Chief drugs containing phenylpropanoids include sources of essential oils whose major constituents are allyl- and propenylphenols (e.g., essential oils of clove, sassafras or Apiaceae): their structures and the biological properties that some of them impart to the drugs containing them will be indicated in the corresponding chapter (see essential oil-containing drugs). In addition, esters of gallic acid and glucose (i.e., hydrolyzable tannins), since they have physico-chemical and biological properties similar to those of condensed tannins, will be studied together (see tannin-containing drugs).

Accordingly we shall cover: first, simple phenols and phenolic acids, then balsams, coumarins, and lignans; and second, chain elongation products of phenylpropane.

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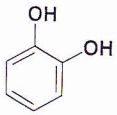
Phenols and Phenolic Acids

1. GENERALITIES

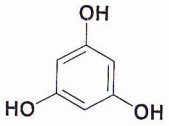
The term phenolic acid applies to all organic compounds with at least one carboxyl group and one phenolic hydroxyl group. However the current practice among phytochemists is to reserve this term to benzoic and cinnamic acid derivatives only. Some authors are even more restrictive: they call phenolic acids only compounds having a C_6-C_1 unit, and include cinnamic derivatives in the larger group of phenylpropanoids.

Because their chemical and analytical properties are not very different, and because their pharmacological interest is relatively limited, we shall present benzoic (C_6-C_1) and cinnamic (C_6-C_3) derivatives in the same chapter.

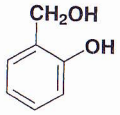
Simple Phenols. Simple phenols (e.g., catechol, guaiacol, phloroglucinol) seldom occur naturally, except for hydroquinone which is found in several families (including Ericaceae and Rosaceae), most often as the glucoside of the diphenol (arbutin) or of its monomethyl ether. Alkylphenols and their depsides arise from the metabolism of a polyketide and are characteristic of Lichens. Also known are a few alkenylphenols (urushiol) and phenolic monoterpenes (thymol).



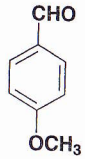
Catechol



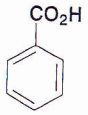
Phloroglucinol



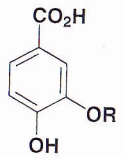
Salicylic alcohol



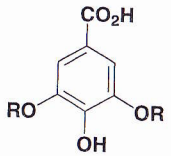
p-Anisaldehyde



Benzoic acid

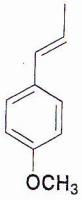


R = H, *Protocatechic acid*
R = CH_3, *Vanillic acid*

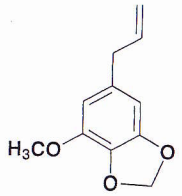


R = H, *Gallic acid*
R = CH_3, *Syringic acid*

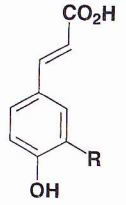
Homogentisic acid



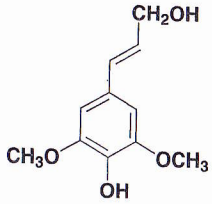
E-Anethole



Myristicin



R = H, *4-Coumaric acid*
R = OH, *Caffeic acid*
R = OCH_3, *Ferulic acid*



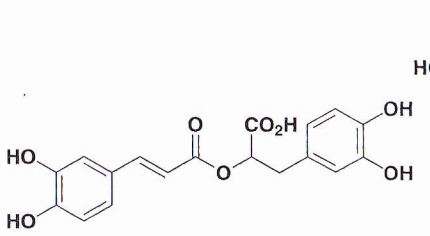
Sinapyl alcohol

Phenolic Acids Derived from Benzoic Acid. C_6-C_1 Phenolic acids that are hydroxylated derivatives of benzoic acid are quite common in the free state, as well as combined into esters or glycosides. Gallic acid and its dimer (hexahydroxydiphenic acid) are constituents of hydrolyzable tannins.

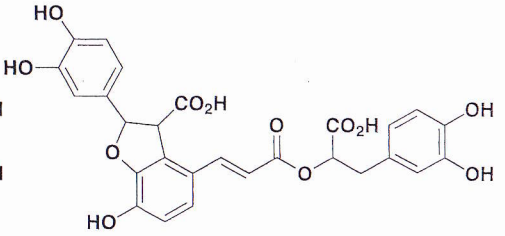
Also known are the aldehydes corresponding to these acids: vanillin (the most widespread), anisaldehyde (in some essential oils), and salicaldehyde, among others.

Phenolic Acids Derived from Cinnamic Acid. Most C6-C3 phenolic acids (4-coumaric, caffeic, ferulic, sinapic acids) are very widely distributed; others (2-coumaric) are uncommon. They occur rarely in the free state, except as extraction artefacts, and are very often found esterified:

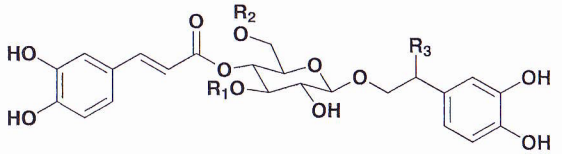
- esters of aliphatic alcohols (mono- and dicaffeoyltartaric acids of Vitaceae or of *Orthosiphon stamineus*, feruloyltartaric acid of *Echinacea* and of other Asteraceae, and caffeoylmalic acid of *Parietaria officinalis*, to name only a few);
- esters of quinic acid (chlorogenic acid, widely distributed) and depsides (rosmarinic and lithospermic * acids), specific to the Lamiaceae and Boraginaceae.



