Journal of
Dementia and Alzheimer's Disease

MDPI

Review

Tiny Carriers, Tremendous Hope: Nanomedicine in the Fight against Parkinson's

Nitu Dogra, Ruchi Jakhmola Mani and Deepshikha Pande Katare *

Proteomics and Translational Research Lab, Centre for Medical Biotechnology, Amity Institute of Biotechnology, Amity University, Noida 201301, India; twinkledogra@gmail.com (N.D.); drruchijakhmola@gmail.com (R.J.M.)
* Correspondence: dpkatare@amity.edu

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms due to the loss of dopamine-producing neurons and the presence of Lewy bodies in the brain. While current treatments such as dopamine replacement with levodopa and deep brain stimulation mainly manage symptoms and do not stop disease progression, recent advancements in nanomedicine provide promising new therapy options. These include drug-loaded nanocarriers that improve drug delivery to the brain, enhancing effectiveness and reducing side effects. This review explores novel nanomedical approaches like solid lipid nanocarriers (SLNs), which could improve drug profiles and decrease the adverse effects seen with traditional PD treatments. Additionally, it discusses the challenge of crossing the blood–brain barrier, which is crucial for treating central nervous system disorders, and how nanocarriers facilitate targeted brain delivery. Despite these advancements, the review emphasizes more research into the safety and long-term impacts of nanomedicine in PD, highlighting the challenge of moving these treatments from lab to clinical use.

Keywords: Parkinson's disease; nanomedicine; drug delivery systems; neurodegeneration; blood–brain barrier; solid lipid nanocarriers

check for updates

Citation: Dogra, N.; Jakhmola Mani, R.; Pande Katare, D. Tiny Carriers, Tremendous Hope: Nanomedicine in the Fight against Parkinson's. *J. Dement. Alzheimer's Dis.* **2024**, *1*, 3–21. https://doi.org/10.3390/jdad1010002

Academic Editors: Zahoor Shah and Faheem Shehjar

Received: 25 April 2024
Revised: 3 June 2024
Accepted: 6 June 2024
Published: 22 June 2024

1. Introduction

Parkinson's disease (PD) is a chronic, progressive extrapyramidal neurodegenerative disorder. The normal age of onset of PD is 55–62 years, and approximately 1.5% of those over the age of 62 are usually affected, with the incidence increasing significantly with older age. According to the World Health Organization (WHO), 10 million individuals have PD globally, and this number is expected to exceed 12 million in the next 30 years [1,2]. The disease is characterized by both motor symptoms (e.g., tremors, slowed movement, muscle rigidity) and non-motor symptoms (e.g., dementia, anxiety, depression), resulting in significant neuronal impairment [3,4]. Current therapy options temporarily alleviate motor symptoms but fail to cure or slow the disease's pathology, largely due to low brain-target-site specificity and significant side effects [5].

Nanomedicine has emerged as a promising field offering new hope in the treatment of PD. Nanomedicine involves using nanotechnology to create nanoscale materials, such as nanoparticles and nanocarriers, to improve drug delivery systems. These nanoscale materials can cross the blood–brain barrier more effectively, ensuring higher drug concentration at the target site, reducing side effects, and enhancing therapeutic efficacy. For example, gold nanoparticles (AuNPs) are known for their biocompatibility, antioxidant activities, and ability to be functionalized for targeted drug delivery, protecting dopaminergic neurons and reducing oxidative stress. They also enhance imaging techniques like MRI and CT, making them useful for early disease detection and follow-up [6]. Similarly, iron oxide nanoparticles (IONPs) enhance MRI contrast, enabling better visualization of brain structures and PD progression. IONPs can be functionalized for targeted drug delivery and have shown potential for reducing neuroinflammation [7].

In this review, we discuss the current therapies available for PD and their associated side effects, and we highlight the landmark discoveries in the field of nanomedicine focusing on PD treatment. By exploring the advancements in nanomedicine, we aim to shed light on how these tiny carriers can bring tremendous hope in the fight against Parkinson's disease.

2. Etiology of Parkinson's Disease

The major pathological hallmarks of PD are dopaminergic neuronal loss in the substantia nigra pars compacta region of the midbrain and the presence of Lewy bodies (eosinophilic cytoplasmatic inclusions) formed of aggregated misfolded α-synuclein (α-syn) protein. The Lewy bodies disrupt the microtubule-based subcellular transport and hence contribute to neuronal homeostasis disturbance and synaptic dysfunction. Furthermore, numerous reports have demonstrated the spreading of toxic α-syn protein aggregates throughout the brain, much like prion virus disease, via the vagus nerve. Despite the presence of pathological hallmarks in post-mortem patient's brain autopsies, the primary reason for the PD's early stages remains unknown [8].

Several studies have suggested that epigenetic and pathogenic mechanisms such as proteasome and lysosomal dysfunction, mitochondrial failure, oxidative stress, and neuroinflammation (astrocyte and microglial impairment) must underlie the onset of the disease. As depicted in (Figure 1), all these associated pathogenic events result in dopamine depletion, brain homeostasis disruption, synaptic dysfunction, and eventually, neuronal cell death. Age, environmental factors, genetic factors, and lifestyle habits are all potential risk factors for the development of PD. Most people suffering from PD are idiopathic; about 14% usually have a familial history, and 10–12% have a monogenic type of pathology. According to the literature, there are about 22 loci and 20 pathology-imitating genes, including 9 autosomal recessive and 10 autosomal dominant genes [9–11]. Based on the particular gene-level mutation and pathophysiological biomarkers, the clinical manifestations differ. Certain gene mutations are associated with α–syn protein accumulation and function disruption. For example, LRRK2 (leucine-rich repeat kinase 2), PARK 1, and PARK 4 are associated with α–syn dysfunction and its aggregation [12].

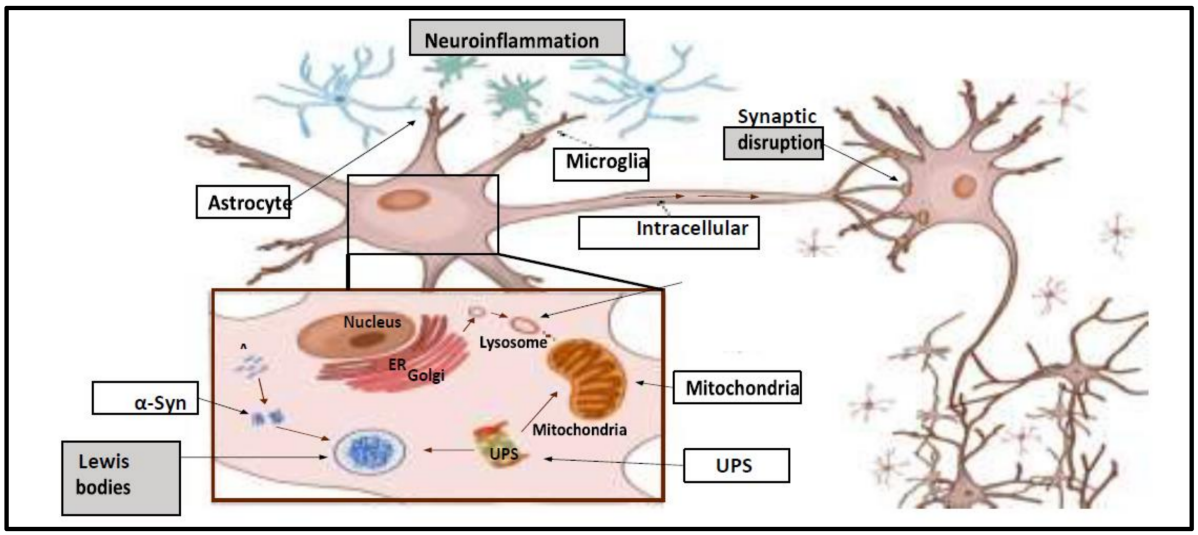

Figure 1. The image highlights key features of PD, including Lewy body formation, which involves the accumulation of abnormal α–syn protein. Neuroinflammation, driven by activated microglia and astrocytes, contributes to neuronal damage. Dysfunction of the ubiquitin-proteasome system (UPS) leads to the buildup of toxic proteins. Synaptic disruption impairs neurotransmission, exacerbating motor and cognitive symptoms. Neurodegeneration, particularly the loss of dopaminergic neurons in the substantia nigra, underlies the disease's characteristic motor deficits.

Furthermore, mutations in genes like UCHL 1 (Ubiquitin carboxyl-terminal hydrolase L1), PARKIN (E3 ubiquitin-protein ligase), and PINK 1 (PTEN-induced kinase 1) have been related to autophagy and ubiquitin linked proteasome system dysfunction. These biological mechanisms enable the effective clearance of α–syn aggregates and the repositioning of mitochondrial-disrupted fragments in the neurons. The failure of these regulatory processes allowed misfolded proteins like α–syn to accumulate, resulting in the formation of Lewy bodies. Furthermore, lysosomal dysfunction has been related to PD and mutations in the ATP13 A2 gene [13]. Environmental variables like exposure to some chemicals, pesticides (rotenone and paraquat), narcotic medicines, and various solvents have also been linked to an increased chance of developing PD.

3. Management of Parkinson's Disease

Several drug treatments are currently available for the management of PD patients. They all have different safety and effectiveness profiles as well as varying indications. The fundamental aim of novel strategies for PD treatment is to restore dopaminergic neurons in the substantia nigra pars compacta and striatum. The most prevalent treatment for PD is pharmacotherapy, which is a pharmacological drug treatment strategy [14]. However, each of the medications has its own set of limitations that could make it difficult to achieve the intended therapeutic impact. Fortunately, a recent therapeutic approach involving nanomedicines in which the drug is combined with nanocarriers has resulted in a considerable improvement in treatment outcomes. This innovative encapsulated drug delivery method significantly improved target-site delivery and enhanced the half-life of the drug. Immunotherapy, gene therapy, surgical therapy, and behavioral therapy are some of the additional therapeutic interventions for PD [15].

Surgical treatment was chosen after long-term usage of drugs, which resulted in drug-induced motor complications or maybe drug resistance in PD patients [16]. Deep brain stimulation, which proved to be a gold-standard treatment for some advanced-stage PD patients, involves the surgical implantation of electrodes. Thalamic stimulation, pedunculopontine nucleus stimulation, and pallidal stimulation are examples of deep brain stimulation [17]. It is beneficial to early-stage PD patients with improvement in tremors and for treating motor fluctuations and symptoms such as tremors, stiffness, and bradykinesia. Unfortunately, dopamine-deficiency symptoms, including gait disruption and postural disability, are not helped by it [16,18]. Neuropsychiatric problems, disordered cognition, and speech are some of the negative consequences of the treatment.

