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Insights into Effects of Ellagic Acid on the Nervous System: A Mini Review

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Abstract: Multiple lines of evidence suggest that disease-related neurodegeneration seems to be a multifactorial process that involves different cytotoxic pathways converging in cell death. Neuropathological evidence indicates that neuroinflammation, excitotoxicity, redox-active metals, increased reactive oxygen and nitrogen species, abnormalities in the activity of the ubiquitin-proteasome system, impairments in endogenous antioxidant defense mechanisms, mitochondrial dysfunction, as well as a reduction in the expression of trophic factors in neuronal tissues might play a role in the pathobiology of disease. In addition, increased expression of proapoptotic proteins, which leads to neuronal cell death, plays an important role in the onset and progression of neurodegeneration. With respect to the inefficacy of single-target drugs for the treatment of numerous neurodegenerative disorders, much attention has been paid to natural products with pluripharmacological properties as well as negligible adverse effects. Ellagic acid is known as an important natural phenolic antioxidant, that is widely found in different fruits and vegetables. Recent studies have shown that ellagic acid may invoke a spectrum of cell signaling pathways to attenuate or slow down the development of neurodegenerative disorders. Ellagic acid possesses potent neuroprotective effects through its free radical scavenging properties, iron chelation, activation of different cell signaling pathways, and mitigation of mitochondrial dysfunction. The aim of this review is to critically summarize and analyze the available literature regarding the neuroprotective effects of ellagic acid with emphasis on its molecular mechanisms of action. In addition, we also discuss the biosynthesis, sources, bioavailability, and metabolism, of ellagic acid to provide as accurately as possible the much needed information for assessment of the overall protective effects of this compound in the central nervous system.

Keywords: Antioxidant, ellagic acid, elligatannins, neurodegeneration, neuroprotective effects.

INTRODUCTION

Neurodegeneration is a complex process affected by many pathological factors such as impaired neuronal function and deficit in neurotransmitters which finally cause to synaptic loss and neuronal death, inflammation, oxidative stress, purinergic signaling, mitochondrial dysfunction, metal accumulation, etc., which are associated with a number of diseases including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease, and many others [1-7]. Since these diseases have complicated pathophysiology, the treatment approaches are quite limited and there is certainly a great need for more research to explain their exact pathology through the understanding of factors and processes that contribute to neurodegeneration. Consequently, neurodegenerative diseases are highly challenging in regard with discovering new drug molecules and much still remains to be learned for human being on this scope.

Recent opinion suggests that oxidative stress may play a causal role in the complex neuronal pathology observed in neurodegenerative disorders [8-10]. Reactive oxygen species (ROS) such as the hydroxyl radical (·OH), superoxide anion (O_2·), nitric oxide (NO·) and hydrogen peroxide (H_2O_2) are generated as by-products of respiration and oxidative metabolism. Under normal physiological conditions, a balance between ROS production and ROS detoxification is crucial to ensuring cellular damage is ameliorated by endogenous antioxidant defence systems (enzymes and antioxidant vitamins) [8-10]. Ellagic acid is an excellent scavenger and its long-term administration is potentially applicable as strategy for neurodegeneration prevention [11-16].

The antioxidant potential of natural compounds have been proven to be irrevocable and continuous sources for developing new drugs and are always attracting targets as leads in drug research that serve as templates for novel molecules [17-22]. Although their importance in drug discovery has been partly diminished for a moment in last decades, contemporary drug research has re-focused on this area using new techniques, *i.e.* combinatorial chemistry, high-throughput screening, and metabolomics [23]. In fact, it has been reported that more than 60% of the drugs available in the market are derivatives of natural products [24-26]. Furthermore, importance of natural compounds is also due to their special selectivity to cellular targets in biological systems, ability to interaction with many receptors as well as their vast chemical structural properties [27, 28].

Ellagic acid is a natural polyphenol widely found in berry-type of fruits, pomegranates, and nuts, and some other medicinal plant species [29]. Latest research show that it exhibits a great number of pharmacological effects such as anti-diabetic [30], anti-hepatotoxic [31], anticancer [32], neuroprotective [33], anti-obesity [34], anti-hypertensive [35], antinociceptive [36], antiviral [37], etc. Given this background, we herein aim to focus our thoughts particularly on potential of ellagic acid in nervous system and also articulating its biosynthesis, sources, and other relevant pharmacological activities.

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BIOSYNTHESIS AND SOURCES OF ELLAGIC ACID

The sources and chemistry of ellagic acid have been recently reviewed [38, 39], hence, we herein provide a brief summary. Elligatannins are esters of hexahydroxydiphenic acid with a sugar moiety, usually glucose (see Fig. **1** for examples). Acid-catalyzed hydrolysis of elligatannins can release the hexahydroxydiphenic acid moiety, which subsequently undergoes lactonization to give ellagic acid (Fig. **1**). The microbiological fermentation of plant by-products to produce ellagic acid have been recently investigated [40, 41].

The main dietary sources of ellagic acid are raspberries, blackberries, and strawberries [42], while nut trees, leaves, and some other fruits are also known to be rich in ellagic acid (approximately 1–3 mg/g) [43]. Table **1** lists some sources and their respective yields of ellagic acid. Unfortunately, there seems to be some inconsistencies in the reported yields of ellagic acid. Some authors report free ellagic acid, while others list total ellagic acid content. In addition, the yields vary considerably depending on cultivation, seasonality, maturity, hydrolytic conditions, and detection methodologies. The most common method for the quantification of ellagic acid has been reverse-phase HPLC using DAD and/or MS detection [44, 45]. However, square-wave voltammetry has also been recently preferred to quantify ellagic acid concentrations in fruits [46].

BIOAVAILABILITY AND METABOLISM OF ELLAGIC ACID

The metabolic fate of ellagitannins and ellagic acid has been extensively reviewed [38, 39, 47]. Briefly, ellagitannins are relatively stable to the physiological pH of the stomach and are not hydrolyzed to produce ellagic acid. The stomach is the first place, where ellagic acid is absorbed. However, ellagitannins can be catabolized by intestinal microflora to produce ellagic acid [48, 49]. Ellagic acid is metabolized by gut microflora in the intestines to produce the urolithins, by way of lactone ring hydrolysis and decarboxylation, followed by dehydroxylation (see Fig. **2**) [48, 49]. The urolithins produced undergo enterohepatic circulation with concomitant conjugation in the liver *via* UDP-glucuranyl transferase (UGT) or sulfotransferases (ST) to the corresponding glucuronides or sulfates, respectively (see Fig. **3**). Upon absorption, ellagic acid is methylated *via* catechol *O*-methyl transferase (COMT) to produce monomethyl and dimethyl ethers (see Fig. **3**). These methylated derivatives are, then, conjugated to the corresponding glucuronides or sulfates.

Several studies have reported that ellagic acid is rapidly absorbed in humans and reaches a maximum plasma concentration within one hour after ingestion [50, 51], where their metabolic derivatives, the urolithins, reach maximum concentrations in the plasma between 24 and 48 hours after ingestion. Bioconjugates of urolithins A and B as well as ellagic acid dimethyl ether circulate in the blood and, therefore, are able to reach target organs. Circulating ellagic acid conjugates and/or conjugates of urolithins are likely to be responsible for the *in vivo* health benefits of ellagitannin- and ellagic acid-rich foods [47, 52-55].

REACTIONS OF ELLAGIC ACID

Reactions of ellagic acid can be conveniently divided into three general types: (a) oxidation of ellagic acid by reactive free radicals, (b) reactions of the nucleophilic hydroxyl groups of ellagic acid, and (c) electrophilic aromatic substitution of the electron rich aromatic rings of ellagic acid.

Ellagic acid has shown a notable activity as a scavenger of free radicals [56] and can, therefore, inhibit the deleterious effects of reactive oxygen species (ROS) such as lipid peroxidation [57]. Marković and co-workers [58] used a density functional theory (DFT) analysis to conclude that in aqueous solutions, the predicted mechanism is loss of a proton from ellagic acid, followed by electron transfer to free radicals, whereas in the gas phase or in nonpolar solvents, the reaction is predicted to be a hydrogen atom transfer to free radicals. In contrast, based upon their theoretical work, Galano and co-workers have concluded that the mechanism for hydrogen atom transfer takes place exclusively regardless of the polarity of the environment.