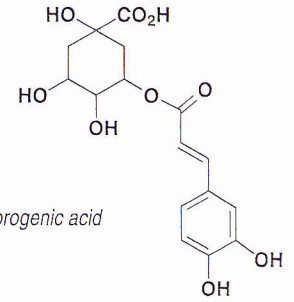
Rosmarinic acid



Lithospermic acid



R_1 = rha, R_2 = R_3 = H, Verbascoside
R_1 = glc, R_2 = R_3 = H, Plantamajoside
R_1 = glc, R_2 = H, R_3 = OH, Hellicoside
R_1 = R_3 = H, R_2 = rha, Forrsythiaside
R_1 = rha, R_2 = glc, R_3 = H, Echinacoside
R_1 = R_2 = rha, R_3 = H, Poliumoside



Chlorogenic acid

* Lithospermic acid (formally a neolignan!) has been described as a caffeic acid trimer [Kelley, C.J. *et al.* (1975). *J. Org. Chem.*, **40**, 1804-1815]; recently, the same name was used to designate a tetramer, namely lithospermic acid B, isolated from *Salvia miltiorrhiza* as Mg, and K and NH4 lithospermates (see Tanaka, T. *et al.* (1989) *Chem. Pharm. Bull.*, **37**, 340-344). Isomeric tetramers (unnamed) of unspecified stereochemistry have also been isolated from *Orthosiphon aristatus*: see Sumaryono, W. *et al.* (1991) *Planta Med.* **57**, 176-180.

They can also be amides (spermidine, tyramine, or putrescine derivatives), or combinations with sugars: glucose esters (most commonly) or glucose ethers (especially in the Apiaceae and Brassicaceae).

Note also that these acids frequently esterify the hydroxyl groups of many secondary metabolites: flavonoids, anthocyanins, alkanols, saponins, and even, although less commonly, alkaloids.

Glycosidic Phenylpropanoid Esters. Another group of phenylpropanoid derivatives consists of phenylpropanoid esters of a glycoside comprising an oligosaccharide (di- or trisaccharide) and a dihydroxyphenylethanol molecule. The phenylpropanoic acid is, most of the time, caffeic acid, although compounds have been isolated (for example from plantains) in which it is *p*-coumaric or ferulic acid instead. Similarly, the dihydroxyphenylethanol can be engaged in an ether linkage, or, in rare cases, hydroxylated at C-2: 2-(3',4'-dihydroxyphenyl)-1,2-dihydroxyethane.

These compounds are mostly found in gamopetalous plants, especially in the Lamiales, Oleales, and to a lesser extent, in the Asterales.

2. PHYSICO-CHEMICAL PROPERTIES, CHARACTERIZATION, AND EXTRACTION

In general, phenols are soluble in polar organic solvents; they are soluble in sodium hydroxide and carbonate solutions. Phenolic acids are solubilized by bicarbonates; they can be extracted with organic solvents in slightly acidic conditions. The glycosides of these phenolic compounds are, classically, soluble in water.

All of these compounds are unstable. All phenols are readily oxidized, especially in alkaline conditions. Cinnamic derivatives tend to isomerize (*E*/*Z*) in aqueous solution under UV. Cinnamic esters of hydroxyacids (e.g., caffeoylquinic acid) readily isomerize in acidic or alkaline conditions and yield mixtures of positional isomers (chlorogenic acids).

The analysis of simple phenolic compounds from a plant is commonly carried out by TLC, or by GC (following silylation), HPLC, or both. The TLC solvents are mixtures which contain an acid most of the time (acetic, formic) and the TLC plates are coated with cellulose or silica gel or a mixture of the two. The spots are visualized using general reagents for phenols (ferric chloride, vanillin and hydrochloric acid, 2,6-dichloroquinone chlorimide in alkaline conditions) or using more specific reagents (e.g., 2,4-dinitrophenylhydrazine for aldehydes). The analytical method of choice is HPLC. In general it is carried out on reverse phases (e.g., C_{18}) and eluted with mixtures of water, alcohols (or acetonitrile or both) and acids (to limit ionization).

These compounds are generally extracted, preferably from fresh plant material, with an alcohol, or alternatively, to extract less lipophilic substances and avoid partial esterification of the phenolic acids, with an alcohol and water mixture. Considering the fragility of these molecules, it is best to work in an inert atmosphere, to avoid extreme pHs, and to concentrate the extracts at low temperature (30°C). Back extraction of the aqueous solution with nonmiscible solvents of increasing polarity separates compounds in the free state, esters, and glycosides.

Separation of the constituents of mixtures can be achieved by classic chromatographic techniques on polyamide, cellulose, silica gel, or, in the case of phenylpropanoic esters, on gels and on ion exchange resins.

3. PHARMACOLOGICAL APPLICATIONS AND USES

The physiological or ecological role of these molecules is little understood. Their therapeutic interest is very limited: urinary antiseptic properties of arbutin, and anti-inflammatory properties of salicylates. The properties that tradition attributes to drugs such as rosemary or artichoke, are said to be due, in part, to esters of cinnamic derivatives; however, pharmacological data are limited, and clinical trials are either nonexistent or of questionable methodology. The only drugs in this group that are currently utilized are commonly used crude, or as simple galenical preparations (powders, extracts, tinctures).

Glycosidic phenylpropanoid esters have interesting pharmacological potential. Some are enzyme inhibitors: cAMP phosphodiesterase inhibition (forsythiaside, plantamajoside), aldose reductase inhibition (verbascoside = acteoside). Verbascoside, forsythiaside, and their homologs inhibit 5-lipoxygenase in human granulocytes, as well as in rat peritoneal cells; as a result, the formation of hydroperoxides and leukotrienes is inhibited, and this may be the basis of the use, in traditional oriental medicine (China, Japan), of *Forsythia* fruits for the treatment of inflammatory or allergic diseases (*Lianqiao*, *F. suspensa* (Thunb.) Vahl., Oleaceae). Several compounds in this series have antibacterial and antifungal properties, particularly against phytopathogenic organisms.

