Neuroprotective Effects of Medicinal Plants and Their Constituents on Different Induced Neurotoxicity Methods: A Review

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ABSTRACT

In the traditional medicine, numerous plants have been used to treat cognitive disorders. Natural products play an essential role in prevention and therapy of various neurodegenerative diseases, and neuronal dysfunctions. Different studies suggest that natural products, such as polyphenolic and alkaloids compounds that isolated from plants potentially delayed the neurodegeneration and also improve memory and cognitive function. Ethnomedical sources have provided information to identify potential new drugs from plant sources. Recently many drugs which available in medicine were originally isolated from plants or their constituents including, anticholinesterase (Anti-ChE) alkaloids isolated from plants have been investigated for their potential in the treatment of Alzheimer's disease (AD). Anti-inflammatory and antioxidant activities of plants and isolated components form plants were used in improvement neuro-inflammation, anxiety, convulsion and etc. Medicinal plants have beneficial properties due to presence of various complex chemical substances for treatment of toxicity in the nervous system. This review article evaluated the some of the medicinal plants and their active constituents that have been used in different methods induced neurotoxicity.

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Introduction

In the neurodegenerative diseases, central nervous system (CNS) are lost leading to either functional loss or sensory dysfunction [1]. Nowadays, these diseases, which are associated with different multifactorial etiologies, have created massive medical, social, and financial problems [2]. The pathological signs of neurodegenerative disorders are aging, disability and mortality. The neurodegenerative diseases are including Alzheimer’s Disease (AD), Parkinson’s disease (PD), Multiple Sclerosis (MS) and etc. [1, 2]. Irreversible memory impairment, cognitive and behavioral disturbances are prevalent AD symptoms [3].

Pathologic processes including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and genetic factors lead to neuronal degeneration in PD [4]. Laboratory analysis of patients brain have shown that elevated lipid peroxidation may destroy cholinergic neurons in AD [5] and dopaminergic neurons in PD [6]. There are different antioxidants in the brain, like superoxide dismutase (SOD) as enzymatic antioxidant [7] and thiol containing molecules such as glutathione (GSH) as non-enzymatic antioxidant [8]. CNS which contains high level of polyunsaturated fatty acids is more sensitive to peroxidation reactions (9). But, CNS is not particularly enriched in antioxidant defenses. Human brain has high levels of ascorbate in general and iron in certain regions. Actually, antioxidant activity of the brain is lower than other tissues. So, neural cells are more susceptible than other tissues to oxidative damage [9].

In herbal medicine, plant organs including: leaves, stems, roots, flowers, fruits and seeds were used as alternative and complementary therapy. Some herbs which are include resveratrol, curcumin, ginsenoside, polyphenols, triptolide, etc. which have neuroprotective characteristic [10]. Herbal products contain of complex active components or phytochemicals like flavonoids, alkaloids and isoprenoids. Therefore, it is frequently difficult to determine which component(s) of the herb(s) has more biological activity [11, 12]. In the present review study, it was aimed to highlight the useful effects of different plants and their constituents on different induced methods for neurotoxicity.

Materials and Methods

The data of this review article was collected by searching only in English language for the keywords “Medicinal plants”, “extract”, “neurotoxicity”, “plants constituent” and “neuroprotective effect” in databases namely ISI Web of Knowledge, Medline/ Pubmed, Science direct, Scopus and Google Scholar. The published papers until Jan 2016 were considered.

Results

Salvia officinalis L. one of the members of the family Lamiaceae is used against degenerative diseases such as brain dysfunction and declining mental functions [13]. The pharmacological leaves of this plant due to the presence of flavonoids, phenolic compounds [14] have anti oxidative properties [15]. The leaves of Salvia officinalis ethanolic extract decreased malondialdehyde (MDA) levels, Also this extract increased activity of brain acetylcholinesterase and glutathione (GSH) levels in STZ injected rats [16]. Treatment of male rats with Salvia officinalis nanoparticles decreased reactive oxygen species (ROS) production and increased glutathione peroxidase (GPx) activity in the cerebral cortex injected MeHg rats [17]. Flavonoids, as natural neuroprotective polyphenol compounds, are attributed to a variety of biological activities due to their anti-inflammatory and anti-apoptotic activities [18].

