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REVIEW OF NATURAL PRODUCTS ON PARKINSON'S DISEASE PATHOLOGY

M.M. Essa[1,2], N. Braidy[3], W. Bridge[4], S. Subash[1,2], T. Manivasagam[5], R.K. Vijayan[1], S. Al-Adawi[2,6], G.J. Guillemin[7]

Abstract: This review examines evidence of plant-derived natural products and their constituents that have been shown to slow down or reverse the underlying neuronal degeneration observed in Parkinson's disease (PD), with a focus on their effect on the modulation of dopaminergic neurotransission levels and motor function. During the last decade, there have been over 140 studies published that have investigated the anti-PD therapeutic potential of herbs, fruits, vegetables and spices, ornamental and parasitic plants, and fungi. Empirical evidence implicates phytochemicals may play a role in the prevention and mitigation of some of the intractable signs and symptoms of PD. The anti-PD effects exhibited by these natural products are considered to be due to their ability to modulate; reactive oxygen species production, neuroinflammation, dopamine production, excitotoxicity, metal homeostasis, mitochondrial function, and cellular signaling pathways, which are all disrupted in the PD brain. However, the precise neuroprotective mechanism of action of natural products for PD remains unclear. Research is necessary to further elucidate the mechanisms by which these compounds are efficacious in attenuating PD or controlling PD-related symptoms.

Key words: Polyphenols, Parkinson's disease, oxidative stress, mitochondrial dysfunction, neurodegeneration.

Introduction

Parkinson's disease (PD) is the world's second most common neurodegenerative disorder, which can significantly impair the quality of life, create dependency and trigger premature mortality of affected individuals (1). The prevalence rate of PD is 0.5-1% among people aged 65-69 years and 1-3% among those aged 80 and above (2). Clinical manifestations include bradykinesia, tremors, rigidity, and postural instability (3). Spectrums of non-motor symptoms are also common, including cognitive impairment, and emotional and behavioral dysfunction (4).

As yet, no definite etiological factors have been identified to contribute to the development and progression of PD, although many factors have been previously proposed (5). Pathologically, PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta region of the brain (7, 8). Intracytoplasmic proteinaceous inclusions termed Lewy bodies (LBs) and dystrophic neurites (Lewy neurites) are present in surviving neurons of PD patients (8). Genetic factors such as mutations to the α-synuclein or the parkin gene, and environmental factors such as neurotoxic pollutants have also been proposed to contribute to the onset of PD (9-11).

The neurochemical events associated with the pathology of PD include increased levels of free radicals, oxidative stress, inflammation, mitochondrial dysfunction, and α-synuclein aggregation. Additionally, increased concentration of redox active metals such as iron and copper, reduced glutathione levels, and increased lipid peroxidation have also been reported in PD (12, 13). Currently available pharmacological interventions provide only limited symptomatic relief for patients with PD and have little efficacy in reversing the underlying neuropathological changes associated with the disease. Therefore there is a clinical need to identify therapeutic agents that can ameliorate, or slow down the deleterious processes associated with PD. One such paradigm is to explore the possible contribution of

1. Department of Food Science and Nutrition, College of Agriculture and Marine, Sciences, Sultan Qaboos University, Oman; 2. Ageing and Dementia Research Group, Sultan Qaboos Unviersity, Oman; 3. Centre for Healthy Ageing, School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, Australia; 4 School of Biotechnology and Biomolecular Sciences, Faculty of Science, University of New South Wales, Sydney, Australia; 5. Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Tamil Nadu, India; 6. Department of Behavioural Medicine, College of Medicine and Health Sciences, Sultan Qaboos University, Oman; 7. Neuropharmacology group, MND and Neurodegenerative diseases Research Centre, Macquarie University, NSW, Australia

Corresponding Author: G.J. Guillemin, Neuroinflammation group MND and Neurodegenerative diseases Research Group, Australian School of Advanced Medicine (ASAM), Macquarie University, NSW, 2109 Australia. Tel.: +61 02 9850 2727; fax: +61 02 9850 2701. E-mail address: gilles.guillemin@mq.edu.au

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natural products that might interfere with PD pathology (14). Natural products have been increasing found to have specific molecular or pharmacological effects that are likely to contribute to the development of neuroprotective agents against PD (15).

Bioactive derivatives of plants such as flavonoids, stilbenoids and alkaloids possess potent anti-oxidative and anti-inflammatory properties that are of considerable interest for the treatment of PD. These naturally occurring phytochemicals can also promote mitochondrial function and serve as important cognitive enhancers (15). Moreover, these compounds act as inhibitors for α-synuclein aggregation, c-Ju N-terminal kinase (JNK) activation, and monoamine oxidase production, and are agonists for dopaminergic neurons (16, 17). Considering the socioeconomic burden and undesirable side effects of synthetic drugs, natural remedies are promising avenues in the treatment of PD.

