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Natural Compounds Used as Therapies Targeting to Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease that occurs throughout the world with no racial, ethnic or socioeconomic boundaries. Despite its high morbidity and mortality, there are limited medications available for ALS that may increase survival in patients with amyotrophic lateral sclerosis by approximately 2-3 months. Inasmuch as negative effects of riluzole on muscle atrophy and wasting, weakness, muscle spasticity, dysarthria, dysphagia, and overall patient quality of life and its different adverse effects, much attention has been paid to natural products and herbal medicines. Overall scientific reports indicate that natural products have beneficial effects on patients with ALS low side effects and multiple targets. In the present paper, we review the scientific reports on beneficial role of natural polyphenolic compounds in treatment of ALS.

Keywords: Amyotrophic lateral sclerosis, natural substances, polyphenol, oxidative stress.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) is a debilitating, irreversible and rapidly progressive neurological disease which is characterized by motor neurons death in some parts of the central nervous system such as cerebral cortex and spinal cord [1, 2]. It is usually classified into two major types, including sporadic and familial [3]. Muscle atrophy, wasting, weakness, muscle spasticity, dysarthria, dysphagia, and respiratory failure are the most common clinical symptoms of ALS [2]. Although the molecular mechanisms of ALS are still largely unknown, it is supposed that oxidative stress plays an important role in the development and progression of this disease [4]. It also been reported that ALS induces mutation on SOD1 [5] and upregulates the expression of certain cytokines as well as different enzymes such as cyclooxygenase-2 [6] and matrix metalloproteinases [7]. Furthermore, it has been reported that ALS is associated with glutamate excitotoxicity, protein misfolding, mitochondrial dysfunction, skeletal muscle dysfunction, calcium toxicity and autoimmune response [1, 8].

According to recent statistical report, approximately 350,000 people suffered from ALS worldwide [9, 10].

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Although ALS is a fatal neurological disease, early diagnosis and treatment can mitigate the abnormality and severity of this pathology and increase quality of life in the patients [11]. Up to now, riluzole (Fig. **1**) is the only pharmacological intervention which is recommended by the National Institute for Clinical Excellence and approved by Food and Drug Administration [12]. Riluzole can slightly mitigate the respiratory failure and increases the survival time up to 3 months. On the contrary, there are no scientific reports about the beneficial role of riluzole on muscle atrophy, wasting, weakness, muscle spasticity, dysarthria, dysphagia and life quality in the ALS patients [12].

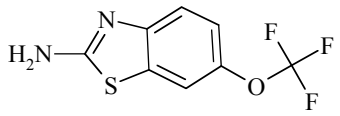

Fig. (1). Chemical structure of riluzole.

On other hand, inasmuch as the potential role of oxidative stress in pathophysiology of ALS, recently much attention has been paid to natural products with high antioxidant potential and low side effects [13].

During last decades extensive research has been performed on plant species, especially some medicinal and culinary species, as a rich source of antioxidant phytochemicals such as polyphenols [14-19]. Polyphenolic compounds (Fig. **2**) can

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be classified into different classes, according to the number of phenolic rings in their structure and the substituents linked to the rings [20, 21]. Especially, there are 4 groups including phenolic acids, phenolic diterpenes, flavonoids, and volatile oils [22]. Phenolic acids are a class of aromatic acids which contain phenolic ring and an organic carboxylic acid moiety in their skeleton [22-25]. The antioxidant effects of phenolic acids are generally the result of their free radicals trapping actions. Terpenophenolic compounds are a type of polyphenolic compounds which contain a terpenoid group and a phenolic ring in their chemical structures [22, 26].

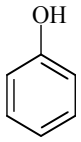


Fig. (2). Basic molecular structure of phenols.

Basic 15-carbon flavan structure is the common characteristic of the flavonoids (Fig. **3**). In the flavonoids structure, carbon atoms are presented in A, B, and C rings [27, 28]. The differences among flavonoids are based on the level of the C ring saturation [27]. However, differences in the substitution pattern of both A and B rings affect antioxidant activity and phenoxyl radical stability of flavonoids [27, 28].

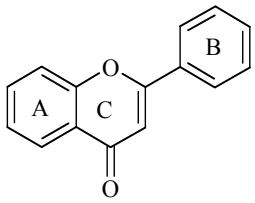


Fig. (3). Basic molecular structure of flavonoids.

