

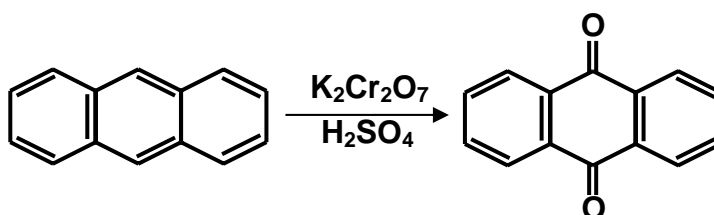
# ANTHRAQUINONES IN COSMETICS.

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Sweden has given the world many outstanding scientists: Arrhenius, Nobel, Scheele, Berzelius, Ångström, Rydberg, Celcius, Bøhlin, and many others. And of course Carl von Linné, better known as Linnaeus. In 1735, 28 year old, he went to Harderwijk in The Netherlands to obtain his degree in medicine. The Harderwijk University does not exist anymore and today the only attraction of Harderwijk is the dolphinarium where in the past Gudrun the orca stole the hearts of thousands. Linnaeus continued his study in Leiden and there his first classification of living things, the *Systema Naturae*, saw daylight. He classified living species on morphological properties, a system that is still used today.

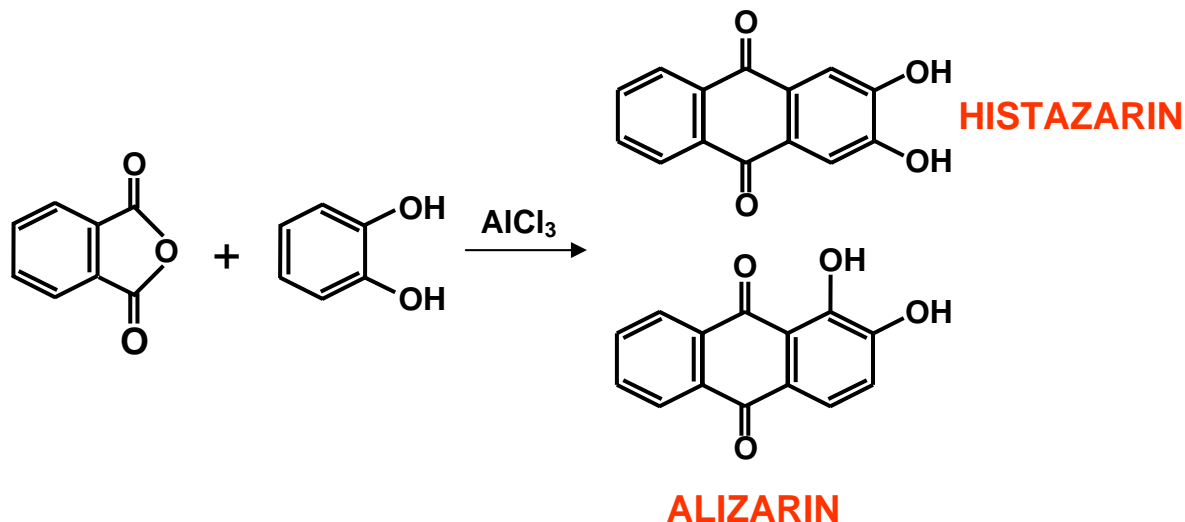
Classification of living things (plants, animals, microorganisms) can also be done based on chemical principles, chemotaxonomy. The presence and distribution of various chemical compounds in plants serve as taxonomic evidences. Nearly 33 different groups of chemical compounds have been identified for their taxonomic significance. Chemotaxonomy is a young science; the foundations have been properly shaped only in 1987 (Wayne), having said that this part of botanical science is still very much *in statu nascendi*. To put it in simple: particular plants produce particular terpenoids, particular steroids, particular alkaloids, particular anthraquinoids, or other particular products that are characteristic for a plant or genera of plants and not produced by other genera of plants. In the past, we presented papers to you on steroids, flavonoids and alkaloids, and now anthraquinones are on the role.

Anthraquinones are condensed aromatic structures; the parent compound is anthracene. This highly crystalline aromatic hydrocarbon occurs in coal tar and melts at 218°C°. It is insoluble in water but readily soluble in most organic solvents such as carbon disulfide, aliphatic hydrocarbons, alcohols, esters, aromatics benzene and halogenated solvents. Upon oxidation of anthracene with potassium dichromate/sulphuric acid anthraquinone is obtained, a substance that is parent compound for a large class of dyes and pigments.



Anthracene belongs to the family of polycyclic aromatic hydrocarbons, which we briefly discussed with you before, and is not a friendly chemical. It is a severe irritant and sensitiser, both to the skin and eyes, and when taken orally it causes severe damage to the liver, kidneys and mucous membranes. Upon inhalation severe lung damage will occur. However, the toxic properties of anthracene are knitty gritty compared to other polycyclic aromatic compounds such as benz[a]pyrene and dibenz[a,h]anthracene. On the other hand, anthraquinone (formal IUPAC name 9,10-dioxoanthracene) is relatively non-toxic: The  $LD_{50}$ -value (rat, oral) has been determined as 15 g/kg body weight.

