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Resveratrol: A Multifunctional Phytochemical with Challenges and Advances in Nanotechnological Drug Delivery Systems

Shoeb Ansari[1*], Dr. Rajkumar Dube[2]

[1]Research Scholar (M Pharm), L. H. Hiranandani College of Pharmacy, Ulhasnagar, Maharashtra, India.
[2]Associate Professor, Dr.L.H.Hiranandani College of Pharmacy, Ulhasnagar-03, Dist- Thane, Maharashtra

Corresponding Author
Email Id: ansari.shoeb@dlhhcop.org

ABSTRACT

The polyphenolic phytoalexin resveratrol, which is mostly found in peanuts and grapes, has drawn a lot of interest because of its varied pharmacological profile, which includes antioxidant, cardioprotective, neuroprotective, and anti-inflammatory properties. Resveratrol's clinical utility is severely limited by its low water solubility, high metabolism, and low oral bioavailability, despite its enormous potential as a therapeutic agent. Presently, current developments in the field of nanotechnology can be used to address issues related to the stability and bioavailability of resveratrol. This paper's main goal is to go into great detail about the pharmacokinetic limitations, modes of action, and therapeutic effects of resveratrol. Special attention is paid to delivery strategies based on nanotechnology, cyclodextrin inclusion complexes, lipid nanoparticles, and co-administration with bioenhancers because of the potential to maximize treatment effectiveness, particularly in neurodegenerative illnesses.

Keywords: *Resveratrol, bioavailability, nanotechnology, neuroprotection, delivery system, phytochemicals.*

INTRODUCTION

A naturally occurring stilbene derivative, resveratrol is mostly found in the skins of peanuts, berries, and red grapes. This substance has the chemical formula 3,5,4'-trihydroxy-trans-stilbene. It was initially identified in 1940 and gained attention because of its connection to the "French Paradox," which is the low incidence of coronary heart disease in French individuals despite their high consumption of saturated fat, primarily as a result of their moderate consumption of red wine, which contains resveratrol. [1]

Anti-inflammatory, cardioprotective, neuroprotective, antioxidant, and anti-cancer capabilities are just a few of the surprising biological effects of resveratrol. Multiple molecular targets of resveratrol, pain transduction or PGE2 signaling pathways, including SIRT1, AMPK, NF-κB, and numerous other mitochondrial enzymes, are responsible for these pleiotropic effects. Because of its capacity to penetrate the blood-brain barrier and influence oxidative stress and neuronal signaling pathways, the molecule has demonstrated promise in the control of neurodegenerative diseases, such as Parkinson's and Alzheimer's. [2]

Despite resveratrol's potential as a pharmaceutical treatment, translational clinical development is inherently limited. Low aqueous solubility, physiologic instability, first-pass metabolism, and an overall short half-life are the main obstacles to resveratrol's clinical

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translation. These factors also affect the systemic bioavailability following oral treatment, which has been reported to be less than 1%. [3]

Nanotechnology-based drug delivery systems offer a useful way to rationally get around the aforementioned restrictions. Nanocarriers (solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and polymeric nanoparticles) increase the pharmacokinetics and efficacy of resveratrol through improved solubility, stability, and targeting, commonly known as pharmacokinetics. [4]
With special attention to concerns regarding its bioavailability and how nanotechnology is transforming its distribution in medication formulations, this review attempts to present a thorough overview of the sources, chemical profile, pharmacology, and mechanism of action of resveratrol.

Sources and Chemistry of Resveratrol

Plants actively respond to harsh external environmental stimuli (such as pathogen attack and sunlight's harmful UV rays) by producing resveratrol, a phytoalexin (a plant source of biological activity). Recognized natural sources of resveratrol include the following:

1) Vitis vinifera, (Grapes)
2) Arachis hypogaea (Peanuts)
3) Vaccinium spp. (Berries)
4) Polygonum cuspidatum (Japanese knotweed)

Resveratrol has two isomers: trans-resveratrol and cis-resveratrol. In physiological systems, the trans-isomer is the more stable and physiologically active isomer because cis isomerizes into trans when heated or exposed to light.

Two phenolic rings joined by an ethylene bridge make up the stilbene resveratrol. The phenolic rings have the ability to scavenge reactive oxygen species (ROS), chelate metals, and modify the oxidative state of cells.

Nevertheless, resveratrol's extremely low water solubility (~0.03 mg/mL) makes pharmaceutical manufacturing difficult. Resveratrol will also quickly isomerize and break down when exposed to UV light because it is a photochemically unstable molecule. Therefore, unless resveratrol is stabilized in a delivery method, its shelf life and therapeutic usage may be restricted. [5-8]

Pharmacological Property: [9]

The pharmacological profile of resveratrol is broad and includes a variety of medicinal applications.