There is close correlation between free radical scavenging activity of polyphenolic compounds and both number and location of free −OH groups presented in flavonoid structures [27]. In the flavonols, B ring substitution pattern has a crucial role in the free radical scavenging activity (Fig. **4**) and hydrogen bond force plays a crucial role in their free radical scavenging effects [27, 29].

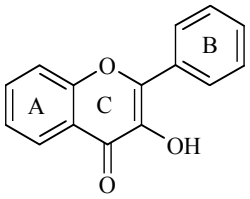


Fig. (4). Basic molecular structure of flavonols.

Finally, there is a close correlation between the number of hydroxyl groups present in the flavonoids skeletons with their antioxidant abilities [27, 29]. Geldof and Engeseth [30] showed that the presence of ortho-3,4-dihydroxy in the flavonoids structures increases their antioxidant capacity. This review aims to critically review and summarize the main scientific findings which indicate the therapeutic potential of natural compounds on ALS. We also discuss on the molecular mechanisms and the potential therapeutic role of these compounds and thereby we offer some recommendation for future studies on ALS.

MATERIALS AND METHODS

Data Sources and Search Strategy

The data for this review were collected through Cochrane databases, Medline, Pubmed, Scopus, Web of Science (ISI Web of Knowledge), Science Direct, Embase, searching these terms: “polyphenols and amyotrophic lateral sclerosis”, “antioxidant and amyotrophic lateral sclerosis”, “traditional herbal medicines and amyotrophic lateral sclerosis”.

Selection Criteria and Data Analysis

Inclusion and exclusion criteria for this review were examined by two authors (MD and SMN). The selected data were extracted and analyzed by two authors (MD and SMN) through the scientific standard of conduct. In general, we opted to consider publications from the past 5 years, but did not neglect highly regarded related publications. Furthermore, we used the reference lists of aforementioned publications and selected those we have judged relevant.

RESULTS AND DISCUSSION

The literature review identified several studies that have evaluated therapeutic role of polyphenols for treatment of ALS. Results showed that there are 8 animal studies, 4 *in vitro* studies, 1 systematic review and 1 unsystematic review (Fig. **5**).

Polyphenols and Amyotrophic Lateral Sclerosis

Ginkgo biloba L.

Ginkgo biloba L. or maidenhair tree is a well-known medicinal plant, native to China, belonging to Ginkgoaceae family, which has long been cultivated in some countries such as Japan, Vietnam and Korea [32]. *Ginkgo biloba* leaves extract is a rich source of some terpene trilactones, called ginkgolides (A, B, Cand J), which differ in the number and position of their hydroxyl groups, and the sesquiterpene trilactone bilobalide. Moreover, in *Ginkgo biloba* extract occurs some flavonol glycosides (such as myricetin, kaempferol, and quercetin) (Fig. **6**) [31]. Proanthocyanidins, carboxylic acids, ginkgolic acids, ginkgols and bilobols and some non-flavonoid glycosides are the other constituents of *Ginkgo biloba* [32],which is known as the most common and popular herbal preparation in the world [31].

According to www.ClinicalTrials.gov and http://www.ncbi.nlm.nih.gov/pubmed, more than 397 clinical studies have evaluated the beneficial role of *Ginkgo biloba* on different human disorders, such as cognitive disorders, memory impairment, dementia, Alzheimer's disease, schizophrenia, pulmonary vascular diseases, migraine aura, brain tumor, sexual dysfunctions, autistic disorders, thyroid carcinoma, blood pressure, metabolic syndrome, migraine, chronic heart

