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A New Look at an Old Devil

by Paul Bergner

It possesses antidiabetic, anti-inflammatory, antioxidant, cholagogue, hepatoprotective, neuroprotective, and antidepressant effects. Regular consumption reduces the incidence of cardiac-related and all-cause mortality in a dose-dependent manner. It is the only herbal remedy shown consistently to extend life in epidemiological studies. It has been proposed as a 'functional food' by the prestigious *British Journal of Nutrition* (DÓrea). This panacea would undoubtedly be named 'Herb of the Century' but for its name: Coffee. Research over the last ten years has seen the emergence of scientific consensus on the broad health benefits of *Caffea arabica,* one of the world's most frequently consumed herbal decoctions.

Coffee, lumped with such agents as nicotine and alcohol, has been demonized not only in contemporary alternative and conventional medicine; but also going back centuries in the history of Arabia and Islam, and more recently in temperance movements in Europe and North America. Moral judgments about coffee invariably arise from the stimulating and habit-forming character of caffeine. In the Ottoman Empire, religious debates raged about whether it was an intoxicant like alcohol or opium, or was otherwise 'legal' in Islamic law. The eventual edict was that although it was an intoxicant, it was similar to the "wine of Paradise" described in the Quran, "that will neither pain their heads nor cloud their reason" and it is not considered an intoxicant by Islamic scholars today. The criterion is that it does not impair judgment. European and North American Christian temperance movements militated against coffee and tea as well as alcohol; and the first version of the FDA regulation of opium and marijuana also proposed making coffee and caffeine into illegal or controlled substances.

Negative attitudes bordering on puritanical fundamentalism persist today in the field of alternative medicine, where a high priority is often placed on removal of coffee or caffeine from the diet without consideration of its actual harmful or beneficial effects on a patient's chief presenting complaint, constitution, or overall health; and usually with complete ignorance of its potential benefits. Below, we describe the potential benefits and harms of coffee consumption so the practitioner may make an informed judgment as to the priority that might be placed on removal or reduction of coffee consumption in any particular case.

The Health Benefits of Coffee

EFFECTS ON LONGEVITY

Coffee has a well-documented benefit on overall mortality, and in light of this it must be considered a tonic to the cardiovascular system and overall health. Early population studies suggested that coffee drinking might increase overall mortality, but recent large and better-controlled investigations show just the opposite. A prospective study of more than 120,000 subjects by the Harvard School of Public Health found that individuals at the highest level of coffee consumption (6 or more cups per day) had about a 20% reduced overall mortality rate (in either men or women) compared to those who drank coffee less than once per month. Some benefit was also seen in women who consumed 2–4 cups per day, and in men who drank 4–6 cups. The decrease in overall mortality was mainly due to a decrease in cardiac deaths (Lopez-Garcia et al., 2008). Recent studies in Finland and Japan also found reduced overall mortality for coffee drinkers compared to non-drinkers (Happonen et al.; Iso et al.). The Finnish trial showed that each additional cup of coffee per day reduced the overall mortality rate by about 4% – results very similar to those from the Harvard study.

CARDIOVASCULAR DISEASE

In the Harvard trial cited above (Lopez-Garcia et al.), overall cardiac mortality was lower in heavy coffee drinkers than in non-drinkers. Significantly, the trial was controlled for smoking, an adjustment omitted in many earlier studies that suggested a link between coffee drinking and heart attacks. This was confirmed in another recent prospective trial of 127,000 patients enrolled in a Kaiser Permanente plan in California. After seven years, diagnosed coronary artery disease (CAD)

was found to be related to coffee only among current or former smokers. For those who had never smoked, coffee had no significant correlation to CAD. The researchers concluded that the disease in smokers was unrelated to coffee drinking (Klatsky et al.). Coffee consumption likewise did not elevate coronary risk in a recent meta-analysis of 23 studies (Sofi et al.). The results were similar to those from a 1994 meta-analysis (Kwachi et al.).