1) **The Impact of Antioxidants**
   Resveratrol exhibits enhanced endogenous antioxidant defenses, such as superoxide dismutase and catalase, as well as the ability to scavenge free radicals. Nrf2, the main regulator of antioxidant genes, is activated by resveratrol.

2) **Impact on Inflammation**
   Resveratrol inhibits pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) as well as cyclooxygenases (COX) and lipoxygenases (LOX). By blocking the NF-κB and STAT3 pathways, resveratrol alters the expression of pro-inflammatory genes.

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3) **Effects on Cancer Prevention**
The main mechanisms by which resveratrol inhibits the development of tumor cells and induces apoptosis include checkpoint modulation of p53, down-regulation of Bcl-2, and activation of caspase-3. There have also been reports of anti-angiogenic and anti-metastatic actions.

4) **Protection of the Heart**
Additionally, resveratrol reduces cardiac ischemia-reperfusion injury, lowers LDL oxidation, and boosts activation of endothelial nitric oxide synthase (eNOS).

5) **Protection of the Nerves**
Neuroprotection is particularly crucial. Resveratrol reduces neuroinflammation brought on by oxidative stress, tau phosphorylation, and amyloid beta aggregation. The ability of resveratrol to permeate the blood-brain barrier increases its clinical utility in the treatment of neurodegenerative diseases.

Mechanism of Action

Resveratrol's pharmacological effects are facilitated by its interactions with many molecular and cell-type mechanisms. Resveratrol can function as a pleiotropic therapeutic and preventative drug through a variety of modes of action, including tissue-specific and poly-targeted mechanisms.

1) **Activation of SIRT1**
Resveratrol is a strong agonist of sirtuin 1 (SIRT1), a well-known NAD+-dependent deacetylase that controls a number of critical biological functions, such as mitochondrial function, aging, and apoptosis. After resveratrol activates SIRT1, SIRT1 acts on PGC-1α, a coactivator that regulates fatty acid oxidation and mitochondrial biogenesis. This leads to increased fatty acid oxidation and mitochondrial biogenesis, which has cardioprotective and neuroprotective effects.

2) **Activity of Estrogen Receptors**
Because of its well-known phytoestrogenic qualities, resveratrol alters gene expression by binding to the estrogen receptors (ERα and ERβ). In the context of neuroprotection, ERβ binding is very crucial.

3) **The Signaling Pathways of MAPK and NF-kB**
Both the nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK) pathways, which mediate inflammation and apoptosis, are modulated by resveratrol. Pro-inflammatory cytokines and stress-response genes are down-regulated as a result of the compound's inhibition of JNK and p38 MAPK phosphorylation. Resveratrol suppresses NF-kB translocation to the nucleus by lowering IκB kinase activity, which in turn lowers the production of inflammatory genes.

4) **Protection of Mitochondria**
By preventing oxidative damage and changing the potential of the mitochondrial membrane, resveratrol shields the mitochondria against malfunctions. Additionally, the chemical may activate AMP-activated protein kinase (AMPK), which is essential for

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maintaining cellular energy homeostasis, particularly in response to stress. Neurons and cardiomyocytes depend on healthy mitochondria.

5) **The Cell Cycle and Apoptosis**
Through both intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic mechanisms, resveratrol causes malignant cells to undergo apoptosis. Resveratrol causes malignant cell death but not genuine cell death by increasing the expression levels of pro-apoptotic proteins (like Bax and caspase-3) and decreasing those of anti-apoptotic proteins (like Bcl-2).[10-12]

Pharmacokinetics and Bioavailability Challenges

Although resveratrol has several positive pharmacological benefits, its pharmacokinetic qualities limit its use in almost all pharmacologic applications.

1) **Oral Bioavailability of Resveratrol**
Resveratrol has an extremely low oral bioavailability of less than 1 to 5% because of its poor water solubility and first-pass metabolism. Trans-resveratrol, the physiologically active version, rapidly decreases with metabolism, despite the possibility of high plasma levels.

2) **Metabolism's Range**
When taken orally, resveratrol undergoes a highly extensive phase II metabolism, conjugating to glucuronide and sulfate conjugates via sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs). But compared to the parent molecule, the metabolites' biological activity is much lower.

3) **The First-Pass Impact**
The systemic availability of resveratrol is significantly reduced by the hepatic first-pass effect. Only a portion of the resveratrol that enters the body is available for systemic circulation because it is quickly metabolized in the liver and quickly absorbed in the gut after oral administration.

