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Review Article

The therapeutic effects and antioxidant properties of epigallocatechin-3 gallate: A new review

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Abstract: The aim of this review is to investigate the possible protective and preventive effects of epigallocatechin-3 gallate (EGCG) in terms of human health including hepatoprotective, neuroprotective, cardioprotective, nephrotoxicity and anticancer effects. Green tea is one of the most consumed beverages in many countries, especially in Turkey and it plays protective roles in the treatment of various diseases via the polyphenol it contains. It is known that EGCG, which is the main bioactive polyphenol in green tea, has versatile bioactivities. It has been determined that EGCG has the highest free radical scavenging ability among common phenolic compounds. It regulates gene expression and molecular signaling pathways by inhibiting oxidative stress and inflammation. In addition, it prevents cell death by suppressing cytokine production and neutrophil migration in inflammatory diseases. With the studies conducted in the last decade, it has been determined that EGCG has anticancer, antioxidative, antiinflammatory, antidiabetic, antitumor, antihypertensive and neuroprotective activities. Especially, its anticancer effect has been found to have chemopreventive and chemotherapeutic activities in various cancer types such as colon, lung and breast cancer with *in vivo* and *in vitro* studies conducted to investigate molecular targets. This review was written to examine the possible protective and preventive effects of EGCG in terms of human health, including its hepatoprotective, neuroprotective, cardioprotective, nephrotoxicity and anticancer effects.

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1. INTRODUCTION

1.1. General Properties of Epigallocatechin-3 Gallate

Antioxidants and polyphenols, which have a distinctive feature in terms of human health and which are found in many plants, prevent damage to cells by reacting with free radicals (Gumuscu, 2019). Polyphenols, a group of plant metabolites that are abundant in plants and that have strong antioxidant properties, provide protection against various chronic diseases caused by oxidative stress. The consumption of dietary polyphenols by humans is of great interest due to their prevention effects of degenerative diseases and possible health benefits (Ganesan & Xu, 2017).

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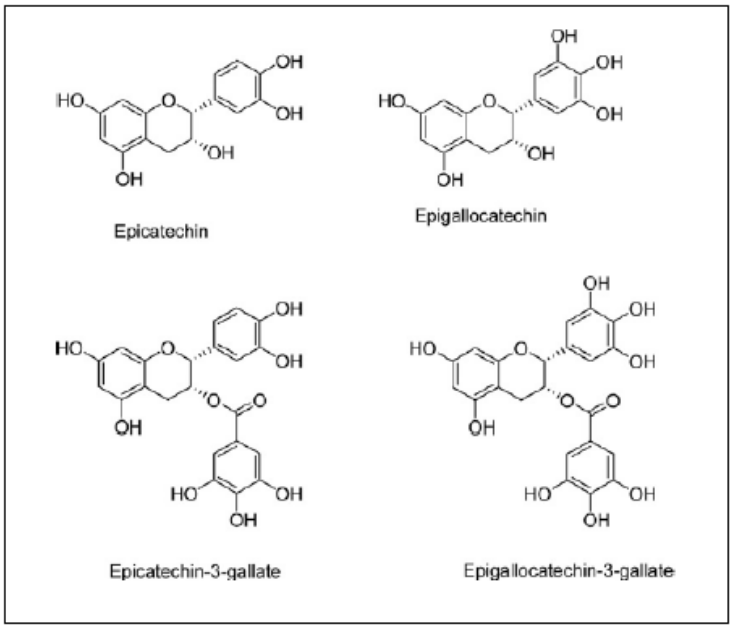
Plant-based products such as fruit, tea and coffee are very rich in polyphenol and antioxidant content (Figure 1). Tea is one of the most popular beverages around the world, both hot and cold. Different tea products such as black tea, green tea, and white tea are produced from the leaves of the *Camellia sinensis* plant with different methods applied during harvesting and processing. Since green tea is produced without oxidation, it is a rich source of unoxidized catechin (Elmas & Gezer, 2019).

Figure 1. Green tea plant (*Camellia sinensis* L.) (Guzeldir, 2015).

There are 80% polyphenols and flavonoids in the structure of green tea. Polyphenols are cyclic organic compounds bearing hydroxyl or carboxyl groups in their structures (Figure 2). Thus, they easily capture and neutralize free radicals (Sarıca, 2014; Legeay *et al.,* 2015). The phenolic compound is found in the raw extracts of green tea which consists of catechin and flavonol glycosides. Epigallocatechin-3-gallate (EGCG) is the most abundant catechin which is the main polyphenol component of green tea, nearly 50-80% of total green tea catechins. Green tea catechins have two benzene rings known as A and B rings. EGCG has two isomers in trans configuration. In addition, it has a higher capacity than vitamins C and E in terms of antioxidant capacity (Nikoo *et al.,* 2018). Green tea leaves contain carbohydrates such as cellulose, glucose, sucrose, fructose, pectins, as well as proteins, minerals, small amounts of lipids, sterols, vitamins, pigments, and volatile compounds (Figure 2) (Bilcanoglu, 2019).

Figure 2. Molecular structure of major green tea polyphenols (Guzeldir, 2015).



Recently some studies determined that EGCG, the most abundant polyphenolic catechin in green tea, has a strong antioxidant, antiinflammatory, antidiabetic, antitumor properties as well as anticarcinogenic properties. EGCG, the most active component of catechins in tea, has a very important role in ensuring DNA stability and in healthy life (Gumuscu, 2019).

