Rx: Caffeine

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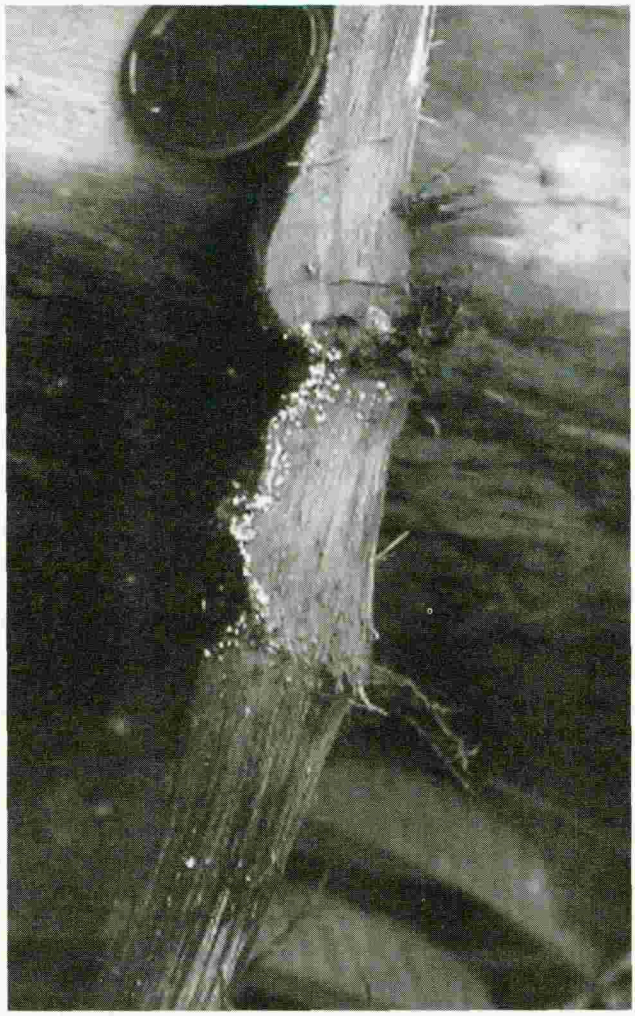
That tall cup of latte, perhaps topped off with a dollop of fresh whipped cream, is one of the great joys of modern life and an invigorating way to start off the workday. Try to bypass the specialty coffee shop in your neighborhood for even a morning and you feel the difference–that special "kick" is not present, and the rest of the day simply drags by. Far from a modern habit, or addiction, the use of caffeine-rich plants to jump-start the body's process of waking up is as old as human society. The late Harvard professor and ethnobotanist Richard Evans Schultes wrote of the discovery of caffeine-rich leaves of *Ilex guayusa*, a species of holly, in the tomb of a shaman from highland Bolivia dating from around 500 AD.[1] He surmised that burial of the leaves with the shaman indicated the respect and reverence people had for the caffeine-rich beverage made from this rare plant. Yet, it still is for sale in South America, appearing in local markets such as in the Colombian city of Pasto, where it is referred to as "*guayusa.*" Few botanical collections exist of this species, one of which is a collection of leaves, folded together in small packets and strung on a piece of twine, collected by Schultes' student Homer Pinkley, from a nearby region of Ecuador. It is one of the few examples of this commercial product in a museum collection and can be seen in the Gothenburg Ethnographic Museum in Norway.

