Review article

Unravelling the cardiovascular symphony: Decoding the intricate influence of green tea polyphenols from leaf to heart

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ABSTRACT

The extensive exploration of green tea's therapeutic potential in relation to cardiovascular ailments has sparked considerable global interest. The green tea polyphenols notably EGCG, ECG, EGC, EC, and various catechins, exhibit considerable promise as agents with cardioprotective attributes. The green tea polyphenolic compounds effectively counteract the detrimental impact of reactive oxygen species while concurrently modulating intricate cellular signalling pathways, thereby ameliorating the adverse effects of oxidative stress—a pivotal contributor to cardiovascular diseases. Furthermore, these compounds have demonstrated a capacity to function as antihypertensive agents, primarily through their facilitation of vasodilation, inhibition of angiotensin-converting enzyme activity, and deterrence of excessive vasoconstriction. Moreover, green tea polyphenols exert their influence on lipid profiles and cholesterol metabolism, presenting an additional avenue for cardiovascular health maintenance. By inhibiting key enzymes, namely ACAT and HMG-CoA reductases, involved in cholesterol esterification and synthesis, respectively, green tea polyphenols actively contribute to the preservation of a favourable lipid profile, effectively mitigating the risk of atherosclerosis development. In evaluating the bioavailability of green tea polyphenols, it is observed that they exhibit considerable stability in gastric conditions. However, substantial metabolic transformations occur within the intestinal and hepatic *milieu*, consequently influencing their availability and physiological activity within the human body. This comprehensive review proffers an array of interdisciplinary methodologies, encompassing *in silico* modelling, omics technologies, and innovative research approaches. These multifaceted avenues possess immense potential in unravelling novel insights and enhancing therapeutic strategies. Future investigations should seek to explore captivating prospects, including the identification of specific polyphenolic constituents or synergistic combinations that exhibit pronounced cardioprotective effects, thus guiding the development of targeted therapeutic interventions. By elucidating the molecular mechanisms underpinning the cardiovascular effects of green tea polyphenols, a greater understanding of the therapeutic targets involved in the prevention.

Keywords: Cardiovascular green tea; polyphenols; epigallocatechin gallate; epicatechin; lipid profile; atherosclerotic plaques.

INTRODUCTION

Cardiovascular diseases (CVDs) pose a significant and complex global health challenge, characterized by a considerable burden of morbidity and mortality. Afflictions such as coronary artery disease, stroke, and heart failure pervade populations, presenting formidable threats to individuals and healthcare systems on a worldwide scale (1). Unhealthy dietary patterns, sedentary lifestyles, and an array of other detrimental lifestyle factors play pivotal roles in the initiation and progression of CVDs. However, a growing body of scientific evidence strongly indicates that embracing healthier lifestyle choices, such as the incorporation of a balanced diet and regular physical exercise, can effectively mitigate these risks and foster cardiovascular well-being (2).

In recent times, scientific investigations have prominently shifted their attention towards exploring the potential contributions of naturally occurring compounds in the prevention and management of CVDs. Within this context, green tea has garnered significant interest as a beverage of choice due to its captivating sensory attributes and compelling medicinal characteristics (3,4). Its consumption, deeply rooted in centuries-old traditions, is widely acknowledged for its refreshing flavour, cultural significance, and therapeutic properties. Consequently, integrating green tea into daily regimens stands as a straightforward yet impactful measure aimed at enhancing health, owing to its status as a readily available and naturally sourced beverage (5,6).

Green tea, derived from the botanical source *Camellia sinensis*, showcases a profuse phytochemical repertoire. Of noteworthy significance are its polyphenolic constituents, encompassing flavonoids and catechins, renowned for their multifaceted biological attributes (4,5). These bioactive compounds, collectively acknowledged as green tea polyphenols, have attracted considerable attention for their potential to confer protection against cardiovascular disorders. Acquiring a comprehensive understanding of the intricate impact exerted by green tea polyphenols on cardiovascular well-being holds the promise of unveiling novel avenues for the prevention and management of CVDs (7).

Polyphenolic compounds have gained renown for their pronounced antioxidant attributes, which counteract the detrimental effects of oxidative stress—an underlying catalyst in the development of cardiovascular diseases (CVDs). Oxidative stress ensues from an intricate imbalance between the generation of reactive oxygen species (ROS) and the intricate antioxidant defence mechanisms intrinsic to the human body. Unfavourable lifestyles characterized by suboptimal dietary patterns and sedentary behaviours exacerbate the propensity for oxidative stress, culminating in deleterious repercussions for blood vessels and cardiac tissues (8). Green tea polyphenols, owing to their formidable antioxidant prowess, effectively scavenge ROS species, thereby conferring robust protection against cardiovascular impairments. Moreover, green tea polyphenols exert pleiotropic effects on diverse aspects of cardiovascular physiology. Particularly noteworthy is their capacity to enhance endothelial function, a pivotal determinant of vascular homeostasis (9). Endothelial dysfunction, characterized by impaired vasodilation, heightened inflammation, and an augmented propensity for thrombosis, represents a prominent feature of numerous cardiovascular disorders. By fostering the preservation of endothelial integrity, green tea polyphenols actively promote optimal blood flow dynamics and mitigate the likelihood of adverse cardiovascular events (10).

Nutritional factors assume a pivotal role in the intricate pathogenesis and advancement of CVDs, with suboptimal dietary practices emerging as a prominent causative factor. Introducing green tea into habitual dietary patterns presents a straightforward yet influential strategy for augmenting cardiovascular well-being (11). Diverging from a myriad of interventions, green tea consumption manifests unparalleled accessibility, seamlessly assimilating into pre-existing dietary regimens. The prospective merits of green tea polyphenols, spanning a wide spectrum encompassing blood pressure modulation, lipid metabolism regulation, platelet functionality, and atherosclerotic processes, firmly establish them as promising contenders for both preventive and therapeutic interventions against the formidable backdrop of CVDs (12).

