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In Vivo Studies of various Antiparkinson's agents: A Systematic Review

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder which is characterized by typical symptoms including gradual progressive muscle rigidity, tremor and loss of motor skills. Although there is no definitive cure for PD, the extract of some medicinal plants and their ingredients have been suggested to relieve its symptoms and to prevent disability in patients. This review is focused on therapeutic effects of some anti-Parkinson's agents. The findings presented in this review were collected from experimental studies in databases including PubMed, Web of Science and Google Scholar until the end of dec 2021. The keywords "Parkinson's disease" or "neuroprotective" and "Medicinal plants", "MPTP", "6 OHDA", "Rotenone", and "haloperidol", were searched. Based on the results of animal studies, according to animal model various anti Parkinson's agents with their proposed mechanism are discussed in this review. This data will help to find new potential therapeutic agents for parkins disease treatment.
Keywords: Parkinson's disease, Neuroprotective, MPTP, 6 OHDA, Rotenone, Haloperidol.

I. INTRODUCTION

Parkinson's disease (PD) is primarily characterized by degradation of dopamine-carrying neurons in the substantia nigra with the extrapyramidal symptoms such as tremors, bradykinesia, rigidness, and inability to maintain the normal posture [1]. The neuronal death in PD is due to the damage to free radicals, Lewy's bodies formation [2]. It has been prevalent in 10 million people around the globe with incidence rate of 219/100000 people in Pakistan [3]. There has been evidence that suggests the oxidative stress, accumulation of misfolded protein and the loss the dopaminergic neurons in substantia nigra pars compacta as the main hallmarks of PD pathogenesis [4]. The neurodegeneration has been accounted for the loss of 80% dopaminergic neurotransmission in striatum that leads to significant neuromuscular dysfunction along with some cognitive deficits at advanced stages [5]. Levodopa is the primary gold standard approach to symptomatically manage the PD but its chronic use has also been associated with development of dyskinesia [6]. Moreover, we have no therapeutic options that provides the neuroprotection or relieve the progression of PD. Therefore, it is the need of time to develop the therapeutic modalities that changes the course of PD progression along with treating it symptomatically.

One well-accepted and commonplace parkinsonian animal model is generated by intraperitoneal (i.p.) injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is converted by monoamine oxidase type B (MAO-B) to its metabolite 1-methyl-4-phenylpyridinium (MPP+). MPP+ exhibits a high affinity for the dopamine transporter (DAT) and is transported into DA neurons, where it impairs respiration by inhibiting mitochondrial complex-1. This results in increased reactive oxygen species (ROS) production. ROS promotes cell death via oxidatively damaging molecules such as superoxide radicals and hydroxyl radicals and causes lipid and protein peroxidation. Eventually, the affected DA neurons can degenerate by either necrosis or apoptosis [7].

Table 1: Anti Parkinson's agents effective in MPTP induced Parkinson's disease.

Sr. No	Name	Parts and Family/ Extracts/Fraction	Maximum tolerated dose (MTD)/ Therapeutic doses (mg/kg)	Constituents/Possible mechanism responsible for this effect
1.	(-) Epigallocatechin-3-gallate[8]		25 50	EGCG serves neuroprotective effects in an MPTP-induced PD mice model and may

