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REVIEW ARTICLE

Green Tea, A Medicinal Food with Promising Neurological Benefits

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Abstract: Neurological disorders and their sequelae, as of the widespread and critical humans' complications, affect the body's nervous systems, organ functions, and behaviors. According to WHO, neurological disorders are currently predicted to affect more than one billion people globally. It is well-established that complementary medicine is one of the high accepted interventions that could have been considered for the management of neurological ailments. The current review aimed to compile all the crucial data reporting the investigation on the conspicuous intervention of green tea (made of Camellia sinensis) and related lead compounds (especially l-theanine, epigallocatechin-3-gallate, epicatechin-3-gallate, epicatechin, and epigallocatechin) for their neurological activities, mechanisms of action, and clinical properties. According to the documents, green tea exhibits antidepressant, anti-neurodegenerative (*e.g.*, anti-Parkinson and anti-Alzheimer), as well as neuroprotective effects.Chief among them, for offering novel work, it is worth focusing on several related assessments with great attention to more extensive standardized clinical trials, and subsequently more in-depth pharmacokinetic studies to safely introduce this beneficial medicinal food as a neuro-effective agent.

Keywords: *Camellia sinensis*, green tea, complementary medicine, neurological disorders, polyphenol, review.

1. INTRODUCTION

Originated from China, currently, tea is the most common beverage that is consumed worldwide and second-ranked drink after water. Tea is derived mainly from the leaves, buds, or delicate stems of the plants of genus *Camellia sinensis* (L.) Kuntze. The plant entails a long history from 2737 BC that spans across the world over the past centuries [1, 2]. Now, statistics show that every year, nearly 3 million tons of tea is produced and consumed [3]. Steaming or roasting of green tea will inactivate the polyphenol oxidase and finally will conserve the natural polyphenolic structure of green tea in parallel with overall composition [4, 5]. Tea generally consists of polyphenols, caffeine, minerals, and trace vitamins, carbohydrates, and amino acids, such as L-theanine. As mentioned previously, the degree of fermentation is significant in the determination of the tea type.

Furthermore, various tea types will have different characteristics and different structures, and finally, even the amounts of minerals like magnesium vary considerably [6]. There are distinct polyphenolic components found in green tea, in which the most bioactive compounds are flavanol monomers (catechin) containing about 30% of its leaves dry weight. Among numerous phytochemical compositions, these compounds are recognized by hydroxyl groups on rings and include epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epicatechin, and epigallocatechin (EGC). Like many herbal metabolites with potent antioxidant activities, EGCG is the most abundant and the leading cause of the observed bioactivities among those compositions [7, 8].

From physicians' views, tea was a common remedy in ancient medicine in Asia, especially in Chinese medicine, for the treatment of many illnesses [9]. Currently, considering many properties of green tea, including antioxidant activity, an enormous number of researches have shown the potential effect of green tea on a broad spectrum of medical conditions. Many biomedical applications such as employment as a critical role in prevention or treatment of alcoholic liver disease and rheumatoid arthritis-related vascular inflammation [10, 11], extended applications in cancer therapy [12, 13], different anti-infective properties [14] have been reported for green tea in different papers.

For reviewing the neurological properties of green tea, critical studies relevant to the neurological aspects of this

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medicinal plant have been gathered and discussed in the current work.

2. METHODS

The databases PubMed, Scopus, Web of Science, and ScienceDirect, were searched for the term, "Green tea" with the specificity of neurological activities and properties concerned with neurology to gather the respective papers from the beginning up to 1st Sep 2019. All documents related to agricultural science, genetics, and those mentioning the phytochemical and chemistry, as well as papers dealing with other pharmacological and biological activities were excluded.

3. RESULTS AND DISCUSSION

Among all filtered documents, 52 papers, directly or indirectly, have dealt with the neurological effects of green tea. Table (**1**) represents all related activities that have been reported previously by researchers. In this table, the specified properties, method of the concerned assay as well as primary or a significant outcome have been cited. From those activities, the neuroprotective effect of this medicinal plant has been cited numerously. The herb's chemical fractions have exerted nerve growth cell activities, CNS stimulant, and antidepressant properties as well as neuroprotection *via* attenuating the induced injuries. There were considerable antioxidant activity assessments, which among those, the neuroprotective effects of green tea were concluded. Moreover, green tea could exert an anti-neurotoxicity impact, which has been evaluated in some studies.

