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The role of catechins of *Camellia sinensis* leaves in modulating antioxidant enzymes: A review and case study

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ABSTRACT

Free radicals are generated in the body due to pollution and unhealthy lifestyle. Unbalanced levels of free radicals and natural antioxidants in the body may induce oxidative stress (OS). OS is responsible for several illnesses, including diabetes mellitus, cancer, and cardiovascular disease. The antioxidants can potentially increase the defense mechanism against OS and protect human health. The study aimed to analyze the catechins' role as antioxidants. The catechins can upregulate antioxidant enzymes, scavenge free radicals, protect the DNA by intercalating to the helixes, and create chelation due to numerous hydroxyl moieties attached to the aromatic ring, which protects the structural integrity through electron delocalization. Epigallocatechin gallate (EGCG), a catechin with the greatest antioxidant capacity, has ortho-phenolic hydroxyl groups which potentially in binding free radicals. Moreover, the case study showed that dose-dependent treatment of tea had some benefits for human health. Humans with anemia and menopause cannot consume tea in high doses, which could worsen the condition. Conversely, humans with thalassemia are suggested to take tea to decrease the iron in their bodies. This review is expected to be a further study reference, mainly to clarify the EGCG process in restoring antioxidant enzymes and activating the thioredoxin antioxidant system.

INTRODUCTION

Unstable molecules, free radicals, are incomplete electrons in their external shell of molecules. This instability is promoted by the reactive free radical that eventually induces the tendency to bind nearby electrons (Elsayed Azab *et al*., 2019; Gutowski and Kowalczyk, 2013; Liguori *et al*., 2018). Free radicals, such as superoxide radical ($\bullet O_2$), hydroxyl radical (•OH), nitric oxide (NOX, NO•), and hydrogen peroxide (H_2O_2), could react with other molecules, causing various damage to cells, tissues, and organs (Wu, 2020). The increasing level of free radicals in the body caused by pollution, cigarette, and poor lifestyle may generate an imbalance of free radicals and antioxidant enzymes response, defined as oxidative stress (OS). OS generates biomolecular damage and causes many diseases, such as heart disease, cancer, neurological disorder, diabetes mellitus (DM), and cardiovascular disease (CVD). (Costantini, 2019; Hajam *et al*., 2022; Lushchak and Storey, 2021; Silveira *et al*., 2021). Antioxidants are chemically capable of inhibiting the excessive oxidation process in the body and suppressing OS. These agents are also known as free radical scavengers (Haider *et al*., 2020). Antioxidants possess many mechanisms against OS, such as stimulating antioxidant enzymes, scavenging the free radical directly, intercalating to DNA to prevent DNA damage, and other mechanisms. One type of antioxidant agent is catechins. Catechins are the primary phytochemical contained in tea (Dias *et al*., 2018).

The antioxidant activity of white tea (WT) (Dias *et al*., 2013), green tea (GT) (Zhao *et al*., 2022), and the potential of *Camellia sinensis* (*C. sinensis*) constituents as an antioxidant in lipid system (Gramza and Korczak, 2005) have been discussed. Moreover, the role of GT in auto-photoaging, stress resistance, neuroprotective agent, and autophagy, which involves antioxidant

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activity, has also been reported (Prasanth *et al*., 2019). Recent studies have also exposed some of the antioxidant mechanisms of polyphenol compounds in tea (Yan *et al*., 2020). However, the role of catechins of *C. sinensis* in modulating antioxidant enzymes still needs to be thoroughly described. This review focuses on catechin's ability, especially on epigallocatechin gallate (EGCG), to stimulate the release of antioxidant enzymes in cells, animals, clinical study, and molecular mechanisms in antioxidant enzyme modulation based on the selenium level. Furthermore, a review of the case reports on the effect of drinking tea is also provided.

CATECHIN CLASSIFICATION

Catechins are polyhydroxylated polyphenols found in abundant levels in tea leaves (Huang *et al*., 2019). High-performance liquid chromatography analysis reported several types of catechin compounds (Fig. 1), which includes EGCG, epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin (EC) (Ahmed *et al*., 2019; Cao *et al*., 2020; De Almeida Gonçalves *et al*., 2015). All catechins and their diastereoisomers contain numerous phenolic hydroxyl groups connected to a benzene ring as their chemical structure. As a proton donor (H^+), the hydroxyl group helps stabilize the free radical, and the aromatic ring plays a role in maintaining the proxy stability via electronic resonance. The antioxidant activity of each catechin is different depending on the number of hydroxyl groups attached to the structure. The more the hydroxyl groups attached, the more the protons are available for donation for free radical stabilization (Reddyvari *et al*., 2017). The antioxidant characteristics of each catechin are presented in Table 1. Based on their ability as antioxidants, catechins were categorized into EGCG > ECG > EGC > EC. Considering the highest antioxidant activity of EGCG, most studies have concentrated on evaluating the potential of this particular catechin (He *et al*., 2018).

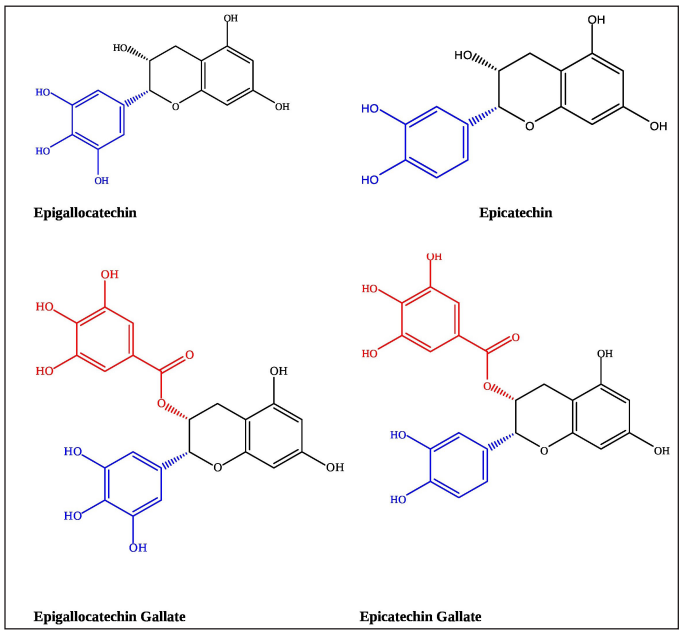


Figure 1. 2D structure of catechins: (a) EGC; (b) EC; (c) EGCG; (d) ECG.

EGCG, the primary polyphenol in C. *sinensis* leaves, has revealed numerous health-promoting effects, including antioxidants. Many studies have proven the EGCG activity as an antioxidant to suppress OS by forming chelate, donating hydrogen ions (H^+), and stimulating endogenous antioxidant enzymes (Abdel-Moneim *et al*., 2018). EGCG is produced through the esterification of EGC, with moiety gallate linked to the C ring via an ester link. Due to its powerful reduction ability, EGCG possesses a potent antioxidant effect (Huang *et al*., 2019). EGCG has eight hydroxyl sites that play an important role in forming free radicals, and radicalization reactions will produce antioxidant radicals with minimal reactivity. Proton donors in the ortho-hydroxyl group in ring B will create oxidized EGCG, which is more stable than meta-hydroxyl (Chiodo *et al*., 2010; Hashim and Fry, 2020; Wagner *et al*., 2006). EGCG has the most vigorous antioxidant activity among all catechin monomers because having six hydroxyls site in the ortho position (Xie *et al*., 2020); hence, it has excellent potential as an iron chelation agent and free radical (Bernatoniene and Kopustinskiene, 2018). After contributing a proton, EGCG creates a resonance to stabilize the antioxidant radical, which is more stable than free radicals (Phimphilai *et al*., 2021). The splitting of covalent bonds in organic molecules forms new free radicals, which initiate a chain reaction (Pan *et al*., 2019). In the complex formed by the chelation of EGCG, the gallate group works to trap •OH. The binding of •OH by such gallate is believed to have no prooxidant effect on EGCG (Lo´pez-Burillo *et al*., 2003).

THE EFFECT OF EGCG IN STIMULATING ANTIOXIDANT ACTIVITY IN CELL LINES

Reactive oxidative stress (ROS) elimination occurs physiologically through free radical scavenging and the upregulation of antioxidant enzymes. Several studies have demonstrated that EGCG acts as a potent antioxidant via activating the nuclear factor-erythroid-2 related factor 2 (Nrf2) pathway. Activation of Nrf2 is the primary regulatory route of the antioxidant response to the decrease of OS (Xie *et al*., 2020), transcription factors that induce antioxidant genes, and detoxification of the exogenous and endogenous OS (Yang *et al*., 2015). Another study showed an increased role of antioxidant activity in the nuclear maturation process of bovine oocytes. The antioxidant modulation mechanism was assumed to be caused by Nrf2 pathway activation, which increases the action of the messenger ribonucleic acid superoxide dismutase (mRNAs SOD1), catalase (CAT), and glutathione peroxidase-4 (GPx4). EGCG could also surge the Nrf2 translocation to the nucleus and heme oxygenase-1 (HO-1) in human intestinal epithelial cells (HIEC), resulting in elevated levels of GPx4 and Solute Carrier Family 7 Member 11 (SlC7A11) in response to ionizing radiation (IR). This work demonstrated the antioxidant effect of EGCG not only via activating the Nrf2 pathway but also by preventing the production of 8-hydroxy-2-deoxyguanosine (8-Ohdg), which damages intestinal epithelial cells when exposed to infrared light. (Xie *et al*., 2020)—the antioxidant mechanism via activation of Nrf2 pathway in mouse hippocampal neuronal cell line (HT22 cells) by GCG. GCG has been shown to protect neuronal cells from injury by inhibiting glutamate induction and stimulating N-acetylcysteine (NAC) production. The reduction

in glutamate synthesis avoids cellular ROS and Ca^{2+} storage and modulates Nrf2/HO-1 signaling, releasing NAC, a glutathione (GSH) antioxidant percussor capable of controlling glutamate production lines (Park *et al*., 2021). GCG is an epi-isomer of EGCG, which is not commonly detected in fresh tea. GCG is only contained in tea products after being processed by drying, lighting, or extreme pH conditions during processing and storage (Wang *et al*., 2021).

The existence of a mechanism of antioxidant enzyme overexpression via the signalling activation pathway of mitogen-activated protein kinase (MAPK) owing to phosphorylation of mitogen p38 and extracellular-signal-regulated kinase (ERK ½) has been proven. The activation of the MAPK signaling pathway will regulate Nrf2, thus elevating the expression of HO-1, which is responsible for enhancing antioxidant defense by upregulating antioxidant enzymes. HO-1 is one of the detoxifying pathways for phase 2 enzymes (Yang *et al*., 2015; Zhao *et al*., 2019). Moreover, EGCG has revealed an antioxidant activity in OS-induced human umbilical vein endothelial cells (HUVECs) and an increase in SOD1, CAT, and GPx activity in Ultraviolet B (UVB)-induced human epidermal keratinocyte cell line (HaCaT cells) (Yang *et al*., 2015). In HaCaT cells, EGCG was thought to prevent the activation of the caspases-8 and caspases-3 pathways and the production of hyaluronidases (HYALs) limiting the number of radicals generated by UVB and sodium nitroprusside (SNP) exposure (Kim *et al*., 2018). Table 2 summarizes the effects of EGCG on various OS-induced cell lines.

