Resveratrol (3,5,4'-trihydroxystilbene) and its properties in oral diseases (Review)

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Received August 30, 2016; Accepted December 19, 2016

DOI: 10.3892/etm.2017.4472

Abstract. Health promotion strategies and lifestyle changes are important in disease prevention. Oral health has received a large amount of attention previously as it is a fundamental component of general health and it contributes to the quality of life. Therefore, the study of associations between diet, health and the presence of bioactive compounds in food is receiving a substantial amount of attention. In the present review the effects and targets of a natural polyohenolic stilbenoid compound; resveratrol (3,5,4'-trihydroxystilbene; RSV) is assessed, and the future prospects for RSV in promoting oral health are considered. RSV is a phytoalexin, synthesized by a wide range of plants and abundantly extracted in grape skin, it has been purported to exert a multiplicity of anti-inflammatory, anti-viral, anti-microbial, estrogenic, anticancer, cardioprotective, neuro-protective and immunomodulatory functions. In this review, following an introduction documenting the biochemistry of RSV and RSV glucosides, the bioavailability and pharmacokinetics of RSV are described. Considering its multiple properties, the present review has focused on the potential benefits of RSV as an antioxidant and chemopreventive agent.

Contents

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Key words: resveratrol, oral squamous cell carcinoma, chemoprevention, oral disease, oxidative stress

1. Introduction

The importance of preventing lifestyle-related diseases including heart disease, cerebrovascular disease, diabetes and cancer has been increasing. In particular, the Global Oral Health Programme of the World Health Organization (WHO) has prompted worldwide vigilance of oral health as it is a matter of considerable importance for general health and quality of life (1,2). Considerable attention has been given to the effective use of fluoride (3), controlling tobacco use (4), oral health at each age, from children to the elderly (5) and healthy diet and nutrition (6,7).

In order to prevent oral diseases, early detection and diagnosis is vital. As there is a potential link between poor oral health and chronic disease, it is important to integrate the prevention of oral diseases with general health promotion to enable the prevention of chronic diseases and improve oral health. Oral diseases affect a large proportion of individuals, for example oral cancer is the 8th most commonly diagnosed cancer in the world and its incidence ranges from one to 10 cases per 100,000 people globally (8). Therefore, a major priority is to establish innovative health promotion strategies by developing novel beneficial agents capable of improving the prevention of oral diseases, for example by integration of oral health into public health programmes or by supportive school policies. The physical environment and skills-based health education are essential in maintaining oral health and reducing risk factors (2).

The study of associations between diet, health and the presence of bioactive compounds in foods has previously received attention. A large number of natural substances, including curcumin (9), quercetin, genistein (10) and epigallocatechin-3-gallate (11) have been identified, which may provide safe, non-toxic alternative pharmacological treatments to prevent the onset of oral diseases. Nutraceutical substances may be used either as individual compounds in their natural form (isolated from matrixes of plant origin) or obtained from chemical synthesis and used alone, or in combination with alternative therapeutic agents, such as phytochemical compounds (10,12).

Traditional Chinese medicine has purported a wide range of remedies made from herbs rich in polyphenols,

including Radix Curcumae formula to treat cardiovascular disease (13) and Yi Shen Juan Bi Tablets to treat rheumatoid arthritis (14), which are responsible not only for providing therapy for specific diseases but also for improving general health (15). The scientific evidence accumulated over the past 20 years has suggested that resveratrol (RSV), a natural polyphenolic compound, exhibits a number of pharmacological activities (16,17) with beneficial health effects. Evidence has indicated that RSV is involved in the modulation of numerous cell-signaling pathways (18,19), thus exerting a variety of antioxidant (20), anti-inflammatory (21), anti-viral, anti-microbial, estrogenic (22), anticancer (23,24), cardioprotective (25), neuroprotective (26) and immunomodulatory (27) functions. The potential beneficial effects of RSV have been linked with a wide variety of chronic diseases, including cancer and the analogues of RSV (28-30) are being investigated specifically as chemopreventive agents in humans (31). RSV has also been linked with cardiovascular diseases (32), skin disorders (33), diabetes (34), arthritis (35), neurological diseases (36) and the aging process (37).