However, the claims that many natural products available to the general population are therapeutically beneficial for PD are based solely on empirical or preliminary data. Therefore, the purposes of this review are to highlight available evidence on the role of specific bioactive molecules present in a wide range of natural flora, and to present information on the potential mechanism of action of these natural products, and their relationship to neuropathological events associated with PD.

Summary of the literature cited

There are over 140 studies published in the last 10 years associated with the beneficial effects of plant-derived natural products and PD. This review included electronic searches of the PubMed, Medline, Scopus, EMBASE, CINAHL, AMED, PsycInfo, CNKI, 7 Korean Medical Databases, J-East and Web of Science with the search terms as follows: "Parkinson's disease therapy", "natural products parkinson's disease", "phytochemicals", "antioxidants" and "plant extracts" in various combinations. The "Dopamine and PD" section is provided since the etiology of PD is thought to be due to an imbalance in brain dopamine levels. This review presents a summary of literature on the relationship between dopamine (DA) levels and motor function in PD, and the beneficial effects of natural products which demonstrate potential anti-PD properties. This also review summarizes recent progress in determining the potential mechanism of action on PD.

Dopamine Levels and Parkinson's Disease

DA is a neurotransmitter produced from the dietary amino acid tyrosine and plays significant roles in a variety of motor, cognitive, motivational, and neuroendocrine functions (18). The rate-limiting enzyme responsible for DA synthesis is tyrosine hydroxylase (TyrH), which catalyzes the hydroxylation of tyrosine to DA. The biosynthetic pathway leads to the production of a number of different catechol monoamines, such as epinephrine and norepinephrine. These products play significant roles in many brain functions, including attention, memory, and cognition. Therefore, deficits in catecholamine synthesis can lead to several deleterious processes, such as hypertension, depression, and dystonias (reviewed in 19). As TyrH is the slowest enzyme in this pathway, its mechanisms of regulation are of considerable interest to neuroscientisits.

The activity of TyrH is regulated by protein-protein interactions with other enzymes in the DA synthesis pathway or the tetrahydrobiopterin pathway , an important cofactor in several redox reactions and acts as a chaperone for the maintenance of normal neuronal oxidative status (19). TyrH is also regulated by protein which transfer DA into synaptic vesicles. Recent studies have shown that TyrH is localized in close proximity to effector proteins near neuronal vesicles and mitochondria, along with protein phosphatases, and aromatic amino acid decarboxylase (AADC), and the vesicular monoamine transporter-2 (VMAT). These vesicles contain the enzyme dopamine beta-hydroxylase, thus ensuring that DA is stored in secretory vesicles rather than freely located in the cytosol (19). TyrH activity is inhibited by reversible glutathionylation during chronic oxidative stress, and the effect may be attenuated by natural phytochemicals which exhibit potent antioxidant potential (20).

DA is unstable and cannot cross the blood brain barrier (BBB). It is formed in the brain by conversion of its precursor L-DOPA. In PD, L-DOPA (Levodopa) can be administered in conjunction with a DA agonist, or the decarboxylase inhibitor carbidopa, which increases plasma concentration of L-DOPA by blockage of peripheral degradation of L-DOPA to DA. This allows more L-DOPA to BBB (21). L-DOPA is naturally found in beans, especially Mucuna spp, which has been proven experimentally to enhance DA levels in the brain (22).

DA receptor agonists (e.g. bromocriptine, cabergoline, pergolide, rotigotine, apomorphine, ropinirole and pamipexole) are the main class of drugs used to treat PD symptoms. Parkinson's symptoms occur in response to reduced levels of the chemical messenger DA, due to the progressive loss of neuronal cells in the brain that synthesize it. These drugs activate DA receptors by bypassing the presynaptic synthesis of DA. Like DA, these DA agonists serve as endogenous free-radical scavengers, regulating DA synthesis and ameliorating excitotoxicity by suppressing subthalamic nucleus overactivity and exerting anti-apoptotic effects (23-25). Additionally, DA receptors can regulate adenylyl cyclase activity and cAMP synthesis (26, 27), and are involved in modulating voltage dependent Ca2+ and K+ channels

(28). Compared to levodopa, DA agonists provide modest symptomatic relief but are associated with higher incidence of adverse effects including hallucinations, edema, sudden sleep attacks, and impulse control disorders (ICD). Interestingly, motor fluctuations such as dyskinesias are less frequent following administration with DA agonists. Naturally occurring protoalkaloids and ergot alkaloids are phytochemicals that exert dopaminergic or DA receptor activity. For example, apomorphine derived from opium alkaloids is used as a DA agonist (29).

