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REVIEW ARTICLE

Chlorogenic Acid and Mental Diseases: From Chemistry to Medicine

Seyed Fazel Nabavi[1], Silvia Tejada[2], William N. Setzer[3], Olga Gortzi[4], Antoni Sureda[5], Nady Braidy[6], Maria Daglia[7], Azadeh Manayi[8] and Seyed Mohammad Nabavi[1,*]

[1]*Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran;* [2]*Experimental Laboratory, Research Unit, Son Llàtzer Hospital, IUNICS, Ctra. Manacor km 4, E-07198, Palma de Mallorca, Balearic Islands, Spain;* [3]*Department of Chemistry, University of Alabama in Huntsville, Alabama 35899, Huntsville, USA;* [4]*Department of Food Technology, Technological Educational Institution of Thessaly Terma N. Temponera Str. Greece;* [5]*Grup de Nutrició Comunitària i Estrès Oxidatiu (IUNICS) and CIBERobn Universitat de les Illes Balears, Palma de Mallorca, Spain;* [6]*Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydneyy, Australia;* [7]*Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Pavia, Italy;* [8]*Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract: ***Background*:** At present, much attention has been focused on the beneficial effects of natural products on the human health due to their high efficacy and low adverse effects. Among them, polyphenolic compounds are known as one of the most important and common classes of natural products, which possess multiple range of health-promotion effects including anti-inflammatory and antioxidant activities. A plethora of scientific evidence has shown that polyphenolic compounds possess beneficial effects on the central nervous system.

***Methods*:** Data were collected from Web of Science (ISI Web of Knowledge), Medline, Pubmed, Scopus, Embase, and BIOSIS Previews (from 1950 to 2015), through searching of these keywords: "chlorogenic acid and mental diseases" and "chlorogenic acid and neuroprotection".

***Results*:** Chlorogenic acid is known as one of the most common polyphenolic compounds, and is found in different types of fruits and vegetables, spices, wine, olive oil, as well as coffee. The potential neuroprotective effects of chlorogenic acid have been highlighted in several *in vitro* and *in vivo* studies. This review critically analyses the available scientific evidence regarding the neuroprotective effects of chlorogenic acid, and its neuropharmacological mechanisms of action. In addition, we also discuss its biosynthesis, sources, bioavailability and metabolism, to provide a broad perspective of the therapeutic implications of this compound in brain health and disease.

***Conclusion*:** The present review showed that chlorogenic acid possesses neuroprotective effects under the both *in vitro* and *in vivo* models.

Keywords: Antioxidant, chlorogenic acid, inflammation, neuroprotective, oxidative stress, polyphenolic.

INTRODUCTION

Polyphenols have favourable effects on human health, exhibiting several biological properties such as anti-inflammatory and antioxidant activities. The beneficial effects of polyphenols have been well established, acting against metabolic and cardiovascular alterations, cerebral ischemia, obesity and lipid metabolism [1-6]. Moreover, several studies have explored the neuroprotective effects of polyphenols [7, 8]. Polyphenolic compounds have been shown to modulate several molecular cascades, attenuate oxidative stress, and ameliorate neuroinflammation [9-13]. The pathobiologies of several neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), have been associated with chronic oxidative stress and proinflammatory mechanisms, which lead to neuronal damage [8, 14]. Therefore, compounds that reduce the production of reactive oxygen and nitrogen species may prevent oxidative damage to macromolecules and restore normal cellular homeostasis [15-17].

Numerous studies have reported that coffee can exert positive effects against depression [18, 19]. The beneficial effects of coffee intake have also been reported in several preclinical and clinical studies of AD and PD [20-22]. In fact, coffee has been widely studied due to its high content of polyphenols, which include chlorogenic acid.

Chlorogenic acid is a polyphenol that can be found in several plant tissues and foods such as fruits, spices,

*Address correspondence to this author at the Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, P.O. Box 19395-5487, Iran; Tel/Fax: +98 21 88617712;
E-mail: Nabavi208@gmail.com

