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Polyphenols: Well Beyond The Antioxidant Capacity: Gallic Acid and Related Compounds as Neuroprotective Agents: You are What You Eat!

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Abstract: Gallic acid (3,4,5-trihydroxybenzoic acid) is a phenolic acid widely distributed in many different families of higher plants, both in free state, and as a part of more complex molecules, such as ester derivatives or polymers. In nature, gallic acid and its derivatives are present in nearly every part of the plant, such as bark, wood, leaf, fruit, root and seed. They are present in different concentrations in common foodstuffs such as blueberry, blackberry, strawberry, plums, grapes, mango, cashew nut, hazelnut, walnut, tea, wine and so on. After consumption, about 70% of gallic acid is adsorbed and then excreted in the urine as 4-O-methylgallic acid. Differently, the ester derivatives of gallic acid, such as catechin gallate ester or gallotannins, are hydrolyzed to gallic acid before being metabolized to methylated derivatives. Gallic acid is a well known antioxidant compounds which has neuroprotective actions in different models of neurodegeneration, neurotoxicity and oxidative stress. In this review, we discuss about the neuroprotective actions of gallic acid and derivatives and their potential mechanisms of action.

Keywords: Gallic acid, neuroprotective activity, polyphenos, protective activity.

1. INTRODUCTION

The investigations performed in the last three decades have shown that plant foods and beverages are complex mixtures of secondary metabolites (such as polyphenols, sulphur-containing compounds, terpenes, and alkaloids) that can play an important role in the protection of human health. Among phytochemicals, the most studied compounds are polyphenols, which have been found to be beneficial in promoting good health, reducing the risks and even preventing some diseases, such as some form of cancers, diabetes, cardiovascular and neurodegenerative pathologies and microbial infections. The protective effect of polyphenols has a close correlation with their antioxidant and free radical scavenging activities, metal chelating effects, inhibition of different enzymes, including telomerase, cycloxygenase, and lipoxygenase, as well as potential capacity to interact with the signal transduction pathways and cell receptors [1].

Gallic acid (GA) and its structurally related compounds are widely distributed in plants and many investigations have demonstrated some functional properties, which make these substances a very promising class of compounds to be studied for effective neuroprotective treatments.

The object of this review is to summarize the knowledge about the chemical structure and distribution of GA and derivatives in the most common plant foods and beverages. Moreover, the metabolism of these compounds and their protective activity against some diseases, with particular attention to neurodegenerative pathologies, has been reviewed.

2. CHEMICAL STRUCTURE AND DISTRIBUTION OF GALLIC ACID AND DERIVATIVES

Gallic acid (3,4,5-trihydroxybenzoic acid, Fig. **1**) is a plant secondary metabolite that is mainly formed from the 3-dehydroshikimic acid through the shikimic acid pathway, which converts simple carbohydrate precursors [2].

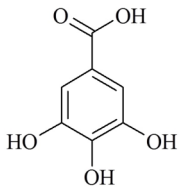

Fig. (1). Chemical structure of gallic acid.

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1873-4316/14 $58.00+.00

GA in free state is ubiquitously present in plant foods. Therefore, it can be considered the main polyphenol dietary compound. The amounts of GA vary according to the plant species, and, within a plant species, according to different environmental factors such as UV radiation, microbial infections, insect attack, and chemical stressors.

Red fruits (i.e. raspberries, blueberries, strawberries, black and red currants, and gooseberries) are important sources of GA. Moreover, GA in free form has been found in red *Vitis vinifera* L. and *Vitis aestivalis* Michx. grapes, which contain up to 4 g/kg fresh weight of phenolic compounds, and in red and white wine, in concentrations ranging from a few milligrams to several tens of milligrams in a glass of wine [3, 4].

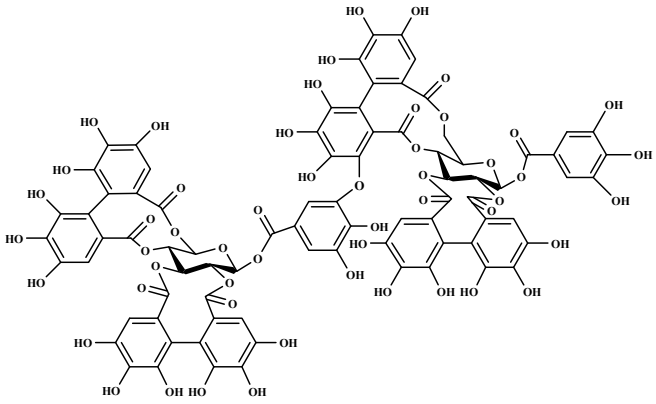
GA is also present in green and black tea, with higher content in black teas (on average 125 mg/L) than in green teas (on average 6 mg/L) [5]. It is also present in some rice (*Oryza sativa* L.) varieties (at concentrations ranging from 17 to 35 mg/Kg) [6], and in oat flour (*Avena sativa* L.) [7].