3.1. Effects of Neuroprotection

In aerobic conditions, energy is produced in the shape of ATP *via* electron transfer, in which the oxygen will be the final electron acceptor in the cell membrane. The free radicals in the cells, such as reactive species (ROS) and reactive nitrogen spices (RNS), are formed by the transfer of free, uncoupled electrons. These serve as mobile health messengers and indicators of cellular functions [15, 16]. The free radicals initiate the oxidative stress process in which may affect numerous biological activities. Excess amounts of these molecules will damage cellular structures and components, which may induce mutation and interfere with the physiologic process [17]. The cell used a complexly complicated network of the antioxidant enzyme to counteract these processes. There are multiple endogenous antioxidants substitute in the cells, such as Catalase, Superoxide dismutase, and Glutathione peroxidase. Any shift in the cellular microenvironment may be resulted by the underproduction of antioxidants and the overproduction of free radicals [18]. Flavonoids are one of the most abundant sources of antioxidants in the diets. They are well known to protect the body against multiple diseases such as cardiovascular diseases, cancers, neurological diseases, and other age-related ailments [19]. Additionally, phenolic acids are widely known for its medicinal antioxidant effects [20]. Having several components such as those mentioned above, green tea extract is a naturally potent free radical scavenger. It has a wide range of applications with negligible drawbacks [21]. Mostly, the papers have demonstrated the antioxidant and radical scavenging activities of green tea flavonoids and polyphenols (catechins) in CNS and PNS cells. Chemically, the presence of hydroxyl groups and conjugated rings in phenolic compounds could be a potential property to exert antioxidant or radical scavenging activities [22]. These compositions, directly or indirectly, have a critical role in enhancing the total antioxidant capacity of plasma [23]. This may be related to providing vitamin C or stimulating the indigenous production of urate as a physiological antioxidant or pro-oxidant [24]. According to numerous experimental and preclinical studies, antioxidants have profound medical impacts on neurologic diseases [25]. Also, green tea serves as an antioxidant agent. Electron traps and scavengers of free radicals, as polyphenols play an essential role in the antioxidant effect. The phenol rings in the structure of EGCG trap the oxidants and protect the nerve and the human body from the oxidation process [26, 27]. According to different studies, the mechanism of ECGC against the oxidation action was documented. However, various mechanisms and pathways were reported as the leading causes of it, but the increased expression of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase, is so Impressive [22, 23]. One study showed that EGCG could protect spinal cord neurons and neutralize the oxidative stress of hydrogen peroxide [28]. An animal study, *via* intraperitoneal administration of ECGC, has revealed the upregulation of glutathione reductase which was attributed possibly to indirect activation of transcription factors or related enzymes. EGCG also diminishes the isoprostanes, a crush induced oxidative agent [29]. An electrophysiological and morphological study showed that EGCG can be suppressive to Bcl-2-associated X protein (BAX) expression and is protective of cortical neurons during UV irradiation [30]. The reduction of malondialdehyde as a marker of oxidation in various animal studies indicated the strong effect of green tea, especially on the protection of biological organs [24, 25, 31] . Moreover, green tea exhibits anti-inflammatory properties as well. In one study on rats, catechins could diminish the inflammation induced by Adriamycin (anti-tumoral agent). In this study, the expressions of inflammatory cytokines such as tumor necrosis factor (TNF), inducible nitric oxide synthetase and nuclear factor kappa-B were significantly diminished following administration of catechin [32]. Furthermore, multiple studies have shown that catechins may benefit patients with inflammatory bowel disease [33, 34]. (-)-epigallocatechin-3-gallate (EGCG) can modulate macrophage and neutrophilic infiltration in gastrointestinal mucosa [35, 36]. Moreover, it has been shown that epicatechin, as catechin, can tighten and enhance the upregulation of gap junction between intestinal cells and could impede the progression of the intestinal lesion to malignancy [37]. Another study on mice showed that EGCG administration could lead to the pro-inflammatory cytokines release and subsequent fibrosis in those with liver injury [38]. L-theanine, as a crucial compound, is found exclusively in green tea extract. In one study, reserpine induced orofacial dyskinesia was used as a

