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REVIEW ARTICLE

Plant-Derived Natural Compounds for the Treatment of Amyotrophic Lateral Sclerosis: An Update

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Abstract: ***Background*:** Amyotrophic lateral sclerosis (ALS) is a motor neuron disease (MND) that typically causes death within 3-5 years after diagnosis. Regardless of the substantial scientific knowledge accrued more than a century ago, truly effective therapeutic strategies remain distant. Various conventional drugs are being used but are having several adverse effects.

***Objective/Aim*:** The current study aims to thoroughly review plant-derived compounds with well-defined ALS activities and their structure-activity relationships. Moreover, the review also focuses on complex genetics, clinical trials, and the use of natural products that might decrypt the future and novel therapeutics in ALS.

***Methods*:** The collection of data for the compilation of this review work was searched in PubMed Scopus, Google Scholar, and Science Direct.

***Results*:** Results showed that phytochemicals like-Ginkgolides, Protopanaxatriol, Genistein, epigallocatechingallate, resveratrol, cassoside, and others possess Amyotrophic lateral sclerosis (ALS) activity by various mechanisms.

***Conclusion*:** These plant-derived compounds may be considered as supplements for conventional (ALS). Moreover, further preclinical and clinical studies are required to understand the structure-activity relationships, metabolism, absorption, and mechanisms of plant-derived natural agents.

Keywords: Plant-derived products, SOD1 mutations, CNS disorders, SAR, clinical trials, Therapeutic effects.

1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also termed as Lou Gehrig's disease, is an idiopathic, fatal cumulative neurodegenerative disease initiated by motor neurons dysfunction in the spinal cord and brain within weeks or months, which progresses into paralysis and finally death [1, 2]. There is no treatment available to cure this destructive disease. The majority of the deaths in ALS patients occur due to respiratory failure within 3 to 5 years from the onset of various signs and symptoms [3, 4]. The incidence of ALS in Western European countries is 2-3 in 100,000 individuals per year and has a prevalence of 4.6 per 100,000 [5-7]. ALS is more commonly found in men than women, affecting 1.2–1.5 men for every woman [8]. Evidence indicates that the incidence and prevalence are lesser in mixed ancestral origin populations than European people, with differences in age of onset in genetically heterogeneous populations [9]. Compared to Alzheimer's disease, the maximum occurrence of the disease is between the age of 50 to 75 years and decreases after that [7]. However, chances of lower incidences among non-Caucasian populations or American Indians and Eskimos are still controversial, but most epidemiological studies accord with insignificant male/women predominance of 1.2-1.5/1 [10-12].

The etiology of ALS is highly multifactorial [1, 13]. It is associated with multiple cellular pathologies that are restricted to oxidative stress, loss of neurotrophic factors, glutamate-induced excite-toxicity, inflammation, insufficient protein quality control, accumulation and misfolding of proteins, and mitochondrial dysfunction [14, 15]. The clinical manifestations of sporadic amyotrophic lateral sclerosis (sALS) and familial amyotrophic lateral sclerosis (fALS) are almost very similar, and the median age of onset of sALS is around

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60 years, and the age of onset for fALS is about ten years earlier than sALS. In juvenile ALS (JALS) families, mutations in *ALS2* and *SETX* genes have been reported [16, 17].

Due to the secondary phenomena, deficiencies in a few of these pathways occur. To identify the primary pathophysiological processes underlying ALS, genetics would be the rational primary perspective. The ALS shows genetic predisposition, about 5-15% of patients diagnosed with ALS have a family history of the disease. A single defect in genetics is believed to lead ALS [18, 19]. While most people lack family background of ALS, in such cases, it is accepted that both genetic and environmental risk factors contribute to the development of disease [20]. Several genetic risk factors have been recognised that are involved in sporadic ALS. However, environmental risk factors exploration has been less successful. Many genetic and molecular pathways are most likely responsible for developing and progressing neurodegenerative changes in ALS.

Several pathological pathways have been suggested, yet no authenticated target for researchers while designing new molecules to impact the disease has been evidenced. To date, various molecules have failed in clinical trials so far while targeting the above-mentioned potential pathways. Thus, attempts carried in this field so far have not provided any success in new drug development [15]. Therefore, to successfully develop new medicine that will change the motor neuron degeneration process, several pathways need to be targeted due to the involvement of multiple pathways. Despite various preclinical and clinical studies, the accurate pathway of pathogenesis and progression of ALS is still not fully known. Thus, the development of successful and targeted therapy is challenging and is a major problem faced by scientists to treat ALS. Over the past two decades, the only FDA approved drug is riluzole, an anti-glutamatergic agent that acts by blocking glutamatergic neurotransmission in the CNS. However, riluzole's efficacy is questionable, without any effects on disease symptoms and nominal therapeutic benefits of about 2-3 months of survival increase in ALS patients [21, 22]. After 22 years, another drug, edaravone, a free radical scavenging agent, was approved by FDA in May 2017, which was found to be effective in slowing ALS progression but its mechanistic pathway in ALS is not fully known yet [23, 24].

2. MATERIALS AND METHODS

2.1. Data Sources and Search Strategy

Databases like Scopus, Science Direct, Pubmed, Google Scholar, Web of Science were used to collect literature for the compilation of the present review by searching the terms including plant-derived bioactive compounds against (excitatory amino acid toxicity, neuroinflammation, calcium cytotoxicity and oxidative stress) in amyotrophic lateral sclerosis, traditional herbal medicines and.

