Camellia sinensis (L.) O. Kuntze

Purine Bases

1. GENERALITIES

Purine bases are compounds comprising a heterocycle, which, in theory, results from the annellation of a pyrimidine nucleus onto an imidazole nucleus. Because their synthetic origin does not involve an intact amino acid, and because of their amphoteric character, and peculiar solubility (in warm water and in chlorinated solvents), these compounds are most often considered non-alkaloids. This is obvious for the nucleotides, which are ubiquitous, but it is less obvious for certain compounds with marked pharmacological properties, like caffeine, theophylline, or theobromine: numerous authors and books refer to them as "purine alkaloids".

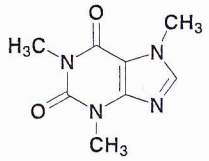
Except for the nucleotides that are constituents of the nucleic acids (adenine, guanine) and the phosphoric esters of the nucleosides (ATP), the purine nucleus is not very common in higher plants.

Caffeine (1,3,7-trimethylxanthine, with xanthine = 2,6-dioxopurine), the first purine base to be isolated in 1820, occurs in the seeds of the coffee plant (1-2%), of the kola plant (1-3%), and in tea leaves (2-4%). It is also found in the leaf of mate and the seed of guarana, two South American drugs used to prepare stimulating beverages.

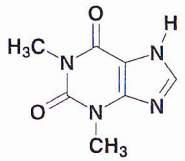
Theophylline (1,3-dimethylxanthine) occurs in small quantities in tea leaves and in kola nuts. Theobromine (3,7-dimethylxanthine) accumulates (0.9-3%) in cacao beans.

The other known purine bases will not be covered here, including (*E*)-zeatin, a cytokinin, and its derivatives, triacanthine from *Gleditsia triacanthos*, or the purine derivatives isolated from sponges or micro-organisms.

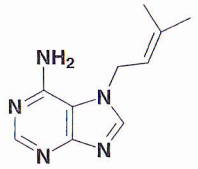
Black tea (leaf), green tea (leaf), and green coffee (seed) are the subjects of monographs in the 10th edition of the French Pharmacopoeia.



Caffeine



Theophylline



Triacanthine

Caffeine and theophylline are used in therapeutics: the former is widely available (a by-product of decaffeinated coffee), and the latter is readily produced by synthesis.

2. TESTS FOR OFFICIAL DRUGS CONTAINING PURINE BASES

The identity of the drugs listed in the French Pharmacopoeia must be verified by a morphologic and a microscopic examination, and possibly by simple chemical reactions. The very classic "murexide" reaction has become archaic: it is no longer used, except to identify guarana (which cannot be identified under the microscope because of the way it is prepared). After extraction (CH_2Cl_2), filtration, and solvent evaporation, the dry residue is treated with hydrogen peroxide in the presence of dilute hydrochloric acid. After evaporation to dryness, a bright red color develops, which turns purple upon addition of dilute aqueous ammonia.

The assay *per se* includes mainly loss on drying, total ash, and a TLC analysis of a tincture in 60% ethanol (visualization: KI + I_2 after spraying the plate with an ethanolic solution of hydrochloric acid).

Caffeine is quantitated by HPLC on a C-18 column eluted with an ethanol-water mixture (35:65 v/v). The solution to be injected is obtained by extracting the drug with hot methanol. After filtration, an aliquot of the methanol solution is evaporated to dryness and redissolved in the mobile phase.

3. PHARMACOLOGICAL ACTIVITY OF PURINE BASES

Caffeine

Caffeine acts chiefly on the CNS and on the cardiovascular system.

- CNS activity. A cortical stimulant, caffeine enhances alertness, facilitates thought formation, and decreases the sensation of fatigue. Very high doses can induce nervousness, insomnia, and tremors. It stimulates the respiratory center in the brain stem by increasing its sensitivity to carbon dioxide.

- Activity on the cardiovascular system. Caffeine has a positive inotropic action, and causes tachycardia and an increase in cardiac output, slight peripheral vasodilation, and has a mild diuretic effect.

