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REVIEW



Epigallocatechin gallate as a nutraceutical to potentially target the metabolic syndrome: novel insights into therapeutic effects beyond its antioxidant and anti-inflammatory properties

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ABSTRACT

Epigallocatechin gallate (EGCG) is one of the most abundant and powerful flavonoids contained in green tea. Because of the global increase in green tea consumption, there has been a general interest in understanding its health benefits, including its bioactive compounds like EGCG. Indeed, preclinical evidence already indicates that EGCG demonstrated a strong antioxidant and anti-inflammatory properties that could be essential in protecting against metabolic syndrome. The current review explores clinical evidence reporting on the beneficial effects of EGCG supplementation in obese subjects or patients with diverse metabolic complications that include type 2 diabetes and cardiovascular disease. The discussion incorporates the impact of different formulations of EGCG, as well as the effective doses and treatment duration. Importantly, besides highlighting the potential use of EGCG as a nutraceutical, the current review also discusses crucial evidence related to its pharmaceutical development as an agent to hinder metabolic diseases, including its bioavailability and metabolism profile, as well as its well-known biological properties.

KEYWORDS

Antioxidants;
epigallocatechin gallate;
green tea;
inflammation;
metabolic syndrome;
nutraceuticals

Introduction

Over the last few years, plants and their derivative bioactive compounds have attracted considerable attention for their potential health benefits. Certainly, there is also a long-term research interest and papers about plant polyphenols and their application on human health benefits (Rasouli, Farzaei, and Khodarahmi 2017; Cory et al. 2018; Fraga et al. 2019). Of interest are the polyphenolic compounds, which are enriched in many plants, and these include dietary sources such as vegetables, fruits, and herbal teas (Pandey and Rizvi 2009). Polyphenols are grouped into at least four major categories such as phenolic acids, flavonoids, lignans, and stilbenes, with flavonoids representing approximately 60% of dietary polyphenols (Pandey and Rizvi 2009). For example, *Camellia sinensis*, a flowering plant used to produce tea, is known to contain abundant levels of polyphenols (Khan and Mukhtar 2007). Tea exists in different forms depending on the oxidation process such as green, oolong, and black teas. In fact, the fermentation process involved in the production of oolong and black teas can also define their chemical composition, including the distribution of

their encompassed biologically active compounds (Wang, Provan, and Helliwell 2000). Green tea is predominantly rich in the flavanol group of polyphenols known as catechins (80–90%), while the degree of oxidation can promote the conversion of most of these compounds to theaflavins during the production of oolong and black tea (Wang, Provan, and Helliwell 2000). Indeed, the composition of theaflavins can reach 60% of total flavonoids in black tea, whereas catechins may account for 20–30% (Wang, Provan, and Helliwell 2000). Generally, tea contains low levels of caffeine, which is a central nervous stimulant, while the polyphenolic content is estimated to be 30% of the dry leaf weight (Wang, Provan, and Helliwell 2000). The foremost flavanols found in tea include catechins, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate (EGCG). Interestingly, the latter is considered the most important bioactive compound found in tea, responsible for its health-promoting properties.

At present, many review papers have been published on the potential health-promoting properties of EGCG. Such evidence ranges from deliberating on its absorption, metabolism, and molecular targets that might involve its anti-cancer

effects (Gan et al. 2018; Negri et al. 2018). This involved its capacity to control mechanisms such as regulating cancer cell growth, survival, angiogenesis, and metastasis, to potentially hinder cancer (Singh, Shankar, and Srivastava 2011; Almatroodi et al. 2020). Alternatively, Steinmann and colleagues illustrated that EGCG might target the cytoplasmic enzyme dihydrofolate reductase to influence the folic acid metabolism of bacteria and fungi (Steinmann et al. 2013). While, reviewed *in vitro* evidence suggests that metabolites of EGCG may play a central role, together with the beneficial actions of EGCG, in reducing neurodegenerative diseases (Pervin et al. 2019). Importantly, the strong antioxidant and anti-inflammatory effects of this tea polyphenol appears, like many other polyphenolic compounds, to be crucial in its biological properties (Chu et al. 2017; Muvhulawa et al. 2022). However, beyond this, others brought have new insights into the potential therapeutic effects of EGCG, consistent with other polyphenolic compounds like resveratrol and curcumin in regulating gene expression and influencing the activity of transcription factors and modulating microRNAs to hinder various metabolic complications (Cione et al. 2019; Mokgalaboni et al. 2021). Moreover, Kim and coworkers did evaluate evidence indicating that EGCG can directly interact with proteins and phospholipids in the plasma membrane and thus modulate signal transduction pathways, DNA methylation, transcription factors, mitochondrial function, and autophagy to potentially protect against the development of many diseases (Kim, Quon, and Kim 2014). With recently published clinical evidence showing controversial results. For example, Chatree and coworkers showing that supplementation with EGCG for 4 or 8 weeks did not affect body weight, body mass index, waist and hip circumferences, nor total body fat mass in obese human subjects (Chatree et al. 2021). However, others showing that perhaps extended treatment (for approximately 12 weeks to 2 months) with green tea extract containing high levels of EGCG could significantly promote weight loss, together with other metabolic features like lipid profiles (Chen et al. 2016; Bazyar et al. 2021).

Extending from previously reviewed evidence (Gan et al. 2018; Negri et al. 2018; Singh, Shankar, and Srivastava 2011; Almatroodi et al. 2020; Steinmann et al. 2013; Pervin et al. 2019; Chu et al. 2017; Cione et al. 2019; Kim, Quon, and Kim 2014), the current study focuses on critically discussing clinical data on the therapeutic benefits of EGCG against diverse metabolic complications, especially those implicating obesity, type 2 diabetes (T2D) and cardiovascular diseases (CVDs). This current manuscript particularly focused on these three chronic medical conditions because of substantial epidemiological data indicating their significant contribution to the increase in global deaths (International Diabetes Federation 2022; World Health Organization (WHO) 2022). Moreover, it is currently acknowledged that only a few individuals adhere to stringent interventions like regular physical exercise (McArthur et al. 2014; Collado-Mateo et al. 2021), which are known to improve metabolic function or cellular function (Lakka and Laaksonen 2007; Nyawo et al. 2021; Mthembu et al. 2022). Further indicating the need to explore

additional ways to improve metabolic health in the general population, which may be essential to eliminate the development of chronic diseases like obesity, diabetes, and CVDs.

Data collection for the related references was attained through computerized systematic literature searches in PubMed, Web of Science and Google Scholar databases to retrieve the pertinent clinical studies, published until the end of May 2022. The search keywords used included, but were not limited to, “green tea”, “catechins”, and “epigallocatechin gallate” in combination with the terms like “obesity”, “diabetes”, and “cardiovascular diseases”. Besides highlighting the potential use of EGCG as a nutraceutical, the current review also explores crucial evidence related to its pharmaceutical development as an agent to hinder metabolic diseases, including its absorption and metabolism profile, as well as its well-known biological properties.

A brief overview of EGCG

Currently, it is well acknowledged that, besides water and coffee, tea is the most popular beverage worldwide (Khan and Mukhtar 2013). Indeed, green tea has become extremely popular due to its health-promoting benefits, especially in Asian countries. One of the major health-promoting components found in green tea is a flavonoid that belongs to the flavan-3-ols group usually known as catechins (Yang, Prabhu, and Landau 2001). These catechins include (–)-epigallocatechin gallate (EGCG; PubChem CID: 65064), (–)-epigallocatechin (EGC; PubMed CID: 72277), (+)-epicatechin-3-gallate also known as (–)-epicatechin gallate (ECG; Pub Med CID: 65056) and (–)-epicatechin (EC; PubMed CID: 72276) (Khan and Mukhtar 2007). Of these, EGCG is the most abundant in green tea leaves (approximately 65%) and has a rich history of having the most interest in the field of medicinal chemistry (Mukhtar et al. 1992; Alipour et al. 2018; Nagle, Ferreira, and Zhou 2006). Briefly, EGCG is classified as an ester of epigallocatechin and gallic acid, with IUPAC name [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl], 4, 5-trihydroxybenzoate, a molecular formula of $C_{22}H_{18}O_{11}$ (MW 458.4 g/mol), a four-ring structure with eight hydroxyl groups and a melting point of 140–142 °C (Figure 1). Over the years, EGCG has been extensively studied and been reported to render versatile cellular and molecular effects relating to its health-promoting benefits such as anticancer (Stuart, Scandlyn, and Rosengren 2006; Mukhtar et al. 1992; Hayakawa et al. 2020; Aggarwal et al. 2020; Sinha et al. 2017), antioxidant (Hosseini et al. 2020; Wang et al. 2020), antimutagenic (Mukhtar et al. 1992; Huseynov and Abdullaev 2021), anti-inflammatory (Ohishi et al. 2016; Musial, Kuban-Jankowska, and Gorska-Ponikowska 2020; Braegelman et al. 2022), antiobesity activity since it has been shown to reduce diet-induced obesity in mice, rats, and humans (Suzuki et al. 2016; Moon et al. 2007; Legeay et al. 2015), antidiabetic (Tsuneki et al. 2004; Wu et al. 2004; Wolfram et al. 2006; Hosseini et al. 2020; Ferreira et al. 2016; Liu et al. 2015) and stroke alleviating properties (Legeay et al. 2015; Singh, Mandal, and Khan 2015; Xicota

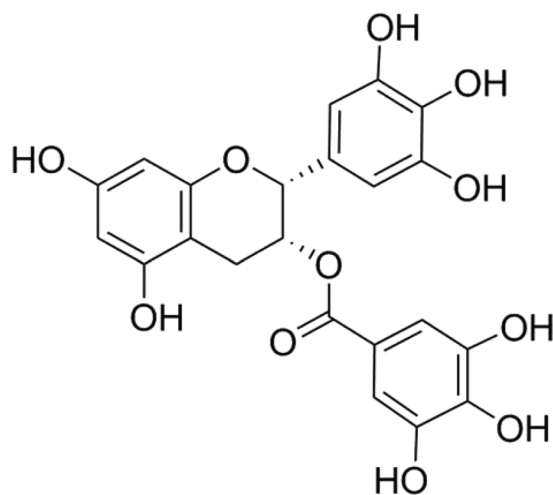


Figure 1. Chemical structure of epigallocatechin gallate (PubChem CID: 65064).

et al. 2017). Hence, as a dietary component or nutraceutical, EGCG has numerous health benefits (Lim et al. 2022).