Coal tar is not used anymore to produce anthraquinone. The anthraquinone skeleton can also be made by means of a Friedel-Crafts reaction of phthalic anhydride with e.g. catechol (1,2-dihydroxybenzene) using a strongly acidic catalyst such as anhydrous aluminium chloride or zinc chloride. The first reaction product is o-(3,4-dihydroxybenzoyl)-benzoic acid, and in a second Friedel Crafts reaction this product a mixture of two anthraquinone dyes is formed alizarin & histazarin.



Alizarin forms orange-red needles, is poorly soluble in water, but easily soluble in ethanol and acetone. The value for  $\lambda_{\text{max}}$  in alcohol is 435 nm ( $\log(\epsilon)=3,8$ ). Histazarin forms yellow-brown needles, is insoluble in water and only poorly soluble in ethanol and acetone. Because of the presence of the two phenolic hydroxyl groups, both alizarin and histazarin are easily soluble in alkali.

Two monohydroxyanthraquinones are known, but they do not have any commercial value. Thirteen dihydroxyanthraquinones are possible, and all are known. The most important ones, next to alizarin and histazarin, are purpuroxanthin (1,3), anthrarufin (1,5), chrysazin (1,8) and anthraflavin (2,6). All of these occur naturally.

Alizarin is the main dye found in madder root (*Rubia tinctorium*, *Rubia cordifolia*), used already by the Egyptians and found in excavations in Pompeii. It is also known as Pigment Red 83 or CI 75330. The alizarin pigment is present in madder root as its water-soluble glycoside; the aglycon is obtained by fermentation. The fermentation used to be a highly polluting process, reason why synthetic alizarin was preferred since the beginning of the 20<sup>th</sup> century.

Madder extract is allowed in personal care & cosmetic products for hair dyeing without any restriction, and that is also valid for Pigment Red 83. Funny enough CI 75330 is not an allowed INCI name. Next to alizarin madder contains another dye in high concentration, a phthalocyanin with the name purpurin, next to a variety of substituted dihydroxyanthraquinones, quite frequently as their methyl ethers, carboxaldehydes, or with a methyl group on the 2-position: 1,4-dihydroxy-2-methyl-anthraquinone is known as an effective termitifuge.

Alizarin itself has also 5-alpha-reductase inhibitor properties, making madder root functional to stimulate hair growth. It has also anti-leukaemia and anti-mutagenic activity and has been described because of its hepatoprotective properties. Alizarin

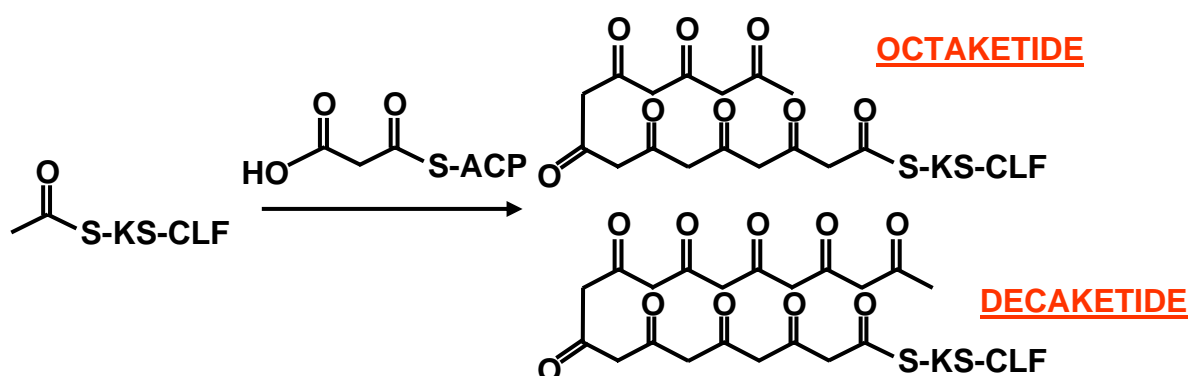
also occurs in noni, *Morinda citrifolia*, which is frequently recommended a nutritional supplement for the treatment of leukaemia. At present the FDA does not accept these claims although quite a bit of study is going on.

## **BIOSYNTHESIS OF ANTHRAQUINONDS.**

You may recall that malonyl-CoA plays an important role during synthesis of steroids and flavonoids. It is also the starting point for the biosynthesis of anthraquinones via the formation and polymerisation of malonyl-CoA (MAT) units by polyketide synthases (PKS's).



