[Template:About](/wiki/Template:About" \o "Template:About) [Template:Pp-semi-indef](/wiki/Template:Pp-semi-indef) [Template:Pp-move-indef](/wiki/Template:Pp-move-indef) [Template:Use dmy dates](/wiki/Template:Use_dmy_dates) [Template:Infobox drug](/wiki/Template:Infobox_drug) **Caffeine** is a [central nervous system](/wiki/Central_nervous_system) (CNS) [stimulant](/wiki/Stimulant) of the [methylxanthine](/wiki/Methylxanthine) [class](/wiki/Chemical_classification).[[1]](#cite_note-1) It is the world's most widely consumed [psychoactive drug](/wiki/Psychoactive_drug). Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. There are several known [mechanisms of action](/wiki/Mechanism_of_action) to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of [adenosine](/wiki/Adenosine) on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the [autonomic nervous system](/wiki/Autonomic_nervous_system).

Caffeine is a bitter, white crystalline [purine](/wiki/Purine), a [methylxanthine](/wiki/Methylxanthine) [alkaloid](/wiki/Alkaloid), and is chemically related to the [adenine](/wiki/Adenine) and [guanine](/wiki/Guanine) bases of [deoxyribonucleic acid](/wiki/DNA) (DNA) and [ribonucleic acid](/wiki/RNA) (RNA). It is found in the seeds, nuts, or leaves of a number of plants native to South America and East Asia and confers on them several survival and reproductive benefits. The most well known source of caffeine is the [coffee bean](/wiki/Coffee_bean), a misnomer for the seed of [*Coffea*](/wiki/Coffea) plants. [Beverages](/wiki/Beverages) containing caffeine are ingested to relieve or prevent drowsiness and to improve performance. To make these drinks, caffeine is extracted by [steeping](/wiki/Steeping) the plant product in water, a process called [infusion](/wiki/Infusion). Caffeine-containing drinks, such as [coffee](/wiki/Coffee), [tea](/wiki/Tea), and [cola](/wiki/Cola), are very popular; in 2005, 90% of North American adults consumed caffeine daily.[[2]](#cite_note-2) Caffeine can have both positive and negative health effects. It can be used to treat [bronchopulmonary dysplasia](/wiki/Bronchopulmonary_dysplasia) of prematurity, and to prevent [apnea of prematurity](/wiki/Apnea_of_prematurity): [caffeine citrate](/wiki/Caffeine_citrate) was placed on the [WHO Model List of Essential Medicines](/wiki/WHO_Model_List_of_Essential_Medicines) in 2007.[[3]](#cite_note-3) It may confer a modest protective effect against some diseases,[[4]](#cite_note-4) including [Parkinson's disease](/wiki/Parkinson's_disease)[[5]](#cite_note-5) and certain types of cancer. One meta-analysis concluded that [cardiovascular disease](/wiki/Cardiovascular_disease) such as coronary artery disease and stroke is less likely with 3–5 cups of non-decaffeinated coffee per day but more likely with over 5 cups per day.<ref name=Ding2014>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Some people experience [insomnia](/wiki/Insomnia) or sleep disruption if they consume caffeine, especially during the evening hours, but others show little disturbance. Evidence of a risk during pregnancy is equivocal; some authorities recommend that pregnant women limit consumption to the equivalent of two cups of coffee per day or less.<ref name=MayoPreg2>[Template:Cite web](/wiki/Template:Cite_web)</ref>[[6]](#cite_note-6) Caffeine can produce a mild form of [drug dependence](/wiki/Drug_dependence) – associated with [withdrawal symptoms](/wiki/Drug_withdrawal) such as sleepiness, headache, and irritability – when an individual stops using caffeine after repeated daily intake.[[7]](#cite_note-7)[[8]](#cite_note-8)[[9]](#cite_note-9) [Tolerance](/wiki/Drug_tolerance) to the autonomic effects of increased blood pressure and heart rate, and increased urine output, develops with chronic use (i.e., these symptoms become less pronounced or do not occur following consistent use).[[10]](#cite_note-10) Caffeine is classified by the [Food and Drug Administration](/wiki/Food_and_Drug_Administration) as "[generally recognized as safe](/wiki/Generally_recognized_as_safe)" (GRAS). Toxic doses, over 10 grams per day for an adult, are much higher than typical doses of under 500 milligrams per day. A cup of coffee contains 80–175 mg of caffeine, depending on what "bean" (seed) is used and how it is prepared (e.g. [drip](/wiki/Drip_brew), [percolation](/wiki/Coffee_percolator), or [espresso](/wiki/Espresso)). Thus it requires roughly 50–100 ordinary cups of coffee to reach a lethal dose. However pure powdered caffeine, which is available as a dietary supplement, can be lethal in tablespoon-sized amounts. [Template:TOC limit](/wiki/Template:TOC_limit)

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## Uses[[edit](/index.php?title=(none)&action=edit&section=1)]

### Medical[[edit](/index.php?title=(none)&action=edit&section=2)]

Caffeine is used in:

* [bronchopulmonary dysplasia](/wiki/Bronchopulmonary_dysplasia) in [premature](/wiki/Premature_birth) infants for both prevention[[11]](#cite_note-11) and treatment.[[12]](#cite_note-12) It may improve weight gain during therapy[[13]](#cite_note-13) and reduce the incidence of cerebral palsy as well as reduce language and cognitive delay.[[14]](#cite_note-14)[[15]](#cite_note-15) On the other hand, subtle long-term side effects are possible.[[16]](#cite_note-16)\* [apnea of prematurity](/wiki/Apnea_of_prematurity) as a primary treatment,[[17]](#cite_note-17) but not prevention.[[18]](#cite_note-18)[[19]](#cite_note-19)\* [orthostatic hypotension](/wiki/Orthostatic_hypotension) treatment.[[19]](#cite_note-19)[[20]](#cite_note-20)

### Enhancing performance[[edit](/index.php?title=(none)&action=edit&section=3)]

Caffeine is a [central nervous system](/wiki/Central_nervous_system) stimulant and is used to reduce physical [fatigue](/wiki/Fatigue_(medical)) and to prevent or treat [drowsiness](/wiki/Drowsiness).[[1]](#cite_note-1) It produces increased wakefulness, increased focus, and better general body coordination.[[21]](#cite_note-21) The amount of caffeine needed to produce these effects varies from person to person, depending on body size and degree of tolerance.[[21]](#cite_note-21) Desired effects begin approximately one hour after consumption, and a moderate dose usually subsides in about three or four hours.[[22]](#cite_note-22) Caffeine can delay or prevent [sleep](/wiki/Sleep), and improves task performance during sleep deprivation.[[23]](#cite_note-23) Shift workers have fewer mistakes caused by drowsiness.[[24]](#cite_note-24) At normal doses, caffeine has variable effects on learning and memory, but it generally improves [reaction time](/wiki/Reaction_time), arousal, and concentration.<ref name=Cog10>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> A 2014 systematic review and meta-analysis found that concurrent caffeine and [Template:Smallcaps all](/wiki/Template:Smallcaps_all)-theanine use has synergistic psychoactive effects that promote alertness, attention, and [task switching](/wiki/Task_switching_(psychology));[[25]](#cite_note-25) these effects are most pronounced during the first hour post-dose.[[25]](#cite_note-25) Both caffeine and [coffee](/wiki/Coffee) are proven [ergogenic aids](/wiki/Ergogenic_aids) in humans.[[26]](#cite_note-26) Caffeine improves athletic performance in [aerobic](/wiki/Aerobic_exercise) (especially [endurance sports](/wiki/Endurance_sports)) and [anaerobic](/wiki/Anaerobic_exercise) conditions.[[26]](#cite_note-26) Moderate doses of caffeine (around 5 mg/kg[[26]](#cite_note-26)) can improve sprint performance,[[27]](#cite_note-27) cycling and running time trial performance,[[26]](#cite_note-26) endurance (i.e., it delays the onset of [muscle fatigue](/wiki/Muscle_fatigue) and [central fatigue](/wiki/Central_fatigue)),[[26]](#cite_note-26)[[28]](#cite_note-28)[[29]](#cite_note-29) and cycling power output.[[26]](#cite_note-26)