				exert this through modulating peripheral immune response.
2.	Acanthopanax senticosus harms[9]	Root and Rhizome Ethanolic	182 45.5	It can increase the level of DA in striatum, balance the behavioral activation/inhibition at a striatal level and protect DA neurons from dying by apoptosis in Parkinson's disease mice.
3.	Apium graveolens L. [10]	Whole plants Chinese medicine methanolic	125, 250 375	Extract is able to ameliorate behavioral impairments, improve oxidative stress parameters, decrease the activity of MAO-A and B, and protect dopaminergic neurons.
4.	Apomorphine [11]		10	(a) its radical scavenging and iron-chelating properties; (b) its ability to protect against hydrogen peroxide, 6-OHDA, and iron-induced neurotoxicity in PC12 cell culture; (c) its ability to protect against MPTP induced neurotoxicity in vivo in mice; (d) its ability to inhibit mitochondrial iron-induced lipid peroxidation and protein oxidation; (e) its ability to prevent 6-OHDAinduced inhibition of mitochondrial complex I activity; and (f) its ability to inhibit MAO-A and B.
5.	Chinonin [12]		10 20 40	Antioxidative property
6.	Cordycepin [13]		10 20	By inhibiting TLR/NF-κB signaling pathway
7.	Dendropanax morbiferus [14]	Leaves Aqueous	200	It effectively curbs the microglia-stimulated neuroinflammation by modulating the NF-κB/IκB-α and JNK-MAPK signaling pathways.
8.	Dexrazoxane [15]		1.5 5 15 3 10 30	Via attenuation of oxidative stress and ER stress, as well as the suppression of systemic inflammation in both peripheral tissues and brain.
9.	Entacapone [16]		12.5	To avoid pulsatile dopaminergic stimulation and provides increased therapeutic response without additional risk of dyskinesia induction over and above that found with a dopamine agonist alone.
10.	*Eucommia ulmoides* Oliv. [17]	Bark Ethanol	2.5 g 5 g 10 g	It is mediated by downregulating p38/JNK-Fosl2 gene expression to alleviate neuroinflammation.
11.	Eupatilin [18]		10	Inhibition of neuroinflammation and apoptosis associated with down-regulation

				of NF-κB signaling and up-regulation of Akt/GSK-3β signaling.
12.	Evernic Acid [19]		5 80	Neuroprotective and anti-inflammatory effects
13.	Fasudil [20]			Reduction of glial cell aggregation around the striatum and SN; Inhibition of ROCK expression; Induction of Nrf2/HO-1 antioxidant pathway; and regulation of NMDAR and AMPAR.
14.	Geniposide [21]		100	Geniposide exerted its neuroprotective effect by enhancing growth factor signaling and the reduction of apoptosis
15.	Gentisic acid [22]		80	Inhibition of oxidative stress
16.	Ginkgetin [23]		80 100	Neuroprotection and demonstrated its potential use as an antioxidant for the mitigation of PD.
17.	Isobavachalcone [24]		50 10	Isobavachalcone decreased the LPS-induced oxidative stress and the expression of inflammatory cytokines, and provided a neuroprotective effect by antagonizing microglia-mediated inflammation.
18.	Isolongifolene [25]		5, 10, 20	ILF showed the potential to arrest apoptosis through the inhibition of caspase activity and rebalancing of the Bax/Bcl-2 ratio in rotenone-treated rats.
19.	Lycopene [26]		5 10 20	Lycopene reverses neurochemical deficts, oxidative stress, apoptosis and physiological abnormalities in PD mice
20	Magnolol [27]		10 mL/kg	It may reverse the neuronal damage in the MPTP-lesioned PD mice.
21.	Norfluoxetine [28]		1 5 10	It is associated with neuroinflammation and microglia-derived oxidative stress.
22.	Ocimum sanctum [29]	Leaf Ethanolic	1.75, 4.25 8.5	Dopamine facilitatory and antioxidant properties.
23.	Oleanolic acid [30]			Inhibits the increase in reactive oxygen species which play a primary role in neurodegeneration in Parkinson's disease.
24.	Piperine [31]		10	Anti-apoptotic and anti-inflammatory mechanism on 6-OHDA induced Parkinson's disease
25.	Portulaca oleracea [32]	Seed Methanolic	2000/ 200 400	Inhibition of oxidative stress
26.	Quercetin [33]		30	Increased the activity of several antioxidant enzymes.