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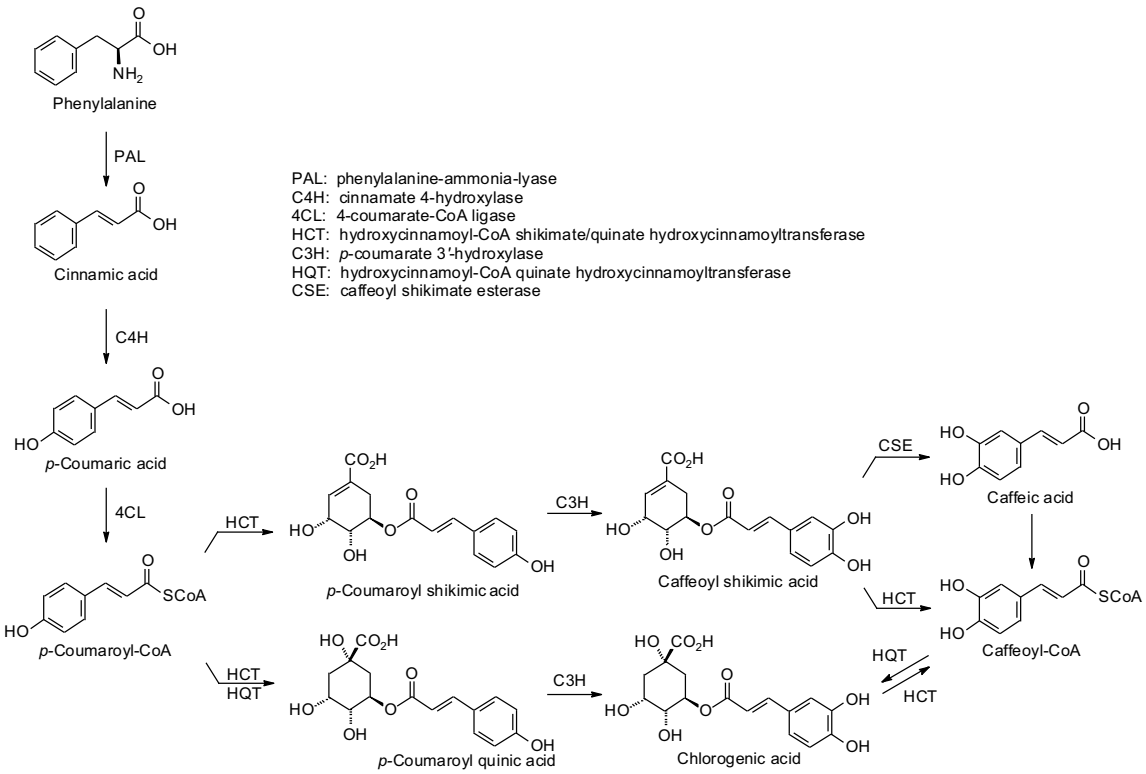

Fig. (1). Biosynthesis of chlorogenic acid in plants [37].

vegetables, wine, olive oil, and coffee [23-26]. In fact, chlorogenic acid and caffeic acid are the main polyphenolic representatives of hydroxycinnamic acids. While several studies have focused on caffeine as a neuroprotective agent against neurodegenerative disorders, chlorogenic acid is also an important active component of coffee. The literature describes this polyphenol as having several biological effects, including antioxidant, antibacterial, antihistaminic, anti-inflammatory, analgesic, hepatoprotective, anticancer, and neuroprotective properties [27-33]. Due to these properties, there are current studies focusing on the potential benefits of chlorogenic acid consumption. However, the exact mechanism(s) related to the neuroprotective effects of this acid have not yet been clearly established, though promising results are emerging in literature.

BIOSYNTHESIS AND SOURCES OF CHLOROGENIC ACID

The biosynthesis of chlorogenic acid (3-*O*-caffeoylquinic acid) has been shown to involve the shikimic acid pathway (see Fig. **1**) [34-37]. In brief, phenylalanine is converted to (*E*)-cinnamic acid by phenylalanine-ammonia-lyase [38], which is then hydroxylated by cinnamate 4-hydroxylase to *p*-coumaric acid. Conjugation of *p*-coumaric acid with coenzyme A is catalyzed by 4-coumarate-CoA ligase. Transesterification of *p*-coumaroyl-CoA with shikimic acid gives *p*-coumaroyl shikimic acid while quinic acid gives *p*-coumaroyl quinic acid [39]. Hydroxylation of *p*-coumaroyl quinic acid by *p*-coumarate 3′-hydroxylase gives chlorogenic acid [40]. Alternatively, *p*-coumaroyl shikimic acid can be hydroxylated to caffeoyl shikimic acid, which can be converted to caffeic acid or to caffeoyl-CoA. Caffeoyl-CoA can then be transesterified with quinic acid to give chlorogenic acid [41].

