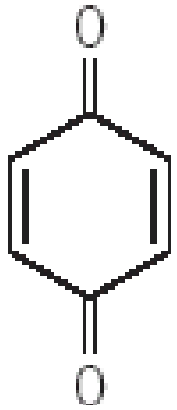
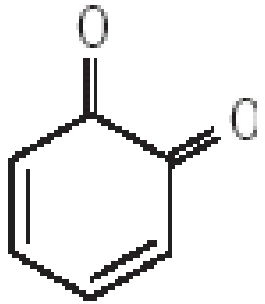
Quinones

Prof. Dr. Ali Hikmet Meriçli

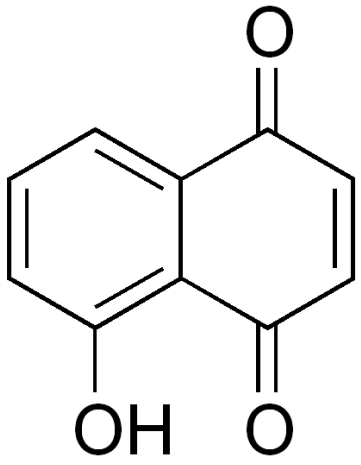
Quinones are oxygen-containing compounds which are essentially the oxidized homologs of aromatic derivatives, and are characterized by a 1,4-diketo-cyclohexa-2,5-diene pattern (para-quinones), or possibly, by a 1,2-diketo-cyclohexa-3,5-diene pattern (ortho-quinones). In naturally occuring quinones, the dione is conjugated to an aromatic nucleus (benzoquinones), or conjugated to a condensed polycyclic aromatic system: naphthalene (naphthoquinones), anthracene (anthraquinones)
1,2-benzanthracene (anthracyclinones), naphthodianthrane (napyhrodianthrones), perylene, phenanthrene, and so on.



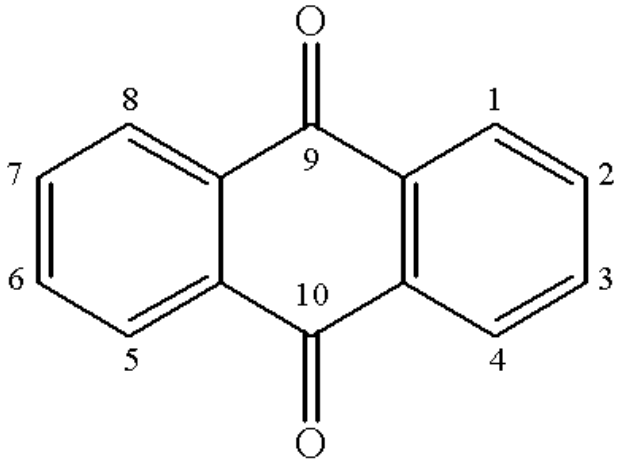
p-Quinone



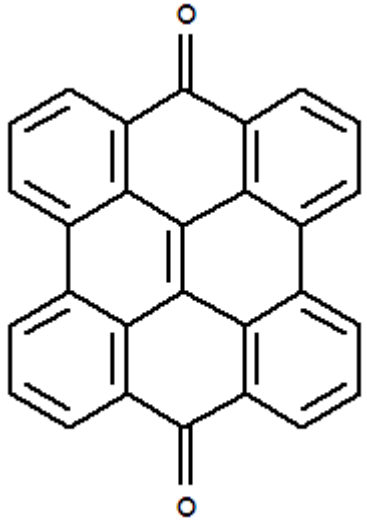
o-Quinone



Naphthoquinone



Anthraquinone

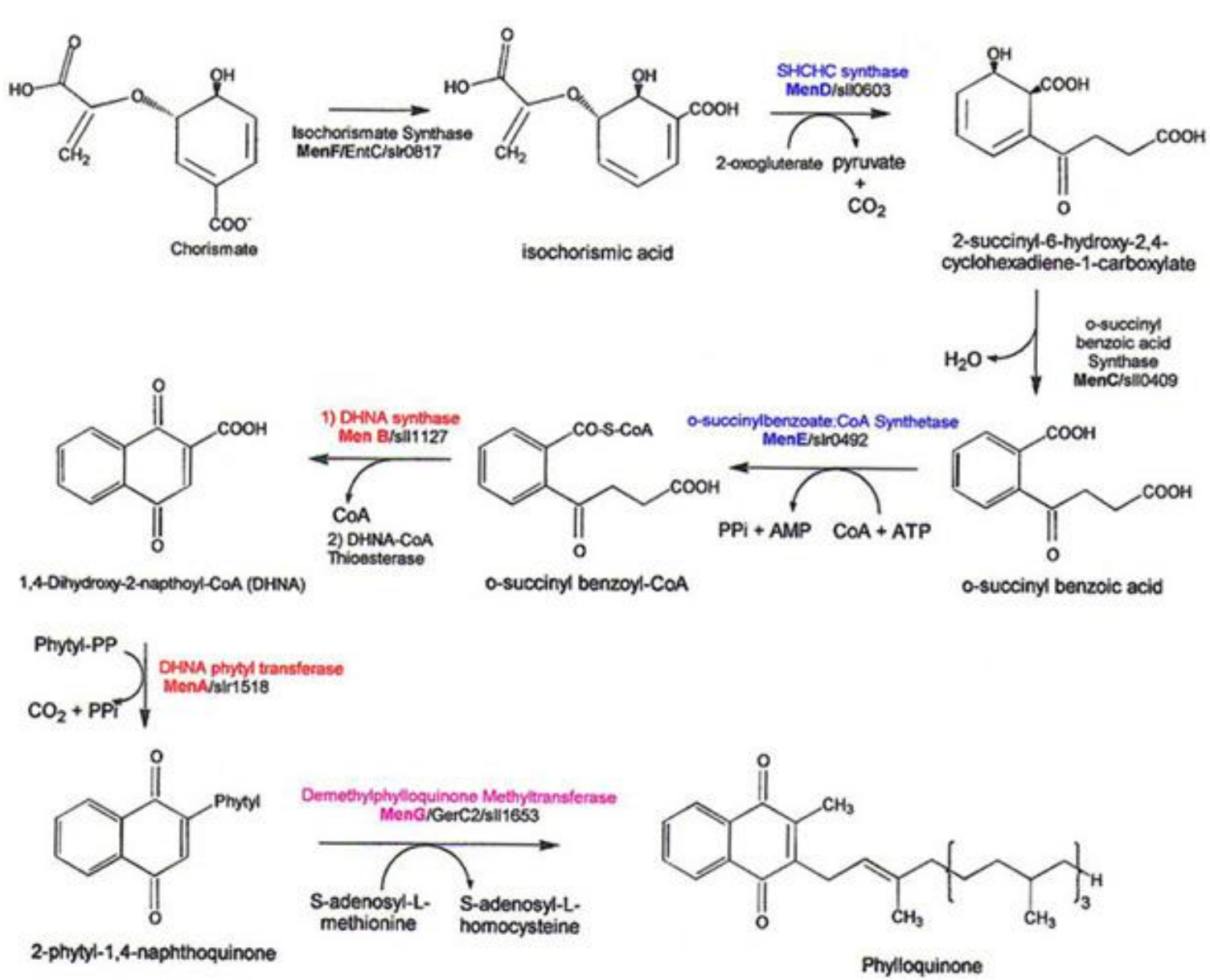


Naphthodianthrone

BIOSYNTHESIS

Quinone biosynthesis is characterized by the diversity of the metabolic pathways which allow the various living organisms to elaborate them from a rather limited number of precursors: acetate and molonate, mevalonate, and phenylalanine.

