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Review Article

Phytopharmaceutical Benefits of Resveratrol in the Management of Diseases and Health Maintenance: A Review

Kenneth Chinedu Ugoeze[1], Inderbir Singh Bakshi[2], Bruno Chukwuemeka Chinko[3, *], Kennedy Emeka Oluigbo[4], Ngozi Augustine Okoronkwo[5], Christian Arerusuoghene Alalor[6]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Port Harcourt, Nigeria

[2]Department of Pharmaceutics, Chitkara College of Pharmacy, Chitkara University, Punjab, India

[3]Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, Port Harcourt, Nigeria

[4]Department of Clinical Pharmacy and Biopharmaceutics, Faculty of Pharmaceutical Sciences, Enugu State University of Science and Technology, Agbani City, Nigeria

[5]Department of Zoology & Environmental Biology, Michael Okpara University of Agriculture, Umudike, Nigeria

[6]Department of Pharmaceutics and Industrial Pharmacy, Delta State University, Abraka, Nigeria

Email address:

bruno.chinko@uniport.edu.ng (Bruno Chukwuemeka Chinko)

[*]Corresponding author

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Abstract: In the last few decades, natural products have enjoyed an extensive range of acceptability for the prevention, treatment and management of various health conditions. Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is a common phytoalexin found in grapes, peanuts, cocoa, and berries of Vaccinium species, together with blueberries, bilberries, and cranberries. Research interest in resveratrol has been increasing due to growing evidence of its many health benefits. This review is aimed at highlighting the various benefits of resveratrol in health and diseases. The present study reviewed published advances in the health-promoting benefits of resveratrol in human clinical trials as well as in animal experimental models with a focus on postulated molecular mechanisms of action. We discussed the sources, biochemistry, bioavailability and biological effects such as antioxidant, anti-inflammatory, anti-cancer, anti-platelet, anti-diabetic, immunomodulatory and cardio-protective, anti-obesity and neuroprotective effects. The study observed that these varieties of biotic influences are initiated by multiple molecular targets and pathways involving cyclooxygenases/lipooxygenases, kinases, sirtuins, transcription factors, cytokines, DNA polymerase, adenylyl cyclase, ribonucleotide reductase and aromatase and thus, enhancing their potential to influence many physiological processes. The study concludes that resveratrol has demonstrated a potent effect against several disease conditions, however, its low bioavailability greatly limits its applications. This review recommends further research direction in the development of health maintenance and therapeutic agents from resveratrol.

Keywords: Resveratrol, 3,4′,5-trihydroxy-trans-stilbene, Antioxidant, Phytopharmaceutical

1. Introduction

Phytopharmaceuticals are natural or formulated herbal remedies that are effective due to their content of one or several plant substances or active ingredients generally referred to as phytochemicals [1, 2]. The expansion of phytopharmaceutical practice became essential to showcase

herbal medicines whose therapeutic essence is based on some plant constituents or biologically active ingredients [3]. Commonly regarded as phytomedicine or phytotherapy, it emphasizes the use of plant-based therapeutic formulations to relieve unwholesome health conditions. The World Health Organization (WHO) recognized that more than 80% of the world's population depends on therapeutic biologically active ingredients from plant sources for their major healthcare requirements [4, 5]. The use of phytopharmaceuticals in the health maintenance and management of diseases is largely dependent on acceptability, and satisfactoriness with little or no side effects [6].

Polyphenols are naturally occurring chemical compounds found mainly in vegetables, fruits and cereals [7]. They are natural complexes or phytochemicals derived exclusively from plants. Their biochemical characteristics are connected with their phenolic elements which stimulate potent antioxidant properties and function to protect the human body from free radical impairment and defence against UV radiation or antagonism by pathogens [7, 8] Several studies have continued to highlight that the intake of these polyphenols offered better defence against chronic diseases such as cancers, cardiovascular diseases, cerebrovascular diseases, diabetes, ageing and neurodegenerative diseases [9, 10]. Natural phenols are classes of natural ingredients comprising two phenyl rings and at least one or more hydroxyl substituents. Polyphenols are extensively distributed in plant tissues where they mainly exist in form of glycosides or aglycones They are classified into flavonoids and non-flavonoids [11].

