

Pharmacokinetic profiles and improvement of resveratrol and derived stilbenes

Jie Peng^{a,#}, Wenyu Zhang^{b,#}, Yixing Zhu^b, Haiqing Zhu^b and Chi-Tang Ho^{a*}

^aDepartment of Food Science, Rutgers University, New Brunswick, New Jersey, USA

^bCollege of Food Science and Pharmacy, Xinjiang Agricultural University, Urumqi 830052, China

[#]These authors contributed equally to this work.

*Corresponding author: Chi-Tang Ho, Department of Food Science, Rutgers University, 65 Dudley Road, New Brunswick, NJ 08901, USA. E-mail: ctho@sebs.rutgers.edu

DOI: 10.26599/JFB.20xx.000xx

Received: May 29, 2025; Revised received & accepted: June 18, 2025

Citation: Peng, J., Zhang, W., Zhu, Y., Zhu, H., and Ho, C.-T. (2025). Pharmacokinetic profiles and improvement of resveratrol and derived stilbenes. J. Food Bioact. 000: 000–000.

Abstract

Numerous studies have demonstrated the health-promoting benefits of resveratrol and its close derivatives in various aspects of disease prevention and management, yet due to their highly conjugated 1,2-diphenylethylene structural skeleton, the *in vivo* application of stilbenoids could be limited. Therefore, the metabolic profiles of these stilbene compounds warrant further attention and investigation. The bioavailability of a nutrient or a drug is significantly influenced by ADME (absorption, distribution, metabolism and excretion). In this review, we summarize the study results of drug metabolism and pharmacokinetics (DMPK) profiles of resveratrol and its close oligomeric derivatives, including oxyresveratrol, piceatannol, pterostilbene, rhaponticin, rhapontigenin and 2,3,5,4'-tetrahydroxystilbene-2-O- β -glucopyranoside (THSG). This review also addresses explored delivery strategies, such as stilbenoids-loaded nanoparticles or Pickering emulsions, to enhance their aqueous solubility, stability, and thus bioavailability.

Keywords: Resveratrol; Resveratrol related stilbenes; Bioavailability; DMPK profile; Pterostilbene.

1. Introduction

Resveratrol represents a family of monomeric stilbene phytochemicals heterogeneously distributed in plants, many of which are edible plants, usually fruits and vegetables such as grapes and berries. This family of 1,2-diphenylethylene derivatives is mainly found in dietary plants. In chemistry, resveratrol and its structural analogs are a group of stilbene compounds with benzene rings whose hydrogen atoms are replaced by varying numbers of hydroxyl and methoxy groups, among others (Peng et al., 2024; Wang, Zhao et al., 2020). It has been revealed that these stilbene compounds possess antioxidant and inhibitory effects on chronic inflammation (Soufi et al., 2015; Truong, Jun, and Jeong, 2018), which are closely associated with their potential protective effects in metabolic syndrome (Hou et al., 2019), particularly in diabetes and its complications (Huang et al., 2020; Peng et al., 2024). These

stilbenoid compounds also exhibited beneficial effects in liver injury (Jia et al., 2019; Wu et al., 2019), brain diseases such as brain injury, dementia and Alzheimer's disease (Hornedo-Ortega et al., 2018; Pasinetti et al., 2015), cardiovascular disease (Fan et al., 2022; Breuss and Atanasov, 2019), anti-aging effect (Li, Li and Lin, 2018) and the modulation of gut microbiota is involved in the mitigation of some diseases (Koh et al., 2020).

However, despite potential health effects exhibited by phytochemicals from the stilbene family, their utilization as therapeutic candidates either as supplements or potential medications is hindered by a few factors. In the last few decades, researchers have studied the pharmacokinetic profile of resveratrol and its structural analogs, although much less investigation has been conducted for the latter. These works provide us with important insight into how they are absorbed and metabolized and identify potential factors contributing to their low bioavailability, such as poor solubility

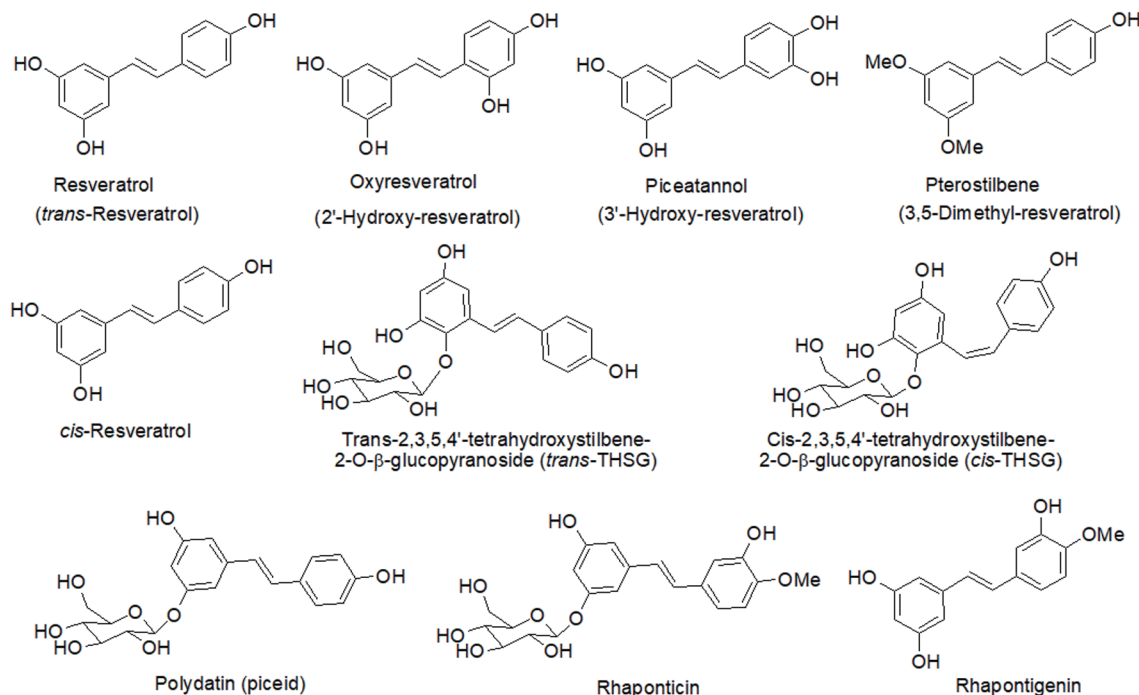


Figure 1. Chemical structures of resveratrol and its close derivatives.

and absorption and fast blood clearance. To solve these limitations associated with not only stilbenes but also many other natural phytochemicals, various formulation systems were created to enhance their stability against environmental stress and bioavailability.

To date, several delivery systems have been investigated for stilbenes compounds. A key strategy employed in these delivery methods is to protect these bioactive substances by encapsulating them within shell-like structures. This could be achieved by structuring lipid- or polymer-based nanoparticles, nanostructured lipid carriers (NLS), or liposomes, among others approaches. Alternatively, strategies often focus on reducing the droplet size or improving the product's permeability through cell membrane to boost bioaccessibility. Nanoemulsions and Pickering emulsions are two representative choices.

