Resveratrol: A Vital Therapeutic Agent with Multiple Health Benefits

Authors
Arshpreet Kaur[1], Ruchi Tiwari[1], Gaurav Tiwari[1], Vadivelan Ramachandran[2]

Affiliations
1 Institute of Pharmacy, Pranveer Singh Institute of Technology, Bhauti, Kanpur, Uttar Pradesh, India
2 Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India

Key words
RSV, Therapeutic properties, Mechanism of action, Side effects, Future prospects

received 17.05.2021
revised 14.07.2021
accepted 19.07.2021
published online 19.08.2021

Bibliography
Drug Res 2022; 72: 5–17
DOI 10.1055/a-1555-2919
ISSN 2194-9379

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Ruchi Tiwari
Associate Professor & Research Co-ordinator
Pranveer Singh Institute of Technology
Kalpi Road, Bhauti
Kanpur-208020
Uttar Pradesh
India
Tel: 7376890719,
dr.ruchitiwari@psit.in

ABSTRACT

Resveratrol (RSV), the most effective stilbene phytoalexin synthesized naturally or induced in plants as part of their defense mechanism, is a key component of natural phenolic compounds and is being considered as a treatment option for a variety of diseases. RSV was discovered in the skin of red grapes, mulberries, peanuts, pines, and *Polygonum cuspidatum* weed root extracts. It was first extracted from white hellebore (*Veratrum grandiflorum O. Loes*) roots in 1940, then from *Polygonum cuspidatum* roots in 1963. However, RSV's use as a drug is limited due to its initial conformational strength and poor stability. The research focused on a set of RSV biological activity data. RSV has been the subject of growing concern, despite its wide range of biological and therapeutic applications. According to the literature, RSV has antioxidant, anticancer, cardioprotective, neuroprotective, anti- inflammatory, anti-microbial, immunomodulatory, and radioprotective properties. The current analysis summarized biological applications of RSV, their mechanisms of action, and recent scientific development in the area of their delivery. It is possible to infer that RSV has many effects on infected cells' cellular functions.

ABBREVIATIONS

AD	Alzheimer's disease
Akt-1	Alpha serine/threonine protein kinase
AMP	Activated protein kinase
AMPK	Adenosine monophosphate activated protein kinase
AOX	Adsorbable organic halides
ASC	Adipose-Derived Stem Cells
AZA	Azacytydine
Aβ	β-amyloid
BCS	Biopharmaceutical Classification System
BNP	Brain Natriuretic Peptide
BSA	Bovine Serum Albumin
CA	Caffeic Acid
CAA	Cellular Antioxidant Activity
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8

CHD	Coronary Heart Disease
COX	Cyclooxygenase
COX-2	activation Celecoxib
CTL	Cytotoxic T Lymphocytes
CTLs	Cytotoxic T Lymphocytes
DAMPs	Release Damage associated molecular patterns
DNA	Deoxyribonucleic Acid
DSA	Dual space analysis
DSB	Double stand break
DSC	Differential Scanning Calorimetry
EDA	Exploratory Data Analysis
EEs	Encapsulation Efficiencies
EMS	Equine Metabolic Syndrome
eNOS	Endothelial Nitric-Oxide Synthase
EOES	Excess Orbital Energy Spectrum
FRAS	Ferric Reducing Antioxidant Strength
GSH	Glutathione
GSK-3	Glycogen synthase kinase
HIF-1α	Hypoxia-inducible factor 1-alpha
HSPs	Heat Shock Proteins
IFN	Cytokines Interferon
IKK	Inhibitory –κB Kinase
IL	interleukin
INOS	Nitric oxide synthases
iNOS	Nitric oxide synthase
JA	Jasmonic Acid
LAK	Lymphokine Activated Killer
LDL	Low-Density Lipoprotein
LKB	Serine-threonine kinase 11
LOX	Lipoxygenase
LPS	Lipopolysaccharides
M1	Microglia Activation
M21	Melanoma Cell line
MAPKs	Mitogen activated protein kinase
MEK-1	Dual specific protein kinases
MKP-1	Mitogen activated protein kinase
MyD88	Myeloid differentiation primary response-88
NADPH	Nicotinamide adenine dinucleotide phosphate
NFAT	Nuclear factor of activated T-cells
NF-κB	pathway Nuclear factor kappa light chain enhancer of activated B cells
NK	Natural killers
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
NQO2	N-Ribosyldihydronicotinamide:Quinone Oxidoreductase
NXS2	Neuroblastoma Cell line
ORAP	Oxygen Radical Absorbance Potential
PBMC	Peripheral Blood Mononuclear Cells
PGC1	Peroxisome proliferator activated receptor γ coactivator 1
PGE	Prostaglandin E
PKC	Protein kinase C
PPAR-γ	Peroxisome proliferator activated receptor gamma
ROS	formation Reactive oxygen species
RSV	Resveratrol
RVL	Trans-Resveratrol
SA	Salicylic Acid
SCE	Sister Chromatid Exchange
SCF	Supercritical Fluid
SEM	Scanning Electron Microscopy
SIRT1	Sirtuin 1
SLN	Solid Lipid Nanoparticle
SOD	Superoxide Dismutase
SSB	Single stand break
STAT3	Signal transducer and activator of transcription 3
T reg	Regulatory T Cells
TEM	Transmission Electron Microscopy
Th2	T Helper cells Orchestrate protective type 2 immune response
TLR-4	Toll-like receptor-4
TNF	Tumor Necrosis Factor
TNF	Tumor necrosis factor
TNF-alpha	Tumour necrosis factor alpha
TNF-α	Tumor Necrosis Factor A
XRD X-Ray	Diffraction

Introduction

Stilbenes and natural phenolic compounds can be found in a wide range of plant foods, especially berries [1, 2]. In 1940, RSV was isolated from the roots of white hellebore (*Veratrum grandiflorum O. Loes*), and in 1963, it was isolated from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine as an anti- inflammatory and anti-platelet agents. RSV is commonly found in the skin of red grapes, mulberries, peanuts, pines, and weed root extracts of *Polygonum cuspidatum* [3, 4]. RSV acts as an antifungal agent in these plants, protecting them from a variety of infections. Grapes are often contaminated with *Botryis cinerea*, which raises RSV levels in nearby grapes [4].

Fungi, stress, injury, infection, or UV radiation all cause RSV to be produced within these plants[5, 6]. Environmental stress (UV light and heavy metals) also has an impact on the overall increased levels of RSV in plants [7, 8]. The Biopharmaceutical Classification Scheme classifies RSV as a Class II compound since it is a poorly water-soluble natural products with high membrane permeability [9]. RSV accumulation in grapes is dependents on the grape cultivar, genotype, location, environmental conditions, and growing seasons. Grape skin, seed, stem, shoot, bud, root, and leaf have all been found to contain varying quantities of RSV [10, 11]. Grape skin, on the other hand, contains a higher concentrations of RSV than grape juice or wine. The global demand for RSV is rising, but natural RSV synthesis and accumulation in grapes is very low. As a result, ongoing attempts to induce RSV accumulation in grape skin are underway. Fungi [12–14], UV-C irradiation, jasmonic acid (JA), salicylic acid (SA), H_2O_2, and $AlCl_3$ are all examples of biotic and abiotic factors that can induce RSV in grapes. RSV is naturally found in a few plant species, including grapes. As a result, grapes and grape-processed products are the most promising sources for both

natural and enhanced production of this compound. RSV has been used as an anticancer and anti-aging agent in the nutraceutical industry. Thus, using single or mixed external stimuli, it will be worthwhile to investigate the full induction of this compound in grapes. As a result, our research summarizes the impact of various biotic and abiotic stimuli on RSV accumulation in grapes. We've also summarized the impact of various external stimuli on RSV biosynthesis, which is regulated by an enzymatic pathway.

