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CURRENT TOPIC

Neuroprotectives: Herbs vs Heterocyclics

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Abstract

Neurodegenerative diseases are described as the ones associated with the loss of any specific nerve function which results in either cell death or abnormal functioning of associated organ such as memory loss, tremors, difficulty in speaking and walking, loss of senses and numbness. A number of heterocyclic nuclei containing compounds are available in the market to treat neurodegenerative disorders and associated symptoms due to their concerned therapeutic potential. Ongoing research on these heterocyclics have confirmed their tremendous potential towards the treatment of neurodegenerative diseases. Although a number of heterocyclic containing compounds are already there in the market against various neurodegenerative diseases, but till date no specific treatment is available against any of the neurodegenerative disease, thus opening new area of research. Herbs are emerging as new area of research due to their wide availability and with lesser or no side effects. These days researchers are gaining interest towards the development of newer neurodegenerative agents derived from plants. This review is focused towards the comparison of various available herbs, heterocyclics and the compounds under clinical trials, against neurodegenerative diseases primarily focusing on Parkinson disease and multiple sclerosis.

Key words: Central nervous system; Peripheral nervous system; Herbal medicine; Parkinson disease; Multiple sclerosis.

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Introduction

Parkinson disease (PD) is an age-related neurological illness that progresses over time and has an unknown cause.[1] Degeneration of the dopaminergic nigrostriatal system in the subthalamic nucleus, *globus pallidus* (internal and exterior segments), *striatum, substantia nigra pars compacta* and *substantia nigra pars reticulata* are its defining characteristics.[1, 2] In order to generate appropriate movement, planning, execution and locomotion, these areas are engaged in processing sensory-motor information.[2] Bradykinesia, rigidity, postural irregularities, resting tremors and some non-motor characteristics are among the disease's symptoms.[3] Unlike Alzheimer's disease and PD, multiple sclerosis (MS) affects mostly the young women usually at the age of 20-40 years.[4] Although MS is idiopathic but genetic and environmental risk factors influence the disease susceptibility.[5] MS is an autoimmune inflammatory disease where autoantibodies kill oligodendrocytes, the myelin-producing neuroglia of the CNS causing demyelination of neurons, hence axons remain unprotected leading to abnormal impulse transmission to the effector organs (Figure 1). The symptoms of the disease include paralysis, numbness or partial loss of sensation, diplopia and loss of spinal cord reflexes which include urination and defecation.