Hypericum perforatum

Phenolic contents of Hypericum perforatum alcoholic extract have significant neuroprotective effect [19]. Alcoholic extract of Hypericum perforatum is very effective in treatment of depression [20], lipid peroxidation decreasing and cell protecting against Amyloid - β induced toxicity [21]. The ethanolic extract of aerial parts of Hypericum perforatum can regulate neurotransmitters receptors like D₂ and 5-HT₂A [22].
Neuroprotective effects of medicinal plants and their constituents

Lavandula angustifolia

Researches indicate that Lavandula angustifolia can put down and glutamate-induced neurotoxicity via inhibition cholinesterase [23]. It has been reported that Lavandula angustifolia extract is benefit for cognitive dysfunction [24].

Opuntia ficus-indica

The fruits and stems of Opuntia ficus-indica have been reported to exhibit antioxidant actions [25]. The methanol extract of this fruits reduced neuronal damage induced by radicals in hippocampal CA1 region of the gerbils and mouse cortical cultures [26]. It was found butanol fraction prepared from Opuntia ficus-indica was able to inhibit lipid peroxidation initiated by Fe2+ and L-ascorbic acid in rat brain homogenates [27].

Curculigo orchioides

Curculigo orchioides Gaertn. (Amaryllidaceae family), contains of plentiful cell protective flavonoids and polyphenols [28]. The results of study showed that this plant has cell protective effects in cisplatin-induced cell damage [29]. Similarly C. orchioides methanol extract promoted restoration of catalase (CAT), SOD, and GSH levels and decreased MDA levels in cyclophosphamide-induced neurotoxicity [28].

Ficus sycomorus

Different studies reported that some Ficus species have been used for treatment of epilepsy [30]. Anticonvulsant and sedative activity of Ficus sycomorus in animal models were also reported [31]. According to the previous studies Ficus religiosa has acetylcholinesterase inhibitory [32] and antianxiety [33] activity. Methanol extract of figs or fruits of this plant showed inhibitory effect in seizures induced by maximum electroshock (MES) and picrotoxin in a dose dependent manner [34]. The Figs contain high amount amino acids [35] and serotonin (5-HT) [34]. Serotonin is useful in protection neurons of induced seizures animals via modulating GABAergic and glutamatergic neurons [36].

Angelica sinensis

Angelica sinensis is used as sedative pharmacological plant [37], Angelica sinensis extract modulated ROS, MDA and GSH contents in Amyloid β - induced damaged cells. Furthermore, this extract was able to protect cell viability against oxidative stress [38], Main compounds of Angelica sinensis are liguistilide, phthalides, ferulic acid (4-hydroxy-3-methoxycinnamic acid) and polysaccharides [38], Administration ferulic acid improved Amyloid β- induced memory impairment in mice [39], Ferulic acid is an antioxidant phenolic compound that protects cells against oxidative stress via conformation changing of synaptosomal membrane proteins [40], Ferulic acid can scavenge intracellular ROS. It also can increase expression protective genes like heme oxygenase-1 and heat shock protein 72. Therefore, this compound has neuroprotective effect in primary hippocampal cultures against Aβ1-142 induced cytotoxicity [41].

Cassia fistula

Hydroalcholic extract of Cassia fistula leaf was able to improve injuries in alcohol induced peripheral neuropathy rats [42].

Dichrostachys cinerea

Tribes of Chittoor used Dichrostachys cinerea root juice against paralysis [43], Dichrostachys cinerea fruit contains high amounts of phenols, triterpenoides and tannins [44], Alcoholic extract Dichrostachys cinerea has a CNS depressant activity [43], Saponins, carbohydrates and tannins of Dichrostachys cinerea may are responsible of CNS depressant activity [45].