4. SIMPLE PHENOL-CONTAINING DRUGS

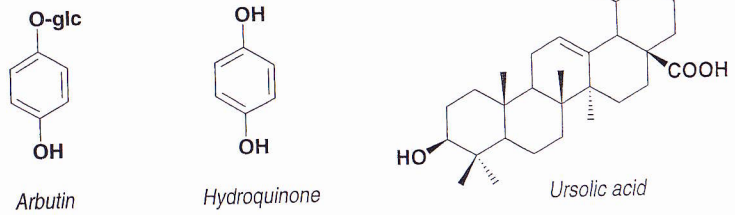
• BEARBERRY, *Arctostaphylos uva-ursi* (L.) Spreng., Ericaceae

Dried bearberry leaf, entire or in fragments (Eur. Ph., 3rd Ed.) is traditionally used to treat urinary tract infections.

The Plant, the Drug. Bearberry, whose Latin name uva-ursi means bear's grape, is a small shrub growing in the mountains of the northern hemisphere, with creeping stems, leaves entire and indeciduous, bell-shaped pinkish-white flowers, and bright red globose berries which are edible. The leaf blade is coriaceous, attenuate at the base, on a short petiole, and obtuse or retuse at the tip (retuse =

rounded with a shallow notch down the middle); the glossy, grainy, dark green upper side and the lighter underside have a network of fine pinnate veins.

Chemical Composition. The active principles are phenolic glycosides, represented by arbutin (6-10%) and methylarbutin. Upon hydrolysis, arbutin releases a diphenol which is immediately oxidized to hydroquinone. Note the presence of a substantial quantity of gallotannins derived from pentagalloylglucose (15-20%). Flavonoids, triterpenes, monotropein (an iridoid), and picein (a glycoside of 4-hydroxy-acetophenone) have also been characterized in the drug.



Arbutin *Hydroquinone* *Ursolic acid*

Tests. The European Pharmacopoeia requires verifying the identity by microscopic examination of the pulverized leaf and by TLC of an aqueous and methanolic (50:50 v/v) extract: hydroquinone, arbutin, and gallic acid are visualized by spraying with dichloroquinonechlorimide and sodium carbonate. The quantitation includes an aqueous extraction of phenolic glycosides, the formation of a quinone-methide by reaction of hydroquinone (formed in oxidizing alkaline conditions: NH_4OH, potassium ferricyanide) with aminopyrazolone, and a colorimetric estimate of the quinone-methide after chloroform extraction. The dried drug must contain not less than 8% hydroquinone derivatives, expressed as anhydrous arbutin.

Pharmacological Properties and Uses. Experiments in the rat show that hydroquinone (whose bacteriostatic properties have been demonstrated *in vitro*) is excreted in urine after conjugation as glucuronide and sulfate. In order for the antiseptic activity to occur, the urine must be alkaline (to allow hydrolysis of the conjugates) and the hydroquinone concentration sufficient (>60 µg/mL). The diuretic activity has been shown by some authors and questioned by others. Hydroquinone is toxic at high doses (i.e., 1 g).

In the absence of clinical trials, bearberry-based medications may claim the following indications [French Expl. Note, 1998]: "traditionally used as adjunctive therapy in the diuretic treatment of benign urinary disorders, and to enhance the renal excretion of water (oral route)". Phytotherapy normally uses the infusion, although some authors prefer cold maceration which produces a preparation less rich in tannins.

The German Commission E monograph lists indications of the same type (inflammation of the urinary tract) and specifies that bearberry leaf can cause nausea in persons with a delicate stomach. Bearberry leaf is contraindicated

in pregnant and breast-feeding women. It must not be used in children under 12 years of age. Bearberry-based preparations must not be taken at the same time as substances that can potentially acidify the urine (this would diminish the antibacterial effect). The treatment (3g/150 mL of water, 4 times per day) must not be prolonged beyond one week or administered more than 5 times per year without medical advice.

OTHER ERICACEAE. The French Explanatory Note of 1998 allows the same indications for phytopharmaceuticals based on the flowers of twisted heath (*Erica cinerea* L.) or on the flowering tops of Scotch heather (*Calluna vulgaris* (L.) Hull. = common heather). Note however that these drugs contain no arbutin (twisted heath) or else very little (Scotch heather); they contain, among others, proanthocyanins and numerous flavonoids. In Germany, the usefulness of Scotch heather is deemed insufficiently substantiated to justify therapeutic use; however, it may be used in mixtures.

HYDROQUINONE. Hydroquinone and its derivatives (e.g., monomethylhydroquinone = mequinol) are inhibitors of melanin synthesis. Therefore, they are used in the composition of pharmaceuticals indicated for the treatment of melanin hyperpigmentation such as scar tissue hyperpigmentation, melasma, chloasma (the mask of pregnancy), freckles, and senile lentigines (age spots). In addition, French regulations allow up to 2% hydroquinone in cosmetic products. The inhibitory action of hydroquinone on melanin synthesis appears to be spotty and can induce unwanted cosmetic effects such as melanoleukoderma (marbled skin) and depigmentation at a distance from the treated areas. For these reasons it is best to limit treatment to small areas, to avoid repeated or prolonged applications, and to avoid exposing the treated areas to sunlight. In Africa, the use of depigmenting products—hydroquinone, corticosteroids, mercury salts—is increasingly popular * in some cities. Side effects are frequently observed, especially because some of the available products are very concentrated (e.g., ointment with 5% hydroquinone). Arbutin has the same skin bleaching properties as hydroquinone. In tests conducted on cultured melanocytes, it inhibits the production of melanin, probably by competing for the binding site of tyrosine on tyrosinase (the enzyme that converts tyrosine into dopaquinone). The cosmetics industry is developing, in addition to novel galenical forms of hydroquinone and less aggressive formulations, products based on arbutin or on extracts of plants rich in arbutin, particularly leather bergenia, *Bergenia crassifolia* (L.) Fritsch (Saxifragaceae). A product based on *Mitracarpus* sp., Rubiaceae has also been marketed; it contains a naphtho[2,3β]pyran diglycoside dihydroxylated at C-1and C-10 (harounoside).

