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Neuroprotection by resveratrol: A review on brain delivery strategies for Alzheimer's and Parkinson's disease

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ABSTRACT

Alzheimer's (AD) and Parkinson's (PD) are the two most common neurodegenerative disorders that affect millions of people worldwide, but their therapeutic opportunities are limited. Resveratrol, a hydrophobic stilbene flavonoid from various sources, including red wine, peanuts, and grapes, has been reported for its effectiveness in multiple diseases, including cancer, cardiovascular disease, and neurological disorders. The mechanism and effect of Resveratrol in AD and PD are also elaborated in detail. Resveratrol can cross the blood–brain barrier (BBB) to exert its pharmacological action. However, the therapeutic dose for its action was not achieved due to its extensive metabolite formation with glucuronide and sulfate. Hence, the discussion on the same has also been reviewed in this article. The development of promising approaches to improve the resveratrol to traverse across the BBB may help the challenges associated with brain delivery. Various studies have reported that nanotechnology-based resveratrol delivery could enhance the multiple outcomes in neurological disorders. Furthermore, preclinical and clinical findings are required to prove the effectiveness of managing AD and PD.

INTRODUCTION

Neurological disorders (NDs) ranked top 50 causes of disability—adjusted life years (DALYs), and it is the most common cause of death worldwide. From the global burden of estimation of disease, the reason for the prominent cause of disability is neurological diseases. Nearly one-third of people in the total population are affected by neurological disorders, and from 1990 to 2019, the death rate has also increased by 39%, and DALYs declined by 15% (Thakur *et al*., 2016). Neurodegenerative diseases (NDDs) are reported as the most challenging disease and a heterogeneous disorder from all the NDs. This is described by the gradual development in degeneration of the function and structure of a nervous system that can either be in central nervous system (CNS) or peripheral nervous system (PNS), followed by the death of the neuronal cell (Feigin *et al*., 2020; Kalia and Lang 2016). NDDs are referred to a greater extent as a severe global social health burden with the progression of the diagnosis of certain NDDs, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease, and prion disease. The pathology involved in these diseases is similar, which involves abnormal aggregates of amyloid protein that can cause selective damage in the neuron cells. Factors including inflammation, oxidation, and aggregates of proteins in the neurons can be the source of neuronal signal disruption that leads to chronic neurological disorders. The current treatment strategies for NDDs are intended for symptomatic relief, replacing certain neurotransmitters that may or may not affect the curative property in disease progression. The strategies used to manage NDDs are implicated in stopping or slowing the further degeneration of neuron cells using antioxidants, anti-inflammatory agents, and anti-amyloid drugs (Maiti and Dunbar 2018).

Resveratrol (Resv), a stilbene flavonoid (3, 4′, 5-trihydroxystilbene), because of its various exciting pharmacological action, has gained attention in the past few years. The stilbene compounds are referred to as phytoalexin as it is known for their resistance to fungal and microbial infections (Bavaresco *et al*., 1997). It can be obtained from various sources, including grapes, peanuts, wines, and berries. Stilbene compounds are

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presently available in larger quantities in injured, UV-treated, and deceased leaves (Langcake and McCarthy, 1979). Resv is a natural substance, and it can be used as a therapeutic compound for several diseases such as Sirtuin 1 (SIRT1) activator (Chung *et al*., 2010), anti-cancer agent as it directly promotes the apoptotic pathway in three stages of cancer disease by inhibiting the IGF-1R/Akt/Wnt pathway, (PI3K)/Akt pathway (Sarkar *et al*., 2009; Vanamala *et al*., 2010), anti-inflammatory agent by inhibiting the production of prostaglandins by inhibiting cyclo-oxygenases enzyme (Kundu *et al*., 2006), anti-hypertensive agent and prevent atherosclerosis by prohibiting the expression of vascular cell adhesion molecule (VCAM) (Stocker and Keaney, 2004), anti-platelet agent (Pace-Asciak *et al*., 1995), and also acts as a therapeutic agent for NDDs. Among several therapeutic effects of Resv, the neuroprotective effect of Resv has gained more attention. The Resv can protect the neuron cells by exhibiting several properties like antioxidant effect, antiamyloidogenic, antitauopathy, anti-inflammatory, Aβ (β-amyloid peptide)—clearance, mitochondrial dysfunction diminution. Also, it is involved in the anticancer activity in Glioma tumors (Bellaver *et al*., 2014; Min *et al*., 2010; Palle and Neerati, 2018; Vingtdeux *et al*., 2010).

With the knowledge of the present literature, we focus on the therapeutic mechanism of Resv involved in the treatment and prevention of neurodegenerative disorders like Alzheimer's and PD. We aimed to offer an extensive overview of development concerning strategies involved in the nano carrier-based delivery of Resv to the brain and highlight its pharmacokinetics.

BIOAVAILABILITY OF RESVERATROL

Resv exhibits two isomeric forms, namely, trans-Resv and cis-Resv. The trans-isomer was reported as more stable compared to the cis-isomer. The better stability of trans-isomer is due to its stability in a light-protected environment for about 42 hours and in pH 1–7 for about 28 days. In contrast, the cis-isomer of Resv was reported stable only when it is completely shielded from light and at pH 7 (Trela and Waterhouse, 1996). The trans-form of Resv shows more biological activity than the cis form, which may be due to the non-planar conformation of the trans-isomer (Fulda, 2010; Rius *et al*., 2010). Hence, most studies have been performed (both pharmacological and drug delivery studies) using trans-isomer of Resv. To find out the bioavailability of Resv, several *in vitro* and *in vivo* studies have clarified the Pharmacokinetics of Resv.

Single dose and repeated doses for the absorption and bioavailability of Resv were reported in the literature. In the single dose of Resv, 25 mg was used, related to the average consumption of red wine. The *C*max was reported to be less than 10 ng/ml after 2 hours of oral administration, and the total plasma concentration of Resv metabolites was markedly high, reported between 400 and 500 ng/ml. From the study, the oral absorption was said to be around 75% based on the assessment of the radio-labeled dose of total Resv metabolites in urine excretion (Goldberg *et al*., 2003; Walle *et al*., 2004). The absorption of Resv is remarkably high because of the low solubility in aqueous media, and the consistent result has been reported in the study of absorption in the human intestine using Caco2 cell lines.

The transport of Resv is taken place by trans-epithelial diffusion (Delmas and Lin, 2011). The transport of resveratrol was independent of the time, and the absorption is nonlinear with the extensive formation of metabolites. It is reported that the metabolism of Resv may be the rate-limiting step for the transport of Resv to the systemic circulation. The Resv metabolites can be transported to the systemic circulation by an active transport mechanism (Walle, 2011). The repeated dose study has been done for enhancing the absorption and bioavailability of Resv to improve the efficacy of the treatment. The linearity was reported between plasma concentration and administered dose when the range was 25 to 5,000 mg. Since the high amount of 5,000 mg was administered, the peak level of plasma was reported only approximately 500 ng/ml, which may be due to poor aqueous solubility of Resv. The enhanced bioavailability might be achieved by saturation of metabolism by administering the dose repeatedly (Almeida *et al*., 2009; Boocock *et al*., 2007).

Studies have also been carried out using rats to quantify trans-Resv in the tissues, including the brain. After 30 minutes of administering polyphenol intravenously, Glucuronide conjugate increased from 33% to 79%, Resv decreased from 59% to 12%, and sulfate conjugate does not have a stable peak as it might have undergone extensive urinary excretion. Therefore, the author reported that the glucuronide conjugate concentration in plasma shows 4.9-folds more than sulfate conjugate. It implied that the leading metabolic pathway of Resv in the rat was glucuronidation. The trans-Resv extractions from the different tissues were done by the liquid extraction method. From this study, at 90 minutes from the time of administration of trans-Resv 15 mg/kg intravenously, the quantity detected in the kidney and lungs were higher than the tissue extracts of the brain and testes. The amount (Juan *et al*., 2010) is determined as represented in Table 1.