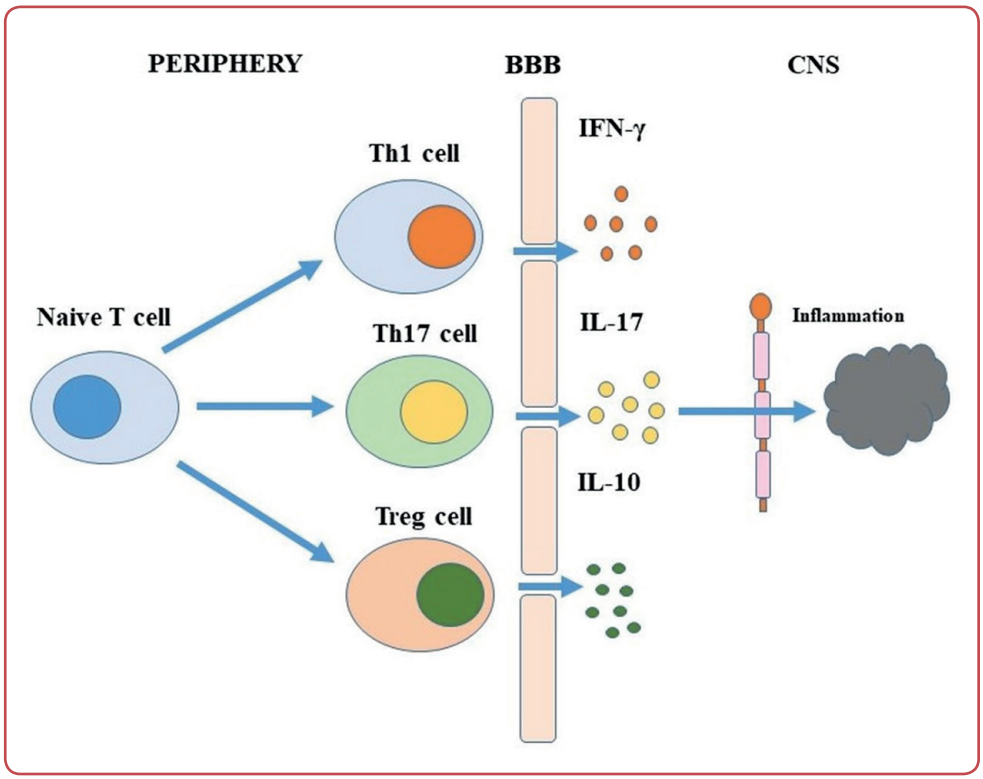


Figure 1: Occurrence of inflammation in multiple sclerosis

BBB: blood-brain barrier; CNS: central nervous system; IFN-γ: interferon gamma; IL: interleukin;

Management of neuro-degenerative diseases by herbs

Currently, neurodegenerative diseases are not curable, so the treatments being used are working as a supportive therapy which manages the sign and symptoms, or silence the progression of the disease.

Management of Parkinson disease

The strategy for treating PD is emphasised on optimising the level of dopamine, by administration of a dopamine precursor levodopa or L-DOPA (L-3, 4-dihydroxyphenylalanine).[6, 7] L-DOPA offers short-term benefit by slowing the progression of the disease, but long-term benefits are unlikely.[8] When L-DOPA is given concomitantly with peripheral decarboxylase inhibitor (like carbidopa), the side effects of L-DOPA, including cardio-vascular and gastro-intestinal problems are alleviated.[7] One more therapeutic approach is about using monoamine oxidase B (MAO-B) inhibitors. MAO-B enzyme activity is increased during dopamine metabolism which lifts oxidative stress and mitochondrial dysfunctions.[7] Nowadays, the natural extracts from medicinal plants are under study which are showing beneficial pharmacological activities against PD.[9] The reactive oxygen species (ROS) in mitochondria are considered as the key target and molecular mechanism of these medicinal products.[10-12]

Acanthopanax senticosus

Ethanolic extract of *Acanthopanax senticosus* (Rupr et Maxim) Harms dried roots and rhizomes (80 %) found to have protective effect on dopaminergic neurons in mice model of PD.[13] The stem bark of *A senticosus* Harms is also effective on *in vivo* model of PD.[14] A 100 % ethanol and 50 % hydroalcoholic extract had preventive effect on MPTP-induced PD in rats and increased the level of dopamine (DA) and noradrenaline (NA) in PD rat model. Sesamin and eleutheroside B, two bioactive substances from *A senticosus*, have anti-PD action. In the rotenone-induced rat model, sesamine had a preventative impact on behavioural dysfunction and pivomolar dosages of sesamine shielded neuronal peochromocytoma cells (PC)-12 from cellular death brought on by methyl phenyl pyridinium (MPP+).[15]

Albizia adianthifolia

A common medicinal plant in Cameroon and Africa is *Albizia adianthifolia*. Its aqueous extract demonstrated anti-PD action at dosages of 150 mg/kg and 300 mg/kg by increasing superoxide-dismutase (SOD), glutathione-peroxidase (GPX) and glutathione (GSH) levels and decreasing protein carbonyl and malondialdehyde (MDA) levels.[16]

Allium sativum

An ethanolic extract of *Allium sativum* demonstrated considerable anti-PD activity at the doses of 200 mg/kg and 400 mg/kg in haloperidol induced PD in rats. In a subacute MPTP PD model in mice, the bioactive S-allylcysteine component of *A sativum* reduced the production of tumour necrosis factor (TNF)- and inducible nitric oxide synthase (NOS).[17, 18]

Alpiniae oxyphyllae

The dried, ripe seeds of *Alpiniae oxyphyllae* have a protective effect on PC12 cells and dopaminergic neurons in zebrafish against 6-OHDA- induced PD model.[19] Additionally, it lessens the cell death brought on by H_2O_2 or sodium nitroprusside in PC12 cells and inhibits apoptotic morphology and lowers tyrosine hydroxylase (TH) expression and cytotoxicity in PC12 cells treated with MPP+.[20]

