



## Review Article

# Natural products: An emerging tool in parkinson's disease therapeutics

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## ABSTRACT

Parkinson's disease is a age associated chronic neurodegenerative disorder of central nervous system characterized by selective loss of dopaminergic neurons in substantia nigra pars compacta which causes functional impairment of midbrain. Although the cause of PD is still not known, but there are several factors such as oxidative stress, genetic mutations, mitochondrial dysfunction, aggregation protein specifically  $\alpha$ -synuclein and neuroinflammation play a pivotal role in pathogenesis of PD. The current treatment primarily includes dopaminergic and non-dopaminergic medications which only provides symptomatic relief and when drug therapy fails to provide relief, the next step is surgical treatments. Unfortunately the current regimens have certain limitations with multiple side effects and possess economic burden thus, there is a need to discover new therapeutic approaches which have antiparkinsonian potential and minimum adverse effects. For many years, some phytoconstituents from natural products have provided a competent resource for the revelation of potential therapeutic agents. The anti-PD potential of these phytoconstituents is because of their well appreciated anti-oxidative, anti-inflammatory activities, their repressive role on aggregation of protein and the regulatory effects of PD cognate pathways. The intention of this review article is to cover the potential of phytoconstituents against the neurodegeneration in PD and to encourage the improvement in future novel treatment strategies predicated on natural sources.

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## 1. Introduction

Parkinson's disease (PD) is age associated second most prevalent neurodegenerative disease of the central nervous system [First is Alzheimer's disease (AD)] and mainly disturbs the motor function of the human body.<sup>1</sup> The incidence of Parkinson's disease is less in early ages, but as the age increases the prevalence also increases rapidly. The incidence of PD is more in females than male.<sup>2</sup> PD is first introduced by English surgeon James Parkinson who first described the syndrome which he called as the 'shaking palsy'.<sup>3</sup> Parkinson's disease is characterised by the degradation of dopaminergic neurons in the SNpc (part of midbrain) leading to disability in normal movements.<sup>4</sup> Apart from dopaminergic degeneration, genetic mutations and environmental factors additionally play a paramount

role in this disease.<sup>5</sup> Lewy bodies are result of  $\alpha$ -synuclein protein mutations, thereby contributing to the degeneration of dopaminergic neurons.<sup>6</sup> In addition, mitochondrial dysfunction causes decline of ATP leading to decline of energy and also enhances reactive oxygen species (ROS), and both of these cause initiation of apoptotic pathways and consequent neuronal death.<sup>7</sup> The neuro-inflammation which is initiated by ROS also plays a crucial role for development of PD.<sup>8</sup> The neurotoxins and cytokines released from the cells destroy the dopaminergic neurons in striatum and substantia nigra.<sup>9</sup> Neuro-inflammation occurring in the striatum and substantia nigra leads to behavioural and biochemical deficiency in PD.<sup>10</sup> Apart from this, the several pathways which are proximately associated with development and progression of PD includes, the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt)<sup>11,12</sup> signalling pathway (the nuclear factor erythroid 2-cognate factor 2 (Nrf2)

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signaling pathway<sup>13,14</sup> the P38 mitogen activated protein kinase (P38MAPK) signaling pathway,<sup>15,16</sup> the glycogen synthase kinase-3b (GSK-3b) signaling pathway,<sup>17,18</sup> the c-jun-N-terminal kinase (JNK) signaling pathway<sup>19,20</sup> the nuclear transcription factor-kB (NF-kB) signaling pathway,<sup>21,22</sup> the Wnt signaling pathway<sup>23,24</sup> and the autophagy lysosome pathway (ALP).<sup>25,26</sup>