Ablative surgical treatments such as thalamotomy and pallidotomy were also used to treat the tremor, but they were considered unfavorable due to their higher risks of severe side effects. Aside from surgical techniques, new regenerative therapeutic approaches like immunotherapy, cell transplantation, and gene therapy are entering clinical trials. A stem cell has the efficiency to be used in the future for the treatment of PD. Human embryonic stem cells (pluripotent) are the cells of choice for transplantation into the striatum of PD patients. Human embryonic mesencephalic cells with dopaminergic neuronal cells were transplanted into the PD patient's midbrain and showed to dramatically ameliorate PD-like symptoms, such as tremors, bradykinesia, and muscle rigidity [19,20]. The introduction of disease-modifying transgenes targeting GABA and dopamine production is a novel breakthrough in PD treatment. Another recent immunotherapy technique aims to eliminate α-syn protein overexpression [21]. Controlling postural instability, gait, and balance requires speech and physical therapy. Patients participate in community activities and work as part of occupational therapy. Patients with impulse control issues, depression, and sleeplessness may benefit from cognitive behavioral therapy. All these therapy approaches manage the pathology and provide symptomatic relief, but they do not cure it. Despite being the gold-standard treatment for PD, patients who do not respond to L-DOPA (levodopa) confront a variety of challenges. Despite appropriate L-DOPA therapy, several motor features do not improve and eventually deteriorate [22]. L-DOPA also exacerbates orthostatic hypotension, mental dysfunction, hallucinations, and a variety of non-motor

parkinsonian symptoms. Unfortunately, within a few years of starting L-DOPA medication, almost half of the patients experience complications like dyskinesia and substantial wear-off effects. Eventually, synthetic levodopa becomes least responsive as the disease progresses with dopaminergic neuronal loss [23].

4. Current and Emerging Therapeutic Strategies

Currently, there are no treatments available that can reverse the underlying pathology of PD; the only treatment options are dopaminergic medications. Some of the alternatives include drugs, procedures, counseling, and a combination of treatments (Table 1). They must also be altered as the disease advances because some traditional treatments, including L-DOPA, lose efficacy with time. Treatment of pathology with available market drugs and therapies provides beneficial clinical benefits; however, none can reduce the disease pathology progression [24,25]. For initial treatment, no medicine is better than the other; instead, the pathology must be treated based on the severity [25].

Table 1. Treatments available for Parkinson's Disease.

Treatment Class	Effects	Advantages	Disadvantages
Monoamine oxidase inhibitors (MAOIs)	Preventing the dopamine and levodopa breakdown.	■ Minimal dose is required. ■ It prevents cognitive deterioration. ■ It improves the L-DOPA-induced dyskinesia problem.	■ Does not give better results in advanced-stage PD. ■ It is usually supplemented with other classes of drugs for effective treatments, like COMT inhibitors.
Dopamine Drugs	It is taken orally or via intraperitoneal route (IP).	■ Gold-standard treatment. ■ Highly beneficial in idiopathic PD patients. ■ Effective in treating motor and non-motor symptoms. ■ Recommended to advanced-stage PD patients suffering from severe life-threatening symptoms.	■ Not recommended in early-stage PD. ■ Requires a heavy dose of levodopa over time.
Glial cell line-derived neurotrophic factor (GDNF)	It is a glial cell line-derived neurotrophic factor implanted in the midbrain.	■ Improves motor symptoms. ■ It raises the striatum dopamine level. ■ It protects the dopaminergic neurons in the midbrain region from neurotoxic effects.	■ Unable to cross BBB. ■ Emerging treatment, more research is required.
Anticholinergics	These are the oral drugs that reduce the excessive acetylcholine level and activity.	■ Quick absorption is generally recommended for treating tremors in PD. ■ Effective in early-stage PD.	■ Low tolerance in old-age PD patients ■ Less PK–PD (Pharmacokinetic–Pharmacodynamic) information.
Nanomedicine	Formulation of drug-loaded nanocarriers for the target site.	■ Can bypass BBB. ■ Sustained and target-site drug delivery. ■ Biocompatible.	■ As this is an emerging field, more research work is needed.
Surgery	Incision into the hypothalamus, global pallidus, or subthalamic nucleus, which may be either unilaterally or bilaterally.	■ Better performance, improved rigidity, reduced tremor scores and hypokinesia.	■ It may lead to permanent side effects.

Table 1. *Cont.*

Treatment Class	Effects	Advantages	Disadvantages
DBS	Basal ganglia are stimulated via high electric frequency.	■ It gives better results than surgical therapy. ■ Used in advanced stages of PD. ■ Beneficial in treating both motor and motor symptoms. ■ It improves L-DOPA-induced symptoms like bradykinesia and tremors. ■ Its benefits last for more than 10–12 years in PD patients.	■ Battery life is limited. ■ Proven to be less effective in improving symptoms like speech disability, body balance, and gait. ■ In certain cases, it may induce dyskinesia and movement imbalance. ■ Costly.
Gene Therapy and Stem Cell Transplantation	Stem cell transplantation into the brain striatum and insertion of transgenes as a disease-modifying agent.	■ Helpful in replacing the damaged neurons with long-term effects. ■ Helps in improving the dopaminergic neuronal pathways for treating the pathway at a genetic level.	■ Ethical issues ■ More research work is required.
Physical Therapy	Addresses mobility and motor-related symptoms through physical training.	■ Improve the quality of life of patients. ■ Therapy helps in treating multiple symptoms. ■ PT comes in a variety of.	■ Other treatments are required with disease progression.
Speech Therapy	Voice exercises are required for speech improvement.	■ Improve vocal issues. ■ Improves patients' quality of life.	■ Effective for treating speech issues.
Occupational Social Therapy	Motivate patients to engage themselves in leisure, work, and self-care activities.	■ Promotes independence. ■ Allows one to participate in a meaningful way. ■ Considers the social and environmental consequences and issues.	■ Requirement of PT with it, as well as additional treatments. ■ Does not address PD on a physiological basis. ■ Patient involvement and motivation are limiting factors.
Cognitive Therapy	Behavioral training practice for symptomatic relief.	■ Alternative drug therapy is used simultaneously for better results. ■ No adverse effects. ■ Equally effective as other drugs at treating insomnia. ■ Managed remotely.	■ Effective for managing one symptom. ■ More tests are required. ■ Totally dependent on patient willpower.

PD affects multiple neural circuits in the brain. Synthetic levodopa, the precursor of dopamine, is the most commonly used pharmacological treatment, particularly when paired with a dopa-decarboxylase inhibitor, which helps to lessen some of the side effects, such as nausea. Ropinirole is a dopamine agonist. MAOB inhibitors such as selegiline and rasagiline, as well as COMT inhibitors like entacapone, can regulate endogenous dopamine metabolism. By restoring dopaminergic activity in the striatum, these drugs can help people with PD improve their motor symptoms. However, they are not capable of treating all the motor symptoms that are common in people with PD. Non-motor symptoms such as neuropsychiatric difficulties and postural instability may be aggravated by treatments in certain cases [26]. Though these drugs can help with the motor symptoms of PD, particularly in the early stages, long-term usage of L-DOPA, in particular, has major side effects that are an important part of the clinical features in advanced-stage PD. Non-physiologically sustained delivery of dopamine to the striatum causes problematic dyskinesias, which eventually leads to significant fluctuations in motor activities and variable transit of L-DOPA into the midbrain, resulting in a rise in on–off phenomena [27] (Figure 2). Deep brain stimulation is a therapy that helps with the mobility issues associated

with PD. However, it is ineffective for non-motor symptomatic features. Though DBS (Deep Brain Stimulation) is a safe therapeutic option, it can have side effects such as psychiatric instability and speech impairment in addition to the usual issues that come with a neurosurgical procedure, and it is only acceptable for a tiny fraction of PD cases [16].

The usage of levodopa-intestinal gel is more appropriate for prolonged dopamine release than oral formulations, making it one of the finest options for providing dopamine more physiologically. This is beneficial in reducing the motor and non-motor symptoms caused by dopaminergic medication delivery. On the contrary, therapy is very expensive, and the surgery needed for its insertion is linked with significant health problems [14]. Furthermore, patients are attached to a device that must be worn at all times, similar to DBS and apomorphine pumps, which is problematic for many people.

While there are effective therapies for the motor and non-motor symptomatic features of PD, they all have limitations, and none of them can slow the progression of the disease or alleviate the severe non-motor symptoms. These medications are, in fact, responsible for some of the non-motor features. Therefore, novel technologies for restoring the normal levels of dopamine in the striatum in a bio-physiological manner and treatments to prevent disease development and neurodegeneration are needed.

