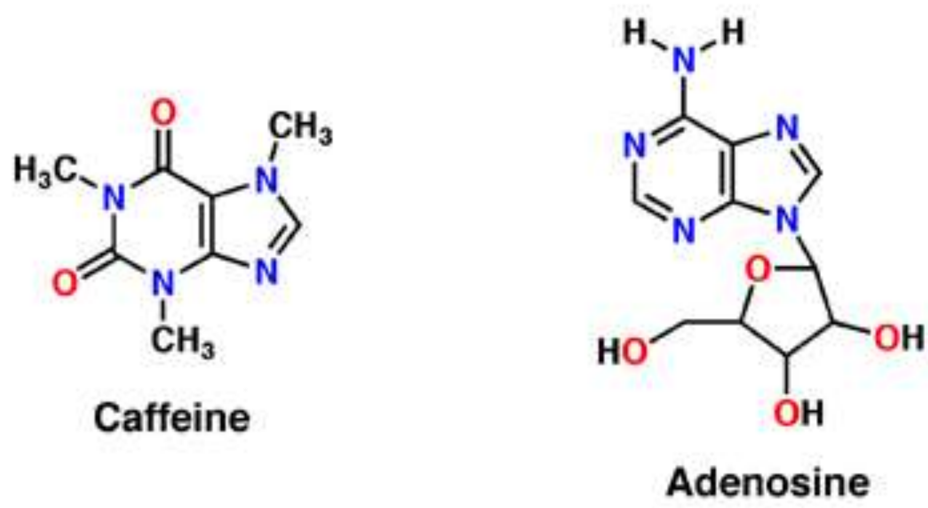
Caffeine: The chemistry behind the world's most popular drug

What are the short-term effects of caffeine?

From coffee and energy drinks to tea and soda, about 90% of adults in North America consume caffeine daily. This widespread popularity makes caffeine the world's most commonly used drug. Caffeine acts as a central nervous system (CNS) stimulant in humans. Generally, CNS stimulants speed up physical and mental processes. Specifically, caffeine is well known for its ability to reduce drowsiness and make us more alert and awake. [1]

The caffeine molecule has several aspects that make it a perfect molecule to act as a CNS stimulant. First, it is able to easily cross the brain's blood barrier, similarly to other drugs such as alcohol, nicotine, and antidepressants. The brain blood barrier serves to protect the CNS by preventing viruses and other molecules from crossing into the brain. This barrier is so effective that many drugs cannot pass through it, and those that can pass through typically enter it slower than other membranes. However, caffeine passes through the blood barrier incredibly easily.

The exact reason for this is not yet clear, but there are a few possible reasons. Caffeine is both water and fat-soluble, which allows it to pass through nearly all membranes easily. Also, caffeine could be helped across the barrier by attaching to a transporter that is usually associated with adenosine, a molecule created in all human cells. [4]

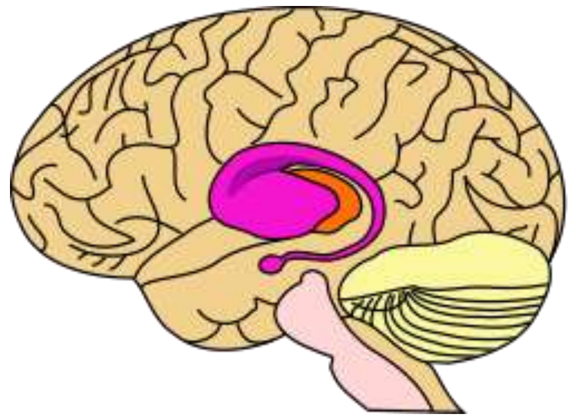


Caffeine and adenosine have similar structures, which allows it to affect the brain. [7, 9]

