**Review**

# Impact of Caffeine on Glucose Metabolism: A Review of Molecular Mechanism of Action

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## Abstract

**Introduction:** Caffeine, a widely consumed psychostimulant, is present in various foods and beverages, with its intake differing across populations. Its role in glucose metabolism remains controversial, with conflicting findings suggesting it may either raise or lower blood glucose levels. This review explores the molecular mechanisms underlying caffeine's effects on glucose metabolism.

**Methodology:** A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, Google Scholar, Springer, and Science Direct, focusing on studies published in English with keywords such as "Glucose metabolism OR antidiabetic AND caffeine AND molecular mechanism of action."

**Result:** Findings suggest that acute caffeine consumption may enhance insulin sensitivity by promoting glucose uptake in skeletal muscles through adenosine receptor modulation. Additionally, caffeine stimulates insulin secretion in pancreatic beta cells via the PI3K/AKT insulin signaling pathway and activates the AMP-activated protein kinase (AMPK) pathway. However, chronic caffeine intake may lead to tolerance, diminishing its insulin-sensitizing effects. Mechanisms such as stress hormone regulation, mitochondrial function, adenosine receptor blockade, and glucagon secretion could contribute to impaired glucose metabolism with prolonged caffeine use.

**Conclusion:** caffeine's impact on glucose metabolism is complex and influenced by individual variations and consumption patterns. While acute caffeine intake may improve insulin sensitivity, long-term use may counteract these benefits, potentially leading to elevated blood glucose levels. Further research is necessary to fully elucidate the intricate relationship between caffeine and glucose metabolism.

**Keywords**: Caffeine, Glucose metabolism, insulin signaling pathway, diabetes



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## Introduction

Caffeine is the most used psychostimulant globally with more than 80% taking it globally. Caffeine use varies widely daily; some sources in the United States claim that the typical American consumes 142 mg of caffeine daily, which is less than in previous years [22]. Any foods and beverages contain products made from kola nut and coffee, where caffeine turns into an active biological component of the coffee and is the main source of the suggested health benefits of coffee consumption. Caffeine is an ergogenic substance, and several plants' seeds, leaves, and fruits contain the substance in varied degrees[60]. While daily caffeine intake in the United States and Canada varies from 210 to 238 milligrams per person, it reaches 400 milligrams daily in Sweden and Finland[55]. As a consequence, each person consumes 76 mg of caffeine daily from all sources. While some surveys suggest that 90% of people regularly use caffeine [14].

It is quite evident that caffeine is not a benign drug and can cause significant toxicity as well as lethality when ample amounts are consumed (most frequently by a myocardial infarction or an arrhythmia), even though it is commonly believed to be harmless when used in little doses (400 mg daily) by healthy adults (70kg) [62]. Some sensitive persons may also experience toxicity and fatality at doses not typically associated with such outcomes [45, 40].

Caffeine has such a broad range of effects on different parts of the human body due to its chemical mode of action at the cellular level, which has led to its enormous attention[55]. Numerous studies have demonstrated that the scientific interest in caffeine is due to its bio-molecular activity. It has been demonstrated to be effectively optimistic by acting as a stimulant for increasing alertness, and wakefulness, protecting the nervous system from any oxidative stress, improving muscle endurance by sparing muscle glycogen, and also regulating glucose uptake[55]. Antagonizing P1 receptors is caffeine's main mechanism of action. Adenosine is a purine that is secreted locally and acts on a variety of receptors [34, 60].