In recently conducted *in vitro* and *in vivo* studies, EGCG suppresses cytokine production, endothelial activation and neutrophil migration in inflammatory disease models. In addition, it has a protective effect against ischemia-reperfusion damage in various organs, has strong antioxidant properties, and provides protection against many oxidative injuries (Chen *et al.,* 2016; Kasper *et al.,* 2016). In addition to its antioxidant, cholesterol-lowering, hypoglycemic and antihypertensive activity, it is also known as an important catechin with neuroprotective effect (Yamamoto *et al.,* 2017). It has been suggested that EGCG is a potential candidate for treatment of aging memory loss. As a neuroprotective agent, it is able to modulate various intracellular signaling pathways to alter the expression of genes involved in the regulation of cell survival and apoptosis, thereby maintaining cellular homeostasis. It is known that EGCG has some advantages in the treatment of neurodegenerative disorders and other diseases, as well as regulating cellular signal transmission pathways in cases such as antioxidation, antiapoptotic and metal chelation (Srividhya *et al.,* 2012; Zhao *et al.,* 2017). EGCG has a protective effect in normal cells against mortality and cell death due to the γ-radiation. In addition, it has been shown that it has antiproliferative and chemopreventive effects against various types of cancer such as colon cancer, lung cancer, and breast cancer (Ko *et al.,* 2013; Zhao *et al.,* 2017).

2. THE EFFECTS OF EPIGALLOCATECHIN-3 GALLATE ON HEALTH

2.1. Cardioprotective Effects of Epigallocatechin-3 Gallate

Cardiovascular diseases occur due to the abnormal function of the heart and blood vessels, being one of the leading causes of deaths worldwide. In recent years, herbal medicines are used in the treatment of cardiovascular diseases due to their low side effects rather than pharmaceutical drugs. In many herbal medicines, it has been determined that green tea has a high therapeutic potential against cardiovascular diseases. EGCG, a bioactive polyphenol in green tea, has a lot of biological and pharmacological activities in the treatment of many diseases other than its cardiovascular protection (Liu *et al.,* 2014; Luo *et al.,* 2017).

Eng *et al.* (2018) reported that EGCG inhibits the activation of the NF-κB signaling pathway. Oyama *et al.* (2017) stated that EGCG has an effective role in protecting the cardiovascular system. Othman *et al.* (2015) investigated the potential protective effect of EGCG against cardiovascular diseases caused by type-2 diabetes and stated that glutathione levels and catalase activities increased in the EGCG treatment groups. Saeed *et al.* (2015) investigated the protective role of EGCG against doxorubicin (DOX) induced cardiotoxicity in rats and reported that EGCG provides protection against DOX-induced cardiomyopathy. In addition, Al Hroob *et al*. (2019) stated that EGCG has a therapeutic effect against the processes involved in the pathogenesis and progression of diabetic cardiomypathy and found that EGCG therapy is a promising drug to reduce diabetes-related morbidity and mortality. Meng *et al.* (2020) concluded that EGCG induces autophagy by targeting the autophagy-related PI3K-AKT-mTOR pathway and that EGCG prevents and treats oxidative stress-induced cardiovascular diseases. Zeng *et al.* (2021) investigated the protective effects and molecular mechanism of EGCG against myocardial ischemia/reperfusion injury (I/RI) and noted that EGCG protects against myocardial I/RI.

2.2. Effects of Epigallocatechin-3 on Nephrotoxicity

The kidneys are responsible for keeping the osmotic pressure of the blood stable by maintaining fluid-electrolyte balance, cleansing the body from metabolic wastes such as urea, creatine, uric acid and contributes to the regulation of acid-base balance. In addition, the kidneys are a

homeostasis center, the production site of some vital hormones such as renin and erythropoietin, thus they balance the uptake, production, excretion and retention of many organic and inorganic compounds (Yıldıran & Gencer, 2018; Koken, 2018).

This balance ensures that the kidneys retain water and water-soluble substances and the content of body fluids by excreting water according to body needs (Yıldıran & Gencer, 2018; Koken, 2018). Kidney diseases are an important public health problem in the world and in our country. Approximately 10% adults of all over the World are in various stages of kidney disease, while this has been estimated to be approximately 15.7% in Turkey. Increasing use of medicinal plants offers new solution possibilities in the treatment of kidney diseases, which are the target of many cytotoxic substances. In recent studies, it has been determined that EGCG protects kidney tissue against oxidative stress and nephrotoxicity (Cellat & Kılıcalp, 2010; Yalcın *et al.,* 2017). Thanks to its antioxidant effect, EGCG has been determined to protect kidney tissue against oxidative stress and necrosis, cleanses free radicals, and treats kidney tissue damage. In addition, it has been determined that it prevents the loss of function of kidney (Cellat & Kılıcalp, 2010; Yalcın *et al.,* 2017).

Zhang and Zhang (2018) found that EGCG significantly reduces the nephrotoxic effect in kidney tissue by providing antioxidant defense. Zhu *et al.* (2018) demonstrated that EGCG has potential value in the treatment of significant hypouremic and hyperuricemia. Peng *et al.* (2011) investigated the effects of EGCG on immune-mediated glomerulonephritis (GN) and concluded that EGCG significantly reduces renal impairment. They also concluded that EGCG has a therapeutic effect for the treatment of immune-mediated GN and other immune-mediated diseases.

