ANTHOCYANINS

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Anthocyanins

- Anthocyanins = antocyan glycosides, Anthocyanidins = aglycons

**Aglycons**
- Anthocyanidins occur in acidic medium as cations.
- They are always hydroxylated at C-3 and, most often, penta(3,5,7,3’,4’) or hexasubstituted (3,5,7,3’,4’,5’) by hydroxyl groups, or methoxyl groups, or both.
- The most common aglycones (they are virtually ubiquitous) are pelargonidin (scarlet), cyanidin (crimson), and deiphinidin (purple).

![Structures of the chief anthocyanidins](image)

- \( R_1 = R_2 = H: \text{Pelargonidin} \)
- \( R_1 = \text{OH}, \ R_2 = H: \text{Cyanidin} \)
- \( R_1 = \text{OCH}_3, \ R_2 = H: \text{Peonidin} \)
- \( R_1 = R_2 = \text{OH}: \text{Delphinidin} \)
- \( R_1 = \text{OCH}_3, \ R_2 = \text{OH}: \text{Petunidin} \)
- \( R_1 = R_2 = \text{CH}_3: \text{Malvidin} \)
Anthocyanins

Glycosides

• At least one hydroxyl group at C-5, C-7, or C-4’ must remain free to allow the formation of the colored quinonoid structures.

• (In contrast, anthocyanidins are unstable because their 3-hydroxyl group makes the flavylium ion very reactive.)

• In fact, the 3-hydroxyl group is always linked to a sugar (very often glucose) to form a stable and water soluble anthocyanin.

• 3- monosides and 3,5-diglycosides are the most common forms, 3,7-diglycosides and triglycosides (for example 3,5,3’-triglycosides) are less common.

• Sugar residue: can be a monosaccharide (e.g., glucoside, galactoside, rhamnoside), a disaccharide (e.g., rutinoside, xylosylglucoside), or, less often, a trisaccharide.

• Acylation: frequent, by phenylpropanoic acids (e.g., p-coumaric, caffeic, ferulic, sinapic acids) or benzoic acids (gallic acid), generally at C-6’; Also known by dicarboxylic aliphatic acids (e.g., malonic, malic, oxalic, succinic acids).
Biosynthetic Origin → general metabolism of flavonoids → precursors: 2,3-trans-dihydro-3,4-cis-dihydroxyflavonols → the diols undergo a hydroxylation (at C-2) and a double dehydration → glucosylation (UDP-glucose) probably occurs late.
Properties of 2-phenylbenzopyrylium cation: a weak diacid and a good electrophilic reagent.

- **Anhydrobase:**
  - Ionized: blue
  - Neutral: blue

- **Quinonoid forms**

- **Carbinol pseudobase:**
  - Colorless

- **Structural transformation of anthocyanins in aqueous solution (shown for pelargonidin 3,5-diglucoside)**

- **Properties:**
  - Weak diacid
  - Good electrophilic reagent

- **Dilution with water:**
  - Cationinic form: red
    - (pH < 3)

- **(pH 4-6):**
  - Anhydrobase: ionized: blue
Anthocyanins interaction. (A) self-association, (B) intramolecular copigmentation, (C) metal complexation, (D) intermolecular copigmentation (Castañeda-Ovando et al.).

Co-pigmentation is a phenomenon in which the pigments and other colourless organic compounds, or metallic ions, form molecular or complex associations, generating a change or an increment in the colour intensity.

Some investigations suggest that the co-pigmentation of anthocyanins with other compounds (co-pigments) is the main mechanism of stabilisation of colour in plants.

http://dx.doi.org/10.1016/j.foodchem.2008.09.001.
EXTRACTION AND CHARACTERIZATION

• Anthocyanins are **soluble in** water and alcohols, **insoluble in** apolar organic solvents, and

• They are **unstable in** neutral or alkaline medium.

• They are **generally extracted with an alcohol** (methanol, preferably ethanol if the product is intended for use in food) **in the presence of** a small amount (0.1-1%) of **hydrochloric acid**.