### Specific populations[[edit](/index.php?title=(none)&action=edit&section=4)]

#### Adolescents and adults[[edit](/index.php?title=(none)&action=edit&section=5)]

[Health Canada](/wiki/Health_Canada) has not developed advice for adolescents because of insufficient data. Nonetheless, they suggest that daily caffeine intake for this age group be no more than 2.5 mg/kg body weight. This is because the maximum adult caffeine dose may not be appropriate for light weight adolescents or for younger adolescents who are still growing. The daily dose of 2.5 mg/kg body weight would not cause adverse health effects in the majority of adolescent caffeine consumers. This is a conservative suggestion since older and heavier weight adolescents may be able to consume adult doses of caffeine without suffering adverse effects. For the rest of the general population of healthy adults, Health Canada advises a daily intake of no more than 400 mg.[[30]](#cite_note-30)

#### Children[[edit](/index.php?title=(none)&action=edit&section=6)]

In healthy children, caffeine intake produces effects that are "modest and typically innocuous".[[31]](#cite_note-31) For children age 12 and under, Health Canada recommends a maximum daily caffeine intake of no more than 2.5 milligrams per kilogram of body weight. Based on average body weights of children, this translates to the following age-based intake limits:[[30]](#cite_note-30){| class="wikitable" |- ! Age range ! Maximum recommended daily caffeine intake |- | 4–6 | 45 mg (slightly more than in 12 oz of a typical soft drink) |- | 7–9 | 62.5 mg |- | 10–12 | 85 mg (about ½ cup of coffee) |}

## Side effects[[edit](/index.php?title=(none)&action=edit&section=7)]

[thumb|upright=1.2|Side effects of caffeine](/wiki/File:Health_effects_of_caffeine.svg)

### Physical[[edit](/index.php?title=(none)&action=edit&section=8)]

Caffeine can increase blood pressure and cause [vasoconstriction](/wiki/Vasoconstriction).[[32]](#cite_note-32)[[33]](#cite_note-33)[[34]](#cite_note-34) Long term consumption at sufficiently high doses has been associated with chronic arterial stiffness.[[34]](#cite_note-34) Coffee and caffeine can affect [gastrointestinal motility](/wiki/Gastrointestinal_motility) and [gastric acid](/wiki/Gastric_acid) secretion.[[35]](#cite_note-35)[[36]](#cite_note-36)[[37]](#cite_note-37) Caffeine increases [basal metabolic rate](/wiki/Basal_metabolic_rate) in adults.[[38]](#cite_note-38)[[39]](#cite_note-39)[[40]](#cite_note-40) In postmenopausal women, high caffeine consumption can accelerate [bone loss](/wiki/Osteoporosis).[[41]](#cite_note-41)[[42]](#cite_note-42) Doses of caffeine equivalent to the amount normally found in standard servings of tea, coffee and carbonated soft drinks appear to have no diuretic action.[[43]](#cite_note-43) However, acute ingestion of caffeine in large doses (at least 250–300 mg, equivalent to the amount found in 2–3 cups of coffee or 5–8 cups of tea) results in a short-term stimulation of urine output in individuals who have been deprived of caffeine for a period of days or weeks.[[43]](#cite_note-43) This increase is due to both a [diuresis](/wiki/Polyuria) (increase in water excretion) and a [natriuresis](/wiki/Natriuresis) (increase in saline excretion); it is mediated via proximal tubular adenosine receptor blockade.[[44]](#cite_note-44) The acute increase in urinary output may increase the risk of [dehydration](/wiki/Dehydration). However, chronic users of caffeine develop a [tolerance](/wiki/Drug_tolerance) to this effect, and experience no increase in urinary output.[[45]](#cite_note-45)[[46]](#cite_note-46) Caffeine in low doses may cause weak bronchodilation for up to four hours in asthmatics.[[47]](#cite_note-47)

### Psychological[[edit](/index.php?title=(none)&action=edit&section=9)]

Minor undesired symptoms from caffeine ingestion not sufficiently severe to warrant a psychiatric diagnosis are common, and include mild anxiety, jitteriness, insomnia, increased sleep latency, and reduced coordination.[[21]](#cite_note-21)[[48]](#cite_note-48) Caffeine can have negative effects on [anxiety disorders](/wiki/Anxiety_disorders).[[49]](#cite_note-49) According to a 2011 literature review, caffeine use is positively associated with anxiety and panic disorders.[[50]](#cite_note-50) At high doses, typically greater than 300 mg, caffeine can both cause and worsen anxiety.[[51]](#cite_note-51) For some people, discontinuing caffeine use can significantly reduce anxiety.[[52]](#cite_note-52) Low doses of caffeine cause increased alertness and decreased fatigue.[[53]](#cite_note-53) In moderate doses, caffeine may reduce symptoms of depression and lower [suicide](/wiki/Suicide) risk.<ref name=Psyc10>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

### During pregnancy[[edit](/index.php?title=(none)&action=edit&section=10)]

Caffeine consumption during pregnancy does not appear to increase the risk of [congenital malformations](/wiki/Congenital_malformations), [miscarriage](/wiki/Miscarriage) or [growth retardation](/wiki/Growth_retardation) even when consumed in moderate to high amounts.[[54]](#cite_note-54) However, as the data supporting this conclusion is of poor quality, some suggest limiting caffeine consumption during pregnancy.[[55]](#cite_note-55)[[56]](#cite_note-56) The UK [Food Standards Agency](/wiki/Food_Standards_Agency) has recommended that pregnant women should limit their caffeine intake, out of prudence, to less than 200 mg of caffeine a day – the equivalent of two cups of instant coffee, or one and a half to two cups of fresh coffee.[[57]](#cite_note-57) The [American Congress of Obstetricians and Gynecologists](/wiki/American_Congress_of_Obstetricians_and_Gynecologists) (ACOG) concluded in 2010 that caffeine consumption is safe up to 200 mg per day in pregnant women.[[6]](#cite_note-6) Although the evidence that caffeine may be harmful during pregnancy is equivocal, there is some evidence that the hormonal changes during pregnancy slow the metabolic clearance of caffeine from the system, causing a given dose to have longer-lasting effects (as long as 15 hours in the third trimester).[[58]](#cite_note-58) There is also some evidence that caffeine intake by pregnant women is associated with a higher risk of giving birth to a [low birth weight](/wiki/Low_birth_weight) baby.[[59]](#cite_note-59) Caffeine's potential impact on female fertility, and its precise impact on pregnancy, is still being studied, but (as with many other substances in these circumstances) caution and moderation is warranted in any case until further information is known. For women of childbearing age, Health Canada recommends a maximum daily caffeine intake of no more than 300 mg, or a little over two 8 oz (237 mL) cups of coffee.[[30]](#cite_note-30)

### Reinforcement disorders[[edit](/index.php?title=(none)&action=edit&section=11)]

#### Addiction[[edit](/index.php?title=(none)&action=edit&section=12)]

Whether or not caffeine can result in an addictive disorder depends on how addiction is defined. Some diagnostic models, such as the [Template:Nowrap](/wiki/Template:Nowrap) and [ICD-10](/wiki/ICD-10), include a classification of caffeine addiction under a broader diagnostic model.[[60]](#cite_note-60) Some state that certain users can become addicted and therefore unable to decrease use even though they know there are negative health effects.[[61]](#cite_note-61)[[62]](#cite_note-62) Some state that research does not provide support for an underlying biochemical mechanism for caffeine addiction.[[7]](#cite_note-7)[[63]](#cite_note-63)[[64]](#cite_note-64)[[65]](#cite_note-65) Other research states it can affect the reward system.[[66]](#cite_note-66) "Caffeine addiction" was added to the ICDM-9 and ICD-10; however, its addition was contested with claims that this diagnostic model of caffeine addiction is not supported by evidence.[[7]](#cite_note-7)[[67]](#cite_note-67)[[68]](#cite_note-68) The [American Psychiatric Association's](/wiki/American_Psychiatric_Association) [Template:Nowrap](/wiki/Template:Nowrap) does not include the diagnosis of a *caffeine addiction* but proposes criteria for the disorder for more study.<ref name=Add2014>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[69]](#cite_note-69)