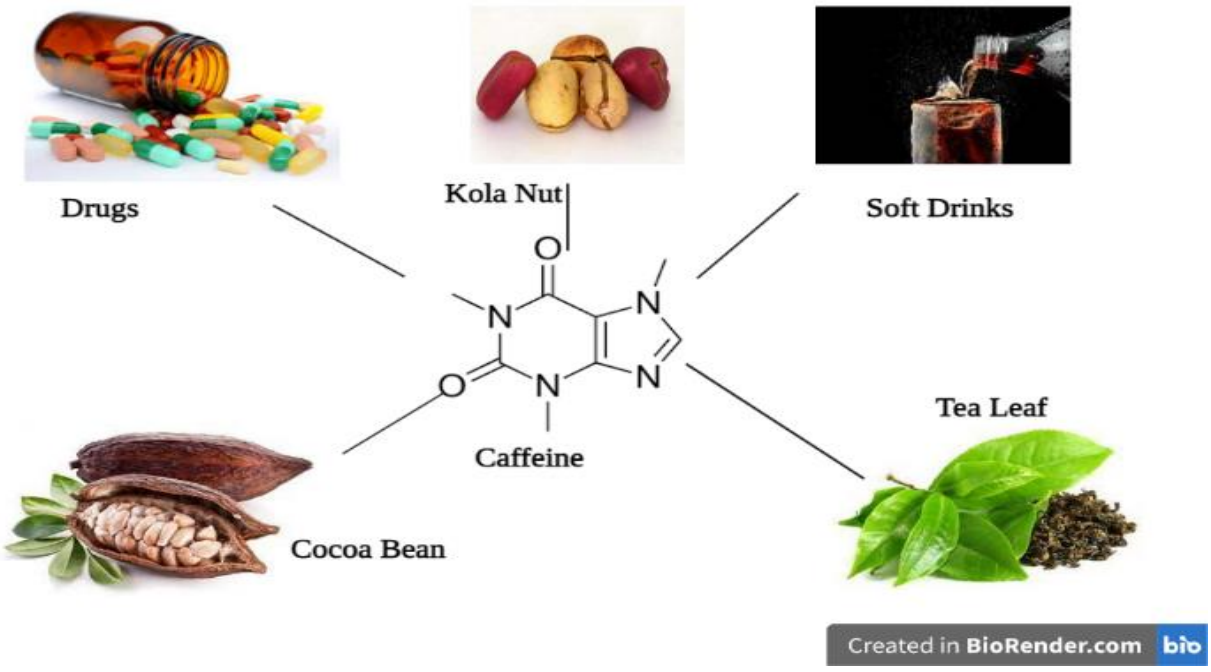


**Figure 1: Natural Sources of Caffeine**

However, this review covers the general uses of caffeine, the importance of caffeine as a drug adjunct, and certain aspects of the molecular basis of caffeine such as its effect on CNS, skeletal muscle, Blood glucose, and Pharmacokinetics.



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**Table 1 Natural Source of Caffeine**

| Plant Source | Local Name | Location (Country) | Percentage of Caffeine | Traditional Uses | Reference |
|---|---|---|---|---|---|
| **Coffee** | Coffea arabica, (75% C. canephora (25%), C. Liberia (1%) | Ethiopia, Brazil, India, Vietnam, Mexico, Nepal Guatemala, Indonesia, and Sri Lanka. | 2–3% | as a key element in sacred ceremonies and ritual celebrations associated with indigenous religions.<br>a ceremonial role and its consumption as part of a ritual meal is thought to bring blessings from God through invocations and prayers<br>as a commodity | 57<br>61 |
| **Cocoa** | Theobroma cacao (tropical evergreen tree)<br>baba de cacao | New World tropics<br>Western Africa<br>tropical Asia<br>lowland rainforests of the Amazon and Orinoco River basins<br>South and Central America | 91% - 93%, | The cultural medicinal use of cacao, or chocolate, both as a primary remedy and as a vehicle to deliver other medicines, originated in the New World and diffused to Europe in the mid-1500s. These practices originated among the Olmec, Maya, and Mexica (Aztecs).<br>We have known cocoa since time immemorial, our great-grandparents started it. It is the national product of Ghana<br>it's the backbone ofthe nation's economy | 32<br>28<br>20<br>12 |
| **Kola** | Kola nitida<br>Bitter kola | West and Central Africa | 46%<br>7.40% | application in several human social activities, these include ancestors' venerations, ceremonies, weddings, and funerals.<br>an active ingredient used for the flavoring of chocolates, soft drinks, and other non-alcoholic beverages | 4 |



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## Methodology

A comprehensive literature search was conducted using multiple scientific databases, including PubMed, Scopus, Web of Science, Google Scholar, Springer, and Science Direct. The review focused on manuscripts published in English, employing specific keywords such as "Glucose metabolism OR antidiabetic AND caffeine AND molecular mechanism of action." The selection process prioritized studies that examined the molecular pathways through which caffeine influences glucose metabolism, insulin sensitivity, and related metabolic processes.

Studies included in this review covered both human and animal models to ensure a broad perspective on caffeine's metabolic effects. Articles were critically evaluated based on their relevance, methodology, and scientific rigor. Both experimental and observational studies were considered to capture a comprehensive understanding of caffeine's acute and chronic effects. Mechanistic insights were analyzed by focusing on key signaling pathways, including the PI3K/AKT insulin signaling pathway, AMPK activation, and adenosine receptor interactions.

To mitigate bias, only peer-reviewed studies from reputable journals were included. Conflicting results were analyzed to highlight areas of debate within the scientific community. The synthesis of findings aimed to provide a balanced discussion on the benefits and potential risks associated with caffeine consumption in relation to glucose metabolism.