Table 1. Neuropharmacological and clinical activities of Green tea

S. No.	Medicinal Properties	Method/ Assay or Aim*	Outcomes and Conclusion*
1	**Effects on neuroprotection**	Electrophysiology, histology, transmission electron microscopy	- Improvement of sciatic nerve deficiencies in GTPs - Pretreat Nerve allografts - Nerve regeneration enhancement [42]
-	-	Superoxide dismutase activity/gene expressing	Spinal cord neurons protection from oxidative stress conditions (by GTPs) [28]
-	-	Use of l-theanine / Reserpine induced orofacial dyskinesia (*in vivo*)	- Neuroprotective effects (Anti-oxidation Neurotransmitter deficiency prevention, anti-neuro-inflammation, Anti-apoptosis) [39]
-	-	Hydrocephalus oxidative damage/EGCG (50 mg/kg)	- ↓ MDA levels in periventricular white matter [88]
-	-	Fluoro-Jade-B (FJB) staining/PCA (30 mg/kg) IP injected	- ↓ Neuronal death and oxidative stress in the hippocampus - ↓ Seizure-induced microglial activation [89]
-	-	Cd-induced brain injury/treated with l-theanine (200 mg/kg/day)	- ↓ Brain cadmium level, oxidative damage, MDA, and neuronal cell death Increase in Glutathione level, Inhibition of GSK-3β activation [90]
-	-	Diminution of MnO_2 nanoparticles neurotoxicity	- Prevention of arsenic neurotoxicity effects (↓ Oxidative stress and lipid peroxidation induced by arsenic [91]
-	-	Rats exposed to trivalent inorganic arsenic/ Green tea (GT) gavage	- ↓ DNA fragmentation, TP53, and COX-II genes expression to attenuate deltamethrin-induced neurotoxicity [92]
-	-	Administration of 3-nitropropionic acid (21 days, rats)/ GT aqueous extract	- ↓ Harmful NO production, Prevention of striatal neurotransmitters levels alteration, Anti-inflammatory activity (l-theanine treatment) [40]
-	-	Male Wistar rats/Induction of crush injury/intraperitoneal administration of EGCG	- Upregulation of glutathione reductase (EGCG may indirectly act *via* enzymes induction of transcription factors) - ↓ Crush induced production of isoprostanes - ↑ Total antioxidant capacity recovery (motor and sensory impairment alleviation, histo-morphological evidence of neuronal regeneration following sciatic nerve injury [29]
-	-	Animal study Two weeks of treatment with EGCG/ *in vivo*, *in vitro*	- ↓ Transient putrescine levels increment ischemic- induced due to EGCG delayed administration [93] - ↑ Cell survival, ↑ Population of doublecortin -expressing cells, ↓ Apoptotic cells, Increase in net neurogenesis, and hippocampal phospho-AKT levels [94] - Preservation of peripheral nerve segments by harvesting in DMEM containing GTPs [41]
-	-	Electrophysiological and morphological studies	- Cortical neurons protection from UV light irradiation-related injury by GTPs through inhibition of active BAX expression [30]
2	**Effects on the motor, memory/cognitive function, and anti-neurodegeneration**	-	-
A	***Effect on Alzheimer's disease (anti-amyloid effect and others)***	Clinical trial & *in vitro* assay	- Synergistic inhibitory effect of EGCG and fish oil on cerebral β-amyloid deposits and noticeable therapeutic efficacy for AD treatment [95] - ↓ Oxidative markers such as MDA, 8-OGdG, and carbonyl, ↑ MMSE score and total antioxidant capacity of plasma [96]