Structure of RSV *(Cis and Trans)*

One of these stilbene compounds, RSV (3, 4', 5-trihydroxystilbene, RSV), has two known isoforms: trans-RSV and cis-RSV, with trans-RSV being the more stable of the two [15, 16]. UV light and high pH are the two factors that allow the trans-isoform to isomerize to the cis isoform. Visible light, high temperatures, and low pH, on the other hand, affect cis to Trans isomerization [17, 18]. RSV is a C = C double-bonded polyphenol stilbene. Trans (E) and cis (C) are the two major (geometric) isomers (Z). Although trans-R appears to be the more common and stable natural form, cis-R has never been discovered in grape extract [19–21]. When the trans-R is exposed to solar [22, 23] or ultraviolet radiation [24], for example, cis-isomerization may occur. This review investigated the chemical change of specific carbon sites in the trans-R and cis-R isomerization for information on through space and through bond interactions. Dual space analysis (DSA) [25], which shows the cross sections of an orbital in momentum space and is thus sensitive to the shape of an isomer [26–29], excess orbital energy spectrum (EOES) [30, 31], which extracts conformer structural details on individual orbitals, and energy decomposition analysis are some of the theoretical methods (EDA) [32, 33]. It is possible to expose physical relations between the energy terms in the isomers of RSV and NMR spectroscopy using isomer-specific methods.

Versatile therapeutic applications of RSV

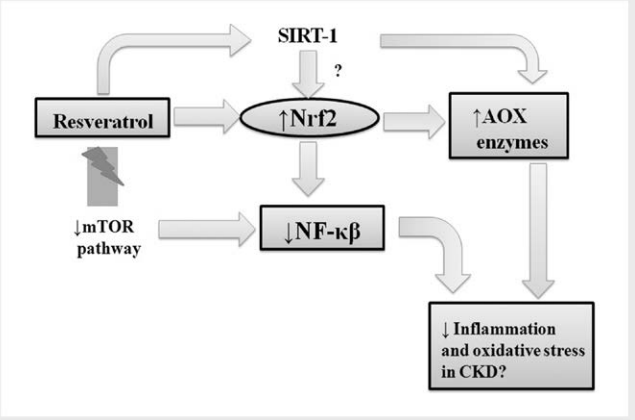
RSV is currently used to treat cancer, slow ageing, cardio-vascular disease, antiviral therapies, inflammation, platelet aggregation, and a number of other disorders [34, 35]. RSV has been related to regulatory pathways that have both growth and death properties as anticancer treatment [35]. RSV can also help to preserve genome stability, according to new evidence [35]. RSV, a polyphenol present in red wine, and similar polyphenols contribute to the inhibition of cancer caused by genomic instability by activating DNA double-strand break (DSB) repair. The use of RSV on a regular basis helps to maintain genomic stability. Given that mouse embryonic fibroblasts (MEFs) often immortalize when the ARF/p53-dependent barrier is broken, RSV may prevent cancer-driver gene alterations by maintaining genomic stability. RSV has been shown in other research to be a cancer chemo preventative drug, with the potential to suppress tumor growth in a wide range of cancers [35]. In recent years, the use of antioxidants in dietary and skin care products has grown in popularity. RSV has been the focus of extensive study for the past two decades [36]. RSV is a very potent antioxidant, making it a special candidate for having beneficial anti-aging results in cosmetic products. Polyphenols present in wine have been shown to be some of the strongest antioxidants, frequently many times more powerful than vitamins A, C, and E [36]. RSV can also be used as a precautionary and/or therapeutic agent, particularly in cases of male infertility due to testicular toxicity [37]. As a result, determining the precise safety range and therapeutic efficacy of particular RSV doses on specific populations is difficult. In this context, patients should be appropriately recommended for successful care with minimal side effects before being administered RSV [38, 39].

Antioxidant Activity

The arrangement of functional groups on the nuclear structure defines the antioxidant activity of RSV. As a result, many mechanisms of antioxidant action, such as radical scavenging and metal ion chelation, are heavily influenced by configuration, substitution, and total hydroxyl group amount. The use of density functional quantum chemistry and computational kinetics methods to investigate the antioxidant effect of trans-RSV against hydroxyl (• OH) and hydroperoxyl (• OOH) radicals in aqueous simulated media revealed that trans-RSV can act as an effective • OOH, and presumably • OOR, radical scavenger [40] (▶ **Fig. 1**). As previously mentioned, RSV is a potent antioxidant, but its beneficial effects are limited due to its poor bioavailability. Many attempts have been made to produce RSV derivatives via the esterification process in order to enhance their lipophilicity and use in lipid-based foods and biological environments. There have been approximately 12 different esterified acyl chlorides synthesized, including [41]; Butyryl Chloride, Caproyl Chloride, Capryloyl Chloride, Capryl Chloride, Docosahexaenoyl Chloride, Eicosapentaenoyl Chloride, Lauroyl Chloride, Myristoyl Chloride, Oleoyl Chloride, Palmitoyl Chloride, Propionyl Chloride, and Stearoyl Chloride. Copper ion-induced low-density lipoprotein (LDL) oxidation and hydroxyl radical-5 induced DNA scission were both effectively inhibited by these derivatives [41]. These findings showed that RSV derivatives could potentially act as antioxidants in foods and biological systems.

RSV's Antioxidant Activity and Cell Cycle Effects are caused by Specific Structural Determinants [42]

RSV (3,4 * ,5-trihydroxy-trans-stilbene) is a natural phytoalexin that has antioxidant and antiproliferative properties. It is present in



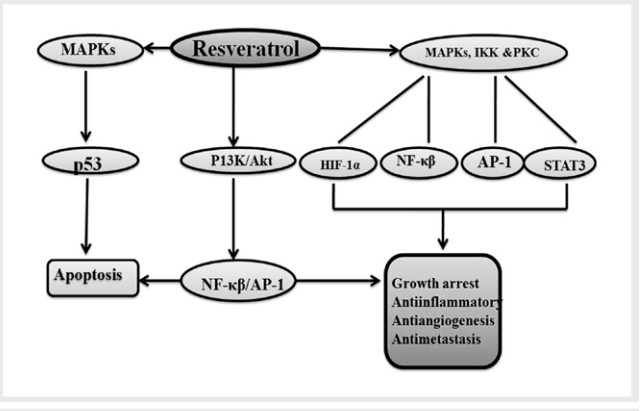
▶ **Fig. 1** Mechanism showing antioxidant activity of RSV, m TOR pathway- Mammalian target. of rapamycin, NF-κβ- Nuclear factor kappa light chain enhancer of activated B cells, Nrf 2- Nuclear factor erythroid 2-related factor 2, AOX- Adsorbable organic halides, CKD- Chronic Kidney Disease.

grapes and wine. We investigated whether these properties are influenced by the same or different structural determinants of the molecule in this analysis. RSV derivatives with all or single hydroxylic functions selectively substituted with methyl groups were synthesized for this purpose. The stereoisomer of analogues with the stilbenic double bond reduced or modified was also investigated. The inhibition of citronellal thermo-oxidation or the reduction of the 2, 2-diphenyl-1-picrylhydrazyl radical is used to assess the antioxidant function of these compounds. Furthermore, the defense against lipid peroxidation in rat liver microsomes and human primary cell cultures was investigated. A clonogenic assay was used to assess antiproliferative activity, as well as cell cycle progression and DNA synthesis analysis. The findings revealed that antioxidant activity is not solely determined by the hydroxyl group in the 4 * position. The presence of 4 * -OH and stereoisomer in the trans-conformation (4 * -hydroxy styryl moiety) was, on the other hand, completely required for cell proliferation inhibition. *In vitro* enzyme assays revealed that RSV inhibited DNA synthesis through a direct interaction with DNA polymerases a and d.