In this comprehensive review, we aim to decipher the cardiovascular symphony orchestrated by green tea polyphenols, encompassing their bioavailability, metabolism, mechanisms of action, and their impact on blood pressure regulation, lipid metabolism, platelet function, and atherosclerosis. Through an intricate exploration of this symphony, we aim to unravel the scientific underpinnings substantiating the potential cardioprotective effects of green tea polyphenols. Moreover, we will scrutinize clinical evidence and examine the translational prospects of these compounds, while identifying opportunities and challenges associated with harnessing their benefits for enhanced cardiovascular health.

Green tea polyphenols

Polyphenols constitute a diverse group of naturally occurring compounds that are widely distributed throughout plant-based sources. Their chemical framework comprises multiple phenol rings, imparting distinctive structural and functional attributes (13). This class encompasses various subclasses, notably flavonoids, phenolic acids, and stilbenes, each distinguished by its own molecular arrangement and biological characteristics. The health-promoting potential of polyphenols has engendered substantial scientific interest owing to their exceptional antioxidative and anti-inflammatory capabilities, which underlie their prophylactic effects against chronic ailments (6). A multitude of epidemiological investigations has established a compelling association between polyphenol intake and a diminished susceptibility to cardiovascular disorders, encompassing coronary artery disease, cerebro- vascular incidents, and hypertension (14).

In cardiovascular health, polyphenols exhibit remarkable cardioprotective properties, owing to their profound antioxidant activity that effectively combats oxidative stress, a fundamental driver behind the development of CVD. By diligently scavenging free radicals and mitigating oxidative damage, polyphenols significantly contribute to the preservation of sound vascular structures and cardiac tissues (15). Moreover, these compounds have demonstrated the ability to enhance endothelial function, bolster nitric oxide production, and mitigate inflammatory processes, all of which are indispensable for the attainment of optimal cardiovascular well-being. Notably, the cardioprotective effects of polyphenols have been extensively investigated in the context of green tea (16). Green tea stands out for its diverse assemblage of polyphenolic compounds, among which catechins emerge as the most prevalent constituents. Within green tea, catechins such as epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin (EC) manifest as noteworthy examples (9).

Catechins, are known for their robust antioxidative capacity, assume a fundamental role in the defence against CVDs. Through their remarkable ability to impede the oxidation of low-density lipoprotein (LDL) cholesterol, catechins thwart the formation of atherosclerotic plaques, a hallmark of CVD pathogenesis. Furthermore, these polyphenolic compounds exert regulatory effects on blood pressure dynamics by fostering vasodilation and mitigating arterial rigidity. Notably, catechins' anti-inflammatory attributes encompass the suppression of pro-inflammatory mediators that contribute to the initiation and progression of cardiovascular maladies. By virtue of their multifaceted mechanisms, catechins exhibit immense potential as therapeutic agents for the prevention and management of CVDs (17).

Polyphenols can be classified into several subclasses based on their chemical structure and characteristics as follows:

Flavonoids

Green tea, a widely consumed beverage, harbours an extensive assortment of flavonoids, which contribute significantly to its multifaceted spectrum of health benefits (18). Flavonoids, a class of polyphenolic compounds exhibiting diverse chemical structures and exerting varied biological activities, have been the subject of numerous scientific investigations. These studies have shed light on the remarkable cardioprotective attributes of green tea flavonoids, underscoring their potential for preventing and managing cardiovascular diseases CVDs (19).

Among the extensively scrutinized flavonoids present in green tea, EGCG stands out as a prominent constituent. This bioactive compound showcases formidable antioxidant properties by effectively scavenging free radicals and inhibiting oxidative stress. Remarkably, EGCG demonstrates a capacity for reducing the oxidation of LDL cholesterol, a pivotal factor in atherosclerosis development. (19). Furthermore, EGCG exerts a beneficial impact on endothelial function by augmenting nitric oxide production and facilitating vasodilation. Consequently, these actions lead to enhanced blood flow and diminished blood pressure. Notably, EGCG's anti-inflammatory potential has also been substantiated, wherein it effectively curtails the release of pro-inflammatory molecules implicated in CVD progression (20). Another flavonoid abundant in green tea, ECG, has exhibited noteworthy cardioprotective effects. ECG has demonstrated the ability to ameliorate endothelial function and augment nitric oxide-mediated vasodilation, resulting in enhanced hemodynamic perfusion and diminished susceptibility to cardiovascular events. Furthermore, ECG manifests compelling antithrombotic properties through its inhibition of platelet aggregation, thereby mitigating the propensity for thrombus formation that precipitates myocardial infarctions or cerebral infarctions (21,22).

Quercetin, a flavonoid abundantly present in green tea and various other botanical sources, has garnered significant interest owing to its potential cardioprotective properties. This bioactive compound showcases remarkable antioxidant and anti-inflammatory attributes and has demonstrated efficacy in reducing blood pressure and ameliorating endothelial function. Moreover, quercetin may exert inhibitory effects on the oxidation of LDL cholesterol, thus mitigating the risk of atheroma formation within the arterial vasculature (23,24).