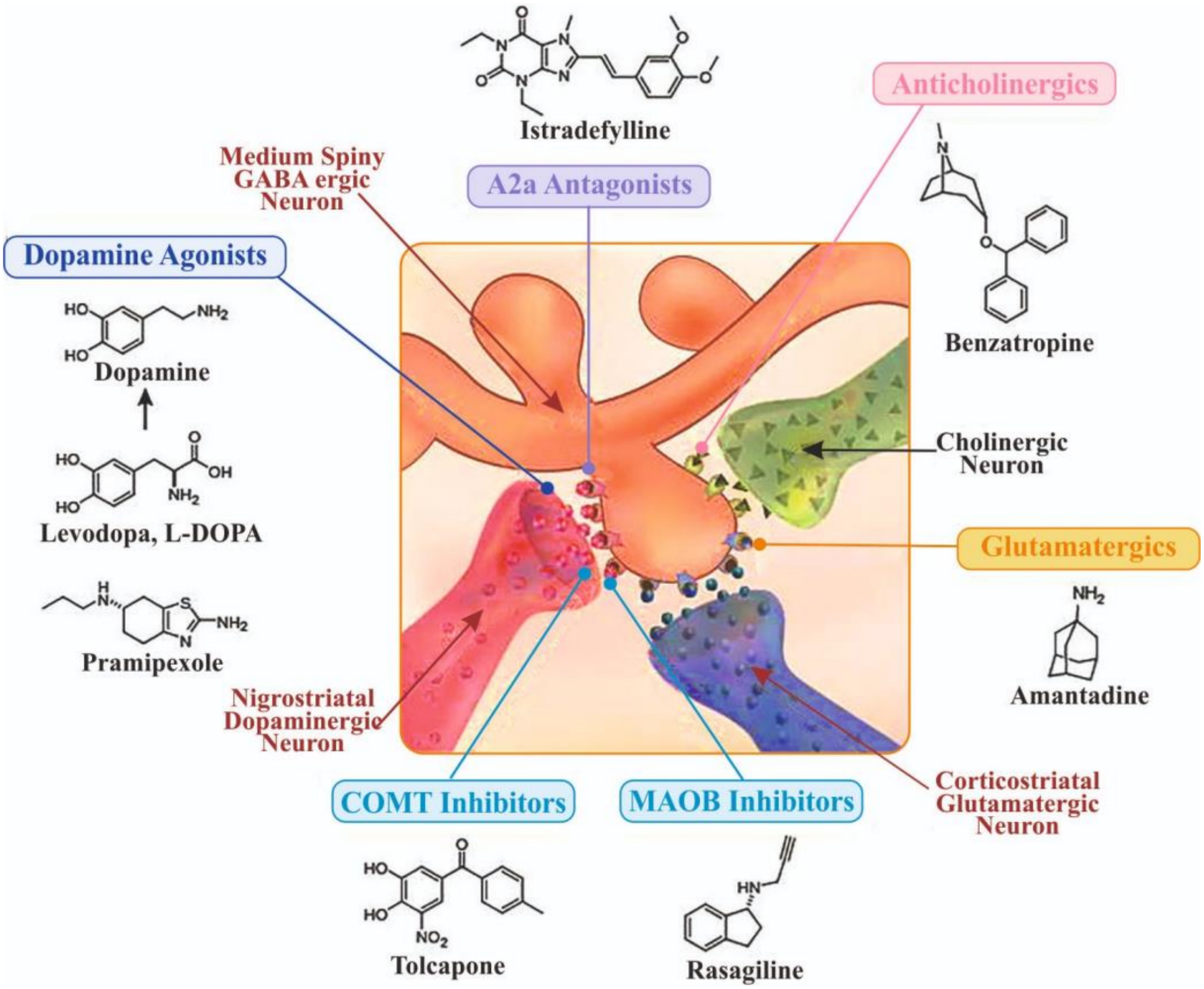

Figure 2. Therapeutic approaches for PD.

5. Integrating Traditional and Modern Approaches

Medicinal herbs have been discovered all over the world for thousands of years. These plants have been utilized in many communities and countries for generations because of their safety, efficacy, acceptability, and comparably fewer bad effects than chemical

drugs [28]. In addition to their economic value, research has shown that the antioxidant qualities of phenolic chemicals found in these plants give them a unique place in many societies' health and well-being. Plants are being used in a variety of therapeutic procedures and novel methods of drug delivery to treat diseases. There is always a demand for new oral medicines that are free of adverse effects [29].

Medicinal herbs and their active components have been reported to be used to prevent and cure PD. Most of the research has focused on the medicinal plants' antioxidant, anti-inflammatory, and immunomodulatory characteristics [30–36]. In a variety of animal models of PD, tea polyphenols have been demonstrated to protect against brain damage. Studies have used a single component, such as EGCG (Epigallocatechin gallate), or a combination of tea extracts. In rats and mice given parkinsonism-inducing neurotoxins such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and 6-OHDA (6-hydroxydopamine), individual EGCG and black tea polyphenol extracts were reported to diminish striatal dopamine depletion and death of substantia nigra dopaminergic neurons [37]. Albizia adianthifolia leaves are high in antioxidants and can aid with PD-related neurological abnormalities. Apigenin is the major flavone component and, hence, the source of the cognitive-enhancing effects in the 6-OHDA-lesion rodent model of PD, according to HPLC analyses.

According to the Morris water maze test, apigenin and related substances increase learning and memory in adults by encouraging neuronal development [38]. The pathogenesis of PD is currently attributed to the formation of reactive oxygen species (ROS) and the onset of oxidative stress, which leads to damage to the substantia nigra pars compacta, considerable changes in the antioxidant enzyme activity (CAT, GST, SOD), iron content, loss of mitochondrial integrity, and oxidative damage to DNA, proteins, and fats. GSH deficiency is linked to the development of Lewy bodies (Figure 3). The biochemical marker GSH may be the most crucial factor in nigral cell death. GSH depletion may not be the main cause of nigral neuron injury, although it may enhance vulnerability to free radical exposure [39]. Most medicinal plants and active compounds raise glutathione, superoxide dismutase, and catalase levels in the brain, resulting in neuroprotective benefits. Most of the medicinal plants and active compounds with neuroprotective benefits are discussed in Table 2.

Inflammation itself plays a crucial role in the pathophysiology of PD. The number of activated microglia in the striatum and substantia nigra increases in people with PD. Activated microglial cells respond to a variety of unfavorable conditions by rapidly hypertrophic growth and the release of cytokines. Active microglia secrete many pro-inflammatory cytokines via overexpressing the cell surface biomarkers like macrophage antigen complex 1. Cytokines, such as TNF, IL-6, IL-1α, and IL-1β, play a major role in neuroinflammation [40]. The therapeutic effects of many plant-based products could be due to synergistic effects. Several herbal extracts have been used to treat PD because of the numerous bioactive chemicals they contain, but none have proven to be successful in PD treatment or in halting the pathology [41,42].

Table 2. List of herbal plants and their mode of action.

Plant	Animal Model	Dose	Effects	References
Tinospora cordifolia	Rat treated with 6-OHDA	400 mg/kg b.w	▪ Rise in dopamine content ▪ Reduced iron ratio ▪ Reduced LPO ▪ Enhanced mitochondrial complex I activity. ▪ Improvement in body balance	[34]
Sesame seed oil	Mice treated with 6-OHDA	Sesame oil mix diet	▪ Rise in CAT, GSH, GPx, GR and GST ▪ Inhibition of Nox2 and Cox2 activities ▪ Restoration of MnSOD level.	[43]

Table 2. *Cont.*

Plant	Animal Model	Dose	Effects	References
Carthamus tinctorius	Rat treated with MPTP	35 mg/kg b.w	▪ Improvement in behavioral activities ▪ Suppressed overexpression of α-syn protein ▪ Suppressed astrogliosis	[33]
Chaenomeles speciosa	Rat treated with 6-OHDA	1000 mg/kg b.w	▪ More positive tyrosine hydroxylase neurons ▪ Rise in D8 cell viability.	[44]
Portulaca oleracea	Mice treated with 6-OHDA	400 mg/kg b.w.	▪ Increased rearing, centrality, and number of crossings in open field test.	[31]
Paeonia suffruticosa	Rat treated with MPTP	50 mg/kg b.w	▪ Increased rearing, centrality, and number of crossings in open field test ▪ Increased striatum dopamine level ▪ Attenuation in the loss of dopaminergic neurons.	[45]
Mucuna pruriens	Rat treated with 6-OHDA	120 mg/kg b.w	▪ Decreased dyskinesias ▪ Rise in nigrostriatal catecholamine level	[46]
Hyoscyamus niger seeds	Rat treated with rotenone	500 mg/kg b.w	▪ Improvement in motor performance ▪ Rise in the content and activities of GSH, CAT, SOD and GPX.	[30]
Hibiscus asper leaves	Rat treated with 6-OHDA	100 mg/kg b.w	▪ Rise in the content and activities of GSH, CAT, SOD and GPX ▪ Reduction in LPO.	[47]
Gynostemma pentaphyllum	Rat treated with MPTP	30 mg/kg b.w	▪ Restoration of dopamine, norepinephrine, homovanillic acid, and 3,4 dihydroxyphenylacetic acid in the midbrain. ▪ More positive tyrosine hydroxylase neurons in the midbrain striatum.	[48]
Ginkgo biloba	Rat treated with 6-OHDA	150 mg/kg b.w	▪ Increased number of crossings and rearing in open field test ▪ Increased striatum dopamine level ▪ Attenuation in the loss of dopaminergic neurons ▪ Rise in the content and activities of GSH, CAT, SOD and GPX ▪ Reduction in MDA level.	[49]
Fructus alpiniaoxyphylla	Zebrafish	20% solution	▪ Restoration of dopaminergic neuron ▪ Improved movement activity ▪ More viable PC12 cells.	[44]
Delphinium denudatum	Mice treated with 6-OHDA)	600 mg/kg b.w	▪ Reduced LPO ▪ Rise in GSH content and GST activity ▪ Rise in CAT, SOD activities ▪ Rise in dopamine level	[50]
Bacopa monniera Linn	Mice treated with 6-OHDA)	40 mg/kg b.w	▪ Reduced MDA levels ▪ Rise in GSH content ▪ Rise in CAT, SOD activities ▪ Rise in dopamine level.	[36]

Table 2. *Cont.*

Plant	Animal Model	Dose	Effects	References
Althaea officinalis L.	Rats treated with 6-OHDA	10 mg/kg b.w	▪ Increased rearing, centrality, and number of crossings in open field test. ▪ Increased striatum dopamine level. ▪ Increased dopaminergic neuronal cells. ▪ Rise in enzymatic and non-enzymatic antioxidants (GSH, CAT, SOD and GPX). ▪ Reduction in LPO.	[51]
Valeriana officinalis	SH-SY5Y cells treated with rotenone	0.049 mg/mL b.w	▪ Increased viability of Neuronal cells.	[52]
Panax ginseng	Rat treated with rotenone	100 mg/kg/b.w	▪ Restoration of dopaminergic neuronal cell ▪ Formation of Lewy bodies.	[53]
Safflower	Rat treated with 6-OHDA	70 mg/kg/b.w	▪ Increases in Tyrosine hydroxylase expression. ▪ Rise in dopamine levels. ▪ Reduced acetylcholine levels.	[54]
Hypericum perforatum	Mice treated with MPTP	200 mg/kg/b.w	▪ Improvement in behavioral performance. ▪ Suppressed α-syn protein overexpression. ▪ Suppressed astrogliosis.	[55]
Oxalis corniculata	Mice treated with 6-OHDA	500 mg/kg/b.w	▪ Rise in catalatic and SOD activity.	[56]

