# The Multifarious Influence of Caffeine on Metabolic and Cognitive Functioning

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## ABSTRACT

The use of caffeine as a psychotropic and medicinal drug has been in existence since the 19th century. It is a natural plant alkaloid used extensively all around the world. In recent years, caffeine has been incorporated into scads of products encompassing food, cosmetics, medicine, and several other industries. In this review, we have accentuated the chemistry of caffeine, its metabolism and processing in the body, its mechanism of action, and several other effects on bodily and cognitive functions. With substantial antioxidants, caffeine is utilised in numerous ailments, including cancer, and is known to enhance longevity. The effect has also been reported in neurodegenerative disorders, anxiety, cardiovascular health, diabetes, and many other significant afflictions. As caffeine is a non-selective antagonist of adenosine receptors, it binds to such receptors and prevents us from being in a torpid state. This further helps to augment alertness and cognitive functions. Caffeine's role in weight loss, kidney dysfunction, and its hepatoprotective and neuroprotective effects have also been emphasized. A fragment of our review also apprises an introduction to decaffeinated coffee, which is transpiring as a sought-after drink. Owing to its extensive use, high caffeine intake may induce "caffeinism," which could be life-threatening. This makes it crucial to comprehend caffeine toxicity and shed light on some of the treatments used. We also scrutinised some gaps in the literature, which could ameliorate the current research and pave the way for novel effects and efficacy of caffeine.

**Keywords:** *Caffeine, Metabolism, Caffeinism, Antioxidants, Cardiovascular Disease, Neurodegenerative Disorders, Decaf, Diabetes, CYP1A2*

## 1. Introduction

Caffeine, a plant alkaloid, is a natural chemical present in at least 63 plant species worldwide in leaves, seeds, or fruits (Gebeyehu and Bikila, 2015). The scientific name of caffeine is 1,3,7-trimethylxanthine. It is also known as Coffein or Theine. Caffeine is a cognate of purine, containing a ketone group at carbons 2 and 6 of the purine component (Heckman et al., 2010). Two different forms of alkaloids are present in coffee plants; purine alkaloids, i.e., caffeine (1,3,7-N-trimethylxanthine), theobromine (3,7-N-dimethylxanthine), and the alkaloid pyridine, i.e., 1-N-methylnicotinic acid (Ashihara, 2006). Caffeine has various metabolites, but paraxanthine is the most significant. When these metabolites are further modified, they have a comparable chemical composition, and the half-life of caffeine can be readily determined in biological samples.

Caffeine is widely used as a stimulant all around the world. The activated nerve cells release the epinephrine (adrenaline) hormone (Chen et al., 2013), which enhances heart rate, blood pressure, and muscle blood supply, improves blood flow to the skin and organs, has psychotropic (mood-altering) effects, and serves as a moderate diuretic. Caffeine also escalates the levels of the neurotransmitter dopamine (Ferré, 2016). For the majority of healthy people, up to 400 milligramms (mg) of caffeine, a day appears to be safe. According to a study that varies among individuals with diseases, the mean serum caffeine half-life for the stable participants is around 5.7 hours (Statland and Demas, 1980). The removal half-life of caffeine, however, can differ between 1.5 and 9.5 hours, and its total plasma clearance rate is estimated to be 0.078 L/h/kg (White Jr et al., 2016).

Caffeinated drinks are widespread and popular beverages in the world due to their harsh flavour and antioxidant properties. Furthermore, recent research has linked them to weight loss and have mediated in increasing focus abilities. Caffeine also has a direct impact on longevity and, when taken regularly and in controlled amounts, can reduce multiple liver, kidney, and cardiovascular diseases. Furthermore, to lessen any lethal impact of caffeine, decaffeinated coffee has been introduced in the market, which is highly popular as it has reduced the fatal side effects of caffeine.