The second way caffeine is able to affect the brain so strongly is because of its structural similarity to adenosine. Adenosine is a molecule produced by all humans, and has various functions throughout the body. In the brain, adenosine acts as an inhibitory neurotransmitter, or CNS depressant. It bonds to neurotransmitters in the brain, and this binding creates a pathway that slows the activity of nerve cells and causes brain blood vessels to dilate, leading to a feeling of drowsiness. Since adenosine is being continually made by the body, the amount of adenosine increases throughout the day. As a result, as the day goes on and adenosine continues to build up, drowsiness increases. [3]

When adenosine enters the brain, it binds to specific receptors at the surface of brain cells. Each of these receptors is specifically tailored to the shape of adenosine, and adenosine binding to these receptors creates a neurological response which increases drowsiness. However, caffeine is so close in structure to adenosine that it is able to bind to the receptors which are specific to adenosine. Caffeine acts as an “antagonist” molecule; it binds to adenosine receptors on cell surfaces without activating them. In this way, the molecule is a competitive inhibitor for adenosine. Since the molecules are bound to adenosine receptors, the adenosine is blocked from attaching to them and cannot cause the typical response of sleepiness. Additionally, even though there is something bonded to the receptors, caffeine’s status as an antagonist molecule means that the receptor doesn’t do its usual job of causing drowsiness. In fact, caffeine binding to adenosine receptors causes the opposite effect: nerve cell activity speeds up, and brain blood vessels constrict. Thus, consuming caffeine prevents the brain from taking the usual steps to make us tired.

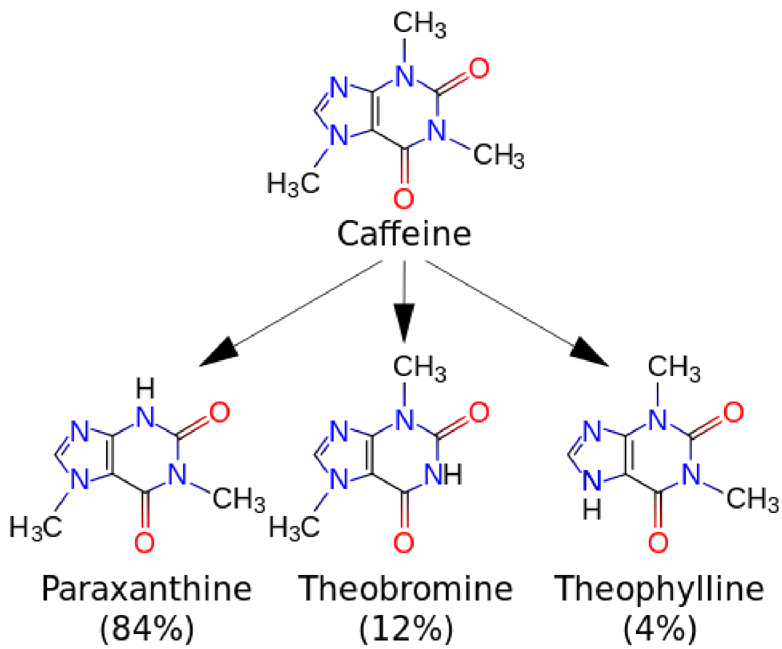
As caffeine binds to adenosine receptors, it actually makes the neurons fire more. The pituitary gland of the brain, which regulates the release of many hormones, takes this increase in activity as a signal to release hormones to produce adrenaline, or epinephrine. This adrenaline release leads to other common effects associated with caffeine, such as the heart beating faster or feeling excited. [7] (See "What are the long-term effects?" for information about how this effect changes over time)



When adenosine receptors in the striatum of the brain are blocked by caffeine, dopamine receptors are able to function at higher levels [5].

