Chapter

Tea Is an Elixer of Life

Tamilselvan Hema, Mathan Ramesh, Selvaraj Miltonprabu and Shanmugam Thangapandiyan

Abstract

Green tea is a commonly consumed beverage in the world and it is a rich source of polyphenolic compounds, which are known as the tea flavonoids. Polyphenolic compounds are effective against oxidative damage in various pathological conditions. Many herbal medicines are used in traditional medicine for their protective and therapeutic properties against various diseases. Among their bioactive components, tea catechins have been found to be active against all kind of diseases including cancer. Extensive report is available that green tea displays a wide range of healthy properties, such as antioxidative, anti-inflammatory, anti-apoptotic and chemopreventors against reactive oxygen and nitrogen species. This review aims to critically analyze the available literature regarding the effects of green tea or tea catechins with special emphasis on its phytoremediation against various health disorders elicited by different chemical compounds. Overall, data in literature show tea catechins appear to be a promising elixir to recover the illness of human beings.

Keywords: green tea, catechins, EGCG, elixir of life, tea

1. Introduction

Tea is the second most frequently consumed daily beverage in the world [1]. The tea plant, *Camellia sinensis,* is a member of Theaceae family, and is produced from its leaves. It is an evergreen shrub or tree [2]. The origins of tea drinking date back to 2737 BC [3]. It is legendarily attributed to the Chinese emperor Shen Nung, the divine cultivator who also apparently invented agriculture and herbal medicine [4]. Since tea is important to human life, a vast number of researchers have investigated the function of tea. It has been found that tea has beneficial effect on both physical health and cognition [5–7]. All tea is produced from the leaves of *Camellia sinensis*, but differences in processing result in different types of tea. In the processing of green tea, fresh tea leaves are steamed or heated immediately after harvest, resulting in minimal oxidation of the naturally occurring polyphenols in the tea leaves. On the other hand, in the processing of black tea, the tea leaves are dried and crushed upon harvesting to encourage oxidation, which converts indigenous tea polyphenols (primarily catechins and gallatecatechins) to other polyphenols (mainly theaflavins and thearubigins). Finally, partially oxidized tea leaves yield oolong tea [8]. Among all of these, however, the most significant effects on human health have been observed with the consumption of green tea [9].

2. Bioactive components of green tea

Tea, from a biological standpoint, is a mixture of larger number of bioactive compounds including catechins flavonols, lignans, and phenolic acids. A typical cup of green tea, brewed with 2.5 g of dry leaves in 250 ml of hot water (called a 1% tea infusion), contains 620–880 mg water extractable materials, of which 30–40% are catechins and 3–6% caffeine [10]. The high-performance liquid chromatography data, green tea leaves (**Figure 1**, *Camellia sinensis*) contain 26% fibers, 15% protein, 2–7% lipids, and 5% vitamins and minerals. They also contain secondary metabolites such as pigments (1–2%), polyphenols (30–40%), of which at least 80% are flavonoids and methylxanthines (3–4%) [8, 9]. Catechins polyphenols are believed to be the most important active component in green tea (GT). They are secondary metabolites possessing antioxidant activity, which is 20 times higher than that of vitamin C [11]. Green tea extract are marketed and generally used for weight reduction and maintenance of homeostasis, however their use carries a risk of hepatotoxicity [12, 13].

The characteristic polyphenolic compounds in green tea known as catechins. Tea catechins were first isolated by Michiyo Tsujimura in 1929 in Japan [14], which include (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC). Tea leaves also contain lower quantities of other polyphenols such as quercetin, kaempferol and myricetin as well as alkaloids such as caffeine and theobromine. A typical brewed green tea beverage (e.g. 2.5 g of tea in 250 ml of hot water) contains 240–320 mg of catechins of which 60–65% EGCG and 20–40 mg of caffeine [15] **Figure 2**; tea polyphenolic compounds (catechins).

