8. Resveratrol

Review Article

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Abstract

Phytochemicals are being increasingly known as the "future prescription". Resveratrol is the most envisioned phytochemical belonging to family of phytoalexin polymers. Humans have been unknowingly consuming this compound since ancient times in the form of wine. It is widely distributed throughout the plant kingdom and has been recently considered for its role in health regulation and promotion. Various studies have been conducted on experimental animal models and some of them have been extrapolated on human subjects as well. It was observed that even though more than 70% was absorbed via oral route, its bioavailability was less due to rapid metabolism and excretion. The results can be used with a greater confidence level given the toxicity, absorption and metabolism of resveratrol is studied in detail. By increasing the bioavailability and optimizing the dosage this "red wine compound" can open up new frontiers in the treatment of fatal diseases. This review is an attempt to promote application of resveratrol as a nutritional supplement by highlighting its health benefits.

1. Introduction

Phytochemicals are naturally occurring, biologically active chemical compounds in plants, acting as their natural defence system. These plant components offer discrete bio-activities that affect the human biochemistry and metabolism, and are increasingly being considered as nutritionally active ingredients. Such phytochemicals include terpenoids, phenolics, alkaloids and fibres. Resveratrol (3,5,4′-trihydroxystilbene) is a natural polyphenolic phytochemical. It is the parent molecule of viniferins, a family of phytoalexin polymers that prevent the progression of fungal infections in plants. Increased consumption of monomeric resveratrol and/or resveratrol-containing foods may be associated with health promotion. These health benefits are attributed to its diverse range of biological

activities. This review is an attempt to discuss various aspects of resveratrol including bioavailability, antioxidant capacity, cardio-protection, anticancer activity, anti-diabetic effects and other health benefits.

2. Occurrence

Resveratrol is found in at least 72 plant species and is formed via a condensation reaction between 3 molecules of malonyl CoA and 1 molecule of 4-coumaroyl CoA [11] (Figure 1). Resveratrol synthase facilitates this condensation reaction, which also produces 4 molecules of CO_2. Resveratrol exists in 2 structural isomeric forms, cis and trans (Figure 2), with the trans form being more biologically active. Polygonum cuspidatum, a weed, is one of the richest sources of this compound. The primary dietary sources which are a part of the human diet are blueberries, mulberries, peanuts, red grapes. Due to its presence in grapes, it is no surprise that resveratrol is also found in wines. The resveratrol concentration in wine varies, with grape variety and the growing conditions. Vinification which is the conversion of fruit juice to wine through fermentation also influences the resveratrol concentration. [11] The fermentation of grape flesh with the skin in red wine production allows red wines to have greater resveratrol concentrations than white wines, which are produced by fermentation of the flesh only. This is the reason why it is also referred to as the "red wine compound".

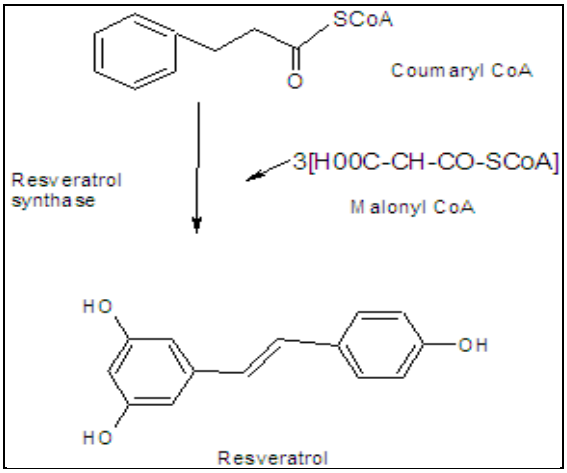

Figure 1: Synthesis of Resveratrol [11]

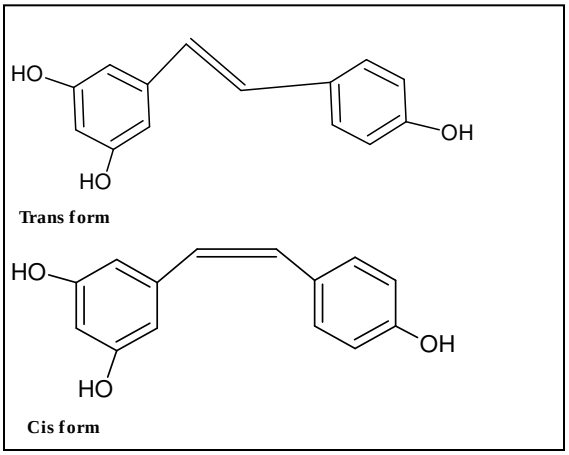

Figure 2: Resveratrol isomers [11]