In contrast, the trans-Resv and its sulfate and glucuronide conjugation were comparatively low in the testes and brain. This may be due to eliminating xenobiotics by using ATP binding cassette (ABC) transporters from various organs (Dauchy *et al*., 2008). Despite the *in vitro* study that reported the conjugation of Resv with glucuronide in the brain (Sabolovic *et al*., 2007), the excretion of the glucuronide conjugate can occur by breast cancer-resistant protein (BCRP) and multidrug resistant

Table 1. Quantity of resveratrol in different organs after 30 minutes of Intravenous administration.

Tissues	Concentration of trans-Resv	Concentration of glucuronides conjugates	Concentration of sulfate conjugates
Kidney	1.45 ± 0.35 nmol/g	2.91 ± 0.19 nmol/g	Sulfate conjugate was not detected.
Lungs	1.13 ± 0.34 nmol/g	0.28 ± 0.02 nmol/g	0.42 ± 0.10 nmol/g
Brain	0.17 ± 0.04 nmol/g	Glucuronide conjugate was not found in the brain	0.04 ± 0.10 nmol/g
Testes	0.05 ± 0.01 nmol/g	0.70 ± 0.35 nmol/g	0.23 ± 0.01 nmol/g

protein 2 transporters. In another study, diffusion efficiency and bioavailability of Resv were determined by observing the concentration in the brain by administering it through different routes for CNS tumors. From this study, the systemic application of Resv can only reach the brain when an excessive quantity is administered. These reports suggest that Resv can cross blood–brain barrier (BBB), but the systemic route of administration did not achieve the curative level. They have administered Resv by different routes intraperitoneal, intrathecal, and external carotid artery (ECA) to achieve a therapeutic level of bioavailability in the brain. From the results, the LP route achieved a 5-fold higher drug peak concentration in the entire brain. Also, the brain's bioavailability achieved by the LP route shows 8.5–38.5 times more than the IP route of administration when the dose was 6% lower than the IP injection. The author suggests that the bioavailability of the drug reaching the intracranial part of the brain was considerably higher in LP than in ECA injection (Shu *et al*., 2015).

Phase I clinical trials (Boocock *et al*., 2007) were conducted with a single dose of oral administration of Resv in the healthy volunteers to ensure safety and efficacy profile. In this study, after oral ingestion of Resv in different amounts of 0.5, 1.0, 2.5, and 5.0 g, the drug appears to be absorbed rapidly into the systemic circulation and achieved plasma peak concentration in 0.83 to 1.5 hours. The plasma peak concentration of the source compound from the administered dose ranges between 73 and 539 ng/ml. The concentration of metabolites increased by 20-folds than that of the parent compound, and the major metabolites were found to be two monoglucuronide conjugate and Resv 3-sulfate conjugate. Resv 3-sulfate conjugate shows higher concentrations between 1,135 and 4,294 ng/ml in all three major metabolites, almost 2-folds higher than monoglucuronide conjugates. In addition, Resv and metabolites have shown rapid excretion. Nearly 77% of the compound and its metabolites are excreted in 4 hours after the administration of 500 mg dose, and the author suggested that the repeated dose could enhance the bioavailability of Resv. Almeida *et al*. (2009) investigated the safety and pharmacokinetics of oral-multiple-dose regimens of four different doses in healthy volunteers, and the doses were administered every 4 hours. The author has reported that there was no severe adverse reaction throughout the study. The minimum quantity required to show desired pharmacological action was more than 5 µm/l, and after the repeated dose of Resv, the plasma concentration required for therapeutic activity was not achieved. The plasma peak concentration of Resv for four different doses (25, 50, 100, and 150 mg) was 3.89, 7.39, 23.1, and 63.8 ng/ml, and the half-life was improved from 1 to 2 hours followed by single administration to 2–5 hours followed by the repeated dose. The author concluded that the Resv tolerance in *in vivo* was in the desired range. However, the periodic dosing regimen was low, followed by the plasma concentration even in high amounts of Resv.

Sawda *et al*. (2017) carried out phase II clinical to study the safety and high dose tolerability of Resv. The author investigated it with randomized 119 participants, double-blind, placebo-controlled in patients with mild-to-moderate AD. The 119 patients were randomized for placebo or Resv (pure synthetic) started with 500 mg once a day orally with dose intensification by 500 mg once in 13 weeks until 2,000 mg was reached per day. From the study of 52 weeks, the oral dose of 2,000 mg of Resv was safe and had good tolerability in the patients with mild-to-moderate AD (Sawda *et al*., 2017). The bioavailability of resveratrol in the brain using various nanocarriers has been summarized in Table 2.

PHARMACOLOGICAL ASPECTS OF RESVERATROL IN ALZHEIMER'S AND PARKINSON'S DISEASE

As the Resv possesses multiple target strategies, it acquired significant attention. Due to its numerous target strategies, it regulates various pathways related to disease pathology. Furthermore, it plays a role in overcoming the resistance connected to specific drug targets. Since Resv possesses multiple targeting strategies, the interaction has a lower affinity than single-target drugs. Due to its lower affinity than single-target drugs, it has lesser side effects. Resv, a non-flavonoid compound, is well known for its pharmacological properties, including antioxidant, anti-inflammatory, neuroprotective, antiviral, anticancer, and antiphoto aging effects. NDDs are a significant cause of global disease burden with increasing population and average lifespan. Globally, there is an increase in the prevalence of the neurodegenerative disease. Alzheimer's Association report states that in the United States, about 5.8 million individuals are leading their lives with AD. This disease is reported as the primary neurodegenerative

Table 2. Bioavailability of resveratrol in the brain followed by intranasal administration of nanocarriers.

Reference	Animal	Administered dose	Dosage Form	Bioavailability in brain
Pangeni *et al*. (2014)	Wristar rat	Dose equivalent to 2.7mg/kg	Nanoemulsion	3,976.25 ± 118.62 ng/ml
			Solution	2,792.76 ± 137.21 ng/ml
Nasr (2015)	Albino rats	50 µl	Nanoemulsion	1,937.9 ± 221 ng/g
			Solution	279.57 ± 43.4 ng/g
Hao *et al*. (2016)	Albino mice	Dose equivalent to 2.0mg/kg	Nanosuspension (insitu gel)	60.42 ± 35.14 ng/g
Ahirrao and Shrotriya (2017)	Wristar rat	Dose equivalent to 1.29mg/kg	Cubosomal (insitu gel)	564.49 ± 2.24 ng/ml
			Solution	133.7 ± 4.1 ng/ml
Rajput *et al*. (2018)	Male Sprague-Dawley (SD) rats	Dose equivalent to 2 mg/kg	NLC (Insitu gel)	No PK reported
Kotta (2021)	Wristar rats	Dose equivalent to 2.0 mg/kg	Nanoemulsion	5,762.30 ± 316.9 ng/ml
			Suspension	3,069.27 ± 215.2 ng/ml

disease, and it is more common among older people. Almost 96% of the total Alzheimer's population falls above 65 years of age. From the study by the PD foundation, more than 10 million people are affected by PD, and it is reported as the second most common neurodegenerative disease.

Alzheimer's is referred to as AD; it is a disease with neurological reasons that ends in the loss of cortical and hippocampal neurons. It can be referred to as the gradual destruction of cognitive functions followed by disinhibition, disorientation, and aphasia. AD is most common in older adults with neurodegeneration, and the disease progression is mainly due to misfolding of tau and β-amyloid peptides (Hardy, 2006). Neuritic plaques and neurofibrillary tangles alter the peptides (Wang *et al*., 2017a). These altered peptides in the brain cause generation of reactive oxygen species (ROS), neuro-inflammations, and neuronal death (Heneka *et al*., 2015; Wyss-Coray and Rogers, 2012).

Resv shows its activity in various aspects that helps in the management of disease, including reducing oxidative stress by ROS prohibition, reducing glutathione levels, and elevating enzymes such as glutathione and superoxide dismutase. The decline in oxidative stress can also be claimed by decreased lipid peroxide. Resv involves in the management of neuro-inflammation by reducing inflammatory cytokines including IL6, IL-1β, and TNF-α. Also, the inhibition of microglial signaling by the transcription factor (NF-kB) manages the neuro-inflammation by decreasing the formation of enzymes such as COX-2, NO-synthase (Kim *et al*., 2006). Resv increases anti-apoptotic Bcl-2 and decreases the expression of pro-apoptotic protein Bax. In general, the Bcl-2 proteins family has contradictory functions in apoptosis regulation. The regulation of cell death or survival can be determined by interpretation of the relative ratio of antiapoptotic and pro-apoptotic protein. Resv plays a role in biological aging by activating the SIRT1 enzyme that prevents oxidative stress and cell apoptosis, thereby acting as an antiaging agent. Resv also has a pharmacological activity on other NDDs because of its well-known motor and cognition-based enhancements along with its antioxidant, anti-inflammatory, and antiapoptotic properties. This polyphenol eradicating the root cause of disease induces scavenging and degradation of accumulated and aggregated amyloid-β. Several studies reported that Resv could prevent misfolding of tau protein and showed reduced tau-protein levels in rat models (Al-Bishri *et al*., 2017).