2.1 Pharmacological properties of tea

The tea possesses diverse pharmacological properties (**Figure 3**) which include anti-oxidative, anti-inflammatory, anti-mutagenic, anti-carcinogenic, anti-angiogenic, apoptotic, anti-obesity, hypocholesterolemic, anti-arterisclerotic, anti-diabetic, anti-bacterial, anti-viral and anti-aging effect [16–28]. The prevention of disease by tea consumption, many studies have demonstrated beneficial effects of tea and catechins in the prevention of cancer and cardiovascular disorders. The green tea is a potent anti-oxidant with anti-oxidative activity greater than vitamins C and E [29]. Tea catechins are strong antioxidants, which scavenge free radicals,

Figure 1.
Tea leaves (Camellia sinensis). Sources from: https://www.istockphoto.com

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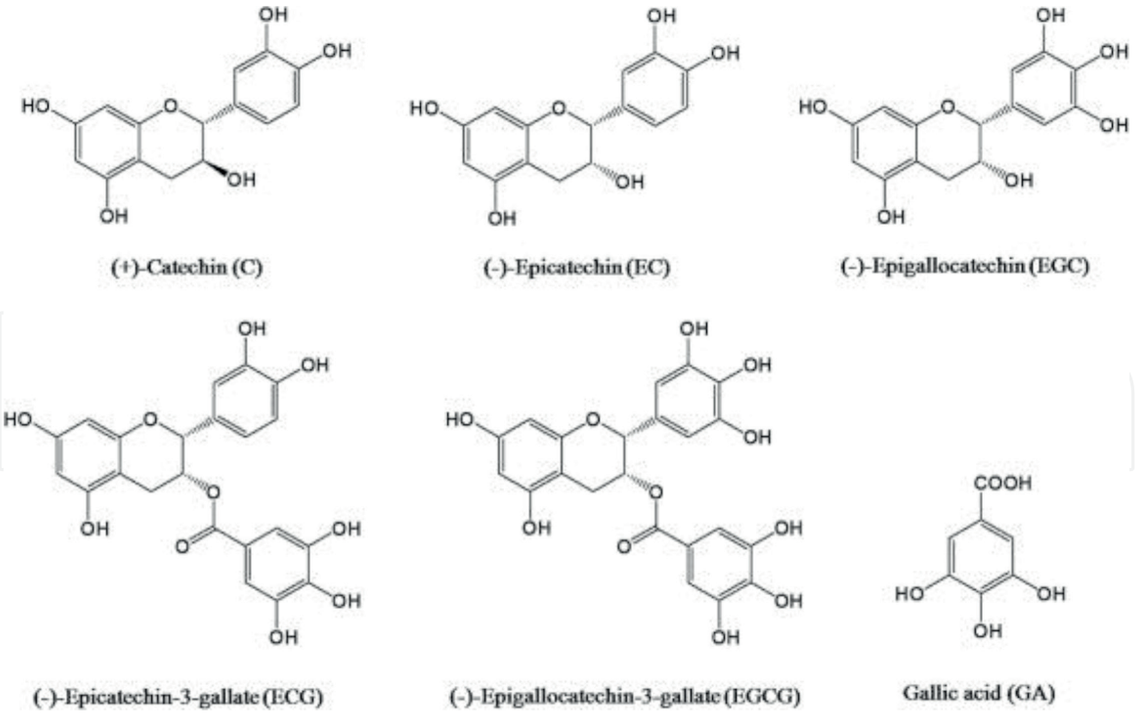

Figure 2.
Green tea polyphenolic compounds. Sources from: https://ars.els-cdn.com.

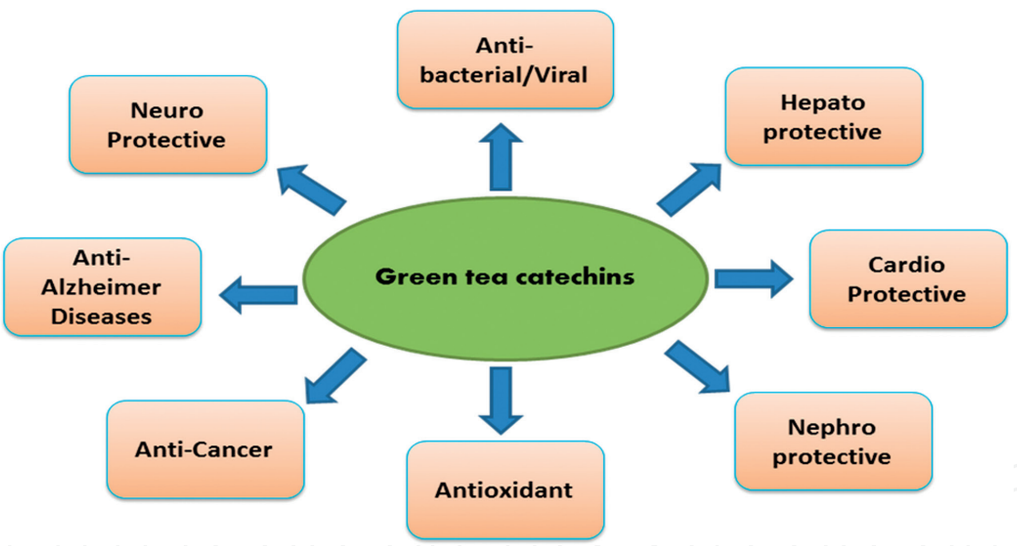

Figure 3.
Pharmacological properties of tea catechins.