- Mevalonic and Chorismic Acid Pathway
- Polyketide Pathway
- 4-Hydroxybenzoic Acid Pathway


Chorismate
Isochorismate Synthase
MenF/EntC/slr0817
isochorismic acid
SHCHC synthase
MenD/sll0603
2-oxogluterate
pyruvate
+
CO2
2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate
H2O
o-succinyl benzoic acid Synthase
MenC/sll0409
o-succinyl benzoic acid
o-succinylbenzoate:CoA Synthetase
MenE/slr0492
PPi + AMP
CoA + ATP
o-succinyl benzoyl-CoA
1) DHNA synthase
Men B/sll1127
CoA
2) DHNA-CoA Thioesterase
1,4-Dihydroxy-2-napthoyl-CoA (DHNA)
Phytyl-PP
CO2 + PPi
DHNA phytyl transferase
MenA/slr1518
2-phytyl-1,4-naphthoquinone
Demethylphylloquinone Methyltransferase
MenG/GerC2/sll1653
S-adenosyl-L-methionine
S-adenosyl-L-homocysteine
Phylloquinone

PROPERTIES, EXTRACTION, SEPARATION, AND CHARACTERIZATION

Free quinones are practically insoluble in water, can be extracted by the common organic solvents, and their separation requires the common chromatographic techniques. Benzoquinones and naphthoquinones can be steam distilled. Glycoside extraction is achieved with water or with rather dilute hydroalcoholic solutions. Recovering the reduced forms (quinols, anthrones) is delicate: working at low temperaure, away from light, and under nitrogen is required to avoid their spontaneous oxidation during the extraction.

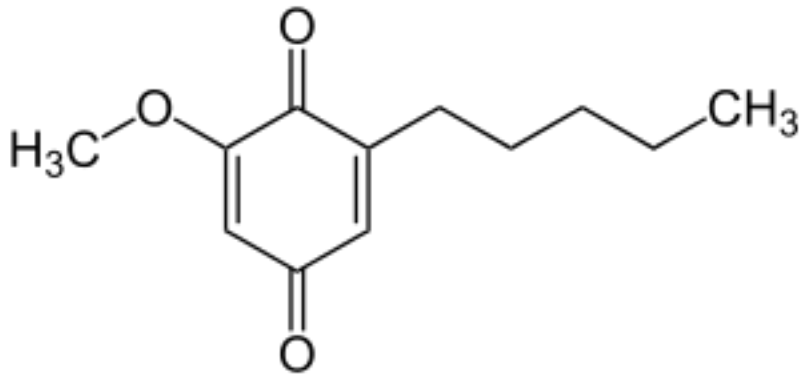
Various color reactions can be used to charactirize quinones. The main one is **Borntraeger's reaction**, obtained by dissolving the quinone in alkaline medium: the solution develops a vivid color which ranges, depending on the structure and the substituents, from **orangy-red** to **purplish-violet**, it also can be used by coloring TLC plates.

BIOLOGICAL PROPERTIES AND USES OF QUINONE-CONTAINING DRUGS

Natural benzoquinones in the strict sense of the term have no therapeutical application. Note, however, that the reduced form of 1,4-benzoquinone (i.e., hydroquinone) occurs as a glycoside, namely arbutin, and that this molecule possesses strong urinary antiseptic properties. Many naphthoquinones are antibacterial and fungicidal. Antiprotozoal and antiviral activities have been described. **Drugs containing 1,8-dihydroxyanthraquinone derivatives have laxative properties, and have been prized for this activity for centuries** (*Cassia, Rhamnus, Rheum*). For a long time, some quinone-containing drugs had been prized as dyes (*Rubia tinctorium* alizarin, *Alcanna tinctoria* alkannin). They also included products of animal origin (*Kermococcus vermilio, Coccus cacti*)

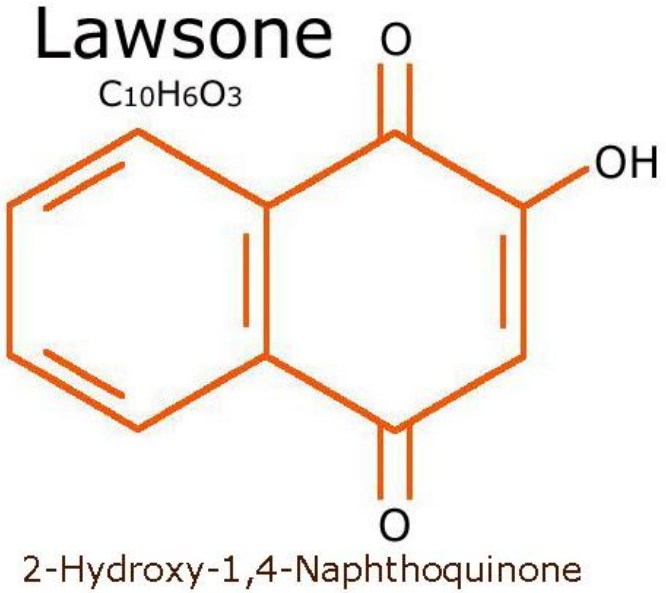
QUINONES AND ALLERGY

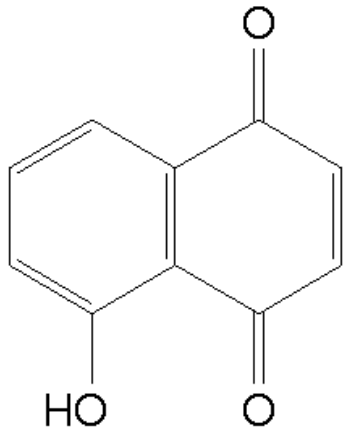
The allergenic potential of many quinones (benzo- and naphtoquinones) is due to the fact that they act as heptens: by combining themselves, through their nucleophilic centers, with amine and thiol functions on macromolecules, they induce dermatitis by sensitization. For example some primrose species of Asian origin can cause , in gardeners and florists, localized pruriginous reactions and urticaria- or erysipetaous-type rushes on the eyelids, cheeks, chin, fingers, hands,and forearms. The responsible quinone is 2-methoxy-6-pentylbenzoquinone (primin).



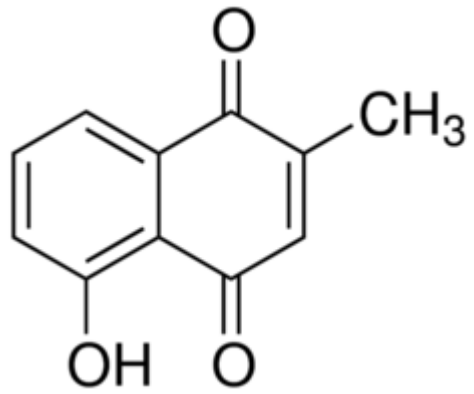
NAPHTHOQUINONE-CONTAINING DRUGS

Naphthoquinones are yellow or orangy pigments essentially from plants, and are characteristic of some Angiosperm families, including Ebenaceae, Droseraceae, and Bignoniacee. They are almost 1,4-naphthoquinones, and they are in very rare cases 1,2-naphthoquinones.





