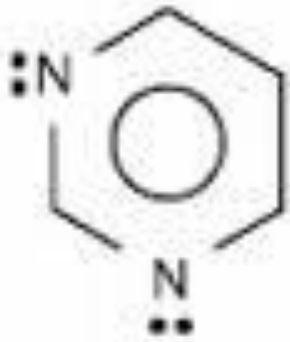


Purine Bases

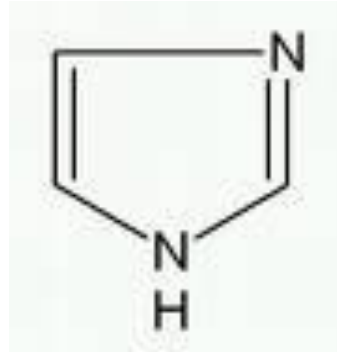
Prof. Dr. Ali Hikmet Meriçli

GENERALITIES

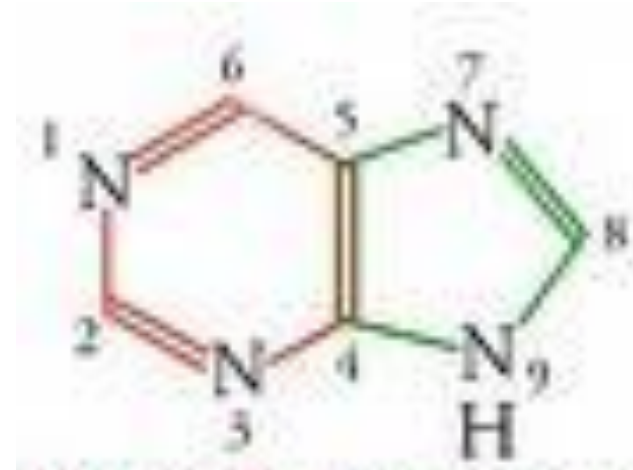
Purine bases (**Xanthine alkaloids, purine alkaloids**) are compounds comprising a heterocycle, which in theory, results from annellation of a pyrimidine nucleus onto an imidazole nucleus. Because their synthetic origin does not involve an intact amino acid, because their amphoteric character, and peculiar solubility (in warm water and in chlorinated solvents), these compounds are most often considered non-alkaloids.



Pyrimidine

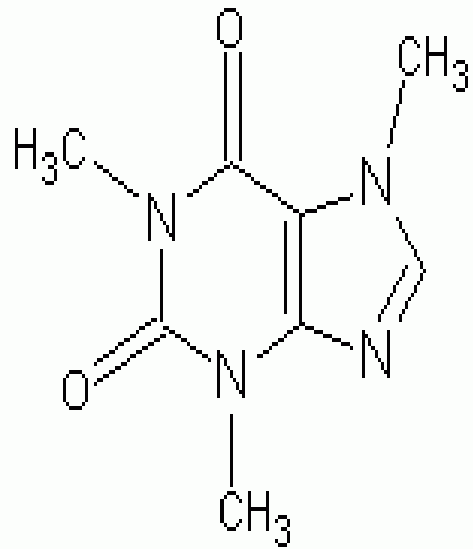


Imidazole

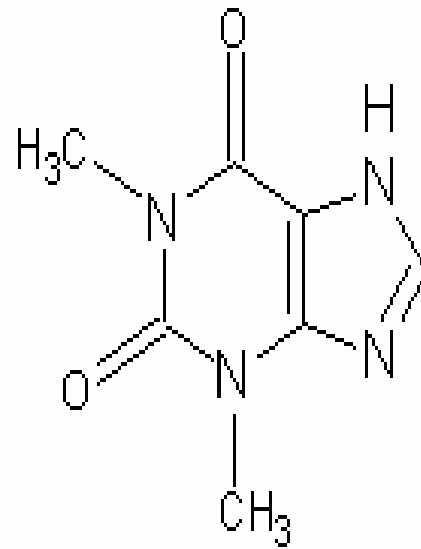


Purine

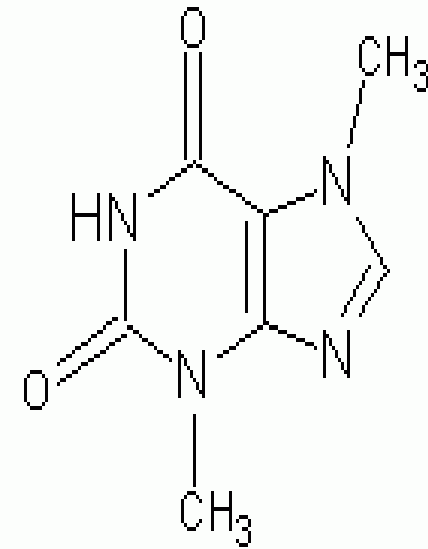
The most important compounds are caffeine, theophylline and theobromine.



