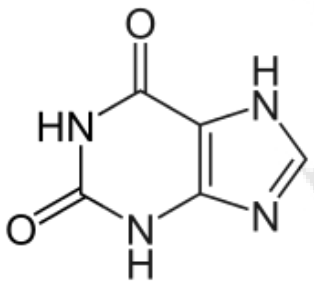
Purine Alkaloids



They are secondary metabolites and are derivatives of xanthine

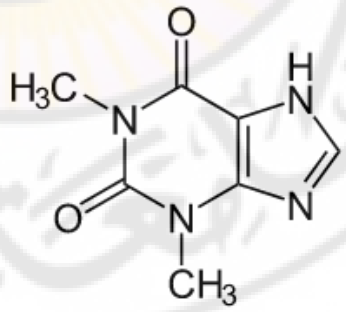
Three well-known examples are :

- **Caffeine** (1,3,7-trimethylxanthine)
- **Theophylline** (1,3-dimethylaxantine)
- **Theobromine** (3,7-dimethylxanthine)

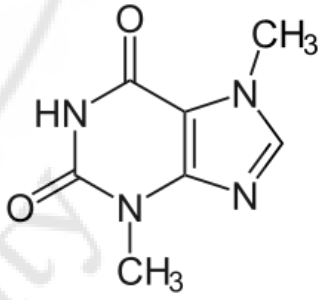


Xanthine

Caffeine



Theophylline



Theobromine

Table 3.4. Percentage content of methylxanthines in dried herbs, n.d. = not detectable (Ploss, 1994).

Herbal drug	Caffeine	Theobromine	Theophylline
Coffee	0.9–2.6	0.002	0.0005
Cola nut	2.00	0.05	n.d.
Tea leaf	2.5–5.5	0.07–0.17	0.002–0.013
Cocoa bean	0.2	1.2	n.d.
Maté	0.5–1.5	n.d.	n.d.
Guarana	2.95–5.8	0.03–0.17	0.02–0.06

- **Caffeine** is lipid-soluble, so it is readily absorbed from the gastrointestinal tract.
- The monographs state that caffeine and caffeine-containing herbs are useful for the short-term relief of symptoms due to mental or physical fatigue.
- **Caffeine citrate** is on the **WHO** Model List of Essential Medicines
- Caffeine is classified by **FDA** as generally recognized as safe (**GRAS**)
- The **possible side effects** of caffeine-containing herbs include stomach upset, nervousness, and sleeplessness.

Essential Oils

- **Analeptic** is an older term denoting a restorative remedy for states of weakness that are frequently accompanied by dizziness and fainting.
- Traditional formulas for analeptics contained aromatic substances that **stimulated** the olfactory nerve and the sensory trigeminal nerve endings, causing a reflex stimulation of respiration and circulation.
- Among these substances were essential oils derived from aromatic herbs (plants containing volatile oils).
- **rosemary leaves** (indicated for circulatory problems)
- **lavender leaves** (indicated for functional circulatory disorders)

as aromatic herbs for external use in balneology.

❖**Rosemary leaves (*Salvia rosmarinus*, Lamiaceae)** contain at least **1.2%** volatile oil.

A hot infusion is prepared from about **50 g** of the crude drug and is added to the bath.

❖ **Lavender leaves (*Lavandula angustifolia* , Lamiaceae)** contain at least **1.5%** volatile oil. About **100 g** of lavender leaves are used to prepare a hot infusion for adding to bathwater.

❖**Camphor** : is indicated for hypotensive regulatory disorders .

Camphor is obtained from the wood of the camphor tree (***Cinnamomum camphora***) by steam distillation and consists of at least **96%** 2-bornanone.

- It is likely that these aromatic herbs are effective only when the molecules of their volatile oils come in contact with the nasal mucosa through inhalation.
- The classic prototype is smelling salts, a preparation that is no longer manufactured today.
- But a homemade version can be prepared by placing 1-4 drops of essential oil on a sugar cube that is then slowly dissolved in the mouth.
- Essential oils should not be used in infants and small children due to the danger of reflex respiratory arrest.

Phytotherapy of Hypertension

- hypertension is present when the blood pressure exceeds 160 mm Hg systolic and 95 mm Hg diastolic.(According to the WHO definition)
- Blood pressures in the range of 140-160 systolic and 90-95 diastolic are classified as borderline hypertension, which is usually managed by non pharmacologic means (weight loss, low-salt diet, exercise).

- An herbal remedy that has been used in the treatment of mild to moderate hypertension is the whole extract made from the dried roots of Indian snakeroot *(**Rawolfia serpentina**)*.
- The extract contains more than 50 different alkaloids, including the sympatholytic agent **reserpine**.
- **Reserpine** is not only one of the oldest antihypertensive agents, it is still one of the most economical.

