IJPSR (2015), Vol. 6, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 February, 2015; received in revised form, 18 April, 2015; accepted, 29 May, 2015; published 01 September, 2015

RESVERATROL: RECOMMENDING ITS WIDE INCREASE – A PREMATURE DECISION OR NOT? A REVIEW

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Keywords:
Resveratrol,
Health Effects, Adverse Effects

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ABSTRACT: Resveratrol, an antioxidant found in red wine and certain foods, has been touted as a natural way to slow aging and fight cancer, obesity, heart disease, and diabetes. It also could be accounted as an agent, which has effects to reduced risk of inflammation and blood clotting. In addition there are some studies showing that resveratrol may actually reduce the positive effect of exercise on the heart in older men, but it's important to know that its effects only last a short time after drinking red wine. As promising as it sounds, it is not yet established how resveratrol affects humans, since most studies have been conducted on animals and microbes. Because the information on resveratrol, presented in literature, pointing its health and adverse effects is full with contradictions, especially with respect to the human response, we tried to present the available information with minimal commentary, remaining as neutral as possible and allowing the reader to draw its own conclusion on recommendation of the wide increase usage of resveratrol and a prematurity of such a decision.

INTRODUCTION: Resveratrol (3, 4′, 5 trihydroxystilbene) is a naturally occuring phytoalexin, which belongs to a class of polyphenolic compounds called stilbenes.[1] The first mention of resveratrol was in a Japanese article in 1939 by Michio Takaoka, who isolated it from the poisonous, but medicinal, *Veratrum album*, variety *grandi florum*. [2] The name presumably comes from the fact that it is a resorcinol derivative coming from a *Veratrum* species. Resveratrol is a type of antioxidant produced by some types of plants in response to stress, injury, invading pathogens, fungal infection, or ultraviolet (UV) radiation.[3]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(9).3641-53

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(9).3641-53

This phenolic compound has been associated with the so called "French Paradox" – a statistically lower risk for cardiovascular disease among French people that is thought to be due, in part, to higher levels of red wine consumption in that culture, according to the University of Maryland Medical Center.[4-8] Considerable scientific research has revealed numerous potential health benefits of resveratrol, which is found in high concentrations in a few commonly consumed plant foods.[9-18]

Chemical and physical properties:

Resveratrol is a fat-soluble compound that occurs in a *trans* and a *cis* configuration (**Fig. 1**).

Both *cis*- and *trans*-resveratrol can be either free or bound to glucose as glucosides. Resveratrol-3-*O*-beta-glucoside is called piceid.[19] The *trans*- form can undergo isomerisation to the *cis*- form when exposed to ultraviolet irradiation (**Fig. 2**),[20] a process called photoisomerization.[21]

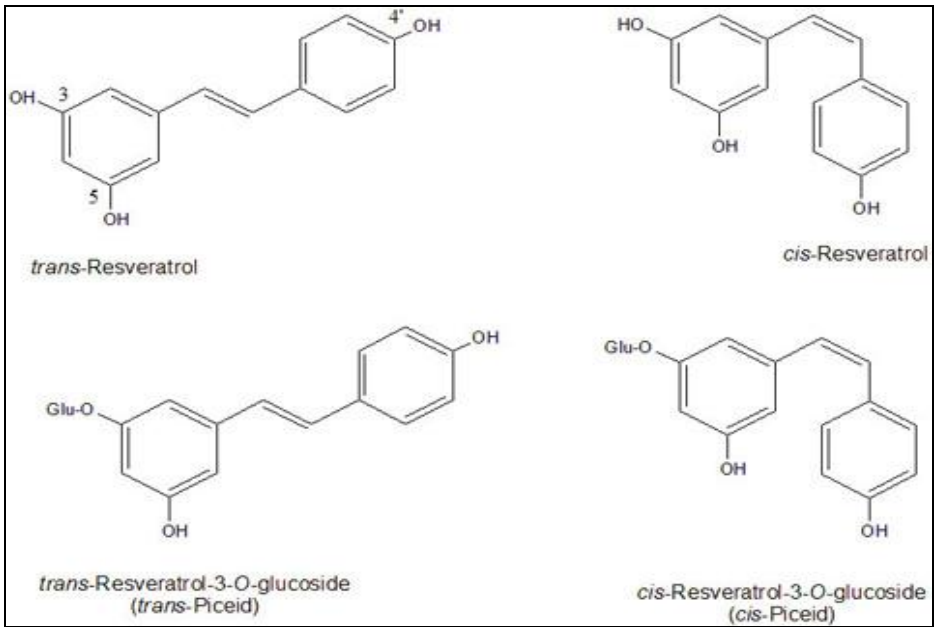

FIG.1: CHEMICAL STRUCTURES OF RESVERATROL AND RESVERATROL GLUCOSIDE (PICEID)