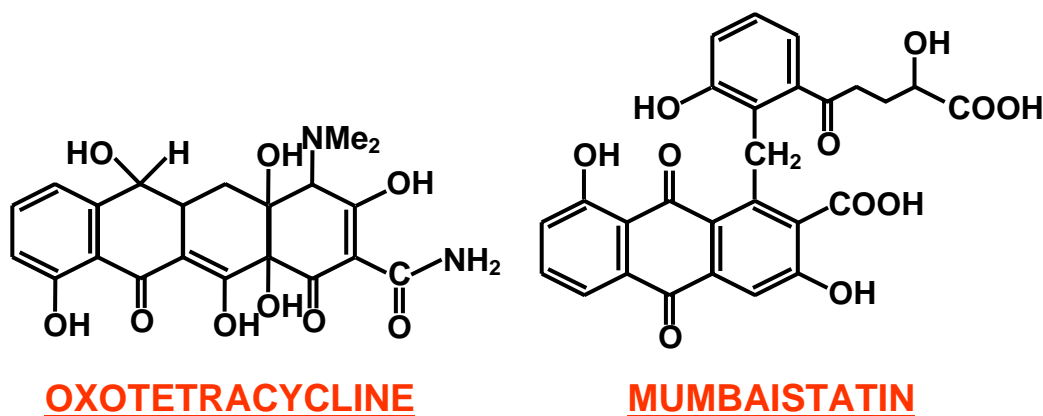
Malonyl-CoA is condensed with a Keto Synthase-Chain Length Factor (KS-CLF) whereby a acetic acid moiety is released; the formation proceeds via an Acy Carrier Protein (ACP). Formation of the chain start by means of condensing additional malonyl-CoA units to the base unit under the influence of either an octaketide or a decaketide synthase. The highly complex biochemistry of these reactions has largely been unravelled (Tang, Lee & Khosla; 2004). Through the activity of particular enzymes such as octaketide kinase and decaketide synthase complex products are obtained, identified as octaketide and decaketide.



Ketides are a large group of molecules with highly diverse structural properties. Quite a number of antibiotics and anti-tumour drugs are derived from the polyketides such as tetracycline and doxorubicin (O'Hagan; 1991) and it is noteworthy that a small unit such as malonyl CoA using polyketide synthases results in a tremendous biosynthetic variability. Microorganisms produce these products. It is thought that micro-organisms such as *Actinomyces* and *Streptomyces* species, that live in symbiosis with particular plants, offer protection to the plants while the host offers excellent hospitality to these micro-organisms.

The geometry of the polyketides already betrays the identity of particular molecules, such as naphthoquinones, tetracyclines, and also anthraquinones. Also heterocyclic systems may be formed containing one or more oxygen atoms. In all cases these products are pharmacologically active.

Sometimes the results are extremely challenging: Vertesy et.al. (Aventis, 2001) found that mumbaistatin, a rather complex 1,6-dihydroxy-7-carboxyanthraquinone with a complex side chain on the 8-position produced by a *Streptomyces* species is the most powerful glucose-6-phosphatase translocase inhibitor known ( $IC_{50}=5$  nMole). This enzyme controls in the liver the conversion of glycogen to glucose. This is an extremely important tool for the treatment of diabetes mellitus type II.



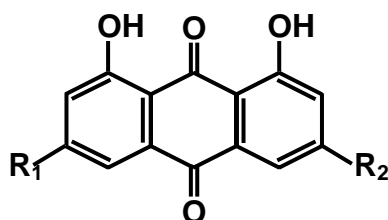
Using botanical extracts from plants that live in symbiosis with particular microorganisms, it is inevitable that these extracts also contain metabolites produced by these microorganisms. In quite a number of cases, it has been shown that a significant part of the physiological activity of botanical extracts can be attributed to the work done by microorganisms.

That does not mean that the production of these physiologically active products is the monopoly of microorganisms (bacteria, fungi). Also particular plants themselves are able to produce them. Related to polyketide synthases are chalcone synthases and stilbene synthase. These enzymes catalyse the stepwise condensation between acyl co-enzyme A esters in the biosynthesis of flavonoids, stilbenes and other aromatic polyketides. All these enzymes have as a similar structural property a highly conserved cysteine residue that is essential for the polyketide synthase activity. This is different for bacterial or fungal polyketide synthases where this cysteine residue is not pronouncedly present.

The chemistry of flavonoids, steroids, anthraquinoids, but also fatty acids, antibiotics, and numerous other products looks so different, but the biochemical pathways are not so different at all. In all cases, the same building blocks are used, acetyl co-enzyme A or malonyl co-enzyme. In all cases large sets of enzymes are used and it is truly a miracle that the chemical sequences function: they have to be present on the right moment in the right concentration and are made to order. If we even would come close to the logistic abilities of a "simple" organism like a bacterium, we would live in a different world. In the divined selectivity and specificity of the enzyme systems the hand of God is recognised, which is a guarantee for the ultimate chemical beauty. By all means, it is chemistry in optima forma, but the same chemistry is so often condemned.