Slowness of movement, resting tremor, rigidity of muscles, joints and difficulties in both speech and writing are some of the disturbing motor symptoms of the said disorder<sup>27</sup> whereas the non-motor symptoms of PD include neuropsychiatric disturbances, autonomic dysfunction, sleep disorders, gastrointestinal symptoms.<sup>28</sup> All these symptoms decrease the quality of life of the patients in addition to reduction in daily functioning.<sup>29</sup> While the causative factors of the disorder is difficult to deal with, the healthcare society has worked hard at least ameliorate the difficulties and provide symptomatic relief by providing several pharmacological agents, such as L-dihydroxyphenyl alanine (L-DOPA), monoamine oxidase-B(MAO-B)inhibitors and Dopamine(DA)agonist are commonly used which are presently prescribe to the affected person according to the extent of need and severity of symptoms.<sup>30</sup> As known from long term, L-DOPA which has been considered as gold standard for treatment of PD. A serious limitations in that it causes motor fluctuations, dyskinesia or both thereby enhancing symptomatic stress in the patient.<sup>31</sup> Also other drugs that are prescribed along with L-DOPA are not so efficient as they cause confusion, hallucination and hepatotoxicity and fails to prevent dopaminergic neuro-degeneration and thus the progression of disease.<sup>32</sup>

The current regimens are hindered by therapeutic inhibitions and with certain deleterious effects; thus, there is a desideratum to develop novel drugs having maximum efficiency and minimum adverse effects. hence to promote the development of future novel treatment strategies predicated on natural sources to fight neurodegeneration is the current aim of this review.

### 1.1. Pathogenesis of PD

Parkinson's is a multifactorial neurodegenerative disease, and there are number of factors responsible for neurodegeneration in parkinsons disease.

### 1.2. Protein stability and aggregation in parkinson's disease

Protein misfolding is a phenomenon caused of neurodegeneration where the normal protein structure changes to the 3-dimensional structure within the nerve cell.<sup>33</sup> mutations in different genes like, *SNCA*, *PARK2*, *PINK1*, *DJ-1* and *LRRK2* causes Protein misfolding and leading to affect neuronal function.<sup>34–36</sup> Normally neurotrophic

factors inhibit the Protein misfolding however it is reported that the neurotrophic factors have been reduced in the PD. Due to relative reduction of these growth factors, accumulation and aggregation proteins occurs, within a nerve cells.<sup>37</sup> The abnormal aggregation of mis-folded proteins is also called as “Lewy Body”(LBs).<sup>38</sup> The main component of LBs is alpha synuclein which is prone to misfolding and aggregation.<sup>39</sup> The alpha synuclein is a protein involves in axonal transport, synaptic vesicle function, and neuronal plasticity.<sup>40</sup> The genetic mutation, oxidative and nitrosative stress, mitochondrial dysfunction can influence aggregation and misfolding of synuclein in protofibrils, fibrils, and filaments.<sup>41</sup> Anomalously aggregated protein affects ubiquitin proteasomal and chaperone mediated autophagic system which inhibit neuronal function and axonal transport.<sup>42</sup> The alpha synuclein in LBs further leads to neurodegeneration by interfering with mitochondrial function, autophagy, vesicular homeostasis and neuroinflammation.<sup>43</sup>

### 1.3. Mitochondrial dysfunction

Mitochondria are the intracellular organelle which carry the biological oxidation and produces energy in mammalian cells and mainly function as energy generation in the form of adenosine triphosphate (ATP).<sup>44</sup> Dysfunction of the mitochondria leads to the pathogenesis of PD. For example, environmental neurotoxin 1-methyl-4-phenyl-1,2,3,4 -tetrahydropyridine (MPTP) produces parkinsonism.<sup>45</sup> MPTP is metabolised into toxic cation named 1-methyl-4-phenylpyridinium (MPP+) under the enzymatic action of MAO-B which further interferes with electron transport chain (ETC), ultimately causing mitochondrial dysfunction.<sup>46,47</sup> Also, MPP+ is as an active substrate of the DA transporter and accumulates into dopaminergic neurons of the brain causing neuronal death.<sup>48</sup> This phenomenon results in ROS generation with increased oxidative stress and decrease ATP production, also resulting in a high intracellular calcium concentration, nitric oxide (NO) and excitotoxicity-mediated neuronal damage.<sup>49</sup> The decrease in ATP production leads to the UPS dysfunction resulting in an activation of pathways involved in aggregation and apoptosis.<sup>50</sup> The initiation of the mitochondrial apoptotic pathways and release of pro-apoptotic proteins from the inter-membranous space including cytochrome C, that induce caspase-dependent cell death and apoptosis inducing factor (AIF) and endonuclease G that translocate to the nucleus and induce caspase-independent nuclear DNA fragmentation.<sup>51</sup>

