Caffeine: Benefits, Risks and Effects-A Review

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Abstract

Caffeine, the world's most widely consumed psychoactive drug is a central nervous system(CNS) stimulant of the methylxanthine class. It is a white crystalline purine, a methylxanthine alkaloid which is bitter in taste. Caffeine is structurally related to the adenine and guanine bases of DNA and RNA. It is found in the nuts, seeds or leaves of a number of plants native to East Asia, Africa, and South America, and its natural function is to prevent germination of nearby seeds and to protect them against predator insects. Caffeine can have both positive and negative impact on human health. It can be used to treat and prevent the premature infant breathing disorders such as bronchopulmonary dysplasia of prematurity and apnea of prematurity. Caffeine citrate is on the WHO Model List of Essential Medicines which confers a modest protective effect against some diseases, including Parkinson's disease. Caffeine is classified by the US FDA as generally recognized as safe(GRAS). Toxic doses are over 10 gm/day for an adult, which are much higher than the typical dose of under 500 mg/day. However, pure powdered caffeine, available as a dietary supplement, can be lethal in tablespoon-sized amounts. In this review article, we discuss about the health benefits and adverse effects of caffeine along with its future prospects.

Keywords: *Caffeine, coffee, dependence, safety doses, toxicity.*

Introduction

The world was and still continues to be a big fan of coffee, the beverage that is globally accepted with open arms. Coffee is a major source of caffeine for most populations[1]. Coffee is often produced from the roasted beans of great variety of coffee crops[2]. The two most economically important species-Coffea canephora and Coffea arabica[3,4]. The world coffee trade is increasing each year showing the importance of coffee to the global economy. The composition of the two main coffee species (Arabica and Robusta) varies consistently with the origin, storage and terroir conditions. During the roasting process a number of reactions give rise to the organoleptic properties of coffee[5]. Coffee contains mineral ingredients such as Ca, K, Fe, P, Ni, Mg, and Cr[6,7,8] among others. The bioactive compounds of coffee include the following: methylxanthines (caffeine, theobromine and theophylline), diterpenes (kahweol and cafestol), phenolic compounds (chlorogenic acid and its derivatives), nicotinic acid[9]. These compounds have been associated with many potential health benefits. For example, diterpene alcohols and chlorogenic acids(CGA) have chemo-preventive and antioxidant activity, whereas caffeine reduces risk of developing neurodegenerative disease[10].

Caffeine, the common name for 1,3,7□ trimethylxanthine ($C_8H_{10}N_4O_2$), was derived from the German word kaffee and the French word café.

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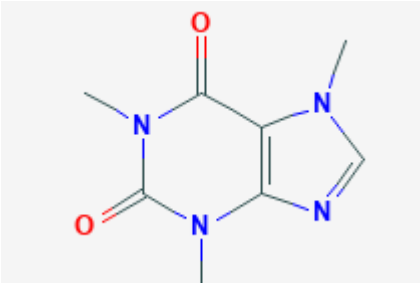

Fig 1: Structure of caffeine[11]

Caffeine is the most widely consumed psychoactive substance in the world[11]. The psychostimulant properties of caffeine are due to its interaction with neurotransmission in different regions of the brain, to promote behavioral changes, such as attention, mood, vigilance, and arousal[12]. By suppressing the actions of adenosine, caffeine increases neural activity in the brain, which leads to a temporary increase in mental alertness and thought processing, while reducing drowsiness and fatigue. At low to moderate doses of caffeine, the most prominent behavioral effects are amplified alertness and attention. Higher doses of caffeine encourage negative effects such as anxiety, insomnia, restlessness and tachycardia[13].The WHO identifies caffeine dependence as a clinical disorder[14]. Caffeine is found in common beverages, in products containing cocoa or chocolate, and in medications (Table 1).

Table 1: The average amounts of Caffeine in various food products.(Food Regulation Standing Committee, Caffeine Working Group. (2013))

Product	Average caffeine content (mg/100 ml)
Red Bull®	32.0
Mountain Dew®	15.0
Coca Cola®	9.7
Diet Coke®	9.7
Coke Zero®	9.6
Brewed black-tea	22.5
Brewed green-tea	12.1
Coffee (cappuccino)	101.9
Coffee (flat white)	86.9
Coffee (long black)	74.7
Coffee (from ground coffee beans)	194.0
Chocolate (milk-added milk solids)	20.0
Chocolate (dark-high cocoa solids)	59.0

Synthesis: The biosynthesis of caffeine is considered as an example of convergent evolution among different species. Primary substrates for Caffeine synthesisare malonic acid and dimethylurea. For commercial use, caffeine is produced as a byproduct of decaffeination.