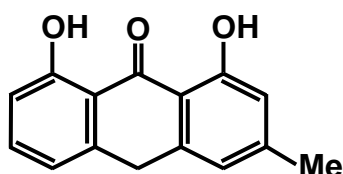
## ALOE VERSUS RHUBARB.

More than 400 Aloe species have been described, mainly occurring in Africa. The most well-known representatives are Aloe vera and Aloe ferox, which are of sincere cosmetic and medicinal value. Topically, aloe is used for burns, wound healing, psoriasis, sunburn, frostbite, inflammation, osteoarthritis and cold sores. It is also applied topically as an antiseptic and as a moisturizer. Aloe vera contains a large number of different anthraquinones, such as 1,8-dihydroxyanthraquinone (danthron). This occurs as red or reddish-yellow needles or leaves and has a melting point of 193-195°C. Danthron is very soluble in alkaline conditions, is well soluble in acetone, chloroform, ether and ethanol, but practically insoluble in water. It has been widely used as a laxative, but in 1987 the FDA ordered its withdrawal from the market. It is currently used as an antioxidant in synthetic lubricants, in the synthesis of experimental anti-tumour agents, and as a fungicide for control of powdery mildew.



$R_1 = H;$	$R_2 = Me$	: <b>CHRYSOPHANOL</b>
$R_1 = H;$	$R_2 = CH_2OH$	: <b>ALOE-EMODIN</b>
$R_1 = H;$	$R_2 = COOH$	: <b>RHEIN</b>
$R_1 = OH;$	$R_2 = Me$	: <b>EMODIN</b>
$R_1 = H;$	$R_2 = H$	: <b>DANTHRON</b>

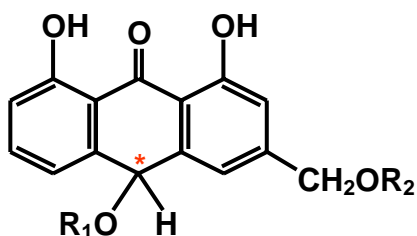
Chrysophanol has haemostatic and bactericidal properties, and is also found in the roots of regular rhubarb (*Rheum rhabarbarum*) and (in a large amount) in Chinese rhubarb (*Rheum palmatum*); more than 350 rhubarb species are known and most of these are edible. Chinese rhubarb, also named Da Huang, is used medicinally as a laxative, which activity boils down to the presence of the anthraquinoids. Next to chrysophanol Chinese rhubarb also contains rhein (antiviral, bactericide, viricide), emodin (anti-inflammatory, anti-tumour [breast], vasorelaxant, viricide) and aloe-emodin (anti-herpetic, anti-leukemic, viricide). According to the Chinese Pharmacopoeia Chinese rhubarb is used for the treatment of painful and swollen eyes, sore throat and painful and swollen gums. These two syndromes are treated by combining Chinese rhubarb with coptis root (*Coptis trifolia*) and Baikal skullcap, a formula known as Xiexin Tang.



**CHRYSAROBIN**

Chrysarobin is related to chrysophanol. This molecule lacks the carbonyl group on the 10-position of the anthracene system. Crude chrysarobin is also known as Bahia Powder or Goa Powder, and is obtained from the trunk of Andira Araroba. In the British Pharmaceutical Codex, it is named Araroba. Although Goa powder may act as a severe skin irritant, it has been demonstrated to be effective for the treatment of acne and eczema, and used for the treatment of ringworm. It is probably the most effective treatment known for psoriasis. However, when taken orally it readily causes gastroenteritis and colours the urine dark yellow. Upon alkalinisation of the urine a violet colour develops.

Aloe and (Chinese) rhubarb also contain water soluble anthraquinoids. These originate from oxidation of the methyl group in chrysophanol to the corresponding hydroxymethyl group (aloe-emodin). The carbonyl group on the 10-position is converted into a hemiacetal with rhamnose, and this product is named aloin. The consequence thereof is that the carbon atom on the 10-position becomes chiral, and thus two optical isomers of aloin exist: aloin A and aloin B. The racemate is named barbaloin.



**BARBALOIN (ALOIN):**  
**R1=H; R2=  $\alpha$ -L-RHAMNOSYL**

**ALOINOSID:**  
**R1=R2=  $\alpha$ -L-RHAMNOSYL**

These glycosides are frequently subject to hydrolysis and subsequent oxidation, resulting in precipitation of water-insoluble aloe-emodin. This procedure is also followed during processing of aloe vera gel. The gel is removed from the leaves and is obtained as a gel-like substance, comparable to a high viscous carbomer gel. Upon oxidation of the whole gel with hydrogen peroxide the gel structure is destroyed and the water-soluble anthraquinoids are converted into water-insoluble products that can be filtered of.

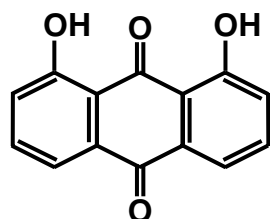
Barbaloin has antibacterial, antihistaminic and laxative properties. Upon oxidation of chrysophanol the corresponding acid, chrysophanic acid, is obtained, which acts as a calcium antagonist and has anti-spasmodic properties.