Monoamine inhibitor (MAOI) activity of plant derived alkaloids is another therapeutic target for PD. Monoamine oxidases (MAO A & MAO B) are flavin-containing enzymes in the central and peripheral nervous systems that catalyze the conversion of neurotransmitters to hydrogen peroxide (H2O2), aldehydes, and ammonia. In the PD brain, MAOI regulates the breakdown of DA to its metabolites (30, 31). Therefore, MAOIs can be used therapeutically to maintain optimum DA levels (32).

Herb Derived Anti-parkinsonian Compounds

The neuroprotective potential of natural products derived from herbs, fruits, vegetables, and spices against PD relies on the presence of flavonoids, steroidal lactones, ginsenosides, alkaloids, caffeine, stilbenoids, ginkgolides, bilobalides , xanthones, saponins, oligosaccharide esters, glycosides isoflavonoids, polymethoxyflavones, catechins, anthocyanins, S-Allylcysteine, lycopene, thymoquinone, sesaminoids,curcuminoids, zingerone, eugenol, and chrysotoxine. enoids, catechols and glycosides. Flavonoids, the major polyphenol group, consist of aromatic rings possessing a phenolic hydroxyl group and a 3-OH group offering potent antioxidant and iron chelating properties (33-35). Based on their alkylation, glycation, and hydroxylation patterns, flavonoids are classified into flavones, flavanones, flavanonols, flavanols, anthocyanidins, and isoflavones (36). Apart from their antioxidative properties, the potential mechanism of action of flavonoids is their interaction with neuronal signaling cascades such as PI3K/Akt, protein kinase C, and MAPK which leads to decreased apoptosis and enhanced neuronal survival (37). Additionally, flavonoids induce angiogenesis and neurogenesis and act directly to counteract neurotoxic and proinflammatory agents (38). Moreover, flavonoids exert antioxidant effects by scavenging free radicals and reactive oxygen species (ROS) (39, 40). As oxidative stress is thought to be the leading cause of dopaminergic neuronal loss in the substantia nigra, neuroprotective molecules that ameliorate oxidative stress and excitotoxicity are of primary importance (41-43).

Camelia sinesis (Green tea) is a shrub native to Asia. Green tea is widely consumed as a beverage in Japan, China, and other Asian nations. Tea flavonoids exert antioxidant, anti-inflammatory and neuroregenerative effects (44, 45). Epicatechin-3-gallate (EGCG) is the tea's most abundant polyphenol which offers antioxidant and neurogenerative effects (46-48). Epidemiological studies showing the alleviation of PD risk in tea drinking populations and its low prevalence in Chinese populations provides additional support for its neuroprotective effects in PD (49-51). In vivo studies in MPTP-induced parkinsonian mice have shown that green tea extract can attenuate DA depletion and dopaminergic neuronal survival in the substantia nigra region of the brain (51). The catechol-like structure of EGCG exerts an inhibitory effect on DA uptake by blocking uptake of the neurotoxin MPP+ (1-methyl-4-phenylpyridinium) and protecting dopaminergic neurons against MPP+ injury (52). Moreover, EGCG regulates extracellular signaling kinases (ERK1/2 and mitogen activated protein kinases), the major impediment to neuronal damage and oxidative stress (53). Additionally, the metal chelating ability of green tea flavonoids can attenuate iron dyshomeostasis observed in PD (54). Supplementation with green tea extract also mitigates NF-kB immunoreactivity and oxidative stress induced in SHSY-5Y cells (55).

Withania somnifera (Ws) is an Indian Ayurvedic traditional medicinal herb grown in India, Africa, and the Mediterranean region. The root extract is rich in steroidal lactones including withanone, withaferin, withanolides, withasomidienone, and withanolide (56). These compounds have been reported to inhibit metastasis and quinone reductase activity, .and preferentially affect the cholinergic signal transduction cascade of the cortical and basal forebrain, and thus may be beneficial for the treatment of PD. One study recently showed that withanolides are potent suppressors of NF-κB activation mediated by a number of inflammatory agents, and that this suppression occurs through inhibition of IκBα kinase (IKK) complex consisting of IKK-α, IKK-β, IKK-γ (also called NEMO), IKK-associated protein 1, FIP-3 (type 2 adenovirus E3-14.7-kDa interacting protein), heat shock protein 90, and glutamic acid, leucine, lysine, and serine–abundant protein. Experimental studies have also shown that MPTP-administered parkinsonian mice showed improvement in neuronal survival and locomotion after administration of Withania somnifera (Ws) root extract. Importantly, there was a significant increase in catacholamines such as DA, glutathione (GSH), and glutathione (GSH) peroxidase enzyme in Ws ingested PD mice compared to control. Also, there was a remarkable increase in the level of DA metabolites, 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA) (57). Further evidence supporting the antioxidative effect of Ws root extract against PD mice is notable. Treatment with Ws root extract (100mg/kg) for a period of 7 days correlated with a significant reduction in aggravated levels of malondialdehyde, superoxide, and

