

Brain-Targeted Nanocarriers Of Resveratrol For The Treatment Of Parkinson's Disease: A Comprehensive Review

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Abstract:

Background: Parkinson's disease is a progressive neurodegenerative condition marked by the loss of dopaminergic neurons along with the emergence of both motor and non-motor symptoms. Natural polyphenols, like resveratrol, have shown considerable neuroprotective effects due to their antioxidant and anti-inflammatory qualities. Nevertheless, the clinical use of resveratrol is hindered by its poor solubility, rapid metabolism, and low bioavailability. The purpose of this review is to highlight recent developments in brain-targeted nanocarrier systems aimed at enhancing the delivery and therapeutic effectiveness of resveratrol for treating Parkinson's disease. A thorough search of the literature was performed using electronic databases, such as PubMed, Scopus, ScienceDirect, and Google Scholar, focusing on studies published between 2018 and 2026. Keywords associated with resveratrol, nanocarriers, targeting the brain, and Parkinson's disease were utilized. After applying specific inclusion and exclusion criteria, around 40 pertinent studies were selected for analysis. Findings: Different nanocarrier systems, such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions, have been explored to improve the delivery of resveratrol to the brain. These systems enhance drug stability, increase bioavailability, aid in crossing the blood-brain barrier, and support targeted delivery to neurons. Numerous experimental studies have shown that nano-formulated resveratrol exhibits greater neuroprotective effects compared to free resveratrol. In conclusion, drug delivery systems based on nanocarriers are a promising way to get around the pharmacokinetic problems with resveratrol and make treatment for Parkinson's disease more effective. Subsequent research concentrating on clinical assessment and sophisticated targeting methodologies may augment the efficacy of nano-resveratrol formulations in the management of neurodegenerative diseases.

Keywords: Resveratrol, Nanocarriers, Brain targeting, Parkinson's disease, Neuroprotection, Nanomedicine

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1. Introduction

Bradykinesia, postural instability, tremor, and muscular rigidity are the main motor symptoms of Parkinson's disease (PD), a progressive neurological disorder (1,2). Degeneration of dopaminergic neurons in the brain's substantia nigra, which lowers dopamine levels in the striatum, is the main cause of this disorder (3). Currently, the second most prevalent neurodegenerative condition after Alzheimer's disease, Parkinson's disease is an important global health problem (1,4).

The prevalence of Parkinson's disease has dramatically increased globally in recent decades due to population aging and advancements in diagnostic methods (4,5). According to epidemiological research, Parkinson's disease affects about 10 million individuals worldwide, with incidence rates significantly rising beyond the age of 60 (5). Patients' quality of life is greatly impacted by the disease's non-motor symptoms, which include cognitive impairment, mental illnesses, sleep abnormalities, and autonomic dysfunction (6).

Parkinson's disease symptoms are currently managed using a number of pharmaceutical treatments, such as levodopa, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors. However, rather than altering the course of the disease, these therapies mostly relieve symptoms (2). The need for innovative therapeutic strategies that can offer neuroprotection and reduce the progression of disease is highlighted by the fact that long-term use of traditional medications is usually linked to side effects including dyskinesia and motor fluctuations (2,3).

Resveratrol, a naturally occurring polyphenolic molecule found in grapes, berries, and peanuts, has drawn a lot of attention as a potential medicinal agent due to its strong anti-inflammatory, neuroprotective, and antioxidant qualities (7). Resveratrol is a viable treatment option for neurodegenerative diseases like Parkinson's disease since it has been demonstrated to lower oxidative stress, inhibit neuroinflammation, and shield dopaminergic neurons (7,8).

Resveratrol's poor aqueous solubility, quick metabolism, low bioavailability, and restricted blood-brain barrier (BBB) penetration limit its clinical use despite its encouraging therapeutic potential (8). These restrictions limit the drug's therapeutic efficacy by drastically lowering the concentration of the medication that reaches the brain. The creation of brain-targeted nanocarrier systems that may improve delivery of medication to the central nervous system has been made possible by recent advances in nanotechnology. Drug stability, bioavailability, and blood-brain barrier trafficking have all been shown to be improved by nanocarriers like liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions (8).

As outcome, utilizing brain-targeted nanocarriers to carry resveratrol has emerged as a viable approach to enhancing Parkinson's treatment outcomes. This review aims to summarize recent advances in nanocarrier-based delivery systems for resveratrol, highlighting their potential to enhance brain targeting, improve drug bioavailability, and provide neuroprotective effects in Parkinson's disease.

