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Advances in the Study of Oxyresveratrol

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Abstract: As a representative substance of stilbenes, oxyresveratrol has various kinds of biological activities including antineoplastic activity, antioxidant activity, tyrosinase inhibitory activity and ability of boosting the immune system. In this study, physical and chemical properties, extraction and separation, structural identification, medicinal activity and pharmacokinetics of oxyresveratrol and its derivatives were reviewed. Future perspectives and challenges involved in the use of oxyresveratrol were also very key discussed.

Key words: Oxyresveratrol, physical and chemical properties, extraction and separation, biological activities and pharmacokinetics, derivative

INTRODUCTION

Oxyresveratrol is a hydroxyl-substituted stilbene found in the roots, leaves, stem and fruit of many widely distributed plants including Moraceae, Liliaceae, Gnetaceae, etc., (Xiong *et al*., 2008; Ti *et al*., 2011) in China. The common representatives of plants harboring oxyresveratrol are *Smilax china* L. (Smilacaceae) (Xiong *et al*., 2008; Ruan *et al*., 2005; Huang *et al*., 2008a, b; Zhao *et al*., 2008; Huang *et al*., 2009a; Ban *et al*., 2006a, b; Ban *et al*., 2007; Jeon *et al*., 2007), *Morus alba* L. (Moraceae) (Zhang *et al*., 2009; Fu *et al*., 2005; Hu *et al*., 1996; Xu *et al*., 2009; Schultz *et al*., 1995; Andrabi *et al*., 2004; Qiu *et al*., 1996a; Lee *et al*., 2003; Djapic *et al*., 2003; Chung *et al*., 2003; Syah *et al*., 2004; Ferlinahayati *et al*., 2008; Shi *et al*., 2012), *Artocarpus heterophyllus* L. (Moraceae) (Fang *et al*., 2008; Chuanasa *et al*., 2008; Sasivimolphan *et al*., 2009; Likhitwitayawuid *et al*., 2005; Likhitwitayawuid *et al*., 2006a; Hakim *et al*., 2002; Maneechai *et al*., 2009; Qiao *et al*., 2011; Maneechai *et al*., 2012), *Veratrum nigrum* L. (Liliaceae) (Zhao *et al*., 2008) and *Scirpus maritimus* (Cyperaceae) (Powell *et al*., 1987). Oxyresveratrol can be transported to tissues at high rates and can result in a bioavailability of around 50% in plants (Qiu *et al*., 1996b). In addition, oxyresveratrol not only has a potent inhibitory effect on cyclooxygenase activity (Shin *et al*., 1998b), rat liver mitochondrial ATPase activity (Nimmanpisut *et al*., 1976) and dopa oxidase activity (Song *et al*., 2007) also possesses antitumor activity (Li *et al*., 2010; Mouihate *et al*., 2006), antiviral activity (Chuanasa *et al*., 2008; Sasivimolphan *et al*., 2009; Likhitwitayawuid *et al*., 2005; Lipipun *et al*., 2011; Galindo *et al*., 2011; Jagtap and Bapat, 2010) and neuroprotective activity (Horn *et al*., 2003; Breuer *et al*., 2006). According to recent studies (Song *et al*., 2007; Choi *et al*., 2004, 2006; Chun *et al*., 2009; Likhitwitayawuid *et al*., 2006b; Rodriguez-Bonilla *et al*., 2010; Han *et al*., 2007; Guengerich *et al*., 2003; Chun *et al*., 2001), oxyresveratrol derivatives have important and significant biological activities than itself. Thus, oxyresveratrol is a potential substance to be utilized to produce medicines, cosmetics and health supplements.

Resveratrol (3, 5, 4'-trihydroxysitlbene), a well-known representative of stilbene, is a phytoalexin used to improve the ability of plant against pathogens and against environmental deterioration. Due to the similar structure, oxyresveratrol may be an important plant natural substance with the same physiological functions. Now though oxyresveratrol have been found to possess a wide range of pharmacological properties and more and more to be of high value in promotion and utilization, no comprehensive report is available for this compound. In order to meet the needs of relevant intellectuals and other researchers, the following provides a detailed review of this particular hydroxystilbene.