• To avoid esterification of the free carboxyl group of acylated anthocyanins by a diacid, and especially **to prevent** their **deacylation**, it is better to use other acids, either **weak acids** (acetic, tartaric, citric) or **volatile acids** (trifluoroacetic), or to work in a **neutral medium** (alcohol mixtures), and to work at **low temperature** (< 30 °C).

• Anthocyanin solutions are very unstable, and they can only be kept under nitrogen, at low temperature, and in the dark.

• **Industrial preparation of anthocyanin extracts.**
  – Classical procedure: extraction in aqueous medium containing sulfur dioxide, followed by acidification to regenerate the anthocyanins.
  – More recent procedures: ultrafiltration on cellulose membranes, chromatography on ion-exchange resins.

• **Separation of anthocyanins** is achieved by **chromatographic techniques** (column chromatography on polyamide supports, on polyvinylpyrrolidone supports, or on ion-exchange resins, preparative TLC on cellulose-coated plates, or semipreparative HPLC).
EXTRACTION AND CHARACTERIZATION

HPLC is the method of choice to analyze anthocyanin-containing drugs.

• The separations are most often carried out on reverse phases with acidic water and alcohol gradients, in which the cationic forms can be detected at about 500-550 nm.

• As for flavonoids, diode array detectors represent a considerable method enhancement.

• The more complex methods (LC-MS, MS-MS) are only available in specialized research laboratories.

As a general rule, anthocyanin quantitation is performed by spectrophotometry.

• At the wavelengths of maximum absorption of these compounds, interferences are exceptional:

• quantitation can be done directly on an acidic solution in alcohol (cationic form) or on an acidified juice.

• To prevent anthocyanin self-association, which would result in a positive deviation from the Beer-Lambert Law, dilute solutions must be used.

Quantitative estimates of the constituents of an anthocyanin mixture are now obtained directly by HPLC.
ANTHOCYANINS

PHARMACOLOGICAL ACTIVITY

• decrease capillary permeability and fragility (confirmed by biological tests on animals based on the diffusion of dyes)
  – participation of the collagen of the vascular wall in the control of the permeability of that wall.
  – inhibition of the proteolytic collagen degradation enzymes (elastase, collagenase); (It has been shown in vitro for black currant extracts)

• antiedema activity,

• increase in regeneration of ‘visual purple’ or rhodopsin (see bilberry

• act like radical scavengers in vitro (antioxidant activity).

USES

• for the symptomatic treatment of venous and lymphatic insufficiency and capillary fragility (in phlebology, proctology, or gynecology).

• in ophthalmology
  – to treat circulatory disorders of the retina or choroid,
  – to improve vision at dusk.
Proposed mechanism for the stabilisation of the cyanidine semiquinone radical (resonance) (Castañeda-Ovando et al.).

http://dx.doi.org/10.1016/j.foodchem.2008.09.001, Chemical studies of anthocyanins: A review,
ANTHOCYANINS, Other uses

The chief industrial application of anthocyanins is coloring

• they are natural pigments for which no animal toxicity has been found, be it acute or chronic.

• Sources:
  – unfermented grape juice: → liquids titrated to contain 0.5-1% anthocyanins, or → nebulisates titrated to contain 1-5% anthocyanins.
  – elderberry or red cabbage leaves, which are more expensive, but provide a more stable coloring agent.

• Difficulties (restricts the scope of applications):
  – instability in aqueous media (high): it results in color changes as a function of the pH, and in sensitivity to heat, light, sulfites (often used as preservatives), and metals (food cans).
  – The common occurrence of proanthocyanidins and gallotannins in the extracts can also be a problem (for example it makes gelatin precipitate in jams).
  – insolubility of anthocyanins in lipids.

• Anthocyanins are extracted from edible fruits and vegetables and may be used as food additives (Eur. id. code E163), for example in beverages (30 mg/L), jams, and confectionery products, to name only a few.
CHIEF ANTHOCYANIN-CONTAINING DRUGS
BILBERRY, *Vaccinium myrtillus* L., Ericaceae

• The bilberry is a subshrub with **coriaceous leaves**.

