



Review Article

Resveratrol: A Phenolic Prodigy

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ABSTRACT

Resveratrol, a naturally occurring polyphenolic compound that performs as a phytoalexin, was isolated for the first time ever in 1940 and has gained attention of the scientific world ever since. Its miraculous properties have made it a phenolic prodigy, and the absence of any negative clinical experimentation or research just goes to prove its never-ending benefits. The conduction of more than 130 clinical trials with the administration of varying doses of resveratrol has showed different results in different settings. The failure to procure established and lasting results has led to a deferral in its use as dietary supplements which could be the reason of its unpopularity. The ultimate fate of resveratrol remains an open-ended question but there is no doubt that this compound certainly has inspired many scientific innovations and advances.

INTRODUCTION

Resveratrol, otherwise known as trans-resveratrol, is a stilbene of paramount importance as it is favorable to human health and its advantages range from simply alleviating hypertension to possessing anticarcinogenic properties [2]. It is a phytoalexin produced in response to stress caused by bacterial and fungal infections, mechanical injury or irradiation [3]. Resveratrol was first discovered in 1940, when it was isolated from white hellebore roots, scientifically known as *Veratrum grandiflorum*. Its second extraction came from *Polygonum cuspidatum* roots in 1963 [4]. Though, curiosity in resveratrol climbed after the release of a paper in 1992 [5], that proposed oral administration of resveratrol has a lowering effect on lipid levels in the livers of rats and red wine, being a rich source of resveratrol, reduces serum lipid levels in humans. By 1997, several

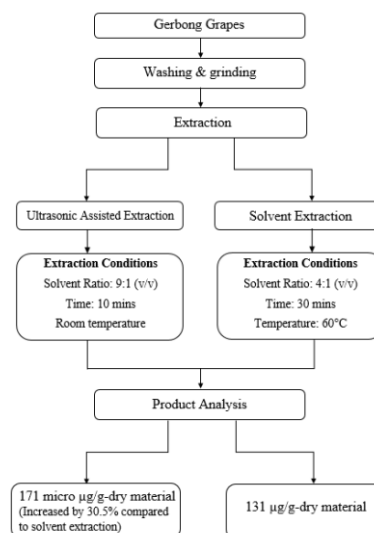


Figure 1: Flowchart comparing ultrasonication and solvent extraction process and result

researches reported its anti-carcinogenic, anti-inflammatory, and antioxidative properties [6-8]. But the main breakthrough came in 2003, in the form of a study that explained its role as an effective SIRT1 activator able to imitate the effects of calorie restriction, [9] discussed in detail further ahead in this article. Stilbenes, including resveratrol, are difficult to extract and collect in large amounts as they are produced by plants only under stressful conditions. Therefore, its extraction from natural sources is very expensive and challenging. Several experimentations [10] to obtain resveratrol and other stilbenes from the yeast *Saccharomyces cerevisiae* by engineering it to release these compounds on mineral media normally used for industrial manufacture. The most effective method for extracting resveratrol from grapes is ultra-sonication assisted extraction, as the extract was observed to be greater by 24 to 30% than simple solvent extraction [11]. In healthy adults, with no chronic illness, short-term safest dosage is 1 to 5 grams. In patients of non-alcoholic fatty liver disease, side effects may manifest at a minor dose of 2.5 grams [12].

CHEMICAL PROPERTIES

Resveratrol, chemically known as 3,4,5-trihydroxy-trans-stilbene and 3,4,5-Stilbenetriol, is a compound consisting of two phenolic rings bound by a double bond that gives rise to its two forms; cis-resveratrol and trans-resveratrol. Trans-resveratrol is more abundant and stable form than cis-resveratrol. Cis-resveratrol usually occurs in nature when trans-form is exposed to ultraviolet, solar, or artificial light of 254 or 366nm wavelength [13].

Absorption: The structure of resveratrol makes it more soluble in organic solvents, such as ethanol, than in inorganic solvents such as water. The most significant property of resveratrol that makes its absorption more enhanced is its ability to form complexes with organic molecules, for instance the addition of acetyl group improves its absorption and cellular uptake [13]. **Metabolism:** Its metabolism takes place in liver. It fuses with glucuronide and sulfates to form five types of metabolites, mainly two different forms of resveratrol monoglucuronide, monosulfate dihydro resveratrol, resveratrol monosulfate and monoglucuronide dihydro resveratrol. The instability of cis-isomer has led it to be less studied about [13].

Bioavailability: The bioavailability of resveratrol differs with different food sources and the way of consumption. Some studies show that its absorption is decreased when intake is accompanied by high-fat meal [13].