and prevent the formation of reactive oxygen species (ROS) by chelating metal ions [30]. Tea also enhances the expression of intracellular antioxidants such as glutathione, glutathione reductase, glutathione peroxidase, glutathione-S-transferase, catalase and quinone reductase [31].

3. Tea is an elixir of life

3.1 Role of green tea in Alzheimer disease (AD)

Alzheimer disease (AD) is a progressive neurodegenerative disorders that represent the most common cause of dementia worldwide. The Alzheimer's Association

estimates that 5.4 million Americans will be affected by Alzheimer disease in 2016 [32]. AD was identified over 100 years ago by Alois Alzheimer and was later termed by Emil Kraepelin and his coworkers as 'Alzheimer's Disease" [33]. AD is currently recognized as the most common cause of dementia (60–80%) [32] and a major cause of death [34]. Recently Helen et al. [35] reported that administration of green to AD-induced rats showed green tea prevent impairments in object and social recognition memories, oxidative stress in the hippocampus of AD-like rats. Similarly, Choi et al. [36] stated that green tea has higher concentration of total catechins, with the highest neuroprotective capacity in the hippocampus and potential to inhibit Aβ-induced neural death and AD. **Table 1** shows the amelioration green tea in various diseases with different animal models. **Figure 4** depicts the normal and Alzheimer-affected brain structure.

3.2 Role of green tea in cancer

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [37]. It is one of the major ailment

S. no.	Experimental animals	Level of green tea	Biomarkers	References
1.	Old male Wister rat	Green, red, black tea (each 13.33 mg/kg) for stereotaxic surgeries for intrahippocampal injection of 2 μl Aβ (25–35).	Avoid short-term memory deficits, long-term memory deficits & social recognition memory deficits, control behavioral tasks, avoid the ↑ of ROS& TBAR levels, inhibit Aβ-induced neural death.	[35, 36]
2.	42 patients oral cancer	500, 750, or 1000 mg/m^2 of green tea extract per day or placebo orally	Disappearance of all lesions (or) greater ↓ in the sum of products of after measured lesions. Against the progression of precancerous lesions in the oral cavity. Against the formation of oral cancer in humans.	[41]
3.	Male Sprague-Dawley rats (170–200 g body weight)	GTE—1.5% w/v Pb acetate—0.4% (oral administration)	Reduced tissue Pb burden, reducing the tissue injury of liver cells, reducing hepatic fat content, ↑ hepatic energy status & functioning as an anti-oxidants.	[52, 53]
4.	Mature male albino rats	Pb acetate – 100 mg kg body weight GT—5 g/l (stomach tube)	Higher activation of antioxidant enzymes, improvement in the antioxidant status, ↑ viability& ↓ lipid peroxidation, strong scavengers against superoxide, hydrogen peroxide, hydroxyl radicals & nitric oxide.	[54, 55]

Table 1.
The amelioration of various diseases with green tea in different animal models.