Schultes' fascination with psychoactive plants led him to identify and describe other stimulants used by indigenous peoples of South America. He described a new species, *Paullinia yoco*, R. E. Schultes et Killip in 1942,[2] based on his fieldwork in the Western Amazon Valley of Colombia and Ecuador. *Yoco*, as the plant is called in this region, is a liana growing wild in the Amazonian forest. According to Schultes, it is a slow growing vine that is apparently not cultivated but rather wild harvested, and, occasionally, when the wild supply runs out, people abandon their settlements and move to another area in which the vine is more plentiful. He calls it one of the most important plants in the diet of the indigenous people in this part of the Amazon: "every Indian household keeps a supply of *yoco* stems, and few natives ever make a trip of more than a day though the forests without carrying two or three pieces."[2] The tribes that use *yoco* include the Kofans, Sionas, Inganos, Koreguajes, Secoyas and perhaps others, shaving the bark into cold water and mashing it, resulting in a beverage with a very bitter taste. These shavings contain a caffeine-rich sap, and approximately 90 to 100 grams of stem material is mixed into a gourd full of water. According to Schultes, chemical analyses of the bark of *yoco* has shown a concentration of 2.73% caffeine–the effects of which are felt within 15 to 20 minutes.[2] It is also used to reduce fevers, but, primarily, it is valued as a daily morning stimulant, not unlike our own cherished cup of coffee or tea.

Another important stimulant plant is *guaraná*, known botanically as *Paullinia cupana* H.B. & K., found in Brazil, Colombia, and Venezuela. This is a vine in the soapberry family–the Sapindaceae–that bears red capsules containing chocolate brown seeds. It is these brown seeds that are valued for their caffeine (sometimes known as guaranine) content–some 4.3% by weight or three to five times as much caffeine as coffee.[3] People who cultivate and harvest *guaraná* prepare it into sticks of dry, hardened paste, which can be stored and transported. The seeds are dried in the sun, cleaned, and baked over heat. They are then ground into a fine powder, mixed with water, and become dough-like in consistency. The mass is formed into sticks, each approximately 1-inch thick by five to eight inches long, and a few coarsely chopped seeds are mixed in. To make a drink from this stick of paste, it is rasped against a rough object to produce a powder–often the dried tongue of a Brazilian species of fish, the *pirarucu,* which has a very rough surface–and the powder is mixed with hot or cold water. *Guaraná* is a very popular beverage in Brazil, where it is sold as a bottled, carbonated beverage under a variety of brands. Of course, this powerful stimulant also found a place in the Western botanical formulary, used in a myriad of commercial products that, among other things, promise extra energy, sexual prowess, or weight loss. "Whether it is dancing till dawn or making it through those incredibly slow days at the office, you should try guaraná!" touts one advertisement.[4] It is not uncommon to see this plant mixed with other stimulants such as *Ephedra*, resulting in a 110-octane super cocktail.

There are over 60 plant species that naturally contain caffeine.[5] So why do so many plants make caffeine? Many experts feel that caffeine evolved as a secondary compound (not essential for a plant's survival) as a natural pesticide.[6,7] Caffeine is poisonous to herbivores and insects. It is also toxic to plants and is stored in special vacuoles or specialized plant compartments, which protect the plant from this toxic stimulant. Thus, caffeine may serve as a "biochemical coevolutionary" strategy for plants to survive against some of their adversaries.[5,7] Today, worldwide consumption of caffeine (from all sources) is estimated to be 120,000 tons per annum or "the approximate equivalent of one caffeine-containing beverage per day for each of the planet's five billion inhabitants."[8] Approximately 210 mg/day of caffeine are consumed daily in the United States, but the distinction for the highest consumption is credited to Sweden where average consumption is 400 mg/day.[9]

Of all the caffeine-containing plants consumed, one of the earliest plants used as a beverage was *Camellia sinensis* Kuntze. Better known as tea, *Camellia sinensis* was discovered in 2737 BC when Emperor Shen Nung was said to be boiling drinking water and the leaves of a nearby bush fell into the pot creating a wonderful smelling drink.



Vine of *yoco (Paullinia yoco)* split to show the caffeine-rich white sap used by indigenous people in the Amazon Valley as a stimulant. Photo by Steven R. King.