In this review, focusing on several key stilbenes, namely resveratrol, pterostilbene, piceatannol, oxyresveratrol, polydatin, rhaponticin, rhapontigenin and THSG, we primarily summarize their pharmacokinetic profiles and current formulation strategies employed to enhance their bioavailability. Formulation such as nanoemulsions, nanoparticles and liposomes are highlighted. Additionally, their structural characteristics, dietary sources, bioactivities and associated mechanisms are briefly discussed.

2. Structure characteristics, dietary sources and brief bioactivities of resveratrol and its close derivatives

The study of structure-activity relationship starts with structural analysis. Stilbenes possess a basic C6-C2-C6 skeleton, comprising two phenyl rings linked by an ethylene group. The diversity among stilbenes arises from distinct substituents on these phenyl rings. As one or multiple hydrogen atoms on the basic skeleton are substituted by hydroxylation, glycosylation, and polymerization among others, more than 400 stilbene phytochemicals have been

identified ((Pecyna et al., 2020; Shen, Wang, and Lou, 2009). The chemical structures of resveratrol and its close analogs are shown in Figure 1.

Resveratrol (*trans*-3,5,4'-trihydroxystilbene), present in plants like berries (e.g. grapes) and is rich in *Polygonum cuspidatum* (Tian and Liu, 2020). According to current reports, resveratrol possesses a few biological functions, ranging from antioxidant, cardioprotective and neuroprotective effects to anti-aging effect (Bastianetto, Ménard, and Quirion, 2015; Bonnefont-Rousselot, 2016; Li, Li, and Lin, 2018; Rauf et al., 2018).

Polydatin, a 3-glycoside derivative of resveratrol (Figure 1), is predominately found in the Vitaceae, Liliaceae, and Leguminosae families and its main plant source is *Polygonum cuspidatum*, which has a long history of use in traditional Asian herbal medicine (Imtiyaz et al., 2024). Similar to resveratrol, polydatin possesses multiple biological activities, such as cardio-protection (Huang et al., 2015), amelioration of diabetes nephropathy (Xie et al., 2012), neuroprotective effects (Chen et al., 2020; Li et al., 2012), and anti-cancer effects (Chen et al., 2020; Imtiyaz et al., 2024). Notably, comparing to resveratrol, polydatin has shown superior effects against oxidative stress *in vivo*, potentially by promoting the activity of serum superoxide dismutase, catalase and glutathione peroxidase (Wang et al., 2015).

Oxyresveratrol (*trans*-2,4,3',5'-tetrahydroxystilbene, Figure 1) is a natural stilbenoid primarily found in the Moraceae family (mulberry family), particularly in *Artocarpus* (jackfruit etc.) and *Moru* genera (white mulberry etc.) (Likhitwitayawuid, 2021). Structurally, it differs from oxyresveratrol by having an extra hydroxyl group at the 2-position of resveratrol's mono-hydroxyl phenyl ring. While sharing similar biological activities with resveratrol (Likhitwitayawuid, 2021), this extra hydroxyl group brings oxyresveratrol stronger antioxidant and anticancer activities (Yang et al., 2019). Its diverse biological and pharmacological activities include anti-melanogenesis effects by inhibiting tyrosinase, anti-inflammatory

activity, gut microbiota modulation, and neuroprotective effects, among others (Likhitwitayawuid, 2021).

Pterostilbene (*trans*-3,5-dimethoxy-4'-hydroxystilbene, Figure 1), a natural 3,5-dimethylated analog of resveratrol with similar biological functions, is notably abundant in blueberries (Lin et al., 2020; Liu et al., 2020). The substitution of the two hydroxyl groups on the A-benzene ring of resveratrol with two methoxyl groups improves its lipophilicity and reduces its overall reaction with phase II metabolic enzymes like glucuronidase in the human body (Dellinger, Garcia, and Meyskens, 2014; Wang and Sang, 2018). Therefore, in comparison with resveratrol, pterostilbene may exhibit higher membrane permeability and metabolic stability, potentially resulting in better bioavailability (Dellinger, Garcia, and Meyskens, 2014; Kapetanovic et al., 2011; Liu et al., 2020).

Rhaponticin (*trans*-3,5,3'-trihydroxy-4'-methoxystilbene 3-O- β -D-glucoside), and its aglycone, rhapontigenin, are primarily found in various rhubarb species from the Rheum family and could accumulate up to 40.8 mg/g in the dry root of *Rheum raphanistrum* (Kolodziejczyk-Czepas and Czepas, 2019; Yang, Dai et al., 2024). Like other stilbenoids, these compounds occur naturally in both *cis* and *trans* form in plants, though chiefly in *trans* isoform. Rhaponticin shares a similar molecular structure with resveratrol, distinguished by a substituted glucose group at 3-position and a methyl group at 4'-position. Notably, rhaponticin exhibits strong anti-inflammatory effects. Both rhaponticin and rhapontigenin have been shown to effectively inhibit pro-inflammatory enzymes and transcription factors (Kageura et al., 2001; Kutil et al., 2015). Moreover, rhapontigenin demonstrates stronger inhibitory activity on NO production than resveratrol in macrophages (Yamamoto et al., 2017).

Structural analysis of resveratrol and its analogs enables us to recognize that structural variations, particularly the numbers and position of hydroxyl or methoxyl groups on the rings, are closely related to anti-inflammation, anti-oxidative and free-radical scavenging capacity, and other redox-related properties, which are believed to be pivotal in their overall bioactivities (Murias et al., 2005).

3. Major mechanisms involved in stilbenoids bioactivities

The antioxidant effects of resveratrol and its stilbene analogs have protected ROS-induced tissue damage in organs like the retina, kidney, heart, and nerves in diabetic complications in *in vivo* studies. Such protection is mediated by various mechanisms, including reduced production of reactive oxygen species (ROS) and nitric oxide (NO) level (Ates et al., 2007; Kutil et al., 2015), attenuated lipid peroxidation (Torres-Cuevas et al., 2021), downregulation of NADPH oxidase (Wu et al., 2016), elevated levels of glutathione (GSH), and detoxifying enzymes such as superoxide dismutase (SOD) (Fang et al., 2018; Sadi and Konat, 2016; Shen and Rong, 2015), glutamine synthetase (GS) (Zeng et al., 2016), catalase (CAT) (Kumar et al., 2007) and glutathione peroxidase (GPx) (Zhang et al., 2019). Key signaling pathways involved in these effects include Nrf2/HO-1 up-regulation (Kosuru et al., 2018; Li et al., 2019; Lv, Du, Zhang and Zhang, 2019; Zhang et al., 2021), PKC inhibition (Giordo et al., 2021), PI3K/Akt/GSK-3 β /Nrf2 activation (Malik et al., 2019), Sirt1/FOXO3 modulation (Wang et al., 2017) and AMPK pathway (Wang, Li et al., 2020). Furthermore, rhapontigenin and polydatin have also shown anti-oxidative effect by reducing lipoxygenase (LOX) level (Ngoc et al., 2008) and activating SIRT1 (Liu, Liu, Xu and Ding, 2024; Kawakami et al., 2014).