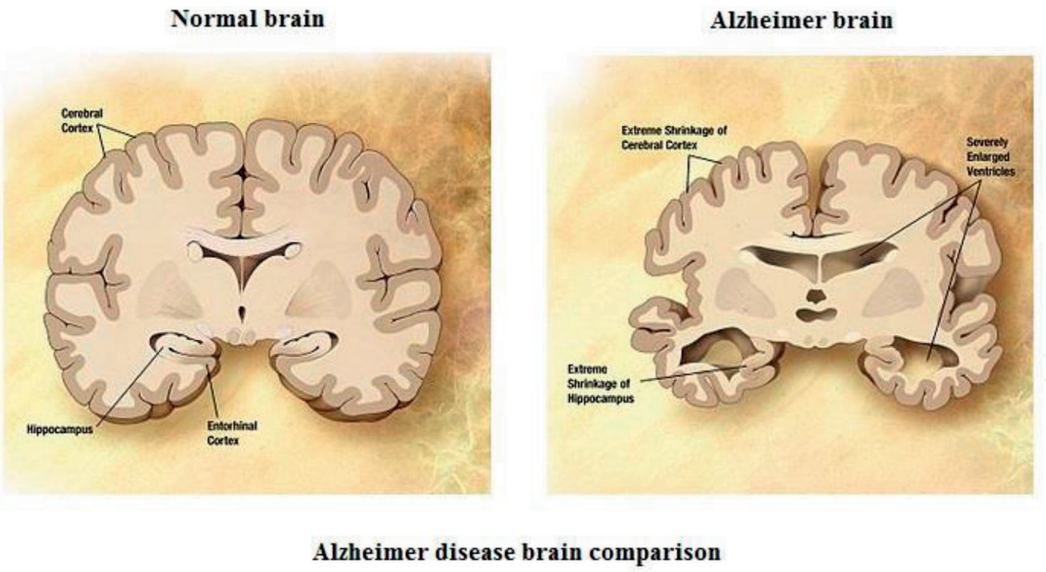

Figure 4.
Shows the normal and Alzheimer affected brain. Source from: https://scialert.net.com.

effecting humankind and remains as one of the leading causes of mortality worldwide, for instance, above 10 million new patients are diagnosed with cancer every year and over 6 million deaths are associated with it representing roughly 12% worldwide death [38]. One third of the human cancers is caused by dietary habits and manipulation of the diet is recognized as the potential strategy against this disease [39]. Chemotherapy has emerged as a practical approach to reducing cancer incidence and therefore the mortality and morbidity with side effects. The use of tea, as a chemopreventive agent has been appreciated in the last 20 years. The first epidemiological report indicating an association between tea consumption in human cancers was published in 1966 [40]. Tsao et al. [41] reported that green tea administration (receive 500, 750, or 1000 mg/m^2 of green tea extract per day or placebo orally) to 42 patients who were affected by oral cancer. The efficacy was determined by the disappearance of all lesions (a complete response) or 50% or greater decrease in the sum of products diameters of all measured lesions (a partial response). At 12 weeks after the initiation of the treatment, 39 patients who completed the trial were evaluated; 14 (50%) of the 28 patients in the three combined green tea extract arms had a favorable response whereas only 2 (18.2%) of the 11 patients in the placebo arm showed the similar response (P for the difference = 0.09). **Table 2** shows the chemotherapeutic efficacy of green tea against various cancers in different animals and in vitro models.

3.3 Role of green tea in heavy metal–induced organ toxicity

Heavy metals are chemical elements with a specific gravity at least 5 times that of water. They are the major pollutant found in the environment has a molecular mass > 5.0 g/cm^3 [42]. Several heavy metals, such as Fe, Mn, Zn, Cu, Co, or Mo are essential for growth of organisms. The specific gravity of water is 1 at 4°C (39°F). Specific gravity is measure of density of a given amount of a solid substance when it is compared to an equal amount of water.

3.3.1 Hepatoprotection

Liver is one of the important organs for heavy metal toxicity. Juberg et al. [43] reported the lead (Pb)-induced hepatic damages. Pb is ubiquitously found in

S. no.	Experimental animals/model	Level of green tea	Biomarkers	References
1.	42 patients oral cancer.	500, 750, or 1000 mg/m^2 of green tea extract per day or placebo orally.	Disappearance of all lesions (or) greater ↓ in the sum of products of after measured lesions. ↑ Against the progression of pre-cancerous lesions in the oral cavity. Protects against the formation of oral cancer in humans.	[41]
2.	MDA-MB-231 human breast cancers.	Green tea (EGCG-solid lipid nanoparticles) at the concentration of 50 μg/mL. Treated with different time points 0, 4, 8, 24, 48 and 96 h.	8.1 fold increase in cytotoxicity of EGCG against MDA-MB–231. ↑ EGCG loaded solid lipid nanoparticles to improve the stability and anticancer activity of EGCG.↑	[56, 37]
3.	Lung and fore stomach cancer in mouse model.	Oral intubation at a dose of 5 mg in 0.2 ml water 30 min prior to challenge with carcinogen.	In the fore stomach tumorigenesis protocol, GTP (green tea polyphenol) afforded 71 and 66% protection against, respectively DEN- and BP-induced tumor multiplicity. In the case of lung tumorigenesis protocol, the protective effects of GTP were 41 and 39%, respectively.↓	[57, 39]
4.	Colon and mammary gland cancer in rat.	Effect of tea, or tea and milk, instead of drinking water. Solutions of 1.25% (w/v) black tea, or 1.85% (v/v) milk in tea were prepared three times per week.	Foci of aberrant crypts in the colon were decreased, after 9 weeks, in the groups on tea, or tea and milk during AOM administration ↓, but not after AOM. Thus, tea decreases mammary tumor induction, and the production of foci of aberrant crypts in the colon. Milk potentiates these inhibiting effects.↓	[58, 39]