## Finding and Discussion

### *General Uses of Caffeine*

Caffeine is a powerful antioxidant that improves mental and physical performance. Caffeine is widely known for its capacity to increase mental performance, improve focus, and increase alertness. Caffeine may improve mood and lessen the signs of depression [47].
Several conditions, such as type 2 diabetes, Alzheimer's disease, and Parkinson's disease may be less likely to develop in people who use caffeine, according to some [53]. In addition to lowering the risk of heart disease and stroke, it lowers the risk of several malignancies, including colorectal and liver cancer, and improves heart function. Through increased lifespan and better general health, the danger is decreased [48, 64].

Caffeine has been extensively studied across various models, revealing its diverse health benefits. In humans, caffeine enhances cognitive performance, reduces fatigue, and improves athletic endurance[21]. It also reduces the risk of depression and suicide[43]. In animal models, caffeine protects dopaminergic neurons in Parkinson's disease, reduces amyloid-beta deposition in Alzheimer's, and improves glucose tolerance and insulin sensitivity in metabolic studies[8]. Additionally, in cellular studies, caffeine inhibits cancer cell proliferation by inducing apoptosis and reducing oxidative stress[10].

### *Importance of caffeine as a drug adjuvant*

An alkaloid purine is what caffeine is known as. 1,3,7-trimethyl-xanthine, which is chemically similar to major endogenous metabolites including purine, xanthenes, and uric acid, was discovered as its chemical structure as early as 1875[5].
In addition to serving as a medication, caffeine also possesses a variety of interesting and unique pharmacological effects. It is a bronchodilator used to treat asthma, and it is listed on the WHO list of important medications for its respiratory stimulating action to be used in newborns with apnea, especially in situations of preterm[24, 5].

In fixed-dose combinations with NSAIDs like ibuprofen, acetylsalicylic acid, or paracetamol, it is also used as an adjuvant analgesic for the treatment of minor pain and headaches, which may provide relief [42]. Caffeine adjuvant, according to [56], does not have an analgesic effect on its own; instead, it improves the effects of other analgesic medicines. Additionally, it has been suggested that caffeine's analgesic adjuvant action may be related to its capacity to quickly lower gastrointestinal pH, which would increase the absorption of analgesics and affect their pharmacokinetics[42].

### *Molecular Mechanism of Caffeine on the Human Body*

According to the dosage, P1 adenosine receptors (ARs) A1R, A2AR, A2BR, and A3R are antagonized by coffee to produce its overall molecular actions [54]. Due to its minor adenosine similarity, caffeine can connect to adenosine-specific receptors. However, all four receptor subtypes are responsive to coffee and other naturally occurring xanthines. While A2A and A2B receptors activate AC activity and raise intracellular cAMP levels, A1 and A3 receptors are negatively linked to adenylate cyclase (AC) and reduce cyclic adenosine monophosphate (cAMP) concentration) [34].



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Although various receptors are localized differently, the results of their blockage are complicated. The A1 subtype is primarily localized in the brain, spinal cord, eye, adrenal gland, heart, and to a lesser extent in tissues like skeletal muscle and adipose, whereas the A2A subtype is primarily localized in the spleen, thymus, striatopallidal GABAergic neurons, and to a lesser extent in the heart, lung, and blood vessels[48].

On the other hand, caffeine's effects are also triggered by the inhibition of phosphodiesterase (PDE) enzymes, which inactivate cAMP and cyclic guanosine monophosphate (cGMP) and result in the formation of 5'-AMP and 5'-GMP, which raises the levels of cAMP and Cgmp [23]. These isoforms' tissue distribution varies, and altering their activity can have of various effects, including bronchodilator and lipolytic effects[55].By causing the release of calcium ions from the Sarcoplasmic Reticulum (SR), caffeine's agonist on the Ryanodine Receptor (Ry) causes the contraction of striated muscles [15].

**Effect on the Central Nervous System**

Caffeine (1,3,7-trimethyl xanthine) as a psychostimulant purine-like alkaloid, [29], has a biological effect that increases alertness and wakefulness, the faster and clearer flow of thought, increased focus, and better general body coordination, and later at the spinal cord(in high doses) through mechanisms such as increased ATP production through cyclic adenosine monophosphate (cAMP) accumulation and inhibition of dopamine re-uptake Even yet, adenosine amplifies the taste receptors' responses to sweetness [17]. Caffeine consumption causes the human body to respond, which, according to some research, can improve performance and communicate to the brain that the body is prepared for action [50, 65].