Bovine serum albumin-caffeic acid conjugate enhanced RSV chemical stability And cellular antioxidant activity in zein nanoparticles [43]

The free radical-induced grafting method was used to make a bovine serum albumin (BSA)- caffeic acid (CA) conjugate in this study. The conjugate had a CA to BSA ratio of 115.7 mg/g. BSA-CA conjugates were found to have higher antioxidant activity than BSA in *in vitro* antioxidant activity assays. The antisolvent method was used to make RSV-loaded zein encapsulated with BSA and BSA-CA conjugate core-shell nanoparticles.

BSA and BSA-CA. The encapsulation efficiencies (EEs) of zein-BSA and zein-BSA-CA nanoparticles were 85.3 percent and 86.5 percent, respectively. Both nanoparticles had smooth surfaces and were spherical with a mean diameter of 200 nm, according to SEM findings. After nanoencapsulation, RSV's thermal and UV light stability improved significantly. The BSA-CA conjugate provided significantly more protection against RSV degradation than BSA. RSV in both zein-BSA and zein-BSA-CA nanoparticles had significantly higher antioxidant activities than RSV alone, according to a cellular antioxidant activity (CAA) study.



▶ **Fig. 2** Figure showing anticancer activity of versatile RSV, MAPKs-Mitogen activated. protein kinase, NF-κβ- Nuclear factor kappa light chain enhancer of activated B cells, Akt- Alpha serine/threonine protein kinase, p53- Tumor Protein, p13K- Phosphoinositide 3-kinase, AP-1- Transcription factor, IKK- Inhibitory –κB Kinase, PKC- Protein kinase C, HIF-1α- Hypoxia- inducible factor 1-alpha, STAT 3- Signal transducer and activator of transcription 310.

The use of a colloidal nanodispersion of BSA-RSV improved RSV dispersibility, stability, and antioxidant activity [44]

RSV's native form has poor aqueous stability and solubility, which limits its use in fortifying foods. UV and fluorescence spectroscopy, oxygen radical absorbance potential (ORAP), and ferric reducing antioxidant strength (FRAS) assays were used to investigate the effect of the BSA-trans-RSV complex on the solubility, photochemical stability, and antioxidant activity of trans-RSV. RSV was solubilized using BSA at a molar ratio of 2.3:1 RSV:BSA, according to the findings. The formation of the BSA-RSV complex was confirmed using FTIR and fluorescence spectroscopy techniques. UV spectroscopy revealed that the complex formation significantly shielded RSV from UV-induced isomerization. RSV-BSA FRAS values were lower than free RSV (57 percent in 30:30 RSV-BSA, 39 percent in 90–90 RSV-BSA, and 25 % in 300:300 RSV-BSA M concentration). After 3 days, ORAP assays revealed a nearly 3-fold decrease in antioxidant activity of RSV; however, ORAP values for BSA-RSV complexes did not change significantly. In an aqueous medium, BSA was successfully used to increase RSV solubility and stability. The use of this device may increase the daily intake of unchanged RSV by consumers of fortified beverages.

Anticancer Activity

Many *in vitro* and *in vivo* studies have confirmed RSV's anticancer properties, demonstrating that it can inhibit all stages of carcinogenesis [45–47]. Many studies have shown that RSV not only serves as a chemo preventive agent, but also as a chemotherapeutic agent due to its anti-inflammatory, antioxidant, pro-apoptosis, and antiproliferative properties [48, 49].

Another *in vitro* study showed that RSV improves chemotherapy efficacy by inactivating the NF-κB protein (a transcription factor) released by cancer cells and regulating the expression of certain genes (▶ **Fig. 2**). Signaling pathways involving extracellular growth factors and receptor tyrosine kinases; formation of multiprotein complexes and cell metabolism; cell proliferation and genome instability; cytoplasmic tyrosine kinase signalling; signal ransduction by the transforming growth factor superfamily; apoptosis and inflammation; and immune surveillance were among the molecular mechanisms of RSV. Cancer cells become chemotherapy-resistant when this factor is present, allowing them to multiply. RSV inhibits this transcription factor, allowing chemotherapeutics to meet their intended targets [50–52].

RSV's anticancer molecular pathway [53]

The stilbene family contains RSV, which is a pleiotropic phytochemical. Despite the fact that it is only found in grape products, a large number of preclinical studies have looked into its anticancer properties in a variety of cellular and animal models. Signaling pathways linked to extracellular growth factors and receptor tyrosine kinases; development of multiprotein complexes and cell metabolism; cell proliferation and genome instability; cytoplasmic tyrosine kinase signaling; signal transduction by the transforming growth factor superfamily; apoptosis and inflammation; and immune surveillance and hormones were among the molecular mechanisms of RSV. In adjuvant therapy, RSV had additive and/or synergistic ef-

fects with 5-fluoruracyl and cisplatin, increasing cancer cell chemo sensitization. RSV has been highlighted as a promising, multi-target anticancer agent, important in both cancer prevention and treatment, due to its ability to operate on multiple pathways at the same time.

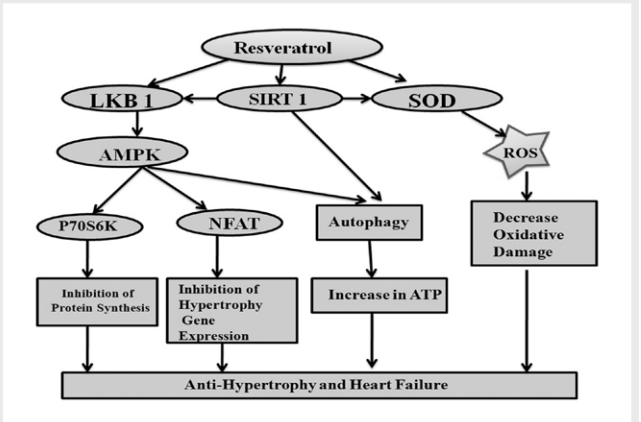
RSV as a Cancer Fighter [54]

Grapes (*Vitis vinifera L.*) are the archetypal paradigms of fruits used not only for culinary purposes but also for exclusive therapeutics due to their antimicrobial, antioxidant, and anti- inflammatory function. Grapes are a rich source of phytochemicals, especially RSV, a phytoalexin antioxidant found in red grapes that has anti-inflammatory and anti-cancer properties. The role of RSV in the prevention of various human cancers has been examined, including breast, cervical, uterine, blood, kidney, liver, eye, bladder, thyroid, esophageal, prostate, brain, lung, skin, gastric, colon, head and neck, bone, ovarian, and cervical cancers.

This analysis examines the literature on RSV's anticancer mechanism, with an emphasis on its antioxidant ability. In addition, this article summarizes the research on RSV as an anticancer agent.

RSV's anticancer and anti-inflammatory properties may be useful in the future [55]

Food-derived phytochemicals have shown promise in treating and managing a wide range of human diseases. RSV is an aromatic stilbene phytoalexin found in grapes, peanuts, berries, turmeric, and other foods. *In vitro*, in laboratory animal models, and in humans, RSV has been shown to have many physiological activities, including anticancer and anti-inflammatory properties. This compound's anticancer activity is primarily due to activation of apoptosis through several pathways, as well as changes in gene expression, both of which result in a reduction in tumor initiation, promotion, and progression. RSV has anti- inflammatory properties by modulating enzymes and pathways that generate inflammatory mediators, as well as inducing programmed cell death in activated immune cells. RSV has been shown to have no harmful side effects except when taken in high doses. As a result, RSV has a lot of promise as a complementary or replacement treatment for cancer and inflammatory diseases.