Chronic exposure of another neurotoxin rotenone causes inhibition of mitochondrial respiratory chain complex-I resulting into selective degeneration of dopamine neurons. Inhibition of complex-I activity, activation of astrocytes and microglial cells, inflammatory reaction, glutamate excitotoxicity and increased nitrosative stress, nitric oxide

and malondialdehyde level, aggregation of  $\alpha$ -synuclein are involved in the mechanism of rotenone -induced parkinsonism.<sup>52</sup> Genetic mutations in mitochondrial DNA (mtDNA) result in mitochondrial dysfunction and the pathogenesis of PD. For example, in patients with PD, the mutation in maternally inherited 12SrRNA may result in a significant reduction of cytochrome oxidase activity which is an essential enzyme that maintains normal mitochondrial functioning.<sup>53</sup> Thus, confirming the relationship between mitochondrial dysfunction and PD.

#### 1.4. Oxidative stress

Whenever there is an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to neutralize their harmful effects, it results in oxidative stress (OS). The excessive OS damages the cellular components like lipids, proteins and DNA. The primary site of ROS generation in brain is mitochondria of neurons and glia.<sup>54</sup> Neuroinflammation, dopamine degradation, mitochondrial dysfunction, aging, GSH depletion, and high levels of iron or  $\text{Ca}^{2+}$  are leading cause for production of these free radicals.<sup>55</sup> ROS production also observed in presence of neurotoxin like Rotenone and MPTP.<sup>56,57</sup> Releasing of dopamine from the vesicle into the cytoplasm coordinate iron molecules (Fe) present in the brain which redox reactions that result in the formation of neuro-melanine (NM) and reactive oxygen species (ROS). Neuromelanine will also coordinate Fe and produce ROS.<sup>58</sup>  $\alpha$ -synuclein is a protein which is responsible for regulation of equilibrium between vesicle bound and cytoplasmic dopamine. The mutations of this protein shift the dopamine equilibrium in favour of the cytoplasm. Presence of Fe and oxidative stress leads to aggregation of  $\alpha$ -synuclein protein causing pigmentation of neurons which are more susceptible to damages.<sup>59</sup> The overproduction of ROS causes mutation of PTEN-induced putative kinase- 1 (PINK1) which is a protein expressed in human tissues which plays a critical role in the fighting against OS and maintaining mitochondrial membrane potential.<sup>60,61</sup> Furthermore, complex-I deficiency caused by ROS leads to activation of certain apoptotic and pro-apoptosis factors and thus the neuronal death.<sup>62</sup>

#### 1.5. Neuroinflammation

The first evidence of involvement of neuroinflammation in PD pathogenesis has been reported by McGeer et al. in 1988, they have found that post-mortem brains of patients who had PD shows increased human leucocyte antigen-DR-positive microglia.<sup>63</sup> In addition to this study, it has been shown that there are increased pro-inflammatory mediators in the striatum and substantia nigra, including TNF, IL $\beta$ , IL6, iNOS and COX2.<sup>64</sup> Microglia is one of the major types of cell which is involved in the inflammatory responses in

