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"Enhancing Resveratrol Delivery for Neuroprotection in Parkinson's Disease by Nano-formulations"

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ABSTRACT

Resveratrol (RV), a polyphenol found in grapes, berries, and peanuts, has garnered attention for its neuroprotective properties and minimal side effects, making it an attractive candidate for the treatment of neurodegenerative diseases like Parkinson's disease (PD). Despite its therapeutic potential, RV faces limitations such as low bioavailability, poor stability, and difficulty crossing the blood-brain barrier (BBB), which hinder its effectiveness in clinical applications. Nanotechnology offers a solution to these challenges by enhancing the delivery and functionality of RV. Through advanced nanoformulation techniques, RV can be encapsulated into nanocarriers that provide targeted brain delivery, controlled release, and improved cellular uptake, all while reducing the required dosage and minimizing systemic side effects. By leveraging nanotechnology, the therapeutic efficacy of RV can be significantly enhanced, positioning it as a promising approach for neuroprotection in PD and other neurodegenerative conditions. This review explores the synergistic potential of nanotechnology in optimizing RV-based therapies, offering new hope for safer and more effective treatments in the management of PD.

KEYWORDS: Nanotechnology, Parkinson's disease, Polyphenols, Resveratrol.

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative illness brought on by a deficiency of dopamine-producing neurons in the brain region responsible for motor coordination, the basal ganglia. Due to dopaminergic neuron degeneration, PD affects millions of people worldwide and is expected to affect 10 million by 2030. PD causes a wide range of motor and non-motor symptoms. It is a long-term, progressive neurological condition characterized by a high level of the intracellular protein alpha-synuclein and an early loss of dopaminergic neurons in the substantia nigra pars compacta. The ensuing dopamine imbalance in the basal ganglia, which causes bradykinesia and other Parkinsonian motor symptoms as stiffness, tremor, and postural instability. Triggering variables in the pathological

cascade of PD include neuroinflammation, oxidative stress, and the excitotoxicity of the N-methyl-D-aspartate (NMDA) receptor (1).

Despite a great deal of research, there are few pharmaceutical alternatives for the condition that can stop the disease from progressing beyond treating its symptoms. As a result, scientists are searching for potentially synthetic or natural substances to use as PD treatments. Due to required continuous consumption of anti-PD medicine to the PD patients, the natural substances are attracting attention recently. Many research has demonstrated the neuroprotective benefits of natural components against dopaminergic neuronal death, with generally harmless side effects that are infrequent, mild, or temporary (2).

A group of secondary metabolites found in plants called polyphenols have become more and more popular because of their many uses as food additives, medicines, and preservatives. They are frequently added to a wide range of foods to improve their flavour, texture, shelf life, and general quality. Effective antioxidants and radical scavengers, polyphenols provide numerous health advantages, including anti-inflammatory and antibacterial properties. Numerous studies have shown that eating more foods high in polyphenols may help lower the risk of cancer and metabolic diseases. However, because of their low solubility in water, instability at low pH levels, and challenges with absorption in the small intestine, their bioavailability is restricted after intake (3).

3,5,4′-trihydroxy-trans-stilbene, (RV), is a polyphenol and phytoalexin which occurs naturally and has drawn a lot of interest due to its neuroprotective and antioxidative qualities in neurodegenerative disease like Parkinsonism. Their enormous potential for therapeutic application was hampered by their low solubility, photostability, and decreased bioavailability. The need for new potent medications is highlighted by the fact that current drugs effectively control PD symptoms but are ineffective in halting the disease's development. A formulation based on convention does not provide the best therapeutic results. In order to overcome these obstacles, new technological procedures as well as the use of polyphenol-loaded nanoparticles and nanotechnology are needed to maintain the biological activities of polyphenols and increase their bioavailability, making them more useful as functional food ingredients and drug delivery systems (3).