Berberis aristata

Berberis aristata methanolic extract demonstrated strong anti-PD efficacy against 6-OHDA- induced rat model by decreasing lipid peroxidation (LPO) and increasing levels of superoxide dismutase (SOD), catalase (CAT), glutathione and total thiols.[21, 22]

Beta vulgaris

The plant *Beta vulgaris* is commonly known as beetroot. In various Parkinson's models, including reserpine- induced model, haloperidol- induced catalepsy and tacrine- induced vacuous chewing movements in rats, pretreatment with methanolic extract of B vulgaris showed potent anti-PD effect at doses of 200 mg/kg and 300 mg/kg by reducing LPO level and restoring the protective antioxidant enzymes SOD and CAT in rat brain.[23]

Carthamus tinctorius

Safflower or *Carthamus tinctorius*, is an annual herbaceous plant with many branches that resembles a thistle and is a member of the *Asteraceae* genus. Kaempferol 3-O-rutinoside (K3R) and anhydrosafflor yellow B (AYB), two compounds isolated from safflower, can protect PC12 cells from rotenone- induced neurotoxicity by decreasing the shrinkage of the cell body and H_2O_2-induced reactive oxygen species while also restoring TH activity. In a mouse model of PD caused by MPTP, safflower flavonoid extracts have also shown a neuroprotective effect. The standardised flavonoid extract of safflower (SAFE) was used to test the anti-PD impact against a 6-OHDA-induced rat model which further demonstrated anti-PD effect by suppressing synuclein overexpression as well as reactive astrogliosis.[24, 25]

Cassia obtusifolia

An 85 percent ethanol extract of this seed has been shown to significantly buffer DA neuronal degeneration brought on by MPTP in the PD mouse model. Strong peroxynitrite- scavenging action is exhibited by alaternin, a component isolated from *C tora*.[26]

Elaeocarpus ganitrus

Elaeocarpus ganitrus is traditionally used for prayer beads in Hinduism and Buddhism. Its ethanolic extract showed neuroprotective activity against haloperidol induced PD mice model. Extract exerts neuroprotective effect by decreasing the malondialdehyde (MDA) levels and increasing level of GSH.[27]

Evolvulus alsinoides

The ethanolic extract of *Evolvulus alsinoides* showed potent antioxidant activity and no toxic effects on the viability of PC12 cells. The methanoic extract of roots of *E alsinoides* has anti-dyskinetic activity in acute reserpine-induced dyskinetic rats.[28]

Gardenia jasminoides

Gardenia jasminoides Ellis, an evergreen flowering plant belonging to the family *Rubiaceae*, contains geniposide as an active component extracted from the fruit. Geniposide exert anti-PD activity against MPTP mouse model by restoring number of dopaminergic neuron in *substantia nigra pars compacta*. Geniposide also exerted neuroprotection *in-vitro* in SH-SY5Y human neuroblastoma cell lines against MPP+ induced neurotoxicity by reducing the level of α- synuclein protein in brain.[29]

Hypericum perforatum

Hypericum perforatum L, its methanolic extract has neuromodulating effect against MPTP-induced mouse model of PD. A flavonoid rich extract of *H perforatum* L has protective effects on PC12 cells against apoptosis induced by H_2O_2.[30, 31]

Magnolia officinalis

Magnolol, a bioactive compound isolated from the bark of *Magnolia officinalis*, exhibited neuroprotective activity against 6-OHDA induced PD in mice by decreasing the levels of TH protein expression in *striatum*.[32]

Morus alba

A 70 % ethanolic extract of mulberry fruit protect SH-SY5Y cells from 6-OHDA induced stress. Mulberry fruit extract showed a preventive effect against PD-like symptoms (bradykinesia) in the sub-acute mouse PD model induced by MPTP.[33]

Tinospora cordifolia

Ethanol extract of *T cordifolia* (TCEE) exhibited significant neuroprotection by increasing the levels of dopamine and complex I in 6-OHDA lesion rat model of PD.[34]

Uncaria rhynchophylla (URH)

Aqueous extract of URH, tested in PC12 cells stressed by 6-OHDA, reduced the cell death, increased level of GSH, generated ROS and inhibited caspase-3 activity. Post-treatment with URH showed reduction in apomorphine- induced rotation and also lowered dopaminergic neuronal loss in *substantia nigra pars compacta*.[35] The list of known medicinal plants used for PD is summarised in Table 1.