Emodin (3-methyl-1,6,8-trihydroxyanthraquinone) has a wide variety of functionality. It has bactericide and viricide properties, is a powerful immune stimulating properties, is active against the cytomegalovirus ( $ED_{50}=1.1 \mu\text{g/ml}$ ) and has vasodilating properties. In high concentration, however, emodin has cytotoxic properties.

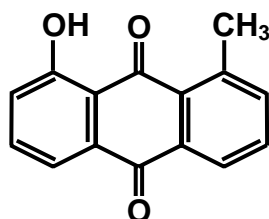
It is interesting to observe, that there is quite a lot of symmetry between the chemical composition of aloe species and rhubarb species, particularly the anthraquinones that are present, despite the fact that the visuals of both plant groups are very different: chemotaxonomy.

Rhubarb never really made it in personal care and cosmetic products: one of the reasons might be that cosmetic marketers could fear that the glossy beauty outlets would be jeopardised by the greengrocer on the corner of the street. This is not

justified as rhubarb has a lot to offer for personal care and cosmetics, and that is not limited to anthraquinoids only.



**1,8-DIHYDROXY  
ANTHRAQUINONE**

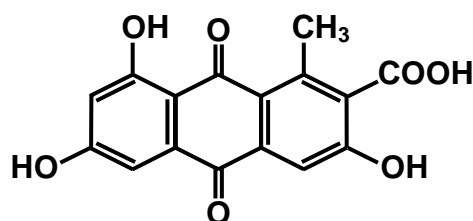


**1-HYDROXY-8-METHYL  
ANTHRAQUINONE**

Recently, several anthraquinones have been isolated from the roots of *Aloe berhana* and *Aloe graminicola* (Dagne, Yenesew; 1994). It was shown that the anthraquinones are formed through two parallel routes of the polyketide pathway, differing in the way the octaketide chain is folded. This leads to two groups of anthraquinones: 1,8-dihydroxyanthraquinones and 1-hydroxy-8-methylantraquinones. 1-Hydroxy-8-methylantraquinones are relatively seldom encountered; examples are aloesaponarin I and aloesaponarin II, and not to forget laccaic acid D.

### **ANTHRAQUINONDS FROM ANIMAL ORIGIN.**

The last one is obtained from *Laccifer lacca*, an insect found in India and Thailand, living in trees and covering themselves with a waxy substance: shellac. Shellac is a hard, brittle wax mainly composed of long chain wax esters (>80%) and some wax acids (~12%). Interesting is the presence of an unusual fatty acid, aleuritic acid (9,10,16-trihydroxy-palmitic acid). Aleuritic acid is an ideal precursor for synthetic ceramides, such as Ceramide HO<sub>3</sub> (Sederma). Aleuritic acid is also applied in fragrance preparations, mainly as its macrocyclic internal ester(s). Shellac wax has many applications, such as citrus fruit coatings, fireworks, microprocessor technology, etc. Shellac contains also a red dye, identified as a representative of the group of 1-hydroxy-8-methylantraquinones, and is named laccaic acid D.



**LACCAIC ACID D**

Three other laccaic acids are known (A,B & C). Laccaic acid is allowed in personal care and cosmetic products without restrictions. It is used for semi-permanent hair dyeing and distinguishes itself by an excellent light and wash fastness.

Another 1-hydroxy-8-methylantraquinone derivative is carminic acid, a red dye also named cochénille (and not to be confused with cochénille red [a red azo dye]). Cochénille compares to laccaic acid D to such an extent that on the 2-position

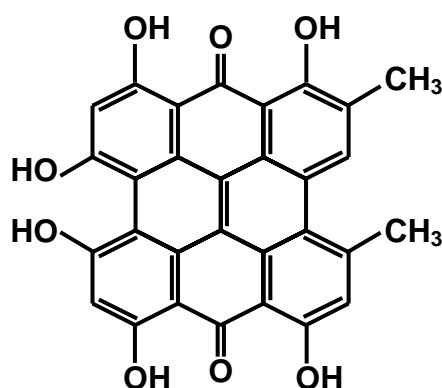
a glucosyl group is present making the dye water-soluble. This food grade dye (E120) is obtained from the insect *Dactylopius coccus*, cactus lice living on opuntia species. Only the females are used as the life span of the males is so short that they are useless for the production of cochénille. Peru is the major producer of cochénille with a market share of ~80%, although in recent times related insects producing cochénille are cultivated in Poland and Armenia.

## **DARK AGES.**

During the dark ages the flowers were collected on the day before St. John's day (June 23<sup>rd</sup>) and hung up in the house to ward off evil spirits, or to drive out the devil from those who were thought to be possessed: St. John's Wort (INCI: *Hypericum Perforatum*). It was believed that if a person would step on the plant after dark he would be transported by a magical horse around the heavens and returned to earth only as the sun rose. (A good excuse for staying late in the local tavern !)