Natural source of EGCG

Epigallocatechin gallate (EGCG) is naturally found in several sources such as different teas including but not limited to green tea (predominantly), black tea and white tea. In addition to teas, trace amounts of EGCG are found in fruits

and vegetables (apples, plums, berries, avocados and onions) and some nuts (pecans and hazelnuts) (Figure 2) (Sinha et al. 2017; Younes et al. 2018; Cione et al. 2019; Aggarwal et al. 2020). In green tea, EGCG is the most abundant and the most bioactive polyphenolic flavonoid due to its 8 hydroxyl groups markedly in 3', 4' and 5' positions and a gallate moiety in C-3 which makes it a better electron donor than the other catechins, ultimately making it the best free radical species scavenger as literature has shown (Evageliou, Panagopoulou, and Mandala 2019). EGCG is marketed as a dietary supplement and has the GRAS status (generally recognized as safe) from the Food and Drug Administration (FDA) and has been widely used in traditional Chinese medicine (>1-3 g per day) and to date no studies have reported on the adverse effects of EGCG in humans (Younes et al. 2018). Literature has shown that the effective concentrations of EGCG can range from 1 to 100 $\mu\text{mol/L}$. Although EGCG has the potential to be a powerful nutraceutical, it is however like many other catechins possess, certain physicochemical limitations such as a highly unstable status where approximately 80% of it degrades after 1 h incubation in simulated intestinal fluid pH 7.4 (Mochizuki et al. 2002; Dettlaff et al. 2017; Evageliou, Panagopoulou, and Mandala 2019; Han et al. 2020). In particular, EGCG may undergo oxidative decomposition under certain intestinal conditions that may include pH, favoring its hydrolysis into other components like epigallocatechin and gallic acid by intestinal

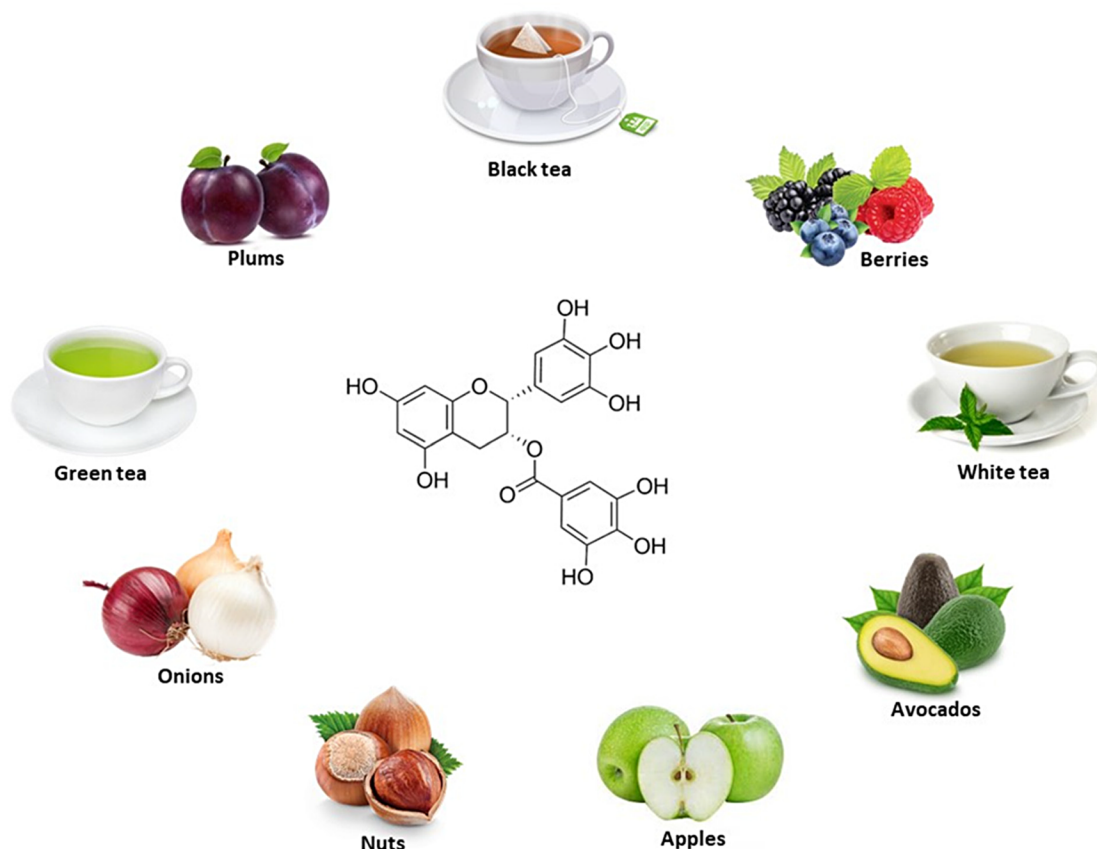


Figure 2. Natural sources of epigallocatechin gallate beverages such as black, white, and green teas, as well as fruits and vegetables such as berries, avocados, apples, nuts, plums, and onions.

microorganisms such as *Enterobacter aerogenes*, *Raoultella planticola*, *Klebsiella pneumoniae* subspecies (*subsp.*) *pneumoniae*, and *Bifidobacterium longum* subsp. *Infantis* (Takagaki and Nanjo 2010; Ma et al. 2021). Nevertheless, catechins are generally considered to be poorly absorbed across intestinal membranes with apparent permeability (Papp) values of 0.8 to 3.5×10^{-7} cm/s which are exceptionally low considering mannitol (the classic poorly permeable compound) ($6\text{--}10 \times 10^{-6}$ cm/s) as has been shown in in vitro studies (Stephens et al. 2002; Yang, Finaly, and Teitelbaum 2003; Zhang et al. 2004; Kadowaki et al. 2008).

Absorption and bioavailability profile of EGCG

Pharmacokinetic studies have reported that green tea catechins, and mainly EGCG, is predominantly absorbed in the jejunum and the ileum, via a paracellular diffusion through epithelial cells without any de-conjugation or hydrolysis (Zhang et al. 2004; Chow and Hakim 2011). However, others have reported on the identification of green tea metabolites in urine, bile and plasma. Indeed, it has already been established that tea catechins can be detected in plasma following ingestion of decaffeinated green tea extract ingestion containing 73 mg of EGCG per g of green tea extract. Results from this study showed that the catechins in human plasma reached peak levels in 1.5 to 2.5 h following 1.5 g ingestion of EGCG, with EGCG having an average peak plasma concentration of 0.71 μ M. Moreover, this study showed that EGCG had a terminal half-life of 4.9 to 5.5 h following oral administration of 1.5 to 4.5 g decaffeinated green tea extract (Yang, Liao, et al. 1998). Consistently, a single-dose administration of EGCG (800 mg) or Polyphenon E (a defined and decaffeinated green tea catechin extract that contains 80–98% total catechins with EGCG at 800 mg) showed a greater oral bioavailability when administered on an empty stomach after an overnight fast in healthy volunteers (Chow et al. 2005). Furthermore, a study by Zhang et al. (Zhang et al. 2004) investigated the absorption mechanism and disposition pathways of catechins from green tea using a Caco-2 cell model, which is a well-established in vitro system to test the intestinal absorption of drugs (Awortwe, Fasinu, and Rosenkranz 2014). In their findings, several metabolites of EGCG were found in the apical chambers during transport experiments and most of these were methylated, sulfated and methylated sulfate metabolites (Lee et al. 2002). Anyhow, clinical evidence on human subjects is very limited, with current findings mostly investigating the absorption profile of EGCG in rats. For example, it has been demonstrated that a single oral dose of 500 mg/kg body weight EGCG peaks at 565 nmol/g within intestinal mucosa, while in the plasma the concentrations can reach 12.3 nmol/mL in rats (Lee et al. 2002; Nakagawa and Miyazawa 1997a). Lambert et al. (Lambert et al. 2003) reported an oral bioavailability of less than 13% for EGCG in mice, while Chen et al. (Chen et al. 1997) demonstrated that this tea polyphenol was only available in less than 2% in the systemic blood of rats. Again, it has been reported that maximum concentration of EGCG can reach a

concentration of 1047 ng/ml (calculated as 0.012% of ingested EGCG) following a single oral supplementation of 56 mg EGCG in fasted rats, while a much lower value of approximately 156 ng/ml (calculated as 0.32% of ingested EGCG) was seen in human plasma after a single oral administration of 97 mg of EGCG, ultimately signifying low bioavailability (Nakagawa and Miyazawa 1997b). Moreover, Warden et al. (Warden et al. 2001) showed that plasma EGCG from black tea monitored increased in response to each successive dose of tea, reaching a plateau at between 5 and 8 h with peak levels of 145, 174 and 20.1 nmol/L, respectively, which returned to baseline levels by 24 h in human subjects. Although such evidence is acknowledged, the clinical data of the bioavailability of catechins in humans is very limited, with available information showing its bioavailability in humans remains low.