Another research attempted to investigate the antioxidant capacity of EGCG in preventing cell damage from ROS caused by gamma radiation water radiolysis. Surprisingly, EGCG has successfully intercalated in DNA helixes and combated ROS directly via hydroxyl groups on aromatic rings (Fig. 2). EGCG can indirectly stimulate SOD and glutathione S-transferase (GST) activities. The study also discovered that EGCG has a greater antioxidant capacity than quercetin and vitamin C (Richi *et al*., 2012). EGCG can defend DNA from free radical attacks and repair DNA damaged by free radicals (Zhao *et al*., 2016). Other studies have confirmed the potential of EGCG as a chemopreventive drug by trapping ROS directly in cancer cells. EGCG also improved cervical cancer biopsy potential by increasing cellular SOD and GPx activity (Hussain, 2017). SOD and GPx activity increases in human lung adenocarcinoma cell line (A549 cells) treated with EGCG (Cromie and Gao, 2015). However, some of these researches still lack explanation on the precise processes involved in enhancing antioxidant activity and sustaining the activity of antioxidant enzymes. Several studies on the effect of EGCG in stimulating antioxidant activity in cell lines are summarized in Table 2.

THE EFFECTS OF EGCG IN STIMULATING ANTIOXIDANT ACTIVITY IN ANIMALS

Several studies on the effect of EGCG in stimulating antioxidant activity in animals have been summarized in Table 3. EGCG could induce antioxidant enzymes and lower serum malondialdehyde (MDA) levels in mice induced by aluminum oxide nanoparticles (Al_2O_3-NPs). A dose of 10 mg EGCG increased creatinine, urea, and uric acid (UA) to near-normal levels, implying no oxidative damage in the form of nephrotoxicity and kidney dysfunction. Antioxidant mechanisms may occur, including stabilizing free radicals via H^+ donors or induction of antioxidant enzymes by activating phase II enzyme production pathways (EI Fattah *et al*., 2018). EGCG can bind metals and form stable conjugate bonds with thiol-carrier compounds. As a result of dimethyl hydrazine (DMH) induction, the direct mechanism of EGCG in scavenging OS caused an increase in the activity of GSH, GST, glutathione reductase (GR), SOD, and CAT in the large intestine of rats (Afzal *et al*., 2021). Another study reported that mice were induced with copper nanoparticles (CNP) and treated with green tea extract (GTE). GTE showed the capability as the hepatoprotective activity of GTE by lowering the activity of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) enzymes, restoring the antioxidant activity of enzymes (SOD and CAT), increasing GSH concentrations, reducing MDA levels, and minimizing DNA fragmentation. The mechanisms underlying its antioxidant activity included directly scavenging free radicals by donating hydrogen, chelating processes that inhibit the Fenton reaction, thereby inhibiting the formation of •OH radicals, and

Table 1. The antioxidant characteristics of catechins based on their chemical structures.

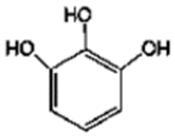
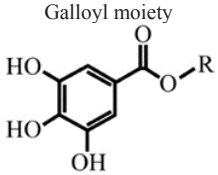
Chemical structure	EGCG	EGC	ECG	EC	Remarks	Ref
Pyrogallol 	Yes	Yes	Yes	Yes	• Pyrogallol provides delocalization electrons. Ortho-dihydroxyl indicates a strong potential as an antioxidant and chelating iron. • The number of −OH affects hydroxylation ability. It has been proven that pyrogallol connected to three OH groups oxidizes more rapidly than pyrogallol with two OHs due to the formation of free radicals.	Bansal *et al*. (2013), Wang *et al*. (2018), Latos-Brozio and Masek (2019), Mokra *et al*. (2023)
Number of OH group	8	6	7	5	More OH groups contribute to more hydrophilicity.	Nakayama *et al*. (2000)
Galloyl moiety 	Yes	No	Yes	No	• Galloyl plays an important role in scavenging °OH radicals. • Galloylated catechin is more effective than nongalloylated catechin. • Galloyl moiety increases hydrophobicity and thus possesses a binding capacity to lipid bilayers.	Ikeda *et al*. (2003), Grzesik *et al*. (2018), Zwolak (2021), Mokra *et al*. (2023)

Table 2. The effects of EGCG on various OS-induced cell lines.

Object of research	Exposure	Treatment	Result	Ref.
HIEC	IR	EGCG	HO-1 ↑ GPx4 ↑ SlC7A11 ↑	Xie *et al.* (2020)
Bovine oocytes matured cells	-	EGCG	SOD1 ↑ CAT ↑ GPX4 ↑	Huang *et al.* (2018)
Mouse hippocampal neuronal HT22 cells	-	GCG	Glutamate ↓ NAC ↑	Park *et al.* (2021)
Human lung cancer A549 cells	-	EGCG	SOD ↑ GPX1 ↑	Cromie and Gao (2015)
HUVEC	Ambient fine particulate matter (2.5)	EGCG	Nrf2-HO-1 expression ↑	Yang *et al.* (2015)
HaCaT cells	UVB irradiation	EGCG	CAT ↑ GPx ↑ SOD 1 ↑	Zhao *et al.* (2019)
HaCaT cells	UVB irradiation SNP	EGCG	Hyaluronic acid ↑ NO ↓	Kim *et al.* (2018)
Murine splenocytes cells	Gamma radiation	EGCG	SOD ↑ GST ↑ DNA Protection ↑	Richi *et al.* (2012)
Human cervical cancer cell line (HeLa) and cervical cancer biopsy	-	EGCG	SOD ↑ GPx ↑	Hussain (2017)

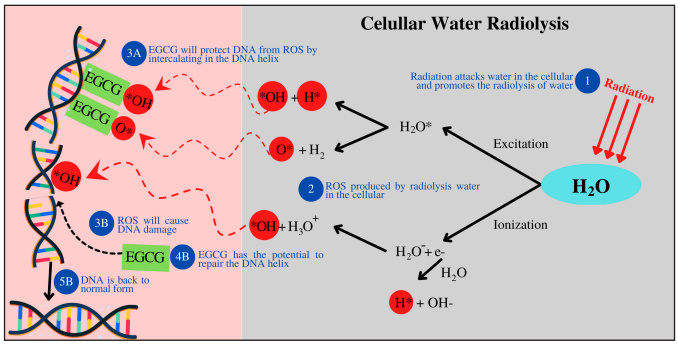


Figure 2. DNA protection from free radicals by EGCG [The concept was made by combining the idea from Reeves and Kanai (2017) and Yousefi and Moazami (2019)].

advanced responses that inhibit the occurrence of lipid peroxidation (LPO). EGCG and other catechins can induce mild OS levels to induce intracellular endogenous antioxidant expression (Ibrahim *et al*., 2015).

Alcohol-induced diabetic rats treated with aqueous GTE exhibited a nonsignificant increase in antioxidant activity (GPx, SOD, GST, and CAT) and GSH concentrations compared to the control group. It concluded that the antioxidant mechanism possibly occurred by involving ROS scavenging (Kodidela *et al*., 2020). A similar mechanism was shown in the study by Bártíková *et al*. (2017). This study did not show increased antioxidant enzyme activity and GSH concentrations in obese rats treated with a GTE-enriched diet. It might be owing to the long delay (7 months) in the induction of monosodium glutamate (MSG) and GTE-enriched diet, which caused severe damage to the body's antioxidant system, making it more challenging to recover (Bártíková *et al*., 2017).

EGCG could improve structural disorders in the corpus cavernosum of aged rats by elevating of SOD activity of the penile, diminishing MDA levels, increasing its ability to counteract free radicals, and donating hydrogen donors to scavenge free radicals directly (Chen *et al*., 2016). Supported by another study, catechins could develop germ cells and increase rat sperm viability by stimulating lactate production in Sertoli cells (Opuwari and Monsees, 2020). Pretreatment EGCG prevents kidney disease and mediates sperm dysfunction in fluoride-exposed male mice. In this case, EGCG antioxidant mechanisms increase mitochondrial transmembrane potential, radical scavenging, and Nrf2-antioxidant response element (ARE) pathway. EGCG has a direct and indirect protective role in antioxidants. EGCG can directly prevent membrane permeability changes and stabilize it by OS induction because of its unique chemical structure. EGCG's chemical characteristics with the gallate moiety esterified (Ring A), the catechol group (Ring B), and the meta-hydroxyl group in Ring C played essential roles in directly scavenging radicals and protecting rat testes from fluoride-induced OS. The direct mechanism of EGCG is reported to be able to reduce the workload of SOD, CAT, and GPx by scavenging free radicals directly. In addition, EGCG can restore the antioxidant enzymes and uphold their activity. The amount of hydroxyl group in the structure of EGCG has electrophilic characteristics and has the potential to modify SH-residue in Keap 1, which causes Nrf2 to accumulate in the nucleus and bind the ARE to upregulate antioxidant enzyme activity (Thangapandiyan and Miltonprabu, 2015).

GTE can restore the antioxidant activity of enzymes (SOD and CAT), raise GSH levels, and limit DNA fragmentation in mice exposed to CNPs. Direct scavenging of free radicals by donating hydrogen and a chelating process, which inhibited the Fenton reaction, is also possible. The cessation of the Fenton reaction causes the inhibition of hydroxyl radicals' production and prevents the occurrence of LPO. EGCG and other catechins can promote intracellular endogenous antioxidant expression by inducing mild OS (Ibrahim *et al*., 2015).

EGCG in another potential has been proven by Ibrahim *et al*. (2019). EGCG acts as a chemopreventive agent, which might be used with an anticancer drug. The study established the efficacy of EGCG as a chemopreventive medication compatible with cisplatin without adverse drug interactions. EGCG in GT has cardioprotective properties, specifically repairing oxidative and cardiac damage caused by cisplatin in cancer treatment by inducing and restoring SOD and GPx. Activation of Nrf2 may boost the expression of genes involved in manufacturing antioxidant enzymes and HO-1 for cell protection and anti-inflammatory signaling pathways (Ibrahim *et al*., 2019). Long-term administration of WT in trained mice elevated endurance because it prevented hepatic tissue from LPO and enhanced trained mice's endogenous antioxidant defenses. The blood antioxidant status of antioxidant enzymes (SOD, GPx, GR, and GSH) improved in response to WT-induced exogenous antioxidants.

Table 3. The effects of EGCG in modulating antioxidant activity in animals.