#### Dependence and withdrawal[[edit](/index.php?title=(none)&action=edit&section=13)]

[Template:Main article](/wiki/Template:Main_article) [Withdrawal](/wiki/Drug_withdrawal) can cause mild to clinically significant distress or impairment in daily functioning.[[70]](#cite_note-70) Mild[[7]](#cite_note-7) to increasingly severe [physical dependence](/wiki/Physical_dependence) and withdrawal symptoms may occur upon abstinence, with greater than 100 mg caffeine per day;[[70]](#cite_note-70) some symptoms associated with [psychological dependence](/wiki/Psychological_dependence) may also occur during [withdrawal](/wiki/Drug_withdrawal).[[9]](#cite_note-9) Caffeine dependence can involve withdrawal symptoms such as fatigue, headache, irritability, depressed mood, reduced contentedness, inability to concentrate, sleepiness or drowsiness, [stomach pain](/wiki/Abdominal_pain), and [joint pain](/wiki/Arthralgia).[[7]](#cite_note-7)[[9]](#cite_note-9) Withdrawal headaches are experienced by roughly half of those who stop consuming caffeine for two days following an average daily intake of 235 mg.[[71]](#cite_note-71) The ICD-10 includes a diagnostic model for [caffeine dependence](/wiki/Caffeine_dependence), but the DSM-5 does not.[[8]](#cite_note-8)[[68]](#cite_note-68) The [APA](/wiki/American_Psychiatric_Association), which published the DSM-5, acknowledged that there was sufficient evidence in order to create a diagnostic model of caffeine dependence for the DSM-5, but they noted that the [clinical significance](/wiki/Clinical_significance) of this disorder is unclear.[[8]](#cite_note-8) The DSM-5 instead lists "caffeine use disorder" in the [emerging models](/wiki/DSM-5#Section_III:_emerging_measures_and_models) section of the manual.[[8]](#cite_note-8) [Tolerance](/wiki/Drug_tolerance) varies for, daily, regular caffeine users and high caffeine users. High doses of caffeine (750 to 1200 mg/day spread throughout the day) have been shown to produce complete tolerance to some, but not all of the effects of caffeine. Doses as low as 100 mg/day, such as a 6 oz. cup of coffee or two to three 12 oz. servings of caffeinated soft-drink, may continue to cause sleep disruption, among other intolerances. Non-regular caffeine users have the least caffeine tolerance for sleep disruption.[[70]](#cite_note-70) Some coffee drinkers develop tolerance to its undesired sleep-disrupting effects, but others apparently do not.<ref name=Fredholm>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

##### Effect of genetics on withdrawal symptoms[[edit](/index.php?title=(none)&action=edit&section=14)]

Gene polymorphism could be associated with caffeine withdrawal symptoms and beta-1 and beta-2 play roles in caffeine withdrawal.[[72]](#cite_note-72) For example, compared to people with homozygous Gly16 allele, people with the heterozygote ADR beta-2 Gly16 Arg gene polymorphism have a higher chance of feeling fatigue after 48 hours of caffeine withdrawal.[[72]](#cite_note-72) It has been suspected that beta2- adrenoceptors are the main cause for this increase in mental fatigue symptoms.[[72]](#cite_note-72) Beta 2- adrenoceptors are receptors that regulate glycogenolysis, secret insulin and intramuscularly transport glucose that is used for cerebral and muscle activity.[[72]](#cite_note-72) Another example is given by the genes ADRbeta1 Gly16 Arg and CYP1A2-163A>C polymorphisms.[[72]](#cite_note-72) They are associated with peoples' mood swings and increased depression level.[[72]](#cite_note-72) Among subjects homozygous for the CYP1A2 allele, ADRbeta1 Gly389 allele carriers are reported to have a higher percentage of depression level increase when compared to Arg389 homozygotes subjects.[[72]](#cite_note-72) Adrenergic receptors, again, play a key role in this symptom, as altered norepinephrine (an adrenoceptor agonist) neurotransmission contribute to the etiology of depression.[[72]](#cite_note-72) This symptom is often seen in faster caffeine metabolizers, because caffeine effects diminish quicker in these people and provide them less opportunity to adapt to caffeine loss.[[72]](#cite_note-72)

### Risk of other diseases[[edit](/index.php?title=(none)&action=edit&section=15)]

Coffee consumption is associated with a lower overall risk of [cancer](/wiki/Cancer).[[73]](#cite_note-73) This is primarily due to a decrease in the risks of [hepatocellular](/wiki/Hepatocellular_carcinoma) and [endometrial cancer](/wiki/Endometrial_cancer), but it may also have a modest effect on colorectal cancer.<ref name=Cancer10/> There does not appear to be a significant protective effect against other types of cancers, and heavy coffee consumption may increase the risk of [bladder cancer](/wiki/Bladder_cancer).<ref name=Cancer10>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> A protective effect of caffeine against [Alzheimer's disease](/wiki/Alzheimer's_disease) is possible, but the evidence is inconclusive.[[74]](#cite_note-74)[[75]](#cite_note-75)[[76]](#cite_note-76) Moderate coffee consumption may decrease the risk of [cardiovascular disease](/wiki/Cardiovascular_disease),<ref name=Ding2014/> and it may somewhat reduce the risk of [type 2 diabetes](/wiki/Diabetes_mellitus_type_2).<ref name=Dam08>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Drinking four or more cups of coffee per day does not affect the risk of [hypertension](/wiki/Hypertension) compared to drinking little or no coffee. However those who drink 1–3 cups per day may be at a slightly increased risk.[[77]](#cite_note-77) Caffeine increases [intraocular pressure](/wiki/Intraocular_pressure) in those with [glaucoma](/wiki/Glaucoma) but does not appear to affect normal individuals.[[78]](#cite_note-78) It may protect people from [liver cirrhosis](/wiki/Liver_cirrhosis).[[79]](#cite_note-79) There is no evidence that coffee stunts a child's growth.[[80]](#cite_note-80) Caffeine may increase the effectiveness of some medications including ones used to treat [headaches](/wiki/Headaches).[[81]](#cite_note-81) Caffeine may lessen the severity of [acute mountain sickness](/wiki/Acute_mountain_sickness) if taken a few hours prior to attaining a high altitude.[[82]](#cite_note-82)

## Overdose[[edit](/index.php?title=(none)&action=edit&section=16)]

[thumb|right|Primary symptoms of caffeine intoxication](/wiki/File:Main_symptoms_of_Caffeine_overdose.svg)[[83]](#cite_note-83)|alt=Torso of a young man with overlaid text of main side-effects of caffeine overdose.