Theophylline

Theophylline receives attention mostly for its bronchopulmonary and respiratory activity. It is a non-specific bronchial smooth muscle relaxant which counteracts the effects of the various bronchoconstricting mediators. The activity of the compound could be due to its ability to cause the accumulation of cAMP by inhibiting phosphodiesterase; it is also possible that it interferes with intracellular calcium movements. Note also a respiratory stimulation, due to an increase in sensitivity of carbon dioxide centers in the brain stem. The other activities are similar to those of caffeine: CNS stimulating activity, modest cardiovascular effects (slightly inotropic); the diuretic activity, linked to an increase in glomerular filtration, is markedly stronger than that of caffeine.

Caffeine and theophylline are rapidly and completely resorbed after oral administration; they are metabolized in the liver and eliminated in the urine. The plasma half-life of theophylline varies greatly among different subjects, which is why the posology must be adjusted individually.

4. USES OF PURINE BASES

Caffeine

Caffeine is available as an injectable solution at 25% for the following indication: stimulation of the CNS respiratory center in case of neonatal apnea. In addition, caffeine is an ingredient of several dozen proprietary products in France, as well as in the United States. For the most part, these are combinations with acetyl-salicylic acid, ascorbic acid, codeine, paracetamol, quinine, and other antipyretics and antalgics. These combinations (which are not always justified) are used to treat fevers, aches and pains, and the symptoms of flu. Caffeine may have been added to the formulation for a specific reason, for example to increase the intestinal resorption of ergotamine, or to counteract the drowsiness induced by phenobarbital. In France, caffeine is also used topically for the symptomatic treatment of localized subcutaneous fat deposits (it is thought to activate lipolysis locally).

The side effects of caffeine *per os* appear at high doses: sinus tachycardia, epigastric pain, nausea, vomiting, headaches, nervousness, insomnia, and tremors. There are few interactions between caffeine (as a drug or as part of a normal diet) and drugs;however, the simultaneous administration of enoxacin (a fluoroquinolone) is discouraged. Enoxacin markedly decreases the hepatic metabolism of caffeine, therefore the caffeine level in the body increases substantially.

Non-pharmaceutical Uses. Caffeine is an ingredient of non-alcoholic beverages and of "energizing" beverages that have appeared recently on the market. To comply with French regulations, the level of caffeine in such beverages must not exceed 150 mg/L (whereas it sometimes exceeds 300 mg/L in other countries of the European Union).

Comment. Caffeine is banned by many sport authorities as a stimulant. Most organizations consider a urine test positive if the caffeine concentration exceeds 12 µg/mL.

Theophylline

Theophylline is generally used as an anhydrous base, in tablets or capsules filled with microgranules for sustained release (50, 100, 200, 300, 400 mg). In various countries, derivatives that are more water-soluble are also used, including theophylline monoethanolamine, theophylline ethylenediamine, and theophylline piperazine.

Theophylline is indicated for the acute attacks of chronic asthma, and reversible bronchospasm associated with chronic obstructive pulmonary disease. The average posology (from 8 to 12 mg/kg/24 h or on average 700 mg/day) must be adjusted gradually in order to completely control the asthma attacks without causing side effects (efficacy is achieved with blood levels of 10-15 µg/mL). High-dose forms are reserved for adults. In children—it is normally contraindicated in children under 30 months of age—it must be used with great caution, given their sensitivity and the fact that doses higher than in adults are often necessary. Theophylline can be used in infants in specialized hospital wards. Contraindications include theophylline intolerance. Gastro-duodenal ulcer, obesity, hepatic insufficiency, cardiac or coronary insufficiency, and hyperthyroidism are all reasons to administer the drug cautiously and with the goal of decreasing the dosage. The simultaneous administration of enoxacin is to be strictly avoided (risk of theophylline overdose by decrease in its metabolism); the same is true for triacetyloleandomycin. The concomitant administration of erythromycin or viloxazine (an antidepressant) increases the plasma concentrations of theophylline: it is not recommended. Many other drug combinations can cause an increase in theophylline blood levels (e.g., macrolides, cimetidine, ticlopidine), or a decrease (enzyme inducers), therefore they are discouraged.

The side effects are usually transient (nervousness, sleeplessness, transient tachycardia) or can be more substantial and include nausea, vomiting, headaches, tremors, epigastralgia, diarrhea, agitation, insomnia, and permanent tachycardia.