BIOLOGICAL ACTIVITIES

Resveratrol displays a number of prodigious physiological activities and that makes resveratrol a miracle nutraceutical compound that takes care of every aspect in

a human body. Some of the activities are:

Antioxidative Activity: Resveratrol's most plush characteristic is the scavenging of free radicals in the body or in other words antioxidation of unwanted particles in the body [14]. The whole mechanism of the antioxidation is based on the blue print of the nuclear structure. Resveratrol plays an important in reducing oxidation of lipids and their toxicity in pharmaceutical products. It conserves the nutritional characteristics of the food compounds and helps increase their shelf life [15]. Resveratrol is engaged in cell protection against UV-irradiation induced apoptosis. Through many cellular antioxidant pathways, resveratrol procures cellular defense by its capability of acting as a direct or indirect cellular antioxidant system inducer which equalizes cellular redox score. [16]. Due to low availability, the antioxidative effect is obstructed that is why through the process of esterification derivatives of resveratrol are being introduced with enhanced ability of fat solubility in fatty foods and other biological environments. After many experimentations it has been concluded that resveratrol derivatives can suffice as a conceivable antioxidant in foods.

Anti-cancerous Activity: Resveratrol has displayed anti-tumor effect that makes it a potential prospect for the prevention and treatment of several kinds of cancer [17]. Through vivo and vitro researches the anti-cancerous quality of resveratrol has been persistent which shows that carcinogenesis stages like initiation, promotion and progression are hampered [18]. Chemotherapeutic characteristics like anti-inflammatory, antioxidative, pro-apoptosis and anti-proliferative actions are also among many other properties that are linked with the functions of chemo-preventive agent [19]. A unique set of components like transcription factors, upstream kinases and their regulators are modulated that targets cell survival and cell apoptosis regulators, anti-inflammatory mediators and metastatic switches of cell cycle [20]. Resveratrol expresses its anti-proliferative quality by initiating a series of commands that include initiation of cell apoptosis, inhibition of angiogenesis; and increasing oxidative stress and mitotic cell death of cancer cells [21]. Resveratrol through direct contact with DNA polymerase initiates inhibition of DNA synthesis. In several types of cancer like in breast cancer resveratrol is a promising preventive and therapeutic agent in a combination therapy; because in many cell vitro systems it has displayed reverse drug resistance by refining the tumor cells to drug intervened response [22]. Resveratrol reduces the nephrotoxicity of ovarian, bladder, testicular and many other cancers because it contains Cisplatin which is a chemotherapeutic agent. Currently globally resveratrol has presented anti-cancerous effect in colon, cervical, prostate, breast and

lungs. In chemotherapy and radiotherapy resveratrol can be adopted as a conventional treatment for cancer because it has displayed beneficial antioxidative effect even if resveratrol-loaded nanoparticles [23].

Cardio-protective Activity: In some cases, cardiac functionality is linked with diabetes but resveratrol has displayed some improved cardiovascular functions which have indicated recovery of ventricular function. This improvement was seen because of the preservation of the functional capabilities of the cardiac stem cell compartments, there is improvement in the cardiac environment by the reduction in the inflammatory state and antagonistic ventricular remodeling of the diabetic heart [24]. There has been reduction in cardiac hypertrophy, contractile dysfunction and remodeling, interstitial fibrosis and low levels of plasma Brain Natriuretic Peptide (BNP). BNP is a peptide hormone that is released when there is stress on the walls of the heart. By the use of resveratrol has there been a significant decrease in the inflammation factor and malondialdehyde levels this indicates oxidative stress markers [25]. Cardiovascular functions are improved when

resveratrol treatment reduces anomalies like myocardial ischemia-reperfusion injury, vasodilation and atherosclerosis. Diversely, use risk. With the evidence at hand it is shown that a resveratrol like Polygonum Caspidatum (A Japanese Herb-Knot wood) used in traditional Chinese medicine helps to prevent hyperlipidemia and arteriosclerosis [26]. Comprehensively, due to the cardio-protective activity of resveratrol there has been a development of novel therapy for atherosclerosis, metabolic syndrome, ischemia and heart failure which might be linked to many molecular targets [27].

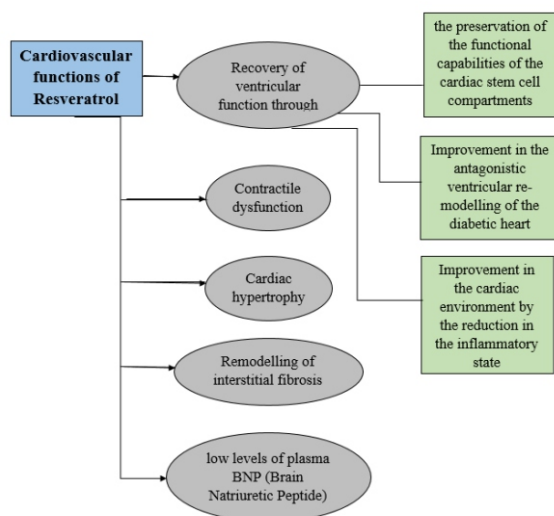


Figure 2: Summarized flowchart of cardiac functions of resveratrol

Anti-Inflammatory Activity: Resveratrol being a stilbene is a non-nitrogenous polyphenol which consists of acidic and amphiphilic attributes with anti-inflammatory effect. Studies have indicated that resveratrol is capable of decreasing the release and expression of inflammatory activity. Resveratrol prevents acute pharyngitis induced inflammation, general inflammation and oxidative stress also it reduces the risk of carcinogenesis. All of this takes place when resveratrol obstructs the activation of microglia (a part of macrophage cell of active immune defense system in the brain and spinal cord); that proceeds with the release of several pro-inflammatory factors and oxidative species which then initiates the signal pathways resulting in neuro-inflammation. Resveratrol with this anti-inflammatory quality has helped improve the lives of many patients [28].