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## 2. Major Properties and Functions of Caffeine

### *Caffeine and its metabolism*

When caffeine is demethylated, paraxanthine is primarily released (84%), followed by theobromine (12%), and theophylline (4%). Caffeine and theophylline have similar chemical structures, but theophylline lacks an N-methyl group and governs more basic actions than caffeine and theobromine. The metabolism of paraxanthine, the major constituent of caffeine, is further processed via two pathways: the first one forms 8-hydroxyparaxanthine, and the other one produces three metabolites, including 5-acetylamino-6-formylamino-3-methyluracil (AFMU), 1-methylxanthine, and 1-methylurate. AFMU is then converted to 5-acetyl-6-amino-3-methyluracil (AAMU), which can be quantified in the urine samples with ease. As a result of active renal tubular secretion, paraxanthine metabolites are excreted almost as quickly in the urine as they are made (Cappelletti et al., 2015).

Theobromine is the next most abundant biologically active metabolite in caffeine (Eteng, 1997).It is quickly ingested, and about 50 percent is excreted in 8–12 hours through the urine (Tarka Jr. et al., 1983).

Caffeine is crucially processed by the enzyme cytochrome P450 in the liver. The enzyme responsible for the metabolism of caffeine is coded by the gene CYP1A2. Also, it is amenable to more than 90% of caffeine removal from the body. The vast variableness of CYP1A2 activity impacts the clearance of caffeine and may be influenced by factors such as gender, race, genetic polymorphisms, disease, and exposure to inducers. A study found that drinking at least three cups of coffee per day increased CYP1A2 gene activity (Fenster et al., 1998). A recent study suggests that caffeine pharmacokinetics do not change after a week of regular ingestion of coffee (Na Takuathung et al., 2019). The digestion of caffeinated beverages occurs through the GI tract and is distributed throughout the body's water. To increase the absorption rate, chewing gums containing caffeine allow absorption through the oral mucosa very rapidly. As a consequence, between 15 and 120 minutes after oral consumption, peak plasma concentrations were observed. Furthermore, caffeine metabolism may be influenced by a variety of other dietary variables (Guest et al., 2021).

### *Stimulatory effects*

Caffeine is taken as a stimulant of the central nervous system, and its derivatives are involved in the treatment of various neurodegenerative diseases.

Conditions that induce stimulation:

- During vigorous muscle contractions, caffeine mobilises $Ca^{++}$ by translocating $Ca^{++}$ across the plasma membrane and the sarcoplasmic reticulum. Higher levels of caffeine also impair the endoplasmic reticulum's calcium absorption (Kuo and Ehrlich, 2015).
- Caffeine also suppresses phosphodiesterase activity, thereby increasing cAMP levels (Echeverri et al., 2010).
- Adenosine, an adenine attached to a ribose sugar and a neurotransmitter in the central nervous system, is structurally similar to caffeine. Its receptors, especially A1 (present in almost all the areas of the brain) and A2A, are the prime targets for caffeine. The effects of caffeine are aggravated after caffeine binds to these receptors. The stimulation of A1 receptors by adenosine can suppress adenylyl cyclase and voltage-sensitive $Ca^{++}$ channels and activate $K^{+}$ channels and phospholipases C and D. The occurrence of presynaptic adenosine A1 receptors regulating the inhibition of transmitter release has been determined in virtually all the neurons (Jasiewicz and Sierakowska, 2020). Therefore, adenosine can modulate the release of numerous neurotransmitters. Caffeine and its theophylline metabolite serve as an adenosine receptor blocker and inhibit the sleep cycle, increasing the capacity to perform usual tasks (Chen et al., 2013).
- Caffeine can also interact with benzodiazepine receptors, though its affinity is lower than that of adenosine receptors (Nehlig et al., 1992). Several studies have demonstrated that high amounts of caffeine could reduce the binding of benzodiazepines, a class of psychoactive drugs (Fredholm et al., 1999; Liu et al., 2017).

### *Antioxidant properties*

Caffeine is recognised as a potent antioxidant. It counteracts many free radicals, such as hydroxyl, singlet oxygen, and peroxide, resulting in PUFA peroxidation. Caffeine has antioxidant properties similar to glutathione and is substantially more potent than ascorbic acid. Caffeine scavenges OH radicals but not HOO, $O_2$ or alkoxy radicals. The mechanism by which the caffeine molecule eliminates the hydroxyl radicals is still uncertain. One hypothesis is that in the C-8 position, the hydroxyl radical binds caffeine molecule synthesizing 8-oxo caffeine, usually appearing up to 60% of that of oxidation products (Jasiewicz and Sierakowska, 2020).