The latter symptoms can reflect overdose and require a decrease in posology. Convulsions are a sure sign of intoxication. Nausea and vomiting at the beginning of the treatment indicate a digestive intolerance to theophylline, in which case therapy must be discontinued.

Theophylline is almost always used alone, but there are still a few combinations on the market (e.g., with caffeine, ephedrine, phenobarbital). Some synthetic derivatives, which retain the basic heterocycle, are also available in many countries: diprophylline (INN, substituted at C-7) and bamifylline (INN, substituted at C-7 and C-8).

Theobromine

Theobromine is seldom used in France. Pentifylline (=1-hexyl-3,7-dimethylxanthine) was still marketed recently as a peripheral vasodilator.

5. TEA, COFFEE, COCOA

Since tea, coffee, and cocoa are agricultural crops of considerable global importance, they have inspired countless studies which are reflected by a plethora of publications: history, botany, optimization, cultivation practices, preparation of the commercial products, sociological aspects, dietary aspects, impact on public health, and so forth. We will not even pretend to present novel information! However, theophylline and caffeine are pharmacologically active substances and ingredients of medications, and the common caffeine-containing drugs are listed in the French Pharmacopoeia: therefore, we shall present them succinctly according to our customary outline.

• TEA, *Camellia sinensis* (L.) O. Kuntze, Theaceae
(= *Thea sinensis* L. = *C. thea* Link)

Green tea or black tea (merely dried or fermented), Oolong tea, in leaves, in tea bags, instant, plain, with mint tea, or with a twist of lemon; first of all tea is one of the beverages most consumed the world around, and it is also a medicinal plant. Is it? In the past few years, green tea has received attention because of the antioxidant properties of its phenolics and its potential role in the prevention of cardiovascular disease and cancer.

The 10th edition of the French Pharmacopoeia includes two monographs on tea: black tea and green tea. Black tea is defined as "the young leaf of *C. sinensis* and of its cultivated varieties, fermented, submitted to a rapid desiccation with applied heat, then dried, [...it...] contains not less than 2.5% caffeine". Green tea is "the young leaf of *Camellia sinensis* and of its cultivated varieties, unfermented, submitted to a rapid desiccation with applied heat, then dried. It contains not less than 2% caffeine".

The "leaf of the tea plant" is also listed in Annex I of the 1998 French Explanatory Note on plant-based medicines.

The Plant, the Drug. Indigenous to the rainy Asian forests (China, Myanmar, Laos, Thailand, Vietnam), the tea plant is currently cultivated in India (black tea), Sri Lanka, China (green tea), in the countries of southeast Asia (Indonesia), and also in Africa (Kenya), Turkey, and Argentina. The world production exceeded 2.7 million t in 1997 and 60% of it came from three countries (India, China, Sri Lanka) [source: FAO].

The tea plant is a small wild tree reaching 5-10 m in height, very branchy, with indeciduous leaves, which are limp and downy when they are young, coriaceous and almost glabrous when they grow old. The leaves can be small (China) or more developed ("var." *assamica* from India). The flowers are solitary or in groups of two or three, regular, and have six to nine white petals. Cultivated tea plants are pruned regularly and kept to a height of about 1.2 m to facilitate the harvest. Since the harvest requires leaf selection, at least for the finest teas, it is most often done manually: only the unopened apical bud (pekoe) is collected, as well as the first leaves, which are young and flexible. Mechanical harvesting is also done in India and Korea.

There is a multitude of commercial grades of tea (depending on the botanical variety, the age of the leaves, the variety of possible treatments, and the geographical origin). The main commercial distinctions are the following:

- green tea, stabilized by dry heating or steaming, rolled, dried rapidly, and more or less roasted. It is consumed in China, Japan, north Africa, and in the Middle East.
- black tea, wilted for about 20 hours, rolled, fermented in a humid atmosphere, then dried with hot air. It represents 80% of the world market.
- Oolong tea. Little known in Erope, it is only partially fermented.