Coffee may slightly elevate blood pressure, but only to a clinically insignificant degree. Pooled data from 18 studies of coffee's effect on blood pressure found that, taken for more than seven days, coffee raises systolic pressure by 1.22 mm Hg, and diastolic pressure by 0.49 mm Hg. The average intake was 24 ounces, given to previous non-drinkers (Noordzij et al.). Another trial examined blood pressure elevation with larger amounts of coffee and for a longer duration. In the 11 studies reviewed, median duration was 56 days and median dose was 40 ounces of coffee per day. Systolic and diastolic blood pressure increased by 2.4 (range, 1.0 to 3.7) mm Hg and 1.2 (range, 0.4 to 2.1) mm Hg, respectively, with coffee treatment compared to control (Jee et al., 1999). The effect of coffee in patients with established hypertension (whether habituated or not) has not been measured, and may possibly be contra- indicated.

Coffee has a well-documented benefit on overall mortality, and . . . must be considered a tonic to the cardiovascular system and overall health.

Coffee can raise total cholesterol, LDL cholesterol, and triglycerides in some individuals – but not with the form of coffee most commonly consumed. A review of 14 trials found average increases in total cholesterol of 12 mg/dl; in LDL cholesterol of 6.5 mg/dl; and in triglycerides of 6 mg/dl. Most of the effect was observed in those who consumed 6 or more cups per day, and was evident *only* in trials of boiled (not filtered) coffee. The filtering process appears to remove the constituents responsible for the elevation of lipids (Jee et al., 2001).

Systemic inflammation is currently recognized as a significant risk factor for cardiovascular disease. Some earlier studies suggested that habitual coffee drinking was correlated with higher measures of systemic inflammation, such as C-reactive protein (Zampelas et al.). Three more recent and better-controlled trials in divergent populations document correlations ranging from no association between coffee consumption and CRP in normal controls, to a protective effect of about 10% lower CRP for each extra cup of coffee drunk by women with type II diabetes (Lopez-Garcia 2006; Williams et al.; Kotani et al.).

DIABETES AND GLUCOSE TOLERANCE

Population studies on three continents have now documented a protective effect of coffee against the risk of type II diabetes. The protection is linear – the more coffee an individual drinks, the lower their risk of diabetes. Individuals drinking 6 cups of coffee per day have about half the risk of those who drink none at all. Studies have found protective effects ranging from 30–60%, increasing as consumption increases (van Dam; Murakami et al.; Legrand and Scheen). The protective effect is not due exclusively to caffeine, and is probably due to chlorogenic acid and/or various other antioxidants in coffee. Either caffeinated or decaffeinated coffee improves glucose tolerance (van Dam).

CANCER

Coffee's connection to various cancers has been studied extensively, due to safety concerns about this widely consumed beverage. A review of ten studies found that coffee consumption is protective against liver cancer. On average, hepatocellular carcinoma was reduced by 30% in moderate coffee drinkers and 55% in heavy users (Bravi et al.). Another meta-analysis of nine studies examined the relationship between coffee drinking and either primary liver cancer or hepatocellular carcinoma, and found similar results. All studies examined found a protective effect. An increase of two cups of coffee per day was associated with a 43% reduced incidence of the two types of liver cancer. This included a 31% decrease in individuals without prior history of liver disease, and a 44% decrease in those with such a history (Larsson and Wolk).

One large population study (The Nurses' Health Study) found a small protective effect of coffee for breast cancer in postmenopausal women, but not in the group overall (Ganmaa et al.). A case-control study found a protective effect in premenopausal but not postmenopausal women with breast cancer who consumed 4 or more cups of coffee per day. The risk was reduced by about 40% (Baker et al.). A large study in Sweden, on the other hand, found no association between coffee consumption and breast cancers in any group (Michels et al., 2002).

Some early studies indicated that coffee may be protective against colon cancer. However, several meta-analyses have failed to find any effect, either protective or causative (Tavani and La Vecchia; Michels et al., 2005; Naganuma et al.).