It is also claimed that on August 29<sup>th</sup>, the day on which John the Baptist was beheaded, blood-red stains appear on the leaves of St. John's wort. Probably the red oil, which is produced on grinding the plant, gave rise to associations with Christian virtues, in that it symbolises the spilled blood of Christ and thus became a weapon against the devil.

The red colour of St. John's wort comes from a dianthron with the name hypericin; it is present in the oil in ~0,12-0,15%. Also present are related substances such as pseudohypericin (one of the methyl groups has been converted into a hydroxymethyl group) and emodinanthranol (which is also found in *Aloe barbadensis*).



**HYPERICIN**

St. John's wort oil has been demonstrated to have a similar efficacy as selective serotonin reuptake inhibitors (SSRI's) such as fluoxetine (Prozac®), sertraline (Zoloft®) and paroxetine (Paxil®). Needless to say that these ingredients are strictly forbidden in personal care and cosmetic products; *Hypericum Perforatum* is not prohibited for use. Taking St. John's wort extract improves mood, decreases anxiety and somatic symptoms, and decreases insomnia related to mild to severe major depression. It was originally thought that hypericin was responsible for the anti-depression activity, but it is now believed that another ingredient present in St. John's wort is active principle, hyperforin. From a molecular point of view, hyperforin is a highly interesting species: it has a bicyclic structure with an enol structure, stabilised by a carbonyl group, with four isoprene side chains, betraying its biosynthetic pathway (via

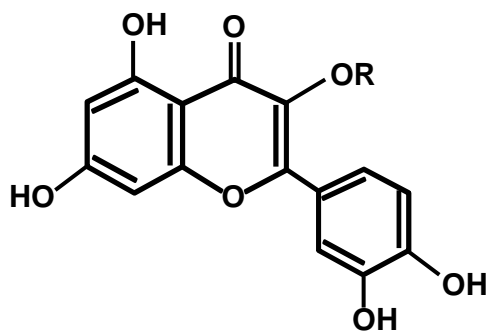


mevalonic acid). St.John's wort can be considered an option for short-term treatment of mild depression.

We prefer to discourage our ever-expanding reading audience to go into treatment of mental disorders by means of personal care and cosmetic products, but isn't it true that the use of our products represent a piece a wellness of the users ? A decent amount of St.John's wort oil in your cosmetic cream or gel, and you will improve the feeling of well-being of your customer. Call it an endorphin-like activity, which is a contraction of the word endogenous morphine. In other words, morphine-like products that are produced in the body, that interact with the opiate receptors when the time is right.

Endorphins improve your mood, relieve pain, make you sleep well, etc. These are peptides produced by the pituitary gland and the hypothalamus, and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. In other words, they might work as "natural pain killers". Three groups of endorphins are known, the  $\alpha$ -,  $\beta$ - and  $\gamma$ -endorphin;  $\beta$ -endorphin is the most active in pain relief, made of a backbone of 31 amino acids. The production of  $\beta$ -endorphin is stimulated by capsaicin, one of the active species of *Piper nigrum*; capsaicin is well-known in the personal care and cosmetic industry for its pain relief abilities, but you'd better not use it in damaged skin. There is now also sufficient evidence that during acupuncture a significant amount of  $\beta$ -endorphin is released giving the patient the feeling that the treatment is beneficial and a general feeling of well-being becomes apparent, frequently associated with healing.

St.John's wort also contains other active species, in particular flavonoids derived from quercetin.



R=GALACTOSE:

HYPEROSIDE

R=RUTINOSE:

RUTIN

R=RHAMNOSE:

QUERCITRIN

R=GLUCOSE:

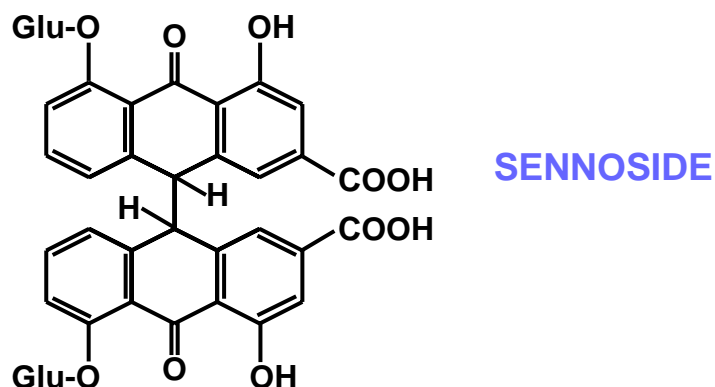
ISOQUERCITRIN

Hyperoside also occurs in coltsfoot (INCI: *Tussilago Farfara*) and has major anti-ageing/anti-wrinkle activity, next to its profound activity to reduce capillary fragility and elastase inhibitory qualities. Isoquercitrin is a useful anti(retro)viral agent; for quercitrin no activity has (yet) been reported. Coltsfoot is under scrutiny (and already forbidden in a number of countries in food supplements) because of the presence of pyrrolizidine alkaloids such as senkirkine and senecionine (see our article on alkaloids).