27.	Resveratrol [34]		10	By inhibiting neuro-inflammation, apoptosis and promoting neuronal survival.
28.	Rolipram [35]		3	By improving the cAMP/CREB signaling pathway in the DG.
29.	Silibinin [36]		280	On the one hand, silibinin alleviates mitochondrial damage in the brain of mice with Parkinson's disease by inhibiting oxidative stress, reducing inflammatory response and α-synuclein aggregation. On the other hand, silibinin can protect dopaminergic nerve by promoting mitophagy to remove damaged mitochondria in the brain of mice with Parkinson's disease
30.	Simvastatin [37]		1	Via inhibition of A1 reactive astrocytes in the MPTP mouse model of PD.
31.	Stemazole [38]		10 30 50	To enhanced anti-oxidative capacity, which may have resulted in the repair/restoration of dopaminergic neurons.
32.	Tripchlorolide [39]		1 µg/kg	Marked increases in neurochemical and immunocytochemical indices of midbrain dopaminergic pathways by TW397 in MPTP parkinsonian model mice
33.	Troxerutin [40]		150	Amelioration of apoptosis, astrogliosis, and oxidative stress and part of its effect is mediated through PI3K/ERβ pathway.
34.	Ursolic acid [41]		5 10	The oxidative stress and inflammation triggered by rotenone was significantly diminished by UA.
35.	Usnic acid [42]		25	Inhibited MPP^+-induced glial activation in primary astrocytes by blocking NF-κB activation.
36.	Valerenic acid [43]		2	Inhibition of NF-κB and activation of the 5-HT5A receptor by its agonist valerenic acid in astrocytes.

6-Hydroxydopamine (6-OHDA) is a specific neurotoxin for catecholaminergic pathways (Perese et al. 1989; Sachs and Jonsson 1975). Being structurally similar to the catecholamines,
it uses the respective transport system to enter the neurons and destroys them. 6-OHDA has been reported to produce some of the behavioral, biochemical, and pathological changes that are encountered in Parkinson's disease (PD) (Bloem et al. 1990) and, because of established
stereotactic techniques and relatively low maintenance costs, is currently the most commonly used animal model for the disease (Breese and Breese 1998). These toxic effects of 6-OHDA are attributed to the formation of various oxidants and free radicals (Cohen 1984), lipid peroxidation (Slater 1984), protein damage, and amino acid modifications (Dean et al. 1985). In addition, studies have demonstrated that 6-OHDA leads to reduction in glutathione (GSH) content and superoxide dismutase (SOD) and catalase (CAT) activity, and an increase in lipid peroxidation (Perumal et al. 1992; Kumar et al. 1995; Zafar et al. 2003a, b; Ahmad et al. 2005a, b) in striatum. [44]

Table 2: Anti Parkinson's agents effective in 6-OHDA induced Parkinson's disease.

Sr. No	Name	Parts and Family/ Extracts/ Fraction	Maximum tolerated dose (MTD)/ Therapeutic doses (mg/kg)	Constituents/Possible mechanism responsible for this effect
1.	(-)-sesamin [45]		30	Via the activation of transient ERK1/2- BadSer112 system and the inhibition of sustained ERK-p38MAPK-JNK1/2-caspase-3 system in PC12 cells. It showed prophylactic and adjuvant therapeutic effects on long-term L-DOPA therapy in dopaminergic neuronal cells of PD rat models.
2.	Albizia adianthifolia [46]	Leaves Aqueous	150 300	Antioxidant potential
3.	Bacopa monniera Linn [47]	Alcoholic	20 40	It has enhanced the availability of dopamine or might have prevented its breakdown and afford protection.
4.	Baicalein [48]	A flavonoid obtained from the root of Chinese medicinal herb Scutellaria baicalensis	200	By the increasing the number of dopaminergic neurons may have been, in part, caused by anti-apoptotic, pro differentiation and anti-inflammatory mechanisms of baicalein.
5.	Betaine [49]		12.5, 25, 50	Antioxidant and methyl donor properties of Betaine are promising particularly in management of plasma total homocysteine (tHcy) and oxidative stress in dopaminergic neurons of the brain.
6.	Caffeic Acid Phenethyl Ester [50]			The neuroprotective and anti-oxidant properties
7.	Caffeine and taurine [51]		10 8	It had an altering effect against the lesion induced by 6-OHDA as evaluated by behavioral tests and neurochemical analysis of striatal dopamine
8.	Cannabidiol [52]		10	The neuroprotective, anti-inflammatory and symptomatic effects of CBD treatment in an animal model of PD, potentially via the activation of astrocytic TRPV1-CNTF pathway.
9.	Cannabinoids [53]		3	These neuroprotective effects might be due, among others, to the antioxidant properties of certain plant-derived cannabinoids, or exerted through the capability of cannabinoid agonists to modulate glial function, or produced by a combination of both mechanisms.
10.	Cerebrolysin [54]		2.5ml/kg	Counteracting oxidative stress, replenishing dopamine content and enhancing behavioral outcomes.
11.	Curcumin and Desferrioxamine [55]		200 (curcumin) 50 (desferrioxamine)	Attenuated the loss of dopamine and increased antioxidant enzymes, resulting in preservation of dopaminergic neurons.
12.	Curcumin and naringenin [56]		50 (curcumin)	Antioxidant capabilities and their capability to penetrate into the brain.

