REVIEW ARTICLE

Resveratrol: The Multifaceted Roles and Mechanisms of Polyphenol to Improve Longevity, Immunomodulation, and Age-related Diseases

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Abstract

High in polyphenols diet has been known to protect human against chronic metabolic diseases including cancer, diabetes, neurological and cardiovascular disorders. Resveratrol (RSV) is a natural polyphenol that presents in fruits, vegetables, and nuts. The polyphenols content of RSV possesses anti-inflammatory, antioxidant, immunomodulatory, and anticancer properties by influencing the nuclear factor-kappaB (NF-κB), p53, adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathways, enzymatic antioxidants expressions, and the levels of microRNAs. Therefore, this review article will focus on the potential of RSV in improving aging and metabolic diseases, which mostly induced by low-chronic inflammation and oxidative stress. RSV is also known as calorie restriction (CR)-mimetics to activate sirtuins family which improve mitochondrial function, repair DNA and genomic stability and reduce inflammation thus become a promising substance to extend health span and longevity. RSV can be useful as a supplement to prevent aging-related diseases, with a dose range between 250–1,000 mg depending on the intended health benefit and individual factors. More clinical data is needed to determine the impact of RSV metabolites and the relationship between dose, concentration, and effect, particularly in the context of chronic illness.

KEYWORDS: mesenchymal stem cell, extracellular vesicle, exosome, cancer therapy, drug delivery

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Introduction

Fruits and vegetables are rich in bioactive compounds known as polyphenols, which contribute to their distinctive colors, flavors, and medicinal properties.(1) Polyphenols are categorized based on their chemical structures into two main groups: nonflavonoids, which include phenolic acids, stilbenoids, and phenolic amides, and flavonoids, which encompass flavones, flavonols, isoflavones, neoflavonoids, chalcones, anthocyanidins, and proanthocyanidins.(2) Predominantly, these substances are plant metabolites characterized by their multiple aromatic rings with hydroxyl groups.(3) They were divided into distinct classes based on their chemical structures. In the small intestine, some, but not all, polyphenols are absorbed after gastrointestinal digestion, while unabsorbed polyphenols will accumulate in the large intestine, where they are metabolized by the gut microbiota. Digestive enzymes must first hydrolyze unabsorbed polyphenols such as glycosides before epithelial cells can absorb it with high lipid concentrations.(4)

In phase I and phase II enzymatic processes in the liver and enterocytes, dietary polyphenols are extensively degraded and/or poorly absorbed.(5) They are then

extensively biotransformed by the gut microbiota into a wide range of new chemical structures that are readily absorbed to reach the systemic circulation.(6) Only less than 5% of the entire polyphenols consumed are absorbed and reaches the plasma unaltered.(7) Phase I and II metabolites, along with microbial products, are predominant in plasma, while the parent molecule is often undetectable by highly sensitive analytical methods or exists at very low plasma levels that fail to provide sufficient cellular concentrations to support overall efficacy.(8) The low bioavailability/high bioactivity paradox was posited because polyphenols are unquestionably responsible for numerous biological effects despite their poor oral bioavailability. Recent study has demonstrated that metabolites of dietary polyphenols have notable intrinsic bioactivities, which may account for the effects of the parent substances.(9)

Many natural compounds possess antioxidant and anti-inflammatory properties, by acting as reactive oxygen species (ROS) scavenger, and altering the expression of several pro-inflammatory genes such as lipoxygenase, cyclooxygenase, nitric oxide synthases (NOS), and cytokines.(10) Among those natural compounds, resveratrol (RSV) is a natural polyphenol that are naturally present in a wide variety of plant species such as fruits, vegetables, and nuts.

RSV has been described as a phytoalexin, an anti-infectious substance produced in particularly high concentrations by plants in response to environmental stressors like ozone exposure, UV radiation, and other environmental factors, as well as injury, pathogenic-induced damage, nutrient deficiencies, and temperature fluctuations. (11,12) Researchers found that coronary artery disease (CAD) mortality was lower in Southern France than in other developed nations, despite consuming a diet relatively high in saturated fat, interest in RSV, especially the trans isomer, significantly increased in the early 1990s.(13)

RSV is known to be a caloric restriction (CR)-mimetic. CR has been shown to increase longevity in a variety of organisms and even delay the onset of late-life diseases.(14) Autophagy, an evolutionarily conserved mechanism of lysosomal proteolysis in eukaryotes, is one of the processes that CR favours. Many drugs and trophic factors can control autophagy, as well as in response to food restriction. In addition to giving the starved cell energy from broken-down self-components, autophagy eliminates otherwise dangerous proteins, is crucial for the oxidative stress response, and is involved in immunological response and endocrine signaling. Studying autophagy in the context of nutrition is particularly interesting since dietary variables, such as polyphenols, might affect the health benefits linked to autophagy. Somehow, the exact dose of RSV to provide benefits, especially for chronic illness, is still not known.

This review will focus on the potential and safety of RSV among many polyphenols as a supplement to improve metabolic health and prevent aging-related diseases, the immunomodulatory effects of such dietary polyphenols, their anti-inflammatory properties, the various pathways and mechanisms that reduce inflammation, and their role in protecting against various chronic inflammatory disorders, thereby contributing to longevity and driving innovation in the supplement industry. This is a non-structured narrative review that started with framing a research question, drafting the review preparatory work, literature searching (Pubmed and Scopus) with keywords: “resveratrol”; “sirtuin”; “aging”; “polyphenols”; and “caloric-restriction” within 2014–2024, and evaluation, organizing and presenting the results, and creating proper illustrations to aid understanding.