1.1. Flavonoids: Flavones, Flavonone and Flavonols

Flavonoids comprise a group of naturally occurring substances found in vegetables, fruits, grains, wine etc [12, 13]. They possess a variable phenolic structure that arises from disparities in hydroxylation design and oxidation state ensuing in a wide range of compounds. This gives rise to subclasses such as flavanols, anthocyanidins, anthocyanins, isoflavones, flavones, flavonols, flavanones and flavanonols with Flavones, flavonols, flavanones and flavanonols making up the bulk of flavonoid compounds [11]. Flavones are one of the essential subclasses of flavonoids widely existing in leaves, flowers and fruits as glucosides. Celery, parsley, red peppers, chamomile, mint and *Ginkgo biloba* are among the key bases of flavones. Luteolin, apigenin and tangeritin belong to this subclass of flavonoids [14]. Flavonols are the precursors of proanthocyanins and the most prominent are rutin (rich in green tea, grape seeds, red pepper, apple, citrus fruits, etc.) [15] kaempferol (existing in apples, grapes, tomatoes, green tea, potatoes, onions, etc.) [16], quercetin (originating in vegetables, fruits, etc.) [17], myricetin (present in vegetables, fruits, nuts, berries, tea, red wine) [18]. Flavanones are richly found in all citrus fruits and they hesperidin and naringenin [19]. They are valuable health-wise as an antioxidant, anti-inflammatory, and blood lipid-lowering agent. These are made possible due to their free radical-scavenging effects. The flavanones are responsible for the bitter taste of the juice and peel of citrus fruits [20]. They are distinct from other classes of flavonoids and are found in food such as aglycones only (the glycosylated state is excluded). In addition, they may occur as monomeric units, referred to as catechins and epicatechins, and as polymeric forms, denoted as tannins [21]. Tannins, occurring in complexes with alkaloids, polysaccharides, and proteins, could be divided into hydrolysable tannins and condensed tannins (also known as proanthocyanidins [22]. Polymers of catechin, epicatechin, and/or leucoanthocyanidin, traditionally called condensed tannins, are the most abundant polyphenols in woody plants. Condensed tannins got their name as proanthocyanidins due to their capability to convert to anthocyanidins in oxidative situations [23]. They occur in fresh tea leaves, red wine, etc. [24]. Proanthocyanin and anthocyanin are widely distributed pigments in land plants where they serve as stress protectants and health-promoting components because of their potent antioxidant activity [25]. The pharmaceutical benefits of flavonoids include anti-oxidative, anti-mutagenic, anti-inflammatory, anti-carcinogenic properties and enzyme-modulatory properties [13].

1.2. Non-Flavonoids

While the polyphenol structural skeleton comprises numerous hydroxyl groups on aromatic rings, the basic structure of non-flavonoids is a single aromatic ring. Non-flavonoid complexes include phenolic acids, stilbenes, and lignans. One of the most popular stilbenes 3, 5, 4'-trihydroxystilbene (RSV) [26]. RSV is a stilbene polyphenol encompassing two phenol rings connected by a double styrene link and is a polyphenolic phytoalexin manufactured in plants [27]. Phytoalexins are secondary metabolites formed by plants in response to biotic and abiotic stressors in the form of stress, injury, fungal infection, or ultraviolet (UV) radiation [28, 29]. They contribute to a complex defence system which allows plants to regulate attacking micro-organisms [30].