* But also in Europe. Networks for the illicit trafficking of skin bleaching products were dismantled in Paris in 1997. See: Amar, A. (1997). Les produits blanchis[illegible]

5. PHENOLIC ACID-CONTAINING DRUGS

Warning. The decision to include in this chapter drugs such as rosemary, big-flowered Java tea, or the European goldenrod is arbitrary, and is dictated only by the presence, in these drugs, of substantial quantities of phenolic acids. Actually, in most cases, the substances responsible for the activity attributed to these drugs are not known with certainty.

A. Caffeic Acid Derivative-containing Drugs

- **ARTICHOKE,**
  Cynara scolymus L., Asteraceae

The artichoke "radical leaf, whole or reduced to fragments of variable size, and dried" is listed in the 10th edition of the French Pharmacopoeia. It is used for its choleretic properties.

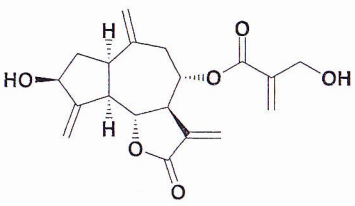
The Plant, the Drug. The artichoke is a large herbaceous perennial plant, with a rosette of pinnatisect leaves, with prominent veins, but not spiny (in contrast to cardoons). The flowers (which appear in the second year) are grouped in big capitulums of 10-15 cm in diameter, borne by hardy ramified grooved stems, with sessile and almost entire leaves. The flowers are violet, tubulous, and inserted on a fleshy receptacle surrounded by bracts which are fleshy at the base and not spine-tipped. The receptacle and the base of the bracts constitute the edible part of this vegetable.

This species is an improved cardoon unknown in the wild and only cultivated. To fulfill pharmaceutical needs, the first-year rosette of leaves is preferred and is harvested from plants produced especially for this purpose. The leaves are either expressed to produce a juice to be concentrated and purified for the preparation of various extracts, or cut into small fragments and rapidly desiccated.

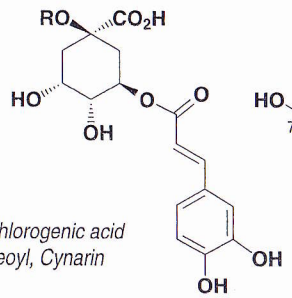
When dried under good conditions (ample ventilation, low temperature) the drug retains its original colors: greenish-gray top side and whitish underside. The microscopic examination reveals the presence of three types of uniseriate covering trichomes, with the most abundant ones comprising a short stalk and a terminal cell shaped like a long and sinuous fiber.

Chemical Composition. The active constituents are said to be phenolic acids and phenolic alcohols. The former are esters of caffeic acid (1%): 5-caffeoylquinic acid (or chlorogenic acid) and 1,5-dicaffeoylquinic acid (= cynarin) in the fresh drug. The latter are commonplace: malic acid (0.8% of the dried drug), and succinic, lactic, fumaric, and citric acids (in the free state?). The drug also contains sesquiterpenoid lactones (cynaropicrin and derivatives) responsible for its strong bitterness and up to 1% flavonoids, which are glycosides of luteolin (7-glucosyl-, 7-gentiobiosyl-, 7-

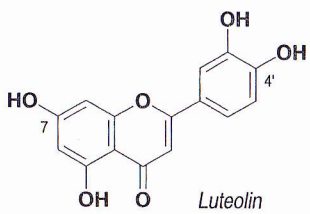
acid composition varies as a function of the extraction procedure because of the potential hydrolysis and transesterifications in aqueous medium.



Cynaropicrin



R = H : Chlorogenic acid
R = Caffeoyl, Cynarin



Luteolin

Tests. The characterization of flavonoids (positive cyanidin reaction) completes the macro- and microscopic identification of the drug. The assay per se includes, in addition to general tests (ashes <15%, water <8%), TLC analysis of a tincture in 60% alcohol, which reveals caffeic derivatives.

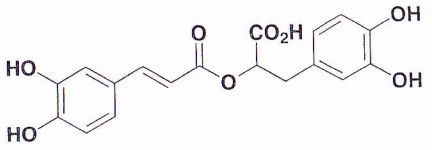
Pharmacological Activity and Uses. The artichoke leaf is a drug known since remote times as a choleretic. Experimentally, 1,5-dicaffeoylquinic acid displays a clear activity on the biliary flow rate in the rat, and *in vitro*, it protects rat hepatocytes against carbon tetrachloride toxicity. Other experiments in the rat show that the mixture of alcohol acids acts as a choleresis regulator (referred to in French as *amphocholérétique*) and that extracts lower blood cholesterol. The antioxidant potential of the aqueous extract has been shown on cultured hepatocytes. In humans, several studies published since the late 1970s report marked decreases in blood cholesterol and triglycerides upon administration of artichoke extracts. They also show, in comparison with a placebo, a clear increase in the biliary flow rate into the duodenum. The fact that there are contradictory data highlights the need for further research.

The tincture, fluid extracts, nebulisates, and other forms are used in proprietary drugs for their choleretic activity. In the opinion of many pharmacologists, the liver disorders that respond to cholagogues and choleretics originate solely from irritations of the gastric mucosa, in which case the purpose of increasing bile secretion or stimulating gallbladder contraction is not clear. Others reason that increased bile acid secretion stimulates intestinal motility and the digestion of fats, hence the beneficial effects on any dyspepsia that is not related to an ulcer and on intestinal "irritation". These comments apply to cholagogues and choleretics as a class, nevertheless artichoke leaf preparations are highly prized. They are traditionally used to enhance urinary and digestive elimination functions, as a choleretic or cholagogue, and to enhance the renal elimination of water [orally, French Expl. Note, 1998]. In general, medications that combine several cholagogues and choleretics (boldo, rosemary, combretum, mineral salts) should not be used in case of bile duct obstruction (a contraindication in Germany). Patients allergic to Asteraceae are at risk for an allergic reaction [...]