Animal	Exposure/physical treatment	Treatment	Result	Ref.
UUO mice model	No exposure and physical treatment	EGCG at a dose of 50 mg/kg (ip, 14 days)	Kidney tissue analysis: SOD ↑ GPx ↑ CAT ↑	Wang *et al.* (2015)
Male albino Wistar rats	Fluoride at a dose of 25 mg/kg b.w/day (intragastric, 4 weeks)	EGCG at a dose of 40 mg/kg/day (oral, 4 weeks)	Renal tissue analysis: SOD ↑ GPx ↑ CAT ↑ GST ↑ GR ↑	Thangapandiyan and Miltonprabu (2014)
Male albino Wistar rats	Natrium fluoride at a dose of 25 mg/kg b.w/day (oral, 4 weeks)	EGCG at a dose of 40 mg/kg/day (oral, 4 weeks)	Testes analysis: SOD ↑ GPx ↑ CAT ↑ GST ↑ GR ↑	Thangapandiyan and Miltonprabu (2015)
Adult male albino rat	Al_2O_3-NPs at a dose of 50 mg/kg b.w (ip, three times a week for 3 weeks)	EGCG at a dose of 5 mg/kg b.w and 10 mg/kg b.w (i.v, 5 weeks)	Blood analysis: GSH ↑ SOD ↑ CAT ↑ MDA ↓ creatinine↑ urea ↑ UA ↑	El Fattah *et al.* (2018)
Male adult Swiss albino mice	Cyclophosphamide at a dose of 100 mg/kg bw (ip, the administration only once an hour after the last treatment; after 14 days of GT treatment)	GT infusion at a dose of 250 mg/kg b.w/day (oral, 14 days)	Testes analysis: SOD ↑ GPx ↑ CAT ↓ GST ↑ Epididymis analysis: SOD ↑ GPx ↑ CAT ↑ GST ↑	Zanchi *et al.* (2015)
Female albino mice	Cisplatin at a dose of 7 mg/kg (ip, only once on the 27th day)	GTE at a dose of 400 mg/kg/day (oral, 30 days)	Cardiac tissue analysis: MDA ↓ SOD ↑ GPx ↑	Ibrahim *et al.* (2019)
Adult male albino Wistar rat	• Streptozotocin (STZ) at a dose of 7 mg/kg (ip, only once administration) • Alcohol (administration using an orogastric tube at a dose for 60 days started from 3 days after STZ induction)	Aqueous GTE (administration using an orogastric tube for 60)	Blood analysis: GPx ↑ SOD ↑ GST ↑ CAT ↑ GSH ↑	Kodidela *et al.* (2020)
Albino Wistar rat	Ethanol 20% at a dose of 5 g/kg b.wt/day (oral, 60 days)	GTE at a dose of 300 mg/kg b.wt/day (oral, 60 days)	Liver tissue analysis: GPx ↑ SOD ↑ CAT ↑ GSH ↑	Reddyvari *et al.* (2017)
Male Wistar rat	Treadmill training and exhaustive tests (once a week for 10 weeks)	WT infusion (oral, every 2 days for 10 weeks)	Serum and liver tissue analysis: GPx ↑ SOD ↑ GR ↑ GSH ↑	Berilli *et al.* (2022)
Male NMRI mice	Newborn male mice were administered an aqueous solution of MSG subcutaneously from postnatal days 2–8. MSG dose 10 mg/day for days 2–6 and 15 mg/day for days 7–8	GTE-enrich diet at a dose of 1 g/kg (oral, 28 days after the age of the mice were 7 months)	Serum and erythrocyte analysis: no change in activity in GPx, CAT, SOD, GST, and GR, as well as GSH concentrations in serum analysis and	Bártíková *et al.* (2017)
Old Wistar male rats	No exposure and physical treatment	• GT at a dose of 500 mg/kg (oral, 9 weeks) • Selenium-GT at a dose of 500 mg/kg (oral, 9 weeks)	Serum analysis: SOD ↑ GPx ↑ MDA ↓ Serum analysis: SOD ↑ GPx ↑ MDA ↓	Wu *et al.* (2022)
Male duckling	AFB1 at a dose of 0.3 mg/kg b.w/day (oral, for 7 days)	EGCG at a dose of 100 mg/kg/day BW (oral, 7 days)	Liver tissue analysis: SOD ↑ GPx ↑ CAT ↑	Wang *et al.* (2022)
Female albino rats	Tamoxifen at a dose of 45 mg/kg/day (ip, 7 days)	GT water extract at a dose of 15% *w/v* (oral, 21 days)	Liver tissue analysis: SOD ↑ GPx ↑ CAT ↑ MDA ↓	Mahboub (2016)
Male Wistar rats	DMH at a dose of 40 mg/kg b.wt (ip, administration on 7th day)	EGCG at a dose 20 mg/kg b.wt (ip, 7 days)	Colon tissue analysis: SOD ↑ GPx ↑ GSH ↑ GST ↑ GR ↑ CAT ↑ MDA ↓	Afzal *et al.* (2021)
Male albino rats	Malathion at a dose of 50 mg/kg b.w/day in 0.2 ml corn oil (oral, 4 weeks)	GT at a dose of 36 mg/kg b.w/day in 0.2 ml distilled water (oral, 4 weeks)	Liver tissue analysis: SOD ↑ GSH ↑ GPx ↑	Elzoghby *et al.* (2014)
Male Kunming mice	Swimming exercise, 1 hour after the final treatment	EGCG at a dose of 200 mg/kg b.w/day in 1.5 ml distilled water (oral, 28 days)	Liver tissue and hind-limb skeletal muscle analysis: SOD ↑ GPx ↑ CAT ↑	Teng and Wu (2017)

*Intraperitoneally administration (ip), intravenously administration (iv).

GPx and antioxidant GSH system in the liver demonstrated higher activity than other antioxidant enzymes, with evidence of reduced peroxidative liver damage. The reaction between H_2O_2 and lipid hydroperoxide (LOOH) will produce MDA as a sign of peroxidative damage (Berilli *et al*., 2022). Wang *et al*. (2022) reported a similar mechanism of antioxidant induction in their study of the reduction of aflatoxin B1 (AFB1)-induced ducks. The elevation in Nrf2 and HO-1 expression is caused by EGCG administration. It indicated the consequences of restoring antioxidant enzyme activity and preventing liver damage in ducks (Wang *et al*., 2022).

The ability of EGCG to increase antioxidant enzyme activity by signaling the Nrf2 pathway was also exhibited in a preclinical investigation using the unilateral ureteral obstruction (UUO) mouse model. EGCG stimulates increasing the nuclear accumulation of Nrf2 and promotes Nrf2-ARE consensus element binding in the kidney UUO to increase antioxidant enzyme activity. Consequently, renal function improved dramatically, and the obstructed kidney gained weight (Wang *et al*., 2015). Pretreatment EGCG in the rats' group induced by fluoride upregulated Nrf2 level by HO-1 signaling pathway. EGCG encourage Nrf2 to translocate to the nucleus and bind the ARE, increasing antioxidant activity in the renal tissue of rat (Thangapandiyan and Miltonprabu, 2014).

The catechins in GTE could also restore the activity of SOD, CAT, GPx, and GSH to near-normal levels following alcohol induction ($p < 0.05$). Antioxidants prevented D-loop mutations in alcohol-induced rat mitochondrial DNA. Mutations in the D-loop, the primary regulatory region for mitochondrial deoxyribonucleic acid (mtDNA) replication and transcription, would influence the stability of mtDNA. It can be hypothesized that the increase in antioxidant activity was due to catechins' capacity to repair SOD, CAT, GPx, and GSH activity (Reddyvari *et al*., 2017). Antioxidant enzyme amelioration in prediabetic rats also occurred after treating WT infusion. Catechins of WT were estimated to rebuild the activity of SOD and GPx to near-normal levels. Although the precise process of enhancing the antioxidant activity of enzymes has not been conclusively elucidated yet, it is believed that activation of the Nrf-2 pathway increases the expression of antioxidant enzymes (Silveira *et al*., 2021). Drinking WT regularly in prediabetic rats led to an increase in CAT levels, efficient ROS clearance, and restoring cerebral cortex antioxidant ability. EGCG, which belongs to the polyphenol group, is believed to have a neuroprotective effect from tea extracts (Nunes *et al*., 2015). EGCG had antifatigue effects in rats because it could potentially improve the activities of SOD, CAT, and GPx to protect corpuscular membranes against LPO. There was no precise mechanism for upregulating the SOD, CAT, and GPx (Teng and Wu, 2017). In another study, EGCG in GT was predicted to prevent memory deficit and hippocampal oxidative damage. EGCG plays a role in diminishing the ROS and thiobarbituric acid reactive substances (TBARS) in ischemic mice hippocampus and avoids the elevation of excitotoxicity, nerve injury, and degeneration induced by OS in the brain (Martins *et al*., 2017).

THE EFFECTS OF EGCG IN STIMULATING ANTIOXIDANT ACTIVITY IN HUMANS

Several studies reported the potential of EGCG in stimulating antioxidant activity in humans and the resume is provided in Table 4. Radiation-induced dermatitis in breast cancer patients following mastectomy could be treated with topical EGCG. EGCG suppresses radiation damage via an antioxidant process, including DNA protection. EGCG intercalated into the DNA to bind the free radicals directly and reduce radiation harm. EGCG prevents DNA from free radicals and repairs the DNA damage induced by free radicals (Zhu *et al*., 2016). Clinical trials of GTE administration on DM 2 patients with comorbid conditions showed the elevation of SOD and GPx activity after 9 months of therapy but declined after the 18th month. Compared to baseline levels, CAT activity increased only in the 18th month. The study also found that GTE had a beneficial effect on LPO markers, such as the lowering of LOOH and MDA, indicating antioxidant activity in the body (Spadiene *et al*., 2014). MDA exhibited LPO-modified low-density lipoprotein is one of the initiators of atherogenesis (Suraphad *et al*., 2017). The antioxidant activity of EGCG also occurred in peripheral blood mononuclear cells of patients with multiple sclerosis. EGCG suppresses NOX overactivity by competitively inhibiting the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme with NADPH. The presence of neuronal calcium is promoted by NOX activation, a pathophysiological mechanism of neuronal dysfunction (Mossakowski *et al*., 2015).

Though the increases were insignificant, GT infusion and GTE treatment increased GSH, GPx, and total antioxidant status (TAS) activity in individuals with metabolic system disease. The findings suggest that catechins selectively enhance endogenous antioxidant capacity in patients with metabolic syndrome by modulating endogenous antioxidant indicators. EGCG also exhibited a drop in iron levels in blood plasma, which was thought to be caused by the chelation process of EGCG (Basu *et al*., 2013). Another research reported the potential of catechins in modulating antioxidant enzymes in chronic cigarette smokers. The rising of GSH, GPx, and SOD activity is due to EGCG's capacity to bind directly to ROS and accumulate the level of antioxidant enzymes, resulting in enhanced antioxidant activity in the blood (Shakeela Begum *et al*., 2018). A clinical study of EGCG and ECG found both catechins in the plasma of healthy subjects given a single dose of decaffeinated GT catechins at random. Decaffeinated GT was generally well accepted by the participants. However, EGCG and ECG are free, whereas other catechins were primarily founded as glucuronide and sulfate conjugates (Chow *et al*., 2005).