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			50(naringenin)	
13.	Curcumin [57]		5 10 20	Regulating intracellular bFGF/NGF/TrkA/Hsp70 expressions, thereby improving neurofunctions in the SN.
14.	Dexrazoxane [58]		1.5 5 15	Via attenuation of oxidative stress and ER stress, as well as the suppression of systemic inflammation in both peripheral tissues and brain.
			3 10 30	
15	Edaravone [59]		30 100 250	Anti-apoptotic effects and radical scavenging activity
16	Eugenol [60]		0.1, 1, 10	Improve the antioxidant response by increasing the production of GSH.
17	Fucoidan [61]		10 20	Suppress the Nox1-triggered oxidative stress in the SNc to protect DA neurons
18	Gallic acid [62]		50 100 200	GA has neuroprotective activity against 6-OHDAinduced oxidative stress *via* enhancement of cerebral antioxidant defense.
19	Garcinia indica [63]	Fruits Methanolic	100, 200, 400	Antioxidant and anti-inflammatory properties
20	Ginkgo biloba [64]		50 100 150	Ginkgo biloba appears to act via antioxidant, free radical scavenging, MAO-B-inhibiting, and DA-enhancing mechanisms that rescue the compromised cells within the dopaminergic lesions.
21	Gynostemma Pentaphyllum [65]	Leaves Ethanol	10 30	Protective effects against neurotoxicity by reducing TH neuronal cell death and normalizing dopamine levels in 6-OHDA-lesioned
22	Hemantane [66]		10	Possesses the antidyskinesic effect against the levodopa-induced dyskinesia disturbances
23	Hesperidin [67]		50	Increasing the DA levels, activity enzymatic and non enzymatic, decreasing the reactive species and improving the behavioral parameters
24	Hibiscus asper [68]	Leaves (Malvaceae) Methanolic	50 100	Antioxidant and antiapoptotic activities in Parkinson’s disease model.
25	Humulus japonicas [69]	Cannabaceae	500	HJ improved the motor dysfunction and notably reduced dopaminergic cell death and fiber loss in the SNc and striatum caused by 6-OHDA.
26	Hypericum Perforatum [70]	Hydroalcoholic	200	Via attenuation of DNA fragmentation, astrogliosis, inflammation, and oxidative stress.
27	Montelukast [71]		10	A potential inhibitor of microglial activation to