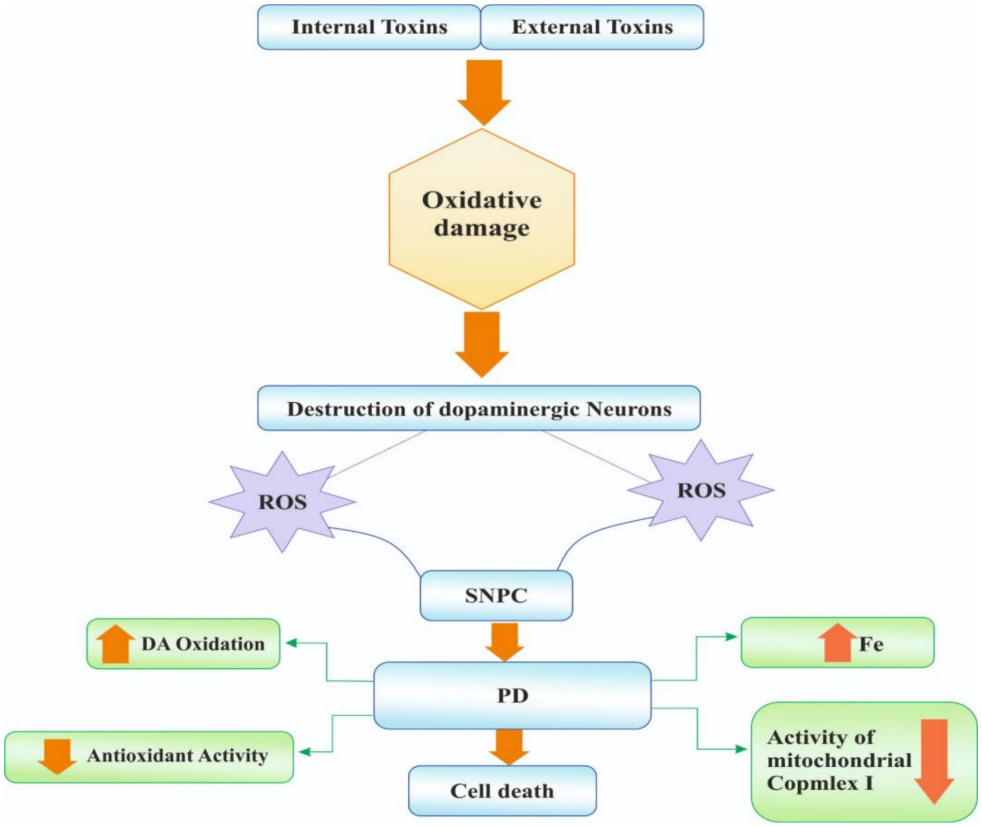

Figure 3. This detailed representation explains how mitochondrial dysfunction and excessive ROS production lead to oxidative stress, impair cellular energy metabolism, disrupt calcium homeostasis, and trigger inflammatory responses, culminating in the progressive loss of dopaminergic neurons in the substantia nigra and the characteristic symptoms of PD.

6. Overcoming the Blood–Brain Barrier: Challenges and Innovations

The presence of the blood–brain barrier (BBB), allowing particular drugs to reach the midbrain region of the brain, is the fundamental hurdle in the treatment of PD. Large hydrophobic charged molecules enter the brain via a facilitated transport system, while only the lipophilic molecules of small size are capable of entering the midbrain. The use of pharmacophore-designed medicines and dopamine is restricted. The BBB consists of pericytes, astrocytes, endothelial cells, and peripheral basal membranes. They are responsible for the closure of brain capillaries. The tight junction is the blood–brain barrier's specialty. It plays an important function in maintaining the brain's homeostasis by inhibiting the entry of a variety of chemicals [57]. Figure 4 depicts the transport of molecules across the BBB. When small lipophilic compounds reach the midbrain, they are identified by the P-glycoprotein and tagged to be disintegrated by endothelial enzymes. Undesirable systemic side effects occur when a drug is liberated from its carrier form prior to reaching the specific region of the brain. These issues can be easily overcome with nanotechnology, in which the medicine is packaged into small nanoparticles (10 nm–1000 nm) that can easily pass the BBB. This technology can be used for target-site drug delivery and reduce the drug's systemic side effects [58]. Receptor-targeted transcytosis is a common phenomenon that includes the transport of large molecules into the brain for simple diffusion. Endothelial cells have unique receptors for binding particular ligands like iron, insulin, and other macromolecules. Internalization of the cell membrane occurs simultaneously with the formation of receptor-ligand complex, resulting in intracellular vesicles processing and recycling the receptors while dissociating the ligands [59].

The internalized chemical attaches to the endothelial cells, releasing the medicine into the brain parenchymal region. Insulin-like growth factor receptors, insulin receptor and transferrin receptors, diphtheria toxin receptors, and BBB transport vehicles are a few receptor-based targets for entering the brain. Another inflow route is adsorption-mediated transcytosis, where polycationic peptides attach to the endothelium surface and pass the BBB. The mechanism is entirely dependent on the electrostatic interaction between positive and negative charges present on proteins and BBB endothelial cells, respectively.

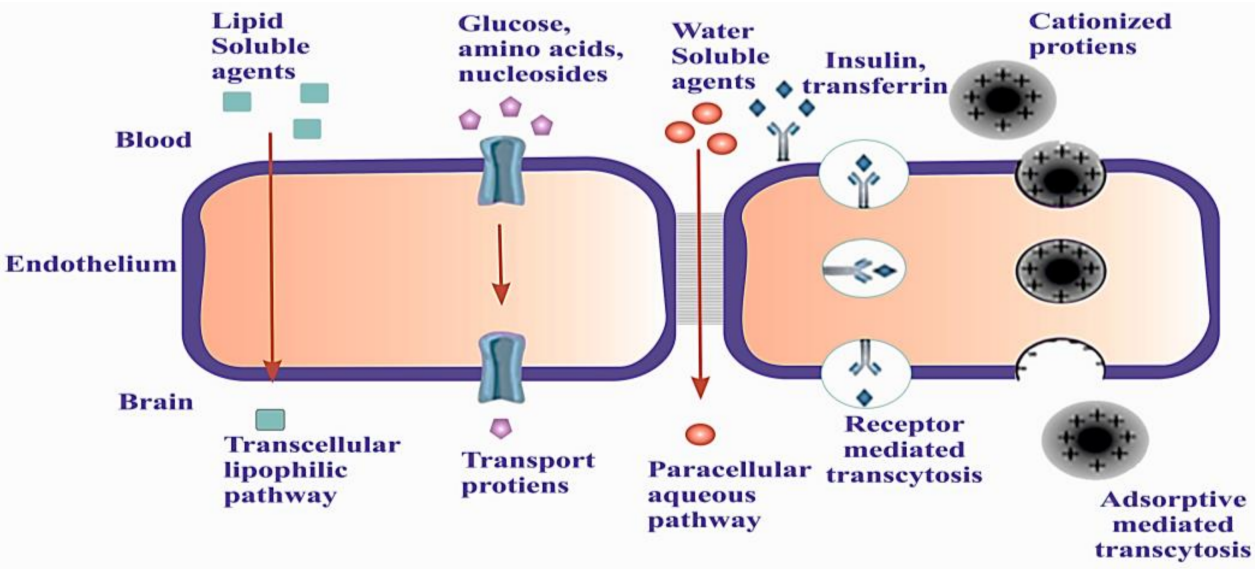

Figure 4. Schematic representation of the blood–brain barrier (BBB) and molecule transport mechanisms.

7. Nanomedicine for Parkinson's Disease

The application of nanomedicine has substantially improved the diagnostics methods and drug delivery, as well as the detection and treatment of several diseases. The drug is transported throughout the body when it is administered into the systemic circulation. This technique is unsuccessful in curing CNS-associated problems due to the limited ability of

the drug to circumvent the BBB, and it also has adverse effects in non-affected areas of the body [60]. Expeditious nanomedicine breakthroughs have enabled us to formulate optimal nanocarriers with appropriate drug loading and release dynamics. The biodegradable capability, lack of toxicity, sustained drug release, particle size lesser than 200 nm, drug encapsulation and release capabilities, and moieties that target the BBB are all essential for nanocarrier development [60]. Nanocarriers have well-maintained sizes, functionalized surfaces, and chemical properties in diverse environments. As a result, nanocarriers provide noninvasive methods to improve drug administration and localization, hence increasing therapeutic dissolution and preservation across the BBB [61]. Cancer, diabetes, lung disorders, inflammatory diseases, cardiovascular diseases, and neurodegenerative diseases all have wide applications in nanomedicine. Nanocarriers are also extensively used in imaging research [62].

Gold and iron oxide nanoparticles hold significant promise for advancing PD diagnosis and treatment. Gold nanoparticles (AuNPs) are known for properties like biocompatibility, antioxidant activities, and the ability to be functionalized for targeted drug delivery, which helps to protect dopaminergic neurons and reduce oxidative stress. They also enhance imaging techniques like MRI and CT, making them useful for early disease detection and follow-up [6]. Similarly, iron oxide nanoparticles (IONPs) are particularly valuable for their magnetic properties, which enhance MRI contrast, enabling better visualization of brain structures and PD progression. Additionally, IONPs can be functionalized for targeted drug delivery and have shown potential for reducing neuroinflammation. Both types of nanoparticles have been engineered to cross the blood–brain barrier effectively, thus providing a potential avenue for the direct administration of therapeutic agents into affected regions of the brain, therefore improving the overall PD prognosis and treatment outcome [7].

Several novel techniques have been proposed for target-site drug delivery in the brain using polysorbate-80 coated nanocarriers. After administration, nanocarriers aggregate in the CNS's blood capillaries. The adsorption and retention of nanocarriers on the capillary walls results in a concentration gradient. The nanocarriers diffuse through the endothelial cell layer as a result of this. Higher fluidization of the membrane is caused by the breakdown of endothelial cell layer fluids [58]. Until the discovery of drug-loaded nanocarriers administration, researchers had a difficult time inserting neurotherapeutics into the brain. Researchers are interested in this form of drug delivery because of its several advantages, including the crossing of the BBB, noninvasiveness, hepatic first-pass metabolism, ease of administration, safety, and practicality. Particle size, Zeta potential, and other surface features are some of the role-determining factors in the manufacturing of nanocarriers. For nanocarriers to establish static repulsion on surfaces and for nanocarriers and cells to interact in vivo, a minimum of 30 mV electric potential is required [63]. Nanocarriers administration through oral route must be biocompatible, cost-effective, scalable for fabrication, suited for the reticuloendothelial milieu, non-toxic, physically stable, demonstrate regulated drug release, and show little drug modification due to nanocarriers-excipient interaction. The nanocarriers must also be able to momentarily disrupt the epithelial layer of the mucosa's tight junctions, allowing the medication to pass freely or be bound with nanocarriers. The process of endocytosis or transcytosis can also be employed to transport nanocarriers across the endothelium. The encapsulated drug must be protected from degradation, and the P-glycoprotein-mediated efflux of medicines must be inhibited. Several pieces of evidence have shown that the drug can be delivered through the oral route to the brain. Oral-route administration of drugs to the brain uses lymphatic and cerebrospinal fluid routes [64].