the central nervous system.<sup>65</sup> As discussed earlier, PD is associated with abnormal aggregation of  $\alpha$ -synuclein which further activates microglia.<sup>66</sup> Oligomers of  $\alpha$ -synuclein activates toll-like receptor 2 (TLR2)-mediated signaling which affects microglia.<sup>67</sup> The characteristic features of neuroinflammation include activation of microglia, reactive astrocytes within the brain and release of various inflammatory mediators including cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6), chemokines, complement cascade proteins, ROS and reactive nitrogen species (RNS). These factors are known to disrupt the BBB permeability.<sup>68</sup> The specific association between these neuroinflammatory mediators and neurodegeneration remains unclear however, it is reported by Witte. et al. that mitochondrial dysfunction and oxidative stress are central to this progression. They suggested that, altered mitochondrial function leads to impaired energy metabolism and induces neuroinflammation via NO and ROS production, which results in neurodegeneration.<sup>69</sup>

#### 1.6. Proteolysis defects

Non-functional and abnormal proteins are removed by three mechanisms: the autophagy-lysosomal pathway, the ubiquitin-proteasome system, and molecular chaperones.<sup>70</sup>  $\alpha$ -synuclein protein is mainly removed through these mechanisms. Inhibition of these mechanisms leads to accumulation of abnormal proteins that can misfold, aggregated and block the normal molecular pathways, leading to cell death.<sup>71</sup> Mitochondrial and UPS functioning is normally regulated by genes namely *PINK1*, *parkin*, and *DJ-1*, *UCH-L1* respectively. Mutation in these genes may turn into dysfunctions of mitochondria and UPS system which further leads to degeneration of DA neurons<sup>72</sup>. Mutation in *DJ-1* upregulate oxidative and nitrosative stress and thus causes dopamine oxidation. Alterations in mitochondrial function also triggers some major pathways which accelerates oxidative stress,  $\alpha$ -synuclein aggregation and further leads to dopaminergic neurodegeneration in PD.

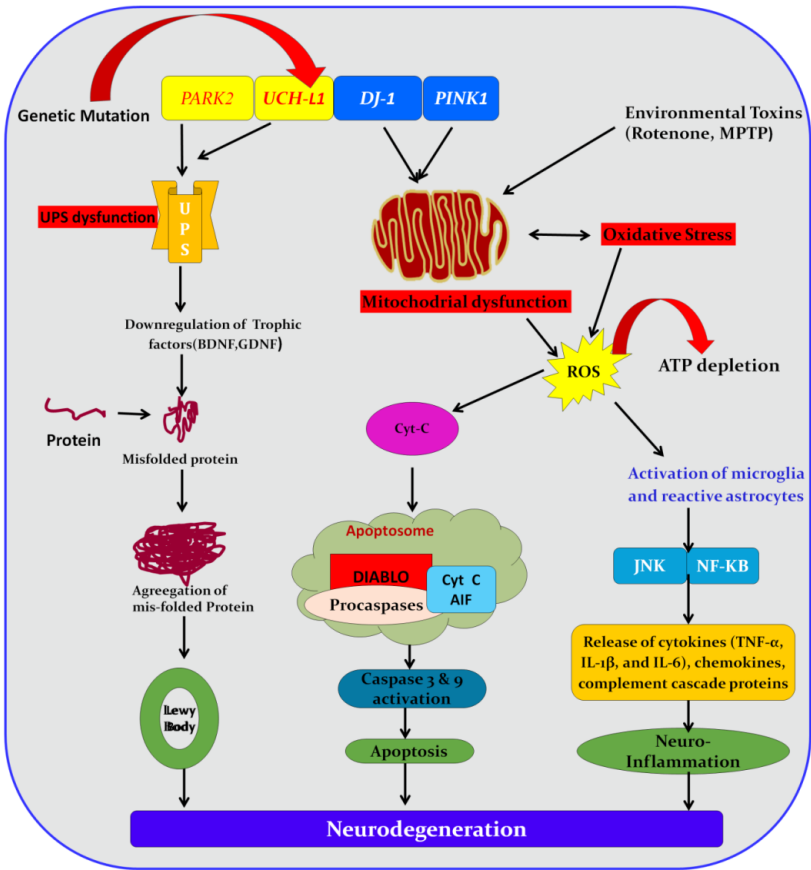


Fig. 1: Pathophysiology of parkinson's disease.