3. PLANT-DERIVED NATURAL COMPOUNDS FOR THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Regardless of the fact that drug design and discovery have a high reliance on synthetic chemistry, the contribution of natural products cannot be ignored [25-30]. WHO's list of essential drugs consists of 252, of which 11% are of plant origin [31]. So, there is an absolute chance of finding a natural molecule having desired ALS activity. The phytochemicals, including flavonoids, alkaloids, terpenes, and saponins from plant sources may instill positive change, which researchers are looking for, as they possess unique chemical diversity. Some of these cannot be synthesized by currently known methods [30, 32]. As a result, these natural compounds as novel drug molecules for ALS treatment remain untapped. Different scientific reports have focused on the validation of the phytoconstituents isolated from various medicinal plants. Scientific investigations claiming various phytochemicals as ameliorative agents in ALS are limited. However, some key findings have demonstrated flavonoids, alkaloids, terpenes, and saponins isolated from multiple medicinal plants exhibit ALS activity. In this review, we have discussed the potential of various plant origin phytochemicals for the treatment of ALS. This review will try to understand the mechanism of action of selected molecules (Fig. **1**), and *in vivo* and *in vitro* activities of these Phytoconstituents will also be covered.

3.1. Phytochemicals Acting against Oxidative Stress

Oxidative stress imparts a major role in the process of neurodegeneration and is one of the most common pathways of all neurodegenerative diseases [33-36]. The death of neurons occurs mainly due to increases in the reactive oxygen species (ROS) generation and malfunctioning of the antioxidative system [37]. Herbal medicines impart a prospective role in oxidative stress regulation by improving the antioxidant activity of various enzymatic and non-enzymatic systems, decreasing the levels of (ROS) and maintaining the expression and regulation of various genes involved in ALS [38, 39]. **Madecassoside,** isolated from *Centella asiatica* is a triterpenoid saponin. It has been reported that in ALS involving transgenic SOD1-G93A mice model, madecassoside safeguards the motor neurons from degeneration and increases the survival time of mice. In another study, it was revealed that madecassoside reduces malondialdehyde levels and enhances the activity of SOD in the brain. In ALS mouse model, madecassoside protects the neurons from apoptosis due to free radicals by increasing the antioxidant activity. It has also been reported that madecassoside improves the LPS mediated neurotoxicity in rats by upregulating the Nrf2-HO pathway [40-44]. **Ampelopsin,** isolated from *Ampelopsis grossedentata,* belongs to the flavonoid class and exhibits prominent antioxidant activity. It has been reported that ampelopsin showed neuroprotective effects against H_2O_2-induced apoptosis in PC 12 cells by suppressing the ROS generation, upregulating the expression of HO-1 protein and hampering the expression of caspase-3. Moreover, in PC-12 cells, 1/2 (ERK1/2) and Akt-dependent signalling pathways play a role in the HO-1 protein upregulation. The studies suggested that ampelopsin could be a strong candidate in the ministration of various neurodegenerative diseases, including ALS [45-48]. **Epigallocatechin gallate (EGCG),** isolated from green tea, is its main constituent and is a water-soluble polyphenolic compound. It was reported to have strong antioxidant activity, besides acting as a radical scavenger mediating antioxidant activity in various neurodegenerative diseases, including ALS. The antioxidant activity of (EGCG)