Apart from these, the other possible mechanisms to remove OH free radicals are:

1. Radical adduct formation (RAF)
2. Hydrogen atom transfer (HAT)
3. Single-electron transfer (SET) (Pizzino et al., 2017).

In a study, showing the possible antioxidant effect of caffeine by utilizing an organic prototype adenine compound and hydroxyl radicals generated by UV photolysis of water (cause of oxidative damage), the result indicated that the scavenging effect of caffeine and its products formed by the reaction of hydroxyl free radicals (1,3,7 trimethyluric acid, paraxanthine, theophylline and theobromine, and, at a lesser extent, 1,3-dimethyluric acid and 3methylxanthine) prevents the adenine deterioration and also converts oxidized adenine (caused by OH) back to adenine by caffeine oxidized products (Vieira et al., 2020).

### 3. Diabetes

Caffeine has been demonstrated as a dynamic chemical, with its functionality varying immensely in conditions such as diabetes. According to a systematic review and meta-analysis published in 2014, the consumption of coffee reduces the probability of the occurrence of diabetes (Ding et al., 2014). Several other studies also indicate an opposite relationship between coffee consumption and the chance of developing diabetes (Odegaard et al., 2008; Van Dam and Feskens, 2002; Van Dam and Hu, 2005; Van Dieren et al., 2009; Zhang et al., 2011).

The compounds in coffee that mediate glucose metabolism are caffeine, chlorogenic acids (CGAs), and magnesium (Muley et al., 2012). Caffeine metabolises into theophylline, which mediates glucose metabolism, thereby exerting its anti-diabetic activity (Pimentel et al., 2009). CGAs restrict the expression of glucose-6-phosphate translocase (Ding et al., 2014), hamper incretin hormones, and suppress oxidative stress on pancreatic beta cells (Pereira et al., 2006). This further inhibits gluconeogenesis and thereby employs its anti-diabetic activity (Zhang et al., 2017).

Coffee polyphenols activate GLP-1, a key intestinal hormone that stimulates glucose-induced insulin release from -cells (Fujii et al., 2015). Magnesium treats diabetes by increasing insulin release and responsiveness, and trigonelline regulates carbohydrate and lipid metabolism through enzymes like glycokinase, glucose-6-phosphate, fatty acid synthetase, and carnitine palmitoyltransferase (Gökcen and Anlier, 2019).

A study published in Diabetes Care in 2004 showed a direct correlation between a high intake of coffee and the amount of fasting insulin (van Dam et al., 2004). Another study, by measuring the increase in skeletal muscle GLUT 4 and 5′-AMP-activated protein kinase (AMPK) protein expression, demonstrated that chronic caffeine consumption, besides regulating glucose and fatty acid levels, also reverses insulin sensitivity (Ribeiro et al., 2013).

According to various studies directed at recognising the relationship between coffee consumption and the incidence of developing type 2 diabetes, there have been variable and inconsistent conclusions. However, a recent meta-analysis indicates that a daily intake of coffee decreases the possibility of developing type 2 diabetes. Due to the disparity among studies, further exploration in this area is needed to unfold new therapeutic possibilities for type 2 diabetes (Carlström and Larsson, 2018).

### 4. Neurodegenerative Disorders & Anxiety

Caffeine is one of the most widely consumed psychostimulants in the world. It is known to boost alertness and lessen fatigue; it leads to improved bodily movement and task performance.

The most elevated blood caffeine concentration is attained after 30-60 minutes of consumption. Owing to its hydrophobic character, it traverses the blood-brain barrier with ease. Prolonged caffeine intake can also enhance oxidative stress and ameliorate mitochondrial functions. However, a study found that it boosts Glutathione-S-transferase activity and suppresses RBC membrane derangement. It is also acknowledged as a hydroxyl radical scavenger (Kolahdouzan and Hamadeh, 2017).

Caffeine provokes human cognitive function and affects the levels of attentiveness, memory, state of mind, learning, psychomotor activity, etc. Consequently, caffeine is related to the slowing down or prevention of disorders involving cognitive decline such as neurodegenerative or neurological disorders namely Parkinson's disease (PD), Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), depressive disorders, etc. It is also known to influence anxiety and stress levels.

