



Mini Review

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Green coffee and green tea as alternative medicines for the treatment of hyperglycemia

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Abstract

Diabetes is a chronic metabolic disorder characterized by the body's inability to regulate blood glucose levels effectively. An autoimmune disease known as type 1 diabetes occurs when the immune system erroneously targets and kills beta cells in the islets of the pancreas. Insulin resistance, a condition in which the body's cells do not adequately respond to insulin, causes type 2 diabetes. As the available hypoglycemic drugs exhibit several side effects, it is important to search for natural remedies to treat hyperglycemia in diabetic patients. The unroasted coffee beans used to make green coffee are rich in chlorogenic acid, a polyphenol with antioxidant effects and several biological activities. According to previous studies, chlorogenic acid improves insulin sensitivity, glycemic management, and glucose metabolism. Similarly, green tea is rich in catechins, particularly epigallocatechin gallate (EGCG), which exhibits several biological properties. Numerous studies have revealed that EGCG may help to enhance insulin sensitivity, insulin secretion, and glucose management. However, more research is required to determine the molecular mechanisms by which these phytochemicals in green tea and green coffee ameliorate the development of hyperglycemia and improve insulin sensitivity.

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1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by a deficiency in insulin production or its action (Baynest, 2015). Type 1 diabetes is caused by an autoimmune disease condition in which the body does not produce sufficient insulin. Type 2 diabetes is mainly caused by insulin resistance brought on by Lifestyle changes (Mukhtar *et al.*, 2020).

According to the World Health Organization (WHO), the global prevalence of diabetes was estimated to be 415 million adults in 2015. The steady increase in the incidence of type 2 diabetes mellitus (T2DM) is associated with unhealthy eating habits, obesity, and inadequate physical activity, resulting in an exponential rise in diabetes-related cardiovascular morbidity

worldwide in recent years (Malone and Hansen, 2019). According to the International Diabetes Federation (IDF), the prevalence of diabetes in Sri Lanka is expected to increase in the coming years (Ogurtsova *et al.*, 2017). As per IDF estimates, 1.3 million adults between the ages of 20-79 years had diabetes in 2019, and, the number of cases is projected to increase to 1.8 million by 2045 (Katulanda *et al.*, 2006).

Common symptoms of diabetes include increased thirst, frequent urination, blurry vision, fatigue, and slow-healing cuts or bruises (Butt, 2022). Over time, diabetes can lead to serious complications such as heart disease, kidney damage, nerve damage, and blindness (Tomic *et al.*, 2022). Maintenance of blood glucose levels is



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important for diabetic patients to avoid these side effects. Type 1 diabetic patients mainly rely on administering external insulin, while type 2 diabetic patients take hypoglycemic drugs that are often associated with several side effects (Ali *et al.*, 2022; Rizzo *et al.*, 2022). The most common side effects include gastrointestinal problems such as nausea, vomiting, diarrhea, abdominal discomfort, low blood sugar (hypoglycemia), weight gain, skin rash, upper respiratory tract infections, headache, gastrointestinal issues, yeast infections, urinary tract infections, and low blood pressure (Modi, 2007).

Since T2DM is a disease mainly associated with the lifestyle, patients with the condition usually have additional risk factors for stroke, such as obesity, hypertension, and dyslipidemia, which multiply the vascular risk in these patients (Tun Nyo Nyo *et al.*, 2017). Therefore, it is important to search for a novel, natural-based alternative treatment to maintain the blood glucose level in diabetic patients. Green coffee and green tea are the most consumed beverages across the globe. Green coffee is made from unroasted beans, which are the same beans used to make roasted coffee known as dark coffee (Farah *et al.*, 2008; Pimpley *et al.*, 2020). Sri Lanka is known for producing high-quality green tea (Ganegoda *et al.*, 2020). Green tea and green coffee contain bioactive compounds (epigallocatechin gallate, catechins, flavonols, caffeine, and L-theanine) that exhibit various biological activities, including antioxidant, anti-inflammatory, and potential hypoglycemic activities (AlHafez *et al.*, 2014). Additionally, these bioactive substances have demonstrated their potential to modify insulin sensitivity and glucose metabolism by stimulating glucose absorption in cells, increasing insulin secretion, and reducing glucose synthesis in the liver. Further, studies have shown that consuming green tea and green coffee extracts may help with weight control, as these beverages have been linked to higher levels of fat oxidation and enhanced metabolic rates. Therefore, the present review aimed to discuss how green tea and green coffee induce different mechanisms to reduce blood glucose levels in people with diabetes.