The only cancer with a possible positive correlation to coffee is bladder cancer. A review of 37 trials found a small increase – about 20% – in bladder cancer among the heaviest coffee drinkers. The authors note that the results could be due to higher rates of smoking in coffee drinkers (Zeegers et al.). Most of the trials were not controlled for nicotine use, and nicotine is a well-established risk factor for bladder cancer. A review of 10 case-control studies in Europe among non-smokers found no relationship between coffee and bladder cancer except in a small group that consumed more than 10 cups of coffee per day (Sala et al.).

Other reviews have found no correlation between coffee consumption and a variety of cancers. A review of 23 studies found no relationship, either protective or adverse, between coffee consumption and gastric cancer (Botelho et al.). A review of 14 trials found no association between coffee and thyroid cancer (Mack et al.). Likewise, on meta-analysis, no correlation was found between coffee consumption and pancreatic (Ilart et al.) or prostate (Dagnelie et al.) cancers.

GASTROINTESTINAL AND GALLBLADDER

Coffee has the same general risks and benefits as other herbs containing bitter principles. A review of coffee's gastrointestinal effects showed that in some individuals it produced gastrointestinal reflux. It was not found to be associated with dyspepsia. Coffee promotes peristalsis in the colon at about the same rate as a 1,000 Kcal meal (Boekema et al.). The recent published reviews of coffee's effect on gallstones all show a dose-dependent protective effect (Boekema et al.; Lammert and Matern; Misciagna et al.; Shaffer). In one representative study, individuals who consumed 2–3 cups of coffee per day had a 40% reduced risk of gall bladder disease. The risk for those who drank four cups or more was even less (Leitzmann et al.).

NEUROLOGICAL CONDITIONS

A Harvard review of 13 studies found a protective effect of coffee for Parkinson's disease. The risk was reduced by about 30% for each 3 cups of coffee consumed (Hernán et al.). The pooled data from four studies conducted between 1990 and 2002 found a protective effect against Alzheimer's disease in coffee drinkers of about 30%. Such protection may be due to the anti-inflammatory or the insulin-sensitizing effects of coffee. Extensive current literature links insulin resistance with hyperinsulinemia as a major contributing factor to Alzheimer's disease (Barranco et al.).

KIDNEY STONES

Because caffeine may increase diuresis and the urinary excretion of calcium, it has been proposed as a risk factor for calcium kidney stones. However, a trial conducted by researchers at Harvard University found about a 40% reduced risk of kidney stones in a group of patients who consumed the most liquids, compared to the least; there was an additional 9–10% reduction in risk for each additional eight-ounce cup of caffeinated or decaffeinated coffee consumed on a regular basis (Curhan et al.).

DEPRESSION AND SUICIDE

No significant research appears on the relationship between coffee, caffeine, and depression. However, coffee drinking appears to be strongly inversely related to the risk of suicide, a natural endpoint of depression. A 10-year study in a group of more than 86,000 women found that those who drank two or more cups of coffee per day had about 40% the suicide risk of non-drinkers (Kawachi et al., 1996). The protective effect was also present in a group of more than 43,000 subjects followed for 15 years. However, in the group consuming greater than eight cups per day, there was an increase in suicide risk. It was impossible to tell from the data whether the high amounts induced depression or whether depressed patients self-medicated with coffee (Tanskanen et al.).

The Adverse Effects of Coffee

INSOMNIA

In occasional users, or those who exceed their habitual intake, caffeine may cause insomnia (especially if it is not cleared from the system by bedtime). See *The Pharmacology of Coffee Constituents* for a discussion of factors that affect clearance. Complete tolerance to the sleep-disrupting effects of caffeine develops after consuming very large doses: 400 mg of caffeine, 3 times per day, for 7 days. Complete tolerance to subjective effects of caffeine was observed to develop after consumption of 300 mg, 3 times per day, for 18 days; and possibly even sooner. Normal doses of caffeine such as are consumed by habitual users do not cause complete tolerance, and some level of sleep disruption may still occur (Griffiths and Mumford).

