Review

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Parkinson's disease caused by diabetes mellitus: pathophysiology and potential treatments

Priyanka Thagunna[1], Priya Chaudhary[1]✉

[1]*Department of Biotechnology, School of Applied and Life Sciences, Uttaranchal University, Dehradun (248007), Uttarakhand, India.*

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Abstract: There have been growing indications that persons with Type 2 diabetes mellitus (T2DM) have a higher risk of getting Parkinson's. Insulin is the hormone responsible for energy metabolism and glucose regulation. However, several reports have demonstrated that insulin can pass across the brain-blood junction and affect multiple processes within the brain. Furthermore, there has been increasing proof that an event similar to peripheral insulin insensitivity takes place in the brains of Parkinson's disease individuals, regardless of diabetes. This brings up the notion that faulty glucose signaling pathways are to blame for the emergence of pathological aspects of Parkinson's disease (PD), implying that the glucose signaling pathway could be an alternative target for disease management. After identifying the linkages between Parkinson's disease and T2DM, it is perhaps not unexpected that medications used to treat T2DM and phytotherapy are among the most effective therapy options being prioritized as innovative treatments for PD. Thus, this study explored the shared pathogenic mechanisms and metabolic pathways that link DM and Parkinson's disease with different PD therapies.

K**eywords:** brain; insulin resistance; Parkinson's disease; signaling pathway; type 2 diabetes mellitus

1. Introduction

The primary metabolic disease in the world, diabetes mellitus (DM), has increased in prevalence and is now associated with increasing death and disability, making it a health burden. Diabetes mellitus (DM) is a diverse collection of illnesses characterized by hyper-glycemia and glucose intolerance. Numerous consequences, including nerve damage, amputation of the leg, coronary artery disease, kidney damage, stroke, and loss of vision, are linked to its advancement. The second most common neurodegenerative illness is Parkinson's disease (PD), which is typified by typical motor symptoms like bradykinesia, stiffness, postural impairment, and resting tremor [1].

Over the past last decade research has drawn greater insight towards much greater connection between neurodegeneration and insulin resistance and their impact in the signaling in central nervous system [2]. The high blood sugar or insulin resistance (IR) leads to synuclein aggregation, autophagy, mitochondrial dysfunction, neuroinflammation, and dopaminergic neuronal loss which are also common metabolic and dysregulated pathways in PD [3].

The PRKN, PINK1 gene that play vital role in mitochondrial dysfunction and autophagy is common molecular pathway both in PD and IR. Mitochondria are the predominant site for reactive oxygen species (ROS) production and play vital role in energy production, redox homeostasis and cell processes [4, 5]. Increased ROS production can initiate the phosphorylation of IR proteins and damage the insulin signaling leading directly to mitochondrial dysfunction and IR [6, 7]. Furthermore, to this the IR can disable mitochondrial biogenesis and cause oxidative stress, membrane depolarisation and increased dopaminergic neuronal degeneration in the substantia nigra (SN), thereby developing PD.

Scientists have proposed PD could be considered "type 3 diabetes mellitus (T3DM)" due to its overlapping pathophysiology and risk factors [1]. Various evidences have assured the relation of diabetes with cognitive impairment and memory decline. Synthetic drugs and phytocompounds focusing insulin resistance, inflammation, and oxidative stress all which directs to neurodegeneration could open doors for better and

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Dr. Priya Chaudhary
Department of Biotechnology, School of Applied and Life Sciences,
Uttaranchal University,
Dehradun, Uttarakhand – 228007, India
E-mail: priyachaudhary@uumail.in

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successful treatment for PD [8]. The pathophysiology of T2DM in the onset of PD and its management are thus discussed in this review.