S. No.	Medicinal Properties	Method/ Assay or Aim*	Outcomes and Conclusion*
-	-	A clinical trial, Four Green tea pills daily for two months	- Prophylaxis effects of a regime containing GT and EGCG modulate against Alzheimer's disease [97]
-	-	*in vivo* (Alzheimer transgenic mice)	- Facilitates hippocampal synaptic transmission through the dopamine D1/5 receptor-PKA pathway - ↑ Memory and hippocampal LTP in AD mice elevates hippocampal dopamine and NA levels in AD mice [59] - Critical protective role of GTPs on prefrontal cortical neurons from amyloid-beta through involving neuroprotective pathway protein AKT [98]
-	-	Orally administered with l-theanine f 0.1 mg/mL (low dose) and 0.4 mg/mL (high dose) *in vivo* (Rats)	- Reversion of phosphatidylcholine deregulated metabolism induced by β-amyloid peptide [60] - ↓ Apoptotic neurons and neurodegeneration memory deficit, oxidative stress, neuroinflammation, and neurodegeneration in hyperhomocysteinemia [61]
B	***Protective Effects against Parkinson's disease***	Fluoro-Jade B staining/ EGCG (*in vivo*) Immuno-histo-chemistry Fly stock and culture/Paraquat toxicity assay/locomotion assay/Antioxidant assay/survival test/western blot analysis/lipid peroxidation/ *in vivo*	- ROS-NO pathway was inhibited by GTPs which resulted in a protective effect against Parkinson's disease [66] - Prevention from a reduction in life span and locomotor activity - ↓ Neurodegeneration and lipid peroxidation [65]
C	**Positive effect on motor/cognitive effect including Spatial learning prevention and impairment of memory**	Morris water maze	- Hippocampus proteins upregulation involved in synaptic plasticity, ↓Aβ142 oligomers (long-term administration of GTC: prevention of spatial learning and memory impairment [49] - Regulation of cAMP-response element-binding protein signaling cascade of the hippocampus (long-term administration of GTC: prevention of spatial learning and memory impairment [49]
-	-	Open field test, Step through the test	- GTPs improved stress-related cognitive impairments [49]
-	-	EEG measurements/ EEG brain mapping instrument	- ↑ The activity of brain waves (putative role of GT in cognitive function) [50]
-	-	IV infusion of EGCG in acutely injured rats' spinal cord/ LSS, pain behavior test	- Anti-neurodegenerative effect (improvement of tactile allodynia, mechanical nociception, and number of neurons, reduction in lesion size area) [51]
3	**Effect on ischemic change**	EGCG (50 mg/kg) effect/Cerebral artery occlusion and reperfusion	- ↓ Infarction volume and neurological deficit total score, ↓MDA level, and oxidized/total glutathione ratio levels (neuroprotective effects) [72]
-	-	Mice middle cerebral artery occlusion and reperfusion/ EGCG	- Proliferation and differentiation improvement of NPCs of Subventricular zone by EGCG (stroke recovery), functional recovery *via* AKT signaling pathway [73]
-	-	Animal and experimental design, Surgery, Control behavioral tests, Memory assessments, Biochemical testing, Brain histology	- Prevents deficits in object and social recognition memories, spatial memories and hippocampal oxidative status, intense necrosis in ischemic necrosis cases [76]
-	-	Western-blot/ RT-PCR/ Tube Formation/ Transwell Migration/ Detection of Apoptosis by Flow Cytometry/ Electron Microscopy/ OGD/R model (*in vitro*)	- Neuroprotective *via* promoting neovascularization, alleviating apoptosis and autophagy, and promoting cell proliferation in HBMVECs of OGD/R [77] - ↓ Infarct volumes and expression of endoplasmic reticulum stress markers and apoptosis, ↑ Neurological scores [75]

