Review Article

Plant-derived neuroprotective agents in Parkinson’s disease

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Abstract: Parkinson’s disease (PD) is one of the most common degenerative disorders of the central nervous system among the elderly. The disease is caused by the slow deterioration of the dopaminergic neurons in the substantia nigra. Treatment strategies to protect dopaminergic neurons from progressive damage have received much attention. However there is no effective treatment for PD. Traditional Chinese medicines have shown potential clinical efficacy in attenuating the progression of PD. Increasing evidence indicates that constituents of some Chinese herbs include resveratrol, curcumin, and ginsenoside can be neuroprotective. Since pathologic processes in PD including inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and genetic factors lead to neuronal degeneration, and these Chinese herbs can protect dopaminergic neurons from neuronal degeneration, in this article, we review the neuroprotective roles of these herbs and summarize their anti-inflammatory, antioxidant, and anti-apoptotic effects in PD. In addition, we discuss their possible mechanisms of action in in vivo and in vitro models of PD. Traditional Chinese medicinal herbs, with their low toxicity and side-effects, have become the potential therapeutic interventions for prevention and treatment of PD and other neurodegenerative diseases.

Keywords: Chinese herbs, resveratrol, curcumin, ginsenoside, Parkinson’s disease, neuroprotection

Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease characterized by motor symptoms of tremor, rigidity, bradykinesia, and postural instability. The main pathological change in PD is progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, though the cause of cell death is unknown [1]. Treatments for PD include oral preparations of levodopa (L-DOPA) and dopamine (DA) receptor agonists and monoamine oxidase-B (MAO-B) inhibitors, and deep brain stimulation of the subthalamic nucleus and globus pallidus by surgically implanted electrodes, and stem cell transplantation into the striatum. Especially in recent years, experimental and clinical research on stem cells for treatment of PD has attracted increasing attention [2, 3]. Such treatments have proven to have some positive results, but at present there is no effective treatment for PD. Neuroprotective treatment does not directly address the etiology of PD, but intervention in some intermediate links in pathogenesis can delay the development of disease. Traditional Chinese medicines have shown potential clinical efficacy in attenuating the progression of PD. Growing evidence indicates that some Chinese herbs contain neuroprotective compounds, such as resveratrol, curcumin, or ginsenoside, green tea polyphenols or catechins, triptolide, etc [4-8]. These herbs can protect dopaminergic neurons against the neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- or 6-hydroxydopamine (6-OHDA)-induced cell degeneration. They may also increase antioxidant activity, impede dopamine loss, inhibit microglial activation and the subsequent reduction of proinflammatory factor release, modulate mRNA levels and protein expression of apoptosis-related factors, and prevent α-synuclein aggregation and fibrillation. In this article, we review the neuroprotective roles of resveratrol, curcumin, and panax ginseng/ginsenoside in PD and discuss their possible mechanisms of action (Table 1, Figure 1).
### Table 1. Neuroprotective effects of resveratrol, curcumin, and ginsenoside on PD