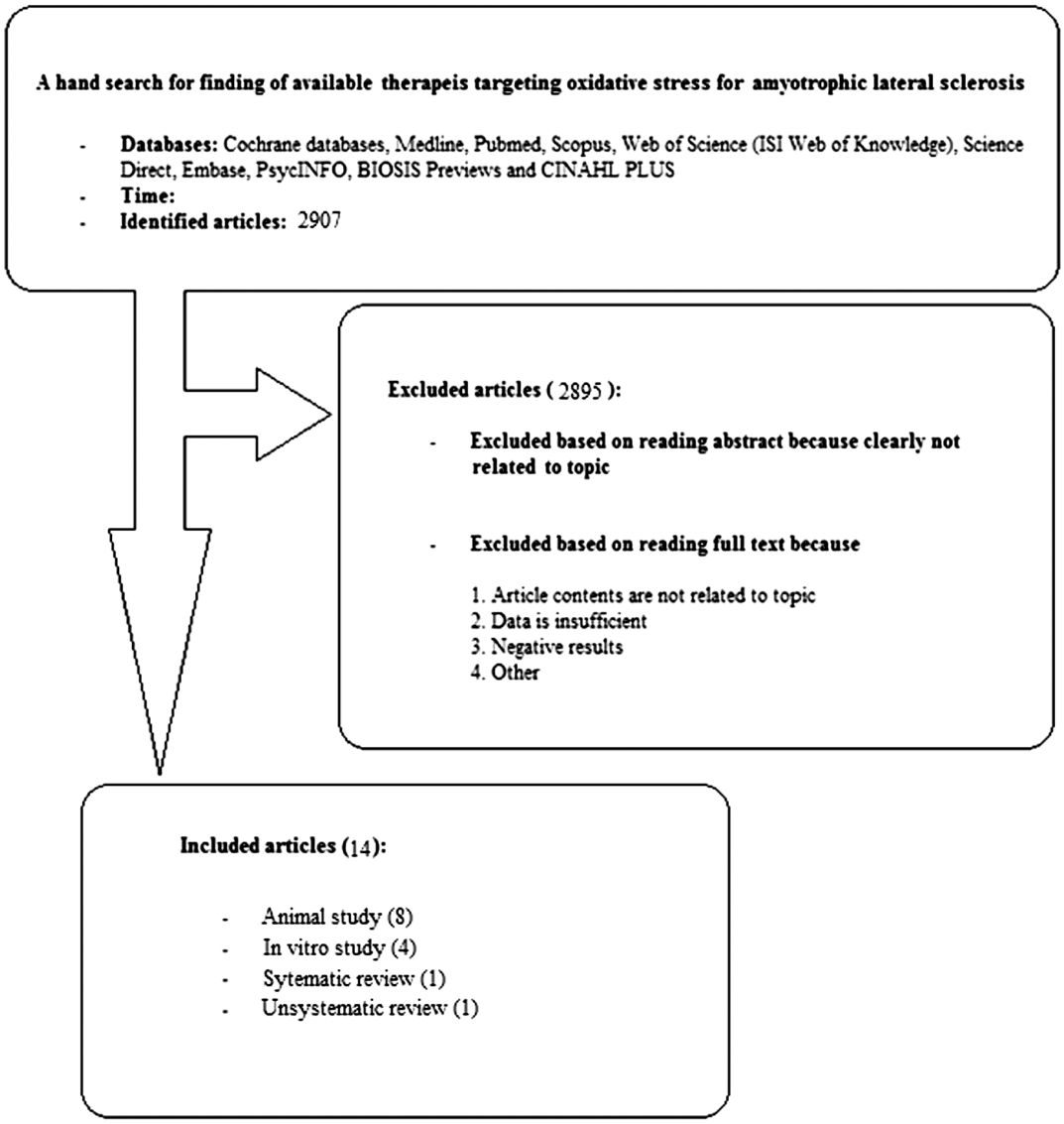


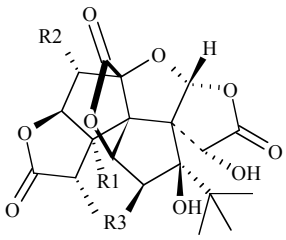
Fig. (5). Data sources and search strategy.

failure, hypertension, premenstrual syndrome, mountain sickness, Graves' disease, hypercholestrolemia, dyslexia, anxiety, hypoxia, acute hemorrhoid attack, equilibrium disorders, circulatory encephalopathy, skin disease, cardiotoxicity, inflammation, type 2 diabetes mellitus, coronary artery disease, depression, ototoxicity, cancers, tardive dyskinesia, vitiligo, Raynaud disease, attention deficit hyperactivity disorder, asthma, peripheral vascular disease, multiple sclerosis, glaucoma, acute ischemic stroke,when given alone or conjunction with dietary compounds.

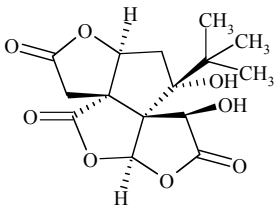
Ferrante *et al*. [33] reported that *Gingko biloba* extract possesses a gender-specific neuroprotective role in transgenic mouse model system (G93A) of ALS. They showed that oral administration of *Gingko biloba* extract significantly mitigates the abnormality in the motor performance and increases the survival time [33]. The same authors [33] also reported that *Gingko biloba* extract significantly decreases the loss of spinal-cord anterior motor horn neurons in the male transgenic ALS mice. They concluded that *Gingko biloba* extract can be used as effective treatment in patients with ALS.