• The **bell-shaped flowers** grow solitary or in pairs at the base of the leaves.

• The fruit is a **multiseeded** tetra- or pentalocular globose **berry** with a fleshy mesocarp;

• On the flattened top, the remains of the style and the calyx form a **small disc with a dull edge**.

• Blueberries are particularly abundant in the woods that grow on siliceous soils in the mountains of the northern hemisphere.

• The French market is largely dominated by imports (from Poland).

• Other species (e.g., *V. corymbosum*, cultivated in Germany) are also used in the food industry.
Vaccinium myrtillus, Chemical Composition

Blueberries

• Water (up to 90%), sugars (3 to 7%), and organic acids.

• Phenolic acids, flavonoids (hyperin = hyperoside], quercitrin), proanthocyanidins (procyanidins B-1 and B-4), and monomeric flavan-3-ols (catechin and epicatechin).

• Anthocyanins (in the fresh fruits: about 0.5%): C-3 O-glucosides, O-galactosides, and O-arabinosides of cyanidin, peonidin, delphinidin, malvidin, and petunidin.

Bilberry leaf

• Phenolic acids, flavonoids (rhamnoglucosyl-, arabinosyl-, and glucuronylquercetin).

• Traces of quinolizidine alkaloids (myrtine, epimyrtine).

• Proanthocyanidins and catechin (up to 10%).

Uses

• Water –soluble bilberry powder titrated to contain 70 % anthocyanins. It is an ingredient of drugs used to treat
  – the functional symptoms of venous and limphatyc vessel insufficiency,
  – cutaneous capillary fragility, and
  – mesopic and scotopic vision (nyctalopia, myopia).
Vaccinium myrtillus, Uses, Indications

In France

• Bilberry fruit, fresh or dried, and bilberry leaf: traditionally used
  – to treat the subjective symptoms of venous insufficiency, such as fullness in the legs, and
  – to relieve the symptoms of piles.

• The fruit, fresh or dried: is traditionally used for the adjunctive therapy of the painful component of functional dyspepsia.

• Only the fresh fruit: for the symptomatic treatment of the functional symptoms of capillary fragility,

• Bilberry leaf or dried fruit: for the symptomatic treatment of mild diarrhea.

In Germany, Commission E:

Bilberry fruit:
  as an adstringent, in case of diarrhoea;
  as a topical anti-inflammatory in case of irritation of the mucous membranes of the mouth and throat.
CRANBERRY, *Vaccinium macrocarpon* Aiton, Ericaceae

- Cranberry grows wild in eastern North America, from the Carolinas to Canada.
- Cultivated in the United States since the beginning of the nineteenth century,
- It produces small dark red fruits
- widely consumed as such (*fresh or frozen*) and as cranberry *juice* (pure or as a cocktail sweetened with corn syrup), cranberry *sauce*, and so on
- The *fresh fruit* is very rich in *acids* (citric. quinic. benzoic);
- it also contains *anthocyanins* (3-O-galactosides and 3-O-arabinosides of cyanidin and peonidin),
- *catechin*, and *flavonoids*.
The beneficial—**bacteriostatic**—effect of cranberry juice in the treatment of urinary infections is confirmed by secular use.

It is now postulated that the activity is due to the **inhibition of bacterial adhesion onto mucous membranes**.

This has been demonstrated in the case of *E. coli* adhesion onto urinary tract epithelial cells, using cranberry juice as well as the urine of mice or humans collected after administration of cranberries.

The active constituent (possibly a procyanidine) inhibiting the adhesins specific to the pathogenic strains of *E. coli* has since been isolated from cranberry juice—and also from bilberry (blueberry) juice.

More recently, a placebo-controlled, double-blind clinical trial showed that the **daily consumption of 300 mL** of a commercially-available cranberry juice **induced**, in elderly women (average age 78.5 years), a very **significant decrease in the frequency of urinary bacterial contamination**, after 4-8 weeks of treatment, a delay which may correspond to an initial action on the intestinal bacterial flora.