catalase in the brains of PD mice (58). The ability of Ws to alleviate gait disorders, inflammation, and brain aging and its potential to upregulate p13 kinase and enhance neuronal growth has also been numerously reported (59, 60).

Ginseng is an adaptogen that resists adverse effects of harmful substances, restoring homeostasis and acting as a psychic energizer (61, 62). Scientific evidence has substantiated the neuroprotective potential of ginseng extract G115 against dopaminergic neuronal loss and gait disturbance in PD mice models (63). Ginsenosides are triterpinoid saponins unique to Panax ginseng species distributed throughout China, North and South Korea, and Russia. These compounds elicit a pleotrophic mechanism of action. The DA uptake inhibiting activity of that ginsenosides have the potential to act as NMDA antagonists and protect neurons from mitochondrial dysfunction and glutamate elevation and excitotoxicity caused by MPTP (64, 65). The potential of ginsenosides to reduce calcium influx and free radical generation and oxidative stress may also play a role in ginseng's disease modifying effects (66, 67).

Caffeine is an Adenosine 2A receptor antagonist present in coffee beans from the Coffea arabica and Coffea canephora plants, which are widely distributed in Asia and Africa. Caffeine exerts neuroprotective effects against dopaminergic neuronal loss in MPTP-induced PD mice (68-70). Furthermore, caffeine causes reversal of motor deficit in PD mice models (71). Caffeine's behavioral and neurobiochemical effects have been shown to cause a reduction in apomorphine-induce rotation and enhanced motor function. In experimentally depletion of dopaminergic neurotransmssion using neurotoxic, 6-hydroxydopamine (6-OHDA), the level of DA and its metabolites have also been shown to recover following caffeine administration (72).

Ginkgolides and bilobalides are unique phytochemicals present only in the Ginkgo biloba tree (73). EGb761, a well-defined mixture of active compounds extracted from its leaves, exerts a protective effect against oxidative stress induced by MPTP in C57BL/6J mice. Mice receiving EGb761 recovered striatal DA levels and tyrosine hydroxylase in the striatum and substantia nigra pars compacta. The neuroprotective effect of EGb761 against MPTP neurotoxicity is associated with its free radical scavenging activity, blockade of lipid peroxidation, and reduction of superoxide radical production (74). Furthermore, G. biloba extract exhibits inhibitory effects on MAO activity on rat mitochondria (75), suggesting that its neuroprotective effects on dopaminergic neurons may be due to its inhibitory action on MAO.

Polygala root extract (PRE) consists of xanthones, saponins, and oligosaccharide esters (76) and is reported to have as neuroprotective effect on dopaminergic neuron in 6-OHDA induced neurotoxicity in both in vitro and in vivo PD models. The possible mechanism of action is due to reduced ROS and nitric oxide (NO) production and altered caspase-3 activity (77). Moreover, oligosaccharide derivatives of PRE act against clinical depression by binding to norepinephrine transporter proteins (78). Furthermore, the 3,4,5-trimethoxycinnamic acid (TMCA) present in PRE exerts anti-stress effects through suppression of norepinephrine (79).

Baicalein and baicalin are flavonoids found in large concentrations in the Scutellaria baicalensis and Bupleurum scorzonerifolfium (S/B) herbs (80). These compounds have been shown to attenuate iron-induced lipid peroxidation and DA depletion in the substantia nigra. They can also augment GSH levels, hinder α-synuclein aggregation, and reduce iron-induced mitochondrial stress and apoptosis. The 3-OH group attached to the benzene ring of the molecular target baicalein is responsible for α-synuclein disaggregation. A significant reduction in nitric oxide synthase and inflammatory markers was also observed in the substantia nigra of neurotoxic rat brain treated with S/B remedies. Furthermore, baicalein ameliorated 6-OHDA induced toxicity by decreasing phosphor-JNK and caspase activity in SHSY-5Y cells (81). Baicalein pretreatment improved behavior in MPTP induced PD mice. The potential mechanism of action may rely on increased DA and melatonin (5-HT) in the striatum (82).