Consumption of 1 – 1.5 g per day is associated with a condition known as *caffeinism.*[[84]](#cite_note-84) Caffeinism usually combines caffeine [dependency](/wiki/Substance_dependence) with a wide range of unpleasant symptoms including nervousness, irritability, restlessness, insomnia, headaches, and palpitations after caffeine use.[[85]](#cite_note-85) Caffeine overdose can result in a state of central nervous system over-stimulation called *caffeine intoxication* ([DSM-IV](/wiki/DSM-IV) 305.90).[[86]](#cite_note-86) This syndrome typically occurs only after ingestion of large amounts of caffeine, well over the amounts found in typical caffeinated beverages and caffeine tablets (e.g., more than 400–500 mg at a time). The symptoms of caffeine intoxication are comparable to the symptoms of overdoses of other [stimulants](/wiki/Stimulant): they may include restlessness, fidgeting, anxiety, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, irregular or rapid heart beat, and [psychomotor agitation](/wiki/Psychomotor_agitation).<ref name=Medline>[Template:Cite web](/wiki/Template:Cite_web)</ref> In cases of much larger overdoses, [mania](/wiki/Mania), [depression](/wiki/Depression_(mood)), lapses in judgment, [disorientation](/wiki/Disorientation), [disinhibition](/wiki/Disinhibition), delusions, hallucinations, or psychosis may occur, and [rhabdomyolysis](/wiki/Rhabdomyolysis) (breakdown of skeletal muscle tissue) can be provoked.[[87]](#cite_note-87)<ref name=Verkhratsky>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Massive overdose can result in death.<ref name=Holmgren>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[88]](#cite_note-88) The LD50 of caffeine in humans is dependent on individual sensitivity, but is estimated to be 150 to 200 milligrams per kilogram of body mass (75–100 cups of coffee for a 70 kilogram adult).[[89]](#cite_note-89) A number of fatalities have been caused by overdoses of readily available powdered caffeine supplements, for which the estimated lethal amount is less than a tablespoon.[[90]](#cite_note-90) The lethal dose is lower in individuals whose ability to metabolize caffeine is impaired due to genetics or chronic liver disease[[91]](#cite_note-91) A death was reported in a man with [liver cirrhosis](/wiki/Liver_cirrhosis) who overdosed on caffeinated mints.<ref name=independent-2013-10-11>[Template:Cite news](/wiki/Template:Cite_news)</ref><ref name=telegraph-2013-10-13>[Template:Cite news](/wiki/Template:Cite_news)</ref><ref name=mirror-2013-10-12>[Template:Cite web](/wiki/Template:Cite_web)</ref>

Treatment of mild caffeine intoxication is directed toward symptom relief; severe intoxication may require [peritoneal dialysis](/wiki/Peritoneal_dialysis), [hemodialysis](/wiki/Hemodialysis), or [hemofiltration](/wiki/Hemofiltration).<ref name=Medline/>

## Interactions[[edit](/index.php?title=(none)&action=edit&section=17)]

### Alcohol[[edit](/index.php?title=(none)&action=edit&section=18)]

[Template:See also](/wiki/Template:See_also) According to [DSST](/wiki/DSST_(standardized_test)), alcohol provides a reduction in performance and caffeine has a significant improvement in performance.[[92]](#cite_note-92) When alcohol and caffeine are consumed jointly, the effects produced by caffeine are affected, but the alcohol effects remain the same.[[93]](#cite_note-93) For example, when additional caffeine is added, the drug effect produced by alcohol is not reduced.[[93]](#cite_note-93) However, the jitteriness and alertness given by caffeine is decreased when additional alcohol is consumed.[[93]](#cite_note-93) Alcohol consumption alone reduces both inhibitory and activational aspects of behavioral control. Caffeine antagonizes the activational aspect of behavioral control, but has no effect on the inhibitory behavioral control.[[94]](#cite_note-94)

### Tobacco[[edit](/index.php?title=(none)&action=edit&section=19)]

Smoking tobacco increases caffeine clearance by 56%.[[95]](#cite_note-95)

### Oral birth control[[edit](/index.php?title=(none)&action=edit&section=20)]

Consumption of caffeine while orally administering birth control can extend the half-life of caffeine; therefore, greater attention should be taken during caffeine consumption.[[96]](#cite_note-96)

## Pharmacology[[edit](/index.php?title=(none)&action=edit&section=21)]

### Pharmacodynamics[[edit](/index.php?title=(none)&action=edit&section=22)]

[Template:Synapse map](/wiki/Template:Synapse_map) [thumb|250px|Caffeine's primary mechanism of action is as an](/wiki/File:Caffeine_and_adenosine.svg) [antagonist](/wiki/Receptor_antagonist) of [adenosine](/wiki/Adenosine) receptors in the brain|alt=Two skeletal formulas: left – caffeine, right – adenosine. In the absence of caffeine and when a person is awake and alert, little [adenosine](/wiki/Adenosine) is present in (CNS) neurons. With a continued wakeful state, over time it accumulates in the neuronal [synapse](/wiki/Synapse), in turn binding to and activating [adenosine receptors](/wiki/Adenosine_receptor) found on certain CNS neurons; when activated, these receptors produce a cellular response that ultimately increases [drowsiness](/wiki/Drowsiness). When caffeine is consumed, it [antagonizes](/wiki/Receptor_antagonist) adenosine receptors; in other words, caffeine prevents adenosine from activating the receptor by blocking the location on the receptor where adenosine binds to it. As a result, caffeine temporarily prevents or relieves drowsiness, and thus maintains or restores alertness.[[97]](#cite_note-97)

#### Receptor and ion channel targets[[edit](/index.php?title=(none)&action=edit&section=23)]

Caffeine is a receptor antagonist at all [adenosine receptor](/wiki/Adenosine_receptor) subtypes ([A1](/wiki/Adenosine_receptor_A1), [A2A](/wiki/Adenosine_receptor_A2a), [A2B](/wiki/Adenosine_receptor_A2b), and [A3](/wiki/Adenosine_receptor_A3) receptors).[[97]](#cite_note-97) Antagonism at these receptors stimulates the [medullary](/wiki/Medulla_oblongata) vagal, vasomotor, and [respiratory centers](/wiki/Respiratory_center), which increases respiratory rate, reduces heartrate, and constricts blood vessels.[[97]](#cite_note-97) Adenosine receptor antagonism also promotes neurotransmitter release (e.g., [monoamines](/wiki/Monoamines) and [acetylcholine](/wiki/Acetylcholine)), which endows caffeine with its stimulant effects;[[97]](#cite_note-97)[[98]](#cite_note-98) [adenosine](/wiki/Adenosine) acts as an inhibitory neurotransmitter that suppresses activity in the central nervous system. [Heart palpitations](/wiki/Heart_palpitation) are caused by blockade of the adenosine A1 receptor.[[97]](#cite_note-97) Because caffeine is both water- and lipid-soluble, it readily crosses the [blood–brain barrier](/wiki/Blood–brain_barrier) that separates the bloodstream from the interior of the brain. Once in the brain, the principal mode of action is as a nonselective [antagonist](/wiki/Receptor_antagonist) of [adenosine receptors](/wiki/Adenosine_receptor) (in other words, an agent that reduces the effects of adenosine). The caffeine molecule is structurally similar to adenosine, and is capable of binding to adenosine receptors on the surface of cells without activating them, thereby acting as a [competitive antagonist](/wiki/Competitive_antagonist).[[99]](#cite_note-99) In addition to its activity at adenosine receptors, caffeine is an [inositol triphosphate receptor 1](/wiki/Inositol_trisphosphate_receptor) antagonist and a voltage-independent activator of the [ryanodine receptors](/wiki/Ryanodine_receptor) ([RYR1](/wiki/RYR1), [RYR2](/wiki/RYR2), and [RYR3](/wiki/RYR3)).[[100]](#cite_note-100) It is also a competitive antagonist of the [ionotropic glycine receptor](/wiki/Glycine_receptor).[[101]](#cite_note-101)

