REVIEW ARTICLE

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Harnessing nature – plant compunds as potential breakthrough therapeutics for Parkinon's Disease

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Abstract

Introduction and Objective. Parkinson disease (PD) is the second most common progressive neurodegenerative disorder. Aetiology evolves around atrophy of dopaminergic neurons located in the substantia nigra. The main ailments that impair motricity include generalized bradykinesia and at least one other symptom of resting tremor or rigidity. In addition to cardinal PD symptoms, the disease can also cause a range of non-motor disabilities. The aim of the review is to describe natural plant-origin substances currently being tested in specific PD models that could become detrimental to PD management in the future.
Review Methods. A search of PubMed was conducted for original articles examining the use of natural plant-derived products in animal or cell models of PD. Two search formulations were used to broaden the scope of the results: 'natural product' and 'plant', and 'Parkinson's disease' and 'natural product, and 'herb' and 'Parkinson's disease'.
Brief description of the state of knowledge. Currently, it is thought that at the molecular level, substantia nigra atrophy may be related to the accumulation of abnormal proteins in the form of Levy bodies (LBs), mitochondrial disorders, neuroinflammation, and disruption of the blood–brain barrier (BBB) function. In recent years, many etiologies of PD have been indicated. Current state-of-the-art treatments for PD are only symptomatic, and causative medication is unavailable.
Summary. The use of natural components is very promising in the current search for effective PD treatments. Their mechanism of action is based on complex molecular mechanisms, the disorders of which are the basis for the occurrence of PD in humans. Harnessing the therapeutic potential of these natural compounds may be crucial for the future treatment of PD patients. However, rigorous evaluation of pharmacokinetics, bioavailability, among others, need to be established.

Key words

dopamine, Parkinson's disease, neuroprotection, natural compounds

INTRODUCTION AND OBJECTIVE

Parkinson disease (PD) is the second most common progressive neurodegenerative disorder [1], characterized by the progressive loss of selectively vulnerable populations of neurons. It mostly presents in later life with a generalized slowing of movements (bradykinesia) and at least one other symptom of resting tremor or rigidity. In addition to cardinal PD symptoms, this disease can also cause a range of non-motor symptoms, including dysarthria or dysphagia, psychiatric disorders, such as depression, anxiety and insomnia, as well as impairment of cognitive functions. PD patients can suffer from autonomic symptoms, such as constipation, urinary incontinence, drooling, erectile dysfunction, hypotension or seborrhea. PD was first described by James Parkinson in 1817, since when the understanding of the etiology of PD has evolved immensely. In 1919, it was first recognized that loss of pigmentation in the substantia nigra of the midbrain is a chronic feature of postmortem brain specimens from patients with PD. In the 1950s, these pigmented neurons that are lost in the substantia nigra were described as dopaminergic, and dopamine deficiency in the subcortical motor circuitry as responsible for movement symptoms in PD patients.

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DESCRIPTION OF THE STATE OF KNOWLEDGE

Currently, it is thought that at the molecular level, substantia nigra atrophy may be related to the accumulation of abnormal proteins in the form of Levy bodies (LBs) [2], mitochondrial disorders [3], neuroinflammation [4], and disruption of the blood–brain barrier (BBB) function [5]. In recent years, many etiologies of PD have been described, including genetic, infectious, autoimmunologic, iron storage, and even intestinal microbiome imbalance [4–10]. Risk factors include older age, male gender, family history, genetic factors, environmental exposures, and possibly head trauma [11]. In industrialized countries, the estimated prevalence of PD is 0.3% in the general population, 1.0% in people older than 60 years and 3.0% in people older than 80 years [12]. Due to the limited options available for treating PD and the increasing prevalence of this disease, there is a constant search for new therapeutic agents, both as symptomatic agents and, more importantly, as causative agents, which are currently unavailable. At present, the only treatment officially recommended for motor symptoms in PD management has evolved around increasing dopamine levels in the nervous system. This consists of four groups of medications: L-DOPA, COMT (catechol-O-methyl transferase) and MAO-B (monoamine oxidase B) inhibitors, dopamine agonists and amantadine. Non-motor ailments are treated according to the respective guidelines. Additionally, a surgical alternative known as deep brain stimulation (DBS) is

currently being used, especially for patients who are resistant to pharmacological therapy [13].