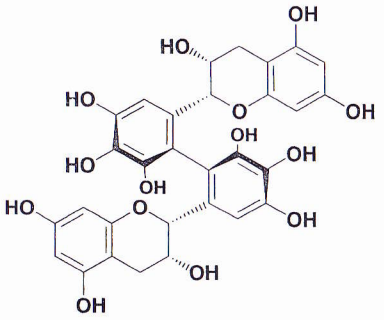
"Fermenting" the tea leaf allows for polyphenol-oxidase activity and modifies its composition, appearance, odor, and the taste and aroma of the infusion. (The phrase partial enzymatic oxidation would probably be more accurate than the term fermentation.) The caffeine concentration is practically not altered by fermentation.

Even though the commercial black tea leaf generally occurs as rolled and brittle fragments, characteristic elements can be recognized, particularly the dentate edge at the apex of the blade, with the teeth comprising a cushion-like structure with a blackish point shaped like a claw. The microscopic examination (cut and powder) is also useful (big ramified sclerites, lower layer of epidermis with stomata).

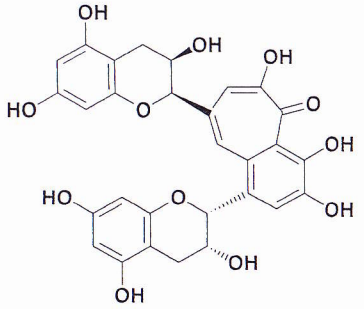
Chemical Composition. The unfermented tea leaf contains proteins (15-20%), amino acids (3%, mainly theanine, i.e., the ethylamide of glutamic acid), sugars (5%), ascorbic acid, group B vitamins, and purine bases chiefly represented by caffeine (2 to 4% depending on the variety). Glycosides of terpenoid, aliphatic and aromatic alcohols are also found: their hydrolysis releases constituents which contribute to the aroma of the infusion.

The phenolics are particularly abundant (up to 20% and more of the dry weight) but their concentration varies depending on the variety, the age of the leaf (the youngest leaves are the richest), and the season (the level is higher in the summer than in the spring). Alongside phenolic acids (chlorogenic acid, caffeic acid), of gallic esters of glucose (gallotannins), and flavonoids (flavonol *O*-glycosides, and in some varieties, *C*-glycosides), the chief constituents are flavan-type compounds, including (–)-epigallocatechin gallate (EGCG, 5-12%), (–)-epicatechin gallate (ECG, 1-5%), the corresponding 3,5-digallates, (–)-epicatechin (0.2-2%), (+)-catechin, and (+)-gallo-catechin. Several proanthocyanidins have also been characterized: procyanidols B-2, B-4, C-1, prodelphinidol 3-*O*-gallates and 3,3'-*O*-digallates, theasinensins (which are bisflavan-type gallates with 6'-2" and 6'-6''' bonds) and, in some varieties, chalcan-flavan dimers, namely the assamicains. One cup of green tea is said to contain 30-400 mg of polyphenols.

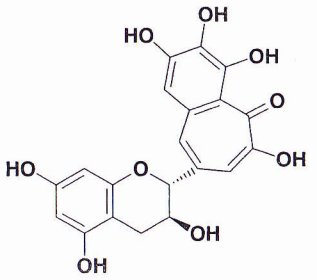
Upon fermentation, the composition changes: the infusion turns from pale yellow (green tea) to reddish-brown (black tea), and the odor becomes clearly aromatic. In addition to the development of the aroma upon formation of volatile products (ketones from carotene degradation, hexenal from unsaturated fatty acid oxidation, miscellaneous heterocycles from oxidation and rearrangement of monoterpenes), an oxidation of the polyphenols (hence the color of the infusion), particularly the formation of benzotropolones occurs: theaflavins and its 3-*O*- or 3'-*O*-mono- and 3,3'-*O*-digallic esters (1-2%), and also theaflagallin and epitheaflagallin. The most abundant compounds are the oxidation and polymerization products of the theaflavins, thearubigins, and their derivatives (10-20%).