In the shikimic acid pathway, GA is converted by a glucosyltransferase into 1-galloyl-β-glucose (named β - glucogallin), which has been proposed as the first intermediate and key metabolite in the synthesis of hydrolysable tannins (HTs, gallotannins and ellagitannin), which belong to the large class of tannins along with condensed tannins.

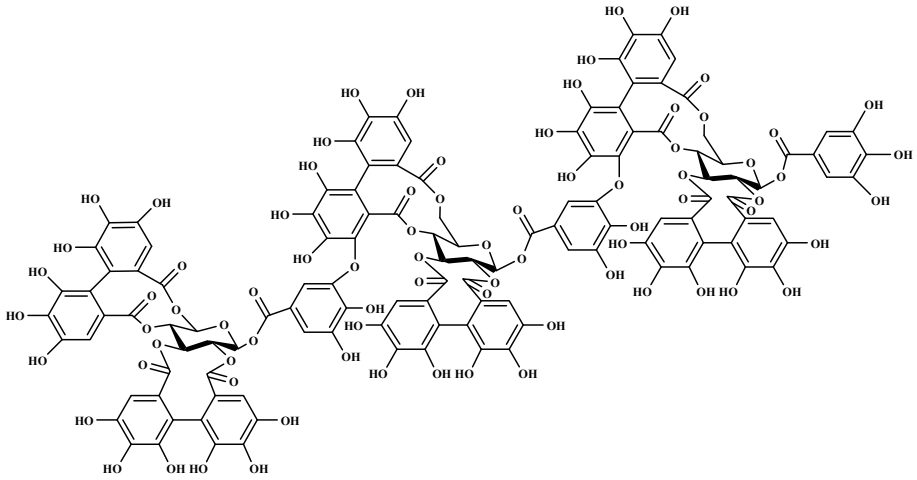
β–Glucogallin, which can act both as acyl acceptor and donor, gives rise to di-, tri-galloylgallotannins through a series of position-specific galloylation reactions of a central core of glucose. This pathway results in the formation of pentagalloyl-glucose, which in turn undergoes a further galloylation up to the production of gallotannins, which show a molar mass ranging from 300 to 3000 Da. As regards to ellagitannins, they are oxidation products of gallyol-glucose in which the galloyl residues form hesahydroxydiphenoyl units [8].

HTs owe their name to the fact that on hydrolysis by acids, bases or enzymes (i.e. tannin acyl hydrolase or tannase), gallotannins produce both glucose and GA, while ellagitannins produce glucose, GA and hexahydroxydiphenoyl residues that undergo spontaneous rearrangement to the lactone, to form ellagic acid (EA).

As regards to the distribution of HTs, gallotannins are not widespread in nature; on the contrary, ellagitannins are more common. The families of *Anacardiaceae (Rhus* sp.), *Leguminosae* (*Caesalpinia* sp.), *Fagaceae (Quercus* sp., *Myroxylon* sp., and *Prosopis* sp.) contain both gallotannins and ellagitannins. *Fagaceae* (*Castanea* sp.), *Combretaceae (Terminalia* sp.), *Myrtaceae (Eucalyptus* sp.), *Rosaceae (Fragaria* sp.*, Prunus* sp., and *Rubus* sp.), *Saxifragaceae (Ribes* sp.),



Sanguiin H-6



Lambertianin C

Fig. (2). Chemical structure of raspberry ellagitannins: sanguiin H-6 and lambertianin C.

Theaceae (Camelia sp) and *Vitaceae (Vitis* sp) contain only ellagitannins [9].

Blackberries, raspberries and strawberries belonging to the *Rosaceae* family contain many different types of ellagitannins. In particular, raspberries are a rich source of two ellagitannins, i.e. sanguiin H-6 and lambertianin C (Fig. **2**). Moreover, mango (*Mangifera indica* L.) contains gallotannins with different levels of galloylation (ranging from 4 to 12) [10-12].

Besides GA in free state and in conjugated form (HTs), many plant foods and beverages contain GA in esterified forms. Green, semi-fermented, and fermented teas (black tea and oolong tea) are the most important sources of these compounds. Green tea contains (-) epigallocatechin-3-gallate (EGCG), (-) epigallocatechin, and (-) epicatechin-3-gallate, which are the GA esterified forms of (-) epicatechin. More recently, a catechin-O-gallate derived from galloylation of catechin was reported, also (Fig. **3**). In oolong and black tea, in which flavan-3-ols is oxidized during the fermentation process by polyphenol oxidases, tea catechins are partially converted into theaflavin, and a mixture of galloyl derivatives, such as theaflavin-3-gallate, theaflavin-3'-gallate and theaflavin-3,3'-digallate, (Fig. **4**) [13].

Less known examples of GA esterified forms are represented by 1) chebulinc acid, occurrs in the *Terminalia chebula* Retz. decotion, which is obtained from its dried fruits [14], 2) di-gallic acid, occurrs in green pods of *Acacia nilotica* (L.) Delile [15], 3) quercetin galloyl-hexoside, in which GA esterifies the sugar linked to the flavonol, as found in many vegetables such as *Hamamelis virginiana* L. leaf extract, and 4) poly-galloyl-poly-flavans occurrs in grape seed extracts that show a large variation in the degree of galloyl substitution [16] (Fig. **5**).

