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Resveratrol A Phytoalexin

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Abstract

Resveratrol has gained popularity as a new therapeutic agent or rightly a phytoalexin -to prevent and manage age-related chronic diseases not only in humans but in animals and poultry as well. Resveratrol is bestowed with antioxidant, antiaging, anticancer and antiinflammatory, immunomodulatory, and metabolic modifier activities that are considered in the treatment and management of a vast array of human diseases such as type 2 diabetes, heart disease, fatty livers and cancer etc. Recent research has also shown resveratrol to be a potential anti microbial and anti-obesity compound. Taking into consideration the potential health benefits for both humans and animals resveratrol can be safely incorporated in the diet without any side effects . This article discusses the current data available on pharmacological effects of resveratrol and whether resveratrol can in fact rightly be termed as a "phyto alexin".

Key words:resveratrol, humans, diseases, animals, anti-aging

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INTRODUCTION

One of the most recognized and widely studied compounds resveratrol (*trans*-3,5,4'-trihydroxystilbene) termed 'phytolaexin' is a polyphenolic compound occurring naturally in various plants, including grapes, cranberries ,peanuts and turmeric, in response to stress, as a defence mechanism against fungal, viral, bacterial infections and damage from exposure to ultraviolet radiation. Although resveratrol was first isolated in 1940 from the roots of white hellebore (Veratrum grandiflorum), the importance of resveratrol was recognized only after the widely publicized historic "French Paradox" associated with drinking of red wine. Having the chemical formula $C_{14}H_{12}O_3$, resveratrol is chemically defined as a stilbene, viniferin or phytoalexin (a Greek-derived term meaning to "protect" (alexin) or to "ward off").

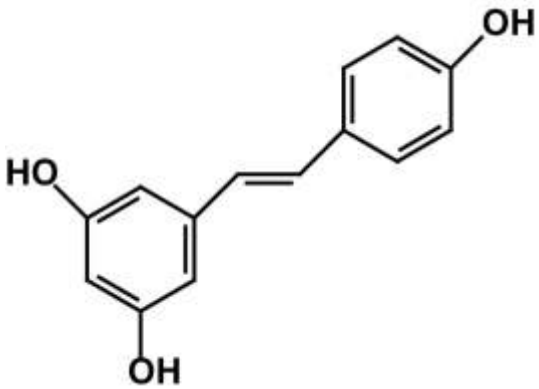

Figure :1 Structure of Resveratrol

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A remarkable range of biological functions have been ascribed to this molecule [1][2] , including cardio protective, antioxidant, anti aging, anticancer and anti inflammatory, immunomodulatory, and metabolic modifier activities that are considered in the treatment and management of a vast array of human diseases. More recently, resveratrol has been proposed as a potential anti-obesity compound. It seems to mimic the effects of energy restriction, thus leading to reduced body fat and improved insulin sensitivity[3][4].

Several mechanisms have been proposed to explain the body fat-lowering effect of resveratrol. It should be emphasized that a great deal of work has been developed in isolated adipocytes, thus limiting the extrapolation of the results to the *in vivo* situation. In this context, results coming from *in vitro* studies, performed in adipocyte types (3T3-L1 cells, pig adipocytes and human adipocytes) have shown that resveratrol increases apoptosis [3][4], decreases proliferation and differentiation of pre-adipocytes [5][6][7] and also reduces lipogenesis [7]. Moreover, in *in vivo* and *ex vivo* experiments resveratrol has been shown to increase mitochondrial biogenesis, thus increasing fatty acid oxidation, and to enhance epinephrine-induced lipolysis[1][4].

Sources of resveratrol

Resveratrol can be easily introduced into the diet by selecting foods such as Red grapes and dark grape juice ,Red wines and white ones(lower resveratrol levels),Blackberries, blueberries, cranberries and their juices, Pistachios, Peanuts with skins and peanut butter.

