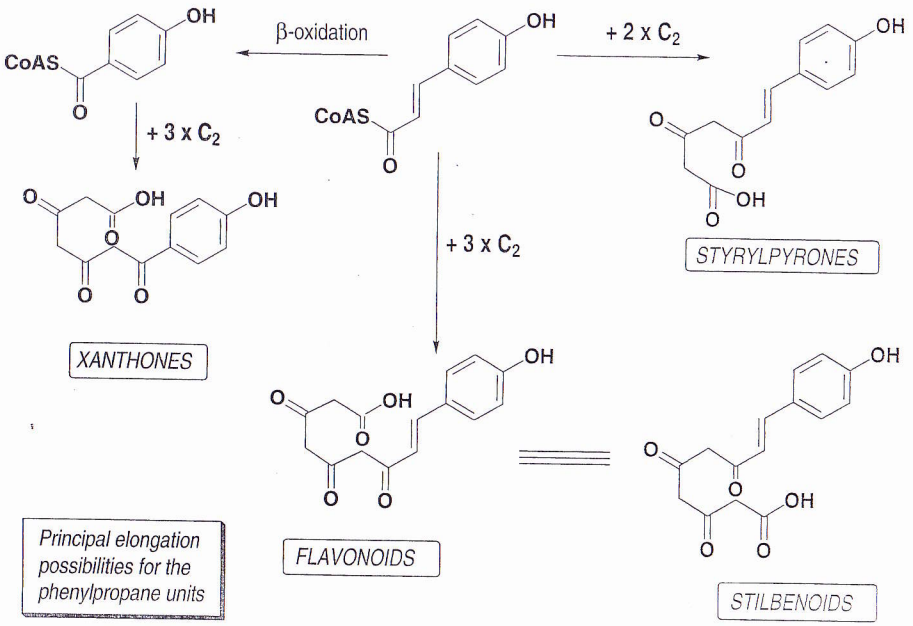
SHIKIMATES
Drugs Containing Phenylpropane Chain Elongation Derivatives

The elongation of compounds of the Ar-C3-type by the stepwise addition of two-carbon units is a common process in plants: it is the origin of styrylpyrones (Ar-C_3 + 2 x C_2), stilbenoids, flavonoids, and isoflavonoids (Ar-C_3 + 3 x C_2).

The mechanism of addition of two-carbon units onto the side chain of cinnamic acids is quite similar to the elongation process of polyacetates: the starter molecule



Principal elongation possibilities for the phenylpropane units

is converted to an ester of coenzyme A and the two-carbon units are provided under the activated form of malonyl-coenzyme A.

In some cases, the starter molecule undergoes preliminary β-oxidation, and the addition is then of the (Ar-C_1 + 3 x C_2)-type. It is a mechanism of this type which is invoked to explain the formation of most xanthones.

Since xanthones and stilbenoids are not used in therapeutics, and since styrylpyrones are of limited interest, we shall place the major emphasis on flavonoids, in other words C_{15} compounds in which two benzene rings are linked by a three-carbon chain (Ar–C_3–Ar): 1,3-diarylpropane (flavonoids), 1,2-diarylpropane (isoflavonoids), or 1,1-diarylpropane (neoflavonoids).

For convenience and although their synthesis is not strictly an elongation process, we shall also cover here diarylheptanoids and arylalkanones, which are molecules built from one or two molecules of a phenylpropanoic acid, most often ferulic acid.

Diarylheptanoids and Arylalkanones

These compounds, including curcuminoids, gingerols, and their derivatives, are specific to several genera of the family Zingiberaceae. They are the coloring substances of turmerics and the pungent principles of ginger. Over the last twenty years, multiple studies have shown that they are pharmacologically active.

- **TURMERIC,**
  Curcuma domestica Val. = *C. longa* L., Zingiberaceae

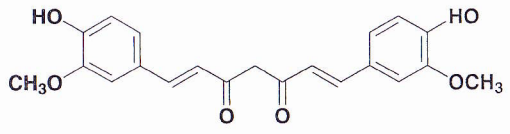
The rhizome of turmeric (= curcuma) is a main ingredient of curry powders, and has been the subject of many studies, mostly by scientists from India who have defined its pharmacological properties.

The Plant, the Drug. 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.