Pueraria thomsonii Benth is a herbal medicine enriched with isoflavonoids such as puerarin, daidzin, daidzein, and genistein (83). The neuroprotective effect of genistein in dopaminergic neurons has been reported, where in 6-OHDA induced nerve growth factor (NF) differentiated pc12 cells, genistein and daidzin showed an inhibitory effect on caspase 3 and caspase 8 activation, thereby preventing apoptosis (84).

Uncaria rhynchophylla is used as a traditional medicine to treat convulsive disorders, tremors, and hypertension (85). The major alkaloids are rhynchophylline, corynoxeine, corynantheine, and hirsutine and the major flavonoids are catechin and epicatechin. All have been shown to have a cytoprotective effect (86). In animal with depleted DA activity using 6-OHDA Uncaria rhynchophylla extract (URE) ameliorated dopaminergic neuronal loss and apomorphine induced rotation. Meanwhile, a significant reduction was observed in ROS generation and caspase 3 activity and a remarkable maintenance of cell viability and GSH levels was observed in neurotoxic PC12 cells.

Polygonum cuspidatum is a perennial herb used primarily in Traditional Chinese Medicine and other Asian cultures. Recent studies have shown the neuroprotective potential of P. cuspidatum-derived resveratrol (RES) in 6-OHDA induced mice. The protective effect is exerted by its antioxidant reducing and antiapoptotic abilities (87). In another study, male Wistar rats pretreated with RES escaped dopaminergic

neuronal loss and neurobehavioral defects following 6-OHD injection. This affect is likely due to upregulation of antioxidant enzyme status and mitigation of DA deprivation (88).

Bacopa monniera is a traditional medicinal plant used extensively to treat anxiety, epilepsy, and memory deficits (89). It has been substantiated that Bacopa moniera extract (BME) exerts a dose dependent protective effect in 6-OHDA-lesioned PD rat models as determined by significant improvements behavioral activity and restoration of GSH, SOD, and catalase activity levels and reduced lipid peroxidation (90). The potential mechanism of action of BME is attributed to its antioxidant, free radical scavenging properties, and DA-enhancing effects (91).

Cassia obtusifolia L. is an annual plant commonly consumed as roasted tea and is widely distributed in Korea and China. Cassiae semen (sicklepod) seed extract (CSE) has been shown to protect against dopaminergic neuronal degeneration in the substantia nigra and striatum of MPTP-induced PD mice models and dopaminergic neurons in vitro. In 6-OHDA induced pc12 cells, CSE supplementation has been demonstrated to mitigate cell damage and attenuate ROS generation and mitochondrial membrane depolarization. MPP+, the neurotoxic metabolite of MPTP, induces dopaminergic neuronal loss by inhibiting the activity of respiratory complex 1 in the mitochondria of dopaminergic neurons (92).

Fruit, Vegetable and Spice derived Nutraceuticals for PD

Levodopa (L-DOPA) was first isolated from the seeds of the leguminous plant Mucuna pruriens, which is native to India and other parts of the tropics including Central and South America (93, 94) and Mucuna spp are considered to be richest natural sources of L-DOPA (95). The administration of 30 grams of Mucuna seed powder has been reported to have antiparkinsonian effects in PD patients, with a more rapid onset of action, shorter latency, and enhanced improvement compared to the standard combination of levodopa (200 mg) and carbidopa (50mg) treatments (96). Vicia faba (broad bean) is an edible bean found in the Mediterranean region and is rich in L-DOPA (97). The ingestion of broad beans in PD patients has been shown to elevate L-DOPA plasma levels which have correlated with cognitive improvement in the same magnitude as levodopa/carbidopa administration (98, 99). Another study suggested that 2,4-epibrassinolide (24-Epi), a natural Brassinosteroid found in V. faba, offers antioxidative and antiapoptotic effect on MPTP induced PC12 cells. The mechanism underpinning the effect was considered to be due to modulation of antioxidant enzymes, Bax/Bcl-2 protein ratio, and cleaved caspase-3.

Chaenomeles speciosa is an East Asian native shrub that is known for its nutritionally edible fruit; the common flowering quince (FQ). FQ is used traditionally to treat neuralgia, migraine, depression, tremors, and dyskinesia (100, 101). Scientific evidence has proven FQ to be a potent DA transport (DAT) inhibitor that can be used as a therapeutic target for PD. In vitro studies have shown that FQ administration attenuates DA uptake by DATs in Chinese hamster ovary (CHO) cells expressing DAT (D8 cells). Additionally, FQ maintains cell viability, tyrosine hydroxylase (TH) activity, and behavioral performance in MPTP induced neurotoxic models of PD.