In large doses, caffeine exerts numerous effects on the brain and spinal cord[35]. Its impact on A2ARs, which is mediated by dopaminergic processes, accounts for the psychomotor stimulating effect. Caffeine alters brain disorders and diseases including Alzheimer's, Parkinson's, epilepsy, pain/migraine, depression, and schizophrenia by inhibiting ARs, which in turn affects brain processes like sleep, cognition, learning, and memory [54, 66] Inhibition of the neurotransmitter acetylcholinesterase (AChE), is another potential mechanism of caffeine's effects on the neurological system[51].

Caffeine consumption is thought to lessen the danger of its antagonistic mechanism in neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. Alzheimer's disease is a neurodegenerative dementia that accounts for 50–70% of cases and is characterized by a gradual loss of synaptic integrity and neuronal tissue [41].

According to Ribeiro & Sebastião the excitatory and inhibitory A1R and A2AR receptors must be objectively activated for caffeine to have stimulatory effects [55]. The adenosine receptors in the brain, particularly the inhibitory A1R and the facilitatory A2AR, are the molecular targets for caffeine at safe concentrations and may exert its effects via inhibiting PDEs Adenosine receptor A1R and A2R expression is elevated in Alzheimer's disease [36]. Parkinson's disease (PD) is caused by the dopamine-producing neurons deteriorating. The motor cortex is stimulated by dopamine-producing neurons, affecting motor control. Loss of dopamine results in loss of cognitive ability, autonomic nervous system, and motor control abilities. According to epidemiological research, as caffeine use increases, the chance of getting Parkinson's disease (PD) reduces. Caffeine inhibits the destruction of dopamine-producing neural cells in the brain and the substantia nigra by binding to the adenosine receptor (A2aR), thereby preventing neural degeneration and loss of motor control (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an experimental neurotoxin known to cause Parkinson's disease)[53].

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It demonstrates that frequent caffeine use was connected to increased pain thresholds for pressure, heat, and other types of discomfort. By inhibiting the receptors that affect pain signaling or peripheral adenosine receptors on sensory afferents, caffeine can lower pain perception analogous to its direct actions on adenosine receptors. Caffeine's supporting and anti-nociceptive effects are due to its antagonistic effects on adenosine receptors and, in some locations, its suppression of cyclooxygenase activity[7]. In light of this, low-dose caffeine is frequently found as an adjuvant in over-the-counter (OTC) pain treatments along with antidepressants, acetaminophen, and non-steroidal anti-inflammatory drugs[19].



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***Effect on Muscle***

According to Bazzucchi et al., caffeine enhances endurance exercise by preventing the decline in neuronal activity by inhibiting the ARs that are linked to the potential for increased muscle fiber recruitment[9].

Caffeine action can cause the ion channel RyRs in muscles and myocytes to open, claim[66]. Myocytes' sarcoplasmic reticulum (SR) stores a reserve of Ca2+ that, when caffeine is present, can be released, improving muscular strength and speed[62]. Caffeine causes calcium to be released from the SR and its reuptake to be inhibited, which promotes contractility during submaximal contractions *(Figure 2)*[13].

On Muscle Filaments and Muscular Strength, it was found that caffeine increases the ratio of globular to filamentous actin in pre-contracted tissues and decreases actin filament binding to phosphorylated myosin heads, leading the authors to the conclusion that caffeine interferes with actin function (decreased binding by myosin, possibly with depolymerization), and as a result, relaxes smooth muscle (*Figure* 2)[59].

Concisely, caffeine's stimulatory effect on the operation of the muscular systems is significant for exercise because it enhances cognitive and exercise performance by blocking ARs, activating RyRs channels, and inducing calcium release.

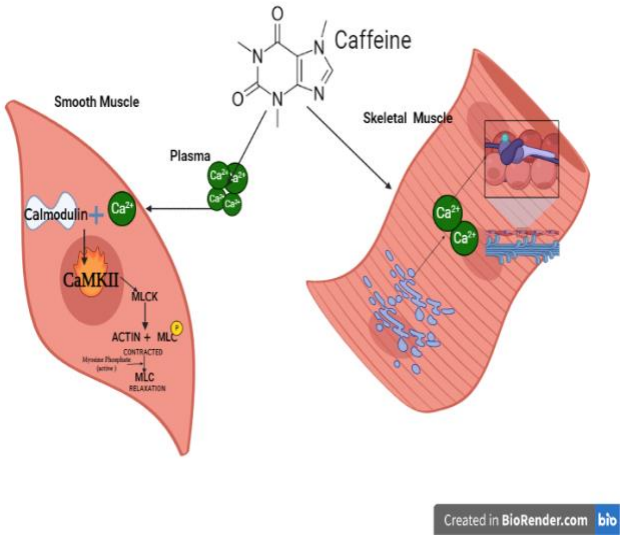


***Figure 2: Action of Caffeine on Muscles***

***Effect on Blood Glucose***

Glucose serves as the principal monosaccharide in metabolism and its sugar diet that accounts for 80% micro molecules of Carbohydrate (CHO) digestion[37]. It's the sole fuel for the brain except during prolonged starvation when liver ketone bodies are oxidized[11].

