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Review Article

Resveratrol: An Overview, Chemistry and Pharmaceutical Applications

Vishva Prakash, Parul Priya, Gaurav Shukla, Amita Verma*, Deepika Singh*

Bioorganic and Medicinal Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, 211007, India

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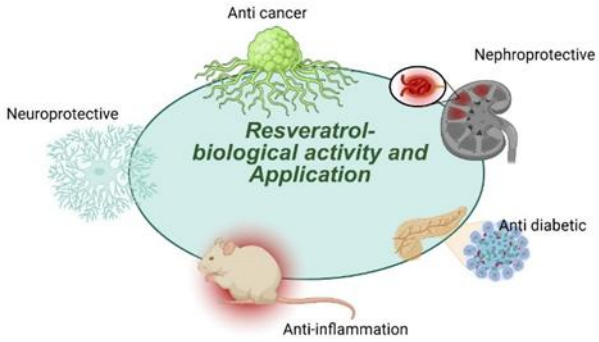
ABSTRACT

As a phytoalexin, resveratrol is a natural polyphenolic compound present mainly in grapes, berries, and peanuts, which has received substantial attention in scientific research for its wide-ranging pharmacological properties and therapeutic applications. This review offers a thorough assessment of its pharmacokinetics, molecular targets, and underlying mechanistic pathways of its bioactivity. Resveratrol exhibits antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and anticancer effects through the modulation of signaling pathways of SIRT1, AMPK, and NF-κB. Besides its pleiotropic effects, resveratrol acts as a potential biomarker for therapeutic response due to its regulation of gene expression and epigenetic factors in disease studies. Its clinical use has been limited by low bioavailability and rapid metabolism, despite promising in vitro and animal studies, which has fueled research into more sophisticated delivery systems and structural analogs. This review highlights the overview, chemistry, pharmacokinetic, and therapeutic potential of resveratrol in the era of personalized medicine and drug discovery.



INTRODUCTION

Resveratrol, a highly compelling polyphenolic compound, is present in various plants such as peanuts and grapes [1]. Initially, it was separated from *Veratrum grandiflorum*, also referred to as white hellebore. Notably, traditional Chinese medicine incorporates resveratrol through extracts derived from *Polygonum cuspidatum*. Compounds originating from natural products have garnered significant interest from researchers due to their powerful effects on inflammation and oxidative stress [2].

A naturally occurring stilbene and nonflavonoid polyphenol, resveratrol (3,4',5trihydroxystilbene) (Figure I), exhibits

*Correspondence: deepi.chhoti@gmail.com, amitaverma.dr@gmail.com, amita.verma@shiats.edu.in
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multiple biological functions, such as antioxidant [3], cardioprotective [4][5], antimicrobial [6], anti-inflammatory [7], and anti-cancer activity [8]. Recent investigations have demonstrated its efficiency in increasing insulin sensitivity and regulating blood sugar levels in patients [9], as well as in preventing obesity [10].

Resveratrol also benefits multiple physiological processes, including oxidative stress, inflammation, apoptosis, angiogenesis, and mitochondrial failure. The market sells resveratrol as a dietary supplement due to its wide spectrum of pharmacological benefits [11]. Resveratrol is primarily taken as a dietary supplement, and several experimental models are used to assess its qualities in vitro or in vivo [12]. Its cardioprotective role is partly attributed to the inhibition of platelet aggregation [13]. Furthermore, resveratrol modulates cellular responses to external stimuli and immune responses to infections by regulating the NF-kB signaling pathway. It may also trigger p53 signaling and block the IGF-1R/Akt/Wnt pathways, which could affect malignancies and cellular progression [14][15][16]. Resveratrol has been demonstrated to efficiently cross the blood-brain barrier. It inhibits tumour cell proliferation, induce apoptosis, and modulates important signaling cascades, including PI3K/Akt, JAK/STAT, and NF-kB. Because of its ability to penetrate the central nervous system, it is a promising therapeutic agent for managing malignancies of the central nervous system [17].

Resveratrol also inhibits the PI3K/Akt pathway, which regulates cell development, differentiation, proliferation, and other associated functions [18]. Multiple studies have illuminated how resveratrol influences the PI3K/Akt pathway. In multicellular carcinomas with increased activity of the mTOR/PI3K/Akt axis, for instance, resveratrol was shown to downregulate Akt signaling, suggesting that it could serve as an adjunct treatment with other PI3K/Akt/mTOR inhibitors [19]. Resveratrol's powerful antioxidant capacities and increased production of nitric oxide (NO) are essential for its cardioprotective benefits [20][21]. Additionally, resveratrol inhibits platelet aggregation and reduces hepatic lipid synthesis [22][23], successfully decreasing the release of reactive oxygen species (ROS) from human polymorphonuclear leukocytes [24]. In relation to vitamin E, it has been suggested to be a more potent antioxidant [25].