Additionally, it modulates hyper-phosphorylation and inhibits aggregation (He *et al*., 2017; Pasinetti *et al*., 2014). Another study also concluded that Resv could protect tau protein's misfolding by stimulating de-phosphorylation that relates to inhibiting CaMKII, GSK-3β, and activating PP2A (phosphatase-2 protein) (Jhang *et al*., 2017). The modulation in the misfolding of proteins has been reported in the phase-2 clinical trial that there is a suppression of amyloid-β levels in both plasma and cerebrospinal fluid (CSF).

PD is the second greatest common neurological movement disorder that affects almost 1% of the global population over 65 years of age (de rijk *et al*., 1997). It can be distinguished by rigidity, bradykinesia, and tremor. The primary pathology of the disease is characterized by a particular loss of dopaminergic neurons and the existence of Lewy bodies. Resv has the ability against the primary pathology of disease due to its cytoprotective activity. Resv can protect neurons by activating AMP activated protein kinase (AMPK) and SIRT1 which regulates the clearance of damaged mitochondria or misfolded proteins. On the other side, SIRT1 and AMPK are activators of the gene PGC-1α that manage oxidative stress and enable the biogenesis of mitochondria (Ferretta *et al*., 2014; Wu *et al*., 2011). Resv promotes the survival of neuron cells by regulating apoptotic and pro-apoptotic proteins such as Bax and Bcl-2 that release neurotrophic factors including Brain, glial-cell, and astroglia-derived neurotrophic factors (Brain derived Neurotrophic factor, Glial cell derived neurotrophic factor, and Astroglia derived neurotrophic factor) on dopamine neurons (Bournival *et al*., 2009; Zhang *et al*., 2012). Furthermore, Resv is also involved in managing secondary factors, including oxidative stress by restoring antioxidant defense, and dopamine in the striatal region was indicated by normalizing denervated neurons (Khan *et al*., 2010). The neuro-inflammation and pro-inflammatory cytokines play an essential role in the formation and progression of PD. It is regulated by reducing the levels of TNF-α, IL-6, IL-1β (inflammatory cytokines), and COX-2 levels (Degan *et al*., 2018; Jin *et al*., 2008; Lofrumento *et al*., 2014). Therefore, Resv holds immense ability to manage Parkinson's and AD (Fig. 1).

NANOTECHNOLOGY-BASED STRATEGY FOR RESVERATROL DELIVERY IN NEUROLOGICAL DISORDERS

Resv has an aqueous solubility of 50 µg/ml, and it has good solubility in organic-based solvents such as Dimethyl sulfoxide, dimethylformamide, and ethanol, and it has PKa value of 11.4, 9.8, and 8.8 (López-Nicolás and García-Carmona, 2008; Robinson *et al*., 2015). It has a partition coefficient of 3.0. The chemical structure of Resv has been illustrated in Figure 2. The rate of transfer of mass across the biological membrane depends upon the aqueous solubility of the compound. Based on the dissolution of the compound and its absorption, the drug can be categorized in the Biopharmaceutical Classification System (BCS) classification. Because of the poor aqueous solubility and high absorption of Resv, it is classified under Class II BCS classification. The limited bioavailability of the drug is due to its poor solubility (Amidon *et al*., 1995; Amri *et al*., 2012; Das *et al*., 2008), and thereby, its clinical uses are restricted (Chan and Stewart, 1996; Hurst *et al*., 2007). Handling the various technologies and techniques can improve the bioavailability of Class II BCS drugs (Krishnaiah, 2010; Kumar *et al*., 2013). Administration of drugs in nanocarrier using surfactant can enhance the solubility (Aliabadi and Lavasanifar, 2006; Rangel-Yagui *et al*., 2005; Vinarov *et al*., 2018). Also, the simple techniques including micronization, co-solvency, precipitation, or evaporation techniques can be used for enhancing the solubility of a poorly soluble drug (Buckley *et al*., 2013; Kalepu and Nekkanti, 2015; Savjani *et al*., 2012; van Hoogevest *et al*., 2011). Noticeably, the utilization of compounds in nanotechnology has offered an essential tool for enhancing solubility and bioavailability of drugs and its capability to targeting the drug to the site of action, including the brain. Also, the drug administered in nanotechnology can minimize the dose-dependent adverse and toxic reaction (Farokhzad and Langer, 2009; Fonseca-Santos *et al*., 2015; Park, 2007, 2013). Resv incorporated in nano carrier-based formulations (Jung *et al*., 2015; Lu *et al*., 2009; Pangeni *et al*., 2014; Siddiqui *et al*., 2015; Summerlin *et al*., 2015) showed enhanced solubility and biological effects, including anti-inflammation, antioxidant, neuroprotective, anti-viral, anti-cancer,

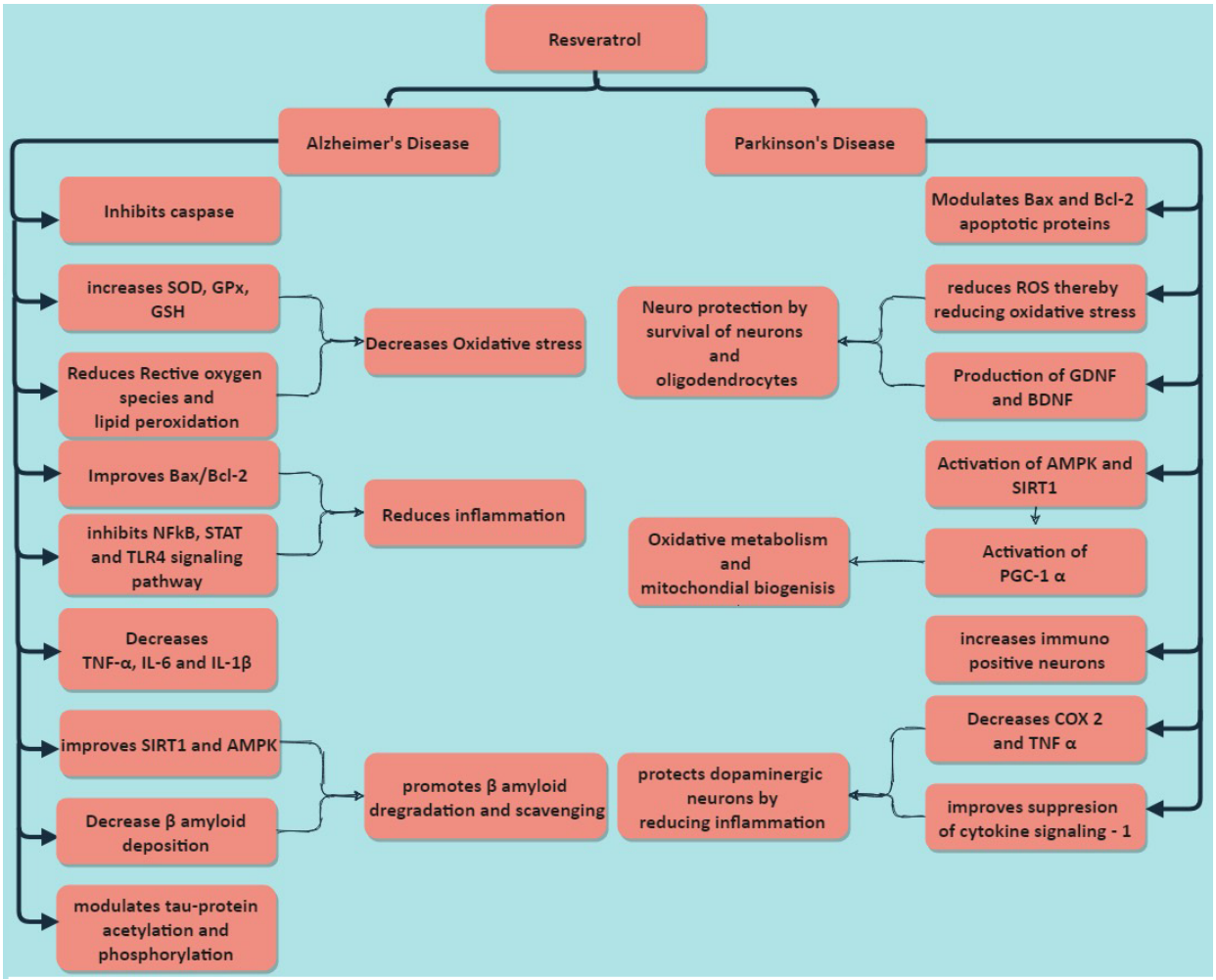

Figure 1. Mechanism of action of resveratrol in AD and PD.

