Review Article

A Comprehensive Review on Pathophysiology and Alternative Therapies for Parkinsons Disease.

ABSTRACT
A neurological disorder is one in which neurons in the cerebral or peripheral nerves gradually lose their ability to operate before dying. Unfortunately, there is presently no treatment for degenerative diseases, only an arrest down of the disease's progression. There are actually several symptomatic treatments available, however degenerative conditions are still incurable. There are certain advantages with western medical treatments, they are Deep brain stimulation, dopamine-producing treatments for Parkinson's disease (PD) and disorders of movement, cholinesterase inhibition for memory problems, antipsychotic medicines to combat the behavioural and mental manifestations of Alzheimer's disease, analgesic medicines for Inflammation, anti-inflammatory agents for transmission, and possibly antipsychotic drugs medications for memory impairment may be used to treat the severe and raising symptoms. Additionally, scientists have sought to discover treatments that might delay the onset of disorders, which include Analgesics (non-steroidal anti-inflammatory in nature drugs) treating dementia, Riluzole treatment fatal motor neuron disease, tremors, and Huntington's chorea. Although specialized medications may assist relieve a few of the signs. There nevertheless remain so many problems with them. Age significantly increases the individual's risk of having a condition that affects the brain. In the future decades, there may be an increase in neurodegenerative illnesses. To better understand the mechanisms behind diseases of the brain, we must come up with novel approaches to both therapy and prevention. Thus we started searching for more treatments for these diseases as a result of this, and we found some options. Such as plant medicine, physiotherapy, stem cell therapy, monoclonal antibiotics.

Key Words: Neurological disorder, Deep brain stimulation, Dopamine-producing treatments, Parkinson's disease, Alzheimer's disease, Physiotherapy, Stem cell therapy, monoclonal antibiotics.

1. Introduction

Usually neurodegenerative is only informally acknowledged and barely addressed in large medical literature it even more Poorly characterized by most sophisticated lexicon. The prefix "neuro-," which indicates cells of the nervous system (i.e.neurons), with the term "degeneration," that describes the phenomenon that an organ or tissue diminishing shape or functioning, make up the word's etymology. A frequently used term with a seemingly clear definition is “neurodegeneration." However, it is considerably harder to define neurodegeneration precisely than one may think. These conditions do not encompass conditions regarding neurological origin that affect brain cells instead of their features, including the destruction of the myelin sheath observed in multiple sclerosis, nor do they include conditions that occur when nerve cells perish from an established factor, which means to be hypoxia, toxic exposure, metabolic problems, or infections. Only a small number of the hundreds of various neurodegenerative diseases have

received the majority of research funding to date, including amyotrophic lateral sclerosis (ALS), Parkinson's disease the pathophysiology is depicted in fig 1, Huntington's disease, and Alzheimer's disease. Even though they are no less deadly, many of the less well-known or publicized neurodegenerative illnesses have mostly gone unnoticed [1].

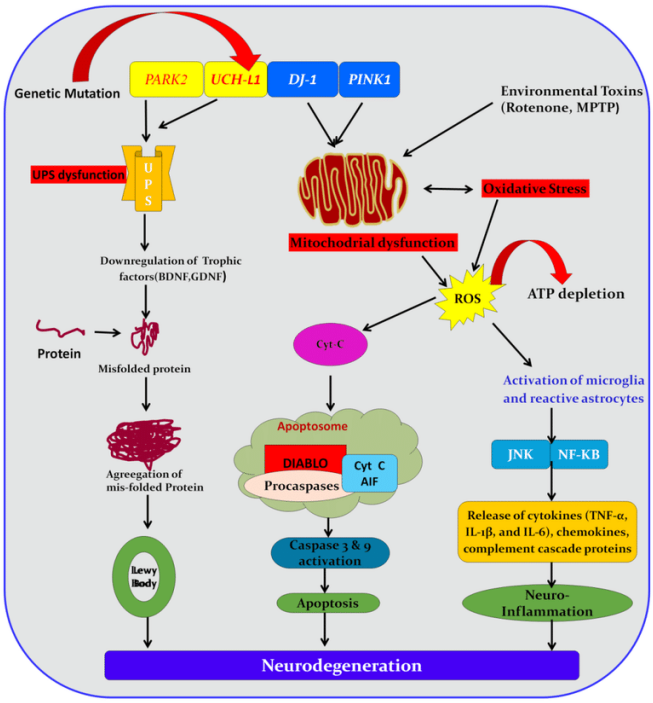

Figure 1 Pathophysiology of Parkinson's disease.