The current review focused on the anticancer effects of RSV assessed *in vivo* and *in vitro* in addition to clinical trials, concentrating on the beneficial effects exerted on oral cancer, specifically the squamous cell carcinoma type that makes up ~90% of oral cancer diagnosed.

2. Biochemistry of RSV and RSV glucosides

RSV is a polyphenolic compound that functionally acts as a phytoalexin and is identified in nature as both cis and trans isomers (Fig. 1). RSV is synthesized by plants as a defense mechanism in response to bacterial or fungal infection (17) and stress factors (such as UV irradiation or ozone exposure (38,39). RSV is synthesized through stilbene synthase by three different condensation reactions between three molecules of malonyl-coenzime A and one molecule of coumaroyl-coenzyme A (40). RSV is naturally occurring in >70 different plant species, such as *Polygonum cuspidatum* (41), eucalyptus (42) and *Picea excelsa* (43), and fruit species, including mulberries, raspberries, pines, peanuts, blueberries and grapes (44). Although these plants and their extracts have been used for various therapeutic purposes by traditional Chinese and Japanese medicine, RSV itself was first isolated in 1940 (45) from the roots of the medicinal herb hellebore (*Veratrum grandiflorum*) (46) and it was identified as a component of wine in 1992 (47,48) However, this compound exists in numerous foods and beverages consumed daily, including cocoa (49), grapes (50) and red wine (51). Red wine, the most notable dietary source of RSV (52), has received special attention and in 1992 an epidemiological study demonstrated a potential correlation between incidence of cardiovascular disease and the consumption of red wine, observed in Mediterranean populations (48).

RSV is composed of two phenol rings, linked by a styrene double bond to generate 3,4',5-trihydroxystilbene. Different conjugate forms of this compound have been detected in plants and trans-resveratrol exists in glycosylated form; trans-isomer is sterically a more stable form and for this reason is considered to be the most abundant form (53). Isomerization is facilitated by UV, light and pH, therefore trans-resveratrol is rapidly converted into cis-resveratrol by visible light, high temperatures or low pH (54).

RSV has a high number of analogues and derivatives, differing in terms of type, number and position of substituents (hydroxyl, methoxyl, halogenated, glycosylated, esterified), the presence of stilbenic double bonds, modified steroisomery and oxidative dimerizations (to form oligomers) (16). Additionally, a number of studies indicate that certain resveratrol analogues and derivatives have pharmacological properties, such as apoptotic and antioxidant activities (55) and chemopreventive effects (56).

A number of RSV derivatives have been identified in the roots of *Poligonum cuspidatum* including piceid 2 (3-O-b-d-glucosyl-resveratrol), resveratroloside 3 (4'-O-b-d-glucosylresveratrol), piceatannol 4 (3,5,3',4'-tetra-O-hydroxyestilbene) and its glucosylated derivative 5 (4'-O-b-dglucosyl-piceatannol) (57). Polyphenols are hydrophobic scaffolds exhibiting poor absorption and solubility, resulting in the very short half-life of RSV in the circulatory system (58). Presence of the glycosylated form of RSV is considered to improve physicochemical properties, such as solubility and partition coefficient in order to facilitate the entry of polyphenols into enterocytes (59) and improve bioavailability (60).

In grapes and wine, RSV has been identified as a free-species and in glycosylated form. In particular, piceid (resveratrol-3-O-beta-D-glucoside, also called polydatin) is a glucoside of RSV in which the hydroxyl group in the C-3 position is substituted by a glycoside group, a hydroxyl group substitute (61). The substitution of the glycosidic group leads to conformational changes occurring in the polydatin that are reflected in changes to the biological properties, greater bioavailability and a higher stability. The piceid maintains the antioxidant properties and the hydroxyl group at C-3, which in this compound is replaced by glycosidic group, is less reactive in regards to the activity of scavenging, undertaken by the hydroxyl group at C-4 that remains unchanged in polydatin (62). The piceid retains the biological activity of resveratrol but has a number of advantages over RSV in drug research: Polydatins are more resistant to enzymatic oxidation than RSV, penetrate the cell via an active carrier mechanism using glucose carrier and due to its solubility in water, it is absorbed from the intestine with greater efficiency (63,64).