All the discussed pathways may have a combined role in brain target-site drug delivery, where one pathway dominates another based on the therapeutic properties and formulation characteristics.

8. Nanotoxicity and Safety Concerns

Nanomedicine is a rapidly evolving field of study, and nanotechnology will undoubtedly play a significant role in the development of diagnostics and therapeutic interventions in the near future. However, much of the nanoparticle's potential toxicity is not known. Because of the growing attention to nanotechnology and the wide range of significant applications, more research into potential health hazards and nanotoxicity is required. Nanotechnology raises concerns regarding potential toxicity and negative effects, not only for patients but also for the environment [65]. According to the available evidence, the toxicity of nanomaterials is influenced by their shape, charge, size, and chemical properties. Certain nanocarriers appear to upregulate genes activated by oxidative stress. In some investigations, positively charged nanoparticles were found to be harmful to neurons and glia. Nanoparticles could disrupt monoamine neurotransmission by changing the shape of cortical neurons. Other nanoparticles, while promising in vitro, turned out to be hazardous in humans [66,67].

To overcome the nanotoxicity challenges, various colloidal carriers have been implemented, like solid lipid nanocarriers (SLN), liposomes, and dendrimers. Among all the colloidal carriers, SLN has become an important area of research on drug delivery because of its biocompatibility property.

9. Solid Lipid Nanocarriers as Drug Delivery System

Phospholipids act as important constituents for lipid-based nano-drug delivery systems due to their properties like biocompatibility, amphiphilic nature, and multifunctionality. Microsimulation, liposomes, and lipospheres carrier systems, on the other hand, have a number of limitations, including a complex production procedure, low degree entrapment efficiency (%), and problematic large-scale fabrication leading to the development of the SLN delivery system. SLNs are typically spherical in morphology, with a size ranging from 50 to 1000 nm [68]. Lipids, which are solid at 30 °C, emulsifiers, active pharmaceutical ingredients, and an appropriate solvent system are the elements required in SLN formulations (Figure 5).

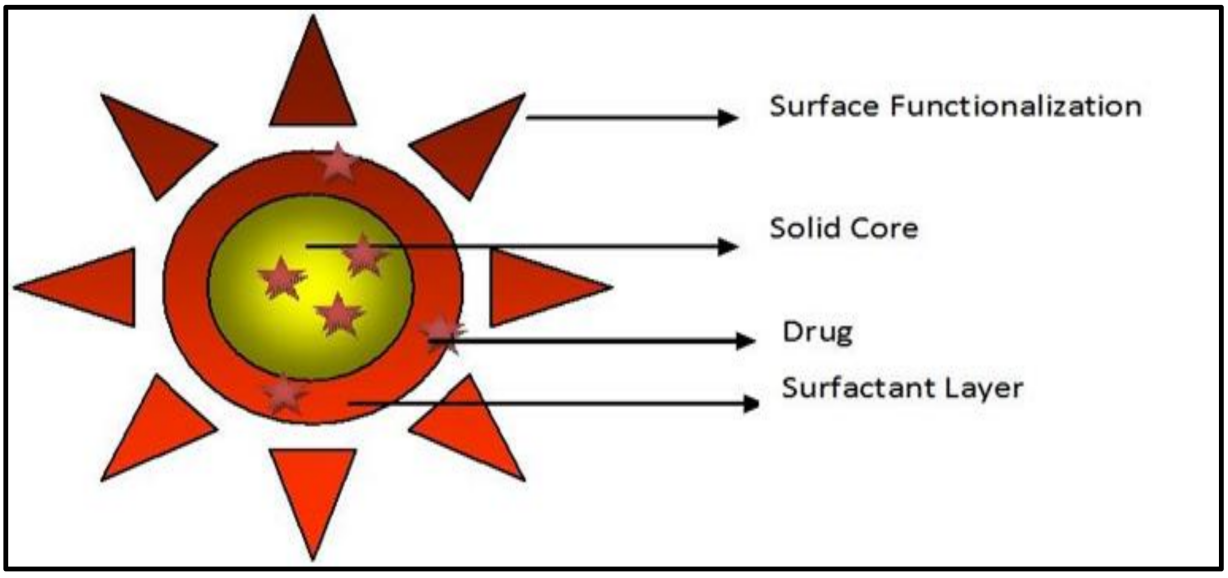

Figure 5. Diagrammatic representation of solid lipid nanocarriers.

The primary reasons for drug development failure are poor bioavailability and pharmacokinetic properties. As a result, the encapsulation of poorly aqueous soluble drugs, nucleic acid byproducts, and proteins in a nanocarrier form may protect them from degradation, providing high solubility and better access to several pathological compartments. The ability of drug-loaded nanocarriers to either pass biological barriers themselves or allow loaded pharmaceuticals to cross them to achieve optimal pharmacological action is critical to their

effectiveness. Nanocarriers may have to overcome various physiological barriers on their way to their target based on the route of administration. SLNs have better PK–PD properties and are also efficient in the biodistribution of therapeutic drugs due to their greater surface-area-to-volume ratio, which limits toxicity via preferential accumulation at the target site. They increase the solubility of hydrophobic substances, allowing them to be administered via parenteral or oral routes. They also improve the stability of a wide range of therapeutic agents due to their smaller size and increased barrier permeability. They can be employed to transport drugs to the central nervous system. The use of biodegradable polymers reduces the risk of hypersensitivity reactions while also allowing for high tissue compatibility. The recent advancement in SLNs for the treatment of PD are summarized in Table 3.

Table 3. Recent studies conducted on SLNs for the treatment of PD.

S. No	Drugs	Studies	Details
1.	Levodopa	In vivo activity of lipid nanocarriers (LN) containing a levodopa prodrug (LD-PD) with therapeutic potential in PD.	Physiologically stable with better entrapment efficiency [69] (Ravani et al., 2015).
2.	Bromocriptine	Bromocriptine encapsulated in nanostructured lipid carriers was evaluated in 6-hydroxydopamine hemilesioned rats, a model of PD.	Drug-loaded SLN was efficient in stabilizing plasma levels, increased target-site drug delivery, and improved half-life. In vivo studies demonstrated better antiparkinsonian properties compared to Bromocriptine alone [70] (Esposito et al., 2008).
3.	Rotigotine	In vitro study of Rotigotine-loaded Solid Lipid Nanoparticles (RTG-SLNs) to improve bioavailability via nose-to-brain delivery.	Nasal route target-site drug delivery was achieved in the form of aerosol formulations. Instant antiparkinsonian results were observed [71] (Prajapati et al., 2021).
4.	Apomorphine	The aim of this work was to investigate whether the oral bioavailability and brain regional distribution of apomorphine could be improved by utilizing solid lipid nanoparticles (SLNs) in a rat model of PD.	Orally administration of Apomorphine-loaded SLN to increase the bioavailability of the drug [72] (Tsai et al., 2011).
5.	Ropinirole	To develop, optimize, evaluate the pharmacokinetic and pharmacodynamic activity of RP-loaded solid lipid nanoparticles (RP-SLNs) and nanostructured lipid carriers (RP-NLCs) and containing hydrogel (RP-SLN-C and RP-NLC-C) formulations for improved oral and topical delivery.	Nasal route Ropinirole-loaded SLN brain-target-site delivery, efficiency in crossing the [73] (Dudhipala et al., 2020.)
6.	Naringenin	Neuroprotective activity of Naringenin–SLN was evaluated using the ROT-induced PD rodent model.	Oral-route brain-target-site delivery of Naringenin-loaded SLN [74] (Mani et al., 2021).
7.	Dopamine	To design and test the neurotherapeutic potential of nanoparticle-based technology composed of albumin/PLGA nanosystems loaded with dopamine (ALNP-DA) in a 6-OHDA PD mice model.	Oral-route brain-target-site delivery of Dopamine-loaded SLN [75] (Monge et al., 2021).

10. Recent Advances in Oral Nanomedicine for PD

Even though the bioavailability of the drug is dependent on its solubility and permeability through the GI tract, oral-route drug delivery is one of the most popular modes of drug administration because it provides a high level of patient compliance, is painless, and is noninvasive. The use of nanotechnology to improve stomach and intestinal drug adsorption, as well as systemic bioavailability, has been extensively researched [76,77]. For

instance, SLN-formulated apomorphine was found to be stable in the presence of gastric juices and pancreatic enzymes and prevented them from degrading; however, particle sizes increased and decreased. According to pharmacokinetic studies, one dose of apomorphine-loaded SLNs had a 25% absolute bioavailability, while an oral solution had just 2.1% absolute bioavailability. These optimized nanocarriers demonstrated stability over 20 days of storage and exhibited a high entrapment efficiency of 89%. This significant improvement highlights the potential of SLN-loaded apomorphine to enhance the effectiveness of PD treatment by overcoming the limitations of traditional oral administration.

Furthermore, in MPTP-treated rats, the oral drug-loaded SLN was able to target the rat's brain in a similar way as the conventional treatment method and, therefore, is considered to be an efficient therapeutic method [76]. Another PD pharmacological medication with limited oral bioavailability and a minimal half-life is selegiline. Selegiline nanospheres were developed by Al-Dhubiab and colleagues to simultaneously increase selegiline's oral bioavailability and therapeutic effect. The ionic gelatin approach was used to create chitosan nanocarriers with an average particle size of 290 nm and an entrapment efficiency of 18.9%, with a zeta potential of 29.17. In vitro drug release tests in a simulated gastrointestinal environment demonstrated a 100% pramipexole release within 5 h with a sustained release of around 49.7% within 60 min [78]. Another study showed that hollow mesoporous silica nanocarriers are effective at incorporating pramipexole. At the same time, the in vitro drug release investigations had shown a consistent pattern of drug release at both intestinal and stomach pH levels. Furthermore, HMS-pramipexole nanocarriers showed no hemolysis, and SH-SY5Y therapy provided a higher antioxidant protective effect than pramipexole alone [79].