The rhizome of the perennial Cyperus rotundus is used as a functional food and medicine in Korea. Reports have suggested that cyperi rhizome extract (CRE) exerts protective effect on 6-OHDA induced PD models. CRE mitigates ROS and NO production and intensifies cell viability and caspase 3 activity. It also modulates mitochondrial membrane potential and dopaminergic neuronal loss in neurotoxic cell cultures (102).

Extracts of the edible fruit of the deciduous Morus alba L. (mulberry) have been demonstrated to have neuroprotective efficacy in in vitro and in vivo PD models, with the efficacy attributed to its content of polyphenols, anthocyanin, rutin, quercetin and α and γ tocopherol (103). In 6-OHDA mediated neurotoxic cell lines, the mulberry extract (ME) elicits antioxidant and antiapoptotic effects. Biochemical assays have shown that ME can stabilize the mitochondrial membrane, and regulate the expression of Bcl-2, Bax, and caspase 3 proteins involved in apoptosisAdministration of ME can also alleviate bradykinesia and dopaminergic neuronal damage in the substantia nigra in vivo (104, 105). Citrus is a family of flowering plants ranging from herbs, shrubs, and trees, including Citrus sinensis (orange), C. lemon (lemon), and C. paradisi (grape fruit). Citrus flavonoids are composed of flavonones, flavone glycosides and polymethoxyflavones (106). It has been reported that polymethoxyflavones present in orange and lemon peel can mitigate the loss of dopaminergic neurons and tyrosine hydroxylase in the substantia nigra of the 6-OHD rat model (107). Similar effects exerted by the flavonoid, naringenin, which is highly present in citrus, in PD models have also been noted (108). Naringenin and another citrus flavonoid, hesperidin attenuates LPS/IFNγ-induced TNF-α production in glial cells and naringenin also represses LPS/IFN-γ induced iNOS expression, p38 mitogen-activated protein kinase (MAPK) phosphorylation, and transcription-1 (STAT-1) which are associated with microglial and astrocyte-mediated inflammatory response (109).

Vitis vinifera (grape) is one of the world's largest fruit crops and is enriched with catechins, epicatechins, anthocyanins, and resveratrol. Grape juice (GJ) administration has been correlated with a decrease in

behavioral deficits in 6-OHDA induced mice (110). Resveratrol has been demonstrated to protect against MPTP induced apoptosis in neuronal cells, with the underpinning mechanism considered to involve the modulation of the expression of pro-apoptotic Bcl-2 gene and antiapoptotic Bax gene. Resveratrol administration has been shown to attenuate MPTP induced mitochondrial release of cytochrome c and caspase 3 activation, and facilitate membrane stabilization and neuronal survival (111). Interestingly, oxyresveratrol, a stilbinoide, contains one extra OH group and is more effective than resveratrol against 6-OHDA toxicity in SHSY-5Y cells. This is probably due to a greater antioxidant potential, more potent inhibition of the JNK pathway and an increase in activity of the nuclear sirtuin enzyme (SIRT1) which is associated with longevity (112).

Allium sativum (garlic), the edible bulb of the Liliacea family, possesses innumerable health benefits. S-allylcysteine (SAC), its most abundant organic sulfur containing compound, possesses radical scavenging activity (113) which when administered to MPTP induced neurotoxic mice improved locomotor function which correlated with increased dopamine production, alleviated lipid peroxidation and superoxide production, and enhanced superoxide dismutase (SOD) activity (114).

Morin (3,5,7,20,40-pentahydroxyflavone) is a bioflavonoid found in Prunus dulcis (almond), Maclura pomifera (osage orange), Maclura tinctoria (old fustic), and in leaves of Psidium guajava (guava) (115). The health benefits of morin have been investigated in in vitro and in vivo PD models. In PC12 cells, morin supplementation at 5-50μmol/L significantly viability losses, apoptosis, and ROS generation following MPTP treatment. In MPTP-induced PD mice models morin administration attenuated behavioral deficits and DA deprivation (116).

Lycopersicon esculentum L. (tomato) is rich in lycopene and well-known for its edible fruit. Pretreatment with a diet containing lyophilized tomato powder correlated with a decreased DA loss in a MPTP-induced PD model (117).

Black cumin (Nigella sativa)seeds are commonly used in culinary preparations. Thymoquinone, its main bioactive component, has been shown to protect against dopaminergic neuronal deprivation in MPP+ and rotenone induced neurotoxic PD models. In primary dopaminergic neuronal cell lines, long term and short term toxicity were reversed by thymoquinone treatment (118).