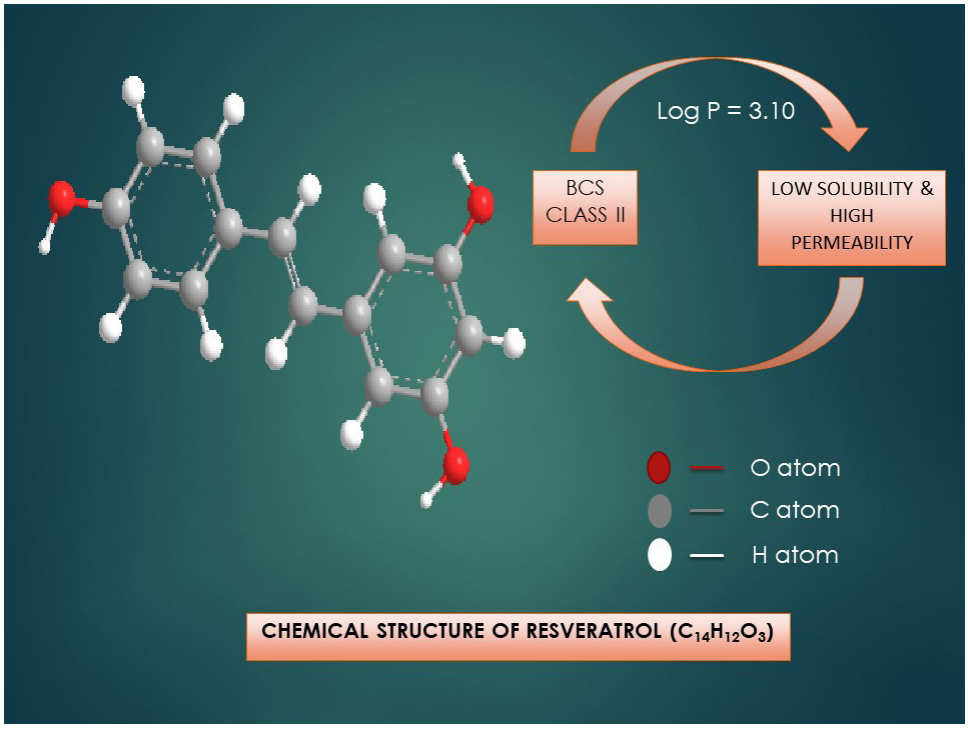

Figure 2. Chemical structure of resveratrol.

and anti-photoaging effects (Alarcón De La Lastra and Villegas, 2007; Chan *et al*., 2015; Csiszar, 2011; Fujimura *et al*., 2016; Quadros Gomes *et al*., 2018; Varoni *et al*., 2016). Additionally, Resv has a beneficial effect on NDDs (Andrade *et al*., 2018; Bastianetto *et al*., 2015; Farooqui, 2012; Singh *et al*., 2013).

For the prevention of foreign molecules entering, the human body is made up of biological barriers. The barrier between the CNS and PNS is considered a vital element. The blood–brain barrier (BBB) and the CSF play a crucial role in the protection of the brain from the numerous foreign molecules, including pathogens, and protect its unique nature (Engelhardt and Liebner, 2014). The BBB acts as a junction between CNS tissues and systemic circulation. Hence, it limits the foreign molecule (including therapeutic drugs) from entering the brain and promotes the passage of essential hormones and nutrients (Patel and Frey, 2015). So, nearly all the drugs with high molecular weight and most of those with small molecular weight cannot enter CNS followed by systemic or oral administration (Pardridge, 2016). Still, there are two fundamental mechanisms through which therapeutic substance nter into the CNS, viz., Active and passive transport through endothelial cells of BBB. But these cells make it impossible for passive transport of therapeutic molecules by tight and rigid junctions (Rankovic, 2014).

The BBB is composed of endothelial cells linked with pericytes and astrocytes, and it acts as a barrier that is responsible for the prevention of almost many drugs, large molecules, and peptides to enter the brain (Abbott *et al*., 2006; Maussang *et al*., 2016; Pardridge, 2005). Several layouts other than pericytes and astrocytes are also responsible the for impermeability of BBB which is preventing the entry of infectious substance and toxic compounds to the brain including tight junction, high expression of proteins which has a role in efflux transport like multidrug-resistance protein-1, P-glycoprotein (P-gp), degrading enzymes, and BCRP (Abbott *et al*., 2010; Gabathuler, 2010). Despite its biological activity, it is considered a significant barrier in managing successful neurological disorders. It is expected that the novel approach and the novel formulations could enhance the penetration of drug molecules through BBB in brain delivery.

The strategy for new formulations is to attain effective treatment for patients with minimal side effects, managing pharmacokinetic profile accuracy, drug release control, and delivering the drug to a specifically targeted cell (Anselmo and Mitragotri, 2014; Bae and Park, 2011; Dong, 2018; Tiwari *et al*., 2012). Formulation based on nanotechnology systems with particle size 1–1,000 nm was used to treat various diseases (Park, 2007) comprising diabetes, cancer, cardiovascular disease, microbial, and inflammatory diseases (Patra *et al*., 2018). These nanotechnology systems exhibit reduced toxicity and adverse effects with economical price and better therapeutic value (Jain *et al*., 2015). It is comprised of various biodegradable ingredients that include lipids, synthetic or natural polymers, and metals. These biodegradable materials are called nanocarriers (Khodabandehloo *et al*., 2016; Suri *et al*., 2007). The various nanocarriers and their formulation strategy in the development of Resv nanocarriers are given in Figure 3.

Nanocarriers

Brain delivery of the drugs can be done in three ways, viz., intracerebroventricular (ICV) injection, oral, or intravenous (IV) injection, and Intranasal administration. Intravenous injection and oral administration are the primary routes that face challenges in targeting the brain due to BBB, leading to low bioavailability and low effectiveness (Agrawal *et al*., 2017). To overcome these bioavailability drawbacks, a novel tool (nanotechnology-based strategy) has been developed as a favorable carrier in the treatment of neurological disorders to transport the drug across BBB (Goldsmith *et al*., 2014; Kreuter, 2014; Patel *et al*., 2012; Srikanth and Kessler, 2012). CNS permeability can be improved by using surface-modified nanocarriers to bypass BBB through