3. BIOAVAILABILITY OF GALLIC ACID AND DERIVATIVES

The metabolism of polyphenols in the human organism and their bioavailability still remain unclear. As regards to GA, it seems to be better absorbed in humans compared with other polyphenols [17]. Glucuronidated forms and 4-*O*-methylgallic acid are the main plasma metabolites of GA. After ingestion of 50 mg of GA, hematic concentrations of its metabolites reach the concentration of 4 μM and the urinary excretion is about 37 % of the ingested dose.

As far as ellagitannins are concerned, they are scarcely bioavailable. In fact, in the upper gastrointestinal tract, ellagitannins are converted into EA which has low bioavailablity. In the lower gastrointestinal tract, gut microbiota metabolize EA and the residual ellagitannins. From this way, urolithin B is produced and persists for few days after ellagitannins ingestion as a conjugated compound with glucuronide acid, at relatively high doses in plasma and urine. So, this latter is considered a biomarker of exposure to ellagitannins and EA [18].

Finally, considering GA in esterified forms, gallate forms of green tea catechin are stable under gastric conditions while are widely degraded after duodenal digestion. Especially, under duodenal digestive conditions, ECG is hydrolyzed to epicatechin, whereas EGCG reacts with different digestive enzymes and thereafter a galloyl derivative is produced [19, 20].

Black tea theaflavins are only marginally absorbed even after the administration of large amounts equivalent to 30 cups of this beverage [21]. After consumption of green and black tea, an increase in the methylated metabolites of gallic acid acid, 3-O-methylgallic acid (3OMGA), 4-O-methylgallic acid (4OMGA) and 3,4-O-dimethylgallic acid has been registered [22].

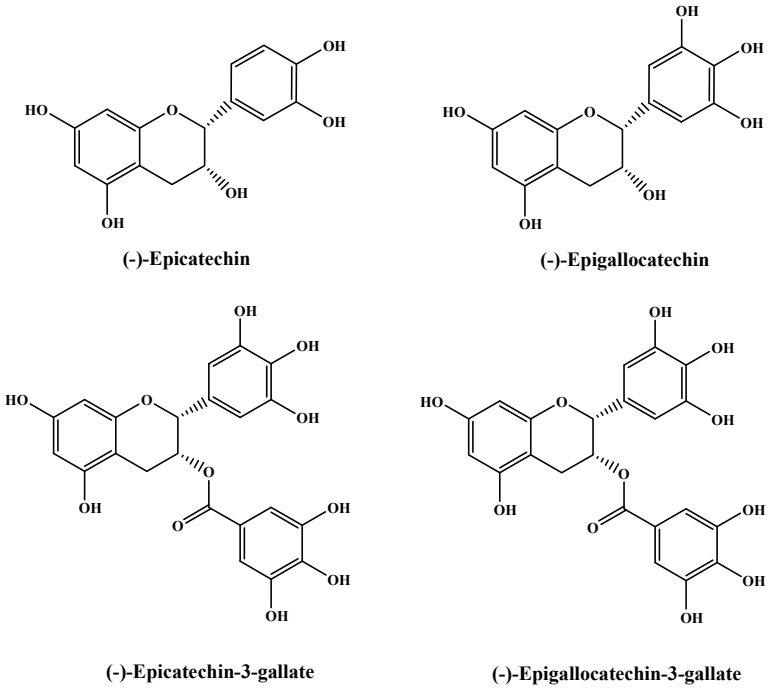


Fig. (3). Chemical structure of tea catechins: (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin-3-gallate, (-)-epigallocatechin-3-gallate.