The Immunomodulatory and Anti-Inflammatory Role of RSV as A Polyphenol

Persistent inflammation has been identified as a significant contributing factor to a number of human conditions, including cancer, type II diabetes mellitus (T2DM), obesity, arthritis, neurological illnesses, and cardiovascular diseases (CVD).(15,16) Numerous studies support the idea that polyphenols can improve the immune system. For example, RSV have cardioprotective effects and an influence on immune cell populations, can alter the generation of cytokines, and the expression of pro-inflammatory genes (17), mainly due to its anti-inflammatory properties (18). Research, both *in vitro* and *in vivo*, has shown that RSV can inhibit cyclooxygenase (COX), deactivate peroxisome proliferator-activated receptor gamma (PPAR-γ), and enhance endothelial nitric oxide synthase (eNOS) in rat and mouse macrophages.(17) Similarly, in RAW (Murine macrophages cell line) 264.7 macrophages, a RSV analog known as RSVA40 suppresses the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6.(19) RSV has been demonstrated to decrease the expression of inflammatory mediators such as prostaglandins and leukotrienes, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), by inhibiting inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1.(20) Additionally, it inhibits

some inflammatory enzymes, such as COX production in mice, lipoxygenase (LOX) in human endothelial cells, mitogen-activated protein kinase (MAPK), and inhibitor of kappa kinase (IKK). Somehow RSV does not block COX expression directly.(21) Moreover, through the activation of the sirtuin 1/forkhead box transcription factor 1 (SIRT1/FOXO1) pathway, RSV helps stabilize adiponectin levels and improve lipid metabolism.(22)

The consumption of polyphenols is directly linked to changes in the number and type of particular immune cells. In male C3H/HeN mice, oral intake of polyphenols from dates is associated with an increase in T helper 1 (Th1) cells, natural killer (NK) cells, macrophages, and dendritic cells (DCs) in the spleen and Peyer's patches.(23) Polyphenols can increase the population of regulatory T cells (also known as suppressor T cells or Treg cells) in humans, which are important in immunological tolerance and autoimmune regulation.(24) RSV enhances the expression of Foxp3, a key transcription factor for Treg development and function, thus may have benefit in autoimmune disease.(25) Furthermore, flavonoids bind to xenobiotic-responsive sites in the promoter regions of some genes, such as Foxp3, increasing their expression and exhibiting an agonistic impact on the aryl hydrocarbon receptor (AhR).(26)

Cytokines are essential mediator proteins that facilitate communication within the immune system. Both pro-inflammatory and anti-inflammatory cytokines can be produced by lymphocytes, monocytes (classical, non-classical and intermediate monocytes), macrophages, mast cells, endothelial cells, fibroblast cells, and stromal cells. Chemokines are a subset of cytokines with chemotactic properties. Studies conducted both *in vitro* and *in vivo* demonstrate that polyphenols affect macrophages by inhibiting key inflammatory response regulators, including TNF-α, IL-1β, and IL-6.(27)

Polyphenols exert their immunomodulatory effects through a variety of common mechanisms, one of which is the modulation of inflammatory cytokines.(28) nuclear factor-kappaB (NF-κB) is an essential transcription factor for the expression of cytokines, and cell survival. It regulates a cellular immune response inflammatory, stress, proliferative, and apoptotic reactions to many stimuli.(29) The target genes of NF-κB are pro-inflammatory genes such as COX-2, vascular endothelial growth factor (VEGF), pro-inflammatory cytokines (*e.g.*, IL-1, IL-2, IL-6, and TNF-α), chemokines (*e.g.*, IL-8, macrophage inflammatory protein (MIP)-1α, and monocyte chemoattractant protein (MCP)-1), adhesion molecules, immuno-receptors, growth factors, and other agents involved in invasion and proliferation.(30) In normal cells, NF-κB presents in cytoplasm in its dormant form, non-DNA-binding form. IκB proteins bind to inhibit NF-κB. IκBs consist of precursors p100 and p105, Bcl-3, Iκ Bα, IκBβ, IκBγ, and IκBε.(31) IKK phosphorylates IκB proteins in response to stimuli, causing ubiquitination and subsequent degradation of the inhibitory proteins. The degradation of IκB causes the release of NF-κB dimer to the nucleus to bind and induce the expression of cause specific genes.(31)

Oxidative stress and protein oxidation are linked to the increased generation of ROS.(32) Protein oxidations in turn cause the release of inflammatory molecules and various inflammatory signals, such as peroxiredoxin 2.(33) Moreover, an excess of ROS can cause tissue damage, which may also start the inflammatory responses.(34) Thus, polyphenols with its traditional antioxidant properties can disrupt the ROS-inflammation cycle, explaining their anti-inflammatory properties. The antioxidant properties of polyphenols are well-known; they scavenge a variety of ROS. RSV exhibits a protective effect against lipid peroxidation in cell membranes and DNA damage caused by ROS and significantly inhibit NF-κB signaling pathway after cellular exposure to metal-induced radicals.(35) Therefore, RSV shows a potent anti-inflammatory property which modulate the immune system.

RSV as CR-mimetics and Autophagy Aging Inducers

Autophagy is a crucial cellular process that involves the degradation and recycling of cellular components through lysosomal pathways. This process is essential for maintaining cellular homeostasis, especially under stress conditions, by removing damaged organelles and protein aggregate. Autophagy is crucial for cellular quality control, especially under stress conditions like nutrient deprivation. As we age, the efficiency of autophagy declines, leading to the accumulation of damaged cellular components. This decline is associated with various age-related diseases.(36) RSV induces autophagy through several pathways, prominently involving the inhibition of the mTOR pathway. It directly inhibits mTOR by competing with adenosine triphosphate (ATP), which is necessary for autophagy induction.(37) In this regard, RSV, either as individual substances (supplements) or as a component of a diet, may be a useful therapeutic tool for healthy aging.(38)

Intracellular proteolysis is another critical cellular process involved in the degradation and recycling of

cellular components. Recent studies suggest that the ubiquitin-proteasome system (UPS) and autophagy are not entirely independent but rather part of a single proteolytic network. They share similarities in substrate selectivity and functionally cooperate to maintain cellular homeostasis.(39) Two primary routes of intracellular proteolysis are proteasomal and lysosomal degradations.(40) Proteins with longer half-lives often degrade in the lysosome, whereas those with short-lived molecules degrade through the proteasomal system.(41) Molecules subjected to lysosomal degradation can reach lysosome through autophagy, phagocytosis, or endocytosis. In yeast, autophagic breakdown happens during periods of low food availability and serves as a survival strategy to recycle cellular components. In higher eukaryotes, however, autophagic proteolysis has grown in importance since it also breaks down molecules, cellular aggregates, microbes, and entire organelles that might otherwise damage the cell. For this reason, autophagy protects neurons and cardiomyocytes from damage and is involved in immunity and tumorigenesis.(42)