Table 2.
The chemotherapeutic efficacy of green tea against various cancers in different models.

environmental and industrial pollutant that has been detected in nearly all phases of environment and biological system (including liver, kidney, heart and etc.,). It was observed that Pb affected liver were significantly higher fatty changes, hydropic degeneration and necrosis of the hepatocytes, were observed as compared to control group. Ingestion of Pb is one of the primary causes of its hepatotoxic effects. The treatment with epigallocatechin gallate, the major flavonoid component of green tea, by oral administration significantly protects the liver after ischemia/reperfusion, possibly by reducing hepatic fat content, increasing hepatic energy status, and functioning as an antioxidant. Similarly, Thangapandiyan and Miltonprabu [44] also reported the hepatic damage by fluoride (Fl) in rat liver. Pre-treatment with EGCG significantly abrogates all the liver damages by Fl and brought the hepatic cells into normal levels. These two results showed the efficacy of EGCG against various heavy metal–induced toxicity in liver.

3.3.2 Cardioprotection

Exposure to arsenic through contaminated groundwater is widespread in certain regions of many countries including Bangladesh, India, and China [45]. Arsenic is a potent cardiovascular toxicant; epidemiological evidence has linked arsenic exposure to ischemic heart disease, cerebrovascular disease, atherosclerosis, and hypertension in exposed human populations. Recently Sun et al. [46] reported with green tea catechins epigallocatechin gallate (EGCG) against Arsenic (Ar)-induced cardiomyopathy in Sprague-Dawley rats. He observed that EGCG fully reversed the Ar-induced morphological changes in the myocardium including necrosis, intracellular edema, myofibrillar derangements, swollen and damaged mitochondria, and wavy degeneration of muscle fibers. Miltonprabu and Thangapandiyan [47] also reported with EGCG significantly reduced fluoride (Fl) accumulation in the hearts of experimental rats and significantly inhibited Fl-induced elevations in the activities of the enzymes CK-MB, and LDL, VLDL in heart tissue. These observations with Green tea catechins against heavy metal–induced cardiotoxicity were proved with its well known antioxidant capacity.

3.3.3 Nephroprotection

Chronic kidney disease (CKD) is affecting the health of more and more people worldwide. The main feature at the end stage of CKD is the accumulation of endogenous uremic toxins. Abdel Moneim et al. [48] reported the deleterious effect of lead (Pb) in rat renal cells with increased lipid peroxides, urea, uric acid and bilirubin. Abnormally high level of lead in human body fluids can result in detrimental effects on the renal, nervous, gastrointestinal and reproductive systems. Administration of green tea extract to lead intoxicated rats showed significant recovery of all the elevated levels of kidney markers as evidenced from histological study. Similarly, Thangapandiyan and Miltonprabu [49] also proved the ameliorative potential of EGCG against fluoride (Fl)-induced nephrotoxicity in rats.

3.3.4 Neuroprotection

El-Missiry et al. [50], reported the protective efficacy of green tea polyphenol EGCG against radiation-induced hippocampal damage in rat. He observed the result after the radiation with increased plasma levels of homocysteine, amyloid β, TNF-α and IL-6 levels and the decrease of dopamine and serotonin. Pretreatment with EGCG about 2.5 and 5 mg/kg BW significantly protected the hippocampus of rat as compared to control. Several studies have demonstrated that green tea components protect the neurons against various chemical compounds. Thangapandiyan et al. [51] also proved the antioxidant efficacy of EGCG against fluoride (Fl)-induced hippocampal dysfunction in rats. Tea catechins are strong scavengers against superoxide, hydrogen peroxide, hydroxyl radicals and nitric oxide produced by various chemicals in brain. They also could chelate the metals toxicity because of the presence of catechol structure.