Important dietary sources of chlorogenic acid are coffee (*Coffea arabica* and *Coffea canephora*) beans [42, 43], potato (*Solanum tuberosum*) tubers [44], apple (*Malus domestica*) fruits [45], prune (*Prunus domestica*) fruits [46], sunflower (*Helianthus annuus*) seed kernels [47], Jerusalem artichoke (*Helianthus tuberosus*) leaves [48], and sweet potato (*Ipomoea batatas*) leaves [49].

Herbal medicinal sources of chlorogenic acid are the flowers and buds of Japanese honeysuckle (*Lonicera japonica*) [50, 51], South China honeysuckle (*Lonicera confusa*) [52], leaves of "guaco" (*Mikania glomerata* and *Mikania laevigata*) [53], Kuding tea (*Ilex latifolia*) [54], and zhi zi (*Gardenia jasminoides*) fruits [55].

BIOAVAILABILITY AND METABOLISM OF CHLOROGENIC ACID

Most studies on chlorogenic acid have been performed using coffee, due to high amounts of this polyphenol (about 400 μmol/200 ml coffee bean cup), yielding evidence of its antioxidant capacity [18-22, 56, 57]. However, the bioavailability of chlorogenic acid is controversial, since its utilization and excretion are unclear. About one-third of ingested chlorogenic acid is absorbed by the small intestine in humans [58] (see Fig. **2**). Most of the ingested chlorogenic acid reaches the colon, largely unaltered, where it is then hydrolyzed by esterases produced by colonic microflora (*e.g.*, *Escherichia coli*, *Bifidobacterium lactis*, and *Lactobacillus gasseri*) [59]. Gastric esterases, most likely located on the apical membrane, release free caffeic acid which then passively