S. No.	Medicinal Properties	Method/ Assay or Aim*	Outcomes and Conclusion*
-	-	Excitotoxicity in primary cultured cortical neurons/ MTT and TUNEL assays	- Modulation of inflammatory cytokines, ↓ Oxidative stress in the ischemic brain [71]
-	-	Experimental ischemia-reperfusion brain injury/ MTT and LDH release/ Cell culture and Trypan blue exclusion/ Immuno-precipitation, Western blot (*In-vivo*)	- ↓ Apoptotic cells and ischemia/reperfusion-related increase of eicosanoid concentration and oxidative damage, recovery improvement from active avoidance inhibition caused by ischemia/reperfusion due to GT extract pretreatment [70, 78] - Dose-dependent protective effect ECG against ischemia-induced hippocampal neuronal damage [74] - Aβ fibrils Formation inhibition/oligomers by ECG resulted in anti-Aβ toxicity action [99, 100] - ↓ SHSY5Y cells DDT death-related by EGCG through ↓ organochlorine pesticide-dependent cell injury [67] - ECG promoting effect on rapid degradation of bad mediated by protein kinase C- and proteasome - Correction of Hyponatremia and improvement [79] - ↓ ROS reduction, ↑ Activity of SOD by GTPs and ERK1/2 inhibitor (PD98059) in VF fibrillation -induced cardiac arrest [101] - ↓ Transient putrescine levels increment induced by ischemia [93] - Reversing the regulation of Akt/mTOR signaling pathway by ROS *via* catechin administration (prevent autophagy-activated apoptosis [80]
4	**Miscellaneous**	-	----------
-	***Effects on action potential***	Functional neurotoxicity/ Orally applied green tea	- ↓ Changes in the action potential of peripheral nerve and spontaneous cortical activity alteration (Diminution of nervous system effects) [85]
-	***Neuronal plasticity improvement***	Synaptic transmission between regions of the hippocampus/ Schaffer collateral (*in vivo*)	- Enhancement of long-term potentiation by EGCG, Alleviation of hippocampal LTP deficiency in a similar fashion as γ-Aminobutyric acid antagonists [87]
-	***Positive effect on depression***	-	- Positive effect of GT and γ-Aminobutyric acid GT against post-stroke depression through decreasing oxidative stress, (restoring normal behavior) behavioral recovery, ↑ endogenous antioxidant defenses and depressive symptoms modulation [86, 101] - Beneficial for anxiety, sleep disturbance, cognitive impairments and depressive symptoms [82]
-	-	Case-control, Antioxidant assay of glutathione, catalase and superoxide dismutase	- Antioxidant activity of catechin may be helpful for the major depressive disorder [83]

Abbreviations: *AD: Alzheimer's disease; DMEM: Dulbecco's Modified Eagle Medium; ECG: Epigallocatechin-3-gallate; EGCG: epigallocatechin-3-gallate; GT: Green Tea; GTC: Green Tea Catechin; GTPs: Green Tea Polyphenols; GSK-3β: Glycogen synthase kinase 3 beta a; HBMVEC: Human Brain Microvascular Endothelial Cell; LDH: Lactate dehydrogenase; LSS: Lumbar spinal stenosis;; LTP: Long-term Potentiation; MDA: Malondialdehyde; MMSE: Mini-Mental State Examination; mTOR: Mammalian Target of Rapamycin; MTT: 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide; NA: Hypernatremia; NO: Nitric Oxide; NPC: Neural Progenitor Cell; 8-OGdG: 8-hydroxy-2-deoxyguanosine; OGD/R: Oxygen-Glucose Deprivation/Reoxygenation; PCA: Principal component analysis; ROS: Reactive Oxygen Species; RT-PCR: Real-time polymerase chain reaction; SOD: Superoxide Dismutase; TP53: Tumor protein P53; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling.

human model for tardive dyskinesia. The result of l-theanine administration was in favor of antioxidant, anti-inflammatory, and anti-apoptosis features of this component [39]. Another investigation showed that l-theanine can decrease the amount of nitric oxide production and may act as an anti-inflammatory agent [40]. An experimental study in rats, showed that the dissected sciatic nerve can be well be preserved in the polyphenol solution for even a month [41]. Another study made a comparison between floating the nerve allograft in the green tea extract versus irradiation. Irradiation is typically done before allogenic nerve transplantation to reduce neuro-immunogenicity, inhibit of early rejection and improve the tissue preservation and minimize the postoperative infections. The study proposed that using green tea polyphenols is better than pretreatment with irradiation [42].