<table>
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<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>In vivo/In vitro model</th>
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<tbody>
<tr>
<td>Resveratrol</td>
<td>Anti-Inflammation</td>
<td>N9 microglial cell</td>
<td>Decrease the mRNA levels of IL-1α and TNF-α; Decrease the levels of COX-2 expression; Decrease the levels of NO, TNF-α, IL-1β, IL-6, MCP-1; Suppress production of IL-12p40, IL-23 and C-reactive protein, and respective receptors; Down-regulate MPO; Modulate the activity of PGC-1α, Akt and NF-kB</td>
<td>[10, 18-21]</td>
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<td>6-OHDA-induced rat</td>
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<td>MPTP-induced mice</td>
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<td>Primary microglia and astrocytes</td>
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<td>Primary mouse astrocytes</td>
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<td>BV2 microglial cells</td>
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<td>Anti-Apoptosis</td>
<td></td>
<td>PC12 cells</td>
<td>Reduce the activity of caspase-3 and the level of Bax; regulate DNA fragmentation and the mRNA levels and protein expression of Bax, Bcl-2, cleaved caspase-3, and cleaved PARP-1; Activate sirtuin deacetylases and PPAR-γ</td>
<td>[12, 24, 25, 27]</td>
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<td>SH-SYSY cells</td>
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<td>MPTP-induced mice</td>
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<td>HtrA2 knockout mice</td>
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<td>Saccharomyces cerevisiae</td>
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<td>Antioxidation</td>
<td></td>
<td>PC12 cells</td>
<td>Diminish superoxide anion; Inhibit ROS generation; Up-regulate the antioxidant status and the expression of MrA; Activate PPAR-γ, AMPK, SIRT1; Raise the mRNA expression of PGC-1α's target genes</td>
<td>[12, 37, 38, 41]</td>
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<td>SKN-MC cells</td>
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<td>6-OHDA-induced rat</td>
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<td>SH-SYSY cells</td>
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<td>Primary fibroblast from PD patients with Park2 mutation Transgenic mice overexpressing PGC-1α DA SN4741 cells</td>
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<td>Curcumin</td>
<td>Anti-Inflammation</td>
<td>MES23.5.5 cells</td>
<td>Increase neurotrophic factors release in the concentration- and time-dependent manners Inhibit NF-κB translocation and AP-1 activation; Inhibit the protein expression of GFAP and iNOS, decrease activation of astrocytes and microglia, reduce pro-inflammatory cytokine, alleviate loss of TH-IR fibers, protect axon</td>
<td>[48-52]</td>
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<td>Primary rat midbrain neuron-glia cultures</td>
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<td>MPTP-induced mice</td>
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<td>Anti-Apoptosis</td>
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<td>PC12 cells</td>
<td>Reduce MMP loss, attenuate MPP⁺⁺⁺⁺-induced an increase in intracellular ROS level, induce overexpression of BCL-2 and antagonize MPP⁺⁺⁺⁺-induced overexpression of iNOS; Ease alphaS-induced toxicity; Protect DA neuron axon; Decrease the Bax/Bcl-2 ratio; Reduce the accumulation of A53Trα-synuclein; Inhibit the JUN/c-Jun pathway; Block MPP⁺⁺⁺⁺</td>
<td>[53-55, 65]</td>
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<td>SH-SYSY cells</td>
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<td>MPTP-induced mice</td>
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<td>6-OHDA-induced rat</td>
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<td>PC12 cells</td>
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<td>6-OHDA-induced rats</td>
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<td>AS3T α-synuclein cell model</td>
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<td>Antioxidation</td>
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<td>MES23.5 cells</td>
<td>Restore MMP, increase level of Cu-Zn superoxide dismutase, suppress ROS; Sustain SOD1 level; reduce the levels of p-p38, cleaved caspase 3 and quinoprotein formation; restore depletion of GSH levels, free radical scaveng; Inhibit oxidative stress and the mitochondrial cell death pathway; activate the Nrf2/ARE pathway; Reduce p53 phosphorylation</td>
<td>[48, 51, 57, 62, 64, 66-68]</td>
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<td>6-OHDA-induced mice</td>
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<td>AS3T α-synuclein cell model</td>
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<td>Prevent α-synuclein aggregation and fibrillation</td>
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<td>SH-SYSY cells</td>
<td>Prevent α-synuclein aggregation and fibrillation; Destabilize preformed alphaS; Specifically binds to oligomeric intermediates</td>
<td>[60, 71-74]</td>
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<td>Ginsenoside</td>
<td>Anti-Inflammation</td>
<td>MPTP-induced mice</td>
<td>Inhibit MDO-B activity</td>
<td>[71, 76]</td>
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<td>BV2 microglial cells</td>
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<td>Rat primary microglia</td>
<td>Suppress NO production and TNF-α secretion, inhibit the mRNA expressions of iNOS, TNF-α, IL-1β, COX-2 and MMP-9, inhibited the phosphorylations of PI3K/Akt and MAPKs and the DNA binding activities of NF-κB and AP-1; Suppress phosphorylation and nuclear translocation of NF-κB/p65, phosphorylation and degradation of αB and the phosphorylation of θ; inhibit the activation of Akt and ERK1/2; Reduce NO-formation and PGE2 synthesis; attenuate up-regulation TNF-α, IL-1β and IL-6 mRNA, and iNOS and COX-2 expression</td>
<td>[5, 84-86]</td>
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<td>Mesencephalic primary cultures</td>
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<td>PC12 cells</td>
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<td>LPS-treated mice</td>
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<td>Anti-Apoptosis</td>
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<td>PC12 cells</td>
<td>Inhibit the activation of caspase-3, reduce iNOS and NO production; Increased the phosphorylation inhibition of Bad through activation of the PI3K/Akt pathway; Enhance the expression of Bcl-2 protein and mRNA, reduce the expression of Bax, Bax mRNA, and iNOS, and attenuate the cleavage of caspase-3</td>
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<td>Primary cultured nigral neurons</td>
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<td>MPTP-induced mice</td>
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<tr>
<td>Antioxidation</td>
<td></td>
<td>PC12 cells</td>
<td>Reduce the generation of ROS and cytochrome c release, reduce MPP, increased the phosphorylation inhibition of Bad through activation of the PI3K/Akt pathway; Decrease iron influx, inhibit IRPs; decrease DMT1-mediated ferrous iron uptake and iron-induced cell damage</td>
<td>[87, 88, 90, 91]</td>
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<td>MES23.5 cells</td>
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<td>Primary cultured nigral neurons</td>
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<td>Neurotrophic-like effects</td>
<td></td>
<td>PC12 cells</td>
<td>Increase neurite outgrowth; Reversed MPTP-induced cell death</td>
<td>[92]</td>
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**Figure 1.** The structures and protective mechanisms of resveratrol, curcumin, and ginsenoside on PD.
Resveratrol