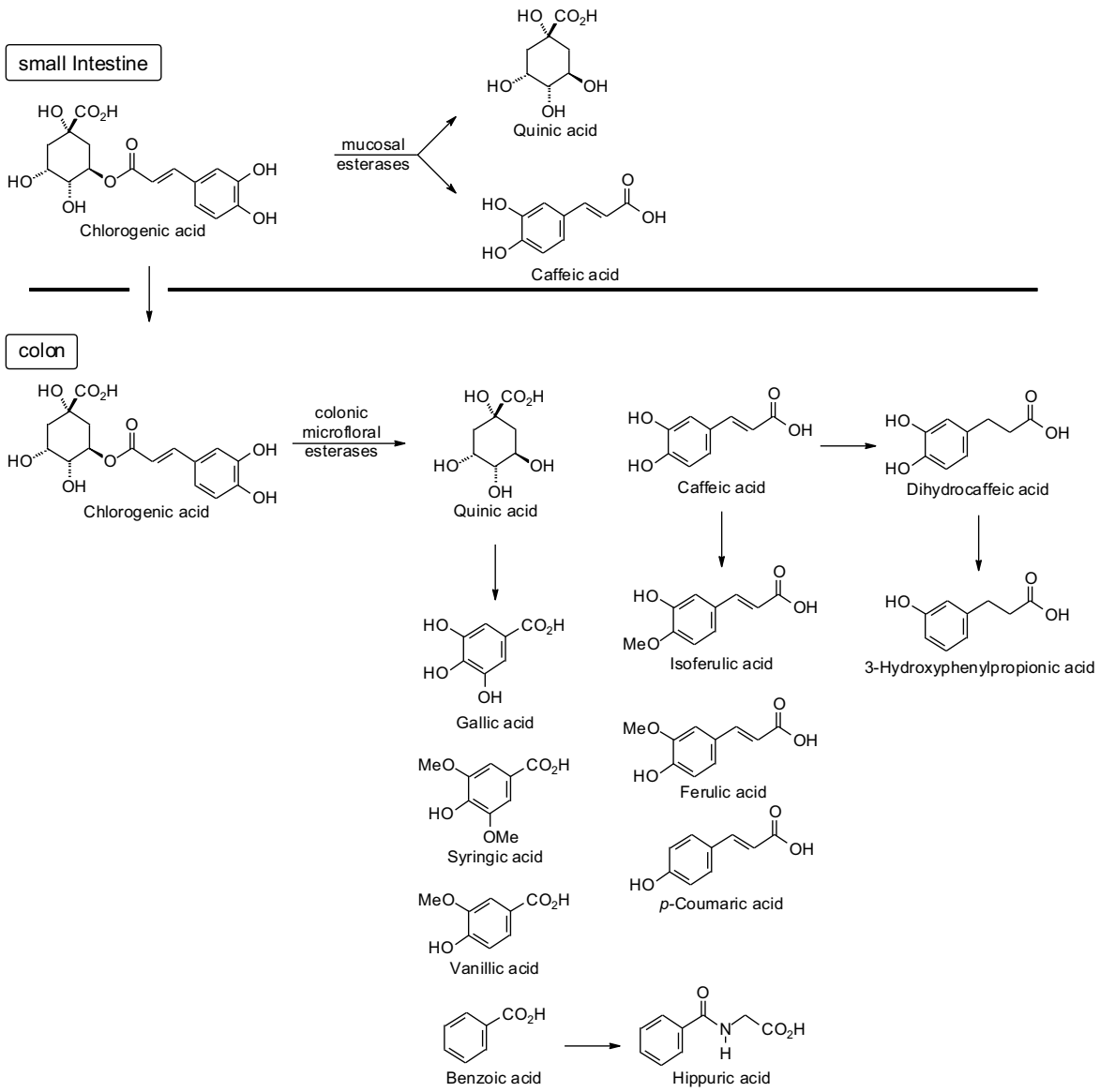

Fig. (2). Metabolism of chlorogenic acid [61, 103, 104].

diffuses across the cell surface [60]. The microfloral metabolites can then reach circulation [61].

Several clinical trials have studied the bioavailability of chlorogenic acid in urine, ileal fluid, and plasma of ileostomist volunteers, who drank different concentrations of chlorogenic acid in coffee. The results seem to indicate that the metabolism of these polyphenols is dependent on gastrointestinal transit time, and that its absorption occurs in the small intestine [56, 62]. However, another study has indicated the key role of the colon in the bioavailability of phenolic compounds in coffee [63]. These discrepancies may be attributed to the low number of subjects that volunteer to participate in these studies, or to differences in methodology.

However, one study has shown that chlorogenic acid is not well absorbed by the digestive tract in a rat model [64], and it was not detected in plasma or bile, suggesting that it may be absorbed and hydrolyzed in the small intestine with the uptake of caffeic acid taking place through the gut mucosa [65]. However, the microbial metabolites of chlorogenic acid represent major components of both urine and plasma of tested rats, indicating that the bioavailability of chlorogenic acid depends on its metabolism by gut microflora [66]. Likewise, urine does not appear to be a major excretion pathway of intact chlorogenic acid in humans [67].

REACTIONS OF CHLOROGENIC ACID

The antioxidant effects of chlorogenic acid are well established [68-74]. Chlorogenic acid can scavenge hydroxyl radicals (•OH) [75], superoxide radicals ($•O_2^-$) [73], 2,2-diphenyl-1-picrylhydrazyl radicals (DPPH•) [69], and 2,2′-azino-bis (3-ethylbenothiazoline-6-sulfonic acid) cation radicals ($ABTS•^+$) [76] in a dose-dependent manner. There are two plausible mechanisms for the radical scavenging activity of chlorogenic acid: (1) a hydrogen-atom-transfer (HAT) reaction where the free radical abstracts a hydrogen atom from chlorogenic acid; (2) a radical adduct formation

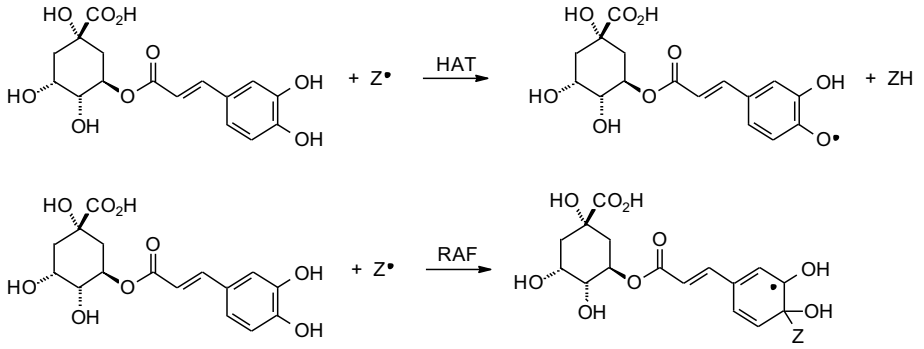

Fig. (3). Possible radical-scavenging mechanisms of chlorogenic acid.