Research on resveratrol originated with the French paradox, a concept introduced in 1992, which highlights the unexpectedly low prevalence of heart disease despite diets rich in saturated fats [26][27]. Since this observation, resveratrol has been extensively investigated, revealing its anti-inflammatory, anti-cancer, antibiotics, anti-angiogenic, and antioxidant characteristics. Among all of these advantages, its effect on oxidative stress is perhaps the most significant. Numerous studies have demonstrated that resveratrol has the potential to

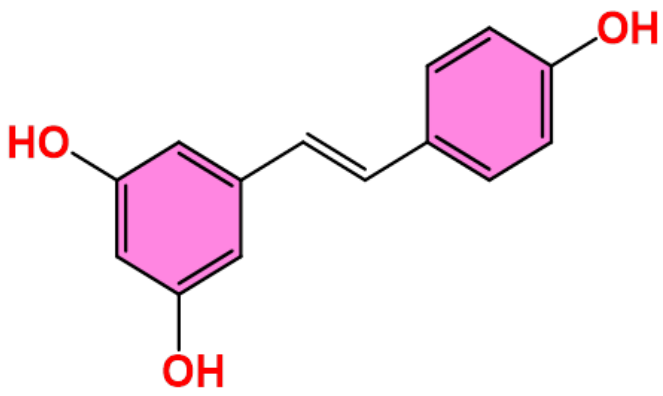

Figure I. Chemical Structure of Resveratrol

mitigate stress and prevent the progression of various ailments, including cancer, aging, and heart diseases [28][29]. Resveratrol has shown exceptional chemopreventive and chemotherapeutic properties against specific cancer forms [30]. Its effects on longevity and cancer resistance are particularly noteworthy. Due to its anti-inflammatory, anti-mutagenic, and antioxidant properties, resveratrol was discovered to possess cancer chemopreventive effects in 1997 across tests that characterized the three main phases of tumorigenesis [31]. According to a 2003 study by Howitz et al. [32], resveratrol extends the lifespan of *Saccharomyces cerevisiae* by activating sirtuin deacetylases. Two significant studies in 2006 demonstrated that resveratrol induces physiological changes associated with increased longevity, such as improved motor function, enhanced insulin sensitivity, elevated activity of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 alpha), and improved mitochondrial function [33][34].

Resveratrol enhances the efficacy of chemotherapeutic interventions. Paclitaxel (PTX), a widely utilized chemotherapeutic drug in oncology, often faces diminished anti-tumor activity due to cancer cell resistance. Pre-treatment with resveratrol increases the vulnerability of tumor cells to PTX, thereby improving the efficacy of the therapy [35][30]. Additionally, resveratrol upregulates DUSP1 expression, augmenting the effectiveness of chemotherapy using cisplatin and assisting in the demise of prostatic tumor cells [36]. Resveratrol also shows promise as a therapeutic agent for neurological disorders (NDs). A recent publication explored its potential in mitigating cognitive impairments. The establishment of microtubule-associated proteins tau and amyloid-beta (Aβ) plaque significantly increases the likelihood of developing Alzheimer's disease (AD. By inhibiting protein tau accumulation, resveratrol markedly reduces cytotoxicity and neuroinflammation, thereby improving memory deficits [37][38][39].

DISCUSSION

Chemistry of Resveratrol

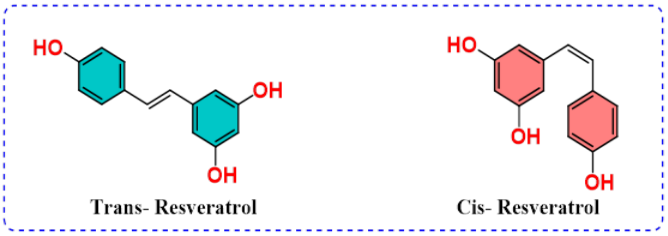

Figure II. Chemical Structure of Trans- resveratrol and Cis-Resveratrol

The molecular structure of resveratrol consists of a pair of aromatic rings joined by a methyl bridge. The two isomeric types of resveratrol are trans-resveratrol and cis-resveratrol, which are found naturally, as shown in Figure II. The known biological processes are predominantly exhibited by the trans isomer [40]. Resveratrol's two phenolic rings are structurally linked by a double bond [41][42]. When exposed to sunlight, ultraviolet (UV) rays, or heat, trans-resveratrol transforms into cis-resveratrol [43][44][45][38–40]. The most active form of resveratrol is the trans-isomer, which is primarily found [46] and boasts larger biological activity [47].