ANXIETY

The acute or chronic effects of caffeine may meet the criteria of acute or chronic anxiety disorder. Turn-of-the-century herbal and medical texts described a syndrome known as caffeinism, which included most of the symptoms of anxiety. The table below compares the symptoms of caffeinism with the conventional diagnosis of chronic anxiety – one form of 'stress' in lay terms. In one study, patients with anxiety disorder rated their symptoms on a standard test. Their levels of anxiety and depression correlated directly with the amount of caffeine they consumed. Another group of six anxiety pa-

Energetics and constitutional affects of coffee

Unani Tibb: According to Avicenna, coffee is hot and dry in the first degree, but he states that other experts consider it cold in the first degree. In Unani (four-humors) medicine, first degree herbs are those that will nudge the patient toward a temperate (neutral) state, but not overshoot the mark to overheat or overly cool the patient. "It fortifies the members, cleans the skin, and dries up humidities that are under it, and gives an excellent smell to all the body (Weinberg and Bealer)."

This nearly-neutral property of coffee allows it to be drunk in larger quantities than would be possible with cold bitter herbs such as Taraxacum, Mahonia, or Gentian. It may, however, aggravate the dry patient, especially those that are dry and cold.

Chinese Medicine: Dr. Subhuti Dharmanada of the Institute for Traditional Medicine has published an extensive article online characterizing coffee according to Chinese medicine (Dharmananda.) He compares its action to that of Bupleurum and states that it is "a valuable therapy for stagnated liver qi, with constricted circulation of blood, and constrained gallbladder function, with constricted elimination of damp and heat.

Summarizing his descriptions:

Flavor: bitter, partly sweet.

Actions: dredges the liver to regulate the flow of liver qi, purges the gallbladder, opens the heart orifices, warms the blood circulation, detoxifies, and gently tonifies.

Cautions: "While coffee dredges the liver qi, it does not necessarily smooth or soothe the liver qi. Therefore, one has to be cautious about the amount consumed and certain individuals will find the otherwise desirable effects distressing: releasing stagnated qi but not regulating its flow."

" Excessive amounts of coffee will agitate the liver yang and even stimulate internal wind. Prolonged use of excessive amounts could thereby damage the blood"

tients who consumed the caffeine equivalent of 1.5 to 3.5 cups of coffee – about the average for Americans – cut their intake to zero. Within 12–18 months, five of the six were symptom-free. Anxiety symptoms do not occur in the majority of individuals consuming 1–4 cups of coffee per day; but in those exhibiting them, caffeine should be considered as a possible cause.

HEARTBURN AND INDIGESTION

Coffee and caffeine may cause or worsen heartburn in some individuals. This may be due to the effects of bitter substances on the secretory apparatus of the stomach. Caffeine itself also increased acid secretions. See The Pharmacology of Coffee Constituents for more details.

PREMENSTRUAL SYNDROME

A number of trials demonstrate a connection between caffeine consumption and the presence and severity of premenstrual syndrome in a dose-dependent manner (Rossignol; Rasheed et al.; Ader et al.; Rossignol et al., 1991). In one trial, risks for PMS increased 700% in women consuming 8–10 cups of coffee per day compared to those who consumed none (Rossignol and Bonnlander). The association has also been found in Asian women consuming caffeinated tea (Rossignol et al., 1989). Caffeine competes with estradiol for clearance via liver p-450 enzymes. Alcohol and various prescription drugs may also compete for clearance – see the accompanying Pharmacology of Coffee Constituents. The pathway is dependent on the nutritional status of a number of micronutrients, especially magnesium, vitamin B-6, and zinc. All three nutrients are commonly deficient in the modern population, and their status may affect the interaction of caffeine and estrogen.