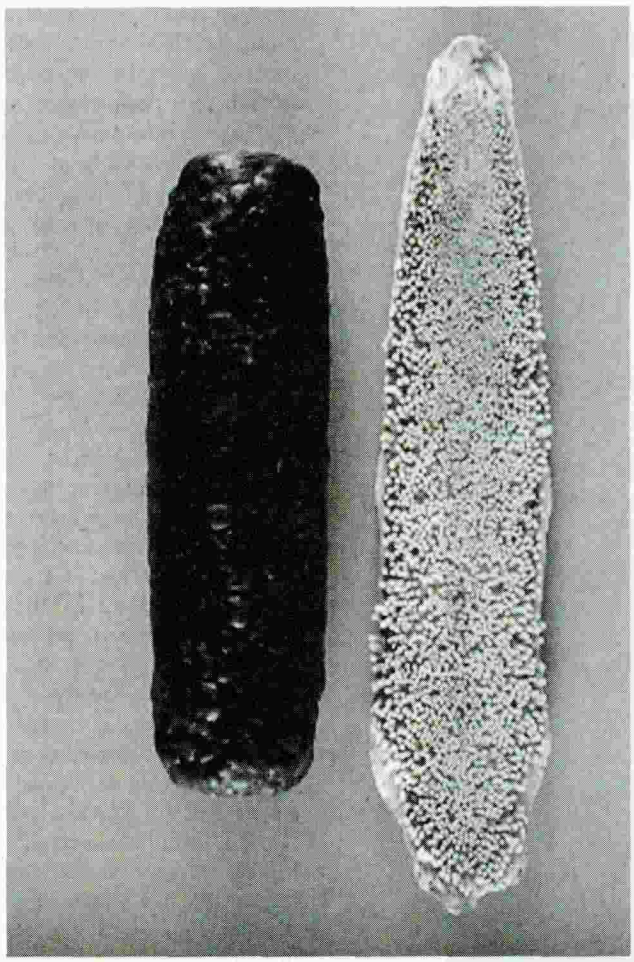
Camellia sinensis is the plant source for black tea (fermented), green tea (unfermented), and oolong (partially fermented). Fermentation is a processing technique that creates an enzymatic oxidation resulting in the black coloration. *Camellia sinensis* is the only plant responsible for making what is labeled as a "true tea."[10] All other teas that do not contain true tea leaves are known as tisanes or herbal infusions. During the T'ang dynasty (618-907 AD), tea drinking was popularized by the Buddhist monk Lu Yu, through the writings on the virtues of tea in his book, the *Ch'a Ching*. Over time, tea drinking spread to other Southeast Asian countries and was taken for trade over the Silk Road, helping to extend tea drinking to Central Asia, Russia, and the Middle East. Tea has over 400 volatile compounds including polyphenols–a group of antioxidants recognized for their health benefits. Undoubtedly, part of tea's popularity was derived from its stimulating caffeine effects.[6] Tea has approximately 35 to 50 mg of caffeine for each eight-ounce serving.[11] However, tea holds second place to coffee in global consumption.

Aside from *Camellia sinensis*, some of today's commonly used caffeine-containing plants include coffee (*Coffea arabica* L. *or Coffea canephora* Pierre ex Froehn.), the kola nut (*Cola acuminata* Schott & Endl.), yerba mate (*Ilex paraguariensis* A. St.-Hil.), chocolate (*Theobroma cacao* L.), and the previously mentioned guaraná (*Paullinia cupana*).

Coffee, native to Ethiopia, was said to be first "discovered" by a local goat herder by the name of Kaldi. Legend has it that he observed an unusual friskiness in his herd after they ate the red berries of a local shrub, so Kaldi experimented and ate them himself, noting the same sensation. Eventually, someone discovered that roasting the beans and brewing them with boiling water made the process of ingestion more palatable.[12] The oldest existing text to document coffee's use as a medicine is written in The Canon of Medicine of the great Islamic physician Abu Ali al-Husain Ibn Abdullah Ibn Sina often referred to as Avicenna (980-1037). In his time, this noble bean was used to "clean the skin, dry up the humidities that are under it, and give a better odor for the body."[13] By the 15th Century, the spread of coffee initially used by some Sufi orders for its energizing effects crossed over into secular use and coffee houses spread throughout the Arab world. In the early 17th and 18th Century, with the explosion of the sea trade, coffee use grew and became commonly available in Europe.[14] Now, coffee ranks as the number one caffeine-containing beverage consumed in the world. A 12-ounce cup of brewed coffee contains 200 mg of caffeine–four times the amount found in a cup of tea.[15]