The intricate mechanisms underlying the cardioprotective attributes of green tea flavonoids are multifaceted (13). These bioactive compounds exert their effects through diverse mechanisms, including potent antioxidative actions that effectively neutralize free radicals, thus abating oxidative stress and safeguarding cardiovascular tissues from damage. Additionally, flavonoids intricately modulate intricate signalling pathways implicated in inflammation, thereby curbing the release of pro-inflammatory molecules and attenuating the inflammatory response within the cardiovascular system (19). Moreover, the exceptional impact of flavonoids extends to the enhancement of endothelial function, wherein they augment the production of nitric oxide; an influential vasodilator, consequently promoting robust vasodilation and optimizing blood vessel calibre and perfusion. These collective effects culminate in reduced blood pressure and diminished susceptibility to atherosclerosis.

Phenolic acids

Green tea, renowned for its health-promoting properties, contains a diverse array of phenolic acids that contribute to its potential cardioprotective effects. Phenolic acids represent a class of polyphenolic compounds distinguished by the presence of a phenolic ring and a carboxylic acid group. Although not as extensively investigated as flavonoids, emerging evidence suggests that phenolic acids present in green tea may confer substantial cardiovascular advantages. Gallic acid has exhibited remarkable antioxidant activity, effectively scavenged free radicals and mitigated oxidative stress (25). Multiple studies have demonstrated that gallic acid possesses the ability to shield against endothelial dysfunction through the enhancement of nitric oxide production, amelioration of endothelial function, and promotion of vasodilation. Furthermore, gallic acid displays potent anti-inflammatory properties by inhibiting pro-inflammatory mediators and cytokines, thereby mitigating the risk of cardiovascular diseases (9).

Caffeic acid, another phenolic acid present in green tea, emerges as an additional agent of cardio protection. Caffeic acid has exhibited remarkable antioxidant properties, effectively shielding against oxidative damage and lipid peroxidation (26). Furthermore, it manifests significant anti-inflammatory effects by hampering the production of pivotal pro-inflammatory molecules, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These anti-inflammatory mechanisms synergistically contribute to the preservation of vascular homeostasis and the prevention of atherosclerosis (27). Among the notable phenolic acids abundant in green tea, chlorogenic acid has garnered considerable attention due to its potential cardioprotective effects. Chlorogenic acid not only exhibits formidable antioxidant properties but also exerts a profound influence on the reduction of oxidative stress and lipid peroxidation, which are recognized as pivotal contributors to the development of CVDs. In addition, chlorogenic acid demonstrates the ability to modulate blood pressure by inhibiting the enzyme angiotensin-converting enzyme (ACE), which plays a crucial role in blood pressure regulation. By inhibiting ACE, chlorogenic acid effectively promotes vasodilation and mitigates hypertension.

The cardioprotective properties of these phenolic acids are mediated through intricate mechanisms involving multiple pathways. Their potent antioxidant activity enables the neutralization of free radicals and the mitigation of oxidative stress, thereby preserving the structural integrity of cardiovascular tissues (9). Additionally, phenolic acids exert regulatory effects on inflammatory pathways by inhibiting key pro-inflammatory mediators, thereby attenuating the inflammatory response within the cardiovascular system. Moreover, their impact on endothelial function, encompassing the augmentation of nitric oxide production and facilitation of vasodilation, contributes to enhanced blood flow, lowered blood pressure, and the safeguarding against atherosclerosis (28).

Stilbenes

Stilbenes represent a class of polyphenolic compounds present in various plant species, including green tea, that have garnered considerable attention due to their potential therapeutic implications for human health. Resveratrol, a particularly well-documented and extensively investigated stilbene compound found in green tea, has exhibited notable cardioprotective properties attributed to its multifaceted mechanisms of action. Remarkably, resveratrol showcases formidable antioxidant properties by efficiently neutralizing harmful free radicals and mitigating oxidative stress within the cardiovascular milieu. This inherent antioxidant activity confers protection against lipid peroxidation and the oxidation of LDL cholesterol, both of which represent pivotal contributors to atherosclerotic pathogenesis. Furthermore, resveratrol exerts potent anti-inflammatory effects by inhibiting the activation of pro-inflammatory signalling cascades, such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs). Through modulation of these inflammatory pathways, resveratrol effectively curtails the production of pro-inflammatory molecules, thereby attenuating chronic inflammation within the cardiovascular system and ultimately reducing the risk of cardiovascular diseases (27).

Resveratrol, apart from possessing remarkable antioxidant and anti-inflammatory characteristics, has demonstrated significant potential in enhancing endothelial function. Its mechanism involves the activation of endothelial nitric oxide synthase (eNOS), which facilitates the production of nitric oxide (NO). This bioactive molecule acts as a potent vasodilator, resulting in vasodilation, improved blood flow, and the maintenance of optimal blood pressure levels. Similarly, pterostilbene, a stilbene compound found in green tea, exhibits comparable cardioprotective attributes. Although it has received less attention in scientific investigations compared to resveratrol, pterostilbene showcases antioxidant properties, effectively mitigates oxidative stress, and contributes to the preservation of endothelial function. Moreover, studies have indicated its ability to inhibit platelet aggregation, a pivotal process in the formation of blood clots. By reducing the risk of thrombotic events, such as heart attacks and strokes, pterostilbene plays a crucial role in cardiovascular health preservation (27).

The cardioprotective effects of stilbenes, including resveratrol and pterostilbene, are mediated through their interactions with diverse molecular targets. These compounds possess the capacity to modulate gene expression, activate intricate cellular signalling pathways, and regulate the enzymatic activities essential for cardiovascular well-being. By virtue of their potent antioxidant, anti-inflammatory, and endothelial protective actions, stilbenes make significant contributions to the prevention and management of cardiovascular diseases.