- the use of **reserpine** has declined in industrialized countries because of its association with objectionable **side effects**, particularly at doses higher than 0.2 mg/day
  - Depression
  - Fatigue
  - Impotence
  - Nasal stuffiness
- but it is still included as a standard antihypertensive agent in the **WHO** list of essential drugs.
- **reserpine** is not considered a phytotherapeutic agent because it is an isolated compound with a known chemical composition

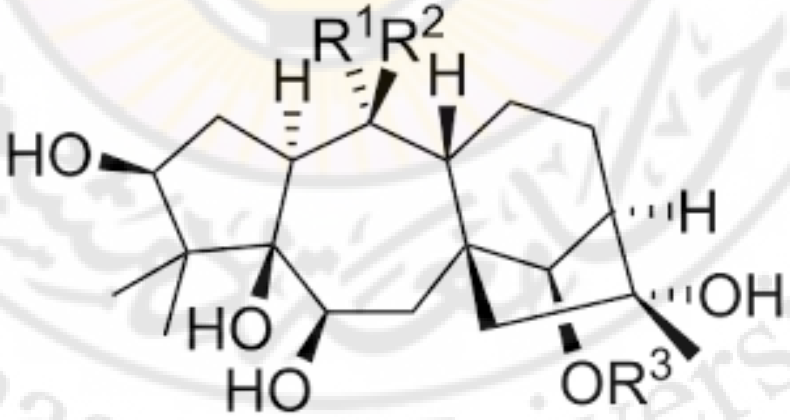
- The whole extract derived from Indian snakeroot has the **same actions and side effects** as reserpine when properly standardized and administered in the proper dose.
- Because of its narrow therapeutic range, *Rauwolfia* extract does not meet the safety criteria of an acceptable phytomedicine
- *Rauwolfia*-extract-based product is standardized to 7% total alkaloids.
- It has no apparent advantage over reserpine therapy which is easier to control

- The parenteral use of mistletoe(***Viscum album,* Santalaceae**) preparations may cause a transient fall in blood pressure
- this is due to an allergic response based on the release of biogenic amines and may not signify real therapeutic benefit for hypertension.

- The dried leaves of the **olive** tree (***Olea europaea,* Oleaceae)** are used in Italian folk medicine as a remedy for high blood pressure
- Olive leaf extract, at the dosage regimen of **500 mg** twice daily, was similarly effective in lowering systolic and diastolic blood pressures in subjects with stage-1 hypertension as Captopril, given at its effective dose of 12.5-25 mg twice daily.

- ***Rhododendron*** (Ericaceae) leaves contain **grayanotoxins**, which lower blood pressure.
- But these compounds are highly toxic, causing nausea, vomiting, diarrhea
- at higher doses : muscular and respiratory paralysis.

- Consequently, rhododendron leaf extract is not considered an acceptable herbal antihypertensive.



- garlic powder (***Allium sativum*** **,** Amaryllidaceae) (600-1200 mg/ day of active ingredient) have mild antihypertensive effects
- with regard to possible side effects and drug-drug interactions (additive effects with other antihypertensives
- garlic powder preparations are the only phytomedicines that can be recommended as adjuncts in the treatment of hypertensive patients.

Atherosclerosis and Arterial Occlusive Disease

Some phytomedicines are useful in the prevention or symptomatic treatment of **atherosclerosis** and its sequelae.

- Particular value is ascribed to certain ***Allium*** species (garlic, onion, ramson) in the prevention of atherosclerosis, and the effects of garlic have been extensively documented by pharmacologic and clinical research.

- The anti -atherosclerotic effects of **garlic** are based mainly on its vasodilating, rheologic, and lipid-reducing actions.

- **Garlic** lowers blood lipids by inhibiting cholesterol synthesis.

- Other lipid-reducing plant constituents for the secondary prophylaxis of atherosclerosis are phospholipids derived from **soybeans**, **oat bran**, and **guar gum**.

Glycine soja

Avena sativa

Cyamopsis tetragonoloba

Garlic

Garlic powder is produced by peeling the cloves, cutting them into slices, and drying them for 3-4 days at a maximum temperature of 50°C to a residual moisture content of less than **5%.** During this process the garlic loses about two-thirds of its fresh weight.

- Drying destroys very little of the sulfur-containing constituents or the enzyme alliinase that causes their breakdown;
- but the residual moisture in the garlic powder leads to a gradual but constant enzymatic decomposition and subsequent volatilization of the sulfur-containing compounds that contribute to garlic's medicinal effects.(**limits the shelf life)**

❖ **garlic oil macerations** (cold oil infusions) using fatty oils.

- In this process the garlic cloves are covered with a vegetable oil (such as corn oil or wheat germ oil), and allowed to stand so that lipophilic compounds can dissolve into the oil.
- A press is then used to separate the oil from the solid residues.
- These preparations **do not contain** the water-soluble constituents of garlic.
- garlic-oil preparations are known to have certain therapeutic effects, they are not nearly as effective as garlic powder and other medicinal garlic preparations.