▶ **Fig. 3** Anti-hypertrophy and Cardioprotective activity of RSV, LKB 1- Serine-threonine . kinase 1, SIRT 1- Sirtuin 1, SOD- Superoxide Dismutase, AMPK- Adenosine monophosphate activated protein kinase, ROS- Reactive oxygen species, P70S6K-Ribosomal protein S6 kinase beta-1, NFAT- Nuclear factor of activated T-cells, ATP-Adenosine triphosphate.

Cardioprotective Activity

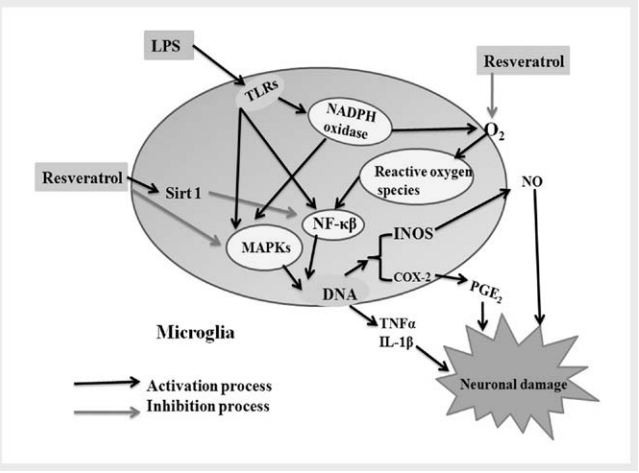
RSV improved left ventricle activity, decreased cardiac hypertrophy, contractile dysfunction and remodeling, interstitial fibrosis, and plasma BNP levels in patients with heart failure [56]. Inhibition of prohypertrophic signalling molecules, enhanced myocardial $Ca2^{+}$ handling, phosphorylation of prosurvival (Akt-1, GSK-3), and stress signaling (MKP-1) pathways, and reduction of oxidative stress and inflammation (iNOS, COX-2 activation, and ROS formation) are some of the molecular mechanisms of RSV action [57]. In rats with diabetes- related myocardial infarction, RSV suppresses phosphorylation of p38 and prevents the expression of endothelial nitric oxide synthase, vascular endothelial growth factor, and endothelial nitric oxide synthase [58] (▶ **Fig. 3**). According to these findings, RSV therapy may enhance cardiovascular function by lowering myocardial ischemia-reperfusion damage, vasodilation, and atherosclerosis [59]. Overall; RSV's cardiovascular protective role has been related to a number of molecular targets, suggesting that it may be useful in the creation of new therapies for atherosclerosis, metabolic syndrome, ischemia/reperfusion, and heart failure [60].

A systematic study of RSV, curcumin, and dietary nitric oxide supplementation's antioxidant and anti-inflammatory effects on human cardiovascular health [61]

Supplemental foods and dietary strategies have been studied extensively over the years for their ability to reduce cardiovascular morbidity and mortality. Many supplements claim to provide cardio protection and lower cardiovascular risk factors, but the functions of many supplements are unclear. Just three supplements have been extensively tested and reliably identified as successful by our clinic patients among the large number of supplements on the market claiming cardioprotective benefits. They had previously used supplements such as fish oil, multivitamins, and calcium, but few were aware of the benefits of RSV, curcumin, and nitric oxide for cardiovascular health. The cardioprotective effects of these dietary supplements have been studied in both animal models and humans, with antioxidant and anti-inflammatory properties being the most common mechanisms of action. RSV is a polyphenol that has been researched extensively and has been shown to have cardiovascular benefits. Preclinical studies have shown that these effects are mediated by enhanced inflammatory markers, atherogenic profile, glucose metabolism, and endothelial function, and clinical trials back this up. Curcumin has a well-known anti-inflammatory effect by controlling a number of transcription factors and cytokines that are involved in inflammation. Curcumin is a possible therapeutic compound since inflammation is an underlying pathology of cardiovascular diseases. Similarly, nitric oxide supplementation has been shown to improve cardiovascular health by reducing inflammation, immune deficiency, and oxidative stress. A systematic study of the cardioprotective effects of these three dietary supplements was conducted in the hopes of providing updated information, raising awareness of these supplements, and sparking potential research into their effects on cardiovascular health.

RSV Protects the Heart and Blood vessels [62]

RSV (3,4,5-trihydroxy-trans-stilbene), a phytoalexin contained in grape skins, peanuts, and red wine, has a variety of biological and pharmacological properties. RSV has been suggested to have cardioprotective properties at low doses. Recent *in vitro* and *in vivo* studies in animal models are described in this article. RSV modulates vascular cell activity, prevents LDL oxidation, suppresses platelet aggregation, and decreases myocardial damage during is-



▶ **Fig. 4** Inhibition mechanism of RSV against Neuronal damage, LPS-Lipopolysaccharide. TLRs- Toll-like receptors, NADPH- Nicotinamide adenine dinucleotide phosphate, SIRT 1- Sirtuin 1, O2-oxygen, MAPKs- Mitogen activated protein kinase, NF-κβ- Nuclear factor kappa light chain enhancer of activated B cells, DNA- Deoxyribonucleic Acid, INOS- Nitric oxide synthases, COX-2- Celecoxib, NO- Nitric Oxide, PGE2- Prostaglandin E2, TNFα- Tumor Necrosis Factor A, IL-1β- Interleukin.

chemia-reperfusion, according to the findings of these studies. Although the recorded biological data suggest that RSV is a highly promising cardiovascular protective agent, further research is required, especially in humans, to determine its bioavailability and *in vivo* cardioprotective effects.

RSV: a cardioprotective substance [63]

Coronary heart disease (CHD) is a leading cause of morbidity and death in the United States, and it is preventable. An epidemiological phenomenon known as the "French paradox" has recently attracted a lot of research attention. This finding relates to the coexistence of high- risk factors and an unexpectedly low incidence of CHD, which is thought to be linked to low- to-moderate red wine consumptions. *In vivo* studies have shown that red wine consumption is more CHD-preventative than other alcoholic beverages; improved cardio protection can be due to grape-derived polyphenols in red wine, such as RSV. This analysis summarizes the findings of *in vitro* and animal studies demonstrating RSV's multifaceted cardioprotective activities, as well as evidence demonstrating the existence of RSV-targeted proteins, such as N-ribosyldihydronicotinamide: quinone oxidoreductase, NQO_2.A structure for learning more about RSV cardio security is suggested, which includes nongenomic and genomic effects as well as a research roadmap.

Neuroprotective Activity

In Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and alcohol-induced neurodegenerative disorders, RSV plays a number of neuroprotective functions [64, 65]. It has been demonstrated that mitochondrial functions and biogenesis enhance RSV protective effects through the SIRT1 (sirtuin 1)/AMPK/PGC1 pathway and vitagenes, which prevent the deleterious effects caused by oxidative stress [65–67]. RSV lowers cholinergic neurotransmission, brain-derived neurotrophic factor expression, and oxidative stress, facilitates the clearance of -amyloid peptides and anti-amyloidogenic cleavages of APP, and lowers neuronal apoptosis [68]. RSV may also boost rat motor skills and deactivate the neuroinflammatory response in the aftermath of an intracerebral hemorrhage (▶ **Fig. 4**). It may be used to treat intracerebral haemorrhage as a novel therapeutic agent [69, 70].