##### Effects on striatal dopamine[[edit](/index.php?title=(none)&action=edit&section=24)]

While caffeine does not directly bind to any [dopamine receptors](/wiki/Dopamine_receptor), it influences the binding activity of [dopamine](/wiki/Dopamine) at its receptors in the [striatum](/wiki/Striatum) by binding to adenosine receptors that have formed [GPCR heteromers](/wiki/GPCR_oligomer) with dopamine receptors, specifically the [A1](/wiki/Adenosine_receptor_A1)–[D1](/wiki/DRD1) receptor [heterodimer](/wiki/Heterodimer) (this is a receptor complex with 1 adenosine A1 receptor and 1 dopamine D1 receptor) and the [A2A](/wiki/Adenosine_receptor_A2a)–[D2](/wiki/DRD2) receptor [heterotetramer](/wiki/Heterotetramer) (this is a receptor complex with 2 adenosine A2A receptors and 2 dopamine D2 receptors).[[102]](#cite_note-102)[[103]](#cite_note-103)[[104]](#cite_note-104)[[105]](#cite_note-105) The A2A–D2 receptor heterotetramer has been identified as a primary pharmacological target of caffeine, primarily because it mediates some of its psychostimulant effects and its pharmacodynamic interactions with dopaminergic psychostimulants.[[103]](#cite_note-103)[[104]](#cite_note-104)[[105]](#cite_note-105) Caffeine also causes the release of dopamine in the [dorsal striatum](/wiki/Dorsal_striatum) and [nucleus accumbens core](/wiki/Nucleus_accumbens_core) (a substructure within the [ventral striatum](/wiki/Ventral_striatum)), but not the [nucleus accumbens shell](/wiki/Nucleus_accumbens_shell), by antagonizing [A1](/wiki/Adenosine_receptor_A1) receptors in the [axon terminal](/wiki/Axon_terminal) of dopamine neurons and [A1](/wiki/Adenosine_receptor_A1)–[A2A](/wiki/Adenosine_receptor_A2a) heterodimers (a receptor complex composed of 1 adenosine A1 receptor and 1 adenosine A2A receptor) in the axon terminal of glutamate neurons.[[102]](#cite_note-102)[[106]](#cite_note-106) During chronic caffeine use, caffeine-induced dopamine release within the nucleus accumbens core is markedly reduced due to [drug tolerance](/wiki/Drug_tolerance).[[102]](#cite_note-102)[[106]](#cite_note-106)

#### Enzyme targets[[edit](/index.php?title=(none)&action=edit&section=25)]

Caffeine, like other [xanthines](/wiki/Xanthines), also acts as a [phosphodiesterase inhibitor](/wiki/Phosphodiesterase_inhibitor).[[107]](#cite_note-107) As a competitive nonselective [phosphodiesterase inhibitor](/wiki/Phosphodiesterase_inhibitor),[[108]](#cite_note-108) caffeine raises intracellular [cAMP](/wiki/Cyclic_adenosine_monophosphate), activates [protein kinase A](/wiki/Protein_kinase_A), [inhibits TNF-alpha](/wiki/TNF_inhibitor)[[109]](#cite_note-109)[[110]](#cite_note-110) and [leukotriene](/wiki/Leukotriene)[[111]](#cite_note-111) synthesis, and [reduces inflammation](/wiki/Anti-inflammatory) and [innate immunity](/wiki/Innate_immunity).[[111]](#cite_note-111) Caffeine also affects the [cholinergic system](/wiki/Cholinergic_system) where it inhibits the enzyme [acetylcholinesterase](/wiki/Acetylcholinesterase).[[112]](#cite_note-112)

#### Off-target effects[[edit](/index.php?title=(none)&action=edit&section=26)]

Caffeine antagonizes [adenosine A2A receptors](/wiki/Adenosine_A2A_receptor) in the [ventrolateral preoptic area](/wiki/Ventrolateral_preoptic_area) (VLPO), thereby reducing inhibitory [GABA](/wiki/GABA) [neurotransmission](/wiki/Neurotransmission) to the [tuberomammillary nucleus](/wiki/Tuberomammillary_nucleus), a [histaminergic](/wiki/Histamine) projection nucleus that activation-dependently promotes arousal.[[106]](#cite_note-106) Disinhibition of the tuberomammillary nucleus is the chief mechanism by which caffeine produces wakefulness-promoting effects.[[106]](#cite_note-106)

### Pharmacokinetics[[edit](/index.php?title=(none)&action=edit&section=27)]

[thumb|250px|Caffeine is metabolized in the liver into three primary metabolites:](/wiki/File:Caffeine_metabolites.svg) [paraxanthine](/wiki/Paraxanthine) (84%), [theobromine](/wiki/Theobromine) (12%), and [theophylline](/wiki/Theophylline) (4%)|alt=A diagram featuring 4 skeletal chemical formulas. Top (caffeine) relates to similar compounds paraxanthine, theobromine and theophylline.

Caffeine from coffee or other beverages is absorbed by the small intestine within 45 minutes of ingestion and distributed throughout all bodily tissues.[[113]](#cite_note-113) Peak blood concentration is reached within 1–2 hours.[Template:Citation needed](/wiki/Template:Citation_needed) It is eliminated by [first-order kinetics](/wiki/Rate_equation#First-order_reactions).[[114]](#cite_note-114) Caffeine can also be absorbed rectally, evidenced by suppositories of [ergotamine](/wiki/Ergotamine) [tartrate](/wiki/Tartrate) and caffeine (for the relief of [migraine](/wiki/Migraine))[[115]](#cite_note-115) and [chlorobutanol](/wiki/Chlorobutanol) and caffeine (for the treatment of [hyperemesis](/wiki/Hyperemesis)).[[116]](#cite_note-116) Caffeine's [biological half-life](/wiki/Biological_half-life) – the time required for the body to eliminate one-half of a dose – varies widely among individuals according to factors such as pregnancy, other drugs, [liver enzyme](/wiki/Liver_enzymes) function level (needed for caffeine metabolism) and age. In healthy adults, caffeine's half-life is between 3–7 hours.[[97]](#cite_note-97) [Nicotine](/wiki/Nicotine) decreases the half-life by 30–50%,[[58]](#cite_note-58) while [oral contraceptives](/wiki/Oral_contraceptives) can double it[[58]](#cite_note-58) and pregnancy can raise it to as much as 15 hours during the last trimester.[[58]](#cite_note-58) In newborns the half-life can be 80 hours or more, dropping very rapidly with age, possibly to less than the adult value by age 6 months.[[58]](#cite_note-58) The antidepressant [fluvoxamine](/wiki/Fluvoxamine) (Luvox) reduces the clearance of caffeine by more than 90%, and increases its elimination half-life more than tenfold; from 4.9 hours to 56 hours.[[117]](#cite_note-117) Caffeine is [metabolized](/wiki/Metabolism) in the [liver](/wiki/Liver) by the [cytochrome P450 oxidase](/wiki/Cytochrome_P450_oxidase) enzyme system, in particular, by the [CYP1A2](/wiki/CYP1A2) isozyme, into three dimethyl[xanthines](/wiki/Xanthine),[[118]](#cite_note-118) each of which has its own effects on the body:

* [Paraxanthine](/wiki/Paraxanthine) (84%): Increases [lipolysis](/wiki/Lipolysis), leading to elevated [glycerol](/wiki/Glycerol) and free [fatty acid](/wiki/Fatty_acid) levels in [blood plasma](/wiki/Blood_plasma).
* [Theobromine](/wiki/Theobromine) (12%): Dilates [blood vessels](/wiki/Blood_vessel) and increases [urine](/wiki/Urine) volume. Theobromine is also the principal [alkaloid](/wiki/Alkaloid) in the [cocoa bean](/wiki/Cocoa_bean) ([chocolate](/wiki/Chocolate)).
* [Theophylline](/wiki/Theophylline) (4%): Relaxes [smooth muscles](/wiki/Smooth_muscle) of the [bronchi](/wiki/Bronchus), and is used to treat [asthma](/wiki/Asthma). The [therapeutic dose](/wiki/Therapeutic_dose) of theophylline, however, is many times greater than the levels attained from caffeine metabolism.[Template:Citation needed](/wiki/Template:Citation_needed)

[1,3,7-Trimethyluric acid](/wiki/1,3,7-Trimethyluric_acid) is a minor caffeine metabolite.[[97]](#cite_note-97) Each of these metabolites is further metabolized and then excreted in the urine. Caffeine can accumulate in individuals with severe [liver disease](/wiki/Liver_disease), increasing its half-life.[[119]](#cite_note-119) A 2011 review found that increased caffeine intake was associated with a variation in two genes that increase the rate of caffeine catabolism. Subjects who had this [mutation](/wiki/Mutation) on both [chromosomes](/wiki/Chromosomes) consumed 40 mg more caffeine per day than others.[[120]](#cite_note-120) This is presumably due to the need for a higher intake to achieve a comparable desired effect, not that the gene led to a disposition for greater incentive of habituation.