Autophagy can be regulated by both genetic and non-genetic factors. Autophagy-related genes (ATG genes) are involved in the formation of autophagosomes and the regulation of autophagy in various physiological contexts. While non-genetic autophagy regulated by transcriptional networks and post-transcriptional mechanisms, including the action of transcription factors, micro-RNAs (miRNAs), and epigenetic regulators.(43)

CR is the only non-genetic autophagy stimulator proven to increase the longevity of model organisms, from yeast to mammals. CR is a dietary intervention characterized by a reduction in 20–50% of calorie intake without malnutrition.(44) CR helps delay or reduce the risk of numerous age-related illnesses by protecting biological processes. The positive effects of CR are driven by several molecular mechanisms, including modifying energy metabolism, lowering oxidative stress, improving insulin sensitivity, reducing chronic inflammation, promoting autophagy, enhancing neuroendocrine function, and inducing hormesis. Key molecular signaling pathways involved in CR's anti-aging impact include SIRT, G-coactivator-1α, AMP-activated protein kinase (AMPK), insulin/insulin-like growth factor (IGF), and the mTOR. These pathways form a highly active interaction network. Scientists are actively searching for natural or pharmaceutical CR-mimetics that can replicate the benefits of CR without reducing food intake, especially for individuals in mid-life to old age, as strict adherence to a CR diet is challenging for most people.(45)

Potential candidates for CR-mimetics include rapamycin, RSV and other polyphenols, 2-deoxy-D-glucose, and other glycolytic inhibitors. The mechanism pathways of these CR-mimetics involve the insulin pathway, activated AMPK activators, autophagy stimulants, alpha-lipoic acid, and other antioxidants.(46) CR depletes intracellular acetyl coenzyme A (AcCoA), which is linked to the deacetylation of cellular proteins, by reducing cytosolic AcCoA, inhibiting its biosynthesis, inhibiting acetyltransferase enzymes that transfer acetyl groups from AcCoA to other molecules, and stimulating deacetylases that remove acetyl groups from leucine residues.(47) *In vitro* and *in vivo* studies show that autophagy can be effectively induced by relatively nontoxic natural compounds that act as AcCoA depleting substances (*e.g.*, hydroxycitrate), acetyltransferase inhibitors (*e.g.*, anacardic acid, curcumin, epigallocatechin-3-gallate, garcinol, spermidine), or deacetylase activators (*e.g.*, nicotinamide, RSV). CR-mimetics can influence the same molecular pathways often activated by short-term fasting or long-term CR by inducing autophagy.(48) Furthermore, a variety of physiological characteristics and circumstances, such as the organism's metabolism, liver health, comorbid illnesses, microbiota characteristics, *etc.*, affect the bioavailability of dietary polyphenols.(49) The amount of polyphenols in food does not directly correlate with their bioavailability in the body upon oral ingestion; since the bioavailability of any natural polyphenol varies.(50)

RSV is known to induce autophagy by activating the SIRT1 protein by activating autophagy-related proteins like LC3 and (Atg) 5 and 7.(51) The indirect pathway is predicated on FOXO1 activation, which triggers Rab7 expression and causes maturation of autophagosomes and endosomes.(52) Furthermore, SIRT1 may activate FOXO3 to trigger Bnip3-mediated autophagy.(53,54) The negative regulation of the mTOR signaling pathway is one of the most significant outcomes of SIRT1 activation brought on by RSV exposure.(51) When taken as a whole, these findings provide credence to the theory that autophagy control and senescence-associated secretory phenotype (SASP) have a close association thus polyphenols that target SASP through autophagy may have anti-aging properties.(38)

RSV Activates SIRTs as The Regulators of Metabolism and Healthspan

A careful balance between energy intake, utilization, and storage is necessary for metabolic management. In excess nutrition, extra energy is conserved for use when resources

are limited. These changes in nutrient intake, use, and storage are governed by a finely tuned regulatory and evolutionarily conserved program that involves both food restriction pathways involving AMPK and SIRTs. Classical food excess signaling pathways involving insulin, IGF1, and TOR (mTOR in mammals).(55)

The class III histone deacetylase (HDAC)-related conserved protein family, known as SIRTs, consists of seven members.(56) Interestingly, SIRTs include a catalytic domain that binds nicotine adenine dinucleotide^{+} (NAD^{+}). Depending on the biological process they are involved in, they may act on distinct substrates. The distinct localization and functions of SIRTs can be partially explained by the differences in their length and sequence in the N- and C-terminal domains.(56) In recent years, an increasing number of studies have demonstrated their involvement in several pathologies, including CVDs, neurodegenerative diseases, muscular disorders, inflammatory and autoimmune diseases, metabolic disorders, and cancer.(57) Numerous cellular functions, including metabolism, mitochondrial homeostasis, autophagy, DNA repair, apoptosis, oxidative/antioxidative balance, and senescence, are regulated by SIRTs.(58,59) Furthermore, mounting data supporting the possible application of SIRT modulators for the treatment of various diseases.(60)

The seven proteins (SIRT1–SIRT7) that make up the SIRT family in mammals differ in their targets, enzymatic activities, subcellular localizations, and tissue selectivity. The significance of SIRTs, particularly SIRT1, in maintaining metabolic homeostasis, preventing age-related illnesses, and limiting caloric intake (as the sole physiological intervention that prolongs lifespan) has been investigated. Consequently, there was a fierce search for pharmacological or nutraceutical SIRT activators, which resulted in the discovery of many SIRT activators. Among these, RSV attracted the most interest.(61) It is believed that activation of SIRTs is advantageous for neurodegenerative disorders like Alzheimer's and Parkinson's as well as metabolic diseases like T2DM and obesity. This is partly due to the fact that SIRTs increase the activity of mitochondria, which are powerhouses of the cell, as well as mitochondrial proteins, which are crucial in the aforementioned diseases.(62)