The total antioxidant capacity of ellagic acid has been previously evaluated using the Trolox equivalent antioxidant capacity (TEAC) assay [59]. The Trolox equivalent antioxidant capacity is the concentration of Trolox required to give the same antioxidant capacity as 1 mM test substance. The study compared a standardized total pomegranate tannin (TPT), punicalagin and ellagic acid,

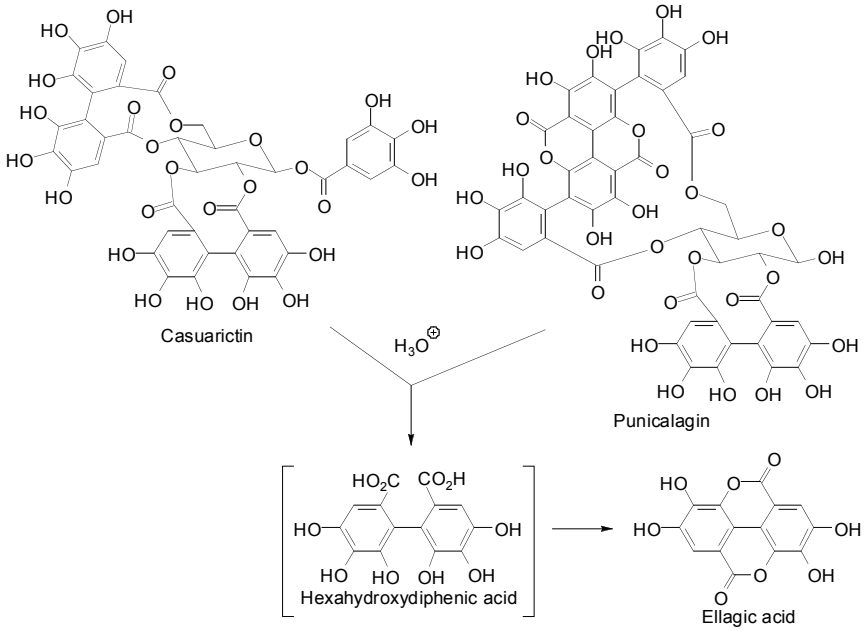

Fig. (1). Examples of ellagitannins and hydrolysis to give ellagic acid.

Table 1. Sources of ellagic acid.

Source	Concentration/Comments	Reference
Açai *Euterpe oleracea*	55.4 mg/kg fresh fruit pulp; 19.5 mg/kg of ellagic acid derivative	[93]
Apple *Malus domestica*	Juice: 0.6 mg/kg.	[94]
Arctic Bramble *Rubus arcticus*	Fruits: 686 mg/kg fresh wt.	[95]
Black Raspberry *Rubus occidentalis*	Dried leaves: 2.06%	[96]
Blackberry *Rubus* spp.	*R. fruticosus* dried leaves: 4.32%. *R. caesius* dried leaves: 4.15%. *R. nessensis* dried leaves: 6.89%. *R. odoratus* dried leaves: 3.76%.	[96]
Blackberry *Rubus* spp.	Fruits: 6.6-26.1 mg/kg fresh wt.	[97]
Blackberry *Rubus* spp.	376.0 mg/kg fresh wt. Determined electrochemically rather than chromatographically.	[46]
Blackberry *Rubus glacus*	Fruits: total EA 438 mg/kg dry wt	[44]
Blackberry *Rubus adenotrichus*	Fruits: total EA 135 mg/kg dry wt.	[44]
Blackberry *Rubus fruticosus*	Fruits: 45.6-84.6 mg/kg	[45]
Blackberry *Rubus adenotrichus*	Fruits: 202-300 mg/kg dry wt	[98]
Cambuci *Campomanesia phaea*	Fruits: 3.3 mg/kg (free EA/fresh wt); 2.67 g/kg (total EA/fresh wt).	[99]
Chestnut *Castanea sativa*	Bark: 0.71-21.6 mg/g of raw bark; 2.83-18.4 mg/g hydrolyzed (MeOH/TFA) bark. Fruit: 1.08-5.98 mg/g pericarp.	[100]
Cloudberry *Rubus chamaemorus*	Fruits: 559-606 mg/kg fresh wt.	[95]
Cranberry *Vaccinium macrocarpon*	Fruit pomace bioprocessed by solid-state hydrolysis using the fungus *Lentinus edodes*: 350 mg/kg dry wt.	[101]
Grape *Vitis vinifera*	Juice: 2.5 mg/kg.	[94]
Grumixama *Eugenia brasiliensis*	Fruits: 85 mg/kg (free EA/fresh wt); 2.70 g/kg (total EA/fresh wt).	[99]
Jabuticaba *Myrciaria jaboticaba*	Fruits: 60 mg/kg (free EA/fresh wt); 3.11 g/kg (total EA/fresh wt).	[99]
Longan *Dimocarpus longan*	Seed: 156 mg/100 seeds	[102]

(Table 1) Contd….

Source	Concentration/Comments	Reference
Mango *Mangifera indica*	Kernel: 118 mg/100 seeds	[102]
Muscadine *Vitis rotundifolia*	Juice: 4.4-102 mg/kg. Wine: 2.3-56.0 mg/kg.	[103]
Muscadine *Vitis rotundifolia*	Juice, free ellagic acid: 13.5-49.7 mg/kg. Juice, total ellagic acid: 360-912 mg/kg.	[104]
Pineapple *Ananas comosus*	Fruit: 1.2 mg/kg fresh fruit.	[105]
Pomegranate *Punica granatum*	Juice: 0.008-0.16 mg/kg	[106].
Pomegranate *Punica granatum*	Seeds: 4.8 mg/kg. Husk: 2600 mg/kg.	[107]
Pomegranate *Punica granatum*	Juice: 14.3 mg/kg.	[94]
Pomegranate *Punica granatum*	Husk: 12.8-33.8 g/kg dry wt.	[43]
Red Raspberry *Rubus* spp.	Fruits: 21-47 mg free ellagic acid / kg fresh fruit; 1198-3235 mg total ellagic acid / kg fresh fruit.	[108]
Red Raspberry *Rubus* spp.	Juice: 0.7-31.5 mg/kg (free ellagic acid); 1.3-53.3 mg/kg (total ellagic acid)	[42]
Red Raspberry *Rubus* spp.	*R. saxatilis* dried leaves: 3.01%. *R. idaeus* dried leaves: 2.45%.	[96]
Red Raspberry *Rubus idaeus*	Fruits: 207-244 mg/kg fresh wt.	[109]
Red Raspberry *Rubus idaeus*	Fruits: 10.13 mg/kg fresh wt. Jam: 25.40 mg/kg fresh jam.	[110]
Red Raspberry *Rubus idaeus*	Fruit: 4.0 mg/kg fresh fruit. Jam: 22.5 mg/kg fresh jam.	[105]
Red Raspberry *Rubus idaeus*	Fruits: 380-1180 mg/kg fresh fruit.	[111]
Red Raspberry *Rubus idaeus*	Fruits: 400.6 mg/kg fresh wt. Determined electrochemically rather than chromatographically.	[46]
Red Raspberry *Rubus idaeus* L.	Fruits: 47.4-164.7 mg/kg.	[45]
Red Raspberry *Rubus idaeus*	Fruits: 708 mg/kg fresh wt.	[95]
Strawberry *Fragaria × ananassa*	Fruit: 14.7 mg/kg fresh fruit. Jam: 20.1 mg/kg fresh jam.	[105]
Strawberry *Fragaria × ananassa*	Fruits: 55.2 mg/kg fresh wt. Determined electrochemically rather than chromatographically.	[46]

(Table 1) Contd….