2. Therapeutic targets of diabetes

The therapeutic targets are mainly focused on reducing hyperglycemia and its complications. Therefore, this section mainly focuses on the main therapeutic targets of diabetes, including the inhibition of alpha-amylase, alpha-glucosidase enzymes, glucose-6-phosphatase, glycogen phosphorylase, dipeptidyl peptidase-4 (DPP-4), protein tyrosine phosphatase 1B (PTP1B) enzymes, and inhibition of the formation of advanced glycation end products (Golovinskaia and Wang, 2023). These enzymes are commonly associated with glucose metabolism and their potential interactions (Agarwal and Gupta, 2016). Alpha-amylase and alpha-glucosidase

are digestive enzymes found in the small intestine. The carbohydrates are broken down into glucose in the lumen of the small intestine (Funke and Melzig, 2006), and alpha amylase breaks down the large, insoluble starch by hydrolyzing the alpha bonds. Alpha amylase is produced by the pancreas and salivary glands and aids in the initial breakdown of starch. The enzyme alpha-amylase acts on the alpha-1,4-glycosidic linkages in starch to break it down into maltose, maltotriose, and alpha-limit dextrins (Kaur *et al.*, 2021). The enzyme alpha-glucosidase catalyzes the final step of the digestion of starch and disaccharides into glucose subunits (Nair *et al.*, 2013), and this enzyme is essential for the release of glucose for use in energy production and regulation of blood sugar levels. Therefore, the inhibitors of alpha-amylase and alpha-glucosidase lead to improve regulation of blood glucose levels by slowing down the release of glucose into the blood stream (Asbaghi *et al.*, 2020a).

The enzyme glucose-6-phosphatase is primarily found in the liver and, to a lesser extent, in the kidneys (Legouis *et al.*, 2022). In the processes of gluconeogenesis and glycogenolysis, which take place predominantly in the liver, glucose-6-phosphatase is essential as it catalyzes the reaction that converts glucose-6-phosphate back into glucose, which is subsequently delivered into the bloodstream to keep blood glucose levels stable (Wen *et al.*, 2021). Inhibiting the activity of glucose-6-phosphatase can help reduce the production of glucose, which in turn lowers blood glucose levels (Guo *et al.*, 2012).

Similarly, glycogen phosphorylase is involved in glycogenolysis, the breakdown of glycogen into glucose (Adeva-Andany *et al.*, 2016). Glycogen phosphorylase acts on liver glycogen and releases glucose into the bloodstream, which helps to maintain blood glucose levels (Todd, 1929). The enzyme dipeptidyl peptidase-4 (DPP-4) plays a role in the degradation of incretin hormones, such as glucagon-like peptide-1 (GLP-1), which are involved in glucose homeostasis. GLP-1 reduces blood glucose levels by inducing insulin secretion in hyperglycemic conditions. DPP-4 plays a role in the quick breakdown of GLP-1 and other incretins in the small intestine, where it is found on the brush edge of intestinal cells. DPP-4 is expressed in pancreatic beta and alpha cells (Sharma *et al.*, 2022). Therefore, natural extracts that inhibit glycogen phosphorylase and DPP-4 help to improve glycemic control.

Protein tyrosine phosphatase 1B (PTP1B) is a phosphatase enzyme that is widely distributed in various tissues and organs in the body, such as the liver, adipose tissue, skeletal muscle, pancreas, and brain (Rocha *et al.*, 2022). The liver is a major organ for the expression of PTP1B, which is highly important for controlling insulin signaling and glucose homeostasis. Acting as a negative modulator of insulin signaling, it reduces insulin sensitivity by dephosphorylating the proteins that

comprise substrates of insulin receptors. Adipose tissue, which controls the metabolism of lipids and glucose, contains PTP1B. PTP1B can impact insulin signaling in adipocytes and aid in the emergence of insulin resistance. Skeletal muscle contains PTP1B, which affects insulin signaling and glucose uptake. Increased PTP1B activity in skeletal muscle has been linked to impaired insulin action and glucose metabolism (Forrester *et al.*, 2020; Sharma *et al.*, 2021). PTP1B is expressed in pancreatic beta cells, which are responsible for insulin production. It can modulate insulin receptor signaling in beta cells and affect insulin secretion (Ferhati *et al.*, 2019). Therefore, the inhibition of PTP1B leads to improved glycemic control *via* the reduction of blood glucose levels.

Advanced glycation end products (AGEs) are harmful compounds, which are formed when proteins, especially hemoglobin, lipids, or amino acids, combine with glucose in an irreversible process known as glycation. It is a non-enzymatic reaction process. This process is accelerated in conditions of high blood sugar, such as diabetes. AGEs can accumulate and contribute to various complications associated with diabetes, including damage to blood vessels, nerves, and other tissues (Song *et al.*, 2021).

3. Manufacturing process of green tea and green coffee

3.1. Green Tea

In the manufacturing process of green tea, the stage at which tea leaves are typically considered green tea is when they have undergone steaming or pan-firing, rolling, shaping, and drying (Figure 1). When the freshly harvested tea leaves are steamed or pan-fired, it helps to halt the oxidation process by deactivating the enzymes responsible for oxidation (Ananingsih *et al.*, 2013).



Figure 1: The appearance of tea leaves after the various manufacturing processes.