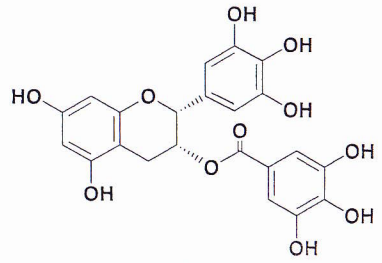
Theasinensin C



Theaflavin



Theaflagallin



(–)-Epigallocatechin 3-O-gallate

Partially fermented tea also contains oxidation products (theaflavins), as well as several theasinensins and bisflavans (occurring in the free state?) with a 4-CH_2-8' bond (*homo*bisflavans).

Pharmacological Activity. Various properties are attributed to tea. In Asia, it was actually used as a medicinal plant before it was used to make a beverage. Its stimulant effect (due to caffeine) and its diuretic action are well known, and it is its antioxidant potential that is currently the focus of attention. Green tea is also known to exert a protective effect against dental caries and its extract could be used as a breath freshener. The flavanols of green tea are antimutagenic *in vitro*, and counteract the formation of mutagens (nitrosamines) and the expression of their mutagenicity (polycyclic aromatic hydrocarbons). In animal experiments, it was established that green tea infusions and EGCG counteract the cancerization of different organs (e.g., skin, lung, duodenum, colon). Like many structurally similar phenols, the tea leaf flavans are free radical scavengers and *in vitro*, they inhibit lipid peroxidation reactions. Finally, note that EGCG blocks urokinase, an enzyme which appears to be implicated in cancer cell proliferation and circulation. In contrast, little data are available on the bioavailability of these polyphenols.

Human data are essentially epidemiological in nature. They are sometimes contradictory, yet they tend to show a negative correlation between the consumption of green tea infusions and the frequency of stomach and esophagus cancer (but the overall diet needs to be taken into account, since tea drinkers often have dietary habits that differ from those of other subjects). Other studies allow the hypothesis that the regular consumption of green tea would significantly decrease cholesterolemia, triglyceridemia, and the LDL/HDL ratio, hence a lower risk of atherosclerosis and a lower prevalence of cardiovascular disease in heavy tea drinkers (four cups or more per day).

As far as black tea is concerned, certain studies suggest that regular consumption (five cups per day) would greatly decrease the risk of cerebrovascular accident. Other studies fail to establish a beneficial effect of black tea on the incidence of cardiac accidents (but the tea drinkers included in the most recent study added milk to their tea, which might have caused the phenols to precipitate and might have prevented their absorption).

Considering the difficulties inherent to this type of retrospective study, intervention studies and other clinical trials (of the teas and of EGCG) are absolutely necessary to prove or disprove the likely virtues of this widely consumed beverage.

Uses (other than as a beverage). According to the 1998 French Explanatory Note, the tea leaf can be used orally, traditionally: 1. for the symptomatic treatment of mild diarrhea, 2. for functional asthenia, 3. as adjunctive treatment in weight loss programs, and 4. to enhance the renal excretion of water. Topically, phytopharmaceutical products based on the tea leaf may claim two indications: as adjunctive treatment in weight loss programs, as adjunctive, emollient and itch-relieving treatment for skin disorders, and as a trophic protective agent for cracks, bruises, frostbite, and insect bites.

• COFFEE, *Coffea* spp., Rubiaceae

Like the tea leaf, the (green) coffee bean is listed in the French Pharmacopoeia, which devotes to it, in its latest edition, a monograph in which it specifies that the drug consists of "the seed, devoid of tegument and dried, of *Coffea arabica* L., of *C. canephora* Pierre ex Froehner and their varieties. Green coffee must contain not less than 1% caffeine".

C. arabica is indigenous to the mountain regions of the southwest of Ethiopia. Initially cultivated by the Arabs, its use spread rapidly to the whole world of Islam. Introduced in Europe by the Venetians (1615), it arrived in France in 1644 (Marseille), appeared at the royal court in 1669, and in the first Paris "*café*" on Place St. Germain in 1672. R. Paris and H. Moyse report that 380 establishments of this type were in business in the French capital in 1720 (there were more than 2,000 of them in London in 1715): the generalization of coffee use could not be slowed by the medical condemnation inspired by pressure... from wine merchants * rather than by objective observations! Despite specific precautions (no coffee bean could be exported outside of the areas under Arab influence without having been heated, therefore without having lost its ability to germinate) several plants were introduced in the Antilles, in Brazil ** (which was to become the world's top producer), in India, and in Sri Lanka. Subsequently, sanitary problems in the Asian plantations led to the cultivation of other species (in tropical Africa [*C. canephora, C. liberica*]), then to that of hybrids.