Source	Concentration/Comments	Reference
Strawberry *Fragaria × ananassa*	Fruits: 403 mg/kg fresh wt.	[95]
Strawberry *Fragaria × ananassa*	Fruits: 24-25 mg/kg fresh wt.	[112]
Strawberry *Fragaria × ananassa*	Fruits (free EA): 6.1-26.0 mg/kg FW. Fruits (total EA): 170-470 mg/kg FW.	[113]
Strawberry *Fragaria × ananassa*	Fruits: 28.6-68.4 mg/kg fresh wt.	[114]
Strawberry *Fragaria × ananassa*	Fruit pulp: 1450 mg/kg dry wt.	[115]

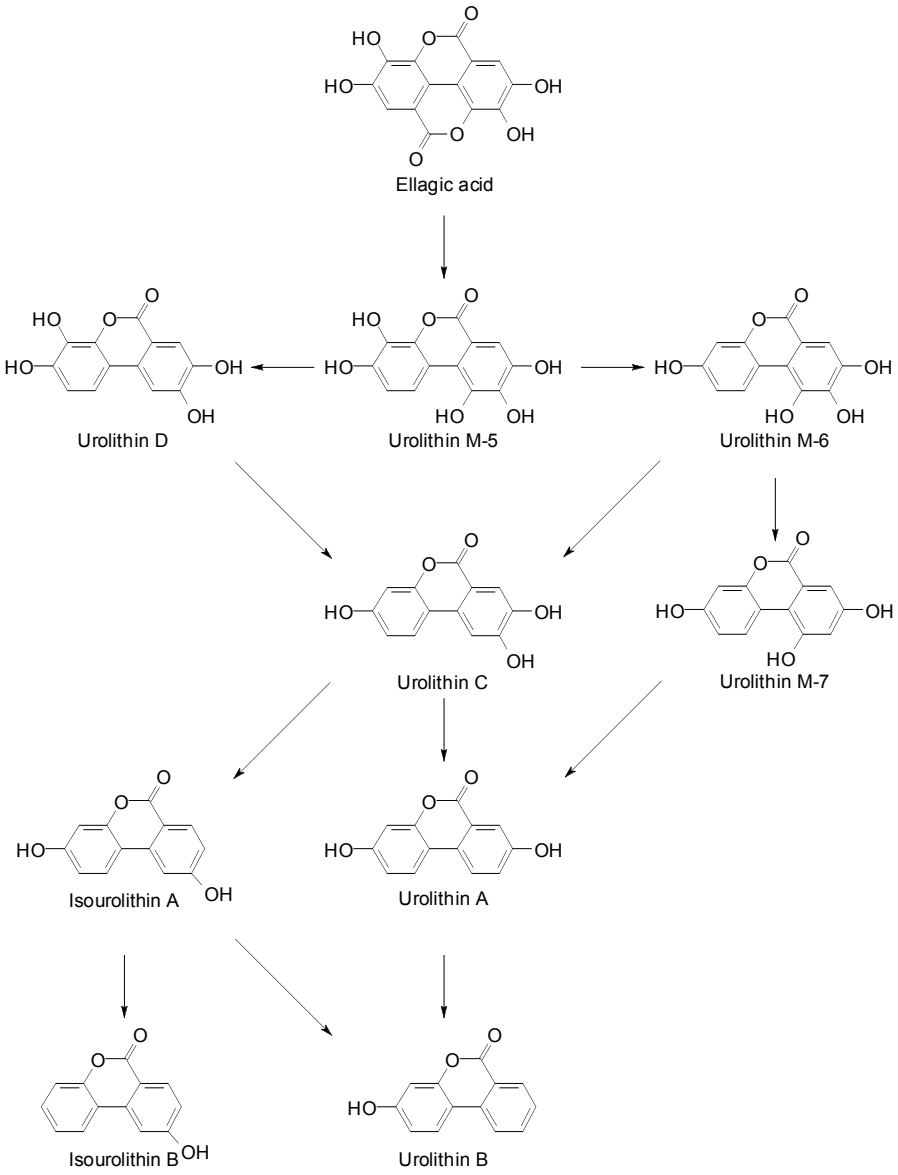

Fig. (2). Gut microfloral metabolism of ellagic acid.

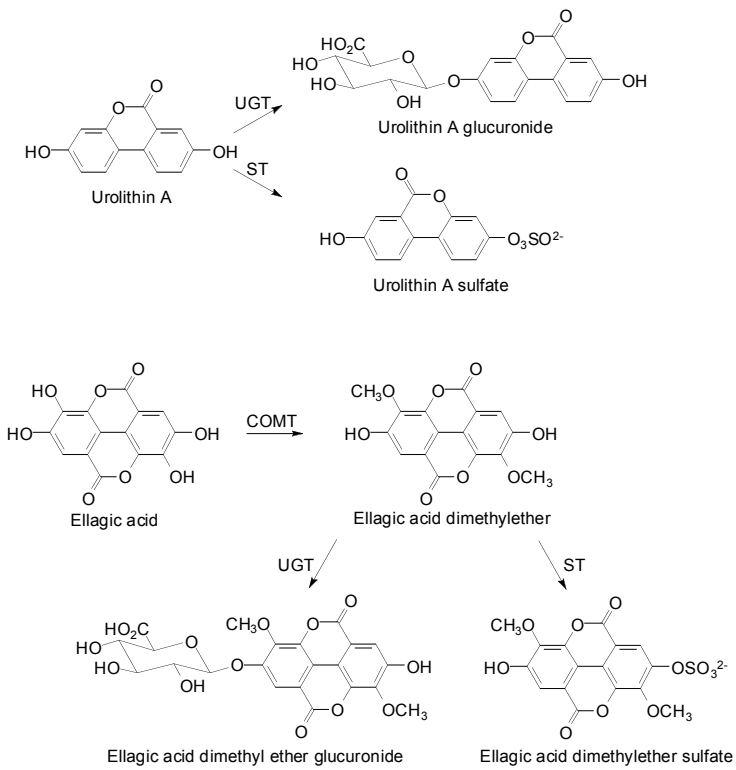

Fig. (3). Phase II (conjugation) metabolism of ellagic acid and urolithin A.

and reported values of 25,591, 100, 90 and 40 μM Trolox equivalents, respectively. The order of antioxidative potency in assay was TPT>punicalagin>ellagic acid [59]. This suggests that ellagic acid may have a lower antioxidant effect compared to tannins and other polyphenolic compounds present in pomegranate juice.

Ellagic acid has been shown to react with (+)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, the ultimate carcinogen of benzo[*a*]pyrene by way of nucleophilic addition of ellagic acid to the electrophilic epoxide (see Fig. **4**) [60, 61]. Reaction of ellagic acid with electrophilic DNA-damaging agents is a possible mechanism for the anticarcinogenic effects of ellagic acid. Ellagic acid undergoes electrophilic nitrosation by reaction with sodium nitrite, mineral acid, and pyridine to produce a red quinone oxime (λ_{max} = 538 nm) [62]. This reaction is the basis for a spectrophotometric analysis of ellagic acid (see Fig. **5**).

Ellagic acid also undergoes interactions with several important biological macromolecules. Ellagic acid has been shown to covalently bind to DNA in explants of bladder, colon, esophagus, forestomach, and trachea of the rat, as well as to calf thymus DNA [63]. DNA-binding of ellagic acid has been suggested to be a mechanism for the known antimutagenic and anticarcinogenic activities of the compound. Ellagic acid has also been shown to be a natural selective estrogen receptor modulator (SERM). Thus, ellagic acid has demonstrated estrogenic activity *via* ERα, whereas it is a complete estrogen antagonist *via* ERβ. Importantly, ellagic acid exhibited potent antiestrogenic activity in MCF-7 breast tumor cells [64]. Ellagic acid, therefore, can be reasonably expected to be an endocrine disruptor. A nuclear hormone receptor docking analysis using "Endocrine Disruptome" has revealed that ellagic acid is predicted to be an androgen receptor (AR) antagonist, an ERβ agonist, and an ERα antagonist [65].