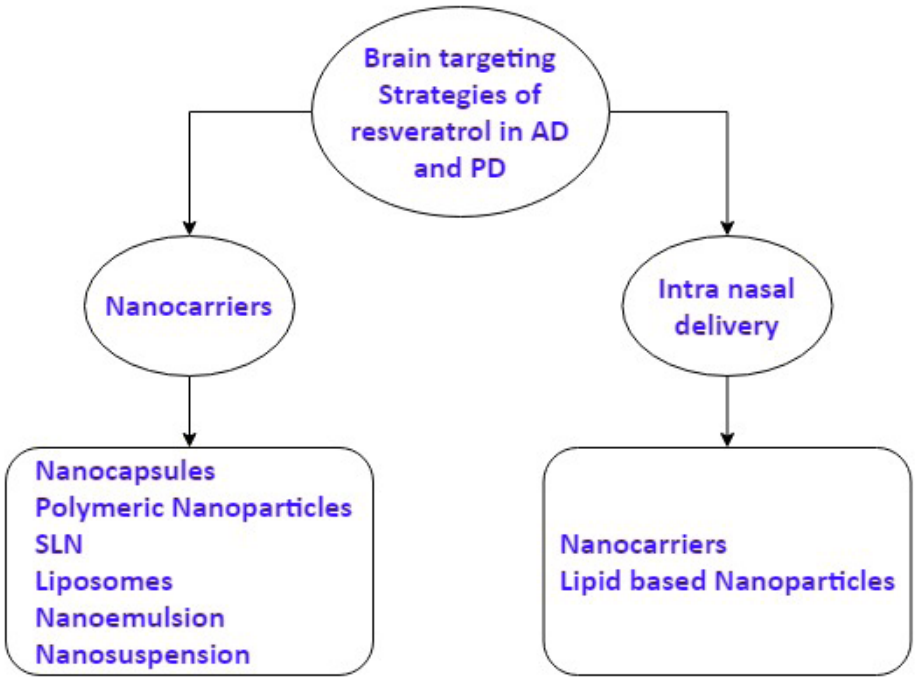

Figure 3. Formulation Strategies of Resveratrol to target the Brain

receptor-mediated endocytosis mechanism (Masserini, 2013; Wong *et al*., 2012). Hence, the application of nanocarriers in delivering resveratrol to the brain has significant importance. Here, we included an overview of several nanocarriers for the resveratrol delivery to the brain in managing Alzheimer's and PD.

Liposomes

Liposomes are spherical vesicles comprised a phospholipid bilayer that has both hydrophilic and lipophilic properties. Liposomes are different in lamellarity and size that depends on the manufacturing procedures and phospholipids composition (Wang *et al*., 2017b). The delivery systems are known for successful brain delivery of specific proteins and growth factors (Rabanel *et al*., 2015). Liposomes have specific properties like delivering both lipophilic and hydrophilic drug candidates with less toxicity and biocompatibility (Barbara *et al*., 2017). Even though liposomes have lipophilic nature that helps in the transportation through biomembrane, the BBB stays as a primary obstacle that precludes the penetration of the molecule from entering the brain. These challenges can be overcome by using surface-modified liposomes to facilitate brain delivery through BBB by receptor-mediated endocytosis mechanism. Wang *et al*. (2018a and 2018b) carried out a study on the formulation and characterization of modified (magnetic) liposomes for enhancing the bioavailability of Resv in the brain. The author had used ferrous sulfate and ferrous chloride by co-precipitation method to formulate modified liposomes followed by the fabrication of resveratrol forming Fe_3O_4 modified resveratrol liposome. The results showed that slow and sustained release was observed in *in vitro* studies. Apart from this, magnetic oxide nano formulation owns enhanced Resv capacity and stability. *The in vivo* result revealed that the magnetic oxide Resv liposome crossed the BBB, followed by the improved drug availability in the brain using an external magnetic field. Hence, the author suggested that this formulation offers a promising platform for treating PD.

Wang *et al*. (2018a) formulated Resv loaded liposomes by using lecithin and cholesterol. It has been tested for its efficiency in rats, and it was reported that Resv liposomes exhibit way more efficiency than free Resv. Another author had formulated polymeric nanoparticles using polysorbate 80, dichloromethane, polyvinyl alcohol, and polylactide. The Resv loaded polymeric nanoparticle and free trans Resv were tested in mice against 1-methyl 4-phenyl- 1,2,3,6- tetrahydro pyridine (MPTP). The Resv loaded polylactide nanoparticles coated with tween 80 showed the promising effect to transport to the brain and in the management of PD (Wang *et al*., 2011). Based on the results, the liposome-based delivery would be more effective in treating NDDs. Upon oral or intravenous administration, it may have some challenges like rapid elimination, accumulation in liver and spleen, or may undergo degradation by gastrointestinal enzymes. Moreover, liposome-based formulations face challenges in mass manufacturing, sterilization techniques, and it has less storage stability (Liu *et al*., 2015; Noble *et al*., 2014).

Polymeric nanoparticle

Nanoparticle-based effective delivery of the drugs to the brain-related disorder provides alternative possibilities for enhanced brain bioavailability. It is a promising approach to overcome the challenges in delivering drugs for treating CNS diseases. These colloidal systems can encapsulate the drugs in both liquid and solid-state. This polymer-based nanoparticulate delivery provides various advantages include biocompatibility, improved absorption, low toxicity, and targeted delivery (Naahidi *et al*., 2013). Primary advantages for delivering the drug to the brain in the polymeric nanoparticle are rapid biodegradability and biocompatibility of the polymer used in the nanoparticle.

Lindner *et al*. (2015) carried out a study investigating the neuroprotective effect of poly (lactide) polysorbate 80 (PLA-PS80) coated Resv nanoparticle in mice models. They used a single emulsion solvent evaporation method to formulate nanoparticles using polysorbate 80 and polyvinyl alcohol. The PLA-PS80 nanoparticle has been used in MPTP-induced PD in mice. They have tested for both biochemical and behavioral changes and reported enhanced activity of resveratrol in the nanoparticulate system as it increases the brain bioavailability. The effectiveness of free Resv in protecting the neuron is limited from MPTP-induced PD as its pharmacokinetics is not favorable for brain delivery. The surface patterns of the nanoparticle can direct the nanoparticle distribution to the brain (Gelperina *et al*., 2010). Based on the knowledge, the fact shows that the PS80 coated nanoparticle improves brain bioavailability through receptor-mediated endocytosis mechanism followed by the P-gp inhibition (Göppert and Müller, 2005; Wohlfart *et al*., 2012). In BBB, the proteins associated with the low-density lipoprotein receptor are expressed (LRP1 & 2). The PS80 coating from the nanoparticle adsorbs the apolipoprotein from the blood that mimics the low-density lipoprotein receptor activity in BBB (Shamenkov *et al*., 2002). P-gp in the BBB limits the passing of exogenic molecules to the brain, and it is extensively available at BBB. The PS80 coated nanoparticle inhibits the P-gp efflux (Kreuter, 2005). These mechanisms can enhance the bioavailability in the brain by acting simultaneously. So, this study with PLA-PS80 enhances the neuroprotective effect of Resv by enhancing the Resv concentration in the brain. The polymeric nanoparticle may undergo prompt clearance from the systemic circulation due to the interaction among the reticuloendothelial system (RES) and the nanocarrier.

Solid lipid nanoparticle (SLN)

The use of lipid nanoparticles suggests an alternate strategy in treating CNS disorders for brain delivery as lipid nanoparticles prolong the elimination by escaping from the interaction with the RES. The mechanism associated with the transport of lipid nanoparticles to the brain would be by receptor-mediated endocytosis (Shah *et al*., 2015; Wen *et al*., 2017). The dispersion of spherical solid-state lipid particles in water or aqueous surface-active agents is referred to as SLN (Kaur *et al*., 2008). These nanoparticles can cross BBB because of their lipophilic property. Loureiro *et al*. (2017) had formulated and evaluated antibody functionalized solid lipid nanoparticles to overcome the challenges from rapid metabolism, elimination, and to improve the permeability of Resv to the brain. They have worked on the formulation of solid lipid nanoparticles encapsulated with Resv by high shear homogenization and ultrasonication method; they used 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol) (DSPE-PEG) and LissRhod-PE for the formulation. SLN assured its stability by size, Zeta Potential (ZP), polydispersity index (PDI), and surface morphology with an average particle size—176 nm and 94% of EE (encapsulation efficiency). To improve brain bioavailability, SLN was conjugated with an antibody (OX-26). The brain targeting efficiency of SLN was tested in *in vitro* model

and reported that antibody functionalized SLN showed 4-fold enhanced transportation to the brain compared to SLN (Loureiro *et al*., 2017). The author has tested the formulation on endothelial cells that are similar to the human brain. This cellular model permits the prediction of drug permeability across BBB to the brain.