In the United States, the recommended use of cranberries is as a dilute juice; dried juice capsules are also available.
BLACK CURRANT, *Ribes nigrum* L., Grossulariaceae

- This bushy shrub is cultivated for its edible fruits (in the Burgundy region of France and in central Europe).
- The black currant leaf as well as the fruit are used in pharmacy (Fr. Ph., 10th Ed.).

- Tri- to pentalobate leaves, the underside of which are pale, pubescent, and scattered with yellow secretory glands.
- Flowers: reddish, grouped in dangling racemes, a pubescent calyx which is longer than the corolla.
- Fruit: a fragrant black berry on top of which the remains of the calyx can be seen.

Constituents

- **Fruit**: sugars (10-15%); organic acids; flavonol glycosides; anthocyanins: cyanidin and dephinidin glycosides.
- **Leaves**: a small amount of essential oil; flavonoids: hyperin, astragalin, rhamnoglucosides and glucoxylosides of quercetin and kaempferol; dimeric and trimeric prodelphinidins.
BLACK CURRANT,

Uses

• Fruit
  – to prepare extracts enriched in anthocyanins
  – With therapeutic indications identical to those of the bilberry

• Leaves (in phytopharmaceuticals, traditionally)
  – to facilitate urinary and digestive elimination functions,
  – to enhance the renal excretion of water, and
  – as an adjunct in weight loss programs.
  – orally and topically, for the symptomatic treatment of minor painful symptoms of the joints.

Contemporary phytotherapy prescribes the preparations based on the buds in the same fashion.
• These are rich in diterpenoid acids (hardwickiic acid), and are
• prized for their essential oil, which is used in food technology.
• Essential oil composition varies with cultivars, but the chief constituents are almost always hydrocarbons (A3-carene, sabinene, phellandrenes, and limonene).
VINE, *Vitis vinifera* L. (tinctoria varieties), Vitaceae

- The term “vine” designates cultivars with black grapes, red pulp, and leaves that turn red in the fall, partially or completely.

- The **dried vine leaf** was the subject of a monograph in the 10th edition of the **French Pharmacopoeia**.

- The pharmaceutical industry also uses **grape seeds**.

**Constituents**
- Anthocyanins (up to 0.3%): 3-O-glycosides of cyanidin and peonidin;
- monocaffeoyltartaric acid, phenylpropanoic acids,
- flavonol glucosides,
- hydrolyzable tannins (esters of glucose and of gallic and dehydrohexahydroxydiphenic acids),
- proanthocyanidins.
VINE

Uses

Vine leaf-based phytopharmaceuticals are traditionally used (orally and topically) to treat
• the functional symptoms of capillary fragility such as ecchymosis and petechiae,
• the subjective symptoms of venous insufficiency such as fullness in the legs, and
• the symptoms of hemorrhoids.
• Topically, they are traditionally used for eye irritation or discomfort of various etiologies (e.g.,
  eye strain, seawater or swimming pool water, or smoky atmospheres).
EUROPEAN ELDER, *Sambucus nigra* L., Caprifoliaceae

- The flower—it is the subject of a monograph in the European Pharmacopoeia.
- The fruit, a source of extracts used as food coloring.

- The European elder is a shrub widespread in western Europe.
- Its bark has small cracks and
- its leaves are imparipinnate.
- Large (20 cm) inflorescences of strong-smelling flowers,
- black berries with their purplish-red juice and three seeds.
- The flower is fairly easy to identify.

- However, to verify the absence, in the drug, of flowers of dwarf elder (*S. ebulus* L)—with red instead of yellow anthers—the French Pharmacopoeia requires a TLC analysis of the flavonoid content of a methanol extract.
- It contains sambunigrin
  cyanogenic glycosides. *S. ebulus* L
EUROPEAN ELDER

Flowers

Constituents
• Flavonoids (>0.8%, Ph. Eur.): rutin, isoquercitrin,
• Derivatives of caffeic acid, free and esterified.
• Triterpenes
• Essential oil
  – smells like muscat grapes, has a pasty consistency,
  – contains fatty acids, 3,7-dimethyl-1,3,7-octatrien-3-ol, linalol, cis-hexenol, and rose oxides, among others.