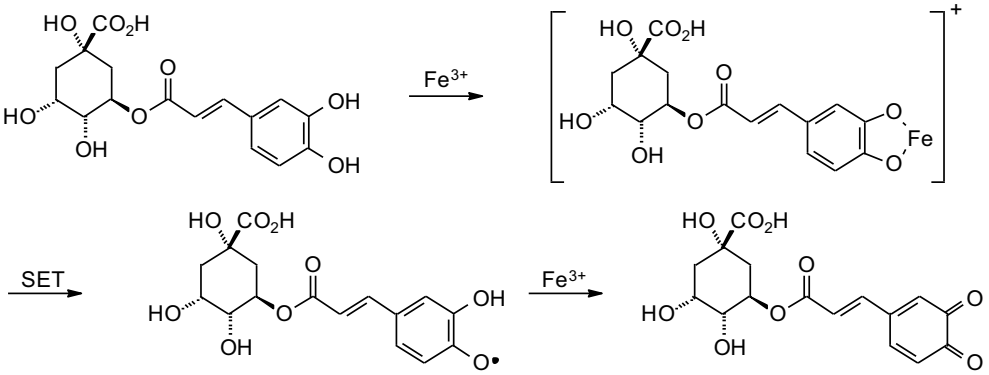

Fig. (4). Oxidation of chlorogenic acid by iron(III).

(RAF) mechanism where the free radical undergoes addition to chlorogenic acid to form a radical intermediate (Fig. **3**) [77, 78]. Chlorogenic acid also reacts with the oxidizing agent peroxynitrite ($ONOO^-$), but the products of this reaction have not been studied [73].

Chlorogenic acid also reacts with redox-active transition metals. In particular, chlorogenic acid reacts with iron(III) to form a chelate between the Fe(III) and the catechol moiety. Subsequent single electron transfer (SET) produces a semiquinone and Fe(II); which then reacts with another Fe(III), producing the corresponding quinone (Fig. **4**) [79]. A similar reaction sequence has been proposed between chlorogenic acid and copper(II) [80]. Chlorogenic acid can be electrochemically oxidized to the corresponding *o*-quinone [81]. The catechol moiety of chlorogenic acid can be enzymatically oxidized to the corresponding quinone [82-84]. The electrophilic quinone can then undergo conjugate addition reactions with suitable nucleophiles such as amines and thiols [85], including glutathione [86].

NEUROPROTECTIVE EFFECTS OF CHLOROGENIC ACID

Ability to Cross the Blood-brain Barrier

It has been reported that chlorogenic acid or its metabolites may cross the blood-brain barrier and exert neuroprotective effects on brain tissue [87-89]. Decaffeinated coffee enriched with chlorogenic acid was administered to 39 healthy older participants, which reported positive effects on mood and cognition, including diminished headaches, and lower mental fatigue in older adults [90]. Similar results were found on mood in 60 healthy individuals following the ingestion of chlorogenic acid. However, no improvement was reported in some mood and cognitive function assessments [91].

Antioxidant Effects in the Brain

Several studies have been performed using animals and human cell lines as models for assessing the protective effects of the chlorogenic acid against oxidative damage in brain tissue [92-94]. The antioxidant effects of chlorogenic acid have also been reported in rats [89], mice [95] and rabbits [96]. Oboh and collaborators [97] observed that chlorogenic acid reduces oxidative stress induced by Fe^{2+} and by sodium nitroprusside in a dose dependent manner. The reduction of ROS production and the inhibition of DNA fragmentation and caspase-3 cleavage have also been reported in PC12 cells following incubation with chlorogenic acid [94].

In contrast, a previous study has shown that chlorogenic acid (100 ng/ml) increases astrocyte viability in cultured cells, but has no direct effect on hydrogen peroxide toxicity in astrocytes. Apart from the free-radical scavenging properties of chlorogenic acid, antioxidant effects have been attributed to the increased expression of neuroprotective ribosomal proteins (PEP-1-rpS3) [98]. Differences in the methodological procedures of different studies may be responsible for the variability of the results reported in the literature.

Antiapoptotic Effects

Despite its antioxidant effects, chlorogenic acid may also inhibit apoptotic processes. For instance, proteins from the B-cell lymphoma 2 (Bcl-2) family act as antiapoptotic

molecules, and the inhibition of Bcl-X_L by hydrogen peroxide was found to be strongly reduced following pretreatment with chlorogenic acid [94].