Juglone



Plumbagin

Droserae rotundifoliae herba **sundew** **drosera**

Drosera rotundifolia **Droseraceae**

Drosera species are insectivorous plants. The other in Eoropa growing species are *Drosera anglica* and *D.intermedia*. All the species contain same constituents and have same activities.

In the fresh plant, a glycoside is found, namely rossoliside, the 4-glucoside of the reduced form of plumbagin. Plumbagin represents about 0.7 to 1% of the dried drug.

Experiments in animals show that sundew tincture is an antispasmodic. Plumbagin has antibacterial properties. It is also active on certain pathogenic fungi and on some parasitic protozoa. At higher doses, plumbagin is cytotoxic. The common form of utilization of the drug is tincture (1-3 g/day). The German Commission E monograph specifies that the drug is used orally for coughing fits and irritation coughs.

Homeopathic *Drosera* preparations

Juglandis folium **walnut tree** **ceviz yaprağı**

Juglans regia **Juglandaceae**

The chief known constituent is juglone (5-hydroxy-1,4-naphthoquinone), which occurs in the fresh plant (leaf) as 1,4,5-trihydroxynaphthalene glycoside (about 0.5% in the leaves), but also in the free state. The leaf and pericarp are rich in hydrolizable tannins. The leaf also contains a small amount of essential oil, ascorbic acid, and flavonoids. Juglone has antibacterial and fungucidal properties.

The seed cotyledons are used as food and as a source of oil. The oil is rich in linoleic (55-65%) and α-linolenic acid (9-15%).

In Germany, the astringent properties recognized by Commission E lead to using the drug only in external application, for superficial skin inflammation, and for excessive foot and hand perspiration.

Lawsoniae folium **henna** **kına**

Lawsonia inermis **Lythraceae**

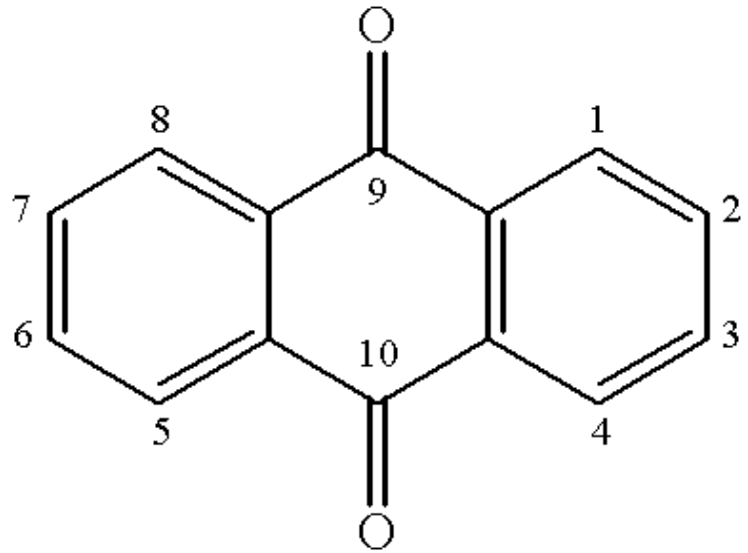
Fresh henna leaves contain glycosides, which release lawsone (2-hydroxy-1,4-naphthoquinone) upon hydrolysis. This quinone dissolves in alkaline aqueous solutions to give an intense orangy-red colour. It is practically non-toxic, and it is a powerful fungucide. The lawsone level in the dried drug is about 1%. Henna leaf also contains flavonoids, coumarins, and xanthones. The ethanolic leaf extract is an analgesic, antipyretic, and anti-inflammatory in rats.

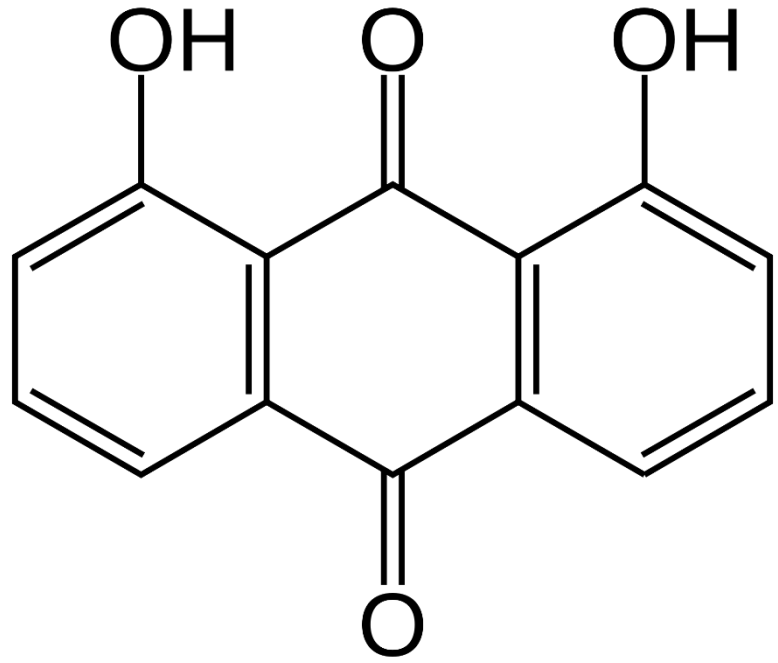
Henna is used in various ways in Ayurvedic medicine: for the treatment of skin ailments, burns, wounds, and diarrhea, also as a taenicide, an antiepileptic, and an abortifacient agent. As a coloring and cosmetic ingredient, it has been in use as a hair color, and nail color. The drug is widely used in cosmetology for its dyeing properties, due to the strong binding of lawsone to the hair.

ANTHRAQUINONE-CONTAINING DRUGS :
LAXATIVE HYDROXYANTHRAQUINONE GLYCOSIDES

The different drugs in this group are characterized by the presence of phenolic and glycosidic compounds, derived from anthracene and have a variable degree of oxidation (anthrones, anthranols, anthraquinones) they are the anthraquinone glycosides. **No matter what their degree of oxidation, these molecules heve in common a double hydroxylation at C-1 and C-8**.

The botanical distribution of the species containing 1,8-dihydroxyanthraquinone glycosides is very limited: Liliaceae (aloe), Polygonaceae (rhubarb), Rhamnaceae (buckthorn, cascara), and Caesalpiniaceae (senna).