Sesame indicum is a flowering plant native to Africa, with high production in India and China. Sesame seed and its oil contain the bioactive molecules sesamin, sesamol, and sesaminol. Sesamin is a lipophilic lignin offering moderate antioxidant and immunomodulatory effects (119, 120). Sesamin has been demonstrated to have a DA enhancing effect in rotenone-induced loss of dopaminergic neurons in mice. Interestingly, MPP+ treated neuronal PC12 cells exhibit a significant decrease in ROS generation and oxidative stress following sesamin treatment. Sesamin modulates the expression of tyrosine hydroxylase (TH), SOD, and catalase, impedes inducible NO synthase (iNOS) protein expression in neuronal cells, and lowers mRNA levels of the potent pro-inflammatory cytokine interleukin-6 (IL-6) in microglial cells (121).

Curcuma longa is a rhizome grown throughout India and is extensively used in food additives and medicines (122). Its diverse cytoprotective action is offered by polyphenolic curcuminoids, consisting of curcumin, demethoxy curcumin (DMC), and bis-demethoxy curcumin (BDMC). In vitro and in vivo models of PD have shown that curcumin demonstrates a disease modifying effect by protecting dopaminergic neurons against LPS and α-synuclein induced neurotoxicity, mitigating DA loss, which allieviates oxidative stress and limits mitochondrial dysfunction (123, 124). The MPTP-mediated depletion of DA and TH immunoreactivity in dopaminergic neurons was reverted following the addition of curcuminoids. The administration of curcuminoids suppressed over-expression of iNOS, reduced pro-inflammatory cytokines, and total nitrite generation in the striatum of MPTP-intoxicated mice (125, 126). Another study has shown that curcumin protects against dopaminergic neurotoxicity induced by MPTP or MPP+ in C57BL/6 N mice and SHSY-5Y cells by inhibiting the JNK pathway (127).

Zingiber officinale (ginger) is a major spice that exhibits neuroprotective effects. Zingerone and 6 shogaol compounds isolated from ginger, impede 6-OHD induced DA loss in mouse striatum (128) and prevent apoptotic neural cell death (129). The DA replacement effect is possibly through up-regulation of the superoxide scavenging activity (SOSA) of SOD. The lipid peroxidation lowering effect of zingerone is also considered to contribute to its cytoprotective effect (130).

Neuroprotective Effects of Ornamental Plants

Paeoniae lactiflora is an ornamental flowering plant known for its dried root. Paeoniflorin (PF), a monoterpene glucoside, is abioactive molecule produced by Paeoniae alba Radix (131) and is reported to have a neuroprotective effect on dopaminergic neurons in an MPTP mouse model for PD. Dose dependent subcutaneous administration of PF restored TH positive cells, dopaminergic neuronal paucity, and ameliorated bradykinesia. The mechanism of action is due to PF acting as an agonist for the adenosine A1 receptor, which down regulates microglial and astrocytic activation and neuroinflammation (132).

Dendrobium nobile Lindl. is an ornamental medicinal plant in the Orchidacea family, which is rich in the bioactive benzyl compound chrysotoxine (133).

Chrysotoxine is reported to protect SHSY-5Y cells against 6-OHDA toxicity through mitochondrial protection and NF-κB modulation. Chrysotoxine pretreatment exerts beneficial effects including attenuation of 6-OHDA-induced intracellular generation of ROS, and activation of p38 MAPK and ERK1/2. Mitochondrial dysfunction is reverted through multiple mechanisms including the decrease of membrane potential, increase of intracellular free Ca2+, release of cytochrome c, imbalance of Bax/Bcl-2 ratio and decrease in activation of caspase-3. An anti-inflammatory response is exerted by suppression of NF-κB activation by blocking its translocation to the nucleus, thereby preventing up-regulation of iNOS and intracellular NO release (134).

Rosmarinus officinalis (rosemary) is an aromatic ornamental plant rich in cytoprotective biomolecules. R. officinalis extracts have been shown to offer neuroprotective potential in a model for H2O2-induced apoptosis of human dopaminergic cells correlating with suppression of of the expression of Bax, caspase-3 and -9 and Bcl-2 genes (135). Rosmaric acid (RA) has been demonstrated to have a neuroprotective effect in a 6-OHDA-lesioned rat model of PD. RA exerts its effect by decreasing iron levels in the substantia nigra and regulating the ratio of Bcl-2/Bax gene expression (136). Carnosol, another major rosemary component has been shown to offer protection against rotenone-induced neurotoxicity by promoting cell viability and down regulating caspase 3 action, withincreased TH, Nurr1, and extracellular signal-regulated kinase 1/2 also likely to be involved (137).