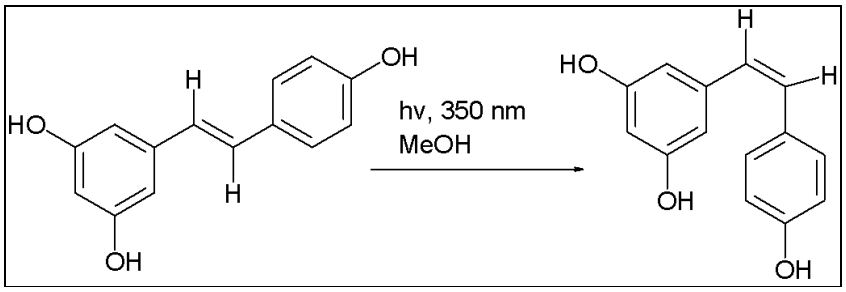

FIG. 2: PHOTOISOMERIZATION OF *TRANS*-RESVERATROL TO *CIS*- RESVERATROL

In some recent studies has been discovered, that the photoisomerization process may induce a further photochemical reaction, which produces a fluorescent molecule named "Resveratrone".[22]

Natural occurrence:

In plants:

Resveratrol was originally isolated by Takaoka from the roots of hellebore in 1940, and later, in 1963, from the roots of Japanese knotweed (*Polygonum cuspidatum*). The major dietary sources include grapes, wine, peanuts, and soy; however, they can also be introduced into the diet through Itadori tea, which has long been used in Japan and China as a traditional herbal remedy for heart disease and strokes. Analysis of grapes, peanuts, and Itadori tea shows that they contain mainly *trans*-resveratrol glucoside. In contrast, red wines are primarily a source of the aglycones *cis*- and *trans*-resveratrol. While peanuts and grapes contain low levels of the stilbenes, Itadori tea and red wine both supply relatively high concentrations of resveratrol.[23]

In foods:

Resveratrol is found in foods such as peanuts,[24, 25] pistachios,[26] grapes, red and white wine, blueberries,[27] cranberries, [23, 28] and even cocoa and dark chocolate.[29] Red grapes and red wines earn star status for their high levels of resveratrol, with Spanish grapes taking the top prize, providing as much as 1,890 micrograms in a 5-ounce glass.[30, 31] Grapes only have resveratrol in the skins and the amount varies according to the type of grape and whether the plant is exposed to fungal infection, a form of stress that the plant responds to by producing resveratrol to fend off infection.[32, 33]

Metabolism and Bioavailability:

Since much of the basic research on resveratrol has been conducted in cultured cells exposed to unmetabolized resveratrol at concentrations, often 10-100 times greater than peak concentrations

observed in human plasma after oral consumption, the information about the bioavailability of resveratrol in humans is important.[34] Although *trans*-resveratrol appear to be well-absorbed by humans when taken orally, its bioavailability is relatively low due to its rapid metabolism and elimination.[35, 36]

The efficacy of orally administrated resveratrol will depend on its absorption, metabolism, and tissue distribution. Although many studies have implicated a role of resveratrol in disease prevention, only a few studies have addressed to its bioavailability and metabolism. However, none of them has provided a conclusive metabolic profile.[37]

It has been suggested, that resveratrol is metabolized according to two pathways: glucuronidation in the human liver and sulfation in both the liver and the duodenum. The major derivatives of resveratrol glucuronidation are trans-resveratrol-3-O-glucuronide, trans-resveratrol-40-O-glucuronide, and trans-resveratrol-3-O-sulfate.[37] Kinetic analysis of resveratrol transformation suggests that in the liver, glucuronidation is favored over sulfation with almost similar rates of reaction. The metabolic modifications of resveratrol can be inhibited by quercetin, a polyphenol also found in wine. Clinical and *in vivo* studies have indicated that free trans-resveratrol in plasma is very sparse and short lived.[16]