Panax ginseng

Active constituents in most ginseng species, are including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols and fatty acids [45]. Panax ginseng (Ginseng) berry ethyl acetate fraction
effectively inhibited the acetylcholinesterase (AChE) activity and decreased MDA levels in mice brain tissues \[^{46}\]. It has been reported that ginsenosid of \textit{panax ginseng} is responsible of protection of dopaminergic neurons against the neurotoxins MPTP- or 6-OHDA- induced cell degeneration \[^{4}\]. Ginseng via suppression of neuro-inflammatory processes, releasing of some neuro-transmitteres and synaptic plasticity regulation has many protective effects on CNS \[^{47}\]. Ginsenosides have anti-inflammatory \[^{48}\] and anti-oxidation effects \[^{49}\] due to ROS, nitric oxide (NO) and tumor necrosis factor-α (TNF-α) suppression.

\begin{flushleft}
\textbf{Aerva lanata}
\end{flushleft}

High levels of flavonoids and phenolic compounds maybe are responsible of \textit{Aerva lanata} antioxidant activity \[^{50}\]. It has been reported that \textit{Aerva lanata} improved behavioral functions \[^{51}\]. Histological studies on brain showed that administration of \textit{A. lanata} might have a protective effect against cisplatin-induced animals \[^{50}\].

\begin{flushleft}
\textbf{Juglans regai}
\end{flushleft}

Different studies have shown that Walnut species such as \textit{Juglans regai} are containing plentiful of polyunsaturated fatty acids and tocopherols \[^{52}\]. Fatty acids and vitamin E can improve learning and memory processes \[^{53}\].

\begin{flushleft}
\textit{Nigella sativa}
\end{flushleft}

\textit{Nigella sativa} as a medicinal plant is well- known for its potent anti-oxidative effects \[^{54}\] and also demonstrated that \textit{N. sativa} seeds could preserve significantly the spatial cognitive ability in rats that challenged with chronic cerebral hypo perfusion \[^{55}\]. Furthermore, \textit{N. sativa} can prevent the damage of spatial memory after scopolamine administration and reduced the AChE activity and oxidative stress of the rats brain \[^{56}\]. The neuroprotective effects of \textit{N. sativa} and its constituents were reviewed previously \[^{57}\].

\begin{flushleft}
\textbf{Crocus sativus}
\end{flushleft}

In Iranian traditional medicine, \textit{Crocus sativus} had been used to treat cognitive disorders and recently \textit{C. sativus} constituents used for treatment of some neural disorders such as depressant \[^{58, 59}\]. The effects of \textit{C. sativus} and its constituents on nervous system was also reviewed \[^{58}\] previously. Crocin, a carotenoid pigment from \textit{C. sativus}, possess potent antioxidant effects by reducing of MDA level \[^{60, 61}\].

\begin{flushleft}
\textbf{Punica granatum}
\end{flushleft}

Potent antioxidants such as polyphenols and tannins which are concentrated in \textit{Punica granatum} L. (pomegranates) can improve degenerative diseases \[^{62}\]. It was reported that variety of Pomegranate juice can change redox function and ameliorate MPTP-induced neurotoxicity \[^{63}\]. Administration ethanolic extract of \textit{Pongamia pinnata} decreased lipid peroxidation and increased GSH, SOD, CAT, serum gamma aminobutyric acid levels in stem bark monosodium glutamate-induced neurotoxicity rats \[^{64}\].

\begin{flushleft}
\textbf{Polygala paniculata}
\end{flushleft}

Most species of Polygala genus possesses significant protective effects against neuronal death and cognitive impairments by reduction of Ca\(^{2+}\), Na\(^+\) and enhancement of K\(^+\) level or ‘anti-glutamateergic’ effect in neurodegenerative disorders related to excitotoxicity \[^{64}\]. Bettio reported that some hydroethanolic extract constitutes of \textit{Polygala paniculata} may have considered as ligand for some receptors like 5-HT\(_{2A}\), α\(_2\), β and D\(_2\) \[^{65}\].