The Plant. The coffee plant is a small tree with entire, indeciduous, coriaceous, and shiny leaves (10-15 x 4-6 cm). The flowers, white and fragrant, are verticillate at the base of the leaves. The fruit is a green drupe, which turns red when ripe, and normally contains two planar-convex seeds with their planar faces together. Although only two species produce the major part of commercial coffee (*C. arabica* and *C. canephora*), there are numerous species of wild coffee growing in the tropical forests of east Africa.

* This was true in France. In Italy, the priests were the people opposed to coffee. In the United Kingdom, its use triggered the wrath of women's leagues because husbands spent more time at the *café* than at home. Charles II shared this distrust... for a short time: 11 days after the proclamation prohibiting the coffee houses, the reverse proclamation was made public! Elsewhere, the dictatorial edicts of Frederick William, King of Prussia had no more success (they were based on the fact that since he drank beer, everyone else should). The most reasonable head of state was probably Gustav III of Sweden, who ordered a clinical trial (of coffee versus tea), to be conducted under medical supervision, on twins who were death row inmates: alas! the judges, doctors, and king all died long before the lucky twins, who lived until the age of 83, sipping the tea and coffee that saved their lives. See Smith, R.F. (1985). A History of Coffee, *in* Clifford, M.N. and Willson, K.C., see bibliography, pp. 1-12.

** Coffee was brought to Brazil by an officer who received it, hidden in a bouquet of flowers, from the wife of the governor of French Guyana, as a token of her fondness!

The Drug. The bean is oval (10-15 x 6-8 mm), convex on the dorsal face, flattened on the ventral face, which has a longitudinal groove or hilum. It is hard, greenish, and odorless. The microscopic examination of green coffee powder shows most of all, fusiform fibers from the tegument and from the albumen cells: these are polyhedral, their wall is pearly and beaded; they contain oily droplets.

The coffee beans are obtained by a wet process (fermentation, washing) or by a dry process (drying then mechanical hulling) from coffee cherries, that is from the drupes. The elimination of the red epicarp and of the fleshy mesocarp leaves the coffee seed surrounded by its parchment. It is after hulling (elimination of the sclerified endocarp) that coffee "beans" are obtained. The world production of coffee (5.5 million t in 1997 according to the FAO) comes mostly from South America (Brazil, 1,200,200 t; Colombia, 600,000 t; Peru), Mexico, and Central America (e.g., Guatemala, Honduras, Costa Rica). Coffee is also cultivated in Asia (e.g., Indonesia, India, Vietnam) and Africa (e.g., Ethiopia, Uganda, Ivory Coast).

Chemical Composition. More than 50% of the dry weight of the green coffee bean is represented by sugars, essentially polysaccharides. Proteins and lipids represent 10-12% and 10-18%, respectively. The unsaponifiable fraction of the crude lipids is substantial (over 10%): alongside sterols, hydrocarbons, and tocopherols, diterpenoid alcohols (cafestol, kahweol, and kaurane-type derivatives) occur in the free state, although mostly, as esters of fatty acids. The coffee bean contains about 5% phenolic acids: quinic acid, caffeic acid, and chlorogenic acid. The concentration of caffeine ranges from 0.6 to 2%, and up to and above 3% for some *canephora* (variety *robusta*).

During the roasting process, the texture and the composition of the bean change drastically. The water content decreases; the bean swells; the polysaccharides are greatly degraded (and form soluble products); pigments form (condensed furan polymers); and the extremely complex aroma develops, (several hundred compounds: alcohols, phenols, aldehydes, furan- and pyrrole-type derivatives, hydrocarbons, thiophenes). Since the study of coffee roasting and of the genesis of the aroma exceeds the scope of pharmacognosy, we refer the interested reader to specialized publications (for example, a good starting point is Clifford, M.N., *in* Clifford, M.N. and Willson, K.C., see bibliography, pp. 305-374 and references therein).