El-Sayed (2023) projected that the range of anticipated values for a normal fasting blood glucose concentration would be between 70 mg/dL (3.9 mmol/L) and 100 mg/dL (5.6 mmol/L) in 2023. It is advised to make lifestyle modifications and check your blood sugar when it ranges between 100 and 125 mg/dL (5.6 to 6.9 mmol/L) while fasting. Diabetes is identified if two independent tests for fasting blood glucose show 126 mg/dL (7mmol/L) or above. Hypoglycemia, or low fasting blood glucose, is defined as a level of less than 70 mg/dL (3.9 mmol/L) and is characterized by symptoms including dizziness, sweating, palpitations, blurred vision, and others that need to be watched for. An increased risk of developing diabetes is indicated by an elevated fasting blood glucose level (hyperglycemia).

According to research that examines the effects of caffeine on glucose and insulin homeostasis in healthy men (23 0.6 years, 74 1.9 kg) using the OGTT (Oral Glucose Tolerance Test), there is an increase in insulin peptide C concentrations following caffeine consumption when compared to the placebo group and the decaffeinated one[7].

According to report depicted that, coffee may cause the pancreatic beta cells to secrete more insulin as a result of an increase in intracellular Ca2+[63]. This is associated with + channel blocking caused by ATP production from glucose metabolism via the insulin-independent glucose transporter protein, glucose transporter 2 (GLUT 2) *(Figure 3)*[52]. According to an article reviewed by[44](Luiz Augusto da Silva1, 2017) Showed that caffeine might increase the glucose consumption by skeletal muscle in rats, due to the rise of intracellularCa2+ and AMPK expression. This demonstration was backed up by the review conducted by DeFronzo, and [2]Ahmadvand et al., that insulin binds itself to its receptor on skeletal muscle, where it triggers the phosphorylation of the receptor's tyrosine which results in the insulin receptor substrate (IRS-1 and 2) to mediate the effects of insulin on glucose metabolism where substrate acts in the activation of phosphatidylinositol (PI)-3 kinase, PKA/AKt and the enrichment of glucose



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transporter 4 (GLUT4) and Glycogen Synthase (GS)[2, 20]. In other Studies, observed that caffeine intake may increase the concentration of different glucose carriers (GLUT), such as glucose transporter 2 (GLUT2) and glucose transporter 4 GLUT4.

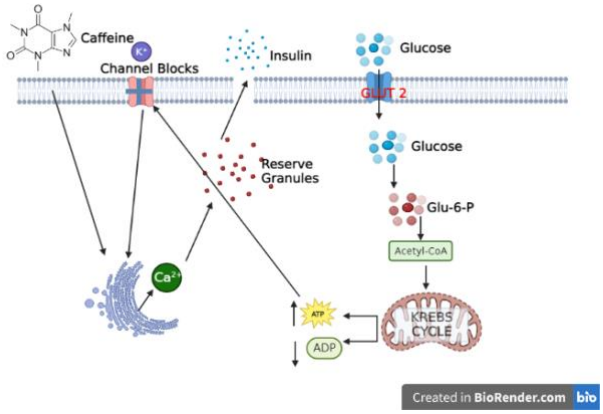
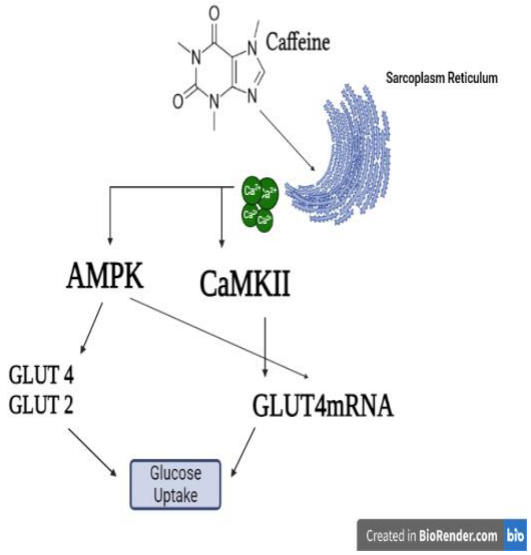