CrossFit exercise and GT ingestion built up aerobic capacity and antioxidant activity. The elevation in UA in plasma, an outcome of purine metabolism, is evidence of increased antioxidant activity. Another mechanism was proven by inhibiting ROS attacks on the bilayer membrane through direct contact with catechins. This study also demonstrated catechins' capacity to balance ROS generation with endogenous antioxidant defenses. The elevation of GSH and SOD levels in the blood, triggered by cellular signaling pathways, indicates a rise in antioxidant activity. Catechins can influence the expression of the first enzyme in the cellular GSH production pathway, namely, glutamyl cysteine synthetase (GCS) (Sadowska-Krępa *et al*., 2019). Supported by other studies, catechins were observed to modulate the expression of γ-GCS as a precursor to increasing the total GSH levels in various organs (Carlsen *et al*., 2003; Moskaug *et al*., 2005). A different result was shown in the study by Jówko *et al*. (2015). GTE supplementation in sprinter athletes after repeated cycles of sprint tests (RST) exhibited a significant elevation in UA and plasma polyphenol levels in total rest. Even higher results were

demonstrated in total plasma after 24 hours of recovery. SOD and GPx revealed different effects, with a decrease in activity followed by a decrease in MDA levels 24 hours after recovery. In this investigation, GTE supplementation elevates plasma antioxidant activity, as seen by an increase in UA and MDA levels, suggesting antioxidant activity in the body. Catechins in GT stimulated antioxidant enzymes were thought to function synergistically to restore the body's equilibrium after RST in sprinter athletes (Jówko *et al*., 2015). The lowering of TBARS oxidation indicated the presence of antioxidant activity, which suppress LPO, due to the presence of catechin-stimulated SOD activity in GT. The great activity of SOD in reducing LPO caused the level of SOD to decrease after treatment lowering (Maeda-Yamamoto *et al*., 2018).

CASE REPORTS OF THE CONSUMPTION OF TEA IN HYPERTENSIVE PATIENTS WITH COMPLICATION

Several previous studies have been explored to investigate the influence of tea drink consumption on pharmacological effects in humans—several case studies are provided in Table 5.

Controlling the use of tea drinks is very important in this regard. People with postmenopause, celiac disease, atrophic gastritis, *Helicobacter pylori* infection, dietary deficits, intestinal resection, and bariatric surgery with gastric bypass cannot consume large doses of tea to avoid iron deficiency. Ingesting in the high level of tea alleviates Ferri's levels—because of the chelating process by catechin—and the amount of hemoglobin in the anemia patients' body leads to the exacerbation of anemia. In addition, excessive tea consumption inhibits the body's absorption of Ferri and other irons. EGCG in high concentration was similarly toxic to hepatocytes (Kucera *et al*., 2015). The occurrence of hepatotoxicity in black tea is relatively uncommon, but this case demonstrated that large-scale black tea consumption possessed a risk of hepatotoxicity (Hadjipanayis *et al*., 2019). This is possible because catechins act as pro-oxidants, replenish the potential mitochondrial membrane, and cause hepatotoxicity (Mazzanti *et al*., 2015).

The case report by Chong *et al*. (2016) showed the occurrence of hypokalemia in patients with regular GT consumption. Still, the exact cause of hypokalemia has not

Table 4. The effects of EGCG in modulating antioxidant activity in humans.

Object of research	Treatment	Result	Ref.
Patients undergoing a modified radical mastectomy	• External beam radiation to the chest wall was administered. • A solution of EGCG (purity ≥95%) at a dose of 660 µmol/l was sprayed over the entire radiation field at 0.05 ml/cm^2 three times a day for 2 weeks after radiation treatment was completed. • Patients were advised not to use deodorants, lotions, creams, perfumes, or other products in areas of the radiation field.	Lowers the effects of dermatitis	Zhu *et al*. (2016)
Adults with the metabolic syndrome	• Group 1: The patient was given a GT drink of 4 cups/day for 8 weeks. One bag of commercial GT brewed in one cup of boiled water for 10 minutes. • Group 2: The patient had been given 2 capsules + 4 cups of water/day for 8 weeks.	Blood analysis: TAS ↑ Fe ↓ GSH ↑ GPx ↑	Basu *et al*. (2013)
Chronic cigarette smokers (have smoked at least 15 to 20 filter cigarettes per day for a minimum of 7 years)	• Respondents received three cups (100 ml) per day for a year.	Blood analysis: GSH ↑ GPx ↑ SOD ↑ CAT ↑ MDA ↓	Shakeela Begum *et al*. (2018)
Students of the physical education faculty volunteered	• Respondents were given a GTE capsule (containing 250 mg of standardized GTE) twice a day for 6 weeks. • Respondents were asked to do a CrossFit exercise within a 5-day-on and 2-day-off workout structure for 6 weeks.	Blood analysis: SOD ↑ GSH ↑ UA ↑	Sadowska-Krępa *et al*. (2019)
Type 2 diabetes patient with complications (Aged 35–80 years)	• Patients were given ECs capsules twice a day for 9 months. • Patients were then given ECs capsules thrice daily at months 9 to 18.	Blood analysis: SOD ↑ GPx ↑ MDA ↓ LOOH ↓	Spadiene *et al*. (2014)
Male sprinters (aged 21.6 ± 1.5 years)	• Respondents were given GTE capsules (contained 980 mg polyphenols daily) for 2 periods (4 weeks/period) • Respondents were asked for two (RST; 4 × 15 seconds, with 1-minute rest intervals) after PL and GTE supplementation. Exercises are performed at the end of each period (every after 4 weeks of treatment) • Respondents were advised not to modify their diet or consume products containing GT and caffeine for up to 1 cup/day.	Blood analysis: MDA ↓ TAC ↑ SOD ↓ GPx ↓ UA ↑	Jówko *et al*. (2015)
Japanese adult (aged 21–55 years) with slightly elevated BP	• GT was extracted with hot water and sprayed dry to create a granulated powder composite containing cyclodextrin. • The product was administered for 12 weeks; however, the dosage administered to volunteers was not specified.	Blood analysis: oxidation marker TBARS ↓ SOD ↓	Maeda-Yamamoto *et al*. (2018)

been explained. Chong *et al.* (2016) suspected that due to the influence of bendroflumethiazide, the drug could cause electrolyte imbalances, causing a decrease in potassium. However, it turned out that hypokalemia also occurred in female patients (67 years old) who did not take the drug. Hypokalemia may be caused by theophylline, which affects the activity of sodium/potassium ATPase, which causes extracellular hypokalemia (Chong *et al.*, 2016). We hypothesized that there are drug interactions with catechin compounds that cause hypokalemia. Lisinopril is a drug used to lower blood pressure (BP) by inhibiting the angiotensin-converting enzyme (ACE) and preventing the formation of angiotensin II. A decrease in angiotensin II causes a reduction in aldosterone secretion, so the reabsorption of natrium in the collecting duct decreases, and so does potassium excretion. It will cause an increase in potassium in the serum of hypertensive patients. Downregulating sodium levels and elevating potassium levels will reduce BP (Lopez *et al.*, 2022; Messerli *et al.*, 2018; Regulski *et al.*, 2015). GTE with a high EGCG content, when consumed with lisinopril, will cause a decrease in plasma concentration and excretion of lisinopril in the urine. It is because EGCG can inhibit the absorption of lisinopril in the gastrointestinal tract. Lowering lisinopril levels will reduce the efficacy of BP-lowering drugs, such as potassium supplements (Misaka *et al.*, 2021).

Patients with high levels of iron in the body, thalassemia, are advised to drink tea regularly. Tea EGCG will reduce iron levels by chelating iron with 3′, 4′-dihydroxy and galloyl groups in its chemical structure (Fan, 2016; Heikal *et al.*, 2013; Jetsrisuparb *et al.*, 2014). Excess iron in cells produced OS through the Fenton reaction, resulting in oxidative cell damage and organ damage. Metal ions can combine with H_2O_2 to form hydroxyl radicals, which are highly reactive and toxic (Ibrahim *et al.*, 2015; Phimphilai *et al.*, 2021). Therefore, iron-chelating compounds will suppress iron levels and improve cellular function in thalassemia patients (Phimphilai *et al.*, 2021). Chelating iron can also inhibit the Haber–Weiss reaction, which causes several chronic diseases (Codoñer-Franch *et al.*, 2010; Valko *et al.*, 2007). Another benefit is that tea can also be an alternative hydration therapy in intracranial hypotension (Petramfar *et al.*, 2016).

MOLECULAR MECHANISM IN MODULATING ANTIOXIDANT ENZYMES

Antioxidant enzymes in the molecular mechanism are divided into two types based on selenium levels. Dong *et al.* (2016) and Wu *et al.* (2022) discovered that selenium levels influence the antioxidant mechanism in EGCG (Dong *et al.*, 2016; Wu *et al.*, 2022). EGCG, in a selenium-rich condition, activates the thioredoxin (Trx) and GSH pathways as the first line of antioxidant defense. Selenium is a component of Trx reductase, which also contributes to the body's antioxidant defense mechanism. Without selenium, EGCG will activate the Nrf2 pathway and increase HO-1 and NADPH levels, hence inducing antioxidant enzymes (Fig. 3) (Dong *et al.*, 2016).

Nrf2 transcriptional activation by EGCG occurs via Michael's reaction between an electrophile of EGCG with the cysteinyl thiol group in Keap 1 (Ma, 2013; Thangapandiyan and Miltonprabu, 2014). Residues C273 and C288 are direct sensors responsible for the induction of the ARE-regulated enzymes when EGCG and free radicals bind the C273 or C288 in the intervening region (IVR) domain (in the Keap 1). The binding will downregulate Keap 1, and Nrf2 will translocate to the nucleus. Nrf will bind with ARE to stimulate gene expression (HO-1 and NADPH quinone dehydrogenase 1 [(human)]) in the nucleus, thereby triggering the release of antioxidant enzymes, such as SOD, GPx, and CAT (Fig. 3) (Guo *et al.*, 2021; Han *et al.*, 2017; Thangapandiyan and Miltonprabu, 2014; Wu *et al.*, 2010).

SOD, GPx, and CAT are the primary antioxidant enzymes found in human plasma (Szczeklik *et al.*, 2016). SOD acts as an antioxidant by neutralizing superoxide (O_2*) (Abolfathi *et al.*, 2012; Didangelos *et al.*, 2020) and converting it into H_2O_2 (Mazur-Bialy *et al.*, 2018; Vranković, 2016). CAT catalyzes the decomposition of H_2O_2 into water molecules (H_2O) and oxygen O_2. Research by Ezeja *et al.* (2022) reported that the elevation of CAT activity after paracetamol administration indicated that CAT could simultaneously detoxify paracetamol. It was reasonable to assume that CAT had nearly the same capabilities as GPx in detoxifying hazardous chemical substances that caused the generation of ROS in the body (Ezeja *et al.*, 2022). GPx detoxifies H_2O_2 and decomposes organic H_2O_2 into appropriate alcohols (Vranković, 2016; Zahra *et al.*, 2021). CAT and GPx avoid the formation of hydroxyl radicals (OH*) by preventing the accumulation of H_2O_2 (Abrahim *et al.*, 2012).