Resveratrol and its related derivatives also exhibit effective inhibition on inflammation. Studies reveal that these oligomeric stilbenoids can suppress inflammation under *in vitro* and *in vivo* conditions and decrease the levels of inflammatory cytokines such as interleukin (I- β), tumor necrosis factor (TNF)- α and IL-6 (Soufi et al., 2015; Cai et al., 2020). The inhibition of NF- κ B with broad upstream and downstream targets is one of the primary anti-inflammation mechanisms (Huang, Xu et al., 2017; Soufi et al., 2015; Xie et al., 2012). Moreover, polydatin demonstrates anti-inflammation effects by regulating ICAM, ICAM-1, NLRP3 and the MAPK pathway (Lv, Du, Liu et al., 2019; Peritore et al., 2021). These stilbenoids also contribute to the inhibition of advanced glycation end products (AGEs) and their receptors (RAGE) (Xian et al., 2020). Furthermore, resveratrol stilbenoids have shown regulatory effects on inflammation-induced stress signals in microglia (Carey et al., 2013) and have attenuated cognitive behavioral dysfunction (Joseph et al., 2008). It was reported that compared to resveratrol, pterostilbene owns a better neuromodulatory activity in aging and Alzheimer's disease (Chang et al., 2011).

The anti-apoptotic effect represents another important bioactivity of these stilbenoids. Resveratrol and its closely derivatives significantly downregulate apoptotic markers such as caspase-3 and caspase-9 while upregulate Bcl-2, hence reducing cell apoptosis and associated tissue damages (Shah et al., 2019; Soufi et al., 2015; Li et al., 2019; Wang, Li et al., 2020). These actions involve the modulation on several signaling pathways, namely the PI3K/Akt/FOXO3a, (Wu et al., 2017), NLRP3 (Li et al., 2018), microRNA-29b/specificity protein 1 (Zeng et al., 2017) and AMPK/Sirt1/PGC-1 α (Li et al., 2017) pathways. In addition, the stimulation of autophagy (Huang, Ding et al., 2017), attenuation of related endoplasmic reticulum stress (Guo et al., 2015), and activation of inositol requiring 1 α (IRE-1 α)/JNK pathways (Wang et al., 2011; Malaguamera, 2019) could also contribute to the actions of these resveratrol-associated stilbenoids.

Beyond the bioactivities described above, resveratrol and associated stilbenes have also demonstrated effects in alleviating pathological changes, such as the inhibition of angiogenesis and fibrosis. For example, in diabetic retinopathy, stilbenoids compound can suppress the proliferation and migration of endothelial cells (Rokicki et al., 2014; Shen and Rong, 2015). The AMPK and PI3K pathways are suggested to contribute to the inhibition of retinal epithelial cell migration (Chan et al., 2013). Extensive studies on resveratrol have been conducted, revealing its effective inhibition of growth factors including vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)- β 1 in retinal and renal cells as well as in diabetic retinopathy rats, thereby mitigating pathological angiogenesis (Chen et al., 2019; Kim et al., 2012; Wen et al., 2013). Studies have also revealed that resveratrol can attenuate renal fibrosis by regulating AMPK/NADPH oxidase 4/ROS pathway (He et al., 2016), decreasing fibronectin production (Gong et al., 2020), inhibiting p38 MAPK and TGF- β 1 (Qiao et al., 2017), suppressing endothelial to mesenchymal-transition (EndMT) by activating SIRT1 (Du et al., 2021), and inhibiting PKC/NADPH oxidase/ROS pathway (Giordo et al., 2021). Similarly, pterostilbene and *trans*-2,3,5,4'-tetrahydroxystilbene (*trans*-THSG) effectively reduced fibronectin secretion by down-regulating TGF- β /drosophila mothers against decapentaplegic protein 1 (Smad1) pathway (Zhang, Ren et al., 2019) and inhibiting renin-angiotensin system (Chen, Yang et al., 2016). Moreover, resveratrol inhibited myocardial fibrosis through its antioxidant function (Wang et al., 2018). It exhibited strong anti-proliferative effects on mouse cardiac fibroblast cells through ROS/ERK signaling pathway and ameliorated myofibroblast cell differentiation through the ROS/ERK/TGF- β /periostin pathway (Wu, Li et al., 2016). Similar

effects were observed in oxyresveratrol, pterostilbene and *trans*-2,3,5,4'-tetrahydroxystilbene, as they exhibited hepatic protective activity via inhibiting liver and renal fibrosis (Long et al., 2019; Yang et al., 2021) by elevating antioxidant activity, inhibiting expression of TGF- β and its downstream activation of ERK1/2 and Smad1/2 (Yang et al., 2021; Zhan et al., 2021).

4. Bioavailability and pharmacokinetics

4.1. Resveratrol and polydatin

Following oral administration, resveratrol undergoes rapid absorption in the gastrointestinal (GI) tract, with peak plasma concentrations ($C_{\max}$) occurring within the first 30 min and 1.5–2 h after low and higher doses in fasting status, respectively (Table 1). Notably, fed states can greatly affect influences its pharmacokinetics. For instance, $C_{\max}$ can be delayed from 3 h to 5 h post-administration in mice or rats when switching from a standard to a high-fat diet (Huang et al., 2019). Urine and feces analyses estimate the absorption of resveratrol in both human and rats at around 75%, mainly attributed to transepithelial diffusion (Li et al., 2003; Soleas et al., 2001; Walle et al., 2004). However, its oral bioavailability is limited due to extensive first-pass metabolism in the intestine and liver, and neither dose escalation nor repeated dosages significantly improved it (Soleas et al., 2001; Walle, 2011). Depending on the solubilizing formulation systems, the absolute oral bioavailability of resveratrol exhibits considerable variability ranging from 2.6% to 46.4% (Ha et al., 2021). While it is challenging to detect the free form of resveratrol in circulating plasma due to extremely low concentration, tissue accumulation has been observed in the kidney, liver, brain, and intestine (Huang et al., 2019; Walle, 2011). This finding is consistent with its relatively high volume of distribution (V_d), indicating substantial extravascular distribution of resveratrol (Huang et al., 2019; Walle et al., 2004). Metabolic studies reveal that resveratrol's major metabolites post-absorption are glucuronides and sulfates, suggesting the involvement of enterohepatic circulation (Wenzel and Somoza, 2005). Unlike resveratrol which is absorbed in the intestine primarily through transepithelial diffusion, polydatin has an additional glucose group at the 3-position. While this enhance its solubility, it may concurrently impede its absorption into the bloodstream as active glucose transporters are required (He et al., 2007). Nevertheless, polydatin concentration in rat serum was observed to be 3–4 times higher than that of resveratrol following a 200 mg/kg oral dose (Wang et al., 2015). Upon oral co-administration of polydatin and resveratrol in the form of *Ramulus Cinnamomi* extract, both compounds were quickly absorbed, reaching $T_{\max}$ within 0.5 h. However, polydatin showed a 4.7-fold greater AUC_{0-t} and 2.5-fold higher C_{max} with a shortened $t_{1/2}$, suggesting an enhanced absorption but more rapid elimination in the blood (Yang, Wang et al., 2024). Notably, it is crucial to recognize that other co-existing components within this herbal extract may have profound impacts on the pharmacokinetic profiles of these two components (Yang, Wang et al., 2024).