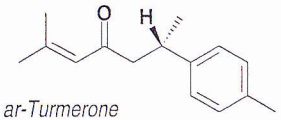
Several cultivars of turmeric are currently grown in India, Sri Lanka, Indonesia, China, and Jamaica. For the most part (80%) the world production comes from India, particularly from the states located on the Bay of Bengal: Andhra Pradesh, Tamil Nadu, and Orissa, among others. The rhizomes are harvested after the aerial parts have dried out, freed of roots, cooked in water which is at one point carbonated, dried in the sun or, to speed up the process, in driers, then polished mechanically to eliminate root residues, scales, and superficial layers.

Commercial turmeric commonly consists of the ovate primary rhizomes ("bulb" or "round" turmeric), the cylindrical secondary rhizomes ("fingers"), or a mixture of both. The fingers have a gray and grooved surface and a diameter of about 1 cm. They break with a clean fracture and look reddish-yellow inside; the odor is aromatic and the taste warm and somewhat bitter.

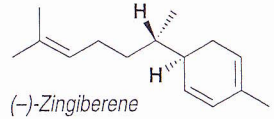
Chemical Composition. Rich in starch (45-55%), the drug contains arabinogalactans (ukonans) and 2.5 to 6% of an essential oil with monocyclic monoterpenes: hydrocarbons (zingiberene, β- and δ-curcumene) and mostly oxygenated derivatives (turmerone, *S*-(+)-*ar*-turmerone, curlone, α- and γ-atlantone). Note, in addition, the presence of monoterpenes. Sesquiterpenes (bisabolanes and germacranes) are also found in the oleoresin and the various extracts, which generally contain more *ar*-turmerone than the essential oil (steam distillation is thought to induce aromatization). The coloring principles in the drug are curcuminoids. These molecules, structurally related to a diarylheptane, occur at a concentration that varies greatly with the cultivar and can reach 8%. The chief component (50 to 60%) is curcumin (= (*E,E*)-1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). The other pigments that are important by weight are feruloyl-(4-hydroxy-cinnamoyl)-methane (or desmethoxycurcumin) and bis-(4-hydroxy-cinnamoyl)-methane (or bisdesmethoxycurcumin). They occur alongside dihydrocurcumin (= 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1-heptene-3,5-dione).



Curcumin



ar-Turmerone



(–)-Zingiberene

Pharmacological Properties. The anti-inflammatory activity of curcumin has been demonstrated on acute inflammation (carrageenate-induced edema in the rat, *median effective dose* (= ED50): 2.1 mg/kg by the intraperitoneal route; 48 mg/kg *per os*) as well as on chronic inflammation models (formaldehyde-induced arthritis, granulomas). 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. A small number of observations reported in India in man highlight the anti-inflammatory potential of this molecule which is apparently devoid of side effects. 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. Note also some activity on the stomach: the ethanolic extract (0.5 g/kg in the rat) is active against ulcers and protects cells (but curcumin may cause ulcers at high doses).

Uses. Turmeric cultivars with the highest curcumin content (e.g., Allepey, > 6.5%) are mostly prized as food coloring (turmeric is sometimes referred to as Indian saffron). Curcumin 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. Commercial curcumin contains not less than 90% curcumin (generally 95%). Other cultivars (e.g., Madras, 3.5%) are a highly valued spice: turmeric is, alongside coriander and other spices, one of the main ingredients of curry powders (these may also contain chili, ginger, clove, fenugreek). The oleoresin is also used in food technology.

Pharmacy uses turmeric rhizomes as a constituent of phytopharmaceuticals with the following indications: traditionally used 1. as a choleretic and cholagogue; 2. for functional dyspepsia attributed to a hepatic origin; 3. as an appetite stimulant [French Expl. Note, 1998]. The German Commission E recognizes uses of the same type, but specifies that biliary tract obstruction is a contraindication.

• 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. It contains starch (30-40%), an essential oil (up to 12%) which is, as is the alcoholic extract, rich in sesquiterpenes, including zingiberene, *ar*-curcumene, (*R*)-(–)-xanthorrhizol, turmerones, bisacurones, bisacumol, and bisacurol. Curcuminoids (1-2%) are represented by curcumin, its monodemethoxylated derivative, and its di-, hexa-, and octahydrogenated derivatives. Monophenolic and non-phenolic analogs have been isolated from rhizomes collected in Thailand.

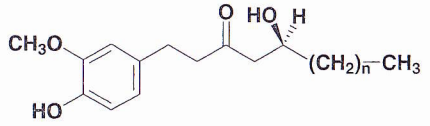
A traditional folk remedy in southeast Asia, the drug has a reputation for being a cholagogue and choleretic, and is used as such: in Germany, Commission E finds its use acceptable for gastrointestinal symptoms, and specifies that biliary tract obstruction is a contraindication and that prolonged use can cause gastric irritation.