#### *Brain and the role of neurotransmitters*

Adenosine is known to make us feel somnolent. Caffeine binds to the adenosine receptors present in the brain in lieu of adenosine, thus preventing us from feeling lethargic. It also promotes the supply of adrenaline, thereby increasing the heart rate and dilating the airways. Also, caffeine obstructs dopamine reabsorption making the feel-good chemical linger in the brain for much longer and making caffeine addictive (DiSalvo, 2012).

Caffeine has been shown to have neuroprotective effects by protecting dopaminergic neurons in investigations using various molecular methods. It has also been illustrated via animal models that caffeine associates with the dopaminergic system bringing about enhancements in neurobehavioral measures of depression or ADHD (Alasmari, 2020). Yacoubi et al. (2001), reported that caffeine impaired neurobiological diseases by regulating dopaminergic pathways.

In a separate study, John et al.demonstrated that caffeine raises glutamate levels in the posterior hypothalamus in adult rats. The relationship between the modulating effects of caffeine on neurobiological outcomes requires further

studies and investigations to come up with a compelling answer (John et al., 2014).

***Alzheimer's and Parkinson's Disease***

AD is one of the most common neurological disorders in the world. Despite the steadily evolving technological and medical advances, many older adults are being afflicted with AD. Caffeine has been of tremendous interest to the scientific community because it is an antioxidant compound and can reduce the oxidative stress caused due to AD (Kolahdouzan and Hamadeh., 2017). A number of studies have found a link between caffeine consumption and a decreased incidence of Alzheimer's disease. Coffee use in midlife has also been shown to reduce the risk of acquiring Alzheimer's disease (Coffeeandhealth.org, 2012).

Caffeine may ameliorate parkinsonian motor symptoms by antagonizing adenosine receptors, which are predominantly expressed in the basal ganglia, according to evidence from in vitro and in vivo investigations. Caffeine administration in conjunction with currently available PD medicines may aid to reduce drug tolerance, implying that caffeine might be used as an adjuvant in the treatment of PD (Roshan et al., 2016). Manalo et al. stated that caffeine generates neuroprotective effects by decreasing the dopaminergic neuronal loss, propounding that caffeine might have therapeutic effects on neurodegenerative disorders; this may spark a positive response for PD patients (Manalo et al.,2018).

***Anxiety and Panic disorders***

Caffeine has been shown to raise levels of cortisol, the major stress hormone, during rest or under mental stress. It also activates the stress axis, raising blood pressure by boosting glucocorticoid and catecholamine levels (al'Absi and Lovallo, 2004). Caffeine may affect blood pressure and stress endocrine responses when consumed during periods of neurotic tension (Lovallo et al., 2005). According to certain studies, persistent coffee use in Panic Disorder patients might cause anxiety and frequent panic episodes (Masdrakis et al., 2009; Nardi et al., 2008). This was demonstrated in a trial that administered 480 mg of caffeine to certain participants with anxiety problems and to those who did not. Patients with anxiety disorders were found to be more prone to have panic attacks (Palmer, 2021).

A study also demonstrates that modest doses of caffeine may also help antidepressant medicines work more effectively in people with major depressive disorder (Nehlig et al., 1992).

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## 6. Cardiovascular Health, Blood Pressure and Hypertension

Several studies have been performed in the past three decades, and despite considerable results and evidence, the effect of caffeine on cardiovascular (CV) health is still unclear; there are large discrepancies and contradictions between earlier and recent studies.

The consumption of caffeine on a regular basis was linked to an increased risk of cardiovascular disease, according to early research, but recent studies show neutral or positive relation (O'Keefe et al., 2018). Fatalities due to coffee intoxication are rare, but there are 92 documented deaths, the leading cause being ventricular fibrillation (Cappelletti et al., 2018).

Studies carried out on healthy patients as well as patients who had a medical history of cardiovascular affliction did not provide a concrete evidence. Lower rates of CV mortality and a range of negative CV outcomes, such as coronary heart disease (CHD), congestive heart failure (HF), and stroke, were linked to habitual coffee consumption; however, the effects of coffee on arrhythmias and hypertension are balanced (Ding et al., 2014), ( O'Keefe et al., 2013), (Turnbull et al., 2017). Although a few are indicative of increased cholesterol, TAG, and homocysteine levels.