\begin{flushleft}
\textbf{Curcuma longa}
\end{flushleft}

Some plants such as \textit{Curcuma longa} contain a natural polyphenol and non-flavonoid compound called curcumin. Curcumin is known for its several biological and medicinal effects, such as anti-inflammatory, antioxidant. Curcumin therapeutic potential for neurodegenerative diseases has garnered great interest in recent years \[^{4}\]. Kulkarni reported that curcumin water soluble extract is able to raise dopamine, norepinephrine and 5-HT levels in CNS \[^{66}\]. The neuroprotective effects of
curcumin in PD also are related to its antioxidant properties. Wang reported that curcumin repress ROS intracellular accumulation \[67\] in human cell line SH-SY5Y exposed to 6-OHDA \[68\]. Administration of curcumin (60 mg/kg, body weight, per oral) for three weeks has amended striatum neuronal degeneration in 6-OHDA lesioned rats \[69\]. Curcumin via restoration of GSH decreased levels protects of neurons against ROS \[70\]. Curcumin increased SOD levels in the lesioned striatum of 6-OHDA mice \[71\] and MES23.5 cells induced the neurotoxin 6-OHDA \[67\]. Curcumin, which is able to do Jun N-terminal kinases (JNK) phosphorylation, protects of axons against LPS degeneration \[72\]. Curcumin neuroprotective effects might be mediated by overexpression of BCl-2 which is inducible nitric oxide synthase (iNOS) antagonist. Therefore, curcumin is effective in improvement of NO-mediated degeneration \[73\]. Oral administration of 150 mg/kg/day curcumin for 1 week reduced pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), TNF-α and total nitrite generation in the striatum of MPTP-induced mice \[74\]. Furthermore, curcumin decreased activation of NF-κB in LPS \[75\] and 6-OHDA-induced inflammatory \[67\].

The protective effects of some traditional medicinal plants (table 1) and their constituents (table 2) on induced neurotoxicity were summarized.
Table 1. Protective effects of plants extracts on induced neurotoxicity

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Animal model</th>
<th>Part of plant</th>
<th>Herbal dose</th>
<th>Drug</th>
<th>Dose of drug</th>
<th>Time protocol</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salvia Officinalis</em> (alcoholic extract)</td>
<td>Rat</td>
<td>leaves</td>
<td>25, 50 and 125 mg/kg, i.p.</td>
<td>Methylmercury (STZ)</td>
<td>10 mg/kg, i.p.</td>
<td>Administration of extracts for 8 week and drug in first day</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50, 100 and 125 mg/kg, i.p.</td>
<td>Streptozotocin (STZ)</td>
<td>3mg/kg, ICV, on day 1 and 3</td>
<td>The extract was administered from day 4 to day 21 following first STZ injection</td>
<td>[16]</td>
</tr>
<tr>
<td><em>Hypericum perforatum</em> (hydroalcoholic extract)</td>
<td>Mice</td>
<td>whole plant</td>
<td>300 mg/kg, p.o.</td>
<td>1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
<td>20 mg/kg, i.p.</td>
<td>Drug administrated with an interval of 2 h in the first day and extract for 7 days</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>Hippocampal neurons of rat</td>
<td>top parts</td>
<td>0.606 55.92 6.650 5.846 6.456 8.114 2.947 12.52 µg compound.ml-1</td>
<td>Amyloid-β peptide (Aβ 25-35)</td>
<td>25 µM</td>
<td>The neurons were exposed to extracts and Aβ for 48 h.</td>
<td>[21]</td>
</tr>
<tr>
<td><em>Lavandula angustifolia</em> (aqueous extract)</td>
<td>Cerebellar granular cell culture of rat</td>
<td>Flower</td>
<td>100 and 1000 µg/ml</td>
<td>Glutamate</td>
<td>10^{-7} M</td>
<td>Extract administrated 32 min before glutamate, then glutamate added to cell culture</td>
<td>[77]</td>
</tr>
<tr>
<td><em>Opuntia ficus-indica</em> (methanol extract)</td>
<td>Mongolian gerbils</td>
<td>Fruit</td>
<td>0.1, 1 and 4 g/kg, p.o.</td>
<td>Ischemia</td>
<td>5 min</td>
<td>Extract administrated every 24 h for 3 day and Ischemia was induced 2.5 h after the final dose of extract, after reperfusion for 3 h before</td>
<td>[26]</td>
</tr>
<tr>
<td><em>Opuntia ficus-indica</em> (butanol fraction)</td>
<td>Rat cortical cells</td>
<td>stem</td>
<td>1, 3, 10, 100, 300 µg/ml</td>
<td>Oxidative stress, excitotoxins, and Amyloid β (Aβ)</td>
<td>50 µg</td>
<td>First the cultures were exposed to the highest concentration and then serially diluted to the</td>
<td>[27]</td>
</tr>
</tbody>
</table>
Neuroprotective effects of medicinal plants and their constituents