2.3. Neuroprotective Effects of Epigallocatechin-3 Gallate

Neurodegenerative diseases occur as a result of advanced degeneration of nerve cells and cause socio-economic negativity on the society. Neurodegenerative diseases such as Alzheimer's and Parkinson's are caused by the accumulation of modified proteins that further trigger inflammation, oxidative stress, and modulation of signaling pathways. EGCG, one of the green tea polyphenols, has a wide spectrum of biological and pharmacological activity and provides very strong protection in the treatment of neurodegenerative diseases. Thus, EGCG prevents neuronal damage by reducing brain inflammation in *in vivo* and *in vitro* studies (Singh *et al.,* 2015).

Zhao *et al.* (2017) revealed that EGCG has neuroprotective and neuro-restorative effects against various brain injuries, including some neurodegenerative diseases. They noted that EGCG therapy has a potential therapeutic drug capacity to prevent neurodegenerative diseases, cerebral trauma, and other related pathogenesis. They also concluded that EGCG treatment could reduce cerebral disorders due to psychological stress in rats.

Khalatbary and Khademi (2020) found that EGCG has neuroprotective effects and is responsible for neuroprotection in various neurodegenerative and neural injury models. Pervin *et al.* (2018) stated that EGCG provides effective protection by preventing abnormal accumulation of fibrous proteins such as Aβ and a-synuclein, inflammation, and neuronal cell dysfunction in the cerebral cortex in Alzheimer's patients.

2.4. Hepatoprotective Effects of Epigallocatechin-3 Gallate

The liver is an important metabolic organ in the body and is responsible for secreting and processing various nutrients into proteins (Zhou *et al.,* 2015). Recently, it has been determined that EGCG treatment reduces acid homeostasis, lipid metabolism, and fatty liver (Huang *et al.,* 2018). Liao *et al.* (2019) stated that EGCG inhibits the proliferation of liver cancer cells as well as the formation and development of liver cancer.

Naito *et al.* (2020) investigated the effect of EGCG treatment on intestinal microbiota, serum acid, and gene expression in the liver in mice fed a high-fat diet and they found that EGCG significantly inhibits excessive fat accumulation in the liver. Tipoe *et al.* (2010) stated that EGCG inhibits the NF-κB signalling pathway due to its antioxidant effects against carbon tetrachloride (CCl_4) induced liver damage in rats. Rishi *et al.* (2017) found that EGCG treatment protects against liver damage.

2.5. Effects of Epigallocatechin-3 Gallate on Visual Impairment

Visual disturbances develop due to age or various factors that affect human life negatively. It makes life difficult not only physically but also spiritually. It is known that EGCG has positive effects in the treatment of visual disorders. Recently conducted studies indicate that EGCG treatment is highly effective in the treatment of eye tissue damage (Lee *et al.,* 2011). Shen *et al.* (2015) stated that EGCG provides protection against the degeneration of retinal ganglion cells in an animal model of glaucoma.

Qi *et al.* (2017) found that EGCG treatment provides highly effective protection against light-induced photoreceptor degeneration in the Balb/c mouse retina. Kumar *et al*. (2017) stated that EGCG treatment has a strong drug potential in preventing the onset of cataracts and in the treatment of cataracts.

Falsini *et al.* (2009) found that EGCG treatment could positively affect the inner retina function of the eyes against glaucoma damage. Lee *et al.* (2011) concluded that EGCG treatment inhibits the inflammatory cytokine expression in the rat cornea dry eye model.

2.6. Anticancer and Antitumor Effect of Epigallocatechin-3 Gallate

EGCG, an ingredient derived from green tea, has many effects on human pathological and physiological processes (Chu *et al.,* 2017). It is known that it plays an important role in the regulation of gene expression and transcription (Chu *et al.,* 2017). These effects come from its polyphenolic compounds (catechins) which are found in green tea. EGCG induces apoptosis in various cancer cells by inhibiting cell proliferation. In addition, it stops the growth of cancer cells by selecting cancer cells without affecting normal cells (Safwat *et al.,* 2020).

Shankar *et al.* (2013) stated that EGCG treatment inhibits tumor growth by decreasing the phosphorylation of genes such as Erk/Akt and suppresses apoptosis by activating caspase-3 expression. Abd El-Rahman *et al.* (2017) investigated the effect of EGCG on 7,12 dimethylbenz[a]anthracene-induced breast tumor metastasis and anticancer in rats. They stated that EGCG decreased significantly the tumor size and tumor amount. Lecumberri *et al.* (2013) stated that when combined with traditional cancer therapies, EGCG can provide an additional synergistic effect in improving cancer therapy side effects along with antiinflammatory and antioxidant activities. Zhu *et al.* (2017) stated that EGCG effectively reduces lung cancer stem cell activity by inhibiting tumor formation and inducing apoptosis. Shirakami *et al.* (2009) investigated the effect of EGCG on hepatocellular carcinoma tumor and stated that EGCG causes a significant decrease in Erk/Akt protein levels.