Caffeine



Theophylline



Theobromine

Caffeine (1,3,7-trimethylxanthine), the first purine base to be isolated in 1820, occurs in the seeds of the coffee plant (1-2%), of the cola 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 to prepare stimulating beverages.

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

TESTS FOR OFFICIAL DRUGS CONTAINING PURINE BASES

Murexide reaction : After extraction (CH_2Cl_2), filtration, and solvent evaporation, the dry residue is treated with hydrogen peroxide or brominated water 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.

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

PHARMACOLOGICAL ACTIVITY OF PURINE BASES

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

CNS activity: Caffeine is a cortical stimulant.

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 tachicardia and 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 other activities of theophylline 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.

USES OF PURINE BASES

Caffeine:

Caffeine is available as an injectable solution at 25% for the following indication: stimulating of the CNS respiratory center in case of neonatal apnea. In addition, caffeine is an ingredient of several dozen products. For the most part, these are combinations with acetyl-salicylic acid, ascorbic acid, codeine, paracetamol, quinine, and other antipyretics and antalgics.

These combinations are used to treat fevers, aches, and pains, and the symptoms of flu.

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 a part a normal diet) and drugs; however, the simultaneous administration of enoxacin 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-alkoholic beverages and of “energizing” beverages that have appeared recently on the market. The level of caffeine in such beverages must not exceed 150-300 mg/l.

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

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. High-dose forms are reserved for adults. Theophylline can be used in infants in specialized hospital wards. The simultaneous administration of enoxacin is to be strictly avoided; the same is true for triacetyloleandomycin. Many other drug combinations can cause an increase in theophylline blood levels (macrolides, cimetidine, ticlopidine), or decrease (enzyme inducers), therefore they are discouraged.

The side effects are usually transient (nervousness, sleeplessness, transient tachicardia) or can be more substantial and include nausea, vomiting, headaches, tremors, epigastralgia, diarrhea, agitation, insomnia, and permanent tachicardia. The latter symptoms can reflect overdose and require a decrease in posology.

Theophylline is almost always used alone, but there are still a few combinations on the market (caffeine, ephedrine, phenobarbital).

Theobromine :

Theobromine is seldom used. Semi-synthetic pentifylline (1-hexyl,3,7-dimethylxanthine) was still marketed recently as a peripheral vasodilator.

TEA (Theae folium) ay yaprađı

***Camellia sinensis* (*Thea sinensis*) Theaceae**

Green tea, black tea, oolong tea..; first of all tea is one of the beverages most consumed the world around, and it is also a medicinal plant.

Black tea is defined as the young leaf (2.5 leaves) of *Camellia 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 no less than 2% caffeine.

The drug : There is a 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 heating or steaming, rolled, dried rapidly, and more or less roasted. It is consumed in China, Japan, north Africa and 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.

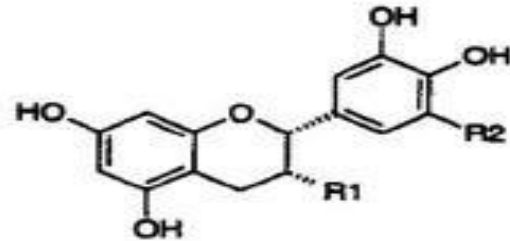
-Oolong tea, little known in Europe, it is only partially fermented.

“Fermenting” the tea leaves allows for polyphenol-oxidase activity and modifies its composition, appearance, odor, and the taste and the aroma of the infusion. The caffeine concentration is practically not altered by fermentation

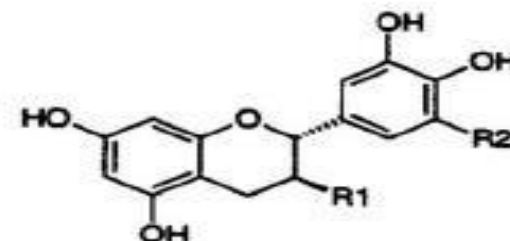
Chemical Composition : The unfermented tea leaf contains proteins (15-20%), amino acids (3%, mainly theanine), sugars (5%), ascorbic acid, group B vitamins, and purine bases chiefly represented by caffeine (2 to 4% depending on the variety). Glycosides of terpenoid, aliphatic and aromatic alcohols are 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), gallotannins and flavonoids, the chief constituents are flavan-type compounds including (-)-epigallocatechin gallate (EGCG, 5-12%), (-)-epicatechin gallate (EGC, 5%) and epicatechin (0.2-2%).