CHARACTERISTICS OF OXYRESVERATROL

Oxyresveratrol (2, 4, 3, 5-tetrahydroxystilbene; Fig. 1) is a derivative of resveratrol. Its linking C = C double bond has a trans conformation and allows the formation of a conjugated system throughout the molecule. Its dihedral angle between the benzene rings is 9.39 degrees. In the crystal, molecules are connected into a three-dimensional architecture through O-H···O hydrogen bonds between hydroxy groups of

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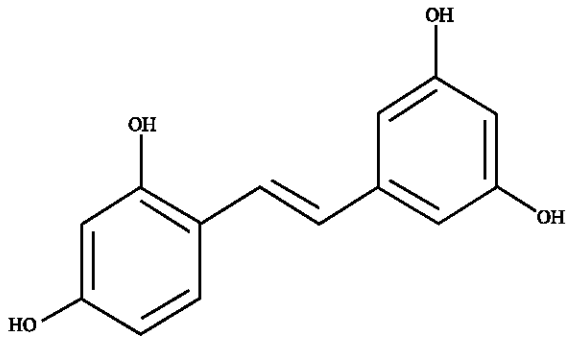

Fig. 1: Molecular structure of oxyresveratrol

oxyresveratrol and solvent water molecules (Deng *et al*., 2012). Additionally, as a natural hydroxystilbene, oxyresveratrol is a yellow solid with a melting-point of 199-204°C (>98%), a molecular formula of $C_{14}H_{12}O_4$ and a molecular weight of 244.24; oxyresveratrol shows blue fluorescence under UV light in a TLC reaction and also turns blue when mixed with $FeCl_3$ (Xiong *et al*., 2008; Ruan *et al*., 2005; Hu *et al*., 1996; Zhao *et al*., 1998). As can be seen from the structure, its chemical properties are unstable. In order to provide a reference for extraction, separation and preservation process, factors that could influence the stability of oxyresveratrol were studied in our laboratory. The results showed that pure water is the most suitable solvent, -40°C is the most suitable temperature, 5.38 is the optimum pH value and dark environment is necessary for the storage of oxyresveratrol (Liu, 2013).

EXTRACTION AND SEPARATION

In recent decades, oxyresveratrol has been isolated by using ethanol bathing from the *Smilax china* L. (Smilacaceae) (Xiong *et al*., 2008; Ruan *et al*., 2005; Huang *et al*., 2008a; Zhao *et al*., 2008; Huang *et al*., 2009a; Ban *et al*., 2006a, b; Ban *et al*., 2007; Jeon *et al*., 2007; Zhang *et al*., 2009), *Morus alba* L. (Moraceae) (Fu *et al*., 2005; Hu *et al*., 1996; Xu *et al*., 2009; Schultz *et al*., 1995; Andrabi *et al*., 2004; Qiu *et al*., 1996a; Lee *et al*., 2003; Djapic *et al*., 2003; Chung *et al*., 2003; Syah *et al*., 2004; Ferlinahayati *et al*., 2008), *Artocarpus heterophyllus* L. (Moraceae) (Fang *et al*., 2008; Chuanasa *et al*., 2008; Sasivimolphan *et al*., 2009; Likhitwitayawuid *et al*., 2005; Likhitwitayawuid *et al*., 2006a; Hakim *et al*., 2002; Maneechai *et al*., 2009), *Veratrum nigrum* L. (Liliaceae) (Zhao *et al*., 2008), *Scirpus maritimus* (Cyperaceae) (Powell *et al*., 1987) and others. Additionally, Tsuruga *et al*. (1991) extracted oxyresveratrol with chloroform and methanol from the fruits of *melaleuca leucadendron* (Myrtaceae).

At present, the main extraction reagents used to obtain oxyresveratrol from plants are ethanol (Maneechai *et al*., 2009), acetone (Djapic *et al*., 2003) and other organic solvents; the procedure begins with bathing the plant in the solvent and then using a chromato bar to purify oxyresveratrol. Lorenz *et al*. (2003) obtained pure solid oxyresveratrol (yield: 1.71 g) from 500 g mulberry wood shavings with 6.0 L of 96% (v/v) ethanol for two days at room temperature. Likewise, Zhang *et al*. (2008) also yielded oxyresveratrol that appeared as yellowish oil (1.04 g, 0.16%) from *Ramulus mori* by cutting the dried samples (6.50 kg) into small pieces followed by soaking with 70% ethanol (30 L) at ambient temperature for 24 h. In order to establish a more effective extraction technology, we optimized the ultrasonic-assisted extraction conditions of oxyresveratrol from the bark of cultured black mulberry. The optimal conditions were as follows: Extraction temperature: 50°C, Ratio of solution to solid (v/g): 20:1, Ultrasonic power: 496.23 W, Extraction time: 113 min, Ethanol concentration: 70.98%, Acetic acid concentration: 0.77% (Xu *et al*., 2013).