Resveratrol



Limitations

- Poor solubility
- Low bioavailability
- Rapid metabolism



Nanocarrier Formulations

- Liposomes
- Polymeric nanoparticles
- Solid lipid nanoparticles
- Nanoemulsions



Improved Drug Properties

- Increased stability
- Sustained drug release
- Enhanced bioavailability



Brain Targeting

- Blood-brain barrier penetration
- Targeted neuronal delivery



Therapeutic Effects

- Reduced oxidative stress
- Anti-inflammatory effects
- Neuroprotection



Management of Parkinson's Disease

Figure 1. Conceptual framework illustrating nanocarrier-mediated delivery of resveratrol for Parkinson's disease treatment.

2. Epidemiology of Parkinson's Disease

Parkinson's disease is one of the most prevalent neurodegenerative diseases affecting the senior population globally (4,9). The prevalence of the illness rises with age, and it mainly affects people over 60 (4,9). According to epidemiological research,

1% to 2% of those over 60 worldwide suffer with Parkinson's disease (9). The global burden of Parkinson's disease is predicted to increase significantly in the upcoming decades due to aging populations and rising life expectancy (5,9).

According to recent estimates, there are currently over 10 million Parkinson's disease sufferers worldwide (5). Geographically, the prevalence varies; North America, Europe, and some regions of Asia have greater rates (9). These regional discrepancies could be explained by changes in lifestyle factors, genetic vulnerability, and environmental exposures (10). In the upcoming decades, Parkinson's disease cases are predicted to rise significantly in nations like China and India that have fast aging populations (9).

The most significant risk indicator for Parkinson's disease seems to be age (9). The disease's incidence sharply rises after age 60 and keeps rising as people age (9,11). Even though younger people can get Parkinson's disease, early-onset instances make up a very small percentage of all cases (11). According to studies, the frequency among those over 80 may be higher than 3–4%, underscoring the robust correlation between neurodegeneration and aging (11).

The epidemiology of Parkinson's disease has also been found to differ by gender. With an approximate male-to-female ratio of 1.5:1, the disease is typically more frequent in males than in women (12). Hormonal impacts, genetic factors, and variations in occupational or environmental exposures are some of the theories put out to explain this discrepancy (12).

Parkinson's disease risk has been linked to a number of environmental and genetic factors, in addition to age and gender (13). A greater likelihood of contracting the disease has been associated with inhalation of heavy metals, pesticides, and herbicides (13). On the other hand, it has been proposed that some lifestyle choices, such as consistent exercise and moderate coffee intake, have protective benefits (13). Although most cases of Parkinson's disease are still sporadic, genetic abnormalities in some genes, such as SNCA, LRRK2, and PARK7, have also been linked to family variants of the disease (14).

Healthcare systems face a major issue due to the rising incidence of Parkinson's disease worldwide (5,9). The disease's progressive nature results in long-term incapacity, higher medical expenses, and a lower standard of living for those who are impacted (5). Effective treatment approaches that address the

underlying neurodegenerative mechanisms of Parkinson's disease in addition to relieving symptoms are therefore desperately needed.

3. Pathophysiology of Parkinson's Disease

Degeneration of dopaminergic neurons in the brain's substantia nigra pars compacta is the main feature of Parkinson's disease, a progressive neurodegenerative condition (1,3). Dopamine, which is essential for controlling motor function, decreases substantially in the striatum when these neurons are lost (3). The hallmark motor symptoms of Parkinson's disease, such as tremor, stiffness, bradykinesia, and postural instability, are ultimately caused by dopamine deficiency (2).

Parkinson's disease is caused by a number of interrelated molecular processes. Oxidative stress, which happens when reactive oxygen species generation surpasses the capacity of cellular antioxidant defense systems, is one of the most significant factors (15). Because dopamine metabolism itself can produce reactive oxygen species, dopaminergic neurons are especially susceptible to oxidative injury. Overexposure to oxidative stress can harm lipids, proteins, and DNA in cells, which can eventually cause neuronal degeneration (15,16).

Mitochondrial dysfunction is another important factor in Parkinson's disease. Cellular energy in the form of adenosine triphosphate (ATP) is produced by mitochondria. Reduced ATP generation and elevated oxidative stress are two consequences of mitochondrial dysfunction in Parkinson's disease that lead to increasing neuronal damage (16,17).

Another important pathogenic aspect of Parkinson's disease is protein aggregation. Lewy bodies are intracellular inclusions that are thought to be a characteristic of the disease due to abnormal accumulation of the protein α -synuclein (18). These protein clumps cause neuronal death, interfere with synaptic transmission, and disturb regular cellular processes.

Furthermore, neuroinflammation is essential to the development of the disease. When brain microglial cells are activated, inflammatory mediators such as chemokines and cytokines are released. Neurodegeneration can be accelerated and neuronal damage can be made worse by persistent neuroinflammation (19).