Pharmacokinetics and Pharmacodynamics

Bailey, H.H., et al., studied the pharmacokinetics of resveratrol in a single dose, with or without piperine, as well as the toxicities associated with the drug in healthy volunteers. The researchers conducted a pilot trial that was randomised, double-blind, and three-arm. In this investigation, participants were given a single dose of resveratrol (2.5 g) combined with piperine at concentrations of either 0 mg, 5 mg, or 25 mg. To determine the quantities of resveratrol and resveratrol-glucuronide in the serum, a sophisticated liquid chromatography/mass spectrometry technique was utilised. Serum samples were analyzed from baseline to 24 hours post-dose, and adverse events were tracked for 30 days. A total of 24 participants were enrolled. No significant association was found between piperine dosage and pharmacokinetic parameters. A near-significant trend (P = 0.057) towards augmentation with piperine was observed in a sex-stratified analysis of the Cmax of resveratrol in females using piperine. For resveratrol, the pharmacokinetic values were as follows: the Cmax value was 18.5 ± 16 ng/mL for resveratrol alone, 29 ± 29 ng/mL for resveratrol plus 5 mg piperine, and 16 ± 13 ng/mL for resveratrol plus 25 mg piperine. The area under the concentration × time curve was 1270 ± 852 ng/h/mL for resveratrol alone, 2083 ± 2284 ng/h/mL for resveratrol plus 5 mg piperine, and 1132 ± 222 ng/mL for resveratrol in combination with 25 mg piperine. All participants tolerated their assigned regimen well, experiencing minimal to no adverse effects, with no discernible differences across the three groups. It was not possible to replicate the significant enhancement seen in murine trials by co-administering resveratrol with piperine at doses of 5 mg or 25 mg, as the pharmacokinetics of resveratrol or resveratrol-glucuronide were not significantly altered [48].

Helal, N.I., et al., examined whether the chemical reactions of celecoxib in normal male volunteers were impacted by traditional drug resveratrol, which acts as an adjuvant soothing substance. Twelve healthy individuals enrolled in an open-label, two-period study. Celecoxib was administered orally as a single dose of 200 mg after the participants had fasted during the control period. Resveratrol (500 mg) was subsequently administered orally as a single dose every day for a period of ten days during the treatment phase. During both phases, blood samples were collected, and evaluated by HPLC (high-performance liquid chromatography). The absorption rate constant, maximum concentrations (Cmax), and area under the curve (AUC) for celecoxib were each significantly enhanced with pre-treatment with resveratrol. Its half-life ($t_{1/2}$) was additionally extended, and its elimination rate constant (k_e), apparent body clearance, and volume of distribution were significantly reduced. The time to achieve maximum concentration (T_{max}) did not change significantly. The findings indicate that resveratrol and celecoxib had an advantageous pharmacokinetic interaction. Thus, celecoxib, an anti-inflammatory medication, and resveratrol, a herbal supplement, could function in tandem to reduce inflammation and osteoarthritis with minimal side effects [49].

Verma, S., et al., examined the combined hepatoprotective benefits of raspberry ketone and resveratrol in rats exposed to carbon tetrachloride for oxidative stress and non-alcoholic steatohepatitis (NASH), followed by a 2-week treatment period. Significant reductions in elevated plasma markers and lipid profiles indicated that oral administration of the combined raspberry ketone and resveratrol regimen provided significantly greater hepatoprotection compared to individual administration of raspberry ketone or resveratrol. Despite increasing GSH levels in the liver, both types of therapy significantly lowered hepatic lipid peroxidation. Significant elevation of anti-inflammatory genes and enhanced MMP-9 protein expression were observed through RT-PCR and immunoblotting analyses, which served to ameliorate the disease. Pharmacokinetic inquiries showed increased synergistic stability in rat liver microsomes and simulated intestinal fluids (FaSSGF, FaSSIF). In addition, co-administration of raspberry ketone and resveratrol enhanced therapeutic efficacy through improvements in mean residence time (MRT0-∞) (h), the volume of distribution (V_d/F) (L/kg), and comparative bioavailability. These pharmacokinetic and pharmacodynamic results indicate interest in adjuvant therapy for the treatment of steatohepatitis [50].

Nguyen et al. investigated the molecular mechanisms underlying resveratrol's protective effects against neurodegenerative conditions like depression, amyotrophic lateral sclerosis (ALS), Parkinson' disease (PD), and cognitive impairment (CI), especially since these illnesses are caused by exposure to a combination of bisphenol A (BPA), bisphenol Sulphide (BPS), and bisphenol F (BPF). The results showed that specific gene targets of resveratrol are responsible for its neuroprotective effects. In addition, the study highlighted the role of microRNAs hsa-miR-377-3p, hsa-miR-1-3p, hsa-miR-128-3p, and hsa-miR-204-5p. Furthermore, transcription factors such as NFE2L2, BACH1, PPARG, and NR4A3 have been shown to be vital in mediating resveratrol's protective responses against the damaging effects of BPA, BPS, and BPF. In silico analyses were carried out to design and test molecular sponges which might block these miRNAs.
The study further examined the physical and pharmacokinetic features of resveratrol, emphasizing its outstanding similarity to drugs, high gastrointestinal absorption, non-substrate status for P glycoprotein, and blood–brain barrier crossing abilities. These characteristics lend credibility to its therapeutic potential in the treatment of depression, PD, ALS, and CI [51].

The potential importance of resveratrol, a naturally occurring phytochemical, in cancer chemoprevention has been thoroughly studied in preclinical settings. However, its low systemic availability—mainly due to its rapid and extensive metabolism—hinders its beneficial relevance and reduces its ability to target tumors that are far removed from the absorption site. Micronization, an approach that reduces particle size, has been utilized to enhance absorption and bioavailability to address this issue.