<table>
<thead>
<tr>
<th>Plant</th>
<th>Model</th>
<th>Concentration</th>
<th>Method of Administration</th>
<th>Duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curculigo orchioides (methanol extract)</td>
<td>Murine model</td>
<td>whole plant 200 and 400 mg/kg, p.o.</td>
<td>Cyclophosphamide 50 mg/kg, i.p.</td>
<td>Administration of extracts for 5 consecutive days and drug in first day</td>
<td>[29]</td>
</tr>
<tr>
<td>Ficus religiosa</td>
<td>Mice</td>
<td>Fig 25, 50 and 100 mg/kg, i.p.</td>
<td>Picrotoxin 5 mg/kg, i.p.</td>
<td>Administration of extracts for 30 min before drug injection</td>
<td>[34]</td>
</tr>
<tr>
<td>Angelica sinensis (ethanol extract)</td>
<td>Neuroblastoma cells</td>
<td>whole plant 50 and 500 µg/ml</td>
<td>Amyloid β (Aβ) 15 µM cell were treated with AB in presence of extracts for 48 h</td>
<td>[38]</td>
<td></td>
</tr>
<tr>
<td>Cassia fistula (hydroalcoholic extract)</td>
<td>Rat</td>
<td>Leaves 50, 100 and 200 mg/kg, p.o.</td>
<td>Axotomy -</td>
<td>After axotomy the extracts for 28 consecutive days administrated</td>
<td>[42]</td>
</tr>
<tr>
<td>Dichrostachys cinerea (ethanolic extract)</td>
<td>Mice</td>
<td>Root 100, 200 and 400 mg/kg, p.o.</td>
<td>Hot plate 55°C</td>
<td>Jumping time of rats measured on the hot plate before and after the extracts administration</td>
<td>[43]</td>
</tr>
<tr>
<td>Panax ginseng (ethanolic extract)</td>
<td>Rat</td>
<td>whole plant 20 mg/kg, p.o.</td>
<td>Acrylamide 50 mg/kg, p.o.</td>
<td>Administration of extract for 11 days and then drug for another 11 days and Vice versa</td>
<td>[78]</td>
</tr>
<tr>
<td>Panax ginseng (ethyl acetate fraction)</td>
<td>C57BL/6 Mice</td>
<td>Berry 20 and 50 mg/kg, orally, mixed in drinking water</td>
<td>High-Fat Diet -</td>
<td>Mice were fed with high-fat diet for 5 weeks and then high-fat diet with ginseng berry fraction for 4 weeks</td>
<td>[46]</td>
</tr>
<tr>
<td>Aerva lanata (ethanolic extract)</td>
<td>Rat</td>
<td>Aerial parts 250 and 500 mg/kg, p.o.</td>
<td>Cisplatin 5 mg/kg, i.p.</td>
<td>Cisplatin injected in the first day and treatment is continued up to 5 weeks</td>
<td>[50]</td>
</tr>
<tr>
<td>Juglans regai (-)</td>
<td>Rat</td>
<td>Fruit %6</td>
<td>Cisplatin 5 mg/kg, i.p.</td>
<td>Co-administration of walnut and cisplatin for 5 weeks</td>
<td>[79]</td>
</tr>
<tr>
<td>Nigella sativa (hydroalcoholic extract)</td>
<td>Rat</td>
<td>Seed 200 and 400 mg/kg, gavag</td>
<td>Streptozotocin (STZ) 60 mg/kg, i.p.</td>
<td>STZ injected in the first day and treatment is continued up to 6 weeks</td>
<td>[80]</td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>Treatment</td>
<td>Concentration</td>
<td>Method</td>
<td>Remarks</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
</tr>
<tr>
<td>Mohebbati et al.</td>
<td>Rat</td>
<td>Seed</td>
<td>350 mg/kg, p.o.</td>
<td>Ciprofloxacin (CFX)</td>
<td>500 mg/kg, p.o.</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Seed</td>
<td>350 mg/kg, p.o.</td>
<td>Pentylentetrazole (PTZ)</td>
<td>60 mg/kg, i.p.</td>
</tr>
<tr>
<td>Crocus sativus (-)</td>
<td>Mice</td>
<td>pure red styles</td>
<td>60 mg/kg, i.p.</td>
<td>Aluminum</td>
<td>50 mg/kg, orally</td>
</tr>
<tr>
<td>Pomegranate (-)</td>
<td>Rat</td>
<td>Fruit</td>
<td>225 mg/kg, gavag</td>
<td>Methotrexate</td>
<td>20 mg/kg, i.p.</td>
</tr>
<tr>
<td>Pomegranate (Juice Extract)</td>
<td>Human Primary Neuronal Cell Cultures</td>
<td>Seeds</td>
<td>1, 10, 50, and 100 μM</td>
<td>1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)</td>
<td>0.05mM</td>
</tr>
<tr>
<td>Pongamia pinnata (ethanolic extract)</td>
<td>Rat</td>
<td>Stem</td>
<td>200 and 400 mg/kg, p.o.</td>
<td>Monosodium glutamate (MSG)</td>
<td>2 g/kg, i.p.</td>
</tr>
<tr>
<td>Polygala paniculata (hydroalcoholic extract)</td>
<td>Mice</td>
<td>Whole plant</td>
<td>100 mg/kg, gavag</td>
<td>Methylmercury (MeHg)</td>
<td>40 mg/l, freely available</td>
</tr>
<tr>
<td>Cipura paludosa (ethanolic extract)</td>
<td>Mice</td>
<td>Bulbs</td>
<td>10 and 100 mg/kg, gavag</td>
<td>Methylmercury (MeHg)</td>
<td>40 mg/l, freely available</td>
</tr>
</tbody>
</table>