Ellagic acid has also been shown to represent a substrate of mushroom polyphenol oxidase [66]. This enzyme catalyses the oxidation of ellagic acid, leading to the production *o*-quinone [66]. Quinones represent an important class of toxicological intermediates that lead to several deleterious processes, including acute cytotoxicity, immunotoxicity, and carcinogenesis [67]. Despite this, a 90-day subchronic study found no changes were reported in males exposed to a diet containing 5% ellagic acid [68]. A slight reduction in body weights was observed with dose-dependence in females. The no-observed-effect level (NOEL) was estimated to be 5% (3011 mg/kg/day) for male rats. In females, the NOEL was <1.25%, and the no-observed-adverse-effect level (NOAEL) was 5% (3254 mg/kg/day) and (778 mg/kg/day) [68]. A human trial showed that pomegranate extract containing 100 mg/day of ellagic acid for 4 weeks attenuated skin pigmentation following irradiation with ultraviolet ray [69]. These doses were much higher than the expected daily intake or the reported effective dose.

EFFECTS OF ELLAGIC ACID ON THE NERVOUS SYSTEM

Ellagic acid is quite stable under physiological conditions in the stomach [70], and therefore, can be a potential phytotherapeutic candidate for the development of neuroprotective drug, which can be administered orally. It is thought that ellagic acid can cross the blood-brain barrier, although there are no definitive studies to prove this. However, ellagic acid may be combined with glucose, and glucose can readily pass through the blood-brain barrier to induce a therapeutic effect on the central nervous system [71]. Ellagic acid possesses multiple pharmacological properties, which are very useful in treatment and management of a variety of nervous system disorders.

Anti-Inflammatory and Analgesic Effects

Ellagic acid possesses anti-inflammatory, anti-edematous and analgesic effects [72]. Moreover, extracts containing ellagic acid as a component have shown a reduction in Tibial & Sural Nerve Transection induced neuropathic pain in a rat model [73]. Ellagic acid treatment attenuated formalin-induced flinching number in early

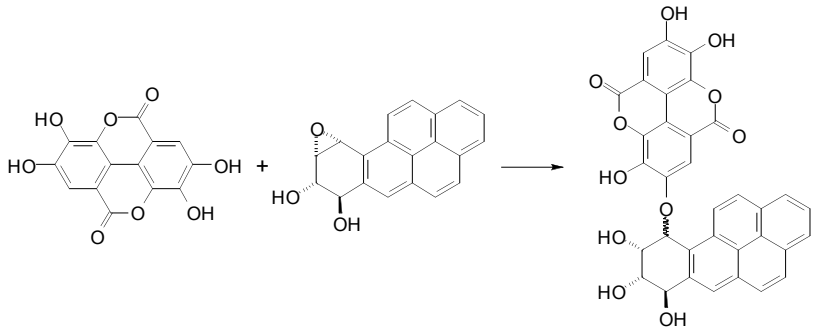

Fig. (4). Nucleophilic addition of ellagic acid to benzo[*a*]pyrene-7,8-diol-9,10-epoxide.

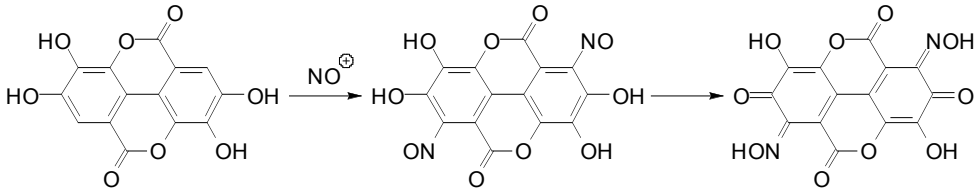

Fig. (5). Electrophilic nitrosation of ellagic acid to form a quinone oxime.

and late phase with the effective dose of less than 2 mg/kg for each phase. When the dosing was increased up to 30 mg/kg, the effect was found comparable to that of morphine (5mg/kg) and indomethacin (10 mg/kg), suggesting ellagic acid as a potent analgesic [74]. Consistently, ellagic acid treatment demonstrated peripheral antinociceptive effect against early and late phases of formalin-induced nociception. Pharmacological studies have demonstrated that the analgesic effects of ellagic acid occur through modulation of opioid receptors [74]. In another study, several routes of administration (oral, intraperitoneal and intracerebroventricular) were employed to elucidate the analgesic effects of ellagic acid in different pain models [75]. The antinociceptive effect of ellagic acid was reversed by naloxone; reaffirming the fact that ellagic acid acts on opioid receptors [75]. Similarly designed studies demonstrated that the antinociceptive effects of ellagic acid were mediated by additional targets, such as, L-arginine-NO-cGMP pathway, and ATP-sensitive K(+) channels [75, 76]. Therefore, it has been suggested that in addition to *in vivo* effects of ellagic acid, topical applications of ointment or cream containing ellagic acid might be a helpful in relieving inflammatory pain states [76].

Antioxidant Effects

Treatment with ellagic acid decreased the generation of reactive oxygen species, and astrocytic cell death due to Cadmium (2+) exposure [77], suggesting that it can be used as an antidote to cadmium-induced neurological disorders. Ellagic acid treatment (on alternative days for three months) decreased the production of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)-induced superoxide anion, lipid peroxidation, and DNA single-strand breaks in several regions of the rat brain. On the contrary, one study indicated that ellagic acid was a less superior protectant than vitamin E succinate in TCDD-induced toxicity in the brain [15]. Excessive production of nitric oxide (NO) in brain tissue has been well-correlated with neurotoxicity and the pathogenesis of several neurodegenerative disorders [78]. Ellagic acid has been shown to decrease (NO) production in lipopolysaccharide and γ-interferon-stimulated C6 astrocytes, however, ellagic acid was not more potent than green tea [78]. Ellagic acid also attenuated rotenone-induced reactive oxygen species and reactive nitrogen species in PC12 cells and resulted in antiapoptotic effects [79]. Ferreres et al. (2013) reported that ellagic acid reduced oxidative stress and has more potent radical scavenging capacity than that of ascorbic acid. Ellagic acid also prevents dopamine and copper-mediated DNA damage due to oxidative stress and cell death, further reaffirming the neuroprotective role of ellagic acid against oxidative stress [80].

Ellagic acid also demonstrated neuroprotective effects against the streptozotocin-induced oxidative stress in rats [12]. Ellagic acid treatment for four weeks ameliorated the decline in paraoxonase, catalase, and total antioxidant capacity to physiological levels in streptozotocin-induced diabetic rats [12]. Ellagic acid (50-100 mg/kg/d) also inhibited sorbitol accumulation in lens, erythrocytes, and sciatic nerve of rats. Taken together, these data suggest that ellagic acid can be used to relieve diabetic complications in multiple organs and the central nervous system in particular [81].

Advanced Glycation Endproducts (AEs) are a heterogeneous group of molecules produced from non-enzymatic glycation. AEs play a key role in the pathogenesis of numerous chronic human diseases, *e.g.* type-2 diabetes and Alzheimer's disease [82]. Ellagic acid was found to be a potent inhibitor of the AEs (more potent than aminoguanidines) [82]. As well, nitrosative stress-mediated S-nitrosylation of protein disulfide isomerase (a housekeeping oxidoreductase) has been implicated in the pathogenesis of sporadic Parkinson's and Alzheimer's diseases. Ellagic acid directly interfered with S-nitrosylation of protein disulfide isomerase formation *in vitro*, suggestive of its potential therapeutic role in Parkinson's and Alzheimer's disease [79].

Anticancer Effects

Ellagic acid treatment (at a dose of less than 500 μM) decreased N-acetylation of 2-aminofluorene (a carcinogen) in the cytosolic preparations obtained from rat cerebrum, cerebellum and pineal gland [16]. In the same study, ellagic acid administered at the dose of 10 mg/kg lead to a reduction in total aminofluorene and its metabolites in the pineal gland, but no significant effect was observed in the cerebellum and cerebrum. This suggests that ellagic acid decreases the N-acetylation of carcinogens in the rat brain [16].

Ellagic acid inhibits growth and promotes apoptosis in human neuroblastoma SH-SY5Y cells in a dose- and time-dependent manner [83] and also induces apoptosis in neuronal tumor cells [84].