4.2. Pterostilbene

The pharmacokinetics of resveratrol and pterostilbene has been comprehensively compared by Wang and Sang (2018). As illustrated in Table 1, pterostilbene exhibits a superior pharmacokinetic profile over resveratrol due to dimethyl ether structure, manifesting as higher metabolic stability and bioavailability (Azzolini et

al., 2014; Liu et al., 2020; Wang and Sang, 2018). Moreover, dose-escalation lead to an increase in $T_{\max}$, suggesting that the pterostilbene absorption is a capacity-limited process (Yeo, Ho, and Lin, 2013). The distribution of pterostilbene in various tissues has been reported, with Deng et al. (2015) specifically highlighting its ability to pass through the blood-brain barrier. In parallel, another research reveals that pterostilbene concentrations in certain tissues can be much higher than that in blood, potentially explaining its bioactivity despite low circulating plasma level (Azzolini et al., 2014). In mice, rats, and human, pterostilbene undergoes phase II metabolism, with sulfation and glucuronidation being the dominant metabolic pathways. In particular, a comparative study in human liver microsomes demonstrated pterostilbene's better metabolic stability over resveratrol, as more than 75% of pterostilbene remained unchanged while 68% of resveratrol went through glucuronidation (Dellinger, Garcia, and Meyskens, 2014). Elimination of pterostilbene occurs mainly through renal and hepatic excretion. Notably, increasing the dosage resulted in a reduced plasma elimination rate, leading to non-linear pharmacokinetics, which indicates the saturation of related enzymes (Yeo, Ho, and Lin, 2013).

4.3. THSG

The pharmacokinetic profile of THSG remains comparatively underexplored. Limited studies in rats show that THSG can be rapidly absorbed after oral administration, with a $T_{\max}$ of 10–30 min and a half-elimination time ($T_{1/2e}$) of 50–120 min (Table 1) depending on the dose (Dong et al., 2014; Sun et al., 2018; Zhao, Cheng, et al., 2013). THSG is widely distributed following absorption, mainly to the heart, kidney, liver, and lung (Zhao, Zhang et al., 2013). This widespread tissue distribution is also supported by a V_d of approximately 3.94 L/kg, thereby suggesting its potential biological function at extrahepatic sites (Zhao, Cheng, et al., 2013). While one study reported that around 81% THSG was present as phase II metabolites (Dong et al., 2014), other two studies revealed a low recovery of unchanged THSG, implying that it was primarily excreted as metabolites through feces, most likely as monoglucuronides (Zhao, Cheng, et al., 2013; Zhao, Zhang, et al., 2013).

4.4. Piceatannol

In rat, the total area under the curve (AUC) of piceatannol (include both intact and conjugate form) is lower than that of resveratrol. However, the ratio of intact piceatannol AUC to total AUC was 3.7- to 4.3-fold higher than that of resveratrol (Table 1), suggesting greater metabolic stability of piceatannol (Setoguchi et al., 2014). While phase I metabolism appears to be insignificant in the metabolism of piceatannol, it can be metabolized to a few compounds following intravenous administration, through glucuronidation, sulfation, and methylation, with piceatannol-monoglucuronide being the most abundant (Dai et al., 2020; Setoguchi et al., 2014). Also, piceatannol can be effectively converted to active monomethylated derivatives, rhapontigenin and isorhapontigenin, after oral administration, compensating for oxyresveratrol's lower plasma exposure as parent compound (Dai et al., 2020). Although piceatannol undergoes extensive hepatic glucuronidation and exhibits a relatively low absolute bioavailability of $6.99 \pm 2.97\%$ (Dai et al., 2020), it has a relatively high V_d of 10.76 L, indicating its wide distribution in tissues (Roupe et al., 2006). It also possesses a long half-life of 2–3 h and is predominantly eliminated via the hepatic pathway with a limited clearance rate (Dai et al., 2020; Roupe et al., 2006). Moreover, the pharmacokinetic pro-

Table 1. Pharmacokinetic values of resveratrol and its derived stilbenes

Stilbenoids	Solubility	Bioavailability	C _{max} (µg/mL)	Time to C _{max}	V _d (L/kg)	T _{1/2} (h)	AUC (µg h/mL)	Major metabolites	References
Resveratrol	<0.05 mg/mL	2.6–46% (human); 20–29% (rat, dose 50 mg/kg)	0.073– 0.539	30 min low dosage; 1.5–2 h high dose	2.24– 2.49	1 to 3	5.05 (mice); 0.179 ± 0.079 (human)	Glucuronides Sulfates	Das et al., 2008; Ha et al., 2021; Kapetanovic et al., 2011; Sergides et al., 2015; Johnson et al., 2011; Wang and Sang, 2018; Wenzel and Somoza, 2005; Yang, Wang et al., 2024
Polydatin	0.16 mg/mL	2.9%	12.63	0.33 h	63.83	2.48 ± 0.99	14.31 ± 0.35	Glucuronides	Yang, Wang et al., 2024
Pterostilbene	0.018 mg/mL	80% (rat, dose 20 mg/kg)	0.415– 1.038	90–300 min	2.5– 3.0	1.57 ± 0.37	4.43 – 11.9 (mice)	Sulfates; Glucuronides	Sun et al., 2018; Dellinger, Garcia, and Meyskens, 2014; Kapetanovic et al., 2011; Remsberg et al., 2008
Trans-THSG	10 mg/ mL	na	31.91	10–30 40min	3.94	0.83 – 2	639.9 ± 347.2 (rat)	Monoglucuronides	Zhao, Cheng et al., 2013; Zhao, Zhang et al., 2013
Piceatannol	<0.5 mg/mL	6.99 ± 2.97% (hu- man); 50.7% (rat, dose 10 mg/kg)	2.0	15 min	10.76	4.23	508.8	Monoglucuronide; Sulfates; methyl- ation; rhapontigenin	Roupe et al., 2006; Seto- guchi et al., 2014
Oxyresveratrol	0.6 mg/ mL	10–15%	1.5	1–2 h	105	1.70 ± 0.77	5.43 ± 1.02 (rat)	monoglucuronide and monosulfate	Huang et al., 2010; Hu et al., 2014; Junsang et al., 2019
Rhaponticin	0.109 mg/mL	0.03%	1.71	10.32 min	62.02	3.0 ± 1.35	52.8	Rhapontigenin monoglu- curonide and monosulfate	Roupe et al. (2006); Zhao et al., 2012
Rhapontigenin	0.11 mg/mL	na	0.18	52.5 min	0.011	3	42	monoglucuronide and monosulfate	Roupe et al., (2006); Navarro- Orcajada et al., 2023

file of piceatannol can be improved when co-administrated with α -cyclodextrin (Inagaki et al., 2016).

4.5. Oxyresveratrol

Based on limited data, oxyresveratrol was rapidly absorbed from the GI tract after oral administration, with a short T_{max} of 15 min. It is further excreted in both bile and urine, predominantly as monoglucuronide and monosulfate (Huang et al., 2010; Huang et al., 2008). Specifically, oxyresveratrol-2-*O*- β -*D*-glucuronide has been identified as the primary glucuronide metabolite in human liver and intestine (Hu et al., 2014). Despite a relatively low absolute bioavailability of around 10% after a single oral dose, oxyresveratrol demonstrates a long residence time in circulation. While dose escalation was correlated with a significantly improved absolute bioavailability, consecutive doses for 1 week did not yield further enhancement (Chen, Yeo et al., 2016). The pharmacokinetic profile of oxyresveratrol was improved when used in combination with piperine (Junsang et al., 2019).