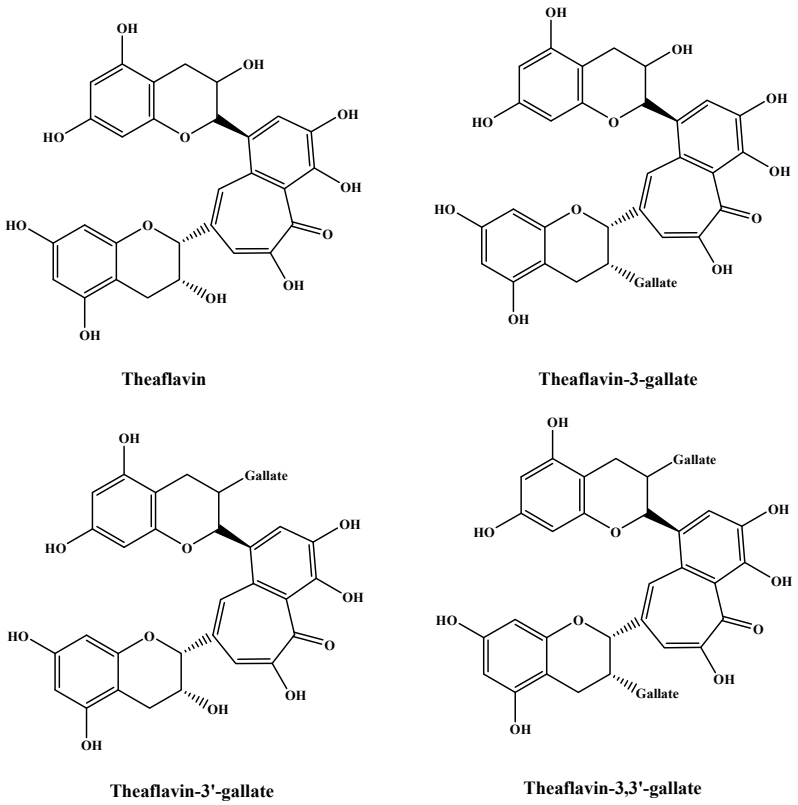


Fig. (4). Chemical structure of theaflavins: theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, theaflavin-3,3'-digallate.

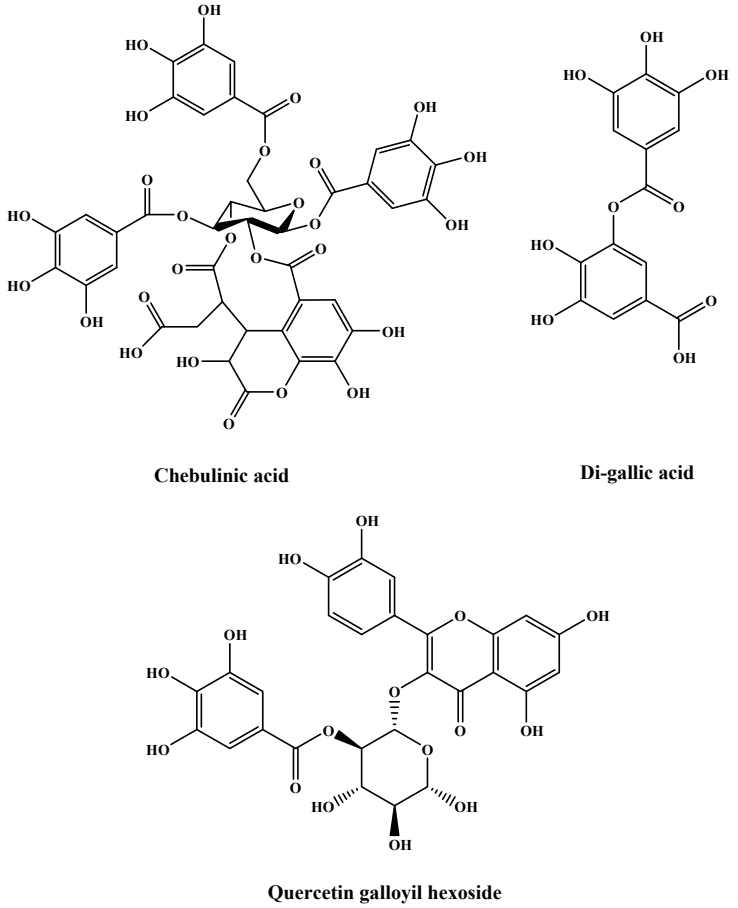


Fig. (5). Chemical structure of chebulinic acid, di-gallic acid, quercetin galloyil hexoside.

4. PROTECTIVE ACTIVITIES OF GALLIC ACID AND DERIVATIVES

The protective properties of GA and derivatives have been investigated from the 90s when the antimutagenic activity of green tea was ascribed to flavan-3-ol and its galloyl derivatives [23].

Since then, many properties have been ascribed to GA. In fact, it affects a number of biochemical pathways and possesses pharmacological activities connected to its antioxidant and anti-inflammatory activities. Among the most studied GA properties there are the anti-tumor potential (cytotoxicity against cancer cells and antimutagenic activity), and neuroprotective effects.

Moreover, GA and its derivatives show hepato-protective, analgesic, antimicrobial and antiallergic properties.

As regards the potential anti-cancer properties, many *in vitro* and *in vivo* studies showed that GA affects a number of biochemical pathways and possesses several pharmacological activities that are important in the oncogenesis. It seems to possess selective cytotoxicity against cancerous cells and no (or low) toxicity against normal cells, such as fibroblast and endothelial cells. Recent studies have shown that GA acts as competitive inhibitor of COX-1 and COX-2 with greater affinity toward COX-2. These cyclo-oxygenases play a significant role in inflammation because they are key enzymes in the synthesis of prostaglandin from arachidonic acid. During the development of different types of cancer such as colon, gastric, esophagus, pancreas and breast cancer, COX-2 is upregulated. The overexpression of COX-2 induces tumorigenesis and makes cancer cells resistant to apoptotic stimuli. It has been reported that one of the most important roles of GA is apoptosis inducing effect in 3T3-L1 pre-adipocytes and several other cell lines [24-29].