## Physical and chemical properties[[edit](/index.php?title=(none)&action=edit&section=28)]

Pure [anhydrous](/wiki/Anhydrous) caffeine is a bitter-tasting white odorless powder with a melting point of 235–238 °C.[[121]](#cite_note-121)[[122]](#cite_note-122) Caffeine is moderately soluble in water at room temperature (2 g/100 mL), but very soluble in boiling water (66 g/100 mL).[[123]](#cite_note-123) It is also moderately soluble in ethanol (1.5 g/100 mL).[[123]](#cite_note-123) It is weakly basic (pKa = ~0.6) requiring strong acid to protonate it.[[124]](#cite_note-124) Caffeine does not contain any [stereogenic](/wiki/Stereogenic) centers[[125]](#cite_note-125) and hence is classified as an [achiral](/wiki/Chirality_(chemistry)) molecule.[[126]](#cite_note-126) The [xanthine](/wiki/Xanthine) core of caffeine contains two fused rings, a [pyrimidinedione](/wiki/Pyrimidinedione) and [imidazole](/wiki/Imidazole). The pyrimidinedione in turn contains two [amide](/wiki/Amide) functional groups that exist predominately in a [zwitterionic](/wiki/Zwitterion) [resonance](/wiki/Resonance_(chemistry)) the location from which the nitrogen atoms are double bonded to their adjacent amide carbons atoms. Hence all six of the atoms within the pyrimidinedione ring system are sp2 [hybridized](/wiki/Orbital_hybridization) and planar. Therefore, the fused 5,6 ring core of caffeine contains a total of ten [pi electrons](/wiki/Pi_bond) and hence according to [Hückel's rule](/wiki/Hückel's_rule) is [aromatic](/wiki/Aromaticity).[[127]](#cite_note-127)

### Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=29)]

Caffeine may be synthesized from [dimethylurea](/wiki/Dimethylurea) and [malonic acid](/wiki/Malonic_acid),[[128]](#cite_note-128)[[129]](#cite_note-129)[[130]](#cite_note-130) but is rarely obtained from synthesis since it is readily available as a byproduct of decaffeination.[[131]](#cite_note-131)[Template:Multiple image](/wiki/Template:Multiple_image)

### Decaffeination[[edit](/index.php?title=(none)&action=edit&section=30)]

[Template:Main article](/wiki/Template:Main_article) [thumb|250px|Fibrous](/wiki/File:CaffeineCrystals_Fibrous_10xDarkField.jpg) [crystals](/wiki/Crystal) of purified caffeine. [Dark field](/wiki/Dark_field) [light microscope](/wiki/Light_microscope) image, the image covers an area of approx. 7 x 11mm.

Extraction of caffeine from coffee, to produce caffeine and decaffeinated coffee, can be performed using a number of solvents. [Benzene](/wiki/Benzene), [chloroform](/wiki/Chloroform), [trichloroethylene](/wiki/Trichloroethylene), and [dichloromethane](/wiki/Dichloromethane) have all been used over the years but for reasons of safety, environmental impact, cost, and flavor, they have been superseded by the following main methods:

* **Water extraction:** Coffee beans are soaked in water. The water, which contains many other compounds in addition to caffeine and contributes to the flavor of coffee, is then passed through [activated charcoal](/wiki/Activated_carbon), which removes the caffeine. The water can then be put back with the beans and evaporated dry, leaving decaffeinated coffee with its original flavor. Coffee manufacturers recover the caffeine and resell it for use in soft drinks and over-the-counter caffeine tablets.[[132]](#cite_note-132)\* **Supercritical carbon dioxide extraction:** [Supercritical carbon dioxide](/wiki/Supercritical_carbon_dioxide) is an excellent nonpolar solvent for caffeine, and is safer than the organic solvents that are otherwise used. The extraction process is simple: [Template:CO2](/wiki/Template:CO2) is forced through the green coffee beans at temperatures above 31.1 °C and pressures above 73 [atm](/wiki/Atmosphere_(unit)). Under these conditions, [Template:CO2](/wiki/Template:CO2) is in a "[supercritical](/wiki/Supercritical_fluid)" [state](/wiki/Phase_(matter)): It has gaslike properties that allow it to penetrate deep into the beans but also liquid-like properties that dissolve 97–99% of the caffeine. The caffeine-laden [Template:CO2](/wiki/Template:CO2) is then sprayed with high pressure water to remove the caffeine. The caffeine can then be isolated by [charcoal](/wiki/Activated_carbon) [adsorption](/wiki/Adsorption) (as above) or by [distillation](/wiki/Distillation), [recrystallization](/wiki/Recrystallization_(chemistry)), or [reverse osmosis](/wiki/Reverse_osmosis).[[132]](#cite_note-132)\* **Extraction by organic solvents:** Certain organic solvents such as [ethyl acetate](/wiki/Ethyl_acetate) present much less health and environmental hazard than chlorinated and aromatic organic solvents used formerly. Another method is to use triglyceride oils obtained from spent coffee grounds.<ref name=Decaffeination/>

"Decaffeinated" coffees do in fact contain caffeine in many cases – some commercially available decaffeinated coffee products contain considerable levels. One study found that decaffeinated coffee contained 10 mg of caffeine per cup, compared to approximately 85 mg of caffeine per cup for regular coffee.[[133]](#cite_note-133)

### Detection in body fluids[[edit](/index.php?title=(none)&action=edit&section=31)]

Caffeine can be quantified in blood, plasma, or serum to monitor therapy in neonates, confirm a diagnosis of poisoning, or facilitate a medicolegal death investigation. Plasma caffeine levels are usually in the range of 2–10 mg/L in coffee drinkers, 12–36 mg/L in neonates receiving treatment for apnea, and 40–400 mg/L in victims of acute overdosage. Urinary caffeine concentration is frequently measured in competitive sports programs, for which a level in excess of 15 mg/L is usually considered to represent abuse.[[134]](#cite_note-134)

### Analogs[[edit](/index.php?title=(none)&action=edit&section=32)]

Some analog substances have been created which mimic caffeine's properties with either function or structure or both. Of the latter group are the [xanthines](/wiki/Xanthine) [DMPX](/wiki/DMPX)<ref name=DMPX>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> and [8-chlorotheophylline](/wiki/8-Chlorotheophylline), which is an ingredient in [dramamine](/wiki/Dimenhydrinate). Members of a class of nitrogen substituted xanthines are often proposed as potential alternatives to caffeine.[[135]](#cite_note-135)[Template:Unreliable source?](/wiki/Template:Unreliable_source?) Many other xanthine analogues constituting the adenosine receptor antagonist class have also been elucidated.[[136]](#cite_note-136) Some other caffeine analogs:

* [Dipropylcyclopentylxanthine](/wiki/Dipropylcyclopentylxanthine)
* [8-Cyclopentyl-1,3-dimethylxanthine](/wiki/8-Cyclopentyl-1,3-dimethylxanthine)
* [8-Phenyltheophylline](/wiki/8-Phenyltheophylline)

## Natural occurrence[[edit](/index.php?title=(none)&action=edit&section=33)]

Around sixty plant species are known to contain caffeine.[[137]](#cite_note-137) Common sources are the "bean" (seed) of the [coffee plant](/wiki/Coffea_arabica) (the quantity varies, but 1.3% is a typical value[[138]](#cite_note-138)); in the leaves of the [tea bush](/wiki/Camellia_sinensis); and in [kola nuts](/wiki/Kola_nut). Other sources include [yaupon holly](/wiki/Ilex_vomitoria) leaves, South American holly [yerba mate](/wiki/Yerba_mate) leaves, seeds from Amazonian maple [guarana](/wiki/Guarana) berries, and Amazonian holly [guayusa](/wiki/Ilex_guayusa) leaves. Temperate climates around the world have produced unrelated caffeine containing plants.