4.6. Rhaponticin and rhapontigenin

The glucose group on the rhaponticin enhance its solubility compared to oxyresveratrol. However, rhaponticin's oral bioavailability was remarkably low, at only 0.03%, primarily due to its rapid metabolism (Zhao et al., 2012). Roupe et al. (2006) reported that rhapontigenin, administrated at a dosage of 10 mg/kg, has a half-life around 3 h in rat plasma, implying a fast elimination from blood, although it is longer than that of resveratrol. The C_{max} of rhapontigenin in murine plasma was only 8.91 μ g/mL 5 min after a 100 mg/kg oral dosage (Zhao et al., 2012) while a lower plasma concentration of rhaponticin at 1.71 μ g/mL was observed. Overall, both rhaponticin and rhapontigenin exhibit characteristics of poor solubility and rapid metabolism (Zhao et al., 2012).

In brief, the therapeutic promise of resveratrol and its close derivatives is often hindered by their pharmacokinetic profiles, characterized by poor oral bioavailability and rapid metabolism and clearance. As the dominance of Phase II metabolism appears as a recurring theme for stilbene metabolism, rapid first-pass metabolism is identified as a major contributor to their low bioavailability. However, studies reported above also demonstrate that structural variation often result in different metabolic patterns and that in some cases, stilbene absorption is a capacity-limited process by which higher dose can mitigate the first-pass barrier. Nevertheless, rhaponticin, despite possessing a higher solubility, still suffers from exceptionally low bioavailability, hence suggesting that improved solubility alone is insufficient to guarantee a favorable pharmacokinetic profile if rapid metabolism and clearance predominates. Therefore, close examination and in-depth understanding of stilbene's metabolic fates are crucial for effective formulation strategies.

5. Improvement of metabolic profiles

In addition to the pharmacokinetic limitations, the poor aqueous solubility and instability against environmental conditions such as moisture, light, heat or high temperature, oxygen and the combination of two or more above factors are also involved (He et al., 2018; Zhang et al., 2014; Zupančič et al., 2015). Therefore, improvement of their water solubility and bioavailability using different strategies is vital for unlocking their preventive or therapeutic potentials. Since structural modification aimed at enhancing

bioavailability may interfere with essential physiological functions and introduce uncertain toxicity, research have focused on developing diverse oral delivery systems, such as the recent trends on nano-based systems (Peng et al., 2018).

5.1. Summary of phytochemical delivery systems

Among nano-based systems, fabrication of stilbenoids-loading nanoparticles is a theme of current relevance as it allows the use of broad biocompatible materials, particularly food-grade materials which are considered safe to use. This nanotechnology enables researchers to design a smart stilbene delivery system in which the timing and spot for the deconstruction of the coating layer can be controlled by choosing materials with different chemical properties. In general, owing to the protection from the coating layer, fabricated nanoparticles of stilbenoids have a higher resistance to the change in pH and metabolic enzymes during digestion and metabolism, thus contributing to better stability, prolonged residence time, and achieving an improved controlled-release profile. Meanwhile, reduced particles size and modified surface facilitate an enhanced cellular uptake of encapsulated compounds. Coupled with increased solubility, these attributes collectively improve their overall bioavailability. Some original research and reviews that reported the improvement in the stability, solubility and/or bioavailability of stilbenoids' nanoemulsions or nanoparticles are summarized in Table 2 and also in the following list: resveratrol (Mohseni et al., 2019; Santos et al., 2019; Yang, Wang, et al., 2019), pterostilbene (Liu et al. 2019; Peng et al., 2018; Tzeng et al., 2021; Zou et al., 2021), THSG (Liu et al., 2022), piceatannol (Aljabali et al., 2020), and oxyresveratrol (Sangsen et al., 2016). Moreover, in the last five years, research focusing on the comparison of bioactivities between free form stilbenoids and their nanoparticles in various disease models (Chung et al., 2020; Yang, Wang, et al., 2019) have gradually emerged, among which a more potent effect of nanoparticles in diabetes and diabetic complications was also indicated (Dong et al., 2019; Mohseni et al., 2019).

5.2. Examples of stilbene delivery systems

5.2.1. Resveratrol

A near-spherical shaped nanosuspension of resveratrol was prepared containing 0.38% of polyvinylpyrrolidone K17 and surfactant F188 (3.63%) and study of in vivo pharmacokinetics revealed that the bioavailability of resveratrol suspension was improved with the increase of C_{max} and AUC values by 3.35- and 1.27-fold comparing to that of resveratrol alone, respectively (Hao et al., 2015). In a solid lipid nanoparticle system with stearic acid as the solid-lipid core, the encapsulation efficiency of resveratrol reached 79.9%. In the oral feeding to Wistar rats, the resulted nanoparticles of SLN-resveratrol exhibited an initial burst release followed by a sustained resveratrol release in natural conditions. Both AUC and C_{max} of SNL-resveratrol were increased compared to those of resveratrol suspension, and $t_{1/2}$ was 2.37 and 11.51 h for suspension and SNL of resveratrol respectively. In terms of efficacy, oral administration of SLN- resveratrol exhibited stronger effect in preventing weight loss and reducing blood glucose levels compared to RES alone (Pandita et al., 2014).

The application of emulsion formulation of resveratrol has been widely explored. Employing liquid and semi-solid self-emulsifying drug delivery systems, micro-emulsions of resveratrol was cre-

Table 2. Delivery examples of resveratrol and close stilbenoid compounds

Stilbene compounds	Delivery methods	Core components	Evaluation model	Results	References
Resveratrol	Nanosuspension	Polyvinylpyrrolidone, mannitol	Wistar rats	Bioavailability (AUC & C_{max}) ↑, Vd ↓	Hao et al., 2015
	Nanoemulsion	long-chain triglycerides	Wistar rats	Bioavailability (AUC & C_{max}) ↑, absorption ↑, permeability ↑	Singh and Pai, 2015; 2016
	Polymer nanoparticles	carboxymethyl chitosan	Wistar rats	Bioavailability (AUC & C_{max}) ↑, t_{max} ↑	Zu et al., 2014
	Protein nanoparticles	Zein	Wistar rats	Bioavailability (AUC & C_{max}) ↑, t_{max} ↑	Penalva et al., 2015
	Solid lipid nanoparticles	Stearic acid	Wistar rats	Bioavailability (AUC & C_{max}) ↑, t_{max} ↑, CI ↓	Pandita et al., 2014
	Cyclodextrin	β-cyclodextrin	SD rats	C_{max} ↑	Das et al., 2008
Polydatin	Liposome	Lethicin, cholesterol	SD rats	AUC ↑, T_{max} ↑, $T_{1/2}$ ↑, MRT ↑	Zhang et al., 2024
Oxyresveratrol	Microemulsion	Tween80®, Labrasol®	Wistar rats	Bioavailability (AUC & C_{max}) ↑	Sangsen et al., 2016
Pterostilbene	Bioenhancement	Piperine	Wistar rats	Bioavailability ↑ (2–6 fold), C_{max} ↑	Junsaeng et al., 2019
	Emulsion	α-Cyclodextrin	SD rats	Bioavailability (AUC _{0-3h} & C_{max}) ↑	Inagaki et al., 2016
	Nanoemulsion	Lipids: MCT, sunflower oil or olive oil	Caco-2 cell monolayer	Bioaccessibility ↑; Apparent permeability coefficient ↑	Liu et al., 2019
	Nanoparticle	Soybean lecithin, D-alpha-tocopheryl polyethylene glycol succinate	N/A	Solubility ↑ anti-tumor activity ↑	Zou et al., 2021
Trans-THSG	Nanoparticle	Carboxymethyl chitosan and chitosan hydrochloride	Simulated environmental stress	Heat and solar radiation stability ↑; Improved pH release profile	Liu et al., 2022
	Vesicles-containing gel system	Oleic acid, calcium chloride, sodium alginate	Franz diffusion cell	Transdermal flux ↑	Lai et al., 2020
Rhaponticin	Vesicles-containing gel system	Polyethylene glycol; Cholesterol, egg phosphatidylcholine, hydrogenated soybean phosphatidylcholine	Female nude mice	C_{max} ↓, T_{max} ↑, $T_{1/2}$ ↑ AUC _{0-1h} ↑	Sun and Zhao, 2012
	Emulsion	Folic acid	Balb/c mice	Water solubility ↑ receptor affinity ↑; Therapeutic effect ↑, toxicity ↓	Liang et al., 2013