Table 1: List of medicinal herbs for management of Parkinson disease

S/N	Name of plant/ Family	Common name	Chemical constituent	Actions performed	References
1	*Bacopa monnieri/ Plantagenaceae*	Brahmi or waterhyssop	Bacoside and bacopaside	• Enhance perception, improves mitochondrial functions, diminish a-synuclein accumulation and apoptosis.	[13-15]
2	*Mucuna pruriens/ Fabaceae*	Velvet bean	Levodopa, glycoside and glutathione	• Enhance behavioural and locomotor activity, ease oxidative stress and metal chelating. Support mitochondrial and synaptic function.	[16], [17]
3	*Withania somnifera/ Solanaceae*	Ashwagandha	Withanolide and Withaferin	• Enhance locomotor activities. • Adjust dopamine, glutathione and tyrosine hydroxylase expression. • Delay iNOS activity and reduce oxidative stress.	[10], [18], [19]
4	*Curcuma longa/ Zingiberaceae*	Turmeric	Curcumin	• Adjust the levels of dopamine and acetylcholine and manage the actions of glutathione peroxidase and superoxide dismutase. Lifting mitochondrial roles and production of adenosine triphosphate. • Hinder a-synuclein fibrillisation and oxidative stress.	[7], [20], [21]
5	*Gingko Biloba/ Ginkgoaceae*	Maidenhair tree	Ginkgolide B, EGB 761	• Adjust the level of dopamine, maintain behaviour and muscle harmonisation. • Lifting mitochondrial role and production of adenosine triphosphate.	[18], [22], [23]
6	*Camellia sinensis/ Theaceae*	Green tea	Polyphenol and catechins classes: epicatechin, epigallocatechin	• Redox equilibrium, constrain path of reactive oxygen species-nitric oxide and metal chelating, guards dopaminergic neurons.	[19], [24], [25]
7	*Camellia sinensis/ Theaceae*	Black tea	Theaflavins: theaflavin (tf1)	• Neuron protection, redox preservative, enhances tyrosine hydroxylase, expression of dopamine transporter, diminish apoptosis.	[16], [18]

8	*Scutellaria baicalensis/ Lamiaceae*	Baicalein	Flavonoids: wogonin, baicalein, oroxylin and wogonoside	• Anti-inflammatory, antioxidant, inhibit glutamate neurotoxicity, protect chondriosomes.	[36]
9	*Panax ginseng/ Araliaceae*	Ginseng	Ginsenosides	Improve behavioural defects, improve loss of dopaminergic neurons, neuroprotective.	[7]

Management of multiple sclerosis

The treatment of MS has three approaches, namely; acute relapses treatment; symptomatic treatment and disease management (treat exacerbations). Along with these, there is a nutritional therapy and other therapies like exercises, physical and speech therapies. The herbs which are used for MS can be categorised into herbal medicine, food and spices and are summarised in Table 2.[11] The usage of essential oil as an aromatherapy is helpful in pain management, improving health and well-being. Therefore, aromatherapy could be used as a method of symptomatic relieve in MS patients due to its ability to serve in sleep, relaxation, movement of joints and muscles, and enhancement of well-being.[12]