Cerezo-Guisado *et al.* (2015) found that EGCG induces cell death in colon cancer cell line (HT-29 cells) and it has cytotoxic effects and has a cancer preventive role. Yang *et al.* (2019) stated that EGCG induces apoptosis by inhibiting proliferation in odontogenic keratocyst keratinocytes by suppressing the WNT/JNK signaling pathway. Jankun *et al.* (2014) stated that EGCG had better efficacy to prevent tumor cell growth than mitomycin C (MMC) when they compared EGCG and MMC in rats with superficial bladder cancer. Tepedelen *et al.* (2021) investigated the role of EGCG in the transcriptional regulation of genes related to inflammation and migration in benign prostatic hyperplasia cells. They stated that EGCG treatment was effective in the treatment of premalignant lesions by reducing NF-κB and FAK protein expression levels.

Luo *et al.* (2020) determined that EGCG treatment increased p53 protein expression and exhibited antitumor activity by decreasing NF-κB and Bcl-2 protein expression levels against doxorubicin (DOX)-induced bladder cancer.

2.7. Antioxidant Effect of Epigallocatechin-3 Gallate

EGCG is classified as an antioxidant according to its chemical structure it acts as scavengers of free radicals with electrons in phenol rings in the EGCG structure, has redox properties like other tea catechins, prevents the formation of reactive oxygen species, and reduces the damage caused by oxidative stress (Chu *et al.,* 2017; Bimonte *et al.,* 2019).

Fouad *et al.* (2017) stated that EGCG can provide testicular protection with its antioxidant, antiinflammatory and antiapoptotic effects in rats induced with cisplatin. Abib *et al.* (2011) stated that EGCG protects rat brain mitochondria against cadmium-induced damage and found that EGCG completely prevents mitochondrial lipid peroxidation due to its antioxidant and chelating effects. Hassan *et al.* (2019) investigated the therapeutic and protective effects of EGCG on infertility due to lead toxicity in male rats and found that EGCG lowers tissue malondialdehyde levels, protects antioxidative enzyme levels, and provides significant protection against testicular toxicity caused by the lead. Tseng *et al.* (2015) stated that EGCG, through its powerful antioxidative activities, has a protective effect in the treatment of memory impairment caused by reserpine. He *et al.* (2017) stated that treatment of PC12 cells with EGCG reduced oxidative stress and alleviated apoptosis, increased superoxide dismutase activity, glutathione levels, but decreased oxidative stress by inhibiting the formation of reactive oxygen species and lipid peroxidation.

Lee *et al.* (2003) found that EGCG, trolox, lipoic acid, and melatonin reduced lipid peroxidation caused by H_2O_2 or iron ion in a concentration-dependent manner. They stated that EGCG is the most powerful antioxidant in inhibiting lipid peroxidation in gerbil brain homogenates under *in vitro* conditions. Zong *et al.* (2021) stated that EGCG is a protective agent against aminoglycoside-induced ototoxicity. They also found that EGCG could significantly reduce the number of apoptotic cells induced by amikacin and gentamicin. Wei *et al.* (2021) determined that EGCG reduces oxidative stress by regulating the activities of antioxidant enzymes (catalase, superoxide dismutase and glutathione peroxidase) and that EGCG could be an effective bioactive compound to reduce cyclophosphamide-induced gastrointestinal toxicity.

2.8. The Effect of Epigallocatechin-3 Gallate on Obesity

Obesity is one of the main health problems of the developed and developing countries today. Obesity is the result of a balance triggered by the consumption of excessive calorie foods and reduced physical activity. It consists of adipocytes, pre-adipocytes, immune cells and endothelial cells and is responsible for the long-term storage of lipids. Accumulating excessive amounts in the body causes oxidative stress and inflammation in the lipid cell. As a result of pharmacokinetic studies, it is known that EGCG increases the burning of excess fat accumulated in adipose tissue and increases the metabolic rate (Legeay *et al.,* 2015).

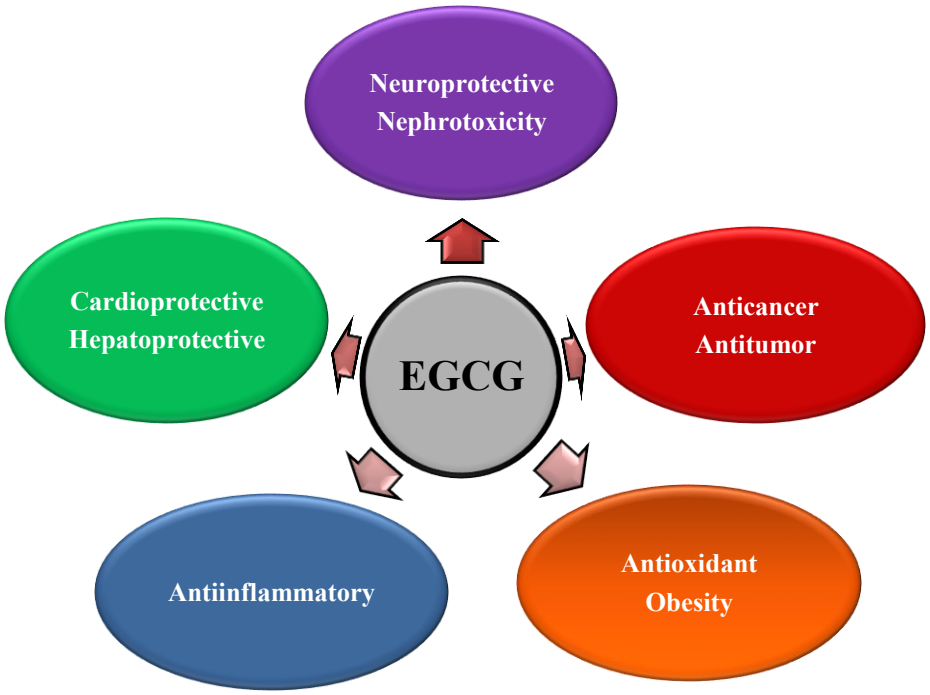
Fiorini *et al.* (2005) investigated the effects of EGCG on obesity in leptin-deficient mice and found that 85 mg/kg EGCG treatment for 5 days accelerates the reduction in body weight in obese mice. Snoussi *et al.* (2014) reported that daily administration of EGCG led to a reduction in body weight within one week in male rats fed a fatty diet (22% fat, 43% carbohydrate and 21% protein). Legeay *et al.* (2015) reported that EGCG can prevent obesity through a modulation involving different organs such as adipose tissue or the liver and also noted that EGCG consumption inhibits pancreatic lipase *in vitro* and suppresses postprandial serum triglycerides in a dose-dependent manner.