1.1 Risk Factors

There are numerous uncommon neurodegenerative disorders with known genetic origins. Mutations cause the early onset of serious neurological illnesses by impairing the activity of genes vital for neurons as well as glial cell functioning. Other variations in genes are associated with risk, which means they contribute to a neurological disease more likely without actually triggering it [2,3].

1.1.1Toxins

Neurodegeneration is a side effect of toxic drugs, such as alcohol or lead, especially when exposed over an extended period of time. Toxins may cause the immediate death of neurons or may hinder the function of neurons or glial cells, causing neurodegeneration [2,3].

1.1.2Impaired Protein Clearance and Protein Misfolding

The misfolding of proteins and the production of aggregates, frequently as the shape to Lewy body masses, tangles of neurofibrillary tissue, or plaques specific to the disease, are linked to a category of neurological conditions known as proteinopathies. One of the primary pathological pathways associated with these neurodegenerative illnesses is assumed to be protein accumulation and cluster growth, which results in protein poisoning. Protein aggregation can result from abnormalities in the ubiquitin-proteasome, autophagolysosome amino acids clearance levels, amino acids types that are prone to clumping together or within the case of prion diseases.

A transmissible form of misfolded protein that can cause unraveling in typical forms of the same protein.

1.1.3Changing Cell Signalling

Since synaptic communication as well as extrinsic signals related to survival are frequently necessary for the vigour and longevity of neurons, improper cell signalling, such as interrupted pre-synaptic input or defective internal signalling pathways, can play a role in the aetiology of neurodegenerative conditions.

1.1.4Hyperoxic Stress

Reactive oxygen species (ROS) are highly created in most neurons due to the large number sustained mitochondrial as well as their elevated levels of function. The antioxidants are essential for neurotransmitters because they can reduce the effects of oxidative stress. Numerous diseases of the brain are associated with diminished the activity of superoxide dismutase or as glutathione breakdown. In addition, neurodegenerative may result from oxidative damage, which may be caused by inflammatory or impaired microglial activity [2].

1.1.5Damage to DNA

Dementia and general cognitive decline, as well as a number of neurodegenerative disorders, have all been related to an accumulation of DNA damage and a decrease in the efficiency about the genome's restoration mechanism [3].

1.1.6The skeleton of cell and transport of axons dysfunction

Technically large cells such as neurons have an important quantity of cytosol that is separated by the perinuclear fluid and all of its digestive apparatus. Axonal transportation, a transfer process along the length of the axon, is crucial to neuronal functioning and health. Lipids, amino acids, vesicles, and organelles are among the metabolites that are carried across the axons in each direction. The payload is pulled through the axonal framework by linking amino acids and energetic transporters, albeit this means of transport can also be quiet. Neuronal function may suffer irreparable damage if the communication system as well as the cytoskeletal framework upon which it depends is disrupted.

1.1.7Neuroinflammation

Various factors, including injury, suppuration, cerebral infarction, toxic metabolites, and autoimmune, can cause inflammation in neural tissue. The deterioration of cell-to-cell connections along with tissues construction, pruning of synapses, problems, and absorption of neuronal plugins, like myelin protein and even the direct induction of apoptosis in cells called glia and cells are all effects of inflammatory reactions. Even though it is frequently reversed, sudden inflammation substantially impairs brain function. Progressive neurotoxicity is frequently the result of ongoing or ongoing inflammation.