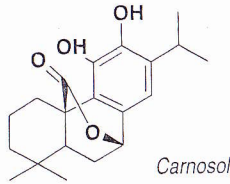
ROSEMARY, *Rosmarinus officinalis* L., Lamiaceae

This bushy shrub with sessile, persistent, opposite, linear, and coriaceous leaves, curled on the edges, grainy on the upper side, tomentose on the underside. The pale blue or light lilac flowers are spotted with purple and grouped in spiciform inflorescences. Rosemary is very common in all of the Mediterranean basin. Used for the production of essential oil and used in phytotherapy, it is also of interest to food technologists because its diterpenes are antioxidants.

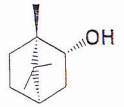
***The Drug*: *Composition*.** The drug (dried flowering tops, Fr. Ph., 10th Ed.) contains 10 to 25 mL/kg of an essential oil in which the chief constituents are camphor, cineole, α-pinene, borneol, and camphene, in proportions that vary with the source and the vegetative stage (see p. 539). Phenolic compounds are represented by flavonoids (glycosides of luteolin, of diosmetin, and of flavones methoxylated at C-6, C-7, or both) and by phenolic acids, particularly by derivatives: caffeic, chlorogenic, and rosmarinic acid. The latter is an ester of caffeic acid and α-hydroxydihydrocaffeic acid. Rosemary is also characterized by the occurrence of tricyclic diterpenes, e.g., carnosolic acid and carnosol (major compounds), rosmanol, epirosmanol, isorosmanol, rosmaridiphenol, rosmari-quinone, rosmadial, and triterpenes (ursolic and oleanolic acid, amyrins).



Rosmarinic acid



Carnosol



Borneol

Tests. Rosemary is identified by macro- and microscopic examination (powder: pluricellular ramified covering trichomes, 8-cellular glandular trichomes, free or attached to epidermis fragments with sinuous cells). The essential oil content is ≥ 15 mL/kg (Fr. Ph.); TLC analysis reveals not less than six distinct spots, corresponding in particular to cineole, borneol and its acetate.

Pharmacological Activity. Rosemary's reputation for being choleretic is only partially confirmed by animal experimentation (tincture, IV, 1-2 g/kg!). It is also a diuretic. Experiments using the aqueous extract of the drug on cultured hepatocytes demonstrates its protective action against the peroxidizing effects of *tert*-butyl hydroperoxide. The spasmolytic activity of the extracts is attributed to the essential oil—primarily borneol. The essential oil is an antibacterial and antifungal *in vitro*. Rosmarinic acid is an anti-inflammatory (carrageenate-induced edema, rat, IV, 1 mg/kg); it is thought to inhibit the activation of complement factor C3. The [...] obtained using supercritical carbon dioxide

or other methods) has been shown on different experimental models and with various food products (lipids, meats, cold cuts). This activity is in part linked to rosmarinic acid, but mostly due to diterpenoid *o*-diphenols, whose efficacy is superior to that of synthetic antioxidants currently in use.

Uses. In France [Fr. Expl. Note, 1998], rosemary is traditionally used, *per os*: 1. for the symptomatic treatment of gastrointestinal disturbances (epigastric bloating, impaired digestion, eructations, flatulence); 2. to enhance urinary and digestive elimination functions; 3. as a choleretic or cholagogue. Topically, it is traditionally used to clear nasal passages and for the common cold, and as a mouthwash for oral hygiene. In Germany, the Commission E monograph requires package inserts to mention the following indications: 1. flatulence, bloating, mild gastrointestinal and biliary cramps (orally); 2. adjunctive treatment of rheumatic ailments (topically). Pregnancy is a contraindication.

Rosemary extracts are used in food technology as antioxidants and preservatives. Upon "dearomatization", the extracts move from the European category of "flavors" to that of "additives", therefore they must undergo safety testing before they are approved.

• ORTHOSIPHON = BIG-FLOWERED JAVA TEA, *Orthosiphon aristatus* (Blume) Miq. (= *O. stamineus* Benth. = *O. spicatus* Backer), Lamiaceae

The drug consists of the leaf and stem apex as dried fragments (Eur. Ph., 3rd Ed., 1998 add.).

The Plant, the Drug. This Lamiaceae grows wild in southeast Asia and is imported from Indonesia to Europe. It is a perennial plant with opposite and irregularly dentate leaves. The flowers are white or lilac and have exsert stamens twice as long as the tube of the corolla (hence the French vernacular name "cat's whiskers" or *moustache de chat*). The leaf is brittle; it has a short quadrangular petiole and an oval to diamond-shaped blade, cuneiform at the base, dark on the upper side, lighter and slightly pubescent on the underside. The veins are pinnate. The principal veins and the petiole are most often purplish.

Chemical Composition. The drug contains substantial quantities of potassium salts (3%), diterpenes derived from pimarane (orthosiphols A-E), triterpenes, less than 0.5 mL/kg of an essential oil rich in sesquiterpenoid hydrocarbons, and about twenty phenolic compounds. These include lipophilic flavones (0.43% as determined by HPLC: sinensetin [0.19%] and other di-, tri-, and tetramethylated derivatives) and caffeic esters: rosmarinic acid (45% of total phenols extractable in hot water), mono- and dicaffeoyltartaric acids (38% of total phenols), and derivatives of lithospermic acid (8%). The presence of a benzopyran derivative (4%) could not be confirmed.

Pharmacological Activity and Uses. Apparently this drug has not been studied substantially from the pharmacological point of view. One study, however, reported significant activity of the aqueous extract on ion excretion (in the rat, *per os*). This activity might be compared with the known effects of lithospermates on renal function (see footnote * p. 241, and *Salvia miltiorrhiza* monograph, "diterpenes" chapter, p. 653). The lipophilic flavonoids inhibit 15-lipoxygenase and are weak free radical scavengers *in vitro*. There are no clinical data to confirm the properties attributed to this drug.