The result suggests that the OX-26 antibody functionalized enhances the SLN permeability through BBB than LB 509 antibody functionalized SLN and non-functionalized SLN. Another study has been carried out by Neves *et al*. (2016). They developed apolipoprotein functionalized Resv based SLN to enhance the brain bioavailability of Resv by the high shear homogenization technique. The permeability was studied in the cell monolayers of hCMEC/D3 by using free Resv and functionalized SLN. The functionalized SLN showed 1.8 times higher penetration than free Resv. This enhanced permeation may be due to the receptor-mediated endocytosis mechanism in BBB.

Polymeric micelle

Lu *et al*. (2009) formulated Resv loaded polymeric micelle to defend against oxidative stress induced by Aβ. The formulation was developed using Polycaprolactone as block copolymer for the hydrophobic core and PEG as hydrophilic shell, followed by lyophilization and drying. The size of the micelles was reported as less than 100 nm with a uniform spherical shape. The encapsulation efficiency was reported as having a high value of 89%. The polymeric micelles of Resv and free Resv were tested in PC12 cell lines for short-term effect, long-term effect, and 2 hours of pre-treatment for the protection against Aβ. The free Resv was effective and did not report any cytotoxicity in the short-term study, even at a higher concentration of 50 µm. Still, in the long-term study (48 hours), Resv has shown cytotoxicity at the concentration of 5–10 µm to PC12 cells. Also, in pre-treatment for 2 hours, Resv failed to protect the cells against Aβ. The same was treated with Resv loaded polymeric micelles. It was reported that it was protective, nontoxic, and positive against the activity of caspase 3 and oxidative stress against Aβ (Lu *et al*., 2009). Improved brain uptake of resveratrol-loaded polymeric micelles to the brain through intracellular delivery to treating NDDs offers an effective delivery based on the evidence presented in this segment. Additional study is required to validate this delivery system.

Nanocrystals

Xiong *et al*. (2020) had formulated the Resv nanocrystals to improve the bioavailability of Resv in the brain by the antisolvent precipitation method. The Resv nanocrystals were administered orally in the rats and showed better absorption than free Resv with an enhanced concentration in the brain and plasma. From the pharmacokinetic study in the rats, the maximum concentration of Resv (2.61 ± 0.21 µg/ml) was attained at 4 hours after oral administration of Resv nanocrystals (4 mg/kg). The brain bioavailability of Resv may be achieved by absorption into systemic circulation followed by the penetration through BBB to the brain (Chen *et al*., 2016). The hydroxypropyl methylcellulose in the formulation enhances the Resv nanocrystal penetration to the brain. Additionally, the elimination half-life of Resv nanocrystals was delayed in the brain compared to the plasma elimination half-life, which shows that the elimination of Resv in the plasma is more than that of the brain (Xiong *et al*., 2020).

Lipid core nanocapsules

Resv loaded- lipid core nanocapsule (LCNC) had formulated by Frozza *et al*. (2010) to enhance the bioavailability in the brain. LCNC was formulated by interfacial deposition of the polymer using poly (ε-caprolactone), capric triglyceride as a lipid, tween 80 as a surfactant, and span 60 as a stabilizer. The nanocapsules loaded with Resv tested their stability by performing particle size, ZP, and PDI. The Resv loaded LCNC administered in animals reported 6.6-, 3.4-, and 2.5-times higher liver, kidney, and brain concentrations, respectively, than those treated with free trans-Resv. The results from the *in vivo* study show that the Resv loaded LCNC could cross BBB to improve the concentration in the brain (Frozza *et al*., 2010). The other research has been reported in Frozza *et al*. (2013a) by using Resv loaded LCNC on Aβ-induced neuronal inflammation in hippocampal organotypic culture. They underwent both co-treatment and pre-treatment with Resv loaded LCNC for testing against reactive oxygen species and Aβ-induced cell death. The result revealed that pre-and co-treatment Resv loaded with LCNC can reduce Aβ triggered neuronal inflammation in hippocampal culture. Despite its pharmacological action, the free trans Resv showed efficient results only in higher concentrations, while Resv loaded LCNC showed significant neuronal protection in a lower concentration. Also, a higher antioxidant effect was reported by Resv loaded LCNC than free trans Resv. The author concluded in such a way that Resv-loaded LCNC with free Res could be a promising strategy in the prevention or delay of Aβ triggered neuronal inflammation (Frozza *et al*., 2013b). This study has been extended for testing the efficiency of Resv loaded LCNC against ICV (intra-Cerebro ventricular) injection in rats with Aβ1-42 induced memory dysfunction. The free trans Resv protects the rats from Aβ induced disturbances in cell signaling, microglial and astrocyte activation, and behavioral impairments in *in vivo*. The author has used Resv loaded LCNC to observe the brain's concentration. The *in vivo* study reported that this formulation enhances the biodistribution of Resv in the brain (Frozza *et al*., 2013).

Even though various routes like oral, IV, and IP are available to administer the drug-loaded nanocarriers to the brain, intranasal delivery plays a prominent role compared to the routes mentioned earlier because they can directly reach the target region produce the desired activity. For this purpose, we have emphasized the intranasal delivery of resveratrol for the management of AD and PD predominantly. The summary of the nanocarriers used in the formulation of Resv to manage AD and PD was given in Table 3.

Nasal delivery

The intranasal route of administration presents a promising and non-invasive approach for drug delivery directly to CNS through the olfactory region by bypassing BBB and CSFB (100,101). The nasal route can deliver the drug at a faster rate, and high absorption of the drug in the brain can be achieved with better patient compliance (Al Bakri *et al*., 2018; Johnson and Quay, 2005; Ozsoy and Gngör, 2011), but it has some limitations including rapid mucociliary clearance followed by less absorption through nasal epithelium (Marttin *et al*., 1998; Meredith *et al*., 2015). Several drug delivery systems include mucoadhesive systems or nanoscale formulations (Chaturvedi *et al*., 2011; Jiang *et al*., 2010; Mistry *et al*., 2009; Ugwoke *et al*., 2005) and chemical-based penetration enhancers present strategies that could

Table 3. Resveratrol loaded nanocarriers in the management if AD and PD.

Carrier	Formulation materials	Route of Administration	Model	Major findings	Reference
Liposomes	Lipoid S 100, TPGS, Cholesterol	Intravenous delivery	Rats	Formulations improved plasma half-life by up to 18 times, and brain distribution increased by 9 times	(Vijayakumar *et al*., 2016a)
	TPGS, Cholesterol	Intravenous delivery	Rats	When compared to free resveratrol, the formulation had a higher t1/2, AUC, and MRT.	(Vijayakumar *et al*., 2016)
	Soy lecithin, Cholesterol	Oral- Gastric gavage	Rats	Resveratrol loaded liposomes showed a higher protective effect when compared to free resveratrol	(Wang *et al*., 2011)
Polymeric Nanoparticles	Polysorbate 80, dichloromethane, polyvinyl alcohol, and poly lactide	Intraperitoneal delivery	Mice	Resveratrol loaded Nanoparticles showed significance in protecting neurons against neurochemical and behavioral changes induced by MPTP	(Lindner *et al*., 2015)
Magnetic liposomes	TPGS, Cholesterol, Ferreso ferric oxide, ferric chloride, and Chitosan	Intravenous delivery	Rats	The combination of Res-lips@Fe3O4 and an external magnetic field acts as a promising platform for crossing the BBB that effectively treat cerebral disease.	(Wang *et al*., 2018a)
Lipid core Nanocapsules	Poly ε-caprolactone, Caprylic, Tween 80, Span 60	Intraperitoneal route	Rats	The bioavailability of Trans-Resveratrol in the Brain was increased when given as lipid core nanocapsules.	(Frozza *et al*., 2010)
	Poly ε-caprolactone, Caprylic, polysorbate 80, sorbitan monostearate	—	Organotypic hippocampal culture	Resveratrol-loaded Lipid nanocapsule showed its potential in managing the neudegenration process effectively by controlling neuroinflammation and followed Aβ triggered cell death.	(Frozza *et al*., 2013a)
	Poly ε-caprolactone, Caprylic, polysorbate 80, sorbitan monostearate	Intraperitoneal route	Rats	Lipid nanocapsules achieved a robustly increased concentration of resveratrol in the brain.	(Frozza *et al*., 2013b)
Polymeric Micelles	Methoxy polyethylene glycol, poly ε- caprolactone.	—	PC12 Cells	Resveratrol-loaded Nanoparticles protect PC12 Cells against Aβ toxicity while free resveratrol fails to protect them.	(Lu *et al*., 2009)
Solid-lipid nanoparticles	DSPE-PEG-2000, Polysorbate 80, Cetylpalmitate, LissRhod PE	—	Endothelial cell culture- the human brain	SLNs show promising effects in preventing the progression of Alzheimer's disease.	(Loureiro *et al*., 2017)
	Cetyl palmitate, polysorbate 80	—	hCMEC/D3 cells	The apolipoprotein functionalized SLN showed 1.8 times higher penetration than free Resv. This enhanced permeation may be due to the receptor-mediated endocytosis mechanism in BBB.	(Neves *et al*., 2016)
Nanocrystals	Polyvinylpyrrolidone (PVP K90), HPMC	Oral	Rats	The Resv-nanocrystals were administered orally in the rats and showed better absorption than free Resv with an enhanced concentration in the brain and plasma.	(Xiong *et al*., 2020)