Ginseng

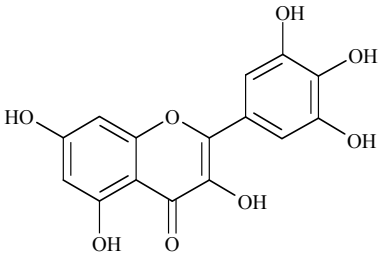
Ginseng, a deciduous perennial plant belonging to the family of Araliaceae, is a very common medicinal herbs from the Panax genus which has a 2000 years history in traditional medicines [34]. There are 13 different species of ginseng throughout the world [35]. *Panax ginseng* C.A. Meyer (Chinese ginseng), which is cultivated in Korea, Japan, China, Russia, and Germany, and *Panax quinquefolius* (American ginseng), which is found in Southern Canada, and United States of America, are the most commonly used species of the Panax genus in the world [35]. It has been reported that ginseng has more than 20 ginsenosides [36]. The main active constituents of ginseng are two types of ginsenosides, i.e. protopanaxatriol and protopanaxadiol (Fig. **7**), which are known as the most pharmacologically active compounds of ginseng [36, 37].



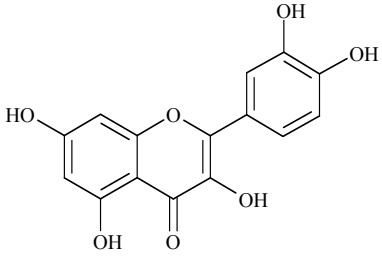
Ginkgolides



Bilobalide



Myricetin

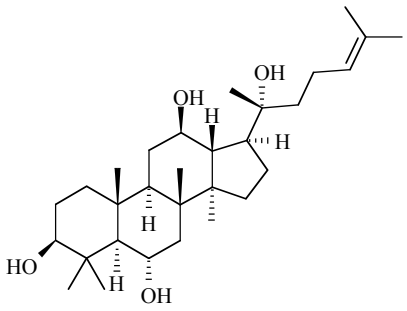


Quercetin

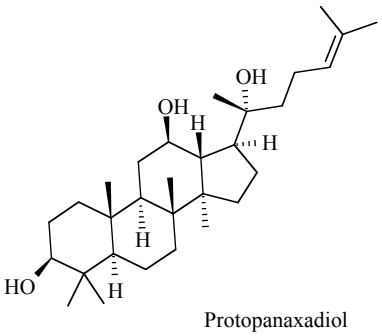
Fig. (6). Chemical structures of some ginkgolides, bilobalide, and some flavonoids (myricetin and quercetin).

Other chemical constituents occurring in ginseng are sugars (i.e. glucose and rhamnose), polysaccharides, peptides, polyacetylenic, alcohols, fatty acids, and some minerals [38, 39]. Numerous scientific reports showed that ginseng has different pharmacological actions such as antioxidant [40], anticancer [41], anti-inflammatory [42], anti-nociceptive [43], neuroprotective [44], and its mechanisms of action include inhibition of DNA damage, regulation of expression of different proinflammatory cytokines and chemokines, induction of apoptosis [45].

Jiang *et al*. [46] reported that 40 and 80 mg/kg of ginseng root extract dissolved in drinking water possesses a beneficial role in B6SJL-TgN(SOD1-G93A)1Gur transgenic mice. They observed that ginseng at the same doses shows similar beneficial role in mitigating the motor impairment as well as increasing survival time in transgenic mouse model of ALS [46]. As regards the potential mechanism of action, the authors reported that the increase in nerve growth factor (NGF) action, the antioxidant effects and an altered nitric oxide level could explain the beneficial effects observed in treated experimental animals, in comparison with controls. They concluded that extract of ginseng root can be used for ALS patients [46].



Protopanaxatriol



Protopanaxadiol

Fig. (7). Chemical structures of the major types of ginseng's ginsenosides, i.e. protopanaxatriol and protopanaxadiol.