The kola nut is derived from two species–*Cola acuminata* and *C. nitida* A. Chev.–native to West Africa. This nut has been chewed for thousands of years and used as an appetite and thirst suppressant and "social lubricant."[16] Traded by West Africa since the 14th Century, the cola nut is exported world wide and naturalized in South and Central America, the West Indies, Sri Lanka, and Malaysia. The value of this nut today is based on its methylxanthine content–the same stimulant compounds found in tea, chocolate, yerba mate, and *guaraná*. These sources of caffeine have been used in natural dietary supplements for appetite suppression and natural remedies to enhance energy and stave off sleep.

Energy drinks boosted with caffeine are the newest caffeine concoctions to enter the market place. Sodas such as Coca-Cola (The Coca-Cola Co., Atlanta, GA), Seven Up (Cadbury Schweppes, Plano, TX), and Sprite (The Coca-Cola Co., Atlanta, GA) contain approximately 30 mg of caffeine per eight ounces. However, these newer so-called energy drinks have significantly raised the level of caffeine to 80 mg per eight ounces. One of the first drinks of this



Dried stick containing ground *guaraná* seeds, processed in the traditional way (L) with the rough, dried tongue of the *pirarucu* fish (R) that is used to grind the *guaraná* stick into a fine powder. Photo by Michael Balick.

type to enter the market place was Red Bull (GmbH, Fuschl am See, Austria) conceived by Autstrian Dietrich Mateschitz, who observed that many rickshaw drivers drank something that kept them energized throughout the day in his travels throughout Asia. Thinking that this would be something the West would embrace, he came up with a formula containing significant amounts of caffeine, vitamins, and amino acids. Since its introduction in 1987, many other energy drinks have entered the marketplace in this unique beverage category, and now there are over 1,000 energy drinks for sale.[17] The source of caffeine for these beverages is often the kola nut, *guaraná,* or caffeine that is derived and purified from the decaffeination of coffee.[18] Red Bull and others like it now have billions of dollars in sales. The success of this genre of beverages, marketed to people under thirty, is appealing because it is touted as a "natural" means to boost energy. An "off label" use of these drinks has evolved, and now these drinks are mixed with alcohol. The combination provides energy, but many erroneously assume that the caffeine negates the sedating effects of the alcohol. In reality, the blood alcohol levels are unaffected by the caffeine, and, when the caffeine wears off, the depressant effects of the alcohol re-emerge.[19] A number of deaths, attributed to the increased levels of caffeine, have been linked to excessive intake of these beverages.

With this renewed interest in caffeine, the big question is, "what health benefits or risks are associated with caffeine use in general"? This subject has been extensively researched and debated for several decades. Despite caffeine's use in traditional cultures via consumption of stimulant enhancing botanicals, it was not until 1820 that caffeine was identified as a chemical structure by the German chemist Friedlieb Ferdinand Runge.[15] Runge's work identified caffeine as a lumpy structure that belonged to a group of chemicals known as methyxanthines. Methylxanthines are stimulants to the nervous system. Methylxanthines are broken down in the liver into several products: theophylline, theobromine, and paraxanthine. Theophylline relaxes smooth muscles in the bronchi or large airways of the lungs and has been used to treat asthma. Theobromine is found in large amounts in cacao beans, the source of chocolate and causes wakefulness. Caffeine works primarily on the central nervous system as a stimulant and mediates this effect by blocking the adenosine receptors A2A and A1. With prolonged wakefulness, adenosine will build up in the central nervous system, generating the urge to sleep. Thus, the net effect of caffeine is to curtail the body's natural tendency to rest after a long period of wakefulness. In extreme situations, prolonged blockage of adenosine can result in over stimulation and seizures. Adenosine 2A receptors are also found in endothelial cells, which line arteries. Caffeine, interacting with the adenosine receptors, will cause vasoconstriction or tightening of these arteries in certain parts of the brain. This effect has been used as treatment for migraine headaches, which are the result of vasodilation of the arteries. In another very specific area of the brain called the *globus pallidus*, caffeine can neutralize A2A receptors, resulting in the inhibition of &gamma-aminobytyric acid (GABA) release. Medications such as Valium (Roche Products Inc, Roche Laboratories Inc., Nutley, NJ) or diazepam and other benzodiazepines tranquilizers enhance GABA release, creating drowsiness.[20] Thus, caffeine can neutralize a benzodiazepine effect. However, unlike other stimulants such as cocaine, amphetamine, or morphine, caffeine cannot activate dopamine release. The dopamine release associated with the other stimulants mentioned above is thought to stimulate centers of the brain that establish strong addictions. Experts feel that the so-called "addictive" properties of caffeine are derived more from the withdrawal or removal of caffeine–with the implication