Steaming is commonly used in Japan, while pan-firing is a traditional method employed in China. Both methods prevent excessive oxidation (Park *et al.*, 2009). Next, the steamed or pan-fired leaves are rolled. Rolling helps to shape the leaves, break down their cell structure, and release some of the juices within the leaves. This process

contributes to the development of the unique flavor and aroma associated with green tea. After rolling, the leaves are shaped (Lee *et al.*, 2013). The shaping process can vary depending on the desired final product and regional preferences. Some popular green tea shapes include twisted or curly leaves, needle-like shapes, or flattened shapes. Finally, the shaped leaves are dried. Drying removes excess moisture from the leaves, preserves their quality, and ensures an extended shelf life. It further helps in preventing oxidation and in maintaining the vibrant green color of the leaves. Once the tea leaves have undergone these stages of steaming or pan-firing, rolling, shaping, and drying, they are considered green tea. The resultant tea leaves are characterized by their fresh, grassy flavor, light liquor color, and high levels of antioxidants and other bioactive compounds (Han *et al.*, 2016).

3.2. Green Coffee

The manufacturing process of green coffee involves several stages (Figure 2), from harvesting the coffee cherries to preparing the beans for export. Some coffee producers may adopt additional steps, such as quality control measures or further processing techniques like polishing or storage methods, to maintain the quality of green coffee beans (Alongi and Anese, 2018).

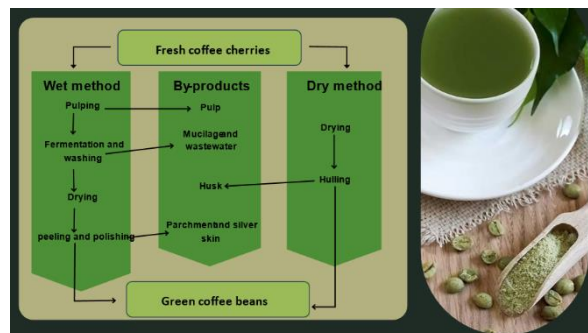


Figure 2: Manufacturing process of green coffee.

Coffee cherries can be processed either by the dry method (natural method) or the wet method (washing method) (Selmar *et al.*, 2008). Harvesting is the first step in the process. Coffee cherries are selectively picked by hand when they are fully ripe. Alternatively, some regions may employ mechanical harvesting methods. Then, coffee cherries undergo a sorting process to remove any damaged, unripe, or overripe cherries and are cleaned to remove dirt, leaves, and other debris. In the depulping process, the outer skin of the coffee cherries is removed using either a mechanical depulper or a fermentation process (Figueroa Campos *et al.*, 2020). This step exposes the coffee beans, which are covered by a parchment layer. Fermentation helps to remove any remaining pulp and enhance the flavor of the beans. Following fermentation, the coffee beans are thoroughly washed to remove any leftover pulp or residue. The washed beans are spread out in thin layers

to dry, either under the sun or using mechanical dryers. This drying process removes the remaining moisture from the beans until they reach an optimal moisture content of around 10-12%. Once the beans are sufficiently dried, the parchment layer surrounding them is removed through a process called hulling. Then, the dried pulp, parchment, and parts of the silver skin are removed with peeling machines. This waste is called husk (Klingel *et al.*, 2020). This exposes the green coffee beans. The green coffee beans are sorted and graded based on various factors, such as size, shape, and color. This step ensures uniformity and consistency in the quality of the beans. The sorted green coffee beans are packed in bags or containers, ready for transportation and export to coffee roasters around the world.

4. Bioactive compounds of green tea and green coffee

4.1 Green Tea

Tea is from the plant *Camellia sinensis*, which is a member of the Theaceae family. Catechins, caffeine, L-theanine, and polyphenols are key bioactive compounds present in green tea (Figure 3) (Ayyadurai and Deonikar, 2021). Green tea contains a lot of catechins (table 1), a type of flavonoid, especially epigallocatechin gallate (EGCG). EGCG is the most prevalent and well-studied catechin in green tea. Tea leaves are the only source of

the amino acid theanine. It has been demonstrated to promote relaxation, reduce stress levels without causing drowsiness, and may even improve cognitive performance (Sang *et al.*, 2011; Khulood *et al.*, 2014). Antioxidant properties found in Catechins can help to protect cells from damage caused by free radicals. Natural stimulants like caffeine can aid to increase mental clarity and focus. Theanine is the most abundant amino acid in all tea samples. It typically amounts to around 3-4% (3.77%) of dry weight. The maximum Theanine concentrations in tea samples were in the following order: green tea > black tea (Yilmaz *et al.*, 2020). L-theanine is known to induce a calming effect without causing drowsiness, which may help to improve focus and concentration (Asbaghi *et al.*, 2020b). Green tea is rich in polyphenols, which are plant compounds known for their antioxidant and anti-inflammatory properties. Green tea also contains Theaflavins, Theaflavin 3'-gallate, and thearubigins, but in smaller quantities when compared to black tea. These compounds are formed during the oxidation process of tea leaves, which is a crucial step in the production of black tea. They compounds contribute to the flavor and color of tea. The bioactive compounds present in green tea have been studied extensively for their potential health benefits, which include antioxidant effects, cardiovascular support, potential cancer prevention, weight management, and cognitive function enhancement, among others (Pradhan and Dubey, 2021).