3.2. Effects on the Motor, Memory/cognitive Function,and Anti-neurodegeneration

Age-related damages start to occur are seen once the grow finishes and aging process become accelerated. Many age-related changes in the brain may result in many problems related to cognition, memory, and learning skills [43]. The central nervous system, brain, and spinal cord are more prone to oxidative damages. Because the system has a high level of oxygen consumption, low availability of a few anti-oxidant systems, and a more elevated amount of iron in the brain tissue [44]. Many medications have been introduced in the market to combat damages induced by free radicals and age-related modifications [45]. These drugs may be useful in the prevention of cognitive impairments such as dementia, learning, and memory difficulties. Numerous studies are suggestive that one of the most important underlying reasons for such a condition is oxidative stress. These stressors may induce neuronal death by cell damage *via* activation of cell signaling process in the apoptosis cascade or necrosis [46]. Accordingly, antioxidants have been frequently used to address these harmfully deleterious events. Natural antioxidants have a pivotal role in this area based on their possible role in modulation of age-related oxidative stress and their widespread availability [47]. An animal study, using water maze, revealed that long term oral administration of green tea catechin compounds could impede impairment of memory and spatial learning. It is medicated *via* decrease in amyloid β (Aβ) peptides 1-42 to form oligomers and *via* rise in synaptic plasticity-related proteins in the hippocampus. This study showed that catechin could stop the reduction of 3 significant proteins in synapse formation and function processes. These proteins are a brain-derived neurotrophic factor (BDNF), post-synaptic density protein-95 (PSD95), and Ca^{+2}/calmodulin-dependent protein kinase-II (CaMK-II) [48]. In order to address stress-related cognitive impairments, an animal study was done using a water maze, open field test, and step-through test. These studies found that the serum level of cortisol, norepinephrine, IL-2, IL-6 were higher in groups of Wistar rats under psychological stress. While a decrease in brain anti-oxidation capacity was also noticed. Subsequent to the stress and memory impairment, it was revealed that all mentioned changes can be improved by using green tea polyphenol (GTP) [49].

To address human psychometric states such as enhancement of attention, relaxation, and mental clarity, Okello EJ *et al.* assessed the EEG of volunteers. They found that alpha, beta, and theta waves were increased 1 hour following the ingestion of green tea. These incline in brain waves, especially theta waves, are suggestive of the putative role of green tea, including better cognitive functions, specifically on alertness and attention [50]. Another study on rats with acute and chronic spinal cord injury revealed that IV administration EGCG is beneficial in many aspects. This compound had positive effects on locomotor activity, pain, and sensory neurobehaviour. EGCG also increased the number of spinal neurons and reduced the size of the lesion area. Also, the protective role of EGCG on neuronal degeneration was implied in this study. By using histochemistry, it was shown that GAP-43 and GFAP showed marked increased following EGCG consumption. Clinically, improvement in tactile allodynia, mechanical nociception, paw withdrawal, and tail-flick latencies were noted [51].

Traditionally, Alzheimer's disease (AD) was a "dualistic histo-clinical diagnosis" in which a patient should have progressive neurological findings such as dementia, impairment of memory, and other related clinical manifestations. The second portion of diagnosis was based on histopathology of the brain, which was neurofibrillary tangles and the existence of senile plaques (a kind of brain tissue lesion), which are also in parallel with deposition of vascular amyloid deposits and lack of synapses [52, 53]. AD was a hub for researchers of both traditional and modern medicine [54]. Various inflammatory processes, oxidative stress, and Aβ peptide accumulation are known to be significant contributors to AD. These factors impair specific enzymatic dysfunctions and programmed neuronal cell death [55]. A recent study on Alzheimer's transgenic mice indicated that EGCG modulates and reduced the level of cerebral Aβ peptide and amyloid precursor protein (APP) [56]. Another *in-vitro* study indicated that a combination of green tea extracts with fish oil reduced cerebral depositing of Aβ [57]. In a clinical trial study, decreasing oxidative markers such as malondialdehyde (MDA), 8-oxyguani- dine-deoxy-guanidine (8-OGdG), and carbonyl and increase inmini-mental state exam (MMSE) score and total antioxidant capacity of plasma was significantly documented by green tea consumption. This promise a protective effect on cognitive function against Alzheimer's disease [26]. In another animal study, the synaptic dopamine pathways in the hippocampal area have been facilitated, and memory improved [27]. In an in-vivo study, combining green tea with fish oil reduced cerebral depositing of Aβ [58]. The evaluation of Alzheimer's transgenic mice in a study showed that green tea could ease the hippocampal synaptic transmission *via* dopamine D1/5 receptor-protein kinase A (PKA) pathway, increase the hippocampal dopamine amount, and improve the memory. Furthermore, it was illustrated that it could activate the protein kinase B (PKB or Akt) protein pathway that is neuroprotective to prefrontal neurons. That can impede the accumulation of the beta-amyloid component [59]. Green tea can also reverse the negative impacts of the β-amyloid peptide, such as dysregulation of phosphatidylcholine metabolism [60]. Another study on rats with hyperhomocysteinemia suggested that green tea and EGCG could improve memory deficit and exerts anti-neuroinflammation, anti-oxidative stress, and anti-neurodegenerative properties [61]. One of the motor-symptom origin disorders is Parkinson's disease (PD). This disease affects more than 10 million people worldwide [62]. This neurodegenerative disease has different obvious clinical symptoms, including; rigidity, bradykinesia (slowness of movement), difficulty in walking, and tremor [42]. Cell death in the brain's basal ganglia dopamine pathway and presence of Lewy bodies leads to lower the level of dopamine [28]. In an animal study, biological tests indicated that the antioxidant effect of green tea based on ROS-NO enzyme systems ameliorated the PD in the 6-hydroxydo-