2. Resveratrol

2.1. History of Resveratrol

Resveratrol (3, 4', 5-trihydroxy-trans-stilbene) was first extracted from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) by Michio Takaoka in 1939 and isolated from the roots of Japanese knotweed in 1963 [31]. The acronym, RSV was coined from their plant source namely: a resorcinol derivative or polyphenol in resin found in Veratrum species and containing hydroxy groups forming alcohol [32]. RSV continued to gain extensive scientific investigations and in 1992, it attracted widespread attention due to its discovery in wine as the basis for the cardio-protective properties of wine [33]. It was suggested that RSV ingestion through modest red wine intake might aid expound the point that French people have a moderately low occurrence of coronary heart disease (CHD) despite feasting on nourishments with elevated saturated fat, a remarkable observation labelled the "French Paradox" [34]. Further

scientific reports have noted that RSV has the potential to prevent or slow the progression of a wide range of diseases including cancer, cardiovascular disease and ischaemic injuries [35]. They are also able to enhance stress resistance while extending the life span of various organisms [36-39].

2.2. Biochemistry of Resveratrol

Resveratrol (3,4',5-trihydroxystilbene) is a member of the stilbene family, a group of compounds that consist of two aromatic rings joined by a methylene bridge. Also known as also as 3,4',5-stilbenetriol with molecular formula $C_{14}H_{12}O_3$ and a molecular weight of 228.25 Da [40]. It is a fat-soluble compound that occurs in two isoforms, trans-RSV and cis-RSV. Although both cis- and trans-resveratrol isomers occur naturally and seem to possess similar biological activity, the actions of the trans-isoform have been more largely investigated and are better known [41].

The trans-RSV is said to be more stable, however, they easily isomerize to the cis-RSV form in the presence of ultraviolet light and higher temperature [42, 43]. The molecular structure of RSV is similar to diethylstilbestrol, a synthetic oestrogen [44].

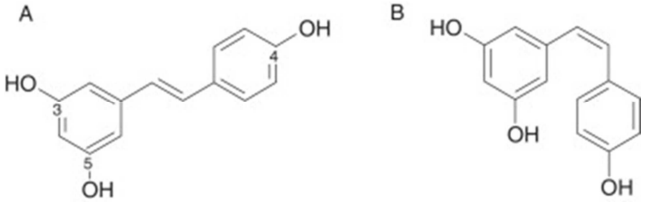

Figure 1. *Chemical structure of trans- (A) and cis-RSV (B).*

2.3. Sources of Resveratrol

Resveratrol has been recognized in more than 70 plant species especially in grapes, wine, grape juice, peanuts, cocoa, and berries of Vaccinium species as well as in blueberries, bilberries, and cranberries [45-48]. RSV has been known to occur only in the skin of grapes with the concentration varying with the geographic origin and exposure to fungal infection [48]. *Polygonum cuspidatum*, a weed used in Japanese and Chinese folk remedies, remains one of the first plants from which RSV was identified in large quantities. In plants like mulberry, lily, peanut, strawberry and eucalyptus, RSV is produced when an external stimulus such as a fungal attack or UV radiation activates stilbene synthase (STS) to produce RSV to protect them from external stimuli. Their seeds and skin contain up to 50 - 100mg/g of RSV. As fungal infections are more predominant in cooler climates, grapes grown here tend to have a higher concentration of RSV [40, 48]. Also, grapes grown around the equator tend to have higher concentrations of RSV due to the impact of ultraviolet radiation [49]. The degree of fermentation time a wine passes in interaction with grape skins is also an essential determining factor of its RSV content. Because grape skins are removed quickly for the period of the production process of white and rosé wines, these wines largely have less RSV than red wines [50].

2.4. Absorption, Bioavailability and Metabolism of Resveratrol

The wide range of phytopharmaceutical effects of RSV is largely dependent on its absorption, bioavailability and metabolism. The chemical structure of RSV causes it to exhibit low aqueous solubility (<0.05 mg/mL) which influences its absorption [51]. It is readily absorbed and transported by both passive and active mechanisms as high absorption of resveratrol (70%) has been observed in human subjects after oral doses [52]. It has been documented that in animals and humans, RSV is rapidly metabolized in the liver and binds to lipoproteins and albumin in the plasma, hence, enabling its entry into cells [53]. Using the method of 14C-labelled RSV, the distribution of RSV in urine, kidney, liver bile and duodenum has been demonstrated. It was observed that RSV had low bioavailability [54].