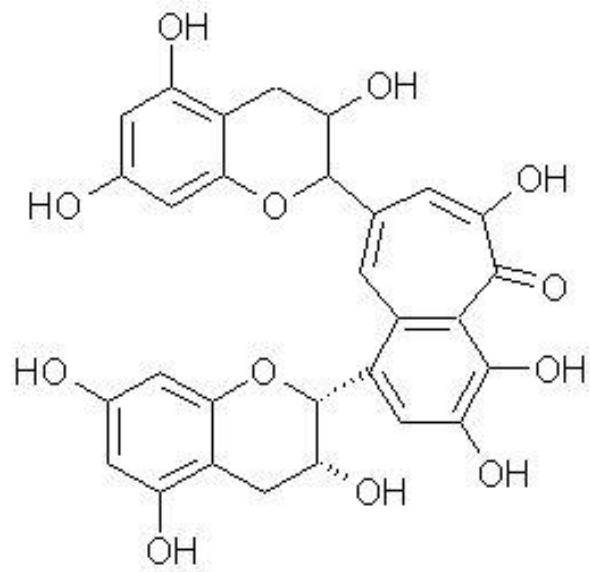
Several proanthocyanidins have also been characterized : procyanidols (procyanidins) B-2, B-4, C-1. One cup of green tea is said to contain 30-400 mg of polyphenols.



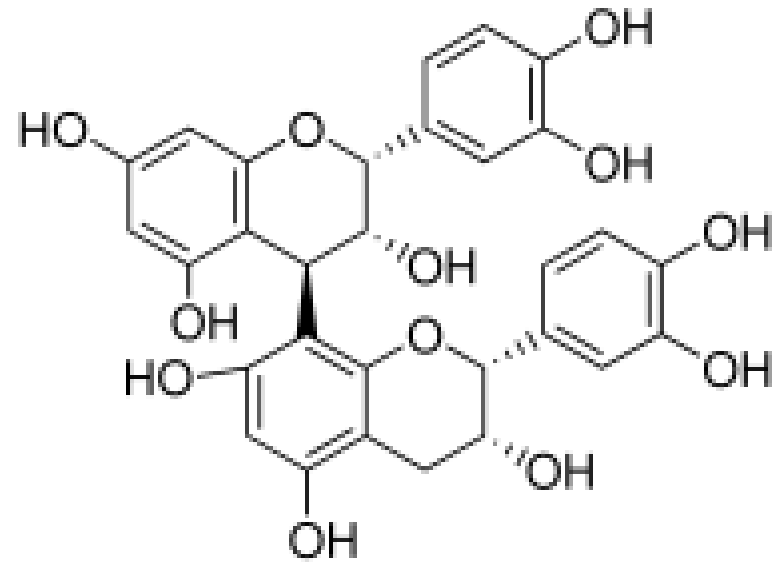
1. (-)-Epicatechin (EC)
R1 = OH
R2 = H
2. (-)-Epicatechin gallate (ECG)
R1 = Galloyl
R2 = H
3. (-)-Epigallocatechin (EGC)
R1 = R2 = OH
4. (-)-Epigallocatechin gallate (EGCG)
R1 = Galloyl
R2 = OH