4) **Solubility and Stability Problems**
Resveratrol has a poor water solubility (~0.03 mg/mL) while being a lipophilic molecule, which presents a number of formulation challenges for conventional dosing forms. In addition to being chemically unstable, resveratrol degrades and photo isomerizes when exposed to heat and light. [13 14]

Strategies to Improve Bioavailability:

To solve the aforementioned problems, a variety of formulation and nanotechnology techniques have been developed.

1) **Nanocarriers Based on Lipids**
Resveratrol can be encapsulated in lipid-based systems such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), which will increase its solubility and absorptivity while shielding it from deterioration. Furthermore, the main benefit of lipid-based carriers for SLNs is the possibility of greater lymphatic absorption, which helps them avoid the overall detrimental effects of the first-pass impact. This is true for both

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usage modes, such as resveratrol. For example, when compared to free resveratrol, resveratrol-loaded SLNs dramatically enhanced oral bioavailability by a factor of five. Additionally, because the lipid matrix of NLCs is composed of both solid and liquid lipids, it offers a better regulated drug release profile and improved drug loading.

2) **Complexation of Cyclodextrin**
The ability of cyclodextrins (CDs) to form inclusion complexes with resveratrol in aqueous solutions has been shown to increase the ingested resveratrol's aqueous solubility while shielding it from photo isomerization.β-CD and hydroxypropyl-β-CD are two of the most commonly used CDs for forming resveratrol inclusion complexes. Furthermore, it was demonstrated that cyclodextrins helped to achieve chemical stability and lessen the degradation of trans-resveratrol in aqueous solutions.

3) **Using bioenhancers in conjunction with medication**
By inhibiting the metabolizing enzymes (like UGTs), the regular use of bioenhancers like piperine with resveratrol may lengthen its half-life and increase its exposure throughout the body. Furthermore, resveratrol concentrations in plasma showed a two-fold rise in preclinical co-administered experiments with piperine.

4) **Liposome and Polymeric Carriers**
Liposome carriers and biodegradable polymeric nanoparticles (such as PLGA and chitosan) offer strong control over release profiles, targeted resveratrol delivery, and degradation resistance. When these systems were modified to bind ligands or peptides that allow penetration across the blood-brain barrier, they demonstrated effectiveness for brain-targeted administration.

5) **Emulsion and Micelle Systems**
To increase solubility and create micelles for lipophilic resveratrol contained in the core, amphiphilic block copolymers can self-assemble. Similarly, oral absorption can be improved by self-emulsifying drug delivery systems (SEDDS) and nanoemulsions. [15 16]

Nanotechnology-Based Delivery System: [17]

Water-poor solubility phytochemicals like resveratrol can have their solubility, bioavailability, and targetability changed via nanotechnology-based drug delivery devices. Resveratrol alone has formulations that may not be clinically useful due to rapid metabolism bioavailability, low aqueous solubility, and thermodynamic instability. Nanotechnology can utilize many different nano-scaled carriers to enhance pharmacokinetics and targeted delivery to specific locations.

1) **Solid Lipid Nanoparticles (SLNs)**
Solid lipids make up SLNs. Drugs that are lipophilic, such as resveratrol, are transported by SLNs. SLNs may also protect resveratrol from degradation which may improve the circulation time and offer prolonged controlled release. One study found that resveratrol SLNs improved delivery and increased antioxidant activity both in vitro and in vivo and showed they may be able to help in prevention or management of neurodegenerative diseases.

2) **Nanostructured Lipid Carriers (NLCs)**
NLCs are complex SLNs, mixtures of liquid and solid lipids that are more efficient when it comes to drug loading capacity allowing better retention of drugs within the carrier.

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This carrier has been shown to enhance oral and topical absorption of resveratrol. It is important to note that the structural composition of NLCs provides a delivery mechanism for drugs through the nasal route allowing targeting to the brain.

3) **Liposomes and Transferosomes**
Liposomes, which consist of phospholipid bilayers, are beneficial for the encapsulation of drugs that are hydrophobic and hydrophilic. They also replicate biocompatibility associated with biological membranes. Liposomes loaded with resveratrol had increased cellular uptake and provided protection against oxidative stress. Transfersomes, which are ultra-deformable liposomes, may provide improved means to deliver resveratrol in topical and intranasal delivery, as they can penetrate desired tissue substantially deeper than liposomes.

4) **Polymeric Nanoparticles**
Biodegradable polymers such as PLGA and chitosan have further been used to create nanoparticles for the encapsulation of resveratrol. This encapsulation allowed for sustained release of resveratrol, as well as enhanced bioavailability for oral delivery. PLGA nanoparticles have been effective in neuroprotective capacity in a model for Alzheimer's disease.