***Figure3: Insulin secretion by β cells to facilitate glucose uptake***

According to a thorough review by Luiz Augusto da Silva1 AMPK is a metabolic sensor that is crucial for maintaining glucose homeostasis and regulating lipid metabolism. It plays a significant role in maintaining glucose homeostasis by lowering hepatic glucose synthesis and increasing skeletal muscle glucose uptake. Caffeine enhances GLUT4mRNA and insulin-independent carriers in skeletal muscle through AMPK-mediated mechanisms, it has been shown. The $Ca^{2+}$ produced by SR, which is the most crucial step in muscular contraction, may serve as a cue for the muscle to take up more blood glucose. To sustain muscle glucose input and provides enough energy for muscular activity, AMPK or $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) are the two parallel routes of glucose uptake activation[43]. (***Figure4***)

Caffeine may cause sarcoplasmic reticulum (SR) to release $Ca^{2+}$, which increases AMPK phosphorylation and activates CaMKII. This enhances the translocation of Glucose Transporter 4 (GLUT4) and results in a higher absorption of glucose. In addition, caffeine promotes $Ca^{2+}$ release in the sarcoplasmic reticulum (SR) by acting on adenosine receptors and activating $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII), which is implicated in other cellular cascades of enzymatic activation *(Figure 4)*[43]




In contrast to the research mentioned above, some studies have indicated that caffeine consumption impairs glucose absorption, causing blood glucose levels to rise. Caffeine consumption results in increased blood glucose levels relative to the fasting condition, suggesting that glucose homeostasis is generally compromised[66].

Studies have shown that consuming coffee while exercising raises blood glucose levels in areas where there is a heavy dependence on fat[16,26]. According to research conducted by [63], the adenosine receptors in the hepatocytes' cell membrane, which are connected to glycogenolysis and gluconeogenesis, are antagonistic to caffeine (*Figure 5*). Additionally, coffee can increase incretins such as the glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), which suggests that it may theoretically improve the pancreas' ability to release insulin. As with caffeine, methylxanthine is a competitive antagonist that does not just affect adenosine receptors. Caffeine has a stronger effect on A2A receptors *(Figure 5)*[17].

The production of stress hormones, notably adrenaline and cortisol, is the second theory put up by Lane demonstrating how coffee inhibits glucose metabolism



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*(Figure 5)*. The release of cortisol and epinephrine in humans is known to be stimulated by caffeine. Cortisol and epinephrine both have hyperglycemic actions that cause them to stimulate the liver's synthesis of glucose while also impairing insulin's ability to function. Evidence from two human investigations supported the notion. According to one study, caffeine's amplified postprandial insulin response and decreased whole-body insulin sensitivity were both reversed by the medication propranolol, which is used to prevent the beta-adrenergic effects of epinephrine. An adult population with tetraplegia in a second trial discovered that coffee had no impact on their ability to tolerate glucose and that they did not respond by producing more epinephrine[39].

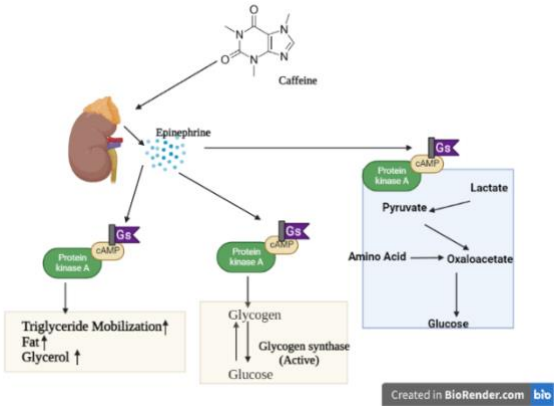


***Figure 5:*** *Action of caffeine on epinephrine*

Novel research that highlights the impairment of insulin sensitivity and glucose tolerance in healthy non-diabetic adults with caffeine usage after an oral glucose tolerance test detected caffeine-induced insulin impairments. They observed that following a caffeine infusion, the body's overall insulin sensitivity drops by roughly 25% [1].

A study focused on the adenosine receptors on cell membranes and noted that caffeine can bind to these receptors, decreasing the affinity for the adenosine molecule to attach. The G-coupled protein receptors A1 and A2, which are both members of 2 distinct types of adenosine receptors, are only two examples. In the presence of adenosine, A1 receptors inhibit adenylyl cyclase whereas A2 receptors activate adenylyl cyclase. This causes caffeine, specifically theophylline, to exert antagonistic actions on both receptors[66].

