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THE ROLE OF EXTRACTS AND COMPOUNDS OBTAINED FROM HERBS IN TREATMENT OF PARKINSON'S DISEASE

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ABSTRACT: Neurodegenerative disorders particularly Parkinson's disease are serious threat for heath society. In addition, treatment, control and managing of Parkinson's disease burden high cost to these patients. Therefore, an efficacy and available treatment strategy is required so that herbs and their bioactive compounds could be good candidates. It has well been demonstrated the herbs are a potential source of antioxidant and have anti-inflammatory property. Interestingly, oxidative stress and inflammation are main reasons neurodegeneration in substantia nigra pars compacta. Here, we review the studies conducted on effects of extracts and compounds obtained from herbs in treatment of Parkinson's disease until 2000 to now by to focus on their effects on different animal model of Parkinson's disease.

INTRODUCTION: Among neurodegenerative disorders, Parkinson's disease is one of their most common, a disease due to obvious reduction of dopamine level in the striatum (**Fig. 1**), which have clinical characterization such as tremor, rigidity, myotonia, dyskinesia and psychosis autonomic dysfunction [1, 2]. It have been proposed that genetic factors (mutation in the α-synuclein, LRRK2 and parkin genes) and environmental factors (neuro-toxic pollutants) have pivotal role in progression of Parkinson's disease [3, 4].

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The prevalence rate of this disease is high so that it have been reported that about 65.6 - 12500 per 100000 and 51.3 - 176.9 per 100000 are the prevalence of Parkinson's disease in European [5] and Asian [6] countries, respectively. Based on a population - based prospective study conducted by Yang *et al.*, 2016 on prevalence of Parkinson's disease in Sweden 1981 to 2010 was found that 66332 patients with Parkinson's disease among 4.6 million Swedish participants [7].

In addition, using statistics database related to English hospital during 2009 -2013 was demonstrated that 324055 cases of admissions were related to patients with Parkinson's disease. Furthermore, £777 million for their hospitalization was spent. In fact, this disease is a threat for health society [8]. The World Health Organization reported that by 2040 mortality related to neurodegenerative disorders

will higher than mortality related to cancer [9]. Given that brain has great need to oxygen, thus it is exposed to oxidative stress, furthermore under oxidative stress condition, endogenous antioxidant defense cannot completely abrogates damages induced by oxidative stress [10]. Oxidative stress and inflammation are two main reasons Parkinson pathogenesis that ordinary occur in nigral neurons [11].

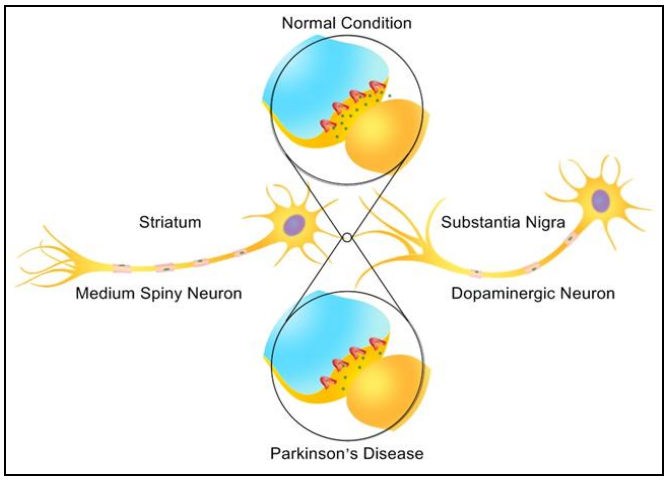

FIG. 1: COMPARISON OF DOPAMINE LEVEL IN NORMAL CONDITION AND PARKINSON'S DISEASE

According to previous studies, oxidative stress and inflammation are commonly observed in Parkinson's disease and they leads to activation of microglial and ultimately neurodegeneration in substantia nigra pars compacta [12, 13]. Besides microglia activation induced by reactive oxygen species (ROS), NADPHoxidase (PHOX) activation is other reason to induce inflammation so that its inactivation leads to free radical formation [14]. Given that mitochondria has pivotal role in electron transport and oxidative phosphorylation thus is a potential source for production of reactive oxygen species (ROS).