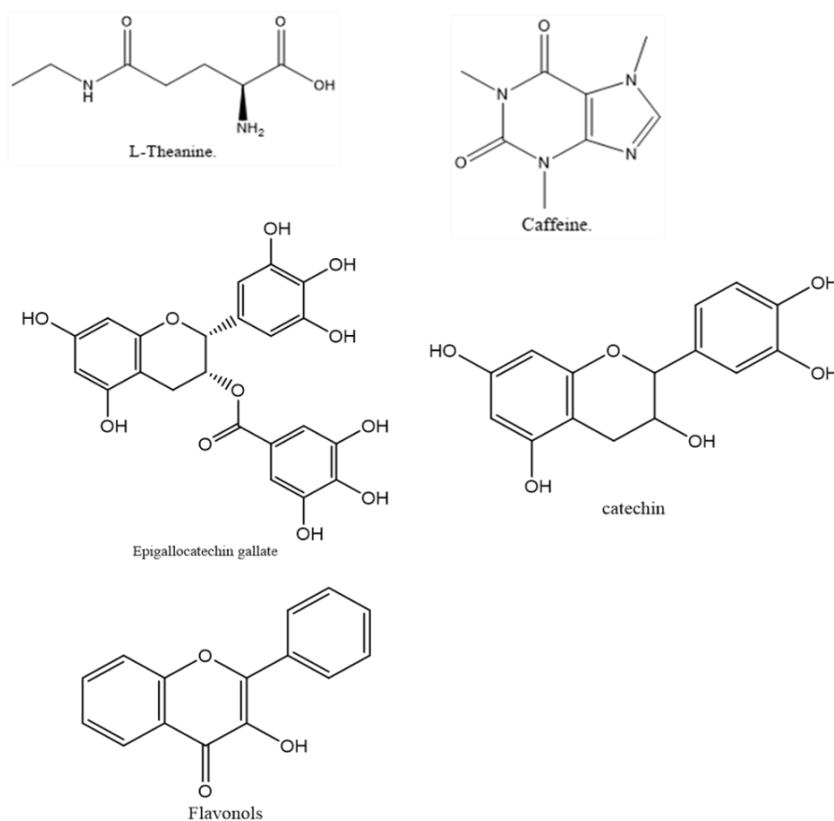


Figure 3: Bioactive compounds of green tea.

Table 1: Comparison of Bioactive Compound Percentages in Green Tea and Black Tea (Lin *et al.*, 2015)

Bioactive Compound	Green Tea	Black Tea
Catechins	Approximately 30-42%	Around 3-10%
Epigallocatechin Gallate (EGCG)	Varies, typically 10-15%	Present, but in lower amounts
Theaflavins	Present, but typically in lower amounts compared to black tea	Major component, typically around 1-3%
Thearubigins	Present, but typically in lower amounts compared to black tea	Major component, typically around 10-20%
Caffeine	Approximately 2-4%	Approximately 3-5%
Other Polyphenols	Can vary, typically around 5-10%	Present, but usually in lower amounts compared to green tea, typically around 5-10%