Uses. Part of the caffeine used in pharmacy comes from decaffeinating coffees. These are prepared by extraction with an organic solvent (trichloroethylene) or, better, with supercritical carbon dioxide. In contrast to tea, coffee is not listed in Annex I of the 1998 French Explanatory Note.

- **CACAO,**
  Theobroma cacao L., Sterculiaceae

The cacao tree is a small tree indigenous to the tropical forests of Central America and the equatorial forests of South America. It is cultivated mostly in West Africa, on both sides of the equator: the Ivory Coast alone produces 38% (i.e., 1.12 million t) of the world production (2.9 million t) and Ghana contributes 12%. The cacao tree is also cultivated in South America (Brazil, 290,000 t) and increasingly in Southeast Asia (Indonesia, 330,000 t; Malaysia, 120,000 t) [source: FAO].

The Plant. The cacao tree is characterized by the direct insertion of its flowers in the trunk and the main branches, as well as by its very typical fruits, the cacao pods, which are indehiscent, voluminous (15-20 x 10-12 cm), and have a coriaceous, yellow to red wall with verrucose grooves. They contain 20 to 40 seeds or beans, contained in a white pulp (see figure). The fresh beans are odorless, very astringent, and bitter: they take on their brown color only after prolonged fermentation and desiccation. Roasting and subsequent rolling give rise to the remarkable taste of cocoa and of its derived products (commercial chocolate).

Chemical Composition. The kernel of the seed of cacao contains about 50% lipids. These constitute "cacao butter" and comprise 75% symmetrical triacylglycerols with an oleic acid at the 2-position. The fatty acid composition varies very little with the geographical origin: C_{16} saturated (25-29%), C_{18} saturated (32-37%), and $C_{18:1}$ unsaturated (34-36%). Phenolics, flavan-3-ols, procyanidins B-1, B-2, B-6, C-1, and their oligomers are also present. It is the oxidation of these polyphenols during the process of fermentation which explains the characteristic color of the drug. Purine bases are represented by theobromine (the principal constituent: 1-3%) and by caffeine (0.05-0.3%).

Uses. Cacao butter can be used as a fatty excipient: it is often advantageously replaced by semisynthetic products that are easier to handle and to store. It is also used in food technology. Several countries now allow the very partial substitution of cacao butter by other fats: sal seed fat—the solid lipid fraction prepared from the seeds of an Indian Dipterocarpaceae (*Shorea robusta* Gaertner *f.*); illipe butter (*Shorea stenoptera* Burk., from Borneo); seed oils from Clusiaceae (kagné, mkani: *Allanblackia* spp.), and others.

6. OTHER DRUGS CONTAINING PURINE BASES

- **KOLA,**
  Kola spp., Sterculiaceae

The French Pharmacopoeia (10th Ed.) indicates that the part to be used is the seed, devoid of tegument and dried, of *C. nitida,* its varieties, and *C. acuminata.* Kola must contain not less than 1.5% caffeine.

The Plants, the Drug. The kola trees are medium-size trees (10-15 m) growing in the equatorial zones of West Africa: from Sierra Leone to Nigeria and to Gabon. The species most often used is *Cola nitida* (Vent.) Schott & Endl. (= *C. vera*

K. Schum.); also cultivated are closely related species such as *C. acuminata* (P. Beauv.) Schott & Endl. (= *Sterculia acuminata* P. Beauv.), *C. verticillata* (Thonn.) Stapf ex A. Chev., and others. The fruits comprise two to six lignified, voluminous (8-12 x 4-8 cm) follicles gathered into a star; they are generally collected before maturity. The follicles are opened and the seeds (5-10/follicle) are recovered and left for several days in a pile or immersed in water. Next, the pulpy tegument, which has disintegrated, is eliminated. In the regions where it grows wild, the kola nut is consumed fresh (as a masticatory).

Depending on the species and the variety, the seed is either white, pink, or light red when fresh; when dry, it is dark mahogany brown, and in the case of *C. nitida*, it splits into two clearly planar-convex cotyledons (kola halves, 3-4 x 2-2.5 x 1-2 cm). In the case of *C. acuminata*, the seed splits into four to six irregular pieces (kola quarters).