Metabolism profile of EGCG

Currently, available information indicates that EGCG can be bio-transformed by the intestinal microbiota, resulting in relative metabolites that offer biological activities (Guo et al. 2019). Moreover, EGCG can be methylated by the human liver enzymes, giving rise to 4'-OH and 4''-OH glucuronides (Okushio et al. 1999; Zhang et al. 2004; Lu, Meng, and Yang 2003). In fact, methylation and sulfation are considered the main biotransformation pathways of green tea catechins. It is suggested that 4',4''-di-O-methyl-EGCG was the main metabolite of EGCG in rats following intravenous administration (Kohri et al. 2001; Zwolak 2021), while available information also indicates that it can be converted into other metabolites such as 4''-O-methyl-EGCG and 4',4''-di-O-methyl-EGCG in the small intestine, colon, and liver of mice after an intragastrical administration of EGCG (Lambert et al. 2006). Similarly, after oral administration of EGCG (100 mg/rat), biliary metabolites of EGCG in both the free (4''-O-methyl-EGCG) and the conjugated forms (4''-O-methyl-EGCG; 3''-O-methyl-EGCG; 4'-O-methyl-EGCG; 3'-O-methyl-EGCG and 4',4''-O-methyl-EGCG) were determined (Kida et al. 2000; Dai et al. 2020). EGCG has been shown to have low bioavailability due to its oxidation, metabolism, and efflux (Kale et al. 2010). However, before its absorption, the gut microbiota is known to play a critical role in its metabolism. For example, EGCG was shown to be almost completely metabolized by the pig intestinal microbiota within just 4–8 h using a pig cecum model (van't Slot and Humpf 2009). The pathways of EGCG degradation through the gut microbiota involve extensive conversions including hydrolysis (Zhang et al. 2004). Takagaki and colleagues reported metabolic hydrolysis of EGCG by rat microbiota to EGC, which subsequently undergoes serial conversion and degradation, and 5-(3,5-dihydroxyphenyl)-4-hydroxyvaleric acid was found as the main metabolite of EGCG both in rat cecal contents and feces (Takagaki and Nanjo 2010). Nonetheless, different techniques such as molecular modification, co-administration of catechins with other bioactive compounds and nanostructure-based drug delivery systems are currently being explored to

advance our understanding of the absorption and metabolic biotransformation of tea catechins, including EGCG, as reviewed elsewhere (Cai et al. 2018).

Potential biological properties of EGCG

Polyphenolic compounds, especially EGCG are progressively explored in preclinical settings for their ameliorative properties against various metabolic complications (Wang, Provan, and Helliwell 2000; Grassi et al. 2013). Similarly, clinical research assessing the beneficial effects of tea on improving human well-being has increased over the past few years (McKay and Blumberg 2002; Chen and Lin 2015; Dlodla et al. 2021). Polyphenols, which are enriched in tea, are generally classified as secondary metabolites that remain crucial for defending plants against invading pathogens or attenuating the harmful effects of oxidative damage. Oxidative stress, together with inflammation are without a doubt the most destructive pathological mechanisms involved in the development of many diseases, including the metabolic syndrome (Fernández-García, Cardona, and Tinahones 2013). The latter categorizes a group of metabolic anomalies that may encompass obesity, dyslipidemia, and hypertension, that orchestrate the risk of developing T2D and CVDs (Grundy 2016). Thus, to contain complications linked with oxidative stress and inflammation, the use of polyphenols including EGCG have garnered significant interest due to their abundant antioxidant and anti-inflammatory properties (Hussain et al. 2016; Nani et al. 2021).

Antioxidant properties of EGCG

Briefly, EGCG is the most potent antioxidant catechin that plays a protective role against oxidative stress caused by an imbalance between free radical generation and antioxidant scavenging activity (He et al. 2018; Joonseo Bae et al. 2020). Several researchers have reported that EGCG is highly effective as a free-radical scavenger against the increased production of reactive oxygen species (ROS) including superoxide anion radicals and hydroxyl radicals, which can cause cellular damage by altering DNA, protein and lipids (Lambert and Elias 2010; He et al. 2018; Zwolak 2021). Uncontrolled production of ROS is mainly due to severely depleted intracellular antioxidant detoxifying systems, especially the reduced glutathione levels (Kwon et al. 2019). For instance, the protective effects of EGCG against retinal degeneration and hepatic oxidative damage are associated with increased total antioxidant capacity as reflected by the increased expression of intracellular antioxidants like catalase, superoxide dismutase and glutathione peroxidase, as well as inhibition of lipid peroxidation in preclinical models (Yang et al. 2016; Perdices et al. 2022). This suggests that the proposed health beneficial effects of EGCG may be attributed to its robust antioxidant activity. Fascinatingly, EGCG has the strongest radical scavenging activity than standard antioxidants such as resveratrol, ascorbic acid, tocopherol, and Trolox, and this could be strongly correlated with the number of hydroxyl and galloyl groups (Yang et al.

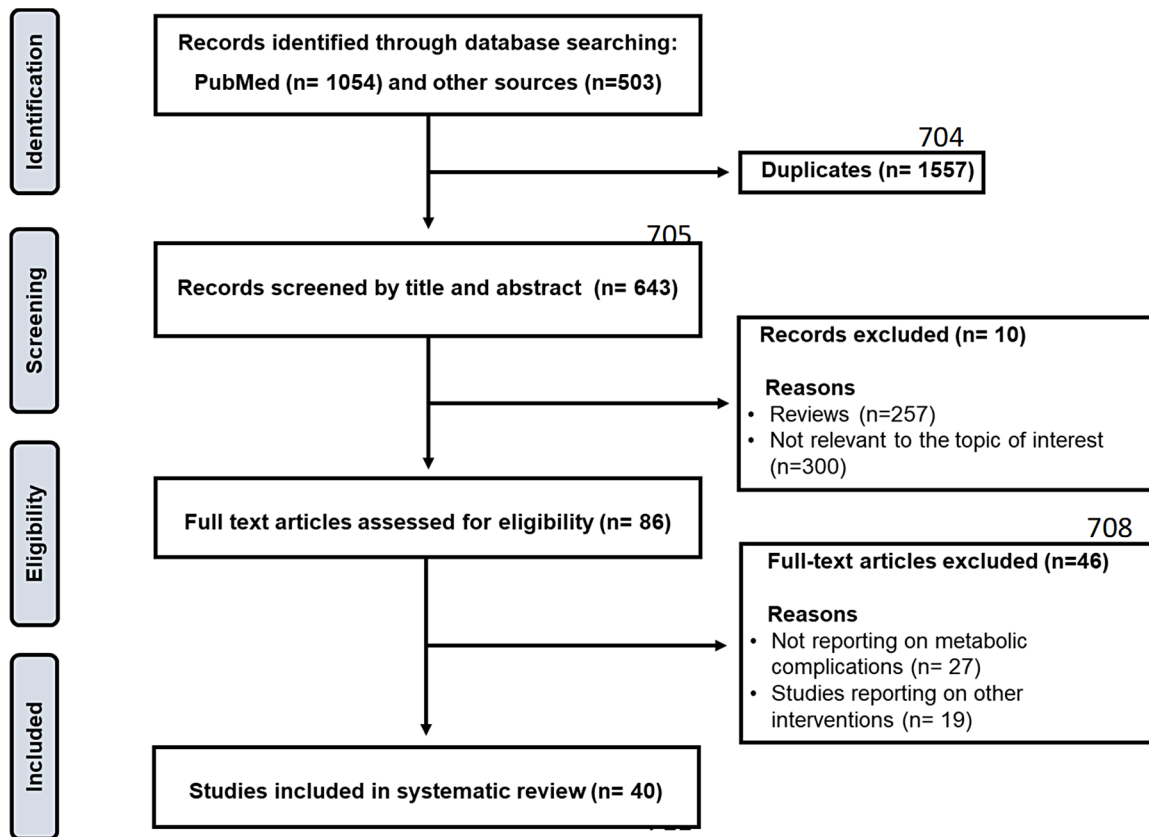
2016; Grzesik et al. 2018; Yamina Boulmouk et al. 2021; Perdices et al. 2022). Indeed, it has been reported that the effectiveness of antioxidants increases as the number of hydroxyl groups present in their aromatic ring(s) increases (Brewer 2011). Thus, the increased number of hydroxyl and galloyl moieties in EGCG structure may enhance its antioxidant activity by acting as electron traps and scavengers of free radicals (Kondo et al. 1999), which in turn inhibits ROS generation and reduce the adverse impact of oxidative stress (Tipoe et al. 2007).

Apart from its well-known antioxidant properties, EGCG displays pro-oxidant properties which could be either beneficial or harmful to human health, depending on certain biological contexts (Kim, Quon, and Kim 2014). Further, in factual physiological doses (1–10 μ M), EGCG can induce the small quantities of ROS production to serve as cell signaling molecules for normal biologic processes and cellular protective mechanisms (Hiroshi Nakagawa et al. 2004; Elbling et al. 2010). This action has been implicated in the anticancer and anti-obesity activity of EGCG (Kim, Quon, and Kim 2014). For anti-cancer activity, EGCG dose-dependently inhibits cell growth, and decreases cell viability mainly due to apoptosis caused by EGCG-induced intracellular ROS production (Yang, Chen, et al. 1998). In the context of obesity in preclinical models, the high doses of EGCG (50–400 μ M) reduce cell viability of preadipocytes, induce DNA fragmentation, and increase the apoptotic enzyme caspase-3 activity which, subsequently decreases preadipocyte proliferation and the fat cell numbers (Hung et al. 2005; Wang et al. 2009). On the contrary, the pro-oxidant effect of EGCG may have implications concerning potential toxicity. For example, a 200 μ M dose of EGCG was demonstrated to induce cytotoxic effects in cultured rat hepatocytes, suggesting a potential hepatotoxicity effect (Kucera et al. 2015). The chemiluminescence analysis of the prooxidant and antioxidant effects of EGCG has revealed the protective effect on DNA at low doses (2–30 mM) and DNA oxidative damage at higher doses (>60 mM) (Tian et al. 2007). This indicates the necessity of understanding the potential toxicity, doses, and usage of EGCG, as presumably the effective dose of EGCG might be close to or higher than the toxic dosage in practical applications, considering its low bioavailability. Hence, more studies should focus on finding the optimal dose at which EGCG could bring more health benefits with lower toxicity.

Anti-inflammatory properties of EGCG

The research into EGCG has been extended to its anti-inflammatory or immunoregulatory properties, which are closely linked with antioxidant properties (Sun et al. 2013). Many studies have registered that EGCG has a positive effect in the experimental models of inflammatory or autoimmune diseases such as arthritis, rhinitis, cancer, diabetes, and CVDs (Zheng, Toborek, and Hennig 2010; Ellis et al. 2011; Fu et al. 2017; Wu et al. 2017; Byun et al. 2018; Liang, Ip, and Mak 2019; Zheng). For example, Ellis et al. (Ellis et al. 2011) have reported that EGCG inhibits

a.)



b.)