Table 2: List of medicinal herbs for management of multiple sclerosis

S/N	Name of plant/ Family	Common name	Chemical constituent	Actions performed	References
1	*Hypericum perforatum/ Hypericaceae*	St John's wort	Hypericin	• Inhibits depression.	[17]
2	*Valeriana officinalis/ Caprifoliaceae*	Valerian	Not defined	• Tranquillity via GABA system.	[17]
3	*Ginkgo biloba/ Ginkgoaceae*	Ginkgo	Ginkgolides	• Reduction of disease exacerbation.	[17]
4	*Oenothera biennis/ Onagraceae*	Evening primrose oil	γ-linoleic acid	• Involved in breakdown of fatty acids. • Affects lymphocyte activity.	[20], [29], [33], [34]
5	*Panax ginseng/ Araliaceae*	Ginseng	Ginsenosoides	• Active in fighting stress, trauma and fatigue by modulating immunity. • Enhance intelligence, learning and motor activity. • Support neuroprotective activity.	[35]
6	*Salvia officinalis/ Lamiaceae*	Sage	Polyphenols, essential oils	• Mental improvement, controls mood. • Memory enhancer.	[11], [35]
7	*Cannabis/ Cannabaceae*	Marijuana	Cannabinoides	• Recovers some symptoms include spasticity, unpleasant feeling, tremor and sadness.	[17]
8	*Curcuma longa/ Gingiberaceae*	Turmeric	Curcumin	• Reduction of disease exacerbation.	[35]
9	*Cinnamomum zeylanicum/ Lauraceae*	Cinnamon	Cinnamaldehyde, sodium benzoate	• Management of relapse- remitting experimental autoimmune encephalomyelitis.	[1], [26], [37-41]
10	*Crocus sativus/ Iridaceae*	Saffron	Crocin	• Diminish clinical symptoms in experimental autoimmune encephalomyelitis mice model. • Overdue onset of illness. • Fight depressed condition.	[34], [35], [38]

11	*Nigella sativa/ Ranunculaceae*	Black seed	Thymoquinone	• Obstructs oxidative stress. • Helpful in muscle spasticity.	[1], [32], [42]
12	*Panax ginseng/ Araliaceae*	Ginseng	Ginsenosides	• Anti-inflammatory. • Anti- oxidant. • Neuroprotective.	[43]

Management of neuro-degenerative diseases by heterocyclics

Last two decades have been marked for the discovery of various novel bioactive moieties by many researchers to get enhanced therapeutic potential with lesser side effects. A number of natural as well as synthetic moieties have emerged as potential candidates to protect neurons against degeneration. Several studies reported the importance of a number of 5- and 6- membered heterocyclics in the treatment of neurodegenerative diseases. Such compounds include pyrrole, purines, pyrimidines, N-heterocyclic compounds (triazolothiadiazoles and triazolothiadiazines) as given in Figure 2.