❖Another process uses steam distillation to obtain **essential garlic oil** from freshly ground garlic.

- Garlic bulbs have about a 0.1-0.5% content of water soluble compounds.
- Analogous to cold oil infusions, the compounds present in essential garlic oil no longer correspond to the original plant constituents as enzymatic and thermal breakdown transform alliin and other thiosulfinates into sulfur-containing products.

- ✓ **Garlic fermentation products** (aged garlics) have been available on the pharmaceutical market for several years now.
- ✓ These odor-free products are fermented for several weeks in the presence of moisture and atmospheric oxygen, resulting in the conversion of all reactive garlic constituents into more or less inert degradation products.

- ✓ One would not expect these fermented products to have significant medicinal actions, nor have such actions been demonstrated in pharmacologic or clinical studies.

- ✓ Sliced draw garlic stored in 15-20% ethanol for more than 1.5 year is refereed to **aged garlic extract**.
- ✓ This whole process is supposed to cause considerable loss of allicin and **increased activity of certain newer compounds**, such as S-allylcysteine, S-allylmercaptocysteine, allixin, derivative of L-arginine, and selenium which are **stable** and significantly **antioxidant**.
- ✓ it has been shown that the aged garlic extract inhibited the binding of ADP-activated platelets to immobilized fibrinogen.
- ✓ Aged garlic extract **inhibited platelet aggregation** via inhibition of the GPIIb/IIIa receptor and an increase in cAMP

Key Constituents

The constituents of garlic are divided into two groups:

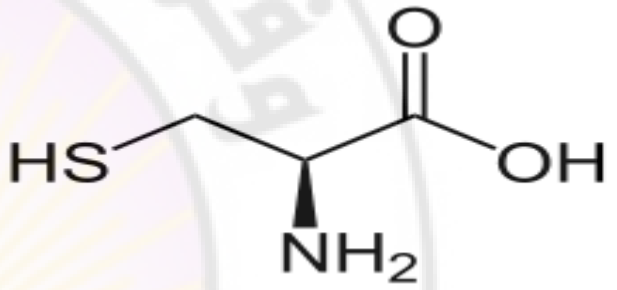
- **sulfur**-containing compounds
- **non-sulfur**-containing compounds.

Most of the **medicinal effects** of garlic are **referable** to the **sulfur compounds** and the alliin-splitting enzyme **alliinase**.

- Thus, commercial garlic preparations are often adjusted or standardized to sulfur-containing ingredients, particularly to the amino acid alliin contained in garlic powder.

The organic **sulfur compounds** in garlic are derived from the amino acid **cysteine** or its derivatives and can be subdivided into

- S-allylcysteine sulfoxide
- y-glutamyl-S-allylcysteines.



➢ the cysteine sulfoxides are stored in the form of y-glutamylcysteines , which undergo a gradual hydrolytic cleavage during germination of the garlic bulb and in products that are stored.

➢ Thus, freshly harvested garlic differs markedly from stored garlic, especially in its content of y-glutamylcysteines.

- **Fresh garlic** contains about 0.5-1% cysteine sulfoxides, mostly alliin, and an equal amount of y-glutamylcysteines.

- **Garlic powder** that has been carefully dried may contain up to twice the concentrations of these constituents.