HMS-pramipexole nanocarriers exhibit a typical particle size ranging from 420 to 570 nm, with a zeta potential of −38 mV. These nanocarriers demonstrated no toxicity up to concentrations of 42.24 nm and provided approximately 15–20% neuronal protection against hydrogen peroxide (H_2O_2) induced oxidative stress. This indicates their potential for safe and effective drug delivery in neuroprotective applications for Parkinson's disease. The development of gastro-retentive drug delivery systems is another technique for effective oral drug delivery. To improve levodopa's pharmacokinetic profile, Ngwuluka and co-authors decided to combine several mechanisms and nanoparticle encapsulation. Overall, the data showed consistent delivery (Table 4).

Table 4. Tabular representation of nanomedicines used for PD treatment.

Group	Drug	Nanocarriers	Synthesis	Animal Model	Effects	References
Dopamine precursor	L-DOPA	PEGb-P (l-DOPA (OAc)2) Nanocarriers	Hot homogenization	Sprague–Dawley rats	Target-site delivery was achieved, and improvement in Akinesia and catalepsy behavior in PD.	[80]
		Chitosan Nanocarriers	Cold technique	Albino mice	The nanocarriers, unlike L-DOPA alone, considerably improved the PD symptoms, reduced toXicity, and caused no dyskinesia. Increased antioxidant activities.	[81]
		SLN	Solvent diffusion method	Mice	The nanocarriers, unlike L-DOPA alone, considerably improved the PD symptoms, reduced toXicity, and caused no dyskinesia.	[82]

Table 4. *Cont.*

Group	Drug	Nanocarriers	Synthesis	Animal Model	Effects	References
Dopamine agonist	Ropinirole	Poly (lactic-co-glycolic acid) Nanocarriers	High-pressure homogenization	Wistar rats	High therapeutic efficiency at lower doses when compared to doses of ropinirole at higher concentrations. Target-site delivery was achieved, and improvement in motor activity was observed.	[83]
	Bromocriptine	SLN	Emulsification	Sprague–Dawley rats	Improved pharmacokinetic parameters and prolonged drug action when compared to bromocriptine singly.	[70]
	Pramipexole	Nanoparticulate Lipid dispersion	Dialysis technique	Mice albino mi	Target-site delivery was achieved, and improvement in Akinesia and catalepsy behavior in PD.	[84]
MAO-B inhibitor	Apomorphine	Chitosan Nanocarriers	Cold technique	Sprague–Dawley rats	Improved motor functions and increased antioxidant level. Bioavailability was increased to several folds, and target-site delivery was achieved.	[72]
	Selegiline	SLN	Emulsification Dawley rats	Wistar rats	Increase in selegiline-loaded SLN concentration in plasma and plasma compared to selegiline administered alone.	[78]

11. Conclusions

In this review, we explored the challenges and recent advancements in using nanomedicine for PD management, focusing on novel pharmacological strategies. Nanotechnology has shown significant promise in sustaining drug concentration, therefore enhancing their half-life, therapeutic effects, and bioavailability of PD treatments. Numerous studies have highlighted the potential of drug-loaded nanocarriers to mitigate L-DOPA-induced dyskinesia more effectively than conventional medications. The nanocarriers ensure targeted and sustained drug delivery with minimal side effects. Despite these advancements, the safety of nanoparticles is still an important issue. Extensive research on the long-term biocompatibility, as well as the possible toxicity of nanocarriers, is essential to ensure these novel therapies do not pose new risks to patients. Though nanomedicine offers substantial potential to revolutionize by improving drug delivery systems and minimizing adverse effects, there is a need for further research on the safety aspects related to nanoparticles. Continued progress in this field might provide more effective and safer treatment alternatives for people affected by PD.

Author Contributions: Conceptualization, D.P.K.; N.D., R.J.M., D.P.K., writing—original draft preparation; N.D., R.J.M., writing—review and editing; D.P.K., supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by University Grant Commision: [Grant Number 324892].

Institutional Review Board Statement: This work does not require any ethical clearances.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors acknowledge Amity University Noida for providing the infrastructure and facilities for the successful completion of this work.

Conflicts of Interest: The authors have no conflicts of interest to report.

References

1. Blesa, J.; Trigo-Damas, I.; Quiroga-Varela, A.; Jackson-Lewis, V.R. Oxidative stress and Parkinson's disease. *Front. Neuroanat.* **2021**, *9*, 91. [CrossRef] [PubMed]
2. De Carolis, L.; Galli, S.; Bianchini, E.; Rinaldi, D.; Raju, M.; Caliò, B.; Alborghetti, M.; Pontieri, F.E. Age at Onset Influences Progression of Motor and Non-Motor Symptoms during the Early Stage of Parkinson's Disease: A Monocentric Retrospective Study. *Brain Sci.* **2023**, *13*, 157. [CrossRef] [PubMed]
3. Larkov, A.; Barreto, G.E.; Grizzell, J.A.; Echeverria, V. Strategies for the treatment of Parkinson's disease: Beyond dopamine. *Front. Aging Neurosci.* **2020**, *12*, 4.
4. Parkinsons Foundation USA. 2021. Available online: https://www.parkinson.org/sites/default/files/documents/Parkinsons_Foundation_2021_Annual_Report.pdf (accessed on 24 April 2024).
5. González-Usigli, H.A.; Ortiz, G.G.; Charles-Niño, C.; Mireles-Ramírez, M.A.; Pacheco-Moisés, F.P.; Torres-Mendoza, B.M.; Hernández-Cruz, J.D.; Delgado-Lara, D.L.; Ramírez-Jirano, L.J. Neurocognitive psychiatric and neuropsychological alterations in Parkinson's disease: A basic and clinical approach. *Brain Sci.* **2023**, *13*, 508. [CrossRef] [PubMed]
6. Chiang, M.C.; Yang, Y.P.; Nicol, C.J.; Wang, C.J. Gold Nanoparticles in Neurological Diseases: A Review of Neuroprotection. *Int. J. Mol. Sci.* **2024**, *25*, 2360. [CrossRef] [PubMed]
7. Qiao, R.; Fu, C.; Forgham, H.; Javed, I.; Huang, X.; Zhu, J.; Whittaker, A.K.; Davis, T.P. Magnetic iron oxide nanoparticles for brain imaging and drug delivery. *Adv. Drug Deliv. Rev.* **2023**, *197*, 114822. [CrossRef]
8. Gómez-Benito, M.; Granado, N.; García-Sanz, P.; Michel, A.; Dumoulin, M.; Moratalla, R. Modeling Parkinson's disease with the alpha-synuclein protein. *Front. Pharmacol.* **2020**, *11*, 356. [CrossRef]
9. Esteves, A.R.; Silva, D.F.; Santos, D.; Candeias, E.; Filipe, F.; Cardoso, S.M. Mitochondria at the base of neuronal innate immunity in Alzheimer's and Parkinson's diseases. *Mitochondrial Dis.* **2018**, *137*. [CrossRef]
10. Jeon, Y.M.; Kwon, Y.; Jo, M.; Lee, S.; Kim, S.; Kim, H.J. The Role of Glial Mitochondria in α-Synuclein Toxicity. *Front. Cell Dev. Biol.* **2020**, *8*, 1297. [CrossRef] [PubMed]
11. Marchetti, B. Nrf2/Wnt resilience orchestrates rejuvenation of glia-neuron dialogue in Parkinson's disease. *Redox Biol.* **2020**, *36*, 101664. [CrossRef]
12. O'Hara, D.M.; Pawar, G.; Kalia, S.K.; Kalia, L.V. LRRK2 and α-Synuclein: Distinct or Synergistic Players in Parkinson's Disease? *Front. Neurosci.* **2020**, *14*, 577. [CrossRef]
13. Meade, R.M.; Fairlie, D.P.; Mason, J.M. Alpha-synuclein structure and Parkinson's disease–lessons and emerging principles. *Mol. Neurodegener.* **2019**, *14*, 29. [CrossRef] [PubMed]
14. Stoker, T.B.; Barker, R.A. Recent developments in the treatment of Parkinson's Disease. *F1000Research* **2020**, *9*. [CrossRef] [PubMed]
15. Sveinbjornsdottir, S. The clinical symptoms of Parkinson's disease. *J. Neurochem.* **2016**, *139*, 318–324. [CrossRef] [PubMed]
16. Koeglsperger, T.; Palleis, C.; Hell, F.; Mehrkens, J.H.; Bötzel, K. Deep brain stimulation programming for movement disorders: Current concepts and evidence-based strategies. *Front. Neurol.* **2019**, *10*, 410. [CrossRef] [PubMed]
17. Pourahmad, R.; Saleki, K.; Esmaili, M.; Abdollahi, A.; Alijanizadeh, P.; Gholinejad, M.Z.; Banazadeh, M.; Ahmadi, M. Deep brain stimulation (DBS) as a therapeutic approach in gait disorders: What does it bring to the table? *IBRO Neurosci. Rep.* **2023**, *14*, 507–513. [CrossRef] [PubMed]
18. Lee, D.J.; Dallapiazza, R.F.; De Vloo, P.; Lozano, A.M. Current surgical treatments for Parkinson's disease and potential therapeutic targets. *Neural Regen. Res.* **2018**, *13*, 1342. [CrossRef]
19. Demiryürek, B.E.; Barut, B.Ö. Surgical Treatment Methods in Movement Disorders: Mechanisms of Action and Indications. *Bezmialem Sci.* **2017**, *5*, 126–134. [CrossRef]
20. Lozano, C.S.; Tam, J.; Lozano, A.M. The changing landscape of surgery for Parkinson's Disease. *Mov. Disord.* **2018**, *33*, 36–47. [CrossRef] [PubMed]
21. Liu, J.; Xu, F.; Nie, Z.; Shao, L. Gut Microbiota Approach—A New Strategy to Treat Parkinson's Disease. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 570658. [CrossRef] [PubMed]
22. Angelopoulou, E.; Stanitsa, E.; Karpodini, C.C.; Bougea, A.; Kontaxopoulou, D.; Fragkiadaki, S.; Koros, C.; Georgakopoulou, V.E.; Fotakopoulos, G.; Koutedakis, Y.; et al. Pharmacological and Non-Pharmacological Treatments for Depression in Parkinson's Disease: An Updated Review. *Medicina* **2023**, *59*, 1454. [CrossRef]
23. Radder, D.L.; Sturkenboom, I.H.; van Nimwegen, M.; Keus, S.H.; Bloem, B.R.; de Vries, N.M. Physical therapy and occupational therapy in Parkinson's disease. *Int. J. Neurosci.* **2017**, *127*, 930–943. [CrossRef] [PubMed]
24. Connolly, B.S.; Lang, A.E. Pharmacological treatment of Parkinson disease: A review. *JAMA* **2014**, *311*, 1670–1683. [CrossRef] [PubMed]
25. Chaudhuri, K.R.; Titova, N. Societal burden and persisting unmet needs of Parkinson's disease. *Eur. Neurol. Rev.* **2019**, *14*, 28–35. [CrossRef]
26. Maiti, P.; Manna, J.; Dunbar, G.L. Current understanding of the molecular mechanisms in Parkinson's disease: Targets for potential treatments. *Transl. Neurodegener.* **2017**, *6*, 28. [CrossRef] [PubMed]
27. Halkias, I.A.; Haq, I.; Huang, Z.; Fernandez, H.H. When should levodopa therapy be initiated in patients with Parkinson's disease? *Drugs Aging* **2007**, *24*, 261–273.