3. Bioavailability and pharmacokinetics

The beneficial properties of RSV have been extensively investigated in the literature with studies *in vitro* (65) and *in vivo* (66); however, there is limited understanding regarding the pharmacokinetics of RSV. A number of studies in animals and humans (46) have demonstrated that unconjugated RSV has a poor *in vivo* bioavailability, due to its extremely rapid metabolism to glucuronide and sulphate derivatives in the liver and intestine (67). The plasma concentration of RSV and its metabolites depend on the dose administered. Marier *et al* (68) have shown that trans-resveratrol in in its aglycone and glucuronide forms exhibited increases in plasma concentrations 4-8 h after oral administration, with terminal elimination half-life of 1.48 and 1.58 h, respectively. Trans-resveratrol in its aglycone form has 38% bioavailability and its exposure was approximately 46-fold lower than that of the glucuronide

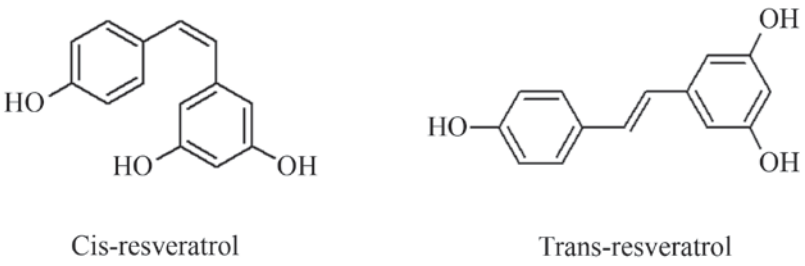

Figure 1. Resveratrol isomers.

form (The area under the curve extrapolated to infinity is 7.1 vs. 324.7 μmol·h/l). Due to its poor water solubility (69) RSV requires binding with serum proteins (70); however, it is able to passively diffuse through the plasma membrane (71). Although there is considerable inter-individual variability, five distinct metabolites may be detected in the urine following the moderate consumption of red wine: Resveratrol monosulfate, two isomeric forms of resveratrol monoglucuronide, dihydroresveratrol monosulfate and dihydroresveratrol (72). Further studies of the activity of its metabolites are required to understand the *in vivo* concentrations of different metabolites from ingested RSV that may be much higher than the concentration of RSV itself.

In vitro glycosylation of natural products is successfully employed to improve physicochemical properties such as solubility and partition coefficient (43,47). Glucosylated polyphenols, are initially deglycosylated at the intestinal wall prior to diffusing into the cells. Following absorption, polyphenol aglycones are conjugated with glucuronic acid or sulphate in the intestinal enterocytes and the liver (72). The presence of a mixture of glucosylated compounds may be of note in terms of the absorption of RSV at the intestinal wall when they are orally administered.

Biasutto *et al* (58) observed that glucosyl groups, added to RSV via a succinate linker, enhanced the bioavailability of RSV. This suggested that the administration of a combination of the aglycone (RSV) and its glycosylated derivative may produce a long-lasting increase in circulating levels of the polyphenols and its metabolites. RSV interacts with a high affinity with albumin and this binding may have a crucial role in improving the distribution of RSV in different body tissues and organs (70). The adsorption and distribution of RSV in organs such as the heart, liver and kidney following oral administration were described for the first time in 1996, by sub-ministration of a daily dose of 6.5 mg/l resveratrol to two different groups of rats (73), and have more recently been confirmed (in the liver, IC50 for the inhibition of resveratrol sulphation was 12±2 pM quercetin, 1.0±0.04 μM fisetin, 1.4±0.1 μM myricetin, 2.2±0.1 μM kaempferol and 2.8±0.2 μM apigenin) (74,75) and extended to the bile, stomach and duodenum (76). To the best of our knowledge, bioavailability of RSV and RSV derivatives is yet to be elucidated.