Resveratrol, a polyphenolic compound naturally present in red wine and grapes, has a number of pharmacological effects including anti-inflammation, anti-apoptosis, antioxidation, antifungal, anticancer, and others [9-12]. It is also able to cross the blood-brain barrier and is water soluble [13]. The pathogenesis of PD is not clear, but in general is considered to be related to neuroinflammation, apoptosis, and oxidative stress [14-16]. Especially since the beginning of the 21st century, many research groups have explored the use of resveratrol in PD [17] and investigated its therapeutic effects from many angles. We summarize the neuroprotective roles of resveratrol in PD and discuss its possible mechanisms of action (Table 1, Figure 1).

Anti-inflammation

Glial activation and neuroinflammation have been found to be closely related to the pathogenesis of PD. Resveratrol strongly decreased the mRNA levels of two proinflammatory genes, interleukin 1-α (IL-1α) and tumor necrosis factor-α (TNF-α), in N9 microglial cells induced by lipopolysaccharide (LPS) [18]. Resveratrol treatment also significantly decreased the levels of cyclooxygenase-2 (COX-2) expression in the substantia nigra in the 6-hydroxydopamine (6-OHDA)-induced PD rat model [19]. Wight RD and colleagues tested the ability of resveratrol to inhibit LPS-induced production of inflammatory molecules by primary mouse astrocytes. They found that resveratrol inhibited LPS-induced production of nitric oxide (NO), cytokines such as TNF-α, interleukin 1-β (IL-1β), and Interleukin-6 (IL-6); and chemokine monocyte chemotactic protein-1 (MCP-1), which play critical roles in innate immunity. Resveratrol also suppressed astrocyte production of Interleukin-12p40 (IL-12p40) and Interleukin-23 (IL-23), which are known to alter the phenotype of T cells involved in adaptive immunity. Finally, resveratrol inhibited astrocyte production of C-reactive protein (CRP), which plays a role in a variety of chronic inflammatory disorders [10]. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, resveratrol significantly reduced glial activation and decreased the levels of IL-1β, IL-6, and TNF-α as well as their respective receptors in the substantia nigra pars compacta (SNpc), according to Western blot, reverse transcription-polymerase chain reaction (RT-PCR), and quantitative PCR analysis [20]. Resveratrol protected DA neurons against LPS-induced neurotoxicity in a concentration- and time-dependent manner through the inhibition of microglial activation and the subsequent reduction of proinflammatory factor release [9]. Resveratrol significantly down-regulated myeloperoxidase (MPO) level (a key molecule in the host defense system against different pathogens), although it did not spark abnormal NO production in microglia and astrocytes. Moreover, resveratrol treatment restored the impaired responses of primary mixed glia from Mpo (-/-) mice to rotenone and attenuated rotenone-induced DA cell death. Furthermore, resveratrol plays the same regulatory roles on MPO levels in microglia treated with 1-methyl-4-phenylpyridinium (MPP)(+) [21]. Resveratrol suppressed the decrease of SIRT1 and increase of TNF-α and IL-6 induced by LPS, indicating that SIRT1 may participate in the regulation of proinflammatory cytokines derived from activated microglial activation [22]. Resveratrol treatment up-regulated the expression of the suppressor of cytokine signaling-1 (SOCS-1), supporting the hypothesis that it protects DA neurons of the SNpc against MPTP-induced cell loss by regulating inflammatory reactions, possibly through SOCS-1 induction [20]. Resveratrol also modulates the activity of numerous proteins, including peroxisome proliferator-activated receptor coactivator-1α (PGC-1α), members of the FOXO family, Akt (protein kinase B), and nuclear factor-κB (NF-κB) [23]. In conclusion, resveratrol protects DA neurons by reducing the inflammatory response.