Genistein

Genistein (4', 5, 7-trihydroxyisoflavone) is a dietary phytoestrogen which is classified as isoflavone [47]. Genistein is produced by intestinal bacteria from genistein (genistein glucoside) [48]. Structurally, genistein has a heterocyclic diphenolic structure (Fig. **8**) and therefore it can bind toestrogen receptor beta in the cells [49]. Genistein possesses a variety of biological and pharmacological actions such as antioxidant, anticancer, antitumor, antiviral, and antiangiogenic properties [50].

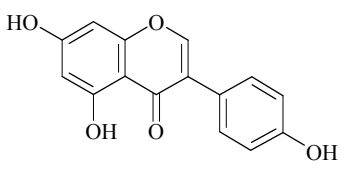


Fig. (8). Chemical structure of genistein.

The inhibition of different tyrosine kinases is the most important molecular mechanism of genistein [51]. Genistein affects different molecular pathways such as activation of

peroxisome proliferator-activated receptors and nuclear factor-like 2 as well as inhibition of topoisomerase, hexose transporter GLUT1, cytosine methylation and DNA methyl transferase [52-54].

Trieu and Uckun [55] reported that genistein at 16 mg/kg (two times per day) delayed the onset of familial ALS and reduced the mortality rate in male human SOD-1 (G93A) mice. However, Trieu and Uckun [55] received negative results from genistein treated females both in the onset of disease and in the mortality rate, which showed that endogenous estrogens probably act *via* common pathways. They concluded that genistein has both estrogenic and non-estrogenic neuroprotective roles and therefore it can be used for familial ALS [55].

Epigallocatechin gallate (EGCG)

EGCG (Fig. **9**), the major flavan-3-ol of green tea, is known as bioactive anticancer natural product in green tea [56].

Despite its scarce stability to digestion and poor bioavailability, EGCG is known as bioactive natural product with a wide range of pharmacological actions such as antioxidant, anticancer, anti-inflammatory activities [57-59]. It has been reported that EGCG, besides its anti-oxidant capacity, affects and alters some molecular targets such as MAPK pathway and activator protein-1 (AP-1) activity, PI3K, angiogenesis through suppressing VEGF phosphorylation, telomerase activity, DNA methyltransferase, dihydrofolate reductase, as well as urokinase-plasminogen activator activity and inhibits the proteasomal chymotrypsin-like and PGPH-like and from this way possesses significant anticancer actions [60-62]. Structurally, pharmacological effects of EGCG may be the result of conjugation of the free hydroxyl groups of EGCG (Fig. **9**) [63].

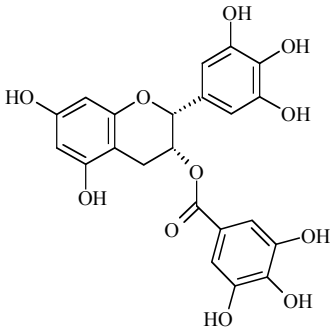


Fig. (9). Chemical structure of epigallocatechingallate.

Xu *et al*. (65) reported that (-)-epigallocatechin-3-gallate has neuroprotective actions in SOD1-G93A transgenic mouse model of ALS. They indicated that oral administration of EGCG at 10 mg/kg significantly delayed the onset of amyotrophic lateral sclerosis and increased the survival times [64]. They also reported that administration of EGCG increased the number of motor neurons, and decreased microglial activation as well as immune-histochemical reaction of nuclear factor-kappaB and cleaved caspase-3 and alsodecreased the protein level of inducible nitric oxide synthase and nuclear factor-kappa B in the spinal cords [64].

Koh *et al*. [65] demonstrated that EGCG possesses a neuroprotective action against oxidative stress-induced apoptosis in both wild type and G93A cells. They reported that EGCG possesses neuroprotection *via* up-regulation of PI3K/Akt and GSK-3 pathways and down-regulation of mitochondrial damage, caspase-3, and PARP [65]. Koh *et al*. concluded that EGCG can serve as potential therapeutic agent for ALS via targeting of oxidative stress [65].

More recently, Koh *et al*. [66] also reported that 60 days orally administration of EGCG at 1.5, 2.9, and 5.8 μg/g body weight per day, shows neuroprotective role in SOD1-G93A mouse model of ALS. They showed that EGCG significantly delayed the onset of ALS symptoms, motor impairment, and increased the survival time [66]. They concluded that the beneficial role of EGCG maybe the result of its influence on different cellular signals i.e. PI3-K and Akt, GKS-3β, cytosolic cytochrome c, cleaved caspase-3, and PARP [66].