In France, the leafy stem of *Orthosiphon* is traditionally used *per os* to enhance urinary and digestive elimination functions, to facilitate the renal excretion of water, and as an adjunct in weight loss programs [French Expl. Note, 1998]. In Germany, the drug is reputed to be a diuretic and a weak spasmolytic. It is used, with suitable fluid intake, for inflammation, urinary tract infection, and renal lithiasis.

B. Salicylic Acid Derivative-containing Drugs

• QUEEN-OF-THE-MEADOW, *Filipendula ulmaria* (L.) Maxim., Rosaceae

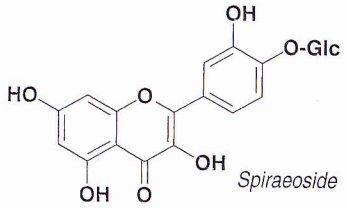
This species is the subject of two monographs in the latest edition of the French Pharmacopoeia: flowering tops and dried flowers. In folk medicine, it has found use as a diuretic and to treat rheumatism.

The Plant, the Drug. The queen-of-the-meadow or meadowsweet is a herbaceous perennial plant. The stem is erect, angular, hollow, grooved, and marbled with red, and bears alternate leaves with angular stipules, with 3-9 pairs of folioles whose color varies with the subspecies (ssp. *ulmaria* and ssp. *denudata* [J. and C. Presl.] Hayek). The flowers are yellowish-white and grouped in irregular corymbs. They have five pubescent sepals, 20-40 exsert stamens, 5 flared petals, and a helicoidal gynoecium and fruit.

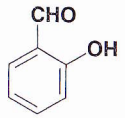
Chemical Composition. The drugs are mainly from eastern and central Europe. They chiefly contain flavonol glycosides (spiraeoside, rutin, hyperin, 1-3% in the flowering tops and up to 6% in the flowers), tannins (10 to 20%, gallic and hexahydroxydiphenic esters of glucose, rugosin D), and glycosides of phenolic acids, which are xyloglucosides of methyl salicylate (monotropitoside) and of salicylaldehyde. Steam distillation of the drugs yields an essential oil containing, among others, methyl salicylate and salicylaldehyde, with the latter being by far the major component in the essential oil of the flowers.

Test. The assay includes a search for foreign matter, especially for leaves in the flowers (<2%) and for large stems in the flowering tops (<1%), and an estimate of the concentration of substances that can be steam distilled (>1 mL/kg for the flowering tops; >2 mL/kg for the flowers), as well as their TLC analysis: methyl

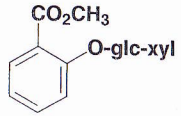
Uses. In the absence of properties truly demonstrated in humans and on the basis of limited animal experimentation (and due to the presence of salicylates), phytotherapeutic products containing queen-of-the-meadow may claim the following therapeutic indications in France [*per os*, French Expl. Note, 1998]: traditionally used for fever and flu-like symptoms, and as an antalgic (headaches, toothaches); for the symptomatic treatment of minor pains in the joints (orally and topically); to enhance urinary and digestive elimination functions; and to enhance the renal elimination of water. In Germany, the drug is used for colds, including those with fever, and to promote urinary elimination. It is to be avoided in case of salicylate idiosyncrasy.



Spiraeoside



Salicylic aldehyde



Monotropitoside

METHYL SALICYLATE. This ester is by far the major constituent of "wintergreen oil", an essential oil generally obtained from the leaves of a shrub from the eastern United States and Canada, *Gaultheria procumbens* L. (Ericaceae), in which it occurs as the monotropitoside. It is also prepared from the bark of *Betula lenta* L. (Betulaceae) and other species in the genus *Gaultheria* (for example, *G. fragrantissima*). Used in North America in the formulation of oral hygiene, cosmetic, and external pharmaceutical products, and as a food flavoring, it is often replaced by synthetic methyl salicylate. Whether natural or synthetic, it is often responsible for intoxications with the same symptoms as salicylate intoxication: 1 mL of methyl salicylate is equivalent to 1.4 g of acetylsalicylic acid, and the quantities ingested are sometimes greater than 10 mL.

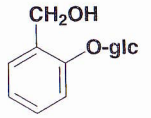
• WILLOW, *Salix alba* L. and other species in the genus, Salicaceae

The various *Salix alba* subspecies (*alba* L., *cærulea* [Sm.] Rech. *fil.*, *vitellina* [L.] Arcangeli) and other willows (*purpurea* L., *fragilis* L., and more) are dioecious trees common in damp regions all over Europe. Official in Germany (DAB 10) and listed in the 1990 BHP, willow bark does not appear in the French Pharmacopoeia, but it is listed in Annex I of the French Explanatory Note of 1998.

Willows are exploited for their bark, which is rich in phenolic compounds and easy to identify by TLC and HPLC: proanthocyanidin dimers and trimers, flavonoids (1-4%, flavanones), and glycosides of phenols and of phenolic acids (from 1 to 11% depending on the species, the source, and the age of the tree). Salicin (glycoside of salicyl alcohol) occurs alongside salicortin and their benzoyl

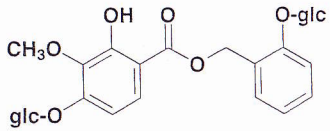
(triandrin, vimalin). The salicortin-type derivatives are thermolabile and are partially converted to salicin if the drug is dried at high temperature. Practically all authors agree to link the anti-inflammatory properties traditionally attributed to the drug to salicylic acid, which arises by oxidation of salicyl alcohol, formed upon intestinal hydrolysis of salicin, itself either native or produced by the slow degradation of salicortin. This slow degradation may explain why the drug activity is more prolonged than that of pure salicylic acid. Nevertheless Tyler * shrewdly noted that the bark doses in use are probably insufficient to be efficacious.

Willow bark is traditionally used orally for fever and flu-like symptoms, and as an antalgic (headaches, toothaches); it is used orally and topically for the symptomatic treatment of minor pains in the joints. The German Commission E monograph specifies that willow bark is used for fever, rheumatic disorders, and headaches.