CI: clearance; MCT: medium chain triglyceride; MRT: mean residence time; SD: Spraw-Darley.

ated with a droplet size of approximately 100 nm. An *ex vivo* study with the jejunum of rats demonstrated that the permeability of the micro-emulsion resveratrol was significantly enhanced, showing an 8.5-fold increase for the resveratrol-nanoemulsion compared to a resveratrol dispersion in an ethanolic medium with the preservation of the intestinal functional viability (Mamadou et al., 2017).

The encapsulation of resveratrol in liposomes has also demonstrated effectiveness. A study by Soo et al. (2016) developed a dual carrier system to co-encapsulate pure resveratrol with cyclodextrin-resveratrol inclusion complexes in both the lipophilic and hydrophilic compartments of liposomes. The final formulation exhibited a particle size of 131 ± 1.30 nm, a polydispersity index of 0.089 ± 0.005 , and a zeta potential of -2.64 ± 0.51 mV. In contrast to free resveratrol and conventional liposomal formulations that showed a drug release profile of 40–60%, this nanoformulations exhibited complete (100%) drug release within 24 h (Soo et al., 2016). Recently, different particle sizes of resveratrol nanoliposomes were created using a thin-film hydration technique and results showed that small size liposomes (<100 nm) more effectively enhanced aqueous solubility, cellular permeability and cellular antioxidant activity (Baek, Jeong and Lee, 2023).

5.2.2. Polydatin

A liposome formulation of polydatin has been developed using a membrane dispersion method (Zhang et al., 2024). The liposome was prepared from lethicin, DSPE-PEG-2000 and cholesterol. The resulted polydatin liposome had a sustained release of polydatin, prolonged *in vivo* circulation time and dramatically improved bioavailability. Comparing to free polydatin, the yielded polydatin liposome had an increased $T_{\max}$ (60 min vs 30 min), $T_{1/2}$ (5.15 ± 0.47 vs 1.02 ± 0.07 h), AUC (13.03 ± 0.30 vs 3.58 ± 0.14 mg h/mL), and mean residence time (MRT, 12.02 ± 2.28 vs 3.32 ± 1.20 h) in SD rats bioavailability evaluation (Zhang et al., 2024). Moreover, the liposome of polydatin demonstrated more effective hypoglycemic effects than that of free form.

5.2.3. Oxyresveratrol

Formulation of oxyresveratrol has been challenging for its low aqueous solubility, poor bioavailability and instability. Cyclodextrins were often used for oxyresveratrol encapsulation to improve bioavailability and stability. Solid lipid nanoparticles were also used to entrap oxyresveratrol to improve stability and bioavailability (Likhitwitayawuid, 2021). Sangsen et al. (2016) examined the influence of different ratios of surfactants in oxyresveratrol microemulsifying on the bioavailability enhancement and they found that $C_{\max}$, AUC and relative bioavailability were increased dramatically compared to free form of oxyresveratrol. For example, for oxyresveratrol delivered in the microemulsion using high percentage of Tween80®, $C_{\max}$ increased to 2.36 µg/mL from 0.66 µg/mL of unformulated oxyresveratrol (Sangsen et al., 2016). Another bioavailability-enhancing method was the combination of oxyresveratrol with a bioenhancer piperine (Junsang et al., 2019). The combination increased oxyresveratrol bioavailability by 2–6 folds, and the $C_{\max}$ reached 1.5 mg/mL within 1–2 h after oral dosing to rats.

5.2.4. Piceatannol

α -Cyclodextrin has been used in the emulsion formulation of piceatannol (Inagaki et al., 2016). When mixed with artificial gastric juice,

the solubility of piceatannol was higher as a result of co-formulation with α -cyclodextrin and reached 35.0 ± 0.8 mM immediately, while that of piceatannol in its free form is about 10 folds lower (3.2 ± 0.1 mM). The bioavailability of piceatannol was significantly enhanced, indicated by the increase in AUC_{0–3h} from 4.8 to 7.0 µmol h/L or more, depending on the amount of α -cyclodextrin used among different formulations. The $C_{\max}$ value of piceatannol increased from 2.5 µmol/L in its free form to 5.3, 4.8 and 5.8 µmol/L when formulated with low, medium and high concentration of α -cyclodextrin in emulsions, respectively (Inagaki et al., 2016).

5.2.5. Pterostilbene

By encapsulating pterostilbene in oil-in-water nanoemulsion through high pressure homogenization, Liu et al. (2019) reported delivery systems that enhanced its solubility and bioavailability and demonstrate the potential impact of lipid compositions on the stability and performance of nanoemulsion. To mimic the *in vivo* digestion process, pterostilbene loaded-nanoemulsions was exposed to simulated stomach and intestinal conditions and after digestion, the bioaccessibility of pterostilbene in MCT oil-nanoemulsion ($98.7 \pm 3.9\%$) was significantly higher than control ($< 20\%$) and other two nanoemulsions that utilized oils with a higher content of long-chain fatty acids such as sunflower oil ($41.3 \pm 0.4\%$) and olive oil ($32.9 \pm 1.9\%$). In addition, Caco-2 cells were used to simulate intestinal epithelial cell barrier in gut and further assess the effect of nanoemulsion formulation on the permeability and bioavailability of pterostilbene. The apparent permeability coefficients of pterostilbene in micelles obtained from digesta of MCT based-nanoemulsion was the higher than that of unencapsulated pterostilbene by 5.7-fold, reaching $8.21 \pm 2.09 \times 10^{-6}$ cm S⁻¹, which was attributed to higher solubility of pterostilbene in MCT oil.