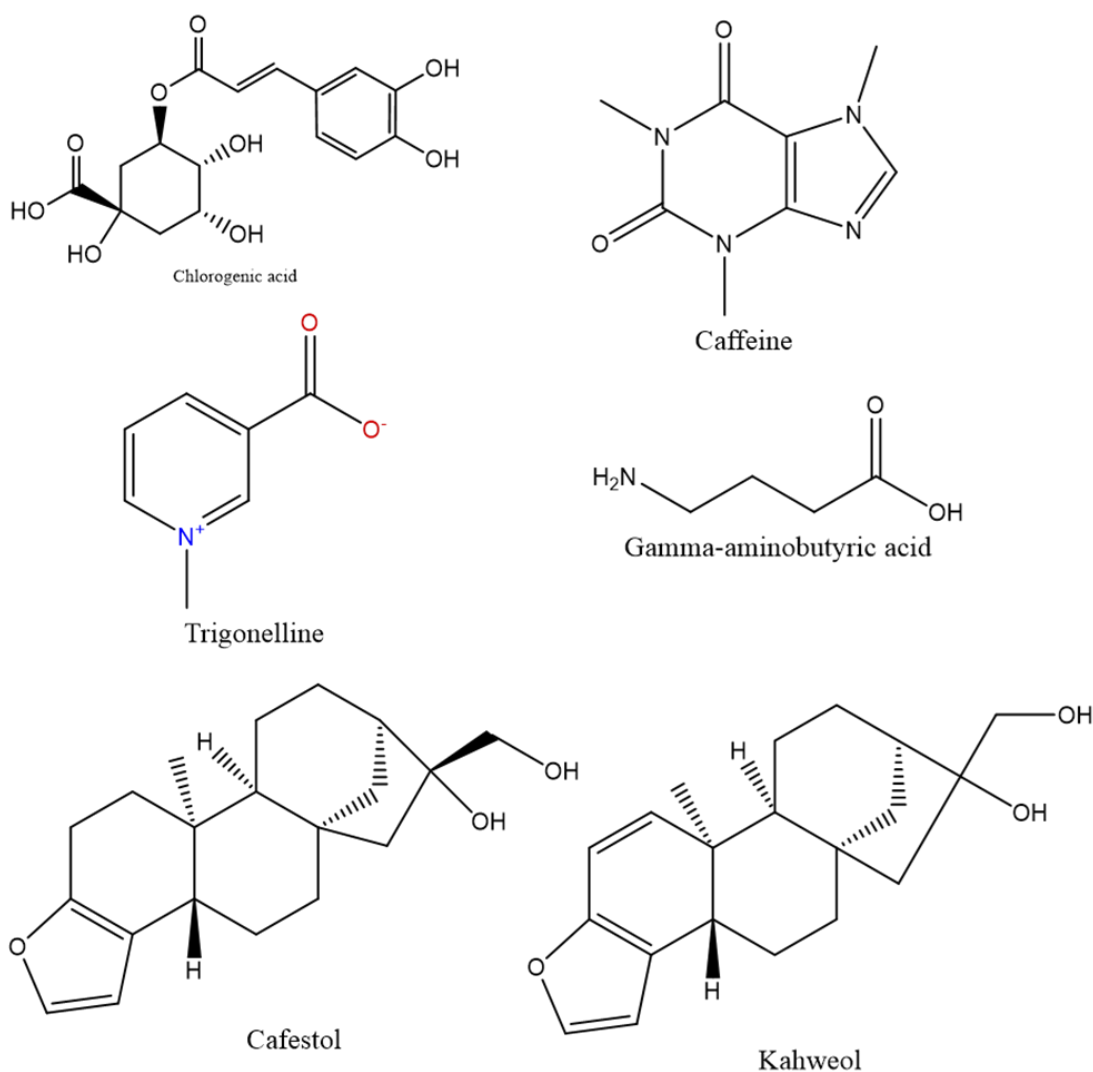


Figure 4: Bioactive compounds of green coffee.

4.2 Green Coffee

Green coffee refers to coffee beans that have not been roasted. These beans have a greenish color and a slightly bitter taste. Green coffee beans contain high levels of chlorogenic acid, a type of polyphenol that has been

studied for its potential health benefits, including weight loss and improved blood sugar control (Vincent, 1987; Holscher and Steinhart, 1995; Wei and Tanokura, 2015).

Green coffee contains a variety of compounds, including chlorogenic acid, caffeine, trigonelline, gamma-aminobutyric acid (GABA), phenolic acids, diterpenes, cafestol, kahweol, and fiber (Figure 4). Chlorogenic acid is a type of polyphenol that is found in high levels in green coffee. It has been studied for its potential health benefits, including its ability to improve blood sugar control and support weight loss (Vinson *et al.*, 2019). Green coffee also contains caffeine, a natural stimulant that can have a variety of effects on the body, including increased metabolism and increased fat burning (Sanlier *et al.*, 2019). Theobromine is another natural stimulant that is found in green coffee. It has a similar effect to caffeine but is less potent (Bosso *et al.*, 2023). Trigonelline is an alkaloid that is found in green coffee. It has been studied for its potential anti-inflammatory and antioxidant effects (AlAmri *et al.*, 2020). Gamma-aminobutyric acid (GABA) is an amino acid that is found in green coffee. It has been studied for its potential calming and anti-anxiety effects. Green coffee contains diterpenes, such as cafestol and kahweol, which are present in small amounts. These compounds have been studied for their potential cholesterol-raising effects but also possess antioxidant properties. These diterpenes are largely removed during the roasting process (Mehaya *et al.*, 2020). In addition to chlorogenic acids, green coffee beans contain other phenolic acids, such as caffeic acid and ferulic acid. These compounds contribute to the antioxidant capacity of green coffee and may have protective effects against oxidative stress. The dietary fiber in green coffee beans can aid in digestion, promote satiety, and support a healthy digestive system (Getachew and Chun, 2016).

5. Hypoglycemic Effect in Type 2 Diabetes

Green tea and green coffee contain bioactive compounds that may have potential hypoglycemic effects. These effects are primarily attributed to the inhibition of enzymes involved in carbohydrate digestion, glucose absorption, and glucose production (Lee *et al.*, 2022).

5.1 Green Tea

Green tea has been studied for its hypoglycemic effects in people with diabetes mellitus, particularly type 2 diabetes. The results of these studies suggest that green tea may have a beneficial effect on blood sugar control (Wu *et al.*, 2004). By increasing insulin sensitivity, green tea may reduce blood sugar levels in one way. People with type 2 diabetes frequently have decreased insulin sensitivity, which can result in high blood sugar levels. According to studies, drinking green tea may increase glucose tolerance and insulin sensitivity, which would lower fasting blood sugar levels and enhance overall blood sugar control (Tsuneki *et al.*, 2004; Lo Piparo *et al.*, 2008). Green tea contains catechins, which have been found to exhibit antioxidant and anti-inflammatory properties. By lowering inflammation and

oxidative stress, which can contribute to the onset and progression of diabetes, these qualities may also help to improve blood sugar control (Mooney *et al.*, 1997).