EGCG shows another antioxidant activity in high selenium level conditions. EGCG can trigger the Trx antioxidant defense mechanism and GSH antioxidant mechanism. Activating mechanism of Trx by EGCG is still unclear (Dong *et al.*, 2016). GSH antioxidant mechanism is another way EGCG stimulates the antioxidant activity in the high selenium level. GSH is a nonprotein thiol that helps coordinate the body's antioxidant defense mechanisms by an electron donor and disulfide bond reducer mechanism (Abolfathi *et al.*, 2012). In the presence of the enzyme GPx, GSH in the GSH antioxidant system is converted into its oxidized state glutathione disulfide (GSSH). GR converts GSSH back to GSH (reduced form) and maintains the average cellular GSH level (Codoñer-Franch *et al.*, 2010; Rakshit *et al.*, 2018; Saravana Kumari and Anuradha, 2016; Valko *et al.*, 2007). GSH at high concentrations can scavenge ROS directly and indirectly (Kodidela *et al.*, 2020). GSH is an indirect mechanism

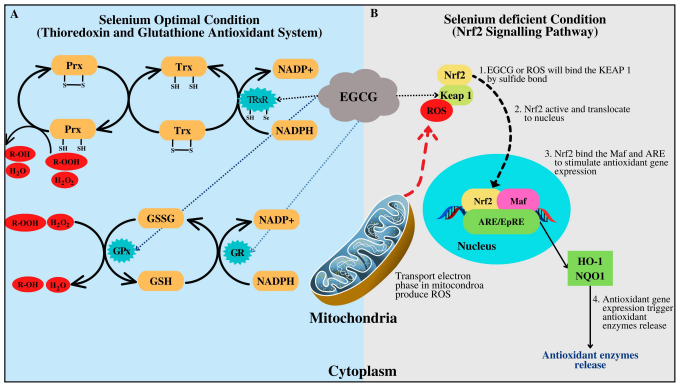


Figure 3. Cellular antioxidant defense pathways depend on selenium status: (A) Trx mechanism and GSH antioxidant enzymes and (B) Nrf2 pathway illustration [The concept was built by the combination concept of Karlenius and Tonissen (2010), Mattmiller *et al.* (2013), Dong *et al.* (2016), Jaganjac *et al.* (2020)].

Table 5. Case reports of the consumption of tea in hypertensive patients with complications.

Patient profile	Symptom/disease	Treatment	Pharmacology effect	Ref.
Woman (32 years old)	• The woman was admitted to the ward because of chronic daily headaches accompanied by nausea, vomiting, and vertigo (2 months). • She had headaches daily, mainly bilaterally in the frontal and occipital areas. • She got positional headaches which were becoming worse in the upright position and got better when lying down. She had an adverse history of lumbar puncture, trauma, or manipulation, and the lumbar punction was a worsening headache factor. There was no fever, chills, dizziness, unsteady gait, blurred vision, diplopia, or photophobia. Regular physical examination results included BP (120/80), pulse (88/minute), respiration (16/minute) peroral temperature (37.2°C). • MRI examination with gadolinium showed meningeal enhancement.	• Epidural blood patching therapy. • Hydration treatment using dextrose water serum. • High caffeine diet. • 200 cc tea (± 800 cc/day) every 2 hours in the daytime (no details about the amount of tea used).	The headache significantly got better after 48 hours of drinking tea	Petramfar *et al.* (2016)
Man (48 years old)	• The disease history was hypertension, DM-2, and previously diagnosed low-grade thalassemia. • The patient was suggested to evaluate for persistent anemia. The patient's symptom involves fatigue, fever, dark-colored urine, persistent diarrhea, abdominal bloating or pain, tarry or fatty stool, change of bowel movement, and weight loss. Physically examination exhibited pale conjunctiva and fingernail beds without cheilosis or koilonychia. The serum ferritin value was 1.6 µg/ml, indicating iron heme deficiency.	The patient had a habit of consuming 1,500 ml/day of GT for 20 years. The patient was advised to stop drinking tea after indicated early-stage anemia. The patient was resumption tea after discontinuing consuming tea for 2 weeks. The patient also proposes administering an intervenous injection of 400 mg ferric sucrose complex once a week and daily oral supplementation of 400 mg ferric hydroxide poly maltose complex for 4 weeks.	The total Hb increased after discontinuing consuming tea. The Hb value again increased after the resumption of tea, even though he got treatment using an intervenous injection and oral supplementation of ferric.	Fan (2016)
Woman (17 years old)	• She got Hb E/β-thalassemia when she is in 6 years old. • She had to do a blood transfusion 1–2 times a year. • She discontinued iron chelator treatments because she had to go abroad to her study. • The historical ferritin serum before tea treatment is 976; 1.125; 802; 1.012; dan 1.090 mcg/l (average: 15–300 mcg/l).	Desferrioxamine 20 mg/kg/day by infusion pump subcutaneously for 10–12 hours, 2–3 days/week (6 days/week at the beginning of treatment) 2 g sachets teabag prepared with 240 ml/day (treatment) Zink sulfate tablet (15 mg) every day.	The ferritin is decreased (600 mgc/l) but lacks zink after drinking tea treatment (≤0.30 mcg/l). The patient was advised to stop consuming tea, and the treatment was continued using zink sulfate; after 1 year, the serum zink was 3.54 mcg/l. The zinc sulfate was discontinued, and the patient was advised to drink tea once or twice weekly.	Jetsrisuparb *et al.* (2014)
Man (73 years old)	The historical disease was hypertension and hypercholesterolemia.	• Amlodipine 5 mg • Lisinopril 10 mg • Bendroflumethiazide 2.5 mg • Atorvastatin 40 mg • Regularly drink eight glasses per day of GT (300 ml)	Sufferers hypokalemia with a potassium serum value was 3.1 mmol/l. The man was suggested to discontinue bendroflumethiazide and alternate the half dose of tea beverage with water (4 cups for tea and 4 cups of water).	Chong *et al.* (2016)
Woman (67 years old)	The historical disease was hypertension and mild hypercholesterolemia.	• Amlodipine 5 mg for hypertension • Lisinopril 20 mg for hypertension • Simvastatin 20 mg for hypercholesterolemia • Regularly drink eight glasses per day of GT (300 ml)	Sufferers hypokalemia with a potassium serum value was 3.2 mmol/l. The woman was recommended to alternate the half dose of tea beverage with water (4 cups for tea and 4 cups of water).	Chong *et al.* (2016)

Continued

Patient profile	Symptom/disease	Treatment	Pharmacology effect	Ref.
Man (12 years old)	The patient presented with a 2-week history of upper right abdomen pain and a 1-day history of itching. Patients reported urine with a dark tint.	• Consume 1.5–2.0 l of black tea every day for 3 months. Product composition: sugar (4.5 g/100 ml) (sugar, fructose), black tea extract (0.09%), citric acid, apricot juice (0.1%), and water.	• Laboratory results showed elevated levels of liver enzymes, γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin. • Abdominal ultrasound results: showed sludge in the gallbladder without increased echogenicity of the liver. • Patients were advised to stop taking black tea, and the examination results showed the gallbladder sludge disappeared, and liver enzymes returned to normal levels after 2 months of discontinuing the excessive consumption of black iced tea.	Hadjipanayis *et al.* (2019)

in conjugating GPx and GST (EI Fattah *et al*., 2018). GSH also aids in detoxifying chemicals via conjugation mechanisms (Heikal *et al*., 2013; Khan *et al*., 2014). Apart from being a substrate for GPx, GSH can directly eliminate free oxygen species, such as superoxide anions, and radical alkoxy, such as H_2O_2, to replace the role of GPx and is primarily responsible for maintaining membrane protein thiols (Fig. 3) (Reddyvari *et al*., 2017).

CONCLUSION AND FUTURE ASPECTS

Camellia sinensis catechins have a variety of antioxidant mechanisms that benefit our bodies. EGCG is the most powerful antioxidant activity compared to other catechins due to its unique chemical composition. EGCG involves eight hydroxyl groups and three benzene rings, contributing to its antioxidant properties. Catechins have several antioxidant mechanisms, including chelating iron to prevent the Fenton reaction, scavenging free radicals, inserting into the DNA helix and binding to free radicals directly, and increasing antioxidant enzymes. The review results reveal that catechins can stimulate antioxidant enzymes. Even though many studies have described the various antioxidant mechanisms of enzymes, some of the mechanisms remain unknown. Further study is needed to elucidate the exact functions of catechins that can replenish and accumulate antioxidant enzymes in the body and the distinction between these methods. Studies about the specific mechanisms of EGCG in activating the Trx antioxidant system are also essential.

LIST OF ABBREVIATIONS

AAPH, 2,2-azobis(2-amidinopropane) dihydrochloride; ACE, Angiotensin-converting enzyme; AFB1, aflatoxin B1; Al2O3-NPs, Aluminum oxide nanoparticles; AFB1, Aflatoxin B1; ALT, Alanine Aminotransferase; ARE, Antioxidant response element; AST, Aspartate transaminase; BTE, Black Tea Extract; CAT, Catalase; CNP, Copper nanoparticles; DMH, Dimethyl hydrazine; ECs, Extract Camellia sinensis; EGCG, Epigallocatechin gallate; ERK, Extracellular-signal-regulated kinase; FBTA, Fuzhuan-brick tea; GPx, Glutathione peroxidase; GR, Glutathione reductase; GSH, Glutathione; GSSH, Oxidized glutathione; GST, Glutathione S-transferase; GT, Green tea; GTE, Green tea extract; HO-1, Heme oxygenase-1; i.p, Intraperitoneally administration; IR, Ionizing radiation; i.v, Intravenally administration; IVR domain, intervening region domain; LDL, low-density lipoprotein; LOOH, Lipid hydroperoxides; LPO, Lipid peroxidation; MAPK, Mitogen-activated protein kinase; MDA, Malondialdehyde; MSG, Monosodium glutamate; mtDNA, Mitochondria deoxyribonucleic acid; NAC, N-acetylcysteine; NADPH, Nicotinamide adenine dinucleotide phosphate; NAF, Natrium Flouride; Nrf2, Nuclear factor-erythroid-2 related factor 2; NQO1, NADPH Quinone Dehydrogenase 1 [(Human)]; NOX, Nitric oxide; SNP, Sodium nitroprusside; SOD, Superoxide dismutase; STZ, Streptozotocin; TAS, Total antioxidant status; Trx, Thioredoxin; UA, Uric acid; UUO, Unilateral ureteral obstruction; UVB, Ultraviolet B; WT, White tea; 8-Ohdg, 8-Hydroxy-2-Deoxyguanosine.