The main aim of the presented review article was to provides details about natural plant-origin substances currently being tested in specific PD models and under consideration for possible PD treatment. It is worth noting that this group of compounds has mostly been used previously in traditional medicine or as supplements, and even as recreational drugs. However, the substances are currently receiving increasing amounts of attention due to their properties, as they may in the future become new drugs or precursors of drugs used in everyday practice in PD [14, 15].

REVIEW METHODS

A search of PubMed was conducted for original articles investigating the use of natural plant-derived products in animal or cell models of PD. Two search formulations were used to broaden the scope of the results: 'natural product' and 'plant', and 'Parkinson's disease' and 'natural product', and 'herb' and 'Parkinson's disease'. Studies written in English from the last 10 years that addressed the main topic of the issue were considered.

RESULTS

As a result of the research, 23 studies were found, of which 11 met the conditions for inclusion in the review and full access to them was obtained. Additionally, other works that outlined the context were used to present the characteristics of given species and substances. Individual substances and plants along with their action characteristics and the PD model in which they were used are summarized in Table 1.

CHARACTERISTICS OF INDIVIDUAL COMPOUNDS OF PLANT ORIGIN

Humulus japonicus. A vine plant that grows in various regions of Asia and is considered a harmful plant due to its rapid growth. Nevertheless, it has been applied in traditional natural medicine where it has been used to treat many diseases, including pulmonary tuberculosis, dysentery and chronic colitis. To date, the properties of the plant's components have been demonstrated to be antibacterial, antioxidant and antitumour [16]. Using the active enrichment fraction, a stronger motor improvement effect was observed in the 6-OHDA-lesioned PD mouse model than in the 70% EtOH extract of H. japonicus. Right forelimb damage (induced rotational asymmetry) was also improved which, in connection with the above data, suggests the neuroprotective effect of active compounds of H. japonicus in diseases such as PD. This effect may be caused by the flavonoids such as luteolin-7-O-glucoside or apigenin-7-O-glucoside and their metabolites: luteolin and apigenin, respectively, which have MAO-B inhibitor properties and angiotensin I converting enzyme inhibitor compounds [17].

Aegle marmelos. A fruit plant found in tropical and subtropical regions. The presence of various compounds, such as alkaloids, flavonoids, and phenolic acids, constitutes a source of medical research on this plant [18]. One such compound that may be used in PD therapy is aegeline, which is an alkaloid-amide that occurs in the leaves of the Aegle marmelos plant. Aegeline is a substance that imitates the action of yeast Sec22p, a SNARE protein essential for Golgi trafficking to the endoplasmic reticulum. The over-expression of Sec22p can reverse a yeast growth blocked by the expression of?-syn or the proapoptotic human protein Bax, which are among the many pathophysiological causes of neurodegenerative processes. Aegeline can block apoptosis via these two pathways. In the case of?-syn-induced apoptosis, it blocks their aggregation by attaching to the?-syn building amino acids. The mechanism of action of aegelin in the case of apoptosis induction by Bax is more complicated and is most likely based on blocking the BH4 domain, and thus preventing its interaction with other ligands necessary for Bax activity [19].