IP: intraperitoneal
ICV: intracerebroventricular
PO: Oral administration (per os)
**Neuroprotective effects of medicinal plants and their constituents**

**Table 2.** Protective effects of plants constituents on induced neurotoxicity

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Effective substance</th>
<th>Model of study</th>
<th>Dose of effective substance</th>
<th>Drug and Dose</th>
<th>Time protocol</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cymbopogon winteri-Anus</em></td>
<td>Citronellol</td>
<td>Albino Swiss mice</td>
<td>(100, 200 and 400 mg/kg, i.p.)</td>
<td>Picrotoxin 8 mg/kg (i.p.)</td>
<td>After 60 min of citronellol Administration</td>
<td>[86]</td>
</tr>
<tr>
<td><em>Carum carvi</em></td>
<td>A,β-epoxy-carvone (EC),</td>
<td>Male mice of Swiss strain</td>
<td>200, 300 or 400 mg/kg</td>
<td>PTZ (60 mg/kg, i.p.)</td>
<td>After 30 min of drug administration</td>
<td>[87]</td>
</tr>
<tr>
<td><em>Mentha spicata L.</em> and <em>Carum carvi L.</em></td>
<td>Carvone (p-mentha-6,8-dien-2-one)</td>
<td>Rat Cell line</td>
<td>5–20 mm</td>
<td>10 V/0.05–0.1 ms isolated rectangular voltage pulses</td>
<td>After 30 min of drug perfusion</td>
<td>[88]</td>
</tr>
<tr>
<td><em>Crocus sativus</em></td>
<td>Kaempferol</td>
<td>Mice</td>
<td>100 and 200 mg/kg</td>
<td>Placed In Pyrex cylinders Which were filled with water</td>
<td>24 hours after their first exposure</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>Kaempferol</td>
<td>Rat</td>
<td>50 mg/kg</td>
<td>Placed In Pyrex cylinders Which were filled with water</td>
<td>24 hours after their first exposure</td>
<td>[59]</td>
</tr>
<tr>
<td><em>Crocus sativus</em></td>
<td>Safranal</td>
<td>Mice</td>
<td>0.15 and 0.35 ml/kg</td>
<td>Sodium pentobarbital, 30 mg/kg, i.p.</td>
<td>Safranal were Administered intraperitoneally, and 30 min afterward, The animals were individually placed at the center of the Plus maze and observed for 5 min</td>
<td>[89]</td>
</tr>
<tr>
<td><em>Crocus sativus</em></td>
<td>Crocin</td>
<td>Rat</td>
<td>15 and 30 mg/kg</td>
<td>STZ-ICV (3 mg/kg)</td>
<td>Three weeks</td>
<td>[90]</td>
</tr>
<tr>
<td><em>Crocus sativus</em></td>
<td>Crocetin</td>
<td>Rat</td>
<td>(25, 50, and 75, BW, i.p.)</td>
<td>6-Hydroxydopamine (6-OHDA) 10 μg unilateral intrastralial injection</td>
<td>Locomotion and rotation were observed on day 23 post-injection and after 4 weeks, striatum and substantia nigra were dissected</td>
<td>[91]</td>
</tr>
<tr>
<td><em>Cassia siamea</em></td>
<td>Barakol</td>
<td>Rat</td>
<td>10, 25, 50, and 75 mg/kg, i.p.</td>
<td>-</td>
<td>Plus-maze 30 min after Barakol injection.</td>
<td>[92]</td>
</tr>
<tr>
<td><strong>Mohebbati et al.</strong></td>
<td><strong>Barakol</strong></td>
<td>Rat</td>
<td>25–100 mg/kg, i.p</td>
<td>PTZ (85 mg/kg, s.c.)</td>
<td>30 min before the administration of PTZ [93]</td>