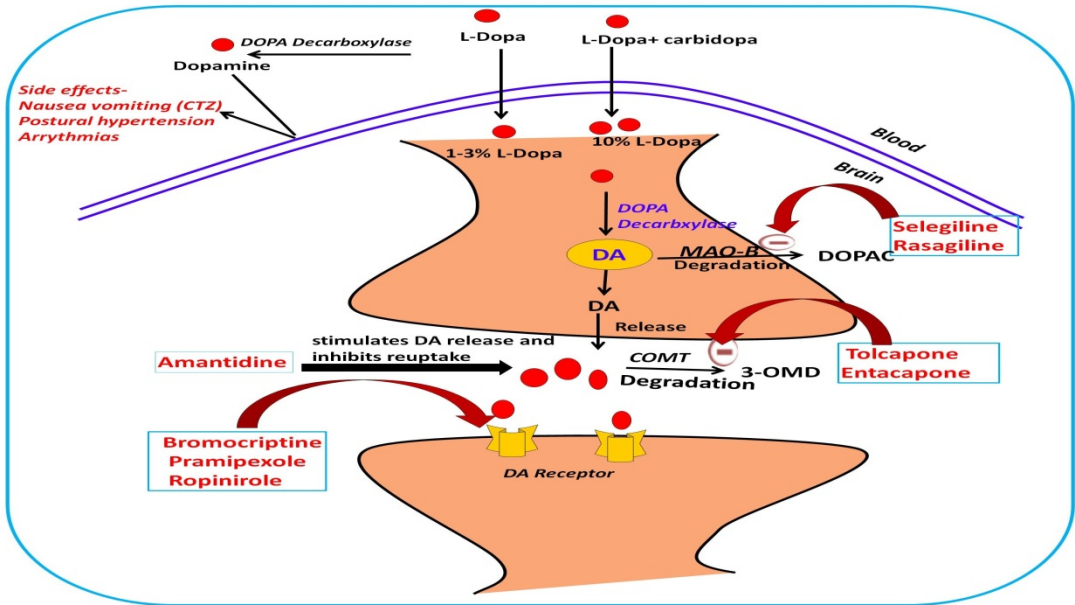


Fig. 2: Current therapeutic management of PD.

Table 1:

S. No.	Compound Name	Plant Source	Class	Mode of Action	
1.	Baicalein	Roots of <i>Scutellaria baicalensis</i> and <i>Scutellaria laterifloras</i> Family: <i>Lamiaceae</i>	flavonoid	Antioxidant, anti-inflammatory, Inhibit $\alpha$ -synuclein aggregation	95-98
2	Curcumin	<i>Curcuma longa</i> . Family- <i>Zingiberaceae</i>	Polyphenolic flavonoids	Strong antioxidant activity, Increased DA, DOPAC Activity and decreased MAO-B activity, ↓ phosphorylation of JNK1/2 and c-Jun, ↓ caspase-3, and thus anti-apoptotic, Enhances autophagy and lysosome biogenesis by activating TFEB	99-103
3	Resveratrol	<i>white hellebore</i> and <i>Polygonum cuspidatum</i> family-	Polyphenols	Reduce $\alpha$ -synuclein aggregation via autophagy induction, Downregulation of a apoptosis-inducing factor (AIF) and upregulate Bcl-2 family protein (an anti-apoptotic protein), Reduce expression of COX-2 and tumor necrosis factor- $\alpha$ and inhibition of microglial activation	104-109
4	Ginkgolides A, B, C, J	<i>Ginkgo biloba</i> family- <i>Ginkgoaceae</i>	Flavonoids and glycosides	Improved locomotor activity, superoxide dismutase(SOD), glutathione(GSH) and tyrosine hydroxylase(TH). BDNF level increase by increasing the levels of phosphorylated CREB Suppression of neuronal apoptosis through activation of the Akt pathway	110 - 113
5	Ginsenoside Rg1, Rd, Rb, Re	plant <i>Panax ginseng</i> , Family- <i>Araliaceae</i>	Steroidal saponins	Decreasing the levels of apoptotic proteins like Bax, Bcl-2, cytochrome c, and cleaved caspase-3, Antioxidant effect by activating Nrf2 transcriptional factor, Alleviates Neuroinflammation by suppressing NF-KB pathway and inhibiting activation of reactive astrocytes and microglia, Neuroprotective effects via Wnt/ $\beta$ -catenin signaling pathway, Upregulation of PI3K/AKT/Nrf2 Pathway.	114-119
6	Bacosides	<i>Bacopa monnieri</i> ( <i>Brahmi</i> ) family- <i>Scrophulariaceae</i>	Glycosides	Attenuates behavioral deformities, reduces the oxidative stress and neuronal cell death Improving TH activity, improves locomotor activity and cognitive functions	120-123
7	L-DOPA	<i>Mucuna pruriens</i> (MP) Family: <i>leguminosae</i>	Flavonoid	Neuroprotection by reducing apoptotic (Bax and caspase-3) and increasing levels of anti-apoptotic protein (Bcl2) expression, Neuronal survival by improving mitochondrial and synaptic functions, increases TH expression, improves locomotion and other motor performance	124-129