Tanacetum parthenium. Commonly called feverfew, is a perennial plant species rich in essential oils and tannins and has been used to treat migraines, arthritis, and as a febrifuge [20]. Parthenolide is a natural compound of sesquiterpene lactones extracted from the buds of feverfew. The parthenolide derivative (ACT001) contains the dimethylaminomicheliolide, the pro-drug of active compound micheliolide. The ACT001 in mice intra-gastrically injected with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to induce PD, at a dose of 20 mg/kg 1 h prior to each MPTP administration every 24 h for 7 days, yielded the following results: the use of ACT001 in combination with L-DOPA substantially improved the results of the open field locomotion activity test and cylinder test, suggesting that L-DOPA has a favourable therapeutic effect on MPTP-induced PD. Similarly, co-administration of ACT001 and a lower dose of L-DOPA resulted in better locomotion in mice, which was equivalent to using a higher dose of L-DOPA without ACT001. The mechanisms at the molecular level that contribute to the improvement of MPTP-induced PD in mice are complex and involve various aspects. Based on immunohistochemical tests the combination of ACT001 and a lower dose of L-DOPA (5mg/kg) did not reduce the amount of tyrosine hydroxylase (TH) positive neurones in the nigrostriatal pathway or in the striatum compared to placebo, and a similar effect was achieved using a higher dose of L-DOPA (8mg/kg) without ACT001. Moreover, co-administration of ACT001 and L-DOPA inhibited MPTP-induced?-syn over-expression in dopaminergic neurons in the striatum. The synergistic effect of ACT001 and L-DOPA was also noticeable in the processes of neuroinflammation and the intensification of apoptotic processes by MPTP, where an inhibition of the increase in the production of pro-inflammatory proteins in the striatum, such as IL-1?, Bax, and cleaved-caspase3, and even a reduction in the level of Bcl-2 are observed. Co-administration of ACT001 and L-DOPA also reduced MPTP-induced astroglial activation and increased neuronal survival. [21].

Boswellia serrata. A medium- to large-sized tree growing in northern Africa, the Middle East and India. Research on the use of this plant in medicine has shown its anti-inflammatory effects on diseases such as enteritis [22, 23]. In a study investigating the effect of Boswellia resin, the main active compound of which is?-boswellic acid, on the activation of the AMPK pathway, increased AMPK

phosphorylation in the striatum was demonstrated after a two-week administration of the extract. Moreover, Boswellia treatment resulted in increased levels of beclin1, a marker of autophagy and decreased phosphorylation of?-syn in the striatum. Boswellia gum extract upregulated the expression of brain-derived neurotrophic factor (BDNF), compared to the control group. In a rotenone-induced toxicity mouse model, Boswellia gum extract significantly attenuated the rotenone-mediated deletion of dopaminergic neurons and of striatal TH-positive neurons. In the case of monoamine levels, a soothing effect of the extract on the decrease in 3,4-dihydroxyphenylacetic acid (DOPAC) and dopamine in mice after the application of rotenone was observed. Boswellia extract also significantly attenuated microglial activation in the substantia nigra. Motor dysfunction was attenuated by treatment with Boswellia extract in the beam test and challenging beam test, and was completely prevented during the cylinder test [24].

Taxus and Tanacetum genus. Another active compound studied in neurodegenerative diseases is myrtenol, an alcoholic monoterpene with a number of health-promoting activities, which is obtained from the Taxus and Tanacetum genus. The effect of myrtenol (5mg/kg) in combination with?-cyclodextrin was investigated in a progressive Parkinsonism model induced by reserpine in mice. Myrtenol treated mice showed better results in tests such as olfactory discrimination tasks and novel object recognition. Compared with those in the reserpine group, delayed and reduced motor deficits and a decreased number of oral movements were also observed in the myrtenol treated group. The study also indicated the protective effect of myrtenol in terms of inhibiting the loss of TH-positive neurons, as well as decreasing oxidative status in the prefrontal cortex [25].

Alpinia oxyphylla. The effectiveness of natural products from Alpinia oxyphylla fruits rich in terpenoids, flavonoids and sterols has also been tested in PD models. These compounds include the R and S enantiomers of oxyphylla A at a concentration of 5 μM, the use of which in the MPTP-induced PD zebrafish model, resulted in an almost complete restoration of the function of dopaminergic neurons that were originally lost after the use of MPTP. The use of oxyphylla A also resulted in improved locomotion of zebrafish, compared to that of the control group, as measured by the length of the distance they swam. The authors also cite the potential possible mechanisms responsible for the effectiveness of (R)-oxyphila A, which include the activation of nuclear factor E2-related factor 2 (NRF2), and the activation of the ubiquitin proteasome system and PKA/Akt/mTOR pathway [26, 27].