Green tea contains several bioactive compounds that have been associated with potential hypoglycemic (blood sugar-lowering) effects. These compounds can interact with various enzymes in the body. Catechins present in green tea have been found to possess alpha-amylase inhibitory activity. EGCG has been studied for its ability to inhibit the alpha-amylase enzyme. EGCG can bind to the active site of the enzyme, preventing its interaction with starch molecules and reducing its enzymatic activity (Sun *et al.*, 2019). By inhibiting alpha-amylase, the bioactive compounds present in green tea delay the digestion of carbohydrates and slow down the rate at which glucose is released into the bloodstream. This can contribute to more stable blood sugar levels and potentially benefit individuals with conditions like type 2 diabetes or impaired glucose metabolism.

Similarly, it has been reported that catechins present in green tea possess alpha-glucosidase inhibitory activity (Yang and Kong, 2016). EGCG is one of the main catechins found in green tea that has been studied for its inhibitory effects on alpha-glucosidase. EGCG can bind to the active site of the enzyme, preventing it from hydrolyzing carbohydrates and reducing the rate of glucose release. Bioactive compounds present in green tea slow down the digestion and absorption of carbohydrates in the small intestine by inhibiting alpha-glucosidase (Yilmazer-Musa *et al.*, 2012). This leads to a more gradual release of glucose into the bloodstream, helping to prevent sharp spikes in blood sugar levels after a meal and promoting better glycemic control.

Green tea catechins have also been found to inhibit the activity of glucose-6-phosphatase, an enzyme involved in gluconeogenesis, which is the production of glucose from non-carbohydrate sources. By inhibiting this enzyme, green tea compounds may help to reduce the production of glucose in the liver (Gamberucci *et al.*, 2006). Green tea may indirectly impact glucose-6-phosphatase activity through its effects on other metabolic pathways. Catechins, (particularly EGCG) have been studied for their potential to modulate glucose metabolism, insulin sensitivity, and related enzymes in animal and *in vitro* studies (Csala *et al.*, 2007; Pari and Rajarajeswari, 2009). For example, EGCG has been found to enhance insulin signaling pathways and improve glucose uptake in certain cell types.

Similarly, EGCG has been shown to have anti-glycation properties (Chen *et al.*, 2016). Other than epigallocatechin gallate, epicatechins, flavonoids, and polyphenols in green tea are reported to exhibit anti-glycation effects (Ladeira *et al.*, 2021).

Consumption of flavonoid-enriched chocolate, containing flavan-3-ols and isoflavones, has

demonstrated significant reductions in peripheral insulin resistance and improvements in insulin sensitivity among patients with type 2 diabetes. In this context, catechins have been significantly associated with a lower risk of developing type 2 diabetes. However, individual intake of flavonoids appears to have no significant effect on diabetes, and data from human clinical trials remain limited (Shi *et al.*, 2016). A meta-analysis of randomized controlled trials indicated that tea catechins could significantly reduce fasting blood glucose levels (Borges *et al.*, 2016).

Liu *et al.* (2014) investigated the effects of green tea extract on glycemic and lipid profiles, as well as hormone peptides, in patients with type 2 diabetes mellitus and lipid abnormalities through a double-blinded, randomized, and placebo-controlled clinical trial. The trial included 92 subjects, randomized into two groups of 46 participants each. One group received 500 mg of green tea extract three times a day, while the control group received cellulose at the same dose and frequency over a 16-week period. Within-group comparisons showed significant decreases in triglycerides and the homeostasis model assessment of insulin resistance (HOMA-IR) index in the green tea extract group. Adiponectin, apolipoprotein A1, and apolipoprotein B100 levels increased significantly in both groups, but glucagon-like peptide 1 (GLP-1) increased only in the green tea extract group. The study concluded that green tea extract significantly improved insulin resistance and increased GLP-1 levels in within-group comparisons, suggesting potential benefits that warrant further investigation (Liu *et al.*, 2014).

The global prevalence of diabetes continues to rise dramatically, despite improvements in outcomes for individual patients. Lifestyle modifications are essential for addressing this issue (van Woudenberg *et al.*, 2012). Green tea extracts may be a promising lifestyle modification for diabetes prevention, as people who drink at least four cups of tea per day have a 16% lower risk of developing type 2 diabetes compared to non-tea drinkers. However, catechins from green tea alone do not significantly impact anthropometric measurements. A meta-analysis found that green tea extract positively influences weight loss and maintenance in obese individuals (Figure 5) (Phung *et al.*, 2010).