Caffeine can operate as a cardiac stimulant by increasing intracellular calcium levels, releasing noradrenaline, and sensitizing dopamine receptors, all of which can cause cardiac rhythm disruption. Caffeine use is believed to trigger atrial arrhythmias, although there is no proof to substantiate this claim; in fact, studies demonstrate that regular use may reduce the risk (Abdelfattah et al., 2018; Artin et al., 2010; Bodar et al., 2019; Cheng et al., 2014; Ding et al., 2014; Mostofsky et al., 2016; Pelchovitz and Goldberger, 2011). In a large cohort study, coffee consumption and caffeine intake were inversely associated with the risk of arrhythmias, particularly atrial fibrillation and other supraventricular arrhythmias (Klatsky et al., 2011).

A rise in blood pressure can be caused by adenosine receptor blockade (Conlay et al., 1997), phosphodiesterase inhibition (Choi et al., 1988), or increased catecholamine release by angiotensin (Robertson et al., 1978). Caffeine may potentially boost water and electrolyte excretion by creating a diuretic effect, resulting in lower blood pressure (Nussberger et al., 1990), (Yu et al., 2016). The disparity in different studies may be due to various factors genetics, age, gender, source of caffeine (filtered, unfiltered, boiled, instant) (Rendón et al., 2018), lifestyle habits (smoking, drinking), presence of ailments.

In their control group investigation, Geethavni et al. found a 17% rise in systolic blood pressure and about 11% rise in mean arterial blood pressure compared to placebo (Geethavani et al., 2014). Caffeine consumption elevates blood pressure acutely, according to a study conducted by the European Food Safety Panel. The dosage ranged from 80 to 300 mg, resulting in an average rise of 3-8 mmHg in SBP and 4-6 mmHg in DBP. Existing evidence shows that blood pressure rises 30 minutes after caffeine use, peaks 60-90 minutes later, and falls to baseline after two minutes (www.efsa.europa.eu, 2015).

An inverse J- shaped relationship has been stated by the author Zhang et al. The results advocate that regular coffee consumption of more than 3 cups per day was not associated with an increased threat of hypertension compared with less than 1 cup per day; however, a slightly upraised risk appeared to be related with light-to-

moderate consumption of 1 to 3 cups per day (Zhang et al., 2011). An investigative study carried out by Soares et al. (2008), indicates that higher DBP is associated with the presence of allele C on the CYP1A2 gene when compared to the AA variant.

Thus, studies on caffeine intake confirm that there is an increase in BP for a short-term period in coffee naïve consumers, although habitual drinkers of caffeine do not show any high risk of hypertension, probably due to tolerance development. There is no concrete evidence to link hypertension with caffeine intake.

## 7. Lipids and Cholesterol

The major component of coffee is caffeine, along with other constituents such as natural diterpenes, cafestol and kahweol might affect hypercholesterolemia. Boiled and unfiltered coffee contain high amounts of diterpenes in contrast to instant or filtered coffee, which contains negligible amounts (Gross et al., 1997; Kurzrock and Speer, 2001). Caffeine consumption was associated with higher levels of TC, LDL-C, and TG, but not HDL-C, according to a meta-analysis of randomized controlled studies (Cai et al., 2012), while a cross-study conducted for 8 weeks showed reduced cholesterol, triglyceride and blood pressure levels (Sarriá et al., 2018).

Urgertet al. (1997), reported that pure Cafestol raised serum cholesterol by 17%, and LDL cholesterol by 19%. In comparison, kahweol raised total cholesterol by just 2% and LDL cholesterol by 4%, indicating that cafestol plays a contributing role in raising cholesterol levels. This is due to the fact that Cafestol is an agonist ligand for Farnesoid X receptor (FXR) and Pregnane X receptor (PXR), and the expression of bile acid homeostatic genes is down-regulated(Ricketts et al., 2007) leading to decreased expression of LDL and elevated secretion of cholesteryl esters in VLDL (Post et al., 2000).