2. Methodology

Related information on Parkinon's disease and diabetes mellitus, their interconnection, pathophysiology, and possible treatments was gathered by performing literature search. More than 60 articles from 2005-2023 were looked up in the electronic databases such as Science Direct, Scopus, Sci-Finder, Web of Science, Google Scholar, and Medline/PubMed with the keywords Parkinson's disease, diabetes mellitus, pathological mechanism/ metabolic pathways, misfolded proteins/ amylin and α-synuclein, impaired homeostasis of calcium, dysregulation of PI3K/ Akt/ GSK3 pathway, activation of NF-kB, pathway involved in autophagy, treatment available for Parkinson's disease, phytotherapy, medicinal plant/ treatment of PD/ *in vitro* studies, phytocompounds/ treatment of PD/ *in vivo* studies, medicinal plant/ treatment of PD/ *in vivo* studies. The inclusion depended on the following sets. (i) The study is available in the English language; (ii) The study includes the general criteria in which papers reported the Parkinson's disease and Diabetes Mellitus; (iii) The research looks into the common pathological mechanism that link DM and PD; (iv) The studies revealed the possible treatment available for PD; and (v) The *in vitro* and *in vivo* research studies reported the therapeutic effect of different medicinal plants or phytocompounds at respective dosages for PD using various cell lines and experimental models. Studies that do not involve the above-mentioned inclusive criteria were excluded from this article.

3. Parkinson's disease and diabetes mellitus

In a study conducted on animal model of transgenic animals excessively express the PED/ PEA protein, found to be increased in patients with T2DM and is overexpressed in the brain. It was reported that the mice developed glucose intolerance and insulin resistance along with neurological dysfunctions such as cognitive impairment, ataxia, movements abnormalities such as delayed locomotor movement, feet clasping, etc. [9]. A study followed for 3 years involving 78 patients concluded T2DM was linked to accelerated development and decline in motor scores, decreased striatal levels of dopamine transporter binding (DAT binding), higher level of tau in cerebrospinal fluid and higher cognitive deterioration in PD individual. In contrast to a healthy person, non-PD diabetes patients showed reduced striatal DAT binding and elevated levels of tau and alpha-synuclein in the cerebrospinal fluid [10]. Several meta-analyses were undertaken to evaluate the relationship between diabetes and Parkinson's disease, and some of them are summarized in Table 1.

Table 1. Association between diabetes mellitus and Parkinson's disease

Study type	Outcome	References
Cohort	The estimated HR of PD was determined to be 1.185 in the DM category, 1.038 in the IFG cohort for DM durations less than five years, and 1.618 for DM durations larger than five years, in contrast to the non-DM group	[11]
Meta-analysis	10.02% was reported to be the mean incidence of DM in empirical research. In observational research, patients with DM had higher odds of acquiring Parkinson's disease	[12]
Meta-analysis	T2DM was linked to the rapid escalation of motor symptoms and cognitive impairment.	[13]
Meta-analysis	Cohort studies show that DM is cause of Parkinson's disease (PD).	[14]

4. Common pathological mechanism and metabolic pathways that link DM and PD

The common pathological mechanisms and metabolic pathways that link DM and PD pathogenesis (Figure 1 and 2) are mentioned as follows:

4.1 Aggregation of misfolded protein: amylin and α-synuclein

The amylin receptors are activated by amyloid-beta proteins. Islet amyloid polypeptide (IAPP), also referred as amylin, is generated by islet of beta cells of pancreas in type 2 diabetes to control the elevated glucose levels in blood with release of insulin. The amylin produced can accumulate in non-pancreatic regions and exhibit toxicity. Moreover, the amylin interacts with several amyloidogenic proteins, including Aβ (amyloid – beta). Furthermore, the amylin may penetrate the brain-blood junction and bind to amylin receptor that is broadly expressed in the brain and coincides with significant areas burden with amyloid beta (basal forebrain, hippocampus, and cortex) [15].