Furthermore, with the development of science and technology, an increasing number of related methods of extraction and separation were invented. Tong *et al*. (2011) used ethanol fractionation, silica gel column chromatography and Sephadex LH-20 gel filtration chromatography to isolate and enrich oxyresveratrol sample from mulberry; used Nuclear Magnetic Resonance (NMR), HPLC-MS to identify its chemical structure and molecular weight; used High Performance Liquid Chromatography (HPLC) to detect its mass fraction (99%). Luo *et al*. (2012) developed a new method for the separation and purification of oxyresveratrol by High-Speed Counter-current Chromatography (HSCCC) from the extract of *Ramulus mori* using n-hexane: ethyl acetate: methyl: water (1:1:1:2, v/v) as the solvent system, the upper phase as the stationary phase, the lower phase as the mobile phase, 2.0 mL min^{-1} of flow-rate, 900 r min^{-1} of rotation speed and 75 mg of injection amount. However, the content of oxyresveratrol in plants is very low, thus only a small amount can be obtained. In this case, our research group (Xu *et al*., 2009) gained a chinese patent on a process of utilizing ethanol and enzymes to extract oxyresveratrol and to convert mulberroside A to oxyresveratrol and the process significantly improved extracting efficiency.

Chemical synthesis is a complex process and can produce considerable toxic waste. Bioconversion, however, is an eco-friendly and efficient method for improving the yield. Organic synthesis is another available method for obtaining abundant oxyresveratrol. Thus, Kim *et al*. (2010) produced oxyresveratrol by

enzymatic hydrolysis of mulberroside a using β-glucosidase. At the same time, Sun *et al.* (2010) also obtained oxyresveratrol with an yield of 30% from 3, 5-dihydroxyacetophenone and 2, 4-dimethoxybenzaldehyde, via methylation, willgerodt-kindler reaction, perkin condensations, subsequent decarboxylation and demethylation isomerization process.

IDENTIFICATION AND ANALYSIS

For oxyresveratrol, there are a variety of determination methods, for instance crystal color and melting point. As mentioned previously, a characteristic blue fluorescence under UV light in a TLC reaction also reflects the presence of oxyresveratrol (Hu *et al.*, 1996; Ruan *et al.*, 2005; Zhao *et al.*, 1998). Based others' studies, Maneechai *et al.* (2009) developed a Thin Layer Chromatogramphy (TLC) method for the quantitative analysis of oxyresveratrol content in *Artocarpus lakoocha* (Moraceae) heartwood and in the traditional drug 'Puag-Haad'.

The reversed-phase high performance liquid chromatography (RE-HPLC) can also be utilized to accurately detect oxyresveratrol. In this procedure, a Zorbax SB-C_{18} column (250×4.6 mm, 5 μm) with a simple linear gradient of acetonitrile-0.04% phosphoric acid at a wavelength of 320 nm and a column temperature of 30°C was used (Huang *et al.*, 2008a). Shao *et al.* (2007) also utilized HPLC (connected an Agilent Zorbax XDB-C_{18} column to a Zorbax XDB-C_{18} guard column) to determinate oxyresveratrol with A (acetonitrile) and B (0.02% aqueous phosphoric acid, v/v) as eluents at the temperature of 30°C. In addition, Ayinampudi *et al.* (2011) further described the methods for quantitative analysis of oxyresveratrol in different parts of mortis species by High Performance Thin Layer Chromatography (HPTLC) and HPLC. These methods were found to be precise and reproducible.