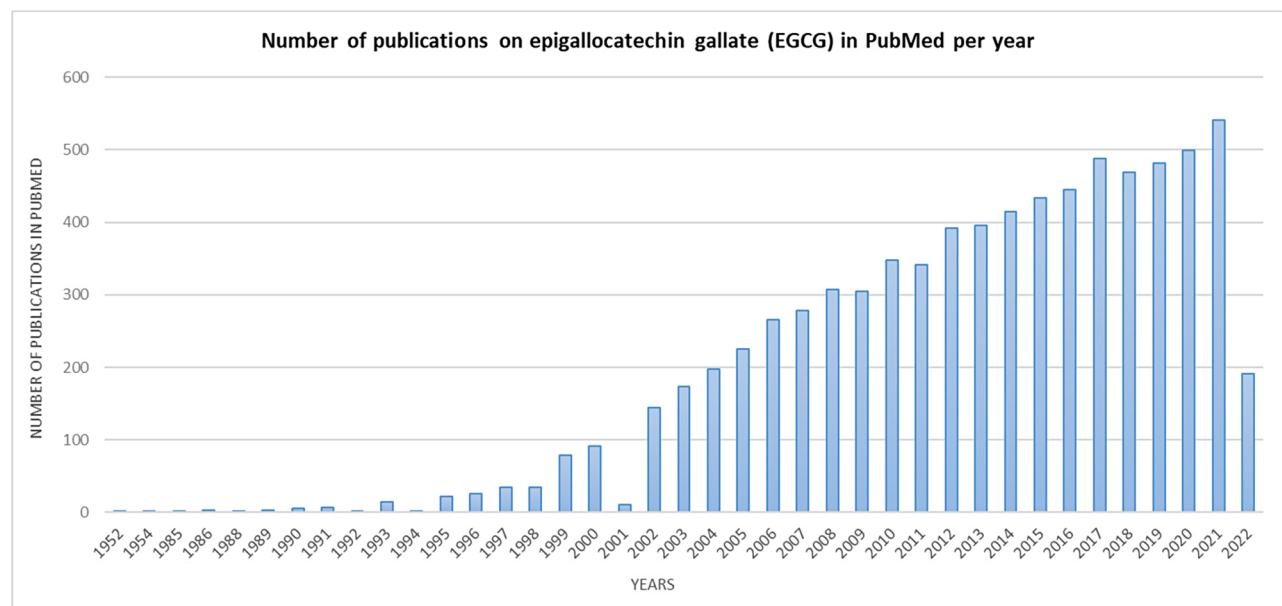


Figure 3. Diagrams representing (a) study inclusion criteria, and (b) the number of publications listed by PubMed per year using the combined search terms “epigallocatechin gallate” AND “tea”. Generally, over 1557 studies were screened for eligibility. However, only 40 studies were included and discussed in the current review, with most literature excluded because of not presenting clinical evidence or reporting on the topic of interest.

inflammasome and interleukin (IL)-1 β secretion to suppress the growth of melanoma, the deadliest type of skin cancer. In the context of CVDs. Interestingly, exacerbated increase of pro-inflammatory markers such as interleukin 1-beta

(IL-1 β), interleukin-6 (IL-6), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α) are implicated in the development of metabolic complications, which eventually increase the risk of developing CVDs (Fernández-Sánchez

et al. 2011; Mahlangu et al. 2020). Notably, EGCG suppresses cigarette smoke-induced inflammation in human cardiomyocytes by attenuating oxidative stress via ROS-mediated mitogen-activated protein kinase and nuclear factor kappa-light-chain-enhancer of activated B cells transcription factors pathways, whose activities are crucial in a multiplicity of downstream pro-inflammatory signaling pathways (Liang, Ip, and Mak 2019). In addition to the aforementioned mechanisms, there is a large body of evidence showing that EGCG inhibits various inflammatory enzymes and cytokines, including the inducible nitric oxide synthase (iNOS), matrix metalloproteinases (MMPs), cyclooxygenase 2 (COX2), chemokine (C-C motif) ligand 2 (CCL2), IL-6, IL- β , IFN- γ , TNF- α , and other mediators of inflammation (Oliviero et al. 2013; Wu et al. 2014; Fu et al. 2017; Reddy et al. 2020). This explains the important role of EGCG and its biological properties in maintaining human health.

An overview of clinical evidence on the impact of EGCG on obesity and related metabolic complications

General characteristics of included clinical studies

Generally, over 1557 studies were screened for eligibility. However, only 40 studies were included and discussed in the current review, with exclusions mainly due to studies presenting preclinical evidence or being out of scope. Figure 3a represents an overview of study inclusion. Briefly, a PubMed diagram shows a significant and gradual growth in the published literature on EGCG (Figure 3b). Interestingly, this publication growth coincides with the increased numbers suggesting a larger volume of tea consumption worldwide (Figure 3b). Consistently, most of the encompassed literature is from countries in Europe like The Netherlands and Spain, with some data from other countries like Iran, the United States, and Taiwan. Importantly, the below sections discuss clinical evidence on the impact of EGCG on diverse metabolic complications, including obesity, T2D, and CVD-related abnormalities. Critical points discussed include variation in dose, treatment duration and study population.

Effects of EGCG supplementation in overweight and obese subjects

Table 1 gives an overview of clinical studies assessing the beneficial effects of EGCG in overweight or obese subjects. Here, it was clear that predominantly summarized studies assessed the beneficial effects of this polyphenol over a treatment period extending for at least 3 months. Kovacs et al. (Kovacs et al. 2004) showed that a green tea extract containing EGCG at 323 mg and caffeine at 104 mg daily for 3 months could not affect weight gain in moderately obese subjects. Also affirming the limited benefits of this tea polyphenol, Mielgo-Ayuso et al. (Mielgo-Ayuso et al. 2014) showed that EGCG at 300 mg daily for 3 months did not affect body weight, fat mass, energy, and fat metabolism, as well as other metabolic parameters such as total

cholesterol, low density-lipoprotein (LDL)-cholesterol, triglycerides, and liver function markers in obese pre-menopausal women. Likewise, Dostal et al. 2017 showed that green tea extract containing EGCG at 843 mg for 12 months did not affect post-prandial responses of leptin, ghrelin, adiponectin, and satiety in overweight and obese postmenopausal women. Interestingly, from the results of the aforementioned three clinical studies (Kovacs et al. 2004; Mielgo-Ayuso et al. 2014; Dostal et al. 2017), different factors such as the dose of EGCG used could affect its bioactive properties. For example, in Dostal et al. 2017, higher EGCG doses of 843 mg (in comparison to an average dose $\leq$ 400 mg) over an extended period of 12 months (in comparison to an average of 3 months) might be less protective. Certainly, beyond the dosage of the compound used, other factors such as the age of the population, gender, and the severity of disease may affect the therapeutic effect of any given drug, as reviewed elsewhere (Soldin and Mattison 2009; Alomar 2014). Nonetheless, overwhelming summarized evidence in the current review favored the beneficial effect of EGCG when supplemented for 3 months (Table 1).

For example, Westerterp-Plantenga and colleagues demonstrated that a green tea-caffeine mixture, at 270 mg EGCG + 150 mg caffeine daily for 3 months, could effectively reduce body weight, waist circumference, respiratory quotient and body fat, while increasing resting energy expenditure in overweight and moderately obese subjects (Westerterp-Plantenga, Lejeune, and Kovacs 2005). Interestingly, others supported these beneficial effects of 3-month supplementation with EGCG (Bajerska, Mildner-Szkudlarz, and Walkowiak 2015; Chen et al. 2016), showing this tea polyphenol at different doses, could promote weight loss, lower blood pressure, and reduce total or LDL-cholesterol levels without any side effects in overweight and obese subjects. Potentially elaborating on the therapeutic mechanisms of this polyphenolic compound, Suliburska and colleagues indicated that supplementation with green tea extract containing EGCG at 379 mg or 208 mg daily for 3 months could reduce body mass index and waist circumference by decreasing serum levels of total cholesterol, LDL cholesterol, and triglyceride (Suliburska et al. 2012). And these positive effects were related while enhancing total antioxidant levels, and serum high-density lipoprotein (HDL) concentrations in obese subjects. To highlight the potential combination or synergistic effects of EGCG with other polyphenolic compounds in overweight and obese subjects, Most and coworkers demonstrated that supplementation with EGCG at 282 mg and resveratrol at 80 mg daily for 3 months could reduce the expression of pathways related to energy metabolism, oxidative stress, inflammation, and immune defense, while blocking cell cycle and apoptosis (Most et al. 2018). A similar research group (Most et al. 2016) went further to show that the combination of EGCG at 282 mg and resveratrol at 80 mg daily for 3 months could reduce bacteroidetes and decrease *Faecalibacterium prausnitzii* in overweight and obese subjects, while also illustrating that baseline bacteroidetes abundance was predictive for the combination treatment-induced increase in fat oxidation in men but not in women. Consistently, it was showed that

Table 1. Clinical studies on epigallocatechin gallate (EGCG) and its impact on metabolic complications linked with overweight and obesity.