Besides the hypercholesterolaemic effect, diterpenes also show a positive impact. Cafestol shows anti-diabetic (Mellbye et al., 2015; Mellbye et al., 2017), anti-cancerous, (Iwamoto et al., 2019; Tsai et al., 2018) anti-inflammatory (Hao et al., 2018; Ren et al., 2019), and anti-oxidant (Hao et al., 2018) properties. An investigative study carried out by Baek et al. (2017), suggests that kahwoel inhibits adipogenesis by up-regulation of AMPK activity. Both kahwoel and cafestol also show chemo-protective and anti-carcinogenic effects (Cavin et al., 2002).

## 8. Other Roles and Effects of Caffeine

### *Role in Cancer*

A study shows that caffeine is a potential modulator for benign and carcinomatous human breast tissues. According to a report, women suffering from benign breast disease experienced symptom relief after eliminating methylxanthines from their diet (Ganmaa et al., 2008). In the case of colorectal cancer (CRC), the intake of caffeine can show effective results (Cui et al., 2020).

### *Effect on the liver and kidneys*

Several shreds of evidence highlight caffeine's hepatoprotective effect. Caffeine impairs the advancement of liver fibrosis through the restriction of adhesion and activation of HSCs (Shim et al., 2013). It also inhibits the onset of alcoholic and non-alcoholic liver cirrhosis (Corrao et al., 2001; Klatsky et al., 2006).

On reviewing the current literature on caffeine's effects on the kidneys, no revelation on its harmful effect is found. It is a well-known fact that caffeine has a diuretic effect, and its consumption shows a markedly increased diuresis and excretion of urine calcium, potassium, magnesium, and other minerals (Bergman et al., 1990; Taylor and Curhan, 2009). An analysis of three cohort studies shows an independent and inverse relationship between caffeine consumption and the chance of developing kidney stones (Peerapen and Thongboonkerd, 2018).

### *White matter, sleep apnea, and weight loss*

Caffeine has also been shown to augment the white matter in premature infants. A study performed at 34–35 weeks of gestational age using cerebral magnetic resonance imaging demonstrated that early caffeine administration increases the microstructural growth of white matter in preterm babies, albeit without any substantial effects on short-term risks linked to prematurity (Liu et al., 2020).

A meta-analysis showed that there was not much evidence that could reveal the interrelationship between caffeine and sleep apnea (disrupted breathing during sleep). Insufficient information has been released to ascertain if sleep apnea is related to caffeine. Further studies are required to shed further light on this potential correlation (Taveira et al., 2018).

Caffeine has been associated with greater weight loss and better weight management in multiple studies. In a six-month placebo-controlled experiment, herbal ephedra and caffeine (90/192 mg/day) aided body weight and body fat loss while increasing blood lipids with no severe side effects (Hills et al., 2001).

CGA, a phenolic acid identified in coffee beans, aids in weight loss by inhibiting the action of glucose-6-phosphatase in the liver. It also counteracts glucose-6-phosphate translocase I, thereby prohibiting glucose absorption in the small intestine. This causes a shift to lipid metabolism as an energy source. Thus, CGA decreases the number of triglycerides, glycated hemoglobin, and fasting glucose and promotes hypocholesterolemia, glucose tolerance, and insulin sensitivity (Naveed et al., 2018).

### *Effects on longevity*

Longevity depends on both internal (genetics, health) and external factors. We consume countless substances, which

can have both detrimental and beneficial effects on longevity. Caffeine is a widely consumed psychoactive drug, which makes it essential for us to know about its influence.

Studies have shown an increased life span in model organisms (Sutphin et al., 2012). Caffeine consumption on a regular basis reduces the risk of developing cardiovascular diseases such as stroke, coronary heart disease, and heart failure, as well as having beneficial to neutral effects on hypertension and cardiac arrhythmias. It also appears to lower liver diseases, cancer, and diabetes and offer protective effects against certain neurodegenerative diseases. However, these conclusions are based on cohort and case-control studies, as well as a few randomised control trials.