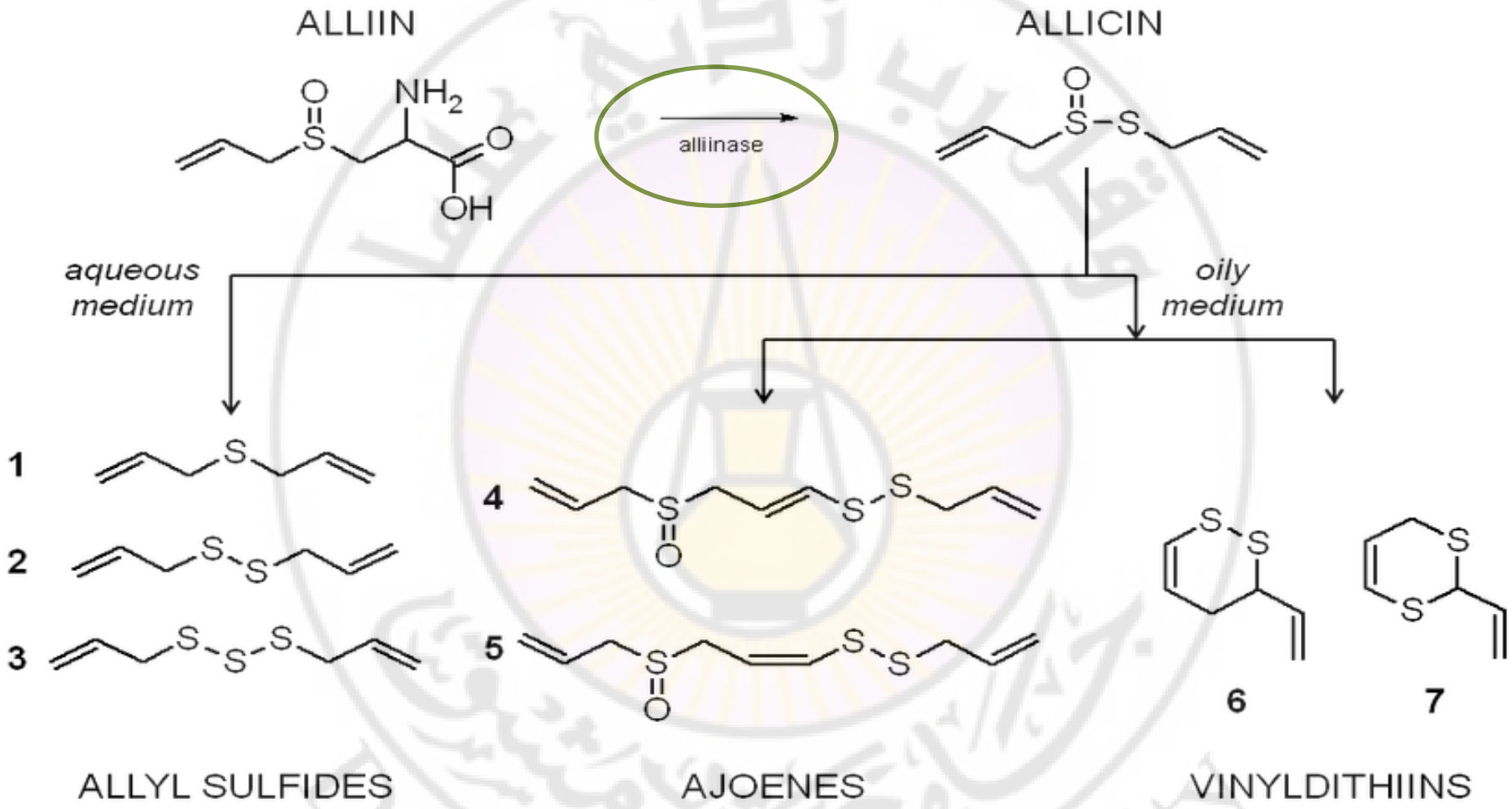
✓ Garlic powder products are usually standardized to a specified content of alliin or of the allicin that is released from alliin by the action of the enzyme alliinase

- **Cold oil infusions** and **distilled garlic oils** contain only the products of alliin degradation.

- **Alliin** is separated from **alliinase** while it is still in the cells of an intact garlic bulb.

- But when the bulb is chopped or crushed, damage to the cells allows the alliin to come into contact with alliinase, and within minutes the enzyme converts the alliin into the volatile compound **allicin**.

- Allicin has an aromatic odor but is unstable in aqueous and oily solution, and within a few hours it degrades into **vinyldithiins** and **ajoene**.


ALLIIN
ALLICIN
alliinase
aqueous medium
oily medium
1
2
3
4
5
6
7
ALLYL SULFIDES
AJOENES
VINYLDITHIINS

The **non-sulfur-containing constituents** of garlic include

- **alliinase and other enzymes**

These enzymes appear to have significant bearing on the bioavailability of garlic principles, and the garlic should be dried in a manner that preserves the enzymes

(e.g., avoiding air temperatures in excess of 50 C).

- **Various amino acids**
- **Proteins, lipids, steroids**
- **Vitamins**, and other trace elements

Table 3.5. Pharmacologic studies using a standardized garlic powder (with 1% alliin). The results of these publications support for the inhibitory effect of garlic therapy on the progression of atherosclerosis.

First author, year	Study material	Effects	Inhibition of atherosclerosis
Betz, 1989	Rabbits	Antiatherogenic	++
Heinle, 1994	Rats	Antiatherogenic	++
Orekhov, 1995	Intimal cell culture	Antiatherosclerotic	++
Orekhov, 1997	Intimal cell culture	Antiatherogenic	++
Abramovitz, 1999	Mice	Antiatherogenic	++
Brosche, 1991	Rats	Inhibition of cholesterol synthesis	+
Gebhardt, 1993	Hepatocyte culture	Inhibition of cholesterol synthesis	+
Gebhardt, 1994	Hepatocyte culture	Inhibition of cholesterol synthesis	+
Gebhardt, 1995	Hepatocyte culture	Inhibition of cholesterol synthesis	+
Gebhardt, 1996	Hepatocyte culture	Inhibition of cholesterol synthesis	+
Siegel, 1991	Human coronary [illegible]	Vasodilation	+
Jacob, 1991	Hypertensive rats	Antihypertensive	+
Das, 1995	Thrombocytes	antiplatelet effect	+
Sabban, 1997	Thrombocytes	antiplatelet effect	+
Brändle, 1997	Hypertensive rats	Life-prolonging	+
Ciplea, 1988	Rats	Cardioprotective	(+)
Ipensee, 1993	Langendorff heart (rat)	Cardioprotective	(+)
Pedraza, 1998	Rats	NO sythetase activating, Vasodilatin	+
Kourounakis, 1991	Hepatic microsomes	Antioxidative	(+)
Popov, 1994	Photochemical radicals	Antioxidative	(+)
Török, 1994	Photochemical radicals	Antioxidative	(+)
Lewin, 1994	LDL particles	Antioxidative	(+)
Siegers, 1999	Granulocytes	Antioxidative	(+)
Siegers, 1992	Colon carcinoma cells	Tumor-protective	–