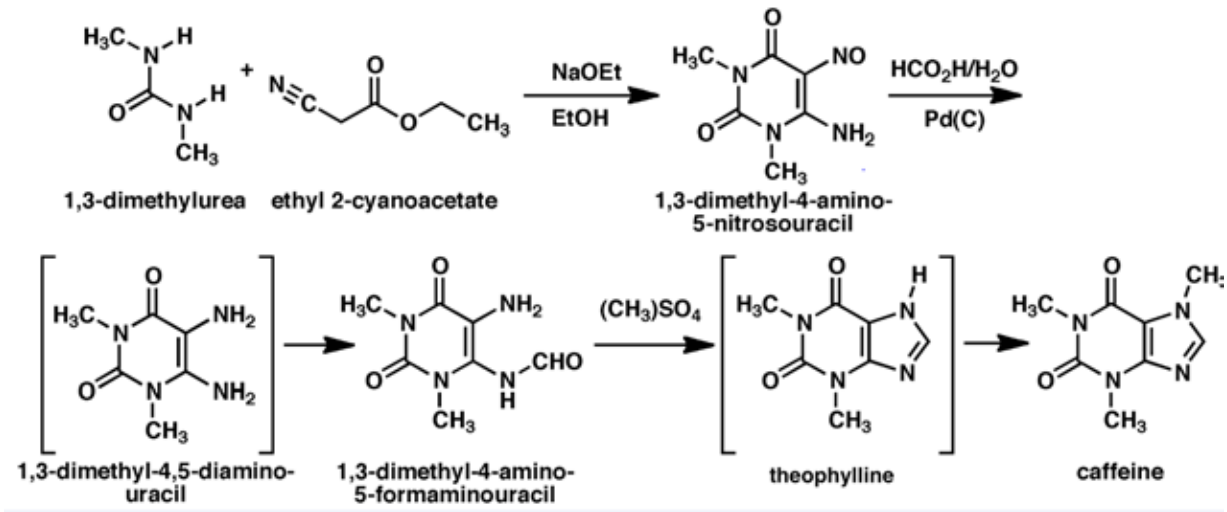

Fig 2: Synthesis of Caffeine

Decaffeination: Caffeine and decaffeinated coffee, are produced by using solvents such as benzene, trichloroethylene, chloroform, and dichloromethane have all been used over the years but for safety reasons, environmental impact, cost, and flavor, they have been superseded by the subsequent main method:

- Supercritical carbon dioxide extraction:

Supercritical CO_2 is an excellent nonpolar solvent usually safer than other organic solvents used regularly. It has gas like properties that enable it to penetrate deep into the beans and also has liquid-like properties that dissolve 97–99% of the caffeine. During the extraction process CO_2 is forced to enter the green coffee beans at pressures above 73atm and temperatures above 31.1°C("supercritical" conditions for CO_2). The caffeine-laden CO_2 is then sprayed with high-pressure water to remove the caffeine. The caffeine is then isolated by charcoal adsorption, distillation, recrystallization or reverse-osmosis.

- Water extraction: Coffee beans are soaked in water. This water is then passed through activated charcoal for removing caffeine. The water is then added back to the beans and evaporated dry, leaving decaffeinated coffee with its original flavor. The recovered caffeine is sold for use in soft drinks and/or over-the-counter caffeine tablets.
- Extraction by organic solvents: organic solvents such as ethyl acetate and use of triglyceride oils obtained from spent coffee grounds is also preferred. these compounds are less hazardous to health and environment compared to aromatic compounds.

Commercia decaffeinated coffee does contain caffeine in some cases. Studies have shown that decaffeinated coffee contained 10mg caffeine per cup, compared to approximately 85mg caffeine per cup for regular coffee.

Pharmacokinetics of Caffeine: The liver is the primary caffeine metabolism site. Rate of metabolism varies across the population; the half-life is diminished in smokers, but augmented during pregnancy and in women taking oral contraceptives[15]. Caffeine is quickly and entirely absorbed from the gastrointestinal tract, with 99% being absorbed within 45 min of ingestion[16].

Peak plasma concentrations take place between 15-120 minutes after oral ingestion. This wide variation in time might be because of variation in gastric emptying time and the presence of other dietary constituents, for example, fiber[17]. Caffeine has a physiological half-life of 3.5 to 6 hours[18,19]. It's physiological impacts are seen in less than 1h. Infants do not metabolize caffeine and therefore have a half-life of around 4 days[20]. CYPP450 oxidase enzyme system is predominantly involved in caffeine metabolism. This metabolic process involves conversion of caffeine by the CYP1A2 isozyme into three dimethylxanthines,[21] paraxanthine (72%), theobromine (20%) and theophylline (8%)[22], each of which effect the body in various ways.