1.1.8Demyelination

An axon is exposed to harmful external factors when the nerve-insulating myelin coverings are lost because of damage, toxins, metabolic changes, or inflammation. This results in an immediate breakdown of the functioning of neurons and the loss of quick, beneficial communication. Energy demands are greatly raised as a consequence of demyelination, and cellular signalling is changed. Neurodegeneration will be caused directly by protracted demyelination [3].

1.1.9Neurologic insufficiency

Glial support is essential to neurons in a number of ways. Glial cells like oligodendrocytes and astrocytes (or Schwann, who cells in the case of the PNS) assist metabolism and transmit critical biological messages to nerves and axons. Furthermore neuronal waste products like harmful metabolites and Radicals are eliminated by the glia that surround Increased neurodegeneration

may be the outcome of, or may even be the direct cause of, diminished glial cell or glia functionality along with acquired glial mortality which is depicted in fig 2.

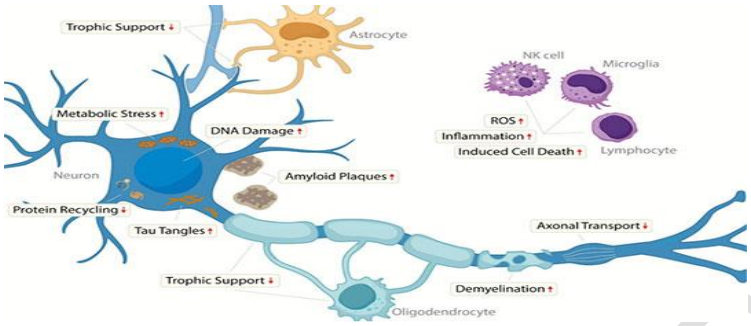

Figure 2 Common manifestations of or contributors to neurodegeneration

1.2 Most Common Neurodegenerative Diseases:

There are numbers of different neurological diseases that have been identified, but just a few of these disorders are prevalent and have a significant effect on society. The bulk of these are neurological conditions associated with ageing, and it is anticipated that as the general population ages, their frequency will rise even more.The two most commonly seen neurological diseases are Parkinson's and Alzheimer's.

1.2.1 The Alzheimer's (AD)

Senile lesions and tangles of neurons are the two main features that define the pathophysiology of AD. Small beta-amyloid peptides that are released through the precursor protein for amyloid make up these clumps that assemble themselves into thick deposits outside the cell and cause dementia and neurological inflammation. As the leading cause of dementia, AD causes the cortex of the brain and several subcortical regions of the brain to atrophy severely in 60–70% of patients.

1.2.2 Parkinson's illness

The next most prevalent neurological disorder, PD frequently shows up as bradykinesia, shaking hands, and other movement abnormalities. The development of alpha-synuclein-ubiquitin protein combination and clumps in Lewy bodies that appear in the substantia nigra neurons and eventual loss of sensory cells in this region of the brain are characteristic for Parkinson's disease (PD). It is still unclear precisely how protein buildup along with cell death is related [3].

2. Alternative Treatments for Parkinson’s disease.

Treatments in alternative neurodegeneration therapies can be categorized into the following categories. Herbal medications, physiotherapy, stem cell therapy, monoclonal antibodies.

2.1 Herbal medication

Plants have consistently remained the foundation forconventional therapeutic processes, and shown to deliverconstant treatments to living organisms for a very long time.Their medicinal capability has been established on thediscovery of their utility since millennium years. Medicinalherbs are considered as a storehouse of numerouscompounds which are biologically active and are utilized dueto remedial functions possessed by them. Antitumor, anti-inflammatory,antiviral, as well as antimalarial functions aresome of the therapeutic abilities manifested by these plants.Understanding of these herbs for the formation of severalmedicines has been of huge importance.These plants for the development of recent years have seen a substantial increase in scientific interest in studying plants as the source of novel drugs used to

treat neurodegenerative illnesses. Different plant extracts are being studied for their biological properties, such as their ability to treat diabetes, scavenge free radicals, reduce inflammation, and fight cancer. Due to their capacity for neuroprotection, medicinal herbs including *Withaniasomnifera*, *Bacopa monnieri*, *Ginkgo biloba*, this herb asiatica, among countless others have received extensive research [4]. Different phytochemicals derived from plants inhibit specific stages of neurodegenerative disorders. This is because they may play a part in maintaining the chemical makeup of the brain by interfering with the action of multiple receptors for important inhibitory neurotransmitters. Due to the therapeutic potential associated with their secondary compounds, medicinal plants play a significant role in the discovery of new medications that may be employed for the development of new curative drugs targeting a particular condition [5,6].