3. Absorption Bioavailability & Metabolism

The oral absorption of resveratrol in humans is about 75% and is thought to occur mainly by trans-epithelial diffusion [13]. The food matrix affects absorption and bioavailability of resveratrol. Nano-encapsulated resveratrol, not being

metabolized in the gastrointestinal tract, is potentially absorbed through the intestinal wall in its active form. [33] Blood circulation and cell surface deposition is attained due to interaction of resveratrol with albumin. 50% to 98% of total resveratrol has been observed non-covalently bound to albumin, LDL (low density lipoproteins) and hemoglobin. Due to its lower molecular weight it has good skin penetration ability and this property of resveratrol is exploited in skin care and anti-ageing formulations. Resveratrol is well absorbed from oral mucosa, but undergoes significant first pass hepatic metabolism after absorption from the gastrointestinal tract. Blood levels indicate no more than 20% overall bioavailability. Resveratrol is metabolized within the intestinal lining to 3 dominant forms, reveratrol-4'-O-glucuronide (M1), resveratrol 3-O-glucuronide (M2) and resveratrol-3-O-sulfate.

A study published in the Journal of Food Science [11] states that following oral administration of pure resveratrol to human subjects, resveratrol glucuronide was the major metabolite detected in the plasma and urine. On the other hand when high oral doses of grape juice were administered, glucuronide and sulfate conjugates were detected in the plasma and urine of the human subjects. Resveratrol sulfate was the major metabolite found in human plasma. Sulfation may be the primary limiting factor in the bioavailability of resveratrol. Grape juice consists of essentially resveratrol glucosides, cis and trans-piceid (piceid is a stilbenoid glucoside and is a major resveratrol derivative in grape juices), with low amounts of the free resveratrol, indicating a lower bioavailability of the glucosides compared to the pure compound. [11] The kidney is the dominant excretion pathway with urinary and faeces recovery of total Resveratrol between 70 to 98% within 24h.

Information about the bioavailability of resveratrol in humans is critical because much of the basic research on resveratrol has been conducted in cultured cells exposed to un-metabolized resveratrol at concentrations that are often 10-100 times greater than peak concentrations observed in human plasma after oral consumption [10].

4. Health Benefits

4.1. Antioxidant Activity of Resveratrol

The antioxidant activity of resveratrol reduces damage to endothelial cells exposed to nitrite radicals and protects skin cells against damage caused by UV radiation. Lipoxygenase is a dioxygenase

with peroxidase activity involved in the synthesis of mediators in inflammatory, atherosclerotic, and carcinogenic processes. Resveratrol is a potent inhibitor of the dioxygenase activity of lipoxygenase, with an IC_{50} (half maximum inhibitory concentration) of 13 μM. Furthermore, oxidized resveratrol is as efficient a lipoxygenase inhibitor as in its reduced form. Resveratrol is able to prevent the increase in reactive oxygen species (ROS) following exposure to oxidative agents (i.e. tobacco-smoke condensate (TAR) and H_2O_2). Pre-treatment of cells with the phytochemical resveratrol resulted in less cellular damage caused by nitrite radicals (could cause atherosclerosis). Resveratrol increases the activity of superoxide dismutase (important antioxidant enzyme that neutralizes superoxide) and glutathione peroxidase (antioxidant enzyme that protects the cells from oxidative damage). It protects ultrastructure of the skin cells and also reduces lipid oxidation and oxidative stress. As per a study resveratrol was the most effective anti-oxidant in reversing cadmium-induced lipid peroxidation. [29]

4.2. Anti-Diabetic Effects of Resveratrol

Diabetes mellitus is a complex metabolic disease, classified into different types; type 1 and type 2 diabetes are the most frequent. Type 1 diabetes results from autoimmune destruction of beta cells. Patients with type 1 diabetes are dependent on exogenous insulin. Type 2 diabetes is characterized by defects in insulin secretion and action. The management of diabetes involves three main aspects: reduction of blood glucose, preservation of beta cells, and improvement in insulin action (type 2 diabetes).