5. NEUROPROTECTIVE EFFECT OF GALLIC ACID AND DERIVATIVES

Over the last decade, much attention has been paid to discovery of neuroprotective agents from medicinal plants [30]. It has been reported that the compounds characterized by high antioxidant activity and hydrophobicity can be useful candidates for preventing and/or protecting against oxidative stress in neural tissues [31]. GA and derivatives are well known antioxidant agents which have high neuroprotective effects under *in vivo* and *in vitro* conditions. It has also been reported that molecular polarity of GA plays a crucial role in its antioxidant activity in different cell systems under *in vitro* and *in vivo* model systems of oxidative stress. Previously, the protective role of GA against neural cells death has been reported [32]. Morever, beneficial role of oral administration of GA against memory deficit and oxidative stress in cerebral tissues of rats has been reported [30]. Mansouri *et al.* [30] demonstrated the beneficial role of GA in prevention and/or protection against neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

5.1. Effects of Gallic Acid and Derivatives on Neuroinflammation

Oxidative stress and oxidative mediated inflammatory response have distinct roles in both initiation and progression of different diseases such as multiple sclerosis, ischemic stroke, Alzheimer's disease (AD), etc. [33-36]. During multiple sclerosis, CD4+Th1 and Th17 cells are suspected to play debilitating role which leads to destruction of myelin sheath [37]. A recent study on the pathogenesis of this inflammatory autoimmune disease shows that tumor necrosis factor, related to apoptosis inducing ligand, which is secreted by activated T cells as death signals, plays a crucial role in axonal inflammatory destruction [38]. A growing body of evidence demonstrates the roles of oxidative stress and inflammation in promotion of multiple sclerosis and the therapeutic role of antioxidant therapy in management of multiple sclerosis [34]. Herges *et al.* [39] studied the effects of EGCG as neuroprotectant and anti-inflammatory agent in addition to Glatiramer acetate in *in vitro* and *in vivo* model of neuroinflammation. The authors found that this combination synergistically reduces neural cell death, enhances axonal outgrowth, and shows a promising therapeutic effect on mice model of multiple sclerosis.

Ischemic stroke, caused by transient or permanent abnormality in the blood supply to the brain, is one of the most common cerebrovascular diseases and the third leading cause of death throughout the world [40, 41]. There is a growing body of evidence that suggests a pivotal role of inflammation in the pathogenesis of ischemic stroke [42]. Following ischemic stroke, brain cells upregulate inflammatory process in ischemic area including: generation of proinflammatory cytokines, activation of microglia, and infiltration of inflammatory cells. These events are synergistically correlated with ischemic damages size [42]. The therapeutic role of anti-leukocyte and anti-inflammatory strategies in amelioration of ischemic injury has been widely studied in animal models of ischemic stroke [43, 44]. In the early phases after ischemic stroke, NADPH oxidase acts as the main source of oxidative stress in brain tissue. Previous reports showed that NADPH oxidase upregulates superoxide radical generation in neural tissue [45]. This NADPH oxidase induces superoxide radical to interact with nitric oxide to produce peroxynitrite [46]. It is reported that peroxynitrite elevates iNOS expression, activates PARP-1, decreases soluble guanylate cyclase, prostacyclin synthase, and mitochondrial Mn-SOD activities, etc., producing mitochondrial dysfunction and ischemic damages [47-49].

Microglial cells are highly sensitive to brain damage [50], clean up damaged cells and exogenous pathogens [51]. They are widely distributed in different parts of brain including hippocampal CA1 regions [52]. Previous reports show that microglia activation is involved in neuroinflammation and neural damages through NF-kB mediated pathways [53]. Wu *et al*. [54] found that EGCG significantly inhibits lipopolysaccharid that induces neuroinflammation and oxidative stress. They found that EGCG and green tea extract normalized ischemic stroke and induced glutathione and the activity of the antioxidant enzymes such as superoxide dismutase in the cerebral cortex and hippocampus. They also reported their anti-inflammatory role in COX-2 and inducible nitric oxide synthase activity in BV-2 microglia cells inhibition [54]. Cai *et al*. [55] studied the potential effect of EGCG on infrasound-induced CNS damages. They found that this GA esters are able to suppress microglia-mediated

inflammation through an NF-κB pathway. According to the results of their study, EGCG administration decreases Iba-1 and pro-inflammatory cytokines. They concluded that EGCG administration also down-regulates NF-κB p65 and phosphorylates IκBα, and normalizes IκB in microglia [55].

Extensive studies showed that β-amyloid aggregation has pivotal role in etiopathogenesis of AD [56, 57]. β-Amyloid is produced by proteolytic cleavage type-I membrane amyloid precursor protein [58]. A growing body of evidence shows that proinflammatory cytokines, complement factors, such as activate microglia etc., in the brains of Alzheimer's patients are higher than in healthy subjects [59, 60]. This phenomenon supports the inflammatory hypothesis of AD. Numerous studies reported that locally inflammation, but not the classical cellular immune mediated response, is the result of β-amyloid accumulation in the brain [61, 62]. Extensive genetic and epidemiological investigations support the view that inflammation has a distinct role in etiopathogenesis of AD [63]. The data obtained from genetic studies show that polymorphisms of proinflammatory cytokines and α1-antichymotrypsin are risk factors of AD [64]. Some clinical studies report that nonsteroidal anti-inflammatory drugs can delay or prevent AD development [65, 66]. Lee *et al*. [67] studied the potential effect of EGCG on cognitive dysfunctions, caused by injection of β-amyloid $_{1–42}$ into mouse brain. They found that EGCG administration improves cognitive functions and increases α-secretase activity as well as diminishes β-, γ- secretase activity and β-amyloid accumulation through ERK/NF-kB pathway. They also showed that EGCG suppresses β-amyloid fibrilization [67].