In more recent publications have been demonstrated, that the translational potential of resveratrol is limited by its specificity, poor bioavailability and uncertain toxicity. In addition some evidences demonstrate that resveratrol modulates sphingolipid metabolism by forming higher order oligomers that exhibit better selectivity and potency in modulating sphingolipid metabolism.[38]

It has been determined, that resveratrol has very low bioavailability and is rapidly metabolized to yield plasma and tissue levels that are several-fold lower than those typically used in experiments with cultured cells. On **Fig. 3** is presented an overview of the proposed metabolism of resveratrol *in vivo* in rodents and humans.[39]

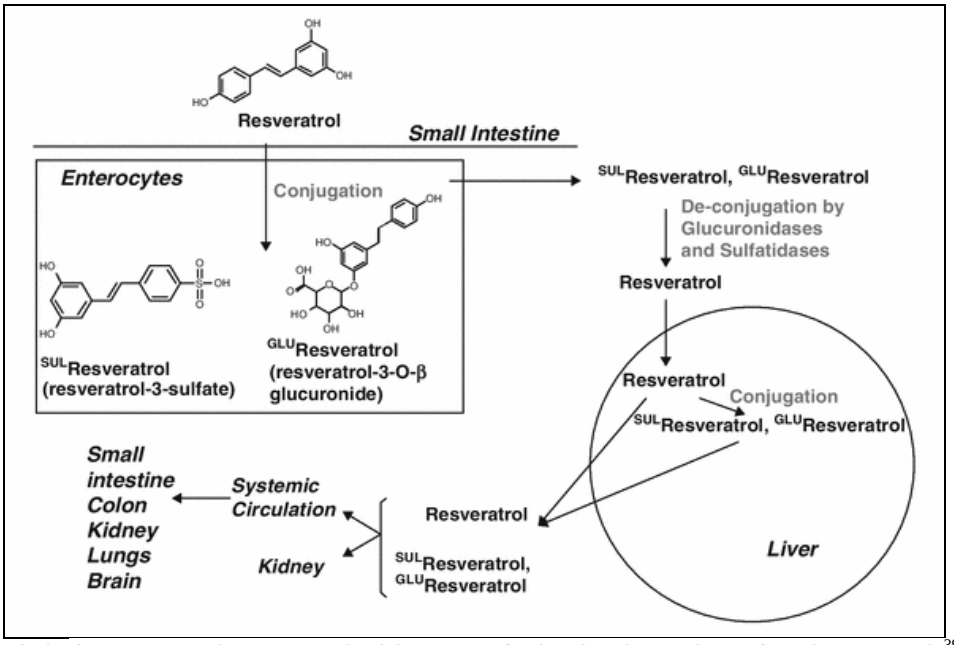

FIG. 3: OVERVIEW OF THE PROPOSED METABOLISM OF RESVERATROL *IN VIVO*.[39]

In addition it appeared that the metabolic by-products of resveratrol metabolism in humans do retain biologic activity, and as such, may be responsible for imparting the protective advantages attributed to the compound.[40-42]

Based on this data is obvious that in order to assess the benefits of resveratrol is important to be able to determine its form in cells and tissues after oral or IP administration. In addition the levels of conjugated and unconjugated resveratrol at the

potential points of action should also be investigated. The bioavailability and metabolic pathways must also be known before drawing any conclusions on the benefits of dietary resveratrol to health.

Health effects:

As phenolic compound, resveratrol contributes to the antioxidant potential of red wine and thereby may play a role in the prevention of human cardiovascular diseases. Resveratrol has been shown to modulate the metabolism of lipids, and to inhibit the oxidation of low-density lipoproteins and the aggregation of platelets. Moreover, as phytoestrogen, resveratrol may provide cardiovascular protection. This compound also possesses anti-inflammatory and anticancer properties.