AUTHOR CONTRIBUTIONS

Jutti Levita (JL) was responsible for the conception and design of the review and checked, finalized, and revised the manuscript. Lidya Cahyo Bawono searched, collected, and

reviewed and wrote the original draft preparation. Miski Aghnia Khairinisa and Supat Jiranusornkul checked the manuscript and collected articles. All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVALS

This study does not include experiments on animal or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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REFERENCES

Abdel-Moneim A, El-Senousy WM, Abdel-Latif M, Khalil RG. Association between antioxidant enzyme activities and *Enterovirus*-infected type 1 diabetic children. Med Princ Pract, 2018; 27:86–91; https://doi.org/10.1159/000486718

Abolfathi AA, Mohajeri D, Rezaie A, Nazeri M. Protective effects of green tea extract against hepatic tissue injury in streptozotocin-induced diabetic rats. Evid-Based Complement Altern Med, 2012; 2012; https://doi.org/10.1155/2012/740671

Abrahim NN, Kanthimathi MS, Abdul-Aziz A. Piper betle shows antioxidant activities, inhibits MCF-7 cell proliferation and increases activities of catalase and superoxide dismutase. BMC Complement Altern Med, 2012; 12:1; https://doi.org/10.1186/1472-6882-12-220

Afzal SM, Vafa A, Rashid S, Shree A, Islam J, Ali N, Sultana S. Amelioration of N,N′-dimethylhydrazine induced colon toxicity by epigallocatechin gallate in Wistar rats. Hum Exp Toxicol, 2021; 40:1558–71; https://doi.org/10.1177/09603271211002884

Ahmed OM, Abdul-Hamid MM, El-Bakry AM, Mohamed HM, Abdel Rahman FEZS. *Camellia sinensis* and epicatechin abate doxorubicin-induced hepatotoxicity in male Wistar rats via their modulatory effects on oxidative stress, inflammation, and apoptosis. J Appl Pharm Sci, 2019; 9:30–44; https://doi.org/10.7324/JAPS.2019.90405

Bansal S, Vyas S, Bhattacharya S, Sharma M. Catechin prodrugs and analogs: a new array of chemical entities with improved pharmacological and pharmacokinetic properties. Nat Prod Rep, 2013; 30:1438; https://doi.org/10.1039/c3np70038k

Bártíková H, Boušová I, Matoušková P, Szotáková B, Skálová L. Effect of green tea extract-enriched diets on insulin and leptin levels, oxidative stress parameters and antioxidant enzymes activities in obese mice. Polish J Food Nutr Sci, 2017; 67:233–40; https://doi.org/10.1515/pjfns-2017-0004

Basu A, Betts NM, Mulugeta A, Tong C, Newman E, Lyons TJ. Green tea supplementation increases glutathione and plasma antioxidant capacity in adults with the metabolic syndrome. Nutr Res, 2013; 33:180–7; https://doi.org/10.1016/j.nutres.2012.12.010

Berilli P, Fanaro GB, Santos JP, Reyes Reyes FG, Iglesias AH, Reis M, Cazarin CBC, Junior MRM. White tea modulates antioxidant defense of endurance-trained rats. Curr Res Physiol, 2022; 5:256–64; https://doi.org/10.1016/j.crphys.2022.06.002

Bernatoniene J, Kopustinskiene DM. The role of catechins in cellular responses to oxidative stress. Molecules, 2018; 23:1–11; https://doi.org/10.3390/molecules23040965

Cao SY, Li BY, Gan RY, Mao QQ, Wang YF, Shang A, Meng J, Xu X, Wei X, Li H. The *in vivo* antioxidant and hepatoprotective actions of selected Chinese teas. Foods, 2020; 9; https://doi.org/10.3390/foods9030262

Carlsen H, Myhrstad MCW, Thoresen M, Moskaug JØ, Blomhoff R. Berry intake increases the activity of the γ-glutamylcysteine synthetase promoter in transgenic reporter mice. J Nutr, 2003; 133:2137–40; https://doi.org/10.1093/jn/133.7.2137

Chen D, Zhang KQ, Li B, Sun DQ, Zhang H, Fu Q. Epigallocatechin-3-gallate ameliorates erectile function in aged rats via regulation of PRMT1/DDAH/ADMA/NOS metabolism pathway. Asian J Androl, 2016; 18:291–7; https://doi.org/10.4103/1008-682X.178486

Chiodo SG, Leopoldini M, Russo N, Toscano M. The inactivation of lipid peroxide radical by quercetin. A theoretical insight. Phys Chem Chem Phys, 2010; 12:7662–70; https://doi.org/10.1039/b924521a

Chong SJK, Howard KA, Knox C. Hypokalaemia and drinking green tea: a literature review and report of 2 cases. BMJ Case Rep, 2016; 2016; https://doi.org/10.1136/bcr-2016-214425

Chow HHS, Hakim IA, Vining DR, Crowell JA, Ranger-Moore J, Chew WM, Celaya CA, Rodney SR, Hara Y, Alberts DS. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of polyphenon E in healthy individuals. Clin Cancer Res, 2005; 11:4627–33; https://doi.org/10.1158/1078-0432.CCR-04-2549

Codoñer-Franch P, Pons-Morales S, Boix-García L, Valls-Bellés V. Oxidant/antioxidant status in obese children compared to pediatric patients with type 1 diabetes mellitus. Pediatr Diabetes, 2010; 11:251–7; https://doi.org/10.1111/j.1399-5448.2009.00565.x

Costantini D. Understanding diversity in oxidative status and oxidative stress: the opportunities and challenges ahead. J Exp Biol, 2019; 222:1–9; https://doi.org/10.1242/jeb.194688

Cromie MM, Gao W. Epigallocatechin-3-gallate enhances the therapeutic effects of leptomycin B on human lung cancer A549 cells. Oxid Med Cell Longev, 2015; 2015; https://doi.org/10.1155/2015/217304

De Almeida Gonçalves G, De Sá-Nakanishi AB, Wendt MMN, Comar JF, Bersani Amado CA, Bracht A, Peralta RM. Green tea extract improves the oxidative state of the liver and brain in rats with adjuvant-induced arthritis. Food Funct, 2015; 6:2701–11; https://doi.org/10.1039/c5fo00548e

Dias TR, Carrageta DF, Alves MG, Oliveira PF, Silva BM. White tea. Elsevier Inc., Amsterdam, The Netherlands, vol. 2024, 2018; https://doi.org/10.1016/B978-0-12-812491-8.00058-8

Dias TR, Tomas G, Teixeira NF, Alves MG, Oliveira PF, Silva BM. White tea (*Camellia sinensis* (L.)): antioxidant properties and beneficial health effects. Int J Food Sci Nutr Diet, 2013; 2:19–26; https://doi.org/http://dx.doi.org/10.19070/2326-3350-130005

Didangelos T, Karlafti E, Kotzakioulafi E, Kontoninas Z, Margaritidis C, Giannoulaki P, Kantartzis K. Efficacy and safety of the combination of superoxide dismutase, alpha lipoic acid, vitamin B12, and carnitine for 12 months in patients with diabetic neuropathy. Nutrients, 2020; 12:1–15; https://doi.org/10.3390/nu12113254

Dong R, Wang D, Wang X, Zhang K, Chen P, Yang CS, Zhang J. Epigallocatechin-3-gallate enhances key enzymatic activities of hepatic thioredoxin and glutathione systems in selenium-optimal mice but activates hepatic Nrf2 responses in selenium-deficient mice. Redox Biol, 2016; 10:221–32; https://doi.org/10.1016/j.redox.2016.10.009

EI Fattah MEA, Abdelgawad MR, EI Boughdady BAE. The protective role of epigallocatechin gallate (EGCG) on oxidative stress in normal and treated rats with aluminum oxide nanoparticles. Int J Adv Biochem Res, 2018; 2:43–52; https://doi.org/10.33545/26174693.2018.v2.i2a.21

Elsayed Azab A, Adwas AA, Elsayed ASI, Quwaydir FA. Oxidative stress and antioxidant mechanisms in human body. J Appl Biotechnol Bioeng, 2019; 6:43–7; https://doi.org/10.15406/jabb.2019.06.00173

Elzoghby RR, Hamoda AF, Abed-Ftah A, Farouk M. Protective role of vitamin C and green tea extract on malathion-induced hepatotoxicity and nephrotoxicity in rats. Am J Pharmacol Toxicol, 2014; 9:174–85; https://doi.org/10.3844/ajptsp.2014.174-185

Ezeja EP, Onuoha NO, Ufere EA. Effects of green tea (*Camellia sinensis*) on paracetamol-induced oxidative stress markers in Wistar rats. J Dietitians Assoc Niger, 2022; 12:30–7; https://doi.org/10.4314/jdan.v12i1.5

Fan FS. Iron deficiency anemia due to excessive green tea drinking. Clin Case Rep, 2016; 4:1053–6; https://doi.org/10.1002/ccr3.707

Gramza A, Korczak J. Tea constituents (*Camellia sinensis* L.) as antioxidants in lipid systems. Trends Food Sci Technol, 2005; 16:351–8; https://doi.org/10.1016/j.tifs.2005.02.004

Grzesik M, Naparło K, Bartosz G, Sadowska-Bartosz I. Antioxidant properties of catechins: comparison with other antioxidants. Food Chem, 2018; 241:480–92; https://doi.org/10.1016/j.foodchem.2017.08.117

Guo C, Bi J, Li X, Lyu J, Liu X, Wu X, Liu J. Immunomodulation effects of polyphenols from thinned peach treated by different drying methods on RAW264.7 cells through the NF-κB and Nrf2 pathways. Food Chem, 2021; 340:127931; https://doi.org/10.1016/j.foodchem.2020.127931

Gutowski M, Kowalczyk S. A study of free radical chemistry: their role and pathophysiological dignificance. Acta Biochim Pol, 2013; 60:1–16

Hadjipanayis A, Efstathiou E, Papaevangelou V. Hepatotoxicity in an adolescent with black iced tea overconsumption. Pediatr Gastroenterol Hepatol Nutr, 2019; 22:387–91; https://doi.org/10.5223/pghn.2019.22.4.387

Haider K, Haider MR, Neha K, Yar MS. Free radical scavengers: an overview on heterocyclic advances and medicinal prospects. Eur J Med Chem, 2020; 204:112607; https://doi.org/10.1016/j.ejmech.2020.112607

Hajam YA, Rani R, Ganie SY, Sheikh TA, Javaid D, Qadri SS, Pramodh S, Alsulimani A, Alkhanani MF, Harakeh S, Hussain A, Haque S, Reshi MS. Oxidative stress in human pathology and aging: molecular mechanisms and perspectives. Cells, 2022; 11; https://doi.org/10.3390/cells11030552

Han XD, Zhang Y, Wang KL, Huang YP, Yang ZB, Liu Z. The involvement of Nrf2 in the protective effects of (-)- epigallocatechin-3-gallate (EGCG) on NaASO2-induced hepatotoxicity. Oncotarget, 2017; 8:65302–12.