It has also been reported that EGCG improves the PKC dependent release of soluble type-I membrane amyloid precursor protein in mice hippocampus, as well as certain types of human cell cultures [68]. Moreover, EGCG modulates type-I membrane amyloid precursor protein cleavage in Alzheimer's transgenic mice [66].

Kim *et al.* [69] studied the ameliorative effect of GA administration as histone acetyltransferase on microglial mediated β-amyloid neurotoxicity and cognitive dysfunction. They found that GA administration decreases proinflammatory cytokines mRNA in both microglia and neuro2-A cells, through the inhibition of NF-kB acetylation. They also reported that GA treatment improves cognitive function in mice [70]. Wang *et al*. [71] also reported that a diet rich in polyphenolic compound (such as GA) prevents β-amyloid deposition and neuroinflammation in mouse model of AD. All the aforementioned reports show the promising effects of GA and its derivatives and suggest that the administration of these compounds might be a useful strategy against neuroinflammation related diseases such as AD, multiple sclerosis, prion, etc.

5.2. Anti-Alzheimer Effects of Gallic Acid and Derivatives

AD is a neurodegenerative disorder and one of the leading causes of dementia and death throughout the world. It is characterized by the accumulation of neurofibrillary pathology and senile plaques containing amyloid β (Aβ)-peptide throughout the cortex by the end step of the disease [70, 72, 73, 74]. In AD patients, neurotoxicity induced by Aβ peptide aggregation occurs in the neural tissues and from this way the severity of AD increases [74]. Despite considerable number of scientific investigations, the exact pathological mechanisms of AD are still controversial. However, a plethora of reports have demonstrated that oxidative stress in different macromolecules such as proteins, DNA and lipid peroxidation plays an important role in the pathogenesis of AD [70, 75].

Therefore, much attention has been paid to antioxidants for reducing the severity of AD *via* mitigation of neurotoxicity and oxidative stress in neural tissues.

GA is known as a bioactive natural compounds with high antioxidant potential and low adverse effects which can protect cells against oxidative damage**.** Previous studies reported the protective role of GA against Aβ-induced neuronal cell death under *in vitro* conditions. Although the exact mechanism of the neuroprotective role of GA against Aβ-induced neuronal injury is still unclear, it is well known that Aβ-peptide induces neurotoxicity *via* Ca^{+2} infestation, glutamate release and activation of ROS. Therefore, it can be concluded that GA suppresses the Aβ-induced neurotoxicity *via* blocking the glutamate release and ROS generation through inhibition of Ca^{+2} infestations in the neuronal cells. Animal studies have shown that the supplementation of GA plays a protective role against AD-induced oxidative stress, neuropathology and cognitive dysfunction [75, 77]. Ferruzzi *et al*. [78] reported that the absorbtion of GA in the brain tissue provides a protective effect against AD. Kim *et al*. [70] showed that GA inhibits neurotoxicity induced by Aβ-peptide via suppressing of microglial-mediated neuroinflammation. They also found that GA reduces Aβ-induced neurotoxicity *via* decreasing of cytokine generation and levels of NF-κB acetylation. Rasoolijazi *et al.* [79] reported that EGCG mitigates the behavioral abnormalities induced by Aβ-peptide in rat model of AD. Yoshiari et al [80] described that EGCG plays a beneficial role in mitigation of AD via suppression of Aβ-induced beta-site APP cleaving enzyme-1 upregulation.

Other reports showed that EGCG mitigates AD and cognitive impairments via suppression of amyloid precursor protein cleavage and decreasing of amyloidosis and mitochondrial dysfunction in the brain [69, 81-83]. Reznichenko *et al.* [84] reported that EGCG regulates the amyloid precursor protein and increases the transferrin receptor and mRNA levels in SH-SY5Y neuroblastoma cells. They found that the beneficial role of EGCG originates from its metal chelating effects specially iron chelating activity [84].