Cardioprotective effects:

Cardiovascular disease (CVD) is one of the major disease burdens worldwide, and even becomes a bigger health concern faced by developing world. CVD also remains the leading causes of death in the world, accounting for 17.3 million deaths per year, a number that is projected to rise to >23.6 million by 2030.[43]

Some data suggests that significant reductions in cardiovascular disease risk have been associated with moderate consumption of alcoholic beverages. Knowing that red wine contains resveratrol and some flavonoids it is believed for this to be the best method of cardioprotection, rather than direct therapy. It's also theorized that cardioprotective effects of resveratrol are a form of preconditioning. This led to the idea that the regular consumption of red wine might provide additional protection from cardiovascular disease.

It has been also demonstrated that resveratrol and proanthocyanidins - the major polyphenol compounds in grapes, mainly presenting in the grape skin and seeds have beneficial effects on cardiovascular health by lowering the systolic blood pressure (SBP) and increasing the nitric oxide (NO) concentrations. It has been established that resveratrol may also have effects like reduce oxidative stress, angiotensin II and ET-1, all of which protect against increasing SBP.[44] In addition hypothesiz exists, that resveratrol would have a favorable effect on the prevention and control of hypertension by regulating blood pressure. A concentration-dependent efficacy has been demonstrate between resveratrol consumption and its reductive SBP effects.[45]

Despite its promising therapeutic potential, few studies have evaluated the safety of long-term resveratrol supplementation in older adults. In some of these studies has been suggested that a low dose of a resveratrol-containing grape product during the first six months, with a double dose provided during the second six-month period, are well tolerated in adult patients with stable coronary artery disease.[46]

In addition the metabolic and safety outcomes of resveratrol supplementation in older individuals have also been evaluated.[47] The results indicate some improvement in insulin sensitivity and post-meal glucose, which suggest that resveratrol is well tolerated in older adults.[47] However the interpretation of the data gave no genuine information on the effects of short-term (90 days) resveratrol supplementation on metabolic and safety outcomes. In additional study was determined, that short-term resveratrol supplementation at doses of 300 mg/day and 1000 mg/day does not adversely affect blood chemistries and is well tolerated in overweight, older individuals. These findings support the study of resveratrol for improving cardio-metabolic health in older adults in larger clinical trials.[48]

Keeping this in mind, a conclusion is drawn that additional high-quality studies are needed to further evaluate the causal conclusions and to determine the cardio-vascular protective effects of resveratrol.

Anti-oxidant effects of resveratrol:

Chronically high levels of ROS are linked to cell dysfunction, cell death and tissue damage, all of which lead to the pathogenesis of cardiovascular disease when it occurs within this system. Elucidating the mechanism of action for some of the naturally occurring antioxidants, such as the potent enzyme mimetics and polyphenols, may lead to new therapeutic targets that can be modulated

through more conventional pharmacological approaches.

It has been previously demonstrated, that resveratrol is able to suppress ROS production and upregulate endogenous antioxidants to protect the cardiovascular system from oxidative damage. The antioxidant effects of resveratrol can protect cells from oxidative damage, which, in turn helps to reduce cardiovascular risk.[49]

In fact, there has not been any convincing evidence that resveratrol acts as a caloric restriction mimetic by extending life in any species under "normal" conditions. However, there are evidences, which indicates resveratrol as an agent providing protection against metabolic stresses induced by high-fat diets or other oxidative reasons in several species, including human, and as a result, presumably extending life span significantly beyond that expected under conditions of such stress.[50] Unfortunately such a statement is far from admittedly since there are sparse clinical evidences confirming these effects in humans. Clearly, further studies are required to understand the effect of ROS on basic cellular functions and the differential responses seen in different cell types and how this in turn impacts on the pathology of different disease states.[16]

Metabolic diseases:

The incidence of metabolic and cardiovascular diseases (MCDs) is increasing globally and has reached a point to be a costly public health issue. Changes in lifestyle including a high-fat diet and reduced activity are key factors in the development of MCD. Investigations on MCD pathogenesis in the last 5 years underscore the importance of many factors contributing to this disease complex including being overweight, central obesity, oxidative stress, vascular and system inflammation, insulin resistance, and endothelial dysfunction. Pharmaceutical and dietary strategies have targeted these disorders to control MCD, and many natural products with excellent pharmacologic properties are good candidates for the control or prevention of MCD.