Numerous studies on diabetic rats revealed the anti-hyperglycaemic action of resveratrol. The ability of resveratrol to reduce hyperglycaemia seems to be the best documented. [18] The anti-hyperglycaemic effect of resveratrol observed in diabetic animals is thought to result from its stimulatory action on intracellular glucose transport. A temporary inhibition of insulin secretion was reported to delay the progress of type 2 diabetes .According to some animal studies; experiments in vitro demonstrated the ability of resveratrol to reduce insulin secretion by freshly isolated rat pancreatic islets. The inhibition of insulin secretion caused by resveratrol was found to result from metabolic changes in beta cells. Resveratrol also ameliorates common diabetes symptoms, such as polyphagia, polydipsia, and body weight loss. In

human clinical trials conducted by Sirtris Pharmaceuticals, it was found that Resveratrol lowered blood sugar levels. [9]

4.3. Anti-Cancer Activity of Resveratrol

Resveratrol not only helps to prevent DNA damage but it also influences the transcriptions of genes responsible for redox metabolism and inhibits proliferation of cancer cells lines, including those from breast, prostate, stomach, colon, pancreas and thyroid.

- Resveratrol decreases tumour growth by inhibiting the enzyme cyclooxygenase-1, which converts arachidonic acid to substances that promote tumour growth. It antagonizes each stage of tumorigenesis and inhibits protein kinase C (PKC), a key mediator of tumour promotion.
- Resveratrol is more effective against tumours on which it can act directly like skin and gastrointestinal tract tumours.
- Resveratrol inhibits activity of certain cytochrome P450 enzymes which trigger carcinogens after metabolism. On the contrary it promotes expression of phase II enzyme (NAD(P)H:quinone) that eliminates potentially toxic chemicals. [10]
- Resveratrol induces apoptosis (Programmed Cell Death) in a number of cancer cell lines and regulates normal cell cycles. It reduces growth of invasive tumours by inhibiting angiogenesis (development of new blood vessels).
- Macrophages produce a cytokine (MIC-1) which has anti-tumorigenic activity. Resveratrol increased (MIC-1) gene expression in pancreatic cancer cells.
- The phytochemical reduced levels of steroid receptor coactivator-3 and growth factor signalling proteins causing reduced cell proliferation and increased apoptosisin colon cancer cell lines.

A study shows that the concentration of resveratrol inhibiting cell growth by 50% (IC_{50}) ranged from about 20 to 100 μM. Thus we can say that resveratrol increases the expression of genes responsible for cell survival, differentiation, proliferation inhibition and apoptosis. Resveratrol therefore has a chemo preventive and anticancer effect.

4.4. Cardiovascular Health and Resveratrol

Coronary heart disease (CHD) is one of the primary causes of death in developed countries and can be prevented by incorporating changes in one's lifestyle & diet. Resveratrol is often touted as the bioactive compound in grapes and red wine, and has particularly been associated with the so-called 'French Paradox'. Thephrase, coined in 1992 by Dr. Serge Renaud from Bordeaux University,

describes the low incidence of heart disease and obesity among the French, despite their relatively fat diet and levels of wine consumption.

Studies published in Annals of the New York Academy of Sciences showed [13] cardio- protective effects of resveratrol, and red wine with and without alcohol:

- Resveratrol inhibits oxidation of LDL, which is considered as the primary event in the initiation of atherosclerosis.
- Resveratrol suppresses proliferation of smooth muscle cells and pulmonary aortic endothelial cells. Migration and proliferation of smooth muscle cells in the intima of susceptible vessels is a requisite for atherogenesis (formation of plaques in the inner walls of arteries).
- Resveratrol is shown to inhibit platelet aggregation—platelets are actively involved in the process of haemostasis, by which injury in the vascular endothelium is rapidly repaired so that the fluidity of the blood is not compromised.

The most accepted mechanism of cardio protection by resveratrol is the inhibition of platelet aggregation. [35] Platelets can be activated by several different factors, including adenosine diphosphate (ADP), collagen, and thrombin. When activated platelets change morphology they aggregate and seal damaged blood vessels. Excessive aggregation can lead to the development of cardiovascular disease. Pre-treatment of platelets with resveratrol has been shown to inhibit lipopolysaccharide (LPS) and LPS + thrombin-stimulated platelet adhesion to collagen and fibrinogen in a non-dose-dependent manner. [37] Using in vitro and in vivo models, it has been [38] demonstrated that resveratrol inhibits ADP, collagen, and thrombin-stimulated human platelet aggregation in vitro.

The cardio protective effects of resveratrol are also attributed to its vasorelaxation properties. The vasorelaxation effects of resveratrol were examined on rat aortic rings with and without intact endothelium.[39] Pre-treatment with resveratrol resulted in a dose-related decrease in noradrenaline (NA) and phenylephrine (PE) induced contraction in endothelium intact rat aortic rings. Endothelium independent rings required higher concentrations of resveratrol before relaxation was observed. Therefore, resveratrol mediates vasorelaxation in endothelium intact and endothelium independent aortic rings via nitric oxide dependent and independent mechanisms, respectively.