First identified in a yeast model (63), silent information regulator 2 (Sir2) has been demonstrated to control a wide range of cellular functions, such as the silencing of ribosomal DNA (rDNA) and telomeric DNA, intracellular signalling related to cell cycle and senescence, and the regulation of metabolism through the deacetylation of not only histones but also a number of transcription factors and cofactors.(64) SIRT1 is the mammalian ortholog that is closest to Sir2. It was first identified as deacetylating histones, but it was subsequently discovered that it also deacetylates additional protein.(65) It is involved in many biological processes, such as DNA repair, cell cycle regulation, apoptosis and inflammation (66), autophagy and aging (67), and it is essential for protecting human against a variety of diseases (68). SIRT1 catalyzes the deacetylation of histone proteins H1, H3, and H4's acetyl-lysine residues. Additionally, non-histone substrates such as p53, Ku70, FOXOs, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), peroxisome proliferator-activated receptor gamma (PPAR-γ), and NF-κB are deacetylated by SIRT1. (69,70) Through the acetylation and deacetylation of these substrates, which changes their transcriptional and enzymatic activity as well as protein levels, SIRT1 plays a significant role in the regulation of cellular senescence and organism lifespan.(71-73)

The p53 was the first non-histone target for SIRT1 to be identified. It is deacetylated and inhibited in response to oxidative stress or DNA damage, which impairs apoptosis. (74,75) Therefore, it was thought that elevated SIRT1 activity might cause tumors, but it appears that the opposite is true.(76) Reversible acetylation also regulates the activity of a transcriptional co-regulator that controls mitochondrial biogenesis and activity, PGC-1α.(77,78) As described in Figure 1, SIRT1 deacetylates PGC-1α, activates and triggers downstream processes of mitochondrial genes expression.(79) Likewise, SIRT1 regulates the acetylation of transcription factors FOXO, which are crucial modulators of glucose and lipid metabolism as well as stress reactions. FOXO transcription factors play a crucial role in regulating apoptosis. FOXO transcription factors (such as FOXO1, FOXO3, FOXO4, and FOXO6) can directly activate the expression of several pro-apoptotic genes, including Bcl-2-interacting mediator of cell death (BIM), p53 upregulated modulator of apoptosis (PUMA), and Fas ligand (FasL). These genes encode proteins that promote apoptosis by triggering mitochondrial outer membrane permeabilization and activating caspases, which are enzymes that execute cell death. SIRT1 deacetylates FOXO proteins, enhancing their ability to induce apoptosis under stress conditions. Under conditions of oxidative stress or nutrient deprivation, FOXO proteins are activated and translocate to the nucleus. In the nucleus, they promote the expression of genes involved in cell cycle arrest, DNA repair, and apoptosis, helping the cell to cope with stress or, if damage is too severe, to undergo apoptosis. It is believed that SIRT1-mediated deacetylation

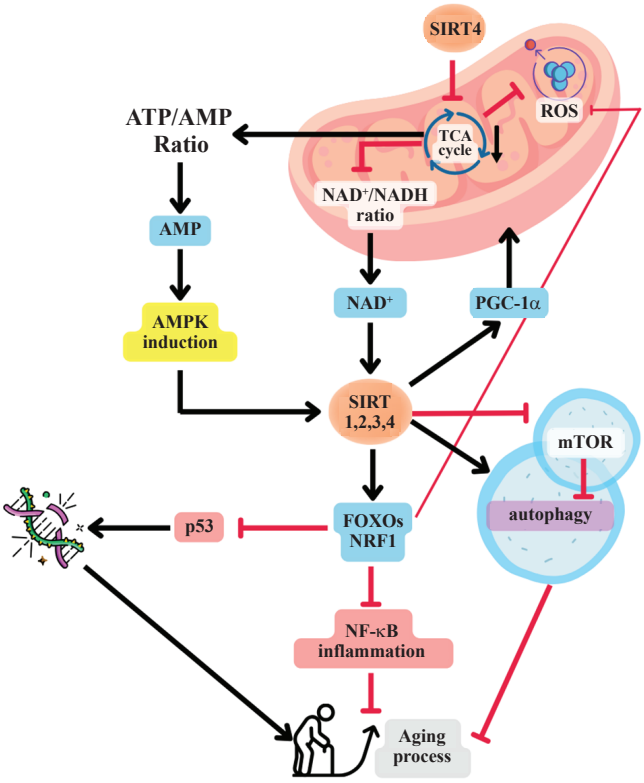

Figure 1. The anti-aging activity of SIRT by modulating a wide range of signal transduction pathways.

adds another level of specificity to phosphorylation-based regulation by preferentially directing FOXO to specific targets rather than merely activating or inhibiting it.(62)

In 2003, the first SIRT1-activating compounds (STACs) were identified, with RSV proving to be the most effective. This discovery was significant as it showed that SIRTs could be activated allosterically. Since then, over 14,000 STACs from various chemical classes, including plant-based stilbenes (such as RSV), chalcones (such as butein), and flavones (such as quercetin), have been discovered through high-throughput screening and medicinal chemistry efforts. (80) Imidazothiazoles (such as SRT1720), thiazolopyridines (such as STAC-2), benzimidazoles (such as STAC-5), and bridging ureas (such as STAC-9) are examples of synthetic STACs.(81,82) Through a K-type allosteric activation mechanism, each of these chemical classes lowers the substrate's Km value to activate SIRT1. It's interesting to note that recent research showed that natural fatty acids at the enzyme's amino terminus can trigger SIRT6 deacetylase activity, suggesting that SIRT6 may potentially be susceptible to *in vivo* activation by synthetic compounds. Given that SIRT6 can improve DNA repair, alter cancer cell metabolism to avoid malignancy, and increase mice lifetime, this discovery offers an intriguing prospect.(83)