The blood–brain barrier (BBB) is a significant obstacle to Parkinson's disease treatment. In addition to shielding the brain from dangerous drugs, the blood-brain barrier (BBB) restricts the admission of numerous therapeutic medicines into the central nervous system (20). Because of this, a lot of traditional medications have inadequate brain penetration, which lowers their therapeutic efficacy. Therapeutic approaches that target these pathways have drawn a lot of attention since oxidative stress, mitochondrial failure, protein aggregation, and neuroinflammation are important factors in the development of Parkinson's disease. Natural substances having neuroprotective and antioxidant qualities have drawn interest as possible medicinal agents in recent years. Because of its capacity to alter several molecular pathways implicated in neurodegeneration, resveratrol has become one of the most promising of these (7,8)

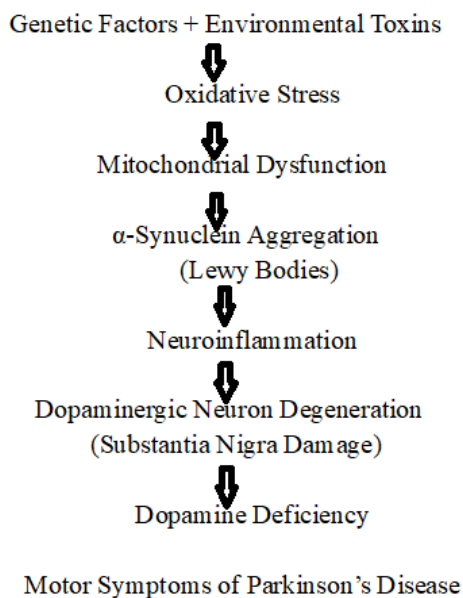


Figure 02: Pathophysiology of Parkinson's Disease

4. Methodology for Literature Search

4.1 Data Sources and Search Strategy

To find pertinent research on resveratrol-based nanocarriers for brain targeting and their possible therapeutic uses in Parkinson's disease, a thorough literature search was carried out. To find research publications published between 2018 and 2026, electronic databases such as PubMed, Scopus, ScienceDirect, and Google Scholar were thoroughly examined.

Keyword combinations pertaining to resveratrol,

nanotechnology, brain targeting, and Parkinson's disease were employed in the search technique. To narrow down the search and find pertinent publications, boolean operators like AND and OR were used.

The following were the main search terms:

- "resveratrol nanoparticles"
- "Nano-resveratrol"
- "Brain-targeted nanocarriers."
- "Drug delivery of resveratrol"
- "Nanoparticles and Parkinson's disease"
- "Drug delivery through the blood-brain barrier"

Boolean operators were used to combine these terms in order to maximize the retrieval of pertinent studies.

4.2 Example Search String

An example of the search query used during database searching was as follows:

("Resveratrol" OR "Nano-resveratrol")
 and ("Nanoparticles" or "Nanocarriers" or "Nanotechnology")
 and ("Brain targeting" or "Blood-brain barrier")
 and ("Parkinson's disease")

4.3 Inclusion Criteria

The following criteria were used to determine which studies were included in the review:

- Studies looking into formulations of nanocarriers based on resveratrol
- Research assessing blood-brain barrier medication distribution or brain targeting
- Studies on neuroprotection or Parkinson's disease
- Articles that have been published in journals with peer review
- Research articles written in English
- Studies released between 2018 and 2026

4.4 Requirements for Exclusion

The review did not include the following studies:

- Research unrelated to resveratrol
- Articles outlining medication delivery methods other than nanotechnology
- Abstracts from conferences without full-text publications
- Publications that are duplicates
- Research unrelated to neurodegenerative or neurological conditions

4.5 Study Selection Process

Initially, titles and abstracts were used to screen every record that was found in the database search. Full-text examination was applied to articles that were

pertinent. The most pertinent studies were chosen for qualitative analysis after the inclusion and exclusion criteria were applied. In order to assess how resveratrol-based nanocarriers can improve brain targeting and therapeutic effects in Parkinson's disease, almost forty research were considered in this evaluation. PRISMA reporting criteria and general principles of systematic review methodology were adhered to during the study selection process (21,22).