MODIFICATION AND DERIVATIZATION

Oxyresveratrol has been reported to have a stronger inhibitory effect on the dopa oxidase activity of tyrosinase than kojic acid (Shin *et al.*, 1998b; Liang *et al.*, 2012). However, another experiment suggested that oxyresveratrol revealed high cell toxicity in the melanoma cell line (Gomez-Cordoves *et al.*, 2001). Furthermore, the quantity of this ingredient was limited in cell transmission and had many synthetic steps for organic synthesis (Zhang *et al.*, 1998; Alonso *et al.*, 1997).

Accordingly, Choi *et al.* (2004) evaluated the effects of synthetic benzyl amide 2,6-dimethoxy-N-phenylbenzamide which is an oxyresveratrol derivative with an amide connection chain between the two benzene rings (Compound 1, Fig. 2) on the ultraviolet B (UV B)-induced hyperpigmentation of the skin and found that (1) The skin returned to its original color after treatment with compound 1when UV B-induced hyperpigmentation was elicited on brownish guinea pig skin, (2) Melanin level in the hyperpigmented area was significantly decreased in the compound 1-treated animals, (3) A 31.7% inhibition of melanin production among the cultured melanoma cells by compound 1 at 100 μM *in vitro*, while the compound had no effect on the tyrosinase enzyme function.

Likhitwitayawuid *et al.* (2006a) studied 8 different oxyresveratrol derivations, the results showed the biological activities of 2, 4, 3', 5'-tetrahydroxybibenzyl and cis-2, 4, 3', 5'-tetramethoxystilbene (compound 2 and compound 3, Fig. 2) were much better than that of oxyresveratrol. Compound 2 exhibited more potent tyrosinase inhibitory activity than oxyresveratrol and had no cytotoxicity. It also was a non-competitive inhibitor of mushroom tyrosinase with L-dopa as the substrate and demonstrated a slightly higher affinity to the enzyme than oxyresveratrol. Compared with the common anticancer agents ellipticine and doxorubicin, compound 3 showed very strong cell toxicity against the human cancer cells KB, BC and NCI-H187. Simultaneously, Choi *et al.* (2006) synthesized 2, 6-dimethoxy-N-(4-methoxyphenyl)-benzamide (DMPB) (compound 4, Fig. 2) using a combination of benzoic acid and aniline, exhibiting significant depigmentation ability on the UV B-induced hyperpigmentation of the brown guinea pig skin without significant cytotoxicity. The results confirmed that DMPB has conquered the shortcoming of oxyresveratrol and could be used to produce cosmetic products.

What's more, Song *et al.* (2007) pointed out that hydroxyl-substituted 2-phenyl-naphthalenes as new inhibitors of mushroom tyrosinase, exerted potent inhibitory effects on cyclooxygenase, rat liver mitochondrial ATPase and tyrosinase. Among them, 7-(3, 5-dihydr-oxyphenyl)-1, 3-naphthalenediol (compound 5, Fig. 2), an isostere of oxyresveratrol, demonstrated an IC_{50} value of 0.49 μM;, 5-(6-hydroxy-2-naphthyl)-1, 3-benzenediol (compound 6, Fig. 2) demonstrated an IC_{50} value of 16.52 μM; 4-(6-hydroxy-2-naphthyl)-1, 3-benzenediol (compound 7, Fig. 2) demonstrated an IC_{50} value of 0.034 μM.

Likewise, Chun *et al.* (2009) results indicated that 2, 2, 4, 6-tetramethoxystilbene (compound 8, Fig. 2), a methoxy derivative of oxyresveratrol, was a very selective and potent competitive inhibitor of human cytochrome P450 1B1 (CYP1B1), as well as a suppressor of CYP1B1 expression, which could be a valuable tool for determining