5.2.6. THSG

To address THSG's sensitivity to environmental stress, a nanoparticle composed of carboxymethyl chitosan and chitosan hydrochloride was developed. This formulation not only improved its stability against heat and solar radiation but also exhibited a great controlled release profile under gastrointestinal pH condition post-administration, thus offering a potential solution for overcoming the current limitations of THSG (Liu et al., 2022). Regarding the enhancement of THSG's bioavailability especially intestinal absorption, one investigated strategy is its co-administration with polysaccharides from *Ophiopogon japonicus*. This approach resulted in a improved solubility and stability of THSG in aqueous solution and further improvement in metabolic profile, increasing the $T_{\max}$, $C_{\max}$ and AUC_{0–1h} to 3.5-, 1.45-, and 2.32-fold, respectively, relative to pure THSG. However, these were accompanied with a slight decrease in permeability (Sun et al., 2018). Another explored strategy is to apply THSG in transdermal drug delivery system through skin. In a recent study, a gel system was developed wherein THSG was loaded in oleic acid-containing vesicles, which were further incorporated into a complex gel matrix. This novel gel system successfully increased the transdermal flux of THSG by about 4-fold, potentially due to the disruption of stratum corneum integrity (Lai et al., 2020).

5.2.7. Rhaponticin and rhapontigenin

Offering multiple health benefits, rhaponticin and rhapontigenin are considered as great candidates for dietary supplement. However,

rhaponticin's poor aqueous solubility and fast metabolism remain significant challenges that must be solved for further development. Therefore, several formulation methods were tested to improve their characteristics. PEGylated liposome, commonly employed in pharmaceutical research and industry, has been utilized to construct carrier for rhaponticin and improve its solubility. Compared to oral administration of free rhaponticin, rhaponticin encapsulation by PEGylated liposome resulted in a smaller C_{max} (0.7-fold), longer T_{max} (4.5-fold) and $T_{1/2}$ (1.9-fold), and higher AUC_{0-t} (5.45-fold), indicating a slower release, yet higher concentration of rhaponticin, and better capacity to withstand plasma clearance. Further *in vivo* study also revealed a stronger anti-tumor effect compared to free rhaponticin, potentially attributed to the delivery of a larger amount of rhaponticin and higher efficiency in cellular uptake (Sun and Zhao, 2012). Another formulation strategy to enhance rhaponticin bioavailability involves the synthesis of folate-targeted rhaponticin conjugate. Due to its linkage with folic acid, this conjugate exhibited improved water solubility and a high affinity for folate receptor-positive cell. Spontaneous release of rhaponticin inside endosomes upon disulfide bond reduction was confirmed, and results from an *in vivo* tumor model showed an enhanced therapeutic effect, along with reduced toxicity (Liang et al., 2013).

6. Conclusion

Resveratrol and related stilbenoids, characterized by a highly conjugated 1,2-diphenylethylene structural skeleton, are widely distributed in food sources. These phytochemicals have been reported to provide health benefits across various conditions, including but not limited to diabetes and its complications, brain and cardiovascular diseases. However, their utilization as therapeutic candidates, either as dietary supplements or as potential pharmaceutical interventions, needs further investigation. Despite extensive research on the pharmacokinetic behaviors of resveratrol over recent decades, comparatively limited works were conducted for other stilbenoid compounds. Collective studies reveal that resveratrol and related compounds share common characteristics such as poor absorption, extensive metabolism and rapid elimination in blood. These characteristics remain primary challenges for the in-depth discovery of stilbenes' true biological effects, as therapeutically relevant concentrations often cannot be reached when delivered in their free form. Therefore, rising trends of investigation on formulation strategies and delivery systems have been observed. Currently, common approaches including nanoparticles, liposome and nanoemulsions are applied, and they are proved effective in improving stability against environmental stress and enhancing bioavailability, either through increased solubility or enhanced pharmacokinetic profiles such as permeability and absorption. However, further validation using *in vivo* study is needed given the prevalence of *in vitro* study in some case studies. In addition, beyond the aforementioned formulation strategies, alternative formulation methods, or the combination of multiple forms of delivery systems are also promising approaches for future research. For instance, incorporating nanoparticles into hydrogel may further enhance their release profiles and allow desired characteristics such as targeted release in the intestinal tract, topical application, or in-situ administration, thereby providing sustained and localized drug delivery with greater efficacy.

References

Aljabali, A.A.A., Bakshi, H.A., Hakkim, F.L., Haggag, Y.A., Al-Batanyeh, K.M.,

- Al Zoubi, M.S., Al-Trad, B., Nasef, M.M., Satija, S., Mehta, M., Pabreja, K., Mishra, V., Khan, M., Abobaker, S., Azzouz, I.M., Dureja, H., Pabari, R.M., Dardouri, A.A.K., Kesharwani, P., Gupta, G., Dhar Shukla, S., Prasher, P., Charbe, N.B., Negi, P., Kapoor, D.N., Chellappan, D.K., Webba da Silva, M., Thompson, P., Dua, K., McCarron, P., and Tambuwala, M.M. (2020). Albumin Nano-Encapsulation of Piceatannol Enhances Its Anticancer Potential in Colon Cancer Via Downregulation of Nuclear p65 and HIF-1 α . *Cancers (Basel)* 12: 113.
- Ates, O., Cayli, S.R., Yucel, N., Altinoz, E., Kocak, A., Durak, M.A., Turkoz, Y., and Yologlu, S. (2007). Central nervous system protection by resveratrol in streptozotocin-induced diabetic rats. *J. Clin. NeuroSci.* 14: 256–260.
- Azzolini, M., La Spina, M., Mattarei, A., Paradisi, C., Zoratti, M., and Biasutto, L. (2014). Pharmacokinetics and tissue distribution of pterostilbene in the rat. *Mol. Nutr. Food Res.* 58: 2122–2132.
- Baek, Y., Jeong, E.W., and Lee, H.G. (2023). Encapsulation of resveratrol within size-controlled nanoliposomes: Impact on solubility, stability, cellular permeability, and oral bioavailability. *Colloids Surf. B Biointerfaces* 224: 113205.
- Bastianetto, S., Ménard, C., and Quirion, R. (2015). Neuroprotective action of resveratrol. *Biochim. Biophys. Act.* 1852: 1195–1201.
- Bonnefont-Rousselot, D. (2016). Resveratrol and cardiovascular diseases. *Nutrients* 8: 250.
- Breuss, J.M., Atanasov, A.G., and Uhrin, P. (2019). Resveratrol and its effects on the vascular system. *Int. J. Mol. Sci.* 20: 1523.
- Cai, T.-T., Ye, X.-L., Li, R.-R., Chen, H., Wang, Y.-Y., Yong, H.-J., Pan, M.-L., Lu, W., Tang, Y., Miao, H., Snijders, A.M., Mao, J.-H., Liu, X.-Y., and Ding, D.-F. (2020). Resveratrol modulates the gut microbiota and inflammation to protect against diabetic nephropathy in mice. *Front. Pharmacol.* 11: 1249.
- Carey, A.N., Fisher, D.R., Rimando, A.M., Gomes, S.M., Bielinski, D.F., and Shukitt-Hale, B. (2013). Stilbenes and anthocyanins reduce stress signaling in BV-2 mouse microglia. *J. Agric. Food Chem.* 61: 5979–5986.
- Chan, C.-M., Chang, H.-H., Wang, V.-C., Huang, C.-L., and Hung, C.-F. (2013). Inhibitory effects of resveratrol on PDGF-BB-induced retinal pigment epithelial cell migration via PDGFR β , PI3K/Akt and MAPK pathways. *PLoS ONE* 8: e56819.
- Chang, J., Rimando, A., Pallas, M., Camins, A., and Casadesus, G. (2011). Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease. *Neurobiol. Aging* 33(9): 2062–2071.
- Chen, G.T., Yang, M., Chen, B.B., Song, Y., Zhang, W., and Zhang, Y. (2016). 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside exerted protective effects on diabetic nephropathy in mice with hyperglycemia induced by streptozotocin. *Food Funct.* 7: 4628–36.
- Chen, W., Yeo, S., Elhennawy, M.A., and Lin, H.S. (2016). Oxyresveratrol: A bioavailable dietary polyphenol. *J. Funct. Foods* 22: 122–131.
- Chen, Y., Meng, J., Li, H., Wei, H., Bi, F., Liu, S., Tang, K., Guo, H., and Liu, W. (2019). Resveratrol exhibits an effect on attenuating retina inflammatory condition and damage of diabetic retinopathy via PON1. *Exp. Eye Res.* 181: 356–66.
- Chen, Y., Niu, J., Li, L., Li, Z., Jiang, J., Zhu, M., Dong, T., Zhang, J., Shi, C., and Xu, P. (2020). Polydatin executes anticancer effects against glioblastoma multiforme by inhibiting the EGFR-AKT/ERK1/2/STAT3-SOX2/ Snail signaling pathway. *Life Sci.* 258: 118158.
- Chung, I.-M., Subramanian, U., Thirupathi, P., Venkidasamy, B., Samynathan, R., Gangadhar, B.H., Rajakumar, G., and Thiruvengadam, M. (2020). Resveratrol nanoparticles: A promising therapeutic advancement over native resveratrol. *Processes* 8: 458.
- Dai, Y., Lim, J.X., Yeo, S.C.M., Xiang, X., Tan, K.S., Fu, J.H., Huang, L., and Lin, H.S. (2020). Biotransformation of Piceatannol, a dietary resveratrol derivative: Promises to human health. *Mol. Nutr. Food Res.* 64: e1900905.
- Das, S., Lin, H.S., Ho, P.C., and Ng, K.Y. (2008). The impact of aqueous solubility and dose on the pharmacokinetic profiles of resveratrol. *Pharm. Res.* 25: 2593–2600.
- Dellinger, R.W., Garcia, A.M., and Meyskens, F.L. Jr. (2014). Differences in the glucuronidation of resveratrol and pterostilbene: altered enzyme specificity and potential gender differences. *Drug Metab Pharmacokinet* 29: 112–119.