4. Conclusions

Nowadays, tea is considered as a source of dietary constituents endowed with biological and pharmacological activities with potential benefits to human health. The health properties of tea extract and its scientific investigation is preventing

several diseases in human life. The green tea extract and their components are partially efficacious in protection and preventing disturbances of antioxidant defense system in the biological systems. These beneficial effect of green tea can result from inhibition of free radical chain reactions generated during oxidative stress caused by xenobiotics from an increase in antioxidant capacity. Further studies are warranted to prove the potent antioxidant ability of tea catechins against various health issues without side effects.

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Conflict of interest

The authors declared that there is "no conflict of interest."

Abbreviations

GT	green tea
GTE	green tea extracts
EGCG	epigallocatechin gallate
ROS	reactive oxygen species
AD	Alzheimer disease
Pb	lead
SOD	super oxide dismutase
GST	glutathione-S-transferase
TAS	total antioxidant stress
Aβ	amyloid β
GSH	reduced glutathione
CNS	central nervous system
ROS	reactive oxygen species
Fl	fluoride
WHO	World Health Organization
Ar/As	arsenic

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References

[1] Hodgson JM, Croft KD. Tea flavonoids and cardiovascular health. Molecular Aspects of Medicine. 2010;**31**(6):495-502

[2] Rani R, Nagpal D, Gullaiya S, Madan S, Agrawal SS. Phytochemical, pharmocological and beneficial effect of green tea. International Journal of Pharmacognosy and Phytochemical Research. 2014;**6**(3):420-426

[3] Chow K, Kramer I. All the Tea in China. San Francisco, CA, USA: China Books and Periodicals; 1990

[4] Clark G. The Eccentric Teapot: Four Hundred Years of Invention. London: Aurum Press; 1989

[5] Shen C, Chyu M. Tea flavonoids for bone health: From animals to humans. Journal of Investigative Medicine. 2016;**64**(7):1151-1157

[6] Einöther S, Martens V. Acute effects of tea consumption on attention and mood. American Journal of Clinical Nutrition. 2013;**98**(6):1700S-1708S

[7] Dietz C, Dekker M. Effect of green tea phytochemicals on mood and cognition. Current Pharmaceutical Design. 2017;**23**(19):2876-2905

[8] Graham HN. Green tea composition, consumption, and polyphenol chemistry. Preventive Medicine. 1992;**21**:334-350

[9] Cabrera C, Artacho R, Gimenez R. Beneficial effects of greentea—A review. Journal of the American College of Nutrition. 2006;**25**:79-99

[10] Oba S, Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsura N, et al. Consumption of coffee, green tea, oolong tea, black tea, chocolate, snacks and the caffeine content in relation to risk of diabetes in Japanese men & women. The British Journal of Nutrition. 2010;**103**:453-459

[11] Hijazi MM, Khatoon N, Azmi MA, Rajput MT, Zaidi SI, Azmi MA, et al. Report: Effects of *Camellia sinensis* L. (green tea) extract on the body and testicular weight changes in adult Wistar rats. Pakistan Journal of Pharmaceutical Sciences. 2015;**28**:249-253

[12] Garcia-Cortes M, Robles-Diaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: A tabular listing and clinical characteristics. International Journal of Molecular Sciences. 2016;**17**

[13] Mazzanti G, Di Sotto A, Vitalone A. Hepatotoxicity of green tea: An update. Archives of Toxicology. 2015;**89**:1175-1191

[14] Snoussi C, Ducroc R, Hamdaoui MH, Dhaouadi K, Abaidi H, Cluzeaud F, et al. Green tea decoction improves glucose tolerance and reduce weight gain of rats fed normal and high-fat diet. The Journal of Nutritional Biochemistry. 2014;**25**:557-564

[15] Sang S, Lambert JD, Ho CT, Yang CS. The chemistry and biotransformation of tea constituents. Pharmacological Research. 2011;**64**: 87-99 [in Eng]

[16] Serafini M, Ghiselli A, Ferro-Luzzi A. In vivo antioxidant effectof green and black tea in man. European Journal of Clinical Nutrition. 1996;**50**:28-32

[17] Mutoh M, Takashi M, Fukuda K, Komatsu H, Enya T, Masushima-Hibiya Y, et al. Suppression by flavonoids of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells: Structure–activity relationship. Japanese Journal of Cancer Research. 2000;**91**:686-791