Continued on next page

Table 1 continued

8	Silymarin	<i>Silybum marianum</i> family - Asteraceae.	flavonolignans	Antioxidant, Anti-inflammatory, cytoprotective and neuroprotective. Increase in DA and serotonin levels and secretions of trophic factors . prevents conversion of DA to DOPAC by MAO-B. downregulate synthesis of inflammatory mediators (TNF-a, TNF-b, iNOS, NO) and apoptotic proteins ( p53 and apaf-1, caspase-9 )	130-136
9	Gastrodin	<i>Gastrodia elata</i> family-orchedaceae	Glycosides	Increased DA concentration and decreased DA turnover in striatum. Anti-apoptotic and Antioxidant activity. blocking obstruct NF- $\kappa$ B signaling pathway and prevent phosphorylation of MAPKs thus inhibit release of cytokines.	137-141
10	Withanolides	<i>Withania somnifera</i> / <i>Ashwagandha</i> family - Solanaceae	Alkaloids	Increasing GSH and glutathione peroxidase (GPx) level, TH positive cells and DA levels in striatum along with improved motor function.	142-146
11	Nicotine	<i>Nicotiana tabacum</i> .Family- Solanaceae	Alkaloids	downregulated cell apoptosis signaling pathways.. Inhibit $\alpha$ -synuclein fibrillation. Inhibit astrocytes and microglia activation in SNpc and increase GDNF in the striatum by Activation of $\alpha 7$ nicotinic acetylcholine receptor ( $\alpha 7$ -nAChRs) Improves learning and memory Trigger pro-survival signaling pathway( Wnt/ $\beta$ -catenin, PI3K, Akt)	147-155
12	Triptolide	<i>Tripterygium wilfordii</i> . Family- Celastraceae	Terpenoid	impedes microglial activation and thus attenuates neuroinflammation. promotes $\alpha$ -synuclein clearance by increasing level of LC3-II protein in autophagy pathway.	156-158
13	Puerarin	<i>Pueraria lobata</i> (PL ) family: Leguminosae	Flavonoid	Increase TH positive neurons, and neurotrophic factor GDNF, protein expression of DJ-1 and superoxide dismutase-2, regulate PI3K/Akt signalling pathway	159-162
14	Magnolol	Plant <i>Magnolia officinalis</i> family: Magnoliaceae	Phenylpropanoid	anti-inflammatory property by down-regulating the expression of Toll like receptor 4 (TLR 4) and p38/ MAPK signaling pathway modulate PI3K-MEK-ERK pathway, PI3K-Akt-FoxO1 and promote neuronal survival. Increase DA and TH	163-167
15	Epigallocatechin-3-gallate (EGCG)	<i>Camellia sinensis</i> family: Theaceae	Polyphenols	inhibits nuclear translocation of NF-K $\beta$ , $\alpha$ -synuclein fibrillation, Increases DA, decreases the TNF- $\alpha$ , nitrite level Modulate MAPKs, PI3k -Akt cell signalling pathways.	168-171