28. Mordeniz, C. *Introductory Chapter: Traditional and Complementary Medicine. InTraditional and Complementary Medicine*; IntechOpen: London, UK, 2019.
29. Chaachouay, N.; Zidane, L. Plant-Derived Natural Products: A Source for Drug Discovery and Development. *Drugs Drug Candidates* **2024**, *3*, 184–207. [CrossRef]
30. Khatri, D.K.; Juvekar, A.R. Propensity of Hyoscyamus niger seeds methanolic extract to allay stereotaxically rotenone-induced Parkinson's disease symptoms in rats. *Orient. Pharm. Exp. Med.* **2015**, *15*, 327–339. [CrossRef]
31. Ebadollahi, S.; Babaei, F.; Zare, S.; Ebadollahi, M. Evaluation of antioxidant properties of hydroalcoholic extract of purslane (Portulaca oleracea) and Its protective effect on 6-hydroxydopamine induced hepatic damage in parkinsonian male rats. *Qom Univ. Med. Sci. J.* **2018**, *12*, 15–25. [CrossRef]
32. Rabiei, Z.; Solati, K.; Amini-Khoei, H. Phytotherapy in treatment of Parkinson's disease: A review. *Pharm. Biol.* **2019**, *57*, 355–362. [CrossRef] [PubMed]
33. Yang, X.; Li, Y.; Chen, L.; Xu, M.; Wu, J.; Zhang, P.; Nel, D.; Sun, B. Protective effect of hydroxysafflor yellow A on dopaminergic neurons against 6-hydroxydopamine, activating anti-apoptotic and anti-neuroinflammatory pathways. *Pharm. Biol.* **2020**, *58*, 686–694. [CrossRef]
34. Birla, H.; Keswani, C.; Singh, S.S.; Zahra, W.; Dilnashin, H.; Rathore, A.S.; Singh, R.; Rajput, M.; Keshri, P.; Singh, S.P. Unraveling the Neuroprotective Effect of Tinospora cordifolia in a Parkinsonian Mouse Model through the Proteomics Approach. *ACS Chem. Neurosci.* **2021**, *12*, 4319–4335. [CrossRef] [PubMed]
35. Khazdair, M.R.; Kianmehr, M.; Anaeigoudari, A. Effects of medicinal plants and flavonoids on Parkinson's disease: A review on basic and clinical evidences. *Adv. Pharm. Bull.* **2021**, *11*, 224. [CrossRef] [PubMed]
36. Singh, B.; Pandey, S.; Rumman, M.; Kumar, S.; Kushwaha, P.P.; Verma, R.; Mahdi, A.A. Neuroprotective and neurorescue mode of action of *Bacopa monnieri* (L.) Wettst in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced Parkinson's disease: An in silico and in vivo study. *Front. Pharmacol.* **2021**, *12*, 169. [CrossRef] [PubMed]
37. Zhen, C.; Li, D.; Wang, H.; Wang, P.; Zhang, W.; Yu, J.; Yu, X.; Wang, X. Tea consumption and risk of Parkinson's disease: A meta-analysis. *Neurol. Asia* **2019**, *24*, 31–40.
38. Beppe, G.J.; Dongmo, A.B.; Foyet, H.S.; Dimo, T.; Mihasan, M.; Hritcu, L. The aqueous extract of Albizia adianthifolia leaves attenuates 6-hydroxydopamine-induced anxiety, depression and oxidative stress in rat amygdala. *BMC Complement. Altern. Med.* **2015**, *15*, 374. [CrossRef] [PubMed]
39. Puspita, L.; Chung, S.Y.; Shim, J.W. Oxidative stress and cellular pathologies in Parkinson's disease. *Mol. Brain* **2017**, *10*, 53. [CrossRef] [PubMed]
40. Gu, J.; Guo, M.; Huang, C.; Wang, X.; Zhu, Y.; Wang, L.; Wang, Z.; Zhou, L.; Fan, D.; Shi, L.; et al. Titanium dioxide nanoparticle affects motor behavior, neurodevelopment and axonal growth in zebrafish (*Danio rerio*) larvae. *Sci. Total Environ.* **2021**, *754*, 142315. [CrossRef] [PubMed]
41. Wang, T.; Li, C.; Han, B.; Wang, Z.; Meng, X.; Zhang, L.; He, J.; Fu, F. Neuroprotective effects of Danshensu on rotenone-induced Parkinson's disease models in vitro and in vivo. *BMC Complement. Med. Ther.* **2020**, *20*, 20. [CrossRef] [PubMed]
42. Tancheva, L.P.; Lazarova, M.I.; Alexandrova, A.V.; Dragomanova, S.T.; Nicoletti, F.; Tzvetanova, E.R.; Hodzhev, Y.K.; Kalfin, R.E.; Miteva, S.A.; Mazzon, E.; et al. Neuroprotective mechanisms of three natural antioxidants on a rat model of parkinson's disease: A comparative study. *Antioxidants* **2020**, *9*, 49. [CrossRef] [PubMed]
43. Ahmad, S.; Khan, M.B.; Hoda, M.N.; Bhatia, K.; Haque, R.; Fazili, I.S.; Jamal, A.; Khan, J.S.; Katare, D.P. Neuroprotective effect of e seed oil in 6-hydroxydopamine induced neurotoxicity in mice model: Cellular, biochemical and neurochemical evidence. *Neurochem. Res.* **2012**, *37*, 516–526. [CrossRef] [PubMed]
44. Zhang, Z.N.; Zhang, J.S.; Xiang, J.; Yu, Z.H.; Zhang, W.; Cai, M.; Li, X.T.; Wu, T.; Li, W.W.; Cai, D.F. Subcutaneous rotenone rat model of Parkinson's disease: Dose exploration study. *Brain Res.* **2017**, *1655*, 104–113. [CrossRef] [PubMed]
45. Sim, Y.; Park, G.; Eo, H.; Huh, E.; Gu, P.S.; Hong, S.P.; Pak, Y.K.; Oh, M.S. Protective effects of a herbal extract combination of Bupleurum falcatum, Paeonia suffruticosa, and Angelica dahurica against MPTP-induced neurotoxicity via regulation of nuclear receptor-related 1 protein. *Neuroscience* **2017**, *340*, 166–175. [CrossRef] [PubMed]
46. Johnson, S.L.; Park, H.Y.; DaSilva, N.A.; Vattem, D.A.; Ma, H.; Seeram, N.P. Levodopa-reduced Mucuna pruriens seed extract shows neuroprotective effects against Parkinson's disease in murine microglia and human neuroblastoma cells, Caenorhabditis elegans, and Drosophila melanogaster. *Nutrients* **2018**, *10*, 1139. [CrossRef] [PubMed]
47. Hritcu, L.; Foyet, H.S.; Stefan, M.; Mihasan, M.; Asongalem, A.E.; Kamtchouing, P. Neuroprotective effect of the methanolic extract of Hibiscus asper leaves in 6-hydroxydopamine-lesioned rat model of Parkinson's disease. *J. Ethnopharmacol.* **2011**, *137*, 585–591. [CrossRef]
48. Park, H.J.; Zhao, T.T.; Kim, S.H.; Lee, C.K.; Hwang, B.Y.; Lee, K.E.; Lee, M.K. Ethanol extract from Gynostemma pentaphyllum ameliorates dopaminergic neuronal cell death in transgenic mice expressing mutant A53T human alpha-synuclein. *Neural Regen. Res.* **2020**, *15*, 361. [PubMed]
49. Yu, D.; Zhang, P.; Li, J.; Liu, T.; Zhang, Y.; Wang, Q.; Zhang, J.; Lu, X.; Fan, X. Neuroprotective effects of Ginkgo biloba dropping pills in Parkinson's disease. *J. Pharm. Anal.* **2021**, *11*, 220–231. [CrossRef]
50. Ahmad, M.; Yousuf, S.; Khan, M.B.; Ahmad, A.S.; Saleem, S.; Hoda, M.N.; Islam, F. Protective effects of ethanolic extract of Delphinium denudatum in a rat model of Parkinson's disease. *Hum. Exp. Toxicol.* **2006**, *25*, 361–368. [CrossRef] [PubMed]