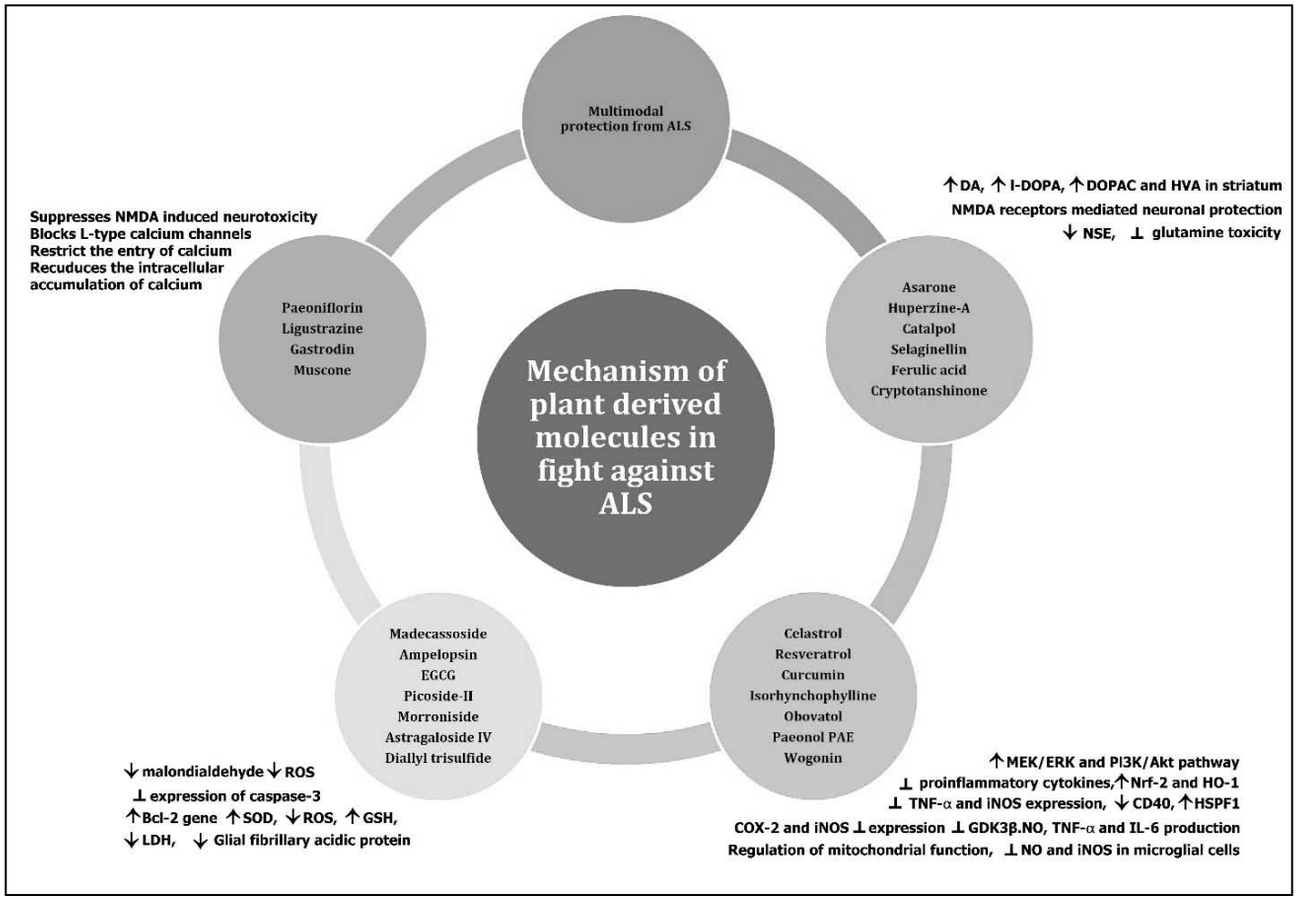

Fig. (1). Plant derived natural compounds for the treatment Amyotrophic Lateral Sclerosis. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

against ALS was further evaluated in transgenic SOD1 mice, where it slows down the beginning of symptoms and prolongs the lifespan. Moreover, upregulation of Bcl-2 gene, which is an anti-apoptotic gene, was also detected with (EGCG), suggesting the antioxidant activity of (EGCG) in ALS is associated with the upregulation of Bcl-2 gene [49-56]. **Picroside-II,** isolated from *Picrorhi zarhizoma* is a type of iridoid glycoside that is widely found in Tibet as well as in India. It was reported that in PC-12 cells, picroside-II strengths nerve growth factor (NGF) mediated neurite outgrowth besides acting synergistically against oxidative stress. Due to their synergistic effect, they are used to manage various nervous disorders, including ALS. Moreover, the neuroprotective activity against oxidative stress of picroside-II was also evaluated in various models, including *in vitro* model of glutamate-treated PC12 cells and *in vivo* model of $AlCl_3$-induced male mice. Picroside -II also enhances the SOD levels in the brain of mice which results in suppression of ROS generation depicting picroside-II protects the brain from a neuronal injury that occurs due to oxidative stress [57-60]. **Morroniside**, isolated from *Cornus officinalis* is a type of iridoid glycoside reported to have a strong neuroprotective activity against oxidative stress. It was also reported that in SH-SY5Y cells, when exposed to H_2O_2-mediated cytotoxicity, Morroniside elevates the levels of cellular GSH and reduces the levels of lactate dehydrogenase (LDH), besides maintaining the Matrix metalloproteinases (MMP) and cell stability. Moreover, it suppresses the intracellular activity of SOD and ROS generation. In addition, Upregulation of Bcl-2 genes was also reported, which confirms the anti-apoptotic and anti-oxidative activity of this compound [61-65]. **Astragaloside IV**, a saponin isolated from *Radix astragali,* is generally used for ALS treatment in China and is reported to have a strong antioxidant activity in various *In-vitro* and *in-vivo* studies. Astragaloside IV also showed a protective role against H_2O_2 mediated oxidative stress in PC-12 cells. Moreover, it also improves the viability of PC-12 cells, activation of HO-1, suppresses the intracellular production of ROS as well as apoptotic cell death [66-70]. **Diallyl trisulfide (DATS)**, an active monomer of allicin isolated from bulbs of *Liliaceae allium,* was reported to exhibit diverse pharmacological activity owing to its capability to pass through the (BBB). It was reported that (DATS) acts as an inducer of phase II enzymes resulting in the amelioration of oxidative stress besides safeguards the activity of various antioxidant enzymes, thus imparting an important role in ALS. Diallyl trisulfide acts *via* multiple pathways in ALS, including activating the heme oxygenase-1 (HO-1), down-regulating the expression of glial fibrillary acidic protein, activating the antioxidant activity of various enzymes [71-76].The various plant-derived phytochemicals (Fig. **2**), along with their diverse mechanistic insights against oxidative stress, are shown in Table **1**.

Table 1. Phytochemicals along with their diverse mechanistic insights against oxidative stress in ALS.