Caffeine in plants acts as a natural [pesticide](/wiki/Pesticide): it can paralyze and kill predator insects feeding on the plant:[[139]](#cite_note-139) high caffeine levels are found in coffee seedlings when they are developing foliage and lack mechanical protection.[[140]](#cite_note-140) In addition, high caffeine levels are found in the surrounding soil of coffee seedlings, which inhibits seed germination of nearby coffee seedlings, thus giving seedlings with the highest caffeine levels fewer competitors for existing resources for survival.[[141]](#cite_note-141) The differing perceptions in the effects of ingesting beverages made from various plants containing caffeine could be explained by the fact that these beverages also contain varying mixtures of other [methylxanthine](/wiki/Methylxanthine) [alkaloids](/wiki/Alkaloid), including the [cardiac](/wiki/Cardiac) stimulants [theophylline](/wiki/Theophylline) and [theobromine](/wiki/Theobromine), and [polyphenols](/wiki/Polyphenol) that can form insoluble complexes with caffeine.[[142]](#cite_note-142)[Template:Clarify](/wiki/Template:Clarify)

## Products[[edit](/index.php?title=(none)&action=edit&section=34)]

[Template:See also](/wiki/Template:See_also)

|  |  |  |  |
| --- | --- | --- | --- |
| Caffeine content in select food and drugs[[143]](#cite_note-143)[[144]](#cite_note-144)[[145]](#cite_note-145)[[146]](#cite_note-146)[[147]](#cite_note-147) | | | |
| **Product** | **Serving size** | **Caffeine per serving (**[**mg**](/wiki/Milligrams)**)** | **Caffeine (mg/**[**L**](/wiki/Litre)**)** |
| Caffeine tablet (regular-strength) | 1 tablet | [Template:Nts](/wiki/Template:Nts) | — |
| Caffeine tablet (extra-strength) | 1 tablet | [Template:Nts](/wiki/Template:Nts) | — |
| [Excedrin](/wiki/Excedrin) tablet | 1 tablet | [Template:Nts](/wiki/Template:Nts) | — |
| [Hershey's Special Dark](/wiki/Hershey's_Special_Dark) (45% cacao content) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | — |
| [Hershey's Milk Chocolate](/wiki/Hershey's_Milk_Chocolate) (11% cacao content) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | — |
| [Percolated](/wiki/Coffee_percolator) [coffee](/wiki/Coffee) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts)–135 | [Template:Nts](/wiki/Template:Nts)–652 |
| [Drip](/wiki/Drip_brew) coffee | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts)–175 | [Template:Nts](/wiki/Template:Nts)–845 |
| [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts)–15 | [Template:Nts](/wiki/Template:Nts)–72 |
| Coffee, [espresso](/wiki/Espresso) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts)–2,254 |
| [Tea](/wiki/Tea) – black, green, and other [types](/wiki/Tea#Processing_and_classification), – steeped for 3 min. | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts)–74[[146]](#cite_note-146)[[147]](#cite_note-147) | [Template:Nts](/wiki/Template:Nts)–418 |
| Guayakí [yerba mate](/wiki/Mate_(beverage)) (loose leaf) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts)[[148]](#cite_note-148) | [Template:Nts](/wiki/Template:Nts) |
| [Coca-Cola](/wiki/Coca-Cola) Classic | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |
| [Mountain Dew](/wiki/Mountain_Dew) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |
| [Pepsi Max](/wiki/Pepsi_Max_(North_America)) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |
| [Guaraná Antarctica](/wiki/Guaraná_Antarctica) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |
| [Jolt Cola](/wiki/Jolt_Cola) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |
| [Red Bull](/wiki/Red_Bull) | [Template:Nowrap](/wiki/Template:Nowrap) | [Template:Nts](/wiki/Template:Nts) | [Template:Nts](/wiki/Template:Nts) |

Products containing caffeine are coffee, tea, soft drinks ("colas"), [energy drinks](/wiki/Energy_drinks), other beverages, [chocolate](/wiki/Chocolate),[[149]](#cite_note-149) caffeine tablets, other oral products, and inhalation.

### Beverages[[edit](/index.php?title=(none)&action=edit&section=35)]

#### Coffee[[edit](/index.php?title=(none)&action=edit&section=36)]

The world's primary source of caffeine is the coffee "bean" (the seed of the [coffee plant](/wiki/Coffea)), from which coffee is brewed. Caffeine content in coffee varies widely depending on the type of [coffee bean](/wiki/Coffee_bean) and the method of preparation used;[[150]](#cite_note-150) even beans within a given bush can show variations in concentration. In general, one serving of coffee ranges from 80 to 100 milligrams, for a single shot (30 milliliters) of arabica-variety [espresso](/wiki/Espresso), to approximately 100–125 milligrams for a cup (120 milliliters) of [drip coffee](/wiki/Drip_coffee).[[151]](#cite_note-151)[[152]](#cite_note-152) [*Arabica*](/wiki/Coffea_arabica) coffee typically contains half the caffeine of the [*robusta*](/wiki/Coffea_canephora) variety.[[150]](#cite_note-150)In general, dark-roast coffee has very slightly less caffeine than lighter roasts because the roasting process reduces caffeine content of the bean by a small amount.[[151]](#cite_note-151)[[152]](#cite_note-152)

#### Tea[[edit](/index.php?title=(none)&action=edit&section=37)]

Tea contains more caffeine than coffee by dry weight. A typical serving, however, contains much less, since tea is normally brewed more weakly than coffee. Also contributing to caffeine content are growing conditions, processing techniques, and other variables. Thus, certain types of tea may contain somewhat more caffeine than other teas.[[153]](#cite_note-153) Tea contains small amounts of [theobromine](/wiki/Theobromine) and slightly higher levels of [theophylline](/wiki/Theophylline) than coffee. Preparation and many other factors have a significant impact on tea, and color is a very poor indicator of caffeine content. Teas like the pale Japanese [green tea](/wiki/Green_tea), [*gyokuro*](/wiki/Gyokuro), for example, contain far more caffeine than much darker teas like [*lapsang souchong*](/wiki/Lapsang_souchong), which has very little.[[153]](#cite_note-153)

#### Soft drinks and energy drinks[[edit](/index.php?title=(none)&action=edit&section=38)]

Caffeine is also a common ingredient of [soft drinks](/wiki/Soft_drink), such as [cola](/wiki/Cola), originally prepared from [kola nuts](/wiki/Kola_nut). Soft drinks typically contain 0 to 55 milligrams of caffeine per 12 ounce serving.[[154]](#cite_note-154) By contrast, [energy drinks](/wiki/Energy_drink), such as [Red Bull](/wiki/Red_Bull), can start at 80 milligrams of caffeine per serving. The caffeine in these drinks either originates from the ingredients used or is an additive derived from the product of [decaffeination](/wiki/Decaffeination) or from chemical synthesis. Guarana, a prime ingredient of energy drinks, contains large amounts of caffeine with small amounts of theobromine and theophylline in a naturally occurring [slow-release](/wiki/Slow-release) [excipient](/wiki/Excipient).[[155]](#cite_note-155)

#### Other beverages[[edit](/index.php?title=(none)&action=edit&section=39)]

* [Mate](/wiki/Mate_(beverage)) is a drink popular in many parts of South America. Its preparation consists of filling a gourd with the leaves of the South American holly [yerba mate](/wiki/Yerba_mate), pouring hot but not boiling water over the leaves, and drinking with a straw, the bombilla, which acts as a filter so as to draw only the liquid and not the yerba leaves.[Template:Citation needed](/wiki/Template:Citation_needed) [Guaraná](/wiki/Guaraná) seeds ("beans") are used in making the commercially sold beverage [Guaraná Antarctica](/wiki/Guaraná_Antarctica), which originated in Brazil and is currently the fifteenth most popular soft drink in the world.[Template:Citation needed](/wiki/Template:Citation_needed)
* The leaves of [Ilex guayusa](/wiki/Ilex_guayusa), the Ecuadorian holly tree, are placed in boiling water to make a guayusa tea, which is both brewed locally and sold commercially throughout the world.[Template:Citation needed](/wiki/Template:Citation_needed)