Anti-apoptosis

Induced in a variety of ways, apoptosis of DA neurons leads to PD. Under microglial-neuronal coculture, treatment with resveratrol successfully reduced the inflammation-mediated apoptotic death of N9 microglial cells [18]. Resveratrol significantly reduced the activity of caspase-3 in neuroblastoma SH-SY5Y cells triggered by 6-OHDA [24], and decreased the level of Bax to the point of attenuating apoptosis [25]. Moreover, under high-glucose (HG) conditions, resveratrol significantly reduces HG-induced apoptosis in DA cells by regulating DNA fragmentation and the expression of several genes, such as Bax, Bcl-2, cleaved cas-
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pase-3, and cleaved poly(ADP-ribose)polymerase 1 (PARP-1) and also prevents the pro-apoptotic increase of p53 in the nucleus induced by HG [12]. Resveratrol showed anti-apoptotic activity in both rat and zebrafish brain synaptosomal fractions exposed to the neurotoxic agent rotenone by MTT assay [26]. Similarly, using PC12 cells, resveratrol greatly reduced PC12 death induced by MPP(+), which was related to modulation of the mRNA levels and protein expression of Bax and Bcl-2 [27]. Numerous studies have demonstrated the neuroprotective capability of resveratrol through activation of silent information regulator 1 (SIRT1) [28]. Resveratrol was shown to increase the lifespan of Saccharomyces cerevisiae [29], which was attributed to its ability to activate sir-2s, members of the histone deacetylase family [30]. There is evidence that resveratrol’s ability to attenuate tissue injury in the brain and restore mitochondrial function is partly attributable to its effect on SIRT1-dependent deacetylation of PGC-1α, a protein factor involved in mitochondrial biogenesis [23, 31], and activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), as a therapeutic target for neurodegenerative disease, due to PPAR-γ ability to protect against mitochondrial damage through upregulation of Bcl-2 [32, 33]. Thus, resveratrol increases the levels of SIRT1 and related enzymes, which could change neuronal transcription profiles and enhance anti-apoptotic activity [34]. Moreover, resveratrol activates AMP-activated protein kinase (AMPK) to affect neuronal energy homeostasis, further contributing to neuroprotection [31]. AMPK and/or SIRT1 are required to induce resveratrol-mediated autophagy, and the AMPK-SIRT1-autophagy pathway plays an important role in neuroprotection by resveratrol in PD cellular models [35]. By activating autophagy, resveratrol prevented PrP (106-126)-induced neurotoxicity and reduction in mitochondrial potential, translocation of Bax to the mitochondria, and cytochrome c release [36]. To sum up, resveratrol plays its neuroprotective function by diminishing DA apoptosis.

Antioxidation

Many evidences showed that resveratrol exerted a neuroprotective effect on DA neurons by antioxidant. Excess reactive oxygen species (ROS) in the brain have been implicated as a likely potential risk factor for the pathogenesis of PD. Resveratrol scavenged ROS in a dose-dependent manner, and its antioxidant effects were further shown by protecting the enzymatic activity of the mitochondrial respiratory electron transport chain (complexes I and II) and pyruvate dehydrogenase in isolated liver mitochondria [37]. Resveratrol up-regulates antioxidant status and lowers DA loss in PD rat models [38], as well as prevents the formation of the DA-DNA adducts that could lead to gene mutations that cause PD [39]. Wang Y et al. showed that pretreatment of PD rats with resveratrol or resveratrol liposome (20 mg/kg per day) for 14 days greatly reduced abnormal rotational behavior and the loss and apoptosis of nigral cells, restored levels of total ROS, and significantly improved the total antioxidant capability of nigral tissues. Furthermore, resveratrol liposome showed even more profound effects than free resveratrol [40]. Methionine sulfoxide reductases A (MsrA) act as a catalytic antioxidant system and refers to the protection of oxidative stress-induced cell injury. Pretreatment with resveratrol up-regulated the expression of MsrA in human neuroblastoma SH-SY5Y cells [30]. It was also found that the expression and nuclear translocation of forkhead box group O 3a (FOXO3a), a transcription factor that activates the human MsrA promoter, were increased after resveratrol pretreatment [41]. In resveratrol (50 μM) coculture, PC12 cell death induced by DA (1 μM)-H₂O₂ (1 μM) was abolished, indicating resveratrol’s anti-oxidant capability [17]. Resveratrol protected DA neurons against HG-induced oxidative stress by diminishing cellular levels of superoxide anion [12]. Activation of PPAR-γ may also target the transcription of SOD and catalase genes through increasing the activity of the NF-E2-related factor 2 (Nrf2)/keap 1 pathway [42]. Many studies have confirmed that resveratrol suppresses neuroinflammation by inhibiting NADPH oxidase and attenuating NF-κB-induced expression of inducible nitric oxide synthase (iNOS), COX-2, and secretory phospholipase A2 (sPLA₂) [9, 43, 44] and by activating the hortmetic pathway, which involves the induction of SOD and catalase genes through stimulating the PI3K/Nrf2/keap 1 pathway [42]. Both in vivo (transgenic mice) and in vitro (SN4741 cells) studies showed that PGC-1α in DA neurons has the important function of resisting oxidative stress and improving neuronal viability,
and resveratrol is neuroprotective via SIRT1/PGC-1α [45]. Nicotinamide is an inhibitor of SIRT1 and prevents resveratrol-induced elevation of FOXO3a and MsR expression, demonstrating that the effect of resveratrol is mediated by a SIRT1-dependent pathway from another direction [41]. Recent research has shown that resveratrol regulates energy homeostasis through activation of AMPK and SIRT1 and raises the mRNA expression of a number of PGC-1α’s target genes, resulting in enhanced mitochondrial oxidative function; resveratrol treatment also causes an increase in complex I and citrate synthase activity, basal oxygen consumption, and mitochondrial ATP production and causes enhanced macro-autophagic flux through activation of an LC3-independent pathway [46].