Therapies based on flavonoids for neurodegenerative diseases in preclinical studies of AD, stroke, and PD. Flavonoids, a large class of polyphenolic substances, exhibit neuroprotective effects. Fruits, veggies, and beverages are the primary sources of these elements in a person's diet. Future research has demonstrated that routine nutritional flavonoids consumption lowers the possibility of Alzheimer, ischemia, and Parkinson's disease. Freestanding oxygen recycling, transitional metal chelation, stimulation of surviving genes and signalling pathways, control of the activity of mitochondria, including regulation of neurological inflammation have all been linked to these advantageous effects [4].

It had been suggested that flavonoids from several chemical categories collaborate on multiple targets when taken together in the context of a diet high in flavonoids, which enables compounds to engage in synergistic effects to explain such a variety of activities. Thus, flavonoid combinations that focus on parallel chemical reactions may encourage synergistic relationships, enabling the use of the least quantity of each component while lowering the possibility of unfavourable side effects. The fact that these substances are highly absorbed and can be ingested in large quantities without harm is an additional draw of this strategy. These characteristics have prompted numerous researchers to suggest that flavonoid-rich extracts of plants should be seriously considered as cutting-edge therapeutics in the management of neurological disorders.

2.1.1 Herbal medicine to treat Parkinson’s disease.

Ginkgo biloba (Ginkgo):An anti-oxidant that enhances the supply of blood to the brain that might aid in dopamine delivery. Many drugs, including blood thinners like warfarin (Coumadin) as well as clopidogrel (Plavix), interact with gingko. Gingko should not be taken without a doctor's prescription. The mechanism of ginkgo is represented in fig 3.

Bacopa monniera (Brahmi): A plant used in Ayurveda occasionally to cure Parkinson's disease. According to studies, it enhances neurological function generally, mood, ability to think, and blood flow to the brain. But Parkinson's disease research has not been done on it. Find a licenced Ayurveda practitioner if you're interested in using brahmi, and never take it without first consulting all of your prescribing physicians[5].

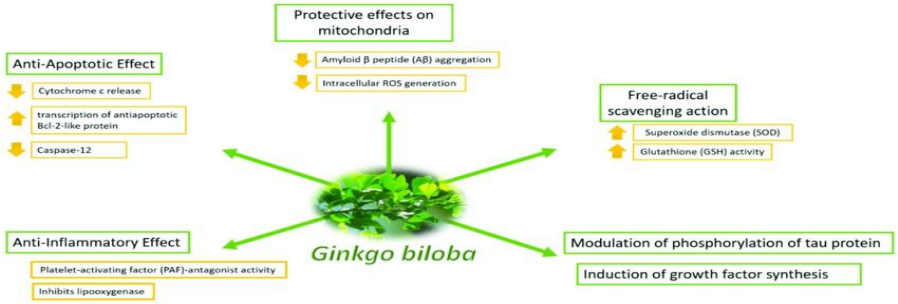

Figure 3 Mechanisms of action of *Ginkgo biloba*

2.2Physiotherapy

Numerous researches investigating the advantages for active living physical activity, along with psychotherapy in PD has been reported recently. However, although denoting different ideas, they have frequently been employed interchangeably, making it difficult to evaluate results and to effectively synthesize and critically assess study findings [7,12]. Additionally, the therapies' level of standardization and the trials' quality of methodology are typically low, frequently producing contradictory or ambiguous outcomes that make it difficult to make recommendations based on strong levels of evidence [8,9,10]. The present evidence needs to be strengthened in order to determine its true efficacy. According to our opinion, exercise should be administered to people with Parkinson's disease with the same care as pharmacological interventions. Collaboration between the disciplines in motor illness and athletic science is required for this to take place.