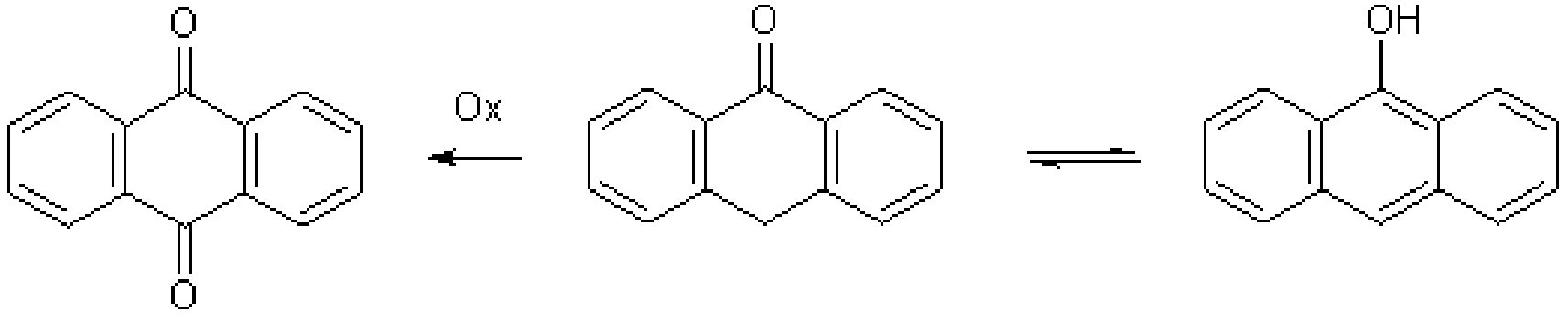


Anthraquinone

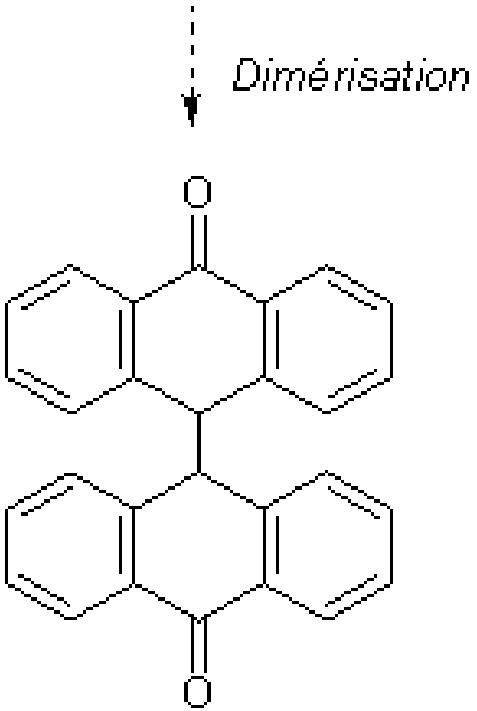
1,8-dihydroxyanthraquinone

Structures of Anthraquinone Glycosides

The aglycones :The degree of oxidation varies. In anthrones, carbon 10 is a mthylene carbon. Depending on the pH, these anthrones can occur alongside their tautomeric forms, the anthranols. In practice anthrones, and anthranols are often designated by the term «reduced forms», and anthraquinones by that of «oxidized forms».

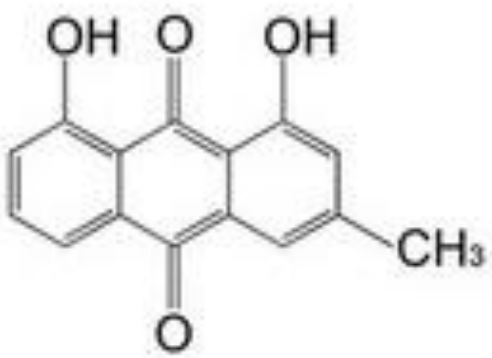


Anthraquinone **Anthrone** **Anthranol**

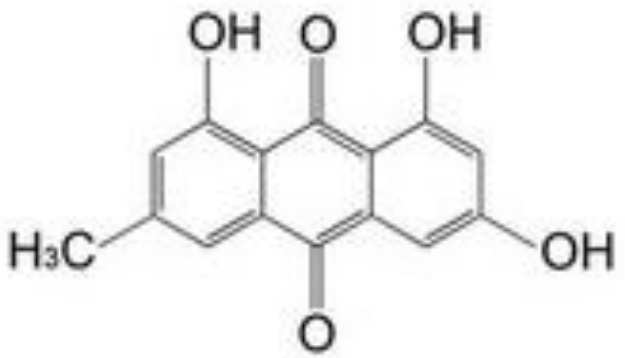


Dianthrone

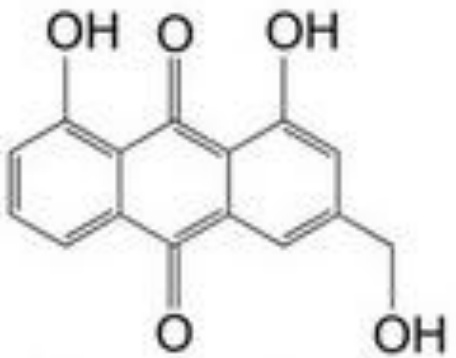
The glycosides: Because anthrones are unstable, the free aglycones that occasionally occur in the drugs are always anthraquinones. The reduced forms on the other hand, exist only in the ombined state, in other words as glycosides. The saccharides within these glycosides are commonplace: glucose, rhamnose, and in rare cases apiose. The bond with the aglycone normally involves the phenolic hydroxyl group at C-8 (in the case of glucose), or the one at C-6 (in the case of rhamnose and apiose). The aglycone may be linked to two sugars; thus , glucofrangulin A is emodin 6-O-α-L-rhamnosyl-8-O-β-D-glucoside. It is not rare for 1,8-dihydroxyanthrones to occur as C-glucosides, with the bond forming between the C-1 of glucose and the C-10 of the aglycone. Moreover these C-glycosides may be O-glycosides as well.



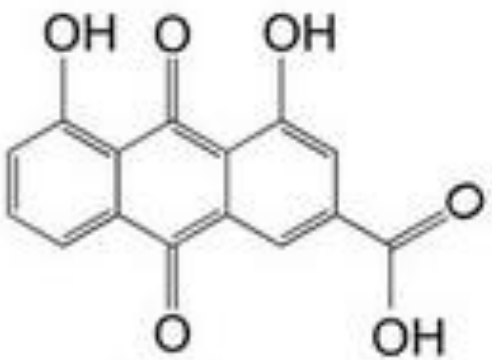
Chrysophanol



Emodin

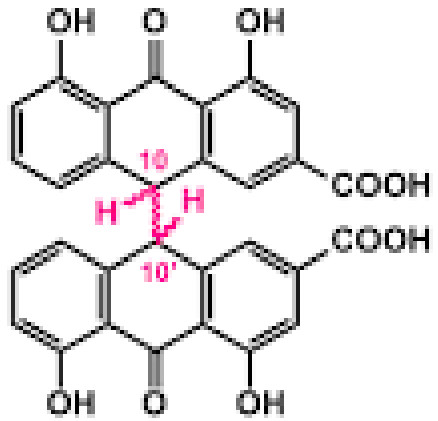


Aloe-emodin



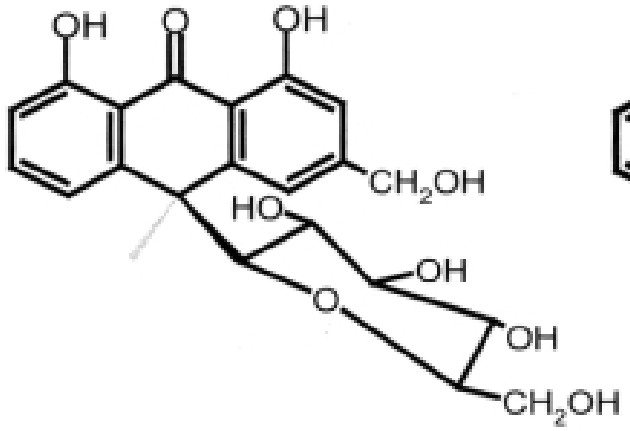
Rhein

Some anthraquinone aglycones

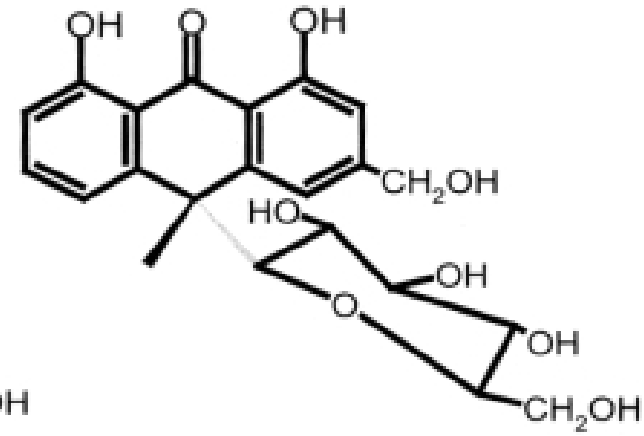


Sennidin A (10S, 10'S)
Sennidin A (10R, 10'R)
Sennidin B (meso form i.e. 10R, 10'S or 10S, 10'R)