Lignans

Lignans, which are polyphenolic compounds abundant in plant-based foods, possess a wide array of biological activities. Despite the comparatively limited research conducted on lignans in green tea relative to other polyphenols, emerging evidence indicates their potential in conferring protection against cardiovascular ailments. Among the significant lignans present in green tea, enterolactone holds particular importance. Enterolactone is synthesized within the body through the microbial metabolism of dietary lignans. Numerous investigations have highlighted the cardioprotective effects associated with enterolactone. Notably, it has been linked to a reduced risk of cardiovascular diseases, including coronary artery disease and stroke. These beneficial effects may be attributed to its multifaceted mechanisms, encompassing antioxidant and anti-inflammatory actions. By scavenging free radicals and mitigating oxidative stress (28), enterolactone safeguards cardiovascular tissues against damage. Moreover, enterolactone demonstrates the ability to modulate inflammatory pathways, thereby suppressing the production of pro-inflammatory molecules and ameliorating inflammation within the cardiovascular system. Another lignan present in green tea is sesamin, which has garnered attention for its potential cardioprotective properties. Sesamin manifests antioxidant characteristics, enabling efficient neutralization of free radicals and consequent mitigation of oxidative stress. Notably, sesamin has demonstrated efficacy in enhancing lipid profiles by diminishing total cholesterol, LDL cholesterol, and triglyceride levels. These lipid-lowering effects assume significance in promoting cardiovascular well-being, as elevated cholesterol and triglyceride levels constitute risk factors for cardiovascular diseases. Furthermore, sesamin exhibits anti-inflammatory actions by impeding the production of inflammatory markers and ameliorating inflammation within the cardiovascular system (28).

Tannins

Tannins, a class of polyphenolic compounds, are widely distributed in plant-derived food sources and beverages. Ongoing research on tannins in green tea reveals emerging evidence of their potential cardioprotective properties. Among the tannins found in green tea, the proanthocyanidins constitute a major group. Proanthocyanidins possess robust antioxidant characteristics and have demonstrated favourable effects on cardiovascular well-being. Their actions involve safeguarding blood vessels and cardiac tissues against oxidative damage, thereby reducing the susceptibility to cardiovascular diseases. Moreover, proanthocyanidins exhibit anti-inflammatory effects by impeding the release of pro-inflammatory molecules and ameliorating inflammation within the cardiovascular system. Additionally, these compounds may contribute to cardiovascular health by enhancing lipid profiles, decreasing total cholesterol and LDL cholesterol levels. An overview of the cardioprotective properties demonstrated by various green tea polyphenols is presented in Table 1.

Metabolic pathways and biotransformation of green tea polyphenols

The metabolic pathways and biotransformation of green tea polyphenols have a pivotal role in elucidating their bioavailability and inherent health advantages. A comprehensive comprehension of these intricate pathways and the myriad factors that exert influence on their metabolism is imperative in deciphering the physiological impact of green tea polyphenols within the human organism. By delving into the intricate intricacies of these metabolic cascades, we can ascertain the optimal utilization of green tea polyphenols, thereby maximizing their potential health benefits.

Upon ingestion, green tea polyphenols undergo extensive metabolic transformations within the hepatic milieu. The liver serves as the principal epicentre for the biotransformation of these polyphenolic compounds, where they undergo a cascade of phase I and phase II reactions, enabling their metabolism and subsequent excretion from the organism. Phase I reactions entail enzymatic modifications that introduce functional groups or modify the chemical architecture of the polyphenols. These reactions are facilitated by a superfamily of enzymes referred to as cytochrome P450 (CYP) enzymes, specifically the subfamilies CYP1A2, CYP2C9, and CYP3A4 (29).

The primary phase I reactions involved in the metabolic fate of green tea polyphenols encompass hydroxylation, demethylation, oxidation, and reduction. Hydroxylation, a paramount process mediated by hydroxylating enzymes, entails the addition of a hydroxyl (-OH) group to the polyphenol molecule. This reaction transpires at diverse positions along the polyphenol backbone, thereby engendering the formation of hydroxylated metabolites. Demethylation, on the other hand, encompasses the removal of a methyl ($-CH_3$) group from the polyphenolic structure, culminating in the generation of demethylated metabolites. Oxidation reactions encompass the incorporation of oxygen atoms into the polyphenol molecule, consequently facilitating the generation of oxidized metabolites. These chemical transformations may lead to the conversion of catechins, a specific class of polyphenols abundantly present in green tea, into quinones. These quinones, acting as reactive intermediates, exhibit the potential to exert diverse biological activities. Conversely, reduction reactions involve the removal of oxygen atoms from the polyphenol structure, resulting in the formation of reduced metabolites (30).

Phase I reactions encompass intermediate metabolites characterized by modified chemical structures in comparison to the original polyphenols. These metabolites possess distinct pharmacological and biological properties relative to their parent compounds. However, it is important to note that these intermediate metabolites often display heightened reactivity and reduced stability when compared to the original polyphenols (30).

Table 1: Cardioprotective mechanisms of green tea polyphenols: Examples and evidence (28)