In a pilot study, Howells et al. treated patients with colon cancer and hepatic metastases who were scheduled for a liver transplant with 5.0 g of SRT501, a micronized form of resveratrol, each day for 14 days and evaluated SRT501's pharmacokinetics, pharmacology, and safety. The average plasma resveratrol levels following a single dose were 1,942 ± 1,422 ng/mL, which is almost 3.6 times higher than the levels reported for similar amounts of non-micronized resveratrol. In addition, hepatic tissue contained resveratrol at quantities of up to 2,287 ng/g. Surprisingly, compared to patients receiving a placebo, there was a significant 39% rise in cleaved caspase-3, a hallmark of apoptosis, in malignant tissue from the liver. The results indicate that further clinical studies are needed for assessing SRT501's potential therapeutic value [52].

With the goal of targeting hepatocellular carcinoma (HCC), Jagwani et al. developed and optimized cationic liposomes encapsulating resveratrol. The improved formulation, known as RL5, displayed a spherical vesicle size of approximately 145.78 ± 9.9 nm, a favourable zeta potential of 38.03 ± 9.12 mV, and an encapsulation efficiency of 78.14 ± 8.04%. In vitro cytotoxicity assay revealed that RL5 exhibited stronger anticancer effects than free resveratrol. Cellular uptake studies supported this, showing that RL5 absorbed more effectively in HepG2 cells than free resveratrol. After three and five hours of incubation, confocal microscopy further confirmed the liposomes loaded with coumarin 6 (C6) were more readily absorbed as free C6. Pharmacodynamics and pharmacokinetics studies were carried out on rats with HCC induced by N-nitrosodiethylamine (NDEA). Compared to free resveratrol, RL5 treatment C_{max} and AUC of revesratrol in cancerous liver tissues by about 2.2 and 3.2 times respectively. Pharmacodynamic investigations showed that animals receiving RL5 exhibited significantly fewer hepatocyte nodules than thos administered free resveratrol. The findings were confirmed by histopathological examinations, demonstrating that RL5 effectively reversed liver damage triggered by NDEA. Based on the study's results, cationic liposomes loaded with resveratrol significantly reduce the severity in HCC and indicate potential as a nanocarrier system for managing the condition [53]..The pharmacological activities and therapeutic potentials of Resveratrol is summarized in Figure III.

Pharmaceutical Applications of Resveratrol

(i) Resveratrol for the Treatment and Prevention of Cancer

Cancer continues to pose a major global health concern, causing more than half of global deaths. Approximately 20 million new cases of the illness were diagnosed in 2022, and 9.7 million individuals lost their lives to the disease. This underlines the urgency with which additional studies, early detection, and effective treatment plans are required to combat this prevalent illness [54]. This approach aims to lower the risk of cancer by acting before a clinically recognized tumor manifests. The potential of natural and synthetic substances, or their combined use in chemoprevention methods, is being explored. For instance, the application of natural compounds together with conventional chemotherapy drugs has significantly boosted patient survival by raising the susceptibility of cancer cells to radiation and chemotherapy [55].

The potential cancer-prevention advantages of resveratrol are found in various fruits and vegetables and have become the focus of numerous studies. Research conducted in laboratories indicates that resveratrol might prevent the development of various cancer cell lines and could interfere with the initiation, advancement, and progression of cancer.

Resveratrol belongs to a group of substances termed stilbenes, which have demonstrated anticancer properties in both animal and human cell culture studies. These compounds appear to function by inhibiting angiogenesis, activating apoptosis (programmed cell death), and altering inflammatory pathways. While the findings are promising, it's crucial to keep in mind that preclinical studies provide almost all of the data. The effectiveness and safety of resveratrol and related stilbenes in

preventing and treating cancer in humans need to be further studied, especially through well-planned clinical trials [54].
With 1.8 million new instances diagnosed every year, colon cancer is the third most prevalent illness globally. Benign polyps in the lining of the intestines or rectum tend to trigger the disease, but they may accumulate genetic changes over time. These polyps have potential to develop into malignant adenomatous polyps if they are not discovered and removed promptly. The development of colorectal cancer is greatly influenced by a variety of environmental and lifestyle factors, such dietary habits, alcohol consumption, tobacco use, and physical inactivity. The impact of these modifying variables on the disease's incidence is being highlighted in numerous studies [56][57].

A nutritious diet is crucial in preventing cancer along with other chronic diseases. The health benefits of a Mediterranean diet, in particular, have been extensively studied. This dietary pattern emphasizes eating foods made from plants, healthy fats, and soothing components to avoid illness [58]. Resveratrol has been studied for its potential anticancer properties, particularly its ability to induce apoptosis in human colon cancer cells. Studies demonstrate that chromatin condensation and the formation of apoptotic bodies are the two mechanisms through which resveratrol may trigger programmed cell death in SNU-C4 intestinal cancer cells [59]. Chromatin condensation and the formation of apoptotic bodies were observed when resveratrol was administered at a concentration of 100 µg/mL, indicating apoptosis in colon cancer cell line (SNU-C4). Compared to untreated control cells, this apoptotic effect is associated with an increase in pro-apoptotic proteins Bax and caspase-3, along with a decrease in the production of the anti-apoptotic gene Bcl-2 [59]. In animal models, researchers investigated the potential of a resveratrol-rich diet, such as red wine, pomegranate, white grapes, and rosemary, for preventing colon cancer. These natural extracts contain polyphenols, particularly resveratrol, which have been proven to possess anti-inflammatory, anti-oxidant, and anticancer properties. Studies indicate that these compounds could prevent the development of cancerous lesions and slow the growth of tumours by altering significant bodily functions such as inflammation and cell proliferation. In addition, resveratrol has shown beneficial synergies in suppressing colon tumor stem cells when paired with other grape-derived compounds [60].