Rapamycin, a medication that was initially identified in an Easter Island bacteria, decreases organ transplant rejection by blocking mTOR. Rapamycin is believed to increase longevity by simulating diets deficient in key amino acids like tryptophan or methionine.(84,85) Metformin also suggested to have longevity effects via an AMPK-activating chemical derived from the Hellebore buttercup plant beside become the first-line treatment for T2DM.(86)

Mechanism of SIRT1 Activation by RSV

SIRTs are desirable therapeutic targets due to their significant role in aging and metabolic control. RSV, a SIRT1 activator, prolongs life expectancy and protects against insulin resistance.(87,88) RSV can impact SIRT activation both direct and indirectly.(89,90) Direct activation and inhibition of SIRT5 and SIRT3 activities may also contribute to physiological consequences in mammals. Consistent with the discovery that piceatannol is a strong inhibitor of SIRT2, the effects on SIRT3 and SIRT5 further demonstrate that RSV is like chemicals that can interact with the conserved SIRT catalytic core rather than the proposed binding to the SIRT1-specific N-terminus.(91) *In vivo* study of RSV showed an opposite effect in higher concentration by inhibiting SIRT1 and SIRT5.(92)

In yeast, gene silencing at the three silent loci requires Sir2.(93) In addition to gene silencing, Sir2 proteins have a key role in a variety of functions, including fatty acid metabolism (94), cell cycle regulation (95), and life span extension (96). The most well-researched human homolog, SIRT1, mediates adipogenesis (97), muscle differentiation (98), transcription regulation (99), p53-dependent activities (100), protection against axonal degeneration (101), and prolong life span (102,103).

Nicotinamide was the sole NAD^+-like metabolite and salvage pathway intermediary that inhibit the regulatory effects on Sir2 enzymes (104) on life span extension (105), making it the most powerful inhibitor of Sir2 enzymes to date (106). Although nicotinamide adenine dinucleotide (NADH) was previously demonstrated to be a competitive inhibitor of NAD^+ *in vitro* (107); the large mm binding constant for NADH suggests that, in the majority of physiological circumstances, cellular NADH levels are unlikely to control Sir2 activity (104). Small compounds including Sirtinol, splitomicin, and splitomicin analogs were shown to be Sir2 inhibitors by phenotypic screening. Furthermore, it was demonstrated that 15 plant phenols, including as RSV, piceatannol, and quercetin, had SIRT1 activating qualities.

(102) RSV was the most effective activator of SIRT1 and, to a lesser extent, of Sir2 among all the small compounds that were discovered.(102)

SIRTs activation seems to be a more promising therapeutic strategy, stronger, more targeted, and more bioavailable substances are available.(91,108) The direct contact between different SIRT isoforms activator and the substrate, however, may settle a contentious issue regarding the potential of SIRT activation.(109) It describes how Sirt activation against the FdL1 substrate requires the C-terminal fluorophore (110,111) and how activation can also be facilitated by other C-terminal extensions, particularly regular amino acids. RSV activation is consistently seen by us and others for both complete substrate proteins and longer peptides without fluorophores.(92,112) According to assay data (92,111,113) and the observation that RSV exhibits Sir2-dependent effects in Caenorhabditis elegans that overlap with but differ from those of Sir2 overexpression (114), this mechanism also explains how the compound can activate, not affect, or inhibit a SIRT depending on the substrate. This sequence dependence implies that each SIRT/substrate pair separately when examining the effects of this class of compounds on SIRT-dependent deacetylation. Current medications only modify the deacetylation of a small number of particular Sirt substrates. RSV, as an alternative concept, suggests that the activator and substrate form a complex in solution, which then acts as an enhanced substrate.(115)

SIRT1 activation needs a fluorophore-containing substrate, even though such activation is independent of peptide sequence. The fluorophore prevents the peptide from tightly binding to the enzyme when coenzyme like RSV is not present. When RSV binds to SIRT1, the enzyme undergoes a conformational shift allowing a stronger fluorophore binding to the whole peptide substrate. RSV activation seems to be specific for SIRT1.(116) RSV-like compounds demonstrate the intriguing potential to create regulators that solely target particular SIRT/substrate combinations and show that a number of mammalian SIRT isoforms can be activated.(117)

Anti-Inflammatory Properties of RSV

Inflammation is one of the body's natural defence mechanism against infection or injury which is important in preserving tissue homeostasis under stressful situations. (118) Inflammation is essential for human health because of this intricate, strictly controlled process, acts as a quick defence to stop possible infections, prevents further tissue damage, and promotes healing processes.(119) All inflammatory responses share a basic mechanism, which generally includes the following steps: 1) The target tissues are impacted; 2) inflammatory pathways are triggered; 3) inflammatory markers are generated; 4) inflammatory cells are recruited; and 5) cell-surface pattern receptors identify harmful stimuli.(120,121) The cardinal signs of inflammation including pain (dolor), heat (calor), redness (rubor), swelling (tumor), and ultimately loss of function (function laesa), are the outcome of this intricate chain of events.(122)

Inflammation can be classified as acute as the body's immediate and early response to harmful stimuli, such as pathogens, damaged cells, or irritants. It typically lasts for a short period, from a few minutes to a few days; or chronic, when inflammation is a prolonged inflammatory response that can last for weeks, months, or even years. (118) Tissue-resident cells identify infections or damage and start the acute phase (the early stage of the body's response to injury or infection) by sending chemical signals that intensify the local response and recruit other cells.(119) Acute inflammatory responses are usually characterized by effective molecular and cellular processes that restore tissue homeostasis and, consequently, the full resolution of inflammation.(123) In low-grade inflammation, however, modifying or extending the inflammatory response's activation might result in the second stage response, known as chronic inflammation, which can harm a host more than the pathogen itself.(124) Recurrent or persistent infections can cause low-grade inflammation to last throughout life, and new research suggests that inflammation plays a key role in the aetiology of a number of chronic illnesses, such as neurological, cardiovascular, pulmonary, and metabolic diseases.(125) Additionally, research has linked inflammation to some cancer types.(119,126)