A third result of caffeine blocking adenosine receptors is an increase in the activity in the neurotransmitter dopamine. Activation of adenosine receptors in the striatum of the brain has been found to reduce the activity of dopamine receptors. Thus, when caffeine blocks the ability of adenosine to bind to receptors, it allows for dopamine receptors to function at higher levels. [5]

Dopamine is commonly known for its role in pleasure; it is released to make humans feel good and to stimulate us to do those pleasurable things again. For example, dopamine is released when we eat. Therefore, since caffeine is linked to an increase in dopamine reception, our bodies link consumption to the reward of pleasure from dopamine. Dopamine is also linked to focus, attention, and movement. Since dopamine improves focus and attention, caffeine's focusing effect can be attributed to an increase in dopamine. Finally, dopamine helps with movement, but its impact can be likened to a tightrope effect. A deficit in dopamine can lead to uncoordinated or delayed movements, but too much can lead to involuntary small movements and tics, similarly to how when one drinks too much caffeine they can start to get jittery. [6]



Caffeine is broken down into paraxanthine, theobromine, and theophylline [2].

Caffeine's effects go further than just what happens when the molecule enters the brain. When caffeine gets to the liver, it is broken down into three molecules: paraxanthine, theobromine, and theophylline. These three molecules are structural isomers of each other, which means that they have the same chemical formula ($C_7H_8N_4O_2$), but are connected differently and have different three-dimensional shapes. Thus, even though they are made of the same number of atoms, they have different properties. Each of these molecules interact with the body in different ways, and various other effects of consuming caffeine can be attributed to their presence.

Most of the caffeine (84%) is metabolized into paraxanthine, which is also a CNS stimulant. Paraxanthine's main effects on the body are to release fat to fuel muscles. This can lead to increased athletic ability. [2] Paraxanthine also has an energizing effect, since it increases the amount of epinephrine in the blood. [8] The next most-produced metabolic product of caffeine (about 12%) is theobromine, which can increase the flow of oxygen and nutrients to the brain. Theobromine also dilates blood vessels and increases urine volume. Finally, about 4% of the caffeine is metabolized into theophylline, which increases heart rate and the force of heart contraction. [2]

All these different effects come together to make caffeine an effective CNS stimulant. The molecule itself affects the brain in numerous ways to make us more alert and awake, and even after being metabolized caffeine contributes to bodies' levels of activity. With all these factors combined, it is unsurprising that caffeine is the world's most popular drug.

What are the long-term effects of caffeine?

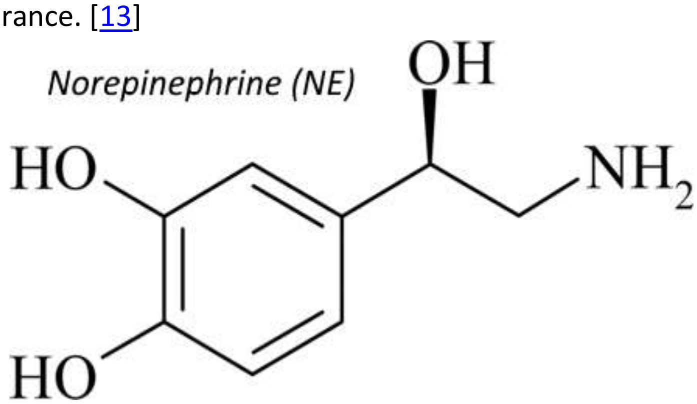
[11] Americans consume coffee at all hours.

Nearly 70 million Americans drink three cups of coffee a day. From college students to working adults, coffee drinkers use the beverage to jumpstart their day and maintain their energy. After it becomes part of your routine, caffeine can have many long-term effects. Withdrawal symptoms, an increased tolerance, and dependence can all result from regular consumption of caffeine. [10]

People who rely heavily on coffee to wake them up and get them through the day may be suffering from caffeine dependence. Caffeine is not actually addictive, even though it is a commonly used term, because it does not meet the definition of “addiction,” according to the National Institute for Drug Abuse. Even though there are many negative side effects, none of them qualify as self-destructive or life threatening, like in nicotine or methamphetamine. [12]

How does caffeine dependence occur? As you read in the previous sections, (See What are the short-term effects?) caffeine is a stimulant enabler that works by binding to adenosine receptors and inhibiting its drowsy effects. Over time, however, regular consumption of caffeine can cause the brain to grow more adenosine receptors. This provides more opportunities for adenosine to bind and take effect. In addition, the brain reduces the number of norepinephrine receptors. Norepinephrine is a stimulant, like caffeine. By reducing the number of receptors, the brain decreases the amount of natural stimulant. Both of these factors compensate for the artificial increase in alertness and can lead to an increased tolerance. [13]