Uses
Elder flower
• In France it is traditionally used
  – to enhance the urinary and digestive elimination functions,
  – as an adjunct in weight loss programs, and
  – to enhance the renal elimination of water

• In Germany, Comission E indications
  – As a sudorific, causing an increase in bronchial secretion
  – Colds and coughs
EUROPEAN ELDER

Fruits

• Constituents
  – Cyanidin glycosides: 3-O-glucosyl-, 3-O-sambubiosyl-, 3,5-diglucosyl-, and 3-sambubiosyl-5-glucosyl-cyanidins.
  – Flavonoids, acids (citric, malic), saccharides, 0.1 mL/kg essential oil.
  – The seed contain cyanogenic glycosides.

• The ripe fruit,
  – edible fresh or as a jam,
  – is the source of an extract used as food coloring (e.g., to color cherry or pomegranate syrup)

• Traditionally used – in France – for medicinal purposes, for the same indications as the leaf.
Phenoloids in Zingiberaceae family (diarylheptanoids and arylalkanones)
TURMERIC, *Curcuma domestica* Val. = *C. longa* L., Zingiberaceae

- **Perennial** by a rhizome,
- turmeric has **large sheathing leaves** with an elliptic blade and pinnate veins.
- The **flowers** are **yellow**, **gathered into a spike** with bracts, and
- have an **irregular corolla** with a developed **posterior petal**,
- an **androecium** reduced to one fertile stamen and staminodes forming a petaloid label, and
- a **gynoecium** with three carpels.

- **Several cultivars** grown in India, Sri Lanka, Indonesia, China, and Jamaica. For the most part (80%) the world production comes from India.
- Commercial turmeric commonly consists of the ovate primary rhizomes ("bulb" or "round" turmeric), the cylindrical secondary rhizomes ("fingers"), or a mixture of both.
- Fingers: gray and grooved surface and a diameter of about 1 cm.
- Break with a clean fracture, reddish-yellow inside; odor aromatic, taste warm, somewhat bitter.
TURMERIC

Chemical Composition

• Starch (45-55%); arabinogalactans (ukonans)

• Essential oil (2.5 to 6%) rich in monocyclic sesquiterpenes:
  – hydrocarbons: *zingiberene*, - and 6-curcumene; their oxygenated derivatives:
    *turmerone*, S- (+)-ar-turmerone, curlone, α- and γ-atlantone;

• Curcuminoids (can reach 8%):
  – The coloring principles in the drug, structurally related to a diarylheptane,
  – *curcumin* (50 to 60%), desmethoxycurcumin, bisdesmethoxycurcumin, dihydrocurcumin.

![Curcumin](image1.png)

![ar-Turmerone](image2.png)

![(-)-Zingiberene](image3.png)
TURMERIC, Pharmacological Properties

Curcumin

• Its anti-inflammatory activity has been demonstrated in animal experiments and promoted by observations reported in India in man.

• Is apparently devoid of side effects.

• The mechanism of action remains poorly-understood:
  – inhibition of the increase in activity of lysosomal enzymes,
  – effect on the synthesis of prostaglandins, or
  – interference with the response of granulocytes to stimuli linked to the inflammatory phenomenon.

The drug has a definite action on the

– Hepatic parenchyma: the hydroalcoholic extract prevents the cytotoxic effects of carbon tetrachloride in vivo in the mouse and in vitro in cultured rat hepatocytes.

– Stomach: the ethanolic extract (0.5 g/kg in the rat) is active against ulcers and protects cells.
TURMERIC

Uses

• **Food coloring:** turmeric cultivars with the highest curcumin content (e.g., Allepey, > 6.5%).