ADDICTION AND WITHDRAWAL

Like many addictive substances, caffeine consumption induces an adaptation which causes withdrawal symptoms when caffeine is removed (See Pharmacology). After habituation, the symptoms of chronic use are much less dramatic than initial symptoms in a non-habit-

Coffee formulation

Spices may be added to hot coffee, or other herbs may be decocted or infused in already-brewed coffee

Caffea and cloves. To enhance antioxidant effects; more stimulating and anticatarrhal.

Caffea and *Cassia cinnamomum*. to enhance antidiabetic effects. Also enhances antioxidation.

Caffea and *Arctium lappa*. Enhances the beneficial effects of both herbs on skin and liver

Caffea and *Urtica spp.* Strong diuretic combination. Drying. Adds nutritional content to coffee.

Caffea and *Paeonia lactiflora.* Enhances calming effects of coffee. Similar to Bupleurum and Paeonia combinations in Chinese medicine.

uated individual; the caffeine user may consume it to prevent withdrawal symptoms.

Withdrawal symptoms may include:

- Headache (50% of subjects)
- Fatigue
- Decreased energy / activeness
- Decreased alertness
- Drowsiness
- Decreased contentedness
- Depressed mood
- Difficulty concentrating
- Irritability
- Foggy / not clearheaded

Symptoms of caffeinism (*)	Symptoms of chronic anxiety (**)
Anxiety	Apprehension
Tremors	Trembling
Insomnia	Isomnia
Nervous irritability	Nervousness
Hysteria	Irrational thinking
Heart palpitations	Heart palpitations
Mental confusion	Difficult concentration
Muscular weakness	Motor weakness
Physical exhaustion	Chronic fatigue
Headaches	Headaches
(Felter and Lloyd)	(Berkow)

Flu-like symptoms, nausea, and muscle pain or stiffness may also occur (Juliano and Griffiths). Severity may be mild to extreme (incapacitating) – clinically significant distress or functional impairment may be present in 10–15% of users on withdrawal. Typically, onset of symptoms occurs 12–24 h after abstinence, with peak intensity at 20–51 h, and for a duration of 2–9 days. In general, the incidence or severity of symptoms increased with higher daily doses. Abstinence from doses as low as 100 mg/day produced symptoms, which may occur after as little as 6–15 days of use.

Caffeine does not meet the scientific criteria for addiction in most individuals, because the unpleasant effect of very large doses effectively produces a 'ceiling' on dose-consumption. Caffeine use also does not have *reinforcing* properties – consumption does not automatically lead to a continuous increase in dosage. Survey data suggest that only 9% to 30% of caffeine consumers may be caffeine-dependent (according to DSM-IV diagnostic criteria for a substance dependence syndrome), including feeling compelled to continue use despite desires and recommendations to the contrary (Dews et al.; Griffiths and Chausmer; Griffiths and Mumford; Griffiths and Woodson).

RISKS IN PREGNANCY

The effect of caffeine on pregnancy outcomes, including miscarriage and birth defects, is controversial. Of concern is the fact that caffeine clearance is reduced during pregnancy; it may concentrate in the fetus at higher levels than in the maternal blood, and is cleared even more slowly there. Whereas the mother may drink two cups of coffee – the second one being taken after the caffeine from the first one has cleared from her system – caffeine from both cups may remain on the fetal side of the placenta. For the mother who consumes larger amounts of caffeine, the problem may be severe.

Many, but not all, epidemiological studies suggest a connection between caffeine and miscarriage. However, a review of fifteen studies, taking into consideration confounding factors and reporting bias, suggests that the connection has not been conclusively demonstrated (Signorello and McLaughlin). One strong confounding factor was demonstrated in a trial that assessed caffeine intake before or early in pregnancy. The researchers found no connection between reported caffeine consumption and subsequent miscarriages. They did find, however, that interviews conducted after a miscarriage tended to over-report caffeine consumption (Savitz). Another recent prospective trial did find a connection between caffeine consumption and miscarriage (Weng et al.).