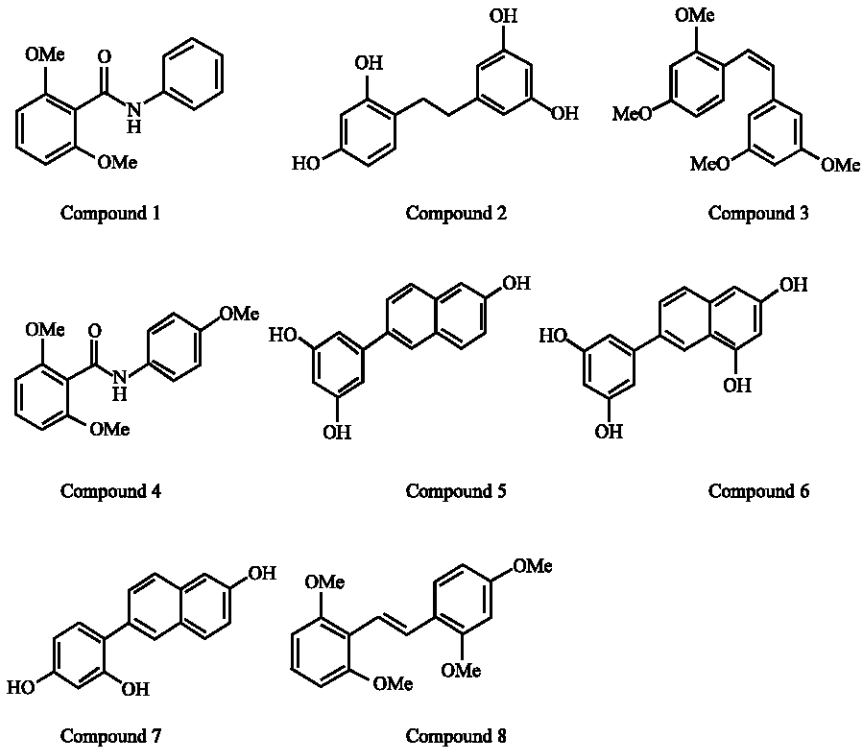

Fig. 2: Structure of compounds 1-8

the enzymatic properties of human CYP1B1. Recently, Song *et al.* (2012) got a more varied approach which increased effect on antityrosinase as well as antioxidant and other activities, as can be expected by azo-oxyresveratrol due to the combination of the chemical properties of azo compounds and oxyresveratrol.

Several problems are associated with low stability and bioavailability of oxyresveratrol and the ease with which it is oxidized by prooxidant agents. These issues have limited its use in the food and pharmaceutical industries. Rodriguez-Bonilla *et al.* (2010) applied cyclodextrins and oxyresveratrol to produce oxyresveratrol/β-cyclodextrin complexes which slowed the rapid metabolism and elimination of oxyresveratrol, thereby its bioavailability was improved.

BIOLOGICAL ACTIVITIES

Antineoplastic activity: There is growing evidence demonstrating the inhibitory effect of oxyresveratrol on cancer. In Hu *et al.* (1996) studied the inhibitory effect of oxyresveratrol on Protein Kinase C (PKC) which probably serves as a receptor for the tumor promoters and found that oxyresveratrol showed noncompetitive inhibition (Nishizuka, 1984). Likewise, Li *et al.* (2010) investigated the cytotoxicity of oxyresveratrol together with resveratrol in HT-29 human colon cancer cells by MTT assay and found oxyresveratrol have about 2-fold more potent cytotoxic activity than resveratrol. Furthermore, a related study (Wu *et al.*, 2010) indicated that oxyresveratrol demonstrated *in vitro* anti-breast tumor cell activity. Accordingly, Mouihate *et al.* (2006) found that oxyresveratrol could dampen neuroimmune responses *in vivo*, suggesting that the oxyresveratrol-induced dampening of neuroimmune responses was largely due to its inhibitory effect on tumor necrosis factor-α (TNF-α) production. However, this study also showed that oxyresveratrol demonstrated no direct effect on the NF-kappa B signaling pathway *in vivo*. Thus the author considered that oxyresveratrol could be used in pathological conditions where excessive detrimental TNF-α was produced.

Whitening and skin care effects: In early, Mongolsuk *et al.* (1957) found oxyresveratrol in *Artocarpus lakoocha* (Moraceae) (Charoenlarp *et al.*, 1981) and proved that it has an obvious whitening effect. Later, the whitening effect of oxyresveratrol had been verified by some related experiments in guinea pigs (Tengamnuay *et al.*, 2003) and humans (Tengamnuay *et al.*, 2006). With in-depth research, more and more studies showed that excessive amount of

