Resveratrol: A therapeutic promise in cancer treatment

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INTRODUCTION

Resveratrol (3,5,4-trihydroxystilbene) is a naturally occurring triphenolic phytoalexin; that mainly exists in cis- and trans- configurations. However, trans-configuration is most commonly used isomeric form due to its greater anticancer and cardiovascular-protective properties than cis-form. It is found in a wide variety of plant species such as grapes, plums, berries and peanuts, and synthesized by plants under stress conditions such as bacterial or fungal infection, UV radiation and exposure to ozone. It is found in considerable amount in red wine as the grape skins are fermented in production of red wine (1).

The first mention of resveratrol was in 1939 in a Japanese article by Michio Takaoka, who isolated it from the poisonous, but medicinal, Veratrum album, variety grandiflorum (2). This name comes from the fact that it is a resorcinol derivative coming from a Veratrum species. Humans have been exposed to resveratrol since ancient times. Approximately 4500 years ago, Ayurveda, ancient medicinal book described “Darakchasava” (fermented juice of red grapes) as a heart tonic (3). More than 100 formulations of resveratrol are available in market. These are mostly available in the form of tablets and capsules. These formulations are marketed as nutritional supplement.

PHARMACOKINETICS

Several in vitro and in vivo studies have helped to clarify the pharmacokinetic characteristics of resveratrol. The in vivo fate of resveratrol following oral administration has been reconstituted based on miscellaneous data obtained in vitro on cell cultures, ex vivo on isolated small intestine models, and in vivo in animals and humans. When trans-form is exposed to ultraviolet irradiation it undergoesomerization (4). Trans-resveratrol was found to be stable under “accelerated stability” conditions of 75% humidity and 40°C in the presence of air in powdered form (5). The absorption of trans-resveratrol in intestine has been studied in vivo in rats using a perfusion method (6). A nutritionally relevant concentration of 25 μmol/L of trans-resveratrol was used to evaluate the absorption across the jejunum. Nearly 72% of the luminaly perfused polyphenol disappeared from the buffer after 30 min, indicating that there was an efficient uptake of this drug. At the same time, the result showed that trans-resveratrol was efficiently conjugated inside the enterocyte with glucuronic acid by UDPglucuronosyltransferase or with sulfate by sulfotransferase, 42% and 12%, respectively, were subsequently pumped back to the luminal side.

The kinetic study of trans-resveratrol was also performed in jejunal and ileal loops perfused with increasing concentrations of resveratrol. The transport rates of the unconjugated polyphenol were directly proportional to the initially applied trans-resveratrol, indicating that the uptake occurs by simple diffusion, without the participation of a mediated transport (6). In a study, Burkon and Somoza showed that more than 90% of free resveratrol was bound to human plasma and that 50% of the plasma trans-resveratrol-3-sulfate, transresveratrol-disulfates and the novel trans-resveratrol-C/O diglucuronides were bound to proteins. The results confirmed the interaction of resveratrol with albumin. Urpiarda et al. reported that resveratrol and its metabolites were recovered in the low density lipoprotein fraction of healthy volunteers after consumption of 250 ml of Merlot wine (7). The results of this investigation confirmed binding of resveratrol to low density lipoprotein. Bertelli’s team described the intestinal metabolism of resveratrol in vivo in rodent model (8).

They measured its absorption in rats by administering red wine with known concentration of resveratrol (6.5 mg/l). The results described that resveratrol was quickly absorbed, reaching its peak concentration approximately 60 min after wine ingestion, with initial concentrations found after 30 min. Further in a study Walle et al., showed that rapid absorption of resveratrol takes place as early as 15 min post-administration and reaching peak concentrations after
30 min (9). The identification of metabolites of resveratrol indicates that trans-resveratrol-3-O-glucuronide and transresveratrol-3-sulfate are the most abundant metabolites, while virtually no unconjugated resveratrol was detected in urine or serum samples of rodents. The sulfation of resveratrol was confirmed in human duodenum samples (10). In 2000, De Santi et al. studied in vitro sulfation and glucuronidation in human liver samples and revealed that resveratrol is a good substrate for human hepatic sulfotransferase and glucuronosyl transferase. Investigations of resveratrol metabolism in vivo in rodent models confirmed that the liver is a major accumulation site for resveratrol and its metabolites, although it is not yet known if accumulation of resveratrol metabolites in the liver takes place due to resveratrol metabolism in the small intestine and its subsequent absorption, or to in situ metabolism (58).