Author, year	Country	Patients, average age	Dose, intervention period	Outcome
Long-term effects of EGCG (treatment duration equivalent to ≥ 3 months)				
Kovacs et al. (2004)	The Netherlands	Overweight and moderately obese subjects (n = 104), with an age between 18–60 years	Received green tea extracts tablets containing EGCG at 323 mg and caffeine at 104 mg daily for 3 months	Did not significantly affect weight gain in subjects on a very-low-energy diet intervention. However, habitual high caffeine consumption was associated with a higher weight regain compared with habitual low caffeine consumption
Westerterp-Plantenga, Lejeune, and Kovacs (2005)	The Netherlands	Overweight and moderately obese subjects (n = 38), with an age between 18 to 60 years	Received a green tea-caffeine mixture (270 mg EGCG + 150 mg caffeine per day) for 3 months	Reduced body weight, waist, respiratory quotient and body fat, while increasing resting energy expenditure
Hill et al. (2007)	Australia	Obese postmenopausal women exercised at moderate intensity (n = 19), with an age between 45–70 years	Received a tablet of EGCG at 150 mg/twice daily (300 mg daily) for 3 months	Reduced waist circumference, total body fat, abdominal fat and intra-abdominal adipose tissue, also reduced heart rate and plasma glucose concentrations
Hursel and Westerterp-Plantenga (2009)	The Netherlands	Overweight and moderately obese subjects (n = 80), with an average age of 44 years	Received green tea-caffeine mixture (270 mg EGCG + 150 mg caffeine) daily in addition to an adequate protein diet for 3 months	Promoted resting energy expenditure, and fat-free mass, whereas respiratory quotient and body fat mass decreased
Suliburska et al. (2012)	Poland	Obese subjects (n = 23), with an average age of 48 years	Received one tablet of green tea at 379 mg or EGCG at and 208 mg daily, for 3 months	Reduced body mass index, waist circumference, and levels of total cholesterol, LDL-cholesterol, and triglyceride, while enhancing total antioxidant level, HDL-cholesterol, and zinc concentration in serum
Mielgo-Ayuso et al. (2014)	Spain	Obese pre-menopausal women (n = 43), with an age between 19–49 years	Received a tablet of EGCG at 300 mg daily for 3 months	Did not affect body weight, fat mass, energy and fat metabolism, homeostasis assessment model for insulin resistance, total cholesterol, LDL-cholesterol, triglycerides, and liver function markers
Bajerska, Mildner-Szkudlarczyk, and Walkowiak (2015)	Poland	Obese subjects (n = 23), with an average age of 53 years	Received 280 and 360 g green tea extract enriched rye bread, providing daily totals of 123.2 and 158.4 mg caffeine, and 188.3 and 242.1 mg of EGCG, respectively, for 3 months	Reduced blood pressure, however, did not influence the maintenance of weight loss, HDL-cholesterol levels, triglycerides levels, and glucose concentrations
Chen et al. (2016)	Taiwan	Women (n = 39) with central obesity, with an average age of 44 years	Received a tablet of EGCG at 856.8 mg daily for 3 months	Promoted weight loss, reduced waist circumference, and a consistent decrease in total cholesterol and LDL-cholesterol plasma levels without any side effects
Dostal et al. (2016)	United States	Overweight and obese postmenopausal women (n = 76), with an age between 50–70 years	Received green tea extract containing EGCG at 843 mg daily for 12 months	Did not affect adiposity or improve bone mineral density
Most et al. (2016)	The Netherlands	Overweight and obese subjects (n = 38), with an average age of 38 years	Received a tablet of EGCG at 282 mg + resveratrol at 80 mg day for 3 months	Reduced plasma triglycerides concentrations, however, did not significantly affect plasma metabolic profile, whole-body fat mass or energy expenditure
Dostal et al. (2017)	United States	Overweight and obese post-menopausal women (n = 30), with an average age of 61 years	Received green tea extract containing EGCG at 843 mg for 12 months	Did not affect post-prandial responses of leptin, ghrelin, adiponectin, and satiety, though it may be involved in the post-meal insulinemic response
Most et al. (2017)	The Netherlands	Overweight and obese subjects (n = 18), with an average age of 38 years	Received a combination of EGCG at 282 and resveratrol at 80 mg daily for 3 months	Reduced bacteroidetes and tended to decrease <i>Faecalibacterium prausnitzii</i> in men but not in women. Moreover, baseline Bacteroidetes abundance was predictive for the combination treatment-induced increase in fat oxidation in men but not in women
Most et al. (2018)	The Netherlands	Overweight and obese subjects (n = 11), with an average age of 36 years	Received a tablet of EGCG at 282 mg and resveratrol at 80 mg daily for 3 months	Reduced the expression of pathways related to energy metabolism, oxidative stress, inflammation, and immune defense. Also, blocking cell cycle and apoptosis

Table 1. (Continued).

Author, year	Country	Patients, average age	Dose, intervention period	Outcome
Short-term effects of EGCG (treatment duration equivalent to < 3 months)				
Boschmann and Thielecke (2007)	Germany	Overweight men (n = 6), with an average age of 40 years	Received a tablet of EGCG at 300 mg daily for 2 days	Did not significantly affect energy expenditure, measured using the respiratory quotient
Brown et al. (2009)	United Kingdom	Overweight or obese male subjects (n = 46), with an age between 40–65 years	Received a table of EGCG at 400 mg for 2 months	Reduced diastolic blood pressure, but did not affect insulin sensitivity, insulin secretion or glucose tolerance
Basu et al. (2010)	United States	Subjects with obesity and metabolic syndrome (23), with an average age of 41 years	Received green tea (4 cups/day), or green tea extract (2 capsules and 4 cups water/day) containing 440 and 460 mg of EGCG, respectively, for 2 months	Both treatments reduced body weight and body mass index. Green tea beverages showed a decreasing trend in LDL-cholesterol and LDL/ HDL-cholesterol ratio versus controls. Green tea beverage also significantly decreased malondialdehyde (MDA) and hydroxynonenals (HNE) levels
Thielecke et al. (2010)	Switzerland	Obese subjects (n = 10), with an average age of 34 years	Received a tablet of EGCG at 300 mg or 600 mg daily for 3 days	A low dose of EGCG was most effective in promoting postprandial fat oxidation in obese men
Brown et al. (2011)	United Kingdom	Overweight and obese subjects (n = 63), with an average age of 50 years	Received a tablet of decaffeinated green tea extract at 530 mg, containing EGCG (40%), twice daily for 6 weeks	Reduced body weight and promoted energy intake, but did not blood pressure or biomarkers of metabolic function
Mangine et al. (2012)	United States	Overweight subjects (n = 25), with an average age of 32 years	Received a mixture of <i>N</i> -oleylphosphatidylethanolamine (120 mg) and EGCG (105 mg) for 2 months	Did not affect body mass; body composition, feelings of hunger, and binge eating
Most et al. (2014)	The Netherlands	Overweight subjects (n = 6), with an age between 20–50 years	Received a tablet of EGCG at 282 mg + resveratrol at 200 mg per day for 3 days	Combined treatment was effective in improving metabolic flexibility, as well as increasing fasting and postprandial energy expenditure
Cazzola and Rondonelli (2020)	Italy	Overweight and class I obese subjects (n = 71), with an average age of 38 years	Received an oily dispersion of EGCG (50 mg) complexed with <i>N</i> -oleylphosphatidylethanolamine (14 mg) for 2 months	In combination with moderate energy restriction, this mixture reduced body weight, including oxidized levels of LDL and enhanced antioxidant capacity
Chatree et al. (2021)	Thailand	Obese subjects (n = 15), with an average age ≥ 18 years	Received a tablet of EGCG at a 150 mg twice a day for 2 months	Reduced fasting plasma triglycerides, decreased systolic blood pressure, diastolic blood pressure, and serum kisspeptin levels. However, did not affect body weight, body mass index, waist circumference, and hip circumferences, nor total body fat mass

consumption of green tea extract enriched rye bread, providing daily totals of 123.2 and 158.4 mg caffeine, and 188.3 and 242.1 mg of EGCG for 3 months, could effectively reduce blood pressure in obese subjects, and this was independent of affecting body weight or serum cholesterol levels (Bajerska, Mildner-Szkudlarz, and Walkowiak 2015). Importantly, such information opens avenues to further clarify whether the combination use of EGCG or its green tea extracts with other bioactive compounds presents an even better efficacy than using it as a monotherapy. However, this aspect needs further investigation since it has already been established that EGCG can block the pharmacokinetics of irinotecan and its metabolite SN-38 in rats (Lin, Wang, and Tsai 2008), which might suggest it potentially interacts with other drugs to limit their efficacy through food-drug interaction.

Table 1 also presents evidence on the short term (treatment duration < 3 months) effects of EGCG supplementation in overweight and obese subjects. In fact, consistent with evidence reporting on the long-term therapeutic effects ($\geq$ 3 months) of EGCG, a few studies (Boschmann and Thielecke 2007; Mangine et al. 2012) showed this tea polyphenol presents with limited activity in reducing body weight or promoting energy expenditure in overweight subjects. With some evidence (Brown et al. 2011; Chatree et al. 2021) indicating that EGCG supplementation may be beneficial in reducing blood pressure overweight in obese subjects, independently of its antiobesity properties. Anyhow, most studies (Chatree et al. 2021) demonstrated that EGCG supplementation, at doses between 150–440 mg daily for < 3 months, is beneficial in decreasing fasting plasma triglycerides, blood pressure in overweight and obese subjects. Whereas both green tea (4 cups/day), or green tea extract (2 capsules and 4 cups water/day) containing 440 and 460 mg of EGCG, respectively, for 2 months could also effectively reduce body weight, body mass index in obese subjects (Basu et al. 2010). With green tea beverage significantly decreasing circulating levels of malondialdehyde (MDA) and hydroxynonenals (HNE) to limit peroxidation in these subjects.

To affirm that the dosage of EGCG might influence its therapeutic effects, Thielecke and coworkers indicated that supplementation with this tea polyphenolic at 300 mg daily for 3 days is more effective (in comparison to 600 mg) in promoting postprandial fat oxidation in obese men (Thielecke et al. 2010). With Most and colleagues (Most et al. 2014) confirming that even used for a short duration (3 days), combination use of EGCG at 282 mg and resveratrol at 200 mg is effective in improving metabolic flexibility, as well as increasing fasting and postprandial energy expenditure in overweight subjects. Notably, because EGCG is considered to have poor absorption, is it likely that its lipid-lowering effect is mediated largely via their influence on the intestinal processes involved in the digestion and absorption of energy compounds. In vitro studies have indicated that the postprandial glucose-suppression effect of green tea may be initiated by its inhibitory effects against gastrointestinal digestive enzymes, which are particularly related to starch digestion, such as α -amylase and α -glucosidase (Huang et al. 2014). Especially, due to the extraordinary nature of human clinical trials, most mechanistic evidence

of the anti-obesity effects of EGCG are mostly plausible, theoretically speculated and or indirectly determined/correlated based on in vitro and in vivo studies. For example, EGCG induced a decrease in phosphorylated extracellular regulated kinase 1/2 in 3T3-L1 preadipocytes (Hung et al. 2005). Additionally, within the same in vitro preclinical model, EGCG could decrease fat accumulation by modulating transcriptional activity of Forkhead transcription factor class O-1, which specially affects adipocyte differentiation via insulin signaling and sterol regulatory element-binding proteins. Such hypothesis is confirmed by Cazzola and Rondanelli (Cazzola and Rondanelli 2020), reporting that supplementation with EGCG (50 mg) complexed with N-oleoyl-phosphatidylethanolamine (14 mg) for 2 months could reduce body weight, including decreasing the levels of oxidized-LDL while increasing antioxidant capacity in overweight and obese subjects. Overall, these results indicate that supplementation with EGCG or its green tea extracts, including its combination use with some other bioactive compounds like resveratrol, potentially reduce body weight or fat mass to improve blood pressure (Figure 4). Interestingly, this is consistent with blocking lipid peroxidation and increasing intracellular antioxidant response in overweight and obese subjects.