In this case, resveratrol has emerged as a potential food constituent with some promising activities.[51]

Diabetes and obesity:

Recent studies suggest that resveratol may have anti-diabetic potential in addition to its other numerous health benefits. At this point almost all research pertinent to Resveratrol's antihyperglycemic effects has been conducted on animals but the results are very promising. The mechanism of resveratrol's action is complex and is demonstrated to involve both insulin-dependent and insulin-independent effects.[11]

The broad spectrum of resveratrol effects is enlarged by new data demonstrating its great potency in relation to obesity. It is well established that resveratrol exerts beneficial effects in rodents fed a high-calorie diet. In some studies, resveratrol was reported to reduce body weight and adiposity in obese animals. The action of this compound involves favourable changes in gene expressions and in enzyme activities.[52]

In a recent publication has been proposed that the mechanism by which Resveratrol exerts favorable effects on obesity is associated with the induction of genes for oxidative phosphorylation and mitochondrial biogenesis.[51] However, the precise molecular mechanism up to this point is not totally clear and since these effects are established mainly on animal models, it is of interest to investigate the antidiabetic and obesity potential of Resveratrol on humans. This warrants further research and determines the necessity for more studies in this area.

Anti-aging activity:

Caloric restriction has been proven to extend the lifespan of a number of species, including mammals. In recent studies have been reported that resveratrol shifts the physiology of middle-aged mice on high-calorie diet towards that of mice on standard diet and significantly increases their survival. It have been shown that obese animals whose diet was supplemented with resveratrol not only lived longer, but were more active and produced fewer cases of the negative effects of a high-calorie diet. In addition also a reduced insulin-like growth factor-1 levels, increased number of mitochondria, and improved motor function have also been observed.[17] However, human studies are still in the initial stages and therefore further

studies are needed in order to be able to determine the anti-aging activity of resveratrol.

Anti-inflammatory effects:

In view of their anti-inflammatory and antioxidant abilities and their capacity to modulate important inflammatory and anti-inflammatory signaling pathways, glucocorticoid efficacy, polyphenols and flavonoids hold great promise as potential therapeutic strategies for controlling lung inflammation and related diseases. In fact, polyphenols and flavonoids may be perceived as future pharmacological agents and may be used as antioxidant and anti-inflammatory enforcements to combat oxidative challenges.[16]

It has been demonstrated, that grape and wine polyphenol resveratrol confers cardiovascular benefits, in part by exerting anti-inflammatory effects. However, the evidence in human long-term clinical trials has yet to be established. In an investigation of the effects of a dietary resveratrol-rich grape supplement on the inflammatory and fibrinolytic status of subjects at high risk of cardiovascular disease has been determined, that 1-year consumption of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic status in patients who were on statins for primary prevention of cardiovascular disease and at high cardiovascular disease risk.[53] These results are in a good agreement with the current guidelines for primary prevention of cardiovascular disease.

In addition, resveratrol is reported to inhibit inflammatory processes, inflammatory-related gene expression and attenuates monocyte adhesiveness to endothelial cells.[13] Thus it may be considered as an important agent in the search for complementary treatments and prevention of inflammation and cardiovascular disease.

Psychological effects:

Depression:

Depression and other mood affective disorders can be chronic, life threatening, and are widespread throughout the population. A wide number of natural or traditional Asian medicines have been investigated as potential anti-depressants or general neuo-protectants. Among the most popular have been polyphenols such as curcumin,[54] fisetin,[55] and resveratrol.[56, 57] Based on literary data for a possible mechanism of mood regulation it has been established, that resveratrol interacts with hippocampal neurotrophic factors, which suggests its potential usefulness in treatment of resistant depression. However no sufficient evidence has been provided that resveratrol alone might be able to fully normalize the depressive characteristics. In this regard possible additive or synergistic effects of resveratrol with other antidepressants should be investigated.[58]

Neuroprotective activity:

Neural dysfunction and metabolic imbalances underlie many progressive neurodegenerative conditions such as Alzheimer's, Huntington's and Parkinson's diseases.[59] Resveratrol is capable of penetrating the blood–brain barrier and exerts strong neuroprotective effects, even at low doses. Resveratrol has been shown to combat the neuronal dysfunction caused in Huntington's and Alzheimer's diseases. In a recent study has been determined, that neither resveratrol nor its conjugated metabolites are detectable in the brain.[60] Nevertheless, resveratrol diminished plaque formation in a region specific manner. Based on this the concept has been accepted, that onset of neurodegenerative disease may be delayed or mitigated with the use of dietary chemo-preventive agents that protect against β-amyloid plaque formation and oxidative damage.[16]