***Pharmacokinetics of caffeine***

Due to its weakly basic nature and pKa of 14 at 25 °C, caffeine has a rapid and complete (i.e., 99%) absorption from the small intestine after oral administration in humans. This is because the more basic environment of the small intestine favors an un-ionized/lipophilic state as opposed to the acidic environment of the stomach, where it is more ionized and less lipophilic. Although some people may fall outside of this range, caffeine is not known to undergo considerable first-pass metabolism and typically reaches peak plasma concentrations within 15-120 min after delivery [33].

While it has been speculated that the rate of consumption of a caffeinated beverage (i.e., drinking an "energy drink" or cold coffee rapidly versus slowly sipping hot coffee or an energy drink) may cause significant changes in the time to reach peak plasma concentrations, a study evaluating such variables did not find any statistically significant difference between the time to reach peak plasma concentrations[32].

Caffeine in the human body is absorbed rapidly by the villi of the small intestine after ingestion into the body within 45 minutes with the average peak value at 30 minutes which might depend directly on the pH and duration of the food intake[58].

Due to its lipophilic moiety or moieties and low plasma protein binding, caffeine is transported throughout the body after being absorbed from the digestive tract (the small intestine in particular), entering all tissues through cell membranes, and entering intracellular tissue water. Additionally, it easily crosses the blood-brain barrier. The volume of distribution varies, like with other pharmacokinetic variables, although an average of 0.7 L/kg is frequently seen. Although caffeine is frequently described as being lipophilic, it is an amphiphilic molecule (i.e., log= -0.07) that, because of certain lipophilic moieties, may diffuse through the lipid bilayer and into the cell [38].

The distribution of absorbed caffeine is eager throughout the entire body. It transports across the blood-brain barrier, into amniotic fluid and the fetus through the placenta, and into breast milk, it has also been detected in semen with a half-life of 1h to 1.5 h[6].

The biotransformation of caffeine is mediated by cytochromeP450in human liver microsomes as hepatic



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microsomal enzymes that undergo selective catalysis[30]. In the liver, the caffeine is primarily metabolized via the isoenzyme CYP1A2 which leads to 3-demethylation to form paraxanthine and 1- and 7- 7-demethylation to form theobromine and theophylline [6].

Although some have highlighted that caffeine may follow non-linear kinetics if the dose is large enough and its metabolism is saturated, a single-compartment model that describes caffeine suggests that it follows first-order, linear kinetics[62]. The CYP isozyme CYP1A2 catalyzes the 3-demethylation of caffeine, which is how caffeine is predominantly metabolized in the liver to 1,7-dimethylxanthine (paraxanthine). The primary metabolite of caffeine biotransformation, accounting for around 80% of the total, is paraxanthine. Though perhaps less hazardous than caffeine, paraxanthine itself is also pharmacologically active). Along with CYP2E1 to some extent, CYP1A2 is also in charge of the 1 and 7-demethylation of caffeine into 3,7-dimethylxanthine (theobromine) and 1,3-dimethylxanthine (theophylline), which are both pharmacologically active compounds. Theophylline makes up around 5% of caffeine compounds, while theobromine makes up about 11%[62]. The main metabolites 1,7-dimethyluric acid, 1,7-dimethylxanthine (paraxanthine), 1,7-acetylamino-6-formylamino-3-methyluracil, 5-acetylamino-6-formylamino-3-methyluridine, and 1-methylxanthine are largely eliminated in the urine. More than 25 metabolites have been discovered in humans after coffee therapy, indicating a very complex metabolism[49]. It is important to keep in mind that other CYP isozymes, including CYP3A4/3A5 and CYP2D6, only become active at relatively high (i.e., millimolar) concentrations as opposed to those that are frequently observed following typical caffeine consumption[6] while according to Willson, just 5% of the caffeine that is taken is excreted unchanged[63].

According to Nawrot et al., illustration, caffeine's half-life is between 3 and 7 hours and can be influenced by several variables, such as sex, age, the use of oral contraceptives, pregnancy, and smoking. Caffeine is said to have a 20–30% shorter half-life in females than in males. The half-life of infants ranges from 50 to 100 hours, but by the age of six months, it progressively reaches that of an adult. There are almost twice as many oral contraceptive steroid users as there are ovulatory females. The metabolic half-life grows progressively in a pregnant woman, rising from 4 hours in the first trimester to 18 hours in the third. Smoking cigarettes increases the rate of caffeine absorption by around two times[46].