3. CONCLUSION

Herbal products have been widely used for the treatment of metabolic diseases all over the world since ancient times. Green tea, one of the plants rich in polyphenols, has powerful therapeutic activities thanks to its epigallocatechin-3 gallate (EGCG) content.

According to the results obtained from epidemiological studies, it has been determined that EGCG positively affects a number of signalling and metabolic pathways, leading to the improvement of various symptoms (Figure 3). Accordingly, EGCG has proven to have an extremely effective drug capacity in terms of human health.

Figure 3. Biological activities of epigallocatechin-3 gallate.



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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship contribution statement

Seda Beyaz: Writing, reading and editing the original draft of the article as well as researching its content. **Ozlem Gok:** Investigation, resources and writing original draft. **Abdullah Aslan:** Writing, reading and editing of article; conducting the study.

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REFERENCES

Abd El-Rahman, S.S., Shehab, G., & Nashaat, H. (2017). Epigallocatechin-3-gallate: the prospective targeting of cancer stem cells and preventing metastasis of chemically-induced mammary cancer in rats. *Am. J. Med. Sci., 354*(1), 54-63.

Abib, R.T., Peres, K.C., Barbosa, A.M., Peres, T.V., Bernardes, A., Zimmermann, L.M., Santos, A.Q., Fiedler, H.D., Leal, R.B., Farina, M., & Gottfried, C. (2011). Epigallocatechin-3-gallate protects rat brain mitochondria against cadmium-induced damage. *Food Chem. Toxicol.*, *49*(10), 2618-2623.

Al Hroob, A.M., Abukhalil, M.H., Hussein, O.E., & Mahmoud, A.M. (2019). Pathophysiological mechanisms of diabetic cardiomyopathy and the therapeutic potential of epigallocatechin-3-gallate. *Biomed Pharmacother., 109,* 2155-2172.

Bilcanoglu, B. (2019). A research on the purification of catechin from green tea waste with macroporous adsorption resins [Master Thesis, Inonu University]. Malatya, Turkey.

Bimonte, S., Albino, V., Piccirillo, M., Nasto, A., Molino, C., Palaia, R., & Cascella, M. (2019). Epigallocatechin-3-gallate in the prevention and treatment of hepatocellular carcinoma: Experimental findings and translational perspectives. *Drug Des. Develop Ther.*, *13,* 611.

Cellat, M., & Kılıcalp, D. (2010). The effect of green tea on prooxidant-antioxidant levels in kidney tissue of guinea pigs exposed to electromagnetic radiation. *Firat Univ Health Sci Vet J.*, *24*(1), 17-21.

Cerezo-Guisado, M.I., Zur, R., Lorenzo, M.J., Risco, A., Martín-Serrano, M.A., Alvarez-Barrientos, A., Cuenda, A., & Centeno, F. (2015). Implication of Akt, Erk 1/2 and alternative p38MAPK signalling pathways in human colon cancer cell apoptosis induced by green tea EGCG. *Food Chem. Toxicol*., *84,* 125-132.

Chen, C., Chang, K., Lin, R., Wang, M., Shih, R., Tseng, H., Soung, H., & Chia, T. (2016). Nitric oxide pathway activity modulation alters the protective effects of (−) epigallocatechin-3-gallate on reserpine-induced impairment in rats. *Behav. Brain Res., 305,* 198–211.

Chu, C., Deng, J., Man, Y., & Qu, Y. (2017). Green tea extracts epigallocatechin-3-gallate for different treatments. *Biomed Res Int.,* 1-9.

Elmas, C., & Gezer, C. (2019). Composition and health effects of the tea plant (*Camellia sinensis*). *Academic Food., 17*(3), 428.

Eng, Q.Y., Thanikachalam, P.V., & Ramamurthy, S. (2018). Molecular understanding of epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases. *J Ethnopharmacol.*, *210,* 296-310.

Falsini, B., Marangoni, D., Salgarello, T., Stifano, G., Montrone, L., Di Landro, S., Guccione, L., Balestrazzi, E., & Colotto, A. (2009). Effect of epigallocatechin-gallate on inner retinal function in ocular hypertension and glaucoma: A short-term study by pattern electroretinogram. *Graefe's Arch Clin Exp Ophthalmol., 247*(9), 1223-1233.