- Both the whole herb and its lipophilic and hydrophilic fractions caused a **50-75%** inhibition of two key enzymes in cholesterol biosynthesis.
- **Allicin** is the most active compound among the sulfur-containing derivatives of alliin.
- Garlic therapy can reduce total **cholesterol** by an average of **9- 12%** with a **13%** average reduction in **triglycerides** compared with placebo.
- These results were obtained at **dose** levels equivalent to **600-900 mg** of garlic powder daily during treatment periods of **at least 4 weeks**

- Garlic has **antihypertensive** effect (based partly on a **direct vasodilating action** of garlic constituents)
- In a series of studies in spontaneously hypertensive rats, the life span of the animals was significantly prolonged by garlic feeding
- garlic is a **potent activator of endogenous nitric oxide synthesis**
  >Nitric oxide is known as a powerful vasodilator
- The activating effect of garlic on fibrinolysis and its inhibitory effect on platelet aggregation have been demonstrated in many experimental studies, (in live animals and in vitro) (it activate the calcium-dependent nitric oxide synthetase).
- The formation of oxygen-derived free radicals leading to lipid peroxidation may play a key role in the pathogenesis of atherosclerosis, and therefore the **antioxidative effects** of garlic could contribute to its **anti atherosclerotic** properties

- Garlic and its aqueous preparations has **antibacterial, antifungal** and **antiviral** properties.

- Garlic has **tumor-inhibiting** properties (sarcomas, bladder tumors, liver cell carcinomas, and isolated colon carcinoma cell)

- A high dietary intake of *Allium* species has a protective effect against certain gastrointestinal tumors. (Antibacterial or antimutagenic effects have been postulated as possible mechanisms)

Other Herbs with Anti-atherosclerotic Properties

- Onion (*Allium cepa* , Amaryllidaceae), like garlic, is useful "for the prevention of age-related vascular changes" (atherosclerosis).
- It must be taken in significantly higher doses than garlic with average daily dose of **50 g** fresh onion bulb or **20 g** dried herb.
- Onion is described as having **antibacterial**, **lipid-reducing** , **antihypertensive**, and **platelet-aggregation-inhibiting** properties.

The chemistry of the onion bulb resembles that of garlic.

- Instead of alliin, onion contains **methyl** and **propyl** compounds of **cysteine sulfoxide**.
- These chemicals are transformed by fermentation into the familiar eye-irritating compounds that induce lacrimation (syn-Propanethial S-oxide).

soybeans

- **reduction** in total **cholesterol** (7-19% of initial levels)
- significant **reductions** in **LDL** cholesterol.
- Triglycerides and HDL cholesterol were unaffected.
- Recommended doses of **1-3 g** of phospholipids per day.

Oat bran

Oat bran (***Avena sativa* , Poaceae**) was found to reduce total cholesterol by **13%** when taken in a daily dose of about **100 g** for **3 weeks**.

(**14 weeks** → **16%** TC reduction and **21%** reduction in LDL)

The cholesterol-lowering effect of oat bran is apparently based on its content of gel-forming dietary fiber; wheat bran does not produce this effect.

Guar gum

A reserve polysaccharide derived from the Indian guar plant (***Cyamopsis tetragonolobus***), lowered

-**Cholesterol** levels by **6-8%**

-**Triglyceride** levels by **13-17%**

when taken in a dose of 15 g/day.

As in the case of oat bran, this effect apparently results from the binding of primarily liver excreted cholesterol to non absorbable bulk materials.

- Owing to their lipid reducing effects, both of these sources of dietary fiber may be beneficial in the secondary prophylaxis of atherosclerosis

Peripheral Arterial occlusive Disease (PAOD)

- Special extracts from *Gingko biloba* leaves have value in the symptomatic treatment of peripheral arterial occlusive disease.

- Another major application of these ginkgo extracts is in the symptomatic treatment of cognitive deficits secondary to organic brain disease .