Cancer effects:

The search for novel and effective cancer chemopreventive agents has led to the identification of various naturally occurring compounds one of which is resveratrol. Resveratrol is known to have potent anti-inflammatory and antioxidant effects and to inhibit platelet aggregation and the growth of a variety of cancer cells. Its potential chemopreventive and chemotherapeutic activities have been demonstrated in all three stages of carcinogenesis (initiation, promotion, and progression), in both chemically and UVB-induced skin carcinogenesis in mice, as well as in various murine models of human cancers. Evidence from numerous *in vitro* and *in vivo* studies has confirmed its ability to modulate various targets and signaling pathways.[14]

However given the multiple effects of resveratrol and the relatively low dose of resveratrol obtained from red wine or other dietary sources, its health benefit may lie in synergistic combinations with other agents. Resveratrol is shown to have a synergistic effect *in vitro* with both quercetin and ellagic acid for apoptosis.[61]

On the other hand the strongest evidence of anticancer action of resveratrol exists for tumors it can contact directly, such as skin and gastrointestinal tract tumors. For other cancers, the evidence is uncertain, even if massive doses of resveratrol are used. It has been found, that Resveratrol treatment appeared to prevent the development of mammary tumors in animal models; however, it had no effect on the growth of existing tumors. Paradoxically, treatment of prepubertal mice with high doses of resveratrol enhanced formation of tumors.[62]

Some animal and human studies have indicated that this polyphenol has low oral bioavailability,[63-65] which may prevent the compound from reaching the target site at therapeutic concentrations *in vivo*. This limitation has been attributed, at least in part, to incomplete intestinal absorption, extensive intestinal metabolism and the activity of ATP-binding cassette (ABC) transporters.[66, 67] That is, once consumed orally, trans-resveratrol enters the enterocyte by passive diffusion, where it is extensively metabolized and its conjugates are secreted back to the intestinal lumen by the members of the ABC family, the Multidrug Resistance Protein 2 (MRP2) and Breast Cancer Resistance Protein (BCRP).[67] All these processes increase the amount of *trans*-resveratrol and its metabolites reaching the large intestine, thus contributing to its potential chemopreventive activity in colon cancer.[68]

In conclusion resveratrol has been found to inhibit the proliferation of a variety of human cancer cell lines, including those from breast, prostate, stomach, colon, pancreatic and thyroid cancers when added to cells cultured outside the body. Inhibition in the development of esophageal, intestinal, and breast cancer with oral administration of resveratrol has been marked in animal models. Some studies suggest that even very high dietary intakes of resveratrol may not result in tissue levels that are high enough to demonstrate the protective effects that resveratrol has shown in cell culture studies. So it is currently unclear whether or not high intakes of resveratrol can help prevent cancer in humans.

Based on the above presented data and given the fact that polyphenols undergo considerable degree of chemical modifications during digestion and absorption and that the modified forms may have altered biological properties and potencies, it is extremely important to practice caution before claiming any definite pharmacological applications for these compounds. Moreover, despite their beneficial health effects, polyphenols have also been shown to have adverse effects too.

Adverse effects:

Resveratrol appears to be well-tolerated by rats continuously at dosages up to 100mg/kg bodyweight,[61] 400mg/kg bodyweight, and no adverse effects have been noted at 750mg/kg bodyweight *trans*-resveratrol.[69] Some adverse effects were noted in animals at 300mg/kg bodyweight, but may have been reflected of increased absorption kinetics by gavage feeding.[70] This may be of a concern to micronized resveratrol (with enhanced absorption) if taken in similar dosages.