BIOCHEMISTRY AND BIOAVAILABILITY

The oral bioavailability of resveratrol is independent from dose and aqueous solubility [8]. Upon oral induction, both resveratrol and methylated resveratrol convert into glucuronide and sulfate forms—with methylated resveratrol being the slower of the 2 (the derivatives have been shown to remain longer in the blood before converting than resveratrol alone). However, the argument of improved bioavailability is somewhat misleading in that the glucuronide and sulfate forms of resveratrol also stay in

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the blood for some time. The question that recently has been raised is whether higher blood levels of the glucuronide and sulfate forms of resveratrol themselves have benefit, perhaps serving as a pool of "time release" sources of resveratrol between times when resveratrol is consumed. Both resveratrol and methylated resveratrol have different rates of conversion into their glucuronide and sulfate forms . It is also likely that resveratrol and its methylated derivatives such as pterostilbene have very different modes of action and physiological effects owing to their different chemical structures.

Pharmacokinetics

Pharmacokinetic studies have revealed that the target organs of resveratrol are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate [9][10] and excreted via feces and urine [11]. No phenolic degradation products were detected in urine or tissues indicating that unlike flavonoids, resveratrol does not serve as a substrate for colonic microflora [12].

Mechanisms of Action

Biological effects of resveratrol have been enormously tested in *in vivo* experiments involving laboratory animals and *in vitro* experiments as well as retrospective clinical trials involving humans:

Anti microbial activity

The antimicrobial activity of resveratrol against bacteria and dermatophytes that are major etiologic agents of human skin infections was evaluated [13] using the broth microdilution protocol of the National Committee for Clinical Laboratory Standards (NCCLS) M7-A5. Growth of the bacterial species *Staphylococcus aureus, Enterococcus faecalis, and Pseudomonas aeruginosa* was inhibited at 171-342 microg/mL of resveratrol in the solvent dimethyl sulfoxide. Using the NCCLS protocol M38-P, activity against the fungal species *Trichophyton mentagrophytes, Trichophyton tonsurans, Trichophyton rubrum, Epidermophyton floccosum,* and *Microsporum gypseum* was also tested and the growth of the dermatophytes was observed to be inhibited at 25-50 microg/mL of resveratrol. Thus a novel application for resveratrol, a molecule of plant defense, to combat human fungal pathogens was indicated..

It has been verified that resveratrol has antibacterial activity against all tested Gram-positive bacteria using both the disk diffusion and broth microdilution methods[14]. Time kill assays of this compound against Gram-positive bacteria showed that its effects on the growth of bacterial cells were due to bacteriostatic action. The addition of resveratrol has allowed the identification of changes in cell morphology and DNA contents, which have been assessed through microscopic analysis and flow cytometry; this suggests that the cell cycle is affected by resveratrol indicating that resveratrol may have potential as a natural antibacterial agent for both food preservation and medicinal use.

The putative candicidal activity of resveratrol is currently a matter of controversy. Here, the antifungal activity as well as the antioxidant response of resveratrol against *Candida albicans*, have been tested in a set of strains with a well-established genetic background .The antifungal activity of resveratrol against human pathogenic fungi was tested to elucidate the antifungal mechanism(s) of resveratrol. Resveratroldisplayed potent antifungal activity against human pathogenic fungi at concentration levels of 10-20 microg/mL. Furthermore, time-kill curve exhibited fungicidal effect of resveratrol on *Candida albicans*, but the compound had no hemolytic activity against human erythrocytes. The destruction of *C. albicans* cells by resveratrol was also confirmed by scanning electron microscopy suggesting that resveratrol could be employed as a therapeutic agent to treat fungal infections of humans[15]. At the doses usually employed in antifungal tests (10–40 μg/ml), resveratrol showed no effect on the exponential growth of the *C. albicans* CAI.4 strain, a tenfold increase (400 μg/ml) was required in order to record a certain degree of cell killing, which was negligible in comparison with the strong antifungal effect caused by the addition of amphotericin B (5 μg/ml). An identical pattern was recorded in the prototrophic strains of *C. albicans* SC5314 and RM-100, whereas the oxidative sensitive trehalose-deficient mutant (*tps1/tps1* strain) was totally refractory to the presence of resveratrol[16]. The serum-induced yeast-to-hypha transition remained unaffected upon addition of different concentrations of resveratrol. Determination of endogenous trehalose and catalase activity, two antioxidant markers in *C. albicans*; revealed no significant changes in their basal contents induced by resveratrol. These results seem to dismiss a main antifungal role as well as the therapeutic application of resveratrol against the infections caused by *C. albicans*.