• **Curcumin (>90%)**:
  – It is a **nontoxic authorized color** (Eur. id. code E100).
  – It is **heat resistant** and scarcely sensitive to changes in pH.
  – It is used as the rhizome powder, or the oleoresin, or extracts and curcumin solutions of variable concentration, sometimes adsorbed onto hydrocolloids.

• **Spice:** Madras (3.5% curcumin) and other cultivars. **Turmeric** is, alongside coriander and other spices, one of the main ingredients of curry powders (these may also contain chili, ginger, clove, fenugreek).

• **Oleoresin** is also used in food technology.

• **In phytopharmaceuticals:** traditionally used
  – as a choleretic and cholagogue,
  – for functional dyspepsia attributed to a hepatic origin,
  – as an appetite stimulant.
  – Biliary tract obstruction is a contraindication (Commission E).
TEMU LAWAQ, *Curcuma xanthorrhiza* Roxb., Zingiberaceae

- Temu lawaq is botanically very close to turmeric, and is a cultivated Indonesian species.
- The rhizome is cut after being harvested, so the drug appears as thin round slices.

### Constituents

- Starch (30-40%),
- Essential oil (up to 12%): rich in sesquiterpenes: zingiberene, ar-curcumene, (R)(−)-xanthorrhizol, turmerones, bisacurones, bisacumol, and bisacurol.
- Curcuminoids (1-2%): curcumin, its monodemethoxylated derivative, and its di-, hexa-, and octahydrogenated derivatives. Monophenolic and non-phenolic analogs have been isolated from rhizomes collected in Thailand.

### Uses

- A traditional folk remedy in southeast Asia: it is used as cholagogue and choleretic.
- In Germany, Commission E:
  - its use acceptable for gastrointestinal symptoms,
  - biliary tract obstruction is a contraindication,
  - prolonged use can cause gastric irritation.
GINGER, *Zingiber officinalis* Roscoe, Zingiberaceae

This *spice*, is used in the oriental traditional medicines, especially for *functional dyspepsia*.

- Originally from India, ginger is cultivated in India, China, and all of southeast Asia (Indonesia, Philippines), and in the tropical regions of Africa (Nigeria).

- Large herbaceous perennial plant,
- lanceolate leaves,
- thick inflorescence with overlapping lateral bracts,
- pale green flowers with purple label.

- The rhizome is ramified within one plane.
- Appearance, depending on the mode of preparation: gray with a wrinkled surface (coated or unscraped), white with a smooth surface (uncoated or scraped), or prepared (preserved).
- Fibrous and granular fracture; odor aromatic, taste warm and pungent.
GINGER

Chemical Composition

• Starch (60%), proteins, fats (10%), from 10 to 25 mL/kg essential oil, and a resin.

• Essential oil (composition highly depends on geographical origin):
  – Sesquiterpene hydrocarbons (30-70%): (—)-zingiberene, (+)-ar-curcumene, (—)-β-sesquiphellandrene, E,E-β-farnesene, β-bisabolene. Monoterpenes aldehydes (citral) and alcohols.

• Gingerols = 1-(3’-methoxy-4’-hydroxyphenyl)-5-hydroxyalkan-3-ones:
  – [3-6]-, [8]-, [10]-, and [12]-gingerols bearing a side chain with 7-10, 12, 14, or 16 carbon atoms, respectively;
  – alongside the corresponding ketones, and dehydration products (shogaols).

• Labdane-type diterpenes, galonolactone and its dialdehyde derivative.
GINGER, Pharmacological Properties

- Used since remote times in India and China.

**Animal experiments:**
- Oleoresin is a cholesterol lowering agent (in rodents),
- [6]-gingerol is a cholagogue (in the rat by the intraperitoneal route),
- [8]-gingerol is a hepatoprotective agent (prevents the toxic effects of carbon tetrachloride in rat hepatocytes).
- The acetone extract and zingiberene have an antiulcer effect in the rat
- The drug has an anti-inflammatory activity (possibly acting on prostaglandin and leukotriene production).