Dianthron aglycone

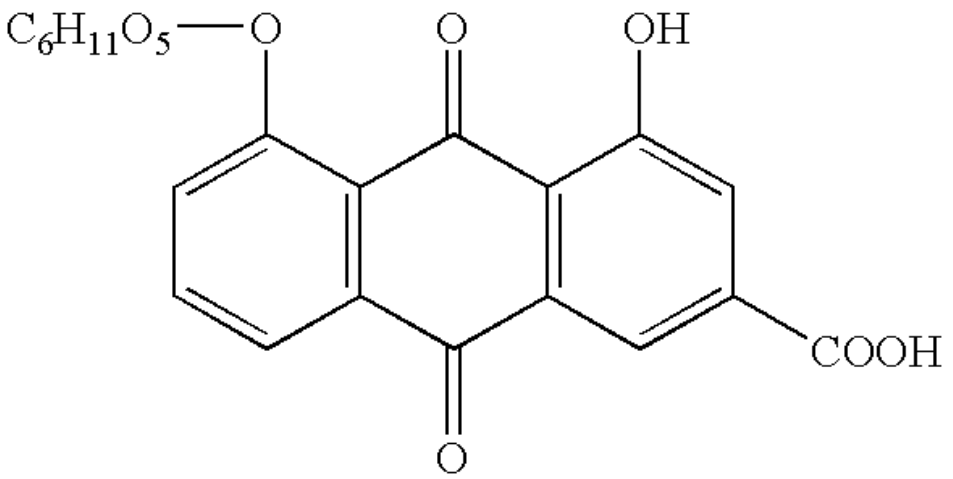


Aloin A



Aloin B

Anthron-C-glucoside



Rhein-8-glucoside

Anthraquinone-0-glucoside

PHYSICO-CHEMICAL PROPERTIES AND CHARACTERIZATION

Anthraquinones are colored, orange-red compounds, sparingly soluble in cold water, and soluble in organic solvents and alcohols. The carboxylic aglycones can be extracted with an aqueous sodium bicarbonate solution. The glycosides are soluble in water and hydroalcoholic solutions. Treating the O-glycosides in acidic medium causes their hydrolysis, but the cleavage of the carbon-carbon bond of C-glycosides can only be obtained in the presence of ferric chloride.

Characterization: The characterization of hydroxyanthraquinone derivatives applies Borntraeger reaction: upon dissolving the quinones in alkaline aqueous medium (KOH), a red color, more or less purplish develops. This reaction is only positivewith the free anthraquinone forms: to characterize the glycosides with this reaction, preliminary hydrolysis is requiried, and if the aglycones are anthrones, they must be oxidized to anthraquinones.

Another color reaction spesific to 1,8-dihydroxyanthraquinones, uses magnesium acetate in methanol. The resulting red color is more intense and more stable to light than that from the simple reaction with potassium hydroxide.

There is a reaction spesific to anthrones: it is based on their ability to react with nitrotetrazolium blue or p-nitrosodimethylaniline to form a colored azomethine.

The C-glucosides of reduced forms can be characterized by the fluorescence of the anthranol forms in the presence of sodium borate (Schouteten reaction).

PHARMACOLOGICAL PROPERTIES

Depending on the dose administered, 1,8-dihydroxyanthraquinone derivatives exetr a more or less violent laxative or purgative activity. At therapeutic doses they are stimulant laxatives. The activity is linked to the structure of these compounds: the most interesting derivatives are the O-glycosides of dianthrones and anthraquinones, as well as the C-glycosides of anthrones. The free aglycones (anthraquinones) are practically inactive.

The glycosides of anthraquinones and dianthrones are polar molecules, are water-soluble, and have a high molecular weight, so they are not resorbed nor hydrolized in the small intestine. In the colon they are hydrolyzed by the β-glucosidases of the intestinal flora, and the freed anthraquinones are reduced : thus, the active forms are the anthrones formed in situ, which explains the latency observed between compound (or drug) intake the laxative effect.

Hydroxyanthraquinone derivatives affect intestinal motility: it has been shown in vivo, that rhein anthrone acts by direct contact with the epithelial cells of the intact intestinal mucosa.

Uses of Anthraquinone Glycoside-containing Drugs

The different drugs in this group, like all of the laxatives, represent a huge market. They are used crude (as herbal teas), or as galenicals (powders, extracts, and titrated extracts) in which the various components act in synergy.

The daily and prolonged use of these stimulant laxatives can cause substantial problems: dependence, and in some cases «cathartic colon» (spastic colitis with diarrhea and abdominal pains, nausea, vomiting, then a melanotic pigmentation of the colon mucosa (=melanosis coli), other alterations of the colon mucosa, waterand elctrolyte imbalances with hypokalemia leading to a deterioration of the overall health, and the risk of drug interactions with cardiac glycosides, diuretics that cause hypokalemia, and more.

Rules for Using of Anthraquinone-containing Drugs

- The packaging of anthraquinone laxative drugs as bulk herbal teas is proscribed.
- The maximum number of laxative drugs introduced in combinations is limited to five with a maximum of two drugs with anthraquinone principles.
- Combinations of drugs containing anthraquinone principles with gums, mucilages, pectins, or fibers is allowed.
- The use of drugs with anthraquinone principles must be limited to short periods of time not exceed eight to ten days.
- Knowing thet the maximum recommended faily adult dose of anthraquinone glycosides is 25 mg.

- The administration of laxatives with anthraquinone principles is contraindicated in children under 10 years of age.
- The information provided to the medicinal and pharmaceutical profession must mention contraindications (organic inflammatory colopathy (ulcerative rectocolitis, Crohn's disease), fecal impaction, intestinal obstruction, undiagnosed abdominal pain). The informaion must also specify that prolonged intake may cause disturbances (cathartic colon, dependence).

The German Commission E has listed the uses that are common to all anthraquinone laxative dugs: for patients needing easier defecation (anal fissures, hemorrhoids, after anal or rectal surgery) and for constipation.