At present, attention is being paid to novel techniques and proposals to promote the bioavailability of these molecules, such as microparticles (77), nanoparticles (78), microsphere (79), microencapsulation (80) and nanoencapsulation (81). Evidence indicates that the reduction of particle size allows an increase in the contact surface, for example, trans-resveratrol is the most commonly used isomeric form due to its numerous health benefits, even though it has poor bioavailability due to low aqueous solubility and slow dissolution rate. However, these parameters increase following treatments to reduce the particle size (82).

With regards to toxicity it has been demonstrated that, unless extremely high doses are administered, there are no signs of toxicity following treatment with RSV. Animal models exhibited no adverse effects following 28 days of RSV administration at 1,000-fold the levels of RSV present in red wine (83).

4. Resveratrol as a potent antioxidant

Previous results have indicated that resveratrol is a free radical scavenger and potent antioxidant, counteracting the oxidative stress that is considered to be associated with the etiology and progression of multiple chronic and acute diseases (84). In clinical studies, oxidative stress has been associated with a number of degenerative diseases including atherosclerosis, cancer, asthma, hyperoxia, arthritis, dermatitis (85,86) and inflammatory conditions (87).

Reactive Oxygen Species (ROS), such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), are by-products of normal aerobic metabolism, which at low levels are fundamental in cell signaling processes (88), including cell proliferation, apoptosis or necrosis, induction or suppression of gene expression. Exogenous factors may cause ROS generation and an imbalance in their production may have negative effects on biomolecules, thus altering normal cell function (89). It has been indicated that ROS are able to induce proliferation, senescence, necrosis, apoptosis or cell death (89). At higher concentrations, ROS induces apoptosis, mediating the post-translational modifications of p53 and altering mitochondrial membrane permeability and apoptotic DNA fragmentation (90). RSV appears to provide protection against DNA damage caused by these ROS (84). Similar to the numerous plant polyphenols, RSV may also exhibit pro-oxidant properties, catalyzing cellular DNA degradation in the presence of transition metal ions (91) and mobilizing endogenous copper, such as chromatin bound copper (92).

The antioxidant system includes a number of antioxidant enzymes such as superoxide dismutase and catalase, non-enzymatic antioxidants such as reduced glutathione (GSH), protein-sulfhydryls and uric acid. It has been demonstrated that RSV significantly activates and prevents the oxidation of these endogenous antioxidant systems. RSV has been demonstrated to reduce the production of H_2O_2, and normalize the

level of oxidized glutathione reductase and myeloperoxidase activities (93).

In a 2004 study by Cao and Li (94) investigating the protective role of RSV in various oxidative cardiovascular disorders, it was determined that RSV increased the level of endogenous antioxidants and phase 2 enzymes in cardiomyocytes. These modifications contribute to the increased resistance of oxidative and electrophilic cardiac cell injury (94). Yen *et al* (95) indicated that RSV, in combination with 4-hexylresorcinol, may exert considerable protection against oxidative DNA damage in human lymphocytes induced by H_2O_2 through modulation of antioxidant enzymes (glutathione peroxidase, glutathione reductase, glutathione-S-transferase) and increased level of GSH, accepted as the most important intracellular hydrophilic antioxidant (96). Another study by Ates *et al* (97) focused on the potential neuroprotective role of RSV and confirmed that an increase in glutathione levels is due to the free-radical scavenging properties of RSV. In a time dependent study of the capacity of RSV to prevent the oxidation of GSH in red blood cells, it was demonstrated that incubating human erythrocytes with resveratrol (10 μM) caused a significant activation of the plasma membrane redox system (41%) and ascorbate free radical reductase (30%) compared with the control (basal level). Furthermore, it was determined that the accumulation of resveratrol inside the erythrocyte is ~89% and does not significantly change after 30 min (86).