**Human studies** (on antiemetic properties)
- Most trials reveal an activity superior to that of a placebo for motion sickness, post-operative nausea, or morning sickness (at the usual dose of 1 g per day).
- These trial results are divergent; (among the reasons: ginger products used were not standardized).

**Antiemetic action:** may be the consequence of direct effects on the gastrointestinal tract: in the mouse, the stimulation of gastrointestinal motility by the acetone extract (75 mg/kg), by [61]-shogaol (2.5 mg/kg), or by gingerols is comparable to that of metoclopramide (10 mg/kg).

- Other authors, however, noted the lack of effect of ginger powder on the rate of gastric emptying in healthy humans.
- The drug is not toxic and has no side effects.
GINGER

Uses

• Used (especially for functional dispepsia) for over 25 centuries in the formulation of countless traditional Oriental remedies (China, Japan).

• **In France**, in phytomedicines: traditionally used **for motion sickness**.

• In Germany: the rhizome powder is used for gastrointestinal distress and to prevent motion sickness (2 g/day).

• Commission E:
  
  – Ginger is a spasmolytic in animals
  
  – in humans, it has antiemetic, positive inotropic, and stimulant effects (intestinal peristalsis, salivary and gastric secretions).
  
  – Ginger must not be used to prevent morning sickness in pregnant women.
KAVA, *Piper methysticum* Forst. f., *Piperaceae*

- *P. methysticum*, a pepper tree which grows in the islands of western Polynesia (Papua New Guinea, Tonga, Samoa, Fiji, Vanuatu) and as far as Tahiti.

- A perennial dioecious subshrub with
- cordate leaves.
- Decaploid and sterile.
- Multiplies by vegetative propagation.

- The term kava designates a beverage prepared by soaking in water the rhizome or root fragments, after grinding them with a pestle or chewing them.
- It has been consumed for centuries according to a ceremonial described in 1875 by Captain Cook.
- This ritual beverage induces a sensation of well-being.
- It continues to play an important role in the culture of that part of the globe.
KAVA

Constituents

- Mono- or di-unsaturated α-pyrones, substituted by a styryl or phenethyl group, itself substituted (methoxyl, methylenedioxy) or not.
  
  - They include yangonin, (+)-methysticin, (+)-dihydromethysticin, (+)-kawain, (+)-dihydrokawain, demethoxyyangonin, and minor products (e.g., dehydrokawain, 7,8-dihydroxyyangonin, 10- and 11-methoxyyangonins).

- Resin content can fluctuate from 3 to 20% depending on cultivars and location (rhizome, lateral roots) and its composition varies with the chemotype.
KAVA, Pharmacological research

- The *pyrones*
  - *induce sleep* in rodents (per os) and *are sedatives* in rodents, cats, and rabbits.
  - cause *muscle relaxation* and several are *anticonvulsant* (strychnine, electroshock).
- The *kavapyrones* (DHK, DHM) are analgesics and weak local anesthetics.
- The *aqueous extract* and the *lipid-soluble fraction* decrease spontaneous movement, but
- the (mild) sedation induced by the aqueous extract is not accompanied by a loss of muscular tone;
- the resin induces sleep, but the aqueous extract does not (mouse, IP).
- *Kava* and *kawain* *induce sleep* by *acting on the limbic system* (EEG in cats)
- *Klinical trials* indicated that a *kava extract* is more *efficacious* than a placebo in patients who suffer from *non-psychotic anxiety*. 
KAVA, Uses

• In Germany, pharmaceuticals based on standardized extracts (i.e., 35-120 mg kavapyrones) were promoted as sleep disorder and anxiety medicines.

• Nowadays their application is contraindicated due to the

• hepatotoxic adverse reactions reported in association with the use of all types of kava products in the South Pacific Islands, Australia, Europe, and the US.

• It appears that poor quality of the kava material was responsible for the liver toxicity.

• Therefore, a sophisticated approach to establish kava quality standardizations is needed for safe human use of kava as
  – relaxing traditional beverages,
  – the anxiolytic drugs, and
  – recreational dietary supplements.