melanin would cause pigmentation disorders which had great harm to human health and tyrosinase was the key enzyme in the production of melanin. The addition of inhibitors that inhibit tyrosinase activity in whitening cosmetics, achieved skin whitening through restraint of melanin formation (Lu *et al*., 2001). Moreover, Shin *et al*. (1998a) concluded the mechanism of whitening effect of oxyresveratrol: *in vivo* tyrosinase could convert tyrosine into dopa quinine and then formed melanin with a series of chemical reactions. When L-dopa was used as a substrate, oxyresveratrol inhibited dopa oxidase activity of tyrosinase in a noncompetitive manner. Additionally, K_i values suggested that oxyresveratrol exhibited about a 150-fold more potent inhibitory effect than resveratrol and exerted more effective inhibition on the enzyme than the well known inhibitors of azelaic acid, curcumin, kojic acid (Zheng *et al*., 2011) and mimosine. The effect was clear even though they were determined by similar assay systems in different laboratories (Lu *et al*., 2001). On the other hand, some similar studies found that compared with mulberroside A, oxyresveratrol had better performance in inhibiting ultraviolet B (UVB) irradiation-induced melanogenesis in brown guinea pig skin (Park *et al*., 2011); compared with dioscin and Mulberroside A, oxyresveratrol showed stronger tyrosinase inhibitory activity (Liang *et al*., 2012; Kim *et al*., 2012). Oxyresveratrol also demonstrated a potent inhibitory effect on mushroom tyrosinase activity, which was 32-fold stronger than kojic acid (Kim *et al*., 2002). Recently, through scientific studies and investigations, Zheng *et al*. (2012) suggested oxyresveratrol as a good source of natural tyrosinase inhibitor with a great potential and it can be used in foods as anti-browning agents and in cosmetics as skin-whitening agents.

Antioxidant activity: As a bioactive compound, oxyresveratrol has demonstrated strong antioxidant activity (Zhang and Shi, 2012; Schonfeld *et al*., 2009; Aftab *et al*., 2010). Especially, it has been shown to effectively scavenge free radicals such as 2,2'-Azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) and 2,2-diphenyl-1-pieryl-hydrazyl (DPPH) with a TEAC value 3.11 mM (Zhao *et al*., 2008). Chung *et al*. 2003 proved that oxyresveratrol could inhibit the expression of nitric oxide synthase and the accumulation of nitrite which produces a protective effect on cells after inflammatory injury and improves the antioxidant capacity of cells. Oxyresveratrol also was found to be nearly twice as strong as resveratrol in antioxidation (TBARS methods) (Nasapon *et al*., 2010). Another study found that compared with resveratrol or trans-4-hydroxystibene, oxyresveratrol was a more effective scavenger for DPPH used as a general free radical model and was a potential protectant against reactive oxygen and nitrogen species (ROS/RNS) (Lorenz *et al*., 2003). In our laboratory, the radical scavenging capacities and antioxidant activities of resveratrol, oxyresveratrol and mulberroside a from Cortex mori also were investigated. The results showed that oxyresveratrol has higher DPPH radical scavenging capacity than resveratrol and mulberroside A (Wang *et al*., 2011). Furthermore, oxyresveratrol demonstrated higher DNA protective effects than both trolox and ascorbic acid (well-known antioxidants) and might become a promising anti-aging drug and riboflavin stabilizer (Chatsumpun *et al*., 2011).

Neuroprotective activity: Oxyresveratrol is a potent neuroprotectant and may be a potential drug for the treatment of acute ischemic stroke (Horn *et al*., 2003). Jagtap and Bapat (2010) reported that oxyresveratrol lowered the activity of neurodegenerative diseases, which destroy microglia and then lead to loss of cell activity after dramatic morphological changes in our brains and in this process nerve tissue would secrete a host of soluble factors, which were beneficial to other major types of glial cells in the brain but could be deleterious to neurons. In addition, oxyresveratrol not only prevented neurological deficits but also reduced the infarct volume and apoptotic DNA fragmentation in middle cerebral artery occluded rats (Andrabi *et al*., 2004).