Fiorini, R.N., Donovan, J.L., Rodwell, D., Evans, Z., Cheng, G., Mayıs, H.D., Milliken, C.E., Markowitz, J.S., Campbell, C., Haines, J.K. Schmidt, M.G., & Chavin, K.D. (2005). Short-term administration of (-)-epigallocatechin gallate reduces hepatic steatosis and protects against warm hepatic ischemia/reperfusion injury in steatotic mice. *Liver Transpl., 11,* 298–308.

Fouad, A.A., Qutub, H.O., Fouad, A.E.A., Audeh, A.M., & Al-Melhim, W.N. (2017). Epigallocatechin-3-gallate counters cisplatin toxicity of rat testes. *Pharm. Biol*., *55*(1), 1710-1714.

Ganesan, K., & Xu, B. (2017). Polyphenol-rich lentils and their health promoting effects. *Int J Mol Sci., 18*(11), 2390.

Gumuscu, S.A. (2019). Investigation of the possible protective effects of *Curcumin* and epigallocatechin gallate against oxidative stress in rats [Master Thesis, Mersin University]. Mersin, Turkey.

Guzeldir, K. (2015). The importance and the place of green tea (*Camellia sinensis* (L.) kuntze) in phytotherapy [Master Thesis, Gazi University]. Ankara, Turkey.

Hassan, E., Kahilo, K., Kamal, T., Hassan, M., & Elgawish, M.S. (2019). The protective effect of epigallocatechin-3-gallate on testicular oxidative stress in lead-induced toxicity mediated by Cyp19 gene/estradiol level. *Toxicol., 422,* 76-83.

He, Y., Tan, D., Mi, Y., Bai, B., Jiang, D., Zhou, X., & Ji, S. (2017). Effect of epigallocatechin-3-gallate on acrylamide-induced oxidative stress and apoptosis in PC12 cells. *Hum. Exp. Toxicol., 36*(10), 1087-1099.

Huang, J., Feng, S., Liu, A., Dai, Z., Wang, H., Reuhl, K., Lu, W., & Yang, C.S. (2018). Green tea polyphenol EGCG alleviates metabolic abnormality and fatty liver by decreasing bile acid and lipid absorption in mice. *Mol Nutr. Food Res., 62*(4), 1700696.

Jankun, J., Keck, R. W., & Selman, S.H. (2014). Epigallocatechin-3-gallate prevents tumor cell implantation/growth in an experimental rat bladder tumor model. *Int J Oncol., 44*(1), 147-152.

Kasper, B., Salameh, A., Salameh, M., Salameh, P., Kostelka, M., Mohr, F.W., & Dhein, S. (2016). Epigallocatechin gallate attenuates cardiopulmonary bypass-associated lung injury. *J Surg. Res., 201,* 313-315.

Khalatbary, A.R., & Khademi, E. (2020). The green tea polyphenolic catechin epigallocatechin gallate and neuroprotection. *Nutr. Neurosci., 23*(4), 281-294.

Ko, H., Yani, Y., Jeon, H., Jeong, M.H., Choi, H.K., Ryu, S.H., Lee, S.W., Yoon, H.G., & Choi, K.C. (2013). TGF-β1-induced epithelial-mesenchymal transition and acetylation of SMAD2 and SMAD3 are negatively regulated by egcg in human A549 lung cancer cell. *Cancer Lett., 335,* 205-213.

Koken, E. (2018). Investigation of the effects of exogenous follistatin in the treatment of cisplatin-induced acute kidney injury in rats [Specialization Thesis in Medicine, Izmir Kâtip Celebi University]. Izmir, Turkey.

Kumar, V., Gour, S., Peter, O.S., Gandhi, S., Goyal, P., Pandey, J., Harsolia, R.S., & Yadav, J.K. (2017). Effect of green tea polyphenol epigallocatechin-3-gallate on the aggregation of αA (66-80) peptide, a major fragment of αa-crystallin involved in cataract development. *Curr. Eye Res., 42*(10), 1368-1377.

Lecumberri, E., Dupertuis, Y.M., Miralbell, R., & Pichard, C. (2013). Green tea polyphenol epigallocatechin-3-gallate (EGCG) as adjuvant in cancer therapy. *Clin. Nutr. 32*(6), 894-903.

Lee, H.S., Chauhan, S.K., Okanobo, A., Nallasamy, N., & Dana, R. (2011). Therapeutic efficacy of topical epigallocatechin gallate (EGCG) in murine dry eye. *Cornea., 30*(12), 1465.

Lee, S.R., Im, K.J., Suh, S.I., & Jung, J.G. (2003). Protective effect of green tea polyphenol (-)-epigallocatechin gallate and other antioxidants on lipid peroxidation in gerbil brain homogenates. *Phytother Res.*, *17*(3), 206-209.

Legeay, S., Rodier, M., Fillon, L., Faure, S., & Clere, N. (2015). Epigallocatechin gallate: A review of its beneficial properties to prevent metabolic syndrome. *Nutr., 7*(7), 5443-5468.

Liao, S., Lin, J., Liu, J., Chen, T., Xu, M., & Zheng, J. (2019). Chemoprevention of elite tea variety CFT-1 rich in EGCG against chemically induced liver cancer in rats. *Food Sci Nutr., 7*(8), 2647-2665.

Liu, D., Zhang, X., Jiana, L., Guo, Y., & Zheng, C. (2014). Epigallocatechin-3-gallate (EGCG) attenuates concanavalin a-induced hepatic injury in mice. *Acta Histochem*., *116,* 654–662.

