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)

\[
\begin{align*}
R_1 = R_2 = H: & \text{ Pelargonidin} \\
R_1 = \text{OH}, R_2 = H: & \text{ Cyanidin} \\
R_1 = \text{OCH}_3, R_2 = H: & \text{ Peonidin} \\
R_1 = R_2 = \text{OH}: & \text{ Delphinidin} \\
R_1 = \text{OCH}_3, R_2 = \text{OH}: & \text{ Petunidin} \\
R_1 = R_2 = \text{CH}_3: & \text{ Malvidin}
\end{align*}
\]
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.

• The most common anthocyanins are 3- monosides and 3,5-diglycosides. Also known are 3,7-diglycosides and triglycosides (for example 3,5,3’-triglycosides).

• 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 phenyipropanoic 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**: neutral: blue
- **Carbinol pseudobase**: colorless
- **Dilution with water**: red (pH < 3)
- **Pine cone forms**: (pH 4-6)

**Structural transformation of anthocyanins in aqueous solution**

*Shown for pelargonidin 3,5-diglucoside*
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 **unstable in** neutral or alkaline medium.

• They are **generally extracted with an alcohol** (methanol, preferrably 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**.
  – The oldest procedura is an extraction in aqueous medium in the presence of 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: obtained extracts are either 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. 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**.
**Vaccinium macrocarpon**

- 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 delphinidin 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.
• The composition of this essential oil 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, Commission 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-saqmbubiosyl-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.
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, \((R)(-)-(\ldots)\)-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. Monoterpane 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-dihydroyangonin, 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)
- Clinical trials indicated that a kava extract is more efficacious than a placebo in patients who
  suffer from non-psychotic anxiety.
- 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.