Tolerance occurs when the body needs more caffeine to produce the same effects of alertness felt the first-time caffeine was consumed. It is a direct effect of the increase in adenosine receptors and decrease in norepinephrine receptors. More caffeine



[15] A decrease in norepinephrine receptors contributes to caffeine tolerance.

is required to bind to enough receptors to keep you awake. [13] Not all people will develop tolerance and it doesn't keep increasing indefinitely. However, complete tolerance is possible as well. Regular doses of caffeine exceeding 750 milligrams (approximately 8 cups of coffee) may produce no noticeable effect. [14]

In addition, the change in receptor patterns explains caffeine withdrawal. [13] Caffeine withdrawal occurs when people who keep a steady intake of caffeine stop abruptly and experience unpleasant side effects. [10] The brain becomes used to operating in highly caffeinated conditions with a greater number of receptors. When caffeine is absent, the brain's chemistry is unbalanced, resulting in an exaggerated effect of adenosine. [13] Headaches, fatigue, irritability, depression, difficulty concentrating, and flu like symptoms are all trademark effects of caffeine withdrawal. [14] Adenosine is a vasodilator, so an increased effect of the chemical would allow more blood flow to the brain. Increased blood flow results in the standard pounding headache. [16] Tiredness is a result of the availability of adenosine to bind to receptors without caffeine blocking it. [17] Caffeine stimulates the production of serotonin. When caffeine is eliminated, serotonin will not be naturally present, causing depressive moods and irritability. [16] It is possible to reverse caffeine dependency. After approximately 7-12 days without caffeine, depending on a person's tolerance, the brain will naturally reestablish the number of chemical receptors. [13]

Negative Effects of Caffeine

Too much caffeine can also have long-term negative effects. These can include anxiety, increased vasodilation, high blood pressure, and decreased fine motor function. It is also linked to infertility, irregular bowel movements, and heartburn. [10] Since caffeine is linked to increased urination, it can result in long-term dehydration, which will decrease the function of major organs. Insomnia is also a common result of consistent caffeine intake. Heavy coffee drinkers have high levels of caffeine, which will continue to stimulate the brain, even after trying to fall asleep. The symptoms of depression are heightened by caffeine intake. The changes in energy levels while drinking coffee throughout the day can affect mood, which may artificially increase depressive symptoms. Both withdrawal symptoms and overstimulation of the nervous system can lead to headaches, one of the most common complaints of long-term coffee intake. [18]

While actually overdosing on caffeine is rare, it is possible. The LD50, or the median lethal dose, of caffeine in humans is approximately 150-200 mg per kg of body mass. This equates to 80-100 cups of coffee in one sitting for an average adult. As a result, death from caffeine is not caused by coffee intake. Instead, it occurs more commonly by overdosing on caffeine pills. [19] (See “How is caffeine formed and used in nature?”)

Health Benefits of Caffeine

Amidst the negative long-term effects of caffeine, there are several medical benefits to drinking coffee. Caffeine is used to treat asthma, improve mood, prevent cavities, and reduce headaches. Coffee drinkers are 80% less likely to develop Parkinson’s Disease, and caffeine derivatives are used to treat the disease. These advantages can be attributed directly to caffeine, even though the coffee bean does have a variety of health benefits. [20] Regular caffeine intake can improve metabolism by 11% and fat burning by 13%. It can enhance your exercise performance by eliminating fatigue [17] and reducing muscle pain. In 2013, a study concluded that both caffeine from coffee and caffeine pills, administered at 5 mg/kg body weight one hour prior, improved performance in aerobic exercise. These effects are likely seen because caffeine increases the amount of adrenaline produced by the brain. In turn, increasing energy and blood flow to muscles. Also, caffeine decreases perceived fatigue, increasing performance. A 2009 study found that caffeine was statistically significant in decreasing reported muscle fatigue from high intensity aerobic cycling. It is also significant that the decrease in reported pain was even higher in groups where caffeine was not consumed regularly. [21]

Caffeine consumption is ingrained into our daily lives, so it is important to understand the long-term effects. While most are not serious, and some are actually beneficial, caffeine is a drug that can have consequences if consumed too often. These range from headaches and dehydration to insomnia, dependence and tolerance. Share this information next time you talk to one of the nearly 70 million Americans that drink coffee three or more times a day.