Continued on next page

Table 1 continued

16	Paeoniflorin	<i>Paeonia lactiflora</i> , family- <i>Paeoniaceae</i>	Terpenoid	Induce autophagy by upregulation of LC3-II protein, also activates ubiquitin-proteasome pathway and promote degradation of $\alpha$ -synuclein, decreases mitochondrial membrane potential, ROS production and increases of Bax/Bcl-2 ratio,	172-176
17	Ligustrazine and tetramethylpyrazine	<i>Ligusticum striatum</i> and <i>Ligusticum wallichii</i> Family- <i>Apiaceae</i>	Alkaloid	Enhance levels of antiapoptotic proteins and downregulate levels of apoptotic proteins, increase amount of phosphorylated Akt while decrease GSK-3 $\beta$ activity by Activation of PI3K/Akt/ GSK3 $\beta$ Signaling Pathway, upregulate the levels of SOD and GSH.	177-180
18	Naringenin	tomatoes, grapefruits,	flavonoids	Shows antiapoptotic effects by inhibiting phosphorylation of JNK and P38, and activation of caspase-9, PARP, and caspase-3 Restores the levels of protective proteins parkin, DJ1, TH, Nrf2 and thus improves antioxidant status	181-185
19	Crocin	<i>Crocus sativus</i> Family : <i>Iridaceae</i>	Carotenoids	improve aversive memory through antioxidant and anti-inflammatory potential. attenuate cholinergic function reduce $\alpha$ synuclein aggregation and fibrillation. inhibition of apoptotic dark neuron formation and inflammatory factors.	186-190
20	Hyoscyamine	Hyoscamine. reticulatus or Hyoscamine niger, family: <i>Solanaceae</i>	Tropane alkaloids	increased GSH GPX, SOD and CAT activity. anticholinergic	191-192
21	Asiatic acid	<i>Centella asiatica</i> Family: <i>Apeaceae</i>	Triterpenoids	Upregulate BDNF, because of the phosphorylation of CREB. Free radical scavenging activity. Neurotrophic activity by increasing the phosphorylation of PI3K, Akt, GSK-3 $\beta$ and mTOR pathway. Decrease $\alpha$ -synuclein aggregation.	193-197
22	salvianolic acid	<i>Salvia miltiorrhiza</i> family: <i>lamiaceae</i>	Phenylpropanoid (coumarin) compounds	protects DA neurons by reducing neuro-inflammation and increasing GDNF expression. Reduce caspase-3 and reduced cytochrome C activity Increases Bcl-x/Bax ratio. Free radicals scavenging activity.	198-201
23	Fraxetin	<i>Fraxinus bungeana</i> , family: <i>oleaceae</i>	Phenylpropanoid	Increase GSH level Reduce ROS mediated apoptosis	202-205
24	MAM(2-methoxy-6-acetyl-7-methyljuglone)	<i>Fallopia japonica</i> . Family : <i>polygonaceae</i>	Napthoquinone compounds	Inhibition phosphorylation of ERK1/2, JNK, and p38-MAPK and shows anti-apoptotic.	206-208