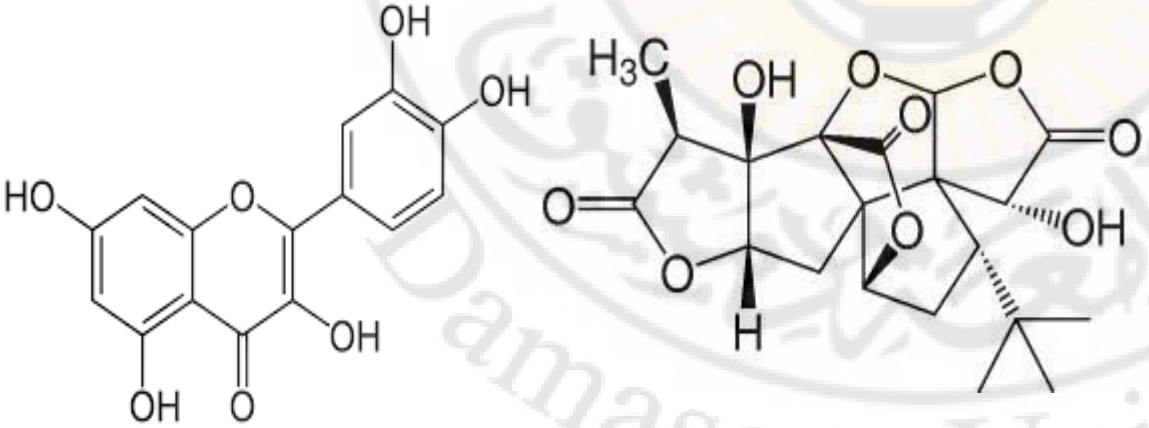
Only two special extracts made from ***Ginkgo biloba*** **(Ginkgoaceae)** leaves (acetone-and-water extracts with an average herb to extract ratio of 50:1) are recommended for therapeutic use.

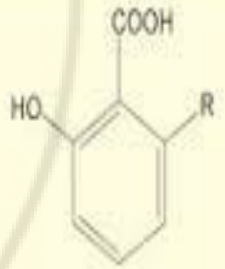
Key Constituents

- 22-27% **flavonoid glycosides**

(quercetin, kaempferol, isorhamnetin)

- 5-7% **terpene lactones** (ginkgolides A, B, and C , bilobalide; and less than 5 ppm ginkgolic acids)





Compound		R
GA C13:0	Ginkgolic Acid C13:0	$C_{13}H_{27}$
GA C15:0	Ginkgolic Acid C15:0	$C_{15}H_{31}$
GA C15:1	Ginkgolic Acid C15:1	$C_{15}H_{29}$
GA C17:1	Ginkgolic Acid C17:1	$C_{17}H_{33}$