The alpha synuclein is a protein which consists of about 140 amino acids and is directed by SNCA gene. When α-synuclein monomers aggregate to form oligomers, they may develop into protofibrils with a beta sheet structure,

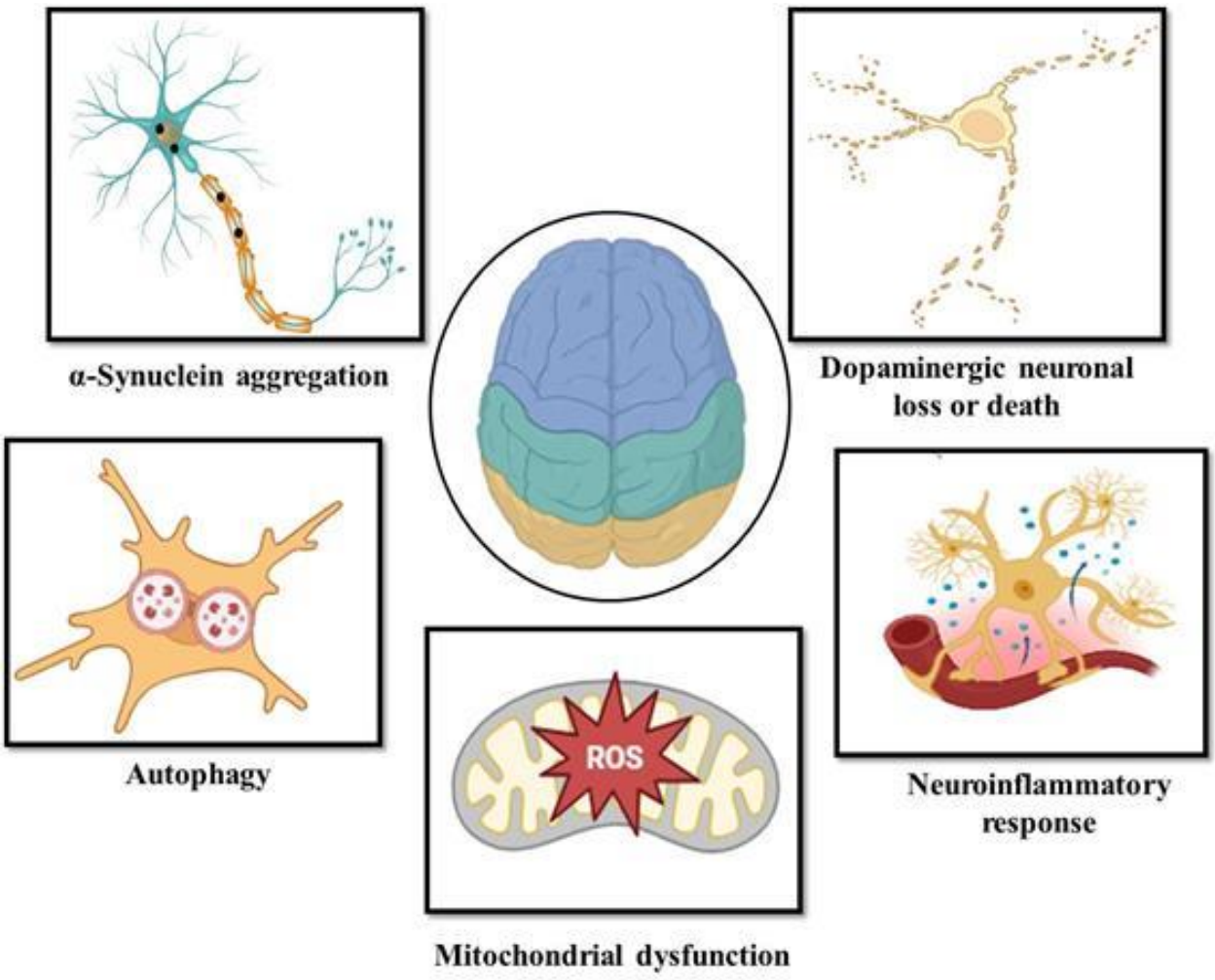

Figure 1. Common pathological mechanisms that link DM and PD.

which have been observed in Lewy body of patients with PD. Moreover, these fibrils with the beta sheet conformation encourage the aggregation of alpha synuclein which maybe result of dysfunction in mitochondria i.e. ubiquitination, truncation or serine phosphorylation [16].