Flow Representation:

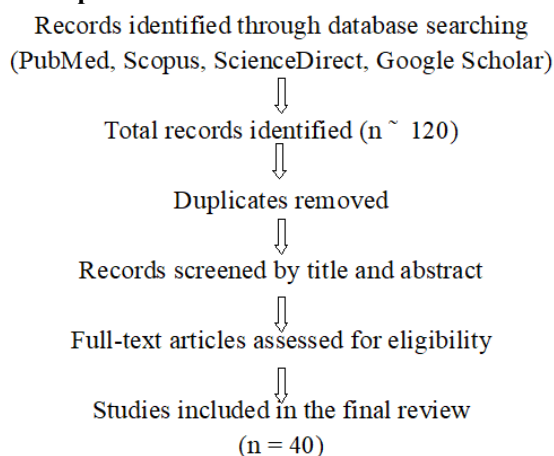


Figure 3. Literature search and study selection process.

5. Resveratrol and Neuroprotection in Parkinson's Disease

5.1 Chemical Nature of Resveratrol

Grapes, berries, peanuts, and red wine are common sources of resveratrol, a naturally occurring polyphenolic molecule that is a member of the stilbene class of phytoalexins. Resveratrol, also known as 3,5,4'-trihydroxystilbene, is primarily found in two isomeric forms: trans-resveratrol and cis-resveratrol. The trans form is thought to be more physiologically active. Its powerful antioxidant qualities are a result of its chemical structure, which consists of two aromatic rings joined by a double bond. Resveratrol's lipophilic properties allow it to interact with intracellular targets and cell membranes, modifying many signaling cascades linked to oxidative stress, inflammation, and neurodegeneration (23, 24). Nevertheless, resveratrol's poor aqueous solubility, quick metabolism, and low bioavailability restrict its clinical uses and therapeutic efficacy despite its considerable therapeutic promise (25).

5.2 Antioxidant Properties

Resveratrol's strong antioxidant impact is one of its most significant biological actions. By producing an excess of reactive oxygen species (ROS) that harm neuronal cells, oxidative stress contributes significantly to the pathophysiology of Parkinson's disease. By scavenging free radicals and boosting natural antioxidant defense systems, resveratrol functions as a potent antioxidant (26).

Research has shown that resveratrol boosts the activity of a number of antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase (SOD), which are critical for neutralizing reactive oxygen species and shielding neuronal cells from oxidative damage (26, 27). Resveratrol slows the neurodegenerative processes linked to Parkinson's disease by protecting dopaminergic neurons in the substantia nigra by lowering oxidative stress.

5.3 Anti-Inflammatory Effects

Another important element influencing the development of Parkinson's disease is chronic neuroinflammation. Inflammatory mediators including cytokines and chemokines are released when microglial cells in the brain are activated, which can worsen neuronal damage. By altering many inflammatory signaling pathways, resveratrol demonstrates strong anti-inflammatory action (28).

According to experimental research, resveratrol can prevent the activation of transcription factors like nuclear factor-kappa B (NF- κ B), which controls the expression of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) (28,29). Resveratrol helps lessen neuroinflammation and shields neuronal cells from inflammatory damage by inhibiting these inflammatory mediators.

5.4 Neuroprotective Mechanisms

Through a variety of molecular mechanisms that target various pathogenic pathways implicated in Parkinson's disease, resveratrol produces neuroprotective benefits. Sirtuin-1 (SIRT1), a protein that controls neuronal survival, mitochondrial function, and cellular stress tolerance, is activated as one of the main pathways (30). Additionally, resveratrol has been shown to prevent the aggregation of α -synuclein, a protein that causes Lewy bodies, an intracellular inclusion that is a pathogenic feature of Parkinson's disease (30, 31). Furthermore, by improving cellular energy

metabolism and lowering oxidative mitochondrial damage, resveratrol enhances mitochondrial function. Additionally, it can promote autophagy, a cellular mechanism that eliminates damaged organelles and proteins. When taken as a whole, these processes support the maintenance of dopaminergic neurons and may halt the advancement of neurodegeneration (31).

5.5 Experimental Evidence in Parkinson's Disease

Resveratrol's neuroprotective effect in cellular and animal models of Parkinson's disease has been shown in a number of experimental investigations. According to preclinical studies, resveratrol therapy can enhance motor function and shield dopaminergic neurons from harm caused by neurotoxins (32).

For instance, research employing MPTP and 6-hydroxydopamine (6-OHDA) animal models has demonstrated that resveratrol considerably improves behavioral outcomes and decreases neuronal loss in the substantia nigra. According to these results, resveratrol may lessen the neurodegenerative processes linked to Parkinson's disease (32).

Resveratrol's poor pharmacokinetic profile, which includes low oral bioavailability and fast hepatic metabolism, limits its therapeutic applicability despite these encouraging findings. Additionally, the amount of resveratrol that reaches the central nervous system is limited by the blood–brain barrier (BBB). In order to enhance resveratrol's stability, bioavailability, and brain targeting, sophisticated nanotechnology-based drug delivery methods have been studied (25,32).