Effects on Signaling Cascade

It is well known that ROS can activate protein kinase cascades [93]. Cho and collaborators [94] observed that pretreatment with chlorogenic acid stimulated JNK and p38 MAPK activation in the PC12 cell line.

Antiamyloidogenic Effects

A study using a human neuroblastoma cell line (MC65) revealed diminished cell viability when cells were treated with β-amyloid proteins (which form the typical extracellular plaques of AD). However, this effect can be prevented by pretreatment with chlorogenic acid. This induces an overexpression of the glycolytic enzyme phosphoglycerate kinase-1, which is associated with ATP production and regulation of neuronal apoptosis [99]. This study agrees with another study conducted using the extracts derived from the plant *Centella asiatica*, which has a high content of chlorogenic acid [100].

Effects Against α-synuclein

PC12 is a useful cell line used to monitor the expression levels of α-synuclein, a pathogenic molecule that induces the overexpression of Parkinson genes and the loss of dopaminergic neurons. Pretreatment with of PC12 cells with chlorogenic acid induces a protective effect against toxicity induced by α-synuclein. Incubation with chlorogenic acid provides protection against oxidative stress which, leads to increased cell viability [101]. In addition, negative effects caused by the oxidized forms of dopamine, and α-synuclein were inhibited by chlorogenic acid [102].

Cognitive Effects

The effects of chlorogenic acid on cognitive performance have been investigated in senescence-accelerated-prone mice 8, by means of the Morris water maze test. Improvements in the execution of this test and diminished latency in reaching the platform were reported in mice treated with chlorogenic acid, compared to control animals [99]. Chlorogenic acid can also protect against anxiolytic and depressive processes by means of reducing the oxidative status in a mouse model [92].

Cholinergic Effects

Chlorogenic acid has been shown to induce neuro-protection in rat brain homogenates by lowering the activities of acetylcholinesterase and butyrylcholinesterase [97]. These enzymatic activities are increased in neuro-degenerative diseases such as AD. Inhibition of these enzymatic activities can result in increased levels of acetylcholine in the synapses leading to an increased communication between neurons [97].

Protective Effects Against Ischemia

In another study of focal cerebral ischemia in rats, animals were treated with different doses of chlorogenic acid in order to assess its potential neuroprotective effects against ischemia. The authors reported that the treated animals had lower brain infarction than the control rats. Moreover, sensory-motor function was improved by the high dose used (30 mg/kg i.p.). Additionally, chlorogenic acid treatment was found to reduce the pressure and compression on brain tissue, and attenuate lipid peroxidation in the brain [89]. Lee and others [89] also described a reduction in lipid peroxidation levels after chlorogenic acid treatment in ischemic rats. The free radical scavenging properties of the acid and inhibition of matrix metalloproteinase 2 and 9 activities are thought to a play a role in the neuroprotective effects of chlorogenic acid. Likewise, another study showed that chlorogenic acid (100 μg/kg i.p.) increased the signal of ribosomal proteins in the hippocampus (CA1 region), and slightly protected neuronal cells in the CA1 region when transient ischemia was induced in Mongolian gerbils [98].

CONCLUSION AND FUTURE PROSPECTS

This review summarises the neuroprotective effects of chlorogenic acid in both *in vitro* and *in vivo* models. The molecular mechanisms of the neuroprotective effects of chlorogenic acid are complex, and its bioavailability and clinical relevance remain unclear. However, it can be hypothesized that its beneficial effects are due to high antioxidant and anti-inflammatory activities. A search of the US governmental clinical trials database (https://clinicaltrials.gov/) with the keyword "chlorogenic acid" (accessed July 15, 2015) showed that there is only one recruited clinical trial regarding the clinical impacts of chlorogenic acid. In view of this, it may be difficult to make a clear decision about its clinical efficacy and to ascertain the most effective therapeutic dose for the treatment and management of diseases of the central nervous system. We recommend that future studies should focus on ascertaining (1) the bioavailability and metabolisms of chlorogenic acid; (2) molecular pathways underlying the neuroprotective effects of chlorogenic acid; (3) toxicological studies to determine the maximum non-fatal doses of chlorogenic acid; and finally (4) clinical studies to examine the efficacy of chlorogenic acid in cognitively impaired humans.

CONFLICT OF INTEREST

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

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