Combining α-synuclein with amylin monomers speeds up coaggregation, which leads to the development of amyloid α-synuclein formation, increasing the possibility of PD in those with T2DM. The amyloid alpha synuclein aggregation leads to neuronal cells damage and death. For example, in an animal model of mice IR in T2DM might accelerate the course of Parkinson through ROS overproduction, mitochondrial dysfunction and increased SNCA signaling, which leads to the aggregation of α-synuclein and its increased production [10].

4.2 Impaired homeostasis of calcium & its role in loss of dopaminergic neurons and mitochondrial dysfunction

Calcium is therefore significant in maintaining appropriate functioning and cellular survival particularly those of neuronal cells. The inter-organelle communication is impaired through calcium dysregulation and numerous organelles including mitochondria, lysosomes, and endoplasmic reticulum (ER) exhibit this process and cause the malfunction [17]. In Parkinsons disease the signal transduction pathways between mitochondria and ER are disrupted which further leads to neuron cell damage and death, the reason is that the ER is major calcium reservoir, when is dysregulated leads to misfolding of proteins and the chaperones that regulate the folding of protein are majorly reliant on the concentration of calcium therefore the impaired calcium homeostasis result in the formation of misfolded alpha synuclein that consist of Lewy bodies and cause neurodegeneration [18]. Additionally, calcium activates numerous proteins and enzymes that affect neurons and synapses in PD, including Cam-kinase-4 (CamK-4), Camkinase-2 (Cam-K2), calpain, calcium-binding proteins, calbindin, calmodulin, and calcineurin, hence the neurons are burdened with an overabundance of ROS as the enzymes activated make up Kreb cycle. The ROS are thus responsible for mitochondrial impairment and promoting process of apoptosis and mitochondrial autophagy. The increased calcium load causes neurodegeneration in PD [19].