3. Review of Biological Effects of Resveratrol

Resveratrol, as a natural food component has been documented in several works of literature [31, 39, 40, 44, 47, 49, 55]. This variety of biotic influences is mostly initiated by multiple molecular targets such as cyclooxygenases/lipooxygenases, kinases, sirtuins, transcription factors, cytokines, DNA polymerase, adenylyl cyclase, ribonucleotide reductase, aromatase, etc. [55]. The ability of RSV to moderate diverse molecular pathways enhances its potential to influence many biological activities. A lot of these influences of RSV are largely due to its antioxidant nature [56, 57]. Biological effects of RSV include cardioprotective [58], antiplatelet [59], anti-inflammatory [60], antioxidant [56, 57], antidiabetic [61], anticancer [61], anti-obesity [62] and anti-neurodegeneration [63].

3.1. Anti-Oxidant and Anti-Inflammatory

It is now widely known that the accumulation of reactive oxygen species (ROS) causes oxidative stress by modification of cellular macromolecules (proteins, lipids and nucleic acids) with deleterious consequences. RSV is a free radical scavenger and hence a potent antioxidant [57]. It has been suggested that RSV is able to exhibit its antioxidant activity by competing with coenzyme Q to reduce the site of ROS generation, scavenging free O_2 radicals and inhibiting lipid peroxidation [64]. RSV can maintain the concentrations of intracellular enzymes such as glutathione peroxidase glutathione reductase, superoxide dismutase and catalase. RSV has been demonstrated to maintain glutathione concentration in peripheral blood mononuclear cells *in vivo*, preventing oxidative damage that was induced by 2-deoxy-D-ribose [65]. In a similar study, it was observed that RSV appeared to cause an increase in glutathione antioxidants (peroxidase, reductase and S-transferase) in a dose-dependent manner [66]. Nitric oxide (NO) is another effective

antioxidant that mediates lipid oxidation (LPO). It typically reacts with peroxyl radicals as a chain-terminating antioxidant. Reports have demonstrated the role of RSV in the regulation of NO production in the brain, kidney, heart and vascular endothelium [58, 67]. RSV is able to increase the concentration of the phosphatase and tensin homolog (PTEN), a well-recognized tumour suppressor that acts by inhibiting the activity of phosphatidylinositol 3-kinase type I (PI3K). In this way, RSV increases the chances of survival against cancer cells [68]. Also, RSV reduces extracellular signal-regulated (ERK) triggered by ROS thereby boosting antioxidant defence [69]. Dietary RSV supplementation can eliminate free radicals effectively while enhancing the activities of antioxidant enzymes.

Inflammation as a cascade of physiological responses to a foreign organism (pathogens and dust particles) has remained a major factor for the aetiology and progression of various chronic diseases like cancer, diabetes, obesity and inflammatory bowel diseases [70, 71]. These include diabetes, cancer, cardiovascular diseases, eye disorders, arthritis, obesity, autoimmune diseases, and inflammatory bowel disease. Inflammatory mediators (chemokines, cytokines and arachidonic acid) release more ROS which stimulates alterations in transcription factors leading to diseases [71]. Several biomedical investigations have shown RSV to possess potent anti-inflammatory actions [60, 72, 73]. These studies (*in vivo* and *in vitro*) suggest RSV is capable of inhibiting anti-inflammatory factors. RSV was shown to suppress the growth of spleen cells induced by concanavalin (ConA), interleukin-2 (IL-2) and alloantigens. It was also effective in preventing lymphocytes from producing IL-2 and interferon-gamma (IFN-γ) and macrophages from making tumour necrosis factor (TNF) or IL-2 [72]. Another study found RSV treatment to significantly reduce the expression of inflammatory factors while improving renal pathology [74]. A natural precursor of RSV, polydatin has been shown to downregulate the levels of interleukins 1 and 6 (IL-1, IL-6), and TNF-α, suggesting the potent anti-inflammatory effect of RSV [75]. Also, RSV was demonstrated to modulate the inflammatory response of the hippocampus after global cerebral ischemia in experimental rats and suppressed neuroinflammation mediated by the microglia [76, 77]. Similarly, RSV treatment was shown to improve neuroimmune dysregulation via inhibiting pro-inflammatory mediators [78].