***Effect on the gastrointestinal tract***

Numerous food supplements can affect the gastrointestinal system and have a variety of consequences. As an additive, caffeine is swiftly absorbed from the intestines, diffuses promptly into human saliva, and dissolves in water with a considerable and essentially pH-independent solubility. The implications of caffeine on stomach emptying, gastric secretion, lower esophageal sphincter pressure, and heartburn have all been the subject of claims (Kumar et al., 2018).

The lower esophageal sphincter is affected by caffeine, a strong activator of stomach acid secretion, which leads to a reduction in pressure (Cohen et al., 1975). In order to isolate the intrathoracic oesophagus, which has negative pressure inside, from the intra-abdominal stomach, which has positive pressure inside, the lower esophageal sphincter (LES) preserves a tonic contraction. Dysphagia or gastroesophageal reflux disease (GERD) are two conditions that can emerge from LES malfunction (Lohsiriwat et al., 2006). It induces chest pain and positive acid-perfusion (Bernstein) tests, re-creating heartburn once it is administered directly into the oesophagus (Cohen et al., 1975). In order to isolate the intrathoracic oesophagus, which has negative pressure inside, from the intra-abdominal stomach, which has positive pressure inside, the lower esophageal sphincter (LES) preserves a tonic contraction. Dysphagia or gastroesophageal reflux disease (GERD) are two conditions that can emerge from LES malfunction (Lohsiriwat et al., 2006). It induces chest pain and positive acid-perfusion (Bernstein) tests, re-creating heartburn once it is administered directly into the oesophagus. Despite the existence of some evidence that caffeine causes dyspepsia, recent research indicates that caffeine has no bearing on the pathophysiology of peptic ulcer disorders (Boekema et al., 1999).

Caffeine has no direct effect on blood glucose levels; however, when consumed with carbs (22-150 g), caffeine's effects on prompt glycemic responses appear to be negligible, though it may cause an exaggerated sugar level and an insulinaemic response at the subsequent meal. As a matter of fact, a modest amount of coffee or caffeine seems to have minimal effect on glycemic control when ingested with a meal laden with carbohydrates (Schubert et al., 2014).

Nevertheless, it is undeniable that caffeine possesses thermogenic properties (Hursel et al., 2013), and prolonged usage of the substance can cause a slight reduction in normal energy intake. Furthermore, research has shown that caffeine enhances the contraction of the gallbladder and the functioning of the colon's motor system (Boekema et al., 1999). Despite not being shown yet, caffeine may have an effect on how many calories a person consumes on a solitary diet. The last point is that caffeine seems to have no effect on gastrointestinal emptying (Gounaris et al., 2020).

**9. Amount of Caffeine Intake**

Caffeine is often consumed in beverages such as coffee (71%), soft drinks (16%), tea (12%), and caffeine gums (90%) (Heckman et al., 2010), but the range varies as the amount of caffeine is present naturally. The proportion of caffeine in chocolate ranges according to the quantity of cocoa it incorporates, with 100% cocoa unsweetened baking chocolate comprising around 240@mg caffeine per 100 g, 55% cocoa bittersweet containing 124@mg caffeine per 100 g, and 33% cocoa milk chocolate holding 45 mg caffeine per 100 g (Kovacs Harbolic, 2020).

The utilisation of coffee in India (as a source of caffeine) is rounded to 0.1 kg per capita, and the ratio between India and the USA is 42:100 in terms of the consumption level. Although India traditionally has a tea-drinking population, green tea consumption is considerably higher than coffee consumption, at 52% and 13%, respectively. Interestingly, green tea contains higher amounts of caffeine than regular coffee (w/w), but a smaller concentration of tea is used to brew a teacup. A cup of 0.25 L coffee has 80–150 mg of caffeine, compared to 60 mg from tea. [TK11]

Although carbonated beverages are not a significant source of daily caffeine intake, statistics show that consumption in India is approximately 28 times lower and 59 times lower than in the United Kingdom and the United States, respectively (fssai.gov.in). However, how sensitive people are to caffeine's effects and how quickly they metabolise it varies greatly (www.fda.gov, 2021;timesofindia.indiatimes.com, 2014; www.everydayhealth.com, 2020).