Pharmacologic actions

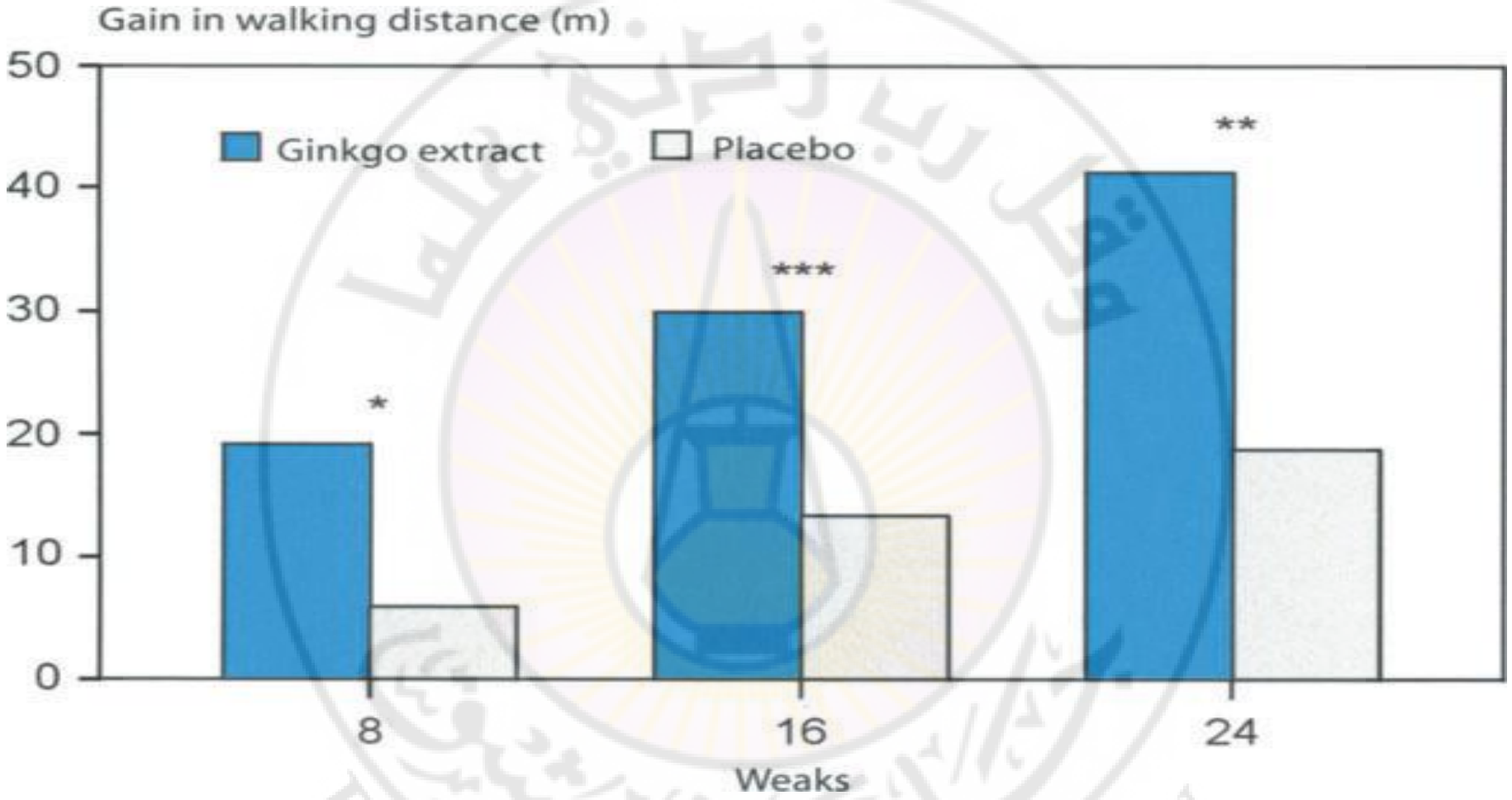
- Increases tolerance to hypoxia, especially in brain tissue
- Inhibits the development of post-traumatic or toxin-induced brain edema and hastens its resolution
- Reduces retinal edema and retinal lesions
- Improves memory and learning capacity
- Improves the rheologic properties of the blood
- Scavenges toxic oxygen-derived free radicals
- Inhibits platelet activation factor (PAP)
- Exerts an neuroprotective effect.

Indications

- Symptomatic treatment of deficits due to organic brain disease as part of a comprehensive therapy program in demential syndromes with these principal features: **memory impairment**, **concentration difficulties**, **depression**, **vertigo**, **tinnitus**, and **headache**.

- Improvement of pain-free walking distance in patients with peripheral arterial occlusive disease (**intermittent claudication**) as an adjunct to physical therapy (The efficacy of the gingko special extract is comparable to that of synthetic drugs in the treatment of intermittent claudication and it more tolerated)

- Vertigo or tinnitus of vascular origin.



Increase in pain-free walking distance in patients with peripheral arterial occlusive disease after 24 weeks treatment with gingko special extract, compared with a placebo

Dosage and form

- Ginkgo is available in **capsule** form, **tablets**, **liquid extracts**, and dried leaf for **teas**.
- Dose : **120 - 240 mg** daily in divided doses for **4 to 6 weeks.**

Side effects

-mild gastric upset (nausea, diarrhea, stomach ache)

- headache

-allergic skin reactions

Chronic Venous Insufficiency

- Chronic venous insufficiency is the term applied to a syndrome resulting from the obstruction or persistent incompetence of deep veins or perforating veins in the lower extremities.
- The symptoms range from **edema**, **cyanosis** or **dermatosclerosis** to **atrophic skin** changes and **crural ulceration**

- Causal therapy in the form of vascular surgery is possible only in a small percentage of patients.

- Conservative treatment options consist of elastic compression (support stockings) and symptomatic pharmacotherapy with so called venous remedies.

- Most pharmacologic and clinical studies on herbs used in the treatment of venous disorders have dealt with **horse chestnut** **extracts** and their constituent **aescins**.
- These agents **act** less on the veins than at the **capillary level**, where they exert **anti exudative** and **anti edematous** effects.
- Commercial products vary widely in quality, however, and only some contain active levels of anti exudative constituents.
- This variable quality of herbal venous remedies is a major reason why their clinical efficacy remains a controversial matter.