5) **Dendrimers**
Dendrimers are branched nanostructures with high surface functionality and payload capacity. By using resveratrol-loaded dendrimers, solubility issues can be resolved and stability issues can be improved while achieving targeted delivery through ligand surface modifications.

6) **Micelles**
Amphiphilic block copolymers can self-assemble to form micelles to solubilize hydrophobic drug molecules such as resveratrol. These systems have much longer circulation time than other systems and improved oral absorption have been noted in preclinical models.

7) **Nanocrystals**
Nanocrystals are pure drug particles stabilized by surfactants and they will exhibit sustained enhanced rates of dissolution, which will lead to increased saturation solubility and better release properties. Specifically, resveratrol nanocrystalline formulations exhibited enhanced oral bioavailability as well as absorption rates compared to the coarse suspension.

8) **In Situ Nasal Gels for Brain Targeting**
Thermosensitive gels (e.g., poloxamer-based systems) offer an advantage of in situ gelling while administering via intranasal delivery. By combining with nanoparticles (i.e., solid lipid nanoparticles (SLNs), nano lipid carriers (NLCs)), you can hope to achieve the aim of targeting resveratrol delivery specifically to the central nervous system (CNS) by avoiding the blood-brain barrier (BBB).

Resveratrol for Neuroprotection:

Because resveratrol may be able to cross the blood-brain barrier (BBB) and modify signaling pathways, reduce oxidative stress and inhibit neuroinflammation, it is an exciting candidate

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for use as a neuroprotectant. Despite the pharmacological value of resveratrol, its poor solubility and availability limits the drug's potential efficacy in neurological diseases. The rise of nanotechnology, especially intranasal delivery, has provided some solutions to the challenges posed by resveratrol and opens the possibilities of drug delivery to the brain.

1) **Blood-Brain Barrier Challenges:** [18]
   The BBB is a selective semipermeable barrier that consists of endothelial cells, astrocytes, and tight junction proteins and maintains homeostasis and protects the brain from harmful toxins and microorganisms. It is a complex barrier that can occasionally make medicine distribution difficult. There is some intrinsic permeability of resveratrol crossing the BBB but it is restricted due to metabolism (quick half-life) and poor aqueous solubility (or slow clearance).

2) **Intranasal vs Oral vs Parenteral Administration:** [19]
   The three primary methods of delivery are parenteral, oral, and intranasal. Intranasal administration provides a unique route to the brain via direct delivery through the olfactory and trigeminal pathways, while protecting the molecule against first pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract. Intranasal resveratrol delivery is better than low systemic oral delivery of resveratrol and better than parenteral administration, which is invasive and poorly accepted by patients. Additionally, the use of nanoformulation for intranasal administration of resveratrol is suggested as advantageous for delivery of resveratrol to the CNS.

   In one study, there was improvement in memory and antioxidant status with intranasal resveratrol-loaded nanostructured lipid carriers (NLCs) in a scopolamine-induced dementia model, which further demonstrated effective targeting of the brain.

3) **Animal and Human Studies:**
   Several preclinical animal studies have demonstrated the neuroprotective effects of resveratrol in different neurological conditions including Alzheimer's disease (AD) and Parkinson's disease (PD), in ischemic stroke and traumatic brain injury. For example, using a rat model of AD, resveratrol improved memory in a spatial memory, while resveratrol prevented Aβ accumulation via activation of the SIRT1 pathway and reducing proinflammatory cytokine major players, such as TNF-α and IL-6.

   In PD models, resveratrol preserved dopaminergic neurons in the model and improved motor function by modulating mitochondrial action along with oxidative stress.

Human studies though few have indicated that long-term resveratrol supplementation can improve cerebral blood flow, memory performance, and glucose metabolism in healthy older adults. One randomized controlled trial (RCT) found sublingual resveratrol to improve memory retention and hippocampal functional connectivity following 26 weeks of oral resveratrol supplementation.

Target Disease: Alzheimer’s, Parkinson’s, Stroke

Alzheimer's Disease [20]
Resveratrol is neuroprotective in AD through:

- Beta-secretase inhibition and prevention of Aβ aggregation
- Stimulate SIRT1 activity and modulate tau acetylation

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- Reduce neuroinflammation mediated by inhibition of NF-κB

Parkinson's disease [21]
In PD, resveratrol will modulate neuroprotection through:
- Stimulating mitochondrial function and biogenesis through PGC-1α
- Preventing α-synuclein aggregation
- Scavenging reactive oxygen species (ROS)

Ischemic Stroke [22]
Resveratrol reduces infarct size and neuronal death in ischemia/reperfusion injury through:
- Activating AMPK and SIRT1 signaling pathways
- Regulating autophagy
- Maintaining and protecting the blood-brain barrier

Clinical Trials and Human Studies
Although promising effects in preclinical studies, resveratrol has not translated well into clinical studies. Nevertheless, several clinical studies have examined the pharmacokinetics, safety, and clinical efficacy of resveratrol in a variety of human diseases.