***Caffeine toxicity***

As caffeine is found in several preparations, such as energy drinks, coffee and its products, supplements, decongestants, stimulants, bronchodilators, drugs, and much more, its toxicity becomes quite prevalent. At concentrations of 80–100 micrograms/ml of blood, harmful doses of caffeine have been recorded, which can

be achieved with an intake of approximately 10 grams or greater (Murray and Traylor, 2021).

Hypokalemia, anorexia, nausea, fatigue, palpitations, headaches, dysrhythmia, and a plethora of other signs, referred to as 'caffeinism', are some of the side effects that can be indistinguishable from extreme persistent anxiety and usually occur with the daily ingestion of 1 to 1.5 g of caffeine per day (Willson, 2018). Arrhythmias, subsequent ventricular fibrillation, seizures, renin excretion, sodium retention, and hypertension can also arise from prolonged consumption of caffeine (Murray and Traylor, 2021; Rudolph and Knudsen, 2010); treatments of caffeine toxicity include oral or intravenous hydration, vasopressors, hemodialysis, beta-blockade, activated charcoal, intralipid therapy, etc. (Kapur and Smith, 2009; Muraro et al., 2016).

## 10. Decaffeinated Coffee

Demand for decaffeinated coffee or decaf is growing since caffeine's stimulatory effects may adversely affect susceptible individuals by causing palpitations, elevated blood pressure, and insomnia (Ogita et al., 2003). Decaffeinated coffee powder, at about 0.05 percent vs. 1.2–2.0 percent of standard coffee, has very low caffeine content. It causes diastolic blood pressure to rise marginally without altering other parameters (Smits et al., 1985). One of the procedures for obtaining decaf coffee involves contacting moist carbon dioxide with coffee in a supercritical state to remove caffeine, which yields significant amounts of decaffeinated coffee (Zosel, 1981).

Decaf coffee may lessen the risks of premature death and diabetes. It is also known to protect against mental decline and acid reflux. It can be a good substitute for people who are sensitive to regular coffee (Bjarnadottir, 2020).

Additional study is warranted on the potential lethal effects on caffeine-restricted patients consuming decaffeinated coffee, which, despite processing, may still contain small amounts of caffeine. Furthermore, subsequent exploration of the potential physical dependence of small doses of caffeine, such as those found in decaffeinated coffee, is merited (McCusker et al., 2006).

## 11. Conclusion

Caffeine is among the most widely used psychoactive drugs, which could have a variety of effects on different bodily functions and behavioural competencies. Caffeine and its metabolites have a similar chemical composition and half-life, making them easier to determine in serum or urine. It also has excellent antioxidant properties, making it capable of counterbalancing detrimental free radical activity. It has also been reported that caffeine can be a potential modulator for several forms of cancer. Therapeutic effects have been seen in patients with neurodegenerative diseases. Caffeine is also used as an antidepressant, but it has been shown to worsen anxiety and cause panic attacks in some people, particularly those who are already under mental stress.

Although a multitude of studies have been conducted on caffeine and its concomitant effects, little concrete evidence exists on its correlation with different conditions. Its impact on cardiovascular health and blood pressure is a matter for further research, as there is not much conclusive evidence. Due to the diuretic effect and enhanced diuresis, the association between caffeine consumption and kidney stones has also been determined. Furthermore, this may lower an individual's blood pressure, but this may be contradicted in caffeine users. It is also crucial to distinguish between the purported protective benefits of coffee and other compounds that might be present. Thus, further experiments on animal models are needed to ascertain its safe dosage and evaluate its beneficial effects on bodily functions.

## 12. References


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## 13. Abbreviations Used

AFMU - 5-acetylamino-6-formylamino-3-methyluracil

AAMU - 5-acetyl-6-amino-3-methyluracil

RAF -Radical adduct formation

HAT - Hydrogen atom transfer

SET - Single-electron transfer

AMPK - 5@-AMP-activated protein kinase

PD - Parkinson's disease

AD - Alzheimer's disease

ADHD - Attention deficit hyperactivity disorder

CV - Cardiovascular

CHD - Coronary heart disease

CF - Congestive heart failure

FXR - Farnesoid X receptor

PXR - Pregnane X receptor

CRC - Colorectal cancer

CGA - Chlorogenic acid

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