pamine (6-OHDA) rat model [63]. The consumption of green tea further caused the attenuation of neurodegeneration and lipid peroxidation in an animal model of PD [64].

An assessment revealed that exposure of wild-type Canton-S flies with the neurotoxicant paraquat (PQ) makes this flies as a useful animal model of PD. This *in vivo* study suggested that EGCG in comparison to other compounds such as propyl gallate and minocycline have positive impacts on locomotion, lipid peroxidation, life-span, and neurodegeneration [65]. An *in-vivo* study done proposed that green tea polyphenols (GTPs) may have a protective role on the dopaminergic neurons *via* inhibition of nitric oxide and reactive oxygen species (ROS) which are crucial in the pathogenesis of the Parkinson's disease. Therein, GTP, as a potent neuroprotective antioxidant, can have protection of the effects on 6-OHDA, midbrain, and striatal dopaminergic neurons. GTP can reduce lipid peroxidation, nitrite/nitrate content, inducible nitric acid synthase, and protein-bound 3-nitro-tyrosine [66]. Another study suggested that EGCG may reduce dichlorodiphenyltrichloroethane (DDT)-induced cell death in dopaminergic human neuroblastoma cell line (SH-SY5Y) cells and might be useful in PD [67].

3.3. Anti-ischemic Effect

An infirmity inwhich there is inadequate blood flow to the brain to meet the metabolic demand is called brain ischemia. Based on WHO, stroke caused around 6 million death in 2005, and it will reach about 8 million death by 2030 [68]. Stroke is also the second preventable leading cause of death and the fourth cause of losing productivity [69]. The brain ischemia is due to inadequate oxygen supply or cerebral hypoxia and, finally, may lead to brain tissue death or cerebral infarction/ischemic stroke [55]. Promoting neovascularization, alleviating apoptosis and autophagy, and promoting cell proliferation in human brain microvascular endothelial cells (HBMVECs) of oxygen-glucose deprivation/re-oxygenation (OGD/R) are fundamental and acceptable mechanisms from green tea extractions for resolving the brain ischemia as well as documented in animal model studies [56, 57, 70]. Green tea polyphenol, especially EGCG gallate, promotes the reperfusion and attenuates the ischemic alignment as shown in different studies [26].