Luo, K.W., Chen, W., Lung, W.Y., Wei, X.Y., Cheng, B.H., Cai, Z.M., & Huang, W.R. (2017). EGCG inhibited bladder cancer SW780 cell proliferation and migration both *in vitro* and *in vivo* via down-regulation of NF-κB and MMP-9. *J Nutr. Biochem*., *41*, 56-64.

Luo, K.W., Zhu, X.H., Zhao, T., Zhong, J., Gao, H.C., Luo, X.L., Huang, W.R. (2020). EGCG enhanced the antitumor effect of doxorubicine in bladder cancer via NF-κB/MDM2/p53 pathway. *Front. Cell Develop. Bio.*, 8, 1-11.

Meng, J., Chen, Y., Wang, J., Qiu, J., Chang, C., Bi, F., Wu, X., Liu, W. (2020). EGCG protects vascular endothelial cells from oxidative stress-induced damage by targeting the autophagy-dependent PI3K-AKT-mTOR pathway. *Annals Trans. Med., 8*(5), 200-212.

Naito, Y., Ushiroda, C., Mizushima, K., Inoue, R., Yasukawa, Z., Abe, A., & Takagi, T. (2020). Epigallocatechin-3-gallate (EGCG) attenuates non-alcoholic fatty liver disease via modulating the ınteraction between gut microbiota and bile acids. *J Clin Biochem. Nutr.,* 20-39.

Nikoo, M., Regenstein, J.M., & Gavlighi, H.A. (2018). Antioxidant and antimicrobial activities of (-)-epigallocatechin-3-gallate (EGCG) and its potential to preserve the quality and safety of food. *Comp. Reviews Food Sci. Food Safety., 17,* 732-753.

Othman, A., El-Sawi, M., El-Missiry, M., & Abukhalil, M. (2017). Epigallocatechin-3-gallate protects against diabetic cardiomyopathy through modulating the cardiometabolic risk factors, oxidative stress, inflammation, cell death and fibrosis in streptozotocin-nicotinamide induced diabetic rats. *Biomed. Pharmacother.*, *94,* 362–373.

Oyama, J.I., Shiraki, A., Nishikido, T., Maeda, T., Komoda, H., Shimizu, T., Makino, N., & Node, K. (2017). EGCG, a green tea catechin, attenuates the progression of heart failure induced by the heart/muscle-specific deletion of MnSOD in mice. *J cardiol., 69*(2), 417-427.

Peng, A., Ye, T., Rakheja, D., Tu, Y., Wang, T., Du, Y., Zhou, J.K., Vaziri, N.D., Zhao, H., Mohan, C., & Zhou, X.J. (2011). The green tea polyphenol (−)-epigallocatechin-3-gallate ameliorates experimental immune-mediated glomerulonephritis. *Kidney Int., 80*(6), 601-611.

Pervin, M., Unno, K., Ohishi, T., Tanabe, H., Miyoshi, N., & Nakamura, Y. (2018). Beneficial effects of green tea catechins on neurodegenerative diseases. *Molecules., 23*(6), 1297.

Qi, S., Wang, C., Song, D., Song, Y., Dunaief, J.L. (2017). Intraperitoneal injection of (−)-epigallocatechin-3-gallate protects against light-induced photoreceptor degeneration in the mouse retina. *Mol. Vision., 23,* 171.

Rishi, P., Arora, S., Kaur, U.J., Chopra, K., & Kaur, I.P. (2017). Better management of alcohol liver disease using a 'microstructured synbox' system comprising l. plantarum and EGCG. *PLoS One., 12*(1), 1-18.

Saeed, N.M., El-Naga, R.N., El-Bakly, W.M., Abdel-Rahman, H.M., El-Din, R.A.S., & El-Demerdash, E. (2015). Epigallocatechin-3-gallate pretreatment attenuates doxorubicin-induced cardiotoxicity in rats: A mechanistic study. *Biochem. Pharmacol., 95*(3), 145-155.

Safwat, M.A., Kandil, B.A., Elblbesy, M.A., Soliman, G.M., & Eleraky, N.E. (2020). Epigallocatechin-3-gallate-loaded gold nanoparticles: preparation and evaluation of anticancer efficacy in ehrlich tumor-bearing mice. *Pharmaceuticals, 13*(9), 254.

Sarıca Y. (2014). Evaluation of protective effects of CAPE and EGCG on PI3K-AKT-mTOR pathways in rat testicular torsion ischemia/reperfusion injury [Master Thesis, Celal Bayar University] Manisa, Turkey.

Shankar, S., Marsh, L., & Srivastava, R.K. (2013). EGCG inhibits growth of human pancreatic tumors orthotopically implanted in Balb C nude mice through modulation of FKHRL1/FOXO3a and neuropilin. *Mol. Cell Biochem., 372*(1), 83-94.

Shen, C., Chen, L., Jiang, L., & Lai, T.Y. (2015). Neuroprotective effect of epigallocatechin-3-gallate in a mouse model of chronic glaucoma. *Neurosci Lett., 600,* 132-136.

Shirakami, Y., Shimizu, M., Adachi, S., Sakai, H., Nakagawa, T., Yasuda, Y., Tsurumi, H., Hara, Y., & Moriwaki, H. (2009). (–)-Epigallocatechin gallate suppresses the growth of human hepatocellular carcinoma cells by inhibiting activation of the vascular endothelial

growth factor–vascular endothelial growth factor receptor axis. *Japanese Cancer Assoc.*, *100*(10), 1957–1962.