5.2 Green Coffee

Green coffee beans contain various bioactive compounds that have been associated with potential hypoglycemic effects (Suárez-Quiroz *et al.*, 2014; Brzezicha *et al.*, 2021). These compounds can interact

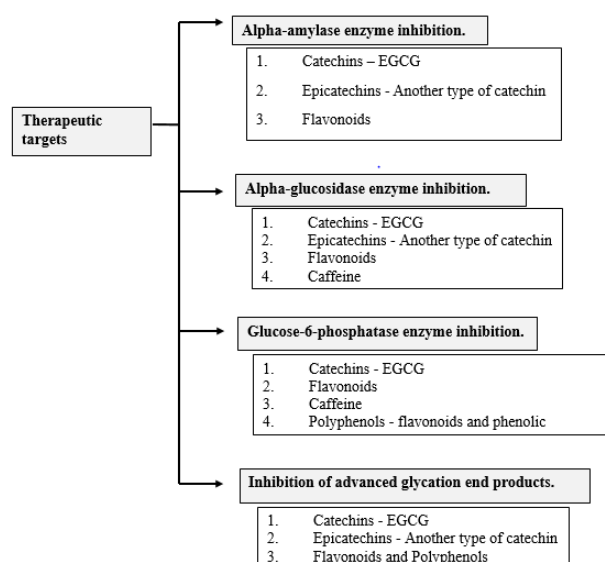


Figure 5: Therapeutic targets of green tea.

with different enzymes in the body. Green coffee is rich in chlorogenic acids (CGA), including caffeoylquinic acids such as 5-caffeoylquinic acid (5-CQA), 3-caffeoylquinic acid (3-CQA), and 4-caffeoylquinic acid (4-CQA) (Li *et al.*, 2021). These compounds are known for their potential health benefits and their interactions with alpha amylase. Green coffee bean extracts have been found to inhibit α -amylase which is an enzyme responsible for breaking down complex carbohydrates into simple sugars. CGA present in green coffee, particularly caffeoylquinic acids, can inhibit the activity of the alpha-amylase enzyme. The chlorogenic acids bind to the active site of the enzyme, impeding its ability to break down complex carbohydrates into glucose molecules. With the inhibition of alpha-amylase, the digestion of complex carbohydrates is slowed down (Hidayati *et al.*, 2022). This results in a slower release of glucose into the bloodstream during the digestive process. The delayed release of glucose helps to regulate blood glucose levels more effectively. By preventing rapid spikes in blood glucose, the bioactive compounds in green coffee contribute to improve glycemic control (Haguet *et al.*, 2023).

Green coffee bean extracts have also been shown to inhibit α -glucosidase, an enzyme involved in the final breakdown of carbohydrates in the small intestine. CGA present in green coffee can inhibit the activity of alpha glucosidase. The chlorogenic acids bind to the active site of the enzyme, preventing its ability to break down complex carbohydrates and disaccharides into glucose molecules (Ayua *et al.*, 2021). Due to the inhibition of alpha glucosidase, the conversion of complex carbohydrates and disaccharides into glucose is slowed down. This leads to a delayed release of glucose into the bloodstream during the digestion process. Inhibition of this enzyme helps to reduce the conversion of complex carbohydrates into glucose, leading to improve blood sugar control (Alongi and Anese, 2018). By preventing

the action of glucose transporters, CGA may also lessen the amount of glucose that is absorbed in the intestines (Zuñiga *et al.*, 2018). Green coffee bean compounds also inhibit glucose-6-phosphatase, an enzyme involved in the production of glucose in the liver and kidneys (Tunnicliffe *et al.*, 2015). Similarly, researchers found the ability of green coffee extracts to inhibit the activity of glucose-6-phosphatase enzyme which in turn help to decrease the release of glucose into the bloodstream (Shokouh *et al.*, 2019). Glycogen phosphorylase is an enzyme involved in the breakdown of glycogen, a storage form of glucose in the body, into glucose-1-phosphate (glycogenolysis) (Abdollahi *et al.*, 2022). CGA inhibits the activity of the glycogen phosphorylase enzyme, potentially helping to regulate blood sugar levels. Similarly, CGA, caffeine, trigonelline, and other polyphenols in green coffee have been shown to exhibit anti-glycation properties.

CGA is a novel insulin sensitizer that potentiates insulin action to reduce blood glucose level, similar to the therapeutic action of metformin. Some early papers in 2008 have reported that CGA induced a significant reduction in the plasma glucose peak in the oral glucose tolerance test, most likely by attenuating intestinal glucose absorption. This indicates that CGA may have a possible role as a glycemic index lowering agent and highlights it as a compound of interest for reducing the risk of developing T2DM (Meng *et al.*, 2013). Using *in vitro* studies, CGA was shown to increase glucose uptake in L6 muscular cells (myoblast cell isolated from the skeletal muscle from a rat), an effect only observed in the presence of stimulating concentrations of insulin. In addition, it was found that CGA stimulates insulin secretion from the INS1E insulin-secreting cell line and rat islets of Langerhans. Clinical trials have also testified that CGA in coffee is able to modulate glucose uptake and gastrointestinal hormone and insulin secretion in humans and that it provides the stimulation of insulin secretion (Liu *et al.*, 2022). Further, CGA has been shown to act as an active principle in glucose metabolism regulation. CGA has been able to improve glucose tolerance and insulin resistance in obese (*fa/fa*) Zucker rats, suggesting that CGA may be a promising candidate for the development of an antidiabetic agent. It provides improving glucose tolerance and insulin resistance (Zhou *et al.*, 2023).

Yang *et al.*, (2015) found that green coffee could be used to substantiate metformin in the treatment of diabetes-induced testicular dysfunction. Oxidative stress may be considered a potent inducer of cell apoptosis observed in this study (Yang *et al.*, 2015).