## **SENNA.**

Another botanical source for anthraquinoids is Senna extract (INCI: *Cassia Italica*). The applicable parts of senna are the leaves and the fruits. Both are stimulant laxatives. Senna contains dianthrone comparable to hypericin (condensed an-

thraquinones) named sennosides A & B, next to minor amounts of sennosides C & D (whereby the one of the carboxyl groups is present as a hydroxymethyl group). The dianthrone glycosides are not present in the fresh leaf, but appear to be formed during the drying process. Hydrolysis of sennoside A results in the formation of rheinanthrone (3-carboxy-1,8-dihydroanthraquinone). Sennocide, frequently offered as the calcium salt, is a well-established laxative.



Sennosides, next to aloe-emodin, emodin and rhein are also found in rhubarb (INCI: Rheum Undulatum). Botanically the more common names are Rheum palmatum (Chinese rhubarb; Turkey rhubarb) and Rheum rhabarbarum (wild rhubarb). Both plants belong to the family Polygonaceae. Rhubarb has very broad leaves and elongated, often reddish, petioles (leaf stalks). The petioles of rhubarb are edible, though the leaves are very toxic. The roots and rhizomes of Rheum palmatum and the roots of Rheum rhabarbarum are used in medicinal treatments. Chinese rhubarb, also named Dahuang, is medicinally considered stronger than American rhubarb. It is interesting to note that several rhubarb species are excellent providers for stilbene derivatives, products going back to the early times of oral contraceptives.

The toxicity of the leaves of rhubarb originates from the presence of large amounts of oxalic acid. Quite interesting to note that oxalic acid in personal care and cosmetics is allowed to a maximum of 5%, but only in hair care products, with the remark "for professional use only". Nobody really bothers if you buy on the corner of the street at your greengrocer a kilo rhubarb to entertain your mother-in-law with a nice rhubarb cake. How funny Legislation can be !

## **BRAZIL.**

The French name for The Netherlands is Les Pays-Bas. Literally translated that means the "Low Lands", and the reasoning behind that name is pretty obvious. The name "Brazil" comes from the Portuguese word "brazá" meaning red. In the early Portuguese times quite a bit of Brazilwood (Caesalpinia brasiliensis) was imported from South America to obtain a red dye to paint textiles. Brazilwood, also named redwood, was quite abundant on the Brazilian coasts, hence the name Brazil. There are even dyestuffs with the names brazilin and brazilein.

The main insoluble redwoods are sandalwood (Pterocarpus santalinus; indigenous to south India); narrawood (Pterocarpus indicus; Burma, Philippines), bar-

wood (*Pterocarpus soyauxii* & *Pterocarpus erinaceus*) and camwood (*Baphia nitida*; West Africa). These redwoods give us dyes with excellent fastness to chemicals and light, that enable to obtain dark red and brown colours. Major colouring matters are also the santalins (first isolated in 1833) and santarubins (condensed biflavonoids) They occur also in e.g. sandalwood, which is today better known because of the essential oil used in fragrances. Hamish McNab of the University of Edinburgh published in 2004 a highly interesting paper on these dyes, in a historical perspective. There are still quite a number of natural anthraquinone dyes around, although their use has been superseded by the use of synthetic dyes because of the price of the natural products.

Alizarin	Madder	CI 75330
Purpuroxanthin	Madder	CI 75340
Rubuadin	Ladies bedstraw	CI 75350
Morindanigrin	Morinda root	CI 75360
Munjistin	Madder	CI 75370
Morindadiol	Morinda root	CI 75380
Chrysophanic acid	Turkey rhubarb	CI 75400
Purpurin	Munjeet	CI 75410
Emodin	Persian berries	CI 75440
Laccaic acid	Coccus laccae	CI 75450
Kermesic acid	Coccus ilici	CI 75460
Carminic acid	Coccus cacti	CI 75470

Table 1: Natural anthraquinone dyes.

Only a limited number of the dyes mentioned in table 1 are also found in the database of the Enterprise, although the extracts of the plants are usually allowed without restriction. Lady's bedstraw (*Galium verum*) is interesting: the Highlanders in Scotland used this plant to dye their tartans, to curdle milk (probably because of the tannins present) and to colour their cheese. This is still practised today in Cheshire, known for its outstanding cheese quality. Lady's bedstraw is used in OTC cosmetic products for poorly healing wounds and to stop bleeding.

Next to the anthraquinones also the related naphthoquinones are used as dyes. Some of those dyes are collected in table 2.