Summary of Available Clinical Data
Many studies have focused on resveratrol supplementation on metabolic, cardiovascular and neurodegeneration diseases. In a large randomized, double-blind, placebo-controlled clinical trial, resveratrol improved insulin sensitivity and mitochondrial structure and function in obese adults after 30-days of 150 mg/day resveratrol supplementation.

In another 26-week study in healthy older people, resveratrol resulted in improvements in memory performance and hippocampal connectivity. [23]

Doses used, Tolerability and Efficacy Outcomes
Doses examined in clinical trials covering the use of resveratrol can vary greatly, from 75 mg/day to 5 g/day. Most studies reported good tolerability up to doses of 1 g/day. When doses went higher, participants experienced more gastrointestinal symptoms such as anxiety, diarrhea and abdominal discomfort.

Efficacy outcomes also changed depending on the disease context. For example, in a study on patients with Alzheimer's disease, resveratrol supplementation of 1 g/day for 52 weeks essentially stabilized cerebrospinal fluid (CSF) Aβ levels; however, cognitive benefits were not robust.

TOXICITY AND SAFETY
Resveratrol is generally regarded as safe with no genotoxic or carcinogenic effects found in either animal or human studies.

Animal Data
Rodent and primate toxicological studies have found no organ toxicity or any deaths at doses as high as 700 mg/kg/day. Nine doses of resveratrol administered over 90 days in rats produced no harmful effects on liver or kidney alterations in urine, hematology, histopathology or whole animal studies.

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Human Tolerability [24]
Studies have shown that resveratrol is very well tolerated by humans at doses of up to 1 g/day for several months. The dose dependent side effects, which were minor, were mostly associated with gastrointestinal mild disturbances, the gastrointestinal effect complaints were mostly experienced as distressful by the volunteers, if they occurred at all. A 29 day study of healthy volunteers found that 2.5 g/day found that the doses could cause diarrhea and abdominal cramps with 5 of the 28 volunteers.

Maximum Tolerated Dose
The maximum tolerated dose level is reported to be 5 g/day in humans, but these levels are uncommon and rarely used due to poor bioavailability and side effects. Nano formulations are to be expected to be recommended to lower per dose and maintain bioactivity.

FUTURE PERSPECTIVES

To further increase the clinical potential of resveratrol, future directions must be directed toward complex drug delivery systems, clinical evidence, and personal therapeutics.

Personalized Nanomedicine [25]
Combining personalized medicine with nanomedicine could improve dosing schedules, targeted release for a given dose, and decrease toxicity. Potentially, genomic and metabolomic analyses could be used to develop patient subgroups that would gain most from resveratrol therapy.

Hybrid Delivery Systems [26]
Hybrid nanoparticles, containing polymeric, lipid, or inorganic components, should improve loading efficiency, stability, and controlled release. Multi-functional delivery systems based on nanocarriers that respond to pH and/or enzymes could enable site-specific release in diseased tissue.

CONCLUSION

Resveratrol is a multifunctional phytochemical with numerous pharmacological properties associated with neurodegenerative, cardiovascular, and metabolic disease. Nonetheless, significant challenges exist to the clinical efficacy of resveratrol with regards to its very low solubility, rapid metabolism, and severe low bioavailability upon oral administration.

Nanotechnology-based delivery systems (solid lipid nanoparticles [SLNs], nanostructured lipid carriers [NLCs], polymeric nanoparticles, and basic liposomes) have made advances to improve the pharmacokinetic profile of resveratrol; however, of these systems, the most effective way to target the brain is still through intranasal administration.

Preclinical models have consistently provided evidence of the neuroprotective properties of resveratrol, while human studies have verified safety and minimal clinical effect, but there remain more issues to address including dosing, available target drug concentrations, and long term safety.

Some planned directions to consider for the future are:
1) PMD based of the use of nanomedicine to have a more targeted and individualized therapy.

2) Hybrid systems that utilize various materials and target methodologies.
3) More in depth clinical studies (randomized controlled trials) to support nanotherapy-based resveratrol formulations.

Incorporating our knowledge from the field of nanomedicine as part of our education in clinical research, there remains great potential for the use of resveratrol for therapeutic intervention in the treatment of chronic disease, especially in targeting the central nervous system.

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