Clinical trials support that coffee drinking has an overall anti-inflammatory action on the body. Two coffee components, trigonelline and chlorogenic acid, have been described to overturn the inflammatory response in cell-based and animal studies, and they are also the probable mediators in the anti-inflammatory properties

of coffee (Dkhil *et al.*, 2020). This study investigated the levels of pro-apoptotic proteins (Bax and caspase-3) and the anti-apoptotic protein (Bcl-2), along with their gene expressions in the kidney tissue of diabetic rats. The levels of the pro-apoptotic proteins Bax and caspase-3 were significantly elevated consistently, while the level of the anti-apoptotic protein Bcl-2 was significantly reduced. Green coffee and metformin treatments demonstrated anti-apoptotic effects by upregulating Bcl-2 and downregulating Bax and caspase-3 compared to the diabetic group. Interestingly, green coffee (100 mg/kg) showed a notable improvement in the levels of Bax, caspase-3, and Bcl-2 compared to the control group (Abdel Mohsen *et al.*, 2021).

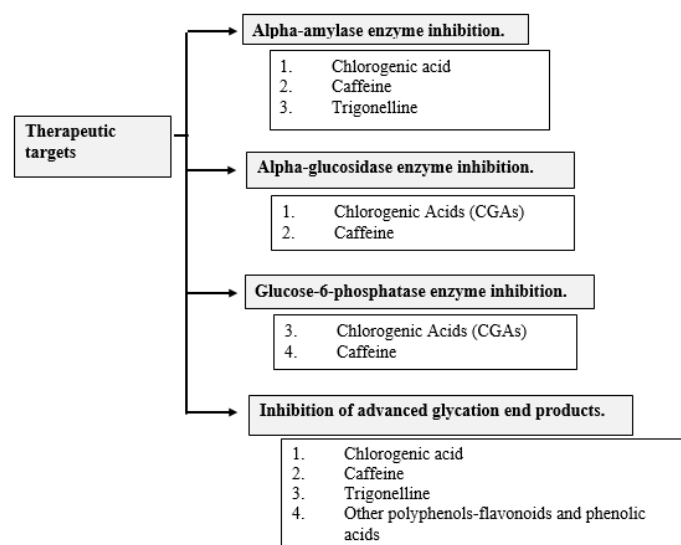


Figure 6: Therapeutic targets of green coffee

Kaundal *et al.*, (2018) reported that diabetic rats showed significant declines in neurotransmitters (DA, NE, and 5-HT), which are crucial for learning and memory. Diabetes disrupts the function of monoamine oxidase (MAO) enzymes, which are involved in metabolizing catecholamines and other substances in the brain and peripheral tissues. This disruption can alter brain amine metabolism levels (Arafa *et al.*, 2016). Chlorogenic acids (CGAs) in green coffee bean water extract (GCWE) have an anti-apoptotic effect by preventing cytochrome c release, caspase cleavages, and reducing intracellular calcium ions. These effects, along with other phytochemicals, contribute to the neuroprotective impact of green coffee bean water extract against diabetic neuronal injury in rats (Figure 6) (Kong *et al.*, 2019).

6. Conclusion

Green coffee and green tea have garnered significant attention as potential alternative treatments for managing hyperglycemia. Extensive research has explored their effects on blood sugar levels, highlighting the abundance of chlorogenic acids in green coffee and

catechins in green tea as key bioactive compounds with potential therapeutic benefits. Notably, chlorogenic acids and catechins, particularly epigallocatechin gallate (EGCG), have demonstrated promising hypoglycemic effects through their inhibition of alpha-amylase and alpha-glucosidase activities. Moreover, the diverse composition of green tea, including caffeine, flavonoids, and polyphenols, presents a multifaceted approach to glycemic control. These compounds exhibit inhibitory effects on enzymes like alpha-amylase, alpha-glucosidase, and glucose-6-phosphatase, as well as the formation of advanced glycation end products, contributing to improve blood sugar regulation. Alongside their therapeutic benefits, it's essential to acknowledge potential side effects associated with green coffee and green tea consumption. Caffeine, present in both beverages, may lead to adverse effects such as insomnia, jitteriness, and increased heart rate, particularly in individuals sensitive to caffeine. Additionally, excessive consumption of green tea extracts, which are rich in catechins, has been linked to liver toxicity and gastrointestinal discomfort in some cases. Furthermore, while the diverse composition of green tea offers a multifaceted approach to glycemic control by inhibiting enzymes like alpha-amylase, alpha-glucosidase, and glucose-6-phosphatase, caution is warranted due to possible interactions with medications and individual variations in response. While existing studies provide valuable insights, further comprehensive research is warranted to elucidate the intricate molecular mechanisms underlying the interactions between these bioactive compounds and diabetes, along with the associated complications. Such investigations hold the potential to unlock new therapeutic strategies and optimize the utilization of green coffee and green tea as adjunct therapies in the management of hyperglycemia.

7. Conflict of Interests

The authors declare there is no conflict of interest.

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