Phytochemical Constituent	Study Type Cellular/Animal/ Clinical	Study Description	Mechanism	Refs.
Madecassoside (1)	*In-vivo* (Transgenic mice SOD1-G93A)	Two dissimilar doses of 61.1 ± 11.0 and 185.6 ±18.7mg/kg/day, markedly increased the time of survival in mice by 11 and 9 days, respectively	Increase the mice survival time and reduces the malondialdehyde levels, and enhances the SOD activity in the brain	[40]
Ampelopsin (2)	*In-vitro* (PC12 cells)	Ampelopsin Neuroprotective effect against H_2O_2-induced cell death in PC12 cells is well observed.	Suppressing the production of ROS, upregulating the expression of HO-1 protein and hampering the expression of caspase-3	[45, 47]
Epigallocatechin gallate (EGCG) (3)	*In-vivo* Transgenic mice SOD1-G93A	EGCG given in doses of 1.5, 2.9, 5.8 µg/g body weight after 60 days of age suggest that it significantly delays the disease onset by 1.4weeks and prolongs the survival time by 1.8 weeks.	upregulation of Bcl-2 gene	[49]
Picroside-II (4)	*In-vitro* PC12 cells *In-vivo* mice AlCl3-induced toxicity	Neuroprotective action of picroside-II has been observed in glutamate-treated PC12 cells and improved SOD activity in the brain of mice	Enhances the SOD levels in the brain of mice, suppression of ROS generation	[58]
Morroniside (5)	*In-vitro* SH-SY5Y cells	Morroniside exhibits both anti-oxidative and anti-apoptotic properties against oxidative stress-induced cell damage	Elevates the levels of cellular GSH and reduce the levels of (LDH), Upregulation of Bcl- 2 genes	[62]
Astragaloside IV (6)	*In-vitro* PC12 cells	It enhances neuronal cellular viability *in vitro*, decreases intracellular production of ROS induced by H2O2 and improves cell survival.	Activation of HO-1 suppresses the intracellular production of ROS	[66]
Diallyl trisulfide (DATS) (7)	*In-vivo* Transgenic mice SOD1-G93A	A dose of 80 mg/kg/day significantly improves life span by 1week	Activating the heme oxygenase-1 (HO-1) Downregulating the expression of glial fibrillary acidic protein	[72]

3.2. Phytochemicals Acting against Neuroinflammation

A strong correlation exists between inflammation and various CNS disorders, particularly ALS. Microglia cells in the CNS impart an essential role in ALS pathogenesis due to their primary role in the release of various pro-inflammatory factors, including (TNF-α), (iNOS), (COX-2). So, one of the targets for ALS involves decreasing the activation of microglia cells, which in turn, inhibits neuroinflammation [77-80]. **Celastrol**, isolated from *Tripterygium wilfordii,* is a triterpenoid pigment that inhibits cancer cell proliferation and inflammation-related various auto-immune diseases. In transgenic mice, SOD1-G93A model of ALS, Celastrol suppresses (TNF-α) and (iNOS) expression, decreased the expression of CD40 and glial fibrillary acidic protein in the lumbar spinal cord section of mice, resulting in delayed onset of disease and improvement in the motor function. Moreover, it was observed that celastrol at the molecular level inhibits LPS mediated activation of mitogen-activated protein kinase/ERK1/2 signaling pathway and (NF-kB), which plays a vital role in the damage to cells and stress. So celastrol suppresses the activation of microglia cells that further

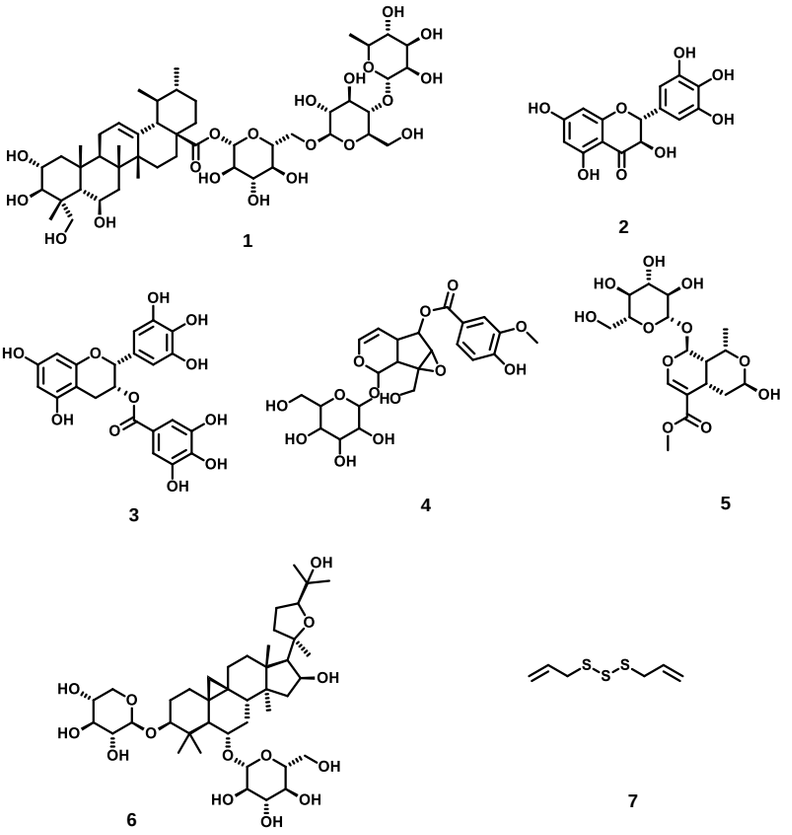

Fig. (2). Phytochemicals against oxidative stress in ALS **(1)** Madecassoside (**2**) Ampelopsin (**3**) Epigallocatechin gallate (EGCG) (**4**) Picroside-II (**5**) Morroniside (**6**) Astragaloside IV (**7**) Diallyl trisulfide (DATS).

