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Review

Neuroprotective mechanisms of plant extracts against MPTP induced neurotoxicity: Future applications in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, affecting about seven to 10 million patients worldwide. The major pathological features of PD are loss of dopaminergic neurons in the nigrostriatal pathway and accumulation of alpha-synuclein molecules, forming Lewy bodies. Until now, there is no effective cure for PD, and investigators are searching for neuroprotective strategies to stop or slow the disease progression. The MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced neurotoxicity of the nigrostriatal pathway has been used to initiate PD in animal models. Multiple experimental studies showed the ability of several plant extracts to protect against MPTP induced neurotoxicity through activation of catalase, superoxide dismutase, and glutathione reductase enzymes, which reduce the cellular concentration of free radicals, preventing intracellular Ca^{++} release and subsequent apoptosis signaling. Other neuroprotective mechanisms of plant extracts include promoting autophagy of alpha-synuclein molecules and exerting an antiapoptotic activity via inhibition of proteolytic poly (ADP-ribose) polymerase and preventing caspase cleavage. The variety of neuroprotective mechanisms of natural plant extracts may allow researchers to target PD progression in different pathological stages and may be through multiple pathways. Further investigations are required to translate these neuroprotective mechanisms into safe and effective treatments for PD.

Contents

Abbreviations: ASK-1, Apoptosis signal regulating kinase-1; BDNF, Brain Derived Neurotrophic Factor; CI, Chrysanthemum indicum Linn; DAT, Dopamine transporter; EGb761, Ginkgo biloba extract 761; EGCG, Epigallocatechin-3-gallate; GR, Glutathione Reductase; H2O2, Hydrogen peroxide; HO-1, Heme-Oxygenase 1; JNK, c-Jun NH2-terminal kinase; LAMP-2A, Lysosome associated membrane protein type 2A; LC3-II, Light chain 3- phosphatidylethanolamine conjugate; MAPK, mitogen activated protein kinases; MDA, Malondialdehyde; MPTP, 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; NADP(H)QO-1, Nicotine-Adenine Diphosphonucleotide, Quinone oxidoreductase 1 (NQO1); NBP, Dl-3-n-butylphthalide; NF-Kb, Nuclear factor- Kappa-B; NO, Nitric oxide; Nrf-2, Nuclear factor-2 Erythroid-2; PARP, Poly (ADP-ribose) polymerase; PC12, Pheochromocytoma cells 12; PCA, Protocatechuic acid; PF, Paeoniflorin; PGC, Peroxisome proliferator-activated receptor gamma coactivator 1; PI3K/Akt, Phosphatidylinositol 3-kinase/Protein Kinase B; ROS, Reactive oxygen species; SAC, S-Allylcysteine; SH-SY5Y, Human Neuroblastoma cells; SOD, Superoxide Dismutase; UPS, Ubiquitin Protease system.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition after Alzheimer's disease, affecting about 1% of the worldwide population above 60 years [1]. The major pathological features of PD are loss of dopaminergic neurons in the nigrostriatal pathway and formation of Lewy bodies [2]. Due to death of dopaminergic neurons, PD patients suffer from motor symptoms such as tremors, rigidity, and bradykinesia which cause disabilities and affect their quality of life [3]. To the moment, there is no effective cure for PD, and current medications aim at controlling the symptoms and improving the quality of life for PD patients [4].

The main pathological pathway, responsible for death of dopaminergic neurons in PD, is not yet known [3]. Population based studies identified mutations in some genetic loci that can predispose to the development of sporadic PD [5,6]. The first identified genetic mutation was found in the alpha-synuclein gene [7]. Alpha-synuclein is an elongated, unstructured presynaptic phosphoprotein that is believed to contribute to the function of synaptic vesicles and is normally cleaved by unidentified synucleinases [8]. Genetic mutations, oxidative stress, dopamine depletion, and proteosomal dysfunction can induce hyperphosphorylation, misfolding and aggregation of alpha-synuclein molecules [9], forming eosinophilic inclusions, known as Lewy bodies [10]. The aggregation of these molecules in a toxic, misfolded form may contribute to neuronal cell death [11]. Another common mutation occurs in the parkin ligase expression gene [12], which codes for a ligase enzyme that adds ubiquitin molecules to mark the target proteins for proteosomal clearance [13]. Loss of its enzymatic function causes accumulation of its substrates such as fructose-1,6-bisphosphatase 1 (FBP1) and aminoacyl-tRNA synthetase-interacting multifunctional protein type 2 (AIMP2), leading to neuronal cytotoxicity [14]. Epidemiological studies showed a link between exposure to environmental factors such as organophosphorus compounds, viral encephalitis, or repeated head trauma and the risk of developing PD [15,16].