### Chocolate[[edit](/index.php?title=(none)&action=edit&section=40)]

[Chocolate](/wiki/Chocolate) derived from cocoa beans contains a small amount of caffeine. The weak stimulant effect of chocolate may be due to a combination of theobromine and theophylline, as well as caffeine.[[156]](#cite_note-156) A typical 28-gram serving of a milk [chocolate bar](/wiki/Chocolate_bar) has about as much caffeine as a cup of decaffeinated coffee. By weight, [dark chocolate](/wiki/Dark_chocolate) has one to two times the amount caffeine as coffee: 80–160 mg per 100 g.<ref name=Erowid/>

### Tablets[[edit](/index.php?title=(none)&action=edit&section=41)]

[thumb|right|No-Doz 100 mg caffeine tablets](/wiki/File:No-Doz.jpg) Tablets offer the advantages over coffee and tea of convenience, known dosage, and avoiding concomitant fluid intake. Manufacturers of caffeine tablets claim that using caffeine of pharmaceutical quality improves mental alertness.[Template:Citation needed](/wiki/Template:Citation_needed) These tablets are commonly used by students studying for their exams and by people who work or drive for long hours.[[157]](#cite_note-157)

### Other oral products[[edit](/index.php?title=(none)&action=edit&section=42)]

One U.S. company is marketing oral dissolvable caffeine strips.[[158]](#cite_note-158) Another intake route is [SpazzStick](/wiki/SpazzStick), a caffeinated [lip balm](/wiki/Lip_balm).[[159]](#cite_note-159) Alert Energy Caffeine Gum was introduced in the United States in 2013, but was voluntarily withdrawn after an announcement of an investigation by the FDA of the health effects of added caffeine in foods.<ref name=NYT5813>[Template:Cite news](/wiki/Template:Cite_news)</ref>

### Inhalants[[edit](/index.php?title=(none)&action=edit&section=43)]

Taking caffeine by inhalation was under scrutiny by some U.S. lawmakers in 2011.[[160]](#cite_note-160)

### Combinations with other drugs[[edit](/index.php?title=(none)&action=edit&section=44)]

* Some beverages combine [alcohol](/wiki/Ethanol) with caffeine to create a [caffeinated alcoholic drink](/wiki/Caffeinated_alcoholic_drink). The stimulant effects of caffeine may mask the [depressant](/wiki/Depressant) effects of alcohol, potentially reducing the user's awareness of their level of [intoxication](/wiki/Alcohol_intoxication). Such beverages have been the subject of [bans](/wiki/Ban_on_caffeinated_alcoholic_beverages) due to safety concerns. In particular, [United States Food and Drug Administration](/wiki/United_States_Food_and_Drug_Administration) has classified caffeine added to malt liquor beverages as an "unsafe food additive".[[161]](#cite_note-161)\* [Ya ba](/wiki/Ya_ba) contains a combination of [methamphetamine](/wiki/Methamphetamine) and caffeine.

## History[[edit](/index.php?title=(none)&action=edit&section=45)]

### Discovery and spread of use[[edit](/index.php?title=(none)&action=edit&section=46)]

[thumb|](/wiki/File:Kahvihuone.jpg)[Coffeehouse](/wiki/Coffeehouse) in [Palestine](/wiki/History_of_Palestine#Ottoman_era), circa 1900|alt=An old photo of a dozen old and middle-aged men sitting on the ground around a mat. A man in front sits next to a mortar and holds a bat, ready for grinding. A man opposite to him holds a long spoon. [Template:Main article](/wiki/Template:Main_article)

According to Chinese legend, the [Chinese emperor](/wiki/Emperor_of_China) [Shennong](/wiki/Shennong), reputed to have reigned in about 3000 BCE, accidentally discovered tea when he noted that when certain leaves fell into boiling water, a fragrant and restorative drink resulted.[[162]](#cite_note-162) Shennong is also mentioned in Lu Yu's [*Cha Jing*](/wiki/Cha_Jing), a famous early work on the subject of tea.[[163]](#cite_note-163) The earliest credible evidence of either coffee drinking or knowledge of the coffee tree appears in the middle of the fifteenth century, in the [Sufi](/wiki/Sufi) monasteries of the [Yemenin](/wiki/Yemen) southern Arabia.<ref name=Bennett>[Template:Cite book](/wiki/Template:Cite_book)</ref> From [Mocha](/wiki/Mokha), coffee spread to [Egypt](/wiki/Mamluk_Sultanate_(Cairo)) and North Africa, and by the 16th century, it had reached the rest of the Middle East, [Persia](/wiki/Safavid_Empire) and [Turkey](/wiki/Ottoman_Empire). From the Middle East, coffee drinking spread to Italy, then to the rest of Europe, and coffee plants were transported by the Dutch to the [East Indies](/wiki/East_Indies) and to the Americas.<ref name = Meyers>[Template:Cite web](/wiki/Template:Cite_web)</ref>

[Kola nut](/wiki/Kola_nut) use appears to have ancient origins. It is chewed in many [West African](/wiki/West_Africa) cultures, individually or in a social setting, to restore vitality and ease hunger pangs.

The earliest evidence of [cocoa bean](/wiki/Cocoa_bean) use comes from residue found in an [ancient Mayan](/wiki/Maya_civilization) pot dated to 600 BCE. Also, [chocolate](/wiki/Chocolate) was consumed in a bitter and spicy drink called *xocolatl*, often seasoned with [vanilla](/wiki/Vanilla), [chile pepper](/wiki/Chile_pepper), and [achiote](/wiki/Achiote). *Xocolatl* was believed to fight fatigue, a belief probably attributable to the theobromine and caffeine content. Chocolate was an important luxury good throughout [pre-Columbian](/wiki/Pre-Columbian) [Mesoamerica](/wiki/Mesoamerica), and cocoa beans were often used as currency.[Template:Citation needed](/wiki/Template:Citation_needed)

*Xocolatl* was introduced to [Europe](/wiki/Europe) by the [Spaniards](/wiki/Spanish_people), and became a popular beverage by 1700. The Spaniards also introduced the [cacao tree](/wiki/Theobroma_cacao) into the [West Indies](/wiki/West_Indies) and the [Philippines](/wiki/Philippines). It was used in [alchemical](/wiki/Alchemy) processes, where it was known as "black bean".[Template:Citation needed](/wiki/Template:Citation_needed)

The leaves and stems of the yaupon holly ([*Ilex vomitoria*](/wiki/Ilex_vomitoria)) were used by [Native Americans](/wiki/Indigenous_peoples_of_the_Americas) to brew a [tea](/wiki/Tea) called *asi* or the "[black drink](/wiki/Black_drink)".<ref name=Fairbanks>[Template:Cite book](/wiki/Template:Cite_book)</ref> Archaeologists have found evidence of this use far into antiquity,[[164]](#cite_note-164) possibly dating to [Late Archaic times](/wiki/Archaic_period_in_the_Americas).<ref name=Fairbanks/>

### Chemical identification, isolation, and synthesis[[edit](/index.php?title=(none)&action=edit&section=47)]

[thumb|upright|Pierre Joseph Pelletier](/wiki/File:Pierre_Joseph_Pelletier.jpg) In 1819, the German chemist [Friedlieb Ferdinand Runge](/wiki/Friedlieb_Ferdinand_Runge) isolated relatively pure caffeine for the first time; he called it *"Kaffebase"* (i.e. a [base](/wiki/Base_(chemistry)) that exists in coffee).[[165]](#cite_note-165) According to Runge, he did this at the behest of [Johann Wolfgang von Goethe](/wiki/Johann_Wolfgang_von_Goethe).[[166]](#cite_note-166)