Lawsone	Henna	CI 75480
Lapachol	Lapachol wood	CI 75490
Juglone	Walnut shells	CI 75500
Deoxysantalol	Sandelwood	CI 75510
Alkannin	Anchusa tinctoria	CI 75520
Anchusin	Anchusa tinctoria	CI 75530
Skikonin (Tokyo violet)	Lithospermum erythrorhizon	CI 75535

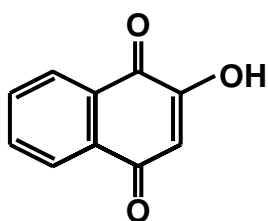
Table 2: Natural naphthoquinone dyes.

Shikonine is produced in the roots of *Lithospermum erythrorhizon* (member of the family Boraginaceae) and has anti-microbial properties. It also has anti-tumour and contraceptive properties. It is externally used to treat nappy rash, burns, cuts, wounds, abscesses, eczema and haemorrhoids. The plant is an ingredient of commercial skin care products, although the commercial impact is limited because of the intense colour that the extract will give to e.g. creams.

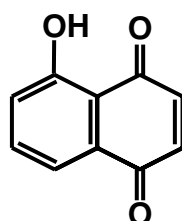
*Anchusa tinctoria* (alkannet), with the INCI name *Alkanna Tinctoria*, provides us with alkannin, a derivative of 5,8-dihydroxynaphthoquinone, better known as alizarin black. It has an isoprenoid side chain carrying a hydroxyl group. Thus, it has a chiral carbon atom, and the optical isomer is the previously discussed shikonine. The medical use of *Anchusa tinctoria* goes back to Hippocrates, doctor and philosopher in Greece (4th century BC). It took until 1976 until Papageorgiou described the results of experiments, which confirmed the wound healing properties and antimicrobial properties of alkannet root extract and was the first to identify alkannin and derivatives thereof as the active components. More recently, such compounds were demonstrated to exhibit significant anti-tumour, antibacterial and anti-inflammatory activity.

The wound healing properties of alkannet are not even spectacular: they are magic. In those cases where synthetic pharmaceutical products fail, the use of alkannet gives a very good chance of success. In addition to the wound healing properties of *Anchusa tinctoria* (and *Lithospermum erythrorhizon*) these extracts have been used effectively in traditional Chinese medicine for hundreds of years as a cancer treatment, with proven efficacy. A beautiful review has been published by Papageorgiou, Assimopoulou, et.al, *Angew.Chemie*, 38,270-300,(1999).

Lawson, 2-hydroxy-1,4-naphthoquinone, comes from the henna plant (INCI: *Lawsonia Inermis*). This dye is still very popular for dyeing hair, but its use has been restricted because of the photochemical activity of lawson. Furthermore, many henna powders in the market place are contaminated with p-phenylene diamine, a well-known carcinogen. On a very frequent basis, the authorities in the European Union recall henna powders from the market, mostly of Indian origin.



**LAWSONE**



**JUGLONE**

Juglone comes from black walnut (*Juglans nigra*), and is toxic to many plants. Topical application results in a {2+2} photoadduct with the cytosine moiety of the genetic material, comparable to the photoadduct of psoralens with cytosine. Consequently cell reproduction comes to a full stop. Juglone is therefore phototoxic and genotoxic. Lapachol chemically compares to lawson, to such an extent that on the 3-position an isoprene unit is present and because of that the {2+2} photoaddition is

less likely to occur due to steric hindrance. Consequently the phototoxicity of lapachol is markedly lower compared to lawsone and juglone.

## **VITAMIN K.**

The naphthoquinone backbone, as it occurs in a number of natural dyes, is also present in vitamin K. Vitamin K, more precisely vitamin K2, is produced in the intestinal tract with the help of *Escherichia coli*. Humans live in symbiosis with this organism that frequently is also less pleasant when the balance is lost. Vitamin K is an oil-soluble vitamin and is encountered in two forms. Vitamin K1, also called phylloquinone, is found in plants. Vitamin K2, with the nickname menaquinone, is produced by bacteria such as *Escherichia coli*. We are forced to live in symbiosis with bacteria to satisfy our needs for vitamin K2.

Vitamin K3, menadione, is a synthetic form of this vitamin which is manmade, with limited activity compared to vitamin K1 & K2. Vitamin K3 is the simplest version identified as 2-methyl-1,4-naphthoquinone. Both phylloquinone and menaquinone are more complex and also have a polymeric side chain on the 3-position identified as a phtyl group (polyisoprene).

Vitamin K is required for the maintenance of normal blood coagulation by facilitating the production and/or release of various plasma proteins required for blood coagulation, including e.g. prothrombin. Although it has been suggested that vitamin K may play a role in electron transport and oxidative phosphorylation in microorganisms, these functions remain to be confirmed in higher animals. Vitamin K is not a regular ingredient in personal care and cosmetic products, and in some countries, it is forbidden (e.g. France).

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Anthraquinones, and also naphthoquinones, offer interesting opportunities for the design of functional personal care and cosmetic products, although their use is once again a demonstration of the fact that there are no boundaries anymore between personal care & cosmetics and pharmacy.