The findings indicated that the number of mucin-depleted foci (MDF) per colon in rates was dramatically decreased when dry wine, pomegranate extracts, and α-tocopherol (a form of vitamin E) were introduced to preserved meat. MDF is believed to be an initial indicator of colon cancerous changes. This suggests that introducing these specific extracts to cooked meats might mitigate some of the cancer risks associated with their consumption [60].

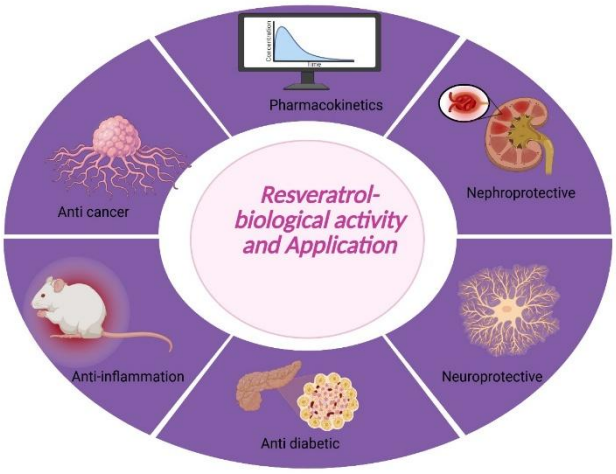

Figure III. Biological activity and application of the Resveratrol

Researchers are investigating how red wine extracts prevent colon cancer cells from proliferating in vitro and inhibit the formation of colonic aberrant crypt foci (ACF) in vivo. Findings indicate that extracts from vinification processes exhibit enhanced anti-proliferative actions against colon cancer cells and can effectively stop ACF. According to these findings, the polyphenolic content and the way these substances alter cellular metabolism may all be important factors in how well red wine extracts prevent colon cancer [61].

(ii) Resveratrol for the Treatment and Prevention of Diabetes

Elevated blood glucose levels caused by impaired insulin secretion, action, or both characterize diabetes mellitus, a metabolic condition. A number of pharmacological and alternative treatments are being utilized with the goal of improving pancreatic insulin production and enhancing insulin sensitivity. Resveratrol has been demonstrated in numerous investigations on humans and in animal models to improve insulin sensitivity, reduce oxidative damage, and alter inflammatory pathways associated with diabetes (Figure IV). Regulation of adipokines, hormones released by fat cells that affect insulin sensitivity, is another indication that resveratrol exerts anti-diabetic advantages. Resveratrol could enhance peripheral tissues' absorption of glucose and insulin responsiveness by modulating adipokine levels. In addition, clinical studies have shown that resveratrol supplementation boosts hemoglobin A1c readings among individuals with type 2 diabetes and improves glycemic control, including reductions in fasting blood sugar and insulin levels [62].

The effect of resveratrol on diabetic peripheral neuropathy (DPN) was investigated in a study by Osmanlıoğlu and Nazıroğlu, focusing particularly on the functioning of the transient receptor potential vanilloid 4 (TRPV4) channel. This calcium-permeable channel allows excessive Ca^{2+} influx. The

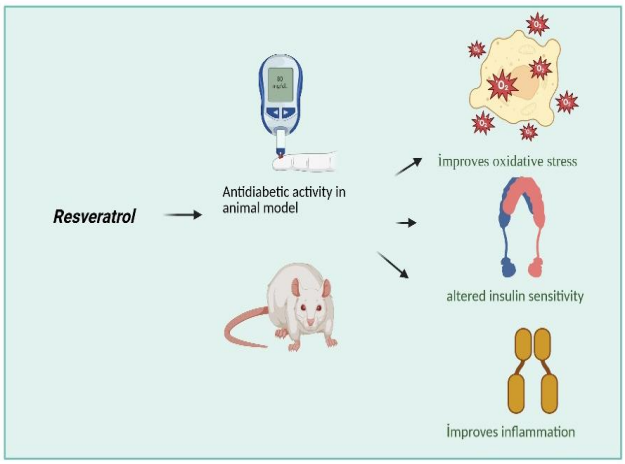

Figure IV. Antidiabetic activity of revesratrol in animal model

capacity of resveratrol, a substance renowned for its antioxidant properties, to alter TRP channels has been studied. Four groups of mice were utilized in this study: control, streptozotocin (STZ)-induced diabetic, resveratrol-treated, and STZ+ resveratrol-treated. Increased TRPV4 activity, enhanced Ca^{2+} influx, increased production of reactive oxygen species (ROS), heightened physical and thermal pain sensitivity, and elevated apoptosis levels were all observed in the STZ-induced diabetic rats., Resveratrol treatment reduced these effects by reducing ROS levels, apoptotic marker expression, Ca^{2+} influx, and TRPV4 activity. Additionally, RESV bolstered antioxidant defences by increasing the levels of glutathione, glutathione peroxidase, vitamin A, β-carotene, and vitamin E in the brain, liver, and kidneys, among other tissues. The findings indicate that resveratrol reduces apoptosis and oxidative stress by modulating TRPV4 channel operation, resulting in neuroprotective properties in diabetic peripheral neuropathy. This research demonstrates the potential of resveratrol as an adjunct treatment for DPN [63].