The No Observable Adverse Effect Limit (NOAEL) of resveratrol appears to be 200mg/kg bodyweight in rats and 600mg/kg bodyweight in beagle dogs.[71]

In humans, up to 5g have been taken with no side effects outside of some intestinal upset[72] and nausea.[73] Micronization of resveratrol at this dosage showed the severity of symptoms decrease, indicating that nausea and intestinal upset are caused by resveratrol's poor bioavailability.[73]

Estrogenic effects:

Resveratrol, subsequently considered a phytoestrogen due to potent estrogenic and even superestrogenic (when combined with E_2) properties in MCF-7 mammary cancer cells,[74] has shown both estrogen agonist and estrogen antagonist effects in cell culture studies. Based on

the similar chemical structure to synthetic estrogen agonists, resveratrol has been established to express estrogen agonistic activity by simulating the effects of endogenous estrogens.[75] Additional studies demonstrated some antagonist activity of resveratrol. It is believed, that these antagonistic effects are due to the fact that it binds to receptor sites, blocking the effects of the hormone.[76] Thus it has been reported that resveratrol function as a mixed agonist/antagonist with ER-transfected cell lines.[76-78]

Pregnancy effects:

Citing the evidence that resveratrol is estrogen antagonistic, some retailers of resveratrol advise that the compound may interfere with oral contraceptives and that women who are pregnant or intending to become pregnant should not use the product, while others advise that resveratrol should not be taken by children or young adults under eighteen, as no studies have shown how it affects their natural development.

However harmful properties of resveratrol may be pronounced in the human fetus, as it has diminished detoxification systems. Therefore, resveratrol as commonly sold combined with other "bioflavonoids", should not be used by pregnant women.[79]

Potential carcinogenicity:

Resveratrol in common with other polyphenols, was found to be a strong topoisomerase inhibitor, sharing similarities to chemotherapeutic anticancer drugs, such as etoposide and doxorubicin.[80, 81] This may simultaneously contribute to both the potential anticarcinogenic and carcinogenic properties of the substance in given circumstances.

Drug interactions:

Resveratrol is well tolerated in healthy subjects without any comedication. However, supplemental doses of resveratrol in the range of 1 g/day or above by far exceed the natural intake through food. Whether resveratrol-drug interactions can be harmful in patients taking additional medications remains unknown. Recent *in vivo* studies and clinical trials indicate a possible drug-drug interaction potential using high-dosage formulations. The known *in vitro* and *in vivo* effects of resveratrol on various cytochrome P450 (CYP) isoenzymes are summarized and discussed in relation to clinically relevant plasma concentrations in humans. It has been concluded that resveratrol may lead to interactions with various CYPs, especially when taken in high doses. Aside from systemic CYP inhibition, intestinal interactions must also be considered. They can potentially lead to reduced first-pass metabolism, resulting in higher systemic exposure to certain coadministrated CYP substrates. Therefore, patients who ingest high doses of this food supplement combined with additional medications may be at risk of experiencing clinically relevant drug-drug interactions.[82]

Resveratrol may interact with several medications. The Linus Pauling Institute reports that resveratrol may inhibit cytochrome 3A4, which may cause interactions with HMG-CoA reductase inhibitors, calcium channel agonists, anti-arrhthmic agents, HIV protease inhibitors, immunosuppressants, antihistamines, and erectile dysfunction medications. In addition, the natural blood pressure-lowering and anti-coagulant effects of resveratrol may cause interaction with blood pressure, anti-platelet, and anticoagulant medication, as well as NSAIDs such as aspirin and ibuprofen.

Gastrointestinal effects:

Although rare, anecdotal gastrointestinal side effects have been reported by resveratrol users. Stomach upset and cramping, diarrhea, and/or decreased appetite may occur with large doses of resveratrol. Dietary supplements affect each individual differently, so some may be more susceptible to digestive side effects than others. In humans, up to 5g have been taken with no side effects outside of some intestinal upset [72] and nausea.[73] Low systemic availability of the parent compound due to rapid and extensive metabolism may confound its usefulness as a potential agent to prevent malignancies in organs remote from the site of absorption.

Micronization of resveratrol at this dosage showed the severity of symptoms decrease, indicating that nausea and intestinal upset are caused by resveratrol's poor bioavailability.[73]

Painful joints:

Resveratrol has been shown to have natural anti-inflammatory effects in the body, according to the Life Extension Foundation. By inhibiting COX enzymes that cause inflammation on a cellular level, resveratrol should theoretically help with conditions such as osteoarthritis.[83] However, some people have reported joint pain and tendinitis with resveratrol use. Commonly affecting the Achilles tendon, resveratrol has also caused joint pain in other areas, sometimes accompanied by tingling and/or numbness in arms, legs, hands and feet. One of the reasons for this side effect may be the fact, that Resveratrol causes lower estrogen levels in the body, which is a normal symptom of joint pain.[84] Another possibility is the fact that some data suggest that resveratrol may act as an aromatase inhibitor.[85] Joint pain is often experienced by women treated with aromatase inhibitors[86] and also by menopausal/post-menopausal women not taking hormone replacement therapy to replace deficient estrogen.