Resveratrol (95 % purity from grapes) failed to inhibit fungal growth on potato dextrose agar media at the concentrations ranging from 0.25,0.05; 0.75; 1.0 and 2.0% v/v but decreased sporulation at 1.0 and 2.0 % levels. Thin Layer chromatography employed to measure aflatoxin production showed the presence of sharp fluorescent bands at all the concentrations showing ineffectiveness of resveratrol in binding aflatoxin B1. Results emphasized that resveratrol was not fungicidal [17] .

Antiviral activity

In test-tube research, resveratrol seems to have some antiviral benefits. For example, it was found to block the influenza virus from transporting certain proteins, thereby restricting the ability of the virus to replicate[18]. Resveratrol also was reported to suppress the activation of herpes simplex virus proteins, and reduce the production of viral DNA[19]. In addition, resveratrol also increased the potency of some antiretroviral drugs against HIV [20].

Anti oxidant effects

Resveratrol is an effective scavenger of hydroxyl, superoxide, and metal-induced radicals[21][22] and increases activities of antioxidant enzymes[23] , such catalase, superoxide dismutase, glutathione peroxidase, NADPH quinone oxidoreductase, and glutathione S-transferase, as well as activates erythroid-derived nuclear factor, a major transcription factor regulating antioxidant response [24]. Resveratrol is highly hydrophilic and lipophilic and likely to be more effective than some other antioxidants, such as vitamin E and C [25][26].

Lipid oxidation is a process that has significant effect on the food industry because it can alter food quality (rancidity,

flavor, odor, and color) and may lead to toxic end product accumulation [27]. Antioxidant agents and some natural substances (e.g., resveratrol) that possess antioxidant potentials are commonly used to control oxidation of polyunsaturated fats in foods. Due to rich nutrient contents (triacylglycerols, phospholipids, and proteins), egg yolk is widely used as an ingredient in various food products and is thus exposed to lipid peroxidation. Dietary supplementation of antioxidant nutrients (e.g., vitamin E, vitamin A, and lycopene) is one of the effective ways to minimize lipid peroxidation in eggs at farm level because these compounds are transferred into egg yolk and meat[28][29][30]. It is also well-established that high dietary antioxidant content improves food quality parameters such as color, tenderness, and storage properties[31].

Resveratrol exerts antioxidant effect via prevention of peroxidation of the apolipoprotein B protein associated with low-density lipoprotein[32] and restoration of tissue glutathione and plasma total antioxidant capacity and tissue malondialdehyde (MDA) and myeloperoxidase activity [33] [34] through acting as an electron donor [35]. Antiinflammatory effects of resveratrol are associated with increased pro inflammatory mediators such as tumor necrosis factor .

Resveratrol has demonstrated antioxidant properties in animal research[36] and it is not clear whether these antioxidant effects are direct, or the result of increased production of antioxidant enzymes by the body. *In vitro* research has shown that resveratrol prevents the oxidation of Low density lipoprotein (LDL) or the bad cholesterol by chelating copper and by directly scavenging free radicals[37]. The attenuation of AflatoxinB1 induced changes were observed upon supplementing resveratrol in feed of broiler birds for a period of 45 days [17] as reflected in the increased activity of the serum biotransformation and antioxidant enzymes while the aflatoxin B1 fed birds elicited low activities.

Anti-aging and longevity

Resveratrol may combat stress, inflammation, insulin resistance and may prolong life by mimicking the effects of caloric restriction (CR) as evident from animal studies. .It was shown that resveratrol significantly extends the lifespan of lower organisms such as the yeast *Saccharomyces cerevisiae [38]* , the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster[39] .T*he ability of resveratrol to improve health and extend life was also provided by a series of experiments in *Nothobranchius furzeri*, a short-lived species of fish[40]. Resveratrol not only extended average lifespan by up to 56%, but also improved motor function and delayed neurodegenerative processes in these animals. These experiments in lower organisms set the stage for testing the effects of resveratrol on longevity in mammals. The reason that resveratrol has these anti-aging effects is unknown, but may be related to the production of proteins by the *SIR2* gene.