3.2. Anti-Carcinogenic Property

Cancers result from abnormal cell growth caused by a large family of diseases that involves abnormal cells arising from genetic mutations or environmental factors which alter the growth and differentiation of normal cells. RSV is known to be effective against colorectal, lung, breast, prostate, liver and gastric cancers. It can interfere with the three major stages of carcinogenesis, namely: initiation, promotion and progression [79, 80]. RSV has been reported to protect against colorectal cancer (CRC). It was observed that RSV inhibited the initiation of colon cancer in rats by reducing the number of abnormal crypt foci [81]. Similarly, RSV has been demonstrated to inhibit the formation of colon tumours while reducing small intestine tumours by direct downregulation of genes that are involved in cell cycle progression and proliferation [82]. Another study showed the ability of RSV to inhibit the production of tumours in a genetically engineered mouse model [82]. Also, RSV has been shown to protect against Ultraviolet B (UVB) induced skin cancer in a mouse model [83] while it also significantly inhibited the induction of epidermal hyperplasia, mediated by multiple UVB by decreasing the proliferation of cell nuclear antigen and the down-regulation of cyclin-dependent kinases (CDK 2, 4, 6) and cyclin-D1 [84]. Generally, these anti-cancer activities of RSV are reported to be mediated via damaging glycolysis, blocking cancer cell growth and proliferation, provoking apoptosis, preserving antitumor immune reactions, and impeding adhesion, migration and invasion of cancer cells by moderating related molecules and gene expression over various signalling pathways [85].

3.3. Effects on Haematological Parameters

Haematological parameters represent a simple and reliable indicator of the overall health status of animals [86, 87]. Studies have indicated that several aspects of haematological toxicities are influenced by RSV. Following fluoride toxicity, RSV has been shown to significantly reduce white blood cell count (WBC). White blood cells are involved in inflammation, hence this effect of reduced WBC in the face of fluoride toxicity was attributed to the anti-inflammatory activity of RSV and suggested a beneficial effect of RSV on bone marrow and hematopoietic progenitor cells [88]. Platelets function to promote blood clotting and reduce blood loss. RSV extracted from fleece flower knotweed (*Polygonum cuspidatum*) significantly reduced platelet count and enhanced platelet disaggregation [89]. This lends credence to the so-called “aspirin effect” of RSV. Studies have implicated platelets as major factors in the aetiology of atherogenic plaque formation and rupture and hence the inhibition of their activity with aspirin reduces the risk of atherothrombotic vascular events and death [90]. Similarly, it has been shown that human platelets treated with RSV and preserved for five (5) days had less thromboxane B2 and prostaglandin E2 showing the ability of RSV to preserve platelets aggregation in response to thrombin. When an *in vitro* model of transfusion and thromboelastography was deployed, it was observed that RSV enhanced cloth strength [91]. The mechanism of RSV’s action on stored platelets is thought to be mediated by decreased apoptosis of platelets which leads to longer half-life in other to preserve haemostatic function. It has also been shown that RSV inhibits platelet aggregation via inhibition of p38 MAPK phosphorylation and an increase in NO/cyclic GMP formation [91]. Another study highlighted the ability of RSV to increase the frequency and total numbers of normal bone marrow hematopoietic stem cells (HSC) following a three-week administration. It went further to show that RSV also enhanced bone marrow multipotent progenitor capacity in vivo. These findings suggest that RSV may have

therapeutic value for disorders of hematopoietic stem and progenitor cells (HSPC) in cases where bone marrow transplantation is involved [92]. Also, a four-week supplementation of RSV on horses showed a significant increase in packed cell volume, haemoglobin concentration, red blood cell counts and a significant decrease in white blood cell counts, neutrophil and eosinophil counts. The study also observed a decreased osmotic fragility of red blood cells. The anti-inflammatory property of RSV ensured a reduction in total white cell counts as well as the differentials while the antioxidant activity of RSV maintained the membrane integrity of red blood cells [87].