Sennae folium **senna** **sinameki**

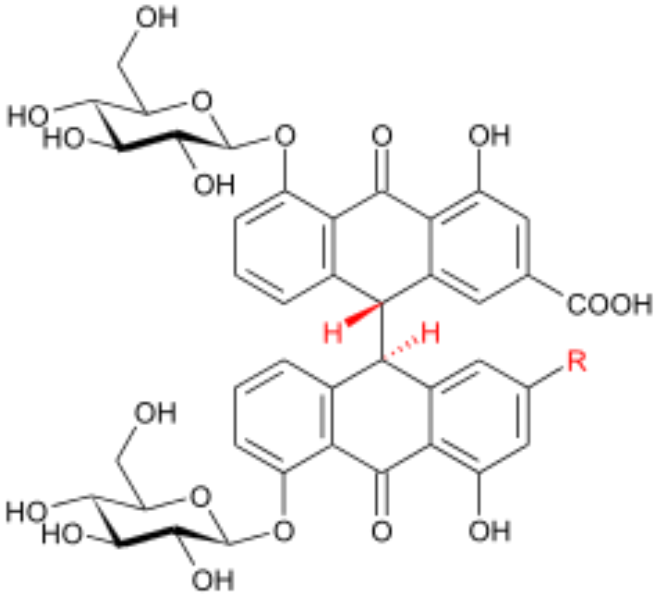
Cassia angustifolia, Cassia senna **Caesalpiniaceae**

Cassia angustifolia
Tinnevelly senna

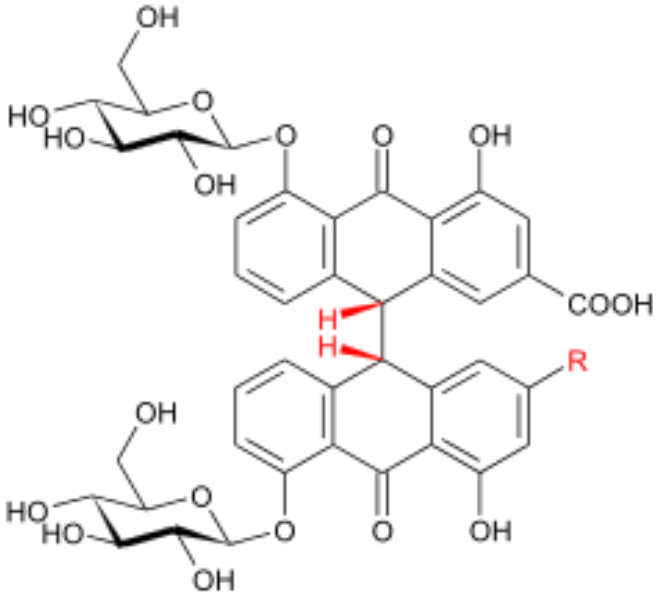
Cassia senna = C. acutifolia
Alaxandria senna

Chemical Composition : The composition of the folioles and pods of the two official species is very similar, and the differences are quantitative rather than qualitative. Both species contain flavonoids, a polyol (pinitol), and anthracene derivatives. The active principles of both drugs are glycosides with 1,8-dihydroxyanthraquinone-type aglycones. The major components of the **dried drug** are sennosides, which are glycosides of dianthrone-type aglycones, in other words sennidins. Sennosides A and B are the major components and they are the 8,8’-diglucosides of a symmetrical homodianthropic aglycone, rhein anthrone.

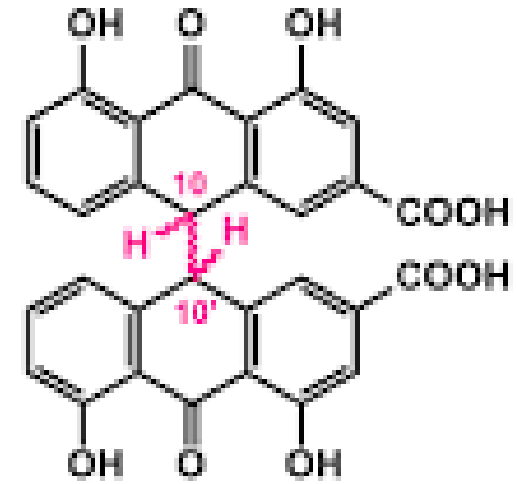
In addition to the substances Tinnevelly senna is characterized by tinevellin glucoside, whereas Alexandria senna contains 6-hydroxymusizin glycoside.



Sennosid A: R = COOH
Sennosid C: R = CH_2OH

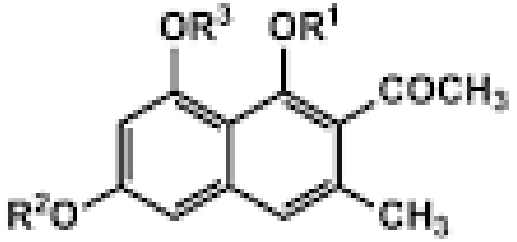


Sennosid B: R = COOH
Sennosid D: R = CH_2OH



Sennidin A (10S, 10'S)
Sennidin A (10R, 10'R)
Sennidin B (meso form i.e. 10R, 10'S or 10S, 10'R)

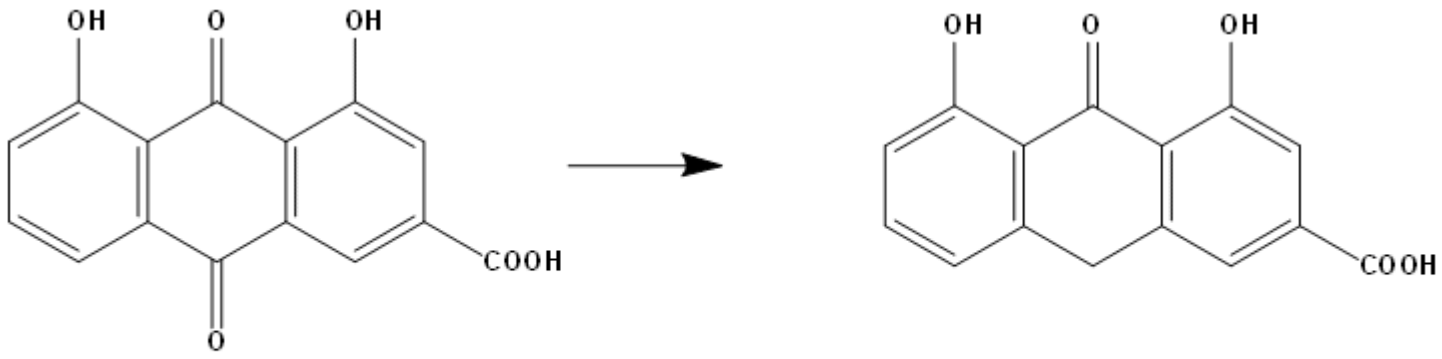
Difference Between Alexandrian and Indian Senna



6-hydroxymusizin glucoside
($R^1 = R^2 = H$ and
R^3 = β-D-glucopyranosyl)

Tinnevellin glucoside
($R^1 = H$, R^2 = β-D-glucopyranosyl
$R^3 = CH_3$)

The dianthrone derivatives do not exist in **fresh senna**, which mainly contains the 8-glucosides of rhein-anthrone and of aloe-emodin anthrone. It is during the drying process, around 40°C, that the anthrone glucosides are dimerized by an enzymatic process. If drying is conducted at a hifher temperature, the glycosidic linkage is cleaved, and the anthrones are immediately oxidized to anthraquinones.