<td></td>
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<tr>
<td><strong>Galanthus nivalis L.</strong></td>
<td>Galantamine</td>
<td>Cultures of hippocampal and glial cells</td>
<td>1–15 μm</td>
<td>Sodium pentobarbital, 60 mg/kg, i.p.</td>
<td>After an initial stabilization period of 30 min [94]</td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>Neuron cell cultures</td>
<td>1 μmol/L</td>
<td>100 μmol/L of NMDA</td>
<td>3-h exposure [95]</td>
<td></td>
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<tr>
<td><strong>Thymus vulgaris L.</strong></td>
<td>Carvacrol</td>
<td>Rat</td>
<td>73 mg/kg, i.p.</td>
<td>Methotrexate 20 mg/kg, i.p.</td>
<td>24 after used of carvacrol, methotrexate was administered [83]</td>
<td></td>
</tr>
<tr>
<td>Carvacrol</td>
<td>Rat</td>
<td>15 and 20 mg/kg (p.o.)</td>
<td>Cisplatin (CP) 6 mg/kg, i.p.</td>
<td>14 days before CP injection and for 7 days after CP administration [96]</td>
<td></td>
<td></td>
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<tr>
<td>Thymol</td>
<td>Rat</td>
<td>20 mg/kg, (p.o.)</td>
<td>Cisplatin 6 mg/kg, i.p.</td>
<td>14 days before CP injection and for 7 days after CP administration [96]</td>
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<tr>
<td><strong>Curcuma longa</strong></td>
<td>Curcumin</td>
<td>Rat</td>
<td>80 mg/kg, (p.o.)</td>
<td>Pilocarpine (380 mg/kg, i.p.)</td>
<td>After 21 days of daily administration [97]</td>
<td></td>
</tr>
<tr>
<td><strong>Nigella sativa</strong></td>
<td>Thymoquinone (TQ)</td>
<td>In vitro (i.v.)</td>
<td>(0.01, 0.1, 1 and 10 μM)</td>
<td>MPP 10 μM on day 10 in vitro (i.v.) For 48 h</td>
<td>On day 8 for 4 days [98]</td>
<td></td>
</tr>
<tr>
<td>TQ</td>
<td>In vitro</td>
<td>(0.1, 1, 10, 100 nm)</td>
<td>Amyloid b-protein 1–42 (2, 5, 10 μM)</td>
<td>Ab1–42 was administered to cell cultures with or without TQ on day 13 for 72 h. [99]</td>
<td></td>
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</tr>
<tr>
<td>TQ</td>
<td>Rat</td>
<td>5 mg/kg/day p.o.</td>
<td>Sodium pentobarbital 30 mg/kg, i.p.</td>
<td>TQ was administered 5 days before ischemia and continued during the reperfusion time (7 days). [100]</td>
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<td></td>
</tr>
<tr>
<td>TQ</td>
<td>Rat</td>
<td>2.5, 5 and 10 mg/kg, i.p.</td>
<td>Acrylamide 50 mg/kg/day, i.p.</td>
<td>Administration of TQ 1 week before administration of ACR and continued during treatment with ACR [101]</td>
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<tr>
<td><strong>Hipericum perforatum</strong></td>
<td>Quercetin</td>
<td>Rat</td>
<td>25 and 100 mg/kg, i.p</td>
<td>Rotenone 2.5 mg/kg, i.p.</td>
<td>60 min before of rotenone injection [102]</td>
<td></td>
</tr>
</tbody>
</table>
Neuroprotective effects of medicinal plants and their constituents