A meta-analysis of ten studies on caffeine consumption during pregnancy and its possible relationship to low birth weight was inconclusive. Three studies showed lower birth weight only with high levels of caffeine consumption, and concluded there was no evidence of a relationship between moderate amounts of caffeine and birth weight (Pacheco et al.). A recent prospective study found restriction of fetal growth strongly associated with caffeine consumption. The increased risk was about 50% for intakes of more than 200 mg caffeine per day (Boylan et al.).

A review of the potential for caffeine to cause birth defects concluded that effects seen with huge amounts of caffeine in animal trials do not represent a credible risk for human mothers (Christian and Brent).

In view of the inconsistent evidence, it would seem prudent to avoid caffeine during pregnancy, although moderate amounts may not provide actual risk. According to one safety review, "Currently available evidence suggests that it may be prudent for pregnant women to

limit coffee consumption to 3 cups/d providing no more than 300 mg/d of caffeine to exclude any increased probability of spontaneous abortion or impaired fetal growth." (Higdon and Frei).

BONE HEALTH

Coffee or caffeine consumption have been proposed as risk factors for osteoporosis, but the evidence is contradictory and reported associations may be due to confounding factors including insufficient intake of dietary calcium in some caffeine consumers. As long ago as 1997, a review of published literature failed to find a connection between coffee intake and markers of bone density (Auquier et al.). Recent literature reviews and one prospective trial similarly find no connection between caffeine and bone density or osteoporosis (Jarupanich; Waugh et al.; Wetmore et al.). One recent cohort study reported an association between osteoporotic fracture and caffeine intake only in women who consumed four or more cups per day and who were simultaneously deficient in dietary calcium intake (Hallström et al.). There was no association of osteoporosis with any level of caffeine consumption in women who consumed the RDA of calcium.

ADRENAL EFFECTS

Normal single doses of caffeine do not affect adrenalin or cortisol levels. See the accompanying article on The Pharmacology of Coffee. At higher experimental doses of concentrated caffeine, both circulating adrenalin and cortisol may be slightly elevated. Increase in levels of adrenal hormones raises the question whether habitual consumption of caffeine may result in adrenal exhaustion or insufficiency. A search of the *PubMed* database of the *National Library of Medicine* produces more than 11,000 articles on the topic of adrenal insufficiency or Addison's disease, but none of these describe any relationship to caffeine or coffee. The adrenalin-promoting effect of higher caffeine doses appears to be due to reduction of adrenaline clearance rather than to stimulation of increased secretion. Caffeine may thus reduce stress on the adrenals by reducing production requirements. The mechanism of increased cortisol at high experimental doses appears to be through increased ACTH from the pituitary.

The exhaustion seen in coffee withdrawal may be due to the exaggerated effects of adenosine rather than to any adrenal effects. See *The Pharmacology of Coffee Constituents*. An empirical argument for this is that the malaise of coffee withdrawal usually disappears after 10–14 days, which would not occur in adrenal exhaustion. Coffee consumption may also indirectly affect adrenal function through the effects of sleep debt. Coffee is often used by the individual in a state of sleep debt to stay alert. Sleep debt is accompanied by elevated cortisol levels, disrupted cortisol daily cycle, and insulin resistance. The endocrine disruption of sleep debt will usually disappear after about three days of 9.5 or more hours of sleep (Bergner).

ACUTE CAFFEINE INTOXICATION

Acute caffeine overdose may occur with doses in excess of about 300 milligrams, depending on body weight and level of caffeine tolerance. Symptoms may include restlessness, nervousness, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, irregular or rapid heartbeat, and psychomotor agitation (*Encyclopedia of Mental Disorders*). In cases of much larger overdoses, mania, depression, lapses in judgment, disorientation, disinhibition, delusions, hallucinations, and psychosis may occur (*Medline Plus*). In cases of extreme overdose, death can result. The LD50 of caffeine in humans is dependent on weight and individual sensitivity and is estimated to be about 150 to 200 mg per kilogram of body mass (roughly equivalent to 80–100 cups of coffee for an average adult) taken within a limited time frame that is dependent on half-life. Though achieving a lethal dose of caffeine would be exceptionally difficult with regular coffee, deaths have been reported from overdosing on caffeine pills; and serious symptoms of overdose requiring hospitalization have occurred from as little as 2 grams of caffeine.