2.2.1 How Do Exercise and Physiotherapy Relate?

Kinesiology is an alternative to drugs therapeutic technique that employs a comprehensive client-centered approach with the goal of maximizing autonomy in function and mobility while promoting patient autonomy and involvement. One of among the most popular treatments in physiotherapy programmes is exercise. It is prescribed to treat functional issues and illness symptoms as well as to prevent further functional decline and, in some situations, disease development. In addition to exercise-based clinic programmes, physiotherapists often recommend home-based exercise programmes based on the unique needs of patients and motivate them to engage in more physical activity each day. Physiotherapy is primarily an exercise-based strategy used in the management of Parkinson's disease (PD) that targets five primary domains: health, payments, mechanical tasks, balance, and gait interventions in programmes for physiotherapy [11,16,17].

2.2.2Therapeutic Intervention by Exercise

Physical activity used as a form of therapy (also known as clinical exercise) applies the body of expertise in sports medicine that deals with psychological, metabolism, and structural reactions as well as recommending rules to both long- and short-term physical activity with clinical significance to the administration of medical terms [18,19]. In several medical specialties, clinical exercise is emerging as a novel, effective treatment strategy. Clinical exercise not only aids in disease management but also enhances physical fitness and is linked to a number of general health advantages, such as bettering cardiovascular and cerebrovascular health, reducing bone loss and age-related sarcopenia, improving mental and autonomous disorders, and acting as a general anti-inflammatory. Therapeutic measures to halt disease progression. For the therapy of symptoms resistant to pharmaceutical and surgical therapeutic methods in Parkinson's disease

professional exercising has been suggested as an adjuvant to pharmacological treatments. It is now acknowledged to be among the more potential treatment approaches for slowing the progression of disease [9,13].

2.2.3 Which Exercise Can Be Prescribed?

Exercising can be categorized as resilience, opposition, mobility, coordination, and multicomponent training, according to the ACSM [9,14,21,22]. All of them raise the metabolic processes, physical in nature, and mechanical demands, which in turn puts more strain on different tissues and biological processes. Supercompensation occurs when the right kind of exercise is carried out at the right intensity, the right length, and the right frequency, leading to an improvement in one's health and function [14]. There is a lot of variation in how different subjects react to exercise due to a mix of lifestyle and genetic variables. It is recommended to consider an individualized exercise prescription that includes all of the exercise components as well as an assessment of the subjects' personal variables, fitness levels, and environmental factors [15,20]. A form of exercise known as endurance workouts (EET) involves using the body's powerful muscles.

2.2.4 Exercises for Balance and Multiple Components

Training for balance involves a variety of exercises intended to strengthen the lower body and lessen the risk of falling [20]. Exercises that combine the aforementioned exercise modalities with the teaching of various motor abilities, including coordination, stability, gait, and agility, as well as proprioceptive training, are referred as multicomponent fitness training (also known as neuro-motor or multimodal training) given below in fig 4[15,21].

Figure 4 Moves to improve stability and prevent injury

2.2.5 Resistance Training

Exercises that require muscles to contract or hold against an external force or weight are referred to as resistance exercise training (RET). RET can be carried out using single-joint workouts that isolate functionally significant muscle groups or active workouts that utilize circular and progressive muscle contractions that simultaneously engage multiples of the primary muscle groups. The following recommendations must be kept in mind in order to maximise the effects of exercise: RET should be performed with proper form and technique throughout every point of movement within the joint; recurrence should be controlled and breathing techniques should be used (i.e., avoid the Valsalva manoeuvre and exhale throughout the phase of concentric motion and inhale during the eccentric phase); antagonist muscles should be used.abdominals and lumbar extensors, for example, should be trained to prevent muscular imbalances; rest intervals between workouts about between forty-eight and seventy-two hours are needed in order to encourage cellular/molecular modifications related to increased muscle mass and power; as well

as education only starring elongated contractions is not recommended because it can lead to muscle imbalances[6,7,8].