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Dose or Concentration</th>
<th>Treatment Details</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>Rat</td>
<td>50 mg/kg</td>
<td>Sodium Pentobarbital (50 mg/kg, i.p.) Administered (i.p.) Twice, 30 min before the first and the second occlusions.</td>
<td>[103]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Cell line (PC12)</td>
<td>12-200 μm</td>
<td>6-hydroxydopamine (6-OHDA) Cells were treated for 6 h with or without different concentrations of quercetin</td>
<td>[104]</td>
</tr>
<tr>
<td>Hypericin</td>
<td>Hacat keratinocytes</td>
<td>2, 5, 10, 15, and 20 μm</td>
<td>Excitation wavelength of 410 nm. Exposure to 30 min of ambient light and 24-h incubation</td>
<td>[105]</td>
</tr>
</tbody>
</table>
Conclusion

In this review we intend to concentrate on different induced neurotoxicity in various studies (in vitro and in vivo) and investigated effects of plants and their constituents on induced toxicity in neural cells. Plants and their constituents play their protective roles via increased SOD and catalase levels, restoration of GSH, decreased MDA levels and also protects of neurons against ROS as antioxidant activities. Anti-inflammatory properties of plants and their constituents as well as due to their interactions with pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and mediated by overexpression of BCl-2 which is inducible nitric oxide synthase (iNOS). Some protective effects of these natural compounds may be due to reduction of Ca2+, Na+ and enhancement of K+ level or ‘anti-glutamatergic’ effect. Furthermore, neuroprotective of plants and their components occur via inhibition of the acetylcholinesterase (AChE) activity and decreased MDA levels in the neural system via modulating GABAergic and glutamatergic neurons, and also increasing amount of amino acids and serotonin (5-HT) in the neurotransmitters systems or as ligand for some receptors like 5-HT2A, α2, β and D2.

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Conflict of interest

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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