Polyphenol	**Cardioprotective mechanism**
Epigallocatechin-3-gallate (EGCG)	Reduces oxidative stress and inflammation in the cardiovascular system, improves lipid profile, enhances endothelial function
Epicatechin	Increases nitric oxide production, improves endothelial function, reduces blood pressure
Catechin	Enhances antioxidant activity, reduces LDL cholesterol oxidation, improves blood vessel elasticity
Epicatechin-3-gallate	Inhibits platelet aggregation, improves blood flow, reduces atherosclerosis
Theaflavins	Inhibits inflammation, reduces oxidative stress, improves lipid metabolism
Thearubigins	Suppresses LDL cholesterol oxidation, inhibits platelet aggregation, improves lipid profile
Gallocatechin	Protects against myocardial ischemia-reperfusion injury, reduces cardiac hypertrophy
Catechin gallate	Enhances endothelial nitric oxide synthase activity, improves endothelial function
Proanthocyanidins	Reduces blood pressure, inhibits inflammation, improves lipid metabolism
Quercetin	Reduces oxidative stress, inhibits LDL cholesterol oxidation, improves endothelial function
Kaempferol	Reduces inflammation, inhibits platelet aggregation, improves lipid profile
Myricetin	Enhances antioxidant activity, improves endothelial function, reduces blood pressure
Rutin	Inhibits platelet aggregation, improves blood vessel elasticity, reduces atherosclerosis
Isorhamnetin	Reduces inflammation, enhances antioxidant activity, improves lipid metabolism
Delphinidin	Inhibits platelet aggregation, reduces oxidative stress, improves endothelial function
Cyanidin	Enhances nitric oxide production, reduces blood pressure, inhibits LDL cholesterol oxidation
Apigenin	Improves endothelial function, reduces inflammation, enhances antioxidant activity
Luteolin	Inhibits platelet aggregation, reduces oxidative stress, improves blood vessel elasticity
Naringenin	Reduces inflammation, improves lipid profile, enhances endothelial function
Phloretin	Enhances antioxidant activity, reduces blood vessel inflammation, improves lipid metabolism
Gallic acid	Inhibits platelet aggregation, reduces oxidative stress, improves endothelial function
Ellagic acid	Reduces LDL cholesterol oxidation, inhibits inflammation, improves blood vessel elasticity

Subsequent to phase I reactions, the intermediate metabolites undergo phase II reactions, renowned as conjugation reactions. Phase II reactions encompass the addition of diverse endogenous molecules, such as glucuronic acid, sulphate, and methyl groups, to the intermediate metabolites. This conjugation process heightens the water solubility of the metabolites, thereby facilitating their excretion from the organism. The catalysis of conjugation reactions is facilitated by specific enzymes known as transferases. Glucuronosyltransferases (UGTs) assume responsibility for incorporating glucuronic acid; sulfotransferases (SULTs) append sulphate groups, while methyltransferases attach methyl groups to the intermediate metabolites. These conjugated metabolites generally exhibit enhanced water solubility, consequently being readily excreted via urine or bile.

The metabolism of polyphenols derived from green tea through both phase I and phase II reactions culminates in the generation of a myriad of metabolites. The destiny of individual polyphenols in terms of metabolism is contingent upon their unique chemical structure, the activity of distinct enzymes, and the intricate interplay between phase I and phase II reactions. This extensive metabolic network substantially influences the bioavailability, pharmacokinetics, and ultimately, the physiological effects of green tea polyphenols within the organism (29).

Phase II reactions assume a pivotal role in the biotransformation of polyphenols derived from green tea by facilitating their conjugation with endogenous molecules. These conjugation reactions are instrumental in augmenting the water solubility of the intermediate metabolites, thereby enabling efficient elimination from the organism. The catalytic prowess essential to the conjugation process resides within specific transferase enzymes, encompassing notable entities such as UGTs, SULTs, and methyltransferases.

Among the diverse array of phase II conjugation reactions, glucuronidation reigns supreme in terms of prevalence and significance. This intricate transformation entails the transfer of a glucuronic acid moiety from uridine diphosphate glucuronic acid (UDPGA) onto the intermediate metabolite, ultimately forging a glucuronide conjugate. The orchestration of glucuronidation reactions is primarily entrusted to a myriad of UGT enzymes, comprising prominent members such as UGT1A1, UGT1A3, UGT1A8, UGT1A9, and UGT2B7. These enzymatic entities demonstrate abundant presence within hepatic tissue and various extrahepatic sites, including the intestines, kidneys, and lungs. Sulfation represents an additional pivotal conjugation reaction within the phase II metabolism of polyphenols derived from green tea. This intricate process relies on the catalytic proficiency of sulfotransferases (SULTs), which mediate the transfer of a sulphate group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) onto the intermediate metabolite, ultimately engendering a sulphate conjugate. Several SULT isoforms, including noteworthy entities such as SULT1A1, SULT1A3, and SULT1E1, actively participate in the sulfation of polyphenols (31). The distribution of these enzymes is predominantly discernible within hepatic tissue, the small intestine, and diverse extrahepatic sites. Methylation, while comparatively less frequent, constitutes a significant phase II conjugation reaction. This intricate transformation involves the addition of a methyl group from S-adenosylmethionine (SAM) onto the intermediate metabolite, ultimately culminating in the formation of a methylated conjugate. Catechol-O-methyltransferase (COMT) emerges as the extensively studied methyltransferase enzyme implicated in the methylation of polyphenols. The discernible presence of COMT is evident within various tissues, encompassing hepatic tissue, renal tissue, the central nervous system, and the gastrointestinal tract.

The conjugated metabolites generated as a result of phase II reactions typically exhibit augmented polarity and enhanced water solubility in comparison to the parent polyphenols. This heightened hydrophilicity expedites their elimination from the organism via excretion through urine or bile. Nonetheless, it is imperative to acknowledge that these conjugates may undergo additional metabolic transformations or deconjugation events prior to excretion. In certain instances, the conjugates can be subjected to hydrolysis by enzymatic action, thereby liberating the original polyphenol or its metabolites (32). This liberation may facilitate their reabsorption or enable further metabolic processes to transpire.