Hashim M, Fry J. Evaluation of direct and indirect antioxidant properties of selected four natural chemical compounds: quercetin, epigallocatechin-3-gallate, indole-3-carbinol and sulforaphane by DPPH radical scavenging assay. J Biomed Res Environ Sci, 2020; 1:389–92; https://doi.org/10.37871/jbres1170

He J, Xu L, Yang L, Wang X. Epigallocatechin gallate is the most effective catechin against antioxidant stress via hydrogen peroxide and radical scavenging activity. Med Sci Monit, 2018; 24:8198–206; https://doi.org/10.12659/MSM.911175

Heikal TM, Mossa ATH, Rasoul MAA, Marei GIK. The ameliorating effect of green tea extract against cyromazine and chlorpyrifos induced liver toxicity in male rats. Asian J Pharm Clin Res, 2013; 6(1):47–55

Huang ST, Hung YA, Yang MJ, Chen IZ, Yuann JMP, Liang JY. Effects of epigallocatechin gallate on the stability of epicatechin in a photolytic process. Molecules, 2019; 24:1–13; https://doi.org/10.3390/molecules24040787

Huang Z, Pang Y, Hao H, Du W, Zhao X, Zhu H. Effects of epigallocatechin-3-gallate on bovine oocytes matured *in vitro*. Asian Australas J Anim Sci, 2018; 31:1420–30; https://doi.org/10.5713/ajas.17.0880

Hussain S. Comparative efficacy of epigallocatechin-3-gallate against H2O2-induced ROS in cervical cancer biopsies and HeLa cell lines. Wspolczesna Onkol, 2017; 21:209–12; https://doi.org/10.5114/wo.2017.70110

Ibrahim MA, Bakhaat GA, Tammam HG, Mohamed RM, El-Naggar SA. Cardioprotective effect of green tea extract and vitamin E on cisplatin-induced cardiotoxicity in mice: toxicological, histological and immunohistochemical studies. Biomed Pharmacother, 2019; 113:108731; https://doi.org/10.1016/j.biopha.2019.108731

Ibrahim MA, Khalaf AA, Galal MK, Ogaly HA, Hassan AHM. Ameliorative influence of green tea extract on copper nanoparticle-induced hepatotoxicity in rats. Nanoscale Res Lett, 2015; 10; https://doi.org/10.1186/s11671-015-1068-z

Ikeda I, Kobayashi M, Hamada T, Tsuda K, Goto H, Imaizumi K, Nozawa A, Sugimoto A, Kakuda T. Heat-epimerized tea catechins rich in gallocatechin gallate and catechin gallate are more effective to inhibit cholesterol absorption than tea catechins rich in epigallocatechin gallate and epicatechin gallate. J Agric Food Chem, 2003; 51:7303–7; https://doi.org/10.1021/jf034728l

Jaganjac M, Milkovic L, Sunjic SB, Zarkovic N. The NRF2, thioredoxin, and glutathione system in tumorigenesis and anticancer therapies. Antioxidants, 2020; 9:1151; https://doi.org/10.3390/antiox9111151

Jetsrisuparb A, Komwilaisak P, Wiangnon S. Green tea consumption prevented iron overload: a case report of thalassemia intermedia. J Hematol Transfus Med, 2014; 24:389–94.

Jówko E, Długołęcka B, Makaruk B, Cieśliński I. The effect of green tea extract supplementation on exercise-induced oxidative stress parameters in male sprinters. Eur J Nutr, 2015; 54:783–91; https://doi.org/10.1007/s00394-014-0757-1

Karlenius TC, Tonissen KF. Thioredoxin and cancer: a role for thioredoxin in all states of tumor oxygenation. Cancers (Basel), 2010; 2:209–32; https://doi.org/10.3390/cancers2020209

Khan G, Haque SE, Anwer T, Ahsan MN, Safhi MM, Alam MF. Cardioprotective effect of green tea extract on doxorubicin-induced cardiotoxicity in rats. Acta Pol Pharm Drug Res, 2014; 71:861–8; https://doi.org/10.3742/opem.2005.5.2.137

Kim E, Hwang K, Lee J, Han SY, Kim EM, Park J, Cho JY. Skin protective effect of epigallocatechin gallate. Int J Mol Sci, 2018; 19:1–14; https://doi.org/10.3390/ijms19010173

Kodidela S, Shaik FB, Chinta V, Mohammad SA, Pasala C, Mittameedi CM, Maddu N, Wudayagiri R, Nallanchakravarthula V. Possible ameliorative role of green tea on chronic alcohol mediated renal toxicity of STZ -induced diabetic rats. Clin Nutr Exp, 2020; 34:1–25; https://doi.org/10.1016/j.yclnex.2020.09.001

Kucera O, Mezera V, Moravcova A, Endlicher R, Lotkova H, Drahota Z, Cervinkova Z. *In vitro* toxicity of epigallocatechin gallate in rat liver mitochondria and hepatocytes. Oxid Med Cell Longev, 2015; 2015; https://doi.org/10.1155/2015/476180

Latos-Brozio M, Masek A. Structure-activity relationships analysis of monomeric and polymeric polyphenols (quercetin, rutin and catechin) obtained by various polymerization methods. Chem Biodivers, 2019; 16; https://doi.org/10.1002/cbdv.201900426

Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Testa G, Cacciatore F, Bonaduce D, Abete P. Oxidative stress and diseases. Oxid Stress Dis, 2018; 13:757–72; https://doi.org/10.5772/2535

Lopez EO, Parmar M, Pendela VS, Terrell JM. Lisinopril. StatPearls Publishing LLC, Treasure Island, FL, 2022.

Lo´pez-Burillo S, Tan DX, Mayo JC, Sainz RM, Manchester LC, Reiter RJ. Melatonin, xanthurenic acid, resveratrol, EGCG, vitamin C and a-lipoic acid differentially reduce oxidative DNA damage induced by Fenton reagents: a study of their individual and synergistic actions. J Pineal Res, 2003; 34:269–77.

Lushchak VI, Storey KB. Oxidative stress concept updated: definitions, classifications, and regulatory pathways implicated. EXCLI J, 2021; 20:956–67; https://doi.org/10.17179/excli2021-3596

Ma Q. Role of Nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol, 2013; 53:401–26; https://doi.org/10.1146/annurev-pharmtox-011112-140320

Maeda-Yamamoto M, Nishimura M, Kitaichi N, Nesumi A, Monobe M, Nomura S, Horie Y, Tachibana H, Nishihira J. A randomized, placebo-controlled study on the safety and efficacy of daily ingestion of green tea (*Camellia sinensis* L.) cv. "Yabukita" and "Sunrouge" on eyestrain and blood pressure in healthy adults. Nutrients, 2018; 10:569; https://doi.org/10.3390/nu10050569

Mahboub FA. The effect of green tea (*Camellia sinensis*) extract against hepato-toxicity induced by tamoxifen in rats. J Food Process Technol, 2016; 7; https://doi.org/10.4172/2157-7110.1000625

Martins A, Schimidt HL, Garcia A, Colletta Altermann CD, Santos FW, Carpes FP, Silva WC, Carpes PBM. Supplementation with different teas from *Camellia sinensis* prevents memory deficits and hippocampus oxidative stress in ischemia-reperfusion. Neurochem Int, 2017; 108:287–95; https://doi.org/10.1016/j.neuint.2017.04.019

Mattmiller SA, Carlson BA, Sordillo LM. Regulation of inflammation by selenium and selenoproteins: impact on eicosanoid biosynthesis. J Nutr Sci, 2013; 2:1–13; https://doi.org/10.1017/jns.2013.17

Mazur-Bialy AI, Kozlowska K, Pochec E, Bilski J, Brzozowski T. Myokine irisin-induced protection against oxidative stress *in vitro*. Involvement of heme oxygenase-1 and antioxidazing enzymes superoxide dismutase-2 and glutathione peroxidase. J Physiol Pharmacol, 2018; 69:117–25; https://doi.org/10.26402/JPP.2018.1.13

Mazzanti G, Di Sotto A, Vitalone A. Hepatotoxicity of green tea: an update. Arch Toxicol, 2015; 89:1175–91; https://doi.org/10.1007/s00204-015-1521-x

Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension. J Am Coll Cardiol, 2018; 71:1474–82; https://doi.org/10.1016/j.jacc.2018.01.058

Misaka S, Ono Y, Uchida A, Ono T, Abe O, Ogata H, Sato H, Suzuki M, Onoue S, Shikama Y, Shimomura K. Impact of green tea catechin ingestion on the pharmacokinetics of lisinopril in healthy volunteers. Clin Transl Sci, 2021; 14:476–80; https://doi.org/10.1111/cts.12905

Mokra D, Joskova M, Mokry J. Therapeutic effects of green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. Int J Mol Sci, 2023; 24; https://doi.org/10.3390/ijms24010340

Moskaug JO, Carlsen H, Myhrstad MCW, Blomhoff R. Polyphenols and glutathione synthesis regulation. Am J Clin Nutr, 2005; 81:277–83; https://doi.org/10.1093/ajcn/81.1.277s

Mossakowski AA, Pohlan J, Bremer D, Lindquist R, Millward JM, Bock M, Pollok K, Mothes R, Viohl L, Radbruch M, Gerhard J, Bellmann-Strobl J, Behrens J, Infante-Duarte C, Mähler A, Boschmann M, Rinnenthal JL, Füchtemeier M, Herz J, Pache FC, Bardua M, Priller J, Hauser AE, Paul F, Niesner R, Radbruch H. Tracking CNS and systemic sources of oxidative stress during the course of chronic neuroinflammation. Acta Neuropathol, 2015; 130:799–814; https://doi.org/10.1007/s00401-015-1497-x

Nakayama T, Hashimoto T, Kajiya K, Kumazawa S. Affinity of polyphenols for lipid bilayers. BioFactors, 2000; 13:147–51.

Nunes AR, Alves MG, Tomás GD, Conde VR, Cristóvão AC, Moreira PI, Oliveira PF, Silva BM. Daily consumption of white tea (*Camellia sinensis* (L.)) improves the cerebral cortex metabolic and oxidative profile in prediabetic Wistar rats. Br J Nutr, 2015; 113:832–42; https://doi.org/10.1017/S0007114514004395

Opuwari C, Monsees T. Green tea consumption increases sperm concentration and viability in male rats and is safe for reproductive, liver and kidney health. Sci Rep, 2020; 10:1–14; https://doi.org/10.1038/s41598-020-72319-6

Pan B, Li H, Lang D, Xing B. Environmentally persistent free radicals: occurrence, formation mechanisms and implications. Environ Pollut, 2019; 248:320–31; https://doi.org/10.1016/j.envpol.2019.02.032

Park DH, Park JY, Kang KS, Hwang GS. Neuroprotective effect of gallocatechin gallate on glutamate-induced oxidative stress in hippocampal HT22 cells. Molecules, 2021; 26; https://doi.org/10.3390/molecules26051387

Petramfar P, Mohammadi SS, Hosseinzadeh F. Treatment of idiopathic intracranial hypotension with tea: a case report. Iran Red Crescent Med J, 2016; 18; https://doi.org/10.5812/ircmj.24620

Phimphilai S, Koonyosying P, Hutachok N, Kampoun T, Daw R, Chaiyasut C, Prasartthong-osoth V, Srichairatanakool S. Identifying chemical composition, safety and bioactivity of Thai rice grass extract drink in cells and animals. Molecules, 2021; 26(22):1–19.