Rhein **Rhein anthrone**

Identification : It is based on the Borntraeger reaction.: extraction (H_2O) and hydrolysis (HCl) of the glycosides, extraction of the aglycones with ether, and elimination of the solvent. Since good quality senna will contain only few anthraquinones, the color obtained upon addition of aqueous ammonia to the evaporation residue should be yellow or orange; the characteristic red color is only obtained after heating the mixture.

Uses : Senna and its preparations are used as laxatives. Senna is used as an infusion (5 to 20 g/l), as a powder, and as extracts (particularly as a titrated extract (5.5-8% hydroxyanthraquinone glycosides). The therapeutic indication is the symptomatic treatment of constipation. The typical daily dose (calculated as sennosides) is 25 mg/day.

Frangulae cortex **buckthorn** **barut ağacı**

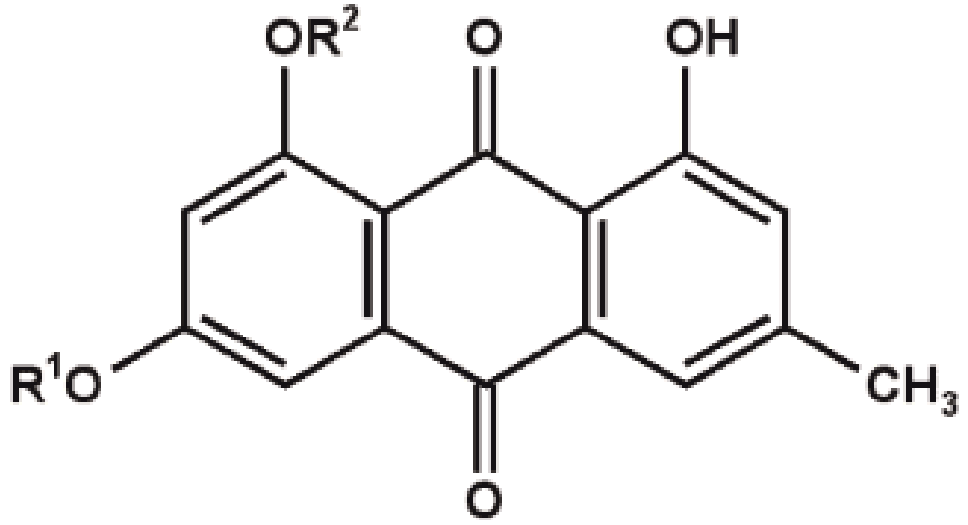
Rhamnus frangula* = *Frangula alnus **Rhamnaceae**

The drug consists of the the dried bark of the twigs and branches. It is used for its laxative properties.

The bark contains flavonoids and

3 to 8% 1,8-dihydroxyanthraquinone derivatives. In the dried drug, stored for over a year or heat treated, anthraquinone derivatives ocur as mono- or biosidic anthraquinone glycosides. The monosides are frangulin A (= emodin 6-O-α-L-rhamnoside) and frangulin B (emodin 6-O-β-D-apioside); the biosides are the corresponding 8-glucosylated derivatives, that is glucofrangulin A and B.

The drug is widely used as a laxative, in the crude form (herbal tea mixtures), as a powder, or as extracts. It is someimes combined with a spasmolytic agent, a bulk laxative, or both. Normally herbal teas of the drug are prepared by a five-minute decoction followed by a two hour infusion.



	R[1]	R[2]
Glucofrangulin A	α-L-Rhamnose	β-D-Glucose
Glucofrangulin B	β-D-Apiose	β-D-Glucose
Frangulin A	α-L-Rhamnose	H
Frangulin B	β-D-Apiose	H
Frangulin C	β-D-Xylose	H

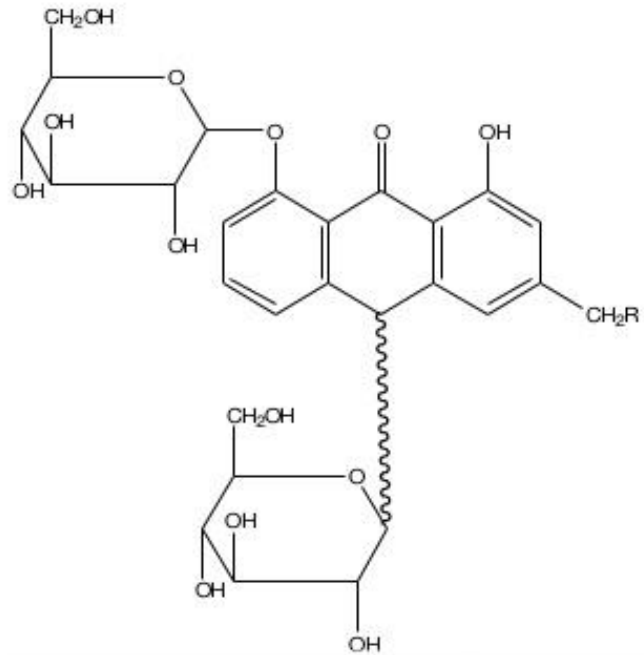
Cascara sagrada = Rhamni purshianae cortex cascara sagrada

Rhamnus purshiana **Rhamnaceae**

Cascara is a tree growing on the West coast of North America. The drug is essentiallyollected from wild trees in the mountains of the West of the United States and Canada. Collection begins in May, and continues until the end of the summer. The bark, cut into small fragments and dried in the shade, is stored for a long time before use. Cascara bark (dry drug) contains 6 to 9% hydroxyanthraquinone glycosides. The chief constituents (70% and more) are O-glycosides of C-glycosides, namely cascarosides A, B, C, and D. These compounds are, respectively, C-10 isomers of aloin (=barbaloin) and chrysaloin 8-O-β-D-glucosides.

Pharmacological Properties: See generalities.

Uses: They are the same as those of Frangulae cortex.



	C-10	R
Cascaroside A	β	OH
Cascaroside B	α	OH
Cascaroside C	β	H
Cascaroside D	α	H

Aloe **aloe** **aloe**

Cape aloe*: Aloe ferox*, **Curaçao aloe: *Aloe vera*** **Asphodelaceae**

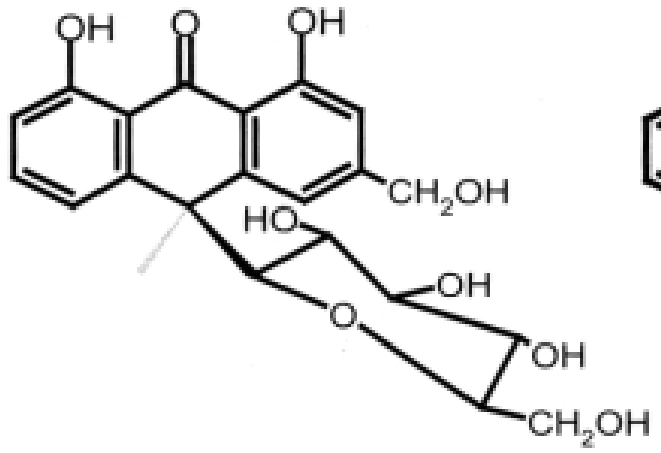
Aloe consists of the dried concentrated juice from the leaves of the *Aloe* species. Aloes also produce a gel which is said to be healing, and is used in the cosmetics industry.