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			20 40	protect DA neurons in the adult brain against PD.
28	Mucuna pruriens [72]		2.5 5 g/kg	Mediated by increasing the mitochondrial complex-I activity and by scavenging the free radicals.
29	Naringenin [73]		70	To activate Nrf2/ ARE pathway to add to the arsenal for treating neurodegenerative diseases
30	oleanolic acid [74]			Inhibits the increase in reactive oxygen species which play a primary role in neurodegeneration in Parkinson's disease.
31	Piperine [75]		10	Anti-apoptotic and anti-inflammatory mechanism on 6-OHDA induced Parkinson's disease
32	Quercetin [76]		30	Increased the activity of several antioxidant enzymes.
33	Sesame [77]	Seed Oil		By enhancing the activities of antioxidant enzymes, decreasing the TBARS content, TH positive expression and increased dopamine and its metabolite DOPAC level.
34	Sorafenib [78]		10	Maintain the normal range of natural antioxidant enzymes in brain tissue.
35	Stereospermum suaveolens DC [79]	Stem barks Methanolic	5000/ 125 250 500	It also contains saponin, a-cellulose, lignin, tannins, flavonoids, and saponins which may be responsible for the observed neuroprotective activity by direct antioxidant properties to detoxify ROS.
36	Syringic acid [80]		20	Via its neuroprotective, antioxidant and anti-inflammatory effects.
37	Thymol [81]		20 30 40	To an antioxidation mechanism
38	Thymoquinone [82]		5 10	Due to the attenuation of lipid peroxidation and this may provide benefits, along with other therapies,
39	Tinospora cordifolia [83]	Aerial parts Ethanol	200 400	By protecting dopaminergic neurons and reducing the iron accumulation.
40	Tricetin [84]			Protect dopaminergic neurons from 6-OHDA- induced neurotoxicity through mitochondrial apoptosis pathway and Nrf2/HO-1 signaling pathway.
41	Troxerutin [85]		150	Amelioration of apoptosis, astrogliosis, and oxidative stress and part of its effect is mediated through PI3K/ERβ pathway.
42	Vanillin [86]		20	Via preserving striatal dopamine levels
43	Varenicline [87]		1	Neuroprotective effect

Experimental as well as epidemiological studies provided evidence that exposure to many types of pesticides is accompanied by a greater risk of developing PD (Uversky et al. 2002; Uversky 2004). Rotenone is a pesticide and a potent inhibitor of complex I in the mitochondria (Naoi et al. 2005). Systemic administration of rotenone to rats produces nigrostriatal dopaminergic degeneration (Betarbet et al. 2000). Additionally, rotenone is well-characterized to be extremely hydrophobic and easily crosses biological membranes (Brown et al. 2006). Hence, rotenone model is a greatly reproducible tool for testing novel neuroprotective interventions for treating patients suffering from PD (Cannon et al. 2009). [88]

Table 3: Anti Parkinson's agents effective in Rotenone induced Parkinson's disease.

Sr. No	Name	Parts and Family/ Extracts/Fraction	Maximum tolerated dose (MTD)/ Therapeutic doses (mg/kg)	Constituents/Possible mechanism responsible for this effect
1.	Agaricus Blazei Murill [89]	Aqueous	273 819	Decreasing oxidative stress in the animal brain by increasing the brain levels of reduced GSH and total proteins and decreasing the levels of nitrite and TBARS.
2.	Agomelatine [90]		40	Increased levels of caspase-3 expression propose apoptosis induced mechanism behind agomelatine induced neuronal loss.
3.	Boswellic acids [91]	Tablets	125, 250	To suppress pro-inflammatory cytokines and neurodegeneration
4.	Caffeic acid [92]		2.5, 5, 10	Anti-inflammatory activity of caffeic acid and highlighted its neuroprotective activity
5.	Carbenoxolone [93]		20	Prevents the mitochondrial dysfunctions and reduces the neuroinflammation caused by rotenone treatment.
6.	Crocin [94]		30	Via activation of PI3K/Akt/mTOR axis and enhanced miRNA-7 and miRNA-221.
7.	Demethoxycurcumin [95]		5, 10, 15	Its anti-inflammatory and antioxidant activities.
8.	Filgrastim [96]	Recombinant human G-CSF (filgrastim)	(20 and 40 µg/kg)	Reduction of rotenone-induced neuroinflammation, apoptosis, and brain-derived neurotrophic factor depletion
9.	Glycyrrhizic acid [97]		50	Its potent antioxidative and anti-inflammatory properties.
10	Hidrox® [98]		10	Antioxidant, anti-inflammatory, prevented the α synuclein from aggregating and Forming accumulations in the