Ferroptosis and the potential medicinal properties of resveratrol were the primary subjects of a study by Li et al. that investigated the mechanisms underlying alveolar osteocyte death in diabetic periodontitis. Male C57BL/6 mice were given either resveratrol or no treatment after developing diabetic periodontitis. Histological analysis and micro-CT imaging was utilized to investigate the progession of periodontitis, and immunohistochemistry was employed to identify ferroptosis in alveolar osteocytes. The results showed that diabetic periodontitis exacerbated the severity of the disease and inhibited alveolar osteocytes from producing two essential antioxidant proteins, GPX4 and SLC7A11. Resveratrol treatment reduced these effects. Resveratrol or the ferroptosis inhibitor ferrostatin-1 reversed the downregulation of these essential antioxidant proteins, reduced malondialdehyde (MDA) levels, restored mitochondrial morphology, and decreased pro-inflammatory mediators, in accordance with in vitro experiments using MLOY4 osteocyte cells that imitated diabetic periodontitis conditions. Additionally, the demonstrated that resveratrol and ferrostatin-1 were able to halt the activation of the NF-κB signaling pathway by downregulating pIKBα and pNF-κB p65 expression in osteocytes. Based to these results, resveratrol can be considered a potential therapeutic agent for slowing the degeneration of alveolar bone caused by diabetes periodontitis [64].

(iii) Resveratrol's Role in Neuroprotection

Significant neuroprotective advantages associated with resveratrol have been observed in both hemorrhagic stroke and ischemic stroke (IS). Resveratrol could decrease atherosclerosis, an established risk factor for IS, by inhibiting the aggregation and activation of platelets mediated by thrombin, collagen, and adenosine diphosphate. The mechanism of action involves either the production of prothrombotic chemicals or the downregulation of tissue factor gene expression. Common consequences of cerebral infarction are cerebral edema and intracranial hypertension, both of which may prove lethal. In experimental animal models, many therapeutic approaches have been established to reduce cerebral edema; some of these have progressed to human trials. Resveratrol, in particular, has demonstrated edema-reducing qualities. Although its hydrophobic nature inhibits penetration across the blood- brain barrier (BBB), resveratrol can be administered via the nasal cavity in the olfactory region, offering a more patient-friendly delivery method. By binding to various enzymes and receptors, resveratrol enhances stress resistance and reduces apoptosis, along with other complex effects on stroke. In addition to apoptosis, other biological processes that lead to damage in the brain and neurons following a stroke include inflammation, oxidative damage, and ionic imbalance [65][66][67][68][69].

Oztak, L., and B.G. Bağca et al. investigated whether the antioxidant resveratrol impacted the levels of metalloproteases and the PI3K/Akt/GSK-3β pathway in a cell-based model of Alzheimer's disease (AD). For each experimental group, in silico analysis was also carried out using the STRING V12.0 database. Apoptosis data revealed that the Differentiated + Resveratrol and resveratrol groups exhibited a 1.5-fold and 2.5-fold decrease in comparison to the control, respectively, even though there were no appreciable changes between the resveratrol and AD model groups. Upon analysing the Real-Time PCR results, it was observed that the levels of gene expression for GSK-3β, TAU, ADAMTS-4, ADAMTS-5, and TIMP-3 were significantly reduced in the Differentiated + β-amyloid (Aβ) + resveratrol group when compared to the Differentiated + Aβ group ($p <. 0.001$). On the other hand, the levels of PI3K (3.38-fold), AKT (3.95-fold), and RELN (1.99-fold) were significantly elevated ($p <.0. 001$). Twenty-three Alzheimer-related Gene Ontology (GO) phrases linked to the Wnt signaling, proteolysis, and extracellular matrix structure pathways showed functional enrichment through network

analysis. In a neurotoxicity environment, resveratrol was founded to stimulate the PI3K/Akt insulin pathway, which inhibits GSK-3β. Resveratrol showed neuroprotective effects via inhibition of TAU, RELN, metalloproteases, all of which have been linked to Alzheimer's desease [70].

In an in vivo rat model, rats were given subcutaneous injections of 50 mg/kg $MnCl_2$ over 4 weeks, either alone or in combination with 30 mg/kg resveratrol. Latronico, T., et al. investigated the role of matrix metalloproteinase (MMP)-2 and -9 in Mn-induced neurotoxicity. Resveratrol mitigated the Mn-induced reduction in superoxide dismutase activity and glutathione levels, while additionally lowering the Mn-induced rise in MMP-9 levels and the production of reactive oxygen species, based on analysis of brain homogenates. Ultimately, Mn exposure induces an increase in MMP-9 through oxidative stress-related processes, which elevates the risk of central nervous system diseases. Resveratrol successfully reduces this risk [71].