decreases the generation of pro-inflammatory cytokines [81-86]. **Resveratrol**, mainly isolated from *Veratrum nigrum* and *Rhizoma polygoni,* is a type of flavonoid (polyhydroxy) diphenyl ethylene, and has intense antioxidant activity due to various hydroxyl groups. Studies also revealed that resveratrol inhibits the release of pro-inflammatory cytokines instigated by LPS in mouse N-9 microglial and rat cortical microglia cells, besides inhibiting the degradation of IkBα and iNOS N-9 microglial cells expression, disclosing the role of resveratrol in the amelioration of various neurodegenerative disease including ALS [87-94]. **Curcumin**, isolated from *Curcuma longa,* is a polyphenolic monomer known for its neuroprotective and anti-inflammatory activity. In LPS stimulated microglia cells, curcumin suppresses the release of nitric oxide and iNOS expression. Moreover, curcumin also upregulates the expression of (Nrf-2) and (HO-1), exhibiting strong neuroprotective activity during inflammatory stress. The neuroprotective role of curcumin in ALS has also been reported due to the downregulation of NF-kB signaling pathway, which suppresses the pro-inflammatory cytokines, including IL-6, IL-1, and TNF-α [39, 95-100]. **Isorhynchophylline (IRN)**, isolated from *Uncaria rhynchophylla,* has been reported to exhibit strong neuroprotective activity due to its ability to inhibit cytokine release like IL-6, IL-1, and TNF-α in LPS stimulated microglial cells. Moreover, the synthesis of inflammatory mediators and expression of mRNA and iNOS has also been reduced by IRN, which impart an essential role in various neurodegenerative disease, including ALS [101-103]. **Obovatol**, isolated from *Magnolia officinalis* leaves, is a type of neolignan. The neuroprotective activity of obovatol has been examined in various models of neuroinflammation mediated by LPS. It has also been reported that obovatol suppresses the release of NO and iNOS in microglial cells by inhibiting the signaling pathways of mitogen-activated protein kinase and NF-kB, besides one of the primary molecular targets of obovatol in microglia is Peroxiredoxin 2 (Prx2), which played an essential role in the various signalling pathways of neuroinflammation [104-106]. **Paeonol,** isolated from the bark of *Paeonia suffruticosa,* acts as a neuroprotective agent by inhibiting inflammation mediated by microglia as well as oxidative stress. In LPS induced inflammation in cortical neurons, paeonol downregulates the expression of COX-2 and iNOS, which results in reduced production of ROS and NO. Moreover, the phosphorylation of ERK induced by LPS was also suppressed by paeonol, which results in an increase in cell viability [107-109]. **Wogonin,** isolated from the *Scutellaria root,* acts as a neuroprotective agent by inhibiting the NO, TNF-α, and IL-6 production. Furthermore, wogonin also shows neuroprotective activity in LPS induced microglia injury by suppressing the various mediators of inflammation [110-112]. The various plant-derived phytochemicals (Fig. **3**), along with their diverse mechanistic insights against neuroinflammation, are shown in Table **2**.

3.3. Phytochemicals Acting against Calcium Cytotoxicity

One of the prime factors that are involved in ALS is calcium toxicity. When the calcium channels are opened up, a massive influx of calcium *via* NMDA receptors piles up in the nuclear cell membrane. This results in nerve cell damage

Table 2. Phytochemicals along with their diverse mechanistic insights against neuroinflammation in ALS.