Effects of EGCG supplementation in subjects with T2D, CVD and other metabolic complications

Table 2 provides an overview of the clinical studies assessing the beneficial effects of EGCG against diverse metabolic complications linked with T2D and CVDs. Consistent with evidence in Table 1, most of these studies reported on the beneficial effects of EGCG during both short- and long-term treatment, extending for less or more than 3-month duration, respectively. In fact, Hsu et al. (Hsu et al. 2010) showed that administration of a very high dose of EGCG, at 856 mg for 4 months, was effective at reducing waist circumference, glycated hemoglobin (HbA1c), homeostasis model assessment for insulin resistance (HOMA-IR), and insulin level in adult patients with T2D. Such evidence is also confirmed by others (Borges et al. 2016; Zhang et al. 2017; Benlloch et al. 2020), indicating that long-term administration of EGCG (> 3 months), at doses between for 500–800 mg, is effective at controlling glucose metabolism and reducing fat mass, while improving neonatal symptoms at birth, including birth weight and, macrosomia, and ameliorating hypoglycemia in patients with T2D or related metabolic abnormalities. Notably, these are the predominant markers of T2D that are consistent with the development of other metabolic complications, including CVDs (Stolar 2010; Ceriello et al. 2022). Correspondingly, de la Rubia Ortí and colleagues showed that supplementation with EGCG at 400 mg twice a day (for a total dose of 800 mg/day) for 4 months could reduce plasma levels of IL-6 and fat percentage while increasing butyrylcholinesterase enzyme and paraoxonase 1 in patients with multiple sclerosis (de la Rubia Ortí et al. 2021). Interestingly, enhanced circulating levels of IL-6, butyrylcholinesterase enzyme, and paraoxonase 1, usually occurring

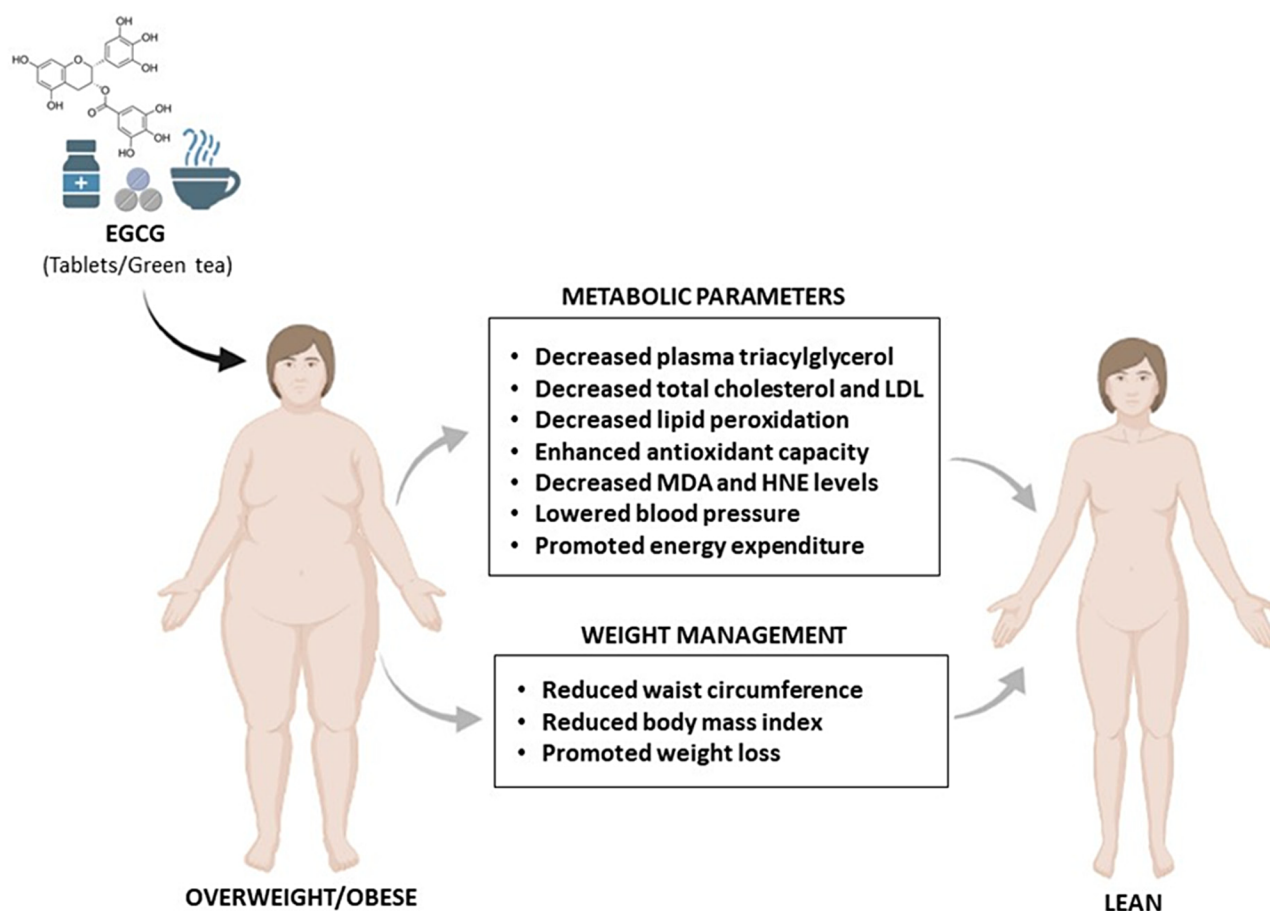


Figure 4. Proposed therapeutic effects of Epigallocatechin gallate (EGCG) in overweight and obese subjects. LDL: low-density lipoprotein, MDA: malondialdehyde, HNE: hydroxynonenals.

consistent with a state of impaired glucose metabolism remain the major determinants of CVD, especially the development of atherosclerotic vascular complications, as reported elsewhere (de la Rubia Ortí et al. 2021; Ndevahoma et al. 2021; Ngcobo et al. 2022).

Summarized evidence further indicated that even during short-term treatment (≤ 3 months), EGCG affects glucose metabolism and attenuate complications linked with atherosclerosis and CVD. For example, Widlansky et al. (Widlansky et al. 2007) showed that supplementation with EGCG at 150 mg twice daily for 2 weeks could improve endothelial function, by positively affecting brachial artery flow-mediated dilation and vascular function in patients with coronary artery disease. Further elucidating the potential cardioprotective mechanisms of EGCG, Huang et al. (Huang et al. 2013) showed that supplementation with a green tea extract providing a daily dose of 300-900 mg EGCG for 2 months could stimulate soluble receptor for advanced glycation of end products (sRAGE) circulation but inhibited RAGE ligand in patients with T2D. Tosco et al. (Tosco et al. 2016, 2017) showed that EGCG supplementation at 270 mg daily for 1 month could increase both cystic fibrosis transmembrane conductance regulator protein and function while restoring autophagy in nasal cells, and this was concomitant to decreasing the levels of chemokine (C-X-C motif) ligand 8 (CXCL8) and TNF- α in the sputum of patients with cystic fibrosis. In fact, beyond effectively reducing some

pro-inflammatory markers such as CXCL8 and TNF- α , evidence from others (Bazyar et al. 2021) indicated that administration of EGCG at 300-500 mg daily for 7 days to 2 months could improve lipid profiles especially the serum levels of triglyceride and total cholesterol, while also lowering diastolic blood pressure, plasma atherogenic index, and mean arterial pressure, by mainly increasing total antioxidant capacity in patients with T2D. These effects were related to reduced plasma levels of both matrix metalloproteinases 2/9 and delayed onset-to-treatment time strata, as evidenced by improved National Institutes of Health stroke scale scores in patients with T2D and acute ischemic stroke (Wang and You 2017).

Although such beneficial effects of EGCG or green tea extracts rich in this polyphenol against complications linked with T2D or CVD were acknowledged, some evidence could not see any positive effects. For example, Basu et al. (Basu et al. 2011) reported that supplementation with EGCG at 110 mg for 2 months could reduce plasma serum amyloid alpha, however, did not significantly affect features of metabolic syndrome or biomarkers of inflammation including adiponectin, C-reactive protein, IL-6, IL-1 β , soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1, and leptin in subjects with metabolic syndrome. While Arazi et al. (Arazi et al. 2014) reported that supplementation with green tea extract containing approximately 75 mg EGCG two times a day for 3 weeks did not affect

Table 2. Clinical studies on epigallocatechin gallate (EGCG) and its impact on diverse complications linked to type 2 diabetes and cardiovascular disease.