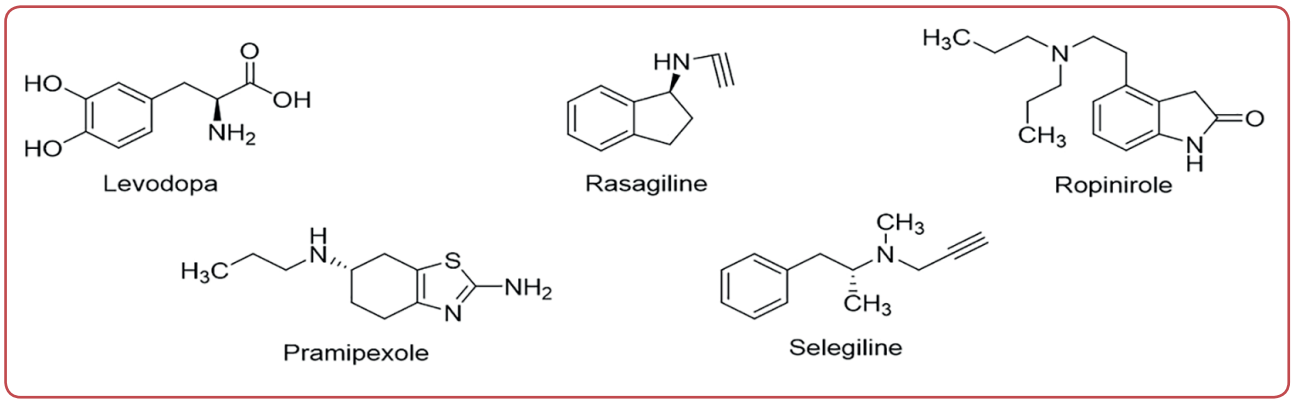


Figure 2: Various heterocyclics as anti-Parkinson disease drugs

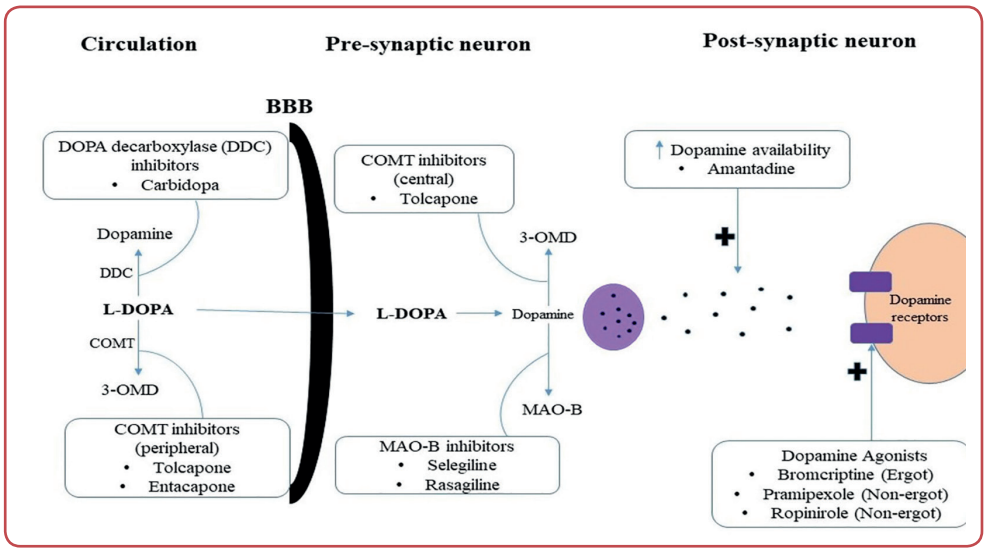


Figure 3: Various targets for heterocyclics against Parkinson disease

BBB: blood-brain barrier; MAO: monoamine oxidase; COMT: catechol-O-methyltransferase;

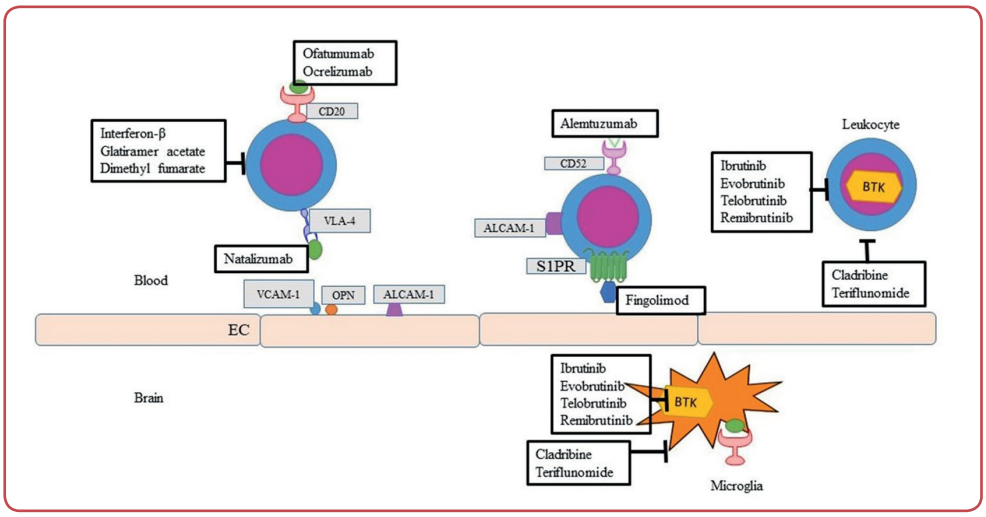


Figure 4: Various targets for heterocyclics against multiple sclerosis

VCAM-1: vascular cell adhesion protein 1; ALCAM: activated leukocyte cell adhesion molecule; VLA-4: alpha4beta1 integrin; S1PR: sphingosine-1-phosphate receptor;