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) (Fig. **10**) is a stilbenoid which occurs in red wine, grapes, berries, peanuts, etc. [67]. Pharmacokinetic reports showed that it has high absorption after oral intake (about 75%), but, due to an extensive metabolism, the bioavailability is low (less than 1%) [68, 69]. Despite its low bioavailability, resveratrol possesses a variety of biological and pharmacological actions including antioxidant, antiaging, anti-Alzheimer, antiviral, anti-inflammatory, antidiabetic, anti-ischemic properties and neuroprotective, cardioprotective activities [70, 71]. Also, resveratrol has beneficial effects on different types of cancer such as melanoma, skin cancer, breast cancer, gastric cancer, pancreatic cancer, leukemia, esophageal tumorigenesis, colorectal cancer, lung cancer, prostate cancer, hepatoma, neuroblastoma, fibrosarcoma [72]. Studies focused on its mechanisms of action at molecular level showed that its antioxidant and anti-inflammatory activities play important role in its anticancer effects [73]. It has been reported that the modulation of carcinogen-metabolizing enzymes activities and inhibition of tumor metastasis, angiogenesis and cell proliferation as well as apoptosis induction and chemosensitization are other molecular mechanisms at the basis of the anticancer effects of resveratrol [74].

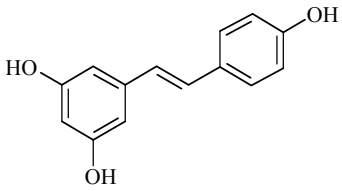


Fig. (10). Chemical structure of resveratrol.

Yáñez *et al*. [75] reported that resveratrol possesses a neuroprotective effect against ALS/cerebrospinal fluid induced neurotoxicity and [Ca(+2)](c) elevation in the brain cortical motor neurons of experimental animals.

Wang *et al*. [76] demonstrated that resveratrol upregulates the sirtuin 1 (SIRT1) expression in the mutant hSOD1-G93A-bearing motor neuron-like cell culture and improves the cell viability and increases the cellular levels of

ATP and prevents from cell apoptosis. Barber *et al*. [77] also reported that resveratrol possesses a protective role in a cell model system of ALS *via* its antioxidant activity.

Markert *et al*. [78] found that resveratrol reduces the severity of ALS via mitigation of abnormality in the p53 acetylation in SOD1 (G93A) mutant mouse model of ALS.

Han *et al*. [79] reported that intraperitoneally administration of resveratrol at 20 mg/kg delays the onset of ALS and improves survival time in G93A-SOD1 transgenic mouse model of ALS, *via* up-regulation of Hsp25 and Hsp70 as well as activation of SIRT1 to deacetylate Heat Shock Factor protein 1 (HSF1).

Mancuso *et al*. [80] demonstrated that treatment with resveratrol significantly delays the onset of ALS as well as improves the lifespan and survival of spinal motoneurons in SOD1G93A transgenic mouse model of amyotrophic lateral sclerosis. These authors found that the beneficial role of resveratrol is associated with up-regulation of Sirtuin 1 and AMPK [80]. They concluded that resveratrol can be served as a promising therapeutic strategy for ALS [80].

CONCLUSION AND RECOMMENDATIONS

In conclusion, there are some natural antioxidant substances which have beneficial effects on amyotrophic lateral sclerosis such as *Ginkgo biloba*, ginseng, genistein, epigallocatechin gallate and resveratrol. Our present review indicates that natural products could be used as new strategy to relieve the severity of ALS symptoms. We also conclude that because of the important role of oxidative stress and long-term inflammation in this pathology, natural substances targeting oxidative stress and inflammation, could be experimented alone or in combination to define new therapeutic methods for the treatment of ALS. Moreover, we showed that natural antioxidant compounds with multi links, multi pathways, or multi targets can be used in modern pharmacology of ALS. For the reasons reported above future studies should focus on the efficacy of natural antioxidants in treatment of amyotrophic lateral sclerosis.

Especially, we recommend that future studies should point their attention on:

- Beneficial role of other natural antioxidants in treatment of ALS.
- Toxicological studies on the active natural antioxidants which have a beneficial effect on this pathology.
- Mechanisms of action at molecular level of the active substances.
- Finding the best effective dose of the active subtances in amyotrophic lateral sclerosis treatment.
- Clinical trials aimed at the definition of their beneficial role in humans.

CONFLICT OF INTEREST

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

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Declared none.

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