The foundation of inflammation therapy is the use of non-steroidal anti-inflammatory medicines (NSAIDs), which have a limited effectiveness and a number of side effects such as gastrointestinal tract injury, which can result from long-term usage of the medication because it inhibits both enzyme isoforms. NSAIDs are strong COX-1 and COX-2 inhibitors. COX-1 is constitutively expressed in many tissues and produces prostaglandins that are involved in maintaining normal physiological functions, while COX-2 is primarily induced at sites of inflammation and produces prostaglandins that mediate pain and inflammation. A novel anti-inflammatory drugs called coxibs was the creation of selective COX-2 inhibitors, which are

selective inhibitors, enhanced the effectiveness of NSAIDs and reduced the harm they caused to the gastrointestinal system, but they also raised the risk of hepatotoxicity and cardiotoxicity.(127)

Phytochemicals found in fruits, vegetables, nuts, and herbs may have pertinent positive benefits because of their inherent anti-inflammatory and antioxidant qualities.(128) Phytochemicals' hermetic qualities trigger adaptive stress response signaling pathways, which boost cells' resilience to damage and illness. As a result, natural compounds have garnered more attention in recent decades as potential sources of novel anti-inflammatory drugs.(129) RSV is known to have similar effects to NSAIDs as COX-1 and COX-2 inhibitors, making it a potential therapeutic agent for managing inflammatory conditions.(130)

Businesses working on food additives and cosmetics as well as the pharmaceutical sector shows growing interest in the use of RSV. RSV became well-known in dermatology applications as a cosmeceutical to enhance skin health because of its promising prospects as a topical anti-aging chemical by downregulating the key transcription factors involved in photoaging.(131) Furthermore, because of its purportedly positive effects on human health, RSV is currently widely available as an over-the-counter nutraceutical.(132) As a result of this heightened interest in RSV activity, numerous *in vitro* and animal studies have been conducted to find out its positive effects. Numerous studies have shown that RSV has both preventive and therapeutic properties in a number of illnesses, such as diabetes, CVDs, and different forms of cancer.(133) These properties are connected by their significant anti-inflammatory action. (132) Additionally, the beneficial biological effects of RSV were linked to lifetime extension in a number of studies using animal models.(134) RSV has a wide range of molecular targets as a pharmacological agent, and it is believed that its effects are the consequence of its simultaneous activity on several targets. RSV typically serves as a strong scavenger of free radicals (135), and exerts its effects by interacting with various enzymes across different groups, including kinases, lipoxygenases, cyclooxygenases, and SIRTs (136). Figure 2 describes the molecular anti-inflammatory effects of RSV.(137)

The pathophysiology of hypertension involves inflammation and oxidative stress in the vascular and renal tissues. RSV improves endothelial function and arteriolar remodelling, which has positive cardiovascular effects, particularly on pulmonary arterial hypertension (PAH). (138) The most common cause of PAH is inactivating mutations in the gene encoding for the bone morphogenetic protein type II receptor (BMPRII) which plays important roles in embryogenesis, and the homeostasis of adult tissues. Patients with PAH have lung pressures higher than 25 mm Hg during the resting state and 30 mm Hg during exercise. Breathlessness, exhaustion, and chest pain are the primary signs of this illness.(139,140) In PAH, combination therapy of anticoagulants, calcium channel blockers, diuretics, and prostanoids is considered standard care.(141,142) The pathophysiology of PAH is significantly influenced by smooth muscle cells (SMCs). Intimal fibrosis results from SMCs dedifferentiating, proliferating, and secreting fibrous material into the subendothelial region.(143) Thus, RSV can support PAH improvement.

Oxidative stress, caused by the accumulation of ROS in the cellular environment, damages proteins, RNA, and DNA. Activating the transcription factor nuclear factor erythroid-related factor 2 (Nrf-2) is one way that cells combat

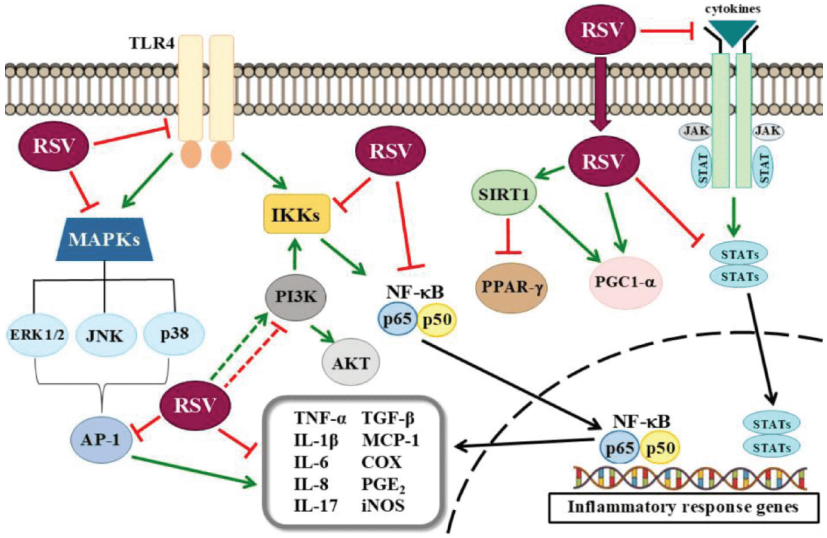

Figure 2. Some of the molecular bases of RSV anti-inflammatory effects.(137) (Adapted with permission from MDPI).

oxidative stress. Nrf-2 stimulates the transcription of genes that detoxify ROS and eliminate damaged proteins in order to increase the overall survival of cells.(144) Therefore, it is crucial to look for ways to restore Nrf-2 function because poor Nrf-2 activation causes inflammation and oxidative stress to be amplified or develop. Animal research has shown that RSV effectively counteracts pro-inflammatory cytokines, which can lead to arterial remodelling and the improvement of endothelial dysfunction. Additionally, RSV has been shown to reduce hypertension, improve small artery remodelling, and stop contractile dysfunction and heart hypertrophy in spontaneously hypertensive rats (SHR).(145,146) Interstitial immune cell infiltration is seen in renal tissue of untreated SHR and is linked to oxidative stress in renal proximal tubular epithelial cells. Nuclear Nrf-2 was markedly reduced in the untreated SHR. RSV treatment improved the progression of hypertension in SHR, decreased oxidative stress in proximal tubular epithelial cells, decreased the number of inflammatory and interstitial angiotensin (ANG) II-positive cells in the kidney, and restored the natural compound activator of Nrf-2. The restoration of Nrf-2 activity and the production of antioxidant enzymes are linked to the reduction of oxidative stress.(147) Glutathione-S-transferase (GST) and superoxide dismutase (SOD) are two examples of antioxidant enzymes that are important in defending cells against oxidative damage and aging.(148) RSV supplementation for an extended period of time raises SOD and GST levels in the SHR.(149)