In addition, the cytochrome C as a trigger of apoptosis is one of the elements of electron chain transport in mitochondria[4]. Parkinson disease pathogenesis is related to mitochondria dysfunction (**Fig. 2**) because it has been reported that defect complex I as a mitochondria dysfunction occur in these patents due to environmental toxin such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine [15-17]. Evaluation of mitochondria lipidomic profiles in Parkinson's disease was showed that cardiolipin redistribution (from the inner mitochondrial membrane to the outer mitochondrial surface) leads to mitophagy so that environmental agents have potential role for this event [18, 19]. The use of herbs is very common among Parkinson's disease patients as it is a healthy lifestyle and protect cell against free radicals and cell death [20]. Because, it has been reported that compounds isolated from herbs are potent anti-oxidant and have potential anti-inflammatory property [21].

According to conducted studies on role of Chinese traditional medicine to treat Parkinson's disease, it has been demonstrated that there are about 22500 medicinal herbs with anti-Parkinson activity throughout China but a few investigations on their abilities were done [22]. Today the major of candidate drugs to control Parkinson's disease such as ginsenoside Rg1 and curcumin, are obtained from herb based on examinations performed on animal models of Parkinson's disease [23]. The purpose of this study was to review effects of the role of extracts and compounds obtained from herbs in treatment of Parkinson's disease based on studies conducted on animal model or cell line.

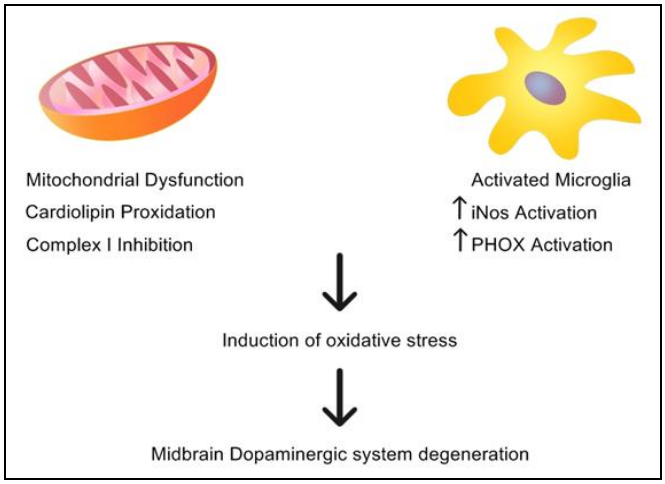

FIG. 2: REASONS OF NEURODEGENERATION DURING PARKINSON'S DISEASE

MATERIAL AND METHOD: Here, the our data source obtained by searching from databases such as web of science, PubMed and Scopus with keywords of "Parkinson's disease and extract of herb and animal model" and "Parkinson's disease and compound of herb and animal model" until 2000 to now. Then, the papers according to topic were categorized and completely read.

Effects of Extracts Isolated from Herbs in Treatment of Parkinson' disease: In a study was evaluated the effect of lyophilized powder prepared from tomato (*Solanum lycopersicum*) on neuro-

toxicity induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in mice. The results were showed that its administration inhibits from reduction of dopamine level in striatal [24] .Our study about effects of *Vitis vinifera* (grape) on 6-hydroxy dopamine-induced neuro-degeneration in rats showed that it has potential effect to influence frequency bands' powers of thalamic VA and to improve post-lesion motor deficits [25].

In addition, it has been reported that grape extract leads to reduction of ROS and protein carbonyl levels as well as increase of activity of complexes I and II related to mitochondrial respiratory electron transport chain and pyruvate dehydrogenase in 2, 2'-azobis (2-amidino propane) dihydrocholoride (AAPH)-induced oxidative stress in rats and human neuroblastoma cells, respectively. Furthermore, it had a potent effect in enhancement of climbing ability at transgenic *Drosophila* expressing human α-synuclein [26]. Study on effect of *Withania somnifera* in parkinsonian mice by maneb-paraquat injection was revealed that it leads to promoting of motor movement, restoring tyrosine hydroxylase activity, increase of catalase activity and reduction of nitrite and lipid peroxidation levels [27].