Recent research studies on resveratrol and its beneficial or harmful effects:

The anti-influenza virus activities of resveratrol derivatives were evaluated using a neuraminidase activity assay. The results demonstrated that the resveratrol derivatives might have a direct effect on viral particle infectivity. It was indicated that the analyzed structures are potentially useful antiviral compounds for new drug design and development for influenza treatment.[87]

The AhR antagonists are of interest for the development of prophylactic as well as curative drugs for major diseases involving AhR activation, such as cancers, atherosclerosis, osteoporosis, skin disorders, and reproductive failures. Based on this some studies have been carried out on stilbene derivatives of resveratrol for their affinity to aryl hydrocarbon receptor (AhR). These studies revealed that the hydrophobic and structural parameters, like the presence of *trans*-geometry in the molecule, positively contribute to AhR activity, which is a premise for increased AhR affinity from the ligand.[88]

The prevalence of metabolic syndrome associated with increased risk for cardiovascular disease, type 2 diabetes, or cancer has been increasing over the past decade.[89, 90] While traditional drug discovery efforts have been tackling these diseases by aiming at individual targets, recent studies in humans have suggested the possibility that the collection of the metabolic degenerative processes can be approached as a whole by controlling diet, especially calorie restriction. Thus much interest in developing pharmacological agents that mimic the effects of calorie restriction arose. Resveratrol, a natural product derived from grapes, is the first reported mimetic of calorie restriction.[91]

Ever since the mode of action of resveratrol was elucidated to activate SIRT1 [sirtuin (silent mating type information regulation 2 homolog) 1] which, in turn, deacetylates p53 and promotes cell survival in a NAD+-dependent manner,[91] numerous efforts have been devoted to discover novel activators of SIRT1. For this reason it has been often used as an initial parameter in the search for new structurally unrelated but more active SIRT1 activators.[92]

Thus from the above presented data may be drawn the following reasons why recommending a population-wide increase of resveratrol usage would be premature:

1. Little is known about the absorption and clearance of resveratrol, the identities of its metabolic products, or its effects on the liver;
2. The research on resveratrol has focused on its short-term effects and has been dominated by *in vitro* studies on non-human models;
3. Its role as a potentiator of breast carcinomas may significantly limit its use, even for its proven benefits;
4. Its main dietary source is red wine, which is not only extremely variable, but possibly harmful to be recommending increased intakes of red wine to the population at this point;
5. In older community-dwelling adults, total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, or cancer or predictive of all-cause mortality. Resveratrol levels achieved with a Western diet did not have a substantial influence on health status and mortality risk of the population.[93]

CONCLUSION: Given the fact that polyphenols undergo considerable degree of chemical modifications during digestion and absorption and that the modified forms may have altered biological properties and potencies, it is extremely important to practice caution before claiming any definite pharmacological applications for these compounds. Moreover, despite their beneficial health effects, polyphenols have also been shown to have adverse effects too.

It is difficult presently to determine if resveratrol may be associated with any additional serious adverse events in humans since there exists only sparse clinical trial data to date. Although the findings thus far, and as summarized in this report appears promising, it is necessary to reiterate that these data derive from cell culture or small animal model systems, with no reports on long-term health or survival in humans or alternate animal models. Thus, the overwhelming consensus from the community is that continued investigation is certainly warranted, but the field needs a more concerted effort directed at establishing a viable translational research strategy, including additional preclinical studies in large animal models such as swine, in order to properly understand and evaluate the biological mechanisms, safety and efficacy of resveratrol and any future potential health benefits it may have in humans.

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How to cite this article:
Georgieva M, Valkova I, Zlatkov B, Andonova L and Zlatkov A: Resveratrol: Recommending Its Wide Increase – A Premature Decision or Not? A Review. Int J Pharm Sci Res 2015; 6(9): 3641-53.doi: 10.13040/IJPSR.0975-8232.6(9).3641-53.