Phytochemical constituent	Study type Cellular/Animal/clinical	Description of Study	Mechanism	Refs.
Celastrol (8)	G93A SOD1 transgenic mouse model of ALS	Transgenic mice were transfected with NSC34 cells and then treated with hydrogen peroxide and celastrol at different doses	Activation in MEK/ERK and PI3K/Akt pathway	[82, 113, 114]
	Transgenic mouse model of ALS	Celastrol was administered to the mice at 30 days of age, and reduction in body weight, improvement in motor function along with delayed onset of ALS was achieved.	Suppresses the TNF-α and iNOS expression Down-regulated the expression of CD40	
	SH-SY5Y neuronal cell model	There was Increased induction of Heat shock proteins (HSPs) after Co-application of celastrol and arimoclomol	Activation of HSPF1.	
Resveratrol (9)	Rat cortical neuron cell model	Cell survival increased up to 75 % on the application of RSV with protection against neurodegeneration	Inhibits the release of pro-inflammatory cytokines	[88, 91, 93, 115-118]
	VSC 4.1 hybrid cell line	Mutant SOD1 expression was induced in the cell line, and on administration of RSV, the cell survival was enhanced with respect to dose, and at highest dose of RSV, cell survival was fully restored.		
	Transgenic SOD mice model	Intraperitoneal administration of RSV led to a significant reduction in motor neuron death along with increased survival rates		
Curcumin (10)	Motor neuron Cell model	Cell line transfected with mutant Q331K and wild TDP43 was treated with curcumin that led to altered membrane permeability of neurons.	Upregulates the expression of (Nrf-2) and (HO-1)	[39, 99, 119]
	Double-blind therapeutic trial for 42 patients	Patients were divided into Group A & B. group A received a placebo for three months followed by curcumin for other three months, while Group B received curcumin for six months		
Isorhynchophylline (IRN) (11)	BM-hMSCs model	Regulation of the intracellular pluripotency mechanisms was examined.	Regulation of mitochondrial function, NMDA subunit, FGFβ levels, BDNF, OXTR, ATP, BM-MSC proliferation and differentiation.	[101, 102, 120, 121]
	Mouse N9 microglial cells	Inhibitory tendencies of RIN and IRN against cytokines and NO were a point of focus	Inhibits the pro-inflammatory cytokines release in LPS stimulated microglial cells	
Obovatol (12)	Microglia BV-2 cell line	LPS induced stimulation was carried out in the cell line to mark changes with respect to NO, cytokines, along with activation of signalling cascades.	Suppresses the release of NO and iNOS in microglial cells	[104, 122, 123]
Paeonol PAE (13)	N9 microglia cell model	Role of PAE in the production of pro-inflammatory markers in LPS stimulated microglia cells and proteins formed in immune signalling cascade were observed	Downregulates the COX-2 and iNOS expression. Involvement of TLR4 signalling pathway to reduce the expression of TRAF6, MAPK molecules, etc.	[107, 109]
Wogonin (14)	SH-SY5Y cells	Aβ changes were observed in the cell line with treatment by wogonin.	GSK3β inhibition *via* the mediation of mTOR signalling pathway	[110, 124, 125]
	Microglia cell	Lps stimulated microglial cells were subjected to treatment to monitor changes with regard to TNF, NO and IL-6.	Inhibiting the NO, TNF-α, and IL-6production.	

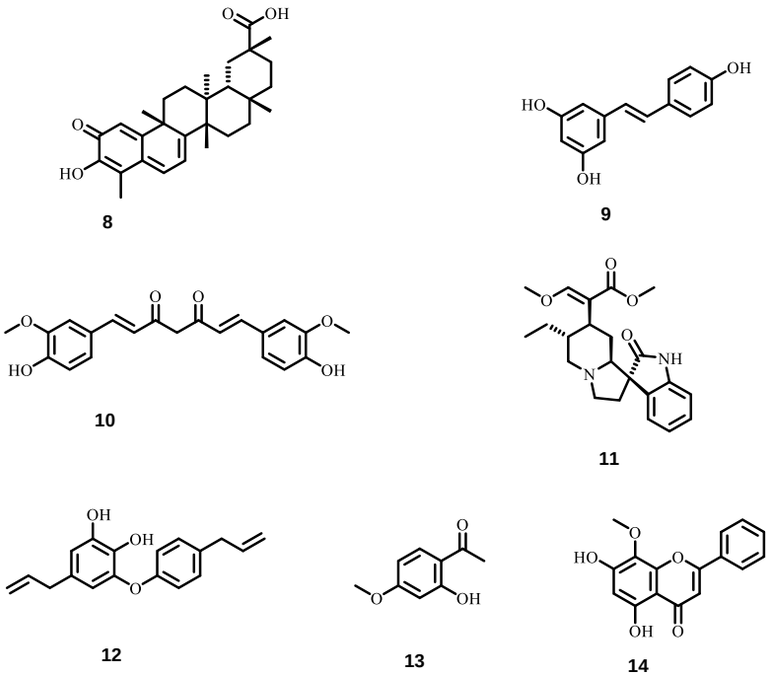

Fig. (3). Phytochemicals against neuroinflammation in ALS (**8**) Celastrol (**9**) Resveratrol (**10**) Curcumin (**11**) Isorhynchophylline (IRN) (**12**) Obovatol (**13**) Paeonol (**14**) Wogonin.

and even death of cells. Nowadays, the focus shifts to herbal medicines to find a phytochemical that can be beneficial in treating ALS [126-128]. **Paeoniflorin,** isolated from *Paeoniae radix*, has an essential role as a neuroprotective agent in ALS management by inhibiting the influx of calcium in cytoplasm in PC12 cell-injury models. Moreover, it also inhibits the extra intracellular level of calcium which is generated due to glutamate and suppresses the apoptosis in PC-12 cells. Further, in PC-12 cells, Paeoniflorin shows its neuroprotective effect by suppressing NMDA induced neurotoxicity [129-134]. **Ligustrazine,** isolated from *Rhizoma chuanxiong*, is known for its neuroprotective activity by blocking calcium channels. It has been reported that in SH-SY5Y cells, ligustrazine blocks L-type calcium channels, which impart a vital role in neurotoxicity development in ALS [135, 136]. **Gastrodin**, isolated from *Gastrodia elata,* can cross the (BBB) and exert its effect on CNS. In SH-SY5Y cells, Gastrodin was reported to limit calcium entry *via* acting on voltage-gated calcium channels, inhibiting the degeneration of neurons due to calcium toxicity [137-139]. **Muscone,** obtained from natural muskies, is its principal active component. In PC12 cells stimulated with glutamate, muscone administration exhibits its neuroprotective activity by reducing the intracellular accumulation of calcium [140]. The various plant-derived phytochemicals (Fig. **4**), along with their diverse mechanistic insights against calcium cytotoxicity, are shown in Table **3**.