The study published in Nutrition & Cardiovascular Diseases, [8] is the first

research to evaluate the acute effects of resveratrol supplementation on circulatory function, revealing that resveratrol improves flow-mediated dilation (FMD)-a marker of cardiovascular function. FMD of the branchial artery is a marker of blood vessel function and cardiovascular health, and is recognized as an independent risk factor for development of cardiovascular diseases (CVD).Impaired FMD is associated with several cardiovascular risk factors including hypertension, and obesity and is characterized by structural and functional changes to the blood vessel endothelium. The cardiovascular benefits of resveratrol include:

- Suppression of platelet aggregation
- Enhanced antioxidant status
- Increased NO(nitric oxide) availability

A key mechanism behind blood vessel endothelial dysfunction is suggested to involve the impaired release of NO causing blood vessels to constrict. Increased availability of resveratrol is suggested to increase NO production.

Due to all the above effects exhibited by resveratrol, it may be partially responsible for the correlation between increased wine consumption and decreased risk of CHDs.

4.5. Longevity

In 2003, David Sinclair and his team from Harvard added life extension to the list of possible benefits with his publication in Nature [9] resveratrol increased survival of yeast cells. Resveratrol protects cells and DNA against free radicals thereby slowing cell aging. Resveratrol was found to increase SIRT1, **(**SIRT1 is an enzyme that deactivates proteins that contribute to cellular regulation**)** activity 13-fold [34] .A study performed on short-lived seasonal fish having a life span of 13 weeks, revealed that if the fish received resveratrol in the early stages of life, their average and maximum lifespan increased considerably in a dose dependent manner [40]. An animal model study on mice was conducted, the results of which showed that when the high calorie fed mice reached old age (114 weeks), greater than 50% had died compared to less than 33% of the high calorie fed mice receiving Resveratrol. [22]

In a nutshell, resveratrol improves mitochondrial function and protects against metabolic disease by activating the SIRT1 enzyme which stimulates the generation of new mitochondria in other bodily tissue, boosting the body's metabolic rate and possibly slowing the effects of aging. From the above observations and, we infer that resveratrol extends life in multiple species. In mice, resveratrol prevents the early mortality

associated with obesity, but there is currently no experimental evidence to suggest that it can prolong life in lean, healthy animals. Although the mouse studies provide a good justification for studying the effects of resveratrol on human health, one cannot ignore the influence of factors such as interspecies differences in metabolism, genetic variation, diet, physical activity, disease, and mental health, when extrapolating from rodent models.

4.6. Anti-Toxic Effects

- Resveratrol protects liver cells from oxidative degradation caused by chronic alcohol consumption. It reduced hepatotoxicity and symptoms such as necrosis, fibrosis and inflammation were less developed.
- Resveratrol alleviated bleomycin, (a chemotherapeutic agent) induced lung injury.
- Resveratrol has a neuroprotective role against cognitive impairment and oxidative stress induced by the drug colchicine.

5. Conclusion

- Resveratrol is a polyphenolic substance possessing extensive physiological activities. However, its application is limited by light instability and poor aqueous solubility. But use of nanoemulsions based on soy lecithin/sugar esters and Tween 20/glycerol monooleate is known to increase physical & chemical stability.
- Along with peanuts and red grapes, chocolate and cocoa are said to be some of the newer sources of trans-resveratrol.
- Resveratrol exhibits antioxidant, cardio protective, chemopreventative, anti-diabetic, anti-toxic, life extension as well as other health benefits (anti-inflammatory effects, neuro-protective effects, estrogenic/anti-estrogenic properties, and modulation of cellular signal transduction pathways).
- Although well-absorbed by humans (via oral route), its bioavailability is relatively low because it is rapidly metabolized and eliminated.
- Its bioavailability is not enough to exhibit chemo preventative effects. Using piperine and deconjugation enzymes (β-glucuronidase and sulfatase) more resveratrol will be available in its free form.
- Further research should focus on translating in vitro findings regarding potential health benefits into in vivo models.

- Understanding the potential toxicity, health effects, bioavailability, and metabolism of resveratrol is necessary before dietary and supplement recommendations can be made.

- Nature-identical Resveratrol is now commercialized and marketed as nutritional supplement having anti-ageing and cardio-protective benefits by Companies like DSM Nutritional Foods under brand name Resvida.

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