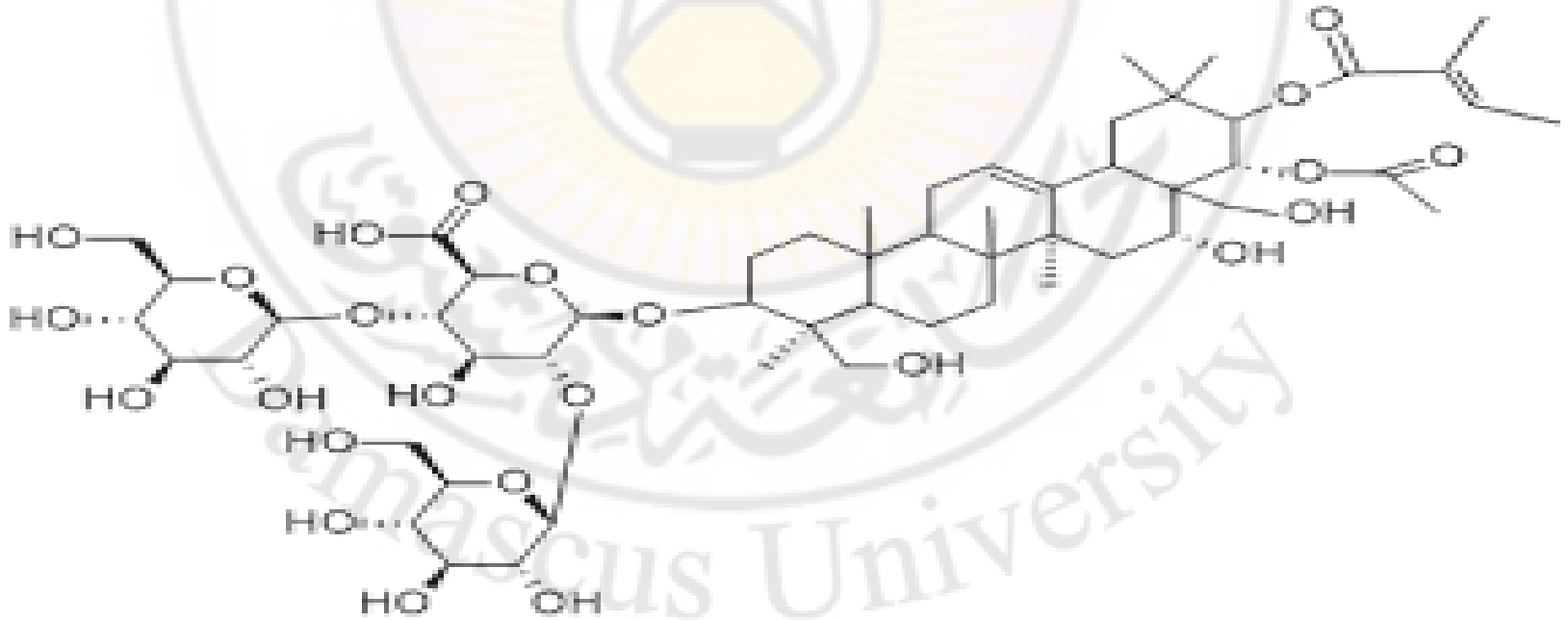
Horse Chestnut Seed

Aesculus hippocastanum

(**Hippocastanaceae , Sapindaceae**).

β-Aescin (triterpene saponin) is considered the main active constituent.

- It has shown clinical efficacy on administration
- It is fairly soluble in water but is poorly soluble in lipid solvents.



Studies in an animal model showed that whole horse chestnut extract was 100 times more active than the same extract with the aescin removed.

- it has been confirmed that **aescin** is responsible for the **anti exudative** properties of horse chestnut extract, even in inflammatory and stasis-related edema,

- This effect was **not blocked** by **phentolamine**, proving that it is not mediated by α-adrenergic receptors.
- Recommended daily dose : **100 mg of aescin** (**300 mg of extract)** in a controlled-release dosage form.

- Horse chestnut extract and aescin have been tested for acute toxicity in several animal species , The "no effect" dose is approximately **8 times higher** than the **dose** recommended for **therapeutic use** in patients.
- Tests for chronic toxicity (34 weeks in rats and dogs) showed no cumulative toxic effects or any evidence of embryotoxic or teratogenic effects.
- The saponins contained in non-controlled-release preparations of horse chestnut extract tend to cause **stomach upset** when the extract is taken at therapeutic doses twice daily

standardized powdered extract of horse chestnut **seeds** (adjusted to a triterpene glycoside content of 16-20% ,calculated as anhydrous aescin) is appropriate for the "**treatment of complaints relating to diseases of the lower extremity veins** (**chronic venous insufficiency**) such as **pain** and a **feeling of heaviness** in the legs, **nocturnal calf muscle spasms**, and **swelling** of the legs.“

- Other preparations made from horse chestnut leaves, bark, and flowers have been negatively appraised and should no longer be prescribed

- Other herbs for remedy of chronic venous insufficiency

-Butcher's Broom **rhizome** (*Ruscus aculeatus*, Asparagaceae)

-Sweet clover (*Melilotus officinalis*, Fabaceae)

-Buckwheat (*Fagopyrum esculentum*, Polygonaceae)

-Grape **leaves** (*Vitis vinifera* , Vitaceae)