Polyphenols including RSV providing anti-inflammatory and anti-cancer benefits by trigger cell death in various cancer types. They alter signaling pathways, reduce the activity of nucleoside diphosphate kinase B, and induce apoptosis in bladder, colon, and lung cancer cells. Numerous biological functions depend on nucleoside diphosphate kinase B (NME2). The oncogene c-MYC, which contributes to the development of cancer, is influenced by NME2 as a transcription factor.(150) By blocking NF-κB pathway, polyphenols also prevent cell proliferation and cell cycle.(151)

Many studies both *in vivo* and *in vitro* showed that polyphenols have been demonstrated to prevent the growth of malignancies of the mouth, gastrointestinal system, liver, lung, breast, and skin.(152) However, there is still much to learn about the molecular mechanisms behind the polyphenols' chemopreventive effectiveness. Oppositely, there are significant differences between polyphenol's clinical results and health advantages. one of the main reason is that polyphenols' non-physiological concentrations are being tested, which may obscure their mode of action at therapeutic dosages.(153) However, there is growing evidence that certain polyphenolic substances influence the epithelial-mesenchymal transition (EMT), one of the primary routes involved in the development and spread of cancer. Cells lose their cell-cell adhesions, cell polarity, and differentiation characteristics as they undergo EMT, changing from an epithelial to a mesenchymal state. (154) The cells become invasive and motile as a result of these alterations, which enable them to migrate through the extracellular matrix and reach distant areas.(155) Flavonoids, ellagic acid, quercetin, silymarins, RSV, and curcumin are just a few of the polyphenolic chemicals that have been shown to dramatically reduce metastasis and invasiveness in a variety of malignancies both *in vitro* and *in vivo*. Therefore, by blocking the EMT signaling pathways in cancer cells, polyphenolic substances may be able to stop or reverse the invasion, metastasis, and progression of cancer.(156)

RSV Improves Mitochondrial Function and Protects Against Metabolic Disease

Utilizing pharmaceutical dosages of bioactive food compounds such as nutrients and phytochemicals present in fruits, vegetables, and spice has become a viable therapeutic strategy to treat the intricate metabolic dysregulations associated with aging and chronic diseases. These substances are known as nutraceuticals, and the field is called nutrapharmacology. These chemicals can effectively alter the oxidative, inflammatory, and apoptotic abnormalities in chronic illness metabolic pathways, according to fundamental science publications.(157,158) More than one decade have passed since the first study revealed RSV's first *in vitro* and *in vivo* proof of cancer chemopreventative action (159), and since then many studies explore RSV in different diseases related to aging and metabolism (160,161), as proposed in Figure 3. The benefits of RSV are closely linked to its ability to improve mitochondrial function by activating SIRT1, which increases NAD^+ levels, promoting mitochondrial biogenesis and improving energy production. It also enhances the expression of antioxidant genes, such as SOD and catalase, which help reduce oxidative stress and protect mitochondria. By activating pathways like AMPK and PGC-1α, RSV improves the efficiency of ATP synthesis, supporting better cellular energy production.(162)

Numerous experimental investigations have shown that the polyphenol RSV inhibits the development of fatty liver disease including non-alcoholic steatohepatitis

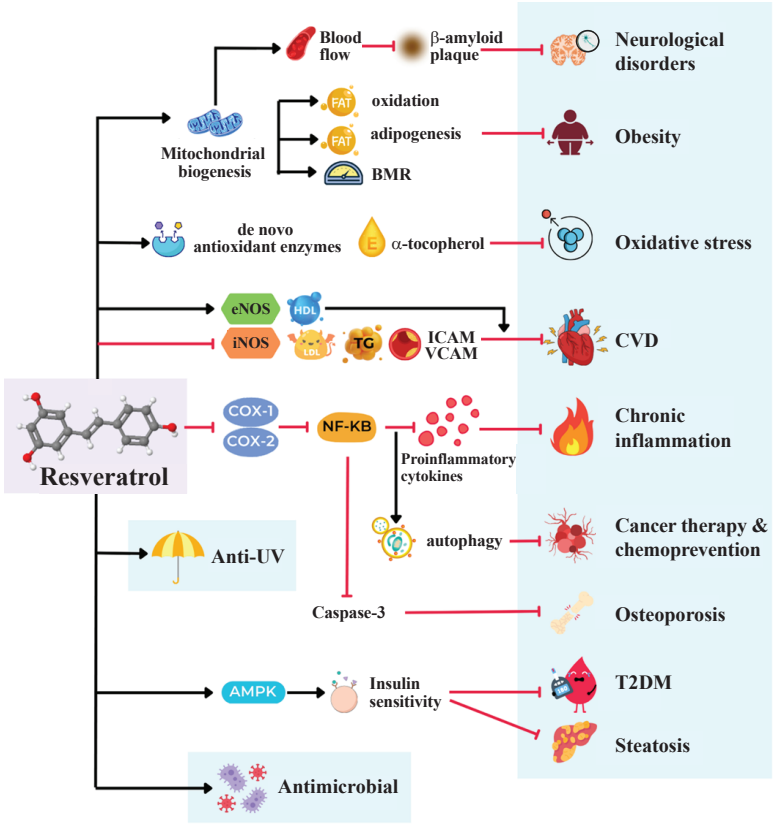

Figure 3. The main proposed mechanisms of action for potential clinical applications of resveratrol in various metabolic related diseases.