- Paraxanthine: Increases lipolysis, causing rise in glycerol and free fatty acid levels[22].
- Theobromine: Along with being the key alkaloid in cocoa bean, it dilates blood vessels and increases urine volume[22].
- Theophylline: Relaxes smooth muscles of the bronchi and are utilized to treat asthma[22].

Further metabolism takes place in each of these metabolites, followed by renal excretion. Caffeine can accrue in people with severe liver disease as expressed before, expanding its half-life[23].

During pregnancy estrogens and gestates inhibit CYP1A2 activity, this increases the half-life time up to 16 hours(3-4 times longer than in non-pregnant women). Since caffeine can't be metabolized by neither fetus nor placenta, caffeine readily crosses the placenta into the fetus. Given the prolonged half-life of caffeine during pregnancy, fetus of caffeine consuming women are exposed to caffeine and its metabolites for a significantly prolonged time. Several genetic and non-genetic factors have been reported that significantly affect caffeine metabolism by CYP1A2 for various population groups. Considering the reduced maternal clearance and prolonged half-life during pregnancy and the fetus' exposure to maternal caffeine plasma levels, the unborn child is the most vulnerable to adverse effects of caffeine among the general population.

Pharmacodynamics Effects: In the absence of caffeine little adenosine is present in neurons. Over time adenosine accumulates in the neuronal synapse, and binds to the adenosine receptors found on certain CNS neurons; this binding of adenosine to its receptors produces a cellular response that increases drowsiness. When caffeine is consumed, it antagonizes 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. It also temporarily increases the production of dopamine, a chemical substance in the brain that is associated with increased concentration.

Four adenosine receptors(A1, A2A, A2B and A3) are present in humans, the distribution of these receptors ultimately effects caffeine activity at various organs and tissues. For example: psychomotor stimulant effect of caffeine is generated by affecting a particular group of projection neurons located in the striatum (high levels of adenosine A2A receptors).

Health Benefits: The positive effects of caffeine consumption have been reported through clinical studies. At a dose of 6 mg/Kg body mass, it exhibited an ergogenic effect, in sedentary men[24].

It's stimulatory activity was tested on Parkinson's disease patients, it seemed to be helpful in managing both motor and non-motor symptoms[25]. In a mouse model, β-amyloid peptides(characteristic feature of Parkinson's disease patients) accumulation reduced with crude caffeine intake[26]. Another study showed that 4.1% of people in the US are suffering from clinical depression. In a Harvard study published in 2011, women who drank 4 or more cups of coffee per day had a 20% lower risk of becoming depressed[27].

Studies show that coffee drinkers have up to a 40% lower risk of liver cancer[28,29]. Similarly, one study in 489,706 people found that those who drank 4–5 cups of coffee per day had a 15% lower risk of colorectal cancer[30].

Investigations have revealed that crude caffeine did possess hydrophilic antioxidant activity (145μmol Trolox equivalent (TE)/g) and lipophilic antioxidant activity (66μmol TE/g), and its administration led to the inhibition of cyclooxygenase-2 enzyme better than aspirin[31].

Adverse Effects

Some of the adverse effects of high doses of caffeine include overstimulation of CNS, decrease tonus of lower esophageal sphincter muscle, and intrauterine growth retardation[32]. High doses of coffee intake during pregnancy increase the risk of miscarriage, independent of pregnancy related symptoms[33].

Caffeine-induced anxiety-disorder is one of four caffeine-related syndromes. Extremely high intake of 1,000mg/day or more have been reported to cause nervousness, jitteriness and similar symptoms in most people, whereas even a moderate intake may lead to similar effects in caffeine-sensitive individuals[34,35].

Increased urination is a common side effect of high caffeine intake due to it's stimulatory effects on the bladder. Most of the research on the compound's effects on urinary frequency has focused on older people and those with overactive bladders[36,37,38]. In one study,12 middle-aged people with overactive bladders who consumed 2 mg caffeine per pound(4.5mg/kg) of body weight daily experienced significant increases in urinary frequency and urgency[37].

Caffeine's ability to keep people awake is one of it's most prized qualities. However, too much caffeine can disrupt the sleep cycle. Studies have found that higher caffeine intake increases the time taken to fall asleep. It may also decrease total sleeping time, especially in the elderly[38,39].