Neuro-Protective Activity: In several neurodegenerative impairments like Huntington's, Alzheimer's, Parkinson's sclerosis and alcohol induced neurodegenerative disease resveratrol plays a significant neuro-protective role. It also improves mitochondrial functions and biogenesis which prevents detrimental effects that are generated by stress of oxidation. Resveratrol reduces cholinergic neurotransmission, neurotrophic expression, promotes β -amyloids peptide reduction and reduces neuronal apoptosis [29]. In a research it has been indicated that resveratrol holds the capability of decreasing Profile of Mood States (POMS) that also includes vigor and fatigue but it does not affect memory and cognitive performance of the brain [30].

Anti-Microbial Activity: Studies has been conducted on the ability of resveratrol to stop the growth of pathogenic microbes like Gram-positive and Gram-negative bacteria and fungi. In certain species like *Candida albicans* resveratrol has efficiently inhibited its growth, [31] which is achieved by the use of dimethoxy resveratrol derivates at a minimum inhibitory concentration (MIC) of 29-37 $\mu\text{g}/\text{mL}$ which also includes 11 other species of *Candida* but these presumed candidacidal activity of resveratrol has become a matter dispute [32]. In one study resveratrol has been declared ineffective against *C. albicans* and in another study, it is stated that at 400 $\mu\text{g}/\text{mL}$ resveratrol has antifungal capabilities against *C. albicans* [33]. Major causes behind bacterial gastroenteritis are the presence of *Campylobacter coli* and *Campylobacter jejuni*. Involved complex of resveratrol like Resveratrol-hydroxypropyl- γ -cyclodextrin improved its solubility and showed antimicrobial effects against these pathogens. Resveratrol's ability inhibit biofilm formation has refined food shelf life and safety [34]. Due to its bacteriostatic action resveratrol is an efficient anti-bacterial agent which also allowed changes in cell morphology and DNA contents.

Resveratrol when supplemented with cultures like *E. coli* and *S. aureus* and then treated with antimicrobial medicines of low concentration they become mutagenic. Resveratrol has the capabilities like Anti-microbial lethality suppression and Mutant recovery promotion which may give rise to various antimicrobial resistant species. When these species are coined with resveratrol its bioavailability increases [35]. Treatment of infectious pneumonia caused by cultures like *S. aureus* are being treated with a potentially effective antimicrobial agent like resveratrol which has a significant role in the easing of diarrhea induced by rotavirus infection.

Anti-Proliferative Activity: Anti-proliferative activity is among the many qualities of resveratrol like neuroprotective, antimicrobial, anticancer, anti-diabetic etc. This function mostly mechanizes in the ovary part of female human body most importantly on the theca-interstitial cells of the ovary. This action is mostly associated with disorders like Polycystic Ovary Syndrome (PCOS). Use of resveratrol may give rise to ovarian-follicular reserve and increases the life span of the ovary which can be an effective anti-aging agent. Resveratrol reduces histopathological and biochemical changes to enforce protective action over the ovary against ischemia-reperfusion injury [12].

Respiratory Activity: Resveratrol also as the ability to sooth pulmonary function of the population and actively protects against respiratory diseases. Resveratrol's main protective function against the respiratory diseases include anti-apoptotic, anti-fibrotic, anti-hypertensive, anti-inflammatory, antioxidant etc. [12].

Aging and Fertility Activity: Resveratrol can be used as a potential therapeutic agent especially in male infertility problems whose leading cause s the testicular toxicity. Among many other specialties of resveratrol helps to protect against several pathological disorders, also against aging problems. Resveratrol has the ability to enhance the function of mitochondria. Low consumption of resveratrol rich foods mostly by the elderly population; symptoms like loss of vision, fatigue skin prevails. These symptoms also include age-related macular degeneration due to lack of antioxidant and anti-proliferative factors in the body [12].

CONCLUSIONS

Resveratrol may provide an alternate and a novel approach towards preventing and treatment of inflammatory diseases such as Osteoporosis, Diabetes Mellitus, Alzheimer's, Macular degeneration and other eye diseases etc. along with improving the biomarkers of these diseases. All studies and researches are still exploratory and have the potential to make a mark in improving the quality of life along with various other bioactive components.

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