The ability of resveratrol to mimic lower energy intake was originally tested in two parallel experiments in mice[41] [42]. In the first, animals were fed a resveratrol-containing diet to test whether it would recapitulate effects of CR. In the second, animals were fed a high-fat diet with or without resveratrol to test whether it could prevent some of the detrimental consequences of obesity. In each case, improvements in physiology were noted, ranging from increased insulin sensitivity in the obese mice, to better motor coordination in both groups, to fewer cataracts and higher bone strength in the lean mice. Strikingly, resveratrol was found to mimic the transcriptional response to CR, both in this study and in a parallel independent study [42] [43]. Resveratrol increased survival in the obese mice such that their life spans were equivalent to those of lean, untreated animals. However, adding resveratrol to the diet of mice on a normal diet did not produce any further increase, suggesting that resveratrol might primarily be counteracting the negative consequences of obesity, rather than slowing aging in a CR-like manner.

Several follow-up studies confirmed that resveratrol did not increase lifespan in healthy mice and increasing the dose of resveratrol to approximately 200 mg/kg had no effect on survival . As many of these studies started with middle-age mice (12 months of age), and CR is reported to have a larger effect on longevity when the treatment starts earlier current studies are targeting younger age groups, though to date no positive results have been reported. Post-mortem analyses of the animals fed high-fat diets support the hypothesis that the life extension that has been observed results primarily from alleviating vascular complications and fatty liver, which are not major contributors to mortality in lean mice[44].

Anti –Inflammatory

Studies aimed on the anti-inflammatory activity of resveratrol prove it to be anti-inflammatory .In asthma the primary allopathic treatment involves the use of steroidal anti-inflammatory drugs to treat lung inflammation. In a study of inflammatory cytokine production in lung epithelial cells ,resveratrol inhibited NF-κB expression, IL-8 release, iNOS, and COX-2 expression [45]. In another cell culture study resveratrol inhibited cytokine release from alveolar macrophages of patients with chronic obstructive pulmonary disease [46]. The anti-inflammatory activity expressed by resveratrol appears to be mediated by an inhibition of the activation of transcription factor nuclear factor –kappa B(NF-κB).The signaling of NF-κB is inhibited by resveratrol which decreases transcription of DNA, down regulating inflammatory cytokine expression. Tumor necrosis factor –alpha (TNF-α) treatment of adipocytes triggered increased NF-κB activation , resulting in increased interleukin-6(IL-6) and cyclooxygenase-2(COX-2) gene expression with resveratrol being known to inhibit NF-κB activation and expression of both IL-6 and COX-2 . Treatment of mice with resveratrol resulted in decreased expression of the inflammatory markers TNF-α ,IL-6,IL-1β,intercellular adhesion molecule-1(ICAM-1),and inducible nitric oxide synthase (iNOS)(Pearson et.al.,2008) .The inhibitory effects of resveratrol on the down stream metabolites of NF-κB in human chondrocytes show that it may be beneficial in prevention of arthritis as well [47][48] and should be explored further for the prophylactic treatment of osteoarthritis in humans and companion animals.

Cyclooxygenase (COX) enzymes produced in humans perform various functions. One such function, inflammation, is necessary as a normal, healthy attempt by the body to heal itself. However, when inflammation gets out of control (such as in the case of arthritis, or other chronic inflammatory disorders) ongoing pain and discomfort is the result. Resveratrol has anti-inflammatory activity, due to inhibition of the COX enzymes, as well as other inflammatory substances including hydroperoxidases, and 5-lipoxygenase and inflammatory cytokines. Some evidence suggests that resveratrol is a more potent anti-inflammatory agent than aspirin, ibuprofen, or indomethacin. Research in animals has shown that injections of resveratrol decreases inflammation and reduces cartilage destruction [49].