3.4. Immuno-Modulatory Effects

Biological activities of RSV such as the induction of CD95 signalling-dependent apoptosis, inhibition of cyclooxygenase, modulation of NF-kB activation and effects on the cell division cycle show a possible effect on the immune response [93]. RSV has been recognized to modulate the immune reaction against pathogenic organisms like viruses, bacteria, etc., by enhancing immune responses and/or reducing immunocyte apoptosis [94]. *In vitro* exposure to RSV was demonstrated to cause a biphasic effect on anti-CD3/anti-CD28-induced development of both IFN-γ, IL2- and IL4-producing CD8+and CD4+ T-cells where stimulation and suppression were observed at low and high RSV concentrations respectively [93]. A similar study observed that RSV at low concentrations reserved the suppressive effect of ethanol on macrophage percentage and macrophage MHC-II molecule expression, hence, enhancing cell-mediated immune response. The study, however, observed that RSV did not have any effect on lymphocyte subtypes [95]. Other studies have shown that RSV enhanced immune response in piglets infected with rotavirus showing results of alleviated diarrhoea and inflammation [96] and also reduced the effect of a bacterial pathogen, *Haemophilus influenza* thus reducing infectious airway inflammation [97]. It has also shown that RSV enhanced spleen lymphocyte propagation,[98] peritoneal macrophages, and CD4+ cells in peripheral blood [98]. In addition to enhancing immune response, RSV is able to inhibit the growth of some pathogenic microorganisms like bacteria and fungi [99]. Indeed, RSV has been shown to inhibit the growth of *Candida albicans* [100], *Campylobacter* and *Arcobacter* [101]. Also, its potency against *Staphylococcus aureus* and rotavirus infection-induced diarrhoea has been demonstrated [102]. While the precise mechanism of action is not clearly understood, it is thought that RSV can affect cells with changes in cell morphology and DNA contents [103]. Its antiviral activity has been evaluated in *Pseudorabies* virus-infected piglets where it was it was found to inhibit virus replication, hence, reducing their mortality [104].

3.5. Cardiovascular Effects

Cardiovascular diseases (CVDs) remain a principal cause of morbidity and mortality worldwide and the use of phytopharmaceuticals like RSV has shown promise in the management and treatment of CVDs [105, 106]. Documented evidence highlights the impactful role of RSV in the treatment of various forms of CVDs like hypertension, congestive heart failure, chemically induced cardiotoxicity, coronary arterial atherosclerosis and myocardial infarction [105, 107] Anti-hypertensive effects of RSV have been demonstrated in several animal models [108, 109], suggesting both a dose-dependent effect and the ability of low-dose RSV to reduce blood pressure in deoxycorticosterone acetate (DOCA) - salt hypertensive rats [110]. Also, RSV treatment in rats fed with high-fat diets caused a significant reduction in their systolic and diastolic blood pressure as a high-fat diet is associated with obesity and vascular dysfunction [111]. The effect of RSV to significantly reduce blood pressure is thought to be mediated through both endothelium-dependent and endothelium-independent mechanisms [112]. For endothelium-dependent actions, RSV has been shown to improve flow-mediated vasodilation and stimulate the relaxation of carotid arteries and aortic rings [113, 114]. These actions are mediated by improvement in the bioavailability of nitric oxide (NO), a potent vasodilator [115]. On the other hand, the endothelium-independent vasodilatory mechanism is via the inhibition of vascular smooth muscle cell contraction [116], reduction in vasopressin and angiotensin II in aortic smooth muscle cells [117] and inhibition of calcium channels leading to vasorelaxation [118]. The ability of RSV to attenuate arteriosclerosis and improve endothelial function makes it able to protect against ischemic stroke [119]. This was attributed to its earlier described anti-platelet activity, antioxidant effects and vasodilatory effects. It has also been shown that RSV preserved the blood-brain barrier, reduced inflammation and protected endothelial cells against recurrent stroke in a rat model [120]. Although human clinical trials on the effect of RSV on stroke patients are scarce, it has been demonstrated that a single dose of RSV enhanced blood cerebral blood flow during a performance task among apparently healthy adult subjects [121].