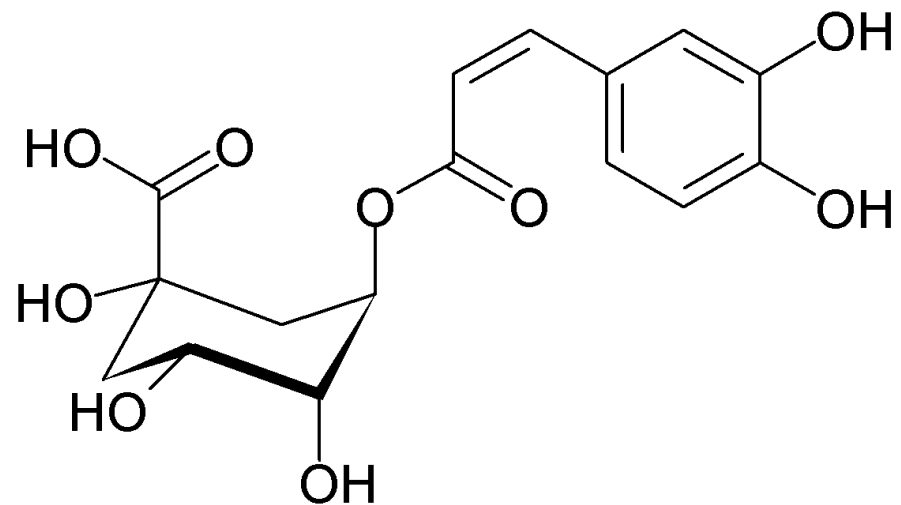
1. (+)-Catechin (C)
R1 = OH
R2 = H



Theaflavin



Procyanidol B-2



Chlorogenic acid

Upon fermentation, the composition changes : the infusion turns from pale yellow (green tea) to reddish brown (black tea), and the odor becomes clearly aromatic. The most abundant compounds are the oxidation and polymerization products of the theaflavins, thearubigins, and their derivatives (10-20%).

Partially fermented tea also contains oxidation products (theaflavins) as well as several theasinensins and 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.

Uses : (other than as a beverage) The tea leaf can be used orally, traditionally 1. for the symptomatic treatment of mild diarrhea 2. for functional asthenia 3. as an adjunctive treatment in weight loss programs, and 4. to enhance the renal excretion of water. Topically, pharmaceutical products based on the tea leaf 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 (Coffeae semen) kahve tohumu

***Coffea* spp. mostly *Coffea arabica* Rubiaceae**

The drug : 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 world production of coffee (5.5 million t) comes mostly from South America (Brazil, Colombia, Peru). Coffee is also cultivated in Asia (Indonesia, India, Vietnam) and Africa (Ethiophia, Uganda, Ivory Coast).

Chemical Composition : More than 50% of the dry weight of green coffee bean is represented by sugars, essentially polysaccharides. Proteins and lipids represent 10-12% and 10-18% respectively. The coffee bean contains about 5% phenolic acids (quinic acid, caffeic acid, chlorogenic acid). The concentration of caffeine ranges from 0.6 to 2%, and up to and above 3% for some varieties.

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; pigments form; and the extremely complex aroma develops, (several hundred compounds; alcohols, phenols, aldehydes, furan- and pyrrole-type derivatives, hydrocarbons, thiophenes).

Cacao (Cacao semen) kakao tohumu

***Theobroma cacao* 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 mostly cultivated in West Africa.

The Drug : The fresh beans are odorless, very astringent, and bitter: they take 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 “cacao butter” and comprise 75% symmetrical triacyl-glycerols with an oleic acid at the 2-position. 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 also used in food technology.

OTHER DRUGS CONTAINING PURINE BASES

Kola (Colae semen) kola tohumu

Cola nitida, C. acuminata Sterculiaceae

Cola acuminata

The cola trees are medium-size trees (10-15 m) growing in the equatorial zones of West Africa (from Sierra Leone to Nigeria and to Gabon). They grow wild and also cultivated. Kola must contain not less than 1.5% caffeine

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 proanthocyanidin 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.

Mate **Mate folium, mate yaprağı**

Ilex paraguariensis **Aquifoliaceae**

Mate is a tree currently widely cultivated and also growing wild in Brasil, Paraguay and north of Argentina. Mate folium does not contain tannins in the strict sense of the term, but up to 10% total chlorogenic acids. In addition it contains 5-10% saponins. Flavonoids and purine bases (1.4-2.6%) are also found and are chiefly represented by caffeine (0.9-1.7%). The particular aroma of the drug is due to a complex mixture of over 250 constituents.

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, however, that the aqueous extracts display antioxidant properties under experimental conditions.

In Germany, the drug is used for physical or mental fatigue (Commission E).

Guarana (Guarana pasta)

***Paullinia cupana* Sapindaceae**

This species is cultivated in the lower Amazon region. 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. 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 seed contains caffeine (3.6-5.8%), saponins and tannins. It is traditionally used to treat mild diarrhea, and as an adjunctive treatment in weight loss programs. In South America, guarana is used to prepare carbonated and flavored beverages whose concentration in caffeine is adjusted by adding guarana.

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