5.3. Anti-Parkinson Effects of Gallic Acid and Derivatives

Parkinson disease (PD), the second most common neurodegenerative and idiopathic disease, causes tremor, rigidity and bradykinesia [30, 31]. PD is pathologically characterized by dopaminergic neurons degeneration in the substantia nigra zona compacta [30, 31]. There are numerous scientific reports on the role of oxidative stress and mitochondrial functions in the pathogenesis of PD [85-88]. In fact, oxidative stress increases Mn superoxide dismutase activity as well as the level of iron in the substantia nigra and also catalyzes free radicals generation, especially hydroxyl radical

[85-88]. It has also been reported that PD causes oxidative injuries in midbrain of patients *via* the induction lipid peroxidation and oxidation to catechol group, protein, and DNA [85-88]. These phenomena lead to the degeneration of dopaminergic neurons of the substantia nigra zona compacta [31, 88]. Due to the role of oxidative stress in the pathogenesis of PD, antioxidants could be used as therapeutic agents for the prevention and/or protection from PD [31]. Sameri *et al.* [89] found that GA mitigates motor dysfunctions and improves gamma wave power in 6-hydroxydopamine-induced dopaminergic neurodegeneration and Parkinson's disease in rats. They found that beneficial role of GA results from its antioxidant and free radical scavenging activities [86]. Mansouri *et al.* [30] demonstrated that the oral administration of GA reduces memory impairment and oxidative stress in hippocampus and striatum of 6-hydroxydopamine-induced Parkinson in rats. They have identified that GA decreases the level of malondialdehyde and increases total thiol levels as well as glutathione peroxidase activity [30]. In addition, there are numerous scientific reports about the beneficial role of EGCG in prevention and/or protection against Parkinson's disease. Mandel *et al.* [90] reported that EGCG possesses a neuroprotective action against serum support withdrawal-induced apoptosis in pheochromocytoma PC12 cells of rats. Levites *et al.* [91] demonstrated that green tea catechin exerts a protective role against N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced oxidative stress and Parkinson's disease in mice. They found that the pretreatment with EGCG mitigates the neurotoxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine *via* the decrease of the activities of antioxidant enzymes, i.e. superoxide dismutase and catalase. Another report by Levites *et al.* [92] showed that the pretreatment with EGCG mitigates 6-hydroxydopamine-induced neuroblastoma (NB) SH-SY5Y cell death *via* modification of the activities of reduced protein kinase C and extracellular signal-regulated kinases. Moreover, EGCG significantly reduces lipopolysaccharide-induced inflammation *via* downregulation of inducible nitric oxide synthase and tumor necrosis factor-α gene expression in both primary rat mesencephalic and dopaminergic cell line SH-SY5Y [93]. Kim *et al.* [94] demostrated that the treatment with EGCG inhibits the expression of inducible nitric oxide synthase and reduces cell death in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice. Oral administration of EGCG decreases the expression of neuronal nitric oxide synthase in the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease [95]. Furthermore, the beneficial role of EGCG against neurotoxicity and apoptosis induced by paraquat in the PC12 cells has been reported above. Hou *et al.* [96] also found that EGCG reduces paraquat-induced toxicity *via* restoration of abnormalities in the mitochondrial membrane, decrease in the activity of caspase-3, as well as down-regulation of the expression of pro-apoptotic protein Smac in cytosol of the PC12 cells. Chung *et al.* [97] also reported that preincubation of EGCG significantly reduces the neurotoxicity of rotenone in human neuroblastoma SH-SY5Y cells through modification of caspase-3 activity and the decrease of intracellular production of reactive oxygen species. Tai and Truong [98] also reported that EGCG has protective role against dichlorodiphenyl-trichloroethane-induced dopaminergic SHSY-5Y cells death.

5.4. Effects on Chemical-Induced Neurotoxicity of Gallic Acid and Derivatives

Nowadays, there is a growing body of evidence showing that many chemicals (more than two hundred) are able to cause clinical neurotoxicity and neurodevelopmental disorders such as memory deficit, learning impairment, cognitive dysfunction, autism, movement disorders, etc. [99]. Everyday exposure to these toxic chemicals causes severe and often irreversible brain damages to humans, especially to fetus [100]. Extensive data from epidemiology and clinical research, performed on individuals who live in industrial areas, support the hypothesis that there is a direct linkage between industrial pollutants and neural dysfunctions as well as behavioral damages [101]. Available therapeutic strategies for these neurodevelopmental disorders are costly, limited and often fail to completely cure disability [102]. Inasmuch as broad application of these chemicals, their limitation are not feasible [103]. However, many efforts have been made to control the sources of these chemicals [99, 104]. Numerous reports showed that oxidative related mechanisms have a pivotal role in the pathogenesis of chemical induced neurotoxicity and antioxidant therapy significantly mitigates chemically induced neurotoxicity [105-106].

Reckziegel *et al.* [107] reported that oral administration of GA for 3 days reduces lead-induced oxidative stress and locomotor injuries in rats. They found that GA treatment significantly decreases blood aminolevulinic acid dehydratase and lipid peroxidation as well as protein carbonyl content. They also found that administration of GA increases the activity of catalase in the brain tissues. Huang *et al.* [108] reported that GA possesses a protective effect against kainic acid-induced seizure and neuronal damages under *in vitro* and *in vivo* conditions. They showed that GA mitigates behavioral dysfunctions and oxidative stress in mice. Huang *et al.* [108] also found that GA reduces p38 mitogen-activated protein kinases and cyclooxygenase-2 genes expression as well as prostaglandin E_2 production in kainic acid-stressed PC12 cells. Nabavi *et al.* [109, 110] reported that GA and methyl-3-O-methyl gallate inhibit oxidative stress and neurotoxicity induced by sodium fluoride *via* increasing the level of reduced glutathione as well as the activities of catalase and superoxide dismutase and also decrease the level of thiobarbituric acid reactive substances in neural tissues. More recently, Curti *et al.* demonstrated that methyl-3-O-methyl gallate (M3OMG), decreasing the expression levels of miR-17–3p and increasing the expression levels of mRNA coding for antioxidant enzymes, allows to these latter to perform their protective effects, suggesting a potential mechanism of action of the protective activity of M3OMG.