Ellagic acid treatment resulted in alterations in the mitochondrial membrane potential, activation of caspases (caspase-9 and caspase-3), DNA-fragmentation, and cell death by apoptosis [84]. Ellagic acid has been employed in biomaterial gels used for the treatment of brain cancer with beneficial outcomes [13],

Neuroregeneration

Ellagic acid derivatives (3,3'-di-O-methylellagic acid and 3,3'-di-O-methyl ellagic acid-4-O-beta-D-xylopyranoside) have been shown to induce neuronal differentiation in neurosphere stem cells very efficiently with no cytotoxic effects. These data show that ellagic acid derivatives may be convenient pharmacological candidates for the induction of neurogenesis [85]. Treatment with ellagic acid reversed traumatic brain injury (TBI)-induced memory impairment and restored hippocampal LTP in rat [11], while it also attenuated TBI-induced inflammation by decreasing the levels of IL-1β and IL-6 at the same time. Similarly, ellagic acid was able to decrease blood brain barrier (BBB) permeability and attenuated damage to the (BBB). According to Farbood et al.'s (2015) findings, ellagic acid was suggested to have potential therapeutic effects to prevent TBI-induced brain damage. On the other hand, maternal dietary supplementation with pomegranate juice (containing ellagic acid as its main constituent) markedly decreased brain tissue loss in the hippocampus and cortex of pups in an animal model of neonatal hypoxic-ischemic brain injury, suggesting that pomegranate juice is neuroprotective to the neonatal brain [86].

Anti-Amyloidogenic Effects

Recently, it has been shown that ellagic acid promotes the formation of Aβ fibril *in vitro*. One study showed that Aβ42 samples co-incubated with ellagic acid showed more fibrils in earlier phases of aggregation [87]. It is believed that plaque formation may represent a protective mechanism, in which the body can sequester toxic Aβ aggregates to render them non-toxic [87]. This was further confirmed by the fact that ellagic acid reduced Aβ42-induced neurotoxicity in SH-SY5Y cells, suggesting the potential role of ellagic acid in the treatment of Alzheimer's disease (AD) [87]. Moreover, ellagic acid treatment was found to be beneficial in a mouse model of AD [88]. The compound has been found to have inhibitory properties on β-secretase (BACE1), the enzyme responsible for the cleavage of amyloid precursor protein (APP) to Aβ fragments, with an IC_{50} value in the range of micromolar concentrations. Ellagic acid also caused non-competitive inhibition of BACE1 and had less inhibitory effect on γ-secretase (TACE) and other serine proteases, *i.e.* trypsin, chymotrypsin, and elastase enzymes, highlighting the huge potential for the treatment of AD [89].

Vascular Effects

Ellagic acid has also been shown to protect against global cerebral ischemia (GCIR) in a rat model [90]. GCIR occurs in in patients suffering from cardiac arrest, asphyxia, and shock. Pretreatment with ellagic acid (100 mg/kg) prevented the reduction in blood pressure due to common carotid artery occlusion in otherwise healthy adult male Wistar rats. Ellgaic acid pretreatment also reduced the levels of malondialdehyde (MDA), a marker for lipid peroxidations, and restored the heart rate to physiologically normal levels [90]. This is the first study to provide evidence for the potential role of ellagic acid in patients with cerebrovascular insult.

Behavioural Effects

Ellagic acid demonstrated antidepressant-like effects in mice exposed to the forced swimming test and tail suspension test. The antidepressant effect of the ellagic acid (25 - 100mg/kg oral doses) was comparable to that of fluoxetine (20mg/kg oral dose) [91], and this effect was suggested to be mediated by modulation of the monoaminergic system [91]. Ellagic acid (25 - 100 mg/kg) also showed anti-anxiolytic effects, which were comparable to diazepam (1 mg/kg). Nevertheless, ellagic acid did not exert hypnotic properties. Subsequently, the study Girish et al. (2013) led to the folowing conclusion that acute and chronic administration of ellagic acid to mice produced anti-anxiety like effects through the involvement of the GABAergic system. Recently, another study reported that ellagic acid displayed a weak inhibitory effect on cholinesterases related to AD, but a very strong antidepressant effect [92].

CONCLUSION AND FUTURE PROSPECTS

Ellagic acid is an important phenolic constituent of a wide variety of fruits and vegetables. A growing body of scientific literature has demonstrated that ellagic acid mitigates neurodegeneration through regulation of different cellular signaling pathways. In addition to this, ellagic acid suppresses neuro-inflammation and cell death in the brain tissues. Ellagic acid is the dilactone of hexahydroxydiphenic acid and the presence of hydroxyl moieties in its chemical structure is responsible mainly for its antioxidant activity. The present review indicates that ellagic acid possesses beneficial effects on brain function and mitigates different hallmarks of neurodegeneration. However, a simple search at https://clinicaltrials.gov/ pointed out to absence of human clinical trials addressing the neuroprotective effects of ellagic acid. Therefore, the clinical efficacy of ellagic acid for the treatment of brain diseases remains unclear, although preclinical studies are quite promising.

Based on this background, we finally recommend that future studies should be designed to (1) Ascertain the best synthetic procedure for production of ellagic acid; (2) Increasing the bioavailability of ellagic acid through nanoparticles loading, nanoparticles encapsulation, as well as its formulation with phospholipid, etc; (3) Examination of acute and sub-acute toxicity of ellagic acid to ascertain its maximum non-toxic doses; (4) Finding the exact molecular mechanisms of neuroprotective effects of ellagic acid; and (5) Conducting clinical trials aimed to evaluate the clinical efficacy of ellagic acid in neurodegenerative diseases through a large patient cohort.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Cavallucci V, Nobili A, D'Amelio M. Emerging role of mitochondria dysfunction in the onset of neurodegenerative diseases. J Biol Regul Homeost Agents 2012; 27: 1-9.

[2] Sorrell ME, Hauser KF. Ligand-gated purinergic receptors regulate HIV-1 Tat and morphine related neurotoxicity in primary mouse striatal neuron-glia co-cultures. J Neuroimmune Pharmacol 2014; 9: 233-44.

[3] Martinc B, Grabnar I, Vovk T. Antioxidants as a preventive treatment for epileptic process: a review of the current status. Curr Neuropharmacol 2014; 12: 527-50.

[4] Chen P, Chakraborty S, Peres TV, Bowman AB, Aschner M. Manganese-induced neurotoxicity: from C. elegans to humans. Toxicol Res 2015; 4: 191-202.

[5] Valadi N. Evaluation and Management of Amyotrophic Lateral Sclerosis. Prim Care 2015; 42: 177-87.

[6] Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. J Mov Disor 2015; 8: 1.

[7] Orack JC, Deleidi M, Pitt D, *et al*. Concise review: Modeling multiple sclerosis with stem cell biological platforms: toward functional validation of cellular and molecular phenotypes in inflammation-induced neurodegeneration. Stem Cells Transl Med 2015; 4: 252-60.

[8] Halliwell B. Oxidative stress and antioxidants, beneficial or pathological? Drug Metab Rev 2010; 42: 23-24.

[9] Halliwell B. Biochemistry of oxidative stress. Biochem Soc Transact 2007; 35: 1147-50.

[10] Halliwell B. Oxidative stress, nutrition and health. Experimental strategies for optimization of nutritional antioxidant intake in humans. Free Rad Res 1996; 25: 57-74.

[11] Farbood Y, Sarkaki A, Dianat M, Khodadadi A, Haddad MK, Mashhadizadeh S. Ellagic acid prevents cognitive and hippocampal long-term potentiation deficits and brain inflammation in rat with traumatic brain injury. Life Sci 2015; 124: 120-7.

[12] Uzar E, Alp H, Cevik MU, *et al*. Ellagic acid attenuates oxidative stress on brain and sciatic nerve and improves histopathology of brain in streptozotocin-induced diabetic rats. Neurol Sci 2012; 33: 567-74.