In addition, treatment with acetone extract obtained from *Eucalyptus citriodora* L. improves climbing ability and moderates oxidative-ant oxidative imbalance in brain of transgenic *Drosophila*, expressing normal human α-synuclein, as an animal model of Parkinson' disease [28]. Siddique *et al*., 2014 evaluated the effect of acetone extract of *Centella asiatica* on transgenic *Drosophila* expression of human α-synuclein. The results were showed the administration of *Centella asiatica* delays loss of climbing ability as well as reduces protein carbonyl and lipid peroxidation and increases content of glutathione, and glutathione-S-transferase activity in brain [29]. Examination of parameters of neuro-inflammation and behavioral after administration of *Ligusticum officinale* ethanol extract tomice with Parkinson model due to 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity was revealed the good effects of this herb to diminish inflammation and behavioral deficit. Indeed, they found that *Ligusticum officinale* has potential anti-inflammatory effect against lipo polysaccharide-induced inflammation in BV-2 cells through inhibition of IκB-α degradation and abrogation of increase in p38-mitogen-activated protein kinase phosphorylation and ultimately reduction of nuclear factor-kappa beta activation. In addition, due to inhibition of 1-diphenyl-2-picrylhydrazyl radicals, it had antioxidant property during *in-vitro* study.

Interestingly, treatment with *Ligusticum officinale* ethanol extract leads to inactivation of microglia and enhancement of behavioral dysfunction in mice with neurotoxicity induced by MPTP injection [30]. It has well been demonstrated anti-Parkinson effects of ethanolic extract prepared from *Mucuna pruriens* on 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) mice model of Parkinson's disease. According to this study, increment of number of tyrosine hydroxylase (TH)-positive cells in substantia nigra and striatum, reduction of expression of inducible nitric oxide synthase (iNOS) and glial fibrillary acidic protein (GFAP) in substantia nigra and nitric oxide level, increase of dopamine, 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic levels and inactivation of microglial were obtained subsequently administration of extract [31].

In another study, it was also revealed that aqueous extract of *Mucuna pruriens* results in reduction of oxidative stress through normalization of catalase activity and reduction of malondialdehyde (MDA) and nitrite levels in brain's mice with neurotoxicity induced by paraquat. This study was also showed improvement of behavioral problem due to increment of hanging time and reduction of narrow beam walk time and foot printing error. In addition, aqueous extract of *Mucuna pruriens* had neuro-protective effect because it increased tyrosine hydroxylase (TH) immunoreactivity in the substantia nigra and striatum [32]. Given that acetone extract of *Bacopa monnieri* enhances climbing ability in transgenic *Drosophila*, expressing human alpha synuclein, thus can be a therapeutic strategy to control Parkinson's disease due to antioxidant and anti-apoptotic properties confirmed in this study [33].

In a study, the effects of ethanol extract prepared from *Bacopa monnieri* and *Mucuna pruriens* on mice with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro pyridine (MPTP)-induced neurotoxicity was compared. The results were indicated that both

herbs have same effect to reduce oxidative stress and to improve behavioral dysfunction, but *Bacopa monnieri* has neuroprotective effect higher than *Mucuna pruriens* because it could significantly normalized activity of tyrosine hydroxylase, caspase-3 and neurogenic gene expression in the substantia nigra [34]. Beppe *et al*., 2014 showed that when rats with neurotoxicity induced by 6-hydroxy dopamine injection treated withaqueous extract obtained from *Albizia adianthifolia* significantly leads to increase of spontaneous alternations percentage, reduction of working memory errors and reference memory errors. Indeed, it had good effect to improve spatial memory [35].

According to study conducted by Perez-Barron *et al*., 2015, administration of methanol extract prepared from *Buddleja cordata* to 1-methyl-4-phenylpyridinium induced neurotoxicity in rats results in increase of dopamine level, reduction of lipid peroxidation and number of ipsilateral rotations. Infact, due to protective effect for inhibition of dopamine level reduction and increase of lipid peroxidation as well as improvement of behavioral dysfunction, *Buddleja cordata* is a promising candidate to treat Parkinson's disease [36]. *Hypericum perforatum* is one of the herbs with anti-Parkinson activity because it has been reported that hydro-alcoholic extract of *Hypericum perforatum* diminishes rotational behavior induced by apomorphine and latency to initiate and the total time on the narrow beam task. Interestingly it had antioxidant property cause by reduction of malondialdehyde (MDA) and increment of glutathione level and catalase activity in striatal. In addition, it was considered as a neuro-protective agent due to reduction of inflammation (inhibition of TNF-α), preventing of DNA fragmentation and astrogliosis. The other properties of *Hypericum perforatum* were significant increase of tyrosine hydroxylase immunore activity and normalization of glial fibrillary acidic protein [37].