(NASH) and non-alcoholic fatty liver disease (NAFLD). It was assumed that RSV might reverse steatohepatitis, including hepatic inflammation and fibrosis. RSV treatment, when started early, partially reduced transaminase elevations, hepatic enlargement, and TNF-induced protein-3 protein expression. However, high hepatic triglyceride levels, histological steatohepatitis, or fibrosis were largely unaffected by RSV treatment.(163)

The major causes of NAFLD and NASH are obesity and inflammation. In affluent nations, NASH affects 2–10% of adults, whereas NAFLD affects 20–33% of individuals. (164-166) Hepatocellular ballooning and intralobular inflammation accompanying steatosis in NASH, can lead to progressive fibrosis and increase the risk of cirrhosis and hepatocellular carcinoma.(165) Additionally, NASH increases the risk of diabetes and ischemic heart disease, which raises the death rate for these individuals.(167,168) A Study on Japanese knotweed contains RSV showed a potential therapy option for NAFLD.(169) It appears that RSV mimics CR and promotes anti-inflammatory and antioxidant effects via activating AMPK and SIRT1.(170)

Mitochondria is the primary energy sources of the cell, which use cellular respiration to convert nutrients into energy.(171) Numerous illnesses, particularly those affecting the cardiovascular and metabolic systems, have been connected to compromised mitochondrial function. (172) Reduced mitochondrial oxidative capacity and ATP synthesis, a lower ratio of oxidative type 1 to type 2 glycolytic type muscle fibers, and, lastly, a decrease in the expression of genes governing mitochondrial activity have all been linked to human muscle insulin resistance. (172) The PGC-1α gene regulates mitochondrial biogenesis and function, which can help with fiber-type switching in muscle and adaptive thermogenesis in brown adipose tissue (BAT). Decreased expression of PGC-1α is reliably linked to diabetes muscle, characterized by muscle weakness, muscle mass loss and fatigue as the impact of diabetes in human or animal studies. A coactivator with pleiotropic properties is PGC-1α.(173,174)

SIRT1 has recently been shown to collaborate with PGC-1α in regulating the genetic programs for gluconeogenesis and glycolysis in the liver, thereby aiding the body's adaptation to CR.(175) Nicotinamide and O-acetyl-ADP-ribose are produced via the catalysis of NAD^+-dependent protein deacetylation, which is catalyzed by SIRT1, one of seven mammalian homologs of Sir2.(176) SIRT1 was first identified as a factor that controls longevity, apoptosis, and DNA repair, and also helps to convert nutritional status changes, which it detects through NAD^+ levels, into adjustments to cellular metabolism.(175)

Current Research Trends on RSV and Future Perspective

Nutraceuticals, such as RSV, are emerging as promising therapeutic agents for addressing metabolic dysregulations in aging and chronic diseases. Studies have shown RSV's potential in treating fatty liver diseases like NAFLD and NASH by mimicking CR and activating AMPK and SIRT1 pathways. Additionally, RSV's role in regulating mitochondrial function and gene expression helps mitigate muscle insulin resistance and supports overall cellular health, making it a valuable compound in nutrapharmacology.

Despite of all aforementioned benefits, RSV is still facing some challenges for optimal clinical application. Even now, there are some contradictory studies regarding the effects of RSV on metabolic and age-related diseases. While many studies highlight its benefits, some research points to limitations and inconsistencies. Different studies have shown that RSV's effects can vary significantly depending on the dosage, duration of treatment, and the specific condition being treated. For example, while RSV has been shown to improve insulin sensitivity in some studies, others have found no significant effect.(177) RSV has low bioavailability, meaning that it is not easily absorbed and utilized by the body. This has led to mixed results in clinical trials, as the effective dose can be difficult to achieve. Nonetheless, high doses of RSV have been associated with adverse effects in some studies, including gastrointestinal issues and interactions with other medications.(178) Studies focusing on improving RSV's bioavailability determining the optimal dose for humans are required.(179)

Recent ongoing research on RSV has focused on enhancing its bioavailability and exploring new therapeutic applications. Some cutting-edge discoveries and ongoing trends including its advance formulation, and expanding the application. Nanoparticle formulations are now developed for RSV-loaded nanoparticles. It was hoped to improve its bioavailability and stability. These formulations have shown enhanced anticancer potency compared to free resveratrol. (180) Scientists are modifying the structure of RSV to create derivatives with improved pharmacological activity and drug availability. These modifications aim to retain the beneficial properties of resveratrol while addressing its limitations. For example, the phenolic hydroxyl group of RSV which is highly susceptible to oxidation was modified with protective groups such as methoxy, ester, amino, benzene sulfonyl, glycoside, etc, The structural modification on the benzene ring of RSV can improve its anti-inflammatory effects. Modification of the linkers between benzene rings can enhance the anti-cancer effects, and some RSV analogues were developed by chemical synthesis, including structures containing naphthalene and its bioelectronic isomers.(181)

The pharmaceutical industry is increasingly interested in RSV for its potential in treating various conditions. Ongoing research is exploring its role in modulating molecular pathways and providing neuroprotective effects. (182) These advancements highlight the potential of RSV as a versatile and valuable compound in various therapeutic areas.

Conclusion

Mitochondrial dysfunction is linked to metabolic, cardiovascular, and neurodegenerative diseases due to its crucial role in cellular metabolism. SIRT1 activators, like RSV, show promise in preventing and treating these conditions by enhancing mitochondrial activity. RSV, a polyphenol, addresses oxidative stress and inflammation, key factors in aging and chronic illnesses. Recommended doses of RSV range from 250 to 1000 mg daily. However, challenges in applying RSV as a nutraceutical include its low bioavailability and the need for more clinical data to understand its effects and optimal dosing as well as advanced formulation and structure modification to increase the benefit. Future research should focus on improving RSV's bioavailability, conducting more clinical trials, and elucidating its mechanisms of action.

Authors Contribution

AM drafted the original manuscript and critically revised the manuscript manuscript. NMD edited and revised the manuscript. AW proposed and concepted the manuscript topic, and gave critical suggestions to the final draft. All authors have agreed with the final revisions of the manuscript.

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