One animal study revealed that EGCG could promote angiogenesis *via* regulation augmentation of nuclear factor erythroid 2-related factor 2 (Nfr2) signaling pathway of ischemic attack. Pathologically, the group that was treated with EGCG, had better outcome, antigen KI-67/Cluster of differentiation 3 (ki67/CD3)-positive vessels, higher vessel density, and increased expression of Nrf2. Moreover, decreased oxidative stress was noticed in the study [71]. Another study on EGCG-treated rats with middle cerebral artery occlusion revealed that the malondialdehyde level and oxidized/total glutathione ratio (oxidative stress and infarction size indicators) was decreased [72]. Another survey indicated that delayed treatment with EGCG is also protective after brain infarction. EGCG might induced neurogenesis following an ischemic stroke [73, 74]. Until recently, the mechanism of how EGCG induces neuroprotection was in a dilemma. A study showed that injecting EGCG after ischemia inhibits expression of endoplasmic reticulum stress (ERS) -related markers, glucose-regulated protein 78 (GRP78), CCAAT-enhancer-binding protein (C/EBP)-homologous protein (CHOP) and caspase-12, exerts antioxidant effects and diminishes apoptosis. Thus, it may improve the neurological status and decrease the infarction size [75].

Another research has addressed the memory deficit compensation and anti-oxidation properties of green tea. The study showed that green tea proved to be useful for the prevention of object and social recognition memory deficit. Green tea was effective in spatial memory and impeding the intense necrosis and other changes in brain tissue [76].

The (-)-epicatechin gallate (ECG) is another significant green tea components that promotes new vessel formation and diminishes autophagy and apoptosis following ischemia/reperfusion in an animal model. Moreover, following the administration of ECG, oxidative stress markers such as ROS, LDH, MDA, and SOD decreased significantly. Moreover, ECG has a positive impact on cell migration and proliferation and, as mentioned, will hinder apoptosis and autophagy by affecting the expression of vascular endothelial growth factor (VEGF), Bcl-2, BAX, light chain 3B (LC3B), caspase 3, mTOR, and Beclin-1 expression [77]. One study confirmed the efficacy of green tea extract to reverse behavior deficit following ischemia/reperfusion-induced brain injury and to decrease the eicosanoid accumulation like Leukotriene C_4, prostaglandin E_2, and thromboxane A_2 [78]. In one study, GTP and extracellular signal-regulated kinases (ERK) inhibitors were used synergistically, and better neurological outcomes and survival were noticed in the rats with cerebral ischemia [79]. Chen *et al*. showed that catechin also prevented apoptosis and cell death of microglial cells of the brain after ischemia. This is done *via* inhibition of the ROS-regulated Akt/mTOR (mammalian target of rapamycin) signaling pathway in microglia [80].

3.4. Miscellaneous Effects

World health organization (WHO) declared that major depressive disorder (MDD) would be the leading health burden in 2030 [81]. A human study revealed that chronic use of l-theanine might be beneficial for MDD, sleep disturbance, cognitive impairments, and anxiety [82]. There is a possibility that catechin decreases the depressive symptoms in rats subjected to chronic stress [83]. Meanwhile, it was reported that catechin might also be useful to inhibit corticosteroid-induced anxiety [84].

An investigation showed that green tea as a material with many antioxidant molecules could lessen the changes in the spontaneous and evoked neuronal activity of cortex as well as peripheral neurons [85]. Hegazi *et al*. in their study showed that green tea could reverse the hyponatremia with lesser neuropathological drawbacks such as focal cell necrosis and locomotor activities [86]. A survey on the mice hippocampus showed that EGCG could promote neuronal plasticity [87].

CONCLUSION

Green tea is widely known as a valuable herbal remedy was used in ancient china. Many positive effects of GTE are suggestive of consuming green tea as an alternative to other beverages. In all, these data could reveal that the administration of green tea as a functional or medicinal daily drink may possess beneficial effects concerning neurological conditions and related disorders. The entire mechanism of action regarding green tea is not transparent. The studies are mainly focused on the activities of l-theanine and EGCG as the main bioactive compounds and antioxidant effects of green tea. Overall, this review clarifies that green tea has a potent neuroprotective effect, especially *in vitro* and *in vivo*. However, it seems that there are future avenues to open by further genomic, molecular, and clinical trials to understand the range and mechanism of action of green tea. Another neglected ring in the chain of green tea administration is about psychological complications. Also, in literature, there is no consensus about the safe amount of green tea consumption for the general population, and this implies that investigations must define the safe amount of green tea to be used in daily routine. Also, these documented effects may enable Alzheimer's patients to consume green tea-containing products, but further molecular research is needed for confirmation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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