What is decaffeination?

Coffee became popular in England in the late 17th century thanks to the supply provided by the British East India Company, and dominated the palates of the American people after the Revolutionary War made tea prohibitively expensive and distinctly un-American. Despite its popularity, it wasn't until the beginning of the 20th century that a decaffeinated version was commercialized; the chemist Friedlieb Ferdinand Runge was the first to chemically isolate caffeine from the coffee bean, but he didn't seek to scale up the process or bring the decaffeinated product to market. [22]

The first commercial decaffeinated coffee was sold as "Kaffee HAG" by the company of the same name in Germany; it was later branded in other countries as "Sanka," a contraction of "sans caffeine." [23] In a process similar to some modern processes for decaffeination, the Bremen-based company prepared green, unroasted beans for caffeine extraction by steaming them for 20-40 minutes to open their pores and allow the solvent fluid to penetrate the beans and extract the caffeine. Initially, the organic compound benzene was used as a solvent to extract the caffeine, shown in Figure 1. Its use was discontinued shortly thereafter for safety reasons; the term "organic compound" simply means that a compound contains the element carbon and usually has a "skeleton" composed primarily of the element, not that it is necessary or beneficial for carbon-based life. Benzene is a human carcinogen, and the chemical is no longer used for anything outside of industries creating products that are not consumed by humans. Its properties as a solvent led it to be used in products like paint strippers and degreasers. [24]

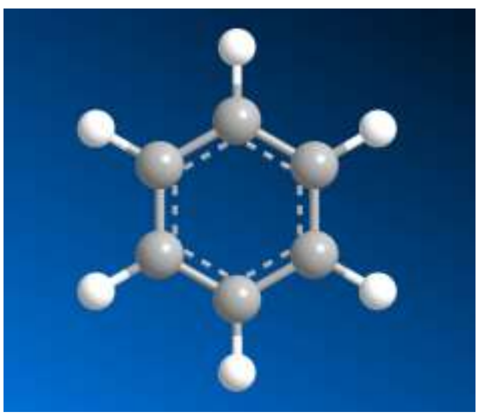
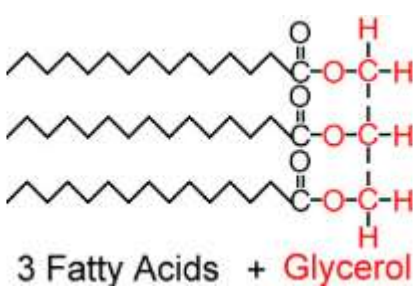


Figure 1 - Benzene Molecule, made in ChemDraw

This process, of first steaming the beans to enable extraction, then soaking them to remove the caffeine, and finally rinsing to remove any leftover solvent, is called the direct solvent process. Contemporary decaffeinated coffees produced by this method use dichloromethane and ethyl acetate as their solvents, given their lower toxicity and greater efficiency. As ethyl acetate can be manufactured in industrial quantities by biological processes like fermentation, coffees decaffeinated using this solvent are sometimes marked "naturally decaffeinated." Historically utilized but discontinued solvents include chloroform and trichloroethylene along with benzene.

Another method of decaffeination is known as "indirect decaffeination." The coffee beans are soaked in hot water for several hours, essentially brewing an enormous pot of coffee; the liquid, containing a significant percentage of the beans' caffeine along with other water-soluble compounds like sugar and various proteins, is drained off and decaffeinated using the same solvents as in the direct method, dichloromethane and ethyl acetate. The water used to soak the beans is recycled continuously through every batch of beans, so after several batches it reaches a concentration equivalent to that of the beans themselves in all of the various proteins and organic compounds that give coffee its taste. The only compound extracted from the beans at this point is the caffeine itself, which is removed from the solvent solution by evaporation.