Resveratrol was shown to play a role in immune regulation as it inhibited the secretion of interferon –gamma(IFN-γ), IL-1,IL-4,IL,-6 and TNF-α but increased the production of IL-10 in lipopolysaccharide-activated macrophages. Immune-regulatory cells CD28 and CD80 were significantly down-regulated.the overall response being a down =regulation of both T-helper-1 and T-helper -2 directed immune activity.

Cardiovascular health

Resveratrol exerts a number of effects that may have protective effects on the cardiovascular system. In both test-tube and animal research, resveratrol has been shown to inhibit platelet aggregation (i.e., the clumping together of blood platelets). This has value since excessive or inappropriate aggregation of platelets can lead to formation of blood clots and subsequent blockages in blood vessels that result in insufficient blood flow, heart attack or stroke. Resveratrol can also promote vasodilation (a relaxed and expanded state of the artery that accommodates increased blood flow) by enhancing the production of a naturally occurring substance in the body called nitric oxide [50]. Some animal studies suggest that high oral doses of resveratrol could decrease the risk of thrombosis (clot formation) and atherosclerosis[51] [52].

Epidemiological as well as experimental studies have revealed that drinking wine, particularly red wine, in moderation protects cardiovascular health; however, the experimental basis for such an action is not fully understood [53]. A growing body of evidence supports the role of resveratrol as evidence based cardiovascular medicine. Resveratrol protects the cardiovascular system in multidimensional ways. The most important point about resveratrol is that at a very low concentration, it inhibits apoptotic cell death, thereby providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis and ventricular arrhythmias. Both in acute and in chronic models, resveratrol-mediated cardioprotection is achieved through the preconditioning effect (the state-of-the-art technique of cardioprotection), rather than direct effect as found in conventional medicine. The same resveratrol when used in higher doses, it facilitates apoptotic cell death, and behaves as a chemo-preventive alternative. Resveratrol likely fulfills the definition of a pharmacological preconditioning compound and gives hope for the therapeutic promise of alternative medicine[53].

Anti-Cancer Effect

Resveratrol's most compelling health effect shown in laboratory studies is its broad-spectrum anti-cancer activity. Experimental models of breast, prostate, lung, blood, skin, brain, tongue, esophagus, kidney, bladder, and colon cancer have reported evidence for beneficial effects of resveratrol. Resveratrol appears to sensitize cells toward cancer therapy agents, improving the benefit of these drugs. Also, when combined with other plant-derived phenolics, resveratrol's anti-cancer actions seem to be enhanced, showing the potential benefits of antioxidant synergy from a mixed diet high in colorful fruits and vegetables rich in phytochemicals. Resveratrol's actions to inhibit inflammatory mediators and the growth of new blood vessels in tumors (anti-angiogenesis), as well as its ability to accelerate the rate of cancer cell death (apoptosis) are synergistic effects in anti-cancer activity. Resveratrol in some studies inhibited enzymes synthesizing nitro-oxygen radicals like nitric oxide that may be involved in cancer development. Resveratrol thus acts against mechanisms controlling the initiation, promotion and progression of tumor cell growth in laboratory models. It is considered one of the most promising natural anti-cancer agents. In *in vitro* studies, resveratrol has been found to inhibit the proliferation of various human cancer cell lines, including those from breast, prostate, stomach, colon, pancreatic and thyroid cancers. In animal research, resveratrol was shown to inhibit the development of chemical induced cancers of the breast [54] , oesophagus [55] and intestine [56] . A mechanism by which resveratrol exerts this effect is by inhibiting angiogenesis (the growth of new blood vessels). For tumors to grow, angiogenesis must take place so that blood vessels can develop in order to feed the tumor while another mechanism is by inhibiting the enzymatic activity of both forms of the cyclooxygenase enzymes. Research results show that long-term inhibition of cyclooxygenase significantly reduces the risk of developing many cancers.