Fruits of *guaraná* growing on a vining stem and enclosing the brown, round seeds that are dried and processed into a caffeine-rich beverage. Photo by Michael Balick.

being that caffeine's withdrawal is a relatively weak phenomenon. Typical withdrawal symptoms include lethargy and fatigue. Symptoms of withdrawal have been recorded to occur with as little as 100 mg/day of caffeine consumption. This is the amount equivalent to one, six-ounce cup of coffee a day or three cans of a caffeinated soft drink.[21]

Chronic ingestion of excessive amounts of caffeine can result in a syndrome called caffeinism. Caffeinism is characterized by restlessness, nervousness, insomnia, increased heart rate (tachycardia), and gastric upset. At extremely high doses (>1000 mg/day), severe psychiatric effects have been reported that are difficult to distinguish from an anxiety disorder.[20] Until 2004, the International Olympic Committee had caffeine on its prohibited substance list. Athletes testing positive for more than 12 micrograms per liter of urine–a level that could be reached by drinking as little as five cups of coffee in a day–were banned from Olympic games.[22]

In previous years, caffeine and coffee consumption have been linked to certain kinds of cancers, including breast, colon, bladder, and pancreatic cancer. However, recent studies have found no correlation in caffeine consumption and cancer risk in humans.[23,24]

Similarly, correlations with caffeine and cardiovascular disease have not been definitively correlated. However, some studies have suggested that nonfiltered coffee can elevate serum low-density lipoprotein (LDL) concentrations (the bad cholesterol fraction)[25,26] and triglycerides.[27]

Other studies have revealed some interesting health benefits of caffeine. Assessment of vigilance and improvement of performance during night operations in soldiers was positively correlated with use of caffeine-infused gum. Soldiers given 200 milligrams of caffeine in two-hour intervals for a total of three doses on the third day of a 27-hour period of sleep deprivation displayed statistically significant improvement of enhanced vigilance and running performance over those assigned to the placebo arm.[28] In another study evaluating physical endurance during intervals of intense cycling, moderate improvement was observed in those given caffeine.[29] In addition, the ratings of perceived exertion were lower in those athletes given caffeine. Increased consumption of coffee has also been correlated with a lower risk of type 2 diabetes.[30] A systematic review of nine cohort studies evaluating 193,473 participants and 8,394 cases of type 2 diabetes showed a substantially lower incidence of diabetes.[30] These findings were also observed in another epidemiological study performed at the Harvard School of Public Health by Frank Hu, MD, and his associates. In his study, those drinking fewer than four cups of coffee per day had a reduced risk of type 2 diabetes by 2% to 7%, whereas those drinking six or more cups of coffee had a reduced risk of 23%.[31]

In summary, caffeine is one of the most thoroughly investigated ingredients in food, and it appears that, when taken in modest amounts, it is safe. Humans, and perhaps other animals as well, ingest caffeine in many different ways, seeking to escape nature's natural patterns of sleeping and wakefulness and for a cup of enjoyment as well.

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