Some companies use a high-tech technique called the "CO_2 method" to extract caffeine from large quantities of low-quality beans. [25] In it, the beans are steamed or soaked in a similar way to the other methods to open their pores, after which supercritical CO_2 is forced through the beans at pressures close to 68 times what we experience everyday under normal atmospheric conditions. "Supercritical" describes a substance when it's at temperatures sufficient for it to be a gas (which is quite low for CO_2; around -78 degrees Celsius or -108.4 degrees Fahrenheit) but is under such tremendous pressure that it takes on part of the properties of a liquid and a gas at the same time. In this state, CO_2 acts as the solvent that extracts the caffeine; after the decaffeination process, the pressurized mixture flows to a separate depressurization chamber where the CO_2 reverts back to its normal gaseous form and the caffeine is deposited in solid crystals. The CO_2 gas can then be recycled into the next batch of beans. This process has a number of advantages that primarily stem from using CO_2, a naturally-occurring substance as a solvent. However, its cost, complexity, and effects upon the beans themselves mean that it is primarily reserved for lower-quality products – being subjected to such tremendous pressures compromises the quality of the coffee produced somewhat. [26]



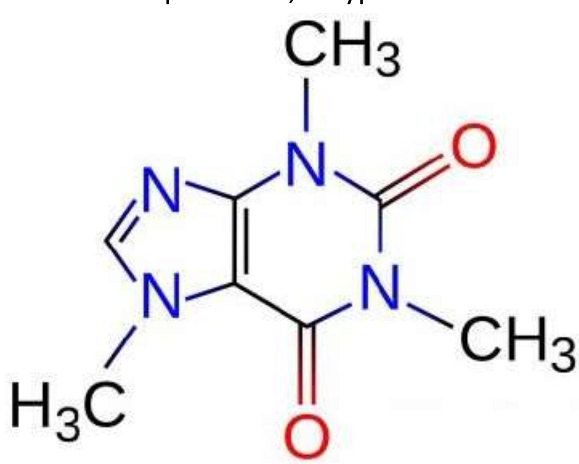
Triglyceride Molecule [27]

An infrequently used but all-natural method of decaffeination uses triglycerides to draw the caffeine out of the beans. The beans are soaked in a hot mixture of water and various oils and triglyceride fats extracted from other beans – coffee grounds are often used. After several hours, the beans are separated and dried for further processing and the heated oil solution is filtered to remove the caffeine so it can be reused to treat the next batch of beans. The caffeine molecule is relatively small as compared to the other compounds responsible for coffee's signature taste, and so can be extracted by the triglycerides and other solvents without compromising the end product. [27]

Demand for decaffeinated coffee has grown over the decades as more and more people like the beverage for its taste and fragrant aroma, but don't want to feel caffeine's stimulating effects. Decaf coffee is often offered to children and the elderly, both of whom for one reason or another shouldn't or can't have much caffeine. However, depending upon the country of origin, decaf coffee may contain anywhere from 1.5% up to 5% or 7.5% of the original caffeine content.[22] Different brands might use the same method for decaffeination but apply it less thoroughly to save money, for example. The resulting product is low enough in caffeine that it wouldn't cause the average person to feel caffeine's stimulating effects. Regardless of the exact concentration of caffeine, decaffeinated coffee is enjoyed by hundreds of millions across the globe and will be for the foreseeable future.

How is caffeine formed and used in nature?