Kumar and Kumar [112] demonstrated that EGCG mitigates cognitive impairments and increases the levels of reduced glutathione, total glutathione and glutathione-S-transferase in different regions of animal's brain. Moreover, EGCG inhibits sodium nitroprusside-induced cytotoxicity and apoptosis in PC12 cells *via* the reduction of reactive oxygen species production and Bax to Bcl-2 expressions [113]. They also found that EGCG inhibits the release of cytochrome c, upregulates the voltage-dependent anion channel, and inhibits the activation of caspase-9, caspase-8 and caspase-3 in the PC12 cells. Bae *et al.* [114] indicated that

that EGCG mitigates alpha-amino-3-hydroxy-5-methyl-4-isoxazolo propionate-induced oxidative stress and cytotoxicity in hippocampal neurons of rats *via* the decrease of the level of hydrogen peroxide and malondialdehyde in the cells as well as survival times of the hippocampal neurons. They also found that EGCG decreases intracellular calcium levels in the hippocampal neurons. Jung *et al.* [115] found that EGCG inhibits Cobalt (II) chloride-induced apoptosis in PC12 cells *via* the decrease of reactive oxygen species production and cell death associates with inhibition of the activities of caspase-9 and caspase-3. They also found that EGCG decreases Bax to Bcl-2 ratio and inhibits the release of cytochrome c. Moreover, this flavan-3-ol inhibits 3-hydroxykynurenine-induced cytotoxicity in the human neuroblastoma SH-SY5Y cell line through the decrease of the levels of reactive oxygen species and also the caspase activity [116]. In addition, Yin *et al.* [117] reported that intraperitoneal administration of EGCG reduces oxidative stress induced by lead in the hippocampus of rats. They found that EGCG increases the level of glutathione and superoxide dismutase and also the mitigation of mitochondrial membrane potential [117].

6. CONCLUSION AND RECOMMENDATIONS

From the above mentioned results, we concluded that oxidative stress plays an important role in neurotoxicity and neuronal cell death. From our review it is clear that neurotoxicity and neuronal cell death are very complex with different targets and pathways. Therefore, it seems that treatment strategies based on a single target and single pathway are not suitable. Thus, natural products with high antioxidant capacities and different molecular targets and pathways can be promising candidates for neuroprotection. GA and its derivatives are known as natural antioxidants with low adverse effects and different molecular targets and pathways. This review provides the evidences about the neuroprotective actions of GA and its derivatives against neuroinflammation, neurodegeneration as well as neurotoxicity. In this review we also discuss about chemistry, bioavailability and different dietary sources of GA and its derivatives to provide a better view about these substances, naturally occurring in food and medicinal plants.

Below recommendations are important for future studies:

- More studies should be performed on pharmacokinetics, and pharmacodynamics of GA and its derivatives;
- More research should be fucused on the improvement of bioavailability of GA *via* employing different drug deliveries;
- More animal studies are needed to understand the exact mechanisms of action of the neuroprotective role of GA and its derivatives;
- Clinical studies should be performed on GA and its derivatives to demonstrate their efficacy in humans.

CONFLICT OF INTEREST

The authors disclose that they have no commercial associations that might create a conflict of interest in connection with this article.

ACKNOWLEDGEMENTS

Declared none.

ABBREVIATIONS

Aß	=	ß-amyloid
AD	=	Alzheimer's disease
Bax	=	bcl-2-like protein 4
Bcl-2	=	B-cell lymphoma 2
CNS	=	central nervous system
COX	=	cyclooxygenase
EA	=	ellagic acid
ECG	=	(-)-epicatechin-3-gallate
EGCG	=	(-)-epigallocatechin-3-gallate
Erk	=	Extracellular-signal-regulated kinases
GA	=	gallic acid
HTs	=	hydrolysable tannins
IκB	=	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
iNOS	=	inducible nitric oxide synthase
Mn-SOD	=	manganese superoxide dismutase
NADPH	=	nicotinamide adenine dinucleotide phosphate
Nf-kB	=	nuclear factor kappa-light-chain-enhancer of activated B cells
PARP-1	=	poly [ADP-ribose] polymerase 1
PD	=	Parkinon's Disease
PKC	=	proteine chinase C
ROS	=	reactive oxygen species
3OMGA	=	3-O-methylgallic acid
4OMGA	=	4-O-methylgallicacid.

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Received: February 17, 2014 **Revised: March 31, 2014** **Accepted: June 06, 2014**