3.4. Phytochemical Acting against Excitatory Amino Acid Toxicity

The primary excitatory neurotransmitter in the CNS is glutamate. To maintain the optimum level of glutamate, various metabolic enzymes, as well as transporters, are available, failure in the function of which leads to excessive accumulation of glutamate in the CNS resulting in various nervous disorders, including ALS [141-143]. Different phytochemicals are involved in maintaining the optimum level of glutamate in CNS, which include: **β-Asarone**, isolated from *Acorus tatarinowii,* acts as a neuroprotective agent due to its ability to cross the (BBB). It was reported that in ALS, β-Asarone suppresses (NMDA) or produces glutamate-induced excitotoxicity. Moreover, in PC-12 cells, β-Asarone increases the survival rate of cells, reduces the leakage of LDH, apoptosis ratio, and intracellular accumulation of calcium [144-147]. **Huperzine-A**, isolated from *Huperzia serrata,* is a novel alkaloid commonly used in the treatment of Alzheimer's disease due to its ability to block glutamate-mediated neurotransmission. (Hup A) also inhibits glutamate toxicity by blocking NMDA receptors. In patients with ALS, (Hup A) acts as a neuroprotective agent by preventing damage to motor neurons [56, 148-150]. **Catalpol**, isolated from *Rehmannia glutinosa,* acts as a neuroprotective agent in various neurological disease, including ALS, by suppressing glutamate excitotoxicity. Moreover, it also increases the viability of cells, protects the neurons from various damages mediated *via* NMDA receptors [151-153]. **Selaginellin**, isolated from *Saussurea pulvinata,* exhibits neuroprotective activity in PC-12 cells by suppressing glutamate toxicity. It also decreases the ROS generation and expression of klotho gene [154-156]. **Ferulic acid**, a phenolic acid monomer mainly present in Chinese herbs, including angelica and Szechwan, crosses the BBB with ease. It shows its neuroprotective activity by preventing damage to neurons due to glutamate excitotoxicity and apoptosis in cortical neurons. Furthermore, it also protects the *In-vitro* PC-12 cells from hypoxia, free radicals, and excitatory amino acids [157-160]. **Cryptotanshinone,** isolated from *Salvia miltiorrhiza,* suppresses glutamate toxicity by activating phosphoinositide 3-kinase signalling pathway and inhibiting the downregulation of Bcl-2, an anti-apoptotic protein. The PI3K/Akt pathway

Table 3. Phytochemicals along with their diverse mechanistic insights against calcium cytotoxicity in ALS.

Phytochemical Constituent	Study Type Cellular/Animal/clinical	Study Description	Mechanism	Refs.
Paeoniflorin (15)	*In-vitro* PC12 cells	Paeoniflorin reverses the amplified intracellular levels of calcium level caused by excitatory glutamate and reduced PC12 cell death in a dose-dependent manner	Suppressing NMDA induced neurotoxicity	[129]
Ligustrazine (16)	*In-vitro* SH-SY5Y cells	Whole-cell patch-clamp technique demonstrated that in the nervous system, there is inhibitory action on the calcium channel due to ligustrazine	Blocks L-type calcium channels	[135]
Gastrodin (17)	*In-vitro* SH-SY5Y cells	The free calcium accumulation can be suppressed by Gastrodin, inhibits the enhanced glutamate to protect neurons	Restricted the entry of calcium by acting on voltage-gated calcium channels	[139]
Muscone (18)	*In-vitro* PC12 cells	It suppresses the calcium overload-induced by glutamate and prevents neuronal cell death	Reducing the intracellular accumulation of calcium	[140]

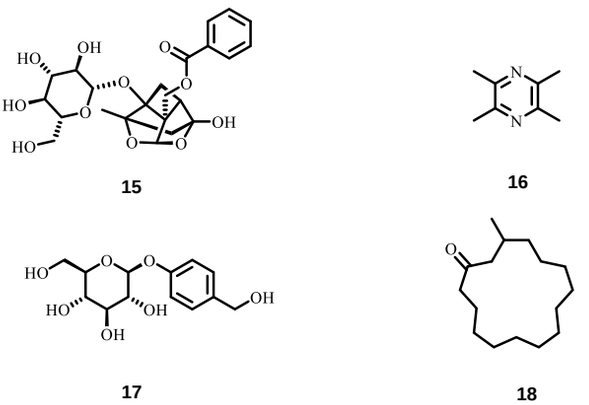

Fig. (4). Phytochemicals against calcium cytotoxicity in ALS **(15)** Paeoniflorin (**16**) Ligustrazine (**17**) Gastrodin (**18**) Muscone.

plays an important role in controlling the pathogenesis of ALS [161, 162]. The various plant-derived phytochemicals (Fig. **5**), along with their diverse mechanistic insights against excitatory amino acid toxicity, are shown in Table **4**.