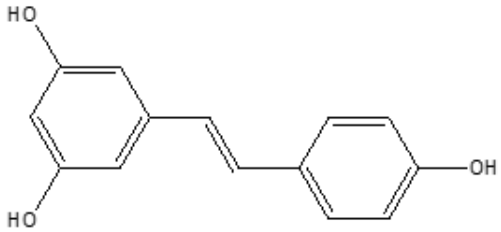

Figure 1: RV chemical structure

2. LITERATURE REVIEW REGARDING RESVERATROL'S NANO-FORMULATIONS USED IN PD

2.1 Solid lipid nanoparticles (SLNs)

Bandiwadekar A et al. (2024) explored intradermal solid lipid nanoparticles (SLNs) to enhance RV stability. In this study, an RV-loaded SLNs (RV-SLNs) microneedle patch was designed for transdermal delivery of RV to improve stability and enhance patient compliance. Characterization studies confirmed favourable sustained drug release profile (78.36 ± 0.74%) and physical properties. Microneedles demonstrated effective skin penetration. *Ex-vivo* permeation studies showed significant drug permeation of 68.39 ± 1.4%. *In-vivo* pharmacokinetic analysis indicated a notable increase in $AUC_{0-t,}$ $T_{max,}$ and C_{max}, values, along with an inferior elimination rate when compared to pure RV delivered *via* microneedles. Treated animals exhibited improvements in behaviour along with elevated antioxidant levels in the brain. Additionally, *in-vivo* skin irritation tests indicated no signs of irritation for up to 24 hours, suggesting the suitability of extended microneedle application Histo-pathological findings revealed changes in the substantia nigra and striatum of the brain, post-treatment. These findings suggest that the RV-SLN loaded microneedle patch (RVSNLMP) offers a novel and promising approach to improving drug efficacy, patient compliance, and therapeutic outcomes in PD treatment (4).

2.2 Nanocrystals

Xiong S et al. (2020) developed a nanocrystal (NCs) formulation of RV to boost its brain delivery and oral bioavailability for the management of PD. RV-NCs were prepared using hydroxypropyl methylcellulose (HPMC) as a stabilizing agent through an antisolvent precipitation technique. The RV-NCs achieved a particle size of 222.54 ± 1.66 nm, a PDI of 0.125 ± 0.035, and a zeta potential of −9.41

± 0.37 mV, with a fast in-vitro dissolution rate. Molecular dynamics simulations indicated an interaction energy of −68.09 kJ/mol and a binding energy of −30.98 ± 0.388 kJ/mol between RV and HPMC, suggesting spontaneous binding via van der Waals interactions. The RV-NCs showed enhanced cellular uptake and superior permeability compared to unformulated RV. Additionally, they provided neuroprotection against MPP^+-induced cytotoxicity without exhibiting significant toxic effects on zebrafish embryos or larvae, preserving their survival and hatching rates. Pharmacokinetic studies in rats showed that orally administered RV-NCs achieved higher plasma and brain concentrations than pure RV. In MPTP-induced PD mice, RV-NCs resulted in notable behavioral improvements, alleviated dopamine deficiency, and elevated levels of dopamine along with its metabolites Overall, RV-NCs present a promising strategy for improving RV's oral bioavailability and brain accumulation, making them a potential treatment modality for PD (5).

2.3 Polymeric nanoparticles

Rahman M et al. (2019) conducted a study to assess the neuroprotective effects of RV delivered *via* chitosan glutamate nanoparticles (RV-CG-NPs) in a PD mouse model induced by MPTP. The nanoparticles were produced using the ionic gelation method with chitosan and tripolyphosphate, and the optimized formulation was administered intranasally. These nanoparticles had a polydispersity index (PDI) of 0.21, good entrapment efficiency (89%), and a particle size of 131 nm. Pharmacodynamic evaluations showed that MPTP significantly, elevated oxidative stress in the striatum, decreased tyrosine hydroxylase expression, and impaired social recognition memory. Biodistribution studies indicated that the nanoparticle formulation achieved significantly higher brain concentrations of RV compared to plain RV solution. The C_{max} (890.12 ng/ml) and AUC (1986.51 ng·h/ml) of the optimized formulation (administered intranasally) were notably higher at all time points compared to the RV solution (intranasally) and the chitosan glutamate-RV-NPs (administered intravenously). Overall, the study demonstrated that nose to brain delivery of RV-loaded nanoparticles enhanced brain targeting and neuroprotection in PD (6).

da Rocha Lindner G et al. (2015) examined the neuroprotective properties of bulk RV with those of RV-loaded polysorbate 80 (PS80)-coated poly(lactide) nanoparticles in a rat model of PD. After receiving intraperitoneal treatment with RV (nanoparticulate or non-nanoparticulate) for 15 days, MPTP was administered once intraperitoneally to C57BL/6 mice, a neurotoxin that induces PD-like symptoms by damaging dopaminergic neurons. MPTP caused significant impairments in olfactory discrimination, social recognition memory, and oxidative stress in the striatum, along with a reduction

in tyrosine hydroxylase expression. Bulk RV did not exhibit the same level of neuroprotection against the behavioural and neurochemical alterations caused by MPTP as did RV-loaded nanoparticles. These results imply that PS80-coated RV-loaded poly(lactide) nanoparticles offer a viable new avenue for PD adjuvant therapy and nanomedical instrumentation (7).