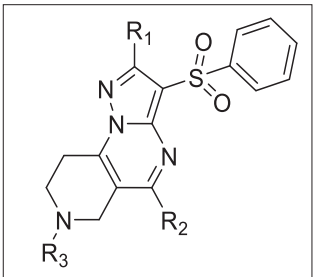
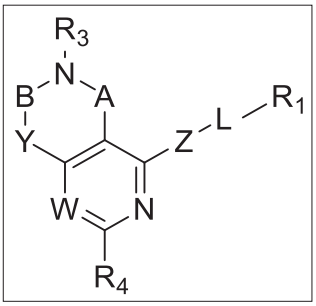
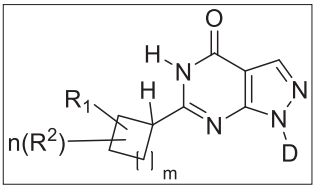
Table 3: Various heterocyclics under clinical trials against neurodegenerative disorders

NCT number	Study title	Study status	Brief summary	Conditions	Phases	Study type
NCT03841604	Effect of safinamide on Parkinson disease related chronic pain.	Completed	To evaluate the potential efficacy of safinamide 100 mg once daily (OD), compared with placebo, as add-on therapy for Parkinson disease-related chronic pain.	Idiopathic Parkinson disease	4	Interventional
NCT01523301	Rotigotine versus placebo to evaluate the efficacy on depressive symptoms in idiopathic Parkinson disease patients.	Completed	The purpose of this study was to show superiority of rotigotine over placebo on improvement of depressive symptoms in subjects with idiopathic Parkinson disease.	Idiopathic Parkinson disease	4	Interventional
NCT00505687	An open-label extension trial to assess the safety and tolerability of long-term treatment of rotigotine in subjects with idiopathic Parkinson disease.	Completed	The objective of this open-label extension is to assess the safety and tolerability of long-term treatment of rotigotine in subjects with idiopathic Parkinson disease.	Idiopathic Parkinson disease	3	Interventional
NCT01300819	Placebo-controlled study in patients with Parkinson disease to evaluate the effect of rotigotine on non-motor symptoms.	Completed	The primary objective of this study was to demonstrate that rotigotine improves non-motor symptoms compared to placebo in subjects with Parkinson disease.	Idiopathic Parkinson disease	4	Interventional
NCT01782222	Trial to evaluate the efficacy of rotigotine on Parkinson disease-associated motor symptoms and apathy.	Completed	This trial is being conducted to assess the effects of rotigotine over placebo on improvement of apathy and motor symptoms in subjects with early-stage and advanced stage idiopathic Parkinson disease.	Idiopathic Parkinson disease	4	Interventional

NCT03325556	Relapse prevention study of pimavanserin in dementia-related psychosis.	Completed	The purpose of this study is to evaluate the efficacy of pimavanserin compared to placebo in preventing relapse of psychotic symptoms in subjects with dementia-related psychosis who responded to 12 weeks of open label pimavanserin treatment.	Dementia-related psychosis	3	Interventional
NCT00322153	Study of the safety and efficacy of memantine in moderate to severe Alzheimer's disease.	Completed	The objective of this study is to evaluate the safety, tolerability, and efficacy of memantine compared to placebo in outpatients diagnosed with moderate-to-severe dementia of the Alzheimer's type on a concurrent acetylcholinesterase inhibitor (AChEI).	Dementia of the Alzheimer's type	3	Interventional
NCT01946243	The feasibility of florbetapir quantitation.	Completed	The overall objective of the study is to assess the feasibility of implementing a quantitative process of florbetapir F 18 scan interpretation.	Alzheimer's disease	4	Interventional
NCT02553928	Comparison of once daily and twice daily dosing on safety and tolerability of memantine in patients with Alzheimer's disease.	Completed	Evaluation of the safety and tolerability of a 20 mg once daily dose of memantine compared with 10 mg given twice daily in patients with dementia of Alzheimer's type and MMSE range 5-18.	Alzheimer's disease	4	Interventional
NCT03724942	Brexpiprazole for the long-term treatment of patients with agitation associated with dementia of the Alzheimer's type.	Completed	To evaluate the safety of brexpiprazole 1 mg or 2 mg after a 14 week treatment regimen for agitation associated with dementia of the Alzheimer's type patients who completed in a double-blind trial, and to investigate the efficacy of brexpiprazole.	Agitation associated with dementia of the Alzheimer's type	4	Interventional
NCT03620981	Brexpiprazole for the treatment of patients with agitation associated with dementia of the Alzheimer's type.	Completed	To evaluate the superiority of brexpiprazole 1 mg or 2 mg over placebo after a 10-week treatment regimen for agitation associated with dementia of the Alzheimer's type in patients who require medication and to investigate the safety of brexpiprazole and identify the optimum dose.	Agitation associated with dementia of the Alzheimer's type	2 and 3	Interventional
NCT03991988	Montelukast therapy on Alzheimer's disease.	Completed	This is a one-year, double-blind placebo-controlled randomised clinical trial that compares montelukast to placebo in individuals with mild cognitive impairment (MCI) and early Alzheimer's disease dementia.	Alzheimer's disease	2	Interventional
NCT03801642	Dapagliflozin in Alzheimer's disease.	Completed		Alzheimer's disease	1 and 2	Interventional

