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Review

Important medicinal herbs in Parkinson's disease pharmacotherapy

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ABSTRACT

Parkinson's disease (PD) is the most common progressive neurodegenerative movement disorder affecting more than 10 million people worldwide. The characteristic hallmark of PD involves progressive loss of dopaminergic (DA-ergic) neuron in Substantia Nigra pars compacta (SNpc) region of the brain, however, aetiology of the disease still remains unclear. Mitochondrial dysfunction and oxidative insult are considered to be the key culprit. The current therapy available for PD primarily relies on Levodopa that offers the potential of slowing down disease progression to some extent but includes lot of side effects. Any potential drug capable of treating or halting the disease still remains to be identified. It is evident that redox stabilization and replenishment of mitochondrial function seem to be an important therapeutic approach against PD as both are required for optimal neuronal functioning. Enormous research done in this field has shown that some natural and synthetic products exhibit neuroprotective and anti-apoptotic potential by improving mitochondrial function and alleviating oxidative stress. Therefore, the present review aims to discuss some of the important medicinal natural herbs (*Bacopa monnieri, Mucuna pruriens, Withania somnifera, Curcuma longa, Gingko Biloba, and Camellia sinensis*) in context to their neuroprotective potential and also in the development of novel therapeutic strategies against PD.

Contents

Abbreviations: ACh, acetylcholine; AD, alzheimer's disease; Bm, *Bacopa monnieri*; BME, bacopa monnieri extract; BBB, blood-brain barrier; Cl, *Curcuma longa*; Cs, *Camellia sinensis*; DA, dopamine; DAT, dopamine transporter; ETC, electron transport chain; Gb, *Gingko biloba*; iNOS, inducible nitric oxide synthase; MAO-B, monoamine oxidase B; Mp, *Mucuna prurient*; MDA, malondialdehyde; MPP+, 1-methyl-4-phenyl-pyridinium iodide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, parkinson's disease; PQ, paraquat; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; TH, tyrosine hydroxylase; Ws, *Withania somnifera*; 6-OHDA, 6-hydroxy dopamine.

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1. Introduction

PD is the most common progressive neurodegenerative movement disorder affecting more than 10 million people worldwide and the incidence of PD increases with the age (http://www.pdf.org/en/parkinson_statistics). It is estimated that 4% of PD cases are identified prior to 50 years of age and that male population is more prone to have PD than their female counterpart [1,2]. In addition, the average medication costs per person suffering from PD is around $2500 per annum and the therapeutic surgery for PD patient may cost around $100,000 (http://www.pdf.org/en/parkinson_statistics). Moreover, the number of PD patients worldwide is increasing exponentially thereby severely affecting the social and personal life of an individual.

The neuropathological characteristic of PD involves progressive loss of DA-ergic neurons specifically in the SNpc region of the brain [3] involving generation of Lewy bodies pathology [4]. The degeneration of DA-ergic neurons is considered to be the root cause of the characteristic classical motor symptoms [5] and non-motor symptoms [6]. Further, the etiology of PD is not yet clear, but the risk of developing PD involves multifactorial heterogeneous risk factors. These risk factors include age, gender, ethnicity [1], environmental and genetic component [7]. Based on the studies, it is known that mitochondrial dysfunction and altered oxidative stress are the two crucial cellular stress parameters playing important role in PD pathogenesis [8–10]. Research has revealed that mitochondrial quality control and dynamics are crucial for optimum neuronal functioning, and any alteration leads to neuronal cell death as summarized in the recent review [11]. This is evident in the brain autopsy sample from PD patients and animal models, where mitochondrial function specifically complex I activity was found to be diminished [12]. Further, mitochondria is involved in mitophagy thereby keeping check of dysfunctional organelles [13]. Also, mitochondria helps in maintaining the synaptic activity at the terminal end of the neurons by optimized distribution of organelles as per the energy demand of neurons [14]. Therefore, mitochondria seem to be one of the primary targets which may lead to neuronal cell loss in neurodegenerative disorders. However, last couple of decade research has provided some important insight but still the present knowledge is superficial for understanding aetiology of the disease.