Prasanth MI, Sivamaruthi BS, Chaiyasut C, Tencomnao T. A review of the role of green tea (*Camellia sinensis*) in antiphotoaging, stress resistance, neuroprotection, and autophagy. Nutrients, 2019; 11:1–24; https://doi.org/10.3390/nu11020474

Rakshit S, Jana S, Dassarma B, Sarkar B, Samanta S. Protective role of green tea extract against cold-restraint stress induced gastric ulcerogenesis in albino rats. J Pharm Chem Biol Sci, 2018; 6:218–27.

Reddyvari H, Govatati S, Matha SK, Korla SV, Malempati S, Pasupuleti SR, Bhanoori M, Nallanchakravarthula V. Therapeutic effect of green tea extract on alcohol induced hepatic mitochondrial DNA damage in albino wistar rats. J Adv Res, 2017; 8:289–95; https://doi.org/10.1016/j.jare.2017.02.002

Reeves KG, Kanai Y. Electronic excitation dynamics in liquid water under proton irradiation. Sci Rep, 2017; 7:40379; https://doi.org/10.1038/srep40379

Regulski M, Regulska K, Stanisz B, Murias M, Gieremek P, Wzgarda A, Niznik B. Chemistry and pharmacology of angiotensin-converting enzyme inhibitors. Curr Pharm Des, 2015; 21:1764–75; https://doi.org/10.2174/1381612820666141112160013

Richi B, Kale RK, Tiku AB. Radio-modulatory effects of green tea catechin EGCG on pBR322 plasmid DNA and murine splenocytes against gamma-radiation induced damage. Mutat Res Genet Toxicol Environ Mutagen, 2012; 747:62–70; https://doi.org/10.1016/j.mrgentox.2012.04.002

Sadowska-Krępa E, Domaszewski P, Pokora I, Zebrowska A, Gdańska A, Podgórski T. Effects of medium-term green tea extract supplementation combined with crossfit workout on blood antioxidant status and serum brain-derived neurotrophic factor in young men: a pilot study. J Int Soc Sports Nutr, 2019; 16; https://doi.org/10.1186/s12970-019-0280-0

Saravana Kumari M, Anuradha R. Effect of green tea extract on lipid peroxidation and antioxidant activity on mercuric chloride induced toxicity in rats. Int J Pharm Sci Rev Res, 2016; 36:67–72.

Shakeela Begum M, Padmavathi P, Saradamma B, Maturu P, Ananda Vardhan H, Varadacharyulu NC, Reddy DV. Effect of green tea consumption on RBC morphology, membrane properties and antioxidant status in chronic cigarette smokers. Indian J Biochem Biophys, 2018; 55:256–63.

Silveira AC, Rato L, Oliveira PF, Alves MG, Silva BM. White tea intake abrogates markers of streptozotocin-induced prediabetes oxidative stress in rat lungs'. Molecules, 2021; 26:1–12; https://doi.org/10.3390/molecules26133894

Spadiene A, Savickiene N, Ivanauskas L, Jakstas V, Skesters A, Silova A, Rodovicius H. Antioxidant effects of *Camellia sinensis* L. extract in patients with type 2 diabetes. J Food Drug Anal, 2014; 22:505–11; https://doi.org/10.1016/j.jfda.2014.04.001

Suraphad P, Suklaew PO, Ngamukote S, Adisakwattana S, Mäkynen K. The effect of isomaltulose together with green tea on glycemic response and antioxidant capacity: a single-blind, crossover study in healthy subjects. Nutrients, 2017; 9; https://doi.org/10.3390/nu9050464

Szczeklik K, Krzysciak W, Mach P, Darczuk D, Cibor D, Rodacki T, Mach P, Darczuk D, Cibor D, Pytko-Polonczyk J, Rodacki T, Owczarek D. Alterations in glutathione peroxidase and superoxide dismutase activities in plasma and saliva in relation to disease activity in patients with Crohn's disease. J Physiol Pharmacol, 2016; 67:709–15.

Teng Y, Wu D. Anti-fatigue effect of green tea polyphenols (-)-epigallocatechin-3-gallate (EGCG). Pharmacogn J, 2017; 13:326–31.

Thangapandiyan S, Miltonprabu S. Epigallocatechin gallate supplementation protects against renal injury induced by fluoride intoxication in rats: role of Nrf2/HO-1 signaling. Toxicol Rep, 2014; 1:12–30; https://doi.org/10.1016/j.toxrep.2014.01.002

Thangapandiyan S, Miltonprabu S. Epigallocatechin gallate exacerbates fluoride-induced oxidative stress mediated testicular toxicity in rats through the activation of Nrf2 signaling pathway. Asian Pac J Reprod, 2015; 4:272–87; https://doi.org/10.1016/j.apjr.2015.07.005

Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol, 2007; 39:44–84; https://doi.org/10.1016/j.biocel.2006.07.001

Vranković J. Age-related changes in antioxidant and glutathione S-transferase enzyme activities in the Asian clam. Biochemistry, 2016; 81:224–32; https://doi.org/10.1134/S0006297916030044

Wagner C, Fachinetto R, Dalla Corte CL, Brito VB, Severo D, de Oliveira Costa Dias G, Morel AF, Nogueira CW, Rocha JBT. Quercitrin, a glycoside form of quercetin, prevents lipid peroxidation *in vitro*. Brain Res, 2006; 1107:192–8; https://doi.org/10.1016/j.brainres.2006.05.084

Wang T, Li Q, Bi K. Bioactive flavonoids in medicinal plants: structure, activity and biological fate. Asian J Pharm Sci, 2018; 13:12–23; https://doi.org/10.1016/j.ajps.2017.08.004

Wang YQ, Li QS, Zheng XQ, Lu JL, Liang YR. Antiviral effects of green tea EGCG and its potential application against COVID-19. Molecules, 2021; 26:3962; https://doi.org/10.3390/molecules26133962

Wang Y, Wang B, Du F, Su X, Sun G, Zhou G, Bian X, Liu N. Epigallocatechin-3-gallate attenuates oxidative stress and inflammation in obstructive nephropathy via NF-κB and Nrf2/HO-1 signalling pathway regulation. Basic Clin Pharmacol Toxicol, 2015; 117:164–72; https://doi.org/10.1111/bcpt.12383

Wang Y, Wu J, Wang L, Yang P, Liu Z, Rajput SA, Hassan M, Qi D. Epigallocatechin gallate and glutathione attenuate aflatoxin B1-induced acute liver injury in ducklings via mitochondria-mediated apoptosis and the Nrf2 signalling pathway. Toxins (Basel), 2022; 14:1–14; https://doi.org/10.3390/toxins14120876

Wu J. Tackle the free radicals damage in COVID-19. Nitric Oxide, 2020; 102:39–41; https://doi.org/10.1016/j.niox.2020.06.002

Wu JH, Miao W, Hu LG, Batist G. Identification and characterization of novel Nrf2 inducers designed to target the intervening region of keap1. Chem Biol Drug Des, 2010; 75:475–80; https://doi.org/10.1111/j.1747-0285.2010.00955.x

Wu M, Wu X, Zhu J, Li F, Wei X, Wang Y. Selenium-enriched and ordinary green tea extracts prevent high blood pressure and alter gut microbiota composition of hypertensive rats caused by high-salt diet. Food Sci Hum Wellness, 2022; 11:738–51; https://doi.org/10.1016/j.fshw.2021.12.031

Xie LW, Cai S, Zhao TS, Li M, Tian Y. Green tea derivative (−)-epigallocatechin-3-gallate (EGCG) confers protection against ionizing radiation-induced intestinal epithelial cell death both *in vitro* and *in vivo*. Free Radic Biol Med, 2020; 161:175–86; https://doi.org/10.1016/j.freeradbiomed.2020.10.012

Yan Z, Zhong Y, Duan Y, Chen Q, Li F. Antioxidant mechanism of tea polyphenols and its impact on health benefits. Anim Nutr, 2020; 6:115–23; https://doi.org/10.1016/j.aninu.2020.01.001

Yang GZ, Wang ZJ, Bai F, Qin XJ, Cao J, Lv JY, Zhang M. Epigallocatechin-3-gallate protects HUVECs from PM2.5-induced oxidative stress injury by activating critical antioxidant pathways. Molecules, 2015; 20:6626–39; https://doi.org/10.3390/molecules20046626

Yousefi T, Moazami HR. Water radiolysis by gamma –irradiation for high quality synthesis of nickel oxide nano sheet. J Nanostruct, 2019; 9:141–5; https://doi.org/10.22052/JNS.2019.01.015

Zahra KF, Lefter R, Ali A, Abdellah EC, Trus C, Ciobica A, Timofte D. The involvement of the oxidative stress status in cancer pathology: a double view on the role of the antioxidants. Oxid Med Cell Longev, 2021; 2021; https://doi.org/10.1155/2021/9965916

Zanchi MM, Manfredini V, Brum D, dos S, Vargas LM, Spiazzi CC, Soares MB, Izaguirry AP, Santos FW. Green tea infusion improves cyclophosphamide-induced damage on male mice reproductive system. Toxicol Rep, 2015; 2:252–60; https://doi.org/10.1016/j.toxrep.2014.12.016

Zhao P, Alam MB, Lee SH. Protection of UVB-induced photoaging by fuzhuan-brick tea aqueous extract via MAPKs/Nrf2-mediated down-regulation of MMP-1. Nutrients, 2019; 11; https://doi.org/10.3390/nu11010060

Zhao T, Li C, Wang S, Song X. Green tea (*Camellia sinensis*): a review of its phytochemistry, pharmacology, and toxicology. Molecules, 2022; 27; https://doi.org/10.3390/molecules27123909

Zhao H, Zhu W, Jia L, Sun X, Chen G, Zhao X, Li X, Meng X, Kong L, Xing L, Yu J. Phase I study of topical epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy. Br J Radiol, 2016; 89:20150665; https://doi.org/10.1259/bjr.20150665

Zhu W, Jia L, Chen G, Zhao H, Sun X, Meng X, Zhao X, Xing L, Yu J, Zheng M. Epigallocatechin-3-gallate ameliorates radiation-induced acute skin damage in breast cancer patients undergoing adjuvant radiotherapy. Oncotarget, 2016; 7:48607–13; https://doi.org/10.18632/oncotarget.9495

Zwolak I. Epigallocatechin gallate for management of heavy metal-induced oxidative stress: mechanisms of action, efficacy, and concerns. Int J Mol Sci, 2021; 22; https://doi.org/10.3390/ijms22084027

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