• Ginger, *Zingiber officinalis* Roscoe, Zingiberaceae

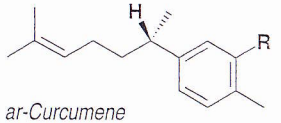
This spice, official in some countries (e.g., BP 1988, whole drug and powder), and widely consumed in Anglo-Saxon countries, is used in the oriental traditional medicines, especially for functional dyspepsia.

The Plant, the Drug. Ginger has botanical characteristics resembling those of turmeric: large herbaceous perennial plant, lanceolate leaves, thick inflorescence with overlapping lateral bracts, and pale green flowers with purple label. Originally from India, ginger is cultivated in India, China, and all of southeast Asia (Indonesia, Philippines), and in the tropical regions of Africa (Nigeria). The rhizome is ramified within one plane. The appearance of the drug varies 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). The drug breaks with a fibrous and granular fracture; the odor is aromatic and the taste warm and pungent. The drug is subject to a standard (NFV32-080). The HPLC quantitation of the pungent principles is also standardized (ISO 13685 [1997]).

Chemical Composition. The rhizome is very rich in starch (60%) and contains proteins, fats (10%), from 10 to 25 mL/kg essential oil, and a resin. The composition of the essential oil varies as a function of the geographical origin, but the major constituents—sesquiterpene hydrocarbons that represent 30-70% of the essential oil—seem to be a constant feature (including (–)-zingiberene, (+)-*ar*-curcumene, (–)-β-sesquiphellandrene, *E,E*-β-farnesene, β-bisabolene). They occur alongside monoterpene aldehydes (citrals) and alcohols found in part (in the fresh drug) as glycosides. The constituents responsible for the pungent taste of the drug are 1-(3'-methoxy-4'-hydroxyphenyl)-5-hydroxyalkan-3-ones. Known as [3-6]-, [8]-, [10]-, and [12]-gingerols, these compounds have a side chain with 7-10, 12, 14, or 16 carbon atoms, respectively; they occur alongside the corresponding ketones, and, in the dried drug, alongside dehydration products (shogaols). Also found are labdane-type diterpenes, galonolactone and its dialdehyde derivative. Cyclic diarylheptanoids were recently isolated from Chinese ginger.



Gingerols (n=1-4,6,8,10)



R = H: *ar-Curcumene*
R = OH: *Xanthorrhizol*

Pharmacological Properties. Ginger rhizome is a drug which has been used since remote times in India and China. Experiments show that the oleoresin is a cholesterol lowering agent (rodents), [6]-gingerol is a cholagogue (in the rat by the intraperitoneal route), and that [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 and several authors have tried to define its action and that of some of its constituents on prostaglandin and leukotriene production (Indian authors report beneficial effects in rheumatic patients).

In humans, about ten studies designed to assess the antiemetic properties of ginger have been published. 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, especially with regard to the potential of ginger to decrease the frequency of nausea subsequent to a gynecological surgical procedure under general anesthesia (but the anesthetic and analgesic therapy used in the published studies were not comparable). These contradictory results are all the more difficult to interpret because the ginger products that were used were not standardized (ginger powder capsules [?]). The antiemetic action, which may not be of central in origin, 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 [6]-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. At least the concensus is that the drug is not toxic and has no side effects.

Uses. Used for over 25 centuries in the formulation of countless traditional Oriental remedies (China, Japan), ginger rhizome is seldom used in France. Yet it was just added to the list of plants allowed in phytomedicines eligible for the abridged application for a French government marketing authorization or *dossier abrégé d'AMM* [French Expl. Note, 1998]; it may claim the following indication: traditionally used for motion sickness. In Germany, where the rhizome powder is used for gastrointestinal distress and to prevent motion sickness (2 g/day), Commission E recognizes that it is a spasmolytic in animals and, that in humans, it has antiemetic, positive inotropic, and stimulant effects (intestinal peristalsis, salivary and gastric secretions). The Commission specifies, with no particular justification, that ginger must not be used to prevent morning sickness in pregnant women. Newall *et al.* ** state that doses that far exceed the quantities used in food must not be taken during pregnancy or while breast feeding.

● Other Zingiberaceae

Other turmerics, such as *C. aromatica* Salisb. or *C. zedoaria* (Christm.) Roscoe (= zedoary), and some *Alpinia* species (e.g., *Alpinia galanga* [L.] Sw. or great galangal, *A. officinarum* Hance or galangal) have, in their country of origin, similar medical applications. They contain an oleoresin with oxygenated sesquiterpenes

* But in some cases, nausea is the direct result of vestibular stimulation.