3.6. Anti-Obesity Effects

Obesity which is characterized by an abnormal increase in adiposity resulting from the increase in the number and size of the fat cell remains one of the leading causes of hypertension, coronary heart disease, type II diabetes mellitus and cancer [40, 122]. A key feature of obesity is chronic low-grade inflammation leading to tissue macrophage accumulation and abnormal cytokine production. RSV has been shown to inhibit TNF-α -induced monocyte chemoattractant protein-1 (MCP-1) secretion which is upregulated in obesity [40, 123]. Studies have evaluated the efficacy of RSV in modulating lipid profiles, fat oxidation, glucose homeostasis and other related energy expenditure and RSV has been shown to affect specific molecular targets involves in obesity. RSV was observed to decrease fat mass and body weight in high-fat diet-induced obesity in mice. It also reduced plasma leptin and lipid levels while modulating insulin and glucose metabolism. It was also found to suppress adipogenic differentiation in pre-adipocytes

and inhibited TNF-induced lipolysis in mature adipocytes [85, 124, 125]. Another study showed that RSV prevented obesity by improving catecholamine production and suppressing pro-inflammatory M1 macrophages and activating anti-inflammatory M2 macrophages in white adipose tissue [85]. Similarly, RSV promoted white adipose tissue in pregnant and lactating mice while promoting white adipose tissue browning and thermogenesis among their male descendants, thereby preventing obesity in the future [126]. Also, by enhancing mitochondrial function and reducing oxidative stress, RSV was demonstrated to reduce sarcopenic obesity [127]. In all, RSV can reduce body weight, affect adiposity gene expression, modulate lipid deposition and promote white adipose browning.

3.7. Antidiabetic Property

Diabetes mellitus presents a significant worldwide health challenge especially among developing nations due to urbanization and increasing inactivity [128, 129]. Several documented studies have shown that RSV is capable of improving hepatic glycogen in diabetic rats, hence attenuating diabetic-induced hyperglycaemia [130]. It has also been observed that treatment with RSV manifested its antidiabetic potential by enhancing insulin secretion and reducing the oxidative destruction of pancreatic beta cells, hence reducing hyperglycemia in streptozotocin-nicotinamide-induced diabetic rats [131]. The antidiabetic effect of RSV could also be non-insulin-dependent as seen in the ability of RSV to regulate the caveolin-1 and caveolin-3 status which are important in glucose transport (via GLUT-4), translocation and uptake [132]. It has also been observed that RSV reversed fat-induced insulin resistance [133] and reduced plasma glucose concentration and triglycerides in diabetic rats [134]. Another study showed the ability of RSV not only to attenuate lipid profiles in diabetic rats but also to reduce the level of serum leptin, resistin as well as TNF-α, and IL-6, hence suggesting a possible modulation of adipocytokines [135].