CONCLUSION

There is currently only one drug available in the market approved by FDA in the treatment of ALS. However, various attempts have been carried out to develop an efficient therapeutic agent against ALS. Majority of the drugs passed the preclinical animal studies, but the results are not promising in human clinical trials. Herbal medicines, on the other hand, act as an alternative and complementary medicinal approach for ALS treatment. The phytochemicals, including flavonoids, alkaloids, terpenes, and saponins from plant sources may instill positive change, which researchers are looking for, as they possess unique chemical diversity. Some of these cannot be synthesized by currently known methods. As a result, these natural compounds as novel drug molecules for ALS treatment remain untapped. Different scientific reports have focused on the validation of the Phytoconstituents isolated from various medicinal plants. The phytochemicals isolated from herbal medicines act *via* multiple pathways, including an antioxidant, anti-inflammatory and an anti-apoptotic agent in ALS. The requirement of natural products to be used in the treatment of ALS has increased because of their safety and efficacy compared to conventional drugs as an alternative treatment measure. The review explains that natural products could be used as a new approach in relieving the intensity of various ALS symptoms. In addition, the review mentions that natural antioxidant compounds with multi targets, multi links, or multi pathways that can be used in the modern pharmacology of ALS. However, all these data underline the importance of testing the tolerability and efficacy of natural products to ameliorate the symptoms or disease progression in ALS in the context of controlled clinical trials.

Table 4. Phytochemicals with diverse mechanistic insights against excitatory amino acid toxicity in ALS.

Phytochemical Constituent	Study type Cellular/Animal/Clinical	Description of Study	Mechanism	Refs.
β-Asarone (19)	*In-vitro* Cultured rat cortical cells	Anti-excitotoxicity effect of isolated α & β asarone as compared to commercially available asarone.	Suppresses (NMDA) or glutamate-induced excitotoxicity	[44, 144, 145, 163]
	In-vivo PD rat model	6-OHDA was used to induce Parkinson's disease in rats that were divided into different groups like untreated, l-dopa, β-asarone and co-administered l-dopa and β-asarone.	Downregulation of NSE and improved levels of DA, l-DOPA, DOPAC and HVA in striatum.	
Huperzine-A (20)	*In-vitro* NSC34 and rat spinal cord organotypic culture	Inducers like staurosporine, hydrogen peroxide, CCCP, THA etc. were used in a cell line, and the effects of huperazine A were noted	Inhibits glutamate toxicity by blocking NMDA receptors	[149]
Catalpol (21)	*In-vitro* PC12 cell lines	Effect of catalpol was observed against Cell injury induced by glutamate	Protects the neurons from various damages mediated *via* NMDA receptors	[44, 120, 151, 152]
Selaginellin (22)	*In-vitro* PC12 cells	Glutamate induced excitotoxicity in PC12 cells was exposed with selaginellin administration	Decreases the ROS generation and expression of klotho gene	[155, 164]
Ferulic acid (23)	*In-vitro* PC12 cells	The protective effects against hypoxia and excitotoxicity were monitored.	Preventing the damage to neurons due to glutamate excitotoxicity and apoptosis in cortical neurons.	[44, 157, 165]
	In-vivo Male Sprague Dawley rat	Protective effects of ferulic acid against hypoxia-induced cerebral injury was the focus of the study	TLR and MyD88 pathways inactivation	
Cryptotanshinone (24)	*In-vitro* Rat cortical neurons	Glutamate was used to entice neurotoxicity in a cell line.	Activating phosphoinositide 3-kinase pathway and inhibiting the downregulating Bcl-2, an anti-apoptotic protein	[120, 161, 162]

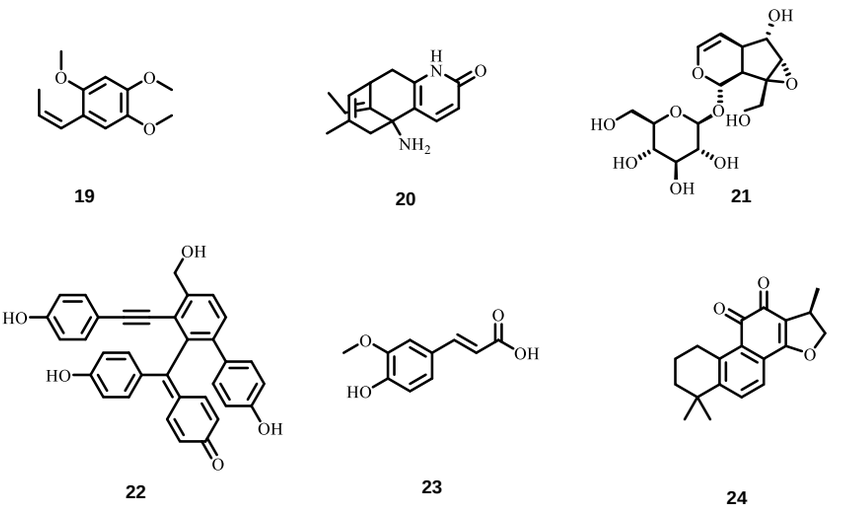

Fig. (5). Phytochemicals against excitatory amino acid toxicity in ALS (**19**) β-Asarone (**20**) Huperzine-A (**21**) Catalpol (**22**) Selaginellin (**23**) Ferulic acid (**24**) Cryptotanshinone.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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