2.3 Stem cell Therapy

Approaches for Healing in Neurodegenerative conditions including treatment with Stem Cells Diseases of protein equilibrium, such as PD, AD, HD, ALS, and FTD, are defined by the loss of particular groups of neurons and insertion bodies made up mainly inflexible and folded proteins. This pathologic process causes a slow paralysis as well as a gradual degradation of sense of touch, cognition, and motor nerve cells. There are still no measurable biomarkers or potent medications to stop the progression of neurological conditions, despite hundreds of millions of dollars spent on clinical studies and enormous strides in understanding their mechanisms[23].

Despite the fact that the use of stem cells remains within its early stages, it has emerged as a promising, helpful, and risk-free method for the treatment of neurodegenerative disorders. Obtaining particular neuronal subgroups and replicating a neural network comparable to the one that has been lost in the illness are the initial goals of stem cell treatment for diseases of the brain. Providing enriching environments to help host neurons by manufacturing BDNF and scavenging toxic substances or constructing supplementary neural networks around damaged areas is another method for treating neurodegenerative diseases. Many approaches use stem cells to produce neuroprotective growth factors (including glial-derived (GDNF), neurotrophic factor derived from the brain (BDNF), insulin-like growth factor one (IGF-1), and the growth factor vascular endothelial growth (VEGF)) from scratch and deliver them to the brain at the location of the sickness to improve the surroundings[23,24].

Researchers have worked hard in recent years to develop neuronal and astrocytes cells from a variety of stem cells and to take advantage of other positive stem cell properties to treat neurological diseases. For the most successful and efficient stem cell therapy for neurological conditions, several stem cell sources have been investigated[25, 26, 27]. The stem-cell-based therapies for neurological disorders have primarily been done in animal models [28,29].The research demonstrated that stem cells may influence endogenous cells, encourage the functional restoration of nervous tissue, develop to neurons and glial cells, as well as lessen motor deficits.Numerous clinical researchesare examining various facets of stem cell therapy for neurological disorders. The data thus far appear to somewhat confirm the findings of animal investigations given in fig 5. The majority of data, for instance, demonstrates that the basic process responsible for the improvements that have been observed in neurodegenerative illnesses is the secretion of growth factors, including neurotrophic factor derived from the brain, neuronal line-derived neurotrophic factor, along with growth factor for nerves. Furthermore, a lot of data suggests that stem cell treatments for neurodegenerative patients can improve neurogenesis[30,31].

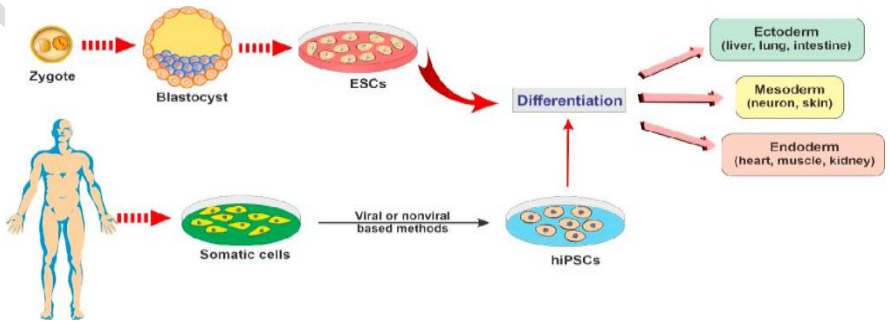

Figure 5 Reprogrammed stem cells implanted into patient with PD.

The primary phases in generating and bringing treatments based on stem cells from the bench to patients include choosing the proper stem cell type, comprehending the mechanism of support, and the particular neurological disorder. For instance, in PD, whereby a particular dopaminergic population is eliminated, biological replacement may be helpful. Contrarily, cellular treatments that improve the regional spinal column environment to sustain the surviving motor neurons are more likely to be beneficial for treating ALS. As a result, we covered the pathophysiology of typical neurodegenerative disorders as well as the process of neurogenesis in the paragraph that follows. Next, we discuss the strategies that are currently being funded and the achievements made in bringing cell therapies from the research facility to the patient's bedside to treat those particular neurodegenerative illnesses[23].