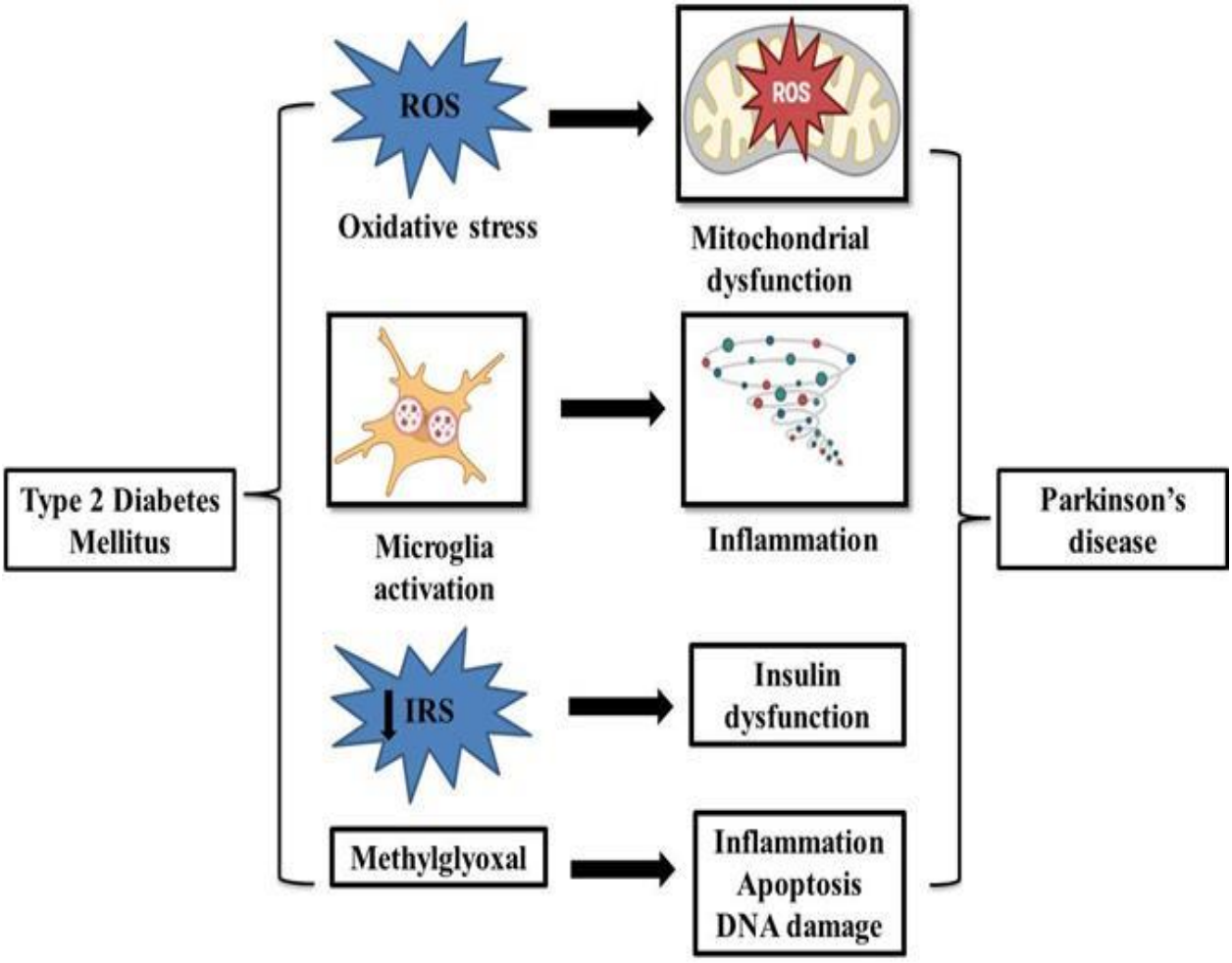

Figure 2. Corelation between Diabetes mellitus and Parkinson's disease. ROS: reactive oxygen species; and IRS: insulin resistance substrate.

4.3 PI3K/ AKt/ GSK-3 and ubiquitin proteosome pathways in neurons death

For the brain tissues to maintain cell integrity, a high concentration of oxygen and glucose is needed. The blood-brain barrier (BBB) is primarily responsible for maintaining the integrity of neurons by facilitating the passing on of chemicals necessary to sustain neuronal activity in brain tissue [20]. In addition, insulin ensures that neurons receive sufficient power and is responsible for the passage of glucose over the blood-brain barrier. The PI3K/ Akt/ GSK-3 pathway and the ubiquitin proteasome are essential for regulating neuronal apoptosis and cell survival in brain tissue. IR oversees the PI3K/ Akt/ GSK-3 pathway dysregulation, which is what causes neurodegenerative illnesses like Parkinson's disease (PD) [21].

4.4 Dysregulation of P13K/Akt /GSK-3 pathway

IR and neuronal oxidative stress are linked to dysregulated PI3K/ Akt/ GSK3β signaling, which may encourage alpha synuclein aggregation, cell death and early onset of PD. When insulin binds to insulin-like growth factor-1(IGF-1), the insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1r) are phosphorylated, initiating the PI3K/ Akt/ GSK3β signaling pathway. The hyper-phosphorylation of IRS-2 and IRS-1 subsequently obstruct Akt, activating GSK3β by dephosphorylation. Activated GSK3β and hyperphosphorylated IRS-2 and IRS-1 have been seen in the cases of PD patient's neurological decline [22].

4.5 Activation of NF-kB pathway and neuroinflammatory response

In individuals with PD, inflammation cytokines and alpha synuclein aggregation cause neuronal inflammation, the cytokine along with α-synuclein aggregates activate the NF-kB pathway chronically. Additionally, this process damages glucose homeostasis, hinders insulin signaling, and raises the risk for onset of IR [23].

4.6 Pathways involved in autophagy

Autophagy is regulated by mechanism such as the P13K/ AKT/ mTOR and AMPK/ mTOR signaling pathways, it

has been observed that P13K/ AKT/ mTOR pathway is hyperactivated in the IR, which may prevent autophagy and cause cellular malfunction. These processes are reported to increase the risk of early onset of PD [24].