** Newall, C.A., Anderson, L.A. and Phillipson, J.D. (1996). Herbal Medicines. A Guide for Health-care Professionals, The Pharmaceutical Press, London.

(guaianes, germacranes). In Germany, the authorities allow the use of galangal, but not zedoary, for dyspepsia and lack of appetite.

Curcuma angustifolia Roxb. is a source of faecula (*arrow-root* of India).

Cardamom seeds (particularly those of *Elettaria cardamomum* (L.) Maton var. *minuscula* Burkill, BP 1988) are used as flavoring agents. They are also used as spices in curries and other mixtures. The same is true for the seeds of the *major* Twaites variety, of many Indian *Amomum* species (*A. aromaticum* Roxb.), and of Indonesian *Amomum* species (*A. compactum* Sol.ex Maton, *A. maximum* Roxb. The seeds of certain *Aframomum* are also used as spices, e.g., grains of paradise (= malaguetta pepper = *A. meleguetta* Schumann) of western Africa or cardamom of Madagascar (*A. angustifolium* [Sonn.] Schumann).

Stilbenoids

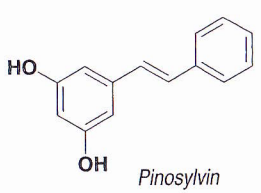
It is customary to group under this name—created to emphasize the biogenetic relationship to flavonoids—phenolic compounds with two benzene rings separated by an ethane or ethene bridge, in other words bibenzyls and stilbenes, as well as products biosynthetically related to them: phenanthrenes *, 9,10-dihydrophenanthrenes, and phenyldihydroisocoumarins.

The stilbenes are generally *E*, occur in the free state or as glycosides, and are sometimes polymers. They are found in many higher plant families.

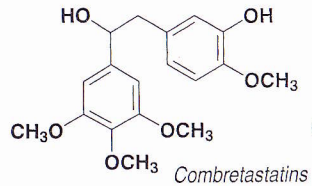
Bibenzyls and their derivatives are characteristic of hepaticas, but are rare in higher plants, in which they occur alongside the corresponding phenanthrene derivatives (Orchidaceae, Combretaceae, Dioscoreaceae) or alongside stilbenes (for example in pines).

These compounds, which are sometimes phytoalexins, are in some cases growth regulators. They often have antifungal and antimicrobial properties: Native Americans of North America used to use many mosses (*Bryum, Mnium, Polytrichum*) to treat wounds, burns, and other skin ailments. They are of limited pharmacological interest: inhibition of thromboxane synthase by lunularic acid, inhibitory activity on 5-lipoxygenase and on calmoduline of linear and cyclic bis(bibenzyls) of *Marchantia, Reboulia, Radula* and other Bryophytes, and cytotoxic properties of these same bis(bibenzyls), but also of closely related, bibenzylic and *cis*-stilbenic structures, isolated from south African *Combretum* species.

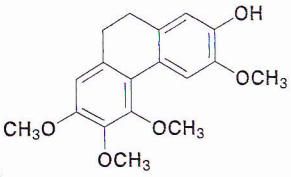
* Not included here are phenanthrene compounds arising from the degradation of alkaloids, or related to quinones.

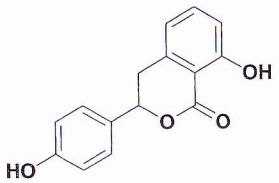


Pinosylvin

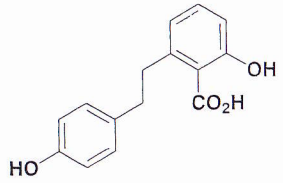


Combretastatins





Hydrangenol



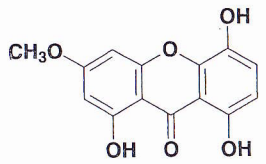
Lunularic acid

trans-Resveratrol is a phytoalexin characteristic of grapes (*Vitis vinifera*). Based on *in vitro* experiments and observations in animals, a preventive effect on atherosclerosis is attributed to it. It is an antioxidant and it inhibits the platelet aggregation triggered by ADP, as well as eicosanoid (thromboxane A2 and leukotriene) synthesis. The clinical significance of these data remains to be established. (See also footnote *, p. 387).

Xanthones

Aglycones and *O*-glycosides have a limited distribution in a small number of families (mainly Clusiaceae and Gentianaceae) whereas *C*-glucosyl xanthones are more common (they have been identified in about twenty families).