				dopaminergic neurons
11	Hyoscyamus niger [99]	Seeds Methanolic	125 250 500	Recovery in locomotor activity which may confer neuroprotection against the underlying dopaminergic neuron degeneration
12	Isolongifolene [100]		5, 10, 20	Anti-oxidant and antiapoptotic properties
13	Monascin [101]		100 200 400	Antioxidation and anti-neuroinflammation via modulating NF-κB and Nrf2 pathway.
14	Nerolidol [102]		50	Its antioxidant and anti-inflammatory activities.
15	Pomegranate Juice (Punica granatum L.) [103]			Its protection against oxidative damage and -synuclein aggregation, the increase in mitochondrial aldehyde dehydrogenase activity, and maintenance of antiapoptotic Bcl-xL protein at the control level.
16	Pulicaria undulate [104]	Essential oil	50 100 200	Anti-inflammatory and antioxidant activities with the ability to reduce a-synuclein gene expression
17	Sesaminol [105]			Reduces α-synuclein expression in the substantia nigra, which suppresses motor dysfunction and the decline of intestinal motor function.
18	Sida cordifolia [106]	Aqueous hexane (HFSC), chloroform (CFSC) and aqueous	50 100 250	Virtue of its antioxidative actions
19	Ursolic acid [107]		5 10	The oxidative stress and inflammation triggered by rotenone was significantly diminished by UA.
20	Vanillic acid [108]		12 25 50	Oxidative stress and attenuated the motor defects indicating the possible therapeutic potential of VA as a neuroprotective in PD.
21	Vitamin E [109]		100 I.U/Kg/ day i.m.	Potential antioxidant role of vitamin E in the nigrostriatal system.

Typical neuroleptic agents like chlorpromazine, haloperidol and reserpine induce a cataleptic state in rodents and these are being used as models to test the extrapyramidal side effects involved with it. Neuroleptic induced catalepsy has been linked to a blockade of postsynaptic striatal dopamine D1 and D2 receptors. Despite this evidence, several other neurotransmitters such as acetylcholine, serotonin, angiotensin, adenosine, or opioids have also been implicated. In addition to implications of various neurotransmitters in catalepsy, many preclinical and clinical studies have proposed reactive oxygen species in haloperidol induced toxicity. Evidence indicates that drugs which potentiate or attenuate neuroleptic catalepsy in rodents might aggravate or reduce the extrapyramidal signs respectively, in human beings. [110]

Table 4: Anti Parkinson's agents effective in Haloperidol induced Parkinson's disease.

Sr. No	Name	Parts and Family/ Extracts/Fraction	Maximum tolerated dose (MTD)/ Therapeutic doses (mg/kg)	Constituents/Possible mechanism responsible for this effect
1.	Achyranthes aspera [111]	Whole plant Hydroalcoholic	2000/ 200 400	Possible antioxidant role of *A. aspera* extract in overcoming the neurochemical and behavioral changes during oxidative stress.
2.	Albizia lebbeck (L.) [112]	Seeds Aqueous Methanolic	100 200 300	Albizia lebbeck (L.) improved the motor functions and reversed the biochemical damages in brain tissue of PD
3.	Beta vulgaris L. [113]	Leaves (*Chenopodiaceae)* Methanolic	2000/ 100 200 300	Augmentation of cellular antioxidants
4.	Brassica juncea [114]	Leaves (Cruciferae)	200, 400, 600	*B. juncea* improved motor functions and enhanced the antioxidant enzymes in brain tissues. reduced the MAO-B levels in the brain
5.	Buspirone [115]		20	Activation of 5-HT1A receptors.
6.	Cannabis sativa [116]	Flowering tops and Leaves	5 10 20	Cannabis alters the oxidative status of the brain in favor of reducing lipid peroxidation, but reduces brain glucose, which would impair brain energetics.
7.	Cucurbita pepo [117]	Seeds (Cucurbitaceae) Methanolic	200 400 600	It has an antioxidant and neuroprotective effect due to phenols, flavonoids and beta-tocopherol
8.	*Cyamopsis tetragonoloba* [118]	Methanol	200 400	Antioxidant potential
9.	Dicyclomine [119]		40, 80, 160	Enhancement of antioxidant defense system
10.	*Elaeocarpus ganitrus* [120]	Elaeocarpaceae	100 200 400	It has anti-oxidant activity and neuroprotective activity
11	Emblica officinalis [121]	Fruit Aqueous	0.8, 2.0 4.0	Due to both its anticholinergic and antioxidant properties.
12	Euphorbia cyathophora [122]	Leaves Ethanolic	2000/ 200, 400	Attenuated the motor defects and also increased the neuro chemical dopamine level.
13	Ficus religiosa [123]	Leaves Petroleum ether	4000/ 100, 200, 400	*Ficus religiosa* treatment significantly attenuated the motor defects and also protected the brain from oxidative stress.
14	Flupirtine [124]		1 10	It synergises with dopaminomimetics, it may prevent development of L-DOPA-induced fluctuations as