Caffeine is defined as an alkaloid, which is a class of nitrogenous organic compounds of plant origin that have pronounced physiological actions on humans. Many of these nitrogen based organic compounds are known for having a bitter aftertaste Other alkaloids include nicotine, morphine, cocaine, and poisons. Caffeine is a natural alkaloid that can be found in about sixty plant species, the most common being: the coffee bean, tea leaf, kola nut, and the cocoa bean. Caffeine is a drug that is a result of millions of years of plant evolution. One mutation occurred and was then replicated many times until finally caffeine was produced, a byproduct of mutations. [28]



Caffeine chemical structure

Caffeine energizes humans (See “What are the short-term effects of caffeine?” and “What are the long-term effects of caffeine?”), but its effect on insects is lethal. Caffeine’s natural plant produced form acts as a pesticide and inhibits enzymes in herbivorous insects’ nervous systems, triggering paralysis and even death. This is why caffeine is commonly used as a pesticide to repel insects from damaging plants. Using caffeine as a pesticide is a highly controversial topic because it can harm other animals who ingest the plants or contaminate water supplies because the decay of caffeine infused plants seeps into the soil. Caffeine isn’t just harmful for insects, but can also negatively impact animals of varying sizes such as frogs, parrots and dogs. The effects of caffeine on these larger animals can induce an increased heart rate, as well as damage of the animal’s liver, kidney and brain neurons. The smaller the body mass of the insect or animal the more lethal the consumption of high doses of caffeine. [29]

Spider web produced by a drug naive spider and a caffeinated spider.

Caffeine consumption has been specifically monitored through bees and the results are quite interesting. You would think that caffeine would cause bees to produce honey at a faster rate equaling more honey, but in fact it has the opposite effect. Caffeine does boost a bee’s memory, helping them to remember the scent of the caffeine linked food. Nectar containing the trace amounts of caffeine will give the bee a jolt which will resonant in the bee’s memories, telling it to return back to that plant. But the caffeine actually leads to a behavioral change in the bees as to where their pollination is targeted toward benefitting the plants and not themselves. The bees in turn will become more attracted to plants with caffeine instead of plants with more nectar. The bees or other pollinating insects will then revisit the caffeine infused plant and spread its pollen further. However overtime other insects that feed on caffeine infused nectar or plants will build up taste receptors that avoid plants with caffeine in them. [30,31]

Plants containing caffeine over time will drop dead leaves onto the group or the plants will decompose leaving high amounts of caffeine in the soil. When caffeine is present in soil it suppresses the seed germination of weeds and surrounding plants which in turn increases the survival rate of the caffeine infused seedlings. This is an extremely useful ability, however caffeinated soil eventually ends up destroying the plants that produce it, that at first thrived because of its caffeine production. Caffeine in soil will eventually reach toxic levels therefore coffee plantations will have to move to new grounds approximately every ten to twenty-five years. [29]

Coffee seed

Specifically coffee is the most mass produced plant containing caffeine. Coffee belongs to the fourth largest family of angiosperms which are vascular seed producing plants. The seed of the coffee plant is the coffee bean. Caffeine starts off as a compound called xanthosine, which then has some of its atoms chopped off by enzymes that the coffee plant produces. Additional enzymes then add on addition atom clusters, finally producing caffeine. Caffeine occurs naturally in the tea plant, Camellia sinensis*,* so all brewed tea contains some amount of caffeine. The caffeine in chocolate comes from the cocoa beans inside the cocoa pods of a cocoa tree. [32,33]

Camellia sinensis (tea plant) and cocoa beans

Caffeine however helpful to humans can be lethal when amounts over 10 grams are ingested. However most sources conclude that about 6 grams per one hundred pounds of body weight, estimate death. To put this in perspective, an average of 1 to 2 mg/kg of caffeine is ingested per beverage. This means that death by caffeinated beverages is very rare due to the large amount of liquid that would need to be ingested at a time. In the few cases where cause of death is caffeine overdose, caffeine pills are the culprit. Caffeine pills deliver large doses of caffeine in a short amount of time. Therefore readers I would encourage you to stay away from caffeine pills and stick to the deliciously caffeinated beverages from your local coffee shop and next time you enjoy a caffeinated beverage think of caffeine's effect in nature. [34,35]

Popular caffeinated beverages (coffee and Monster)

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