Other effects

Resveratrol exerted neurotrophic effects on primary rat midbrain neuron-glial cultures; furthermore it increased the release of neurotrophic factors in a concentration- and time-dependent manner [11]. Polymorphisms of the cytochrome P450 (CYP/Cyp) 2D6 gene are related to PD. Resveratrol ameliorated the neurodegenerative changes by altering the expression of Cyp2d22, a mouse ortholog of human CYP2D6 as well as paracrine accumulation [47].

Curcumin

Curcumin, a natural polyphenol compound derived from the curry spice turmeric, is known for several biological and medicinal effects, such as anti-cancer, anti-microbial, anti-inflammatory, antioxidant, and antiproliferative activities. Curcumin has shown therapeutic potential for neurodegenerative diseases including PD, which has garnered great interest in recent years. We review the neuroprotective roles of curcumin in PD and discuss its possible mechanisms of action (Table 1, Figure 1).

Anti-inflammation

Both in vitro and in vivo studies showed that curcumin can protect DA neurons through anti-inflammatory effect. Curcumin pretreatment significantly inhibited both 6-OHDA-induced NF-kB translocation [48] and LPS-induced morphological changes in microglia, and dramatically suppressed the expression of many LPS-induced proinflammatory factors and their genes. Furthermore, curcumin treatment decreased LPS-induced activation of NF-kB and activator protein-1 (AP-1) [49]. Pretreatment with curcuminoids (150 mg/kg/day, oral administration) for 1 week prevented MPTP-mediated depletion of DA and tyrosine hydroxylase (TH) immunoreactivity and inhibited the protein expression of glial fibrillary acidic protein (GFAP) and iNOS. Likewise, curcumin pretreatment reduced pro-inflammatory cytokine (IL-6, IL-1β, TNF-α) and total nitrite generation in the striatum of MPTP-induced mice [50]. Curcumin alleviated loss of TH-IR fibers and decreased activation of astrocytes and microglia [51]. Recently, using a quantitative microfluidic-based methodology, Tegenge et al. showed that LPS-stimulated microglia release soluble factors, which when applied locally to axons, result in axon degeneration. Curcumin specifically protects axons, but not neuronal cell bodies, from NO-mediated degeneration [52].

Anti-apoptosis

Curcumin also protected DA neurons from apoptosis. It has been reported that curcumin protects PC12 cells against MPP(+) -induced cytotoxicity and apoptosis by reducing the loss of mitochondrial membrane potential (MMP), and its neuroprotective effects might be mediated by the Bcl-2-mitochondria-ROS-iNOS pathway because curcumin attenuates MPP(+) -induced an increase in intracellular ROS level, induces overexpression of BCI-2 and antagonizes MPP+-induced overexpression of iNOS [53]. Research using a PD cell model found that both intra- and extra-cellular alphaS may induce apoptosis of DA neurons; curcumin can ease alphaS-induced toxicity, decrease ROS levels, and protect cells against apoptosis [54]. In addition the death of DA neurons and the loss of DA axons in the striatum were significantly suppressed by curcumin in the MPTP mouse model [55]. Chiu et al. showed that liposomal-formulated curcumin [Lipocurc™] significantly blocked neuronal apoptosis and stimulated DA neurons in the substantia nigra [56]. Using 6-OHDA-induced neurotoxicity in the SH-sY5Y cells, curcumin decreased the Bax/Bcl-2 ratio at mRNA expression and protein level [57]. Curcumin specifically inhibits the JNK/c-Jun pathway [58] and can block MPP(+),
which causes the upregulation of c-Jun N-terminal kinase (JNK) and DA neuronal death [59]. JNK phosphorylation induced by MPTP can cause translocation of Bax to mitochondria and the release of cytochrome c, which can be diminished by curcumin [55]. The axon degeneration induced by LPS is mediated by microglial MyD88/p38 MAPK signaling and concomitant production of NO. Through inhibiting JNK, curcumin protects axons from degeneration involving JNK phosphorylation [52]. Curcumin could reduce the accumulation of A53T α-synuclein through downregulation of the mTOR (mammalian target of rapamycin)/p70S6K signaling [60].