Further, the current therapeutic strategy against PD primarily relies on restoring the optimum level of dopamine (DA) and its associated signalling pathways, for which Levodopa or L-DOPA (L-3, 4-dihydroxyphenylalanine), a precursor of DA is administered to the PD patients [15]. L-DOPA provides initial benefit by slowing down the disease progression; however, long term benefits are unlikely [16]. Moreover, it is also administered in combination with carbidopa, a peripheral decarboxylase inhibitor. This helps in alleviating the side effect of L-DOPA which mainly include gastrointestinal and cardiovascular problems [15]. Another strategy for PD therapy is the use of monoamine oxidase B (MAO-B) inhibitors. The activity of MAO-B enzyme is increased on account of DA metabolism which elevates oxidative stress and mitochondrial dysfunctions [15]. To date, mitochondrial dysfunction and altered oxidative stress are considered to be the possible mechanism leading to neuronal cell death [8,11,17]. Therefore, therapeutic approaches that optimize ROS and ameliorate mitochondrial function are being thoroughly considered in the current scenario. In this milieu, several approaches are being under investigation [18], and pharmacological approach involving a natural extract from medicinal plants has been shown to impart beneficial effect in PD [17,19–26]. Although the exact molecular mechanism of action still remains elusive. However, optimization of ROS production is considered to be a prime target of these natural plant products [17]. Research during the last couple of decade has identified several plants that show medicinal property against neurodegenerative disorders like PD and AD. Therefore, the present review aims to discuss some of the important medicinal natural herbs (*Bacopa monnieri, Mucuna pruriens, Withania somnifera, Curcuma longa, Gingko Biloba, and Camellia sinensis*) in context to their neuroprotective potential and also in the development of novel therapeutic strategy against PD. The summary is given in Table 1.

Table 1
Summary of medicinally important herbs in PD.

Plant	Common name	Important constituents	Functions	References
Bacopa monnieri	Brahmi or waterhyssop	Bacopaside and bacoside	Redox stabilization, improves mitochondrial function, attenuate α-synuclein aggregation, attenuate apoptosis, improves cognition	[20,27–29]
Mucuna pruriens	Velvet bean	Glycoside, gallic acid, glutathione, Levodopa	Improves locomotor & behaviour function, alleviate oxidative stress, metal chelation, mitochondrial and synaptic function, TH expression	[30–33]
Withania somnifera	Ashwagandha or Indian ginseng	Withaferin, withanolide	Alleviate oxidative stress, improve dopamine level, motor function, glutathione level, TH expression, inhibition of iNOS,	[34–38]
Curcuma longa	Turmeric	Curcumin	Improves striatal dopamine level, mitochondrial Complex I activity, Reduces oxidative stress, up-regulate SOD and GPx activity, acetylcholine level, replenish mitochondria membrane potential and ATP production, inhibit α-synuclein fibrillization	[24,39–42]
Gingko Biloba	Maidenhair tree	EGb 761, Ginkgolide B	Improve DA level, behaviour function and muscle coordination, redox stabilization, uplift mitochondria function and ATP production	[34,43–45]
Camellia sinensis	Green tea	Polyphenols, catechins [epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG)]	Redox stabilization, inhibit ROS-NO pathway, metal chelation, Protects DA neurons in nigral region	[19,46–49]
Camellia sinensis	Black tea	Theaflavins [theaflavin (TF1), theaflavin-3-gallate (TF2A), theaflavin-3′-gallate (TF2B) and theaflavin-3,3′-digallate (TF3)]	Neuroprotective, redox stabilizer, Enhances TH & DAT expression, anti-apoptotic	[50,51]

TH: tyrosine hydroxylase; iNOS: inducible nitric oxide synthase; SOD: superoxide dismutase; GPx: glutathione peroxidise; ROS-NO: reactive oxygen species-nitric oxide; ATP: adenosine triphosphate; DA-ergic: dopaminergic; DAT: dopamine transporter.