NCT04538066	Bryostatin treatment of moderately severe Alzheimer's disease.	Completed	To evaluate the safety, tolerability and long-term efficacy of bryostatin 1 (hereafter referred to as bryostatin) for the treatment of moderately severe Alzheimer's disease.	Alzheimer's disease	2	Interventional
NCT03101085	S-Equol in Alzheimer's disease 2 trial.	Completed	Does S-equol, a compound that acts like oestrogen in the body, causes an increase in mitochondrial activity.	Alzheimer's disease	1 and 2	Interventional

Table 4: Various patents filed against heterocyclics for neurodegenerative disorders

S.No.	Patent number	Receptor involved	Heterocyclic compounds	Structure	Effective against disease	Ref.
1	WO2009136814A1	5-HT6 receptors	3-sulphonyl-6,7,8,9-tetra-hydro-pyrazolo[1,5-a]pyrido [4,3-d]-pyrimidines.	 Ar substituted aryl or heterocyclyl R1 hydrogen atom or a substituted lower C1-C3 alkyl R2 hydrogen or a substituted C1-C3 alkyl R3 hydrogen atom substituted C1-C3 alkyl tert-butyloxycarbonyl R4 Hydrogen substituted C1-C3 alkynyl	Alzheimer's disease, Huntington's disease, schizophrenia	[44]
3	US7745451B2	5-HT6 receptors	Tetrahydronaphthyridine and tetrahydropyrido[4,3-d] pyrimidine-fused heterocyclic compounds.		Alzheimer's disease, Huntington's disease, schizophrenia	[36]
4	US9102679B2 and US9328120B2	PDE9A inhibition	6-cycloalkyl-pyrazolopyrim-idinones.		Treatment of CNS disorders by modulating PDE9A	[7]

A number of heterocyclics are already available against PD and MS which are acting at various sites to increase the level of dopamine by restoring dopaminergic neurons and to decrease CNS inflammation respectively some of which are given in Figure 3 and 4.

Researchers are focused towards the development of a multi target approach to synthesise heterocyclic scaffolds to aim towards new biological targets. Therefore, many researchers are working towards improving the properties of drugs through chemical modifications of the starting structure. Other heterocyclic natural compounds

inspired the design of original structures some of which are even under clinical trials as given in Table 3 and 4, respectively.[43]

Conclusion

The actual reason underlying neurodegenerative diseases is still a mystery and may involve various environmental factors such as oxidative stress, mitochondrial defects, inflammation, protein degradation, familial history, ageing and abnormal protein accumulation in neuron. The outcomes obtained by various heterocyclics leave a room for some alternative treatments such as herbals. A number of *in vivo* studies and clinical trials reported that a number of herbal plants and their derived medicinal compounds can prevent or alleviate some neurological disorders and their associated symptoms. Based on these reports, the herbal medicines are becoming popular day by day and gaining more attention towards searching new therapies for neurodegenerative diseases thus opening a new platform for researchers.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Data curation: DDB, PK
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Writing - review and editing: PK, SL

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