6. Brain-Targeted Nanocarriers for Resveratrol Delivery

In the treatment of neurodegenerative illnesses like Parkinson's disease, resveratrol has shown considerable therapeutic promise. However, a number of pharmacokinetic issues, including as poor water solubility, fast metabolism, low systemic bioavailability, and restricted blood–brain barrier (BBB) penetration, restrict its practical use. The amount of resveratrol that reaches the central nervous system is greatly decreased by these restrictions. Drug delivery systems based on nanocarriers have been investigated as a solution to these problems. Drug stability, metabolic degradation protection, bioavailability, and targeted brain administration can all be improved by nanocarriers (33, 34). Furthermore, regulated drug release and increased drug accumulation in brain tissues can be facilitated by nanoscale devices.

To enhance the delivery of resveratrol to the brain, a number of nanocarrier techniques have been studied.

6.1 Liposomes

Both hydrophilic and lipophilic medications can be encapsulated in liposomes, which are spherical vesicles made of phospholipid bilayers. Liposomes are frequently employed for medication delivery in disorders of the central nervous system because of their superior biocompatibility and structural resemblance to biological membranes (35). When compared to free resveratrol, resveratrol-loaded liposomal formulations have demonstrated superior stability, increased bioavailability, and improved brain transport. The ability of liposomes to traverse the blood–brain barrier and concentrate in neuronal tissues can be further improved by surface modification with targeted ligands (36). Because of these qualities, liposomes are a promising delivery system for neuroprotective substances in Parkinson's disease.

6.2 Solid Lipid Nanoparticles

Solid lipids stabilized by surfactants make up solid lipid nanoparticles (SLNs), which are lipid-based nanocarriers. These systems provide a number of benefits, such as better bioavailability, regulated drug release, and increased drug stability (37). SLNs loaded with resveratrol have shown enhanced drug accumulation in brain tissues and better pharmacokinetic characteristics. SLNs may improve resveratrol's therapeutic efficacy in neurodegenerative disorders by shielding it from metabolic degradation and facilitating sustained drug release (38).

6.3 Polymeric Nanoparticles

Colloidal drug delivery systems called polymeric nanoparticles are made from biodegradable polymers like chitosan and poly(lactic-co-glycolic acid) (PLGA). Therapeutic substances can be encapsulated in these nanoparticles and released over long periods of time in a regulated manner (39).

Polymeric nanoparticles loaded with resveratrol have demonstrated better stability and blood–brain barrier penetration. Drug delivery efficiency can be increased by promoting receptor-mediated transport into brain tissues through surface functionalization with targeted ligands (40).

6.4 Nanostructured Lipid Carriers

Second-generation lipid nanoparticles called nanostructured lipid carriers (NLCs) were created to

get over the drawbacks of solid lipid nanoparticles. Higher drug loading capacity and enhanced stability are made possible by the combination of solid and liquid lipids seen in NLCs (41).

According to experimental research, resveratrol-loaded NLCs show better bioavailability, prolonged drug release, and improved brain targeting. In brain cells, the lipid matrix helps sustain therapeutic quantities of resveratrol by preventing its breakdown (42).

6.5 Nanoemulsions

Oil, water, and surfactants combine to form nanoemulsions, which are colloidal dispersions with droplet sizes usually between 20 and 200 nm. These systems improve drug solubility and make it easier for molecules that are poorly soluble in water to be absorbed (43).

It has been demonstrated that resveratrol nanoemulsion formulations improve bioavailability and facilitate efficient transport across the blood-brain barrier. Drug delivery to the central nervous system is improved by the small droplet size, which permits effective penetration across biological membranes (44).

6.6 Dendrimers

Dendrimers are highly branched polymeric nanostructures with several surface functional groups and a clearly defined topology. These characteristics enable surface modification for targeted drug delivery and allow dendrimers to encapsulate substantial amounts of drug molecules (45). Dendrimer devices loaded with resveratrol have been studied for targeted administration to the central nervous system. These nanocarriers are intriguing platforms for neuroprotective medication delivery in Parkinson's disease because they can improve drug solubility, stability, and controlled release (46). All things considered, nanocarrier-based delivery methods offer a viable way to get over resveratrol's pharmacokinetic restrictions and enhance its therapeutic potential in the treatment of Parkinson's disease (47, 48).