4.7 Parkin/ PINK11/ PGC-1α in dysfunction of mitochondria

Parkin along with PINK1 play important role in regulating mitochondrial mitophagy and mitochondrial homeostasis. Disruption in the metabolic functions of mitochondria is involved in key mechanism of pathogenesis of both Parkinson disease and Insulin resistance. Insulin reduces the glucose levels in blood primarily by promoting the absorption of glucose into skeletal muscle and adipose tissue. Neurons and glial cells are the sites for the de novo synthesis of Insulin in human body, the insulin receptors are also present in the brain and perform a vital function in cognitive functions, homeostasis and other brain activities [25].

Insulin resistance is a condition in which the body responds less sensitively to insulin and uptakes lower amount of blood glucose resulting in increased blood glucose levels which hinder the glucose metabolism, this gives rise to several disorders. For instance, formation of damaged and dysfunctional mitochondria and mitophagy due to increased glucose metabolism and ROS production, which further culminate into numerous diseases such as neurological disorders and aging. Through oxidative phosphorylation, mitochondria generate the majority of the power needed for the regular upkeep of human tissues like the cardiovascular system, muscle tissue, and brain in the kind of ATP. Furthermore, the brain consumes the most power when it is simultaneously active and at rest. Furthermore, the mitochondria play a role in the calcium ion balancing process, which is necessary for the stimulation of signaling pathways and synapses [26]. People with T2DM and IR have abnormal mitochondrial regulatory systems, including protein-complex development, biogenesis of mitochondria, and mitochondrial protein post-translation. Nevertheless, α-synuclein aggregations are also linked to the calcium ion equilibrium disruption that results in the mitochondrial membrane's deterioration. This calcium ion stress causes the release of cytochrome C, an oxidative stress linked to PD [27].

According to reports, insulin-resistant individuals or those with type 2 diabetes had 38% less mitochondria in their skeletal muscles than controls, which results in altered function of mitochondria and disruption of metabolic pathways. Mitochondrial dysregulation, which controls the death of dopaminergic neurons, is present in PD-damaged cells [28]. Furthermore, to this, IR and T2DM result in decreased amounts of Parkin and PGC-1α, which regulate the expression of mitochondrial proteins and the genome [29]. PGC-1α interacts with transcription variables, such as NRF2 and NRF1, to regulate the process of transcription of mitochondrial respiratory chain proteins. Further, the response to oxidative stress is linked to the mitochondrial transcription factor (TFAM). Therefore, PGC-1α deregulation may decrease neuronal mRNA and be associated with the pathophysiology of IR and PD [30].

5. Therapeutic strategies available for PD

There is no known cure for the Parkinson's yet, but the symptoms can be treated and controlled. Currently there are many drugs and therapies for treating the symptoms of PD [31].

5.1 Lixisenatide

Lixisenatide, a GLP-1 agonist based on the structure of exendin-4, has acquired FDA authorization for T2DM. It crosses the blood-brain barrier, has neuroprotective qualities, lowers degradation of motor function more than exenatide, and has anti-apoptotic capabilities. Latest, phase 2 clinical investigations are being conducted to determine the effectiveness of lixisenatide for PD treatment. Semaglutide and liraglutide are the examples of GLP-1 agonists investigated as a viable cure for PD [3].

5.2 Dipeptidyl peptidase-4 inhibitors (DPP4i)

DPP4i are utilized as hypoglycemia medicines for the cure of T2DM. DPP4i has been linked to advances in the utilization of glucose by decreasing GLP-1 breakdown and boosting its availability. In addition, it has been proven that DPP4i have neurological protective activities, involving anti-apoptotic signaling and suppression of neuroinflammatory response, and could reduce the chance of growing PD [3].

5.3 Ghrelin

Ghrelin has also been linked to an enhancement of insulin signaling. It is a hormone found in the nervous system and peripheral tissues. It has been shown to improve sensitivity of insulin in neurons while decreasing IR. Therefore, it could be a neuroprotective component in neurodegenerative illnesses such as PD [3]. Other antidiabetic drugs to cure PD are listed in Table 2.