### 1.7. Challenges with current synthetic treatment

Although there are a few medicines given to PD patients but none of them act on actual causal mechanism involved in the disorder. Coming to the mechanism symptoms, that occurs, dopamine loss is responsible for the motor symptoms of PD, that is why dopamine replacement therapies like tablets having carbidopa, levodopa and others are given to serve the replacement of depleted dopamine.<sup>73,74</sup> Apart from the limitations that the gold standard levodopa does not act on the cause, another limitation that lies is on long term administration the symptoms become the more severe.<sup>75</sup> However the chronic use of L-dopa may turn into disabilities in motor symptoms like speech, gait, posture, etc.<sup>76</sup> Another serious problem with L-dopa is that it increases neurodegeneration through oxidative stress.<sup>77</sup> While levodopa possess all these problems, on the other hand sleep disturbances and cognitive problems such as confusion and hallucination arise from other PD medicines like MAO-B inhibitors, COMT inhibitors and anticholinergic drugs.<sup>78</sup>

When drug therapy can no more provide symptomatic relief, surgeries like deep brain stimulations and lesional stimulations are opted by the physicians where areas like thalamus, globus pallidus are stimulated through low current. Out of these deep brain stimulation is more preferred due to its convenience where a medical device is implanted that sends electric impulses to required brain regions.<sup>79,80</sup> Currently DBS in subthalamic nucleus (STN) and the globus pallidus internus (GPi) is the mostly opted surgery due to its great effectiveness.<sup>81,82</sup> But again, DBS also has the same limitations in that it does not stop the disease progression and also does not prevent the worsening of symptoms.<sup>83</sup> Lesion surgeries are also used which includes thalamotomy, pallidotomy, subthalamotomy, etc but their application is much less in the present time because of the risks associated with a surgical lesion.<sup>84</sup> Another fact that has been known is that surgeries in PD lead to brain haemorrhage thereby enhancing the risk of morbidity and mortality.<sup>85</sup> One approach that lacks side effects is rehabilitation therapy but it only improves functional ability.<sup>86</sup> Rehabilitative therapy utilised to treat PD in order to improve functional capacity of individuals by performing day to day exercise like stretching, muscle strengthening, postural exercises, etc.<sup>87,88</sup> It has been observed that physical exercise and treadmill training significantly improves motor functions in Parkinson's patients.<sup>89</sup> Non-conventional strategies like music and dance therapy also seem to be effective in management of affected motor activities.<sup>90</sup>

However the current therapeutic regimen having some major limitations such as, It provides only symptomatic relief, fails to reduce disease progression, safety and life expectancy issues and cost of treatment is also more.<sup>91</sup>

### 1.8. Natural products used in Parkinson's disease therapeutics

Herbal plants have long been utilized to prevent and treat diseases. Nowadays, many people still rely on herbal nutraceuticals for their primary healthcare. More than 50% of the drugs currently in clinical application are of natural product origin.<sup>92</sup> In the last few years, many researchers have investigated the role of various natural products and herbs in the treatment of PD. Some herbs have proved to be effective and more reliable than the usual synthetic drugs.

## 2. Conclusion

PD is one of the most common neurodegenerative diseases worldwide, and effective treatments for it are yet to be found. The causes of PD are unknown, current treatments focus on managing patients' symptoms and on increasing DA levels. Various types of important mechanisms with multiple factors are involved in the pathogenesis of PD. These mechanisms may be targeted by diverse compounds from natural sources that exert anti-Parkinson effects via the modulation of the pathological pathways and/or factors involved. Thus, effective new treatment strategies for PD are urgently needed given the increasing number of PD patients worldwide. With further study of the pathogenesis of PD as well as deeper revealing of the pharmacological effects of various natural products, more and more monomer components derived from natural products are found to

have anti-PD efficacy *in vivo* or *in vitro*. However, many of these monomer components outlined above could not be directly used as drugs for the treatment of PD and related disorders. Therefore, we speculate that detailed investigations into the structure activity relationships of natural products outlined above may guide the design of novel therapeutic drugs in Parkinson's disease which possess enhanced properties *in vivo* (e.g. ability to penetrate the blood brain barrier), but which retain the bioactivity characteristic of the natural product scaffold. Thus, these monomer components outlined above could represent starting points to the development of innovative anti-PD drugs.

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None.

## 5. Conflict of Interest

None.



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