Chemical Composition and Uses. Alongside the purine bases chiefly represented by caffeine (2.5% on average in the dried drug), note the presence of polyphenols, especially flavan-3-ols: (+)-catechin, (–)-epicatechin, and pro-anthocyanidin dimers of group B. Caffeine forms a molecular association with the catechin derivatives, and therefore, the proportions of free and combined caffeine vary depending on whether the drug is fresh, dry, or stabilized.

The drug is rarely used in pharmacy, even though is has been shown that its effects are more gradual than those of caffeine, and even though, in 1998, the French Explanatory Note authorized one indication: traditionally used in functional asthenia. The chief outlet, of course, is the manufacture of carbonated, non-alcoholic beverages.

• MATÉ, *Ilex paraguariensis* St Hilaire, Aquifoliaceae

Maté is a tree currently widely cultivated and also growing wild in Brazil, Paraguay, and in the north of Argentina. The drug—green maté—consists of the leaf "submitted to a rapid desiccation with heat and incised" (Fr. Ph., 10th Ed.). This leaf does not contain tannins in the strict sense of the term, but up to 10% total chlorogenic acids (mono- and dicaffeoylquinic acids, feruloyl- and *p*-coumaroyl-quinic acids). In addition, it contains 5-10% saponins: the matesaponins 1-5 and the J1a-b, J2a-b, J3a-b saponins are mono- and bidesmosides of ursolic acid and oleanolic acid. Flavonoids and purine bases (1.4-2.6%) are also found, and are chiefly represented by caffeine (0.9-1.7%; >1% for the official drug) and theobromine (0.45-0.9%). The particular aroma of the drug is due to a complex mixture of over 250 constituents. Upon roasting, the Maillard reaction produces many heterocyclic compounds: furans, pyrazines, and pyrroles.

The dried leaves are used to prepare an infusion which is a traditional stimulant beverage for the Guaranis Indians. The pharmacological properties of mate (other than as a CNS stimulant) are not well known; it is known, however, that the aqueous

extracts display antioxidant properties under experimental conditions. In France [French Expl. Note, 1998], the preparation of phytopharmaceuticals based on mate leaves and their use for the following indications are permitted: traditionally used to treat functional asthenia and to enhance the renal excretion of water (orally); traditionally used as an adjunctive treatment in weight loss programs (orally and topically). In Germany, the drug is used for physical or mental fatigue (Commission E). Epidemiological data collected recently in South America show a possible correlation between the consumption of mate infusion and a higher risk of lung cancer.

- GUARANA,
  Paullinia cupana Kunth ex H.B.K. var. *sorbilis* (Mart.) Ducke (= *P. sorbilis* C. Mart.), Sapindaceae

This species is cultivated in the lower Amazon region. It is a creeping plant with small bright red fruits whose seeds are used. The seed is normally roasted, freed of its tegument and crushed with water to form a paste which is rolled into sticks and smoked: it is also used grated. According to the French Pharmacopoeia, guarana consists of "the dried paste, obtained by crushing the kernel, and submitted to rapid desiccation with heat and moisture [...] It contains not less than 3% caffeine calculated relative to the dried drug." It occurs as brown cylinders; it tastes astringent and bitter like cacao. The latest supplement to the French Pharmacopoeia devotes a monograph to the "paullinia", in other words the seed desiccated with heat; in this case the concentration of caffeine is not less than 3.5%.

The seed contains caffeine (3.6-5.8%, concentrated in the cotyledons), saponins, and tannins (catechin, epicatechin, and proanthocyanidins). In France, both the seed and guarana may claim three indications (orally, French Expl. Note, 1998): 1. traditionally used to treat mild diarrhea, 2. to treat functional asthenia, and 3. as an adjunctive treatment in weight loss programs (orally and topically). In reality, it is seldom used. In South America, guarana is used to prepare carbonated and flavored beverages whose concentration in caffeine is adjusted by adding guarana. The local industry prepares extracts by lixiviation of the seeds, mechanically hulled and sometimes roasted. In recent years, non-alcoholic beverages containing guarana have appeared in France and in the United States.

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