The Role of SIRT1 in RSV-mediated Neuroprotection in Alzheimer's Disease [71]

Alzheimer's disease (AD) is a neurodegenerative condition of the cortex and hippocampus that causes cognitive decline. While the cause of Alzheimer's disease is unknown, the presence of -amyloid (A) peptides in these learning and memory regions is a defining feature of the disease. As a consequence, inhibiting A peptide aggregation has been suggested as the main therapeutic technique for the treatment of Alzheimer's disease. RSV has been shown in numerous studies to have antioxidant, anti-inflammatory, and neuroprotective effects, as well as the ability to reduce a peptide toxicity and aggregation in the hippocampus of AD patients, promote neurogenesis, and prevent hippocampal harm. Furthermore, RSV's antioxidant activity plays an important role in neuronal differentiation by activating the silent knowledge regulator-1 (SIRT1). SIRT1 is essential for neuronal growth and differentiation, as well as preventing apoptosis by deacetylating and repressing p53 activity; however, the exact mechanisms are unknown. RSV has anti-inflammatory properties since it inhibits M1 microglia activation, which is involved in neurodegeneration, and promotes Th2 responses by increasing anti-inflammatory cytokines and SIRT1 expression. This review will concentrate on RSV's antioxidant and anti-inflammatory neuroprotective properties, as well as its function in SIRT1 and its link to AD pathophysiology.

RSV has a neuroprotective role in the pathology of Alzheimer's disease [72]

Alzheimer's disease is a neurodegenerative disease that causes cognitive and behavioral abilities to deteriorate over time. Alzheimer's disease is characterized by extracellular senile plaques and intracellular neurofibrillary tangles. The aim of researchers is to decipher the molecular mechanisms underlying AD pathogenesis; however, the current therapeutic options for treating this disease are insufficient. Several studies have reported fascinating insights into the neuroprotective properties of the polyphenolic compound RSV (3, 5, 4 –trihydroxy- trans-stilbene) when used with *in vitro* and *in vivo* models of Alzheimer's disease in the lastfew years. A review of possible analogues aimed at raising the bioavailability in plasma is also addressed, since naturally occurring types of RSV have a very short half-life in plasma.

RSV has neuroprotective effects in a variety of neurodegenerative diseases [73]

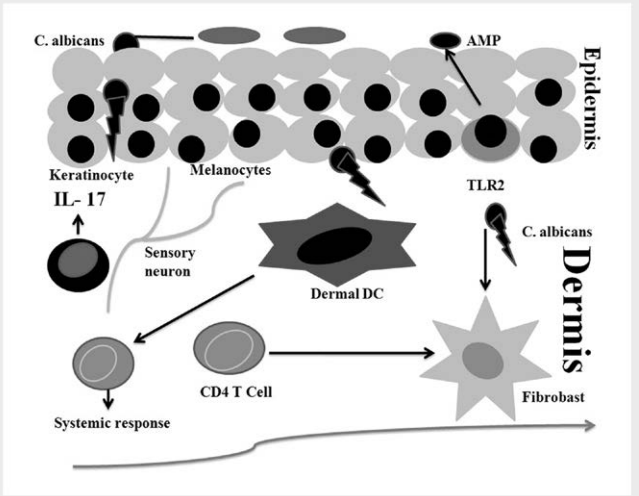
RSV, a natural phytocompound, has long been thought to be a potential anticancer drug, but it has recently attracted the attention of neuroscientists as well, since it has neuroprotective properties and activates the SIRT1 sirtuin family member. Sirtuins are deacetylase enzymes that have a preference for acetyl groups. Seven genes code for human sirtuins (SIRT1-7). SIRT1 is the most researched sirtuin, and it's involved in a number of physiologic and pathologic processes including apoptosis, autophagy, diabetes, cancer, cardiovascular disease, and neurodegeneration. RSV has been shown to be beneficial in ischemic stroke, Parkinson's disease, Huntington's disease, and epilepsy models, as well as *in vitro* and *in vivo* in models of Alzheimer's disease (AD). Here, we summarize the *in vitro* and *in vivo* experimental findings, emphasizing RSV's potential function as a neuroprotective bio factor, with an emphasis on Alzheimer's disease.

Anti-Inflammatory Activity

RSV and other stilbenoids are non-nitrogenous polyphenols with acidic and amphiphilic properties that have anti-inflammatory properties. Many of their targets are cyclooxygenase (COX), 5-lipoxygenase (5-LOX), and protein kinase B [74], which is related to its ability to inhibit COX-1 and COX-2 activity, as well as transcription factors [75]. RSV's anti-inflammatory activity prevents acute pharyngitis-induced inflammation in rabbit models by inhibiting NF-κB, tumour necrosis factor, and interleukin-6 serum levels, macrophage inflammatory protein-2 and cyclooxygenase-2 activity, reactive oxygen species formation, and caspase-3/9.RSV inhibits the activation of microglia, which results in the release of pro- inflammatory factors, the development of reactive oxygen species, and the activation of neuroinflammation signal pathways [76]. In the laboratory at moderate to high concentrations, RSV suppresses the inflammatory response in intestinal cells by inhibiting NF-B activation and preventing mitocin production. *In vivo*, RSV inhibits TNF- and NF-κB activation, reduces neutrophil infiltration in the intestinal mucosa, and suppresses intestinal tumorigenesis by controlling anti-inflammatory miRNA (miR-9 expression, miR-146, miR- miR-21, miR-24, miR-10a) [77, 78]. RSV blocked the TLR-4/MyD88/NF-κB signaling pathway in lysophosphatidylcholine-induced damage and inflammation, suggesting that it may be used to treat arteriosclerosis [79]. RSV, a polyphenolic substance found in grapes and red wine, has anti-inflammatory properties that can reduce cytokine production, limit neutrophil activity, and change the expression of adhesion molecules. RSV also lowers the expression of NF-B and TLR4, a recognised receptor that activates innate immune responses, indicating that it has anti-inflammatory properties. These findings suggest that RSV can prevent inflammation and oxidative stress, lower the risk of carcinogenesis, and be used as an anti-inflammatory agent to improve patient quality of life.

RSV's anticancer and anti-inflammatory properties may be useful in the future [80]

Food-derived phytochemicals have shown promise in treating and managing a wide range of human diseases. RSV is an aromatic stilbene phytoalexin found in grapes, peanuts, berries, turmeric, and other foods. *In vitro*, in laboratory animal models, and in humans, RSV has been shown to have many physiological activities, including anticancer and anti-inflammatory properties. This compound's anticancer activity is primarily due to activation of apoptosis through several pathways, as well as changes in gene expression, both of which result in a reduction in tumour initiation, promotion, and progression. RSV has anti-inflammatory properties by modulating enzymes and pathways that generate inflammatory mediators, as well as inducing programmed cell death in activated immune cells. RSV has been shown to have no harmful side effects except when taken in high doses. As a result, RSV has a lot of promise as a complementary or replacement treatment for cancer and inflammatory diseases.



▶ **Fig. 5** Mechanism showing capacity of RSV to inhibit the growth of pathogenic. microorganisms, AMP- Activated protein kinase, IL-17- interleukin, TLR 2- Toll-like receptor- 2, CD4 T CELL- Cluster of differentiation 4, DERMAL DC-dermal dendritic cells, C albicans- Candida albicans.

Natural stilbenoids have anti-inflammatory effects [81]

RSV and other natural stilbenoids, such as piceatannol, pterostilbene, and gnetol, are well-known anti-inflammatory compounds that have been shown to work *in vitro* and *in vivo*. Inducible nitric oxide synthase, cyclooxygenases, leukotrienes, nuclear factor kappa B, tumour necrosis factor, interleukins, and other molecules are among their molecular targets. This anti-inflammatory activity, along with their antioxidant activity, is thought to be the driving force behind their other beneficial health effects, such as protection against cancer, cardiovascular and neurodegenerative diseases, and diabetes. As a result, they are now referred to as nutraceuticals. They are naturally found in wine, grapes, and berries. However, the true impact of these compounds on human health is the subject of heated debate. It is claimed that the concentration of stilbenoids in food and beverages is too low to have any therapeutic potential, and that their low bioavailability and extensive metabolism further reduces this concentration. As a result, this analysis focuses on *in vitro*, *in vivo*, preclinical, and clinical evidence for various natural stilbenoids and summarizes the anti-inflammatory targets on a molecular basis, compares the importance of laboratory research, examines stilbenoids metabolism and the possible action of their metabolites, and links this information to human health. Furthermore, methods to improve the effectiveness of stilbenoids are proposed, with a particular emphasis on multitargeted therapy and nanocarriers.