The main product of the CYP1A2-mediated clearance, which eliminates the majority of caffeine from plasma, is paraxanthine. According to Faber et al., renal excretion in urine makes up around 85-88% of total elimination since fecal excretion only contributes to about 2-5% of it[25]. The clearance and elimination of half-lives of caffeine also exhibit significant inter-individual variation. Despite a coefficient of variation of around 36% being identified, the typical, average clearance value, for instance, ranges from 1 to 3 mL/kg/min [6]. To make matters more difficult, the clearance of caffeine may considerably decrease as caffeine use rises. For instance, statistics demonstrate that this is still possible even at levels below the conventional limit of 100 mol (19.4 mg/L)[62].

The fatal acute oral dose of caffeine in humans is estimated to be 10–14 g (150–200 mg/kg body weight. Ingestion of caffeine in doses up to 10 g has caused convulsions and vomiting with complete recovery in 6 hours. Extreme side effects were observed in humans at caffeine intakes of 1 g (15 mg/kg), including restlessness, nervousness, and irritability, and progressing to delirium, emesis, neuromuscular tremors, and convulsions. Other symptoms included tachycardia and increased respiration.

**Strengths and Limitations of the Review**

The review extensively explores the molecular mechanisms of caffeine's impact on glucose metabolism, covering its effects on insulin sensitivity, glucose uptake, and metabolic pathways. It integrates findings from multiple studies, enhancing its credibility and providing a holistic understanding of the topic [44]. Additionally, the methodology includes a broad literature search from reputable databases such as PubMed, Scopus, Web of Science, Google Scholar, Springer, and Science Direct, ensuring a wide range of scientific perspectives [30]. The review also distinguishes between the short-term (acute) and long-term (chronic) effects of caffeine on glucose metabolism, which is crucial for understanding its varying impacts on different individuals [39]. Furthermore, the discussion of mechanisms involving adenosine receptors, the PI3K/AKT insulin signaling pathway, and



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AMPK activation provides a detailed biochemical perspective, strengthening the molecular basis of the study.[54] The findings presented are valuable for researchers in physiology, pharmacology, nutrition, and medicine, especially those studying metabolic disorders such as diabetes.[9]

Despite its strengths, the review highlights contradictory findings regarding caffeine's role in glucose metabolism—some studies suggest it improves insulin sensitivity, while others indicate it worsens glucose regulation, making it difficult to draw definitive conclusions. [39, 66] Differences in study design, caffeine dosage, and participant characteristics (e.g., genetic differences, lifestyle factors) across the reviewed literature may have led to varied results, necessitating a meta-analysis or systematic review to quantify the overall effect[68]. Although the review acknowledges that caffeine's impact may differ among individuals, it does not fully explore factors such as age, sex, genetics, and pre-existing metabolic conditions that could influence its effects.[47] Moreover, the reliance on previously published studies presents a potential publication bias favoring positive or significant results over null findings. [51] While the review is well-supported by existing literature, it does not include new experimental data or meta-analytical statistical findings to strengthen its conclusions.[29]

## Conclusion

Caffeine, a globally consumed psychostimulant, exhibits extensive pharmacological effects on various body systems. It has been shown to improve mental alertness, physical endurance, and muscle performance, while also offering protective effects against neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Caffeine plays a role in glucose metabolism, with mixed findings regarding its influence on blood glucose regulation. It is metabolized through well-defined pathways involving cytochrome P450 enzymes, leading to diverse metabolites with unique actions. Despite its well-documented benefits, caffeine's impact varies with dose and individual sensitivity, emphasizing the need for balanced consumption. This review highlights the molecular and systemic mechanisms underpinning caffeine's physiological effects, confirming its therapeutic potential as well as the importance of cautious use to avoid toxicity.

## Declarations

***Authors' Contribution***: All authors contributed to the conception and design of the study. Writing – Original Draft Preparation and Writing – Review & Editing: Abudllahi Adamu Ja'e, Sadiq Muazu Maifata and Kabeer Abubakar; Methodology and Software: Abudllahi Adamu Ja'e and Sadiq Muazu Maifata; Formal Analysis, Investigation, and Visualization: Ahmad Muhammad Rabiu, Sadiq Muazu Maifata and Zayyanu Umar Usman, Supervision, Project Administration, and Funding Acquisition: Zayyanu Umar Usman, Amina Yusuf Jega and Chinedu Onwuchekwa. All authors gave final approval and agreed.

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