6. Phytotherapy

The preference to treat PD with phytocompounds primarily derived from medicinal plants has been growing. At present, PD medications only work to lessen the signs of the disease. Drugs that address the disease's underlying etiology do not yet exist, though. Restoring dopamine levels in the brain is among the most popular kind of treatment. However, there are currently no treatments that

Table 2. List of antidiabetic drugs to cure Parkinson's disease.

Drug	Purpose	Pre-clinical & clinical evidence
Exendin-4	According to several studies Exendin-4 improves dopaminergic neuron loss and even stimulates neurogenesis in PD animal models, enhancing motor and cognitive function [10]	The treatment showed advancement in motor and cognitive function in PD patients. **Motor**: 4.9 points difference, 95% CL:0.3-9.4; P=0.037 **Cognitive**: 6.3 points difference, 95% CI: 2.7–9.9; P = 0.001
DA-CH5	DA-CH5 can cross the blood brain barrier, reduce motor dysfunction, protects dopaminergic neurons by reducing mitochondrial stress and apoptosis through the AKT/JNK signal pathway [32]	In an animal model medication alleviated impairments in three distinct motor tests. • decreased α-syn levels, • decreased proinflammatory cytokine levels • inflammatory response in the substantia nigra and striatum, and regained autophagy and mitochondrial activity
DD4	Facilitate neuroprotective effects via increasing the half-life of GLP-1 receptor, anti-apoptotic signaling, inhibition of phosphorylation of toxin proteins [33]	It has also been hypothesized that in patients with PD, DPP4i has protective benefits to the nigrostriatal dopamine system
Metformin (MPTP)	Metformin is associated with neuroprotective effects as it activates the AMP activated protein kinase effectively regulates cellular energy homeostasis, decreases the oxidative stress which improves mitochondrial functions and lowers the alpha synuclein aggregation [34]	In animal models of MPTP-treated and haloperidol–induced catalepsy mouse *in vivo* studies, the metformin has been reported to exhibit neuroprotective effects

can restore the destroyed brain tissue. Drugs are synthetic, particularly in the field of Western medicine. Typically, the goal of medication creation is to limit adverse reactions by focusing on a single target pathway. There are certain difficulties, nevertheless, in which individuals grow tolerant to the medication with repeated use and dose increases, which results in more adverse effects. New drug development is becoming more and more necessary considering these difficulties. To overcome the limitations of the present therapeutic method, our research investigated substitute natural products. Herbal medications come in a variety of forms and are composed of natural components extracted from plants. This suggests that a single medication can target several pathways, opening new therapeutic alternatives for PD [35].

Since both are necessary for proper brain functioning, redox stability and mitochondrial function replenishment appear to be key therapeutic approaches against PD [36, 37]. Recent studies have demonstrated the potential benefits of herbal medicine in preventing several degenerative diseases. Brahmi, also known as *Bacopa monnieri*, is a perennial creeping herb with several medical uses. It is recognized to possess anti-inflammatory, anti-oxidative, anti-microbial, neuroprotective, and memory-improving qualities. It is also known that *B. monnieri* extract (BME) improves cognitive abilities. Additionally, research has demonstrated that BME has an anti-parkinsonian impact in both transgenic and toxin-induced animal model systems, indicating that it may be effective in treating PD [38].

Tropical legume plant *Mucuna pruriens* (Mp) is well-known for its therapeutic uses. Mp seeds are used to treat nephropathy, ulcers, and helminthiasis. They also have anti-inflammatory properties. Because Mp has been utilized for centuries as an ayurvedic medicine to treat PD symptoms, its significance in the disease dates back thousands of years. Levodopa, the drug included in Mp Seed, is regarded as the gold standard for treating Parkinson's disease [39].

Since the beginning of time, *Withania somnifera* (Ws), also known as ashwagandha, has been utilized as a herbal remedy in India. Given that it is an amorous and may be a nerve tonic that improves learning and recall, Ws has a great deal of medical potential. Ws roots have antioxidant,

Table 3. Protective effect of medicinal plants on PD.