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin that has the ability to cross the blood brain barrier and damage dopaminergic neurons in the nigrostriatal pathway [17]. Although MPTP itself is not toxic, it is transformed by monoamine peroxidase enzyme to MPP^+ which binds to dopamine transporters (DAT), causing inhibition of dopamine uptake and depletion of its cerebral levels [18]. When transported inside the neuronal bodies, MPP^+ passes to the mitochondria and impairs oxidative phosphorylation through inhibition of complex I (NADPH-ubiquinone oxidoreductase I) in the electron transport chain [17,19,20]. This inhibition leads to elevated Ca^{++} levels, formation of free radicals, and impairment of ATP production causing inability of the mitochondria to supply the cell with energy [21]. The MPTP induced neurotoxicity of the nigrostriatal pathway is used to initiate PD in animal models [22,23]. Experiments on MPTP treated animal models led to better understanding of PD pathology including microglial activation and oxidative stress, and allowed investigators to test neuronal replacement therapies for this neurodegenerative condition.

Due to the progressive nature of PD, investigators are searching for neuroprotective agents that can stop the underlying pathological condition and therefore, prevent further neuronal death. The literature suggests that several medicinal plants and their active constituents and extracts exert neuroprotective effects against neuronal cell death [24]. These plants have been traditionally used in folk medicine for centuries [25], and currently, they are widely used in traditional Chinese medicine for treating neurological disorders such as general paralysis, epilepsy, cerebrovascular disorders, and neurodegenerative diseases [26–28]. Recently, scientific research on medicinal plants is getting more attention because the identification of their active ingredients can improve drug manufacturing [29] and studying their mode of action may help identifying new therapeutic targets. In this article, we reviewed preclinical trials that investigated the neuroprotective effects of plant extracts against MPTP induced neurotoxicity.

2. Summary of neuroprotective effects of different plant extracts

Preclinical trials identified several mechanisms, underlying the observed neuroprotective effects of medicinal plants, including antioxidant, anti-inflammatory, antiapoptotic, and neurotrophic mechanisms [30]. Understanding these mechanisms at the molecular level will help developing novel neuroprotective agents for PD.

2.1. Antioxidant activity

This is the most commonly reported mechanism of action for plant extracts in attenuating MPTP induced cytotoxicity and improving cell viability (Table 1). The formation of reactive oxygen species (ROS) results in mitochondrial transmembrane potential collapse and dysfunction of the mitochondrial respiratory chain complex-1, which ultimately leads to increased cytosolic concentrations of Ca^{++} and mitochondrial cytochrome C, initiating apoptosis signaling pathways [24]. Therefore, the reduction of cellular free radicals prevents apoptosis and preserves mitochondrial function [30].

Several plants including those of *Alpinia oxyphylla*, *Chrysanthemum indicum Linne* (CI), and *Chrysanthemum morifolium* Ramat (CM) plants can reduce the production of ROS through direct activation or increasing mRNA expression of reductive enzymes such as catalase, superoxide dismutase (SOD), glutathione reductase (GR), and phase two enzyme [Nicotine-Adenine Diphosphonucleotide (NADP(H))-Quinone oxidoreductase 1 (NQO1)] [31–33]. Moreover, numerous compounds such as *Ginko biloba* extract 761 (EGb761) and S-Allylcysteine (SAC) can attain a free radical scavenging action to inactivate nitrous oxide (NO) and hydrogen peroxide (H2O2) radicals [34,35]. The efficacy of these compounds can be evaluated through measuring the cytoplasmic levels of malondialdehyde (MDA), which acts as an index for lipid peroxidation [36]. In a recent study by Jiang and colleagues (2014), application of gastrodin on MPTP treated SH-SY5Y cells resulted in enhanced nuclear factor-2 Erythroid-2 (Nrf2) nuclear translocation which is upstream of Heme-Oxygenase-1 (HO-1)