[13] Kim S, Nishimoto SK, Bumgardner JD, Haggard WO, Gaber MW, Yang Y. A chitosan/beta-glycerophosphate thermo-sensitive gel for the delivery of ellagic acid for the treatment of brain cancer. Biomaterials 2010; 31: 4157-66.

[14] Hassoun EA, Vodhanel J, Holden B, Abushaban A. The effects of ellagic acid and vitamin E succinate on antioxidant enzymes activities and glutathione levels in different brain regions of rats after subchronic exposure to TCDD. J Toxicol Environ Health A 2006; 69: 381-93.

[15] Hassoun EA, Vodhanel J, Abushaban A. The modulatory effects of ellagic acid and vitamin E succinate on TCDD-induced oxidative stress in different brain regions of rats after subchronic exposure. J Biochem Mol Toxicol 2004; 18: 196-203.

[16] Lin SS, Hung CF, Ho CC, Liu YH, Ho HC, Chung JG. Effects of ellagic acid by oral administration on N-acetylation and metabolism of 2-aminofluorene in rat brain tissues. Neurochem Res 2000; 25: 1503-8.

[17] Nabavi SF, Daglia M, Moghaddam AH, Habtemariam S, Nabavi SM. Curcumin and liver disease: from chemistry to medicine. Compr Rev Food Sci Food Saf 2014; 13: 62-77.

[18] Nabavi SF, Russo GL, Daglia M, Nabavi SM. Role of quercetin as an alternative for obesity treatment: You are what you eat! Food Chem 2015; 179: 305-10.

[19] Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH. In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem 2012; 132: 931-5.

[20] Curti V, Capelli E, Boschi F, *et al*. Modulation of human miR-17–3p expression by methyl 3-O-methyl gallate as explanation of its in vivo protective activities. Mol Nutr Food Res 2014; 58: 1776-84.

[21] Scalbert A, Manach C, Morand C, Remesy C, Jimenez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr 2005; 45: 287-306.

[22] Hipkiss AR. Aging risk factors and Parkinson's disease: contrasting roles of common dietary constituents. Neurobiol Aging 2014; 35: 1469-72.

[23] Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov 2015; 14: 111-29.

[24] Molinari G. Natural products in drug discovery: present status and perspectives. In: ed.^eds., Pharmaceutical Biotechnology. Springer 2009; pp. 13-27.

[25] Nabavi SF, Nabavi SM, Mirzaei M, Moghaddam AH. Protective effect of quercetin against sodium fluoride induced oxidative stress in rat's heart. Food Funct 2012; 3: 437-41.

[26] Nabavi SF, Nabavi SM, Habtemariam S, *et al*. Hepatoprotective effect of gallic acid isolated from Peltiphyllum peltatum against sodium fluoride-induced oxidative stress. Ind Crops Prod 2013; 44: 50-5.

[27] Lagunin A, Filimonov D, Poroikov V. Multi-targeted natural products evaluation based on biological activity prediction with PASS. Curr Pharm design 2010; 16: 1703-17.

[28] Gu J, Gui Y, Chen L, Yuan G, Lu HZ, Xu X. Use of natural products as chemical library for drug discovery and network pharmacology. PLoS One 2013; 8(4):e62839.2013.

[29] Cerdá B, Tomás-Barberán FA, Espín JC. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: identification of biomarkers and individual variability. J Agric Food Chem 2005; 53: 227-35.

[30] Kyriakis E, Stravodimos GA, Kantsadi AL, Chatzileontiadou DS, Skamnaki VT, Leonidas DD. Natural flavonoids as antidiabetic agents. The binding of gallic and ellagic acids to glycogen phosphorylase b. FEBS Lett 2015; 589(15):1787-94.

[31] García-Niño WR, Zazueta C. Ellagic acid: Pharmacological activities and molecular mechanisms involved in liver protection. Pharmacol Res 2015; 97: 84-103.

[32] Cho H, Jung H, Lee H, Yi HC, Kwak H-k, Hwang KT. Chemopreventive activity of ellagitannins and their derivatives from black raspberry seeds on HT-29 colon cancer cells. Food Funct 2015; 6: 1675-83.

[33] Dolatshahi M, Farbood Y, Sarkaki A, Mansouri SMT, Khodadadi A. Ellagic acid improves hyperalgesia and cognitive deficiency in 6-hydroxidopamine induced rat model of Parkinson's disease. Iran J Basic Med Sci 2015; 18: 38.

[34] Woo MS, Choi HS, Seo MJ, Jeon HJ, Lee BY. Ellagic acid suppresses lipid accumulation by suppressing early adipogenic events and cell cycle arrest. Phytother Res 2015; 29: 398-406.

[35] Tang B, Chen GX, Liang MY, Yao JP, Wu ZK. Ellagic acid prevents monocrotaline-induced pulmonary artery hypertension via inhibiting NLRP3 inflammasome activation in rats. Int J Cardiol 2015; 180: 134-41.

[36] Ghorbanzadeh B, Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A. Involvement of L-arginine/NO/cGMP/K ATP channel pathway in the peripheral antinociceptive actions of ellagic acid in the rat formalin test. Pharmacol Biochem Behav 2014; 126: 116-21.

[37] Kang EH, Kown TY, Oh GT, *et al*. The flavonoid ellagic acid from a medicinal herb inhibits host immune tolerance induced by the hepatitis B virus-e antigen. Antiviral Res 2006; 72: 100-6.

[38] Larrosa M, García-Conesa MT, Espín JC, Tomás-Barberán FA. Ellagitannins, ellagic acid and vascular health. Mol Aspects Med 2010; 31: 513-39.

[39] Landete J. Ellagitannins, ellagic acid and their derived metabolites: a review about source, metabolism, functions and health. Food Res Int 2011; 44: 1150-60.

[40] Aguilera-Carbo A, Augur C, Prado-Barragan LA, Favela-Torres E, Aguilar CN. Microbial production of ellagic acid and biodegradation of ellagitannins. Appl Microbiol Biotechnol 2008; 78: 189-99.

[41] Sepúlveda L, Ascacio A, Rodríguez-Herrera R, Aguilera-Carbó A, Aguilar CN. Ellagic acid: Biological properties and biotechnological development for production processes. Afr J Biotechnol 2013; 10: 4518-23.

[42] Rommel A, Wrolstad RE. Ellagic acid content of red raspberry juice as influenced by cultivar, processing, and environmental factors. J Agric Food Chem 1993; 41: 1951-60.

[43] Aguilera-Carbo AF, Augur C, Prado-Barragan LA, Aguilar CN, Favela-Torres E. Extraction and analysis of ellagic acid from novel complex sources. Chem Papers 2008; 62: 440-4.

[44] Mertz C, Cheynier V, Günata Z, Brat P. Analysis of phenolic compounds in two blackberry species (Rubus glaucus and Rubus adenotrichus) by high-performance liquid chromatography with diode array detection and electrospray ion trap mass spectrometry. J Agric Food Chem 2007; 55: 8616-24.

[45] Gasperotti M, Masuero D, Vrhovsek U, Guella G, Mattivi F. Profiling and accurate quantification of Rubus ellagitannins and ellagic acid conjugates using direct UPLC-Q-TOF HDMS and HPLC-DAD analysis. J Agric Food Chem 2010; 58: 4602-16.

[46] Komorsky-Lovrić Š, Novak I. Determination of ellagic acid in strawberries, raspberries and blackberries by square-wave voltammetry. Int J Electrochem Sci 2011; 6: 4638-47.

[47] Espín JC, Larrosa M, García-Conesa MT, Tomás-Barberán F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: the evidence so far. Evid Based Complement Altern Med 2013; 2013.

[48] Espín JC, González-Barrio R, Cerdá B, López-Bote C, Rey AI, Tomás-Barberán FA. Iberian pig as a model to clarify obscure points in the bioavailability and metabolism of ellagitannins in humans. J Agric Food Chem 2007; 55: 10476-85.

[49] González-Barrio R, Edwards CA, Crozier A. Colonic catabolism of ellagitannins, ellagic acid, and raspberry anthocyanins: in vivo and in vitro studies. Drug Metab Disposit 2011; 39: 1680-8.