The metabolism of green tea polyphenols is subject to various influential factors. The chemical structure of the polyphenols themselves stands out as a key determinant. Diverse classes of polyphenols, such as catechins and flavanols, undergo distinct metabolic pathways due to inherent structural variations. The presence and arrangement of hydroxyl groups, glycosylation, and methylation patterns exert a notable influence on the metabolism of green tea polyphenols. Another crucial factor is the interindividual variability in the expression and activity of enzymes. Genetic polymorphisms in enzymes involved in polyphenol metabolism, including cytochrome P450 enzymes and transferases, give rise to dissimilarities in the rate and efficiency of polyphenol metabolism among individuals. This genetic variability contributes significantly to the variations observed in the bioavailability and health effects of green tea polyphenols. Moreover, the gut microbiota plays a pivotal role in the metabolic processes of green tea polyphenols. Certain microbial species residing in the gut possess enzymes capable of metabolizing polyphenols, leading to the formation of smaller metabolites that can be absorbed by the host or further metabolized by host enzymes. The composition and activity of the gut microbiota significantly influence the extent of polyphenol metabolism and the profile of generated metabolites (33).

Additionally, several other factors, such as the food matrix, co-ingestion of other dietary components, and interactions with drug metabolism, can exert an impact on the bioavailability and metabolism of green tea polyphenols. For instance, the presence of dietary fibres, proteins, or other polyphenols in the gut can form complexes or compete for absorption, thereby affecting the overall bioavailability of green tea polyphenols.

Cardioprotective properties of green tea polyphenols

Green tea polyphenols possess extraordinary cardioprotective properties that have undergone extensive scrutiny in scientific research. These polyphenolic compounds, encompassing flavonoids such as catechins, phenolic acids, stilbenes, lignans, and tannins, exert their favourable effects through diverse mechanisms. They manifest remarkable antioxidant activity, effectively scavenging free radicals and mitigating oxidative stress. Moreover, they ameliorate endothelial function, augment nitric oxide production, diminish inflammation, impede platelet aggregation, and regulate blood pressure. The multifaceted nature of these actions contributes significantly to the preservation of robust blood vessels, thereby reducing the risk of atherosclerosis and bolstering overall cardiovascular health. The bioavailability and metabolic processes associated with green tea polyphenols additionally exert a profound influence on their cardioprotective effects, as they undergo extensive biotransformation within the human body (33). Thus, comprehending these intricate mechanisms is pivotal in fully harnessing the vast potential of green tea polyphenols for the promotion of cardiovascular well-being (Fig. 1).