2.4 Liposomes

Wang M et al. (2018) designed Fe3O4-modified RV liposomes (RV-lips@Fe3O4) as a magnetic targeting drug nanocarrier. T2 relaxation times and Factional anisotropy (FA) values were measured using magnetic resonance imaging in RV-lips@Fe3O4-treated rats. The RV-lips@Fe3O4 formulation demonstrated high drug loading capacity, stability, and strong magnetic responsiveness, with slow and sustained drug release *in-vitro*. RV-lips@Fe3O4 efficiently penetrated the blood-brain barrier and raised medication concentration at the target region when exposed to an external magnetic field, according to *in-vivo* tests. Increased T2 relaxation periods and FA values supported the improved therapeutic efficacy of magnetic RV-liposomes. According to these results, RV-lips@Fe3O4 presents a viable platform for effectively overcoming the blood-brain barrier and treating neurological conditions like Parkinson's disease when combined with an external magnetic field (8).

2.5 Nanoemulsion

Pangeni R et al. (2014) formulated a kinetically stable oil-in-water nanoemulsion of RV by employing vitamin E:sefsol (1:1), Tween 80, and Transcutol P as oil, surfactant and co-surfactant respectively for managing PD efficiently. Despite RV's potent antioxidant and pharmacological properties, its low oral bioavailability, attributed to extensive hepatic and presystemic metabolism, was addressed through this nanoemulsion approach. Spontaneous emulsification followed by high-pressure homogenization was used for preparing nanoemulsion, demonstrated favorable characteristics, including a polydispersity index of 0.158 ± 0.02, a zeta potential of −35 ± 0.02, and a globule size of 102 ± 1.46 nm. Drug release studies showed significantly enhanced cumulative release in both *in-vitro* and *ex-vivo* conditions, with 88.57 ± 1.92% and 85.48 ± 1.34% release after 24 hours, respectively. The optimized formulation exhibited strong antioxidant activity, and pharmacokinetic studies revealed a high brain concentration following intranasal administration. Histopathological analyses revealed less degenerative alterations, while GSH and SOD levels were significantly increased and MDA levels decreased, confirming the nanoemulsion's neuroprotective potential in PD (9).

Table 1: Application of few drug delivery carriers containing RV to the brain targeting.

Nano-formulations	Animal	Route	Outcome	Reference
NLCs	Rats	Intra-nasal	NLC-loaded in situ gel results in higher drug distribution in the brain.	(10)
Liposomes		Intra-venous	The formulation outperformed free RV in terms of AUC, $t_{1/2}$, and MRT.	(11)
			Formulations increased the brain distribution by nine times and the plasma half-life by up to eighteen times.	(12)
Nanosuspension		Intra-nasal	Additional distribution and localization revealed a direct brain-to-nose transport pathway.	(13)
Nanoemulsion		Intra-nasal	Increase in Brain AUC after Intranasal administration in Rats.	(14)

3. Conclusion

RV stands out as a potent polyphenol with remarkable neuroprotective properties, making it a promising candidate in the fight against PD. However, its clinical application is hampered by inherent challenges such as poor bioavailability, low stability, and limited ability to cross the BBB. The integration of nanotechnology offers a powerful solution to overcome these barriers. Nanoformulation strategies, including the encapsulation of RV in nanocarriers, enable targeted brain delivery, controlled release, and enhanced cellular uptake, while minimizing side effects and reducing the required dosage. By optimizing RV's therapeutic potential through nanotechnology, we open the door to more effective and safer treatments for PD and other neurodegenerative disorders. This convergence of nanotechnology and RV-based therapy holds significant promise for advancing neuroprotective strategies in clinical practice.

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