2.4 Monoclonal antibiotics

There is no known cure for the degenerative neurological disorder Parkinson's disease (PD), although there are medicines that can reduce symptoms and improve quality of life explained in fig 6. Delaying the onset of motor issues that can cause long-term issues should be the aim for PD clinical research. Nevertheless, considering the sharp rise in PD prevalence rates worldwide, developing novel multi-target treatments with few adverse reactions is a critical problem[32-39].

Lewy body lesions and Parkinson's disease have a very particular association, thus it makes sense to assume because the onset of the condition is closely linked to the aetiology of the condition. Lewy bodies can't currently be created intentionally. Therefore, it is vital to identify the components of these bodies in order to comprehend the development of these corpuscles. This allows for the determination of whether these elements are intrinsically diseased or normal cell elements. In the latter scenario, the components involved in the disease's unique degenerative process can be determined, and possibly even the route taken by a potential etiological factor. Lewy body antigens are analysed using monoclonal antibodies, which are directed against them[40].

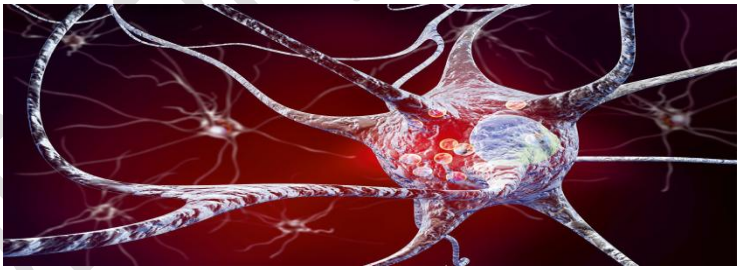

Figure 6 Reprogrammed stem cells implanted into patient with PD.

The amino acid α-synuclein is found in high concentrations in both Lewy body cells and Lewy neuritis. The pathogenesis of Parkinson's disease has been associated with the cytosolic protein -synuclein, which is tiny, naturally unfolded, and capable of misfolding to form associated polymers. A synaptic alpha (SNCA) gene, which encodes the α-synuclein protein, is subject to rare genetic mutations that result in Parkinson's disease (which is inherited by an autosomal dominant manner). Monoclonal antibodies were used in studies on alpha-synuclein transgenic mice (passive immunotherapy), and it was discovered that these antibodies moderated neuronal pathology by lowering intracellular accumulation of synuclein with in cell membranes and synapses.Aimed to improve both cognitive and motor functioning as well as safeguard against synapse loss and gliosis [35-38].The underlying principle therefore relies on the observation that

anti-synuclein gathering therapy primarily increases Lewy body control and cell clearance mechanisms[38].

3. Conclusion

In this article we have discussed about various therapeutic modalities for the Parkinson's disease such as herbal medication, physiotherapy, stem cell therapy and monoclonal antibodies. The medicinalplants and phytochemicals protect against neuronal damage caused by neuronal dysregulation, oxidative stress and inflammation. Phytochemicals called flavonoids have been shown in numerous trials to be useful in treating neurological problems. The cellular response to stress has been found to benefit from flavonoids. Additional research is required to concentrate on its clinical acceptance. To evaluate modified flavonoids' potential as treatments for neurological illnesses, more research on them is required. Because of the good safety profile, easy access, and low cost of exercise interventions, the confirmation of both symptomatic and disease-modifying effects of exercise in this field could have a profound societal impact. Using stem cells appears likely to become a key feature of future clinical strategies for treating neurodegenerative disease by replacing dysfunctional neurons and affording neuroprotective and neuro-restorative functions. In conclusion, we suggest that extracellular alpha-synuclein aggregates are specific targets for use in successful immunotherapy for PD and other synucleinopathy and these specific targets might also be used in development of novel small molecule drugs that mimic the beneficial effects of antibodies without the adverse effects.

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CONFLICT OF INTEREST

No conflict of interest.

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