be applied for overcoming these drawbacks for enhancing nasal absorption (Illum, 2003; Mittal *et al*., 2014; Sood *et al*., 2014). For the respiratory system, the interior structure of the nose or nasal cavity is the access point for the air inhalation and, by that, it builds up the front structure. The nose cavity is branched into binary with a septum in which the mucosal layer completely covers the cavity that provides immediate shelter from allergic and infectious pathogens to the body (Harkema *et al*., 2006).

In addition, the nasal cavity is split into three sections, viz., the nasal vestibule (wider cavity of the nostril), respiratory section (passage for inhaled air), and olfactory section (having olfactory receptors) (Wang *et al*., 2018b). For the sense of smell, the receptors in the olfactory region are responsible. It has the olfactory neuron cells instead of having tiny cilia like another part of the nasal mucosa (Xi *et al*., 2015). The neuronal cells emerge from the olfactory bulb in the nasal cavity and terminate in the neuroepithelium. This neuroepithelium is the only area of CNS that has direct contact with the external environment with the unique characteristics of the regeneration potential. Therefore, this site of the olfactory region is suitable for the utilization of drugs to target CNS. Only the matters/particles with <200 nm have the favorable circumstances to transport through the olfactory neurons (Ahmad *et al*., 2017). The fate of nanocarriers can be influenced by the size of the particle and the carrier (composition) (Samaridou and Alonso, 2018), followed by the administration through intranasal delivery. Apart from the olfactory neurons, the mucosa in the nasal cavity has a supply of maxillary and trigeminal nerves. These nerves provide various sensations to the rest of the areas in the

face. Still, the mechanism of nasal absorption to the CNS is not entirely known. Based upon the research carried out, there are two possible mechanisms of absorption of therapeutic agents. First, transport via neuronal path (olfactory or trigeminal neurons), and the second way comprises a lymphatic system and CSF (Mittal *et al*., 2014). The transport of therapeutic agents from the nasal cavity to the CNS either occurs by one or combined mechanisms. The olfactory neuronal pathway is considered as the primary mechanism of intranasal absorption of drugs to the CNS. Crossing the olfactory epithelium is the prerequisite for drug absorption by the olfactory nerves (Agrawal *et al*., 2018).

This transport of drugs is possible in three ways; para-cellular pathway, passive diffusion, and endocytosis mechanism by neurons. The hydrophilic drugs are transported by the para-cellular path, whereas passive diffusion is responsible for the absorption of lipophilic drugs. The molecular weight and hydrophobicity of the drug automatically alter the mechanism mentioned above (Bhise *et al*., 2008). Trigeminal nerves regulate sensory reports from the oral cavity, nasal cavity, and cornea. These trigeminal nerves innervate one end in the olfactory epithelium. The other end reached two different brain sites, viz., cerebrum, and near the pons, along with the frontal brain and the olfactory bulb to a lesser extent (Crowe *et al*., 2018). Accordingly, the trigeminal nerve pathway can also be the promising drug delivery pathway to the brain. Thorne *et al*. (2004) showed that a significant quantity of insulin-like growth factor-I was reached the brain via the trigeminal path. From the CSF of the brain in subarachnoid space, the lymphatic and CSF pathways are connected to the lymphatic system (nasal) into the perineural space through olfactory nerves. Yu *et al*. (2017) concluded that in the delivery of Evans blue to the brain, the lymphatic system acts as the bridge between nasal mucosa and mystacial pad. Johnston *et al*. (2004) showed evidence of radioactive substances in the cervical lymph node and nasal lymphatic system through the olfactory nerve channels injected into the CNS. Possibly, these pathways can help in the transportation of drugs from the nasal cavity to the CSF, and the perivascular area can distribute the drugs to other parts of the brain. Molecular weight, degree of ionization, and lipophilicity of the therapeutic molecule may influence the transportation and distribution of drugs into the CSF (Nau *et al*., 2010). Better distribution of the drug can be achieved by higher value lipophilicity. The individual input of these pathways to understand the transport of drugs from the nasal cavity to the brain is challenging. Still, the different studies with the radio-labeled molecule can support the perception of drug transport pathways from nose to brain. Although the drug enters the systemic circulation by oral or various route of administration, the drug should enter the brain by crossing BBB if not, there will be no pharmacological action that required for the management of disease (Gomes *et al*., 2016). The BBB has the transporters that allow the neuro-transmitters, nutrients, macromolecules, and amino acids to enter BBB by passing through endothelium (Abbott *et al*., 2010; Chen *et al*., 2004). The transport of drug through BBB can be achieved by triggering the transporter with functionalized nanocarriers with specific ligand-target for respective binding transporters (Abbott *et al*., 2010; Chen *et al*., 2004; Fonseca-Santos *et al*., 2015; Moura *et al*., 2019). The internalization of the drug-loaded nanocarrier can be achieved once the transporter identifies its ligand by promoting conformational change (Tamai and Tsuji, 2000). In the case of CNS disease, these transporters are either upregulated or downregulated. In AD, there is an upregulation of scavenger receptors (Eugenín *et al*., 2016; Wilkinson and El Khoury, 2012) and downregulation of low-density lipoprotein transporter (Helbecque and Amouyel, 2000) and glucose transporter (Gejl *et al*., 2017). In PD, there is an upregulation of glucose receptors (Aviles-Olmos *et al*., 2013). Functionalized nanocarriers and their targeting transporters showed promising results to target the brain (Moura *et al*., 2019).

In a study based on the nanostructured lipid carrier (NLC) *in situ* gel of Resv formulated by melt-emulsification probe sonication method, the author used Cetyl palmitate and capmul mono-diglyceride of medium chain fatty acids (MCM) (Solid lipid and oil) in a 1:1 ratio, using Acrysol K150 as a solubilizer and Poloxamer 188 and Tween 80 as the surfactant, reported the homogenous size with PDI less than 0.33 with singlet peak. The intranasal route was selected for administering for the management of AD, for which it resulted in five times enhanced permeation than the suspension form. The NLC based *in situ* gel showed significant progress in the memory function of rats from the study- amnesia induced model using scopolamine (Morris-water Maze's test) (Rajput *et al*., 2018). This shows the effective use of nanocarriers for brain delivery.

Pangeni *et al*. (2014) has planned to formulate the Resv loaded d- α-tocopherol (vitamin E) Nanoemulsion (NE) to manage PD to brain delivery. They used the Spontaneous emulsification method to formulate the kinetically stabilized product. Nanoemulsion followed high-pressure homogenization; they used vitamin E and Sefsol in a 1:1 ratio as oil phase in o/w type nanoemulsion, Tween 80 and transcutol P as surfactant and co-surfactant, respectively. The PDI and ZP values confirmed nanoemulsion's uniformity and stability, and its insignificant variation ensures a longer shelf life. The percentage of the cumulative release of drug for the post homogenized NE reported 1.5-folds higher release of the drug than pre-homogenized NE. A significant quantity of drugs had reached the brain through intranasal administration (non-invasive method). It enhances the brain bioavailability of NE due to the highly permeable and vascularized nasal area (Pardeshi *et al*., 2013; Pardeshi *et al*., 2013). It also enhanced the drug absorption facilitated by fewer enzymes and a significant surface area of about 150 cm^2. In addition to that, intranasal delivery is a substitute approach that efficiently bypasses the first-pass metabolism and BBB (Haque *et al*., 2012; Mittal *et al*., 2014). Histopathological study revealed that there was a reduced degeneration in the animals that received Resv NE. In the Resv NE treated animal group, there are considerably higher levels of Glutathione and Superoxide dismutase, and there was a decreased level of malonaldehyde.