Excretion of the non-absorbed fraction in isolated perfused rat small intestine represents 40% of free resveratrol, 11% of glucuronide and 3% of sulfate conjugates. Renal excretion is the major route of elimination in animals and humans (11). Total excretion in urine and faeces after oral administration in humans was found to be 71 to 98% (vs. 54–91% after i.v. dose). Renal excretion varied from 53–85% in healthy volunteers with doses of 1 to 0.5 mg/kg, while faecal excretion ranged between 3.3 to 35%.. More recently, the role of microbiota in the intestinal degradation of resveratrol was suggested to explain the urinary excretion of polar metabolites subsequent to bacterial degradation and further enteric absorption (12). Bioavailability Regardless of promising results of the absorption, the clinical use of resveratrol has met only limited success, due to poor bioavailability of resveratrol particularly after its oral administration. It has been observed that only trace amounts (below 5 ng/ml) of unchanged resveratrol could be detected in the blood after 25 mg of oral dose [13]. Resveratrol also has a short initial half-life (8—14 min) and is highly metabolized due to extensive hepatic glucuronidation and sulfation (14). Even when large dose (2.5 and 5 g) was given as an uncoated pill, resveratrol failed to reach the desired concentration level in the blood that is necessary for systemic anticancer effect (15).

**THERAPEUTIC EFFECTS**

Scientific evidence shows that resveratrol has a wide range of desirable biological effects. It is effective on many diseases and ailments. Many studies also have demonstrated that trans-resveratrol has a strong cancer chemoprotective activity and can block initiation, promotion and progression stages of carcinogenesis. It also possesses several other biological activities including antioxidant, antimicrobial, antiinflammatory, diabetes, antiplatelet, anti-peroxidation effects, and neurodegenerative diseases such as parkinson’s disease and alzheimer’s disease (16). It has ability to block each step in the carcinogenesis process by inhibiting several molecular targets such as kinases, cyclooxygenases, ribonucleotide reductase, and DNA polymerases (1, 17). Resveratrol is supposed to be responsible for the "French Paradox" that associates red wine consumption to the low incidence of cardiovascular diseases, probably due to antioxidant properties of trans-resveratrol present in many wines (18). It protects the cardiovascular system by a large number of mechanisms that includes defense against ischemic-reperfusion injury, promotion of vasorelaxation, protection and maintenance of intact endothelium, antiatherosclerotic properties, inhibition of low-density lipoprotein oxidation, suppression of platelet aggregation, and estrogenlike actions (1).

The phenolic nature of resveratrol explains its antioxidant effect. It provides health-promoting benefits such as lowering the incidence of coronary heart disease, and to possess cancer chemoprotective activity and strogenic activity with varying degrees of estrogen receptor agonism, due to its similarity in structure with the synthetic estrogen diethylstilbestrol. Resveratrol has been described to interfere with the arachidonate metabolism by reducing the levels of leukotrienes generated by the lipoxygenase pathway and prostaglandins generated by the cyclooxygenase pathway (19). It shows substantial protection against skin damage from ultraviolet B exposure (20, 21), antimicrobial activity against dermatophytes and herpes simplex virus, and can also be used in the dermocosmetic field because of its role as a phytoestrogen which based on its ability to activate estrogen receptors (22, 23, 24). Evidence suggests that regular wine consumption alleviates perimenopausal symptoms and protects against osteoporosis due to binding with estrogen receptor. Resveratrol has been shown to facilitate the breakdown of beta-amyloid, which is associated with Alzheimer’s disease, via specific mechanisms unrelated to antioxidant effects, (25) and to protect against beta-amyloid toxicity in vitro (26).

Mitogenactivated protein enzymes (MAP kinases), which are active in learning and memory centers of the brain, are up-regulated by resveratrol in neural tissues (27). Resveratrol also activates Neuronal AMP kinases (28). Another potentially important mechanism that is Chapter 1 Introduction Poly (D.L-lactide-co-glycolide) Based Nanoparticles for Improved Delivery of Resveratrol 14 common to both resveratrol supplementation and caloric restriction is the
modulation of autophagy (29). SIRT1 is a hypothesized target of both resveratrol and caloric restriction therefore has been shown to facilitate autophagy by the inhibition of mTOR, which itself negatively regulates autophagy (30). Not only cytokines, but also ROS (Reactive oxygen species) from microglia, are involved in ischemic brain damage and microglia activation. Resveratrol reduces ROS production and microglial activation in the ischemic brain (31).

Adverse effects

A recent phase I clinical trial demonstrated that consumption of even 5000 mg of resveratrol does not cause any serious adverse effects in healthy volunteers, but the peak plasma level remains much below than the minimum required concentration to exert either chemo preventive or chemotherapeutic effect on cultured cells (32).

Limitations (14, 15)

- Low aqueous solubility which is just 0.03 μg/ml.
- Susceptible to enzymatic degradation in stomach and intestine.
- Highly photosensitive.
- Highly metabolized in body due to extensive hepatic glucuronidation and sulfation.
- Less than 1% oral bioavailability.
- Short half-life (i.e. 8—14 min only).

REFERENCES