Curcumin, RSV, and flavonoids are anti-inflammatory, cytoprotective, and DNA- protective foods [82]

Many dietary compounds contained in fruits, vegetables, and spices have been isolated and tested for therapeutic potential in recent years. These compounds include flavonoid and non-flavonoid polyphenols, both of which have anti-inflammatory properties. Since their consumption was linked to a lower risk of cancer, cardiovascular, neurological, respiratory, and age-related diseases, the idea that these plant products had health-promoting properties arose. When the body is exposed to a stressful environment, cell survival is harmed, and the risk of chronic disease increases. Polyphenols protect against a variety of stress-related toxicity by modulating intercellular cascades that inhibit inflammatory molecule synthesis, free radical formation, nuclear damage, and the expression of antioxidant enzymes. These actions have the power to lengthen people's lives. Curcumin, RSV, and flavonoids are the subjects of this review report, which aims to summarize their anti-inflammatory, cytoprotective, and DNA-protective properties.

Antimicrobial Activity

The capacity of RSV to inhibit the growth of pathogenic microorganisms such as Gram-positive and Gram-negative bacteria and fungi has been studied (▶ **Fig. 5**) [83]. RSV has been shown to in-

hibit Candida albicans development effectively [84]. C. albicans was resistant to dimethoxy RSV derivatives. albicans, with MIC values ranging from 29 to 37 g/mL, as well as 11 other Candida species [85]. The putative candidacidal operation of RSV, on the other hand, is a source of debate. In reality, according to one analysis, RSV is ineffective against both C. Non-C. albicans and C. albicans species of albicans [86].

RSV Analogues' Antimicrobial Activity [87]

Stilbenes, especially RSV and its derivatives, have become well-known for their beneficial effects on a variety of medical conditions, as evidenced by numerous published studies. Antimicrobial properties are a field of research that has received less attention. The antimicrobial activity of a series of 13 trans-RSV analogues synthesized through Wittig or Heck reactions was tested on two separate grapevine pathogens that cause severe diseases in the vineyard. The entire collection, along with RSV, was tested first on Plasmopara viticola zoospore mobility and sporulation level. Stilbenes showed a wide range of behavior, from low to high. Six of them, including the most active ones, were then tested for Botrytis cinerea growth. The findings allowed us to identify the most active stilbenes against both grapevine pathogens, compare the antimicrobial activity of the tested series of stilbenes, and discuss the relationship between chemical structure (number and location of methoxy and hydroxy groups) and antimicrobial activity.

RSV-derived monomers and dimers have antimicrobial activity against pathogens that cause food poisoning [88]

Polyphenolic compounds found in plants are thought to be a potential source of new antibacterial agents. The antimicrobial activity of a series of RSV-derived monomers and dimers screened as single molecules against a panel of nine foodborne pathogens was investigated in this report. Two monomers (pterostilbene 2 and (E)-3-hydroxy-4′,5-dimethoxystilbene 9) and three dimers (-viniferin 10, viniferifuran 14, and dehydro— viniferin 15) were found to have significant antibacterial activity against gram-positive bacteria (Actinomyces, Arthrobacter, Bifidobacterium, Corynebacterium, Mycobacterium etc) according to the findings. The exposure of gram-positive foodborne pathogens to 100 g/mL of 2, 9, and 15 resulted in significant cell membrane damage and phospholipid bilayer disruption. Dehydro—viniferin 15, the most promising dimeric compound, was tested against Listeria monocytogenes, and it resulted in a loss of cultivability, viability, and cell membrane potential. TEM analysis showed significant morphological changes to the cell membrane as well as intracellular material leakage, suggesting that the tested derivative's primary biological target was the cell membrane.

RSV, a plant polyphenol, has been studied extensively for its antimicrobial Properties [89]

Because of rising drug resistance and a lack of effective antibiotics, treating certain infectious diseases is becoming more difficult. Alternative microbicides are urgently needed to combat infectious diseases due to the rapid rise in drug resistance. RSV is a small plant polyphenol that is formed and distributed naturally in 72 plant families. Researchers are increasingly turning to natural derivatives, such as RSV, to treat acute and chronic illnesses. The goal of the pre-planned analysis was to analyze and survey RSV's antimicrobial potency in depth. RSV is shown to be a natural antimicrobial agent in this research.

Immunomodulatory activity

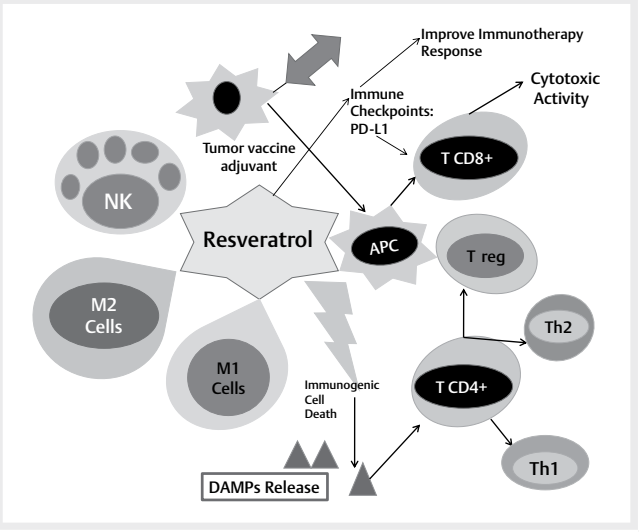
Immunomodulation is a therapeutic technique that involves interfering with the defense system's auto-regulatory processes. The functional status of the humoral immune response, such as hemolysin, is measured by the amount of particular antibody present in the serum. The effect of RSV on hemolysin regulation was investigated in mice immunized with Sheep red blood cells, and the results revealed a dose-dependent increase in hemolysin levels, suggesting that RSV boosted the humoral immune response and increased the formation of antibody cells. RSV was also found to increase the CD4/CD8 ratio, T lymphocyte proliferation, B cell-mediated immune response, and enhanced NK cell function, demonstrating an immunomodulatory effect on mouse lymphocytic leukemia [90] (▶ **Fig. 7**). Another research found that RSV has antiproliferative and immunosuppressive activity in **M21 human melanoma cell line (ATCC)** and NXS2 tumour cell lines (murine neuroblastoma **cell line**), as well as immunosuppressive activity in human and murine immune cells. *In vitro*, the concentration needed for immunosuppressive activity was 25- to 50-fold higher than the peak plasma level achieved in mice after oral administration, demonstrating antitumor activity [91].