51. Rezaei, M.; Alirezaei, M. Protective effects of *Althaea officinalis* L. extract in 6-hydroxydopamine-induced hemi-Parkinsonism model: Behavioral, biochemical and histochemical evidence. *J. Physiol. Sci.* **2014**, *64*, 171–176. [CrossRef] [PubMed]
52. Amaral de Brito, A.P.; Galvão de Melo, I.M.; El-Bachá, R.S.; Guedes, R.C. Valeriana officinalis counteracts rotenone effects on spreading depression in the rat brain in vivo and protects against rotenone cytotoxicity toward rat glioma C6 cells in vitro. *Front. Neurosci.* **2020**, *14*, 759. [CrossRef] [PubMed]
53. Huang, X.; Li, N.; Pu, Y.; Zhang, T.; Wang, B. Neuroprotective effects of ginseng phytochemicals: Recent perspectives. *Molecules* **2019**, *24*, 2939. [CrossRef] [PubMed]
54. Lei, H.; Ren, R.; Sun, Y.; Zhang, K.; Zhao, X.; Ablat, N.; Pu, X. Neuroprotective effects of safflower flavonoid extract in 6-Hydroxydopamine-induced model of Parkinson's disease may be related to its anti-inflammatory action. *Molecules* **2020**, *25*, 5206. [CrossRef]
55. Oliveira, A.I.; Pinho, C.; Sarmento, B.; Dias, A.C. Neuroprotective activity of Hypericum perforatum and its major components. *Front. Plant Sci.* **2016**, *7*, 1004. [CrossRef] [PubMed]
56. Aruna, K.; Rajeswari, P.D.; Sankar, S.R. The effect of Oxalis corniculata extract against the behavioral changes induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in mice. *J. Appl. Pharm. Sci.* **2017**, *7*, 148–153.
57. Bellettato, C.M.; Scarpa, M. Possible strategies to cross the blood–brain barrier. *Ital. J. Pediatr.* **2018**, *44*, 127–133. [CrossRef] [PubMed]
58. Ahlawat, J.; Guillama Barroso, G.; Masoudi Asil, S.; Alvarado, M.; Armendariz, I.; Bernal, J.; Carabaza, X.; Chavez, S.; Cruz, P.; Escalante, V.; et al. Nanocarriers as potential drug delivery candidates for overcoming the blood–brain barrier: Challenges and possibilities. *ACS Omega* **2020**, *5*, 12583–12595. [CrossRef] [PubMed]
59. Pulgar, V.M. Transcytosis to cross the blood brain barrier, new advancements and challenges. *Front. Neurosci.* **2019**, *12*, 1019. [CrossRef] [PubMed]
60. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.; del Pilar Rodriguez-Torres, M.; Acosta-Torres, L.S.; Diaz-Torres, L.A.; Grillo, R.; Swamy, M.K.; Sharma, S.; et al. Nano based drug delivery systems: Recent developments and future prospects. *J. Nanobiotechnol.* **2018**, *16*, 71. [CrossRef] [PubMed]
61. Yusuf, A.; Almotairy, A.R.; Henidi, H.; Alshehri, O.Y.; Aldughaim, M.S. Nanoparticles as Drug Delivery Systems: A Review of the implication of nanoparticles' physicochemical properties on responses in biological systems. *Polymers* **2023**, *15*, 1596. [CrossRef] [PubMed]
62. Baig, B.; Halim, S.A.; Farrukh, A.; Greish, Y.; Amin, A. Current status of nanomaterial-based treatment for hepatocellular carcinoma. *Biomed. Pharmacother.* **2019**, *116*, 108852. [CrossRef] [PubMed]
63. Zorkina, Y.; Abramova, O.; Ushakova, V.; Morozova, A.; Zubkov, E.; Valikhov, M.; Melnikov, P.; Majouga, A.; Chekhonin, V. Nano carrier drug delivery systems for the treatment of neuropsychiatric disorders: Advantages and limitations. *Molecules* **2020**, *25*, 5294. [CrossRef] [PubMed]
64. Zeb, A.; Rana, I.; Choi, H.I.; Lee, C.H.; Baek, S.W.; Lim, C.W.; Khan, N.; Arif, S.T.; Alvi, A.M.; Shah, F.A.; et al. Potential and applications of nanocarriers for efficient delivery of biopharmaceuticals. *Pharmaceutics* **2020**, *12*, 1184. [CrossRef] [PubMed]
65. Joseph, T.M.; Kar Mahapatra, D.; Esmaeili, A.; Piszczyk, Ł.; Hasanin, M.S.; Kattali, M.; Haponiuk, J.; Thomas, S. Nanoparticles: Taking a unique position in medicine. *Nanomaterials* **2023**, *13*, 574. [CrossRef] [PubMed]
66. Soares, S.; Sousa, J.; Pais, A.; Vitorino, C. Nanomedicine: Principles, properties, and regulatory issues. *Front. Chem.* **2018**, *6*, 360. [CrossRef] [PubMed]
67. Dash, D.K.; Panik, R.K.; Sahu, A.K.; Tripathi, V. Role of Nanobiotechnology in Drug Discovery, Development and Molecular Diagnostic. In *Applications of Nanobiotechnology*; IntechOpen: London, UK, 2020.
68. Marinelli, L.; Dimmito, M.P.; Cacciatore, I.; Toto, E.C.; Di Rienzo, A.; Palmerio, F.; Puca, V.; Di Filippo, E.S.; Fulle, S.; Di Stefano, A. Solid lipid nanoparticles for efficient delivery of capsaicin-rich extract: Potential neuroprotective effects in Parkinson's disease. *J. Drug Deliv. Sci. Technol.* **2024**, *91*, 105097. [CrossRef]
69. Ravani, L.; Sarpietro, M.G.; Esposito, E.; Di Stefano, A.; Sozio, P.; Calcagno, M.; Drechsler, M.; Contado, C.; Longo, F.; Giuffrida, M.C.; et al. Lipid nanocarriers containing a levodopa prodrug with potential antiparkinsonian activity. *Mater. Sci. Eng. C* **2015**, *48*, 294–300. [CrossRef] [PubMed]
70. Esposito, E.; Fantin, M.; Marti, M.; Drechsler, M.; Paccamiccio, L.; Mariani, P.; Sivieri, E.; Lain, F.; Menegatti, E.; Morari, M.; et al. Solid lipid nanoparticles as delivery systems for bromocriptine. *Pharm. Res.* **2011**, *25*, 1521–1530. [CrossRef] [PubMed]
71. Prajapati, J.B.; Patel, G.C. Nose to brain delivery of Rotigotine loaded solid lipid nanoparticles: Quality by design based optimization and characterization. *J. Drug Deliv. Sci. Technol.* **2021**, *63*, 102377. [CrossRef]
72. Tsai, M.J.; Huang, Y.B.; Wu, P.C.; Fu, Y.S.; Kao, Y.R.; Fang, J.Y.; Tsai, Y.H. Oral apomorphine delivery from solid lipid nanoparticles with different monostearate emulsifiers: Pharmacokinetic and behavioral evaluations. *J. Pharm. Sci.* **2011**, *100*, 547–557. [CrossRef] [PubMed]
73. Dudhipala, N.; Gorre, T. Neuroprotective effect of ropinirole lipid nanoparticles enriched hydrogel for parkinson's disease: In vitro, ex vivo, pharmacokinetic and pharmacodynamic evaluation. *Pharmaceutics* **2020**, *12*, 448. [CrossRef] [PubMed]
74. Mani, M.; Balasubramanian, S.; Manikandan, K.R.; Kulandaivel, B. Neuroprotective potential of Naringenin-loaded solid-lipid nanoparticles against rotenone-induced Parkinson's disease model. *J. Appl. Pharm. Sci.* **2021**, *11*, 019–028.

75. Monge-Fuentes, V.; Biolchi Mayer, A.; Lima, M.R.; Geraldes, L.R.; Zanotto, L.N.; Moreira, K.G.; Martins, O.P.; Piva, H.L.; Felipe, M.S.; Amaral, A.C.; et al. Dopamine-loaded nanoparticle systems circumvent the blood–brain barrier restoring motor function in mouse model for Parkinson's Disease. *Sci. Rep.* **2021**, *11*, 15185. [CrossRef] [PubMed]
76. Homayun, B.; Lin, X.; Choi, H.J. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics* **2019**, *11*, 129. [CrossRef]
77. Alshawwa, S.Z.; Kassem, A.A.; Farid, R.M.; Mostafa, S.K.; Labib, G.S. Nanocarrier drug delivery systems: Characterization, limitations, future perspectives and implementation of artificial intelligence. *Pharmaceutics* **2022**, *14*, 883. [CrossRef]
78. Mishra, N.; Sharma, S.; Deshmukh, R.; Kumar, A.; Sharma, R. Development and characterization of nasal delivery of selegiline hydrochloride loaded nanolipid carriers for the management of Parkinson's disease. *Cent. Nerv. Syst. Agents Med. Chem.* **2019**, *19*, 46–56. [CrossRef] [PubMed]
79. Tzankov, B.; Voycheva, C.; Yordanov, Y.; Aluani, D.; Spassova, I.; Kovacheva, D.; Lambov, N.; Tzankova, V. Development and in vitro safety evaluation of pramipexole-loaded hollow mesoporous silica (HMS) particles. *Biotechnol. Biotechnol. Equip.* **2019**, *33*, 1204–1215. [CrossRef]
80. De Giglio, E.; Trapani, A.; Cafagna, D.; Sabbatini, L.; Cometa, S. Dopamine-loaded chitosan nanoparticles: Formulation and analytical characterization. *Anal. Bioanal. Chem.* **2017**, *400*, 1997–2002. [CrossRef] [PubMed]
81. Cunha, A.; Gaubert, A.; Latxague, L.; Dehay, B. PLGA-Based nanoparticles for neuroprotective drug delivery in neurodegenerative diseases. *Pharmaceutics* **2021**, *13*, 1042. [CrossRef] [PubMed]
82. Cacciatore, I.; Ciulla, M.; Fornasari, E.; Marinelli, L.; Di Stefano, A. Solid lipid nanoparticles as a drug delivery system for the treatment of neurodegenerative diseases. *Expert Opin. Drug Deliv.* **2016**, *13*, 1121–1131. [CrossRef] [PubMed]
83. Liang, J.; Liu, Y.; Liu, J.; Li, Z.; Fan, Q.; Jiang, Z.; Yan, F.; Wang, Z.; Huang, P.; Feng, N. Chitosan-functionalized lipid-polymer hybrid nanoparticles for oral delivery of silymarin and enhanced lipid-lowering effect in NAFLD. *J. Nanobiotechnology* **2018**, *16*, 64. [CrossRef] [PubMed]
84. Gunay, M.S.; Ozer, A.Y.; Erdogan, S.; Bodard, S.; Baysal, I.; Gulhan, Z.; Guilloteau, D.; Chalon, S. Development of nanosized, pramipexole-encapsulated liposomes and niosomes for the treatment of Parkinson's disease. *J. Nanosci. Nanotechnol.* **2017**, *17*, 5155–5167. [CrossRef]