Author, year	Country	Patients, average age	Dose, intervention period	Outcomes
Long-term effects of EGCG (treatment duration equivalent to ≥ 3 months)				
Hsu et al. (2010)	Taiwan	Patients (n = 68) with type 2 diabetes (T2D), with an age between 20-65 years	Received green tea extract providing a daily dose of 856 mg of EGCG for 4 months	Reduced waist circumference, glycated hemoglobin (HbA1c), homeostasis model assessment for insulin resistance (HOMA-IR), and insulin level. Also, increased ghrelin levels
De la Torre et al. (2014)	Spain	Patients with Down syndrome (n = 13), with an age between 14 to 29 years	Received tablet of EGCG at 9 mg/kg/day for 3 months	Reversed cognitive deficits in individuals with effects on memory recognition, working memory, and quality of life
aus dem Siepen et al. (2015)	Germany	Patients with wild-type transthyretin amyloidosis (n = 9), with an average age of 72 years	Received green tea extract containing EGCG at 600 mg daily for 12 months	Reduced left ventricular myocardial mass, but did not significantly affect left ventricular ejection fraction
Borges et al. (2016)	Brazil	Patients with type 1 (n = 4) or 2 (n = 17) diabetes (T1D/T2D), with an average age of 63 years	Received green tea polyphenols containing EGCG at 800 mg daily for 3 months	Reduced albuminuria, as measured using urinary albumin-creatinine
Zhang et al. (2017)	China	Patients with gestational diabetes mellitus (n = 176) (at the beginning of the third trimester), with an age between 25-34 years	Received a tablet containing EGCG at 500 mg daily, until full-term pregnancy	Improved glucose metabolism and insulin levels, as well as neonatal symptoms at birth, including birth weight, macrosomia, hypoglycemia, respiratory distress, and Apgar scores
Benlloch et al. (2020)	Spain	Patients with metabolic syndrome (n = 27), with an average age of 44 years	Received EGCG at 800 mg, together with 60 ml of coconut oil for 4 months	Reduced cardiac risk associated with a significant decline in waist-to-hip ratio and reduced fat mass, as well as a significant increase in muscle percentage. However, there was an increase in levels of beta-hydroxybutyrate, albumin and paraoxonase 1
de la Torre et al. (2020)	Spain	Subjects with Fragile-X syndrome (n = 27), with an age between 18-55 years	Received a tablet of EGCG at 5-7 mg/kg/day, combined with cognitive training for 3 months	Displayed improved cognition (visual episodic memory) and functional competence (ABAS II-Home Living skills) in everyday life compared to subjects receiving a placebo
Xicota et al. (2020)	Spain	Individuals with Down syndrome (n = 77), with an average age of 23 years	Received a tablet of EGCG at administered at 400, 600, or 800 mg depending on body weight, daily for 12 months	Displayed a modest beneficial effect on weight management. Furthermore, EGCG also has a sex-dependent effect (for males) on lipid profiles that are related to changes in body mass and composition
de la Rubia Orti et al. (2021)	Spain	Patients with multiple sclerosis (n = 27), with an average age ≥ 18 years	Received a tablet of EGCG at 400 mg twice daily (total dose of 800 mg/day) and 60 mL of coconut oil for 4 months	Reduced plasma levels of IL-6 and body fat percentage, while increasing butyrylcholinesterase enzyme, beta-hydroxybutyrate, paraoxonase 1, albumin, and the functional capacity (determined by the Expanded Disability Status Scale)
Short-term effects of EGCG (treatment duration equivalent to < 3 months)				
Widlansky et al. (2007)	United States	Patients with coronary artery disease (n = 21), with an average of 59 years	Received a tablet of EGCG at 150 mg twice daily, for 2 weeks	Improved endothelial function, by positively affecting brachial artery flow-mediated dilation and vascular function
Basu et al. (2011)	United States	Subjects with metabolic syndrome (n = 10), with an average age of 40 years	Received green tea extract containing EGCG at 110 mg for 2 months	Reduced plasma serum amyloid alpha, however, did not significantly affect features of metabolic syndrome or biomarkers of inflammation including adiponectin, C-reactive protein, IL-6, IL-1 β , soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1, leptin, or leptin: adiponectin ratio
Huang et al. (2013)	Taiwan	Patients with T2D, with an average age of 59 years	Received green tea extract providing a daily dose of 300-900 mg of EGCG for 2 months	Stimulated soluble receptor for advanced glycation of end products (sRAGE) circulation but inhibited RAGE ligand in T2D, and ADAM10 (a disintegrin and metalloprotease)-mediated ectodomain shedding of extracellular RAGE was mainly involved in EGCG-stimulated sRAGE circulation

Table 2. (Continued).

Author, year	Country	Patients, average age	Dose, intervention period	Outcomes
Arazi et al. (2014)	Iran	Women with hypertension (n = 16), with an average age of 46 years	Received a green tea extract containing ~75 mg EGCG for twice a day for three weeks	Did not affect systolic blood pressure, diastolic blood pressure and heart rate but may have a favorable effect on mean arterial pressure and rate pressure product responses to an acute resistance exercise during an hour recovery from exercise
Tosco et al. (2016)	Italy	Patients (n = 8) with cystic fibrosis, with an average age of ≥ 6 years	Received cysteamine at 900 mg (<12 years) or 1200 mg (>12 years) in four doses. EGCG was received at 270 mg daily for 1 month	Increased both cystic fibrosis transmembrane conductance regulator protein and function in nasal cells, restored autophagy in such cells, decreased CXCL8 and tumor necrosis factor alpha (TNF- α) in the sputum, and tended to improve respiratory function
Wang and You (2017)	China	Patients with acute ischemic stroke (n = 185), with an average age of 45 years	Received continuous administration of EGCG at 500 mg daily dose for 7 days	Improved treatment outcomes of patients in the delayed onset-to-treatment time strata, as evidenced by improved National Institutes of Health stroke scale scores. Also, reduced plasma levels of both matrix metalloproteinases 2/9
Bazyar et al. (2021)	Iran	Patients with T2D (n = 50), with an average age of 51 years	Received a tablet of EGCG at 300 mg daily for 2 months	Reduced the serum levels of triglyceride, and total cholesterol, decreased diastolic blood pressure, atherogenic index of plasma, and mean arterial pressure. Also, enhanced total antioxidant capacity

systolic blood pressure, diastolic blood pressure and heart rate in women with hypertension. Perhaps this indicates that in addition to variation in the dose or treatment duration many factors including disease severity may limit the beneficial effects of drug treatment (Lim et al. 2022). However, this hypothesis must be confirmed in other well-designed clinical trials.

Nonetheless, the evidence summarized in the current review also indicates that besides its efficacy in managing complications linked with T2D or CVDs, EGCG supplementation could affect other chronic diseases, including patients with Down syndrome. De la Torre and colleagues showed that supplementation with EGCG at 9 mg/kg/day for 3 months could reverse cognitive deficits in individuals with effects on memory recognition, working memory, and quality of life in patients with Down syndrome (De la Torre et al. 2014). The same research group showed that exposure to EGCG at 5–7 mg/kg/day, combined with cognitive training for 3 months, could improve cognition (visual episodic memory) and functional competence (ABAS II-Home Living skills) in everyday life in subjects with Fragile-X syndrome. These data are confirmed by Xicota et al. (2020) indicating that supplementation with EGCG at 400, 600, or 800 mg depending on body weight, daily for 12 months, displayed a modest beneficial effect on weight management, and this was linked with sex-dependent effect (for males) on lipid profile in patients with Down syndrome. Alternatively, other researchers (Kristen et al. 2012; aus dem Siepen et al. 2015) have showed that administration of green tea extract containing EGCG at 600 mg daily for 12 months could reduce left ventricular myocardial mass, albeit not significantly affect left ventricular ejection fraction in patients with wild-type transthyretin amyloidosis. Overall, these data suggest that EGCG or green tea extracts containing this polyphenol potentially induce favorable outcomes by limiting body fat mass and enhancing total antioxidant capacity, especially in combination with interventions like regular exercise, leading to improved outcomes with other major defects involving cognitive function or related chronic diseases (Figure 5).

Potential mechanistic insights into the therapeutic effects of EGCG

Currently, it is acknowledged that various cell lines have been used to investigate the potential modulatory effects of EGCG against metabolic diseases. For example, in various preclinical models of metabolic syndrome, it was evident that EGCG exposure exhibits a broad range of therapeutic properties, mostly affecting insulin signaling mechanisms such as the phosphorylation of insulin receptor substrate-1 via activating AMP-activated protein kinase (AMPK) pathway, to improve metabolic function (Eng, Thanikachalam, and Ramamurthy 2018). Also, affirming the anti-diabetic activity of EGCG, others have showed that EGCG could enhance glycogen synthesis to inhibit lipogenesis in cultured liver (HepG2) or endothelial cells (Kim et al. 2013; Zhang, Zhang, and Liang 2016).

Furthermore, treatment of Wistar rats with 1% EGCG for 4 weeks could reduce plasma lipid profiles such as total cholesterol, triglycerides, and LDL in conditions of high fat diet feeding (Raederstorff et al. 2003). With evidence from this paper further suggesting that EGCG may interfere with the micellar solubilization of cholesterol in the digestive tract, which then in turn reduces cholesterol absorption. Relevant to the potential cardioprotective effects, EGCG protected cardiomyocytes (H9c2 cells) that were exposed to hypoxia/reoxygenation injury by activating survival pathways such as protein kinase 3/protein kinase B pathway, while also down-regulating pro-inflammatory markers like TNF-, and IL-6 (Zeng and Tan 2015). Likewise, others showed that EGCG was able to display anti-inflammatory effects by suppressing nuclear factor kappa B (NF- κ B) target genes such as IL-6, C-reactive protein, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in polychlorinated biphenyl-induced human endothelial cells (Liu, Perkins, and Hennig 2016; Liu, Perkins, and Hennig 2016). Whereas Yin and colleagues proposed that EGCG can protect against oxidized-LDL-induced atherosclerosis in cultured endothelial (HUVECs) cells, in part through modulating the Jagged-1/Notch pathway (Yin et al. 2016). Further indicating its potential therapeutic properties that are consistent with some clinical data.