The neuroprotective effects of resveratrol, urapidil, and their combined administration have been investigated by Çetin, R., et al. in a rat model of ischemia/reperfusion (IR) injury resulting from middle cerebral artery occlusion (MCAO). Significant histological modifications, increased oxidative stress, and enhanced apoptotic and inflammatory protein expression in the IR group compared with the control group ($p < 0.001$) indicate that the MCAO model effectively produced IR injury. All assessed parameters indicated significant improvements in the IR resveratrol group as compared to the IR group (all $p < 0.05$). With the possible exception of caspase-3 and Bcl-2, all metrics in the IR urapidil group were significantly better as compared to the IR group (all $p < 0.05$). When contrasted with the IR group, the IR combination of

Table I. Therapeutic and Biological activity of the Resveratrol.

Drug	Animals	Dose	Application	Mechanism of Action	References
Resveratrol	Rats	20 mg/kg/day, i.p, 28 days	Neuroinflammation	Acts on the SIRT1/NF-κB pathway and improves neuroinflammation.	[91]
Resveratrol	Rats	10 mg/kg	Anti-inflammatory effect	Reduces IL-1β, TNF-α, and IL-6 expression levels and improves the JNK/p38MAPK pathway.	[92]
Liposomal resveratrol	Rats	40 mg/kg	Cardioprotective effects	Improves apoptosis (caspase, Bcl2, and Bax).	[93]
Resveratrol	Rats	20, 40 mg/kg i.p	Life stress-induced depression in rats	Reverses cortisol release, monoamine levels, and oxidative stress.	[94]
Resveratrol	Rats	25, 50 and 100mg/kg b.w.	NSAID-induced intestinal injury	Improves TLR4/NF-κB/IκB protein expression and gut microbiota.	[95]
Trans-resveratrol	Rats	30 mg/Kg	Obesity	Elevates SIRT-1/PGC-1α/Cyto-c/GLUT-4 genes and modulates carbohydrate-lipid metabolism.	[96]
Exercise training and resveratrol	Rats	50 mg/kg, once daily	Lung injury and mortality in rats with obstructive jaundice	Decreases TNF-α and IL-6 levels and macrophage accumulation in lung tissues.	[97]
Resveratrol	Rats	20 mg/kg	Anti-oxidative stress and anti-ferroptotic effects	Elevates FTH1, GPX4, and SLC7A11(ferroptosis resistance-related proteins) and Nrf2, NQO1, and HO-1 (anti-oxidative stress pathway).	[98]
Resveratrol	-	8 mg/kg	Colorectal cancer	Targets the JNK pathway and improves oxidative DNA damage.	[99]
Resveratrol	-	50 mg/kg by gavage;	Exercise-induced fatigue	Elevates the SIRT1/PGC-1α pathway.	[100]
Resveratrol	Rats	20 mg/kg, oral gavage	Hepatotoxicity	Increases hepatic parameters IL-6 and MDA.	[101]
Resveratrol	Rats	-	Diabetic hearts	Reduces the gene expression of GLUT4/SIRT1/PGC-1α in heart tissue.	[102]
Resveratrol	Mice	-	Post-transplantation alterations of inflammatory mediators	Reduces systemic inflammation, NOD-like receptor signaling pathway, and granulocyte implantation.	[103]
Resveratrol	Mice	Intraperitoneally injected 100mg/kg	Postoperative cognitive dysfunction	Improves the expression of SIRT1/CX3CL1/CX3CR1.	[104]
Resveratrol and hesperidin	Rat	20 mg/kg, *p.o.*	Neuroprotective effects	Restores brain anti-oxidant status, reduces neuro-inflammation, and improves brain mitochondrial impairments.	[105]
Resveratrol and naringenin	Rats	-	Nonylphenol-induced oxidatives stress	Improves the content of SOD, CAT, GPx, GSH, and LPO	[106]

resveratrol and urapidil group exhibited the most significant improvements in all metrics (all $p < 0.001$) [72].

(iv) Resveratrol Role in Nephroprotective

Abdallah, A., et al. investigated whether resveratrol repaired renal tissues in Wistar rats with kidney damage from 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).102 male albino rats, weighing 80–90 g and 8–9 weeks of age, participated in the study. Of these, 70 rats were tested for chronic toxicity, and 32 rats were used for evaluating acute toxicity. All the rats were divided into seven groups and received resveratrol at different dose levels. Analysis demonstrated that TCDD-treated groups had significantly higher levels of malondialdehyde (MDA), urea, and creatinine compared to the other groups, but glutathione (GSH) and catalase (CAT) levels were lower. In contrast, the resveratrol-treated group exhibited decreases in MDA, urea, and creatinine, along with greater amounts of GSH and CAT. Resveratrol administration successfully lowered oxidative stress markers and TCDD-induced histological changes [73].