[50] Seeram NP, Lee R, Heber D. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (*Punica granatum* L.) juice. Clin Chim Acta 2004; 348: 63-8.

[51] Stoner GD, Sardo C, Apseloff G, *et al*. Pharmacokinetics of Anthocyanins and Ellagic Acid in Healthy Volunteers Fed Freeze-Dried Black Raspberries Daily for 7 Days. J Clin Pharmacol 2005; 45: 1153-64.

[52] Ishimoto H, Shibata M, Myojin Y, *et al*. In vivo anti-inflammatory and antioxidant properties of ellagitannin metabolite urolithin A. Bioorg Med Chem Lett 2011; 21: 5901-4.

[53] Giménez-Bastida JA, González-Sarrías A, Larrosa M, Tomás-Barberán F, Espín JC, García-Conesa MT. Ellagitannin metabolites, urolithin A glucuronide and its aglycone urolithin A, ameliorate TNF-α-induced inflammation and associated molecular markers in human aortic endothelial cells. Mol Nutr Food Res 2012; 56: 784-96.

[54] González-Sarrías A, Miguel Vn, Merino G, Lucas R, Morales JC, Tomás-Barberán F, Álvarez AI, Espín JC. The gut microbiota ellagic acid-derived metabolite urolithin A and its sulfate conjugate are substrates for the drug efflux transporter breast cancer resistance protein (ABCG2/BCRP). J Agric Food Chem 2013; 61: 4352-9.

[55] Galano A, Francisco Marquez M, Pérez-González A. Ellagic acid: an unusually versatile protector against oxidative stress. Chem Res Toxicol 2014; 27: 904-18.

[56] Priyadarsini KI, Khopde SM, Kumar SS, Mohan H. Free radical studies of ellagic acid, a natural phenolic antioxidant. J Agric Food Chem 2002; 50: 2200-6.

[57] Osawa T, Ide A, Su JD, Namiki M. Inhibition of in vitro lipid peroxidation by ellagic acid. J Agric Food Chem 1987; 35: 808-12.

[58] Marković Z, Milenković D, Đorović J, Marković JMD, Lučić B, Amić D. A DFT and PM6 study of free radical scavenging activity of ellagic acid. Monatshefte für Chemie 2013; 144: 803-12.

[59] Seeram NP, Adams LS, Henning SM, *et al*. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. J Nutr Biochem 2005; 16: 360-7.

[60] Sayer JM, Yagi H, Wood AW, Conney AH, Jerina DM. Extremely facile reaction between the ultimate carcinogen benzo [a] pyrene-7, 8-diol 9, 10-epoxide and ellagic acid. J Am Chem Soc 1982; 104: 5562-4.

[61] Huetz P, Mavaddat N, Mavri J. Reaction between ellagic acid and an ultimate carcinogen. J Chem Information Model 2005; 45: 1564-70.

[62] Wilson TC, Hagerman AE. Quantitative determination of ellagic acid. J Agric Food Chem 1990; 38: 1678-83.

[63] Teel RW. Ellagic acid binding to DNA as a possible mechanism for its antimutagenic and anticarcinogenic action. Cancer Lett 1986; 30: 329-36.

[64] Papoutsi Z, Kassi E, Tsiapara A, Fokialakis N, Chrousos GP, Moutsatsou P. Evaluation of estrogenic/antiestrogenic activity of ellagic acid via the estrogen receptor subtypes ERα and ERβ. J Agric Food Chem 2005; 53: 7715-20.

[65] Kolsek K, Mavri J, Sollner Dolenc M, Gobec S, Turk S. Endocrine disruptome--an open source prediction tool for assessing endocrine disruption potential through nuclear receptor binding. J Chem Inf Model 2014; 54: 1254-67.

[66] Munoz-Munoz JL, Garcia-Molina F, Garcia-Molina M, Tudela J, Garcia-Canovas F, Rodriguez-Lopez JN. Ellagic Acid: Characterization as Substrate of Polyphenol Oxidase. Iubmb Life 2009; 61: 171-7.

[67] Morina F, Takahama U, Yamauchi R, Hirota S, Veljovic-Jovanovic S. Quercetin 7-O-glucoside suppresses nitrite-induced formation of dinitrosocatechins and their quinones in catechin/nitrite systems under stomach simulating conditions. Food Funct 2015; 6: 219-29.

[68] Tasaki M, Umemura T, Maeda M, *et al*. Safety assessment of ellagic acid, a food additive, in a subchronic toxicity study using F344 rats. Food Chem Toxicol 2008; 46: 1119-24.

[69] Kasai K, Yoshimura M, Koga T, Arii M, Kawasaki S. Effects of oral administration of ellagic acid-rich pomegranate extract on ultraviolet-induced pigmentation in the human skin. J Nutr Sci Vitaminol 2006; 52: 383-8.

[70] Usta C, Ozdemir S, Schiariti M, Puddu PE. The pharmacological use of ellagic acid-rich pomegranate fruit. Int J Food Sci Nutr 2013; 64: 907-13.

[71] Kyriakis E, Stravodimos GA, Kantsadi AL, Chatzileontiadou DSM, Skamnaki VT, Leonidas DD. Natural flavonoids as antidiabetic agents. The binding of gallic and ellagic acids to glycogen phosphorylase b. Febs Letters 2015; 589: 1787-94.

[72] Rogerio AP, Fontanari C, Melo MC, *et al*. Anti-inflammatory, analgesic and anti-oedematous effects of Lafoensia pacari extract and ellagic acid. J Pharm Pharmacol 2006; 58: 1265-73.

[73] Jain V, Pareek A, Bhardwaj YR, Singh N. Attenuating effect of standardized fruit extract of Punica granatum L in rat model of tibial and sural nerve transection induced neuropathic pain. BMC Complement Altern Med 2013; 13: 274.

[74] Mansouri MT, Naghizadeh B, Ghorbanzadeh B. Involvement of opioid receptors in the systemic and peripheral antinociceptive actions of ellagic acid in the rat formalin test. Pharmacol Biochem Behav 2014; 120: 43-9.

[75] Taghi Mansouri M, Naghizadeh B, Ghorbanzadeh B, Farbood Y. Central and peripheral antinociceptive effects of ellagic acid in different animal models of pain. Eur J Pharmacol 2013; 707: 46-53.

[76] Ghorbanzadeh B, Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A. Involvement of L-arginine/NO/cGMP/K(ATP) channel pathway in the peripheral antinociceptive actions of ellagic acid in the rat formalin test. Pharmacol Biochem Behav 2014; 126: 116-21.

[77] Yang CS, Tzou BC, Liu YP, Tsai MJ, Shyue SK, Tzeng SF. Inhibition of cadmium-induced oxidative injury in rat primary astrocytes by the addition of antioxidants and the reduction of intracellular calcium. J Cell Biochem 2008; 103: 825-34.

[78] Soliman KF, Mazzio EA. In vitro attenuation of nitric oxide production in C6 astrocyte cell culture by various dietary compounds. Proc Soc Exp Biol Med 1998; 218: 390-7.

[79] Kabiraj P, Marin JE, Varela-Ramirez A, Zubia E, Narayan M. Ellagic acid mitigates SNO-PDI induced aggregation of Parkinsonian biomarkers. ACS Chem Neurosci 2014; 5: 1209-20.

[80] Spencer WA, Jeyabalan J, Kichambre S, Gupta RC. Oxidatively generated DNA damage after Cu(II) catalysis of dopamine and related catecholamine neurotransmitters and neurotoxins: Role of reactive oxygen species. Free Radic Biol Med 2011; 50: 139-47.

[81] Ueda H, Kawanishi K, Moriyasu M. Effects of ellagic acid and 2-(2,3,6-trihydroxy-4-carboxyphenyl)ellagic acid on sorbitol accumulation in vitro and in vivo. Biol Pharm Bull 2004; 27: 1584-7.

[82] Liu W, Ma H, Frost L, Yuan T, Dain JA, Seeram NP. Pomegranate phenolics inhibit formation of advanced glycation endproducts by scavenging reactive carbonyl species. Food Funct 2014; 5: 2996-3004.