Antioxidation

The neuroprotective effects of curcumin to PD also related to its antioxidant properties. In 2005, Zbarsky V et al. pretreated rats with curcumin and showed clear protection of the number of TH-positive cells in the SN and DA levels in the striata [61]. Treatment of DA neurons and mice with curcumin restores depletion of glutathione (GSH) levels, protects against protein oxidation, preserves mitochondrial complex I activity that is normally impaired due to GSH loss [62], and maintains SOD1 levels in the lesioned striatum of 6-OHDA mice [51]. Curcumin protected MES23.5 cells against the neurotoxin 6-OHDA by restoring mitochondrial membrane potential, increasing the levels of Cu-Zn superoxide dismutase, and suppressing an increase in intracellular ROS [48]. The effect of three bioconjugates of curcumin (involving diesters of demethylenated piperic acid, valine, and glutamic acid) against GSH depletion mediated oxidative stress in DA neurons [63]. Curcumin pretreatment of the human DA cell line SH-SY5Y exposed to 6-OHDA improved cell viability and significantly reduced ROS [57]. Curcuminoids were administered to rats (60 mg/kg, body weight, per oral) for three weeks followed by unilateral injection of 6-OHDA (10 μg/2 μL) into the right striatum on the 22nd day. The results showed that curcuminoids appear significant protection against progressive neuronal degeneration due to increased oxidative attack in 6-OHDA-lesioned rats through a free radical-scavenging mechanism [64]. Pretreatment of SH-SY5Y with curcumin I (diferuloylmethane) significantly decreased the formation of quinoprotein and reduced the levels of p-p38 and cleaved caspase-3 in a dose-dependent manner induced by 6-OHDA. Moreover, the levels of phospho-tyrosine hydroxylase (p-TH) were also dose-dependently increased by treatment with curcumin I. These results clearly demonstrate that curcumin I protects neurons against oxidative damage by attenuation of p-p38 expression, caspase-3-activation, and toxic quinoprotein formation and by restoration of p-TH levels [65].

Similarly, pretreatment with a pyrazole derivative of curcumin (CNB-001, 2 μM) 2 h before rotenone exposure (100 nM) to SK-N-SH cells increased cell viability, decreased ROS formation, maintained normal physiological mitochondrial membrane potential, and reduced apoptosis. Furthermore, CNB-001 inhibited downstream apoptotic cascade by increasing the expression of Bcl-2 and decreased the expression of Bax, caspase-3, and cytochrome C [66]. Curcumin has also been shown to detoxify peroxynitrite and protect against mitochondrial complex I (CI) inhibition and protein nitration [67]. Curcumin protects against A53T mutant α-synuclein-induced cell death via inhibition of oxidative stress and the mitochondrial cell death pathway [68]. Pretreatment with curcumin I (diferuloylmethane) protects SH-SY5Y cell from 6-OHDA-induced neurotoxicity. Curcumin I significantly improved cell viability, reduced ROS and p53 phosphorylation [61]. Curcumin has been shown to activate the Nrf2/ARE (antioxidant-response element) pathway that activates transcription of anti-inflammatory and antioxidant genes to produce neuroprotective effects [69]. The protective effects of curcumin against 6-OHDA may be attributable to its iron-chelating capability, suppressing the iron-induced degeneration of nigral DA neurons [70].

Other effects

In addition to preventing α-synuclein aggregation and fibrillation [71], curcumin also inhibits the formation of alpha-synuclein fibrils (alphaS) and destabilizes preformed alphaS at pH 7.5 at 37 degrees C in vitro [72]. Curcumin-glucoside (Curc-gluc), a modified form of curcumin, prevents oligomer formation and inhibits fibril formation. Curc-gluc inhibits aggregation in a dose-dependent manner and enhances the solubility of α-synuclein [73].
Curcumin efficiently reduces the accumulation of A53T α-synuclein [60]; however, fluorescence and two-dimensional nuclear magnetic resonance (2D-NMR) show that it binds not to monomeric α-Syn but instead to oligomeric intermediates [74]. A mixture of curcumin and β-cyclodextrin not only inhibited aggregation but also broke up the preformed aggregates [75].

In addition, curcumin inhibits monoamine oxidase B [71]. Systemic administration of curcumin (80 mg/kg i.p.) significantly reversed the MPTP-induced depletion of DA and dihydroxyphenylacetic acid (DOPAC). MAO-B activity was also significantly inhibited by curcumin and its metabolite tetrahydrocurcumin [76]. However, Ojha's found the MAO-B activity only partially and not significantly altered [50]. In yeast, curcumin prevents formation of polyglutamine aggregates by inhibiting Vps36, a component of the ESCRT-II (endosomal sorting complex required for transport) complex [77].

The leucine-rich repeat kinase 2 (LRRK2) gene is most commonly associated with both familial and sporadic PD [78]. Employing both cell and Drosophila models to investigate the interaction between LRRK2 genetic mutations and oxidative stress, it was found that curcumin significantly reduced LRRK2 kinase activity and the levels of oxidized proteins, and thus acted as not only an antioxidant but also a LRRK2 kinase inhibitor [79].