Lipophilic properties of RSV may improve its antioxidant activity (98,99). In order to increase the evidence demonstrating the involvement of free radicals in numerous disorders and diseases including cancer (100), cardio-vascular diseases and neurological disorders, ageing (16,101,102) and lipid peroxidation, RSV has received increased attention. RSV appears to prevent oxidation of low-density lipoprotein (LDL) by chelating copper and scavenging ROS. Furthermore, a RSV-rich diet has been demonstrated to produce a measurable increase in plasma antioxidant level and decreased lipid peroxidation (103). It has also been reported that RSV reduces intracellular ROS and prevents LDL oxidation in endothelial cells (104).

In 2008, Dani *et al* (105) indicated that RSV has the ability to prevent lipid peroxidation and intracellular oxidation in *Saccharomyces cerevisiae*. Under conditions of oxidative stress in skeletal muscle, it has been determined that RSV is able to alter protein catabolism and muscle function (106).

It is important to note that the protective effects of RSV against lipids and peroxidation occur over a very short time frame (16,107-109). RSV is rapidly absorbed and its peak plasma concentration is achieved within 15-60 min of its administration (73,110).

5. Resveratrol as a chemopreventive

RSV is comprised of a number of polypheinolic compounds, including curcumin (111), rottlerin (112), genistein (113) and quercetin (114,115). RSV has been purported to be of potential use in cancer treatment and evidence indicates that it may inhibit pathways contributing to cell proliferation (116). Yu *et al* (117) demonstrated the inhibitory effect exhibited by RSV on the proliferation of oral squamous cell carcinoma cells through the induction of apoptosis and G2/M phase cell cycle arrest.

Oral submucous fibrosis (OSF) is a precancerous condition that affects the oral mucosa, which currently cannot be treated by specific therapeutic drugs. Moderate-to-severe OSF is irreversible and current treatment strategies include injections or topical application of steroids, oral subministration of lycopene (16 mg daily) and pentoxyfilline (400 mg 3 times daily) (16,118,119). A previous study demonstrated that RSV epigenetically inhibits Zinc finger E-Box binding homeobox 1 expression to suppress the myofibroblast activity of fibrotic buccal mucosal fibroblasts, and may serve as a dietary supplement for OSF patients (120).

Mohan *et al* (121) developed a drug combination of RSV and doxorubicin loaded in liposomal nanoparticles (78). Their evaluation *in vitro* was conducted on a squamous cell carcinoma cell line, NT8e. Their data indicated that the drug-loaded nanoparticle exerted apoptosis inducing effects by controlling the cell cycle and downstream apoptosis by inducing proteins such as caspase-3 and poly (ADP-ribose) polymerase 1.

A study by ElAttar and Virji (122) aimed to evaluate the chemopreventive properties of RSV on oral squamous cell carcinoma cell (SCC-5). The study calculated the average incorporation of ^{3}H-thymidine into nuclear DNA using a hemocytometer and demonstrated that RSV alone, or a combination of RSV and quercetin was able to effectively inhibit growth and proliferation.

Another study demonstrated that RSV inhibited matrix metalloproteinase-9 expression and metastasis in oral cancer cells (SCC-9) by downregulating the signaling pathways of c-Jun N-terminal kinase 1/2 and extra-cellular signal regulated kinase 1/2 signals, thus, exerting beneficial effects in chemoprevention (123).

6. Conclusions

Resveratrol is a promising nutraceutical for the treatment of cancer; however, the molecular mechanisms that explain the chemopreventive role of RSV remain unknown. Currently, there are numerous *in vitro* studies regarding the benefits of RSV as an anticancer agent (12,117,124,125). It is necessary to complete and confirm these effects using *in vivo* studies and clinical trials.

Finally, in order to resolve the primary problem associated with the poor bioavailability of RSV and its complicated pharmacokinetic profile, the development of specific nanotechnology and controlled and targeted-drug delivery systems are required.

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