RSV's immunomodulatory properties include the inhibition of lymphocyte proliferation, the creation of cell-mediated cytotoxicity, and the release of cytokines [92]

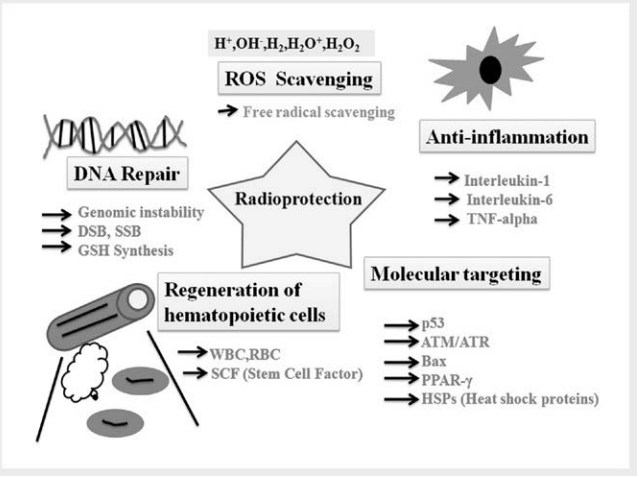
Anti-inflammatory, antioxidant, and antitumor properties have been demonstrated for trans- RSV, a phytoalexin contained in grapes, wine, and other plant products. Many of RSV's beneficial effects necessitate the involvement of immune system cells; however, RSV's impact on the production of immunological responses is unknown. We looked at how RSV affected mitogen/antigen-induced splenic lymphocyte proliferation, the induction of cytotoxic T lymphocytes (CTLs) and lymphokine activated killer (LAK) cells, and the synthesis of the cytokines interferon (IFN), interleukin (IL)-2, tumour necrosis factor (TNF), and interleukin (IL)-12. At 25–50 M RSV, we noticed that mitogen-, IL-2-, or alloantigen-induced splenic lymphocyte proliferation and the production of antigen-specific CTLs were significantly reduced. The suppressive effect of RSV was less sensitive in the generation of LAK cells at similar concentrations. RSV's suppression of cell proliferation and CTL generation was not only reversible, but in some cases, the response was also improved after the cells were pretreated with RSV. RSV also inhibited splenic lymphocytes' development of IFN- and IL- 2, as well as peritoneal macrophages' production of TNF- and IL-12.RSV had an irreversible effect on cytokine development. RSV also inhibited the activation of the transcription factor NF-κB while having no effect on its basal function. RSV inhibits cell proliferation, cell- mediated cytotoxicity, and cytokine production, at least in part, by inhibiting NF-κB activation, according to the latter result.

On Peripheral Blood Mononuclear Cells and Macrophages in Metabolic Syndrome Animals, Immunomodulatory Properties of Adipose-Derived Stem Cells Treated with 5- Azacytydine and RSV [93]

In veterinary medicine and horse breeding, endocrine disorders, such as equine metabolic syndrome (EMS), are a major problem. EMS was also found to alter the cytophysiological properties of adipose-derived stem cells, lowering their therapeutic ability. However, it was discovered that by combining two chemicals, 5-azacy-



▶ **Fig. 6** Figure showing immunomodulatory effects of RSV, NK- Natural killers, PD-L1-. Programmed death ligand, TCD8- Cluster of differentiation 8, APC-Antigen Presenting cell, T reg- Regulatory T Cells, M2- Melanoma Cell line, M1- Microglia Activation, Th 2- Helper cells Orchestrate protective type 2 immune response.



▶ **Fig. 7** Figure showing several mechanisms of RSV for radioprotective action, ROS- Reactive oxygen species, DNA- Deoxyribonucleic Acid, DSB- Double stand break, SSB- Single stand break, TNF-α- Tumor necrosis factor alpha, WBC-White Blood Cells, RBC-Red Blood Cell, SCF-Stem Cell Factor, p53- Tumor Protein, ATM-serin/threonine kinase, ATR-DNA repair protein, Bax-BCL2 Associated X, Apoptosis Regulator, PPAR-γ- Peroxisome proliferator activated receptor gamma, HSPs-Heat shock proteins.

tydine (AZA) and RSV, certain cells can be rejuvenated. We agreed to test the immunomodulatory properties of AZA/RSV- treated adipose-derived stem cells (ASC) isolated from EMS horses in the current research (ASCEMS). As a result, we co-cultured ASC with RAW264.7 macrophages and peripheral blood mononuclear cells (PBMC). The mRNA and protein levels of many cytokines (tumour necrosis factor (TNF-), interleukin (IL)-6, IL-10, and IL-1), as well as regulatory T lymphocytes (TREG), received the most attention. In addition, we looked at the expression of genes involved in autophagy and mitophagy in both PBMCs and ASCs. ASCs were isolated from healthy and EMS horses cultured in control conditions and with AZA/RSV. PBMCs were collected from healthy and EMS-suffering individuals and co-cultured with ASCs from healthy and EMS horses cultured in control conditions. When co-cultured with PBMCs, cells treated with AZA/RSV increased the amount of TREG. Furthermore, co-culturing PBMCs with AZA/RSV-treated ASCEMS resulted in PBMC mitophagy. Furthermore, in co-culture with RAW macrophages, ASCEMS pre-treated with AZA/RSV showed anti-inflammatory properties, with lower levels of TNF-, nitric oxide (NO), and IL-6 in those cells compared to their untreated counterparts. In conclusion, we found that ASCEMS treated with AZA/RSV had more anti-inflammatory properties and could control and activate the TREG- related anti-inflammatory response.

RSV's immunomodulatory activity: in vitro and in vivo immunological effects *are*contradictory [94]

Trans-RSV is a polyphenolic compound found in grapes that has been shown to have significant anti-inflammatory, antioxidant, and chemo preventive properties. In this review, we compared the effects of RSV on mitogen/antigen-induced T cell proliferation, induction of cytotoxic T lymphocytes (CTLs), interleukin-2 (IL-2) induced lymphokine activated killer cells, and cytokine synthesis *in vitro* and *in vivo*. *In vitro*, RSV at a concentration of 25 mM significantly suppressed mitogen/antigen-induced T cell proliferation and the development of allo-antigen specific CTLs (> 90 %). RSV (2 mg daily) intragastric administration to mice for 4 weeks had no effect on age-related body weight gain, peripheral blood cell counts, bone marrow cellularity, or spleen cellularity. RSV therapy had no effect on CD4 and CD8 T cells in the spleen or complete colony-forming units in the bone marrow. Spleen cells stimulated *in vitro* after being separated from RSV-infected mice for 2 or 4 weeks showed no noticeable changes in IL-2 or concanavalin levels (▶ **Fig. 6**). RSV administration did not affect the production of interferon-gamma or IL-12, but it did decrease the production of tumour necrosis factor-alpha. Treatment with RSV was found to only slightly reduce allo-antigen mediated T cell proliferation and the production of CTLs in the draining lymph nodes, even when performed entirely *in vivo*. Despite the fact that RSV inhibits T cell proliferation and the development of cytolytic cells *in vitro*, oral administration of RSV for four weeks causes no hematologic or hematopoietic toxicity and only slightly decreases T cell-mediated immune responses.

Radioprotective activity

Radiation-induced damage to living cells, mediated by the development of free radicals and reactive oxygen species (ROS), is a common issue. The radioprotective properties of various polyphenols have been investigated[95]. When 10 mol of RSV was dissolved in 200 l acetone and applied topically to mice's skin, inhibition of cellular proliferation and protein levels of epidermal COX-2 and ornithine decarboxylase was observed, confirming radioprotective activity mediated by apoptotic elevation (▶ **Fig. 7**). Another radioprotective analysis on RSV found that it reduced the frequency of chromosome aberrations in mouse bone marrow cells [96]. No treatment, RSV only, radiation only, and RSV and radiation were used to divide mice into four groups for this research [97].

Curcumin and RSV have been tested in vitro for their radioprotective properties [98]

Many natural substances have recently been investigated for use as radioprotectors to reduce ionizing radiation-induced damage in mammalian systems, due to their efficacy both before and after irradiation, and for long periods of time without drug-related toxicity. Curcumin and trans-RSV are naturally occurring polyphenols that can be found in the root of *Curcuma longa*, as well as grapes and other berries. Antioxidant, anti-inflammatory, immunostimulant, and anti-carcinogenic effects have been demonstrated for these compounds. The aim of this study was to compare the radioprotective efficacy of curcumin and trans-RSV against radiation-induced chromosomal aberrations *in vitro*. Curcumin and trans-RSV were pre- treated in human blood lymphocytes at concentrations ranging from 0 to 500 mg mL1 for curcumin and 0 to 50 mg mL1 for trans-RSV, respectively. Radiation-induced chromosomal damage was decreased at all concentrations measured, according to the findings. Curcumin's maximum damage protection was observed at a concentration of 5 mg mL1 and trans- maximum RSV's damage protection was observed at a concentration of 0.5 mg mL1. As a results, our findings show that pre-treatment with curcumin and trans-RSV Significantly protects normal lymphocytes from g-radiation-induced cellular damage.