			20	NMDA receptor antagonists do _Chase et al., 1996., it possesses a neuroprotective potential, and _iv. it is devoid of the side effects of NMDA receptor antagonists.
15	Gentisic acid [125]		80	Inhibition of oxidative stress
16	Glucocorticoids [126]		1 2	Anticataleptic action of glucocorticoids.
17	Green coffee extract [127]	Seeds	100 400	Indirectly modulate dopaminergic transmission
18	Lauric acid [128]		0.66 1.32	Neuro-protection against oxidative stress, inflammatory cytokines and behavioral changes in HPD induced rat model of PkD.
19	Metformin [129]		25 50 100	Inhibition of oxidative/nitrosative stress
20	Myrica esulenta [130]	Leaves Methanolic	2000/ 50 100 200	Due to an escalation of cellular antioxidants
21	Nardostachys jatamansi [131]	Dried roots Aqueous	5000 250 500	Antioxidant potential has contributed to the reduction in the oxidative stress and catalepsy induced by haloperidol administration.
22	Ocimum sanctum [132]	Leaf Ethanolic	1.75, 4.25 8.5	Dopamine facilitatory and antioxidant properties.
23	Phaseolus vulgaris [133]	Seeds Methanolic	200	Herb contains L-DOPA and also possess the anti-oxidant activity.
24	Portulaca oleracea [134]	Seed Methanolic	2000/ 200 400	Inhibition of oxidative stress
25	Rhinacanthin-C [135]		5 10 20	The compound improves catalepsy and locomotion by increasing dopamine, serotonin, and norepinephrine concentration in the brain.
26	Tribulus terrestris [136]	Fruits Methanol	100 300 1000	Modulation of AChE, α-Synuclein, TNF-α, and IL-1β
27	Tridax procumbens [137]	Leaves (Asteraceae) Ethanolic	100 200	Due to its neuroprotective and free radical scavenging properties.
28	Varenicline [138]		0.5 1.5 2.5	It can delay the rate of progression of PD, but also alleviates the symptoms of PD.
29	Vigna aconitifolia [139]	Seeds Hydroalcoholic	2000/ 100 200 300	The predictable mode of action of this plant may be due to increased synthesis of dopamine from L-dopa and decreased lipid peroxidation due to the presence of flavonoids and polyphenols.
30	Withania somnifera [140]	Root	1.7, 4.25, 8.5	Antioxidant properties

Table 4.1: Anti Parkinson's agents effective in chlorpromazine induced Parkinson's disease.