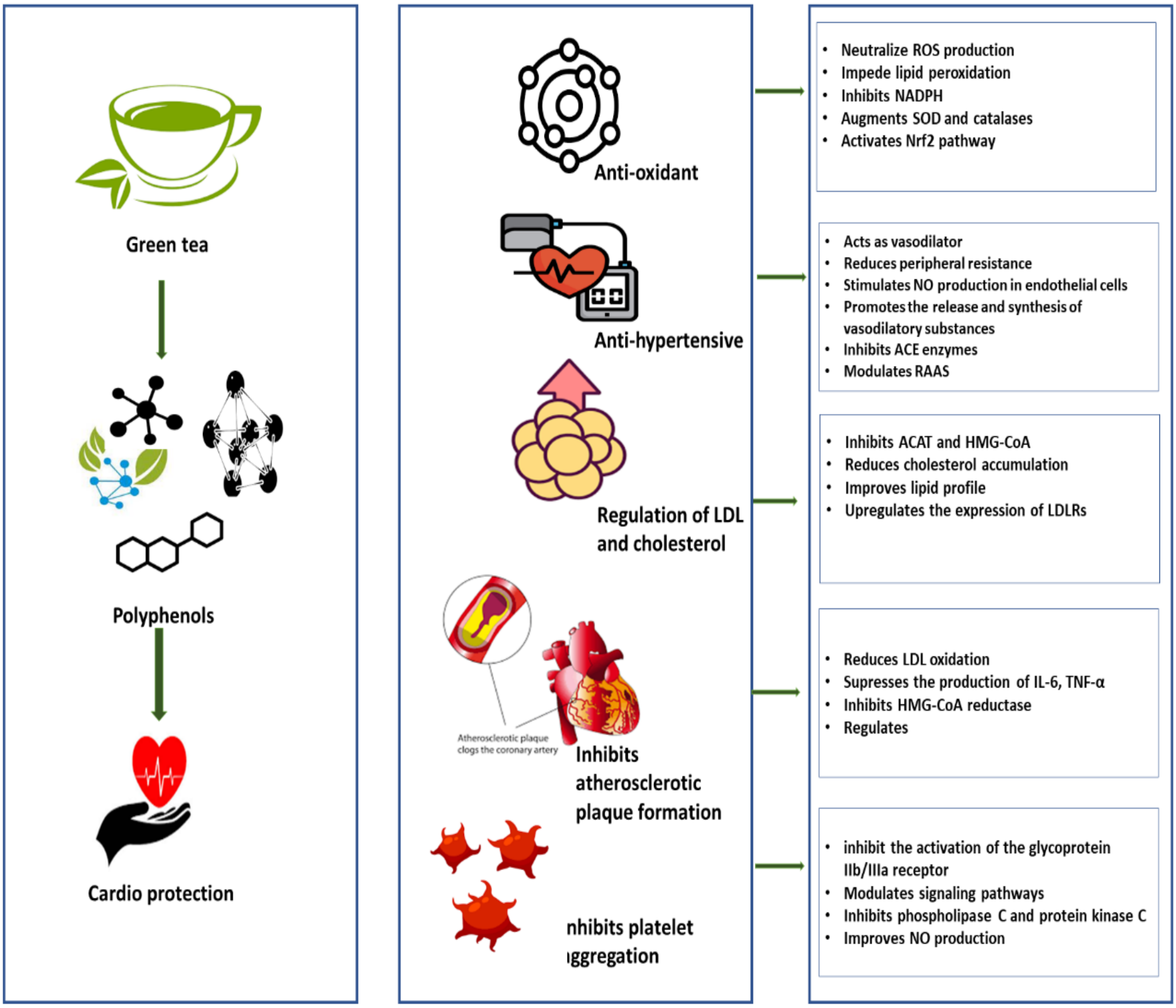

Fig. 1: Cardioprotective effects of green tea polyphenols

Antioxidant properties

Polyphenols encompass a heterogeneous group of compounds renowned for their exceptional capacity to scavenge deleterious free radicals and mitigate oxidative stress, thus safeguarding the cardiovascular system against detrimental consequences. Among these polyphenols, EGCG, a prominent catechin abundantly present in green tea, emerges as one of the most potent and extensively studied molecules. Its antioxidant properties and pivotal role in cardiovascular health have garnered significant attention. The antioxidant potential of EGCG manifests through its ability to neutralize reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals, which inflict oxidative damage upon cardiac tissues. By impeding lipid peroxidation, EGCG upholds cellular membrane integrity and shields against oxidative stress-induced harm. Epicatechin, another notable polyphenol, exerts its antioxidant activity by inhibiting enzymes involved in ROS production, including NADPH oxidase (34). Additionally, epicatechin augments endogenous antioxidants such as superoxide dismutase (SOD) and catalase, thereby further reinforcing cellular defence mechanisms against oxidative stress. Collectively, these actions alleviate the burden of oxidative stress on cardiac cells, promoting optimal cardiovascular well-being. Moreover, green tea encompasses additional polyphenolic compounds, such as catechin and flavanols, which also possess robust antioxidant properties. Catechins like ECG and EGC effectively scavenge free radicals, hinder oxidative enzymes, and modulate cellular signalling pathways to ameliorate oxidative stress within the cardiovascular system. Flavanols, exemplified by quercetin, serve as effective scavengers of free radicals and chelators of transition metal ions, thus diminishing their catalytic potential in ROS formation (34).

The mechanisms underlying the antioxidant effects of green tea polyphenols surpass mere direct scavenging of free radicals. Research has illuminated the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways as a crucial regulator of cellular antioxidant defence systems by these compounds. Stimulation of the Nrf2 pathway engenders an upregulation of diverse antioxidant enzymes, including SOD, catalase, and glutathione peroxidase. By bolstering the endogenous antioxidant capacity of cardiac cells, green tea polyphenols provide a formidable defence against the pernicious impact of oxidative stress.

Regulation of blood pressure

The principal polyphenol EGCG has undergone extensive investigation due to its potential as an antihypertensive agent. EGCG acts as a vasodilator, inducing relaxation and dilation of blood vessels, thus reducing peripheral resistance and facilitating enhanced blood flow. This vasodilatory effect is achieved through multifaceted mechanisms. EGCG stimulates nitric oxide (NO) production in the endothelial cells lining blood vessels. NO serves as a pivotal signalling molecule that promotes vasodilation by relaxing smooth muscle cells in the vessel walls. Through its ability to increase NO production, EGCG enhances endothelium-dependent vasodilation, leading to improved blood flow and contributing to the maintenance of healthy blood pressure levels. Another polyphenol found in green tea, known as catechin, has also exhibited potential in blood pressure regulation. Catechins, including ECG and EC, promote the synthesis and release of vasodilatory substances such as prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) (35). These substances effectively relax blood vessels and reduce blood pressure. Additionally, catechins have been shown to inhibit angiotensin-converting enzyme (ACE), an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. By impeding ACE activity, catechins aid in preventing excessive vasoconstriction, thereby contributing to the maintenance of normal blood pressure levels. Furthermore, green tea polyphenols, such as ECG and EC, have been found to modulate blood pressure by intervening in the renin-angiotensin-aldosterone system (RAAS). The RAAS is a crucial hormonal system involved in blood pressure regulation (35). It encompasses the conversion of angiotensinogen to angiotensin I, which is subsequently transformed into angiotensin II, a potent vasoconstrictor. Angiotensin II also stimulates the release of aldosterone, a hormone promoting sodium and water retention, resulting in increased blood volume and elevated blood pressure. Green tea polyphenols inhibit the activity of ACE, responsible for the conversion of angiotensin I to angiotensin II. Through ACE inhibition, green tea polyphenols effectively reduce angiotensin II production, leading to vasodilation and decreased blood pressure. Additionally, green tea polyphenols have been shown to inhibit aldosterone synthesis, further contributing to the regulation of blood pressure. Moreover, the presence of flavanols in green tea, such as quercetin, has been associated with blood pressure-lowering effects. Quercetin modulates the activity of ion channels, including calcium channels, in vascular smooth muscle cells. By inhibiting calcium influx into these cells, quercetin promotes relaxation of smooth muscle, leading to vasodilation and decreased blood pressure.