Potential use of EGCG as a nutraceutical or dietary supplement

The nutraceutical benefits of green tea catechins are widely obtained via tea infusions, however, consumption of 800 to 1400 L/day (4–7 cups of green tea a day) is required to acquire the expected health benefits of catechins (Kuriyama et al. 2006; Pang et al. 2016; de Oliveira 2012). As the most abundant and most bioactive catechin in green tea, studies to explore the potential development of EGCG as a therapeutic agent for the treatment and prevention of various diseases have attracted considerable attention in the last two decades (Gan et al. 2018; Negri et al. 2018; Singh, Shankar, and Srivastava 2011; Steinmann et al. 2013; Kim, Quon, and Kim 2014; Chu et al. 2017; Cione et al. 2019; Pervin et al. 2019; Almatroodi et al. 2020). Owing to its poor bioavailability after oral administration, the potential to develop EGCG as a therapeutic drug is currently very limited (Cai et al. 2018). Hence, the consumption of green tea extracts (rich in EGCG) as a dietary supplement in food products such as ready-to-drink tea beverages, juice, dairy products, bread, cake, biscuits, or cereal bars with added nutraceutical value has become more popular among the consumers worldwide (Wang and Zhou 2004; Lu et al. 2010; Sharma and Zhou 2011; Hinojosa-Nogueira et al. 2021; Cerbin-Koczorowska et al. 2021). Food additives such as ascorbic acid and sucrose were formulated with green tea extracts and these formulations were shown to increase the intestinal transport of catechins such as EGCG, suggesting that the common practice of co-formulating ready-to-drink green tea beverages with sucrose and ascorbic acid may enhance the bioavailability of catechins (Green et al. 2007;

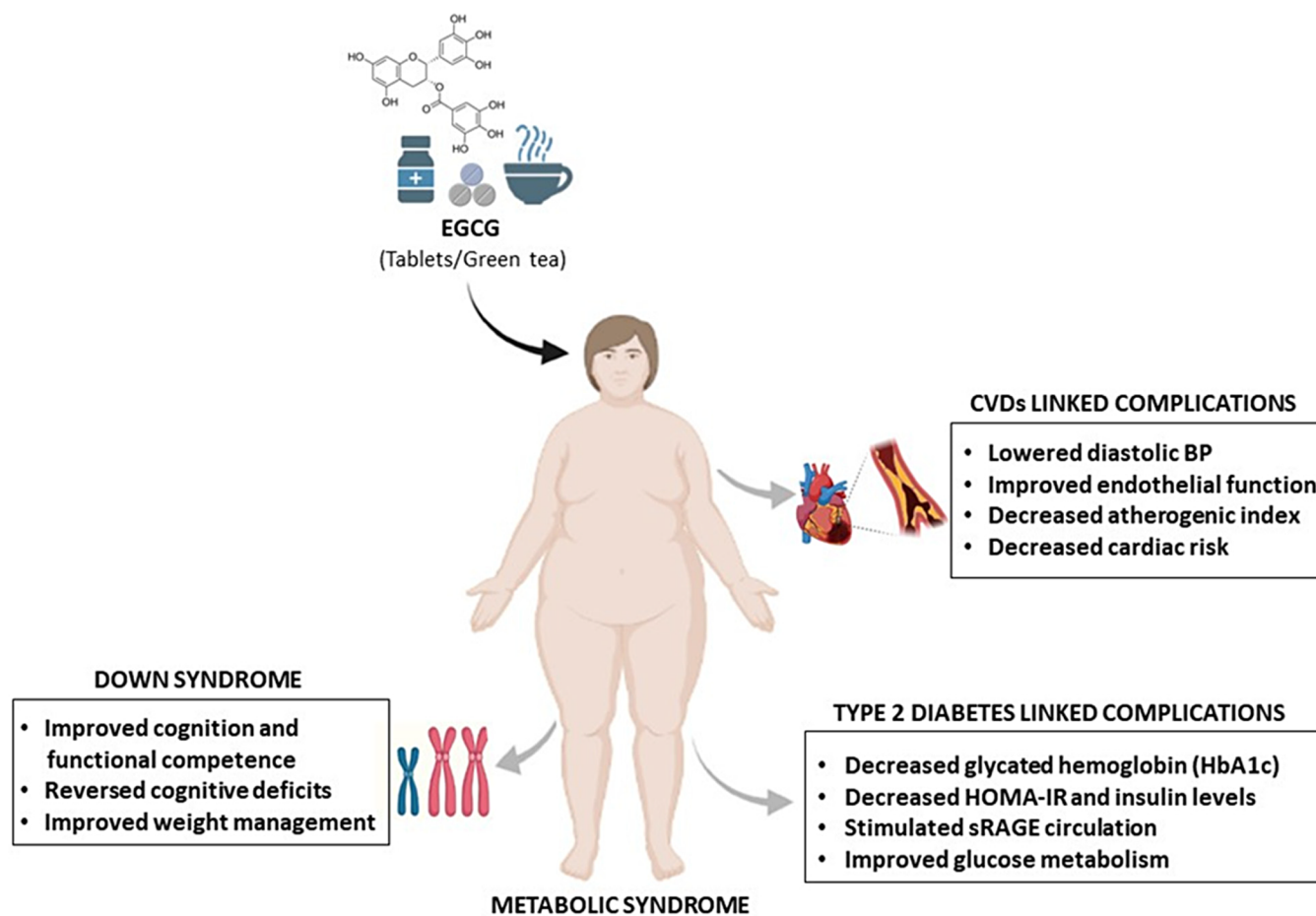


Figure 5. Proposed therapeutic effects of epigallocatechin gallate (EGCG) in metabolic syndrome linked with type 2 diabetes and cardiovascular disease (CVD). HOMA-IR: homeostasis model assessment for insulin resistance, sRAGE: soluble receptor for advanced glycation of end products.

Peters et al. 2010). Similarly, the impact of citrus juice and milk, which are commonly used as ready-to-drink green tea beverage adjuncts, were also investigated by formulating green tea infusion with citrus juice (grapefruit, lemon, lime, and orange) or milk (bovine, soy, and rice), and the results showed improved bioavailability of EGCG (Green et al. 2007).

For clinical studies, EGCG has been mainly administered orally in the form of a green tea extract (Chow et al. 2003; Ullmann et al. 2004; Chow et al. 2005; Naumovski, Blades, and Roach 2015; de la Torre et al. 2016; Scholl et al. 2018; Andreu-Fernández et al. 2020) and various pharmaceutical formulations (capsules, tablets, powder or liquid drops) of green tea extracts are commercialized as dietary supplements with added health benefits. Challenges with many of these products include low EGCG content and the lack of scientific evidence demonstrating their beneficial health effects, oral bioavailability, and safety (Nagle, Ferreira, and Zhou 2006). Standardized commercial nutraceuticals such as Teavigo (capsules of purified green tea extract with 94% EGCG content) and FontUp (a nutritional supplement incorporated with Teavigo and formulated to provide nutrients such as vitamins, minerals, omega-3 fatty acids, carbohydrates, and proteins), improved EGCG bioavailability and increased the stability of EGCG in plasma of healthy subjects (Fernández-Sánchez et al. 2011; Dłudla et al. 2018).

Challenges with the development of EGCG as a nutraceutical or dietary supplement also relate to the increasing concerns about the possible harmful effects associated with the consumption of green tea extracts. These include reported cases of liver toxicity that are strongly associated with green tea catechins and the concentration of their intake (Zheng et al. 2016). Furthermore, a green tea extract (Exolise) marketed as a weight-loss herbal supplement, was withdrawn due to hepatotoxicity events related to its consumption (Gloro et al. 2005). Similarly, SLIMQUICK products containing green tea extracts that are marketed for weight loss were implicated in various cases of severe acute hepatocellular liver injury (Dekant et al. 2017). While there are currently no clear dosage recommendations for EGCG, a safe intake level of up to 338 mg EGCG/day for adults has been proposed for the consumption of green tea extracts, particularly in dietary supplements (Dekant et al. 2017; Hu et al. 2018).

Summary and future perspective

Plants and their phenolic constituents like EGCG have attracted significant interest due to their health-promoting properties (Khan and Mukhtar 2007; Pandey and Rizvi 2009; Mokgalaboni et al. 2021). As such, the current review mainly

explores the potential benefits of EGCG against the metabolic syndrome in clinical studies, especially its capability to attenuate complications linked with obesity, T2D, and CVDs. The majority of summarized evidence here indicates that supplementation with EGCG as a tablet or enriched in green tea extract, at doses between 200–500 mg daily for at least 3 months, remains effective in reducing body mass index and waist circumference concomitant to decreasing serum levels of total cholesterol, LDL-cholesterol, and triglycerides (Table 1). These positive effects are consistent with improved metabolic and CVD-related profiles including HbA1c levels, endothelial function, and blood pressure in either obese subjects or patients with T2D and established CVDs (Tables 1 and 2). Mechanistically, EGCG supplementation may be instrumental in promoting a strong antioxidant response to block lipid peroxidation and reduce predominant markers of inflammation such as IL-6 and TNF- α to improve blood flow and overall cellular function. Nonetheless, although such benefits are acknowledged, from the summarized evidence, an argument persists on whether much lower doses of EGCG (<200 mg) or perhaps a short-term treatment duration (< 3 months), or its combination use with other polyphenols like resveratrol, could be more effective in protecting against metabolic diseases. Pertaining to the clinical application of green tea extracts and EGCG, studies focusing on improving the bioavailability of EGCG are still limited, while the hepatotoxicity associated with consumption of green tea extracts remains unclear. Even so, such information opens avenues for research to further explore the pharmaceutical and nutraceutical development of EGCG for its broad health benefits beyond protecting against the metabolic syndrome.

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Author contribution

YN, BJ, KZ and PVD - concept and original draft; YN, BJ, KZ and PVD- literature search and data extraction; YN, BJ, KZ, SEM-M, BBN, TMN, SEM, SH, PO, LT and PVD- writing and final approval of the manuscript.

Conflict of interests

The authors declare no conflict of interest.

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Ethics approval

This is a review of already published studies and thus it does not require ethical approval.

Consent for publication

Not applicable. No individual person's data has been included in this manuscript.

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Data availability

Data related to search strategy, study selection, and extraction items will be made available upon request after the manuscript is published.

Abbreviations

AMPK	AMP-activated protein kinase;
CVD	cardiovascular diseases;
CCL2	chemokine (C–C motif) ligand 2;
DNA	Deoxyribonucleic acid;
EC	epicatechin;
EGC	epigallocatechin;
ECG	epicatechin gallate;
EGCG	epigallocatechin gallate;
FDA	Food and Drug Administration;
GRAS	generally recognized as safe;
GSH	glutathione;
HDL-cholesterol	high density lipoprotein-cholesterol;
HNE	hydroxynonenals;
HbA1c	glycated hemoglobin;
HOMA-IR	homeostasis model assessment for insulin resistance;
IL	Interleukin-6;
IL-1 β	Interleukin-1 β ;
IL-6	Interleukin-6;
IFN- γ	interferon-gamma;
LDL-cholesterol	low density lipoprotein-cholesterol;
MDA	malondialdehyde;
NF- κ B	nuclear factor kappa B;
RCTs	randomized controlled trials;
sRAGE	soluble receptor for advanced glycation of end products;
SOD	superoxide dismutase;
T2D:	type 2 diabetes mellitus;
TNF- α	tumor necrosis factor-alpha;

Papp apparent permeability;
ROS reactive oxygen species

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