The implications of selected chemopreventive parameters and metabolic conversion of resveratrol *in vivo* in two 8-week long feeding experiments with rats by administering a low-resveratrol diet containing 50 mg resveratrol per kg body weight (bw) a day and a high-resveratrol diet with 300 mg per kg bw / day were investigated [9]. Feeding of different dosages of resveratrol revealed no effect on the different chemopreventive parameters, except for the total antioxidant activity, which was elevated in plasma by 19% after feeding 50 mg resveratrol / kg body weight . The formation of *trans*-resveratrol-3-sulfate,*trans*-resveratrol-4'-sulfate, *trans*-resveratrol-3,5-disulfate, *trans*-resveratrol-3,4'-disulfate, *trans*-resveratrol-3,4',5-trisulfate, *trans*-resveratrol-3-*O*-β-D-glucuronide, and resveratrol aglycone was detected by HPLC analysis, depending on the biological material. Total resveratrol recovery in urine and feces of rats fed on 50 mg resveratrol / kg body weight and day was 15% and 13%, respectively. For rats fed the higher dosage of 300 mg resveratrol / kg body weight and day recovery was 54% and 17%, respectively. This was one of the first studies performed with synthesized standards of relevant resveratrol conjugates. The lack of effect on the chemopreventive parameters was probably due to the formation of various resveratrol conjugates reducing its bioavailability in the rat[9].

Weight loss potential

Obesity is biologically characterized at the cellular level by an increase in the number and size of adipocytes (fat cells) that develop from pre-adipocytes in adipose tissue. Resveratrol has been shown to inhibit pre-adipocytes[57] which may translate into reducing the production of new fat cells. In addition, the *SIR2* gene in the body of animals and humans produces the protein sirtuin 1 or *Sirt 1*. *Sirt 1* promotes fat mobilization in adipose (fat) tissue [58]. Resveratrol is also a known an activator of *Sirt 1*, and was shown in research to protect mice against diet-induced-obesity and insulin resistance. By means of stimulating *Sirt 1* in mice, resveratrol was further shown to improve glucose balance[59]. Mice fed resveratrol for 15 weeks in another study showed better treadmill endurance than controls. This work also supports the role resveratrol has on the activation of *Sirt 1* [60].

Metabolic syndrome /Type 2 diabetes

Resveratrol supplementation in mice fed high-fat diets

demonstrated an inhibition of fat deposition in abdominal organs and an increase in insulin sensitivity [41]. Supplementation with resveratrol also had a significant effect in lowering blood glucose and triglycerides in streptozotocin-induced diabetes in rats. Hepatic glycogen synthesis as well as glucose uptake in tissues was stimulated by resveratrol demonstrating increased insulin sensitivity [61]. Supplementation of resveratrol also showed to be protective of vascular endothelial cells in diabetes and inhibited the typical inflammatory activity in experimental diabetic neuropathy and nephropathy [62] [63][64].

Fatty liver

Resveratrol was shown to inhibit the development of fatty liver in rats fed a high carbohydrate diet and subjected to periodic fasting .. A mouse model of alcoholic fatty liver disease also confirmed the preventive role of resveratrol with reduced lipid synthesis and increased fatty acid oxidation[65] [66].

Bone mineralization

Resveratrol may also augment calcium metabolism. Using ovariectomized rats, it was shown that resveratrol (0.7 mg/kg) supplementation increased bone mineral density and inhibited femur calcium loss associated with estrogen deficiency[67]. .

Cellular stress

Various stress factors including chemical and physiological stress factors (i.e., heat, radiation, toxins, viral infections, ethanol, arsenite, and gene transfer) increase heat shock protein synthesis at the cellular level. Increased heat shock protein protects cells against the additional stress via making the cells resistant to harmful insults and apoptosis [68] . Constitutive expression of Hsp70, a major heat shock protein, mediates the protection against cell lysis induced by the toxic effect of NO, a reactive oxygen intermediate created through oxygen-derived free-radical action [69].Resveratrol activates the vitagene system, which encodes for cytoprotective Hsp70 and heme oxygenase 1, as well as thioredoxin reductase and sirtuins[70]. Through these mechanisms, resveratrol also activates the silent information regulation 2 homolog 1 and 5' adenosine monophosphate-activated protein kinase that are related to extending lifespan and improving metabolic disease [66].