3.8. Anti-Neurodegenerative Effects

Neurodegenerative diseases such as Parkinson's and Alzheimer's are characterized by the excessive accumulation of reactive oxygen species in the brain [136]. The antioxidant capacity of RSV makes it a potent natural therapeutic agent with pharmacological potential against these diseases. RSV has been demonstrated as a possible neuroprotective agent against ß-amyloid peptide (Aß) - induced neurotoxicity, where oxidative stress was evaluated in a cell culture model. RSV was found to maintain cell viability and exerts an anti-oxidative action by enhancing the intracellular free-radical scavenger glutathione [137]. In a similar study, RSV was found to prevent β-amyloid-induced oxidative cell death in cultured rat pheochromocytoma (PC12) cells and reduced β-amyloid-induced cytotoxicity, intracellular reactive oxygen intermediates (ROI) accumulation and apoptotic features [138]. It is known that RSV reduces nuclear factor kappa B (NF-κB), which is essential in the transmission of signals from the activated synapse to the nucleus. This enhances the survival of neurons as NF-κB is also known to accelerate neurodegenerative processes [139]. Other studies have demonstrated that moderate wine consumption is associated with a lower risk of Alzheimer's disease and also improved chances in the case of neuropathology in a mouse model [140]. In another study, RSV was shown to be useful in reducing excitatory neurotransmitter toxicity associated with glutamate and in dopaminergic neurodegenerative disorders such as Parkinson's disease [141]. Also, RSV is successful in upregulating the antioxidant status and lowering dopamine loss [141].

3.9. Effects on Reproductive Function

Studies have shown varied effects of RSV on male and female reproductive function and behaviour. The chemical structure of RSV is similar to that of some estrogens like diethylstilbestrol (DES), hence RSV is considered a natural phytoestrogen acting via the estrogen receptors and possessing the ability to mimic the actions of estradiol [142, 143]. The antioxidant effect of RSV helps in the protection of oocytes from senescence-dependent damage and increases the levels of luteinizing hormone receptors [144, 145]. Hence, RSV is able to arrest declining ovarian function by stimulating the number and function of the ovarian mitochondria. Also, this RSV-induced upregulation of mitochondrial biogenesis can preserve embryogenesis leading to increased pregnancy rates [146]. Results from experimental animal studies as well as human clinical trials suggest that RSV is effective in the treatment of polycystic ovary syndrome (PCOS), dysmenorrhea and endometriosis [146]. On male reproductive function, RSV also plays a similar estrogenic paracrine regulatory role hence acting as a regulator of male reproductive function [147]. The antioxidative capacity of RSV once again ensures the preservation of male fertility by the reduction of the reactive oxygen species (ROS) production, inhibiting lipid peroxidation and enhancing the production of essential antioxidative enzymes like catalase, glutathione peroxidase (GPs), and superoxide dismutase (SOD) [146]. Hence, RSV is able to improve semen quality and function (viability, motility and acrosomal reaction).

3.10. Other Physiological and Therapeutic Effects of RSV

The effects of RSV on several other body functions and health conditions have been fairly documented. RSV has been documented to reduce reducing synovial inflammation caused by rheumatoid arthritis by raising antioxidative enzymes like malonaldehyde and superoxide dismutase [148]. Similarly, RSV has been shown to suppress uterine fibroid growth by reducing the expression of proliferating cell nuclear antigen (PCNA) and fibronectin showing the ability of RSV to inhibit uterine fibroid cell growth [149]. Also, RSV is said to exhibit anti-ageing properties. This is thought to be effected by increasing cell survival, effective energy application with caloric intake and insulin sensitivity, hence increasing life expectancy [150]. Studies have shown that RSV is able to

ameliorate non-alcoholic fatty liver disease (NAFLD) by up-regulating the receptor for low-density lipoprotein and scavenger receptor class type (SRB1). It is also thought to down-regulate adipose differentiation-related proteins and enhance the numbers of CD68+ Kupffer cells and reducing inflammation and ROS production [151, 152].

4. Conclusion

Resveratrol is one of the most explored natural polyphenolic compounds contained in various plants and predominantly found in red wine. The widespread action of RSV derives mostly from its antioxidant and anti-inflammatory properties and hence it has been found useful as an adjuvant agent in reducing risk factors for CVDs, metabolic syndrome, malignancies and neurodegenerative disorders. Studies have identified various molecules and cell structures through which RSV acts, hence the expression of RSV as "one molecule – many targets". Affecting many targets directly and others indirectly. The present review has explored the various health-promoting benefits of RSV and the various postulated mechanisms of action.

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