Aster koraiensis. A perennial herb found mainly on the Korean Peninsula and is used in traditional medicine for respiratory diseases, mainly infections [28]. One of the compounds that may be used to treat neurodegenerative diseases is astersaponin, a triterpene saponin isolated from the EtOH extract of A. koraiensis. The main mechanism responsible for research on astersaponin is its ability to induce autophagy, which is a neuroprotective pathway. Astersaponin significantly increased the expression of microtubule-associated protein 1A/1B light chain 3B in human neuroblastoma (SH-SY5Y) cells, which indicates the induction of autophagy [29].

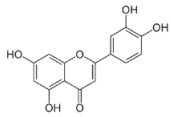
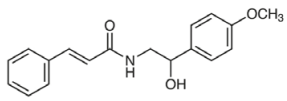
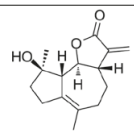
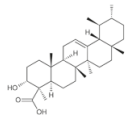
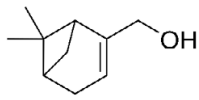
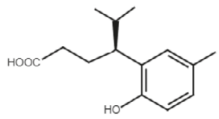
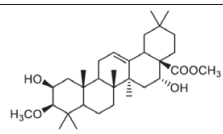
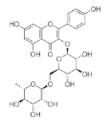
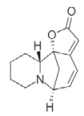
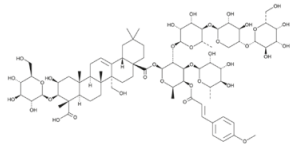
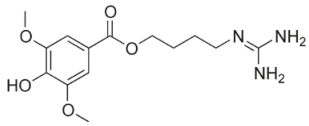
Byrsonima sericea. A widely-known semi-deciduous tree that grows in Bolivia, Peru, Guyana, and French Guiana, and in the northeastern states of Brazil. B. sericea extracts contain antioxidant compounds such as flavonoids and kaempferol-O-hexoside [30]. The ethanolic extract of the leaf of B. sericea (BSEE) was evaluated in a PC12 cell model of Parkinsonism caused by 6-hydroxydopamine (6-OHDA). BSEE contains active compounds, such as kaempferol 3-O-?-rutinosid, geraniin, rutin, isoquercetin and quercetin. BSEE at a concentration of 75 μg/mL blocked the increase in LDH activity and nitrite levels induced by 6-OHDA. Compared with 6-OHDA, 6-OHDA also had a positive effect on cell viability and decreased apoptotic activity. Researchers suggest that the effect of BSEE is due to its ability to scavange reactive oxygen species (ROS) and modulate inducible nitric oxide synthase (iNOS) and NADPH oxidase 2 [31].

Securinega suffruticosa. A plant of Asian origin used in traditional medicine. The natural product obtained from the roots of this plant is the alkaloid securinine. The effects of securinine (10?M) on the production of inflammatory mediators in LPS-treated BV2 cells and mouse primary microglia were examined. Researchers have demonstrated that securinine effectively inhibits LPS-induced and interferon induced NO production and iNOS expression at the mRNA and protein levels in primary microglial cell cultures. Moreover, securinine significantly reduced the expression of proinflammatory molecules such as TNF- and IL-1? in both BV2 cells and primary microglia. A possible protective effect of securinine on the survival of TH-positive neurons in an induced model was also demonstrated. The mechanisms through which securinine is effective include reducing NF B-dependent transcriptional pro-inflammatory activity and repressing the phosphorylation of the p38 MAPK signaling pathway [32].

Polygala tenuifolia, Angelica tenuissima, and Dimocarpus longan. Another tested preparation is the 20% ethanol extract of herbs traditionally used in Asian medicine, namely Polygala tenuifolia, Angelica tenuissima, and Dimocarpus longan. The active compounds contained in the extract include onjisaponin B and its metabolites. The use of the extract (200 mg/kg) to treat MPTP-induced mice significantly improved their results in the latency test and field test results. As with the previous substances, the effectiveness of the extract in the recovery of TH-positive cells in the substantia nigra pars compacta and striatum has also been demonstrated. Treatment with both 100 and 200 mg/kg extract significantly increased the expression level of beclin-1, reduced the mTOR protein expression and reduced the p62 protein expression level. After using the extract, autophagy-related proteins were positively regulated in the 6-OHDA model, as indicated by an increase in the LC3-II/LC3-I conversion ratio and an increase in the level of beclin-1, a protein related to autophagy. In the 6-OHDA-induced cytotoxicity model, pre-treatment with the extract significantly downregulated the protein expression of mTOR, which again led to the conclusion that the preparation has a positive effect on autophagy processes in PD models [33].