Table 01: Summary of Nanocarriers Used for Resveratrol Delivery

Nanocarrier Type	Key Advantages
Liposomes	Biocompatible and capable of encapsulating multiple drugs

Solid Lipid Nanoparticles	Improved stability and controlled release
Polymeric Nanoparticles	Biodegradable and long-lasting drug release
Nanostructured Lipid Carriers	Higher drug loading capacity
Nanoemulsions	Improved solubility and absorption
Dendrimers	Highly customizable and targeted delivery

7. Mechanisms of Brain Targeting Using Nanocarriers

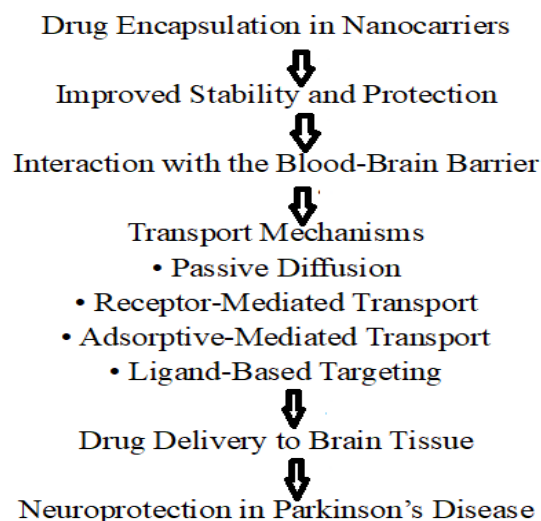


Figure 04: Brain Targeting Mechanism

7. Literature Review

Recent research indicates a substantial advancement in the development of nanocarrier-based resveratrol delivery methods. Numerous nanocarriers, such as liposomes, polymeric nanoparticles, nanoemulsions, and solid lipid nanoparticles, have been investigated to improve the pharmacokinetic profile of resveratrol. These systems enhance a drug's stability, bioavailability, and blood-brain barrier (BBB) penetration. Numerous experimental studies have shown that nano-formulated resveratrol has superior neuroprotective effects when compared to free resveratrol (61,62).

In recent years, a number of studies have evaluated several nanocarrier technologies for the transport of resveratrol to the brain. Albumin-based nanoparticles have been demonstrated to improve blood-brain barrier penetration and reduce oxidative damage in neuronal cell models (63). Similarly, polymeric nanoparticles have demonstrated improved

dopaminergic neuron survival in animal models of Parkinson's disease (64). Liposomal resveratrol formulations have also been shown to enhance neuronal uptake and antioxidant activity in in vitro neuronal models (65). Solid lipid nanoparticle formulations have also been demonstrated to reduce oxidative stress and neuroinflammation in Parkinson's disease experimental models (66).

Numerous recent studies have also shown the advantages of nano-resveratrol formulations. Nanoemulsion-based devices have been shown to increase the solubility and bioavailability of resveratrol (67). Albumin-based nanoparticles have been shown to facilitate medication distribution across the blood–brain barrier and enhance therapeutic targeting in neurological diseases (68). Additionally, solid lipid nanoparticles have demonstrated the prolonged drug release and improved systemic absorption of resveratrol (69). Furthermore, poly(lactic-co-glycolic acid) (PLGA) nanoparticles have been shown to significantly enhance medication stability and brain targeting (70).

Recent research has confirmed the advantages of nanocarrier-based delivery methods. Brain-targeted liposomal formulations have been shown to improve BBB transport and increase neuroprotective effects in both cellular and animal models (71). Solid lipid nanoparticles have demonstrated potential in lowering oxidative stress and neuronal degeneration in Parkinson's disease models (72). Similarly, it has been shown that drug loading capacity and brain drug delivery are enhanced by nanostructured lipid carriers (73). Additionally, polymeric nanoparticles and nanoemulsions have been shown to enhance antioxidant defense systems and increase the solubility of resveratrol (74,75).

Previous experimental studies provide additional evidence for the therapeutic potential of nano-resveratrol formulations. Resveratrol nanoparticles have been shown to improve neuroprotection and reduce neuronal cell death in animal models (76). Targeted liposomal formulations have demonstrated enhanced neuronal uptake and blood–brain barrier penetration (77). Furthermore, polymeric nanoparticles have been shown to prolong medication release and improve drug stability (78).

Over the past ten years, numerous studies have demonstrated the benefits of resveratrol distribution by nanocarrier. Liposomal resveratrol has been shown

to reduce oxidative stress and improve neuronal survival (79). Nanoemulsion formulations have also demonstrated improved behavioral outcomes and increased brain drug accumulation in neurodegenerative experimental models (80).

Overall, the data clearly show that nanocarrier-based administration strategies significantly improve the pharmacokinetic and pharmacodynamic properties of resveratrol. In addition to providing targeted neuronal delivery, these nanoformulations enhance medication stability, increase bioavailability, and facilitate drug passage through the blood–brain barrier. Therefore, a viable treatment strategy for improving neuroprotection and slowing the course of Parkinson's disease is resveratrol administration via nanocarriers.