Choi *et al*., 2010 showed that injection of 6-hydroxydopamine significantly reduced level of dopamine and its metabolites (3, 4-dihydroxy phenylacetic acid, homovanillic acid and nore pinephrine) in the striatum as well as number of tyrosine hydroxylase (TH)-immunopositive neurons in the substantia nigra. While, treatment with ethanol extract obtained from *Gynostemma pentaphyllum* had potential effects to increase dopamine and its metabolites as well as tyrosine hydroxylase (TH)-immunopositive neurons number in rats with 6-hydroxydopamine-induced neuro-toxicity. Therefore, it has obvious anti-Parkinson property [38]. When methanol extract of *Hibiscus asper* Hook. F was administrated to 6-hydroxy dopamine-induced neurodegeneration rats, it was obtained inhibition of depression and anxiety-like behavior as well as improvement of spatial memory performance. In addition, based on *in-vitro* study it was showed obvious free radical scavenging activity [39].

TABLE 1: ROLE OF EXTRACTS ISOLATED FROM HERBS IN TREATMENT OF PARKINSON' DISEASE

Plant	Extract	Animal model/cell line	Finding(s)	Reference
Solanum lycopersicum	Lyophilized powder	MPTP-induced neurotoxicity in mice	To prevent dopamine level reduction in striatal	24
	Ethanol	6-OHDA-induced neurotoxicity in rat	Improvement of frequency bands' powers of thalamic VA and post-lesion motor deficits	25
Vitis v inifera	Regrapex-R	AAPH-induced oxidative stress in rats and human neuroblastoma cells, induction of Parkinson' disease model with expression of human α-synuclein in transgenic Drosophila	To have anti-oxidant effect, improvement of oxidative-induced mitochondria damages and climbing ability	26
Withania somnifera		MB-PQ-induced Parkinson model in mice	Inhibition of oxidative stress and behavioral dysfunction	27
Eucalyptus citriodora	Acetone	Induction of Parkinson' disease model with expression of human α-synuclein in transgenic Drosophila	Reduction of oxidative stress, improvement of motor dysfunction	28
Centella asiatica	Acetone	Induction of Parkinson' disease model with expression of human α-synuclein in transgenic Drosophila	Improvement of climbing ability and antioxidant condition	29

Ligusticum officinale	Ethanol	LPS-induced inflammation in BV-2 cells, MPTP-induced n eurotoxicity in mice	Reduction of inflammation in BV-2 cells, to have free radical scavenging activity, inhibition of microglia activation and improvement of behavioral problem	[30]
Mucuna pruriens	Ethanol	MPTP-induced neurotoxicity in mice	Antioxidant and neuroprotective properties, inactivation of microglia	[31]
	Aqueous	PQ-induced neurotoxicity in mice	Antioxidant activity, diminishing of behavioral problem, increase of TH-cell number	[32]
Bacopa monnieri	Acetone	Induction of Parkinson' disease model with expression of human α-synuclein in transgenic *Drosophila*	Antioxidant and anti-apoptotic activities, improvement of climbing ability	[33]
Bacopa monnieri *Mucuna pruriens*	Ethanol	MPTP-induced neurotoxicity in mice	Reduction of oxidative stress and behavioral problem equally, the neuroprotective effect of *B. monnieri* Higher than neuro-protective effect of *M. pruriens*	[34]
Albizia adianthifolia	Aqueous	6-OHDA-induced neurotoxicity in rat	To improve spatial memory	[35]
Buddleja cordata	Methanol	MPP^+-induced neurotoxicity in rat	Reduction of lipid peroxidation, increase of dopamine level, improvement of behavioral dysfunction	[36]
Hypericum Perforatum	Hydro-alcoholic	6-OHDA-induced neurotoxicity in rat	Antioxidant and anti-inflammatory effects, improvement of behaviors problem	[37]
Gynostemma pentaphyllum	Ethanol	6-OHDA-induced neurotoxicity in rat	Increase of dopamine and its metabolites and TH-immunopositive neurons	[38]
Hibiscus asper	Methanol	6-OHDA-induced neurotoxicity in rat	To have free radical scavenging activity, reduction of depression and anxiety-like behavior and enhancement of spatial memory function	[39]

MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; 6-OHDA: *6*-hydroxydopamine*;* AAPH: 2, 2'-azobis (2-amidino propane) dihydrocholoride; MB-PQ: maneb-paraquat; LPS: lipopolysaccharide; TH: tyrosine hydroxylase; MPP^+: 1-methyl-4-phenylpyridinium

Effects of Compounds Isolated from Herbs in Treatment of Parkinson' disease: Study on anti-Parkinson effect of tangeretin in rats with neuro-toxicity induced by 6-hydroxydopamine injection was confirmed that its administration leads to normalization of reduced number of tyrosine hydroxylase positive (TH^+) cells and reduced-level of dopamine in substantia nigra and striatal, respectively. Interestingly, the result was showed that tangeretin has good bioavailability as well as simply crosses the blood-brain barrier [40].

It has been reported that rutin has neuroprotective effect and reduce neurobehavioral deficit after its administration to rats with 6-OHDA-induced neuro -degeneration. Indeed, this study was showed that rutin results in reduction of thiobarbituric acid reactive substances (a lipid peroxidation marker), increase of glutathione level and glutathione peroxidase and glutathione reductase activity, dopamine and 3, 4-dihydroxy phenyl acetic acid. In addition, it improved increased-rotations and locomotor dysfunction due to injection of 6-hydroxydopamine [41]. Based on previous studies, curcumin is a potent neuro- protective compound due to anti-oxidant and anti-apoptotic properties and inhibition of monoamine oxidase (MAO-B) activity during its administration into PC12 cells with A53T α-synuclein-induced neurodegeneration [42] and mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP)-induced neurotoxicity [43], respectively.

Evaluation of effect of quercetin on damages induced by rotenone in rat was revealed that it is a useful compound to treat Parkinson's disease, as it

had neuroprotective effect due to increase of tyrosine hydroxylase-positive cells and reduction of TUNEL staining in the substantia nigra. Interestingly, the antioxidant effect during either *in-vitro* or in vivo study was confirmed so that it had *in-vitro* hydroxyl radical scavenging activity and reduced oxidative stress in rats with rotenone-induced neurotoxicity through increase of catalase and superoxide dismutase activity and glutathione, mitochondrial complex-I activity up-regulation and inhibition of NADH-diaphorase activity.

In addition, it had obvious effect in increase of dopamine level [44]. Moreover, the improvement of behavioral problems (disturbed motor balance and coordination) and stress oxidative (reduced activity of glutathione peroxidase, superoxide dismutase and Na^+, K^+-ATPase) were showed subsequently quercetin administration to mice with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced neuro toxicity. It was also affective to increase dopamine level and to reduce 4-hydroxy-2-nonenal (4-HNE) immunoreactivity [45].

Furthermore, it have well been demonstrated treatment with quercetin leads to potential effects to diminish stress oxidative and cognitive disorder as well as to inhibit neuron death and ultimately normalization of dopamine level in 6-hydroxy dopamine-induced neurotoxicity in rats [46, 47].

Our study about the effect of ellagic acid on rats with 6-hydroxidopamine-lesioned neurotoxicity demonstrated that it could abrogates hyperalgesic responses and memory and learning dysfunction caused by 6-hydroxidopamine injection in Right medial forebrain bundle's rats [48]. It has well been revealed that injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) increases infla-mmatory condition in mice, while administration of caffeic acid as pre-intake and post-intake reduce induced inflammation. Interestingly, the effect of pre-intake of caffeic acid was higher than effect of post-intake of caffeic acid due to it was showed more level of caffeic acid after its pre-intake.