Phytocompounds	Dosage	Model of study	Effect	References
***In-vitro* studies**				
Astragaloside IV	50, 100, and 200 µM	Primary nigral cell culture	Provide protection to dopaminergic neurons against degeneration	[40]
Oxyphylla A	10-300 µM	PC12/A53T-α-syn cells	Activates the PKA-AKT-mTOR pathway	[41]
Pre-Clinical studies				
Berberine	5, 10, and 30 µM	Rat	Depletion in the tyrosine hydroxylase-associated immune positive cells in the region of substantia nigra	[40]
Carvacrol	10 mg/ kg/ day	Rat	Enhanced catalase activity	[42]
Crocus sativus	0.01% w/v	Mice		
Curcuma longa	560 mg/ kg	Mice	Restriction of enzyme responsible for the metabolization of dopamine in brain	
Duzhong fang (dried ginger, *Rehmanniae radix*, *Dendrobium*, and *Eucommia ulmoides*)	200:2:3:3	C57bl/6 mice	Decreases microglia reactivity state, lba1, inflammation, and locomotor dysfunction; and increases dopaminergic neurons, and striatal dopamine content	[35]
Hesperetin	50 mg/ kg/ day	Wistar rats	Attenuates oxidative stress, astrogliosis marker, and apoptosis	[35]
Mucuna pruriens	2.5, 5, or 10 kg/ d of endocarp form of HP-200	Rat	Elevation of the dopamine concentration in brain cortex	[42]
Paeonol	20 mg/ kg/ day	Mouse	Reduced microglia and interleukin-1β levels, indicating decreased neuroinflammation	[35]
Sesamine from *Acanthopanax senticosu*	250 mg/ kg/ day	Rats	Improvement in the tyrosine hydroxylase	[43]
Clinical studies				
Licorice	5 cc, twice a day	Human	Enhance the total integrated neurological disorder rating scale score, including daily activities, tremor, motor ability test, and rigidity scores	[44]
Nigella sativa	500 mg/ kg	Human	Improvement of intellect, attention, and memory	[42]
Origanum majorana	-	Human	Significant improvement was observed in non-motor symptoms such as depression, anxiety, gastrointestinal and urine problems	[45]
Vicia faba	200 g + carbidopa	Human	Improvement in the level of plasma of L-dopa	[42]

anti-inflammatory, anti-carcinogenic, anxiolytic-antidepressant, and memory-boosting qualities. These demonstrate its effectiveness in treating a variety of illnesses, including Parkinson's disease. Research indicates that Ws root extract increases glutathione (GSH) and glutathione peroxidase (GPx) levels, which tends to restore oxidative stress in MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) induced mice models of Parkinson's disease [46]. A few others' effects on the PD are indicated in Table 3.

7. Conclusion

Alteration in the blood sugar metabolic process may contribute to the advancement of a variety of serious illnesses, particularly neurodegenerative disorders. There is growing proof that alpha-synuclein can disrupt typical signaling of glucose through its effects on inflammatory factors and the AKT pathway. Patients suffering from this illness are being treated with allopathic drugs. However, these treatments simply reduce the disease's course, not cure it. They fail to tackle many non-motor signs such as depression and sleep difficulties, which can result in a variety of adverse reactions. However, in both animal and human tests, a variety of natural compounds have shown few or no negative effects, even at greater oral doses. The issue persists whether the ensuing neuroprotective effects shown in pre-clinical model by focusing this unique mechanism will translate into observable disease change, although preliminary data from human studies are encouraging. There are constraints to producing medications that utilize natural ingredients. Because there are no established techniques for manufacturing natural goods, the quality and content of natural products designed for medicinal purposes can vary widely. Similarly, there is an absence of clinical trials that follow established standards, resulting in inadequate scientific proof for the medical application of natural products. Thus, more clinical investigations and studies are needed to confirm the efficacy of these natural-product-based medicines in the human body using defined criteria. In addition, because natural goods contain a complex mix of molecules that work simultaneously, it is difficult to determine and extract the active components essential for certain therapeutic benefits. Furthermore, studies into the biological pathways via which these particular components work in the body is restricted highlighting the need for additional exploration.

Declarations

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