[83] Fjaeraa C, Nanberg E. Effect of ellagic acid on proliferation, cell adhesion and apoptosis in SH-SY5Y human neuroblastoma cells. Biomed Pharmacother 2009; 63: 254-61.

[84] Alfredsson CF, Ding M, Liang QL, Sundstrom BE, Nanberg E. Ellagic acid induces a dose- and time-dependent depolarization of mitochondria and activation of caspase-9 and -3 in human neuroblastoma cells. Biomed Pharmacother 2014; 68: 129-35.

[85] Tabopda TK, Ngoupayo J, Liu JW, *et al*. Induction of neuronal differentiation in neurosphere stem cells by ellagic acid derivatives. Nat Prod Commun 2009; 4: 517-20.

[86] Loren DJ, Seeram NP, Schulman RN, Holtzman DM. Maternal dietary supplementation with pomegranate juice is neuroprotective in an animal model of neonatal hypoxic-ischemic brain injury. Pediatr Res 2005; 57: 858-64.

[87] Feng Y, Yang SG, Du XT, *et al*. Ellagic acid promotes Abeta42 fibrillization and inhibits Abeta42-induced neurotoxicity. Biochem Biophys Res Commun 2009; 390: 1250-4.

[88] Hassaan Y, Handoussa H, El-Khatib AH, Linscheid MW, El Sayed N, Ayoub N. Evaluation of plant phenolic metabolites as a source of Alzheimer's drug leads. Biomed Res Int 2014; 2014: 843263.

[89] Kwak HM, Jeon SY, Sohng BH, *et al*. beta-Secretase (BACE1) inhibitors from pomegranate (Punica granatum) husk. Arch Pharm Res 2005; 28: 1328-32.

[90] Nejad KH, Dianat M, Sarkaki A, Naseri MK, Badavi M, Farbood Y. Ellagic acid improves electrocardiogram waves and blood pressure against global cerebral ischemia rat experimental models. Electron Physician 2015; 7: 1153-62.

[91] Girish C, Raj V, Arya J, Balakrishnan S. Evidence for the involvement of the monoaminergic system, but not the opioid system in the antidepressant-like activity of ellagic acid in mice. Eur J Pharmacol 2012; 682: 118-25.

[92] Ferreres F, Grosso C, Gil-Izquierdo A, Valentao P, Andrade PB. Ellagic acid and derivatives from Cochlospermum angolensis Welw. Extracts: HPLC-DAD-ESI/MS(n) profiling, quantification and in vitro anti-depressant, anti-cholinesterase and anti-oxidant activities. Phytochem Anal 2013; 24: 534-40.

[93] Del Pozo-Insfran D, Brenes CH, Talcott ST. Phytochemical composition and pigment stability of Acai (*Euterpe oleracea* Mart.). J Agric Food Chem 2004; 52: 1539-45.

[94] Amakura Y, Okada M, Tsuji S, Tonogai Y. Determination of phenolic acids in fruit juices by isocratic column liquid chromatography. J Chromatogr A, 2000; 891: 183-8.
[95] Häkkinen SH, Kärenlampi SO, Mykkänen HM, Heinonen IM, Törrönen AR. Ellagic acid content in berries: Influence of domestic processing and storage. Eur Food Res Technol 2000; 212: 75-80.
[96] Gudej J, Tomczyk M. Determination of Flavonoids, Tannins and Ellagic acid in leaves fromRubus L. species. Arch Pharm Res 2004; 27: 1114-9.
[97] Siriwoharn T, Wrolstad RE, Finn CE, Pereira CB. Influence of cultivar, maturity, and sampling on blackberry (*Rubus* L. Hybrids) anthocyanins, polyphenolics, and antioxidant properties. J Agric Food Chem 2004; 52: 8021-30.
[98] Acosta-Montoya Ó, Vaillant F, Cozzano S, Mertz C, Pérez AM, Castro MV. Phenolic content and antioxidant capacity of tropical highland blackberry (*Rubus adenotrichus* Schltdl.) during three edible maturity stages. Food Chem 2010; 119: 1497-501.
[99] Abe LT, Lajolo FM, Genovese MI. Potential dietary sources of ellagic acid and other antioxidants among fruits consumed in Brazil: Jabuticaba (*Myrciaria jaboticaba* (Vell.) Berg). J Sci Food Agric 2012; 92: 1679-87.
[100] Vekiari S, Gordon M, Garcia-Macias Pa, Labrinea H. Extraction and determination of ellagic acid contentin chestnut bark and fruit. Food Chem 2008; 110: 1007-11.
[101] Vattem DA, Shetty K. Ellagic acid production and phenolic antioxidant activity in cranberry pomace (*Vaccinium macrocarpon*) mediated by Lentinus edodes using a solid-state system. Proc Biochem 2003; 39: 367-79.
[102] Soong Y-Y, Barlow PJ. Quantification of gallic acid and ellagic acid from longan (*Dimocarpus longan* Lour.) seed and mango (*Mangifera indica* L.) kernel and their effects on antioxidant activity. Food Chem 2006; 97: 524-30.
[103] Talcott ST, Lee JH. Ellagic acid and flavonoid antioxidant content of muscadine wine and juice. J Agric Food Chem 2002; 50: 3186-92.
[104] Lee J-H, Johnson JV, Talcott ST. Identification of ellagic acid conjugates and other polyphenolics in muscadine grapes by HPLC-ESI-MS. J Agric Food Chem 2005; 53: 6003-10.
[105] Amakura Y, Okada M, Tsuji S, Tonogai Y. High-performance liquid chromatographic determination with photodiode array detection of ellagic acid in fresh and processed fruits. J Chromatogr A 2000; 896: 87-93.
[106] Mousavinejad G, Emam-Djomeh Z, Rezaei K, Khodaparast MHH. Identification and quantification of phenolic compounds and their effects on antioxidant activity in pomegranate juices of eight Iranian cultivars. Food Chem 2009; 115: 1274-8.
[107] Robledo A, Aguilera-Carbó A, Rodriguez R, Martinez JL, Garza Y, Aguilar CN. Ellagic acid production by Aspergillus niger in solid state fermentation of pomegranate residues. J Ind Microbiol Biotechnol 2008; 35: 507-13.
[108] Bobinaitė R, Viškelis P, Venskutonis PR. Variation of total phenolics, anthocyanins, ellagic acid and radical scavenging capacity in various raspberry (*Rubus* spp.) cultivars. Food Chem 2012; 132: 1495-501.
[109] de Ancos B, González EM, Cano MP. Ellagic acid, vitamin C, and total phenolic contents and radical scavenging capacity affected by freezing and frozen storage in raspberry fruit. Journal of Agricultural and Food Chem 2000; 48: 4565-70.
[110] Zafrilla P, Ferreres F, Tomás-Barberán FA. Effect of processing and storage on the antioxidant ellagic acid derivatives and flavonoids of red raspberry (*Rubus idaeus*) jams. J Agric Food Chem 2001; 49: 3651-5.
[111] Anttonen MJ, Karjalainen RO. Environmental and genetic variation of phenolic compounds in red raspberry. J Food Composit Anal 2005; 18: 759-69.
[112] Cordenunsi BR, Genovese MI, do Nascimento JRO, Hassimotto NMA, dos Santos RJ, Lajolo FM. Effects of temperature on the chemical composition and antioxidant activity of three strawberry cultivars. Food Chem 2005; 91: 113-21.
[113] da Silva Pinto M, Lajolo FM, Genovese MI. Bioactive compounds and quantification of total ellagic acid in strawberries (*Fragaria xananassa* Duch.). Food Chem 2008; 107: 1629-35.
[114] Williner MR, Pirovani ME, Güemes DR. Ellagic acid content in strawberries of different cultivars and ripening stages. J Sci Food Agric 2003; 83: 842-5.
[115] Maas JL, Wang SY, Galletta GJ. Evaluation of strawberry cultivars for ellagic acid content. HortSci 1991; 26: 66-8.

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