Likewise, Breuer *et al*. (2006) demonstrated that oxyresveratrol potentially exerted direct protective effects on the brain by crossing the blood-brain barrier and proved an excellent complementary drug for the treatment of neurodegenerative diseases that involved oxidative/nitrosative stress especially in stroke. Oxyresveratrol non-competitively inhibited β-secretase (Jeon *et al*., 2007), prevented amyloid β protein (25-35)-induced neuronal cell damage by interfering with the increase of Ca^{2+} and inhibited glutamate release and reactive oxygen species generation (Ban *et al*., 2007). Oxyresveratrol was also a potential nutritional candidate for protection against neurodegeneration in Parkinson's disease (Liu and Hong, 2003). Compared with resveratrol, oxyresveratrol exhibited a wider effective dosage range as an intracellular antioxidant for reducing oxidative stress induced by 6-hydroxydopamine, which markedly attenuated 6-hydroxydopamine (6-OHDA) induced phosphorylation of c-Jun N-terminal kinase and c-Jun; Furthermore, oxyresveratrol increased the basal levels of SIRT1, which might disclose new pathways accounting for the neuroprotective effects of oxyresveratrol (Chao *et al*., 2008).

Weber *et al.* (2012) analyzed the neuroprotective ability of oxyresveratrol by using an *in vitro* model of stretch-induced trauma in co-cultures of neurons and glia and by exposing cultures to high levels of glutamate. The results showed that oxyresveratrol significantly inhibited trauma produced marked neuronal death when measured 24 h post-injury but it was not inhibited by oxyresveratrol when cultures exposed to high glutamate for 24 h.

Protective function of hepatic damage: Currently, alcohol toxicosis has been attracted more and more attention. As well known, alcohol is harmful to the liver and can lead to many diseases, such as alcoholic hepatitis, hepatic fibrosis and cirrhosis. Thus, a new drug which can efficiently protect and repair our liver would be an important discover. Zhang *et al.* (2008) studied the activity of oxyresveratrol on the liver of mice intoxicated with ethanol and demonstrated that oxyresveratrol from *Ramulus mori* could protect mice against ethanol-induced hepatic damage. Oxyresveratrol also increased glutathione levels and antioxidant enzymes activities and reduced iron concentration and mitochondrial permeability transition to keep the related physiological indexes to the basal level, as well as attenuated the degree of tissue damage and the regulation of the expression of TNF-α. The molecular mechanisms behind the liver-protecting effects of oxyresveratrol, however, are still unclear and require further study.

Hypoglycemic activity: Oxyresveratrol could decrease the level of blood sugar in mice and inhibits the activity of α-glucosidase, therefore oxyresveratrol could be used to produce a novel hypoglycemic drug that could cure or prevent diabetes mellitus (Lu and Wang, 2010). In addition, Nasapon *et al.* (2010) reported that oxyresveratrol showed strong antiglycation activities, the IC_{50} value was 2.0 μg mL^{-1} (5 times higher than that of aminoguanidine).

Antiviral and antibacterial activities: *Artocarpus lakoocha* (Moraceae), a Thai traditional plant, had shown to possess *in vitro* anti-herpes simplex virus activity and oxyresveratrol was a major constituent previously purified from it (Sasivimolphan *et al.*, 2009; Likhitwitayawuid *et al.*, 2005). In Chuanasa *et al.* (2008) concluded that oxyresveratrol revealed inhibitory activity at the early and late phases of viral replication with pretreatment in the one-step growth assay of HSV-1 and HSV-2 that had significantly delayed in herpetic skin lesion development ($p<0.05$). At the same time, topical application of oxyresveratrol (30%) ointment five times daily markedly delayed the development of skin lesions and protected mice from death ($p<0.0001$). Another study demonstrated that 10% oxyresveratrol in cream form was significantly effective for cutaneous HSV infection (Lipipun *et al.*, 2011). Likewise, oxyresveratrol showed a broad spectrum of anti-varicella zoster virus activity and the mechanism of action was different from that of acyclovir (Sasivimolphan *et al.*, 2009).

In addition, oxyresveratrol possessed potential anti-HIV activity against a wild-type *Human immunodeficiency virus* type 1 (HIV-1) isolate and was found to be a modest inhibitor of HIV (EC_{50} = 28.2 μM) (Likhitwitayawuid *et al.*, 2005). In Galindo *et al.* (2011), a new study showed that oxyresveratrol displayed an excellent inhibitory activity on *African swine fever virus* replication and inhibited viral DNA replication, late viral protein synthesis and viral factory formation but allowed early protein synthesis. In the same year, Mazimba *et al.* (2011) found that oxyresveratrol showed activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus flavus*, *Streptococcus faecalis*, *Salmonella abony* and *Pseudomonas aeruginosa*. Oxyresveratrol also was evaluated for its antifungal activity and its cytotoxicity and its structure was established by 1D and 2D NMR, HRMS, CD and optical rotation measurements (Basset *et al.*, 2012).