Singh, N.A., Mandal, A.K.A., & Khan, Z.A. (2015). Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG). *Nutr. J., 15*(1), 1-17.

Snoussi, C., Ducroc, R., Hamdaoui, M.H., Dhaouadi, K., Abaidi, H., Cluzeaud, F., Nazaret, C., Le Gall, M., & Bado, A. (2014). Green tea decoction improves glucose tolerance and reduces weight gain of rats fed normal and high-fat diet. *J. Nutr. Biochem., 25,* 557–564.

Srividhya, R., Gayathri, R., & Kalaiselvi, P. (2012). Impact of epigallocatechin-3-gallate on acetylcholine-acetycholine esterase cycle in aged rat brain. *Neurochem. Int., 60,* 517-522.

Tepedelen, B.E. (2021). The effect of epigallocatechin-3-gallate on transcriptional regulation of migration and inflammation related genes in benign prostate hyperplasia cells. *Celal Bayar Univ. J. Institute Health Sci., 8*(2), 323-330.

Tipoe, G.L., Leung, T.M., Liong, E.C., Lau, T.Y.H., Fung, M.L., & Nanji, A.A. (2010). Epigallocatechin-3-gallate (EGCG) reduces liver inflammation, oxidative stress and fibrosis in carbon tetrachloride (CCl_4)-induced liver injury in mice. *Toxicol., 273*, 45-52.

Tseng, H.C., Wang, M.H., Soung, H.S., Chang, Y., & Chang, K.C. (2015). (−) Epigallocatechin-3-gallate prevents the reserpine-induced impairment of short-term social memory in rats. *Behav. Pharmacol.*, *26*(8-9), 741-747.

Wei, R., Liu, X., Wang, Y., Dong, J., Wu, F., Mackenzie, G.G., & Su, Z. (2021). (−)-Epigallocatechin-3-gallate mitigates cyclophosphamide-induced intestinal injury by modulating the tight junctions, inflammation and dysbiosis in mice. *Food Func*., *12*(22), 11671-11685.

Yalcın, A.S., Yılmaz, A.M., Altundağ E.M., & Kocturk, S. (2017). Anti-cancer effects of curcumin, quercetin and tea catechins. *Marmara Pharma J., 21,* 19-29.

Yamamoto, N., Shibata, R., Tanida, M., Taniguchi, Y., Ikeda-Matsuo, Y., & Sobue, K. (2017). Epigallocatechin gallate induces extracellular degradation of amyloid β- protein by increasing neprilysin secretion from astrocytes through activation of Erk and PI3K pathways. *Neurosci., 362,* 70-78.

Yang, S.B., Pang, B.X., Xue, J., & Yuan, R.T. (2019). Epigallocatechin-3-gallate inhibits proliferation and induces apoptosis in odontogenic keratocyst keratinocytes. *Oral Dis*., *25*(4), 1175-1184.

Yıldıran, H., & Gencer, F. (2018). Kidney diseases and protein metabolism. *Nutr Diet J., 46,* 7-12.

Zeng, M., Wei, X., He, Y.L., Chen, J.X., Lin, W.T., & Xu, W.X. (2021). EGCG protects against myocardial I/RI by regulating lncRNA Gm4419-mediated epigenetic silencing of the DUSP5/ERK1/2 axis. *Toxicol. Appl. Pharma., 433*, 115782.

Zhang, G., & Zhang, J. (2018). Enhanced oral bioavailability of EGCG using ph-sensitive polymeric nanoparticles: Characterization and *in vivo* investigation on nephrotic syndrome rats. *Drug Des Develop Therapy., 12,* 2509-2518.

Zhao, X., Liu, F., Jin, H., Li, R., Wang, Y., Zhang, W., Wang, H., & Chen, W. (2017). Involvement of PKCα and ERK1/2 signaling pathways in EGCG's protection against stress-induced neural injuries in wistar rats. *Neurosci., 346,* 226–237.

Zhou, B.H., Zhao, J., Liu, J., Zhang, J.L., Li, J., & Wang, H.W. (2015). Fluoride-induced oxidative stress is involved in the morphological damage and dysfunction of liver in female mice. *Chemosphere., 139,* 504-511.

Zhu, C., Xu, Y., Liu, Z.H., Wan, X.C., Li, D.X., & Tai, L.L. (2018). The anti-hyperuricemic effect of epigallocatechin-3-gallate (EGCG) on hyperuricemic mice. *Biomed. Pharmacother., 97,* 168–173.

Zhu, J., Jiang, Y., Yang, X., Wang, S., Xie, C., Li, X., Li, Y., Chen, Y., Wang, X., Meng, Y., Zhu, M., Wu, R., Huang, C., Ma, X., Geng, S., Wu, J., & Zhong, C. (2017). Wnt/β-Catenin

pathway mediates (-)-epigallocatechin-3-gallate (EGCG) inhibition of lung cancer stem cells. *Biochem. Biophys Res. Commun., 482,* 15-21.

Zong, Y., Chen, F., Li, S., & Zhang, H. (2021). (−)-Epigallocatechin-3-gallate (EGCG) prevents aminoglycosides-induced ototoxicity via anti-oxidative and anti-apoptotic pathways. *Int. J. Pediatric Otorhinolaryngol., 150*, 110920.