[18] Steele VE, Kelloff GJ, Balentine D, Boone CW, Mehta R, Bagheri D, et al. Comparative chemopreventive mechanisms of green tea, black tea and selected polyphenol extracts measured by in vitro bioassays. Carcinogenesis. 2000;**21**:63-67

[19] Yang CS, Wang Z. Tea and cancer review. Journal of the National Cancer Institute. 1993;**85**:1038-1049

[20] Jung YD, Ellis LM. Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. International Journal of Experimental Pathology. 2001;**82**(6):309-316

[21] Ahmad N, Feyes DK, Nieminen AL, Agarwal R, Mukhtar H. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. Journal of the National Cancer Institute. 1997;**89**:1881-1886

[22] Han LK, Takaku T, Li J, Kimura Y, Okuda H. Anti-obesity action of oolong tea. International Journal of Obesity and Related Metabolic Disorders. 1999;**23**:98-105

[23] Yang TTC, Koo MWL. Hypocholesterolemic effects of Chinese tea. Pharmacological Research. 1997;**35**(6):505-512

[24] Yang TTC, Koo MWL. Inhibitory effect of Chinese green tea on endothelial cell-induced LDL oxidation. Atherosclerosis. 2000;**148**:67-73

[25] Zeyuan D, Bingying TXL, Jinming H, Yifeng C. Effect of green tea and black tea on the blood glucose, the blood triglycerides, and antioxidation in aged rats. Journal of Agricultural and Food Chemistry. 1998;**46**:875-878

[26] Hu ZQ, Zhao WH, Hara Y, Shimamura T. Epigallocatechin gallate synergy with ampicillin/sulbactam against 28 clinical isolates of methicillin-resistant *Staphylococcus aureus*. The Journal of Antimicrobial Chemotherapy. 2001;**48**:361-364

[27] Clark KJ, Grant PG, Sarr AB, Belakere JR, Swaggerty CL, Phillips TD, et al. An in vitro study of theaflavins extracted from black tea to neutralize bovine rotavirus and bovine coronavirus infections. Veterinary Microbiology. 1998;**63**:147-157

[28] Esposito E, Rotilio D, Di Matteo V, Di Giulio C, Cacchio M, Algeri S. A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes. Neurobiology of Aging. 2002;**23**: 719-735

[29] Wiseman SA. Antioxidants in tea. Critical Reviews in Food Science and Nutrition. 1997;**37**:705-718

[30] Sang S, Lambert JD, Ho CT, Yang CS. The chemistry andbiotransformation of tea constituents. Pharmacological Research. 2011;**64**:87-99 [in Eng]

[31] Valerio LG Jr, Kepa JK, Pickwell GV, Quattrochi LC. Induction of human NAD(P)H:quinone oxidoreductase (NQOI) gene expression by the flavonol quercetin. Toxicology Letters. 2001;**119**:49-57

[32] Alzheimer's Association. Alzheimer disease facts and figures. Alzheimer's Dementia. 2016;**12**(4):459-509

[33] Hippius H, Neundorfer G. The discovery of Alzheimer disease. Dialogues Clinical Neuroscience. Mar 2003;**5**(1):101-108

[34] Murphy SL, Kochanek KD, Xu J, Heron M. National Vital Statistics Reports. 2015;**63**:1-117

[35] Schimidt HL, Garcia A, Martins A, Mello-Carpes PB, Carpes FP. Green tea supplementation produces better neuroprotective effects than red and black tea in Alzheimer-like rat model. Food Research International. 2017;**100**:442-448

[36] Choi SM, Kim BC, Cho YH, Choi KH, Chang J, Park MS, et al. Effects of flavonoid compounds on beta-amyloid-peptide-induced neuronal death in cultured mouse cortical neurons. Chonnam Medical Journal. 2014;**50**(2):45-51

[37] Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry K, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. Journal of the National Cancer Institute. 2015;**107**:djv048

[38] Rady I, Siddiqui IA, Rady M, Mukhtar H. Melittins. A major peptide component of bee venom, and its conjugates in cancer therapy. Cancer Letters. 2017;**402**:16-31

[39] Mann CD, Neal CP, Garcea G, Manson MM, Dennison AR, Berry DP. Phytochemicals as potential chemopreventive and chemotherapeutic agents in hepatocarcinogenesis. European Journal of Cancer Prevention. 2009;**18**(1):13-25

[40] Higginson J. Etiological factors in gastrointestinal cancer in man. Journal of the National Cancer Institute. 1966;**37**:527-545