The drugs: **Aloe Juice** and **Aloe Vera Gel**

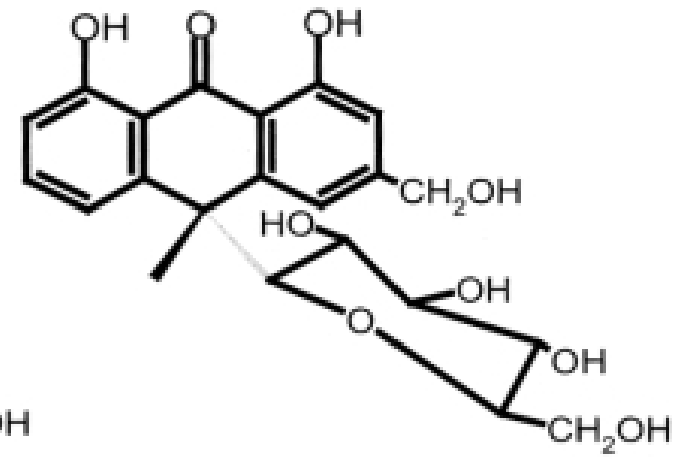
Aloe juice («**aloe**»)is contained in the pericyclic cells, and flows, spontaneously from the cut leaf, whereas **aloe gel** consists strictly of the mucilage from the polyhedral cells of the central region.

Traditionally, the juice that flows spontaneously from the cut leaves is collected and concentrated by boiling. The thickened juice consists of dark brown masses (Curaçao aloe) whith greenish reflections (Cape aloe). The gel is obtained after eliminating the outermost tissues of the leaf.

Aloe Composition: The drug contains 15 to 40% hydroxyanthraquinone derivatives, which are aloe-emodin anthrone 10-C-glucosides: aloin (= barbaloin), hydroxyaloins, and in *Aloe ferox*, aloinoside. Aloin, which is by far the chief constituent, is in fact a mixture of aloin A (10R) and aloin B (10S).



Aloin A



Aloin B

Pharmacological activity and Uses: Both aloes are used to prepare the titrated dried aloe extract, titrated to contain 20±1% hydroxyanthraquinone derivatives. This extract is prepared by aqueous extraction, which eliminates a large part of the resinous material to which most of the side effects of the juice are attributed.

Aloe Vera Gel Composition: very rich in water, it does not appear to contain very specific compounds: amino acids, lipids, sterols, enzymes, and most of all polysaccharides (pectins, hemicelluloses). Tradition attributes to **Aloe Vera Gel** some healing properties. The gel is widely used in cosmetic products as a hydrating ingredient in liquid or creams: sun lotions and shaving creams, lip balms, healing ointments, face packs and creams. It may be employed in the composition of phytomedicines: skin disorders, frostbite, insect bites, sunburn, diaper rush.

Rhei rhizoma **rhubarb**

Rheum palmatum, Rheum officinale **Polygonaceae**

The drug consists of the dried subterranean organs of *Rheum palmatum* or *R. officinale*, or hybrids of the two species, or a mixture, or a mixture of the two species.

Chemical Composition: Many constituents have been isolated from the commercial drugs: galloylglucoses, acylglucoses, tannins, flavan derivatives, proanthocyanidins, napthalenes, stilbenes, and especially between 2 and 5% hydroxyanthraquinone derivatives. In the dry drug, the chief constituents (60-80%) are anthraquinone glycosides, namely emodin, physcion, aloe-emodin, and chrysophanol glycosides.

Pharmacological Activity: Rhubarb remains in use as a laxative, especially as a powder. **Some authors point out that because of the presence of tannins, it is illogical to prescribe it as a laxative. Indeed, at low doses it is an antidiarrheal, and it can even lead to laxative-induced constipation**. Outside of its use as a laxative, the drug is used (as a purified dry extract combined with salicylic acid) for the local adjunctive treatment of inflammations and forinfections of the oral cavity mucosa (irritations due to prostheses, gingivitis, or periodontitis). It is traditionally used for children's teething pains.

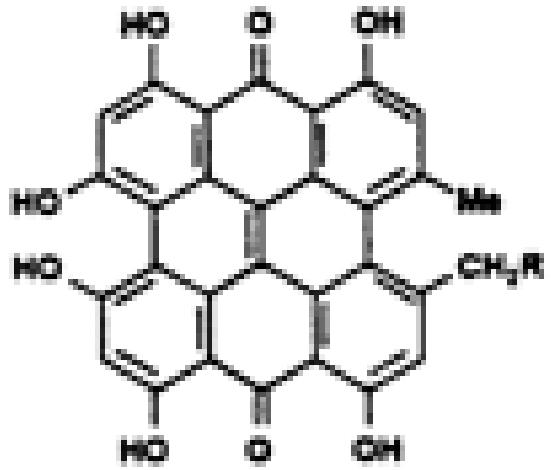
NAPHTODIANTHRONE-CONTAINING DRUGS

Hyperici herba **Saint John’s wort** **kantaron, binbirdelik otu**

Hypericum perforatum **Clusiaceae (Hypericaceae)**

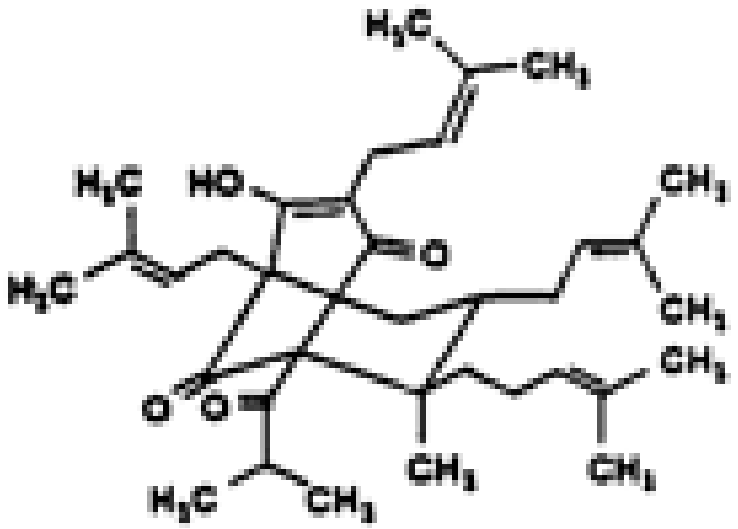
The flowering tops of Saint John's wort are very popular especially in Germany, where it is prescribed, as a standardized extract, for the treatment of mild depression. The drug is also used for its antiseptic and healing properties.

Chemical Composition: The drug contains essential oil, phenolic acids, proanthocyanidins, prenylated derivatives of phloroglucinol (hyperforin 2-4.5%), adhyperforin (0.2-1.8%), and flavonoids. The constituents responsible for the color of the juice contained in the black dots on the leaves and flowers are naphthodianthrones (0.06-0.15%): hypericin, and in the fresh plant, alongside protohypericin and protopseudohypericin.



Hypericin R=H

Pseudohypericin R=OH



Hyperforin

Properties and Uses: Saint John's wort has a reputation for having healing properties. The antibacterial properties of extracts have been demonstrated (hyperforin).
The conventional animal experiments used to detect an antidepressant activity Show that the drug has a stimulant effect on the CNS (hypericin, hyperforin). Saint John's wort extract may also interfere with seretoninergic mechanisms: inhibition of seretonin uptake at synapses. Hypericin has antiretroviral properties.
The drug is used especially in Germany as extracts **to treat mild and moderate depression**. **Commission E warns consumers about the risk of photosensitization, especially in fair-skinned individuals**.

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