Recently Sasivimolphan *et al.* (2012) evaluated the physicochemical properties of the optimized microemulsion and examined the permeating ability of oxyresveratrol in microemulsion and the efficacy of oxyresveratrol microemulsion in cutaneous *Herpes simplex virus* type 1 (HSV-1) infection in mice, demonstrated that topical oxyresveratrol microemulsion at 20-30% (w/w) was suitable for cutaneous HSV-1 mouse infection.

PHARMACOKINETICS

A previous study demonstrated that oxyresveratrol was transported to tissues at high rates in rats (Qiu *et al.*, 1996b). A sensitive and simple HPLC method had been developed and validated for the pharmacokinetic profiles of oxyresveratrol in rat plasma (Huang *et al.*, 2008a) and then oxyresveratrol was quantitatively determined by this method in rat tissues including heart, liver, spleen, lung and kidney after oral administration of *Smilax china* L. (Smilacaceae) extract (Huang *et al.*, 2009a). The cumulative excretion of oxyresveratrol was 0.29% in bile samples and 0.84% in urine samples (Huang *et al.*, 2009b). The main metabolites of oxyresveratrol were monoglucuronided and monosulfated oxyresveratrol (Huang *et al.*, 2010). Mei *et al.* (2012) found that when incubated anaerobically

with intestinal bacteria, the permeation of oxyresveratrol which underwent extensive hepatic glucuronidation and across Caco-2 cells was much more rapid than Mulberroside A. That further revealed a key role of intestinal bacterial conversion in absorption and systemic exposure of oxyresveratrol in the oral route in humans and rats.

CONCLUSION AND FUTURE PERSPECTIVES

With the rapid development of the economy, our lives have greatly transformed. On the other hand, it is easy for us to be infected by diseases, thus the rate of tumour, cerebral and vascular diseases, diabetes and heart disease increases. In addition, the concept of health has attracted more and more attention and women in growing numbers take their appearance into consideration and are eager to find ways to make themselves look more beautiful. These problems have increased the burden of our society but give oxyresveratrol an opportunity to serve mankind.

Oxyresveratrol has anti-tumor and anti-oxidant activities and can lower blood fat and blood sugar levels. Besides, oxyresveratrol can enhance the immune system and inhibit the activity of tyrosinase. Owing to these functions, oxyresveratrol could be utilized to develop and produce cosmetics, health supplements and drugs. Moreover, a lot of substances with important and significant activity could be derived from oxyresveratrol, which would become important in the future. Meanwhile, consumers in developed countries are becoming disillusioned with modern healthcare and are seeking alternatives. Since herbal medicines serve the health needs of about 80% of the world's population, thus oxyresveratrol is an important bioactive phytochemical that can be used as a promising source of medicine. For this purpose, oxyresveratrol should typically be subjected to precise scientific standardization in order to confirm the combination of traditional and modern wisdom in the light of a rational phytotherapy.

It was well known that the *Morus* (Moraceae) plant is adapted to grow all over the world. Every year, there are a large number of waste branches of mulberry especially in China. Many reports had pointed out that oxyresveratrol exists in mulberry and its concentration is low. While mulberroside A concentration is high and it can be converted to oxyresveratrol (Kim *et al*., 2010; Mei *et al*., 2012; Park *et al*., 2011; Wu, 2012). Thus, based on 3-year cooperation with Chongqing Huanshaotang Bio-Tech Co., Ltd and exploratory study on the pilot and the later development of the extraction and separation technology of oxyresveratrol and mulberrosideA, we think mulberry could provide the raw material for exploiting oxyresveratrol in the future.

Currently, the study on oxyresveratrol is a very hot field in scientific research. Oxyresveratrol and its various derivatives possess significant potential as therapeutic agents for a wide range of diseases and ailments. This promise needs to be effectively studied at the clinical level, so as to firmly establish the usefulness of these compounds in the treatment or prevention of diseases in humans.

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