Ginsenoside

Ginseng, a traditional Chinese medicine, is widely used. Most ginseng species contain active constituents with beneficial effects, including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. There are two major categories of ginsenosides: protopanaxadiols (PPD, e.g., Ra, Rb, Rc, Rd, Rg3, Rh2) and protopanaxatriols (PPT, e.g., Re, Rf, Rg1, Rg2, Rh1) [80]. Ginseng has many therapeutic effects, especially on nervous system diseases. Ginseng plays a neuroprotective role in the regulation of synaptic plasticity, neuroinflammatory processes, and neurotransmitter release [6]. In vitro and in vivo studies have determined that ginsenosides, as the active compounds responsible for ginseng’s action, exert pharmacological effects against neuroinflammation, cerebral oxidative stress and radical formation, and apoptosis (Table 1 and Figure 1).

Anti-inflammation

Ginsenosides have clear anti-inflammatory effects. Ginsenoside Rg5 is one of the main constituents of steamed ginseng and belongs to the family of protopanaxadiol ginsenosides [81]. It has been shown to suppress NO production and proinflammatory TNF-α secretion in BV2 microglial cells and rat primary microglia, as well as inhibit the mRNA expression of iNOS, TNF-α, IL-1β, COX-2, and matrix metalloproteinase 9 (MMP-9) induced by LPS [82]. Drug screening determined that ginsenoside Re enhances the function of the defective PINK1-Hsp90/LRPPRC-Hsp60-complex IV signaling axis in PINK1-null neurons by restoring NO levels [83]. In addition, Re (2 μg/ml) protects against LPS (1 μg/ml)-treated microglial cells. The neuroprotective/anti-inflammatory effects induced by Re treatment appeared via the phospho-p38, iNOS, and COX2 signaling pathways in BV2 cells [80]. Rg1 obviously decreased the cytotoxicity induced by H2O2 in PC12 cells and suppressed phosphorylation and nuclear translocation of NF-κB/p65, phosphorylation and degradation of inhibitor protein of κB (IκB), and the phosphorylation of IB-kinase complex (IKK). Rg1 also inhibited the activation of Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) [84]. Rd partially reduced the neurotoxic action of LPS on DA neurons, which could take place through a reduction of NO-formation and prostaglandin E2 (PGE2) synthesis [85]. In an in vivo animal model, pretreatment with Rg3 (orally with 10, 20, and 30 mg/kg 1 h prior to the LPS) significantly attenuated upregulation of TNF-α, IL-1β, and IL-6 mRNA in brain tissue at 4 h after LPS injection. Furthermore, iNOS and COX-2 expression in brain tissue were also attenuated [86]. Also, Rg5 inhibited the phosphorylation of P3K/Akt and MAPKs and the DNA binding activity of NF-κB and AP-1, which are upstream molecules controlling inflammatory reactions [82]. In addition, ginsenoside’s neuroprotective effects via Rd may involve interference with the expression of iNOS and COX-2 [85].

Anti-apoptosis

Ginsenosides have anti-apoptotic effects. Pretreatment with ginsenoside Rg1 obviously...
inhibited the activation of caspase-3. In addition, Rg1 also reduced iNOS protein levels and NO production [87]. Rg1 increased the inhibition of phosphorylation of the pro-apoptotic protein Bad through activation of the PI3K/Akt pathway [88]. Pretreatment with Re markedly increased TH-positive neurons and decreased the TUNEL-positive ratio in a PD mouse model induced by MPTP. Furthermore, Re enhanced the expression of Bcl-2 protein and mRNA but reduced the expression of Bax, Bax mRNA, and iNOS and attenuated the cleavage of caspase-3 [89].

**Antioxidation**

Ginsenosides also have anti-oxidation function. Pretreatment with ginsenoside Rg1 evidently reduced the generation of DA-induced ROS and the release of mitochondrial cytochrome c into the cytosol [87]. Rg1 was shown to reduce rotenone-induced cell death in primary cultured nigral neurons and restored mitochondrial membrane potential. In addition, Rg1 prevented cytochrome c release from the mitochondrial membrane [88]. Because iron accumulation is involved in the neurotoxicity of 6-OHDA, Rg1 pretreatment decreases iron influx by inhibiting 6-OHDA-induced up-regulation of an iron importer protein divalent metal transporter 1 with iron-responsive element (divalent metal transporter 1 (DMT1) + iron responsive element (IRE)), and the effect of Rg1 on DMT1 + IRE expression was due to its inhibition of iron-regulatory proteins (IRPs) by its antioxidant effect [90]. Pretreatment with Rg1 inhibited MPP(+) -induced up-regulation of DMT1-IRE in MES23.5 cells and significantly inhibited ROS production and translocation of NF-κB to nuclei. Rg1 decreased DMT1-mediated ferrous iron uptake and iron-induced cell damage by inhibiting the up-regulation of DMT1-IRE, likely by inhibiting the ROS-NF-κB pathway [91].