Leonurus japonicus. A compound with a completely different action profile than that of previous preparations. It is an alkaloid obtained from the herb Leonurus japonicus,

Table 1. Characteristics of specified substances in various toxicity induced models, along with their effectiveness

Natural products and origin	Examples of chemical structures of potential active components	Animal or Cell Model	Efficiency	Mechanism of action
Active components of *H. japonicus*	 Luteoline	6-OHDA-lesioned mice PD model	Suggested neuroprotective effect. Improvement in motor function and right forelimb damage.	Complicated action in many mechanisms, including as an MAO-B inhibitor and ACE I inhibitor
Aegelin from leaves of *A. marmelos*	 Aegelin	α-syn/Bax induced apoptosis in yeast	Restoring the growth of the yeast with overcoming of the induced apoptosis	Sec22p like substance attaching to the α-syn building amino acids and blocking the BH4 domain in Bax
Parthenolide from the buds of *T. parthenium*	 Micheliolide	MPTP-induced PD in mice model	Statistically improved open field locomotion activity test and cylinder test	Preventing the loss of TH-positive neurons, reducing α-syn expression and neuroinflammation
B. serrata resine	 β-boswellic acid	Rotenone-induced neurotoxicity in mice model	Statistically significant improvement in motor functions; increase in BDNF levels; reducing the loss of TH-positive neurons, dopamine and DOPAC	Activation of AMPK pathway (phosphorylation); increasing beclin-2 and reducing phosphorylation of α-syn
Myrtenol from *Taxus* and *Tanacetum* genus	 Myrtenol	Reserpine-induced PD mice model	Statistically significant improvements in motor function and oral movements; reducing the loss of TH-positive neurons; reducing oxidative stress	Studies indicating the mechanism of action are further needed
R and S enantiomers of oxyphylla A isolated from *A. oxyphylla* fruits	 (R)-Oxyphylla A	MPTP-induced PD zebrafish model	Improved locomotion measured by swimming distance; restoring the function of dopaminergic neurons	Activation of NRF2, ubiquitin proteasome system and PKA/Akt/mTOR pathway
Astersaponin from extract of *A. koraiensis*	 Astersaponin A	Human neuroblastoma (SH-SY5Y) cells	Most likely induction of autophagic processes; more data is needed	Increasing the expression of microtubule-associated protein 1A/1B light chain 3B
Ethanolic extract of the leaf of *B. sericea*	 Kaempferol 3-O-β-rutinosid	PC12 cell model 6-OHDA induced PD	Blocking the increase in LDH activity and nitrite levels; increasing cell viability and decreasing apoptotic activity	Antioxidant effects by reducing ROS and modulating iNOS and NADPH oxidase 2
Securinine from *S. suffruticosa*	 Securinine	LPS-induced activation of microglia and astrocytes in mice cells	Reducing the production of pro-inflammatory cytokines and NO; protection of TH-positive neurons	Reducing NF B-dependent transcriptional proinflammatory activity; repressing the phosphorylation of p38 MAPK signaling pathway; inhibition of iNOS activity
20% ethanol extract of *P. tenuifolia*, *A. tenuissima,* and *D. longan*	 Onjisaponin B	MPTP-induced PD mice model; 6-OHDA induced toxicity	Significantly improved results of the latency test and field test; recovery of TH-positive cells in substantia nigra pars compacta and striatum	Inhibiting the inflammatory process, inducing the autophagy process by modulating protein expression (LC3-II/LC3-I conversion, beclin-1 and mTOR)
Leonurine from *L. japonicus*	 Leonurine	Psychological stress-induced PD mice model, MPTP-induced PD mice model	Mitigating the phospholipid peroxidation of dopaminergic neurons; improving the results of the pole test, rotarod test, and gait analysis	Inhibition of ALOX15 and disrupting ALOX15/PEBP1 interaction; decreasing the level of transferrin receptor protein 1 and prostaglandin-endoperoxide synthase 2