TABLE 2: ROLE OF COMPOUNDS ISOLATED FROM HERBS IN TREATMENT OF PARKINSON' DISEASE

Compound	Animal model/cell line	Finding(s)	Reference
Tangeretin	6-OHDA-induced neurotoxicity in rat	Increase of TH+ cell number and dopamine level, good bioavailability	40
Rutin	6-OHDA-induced neurodegeneration in rat	Antioxidant property, increase of dopamine and its metabolite level, improvement of behavioral problem	41
Curcumin	A53T α-synuclein-induced neurodegeneration in PC12 cells	Antioxidant and antiapoptotic activities	42
	MPTP-induced neurotoxicity in mice	Inhibition of MAO-B activity	43
Quercetin	Rotenone-induced hemi-Parkinson in rat	Conformation of neuroprotective effect and antioxidant property, increase of dopamine level	44
	MPTP-induced neurotoxicity in mice	To have neuroprotective and antioxidant effects, improvement of behavior deficit	45
	6-OHDA-induced neurotoxicity in rat	Antioxidant and neuroprotective properties	46
	6-OHDA-induced neurotoxicity in rat	Enhancement of cognitive problem and oxidant-antioxidant imbalance	47
Ellagic acid	6-OHDA-lesioned neurotoxicity in rat	Reduction of hyperalgesic responses, enhancement of memory and learning dysfunction in MFB's rats	48
Caffeic acid	MPTP-induced inflammation in mice	To have potent neuroprotective and antioxidant effects	49
Gallic acid	6-OHDA-induced neurotoxicity in rat	Improvement of motor problem and pallidal gamma wave power	50
	6-OHDA-induced neurotoxicity in rat	Anti-oxidant property, improvement of passive avoidance memory	51
Hesperidin	Rotenone-induced apoptosis in human neuroblastoma SK-N-SH cells	Anti-oxidant and anti-apoptotic properties	52
Isoflavone	OVX- 6-OHDA-induced Parkinson's disease in female rats	Enhancement of spatial learning and memory, Inhibition of body weight increasing	53

6-OHDA: 6-hydroxydopamine; TH+: tyrosine hydroxylase positive; MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; MAO-B: monoamine oxidase; MFB: medial forebrain bundle; OVX: ovariectomized

This study also was revealed that caffeic acid pre-intake results in down-regulation of mRNA expression of iNOS (inducible nitric oxide synthase), COX-2 (cyclooxygenase-2), GFAP (glial fibrillary acidic protein) and ionized calcium binding adaptor molecule 1 (Iba1), reduction of NO (nitric oxide) and PGE_2 (prostaglandin E_2).

In addition, in association with up-regulation of mRNA expression brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), increase of tyrosine hydroxyllase activity and dopamine level, caffeic acid pre-intake was affective than caffeic acid post-intake [49]. Based on our studies, gallic acid has potential effects to reduce disturbances related to Parkinson's disease. Because it could be affective to reverse motor deficit, pallidal gamma wave power and memory dysfunction (through improvement of passive avoidance memory) due to have prominent antioxidant effects in hippocampus and striatum (through Increase of total thiol level and glutathione peroxidase activity and reduction of malondialdehyde level) in animal model of Parkinson's disease induced by 6-hydroxydopamine injection [50, 51].

Given that, obvious improvement of enzymes activity related to antioxidant defense (catalase, superoxide dismutase and glutathione peroxidase), reduction of ROS formation as well as inhibition of apoptosis result from incubation of human neuroblastoma cell line with hesperidin after induction of apoptosis by rotenone, thus it is a promising agent to treat Parkinson's disease [52]. In conjunction with our examination about effect of soy meal (+/- isoflavone) on post-menopausal cognitive problem and body weight changing in female rats with ovariectomized-6-hydroxy dopamine-induced Parkinson's disease demonstrated that soy meal (+/- isoflavone) ameliorates spatial learning and memory and inhibits body weight increasing. We believe that these effects are related to reduction of degeneration of nigrostriatal dopaminergic system [53].

CONCLUSION: In this study, we reviewed the role of extracts and compound obtained from plant in treatment of Parkinson's disease according to study on different animal models of Parkinson's disease. The antioxidant property is most important of these herbs to abrogate showed neurotoxicity and neurodegeneration in these models that can occurs through increase of enzymes related to antioxidant defense such as catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase as well as reduction of malondialdehyde level (a marker of lipid peroxidation). In addition, apoptosis and mitochondrial dysfunction are common reasons degeneration during Parkinson's disease.

Our review study showed the treatment with extracts and compounds of herbs lead to prominent effects in reduction apoptosis and mitochondrial dysfunction at striatum and *Substantia nigra*. Behaviors dysfunctions commonly occur after induction of Parkinson models by neurotoxic agents. Here, we found that herbs or their compounds potentially improve these problems.

Finally, we concluded that herbs are good candidates for treatment of Parkinson disease, although should be perfume further studies to understand probably their mechanisms and side effects.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding this study.

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