**Other effects**

Ginseng extract has been found to have neurotrophin-like effects. Both Rb1 and Rg1 increased neurite outgrowth of PC12 cells in the absence of NGF after 18 days in culture; in addition, both Rb1 and Rg1 reversed MPTP-induced SN-K-SH cell death [92].

**Conclusion and perspective**

PD is a chronic, progressive, and multifactorial neurologic disorder in which many pathologic processes including inflammation, oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance, apoptosis, and genetic factors lead to neuronal degeneration. Thus, any therapeutic approach that limits itself to drugs against a single pathological process is invalid, and drug combinations with various pharmacological properties are likely to be more effective. Recently, traditional Chinese medicinal herbs, with their low toxicity and side-effects have become a popular topic when discussing new drugs for prevention and treatment of PD and other neurodegenerative diseases. It is known that Chinese herbs play various neuroprotective roles, including antioxidant, anti-inflammatory, free radicals-scavenging, anti-apoptosis, and chelating harmful metals through a variety of mechanisms [4, 6, 93, 94]. Therefore, as therapeutic neuroprotective agents, Chinese herbs are attracting increasing attention for the treatment of PD patients. At present, for the prevention and treatment of PD, traditional Chinese herbs monomer and active ingredients with clear molecular structures contribute to its mechanism research, but there are some problems in the application of Chinese herbs. First, efficacy studies of traditional Chinese medicine monomer or effective ingredients for PD still remain in the stage of cell or animal model, and need further clinical observation and verification. Second, the efficacies of single use of traditional Chinese herbs monomer or effective components are very different from Chinese herbal compound used in clinic, and can not exploit advantages of traditional Chinese medicine on synergy effects and overall regulation of body. Third, some Chinese herbs ingredients have low bioavailability [93]. Future studies should be pay attention to the bioavailability of the traditional Chinese herb composition and the best combination of a variety of traditional Chinese medicine monomer and the effective composition to improve its therapeutic effect.

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Disclosure of conflict of interest

None.

Abbreviations

AP-1, activator protein-1; AMPK, AMP-activated protein kinase; 6-OHDA, 6-hydroxydopamine; JNK, c-Jun N-terminal kinase; CRF, C-reactive protein; COX-2, cyclooxygenase-2; DOPAC, dihydroxyphenylacetic acid; DMT1, divalent metal transporter 1; DA, dopamine; ESCRT, endosomal sorting complex required for transport; ERK1/2, extracellular signal-regulated kinase 1/2; FOXO3a, forkhead box group O 3α; GFAP, glial fibrillary acidic protein; GSH, glutathione; HG, high glucose; iNOS, inducible nitric oxide synthase; IkB, inhibitor protein of κB; IKK, IκB-kinase complex; IL-6, Interleukin-6; IL-1α, interleukin 1-α; IL-1β, interleukin 1-β; IL-12p40, interleukin 12p40; IL-23, interleukin 23; IRPs, iron regulatory proteins; IRE, iron responsive element; L-DOPA, levodopa; LRRK2, Leucine-rich repeat kinase 2; LPS, lipopolysaccharide; MMP-9, matrix metallopeptidase 9; MsrA, methionine sulfoxide reductases A; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP+, 1-methyl-4-phenylpyridinium; MMP, mitochondria membrane potential; MAO-B, monoamine oxidase-B; MPO, myeloperoxidase; Nrf2, NF-E2-related factor 2; NO, nitric oxide; NF-κB, nuclear factor-κB; PD, Parkinson’s disease; PPAR-γ, peroxisome proliferator-activated receptor-γ; PGC-1α, peroxisome proliferator-activated receptor-γcoactivator-1α; PARP-1, poly(ADP-ribose)polymerase 1; PGE2, prostaglandin E2; ROS, reactive oxygen species; RT-PCR, reverse transcription-polymerase chain reaction; sPLA2, secretory phospholipase A2; SIRT1, silent information regulator 1; SNpc, substantia nigra pars compacta; SOCS-1, suppressor of cytokine signaling 1; TNF-α, tumor necrosis factor-α; TH, tyrosine hydroxylase.

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References


[13] Chao J, Yu MS, Ho YS, Wang M and Chang RC. Dietary oxyresveratrol prevents parkinsonian...
Plant-derived neuroprotective agents in Parkinson’s disease


[37] Long J, Gao H, Sun L, Liu J and Zhao-Wilson X. Grape extract protects mitochondria from oxy-
Plant-derived neuroprotective agents in Parkinson’s disease


[55] Pan J, Li H, Ma JF, Tan YY, Xiao Q, Ding JQ and Chen SD. Curcumin inhibition of JNKs prevents dopaminergic neuronal loss in a mouse model of Parkinson’s disease through suppressing mitochondria dysfunction. Transl Neurodegener 2012; 1: 16.


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