Bioactive molecules Derived from Parasitic Plants and Fungi

Cistanche salsa is a parasitic plant used as a Chinese traditional medicine containing acteoside, echinacoside, and tubuloside as its major phenylethanoid glycosides (PHGs). C. salsa extracts containing these bioactive molecules have been shown to restore behavioral deficit and dopamine depletion in strata of MPTP induced C57 mice (138). They has also been demonstrated to protect dopaminergic neurons in the substantia nigra of PD model mice, which correlated with neurobehavior improvements (climbing test) and TH positive neuronal levels (139).

Gastrodia elata (GE) blume is a saprophytic perennial herb used traditionally as a medicine due to its wide range of therapeutic benefits. Protective effects of GE extract against MPP+-induced cytotoxicity in human dopaminergic SHSY-5Y cells demonstrated that GE extract dose dependently improved cell viability maintenance, attenuated oxidative damage, modulated expression of Bcl-2 and Bax, caspase-3, and limited poly(ADP-ribose) polymerase proteolysis (140). Recently, MPP+ induced MN9D dopaminergic cells were shown to exhibit antiapoptotic effects following GE extract treatment. The v anillyl alcohol present in GE was considered to act by attenuating the MPP+ induced elevation of ROS levels and decreasing the Bax/Bcl-2 ratio and poly (ADP-ribose) polymerase (141).

Ganoderma lucidum (GI) is a woody mushroom widely used as an alternative medicine. One study has identified that the neuromodulatory potential of GL on dopaminergic neurons to protect against inflammatory damage induced by microglial activation following exposure to MPP+ and LPS. The mechanism of action is purportedly the ability of GL to protect against the production of the microglia-derived toxic factors NO, TNF-α, IL-1ß, and superoxide (142).

Current and Future Developments

Current pharmacotherapies for PD do not provide the much desired permanent curative benefits to patients. Scientists in the field of nutrition have identified natural products as potential adjuvant treatments to conventional drug therapy to attenuate the PD symptoms and reduce the dose of anti-Parkinson drugs and the incidence of associated adverse events. There is a high rate of dyskinesia and relapse of Parkinsonian symptoms following long-term treatment with levodopa (143). Combination therapy with natural herbal products has demonstrated substantial benefits in lowering levodopa-related complications (144). However, the long term effect of combination therapy has not been investigated, and potential interactions with drugs that are currently used in the PD treatment remain unclear. The dosage regimen for anti-parkinson's drug is of major clinical importance of anti-parkinson's drug due to its lifelong requirement. Adjunct therapy with natural products may ultimately prove useful for reducing the dose of levodopa for managing PD symptoms.

While many natural products appear promising for the treatment of PD and management of dyskinesia, a global initiative to standardize compositions for pharmacological applications is essential to ensure good quality and efficacy. The efficacy of natural formulations are limited due to several problems related to the original species of individual herbs, chemical compositions and indexes, preparations and indications for herbal products (145). Chinese formulas currently available on the market are composed of a variety of natural products and there exists wide heterogeneity between the natural products described in this review. Standardization of single and combinations of natural products in human clinical trials will be a major factor for translating preclinical data to the clinical setting.

Future clinical trials using natural products for the treatment of PD need to be improved methodologically to ensure good reproducibility, to improve clinical benefit,

and to reduce the potential to cause harm. Double blinded studies and the inclusion of placebos should be employed in the study design. Protocols need to be defined prior to commencement of clinical trials to guarantee the transparency of the study finding(s) and prevent publication bias (146).

Conclusion

Prior to the onset of modern medicine, societies all over the world have employed various natural products as 'food for medicine'. With hegemony of biomedical sciences with its reductionism approach, the usage of natural products for the cause of prevention and amelioration of illness was deemed a relic of the past. The idea encapsulating 'food for medicine' was often portrayed as Grandmother's medicine. However, despite decades of the reductionism approach in health and medicine, some of the emerging prevalent conditions such as PD appear to be inaccessible to modern medical interventions. In the age of paradigm shift, interests towards natural product have been rekindled. Rather than being limited to grandmother's empiricism, development of science has rendered the possibility of scrutinizing mechanisms of natural project with lances of modern scientific approach. The evidence suggesting the heuristic value of some of the natural products is abundant. This paper has specifically explored the role of herbs, fruit, vegetable and spice, ornamental plants and parasitic plants and fungi in the trajectory of PD. The evidence appears to be tenderized with notion that the wisdom of Grandmother's medicine is not a relic of the past; the natural product is once again live and kicking. If science would progress on such a quest, natural products may address the underlying pathological processes associated with the development and progression of neurodegenerative diseases, and PD in particular.

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