[41] Tsao AS, Liu D, Martin J, Tang XM, Lee JJ, El-Naggar AK, et al. Phase ii randomized, placebo-controlled trial of green tea extract in patients with high-risk oral premalignant lesions. Cancer Prevention Research. 2009;**2**:931-941

[42] Hodson ME. Heavy metals. Geochemical bogey men. Environmental Pollution. 2004;**129**:341-343

[43] Juberg DR, Kleiman CF, Simona CK. Position paper of the American Council on Science and Health: Lead and human health. Ecotoxicology and Environmental Safety. 1997;**38**:162-180

[44] Thangapandiyan S, Miltonprabu S. Epigallocatechin gallate effectively ameliorates fluoride-induced oxidative stress and DNA damage in the liver of rats. Canadian Journal of Physiology and Pharmacology. 2013;**91**:528-537

[45] Mandal BK, Suzuki KT. Arsenic round the world: A review. Talanta. 2002;**58**:201-235

[46] Sun TL, Liu Z, Qi ZJ, Huang YP, Gao XQ, Zhang YY. (−)-Epigallocatechin-3-gallate (EGCG) attenuates arsenic-induced cardiotoxicity in rats. Food and Chemical Toxicology. 2016;**93**:102-110

[47] Miltonprabu S, Thangapandiyan S. Epigallocatechin gallate potentially attenuates fluoride induced oxidative stress mediated cardiotoxicity and dyslipidemia in rats. Journal of Trace Elements in Medicine and Biology. 2015;**29**:321-335

[48] Abdel-Moneim A-MH, Meki A-R, Attia Salem AM, Mobasher A, Lutfi MF. The protective effect of green tea extract against lead toxicity in rats kidneys. Asian Journal of Biomedical and Pharmaceutical Sciences. 2014;**04**(39):30-34

[49] Thangapandiyan S, Miltonprabu S. Epigallocatechin gallate supplementation protects against renal injury induced by fluoride intoxication in rats: Role of Nrf2/HO-1 signaling. Toxicology Reports. 2014;**1**:12-30

[50] El-Missiry MA, Othman AI, El-Sawy MR, Lebede MF. Neuroprotective effect of epigallocatechin-3-gallate (EGCG) on radiation-induced damage and

apoptosis in the rat hippocampus. International Journal of Radiation Biology. 2018;**25**:1-27

[51] Thangapandiyan S, Sharmilabanu A, Vadivazhagi Y, Miltonprabu S, Ramesh M. A mechanism underlying the neurotoxicity induced by sodium fluoride and its reversal by epigallocatechin gallate in the rat hippocampus: Involvement of NrF2/Keap-1 signaling pathway. The Journal of Basic and Applied Zoology. 2018;**79**:17

[52] Sivaprasad RT, Malarkodi SP, Varalakshmi P. Therapeutic efficacy of lipoic acid combination with dimercaptosuccinic acid against lead-induced renal tubular defects and tubular defects and on isolated brush-border enzyme activities. Chemico-Biological Interactions. 2004;**147**(3):259-271

[53] Mehana EE, Abdel Raheim MA, Fazili MKM. Ameliorated effects of green tea extracts on lead induced liver toxicity in rats. Experimental and Toxicologic Pathology. 2012;**64**:291-295

[54] Khalaf AA, Moselhy WA, Abdel-Hamed MI. The protective effect of green tea extract on lead induced oxidative and DNA damage on rat brain. Neurotoxicity. 2012;**33**:280-289

[55] Rice-Evans CA, Miller NJ, Paganga G. Structure–antioxidant activity relationship of flavonoids and phenolic acids. Free Radical Biology & Medicine. 1996;**20**:933-956

[56] Radhakrishnan R, Kulhari H, Pooja D, Gudem S, Bhargava S, Shukla R, et al. Encapsulation of biophenolic phytochemical EGCG within lipid nanoparticles enhances its stability and cytotoxicity against cancer. Chemistry and Physics of Lipids. DOI: 10.1016/j.chemphyslip.2016.05.006

[57] Katiyar SK, Agarwal R, Mukhtar H. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. Cancer Letters. 1993;**73**(2-3):167-172

[58] Weisburger JH, Rivenson A, Garr K, Aliaga C. Tea, or tea and milk, inhibit mammary gland and colon carcinogenesis in rats. Cancer Letters. 1997;**114**:1-5