Regulation of lipid profile and cholesterol metabolism

Catechins, a class of polyphenolic compounds abundantly found in green tea, have undergone extensive scientific investigation regarding their impact on lipid metabolism. Notably, catechins exhibit inhibitory effects on the enzyme acyl-CoA: cholesterol acyltransferase (ACAT), which plays a pivotal role in cholesterol esterification. Through the inhibition of ACAT, catechins effectively impede the formation of cholesterol esters, thereby mitigating cholesterol accumulation in tissues and promoting a more favourable lipid profile (36). Furthermore, theaflavins, compounds generated during the fermentation process of tea, contribute significantly to the regulation of lipid profiles. Notably, theaflavins have been observed to inhibit the enzyme HMG-CoA reductase, a key enzyme involved in cholesterol synthesis. By impeding the activity of HMG-CoA reductase, theaflavins effectively reduce cholesterol production within the body, leading to improved lipid profiles and a decreased risk of atherosclerosis. Additionally, the polyphenol quercetin, present in green tea, has been associated with lipid-lowering effects. Quercetin exerts its influence on lipid metabolism by upregulating the expression and activity of hepatic low-density lipoprotein receptors (LDLRs). These LDLRs are responsible for the clearance of LDL cholesterol from the bloodstream. Through the enhancement of LDLR activity, quercetin facilitates the removal of LDL cholesterol, ultimately resulting in improved lipid profiles (36). Moreover, gallic acid, another polyphenol present in green tea, has demonstrated the ability to reduce lipid levels by inhibiting the enzyme lipoprotein lipase (LPL). LPL plays a critical role in the hydrolysis of triglycerides within lipoproteins, including LDL and very-low-density lipoprotein (VLDL). By inhibiting LPL activity, gallic acid effectively decreases the breakdown of triglycerides, thereby leading to lower levels of circulating lipids. Collectively, the combined actions of these polyphenols present in green tea play a significant role in the regulation of lipid profiles and cholesterol metabolism. They inhibit cholesterol synthesis, enhance cholesterol clearance through LDL receptors, and reduce the formation of cholesterol esters. These multifaceted effects contribute to improved lipid profiles and a decreased risk of developing cardiovascular diseases.

Effect on atherosclerotic plaque formation

The polyphenolic compounds present in green tea hold considerable potential for the regulation of atherosclerotic plaque formation, a pivotal factor in safeguarding cardiac health. These compounds encompass a diverse array of mechanisms that collectively contribute to the prevention and reduction of arterial plaque deposition. EGCG, for instance, demonstrates inhibitory effects on the oxidation of low-density LDL, a process of paramount importance in atherosclerosis development. The oxidation of LDL prompts an inflammatory response and facilitates the formation of foam cells (37), which play a central role in plaque formation. EGCG counteracts this phenomenon by reducing LDL oxidation, effectively impeding the initiation of atherosclerotic lesions. Catechins, on the other hand, suppress the production of pro-inflammatory cytokines such as IL-6 and TNF-α. By mitigating inflammation, catechins contribute to attenuating the inflammatory processes intrinsic to plaque formation, thereby mitigating the risk of atherosclerosis. Moreover, theaflavins, compounds generated during tea fermentation, have demonstrated the capacity to modulate atherosclerotic plaque formation (37). Theaflavins exert inhibitory effects on enzymes involved in cholesterol synthesis, including 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, culminating in diminished circulating cholesterol levels. By reducing the availability of lipid constituents necessary for plaque formation, lower cholesterol levels effectively impede the progression of atherosclerosis. Epicatechin and quercetin among other polyphenols exhibit antiplatelet effects. Platelet aggregation plays a critical role in the formation of thrombin that can occlude arteries and precipitate cardiovascular events. These polyphenols effectively inhibit platelet aggregation and adhesion, thus averting thrombus formation and reducing the risk of atherosclerotic complications. Furthermore, green tea polyphenols regulate the activity of matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix degradation and plaque destabilization. By impeding MMP activity, green tea polyphenols actively contribute to preserving the stability of atherosclerotic plaques and mitigating the risk of plaque rupture, a principal instigator of heart attacks and strokes (38).

Future prospects

Green tea polyphenols have been the subject of extensive research due to their potential health benefits, particularly in the context of cardiovascular health. To advance our understanding of the effects of green tea polyphenols on the cardiovascular system, researchers have begun to employ interdisciplinary approaches, such as *in silico* modelling, omics technologies, and innovative methodologies, which hold great potential for uncovering novel insights and improving therapeutic strategies.

In silico modelling involves computer simulations and mathematical algorithms to investigate the intricate interactions between green tea polyphenols and cardiac health. By utilizing structural biology techniques, researchers can determine the three-dimensional structures of polyphenols and their targets, including enzymes and receptors involved in cardiovascular regulation. This knowledge can be employed to predict the binding affinities and mechanisms of action of these polyphenols, providing valuable insights into their potential effects on the cardiovascular system. In silico models also facilitate the identification of specific molecular pathways and signalling cascades modulated by green tea polyphenols, aiding in the elucidation of the underlying molecular mechanisms behind their cardioprotective actions.

Omics technologies encompassing genomics, transcriptomics, proteomics, and metabolomics, offer comprehensive insights into the molecular changes induced by green tea polyphenols in the cardiovascular system (103, 104). Genomic analyses can identify genetic variations that influence an individual's response to green tea polyphenols, potentially enabling personalized medicine approaches in the future. Transcriptomic investigations reveal alterations in gene expression patterns, shedding light on the specific genes and pathways influenced by green tea polyphenols (105). Proteomic studies identify changes in protein expression and post-translational modifications, providing insights into the functional consequences of polyphenol treatment (39). Metabolomic profiling detects alterations in metabolite levels, elucidating the metabolic pathways influenced by green tea polyphenols in the heart. Integrating data from these omics approaches generates a comprehensive understanding of the molecular events underlying the cardioprotective effects of green tea polyphenols.

CONCLUSION

Looking ahead, future research on green tea polyphenols and cardiac health can explore several exciting possibilities. Identifying specific polyphenols or combinations of polyphenols that exert the most pronounced cardioprotective effects can pave the way for the development of targeted therapies. Elucidating the molecular mechanisms underlying the cardiovascular effects of green tea polyphenols may reveal novel therapeutic targets for the prevention and treatment of cardiovascular diseases. Additionally, investigating the potential synergistic effects of green tea polyphenols with other natural compounds or pharmaceutical agents holds promise for enhancing their efficacy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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