8. Comparative Analysis:

Table 02: Comparative Analysis of Nanocarriers for Brain Delivery

Nanocarrier Type	Advantages	Limitations	Application in Parkinson's Disease
Liposomes	Biocompatible, good drug encapsulation	Physical instability	Used for the targeted delivery of resveratrol across the BBB
Polymeric Nanoparticles	Controlled drug release, high stability	Possible polymer toxicity	Enhances brain accumulation of resveratrol
Solid Lipid Nanoparticles (SLN)	Improved stability, sustained release	Limited drug loading capacity	Reduces oxidative stress in PD models
Nanostructured Lipid Carriers (NLC)	Higher drug loading than SLN	Complex preparation methods	Improved neuroprotective delivery
Nanoemulsions	High solubility of hydrophobic drugs	Short stability time	Enhances the bioavailability of resveratrol
Dendrimers	Highly controlled structure	Expensive synthesis	Targeted drug delivery

			potential
Polymeric Micelles	Good for poorly soluble drugs	Limited drug loading	Potential carrier for neuroprotective compounds

By increasing medication stability, solubility, and targeted transport to brain regions, nanocarrier systems significantly contribute to the therapeutic efficacy of resveratrol. Among the several nanocarriers studied, liposomal formulations, solid lipid nanoparticles, and polymeric nanoparticles have shown encouraging results in Parkinson's disease experimental models. Resveratrol's neuroprotective effects are improved and its total therapeutic potential is increased by these delivery systems, which also improve neuronal absorption and promote transport across the blood–brain barrier (81–83).

9. Key Findings from Reviewed Literature

The analysis of the selected studies highlights several important findings regarding the use of nanocarrier-based systems for resveratrol delivery in the management of Parkinson's disease.

- Resveratrol's solubility, stability, and bioavailability are greatly increased by nanocarrier systems, increasing its therapeutic potential (84).
- The most extensively researched systems for brain-targeted drug delivery among the several nanocarriers examined are liposomes, polymeric nanoparticles, and solid lipid nanoparticles (85).
- Formulations based on nanoparticles enable better blood–brain barrier penetration, allowing therapeutic drugs to be delivered to neuronal tissues more effectively (84,85).
- In experimental models of Parkinson's disease, nano-resveratrol formulations have better antioxidant and anti-inflammatory properties than free resveratrol, which helps to improve neuroprotection (86).
- However, most of the current research is still limited to in-vitro studies and animal models, indicating a lack of large-scale clinical trials evaluating the safety and therapeutic efficacy of nano-resveratrol formulations in human patients (86).

10. Discussion

The creation of efficient therapeutic approaches for the treatment of Parkinson's disease is one of the main issues facing contemporary medicine. Dopaminergic neurons in the substantia nigra gradually degenerate in Parkinson's disease, resulting in motor symptoms such

bradykinesia, stiffness, and tremors. Neuronal degeneration in this illness is thought to be primarily caused by oxidative stress, mitochondrial malfunction, and neuroinflammation (87).

As possible neuroprotective drugs, natural polyphenolic substances have drawn a lot of interest. Among them, resveratrol has shown notable anti-inflammatory, anti-apoptotic, and antioxidant qualities. Resveratrol has been shown in a number of experimental experiments to lower oxidative stress, block inflammatory pathways, and prevent neuronal cell degeneration. Resveratrol is a promising therapeutic option for the treatment of neurodegenerative disorders because of these pharmacological characteristics (88).

However, a number of pharmacokinetic issues, such as low systemic bioavailability, fast metabolism, and poor water solubility, restrict the clinical use of resveratrol. Furthermore, the transport of therapeutic medicines into the brain is severely limited by the existence of the highly selective blood–brain barrier (BBB). Because of this, only a little portion of resveratrol taken orally can enter the central nervous system (89).

New developments in medication delivery systems based on nanotechnology have shown encouraging ways to get beyond these restrictions. The distribution of resveratrol to the brain has been extensively studied using nanocarrier systems as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions. Drug stability, bioavailability, and targeted administration across the blood–brain barrier can all be improved by these nanocarriers (90).

Numerous studies have shown that, as compared to free resveratrol, nano-formulated resveratrol has stronger neuroprotective benefits. While solid lipid nanoparticles and nanostructured lipid carriers have exhibited improved brain targeting and decreased oxidative stress in animal models of Parkinson's disease, polymeric nanoparticles have been found to offer better neuronal absorption and prolonged drug release (91).