Another author had developed Resv and curcumin-based mucoadhesive lipidic hyaluronic acid nanoemulsion to manage the neurodegenerative disease through the intranasal route to the brain. NE was formulated by spontaneous emulsification method using Labrafac lipophile, Labrafac PG as oil phase, and Cremophor 40, tween 80 as surfactants. PDI and ZP ensured the formulation's spherical morphology and stability. Based on the ZP and PDI value, the formulation was selected for hyaluronic acid encapsulation, conserving the antioxidant property and protecting it from deterioration. From the *in vitro* study results, nearly 60% of the drugs were released from the nanoemulsion by a diffusion-controlled release mechanism. Also, the *ex vivo* study confirmed that 2.86 mg/cm of Resv had been released in the nasal mucosa of the sheep.

Table 4. Intranasal delivery of resveratrol in managing AD and PD.

Carrier	Formulation materials	Route of administration	Model	Major findings	Reference
Nanostructured lipid carrier	Cetyl palmitate, Capmul MCM, Acrysol, Poloxamer 188, Tween 80	Intranasal delivery	Rats	enhanced delivery of Resveratrol to the brain through the nasal mucosa	(Rajput *et al*., 2018)
Nanoemulsion	Labrasol, Transcutol, Tween 80	Intranasal delivery	Rats	Higher Bioavailability of Resveratrol in Brain showed the efficient targeting capability of Nanoemulsion when given intranasally	(Pangeni *et al*., 2014)
	Labrafac lipophile, labarafac PG, Cremophor RH, Tween 80	Intranasal delivery	Rats	Intranasal delivery showed enhanced Bioavailability of Resveratrol in the brain	(Nasr, 2016)
Nanosuspension	Deacetylated gellan gum, ethanol	Intranasal delivery	Mice	Bioavailability of Resveratrol in the brain showed more than 2 folds enhanced availability in the I.N route than the I.V route.	(Hao *et al*., 2016)
Polymeric nanoparticles	Polysorbate 80, dichloromethane, polyvinyl alcohol, and polylactide	Intranasal delivery	Mice	Resveratrol loaded Nanoparticles showed significance in protecting neurons against neurochemical and behavioral changes induced by MPTP	(Lindner *et al*., 2015)
Cubosomes	Glycerol monooleate, poloxamer 407	Intranasal delivery	Rats	Resveratrol-loaded cubosomes showed better permeability and enhanced bioavailability in the brain in the I.N route.	(Ahirrao and Shrotriya, 2017)

Furthermore, the formulated Mucoadhesive NE was reported to be safe on rat nasal tissues. In the *in vivo* study, the Resv aqueous solution showed limitation in bioavailability as it was influenced by BCRP-efflux pump (Scheepens *et al*., 2010). The pharmacokinetic analysis of the mucoadhesive formulation of Resv reveals that the brain bioavailability of Resv increased by seven folds (1,937.9 ng/ml). This study proposes a safe and effective method for brain targeting delivery. Still, further work is required in the future for clinical application (Nasr, 2016).

Hao *et al*. (2016) formulated the Resv nanosuspension (RES-NS) based *in situ* gel for intranasal delivery to target the brain for CNS-related disorders. RES-NS was prepared by the antisolvent precipitation method using ethanol as solvent followed by lyophilization using mannitol as cryoprotectant. In the formulation of *in situ* gel deacetylated gellan gum (DGG) is used as an ion-sensitive polymer, glycerin as an isotonicity agent, and benzalkonium chloride as a preservative. The ZP and PDI assure the morphology and sensitivity of the formulation. 0.6% ion-sensitive polymer DGG showed promising gelling capability and suitable viscosity. A pharmacokinetic study revealed that the RES-NS in situ gel increased 2.88 times compared to Resv suspension *in situ* gel. DTE and DTP The concentration of Resv in the brain followed by intranasal delivery administration was 78.18% and 458.2% of DTE and DTP, respectively. The study shows that the Resv nanosuspension *in situ* gel can increase the resident nasal time and decrease nasal clearance (Hao *et al*., 2016).

Ahirrao and Shrotriya (2017) aimed to improve brain bioavailability by formulating Resv-cubosomes administered by the intranasal route. The cubosomes were prepared by the probe-sonication method using Lutrol F127 and glycerol monooleate. Here, lutrol F127 was used as a gelling agent and glycerol monooleate as monoglycerides. The optimized cubosomes assure its stability by particle size and PDI. The better entrapment efficiency was reported as 83.08% with ZP of -20.9mV, and 67% of the drug was released within 24h in the *in vitro* study. From the *in vivo* study, the intranasally (i.n) administered cubosomal *in situ* gel reported the higher concentration of Resv in the brain (564.49 ± 2.24 ng/ml) than drug solution administered intranasally (133.7 ±4.1 ng/ml) and drug solution administered orally (102.2 ± 9.8) and the author had concluded in a way that the cubosomal *in situ* formulation could be the better possible way to administer Resv to the brain intranasally (Ahirrao and Shrotriya, 2017).

Moreover, the novel strategy to deliver the Resv aerosol to the brain through intranasal delivery may offer a promising way to direct nose to brain transport. Aerosol inhalation offers the deposition of the drug on the nasal mucosa and the olfactory epithelium, followed by transportation to the olfactory region in the brain through the trigeminal or olfactory pathway (Khan *et al*., 2017). The study from another polyphenol reported that the aerosol formulation through the intranasal route enhanced the distribution of drugs in the brain than intravenous administration of the polyphenol (McClure *et al*., 2015). From this proof, intranasal delivery can be an efficient strategy to target the brain by bypassing the BBB that may offer better development in treating NDDs. Even though intranasal delivery offers promising benefits in brain delivery, there are some limitations including, mucociliary clearance, nasal toxicity, and drug degradation. These challenges can be overcome by administering a drug in nano formulation with appropriate delivery devices (Khan *et al*., 2017).The nanocarriers used in the formulation of Resv in managing AD and PD through the intranasal route were summarized in Table 4.

CONCLUSION

Despite having the drugs used in managing PD and AD, neither of them had reported reducing or preventing the neurodegeneration, which can only be used as a palliative treatment. Resveratrol is reported as a harmless phytochemical compound that has the potential efficacy in managing AD and PD. Resv reported various pharmacological effects in different diseases, but its bioavailability is limited due to its extensive formation of metabolites. The drug candidate used to treat CNS diseases should enter the brain by passing through BBB to exert its therapeutic effect. Resv can cross BBB, but its bioavailability is limited in low doses due to its metabolite formation with glucuronide and sulfate. The intranasal delivery of drugs for the administration to the brain

is of growing interest. Suppose the Resv is administered in the solution form in the intranasal route, it will be eliminated from the nasal region due to its mucociliary clearance, resulting in low bioavailability in the brain. The *in situ*-based formulation delivers the Rev using nanocarriers. The gellan polysaccharides used in the *in situ* gel formulation are converted into gels by rapid gelation with cations present in the mucus that increase the resident nasal time of Resv. It favors the nano-carrier-based intranasal delivery.

The lipid-based nanosystem has reported pharmacological activity in NDDs. Since Resv is a hydrophobic candidate, it has a better ability to solubilize lipids that improve the bioavailability in the brain. Conversely, the physicochemical properties of Resv have not been established in preformulation studies, including the stability against enzyme, pH, and light. Also, when Resv is exposed to light, it can be transformed into cis-isomer from trans isomer of Resv in which cis-Resv has low pharmacological action compared to trans-Resv. The advantage of using the nanotechnology-based delivery system is that it protects the Resv against enzymes, light, and pH. Still, there was insufficient information regarding the capability of improving stability. However, many studies reported its pharmacological activity in cell lines. These animal models showed promising results with a nanotechnology-based delivery system, and there is a lack of reports in understanding the mechanism of action with the delivery systems. In the future, we believe that innovative technologies can improve the potential ability of Resv in managing NDDs.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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