Golestaneh, E., et al., examined the therapeutic effects of silymarin (SM) and resveratrol on the morphological damage to renal tubular cells in adult male Wistar rats with diabetes. Twenty-five male Wistar rats were randomly assigned to five groups ($n = 5$): Group I (control), where rats received normal saline orally for 14 days; Group II, where rats received a single intraperitoneal injection of streptozotocin (STZ) at 60 mg/kg and were administered isotonic saline orally for 14 days; Group III, where rats, post-STZ injection, received 100 mg/kg SM via gavage for 14 days; Group IV, treated with 100 mg/kg resveratrol; and Group V, treated with SM and resveratrol at 100 mg/kg. Following sacrifice, kidneys were extracted and prepared for morphological analysis. The level of renal tubular cell damage, including vacuolization, flattening, degeneration, and necrosis, was assessed. There were significant differences between the groups in the terms of morphological damage; renal tubular damage in diabetic rats decreased significantly by both SM and resveratrol ($P < 0.05$). According to the statistics, both SM and resveratrol independently had greater nephroprotective effects against renal tubular cell injury in diabetic rats than when administered together, although SM had a more pronounced protective effect on necrosis and resveratrol on flattening [74].

(v) The Anti-Inflammatory Activity of Resveratrol

Numerous cell types and communication mediators play a role in the complex, multi-stage process that consitutes the response to inflammation. Inflammation is an adaptive mechanism activated by a variety of danger signals, such as tissue damage or microbial invasion [75][76].

(vi) Mechanism of Action of Resveratrol in Inflammation

Resveratrol can modify apoptosis by altering the expression of essential genes such as PUMA, p53, NoxaBak, and Bcl-XL, which are involved in cellular processes through both downregulation and upregulation mechanisms. By regulating nuclear factor-kappa β (NF-κβ) activity, cyclooxygenase-2 function, and prostaglandin synthesis, resveratrol limits cellular proliferation at the G1 and G1/S phases, functioning as a medication for inflammation [77][78]. Moreover, extensive studies have been carried out on its ability to prevent tumor progression, delay the onset of cardiovascular diseases, and exhibit antiviral properties [79]. Trans-resveratrol's anti-inflammatory, antiproliferative, and antioxidant properties are believed to contribute to its major therapeutic advantages [80]. Resveratrol is known to decrease cytosolic peroxide and superoxide radical production in skin fibroblasts in vitro, constrain platelet activation, and halt low-density lipoprotein oxidation [81]. Activation of quinone reductase 2 is linked to its chemopreventive actions via the augmentation of detoxifying enzymes and antioxidants within cells, which increases resistance to a condition known as oxidative stress [82]. The mechanism that provides resveratrol its anti-inflammatory action is its ability to inhibit cyclooxygenase-1 in vitro and cyclooxygenase-2 in murine skin models [83]. Resveratrol's antioxidant properties could stem from its suppression of oxidative enzymes or its capacity to scavenge superoxide and peroxide radicals [84]. Trans-resveratrol has been shown to be an even stronger radical scavenger, and its synergistic benefits increase when coupled with other vitamins [85]. The increase of reactive oxygen species in the skin contributes to various dermatological diseases, including cancer [85].

The cause of cutaneous diseases is greatly impacted by prolonged exposure to ultraviolet (UV) rays, which can damage DNA. The use of medicines to prevent, combat, or mitigate the impact of UV radiation on the human body is known as chemoprevention [86]. Along with chromosomal modifications and mutations, surviving, a vital regulator of cell life and death and a member of the apoptosis regulator gene family, plays a critical role in the formation of cancer cells induced by sunlight [11][87]. By regulating the synthesis and activity of survivin, resveratrol could offer protection against UVB-induced severe skin damage and potential carcinogenic growth [88]. In addition, resveratrol may be utilized as a complementary therapy for melanoma [89]. It enhances temozolomide's cytotoxicity against malignant cells while reducing the lifespan of melanoma cells. Resveratrol also inhibits antioxidant factor 1, making melanoma cells more susceptible to radiation therapy [90].

The pharmaceutical applications of the resveratrol are shown in Table I.

CONCLUSION

Resveratrol has evolved as a versatile bioactive molecule with immense pharmacological potential in a variety of diseases, including cardiovascular diseases, neurodegenerative diseases, cancer, and metabolic syndromes. Its applications stem from its capacity to regulate various molecular mechanisms, including SIRT1 activation, AMPK signaling, and NF-κB inhibition. Furthermore, resveratrol's function as a biomarker adds additional clinical values, as it can reflect disease status, treatment response, and interindividual differences in response to treatment. However, due to its poor bioavailability, rapid metabolism, and inter-individual variability in humans, its clinical translation is still limited.

These limitations could be circumvented by developing new delivery systems, such as nanoformulations, prodrugs, and encapsulated formulation, which could increase the stability and systemic availability of resveratrol. Furthermore, well-designed clinical trials are important for more clearly confirming resveratrol's usefulness and safety in different populations and disease states. Enhancement of therapeutic responses can also be achieved by combining resveratrol with other bioactives or classic drugs. With the development of precision medicine, the use of resveratrol as a biomarker could significantly change personalized treatments, providing a new paradigm in clinical practice. In the future, as a result of further interdisciplinary studies, resveratrol will hopefully rise above being merely an encouraging phytochemical to become an indispensable drug in clinical therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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