Despite these encouraging results, the majority of the evidence that is currently available comes from animal research and in vitro investigations. There are yet few well-designed clinical trials assessing the pharmacokinetic behavior, safety, and long-term therapeutic efficacy of nano-resveratrol formulations in human subjects. Furthermore, the clinical

translation of nanocarrier-based therapeutics is still hampered by issues such formulation stability, large-scale production, and regulatory approval (92).

Therefore, more research and clinical studies are needed to translate these findings into effective treatments for Parkinson's disease, even though nanotechnology-based drug delivery systems offer significant potential in enhancing the therapeutic efficacy of resveratrol.

11. Research Gap

Even though resveratrol delivery methods based on nanotechnology have advanced significantly, there are still a number of critical research gaps. First, in vitro cell culture models and experimental animal models have been used in the majority of research on nano-resveratrol formulations. There are currently few clinical trials assessing these formulations' safety, pharmacokinetics, and treatment efficacy in Parkinson's disease patients (93).

Second, little is known about the toxicity and long-term safety of nanocarrier systems. Comprehensive toxicological assessments are necessary to ascertain the long-term impacts and possible hazards of nanoparticles since they may accumulate in biological tissues (94).

Third, it is challenging to compare findings and create consistent formulations due to notable differences between studies in terms of nanoparticle fabrication methods, particle size, surface modification, and drug loading efficiency (95).

The absence of highly selective brain-targeting delivery devices intended to improve drug accumulation in impacted brain regions like the substantia nigra represents another significant research gap. The creation of targeted techniques mediated by ligands or receptors may greatly enhance therapeutic results (96).

Lastly, the clinical application of nanomedicine-based treatments is still constrained by large-scale production difficulties and regulatory obstacles. Therefore, future studies should concentrate on creating nanocarrier systems that are economical, scalable, and clinically safe (97). In order to improve Parkinson's disease treatment approaches and advance the clinical development of resveratrol therapies based on nanocarriers, it will be crucial to fill in these research gaps.

12. Future Perspectives

Before nano-resveratrol formulations can be widely used in clinical practice for the treatment of Parkinson's disease, a number of issues need to be resolved, despite significant advancements in nanotechnology-based drug delivery systems. The dearth of carefully planned clinical trials assessing the safety and therapeutic effectiveness of resveratrol-loaded nanocarriers in human populations is one of the main obstacles (93). The creation of sophisticated nanocarriers with increased drug loading capacity, stability, and targeting effectiveness should be the main emphasis of future research. The ability of nanoparticles to permeate the blood-brain barrier and deliver therapeutic medicines directly to damaged brain regions may be greatly enhanced by surface modification with certain ligands or antibodies (96). By lowering systemic side effects, such focused administration methods may improve treatment results.

The creation of multifunctional nanocarriers that can deliver several therapeutic substances at once is another potential strategy. In neurodegenerative diseases, combination treatments with resveratrol and other neuroprotective substances may improve overall therapeutic efficacy (98). Furthermore, the creation of non-invasive drug delivery methods, including intranasal nanocarrier systems, may enhance medication administration to the brain even more. By using the olfactory and trigeminal nerve pathways, medicinal drugs can quickly reach the central nervous system and avoid the blood-brain barrier (96).

It is anticipated that developments in biotechnology, nanomedicine, and precision medicine will be crucial to the creation of more potent Parkinson's disease treatments. Nanocarrier-mediated resveratrol delivery may become a viable therapeutic strategy for the treatment of neurodegenerative diseases with more investigation and technical advancement.

13. Conclusion

Degeneration of dopaminergic neurons and the emergence of both motor and non-motor symptoms are hallmarks of Parkinson's disease, a progressive neurodegenerative condition. Because of their anti-inflammatory, anti-apoptotic, and antioxidant qualities, natural polyphenolic substances like resveratrol have shown considerable neuroprotective potential (88). However, resveratrol's low

bioavailability, quick metabolism, and poor solubility restrict its medicinal use (89).

Drug delivery technologies based on nanotechnology have shown promise as ways to get around these restrictions. To enhance the delivery of resveratrol to the brain, several nanocarrier systems, including as liposomes, polymeric nanoparticles, nanoemulsions, and solid lipid nanoparticles, have been studied (90). By enhancing medication stability, bioavailability, and blood-brain barrier transit, these systems improve therapeutic outcomes.

Overall, the use of brain-targeted nanocarriers has the potential to significantly enhance the therapeutic efficacy of resveratrol in the management of Parkinson's disease. Future research on targeted drug delivery methods, enhanced nanocarrier design, and clinical validation may result in the creation of more potent therapies for neurodegenerative illnesses.

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