Toxicity

No biochemical, neurological, electrocardiographical ,serious side effects or toxicity have been reported in repeated dose studies in humans. A very high dose of oral supplementation of resveratrol to rats (20 mg/kg for 20 d), 1,000 times the amount consumed by a 70-kg person taking 1.4 g of *trans*-resveratrol/d,was tested and no adverse effects were reported on growth, water and feed intakes, and hematological and biochemical variables as well as histopathological alteration[71] .

Drug-Nutrient Interactions

Resveratrol inhibits cellular proliferation via an S-phase inhibition of the cell cycle. Two studies have shown a synergistic apoptotic effect of resveratrol and paclitaxel. When the former was introduced prior to the latter to lung cancer cells a significant increase in cell death was observed [72]. Similar effects were reported in non-Hodgkin's lymphoma and multiple myeloma cells[73].However ,some studies have reported interference between resveratrol and paclitaxel as resveratrol prevents tumor cell progression to stage S1 phase where paclitaxel exerted it's apoptotic effect. Resveratrol was also reported to reduce the antitumor efficacy of both paclitaxel andvinblastine in bladder cancer cells but pretreatment with resveratrol enhanced the cell-killing activity of these chemotherapeutic agents[74][75]. Resveratrol enhanced the effectiveness of the chemotherapeutic drugs cisplatin and doxorubicin which are known to be toxic for the heart and kidneys. Resveratrol was reported to decrease the toxicity of doxorubicin in rat heart cells and of cisplatin in rat kidneys [76].

Dosage

The majority of resveratrol supplements contain a very low dose of resveratrol. The potency of most of the nutritional supplements labeled as resveratrol is in the range of 30 mg to 100 mg which is 30 to 100 times lower than doses thought to be in the range for therapeutic effects in humans. A dose of 200-400 mg of trans-resveratrol daily has been shown to be beneficial in inflammatory diseases, anti-aging, cardiovascular diseases and Type 2 diabetes., while higher doses are recommended for cancer chemoprevention. Resveratrol taken in conjunction with synergistic polyphenols like curcumin, quercetin etc has also proven helpful and may further reduce the requirement.Most of the feeding studies published on resveratrol have been in animals, and it is difficult to translate dosages in animal studies into human equivalents. However, a recently published human pharmacokinetic study of resveratrol indicated that a dose of 1000 mg to 5000 mg per day was required to bring the blood level of resveratrol into a range for being a potential cancer preventive.

CONCLUSIONS

Resveratrol is a natural compound obtained from plants. Most of the feeding studies published on resveratrol have been conducted in animals making it difficult to translate dosages in animal studies into human equivalents. Thus research, particularly on long term benefits in animals, needs to be conducted on resveratrol. By consuming blue, red, purple and black-skinned plants rich in resveratrol, the below mentioned protective benefits can be gained:

Increase blood flow and reduce the extent of brain cell damage following stroke
Reduce the activity of brain inflammatory mediators in a model of Alzheimer's disease
Reduce vascular plaque formation in rats given a high-fat diet
Improve the rate of healing in skin wounds
Protect against lipid oxidation in a model of pancreatitis
Protect against cellular pathology in a model of diabetic kidney disease
Protect against liver damage in a model of cholestasis or bile duct occlusion
Protect against cartilage deterioration in a model of osteoarthritis
Stimulate anti-clotting mechanisms in blood
Suppress appetite and in turn contribute to weight control or loss
Enhance sperm production
Inhibit formation of cataracts
Inhibit proliferation of the herpes simplex virus
Resveratrol plays a role as a antimicrobial agent
Resveratrol extends life in multiple species

Resveratrol and its analogs may have wide application to skin conditions may also have promising clinical potentials in diabetic wounds.

Taking into consideration the potential health benefits for both humans poultry and animals in general resveratrol can be safely incorporated in the diet without any side effects . To conclude resveratrol can in fact rightly be termed as a "phyto alexin" .

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Conflict of Interest

Authors declare no conflicts of interest.

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