In vitro assessment of RSV's radioprotective and cytogenetic effects in Human lymphocytes [99]

Trans-RSV is a polyphenol that can be used in grapes and other berries. Antioxidant, anti- inflammatory, immunostimulant, and anti-carcinogenic effects have been demonstrated for this compound. Our aim was to establish the radioprotective efficacy of trans-RSV against radiation-induced chromosomal damage *in vitro*, as well as the genotoxicity and cytotoxicity of this polyphenol in non-irradiated cell cultures. Pre-treatment of human lymphocytes with trans-RSV at concentrations ranging from 0 to 219 lM was used in the experiment. The findings revealed that all of the concentrations examined decreased radiation-induced chromosomal damage as compared to cells that had not been treated. At a concentration of 2.19 lM, maximum damage protection was observed. In terms of genotoxicity, all trans-RSV concentrations tested raised the sister chromatid exchange (SCE) index as compared to no trans-RSV therapy. The cytotoxic indexes (Mitotic and Proliferation Index) revealed that the lowest concentrations boosted cell proliferation rates while the highest concentrations harmed the development of human peripheral lymphocytes.

Trans-RSV SLN for Long Circulation and Improved Radioprotection based on Supercritical Fluid Technology [100]

A radioprotective device with lower toxicity and prolonged operation is needed to minimize the harmful effects of radiations during occupational radiology, radiotherapy, and diagnosis. To mitigate radiation-induced damage, Trans-RSV (RVL) uses a free radical scavenging/antioxidant mechanism. However, its ineffectiveness is hampered by its low solubility and rapid metabolism. The goal is to encapsulate RVL in a long-circulating solid lipid nanoparticle (SLN). Methodology The RVL, Gelucire50/02, and Gelucire50/13 SLN supercritical CO2 solutions were rapidly expanded into an aqueous process comprising Tween 80, sonicated, and lyophilized to obtain SLN. Particle size, polydispersity index (PDI), percent entrapment efficiency (% EE), scanning electron microscopy (SEM), transmission electron microscopy (TEM), differential scanning calorimetry (DSC), X-ray diffraction (XRD), drug release, *in vivo* pharmacokinetics, antioxidant assays, radiation-induced lipid peroxidation, and plasmid DNA relaxation assays were all investigated. Drug degradation and shelf life were studied using stability tests. Conclusions The percent yield, particle size, PDI, percent EE, and percent drug release (after 72 hours) of the optimized formulation (F9) were 68.48 5.73 percent, 276.7 5.33 nm, 0.18 0.032, 62.66 4.52 percent, and 70.05 3.003 percent, respectively. DSC and XRD showed reduced crystalline peaks, while electron microscopy revealed nearly spherical particles. When compared to RVL solution, F9 demonstrated higher AUC and sustained release of RVL in rats (i. v. bolus), as well as improved antioxidant activities and radioprotection. F9 (at 8 °C) was estimated to have a shelf life of more than two years.

Side-Effects, Drawbacks and Limitations of RSV

One of the most intriguing features of RSV for its possible production as a promising drug is that it appears to have no debilitating or toxic side effects. Various *in vivo* and *in vitro* tests have used a wide variety of RSV doses. However, determining the most effective dosage and route of administration is critical. In addition, RSV has been shown to cause cell death in tumour tissues while having little effect on normal adjacent tissues [100]. The disparity in RSV cell uptake between normal and tumour cells may be due to variations in cellular targets and gene expression in cancer cells, rendering RSV tumor-specific. Lower RSV doses may be associated with health benefits, while higher doses devastate tumour cells through pro- apoptotic effects, according to Short-term doses of RSV do not seem to have any side effects (1.0 g). Otherwise, side effects such as nausea, vomiting, diarrhea, and liver dysfunction in patients with non-alcoholic fatty liver disease can occur at doses of 2.5 g or more per day. In long-term clinical trials, no significant side effects were identified. In reality, at doses of up to 5 g/day, either as a single dose or as a fraction of a multiple-day dosing schedule, RSV has been found to be safe and well-tolerated. However, it's important to note that these experiments were conducted on healthy people, and results can differ in sick people. Since orally administered RSV is metabolized by gut microbiota, deciding which effects are attributable solely to RSV or both RSV and its metabolites is difficult. When administered at high doses, RSV has been shown to inhibit cell growth and induce apoptosis in normal cells, supporting its biphasic effects over a broad concentration range. RSV activates MEK-1, Src, matrix metalloproteinase, and epidermal growth factor receptor in a MEK-1, Src, and matrix metalloproteinase dependent manner. At nanomolar concentrations, it stimulates MAPK and endothelial nitric-oxide synthases (eNOS), and at concentrations that are possibly/transiently reached in serum after oral red wine intake. Furthermore, in 1-year-old mice, RSV intake at low doses extend their lifespan. However, when mice were given higher RSV doses (1800 mg/kg), the animals died after 3–4 months. Trans-RSV was well-tolerated by healthy subjects in studies on steady-state pharmacokinetics and tolerability of 2000 mg Trans-RSV, given twice daily with food, quercetin, and ethanol. One disadvantage of taking RSV orally is that it undergoes rapid digestion in the body, limiting the molecule's bioavailability at the site of action. According to recent reports, even low doses of RSV consumed via the com-

mon diet can help to reduce cardio-vascular disease. One major downside of RSV is that the compound is not water soluble, necessitating the use of alternative methods such as organic solvents/oils, which are toxic to the environment and the human body. Furthermore, also in organic solvents, RSV has stability problems. As a result, for any commercially active formulation, RSV's water solubility and stability must be improved.

Future Perspectives of RSV

Natural products, as one of the most valuable tools in drug production, show a wide variety of biological activities for disease prevention, defense, and treatment. RSV is a natural polyphenol that can be found in a variety of foods. The use of RSV for the treatment and prevention of various diseases, especially cancer and Parkinson's disease, has been extensively investigated. In cancer, RSV has been shown to interact with a variety of molecular and cellular targets. Plant extracts are becoming increasingly common as a way to prevent or even cure diseases [100]. RSV is a small, inexpensive, and simple to obtain and functionalize molecule. It has a low toxicity and a variety of biological effects that could be used commercially. This paper summarized research on RSV's recent advancements, emphasizing its plant origins and future clinical applications. The use of RSV molecular derivatization is currently attracting a lot of research interest. Furthermore, with the advancement of technological means, the use of RSV in food would become more widespread. Furthermore, since RSV has a low bioavailability, it is critical to continue modifying and optimizing it in order to find better analogues with high bioavailability and specificity. If cancer cells or essential proteins of interest could be targeted with peptides conjugated to RSV, the effectiveness of RSV would be significantly improved while side effects would be reduced [100].

Conclusion

The use of RSV for biological purposes dates back hundreds of years. Here, the biological requirements of RSV, as well as its properties and side effects, are addressed. RSV is a natural phenolic compound with various biological applications in the pharmaceutical industry. To avoid their non-specific cytotoxic effect, optimization strategies currently rely on the potential use of RSV based on Nanoparticles, Translabial, Dendrimers, and Nanocrystals. Finally, although biological implementation of RSV is still a way off, researchers agree that ongoing research on the subject will eventually enable RSV and its compounds to be considered definitive candidates in a variety of activities in the coming years.

Author Contributions

The study for review, search and data collection, and preparation of the manuscript was done by all of authors. The author read and approved the final manuscript.

Funding/Support

This research was financially supported by the author.

Conflict of interest

The authors declare no conflict of interest.

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