The Pharmacology of Coffee Constituents

Coffee constituents to be considered include:

- Caffeine
- Caffeine metabolites
- Polyphenols
- Bitter principles

Caffeine is highly water-soluble, is rapidly absorbed in the stomach and intestine, and rapidly circulated to all the tissues. It freely crosses the blood-brain barrier and its distribution is close to equal in all tissues and fluids. When taken as coffee, caffeine levels peak about one hour after ingestion.

About 98% of caffeine is biotransformed in the liver to secondary metabolites with the remainder excreted in the urine or other fluids unchanged. The half-life is 3–4 hours in healthy adults, but may vary widely. It increases to 5–10 hours in women taking oral contraceptives, and to

9–11 hours in pregnant women. It is biotransformed by the CYP1A2 subset of the cytochrome p-450 system. In the predominant reaction, one or more of its methyl groups may be removed to yield primarily paraxanthine, a smaller amount of theophylline, and a physiologically negligible amount of theobromine. Secondary metabolites are eventually converted to uric acid derivatives and excreted in the urine. This same CYP1A2 pathway metabolizes estradiol; excess caffeine may compete with estradiol and thus contribute to hyperestrogenism, a common pattern of female reproductive pathology resulting in premenstrual syndrome, fibrocystic breasts, and other pathologies. Some pharmaceutical drugs are metabolized by the same pathway, and caffeine may interact with such medications (See table). Interactions may be aggravated or ameliorated depending on the nutritional status of magnesium, vitamin B-6, and zinc, which are essential for normal functioning of the pathway.

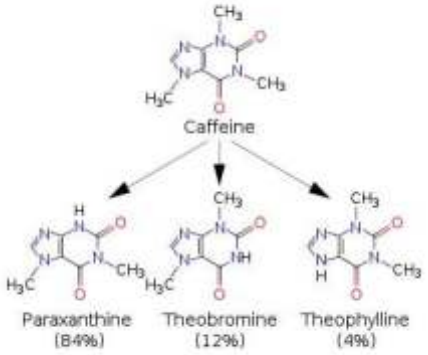
Some substances enhance the activity of the CYP1A2 pathway in the liver, and these may increase both tolerance and the speed of caffeine clearance. Notable on the list are nicotine and insulin. Smokers can drink more coffee with less net caffeine effect. Likewise individuals with hyperinsulinemia secondary to insulin resistance, with or without type II diabetes, may drink more coffee with less net caffeine effect because of enhanced biotransformation and clearance.

PHARMACODYNAMICS OF CAFFEINE

Caffeine binds to receptors for adenosine (a regulatory nucleotide with wide physiological activity) and blocks its effects. In the brain, adenosine is an inhibitory neurotransmitter; blocking it results in stimulation, with increased activity of dopamine and glutamate. Cells rapidly adapt to caffeine by increasing the number of adenosine receptors within 7–10 days. The result is a development of tolerance as the receptors up-regulate, with increasing doses necessary to achieve the same effects. There is a limit to this increase in receptors, and caffeine consumers habituated to high doses do not experience the same effects as non-users. Withdrawal symptoms are primarily due to excess adenosine effects in the caffeine-adapted user, with fatigue, depression, lethargy, and headache occurring until adenosine effects normalize in 5–10 days.

Caffeine increases levels of cAMP in cells via inhibition of the enzyme that normally breaks it down. Increased cAMP in turn reduces the clearance of epinephrine (adrenalin) and drugs that resemble it, including amphetamine and ephedrine; caffeine is thus used as a booster for ephedrine effects in 'herbal pep pills.' The same mechanism causes an increase in hydrochloric acid secretion in the stomach.