which is a Chinese traditional herbal medicine used to treat gynaecological diseases [34]. The mechanisms that increase susceptibility to PD include oxidative stress and increased phospholipid peroxidation caused by the activity of the 15-lipoxygenase-1 (ALOX15) complex, and phosphatidylethanolamine-binding protein-1 (PEBP1) in dopaminergic neurons. Leonurine can mitigate peroxidation through direct inhibition of ALOX15, and thus significantly disrupted the ALOX15/PEBP1 interaction in RSL3 or rotenone-induced ferroptosis models. Moreover, leonurine significantly protected mice from MPTP-induced PD,according to the results of the pole test, rotarod test, and gait analysis. In MPTP-induced PD, leonurine also significantly reduced the binding of ALOX15 and PEBP1, and decreased the levels of transferrin receptor protein 1 and prostaglandin-endoperoxide synthase 2 [35].

DISCUSSION

The pathophysiological mechanisms underlying PD have not yet been fully elucidated. To date, therapeutic strategies for PD patients have focused on alleviating and counteracting symptomatic manifestations because disease-modifying treatments are unavailable.

Currently, plant compounds are attracting interest in the development of new therapeutic strategies due to their multidirectional effects, enabling the simultaneous modulation of multiple outcomes [36, 37]. Natural product-derived molecules have demonstrated good therapeutic effects in neurodegenerative diseases as a less toxic treatment, and results published in the scientific literature highlight the beneficial effects of administering natural molecules in controlling the?-Syn aggregation process [38, 39].

Popular molecules, including caffeine, baicalein, rosmarinus acid, and flavonoids, have been evaluated as potential neuroprotective agents and have demonstrated beneficial effects both in vivo and in vitro. However, their effects are primarily attributed to exogenous and endogenous antioxidant properties, leading to diminished neuroinflammation through the reduction of oxidative stress damage [40–42].

In contrast, several plant compounds, such as securinine from S. suffruticosa or a 20% ethanol extract of P. tenuifolia, A. tenuissima, and D. longan, have therapeutic effects through different pathways in addition to the classical antioxidant Nrf2 and anti-inflammatory NF-?B pathways. Therefore, they can be proposed to modulate PD progression through various mechanisms of action [32, 33].

From a critical point of view, current data on the potential use of natural product-derived molecules as therapeutic strategies for PD are engaging. Nevertheless, more research is required to elucidate the roles these compounds play in other signalling pathways, as well as their selectivity and binding mechanisms to the different forms of?-syn [38].

It is worth noting that most of the mentioned studies were conducted in vitro in animal models. Extensive preclinical studies in animal and cell models are required to identify individual active compounds and elucidate their precise molecular mechanisms of action. Although animal and cell models are essential for advancing our understanding of the molecular pathways involved in various diseases, the results obtained from these models cannot be directly extrapolated to human cells, tissues, or the entire human body. Furthermore, additional data are also required regarding the pharmacokinetic parameters of natural molecules, including absorption, excretion, hepatotoxicity, and BBB permeability. To achieve this, after thorough testing and classification of the selected plant-based extracts, randomized clinical trials are necessary to assess their safety profile. [39].

In future developments, an experimental approach could involve co-administering plant compounds targetting various mechanisms, including the modulation of chaperone activity, direct interaction with different forms of?-syn, and enhancement of proteasomal degradation.

Another compelling challenge could involve combining various therapeutic strategies, such as administering natural product-derived molecules with synthetic peptides, antibodies, or other biologic drugs to mitigate the?-syn burden.

CONCLUSIONS

PD is a complicated disease requiring a comprehensive treatment approach. Potential compounds that could cure or alleviate the course of PD are still being sought for. These include drugs of plant origin, the potentially beneficial effects of which have been demonstrated in many cellular and animal PD models. Natural compounds exert their effects through complex molecular mechanisms, the disorders of which are the basis for the occurrence of PD in humans. In summary, harnessing the therapeutic potential of these natural compounds may be crucial for improving the quality of life of patients, and developing new therapeutic strategies. However, rigorous evaluation of pharmacokinetics, bioavailability and potential drug interactions, is essential to establish evidence-based treatment options.

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