Sr. No	Name	Parts and Family/ Extracts/Fraction	Maximum tolerated dose (MTD)/ Therapeutic doses (mg/kg)	Constituents/Possible mechanism responsible for this effect
1	Camel milk [141]		33ml/kg p.o	Neuroprotective effect of camel milk could be attributed to its antioxidant property.
2	Diclofenac [142]		20	Via preventing dopaminergic neuronal cell death
3	Phaseolus vulgaris [143]	Seeds Methanolic	200	Presence of L-dopa in *Phaseolus vulgaris* in phytochemical screening of herb

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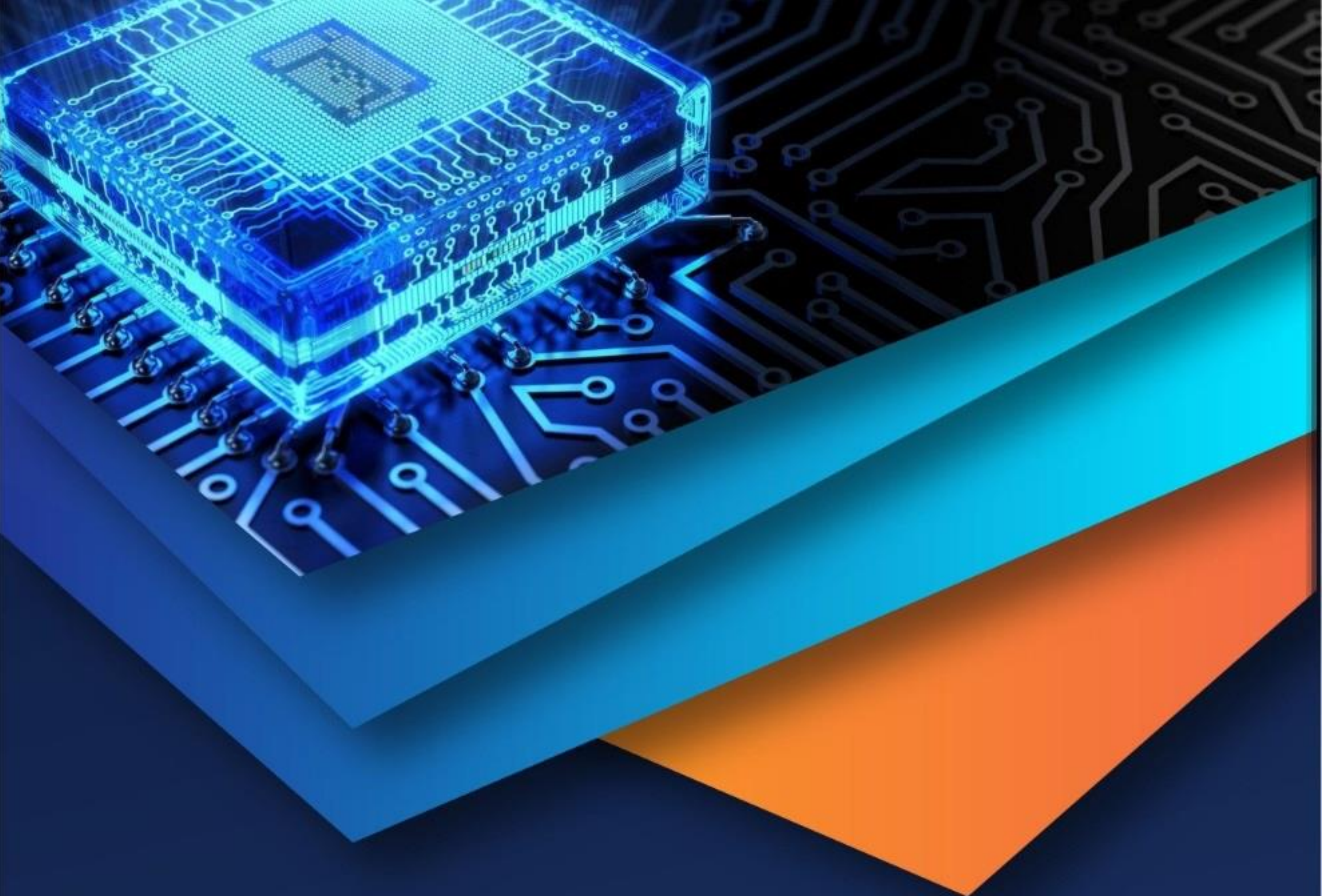

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