Caffeine metabolites



Drug-Herb Interactions

Medications that may have interactions with caffeine via competition for the CYP1A2 subset of the cytochrome p-450 system:

amitriptyline
clomipramine
clozapine
cyclobenzaprine
estradiol
fluvoxamine
haloperidol
imipramine
mexiletine
naproxen
olanzapine
ondansetron
phenacetin
acetaminophen
propranolol
riluzole
ropivacaine
tacrine
theophylline
tizanidine
verapamil

Factors Affecting Caffeine Metabolism

Slows metabolism	Speeds metabolism
Alcohol	Nicotine
Asian ancestry	Caucasian ancestry
Male	Female
Fetus/newborn	Child
Oral contraceptives	Insulin
Liver damage	
Pregnancy	

At a dose of 250 mg, caffeine appears to have no effect on cortisol, epinephrine, thyroid-stimulating hormone, growth hormone, prolactin, or triiodothyronine in individuals habituated to its use (Spindel et al.). At a 300–500 mg *single dose*, a slight elevation of ACTH, cortisol, or epinephrine may occur. A significant body of research into the effects of caffeine on the hypothalamic-pituitary-adrenal axis (HPA) shows that:

- Effects are generally non-existent at lower doses (Spindel; Spindel et al.; Tarnopolsky et al.).
- The threshold for endocrine effects is between 250 and 500 mg caffeine per dose (the equivalent of rapidly consuming 3–5 cups of coffee at a sitting) (Spindel; Spindel et al.; Lane).
- Effects are mild or non-existent in resting individuals not under stress (Spindel et al.; Van Soeren et al.).
- Both epinephrine (adrenalin) and cortisol responses to exercise or stress may be increased at the threshold dose and above (Lane; Lane et al.; Lovallo et al.; al'Absi et al.; Van Soeren et al.).
- Effects may be less in habituated caffeine users (Tarnopolsky et al.; Van Soeren et al.).

Most caffeine is converted to *paraxanthine*, and its pharmacological effects are added to those of caffeine. Paraxanthine increases lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma – a beneficial effect for exercise performance. A smaller amount is converted to theobromine (the principal alkaloid in *Cacao*) which dilates the blood vessels and increases urine volume; this compound is at least partly responsible for the diuretic effect of caffeine in those not habituated to it.

POLYPHENOLS

The polyphenol content of coffee, most notably chlorogenic acid and its derivatives, has been the focus of extensive research in recent years. Chlorogenic acid is a potent antioxidant with an insulin-sensitizing effect on cells. See the accompanying discussion of coffee consumption and diabetes. See also the table below for a ranking of coffee with other foods that are high in antioxidant content. As a reference, a cup of coffee contains more antioxidants than a cup of blueberries, and has about 3.5 times the antioxidant content per serving as green or black tea. Because most coffee drinkers consume more than the one serving of coffee, and because most do not consume the other foods with any frequency, coffee is the highest source of total dietary antioxidants in the average North American diet today. This may be a critical consideration before recommending that individuals remove coffee from their diets.

BITTER PRINCIPLES

The bitter constituents of coffee give the beverage effects similar to those of other bitter herbs: stimulation of digestive secretions and of bile release and flow from the liver. See the effects of coffee on digestion and gall bladder function in the accompanying article.

FOODS WITH THE HIGHEST ANTIOXIDANT CONTENT PER SERVING

Food	Serving	Mmol/serving of antioxidants
Blackberries	1 cup	5.746
Walnuts	1 oz.	3.721
Strawberries	1 cup	3.584
Artichokes, prepared	3 oz.	3.559
Cranberries	1 cup	3.125
Coffee	***1cup***	***2.959***
Raspberries	1 cup	2.870
Pecans	1 oz.	2.741
Blueberries	1 cup	2.680
Cloves, ground	1 tsp.	2.637
Grape juice	8 oz.	2.557
Chocolate, baking, unsw.	1 oz.	2.516
Cranberry juice	8 oz.	2.474
Cherries, sour	1 cup	2.205
Wine, red	3.5 oz.	2.199

(Halvorsen et al.)

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