Salicin

Salicortin



Leiocarposide

C. Other Phenolic Acid-containing Drugs

• EUROPEAN GOLDENROD, *Solidago virgaurea* L., Asteraceae

Tradition attributes diuretic properties to the flowering tops (Fr. Ph., 10th Ed.) of this Asteraceae. There are no data to unequivocally attribute this activity to any particular substance.

The Plant. The European goldenrod is a tall (1 m) perennial herb, common in all of Europe, with a round purplish-red stem, with yellow flowers in radiating capitulums gathered in oblong panicles, and with capitulum bracts shiny on the underside. The disk-flowers are tubular with sepals bordered with silken hairs and the ray-flowers are pistillate only and have a broad ligule. Microscopic examination—of trichome structure in particular—allows one to distinguish the most common species within the genus, often used in place of *S. virgaurea*, especially in Germany (*gigantea* Aiton [incl. subsp. *serotina* (Kuntze) Cronquist],

* Tyler, V.E. (1994). Herbs of Choice. The Therapeutic Use of Phytomedicinals

canadensis L.). The drug assay includes TLC analysis of an aqueous and methanolic extract to characterize flavonoids and phenolic acids.

Chemical Composition. Several categories of metabolites are represented in the drug: tannins, essential oil, diterpenes, flavonoids (1.5-2% including about 20 glycosides identified so far), saponins with an acidic triterpenoid aglycone (virgaureasaponins I and II and other bidesmosides of polygalacic acid, acylated or not), and phenolic acids. The latter are, on the one hand, caffeic esters (chlorogenic acid), and on the other hand, specific compounds, namely virgaureoside A and leiocarposide, a diglucoside of the esters of salicyl alcohol and of 2,4-dihydroxy-3-methoxybenzoic acid (0.1-0.5%).

The other species have a different composition: saponins derived from bayogenin and comprising up to 9 or 10 saccharides in *S. gigantea* and *S. canadensis*; clerodane-type diterpenes found in *S. gigantea*, but not in *S. virgaurea* or *S. canadensis* (they contain labdanes); leiocarposide not found in *S. gigantea* and *S. canadensis*; flavonoid content qualitatively and quantitatively different (*canadensis,* 2.4%; *gigantea,* 4%); variations in essential oil concentration and composition.

Pharmacological Activity and Uses. Leiocarposide is a diuretic, an anti-inflammatory (rat, IP), and an analgesic, but its intestinal resorption is very low. The saponins are antifungal *in vitro*. There are no clinical data to substantiate the properties attributed to this plant.

In France, the European goldenrod is traditionally used, by the oral route, to enhance urinary and digestive elimination functions, and to enhance the renal excretion of water [French Expl. Note, 1998]. In Germany, package inserts are required to mention "to increase urine quantity in case of kidney and bladder inflammation (seek medical advice in case of chronic disorder)".

6. BENZOIC AND CINNAMIC ESTER-CONTAINING DRUGS: BALSAMS AND BENZOINS

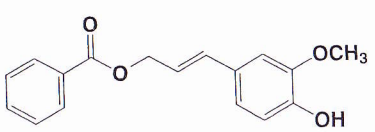
Balsams are defined as oleoresins containing substantial proportions of benzoic acid, cinnamic acid, and their esters. Therefore, studying them immediately after phenolic acid-containing drugs is not illogical.

• PERUVIAN BALSAM,
Myroxylon balsamum (L.) Harms, var. *pereirœ* (Royle) Harms
= *M. pereirœ* (Royle) Klotzsch, = *M. peruiferum* L. *f.*, Fabaceae

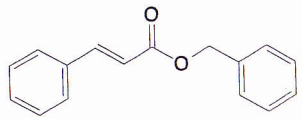
The 3rd edition of the European Pharmacopoeia defines Peruvian balsam as "the product obtained from the [tree] trunk scarified at high temperature".

The Drug, Characteristics and Composition. The species producing this balsam is a tree which grows wild in Central America, especially in El Salvador. When the trunk is beaten, stripped, and in a subsequent step, scorched with a torch, it secretes a pathological exudate which is the balsam. Traditionally, the exudation is soaked up with rags which are then extracted by immersion in boiling water: the insoluble balsam sinks (specific gravity 1.135-1.170) and is recovered by decanting. A portion of the commercial supply is obtained by extraction of the bark. The balsam is a dark brown syrupy liquid with a strong and vanilla-like smell; it does not thicken upon exposure to air; it is insoluble in water, readily soluble in ethanol, and not miscible with oils except for castor oil.

Peruvian balsam contains approximately 6-8% benzoic and cinnamic acids in the free state and 50 to 60% "cinnamein" (a mixture of benzyl benzoate, benzyl cinnamate, and cinnamyl cinnamate). It also contains alcohols (terpenoid and benzylic), vanillin, and a resinous fraction.



Coniferyl benzoate



Benzyl cinnamate

Tests. Peruvian balsam is identified by the green color developed by its ethanolic solution in the presence of ferric chloride, and by TLC analysis of its solution in ethyl acetate to characterize the two chief benzylic esters (visualization under UV). Visualization by phosphomolybdic acid allows the identification of nerolidol, and the verification of the absence of rosin. The French Pharmacopoeia requires a verification of the absence of artificial balsams (insolubility in petroleum ether), fixed oils (clarity of a solution in chloral hydrate), and turpentine (absence of odor for the evaporation residue of the petroleum ether solution). Peruvian balsam must contain not less than 45%, and not more than 70%, esters, chiefly composed of benzyl benzoate and cinnamate, extractible by diethyl ether in alkaline conditions, and measured gravimetrically.