Regulations: The FDA in the US currently allows only beverages containing less than 0.02% caffeine, but caffeine powder,which is sold as a dietary supplement,is unregulated[40]. It is a regulatory requirement for packaged food to show presence of additives such as caffeine in the label. However, there is no regulatory provision for mandatory quantitative labeling of caffeine, (e.g.,milligrams caffeine per stated serving size). There are a number of food ingredients that naturally contain caffeine. These ingredients must appear in food ingredient lists.

Future Prospects and Conclusion

Refined western tastes for specialty blends and developing economies have led to an increase in coffee demand worldwide with the International Coffee Organization expecting the market to grow almost 25% by 2020. With the rising demand,supply is unable to keep up. Coffee supply chain networks are structured to reward roasters and distributors, leaving growers with not much in return for their labor. Poor economic futures combined with the mounting threat to crop yields due to global warming have created a problem that will take time to resolve. As temperatures rise, so will farms. Only 2% of the land currently appropriate for the farming of coffee is actually used to produce the crop. However,a warming climate will cut suitable land in half. Available geographical terrain for coffee production will shift in latitude and increase in elevation. A recent study done by Conservation International reported that tropical forests cover 60% of future farmable land with one-third of that marked as a pristine and protected area. Parts of Central America, the Andes and Southeast Asia are

under the greatest threat of deforestation which would impact and destroy crucial ecosystems that presently assist in carbon storage and provide both freshwater and biodiversity for communities. "Coffee Rust" is the most detrimental disease to coffee plants and has accompanied rising global temperatures.

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References

1. Reyes. C.M., Cornelis. M.C. Caffeine in the diet: Country-level consumption and guidelines. Nutrients 2018, 10, 1772.
2. F. Anthony, B. Bertrand, O.Quiros. "Genetic diversity of wild coffee (Coffea arabica L.) using molecular markers," Euphytica, 2001; vol.118;1; pp.53–65.
3. M. Klein, I.S teffan-Dewenter, and T. Tscharntke, "Bee pollination and fruit set of C.
4. arabica and C.canephora (Rubiaceae)," The American Journal of Botany, 2003;vol.90;1, pp.153–157.
5. A. Lécolier, P.Besse, A. Charrier, T.N.Tchakaloff, and M. Noirot, "Unraveling the origin of Coffea arabica "Bourbon pointu" from la Réunion: a historical and scientific perspective," Euphytica, 2009;vol.168;no.1;pp.1–10.
6. M.Oliveira, S.Casal, S.Morais. "Intra-and interspecific mineral composition variability of commercial instant coffees and coffee substitutes: contribution to mineral intake," Food Chemistry, 2012;vol.130;3;pp.702–709.
7. J.A.Vignoli, D.G. Bassoli & M.T. Benassi, "Antioxidant activity, polyphenols, caffeine and melanoidins in soluble coffee: the influence of processing conditions and raw material,"Food Chemistry, 2011:124:3:863–868.
8. S.I. Mussatto, L.M. Carneiro, J.P.A. Silva, I.C. Roberto, & J.A. Teixeira, "A study on chemical constituents and sugars extraction from spent coffee grounds," Carbohydrate Polymers, 2011; vol.83:2:368–374.
9. Mafalda. C.S, Ricardo. N.M.J.P, Miguel. L, Jorge. M.G.S and Joao. A.L. Bioactive Compounds in Coffee as Health Promotors, pp.180-220(41).
10. Gómez-Ruiz. J.A, Leake. D.S, Ames.J.M "In vitro antioxidant activity of coffee compounds and their metabolites". J Agric Food Chem. 2007, 55:6962–6969
11. Büşra. B, Gökcen & Nevin. Ş. "Coffee consumption and disease correlations" Journal of Critical Reviews in Food Science and Nutrition, 2017.
12. Ian. C.H, Peter. L. "Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials"Sleep Med Rev.2017;31:70-78.
13. Fisone.G, Borgkvist.A & Usiello.A."Caffeine as a psychomotor stimulant: mechanism of action" CMLS, Cellular and Molecular Life Sciences.200 4;Vol.61:7–8:857–872.
14. Finnegan D. "The health effects of stimulant drinks". Nutrition Bulletin.2003;28:147-155.
15. Uddin. M.S, Sufian. M.A, Hossain. M.F, Kabir. M.T, Islam. M.T. Neuropsychological Effects of Caffeine: Is Caffeine Addictive? J.Psychol. 2017;7:295.
16. Liguori. A, Hughes. J.R, Grass. J.A. Absorption and subjective effects of caffeine from coffee, cola and capsules. Pharmacol Biochem Behav 1997;58:721-726.
17. James JE. The influence of user status and anxious disposition on the hypertensive effects of caffeine. Int J Psychophysiol 1990;10:171-179.
18. Parsons.W.D, NeimsA.H.Effect of smoking on caffeine clearance. Clinical Pharmacology & Therapeutics 1978;24:40-45.
19. Aranda. J.V, Cook. C.E, Gorman. W, Collinge. J.M, Loughnan.P.M, Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. The Journal of pediatrics, 1979, 94: 663-668.
20. Aranda. J.V, Sitar. D.S, Parsons. W.D, Loughnan. P.M, Neims. A.H. Pharmacokinetic aspects of theophylline in premature newborns. N Engl J Med, 1976, 295:413-416.
21. Coelho A, Fraichard.S, Le.G.G, Faure.P, Artur.Y. Cytochrome P450-dependent metabolism of caffeine in Drosophila melanogaster. 2015;PloS one 10:e0117328.
22. Fredholm. B.E. Handbook of Experimental Pharmacology: Methylxanthines. Sweden:

Springer. 2011.

23. Verbeeck.R.K. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147-1161.
24. G.Laurence, K.Wallman, and K.Guelfi, "Effects of caffeine on time trial performance in sedentary men," Journal of Sports Sciences, 2012;vol.30;12;pp.1235–1240.
25. R.D.S.Prediger, "Effects of caffeine in Parkinson's disease: from neuroprotection to the management of motor and non-motor symptoms," Journal of Alzheimer's Disease, 2010;vol.20;1;pp.205–220.
26. Y.F.Chu, W.H.Chang, R.M.Black. "Crude caffeine reduces memory impairment and amyloid β1—42 levels in an Alzheimer's mouse model," Food Chemistry, 2012;vol.135;3;pp.2095–2102.
27. Lucas.M, Mirzaei.F, Pan.A, Okereke.O.I, Willett.W.C, O'Reilly.É.J, Koenen.K, Ascherio.A. Coffee, caffeine, and risk of depression among women.Arch Intern Med. 2011:26;171(17):1571-8.22.
28. Susanna.C.L, Alicja.W. Coffee Consumption and Risk of Liver Cancer: A Meta-Analysis 2007;Vol.132;Issue-5;pp-1740-1745 Gastroenterology
29. T.Shimazu, Y.Tsubono, S.Kuriyama, K.Ohmori, Y.Koizumi, Y.Nishino, D.Shibuya, I.Tsuji, Coffee consumption and the risk of primary liver cancer: Pooled analysis of two prospective studies in Japan. International jornal of cancer First published: 08-March-2005
30. Sinha. R, Cross. A.J, Daniel. C.R, Graubard. B.I, Wu.J.W, Hollenbeck. A.R, Gunter. M.J, Park.Y, Freedman. N.D. Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study.American Journal of Clinical Nutrition. 2012;96(2):374-81.
31. Y.F.Chu,Y.Chen,P.H.Brown."Bioactivitiesofcrude caffeine: antioxidant activity, cyclooxygenase-2 inhibition, and enhanced glucose uptake," Food Chemistry, 2012;vol.131;2;pp.564–568.
32. W.Dworzański, G.Opielak, and F.Burdan, "Side effects of caffeine," Polski Merkuriusz Lekarski, 2009;vol.7;161;pp.357–361.
33. Weng.X, Odouli.R, Li.DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. American Journal of Obstetrics and Gynecology, 2008;pp:198-279.
34. Anthony.P.W, Elizabeth.H and Neema.J. Neuropsychiatric effects of caffeine.Advances in Psychiatric Treatment 2005;pp.432-439;Volume-11;Issue-6
35. Smith.A. Effects of caffeine on human behavior. Food Chem Toxicol. 2002;40(9):1243-55.
36. Kosilov.K.V, Loparev.S.A, Ivanovskaya.M.A, Kosilova.L.V. Caffeine as a Probable Factor for Increased Risk of OAB Development in Elderly People. Curr Urol. 2016;9(3):124-131.
37. Lohsiriwat.S, Hirunsai.M, Chaiyaprasithi.B. Effect of caffeine on bladder function in patients with overactive bladder symptoms. Urol Ann. 2011;3(1):14-8.
38. Ying.H.J, Mary.K.T, Gary.C.C, Neil.M.R, and Francine.G. Caffeine intake and risk of stress, urgency, and mixed urinary incontinence. J Urol. 2011;185(5):1775–1780.
39. Watson.E.J, Coates.A.M, Kohler.M, Banks.S.Caffeine Consumption and Sleep Quality in Australian Adults.Nutrients. 2016:4;8(8). pii:E479.
40. Clark. I, Landolt. HP. Coffee, caffeine, and sleep:A systematic review of epidemiological studies and randomized controlled trials. Sleep Med Rev. 2017;31:70-78.