As a general rule, xanthones are formed by cyclization of benzophenones resulting from the addition of two-carbon units (in fact of malonyl-CoA) onto a precursor in C_6-C_1, i.e., a benzoic acid arising from the shortening of a cinnamic acid. The biosynthesis of *C*-glucosyl xanthones is thought to be analogous to that of flavonoids.



Bellidifolin

Mangostin

With regards to the biological properties of these molecules, several in this series (1,3,5,8-tetrasubstituted aglycones) are *monoamine oxidase* inhibitors (of MAO A and, to a lesser extent, of MAO B), and are CNS stimulants. Several xanthones have antifungal and strong antibacterial properties, some inhibit platelet aggregation, and others, such as mangostin, are anti-inflammatory.

Although xanthones are found in certain plants currently in use, their responsibility in the action traditionally attributed to these drugs remains to be proven (gentian root, lesser centaury flowering tops: see iridoid-containing drugs).

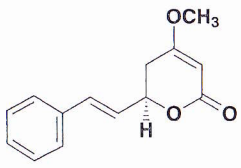
Styrylpyrones

- **KAVA**,
  Piper methysticum Forst. *f.*, Piperaceae

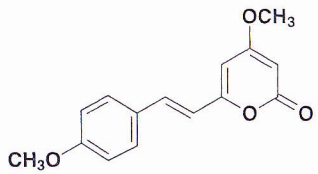
The term kava designates a beverage prepared from the subterranean parts of *P. methysticum*, a pepper tree which grows in the islands of western Polynesia (Papua New Guinea, Tonga, Samoa, Fiji, Vanuatu) and as far as Tahiti. This perennial dioecious subshrub with cordate leaves does not bear fruit: it multiplies by vegetative propagation. Decaploid and sterile, it is thought to have arisen from a wild species for which it is sometimes mistaken, *P. wichmannii* C. DC.

Kava is prepared by soaking in water the rhizome or root fragments, after grinding them with a pestle or chewing them, a preliminary step which would facilitate the emulsification of the resin particles and would yield a more active preparation. The resulting beverage has been consumed for centuries according to a ceremonial described in 1875 by Captain Cook. This ritual beverage, which continues to play an important role in the culture of that part of the globe, induces a sensation of well-being.

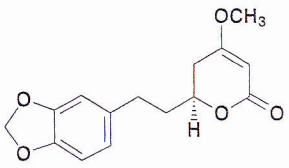
The active ingredients of kava are mono- or di-unsaturated α-pyrones, substituted by a styryl or phenethyl group, itself substituted (methoxyl, methylenedioxyl) or not. They include yangonin, (+)-methysticin, (+)-dihydromethysticin, (+)-kawain, (+)-dihydrokawain, demethoxyyangonin, and minor products (e.g., dehydrokawain, 7,8-dihydroyangonin, 10- and 11-methoxyyangonins). The resin content can fluctuate from 3 to 20% depending on cultivars and location (rhizome, lateral roots) and its composition varies with the chemotype.



Kawain



Yangonin



Dihydromethysticin

Kava, its extracts, the fat-soluble fraction, dihydrokawain (DHK), dihydromethysticin (DHM), and other pyrones have undergone much pharmacological research. The pyrones induce sleep in rodents (*per os*) and are sedatives in rodents, cats, and rabbits. They also 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). The *electroencephalogram* (= EEG) modifications observed in the cat suggest that kava and kawain induce sleep by acting on the limbic system.

At least three trials conducted in humans indicate that a kava extract is more efficacious than a placebo in patients who suffer from non-psychotic anxiety. The effect is relatively rapid and prolonged treatment does not induce dependence. No side effects were noted*. Many German researchers view kava as an alternative to tricyclic antidepressants and to benzodiazepines for the treatment of various types of anxiety.

About 15 pharmaceuticals based on standardized extracts (i.e., 35-120 mg kavapyrones) are currently marketed in Germany; they are promoted as sleep disorder and anxiety medicines.

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* Excessive kava consumption is known to cause neurological symptoms (Spillane, P.K., Fischer, D.A. and Currie, B.J. (1997). Neurological Manifestations of Kava Intoxication, *Med. J. Aust.*, **167**, 172-173 and references therein). A drug interaction with benzodiazepines can also cause problems: Almeida, J.C. and Grimsley, E.W. (1996). Coma from the Health Food Store: Interaction between Kawa and Alprazolam. *Ann. Int. Med.* **125**, 90-941

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