Properties and Uses. Tradition is confirmed by experience when using this balsam as a vulnerary, or at least as a product able to create an environment favorable to the process of tissue repair. It is also an antiseptic. It is irritating when taken orally, and is therefore only used externally. It is mainly in dermatology that Peruvian balsam is still used, as an active principle, or in some proprietary products, as an excipient, in ointments or other preparations for local application, for topical, trophic or antiseptic or both purposes, for the treatment of burns, frostbites, chaps, cracks, erythema, pruritus ulcers, infected dermatitis, and other minor wounds. It is also used in suppositories for the symptomatic treatment of pain, pruritus, and feelings of congestion associated with the acute attack of piles and other anal disorders. It remains an ingredient of

MYROXYLON BALSAMUM (L.) Harms

Peruvian balsam is also used in the manufacture of cosmetic and hygiene products (soaps, detergents, creams, lotions) and in perfumes (fixative). One disadvantage is that it can induce contact dermatitis in some people. Sensitive subjects display cross-reactions with cinnamon, cinnamates, and benzoin.

In Germany, the recommendation is to apply it only to a small area and to not use it for longer than a week.

• Tolu Balsam,

Myroxylon balsamum (L.) Harms
= *M. toluiferum* H., B. & K., Fabaceae

This balsam, which was listed in the French Pharmacopoeia until 1972, is obtained by deep incision of the tree trunk. The species producing it is a tall tree growing wild in Colombia and Venezuela, and cultivated in the Caribbean Islands. The balsam is a grayish and soft semi-solid when fresh, then it slowly dries and becomes hard, resinous, brittle, and reddish-brown. It softens on warming and then smells like vanilla. Chemically, Tolu balsam is a mixture of free acids (benzoic acid, 6-8% and more; cinnamic acid, 10-15%) and benzyl benzoate which is slightly volatile. The drug also contains a resinous fraction, mono- and sesquiterpenoid hydrocarbons and alcohols, and phenylpropanoid derivatives (eugenol, traces of vanillin). The composition of the balsams currently available on the market seems very variable. Tolu balsam is considered an antiseptic and expectorant, and is used internally. Often combined with simple syrup or ipecac syrup—better known in France as Desessartz syrup or *sirop de Desessartz*—it is an ingredient of proprietary drugs designed for the symptomatic treatment of cough in various respiratory ailments; its acts as a vehicle, flavor, and mildly active ingredient. In perfumery, it is a fixative for volatile products.

• Siam Benzoin

Siam benzoin—also called in French, Laos benzoin or *benjoin du Laos*—is the balsamic resin obtained by incising the trunk of *Styrax tonkinensis* (Pierre) Craib ex Hartwich, Styracaceae (Fr. Ph., 10th Ed.). The species producing it is a tree growing wild in Laos, Thailand, and northern Vietnam.

Chemically, the balsam contains 60-80% coniferyl benzoate, 10-20% free benzoic acid, benzyl cinnamate, vanillin, triterpenes, and more.

The drug consists of tears or opaque and granular masses, more or less embedded together, and ranging from yellowish- to reddish-white. It has a distinct vanilla smell. Its identity is confirmed by reacting an alcoholic tincture with ferric chloride and watching for a green color (according to the French Pharmacopoeia, falsification with Sumatra benzoin gives a yellowish-green color instead *p. 258). The assay includes estimating the matter insoluble in 90% ethanol (must be less than 5%), GC

followed by an estimate of the potassium hydroxide in excess. French official benzoin must contain not less than 25% total acids expressed as benzoic acid.

Benzoin is mostly used in cosmetic formulation, perfumery, and food technology. Seldom used in pharmacy, it has antiseptic, vulnerary, and expectorant properties. It must be reserved for external use; however, it is (as benzoin tincture) an ingredient of preparations for inhalation.

The tincture (Fr. Ph., 10th Ed.) is prepared by maceration. In general, it corresponds to one part of drug for five parts of tincture (ethanol content: 71-75%) and contains not less than 5% total acids expressed as benzoic acid (saponification by potassium hydroxide and back titration with a sulfuric acid solution). The absence of Sumatra benzoin in the tincture is verified by TLC: absence of band corresponding to cinnamic acid.

• SUMATRA BENZOIN

This balsamic resin is a pathological product elaborated by *Styrax benzoin* Dryander and *Styrax parallelloneurus* Perkins, two species growing wild in Malaysia and in Indonesia, cultivated in Sumatra, and exported from Singapore. The drug consists of tears and irregular fragments embedded in a resinous, translucent, reddish-brown matrix. Its odor is weak and its taste slightly acrid. When heated in the presence of potassium permanganate, Sumatra benzoin releases a benzaldehyde odor (from oxidation of cinnamic acid), which differentiates it from Siam benzoin.

Sumatra benzoin contains a large proportion (20% and more) of free benzoic and cinnamic acids, with cinnamic acid as the major component by far (up to 80%). Note also the presence of esters (benzoates, cinnamates), triterpenes derived from oleanoic acid, and vanillin. The industrial applications of Sumatra benzoin are essentially outside of the pharmaceutical industry.

Comments.

- 1 - Balsams from *Styrax* spp. must not be confused with storax, a balsam which flows after incision of the trunk of *Liquidambar orientalis* Miller (Levant storax from Turkey) or *Liquidambar styraciflua* L. (American storax, liquid storax, or styrax mainly from Honduras). As indicated by their generic name, the trunks of these tall trees from the Hamamelidaceae family exude, following traumas, a thick *liquid* which is grayish, amber, and contains a large amount of free and combined cinnamic acid, styrene, and an ill-defined resinous fraction. Storax is healing and antiseptic, but is apparently not used in France.

* Evans specifies that Sumatra benzoin does not give this test: Evans, W.C. (1996). Trease and Evans' Pharmacognosy, 14th Ed., W.B. Saunders, London.

- 2 - Cinnamic acid (as cinnamates) is largely used in the formulation of sunscreens. This "chemical filter", like salicylates or *p*-aminobenzoic acid, only screens out UVB radiation (290-320 nm), therefore it is combined with "filters" that absorb some UVA radiation (a benzophenone or dibenzoylmethane), and to physical, reflective screens (mica or titanium oxide).

- 3 - Ferulic acid has been marketed as a biliary drug. It was used for the symptomatic treatment of dyspepsia.

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