- Deng, L., Li, Y., Zhang, X., Chen, B., Deng, Y., and Li, Y. (2015). UPLC-MS method for quantification of pterostilbene and its application to comparative study of bioavailability and tissue distribution in normal and Lewis lung carcinoma bearing mice. *J. Pharm. Biomed. Anal.* 114: 200–207.
- Dong, L.H., Guo, P.P., Yan, W.Y., Zhang, Z.J., and Wang, C.Y. (2014). Comparative study on pharmacokinetics and tissue distribution of cis- and trans-2,3,5,4'-Tetrahydroxystilbene-2-O-beta-D-glucosides in mice. *Zhong Yao Cai* 37: 1627–1632.
- Dong, Y., Wan, G., Yan, P., Qian, C., Li, F., and Peng, G. (2019). Fabrication of resveratrol coated gold nanoparticles and investigation of their effect on diabetic retinopathy in streptozotocin induced diabetic rats. *J. Photochem. Photobiol. B.* 195: 51–57.
- Du, L., Qian, X., Li, Y., Li, Z.-X., He, L.-L., Xu, L., Liu, Y.-Q., Li, C.-C., Ma, P., Shu, F.-L., Lu, Q., and Yin, X.-X. (2021). Sirt1 inhibits renal tubular cell epithelial-mesenchymal transition through YY1 deacetylation in diabetic nephropathy. *Acta Pharmacol. Sin.* 42: 242–51.
- Fan, D., Liu, C., Zhang, Z., Huang, K., Wang, T., Chen, S., and Li, Z. (2022). Progress in the preclinical and clinical study of resveratrol for vascular metabolic disease. *Molecules* 27: 7524.
- Fang, W.-J., Wang, C.-J., He, Y., Zhou, Y.-L., Peng, X.-D., and Liu, S.-K. (2018). Resveratrol alleviates diabetic cardiomyopathy in rats by improving mitochondrial function through PGC-1 α deacetylation. *Acta Pharmacol. Sin.* 39: 59–73.
- Giordo, R., Nasrallah, G.K., Posadino, A.M., Galimi, F., Capobianco, G., Eid, A.H., and Pintus, G. (2021). Resveratrol-elicited PKC inhibition counteracts NOX-mediated endothelial to mesenchymal transition in human retinal endothelial cells exposed to high glucose. *Antioxidants (Basel)* 10: 224.
- Gong, W., Li, J., Chen, W., Feng, F., and Deng, Y. (2020). Resveratrol inhibits lipopolysaccharide-induced extracellular matrix accumulation and inflammation in rat glomerular mesangial cells by Sphk1/S1P2/NF- κ B pathway. *Diabetes Metab. Syndr. Obes.* 13: 4495–505.
- Guo, R., Liu, W., Liu, B., Zhang, B., Li, W., and Xu, Y. (2015). Sirt1 suppresses cardiomyocyte apoptosis in diabetic cardiomyopathy: An insight into endoplasmic reticulum stress response mechanism. *Int. J. Cardiol.* 191: 36–45.
- Ha, E.S., Choi, D.H., Baek, I.H., Park, H., and Kim, M.S. (2021). Enhanced oral bioavailability of resveratrol by using neutralized Eudragit E solid dispersion prepared via spray drying. *Antioxidants (Basel)* 10: 90.
- Hao, J., Gao, Y., Zhao, J., Zhang, J., Li, Q., Zhao, Z., and Liu, J. (2015). Preparation and optimization of resveratrol nanosuspensions by antisolvent precipitation using Box-Behnken design. *AAPS PharmSciTech* 16: 118–128.
- He, J., Guo, F., Lin, L., Chen, H., Chen, J., Cheng, Y., and Zheng, Z.P. (2018). Investigating the oxyresveratrol β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin complexes: The effects on oxyresveratrol solution, stability, and antibrowning ability on fresh grape juice. *Lebensm. Wiss. Technol.* 100: 263–270.
- He, H., Zhao, Y., Chen, X., Zheng, Y., Wu, X., Wang, R., Li, T., Yu, Q., Jing, J., Ma, L., Ren, W., Han, D., and Wang, G. (2007). Quantitative determination of trans-polydatin, a natural strong anti-oxidative compound, in rat plasma and cellular environment of a human colon adenocarcinoma cell line for pharmacokinetic studies. *J. Chromatogr. B.* 855: 145–151.
- He, T., Xiong, J., Nie, L., Yu, Y., Guan, X., Xu, X., Xiao, T., Yang, K., Liu, L., Zhang, D., Huang, Y., Zhang, J., Wang, J., Sharma, K., and Zhao, J. (2016). Resveratrol inhibits renal interstitial fibrosis in diabetic nephropathy by regulating AMPK/NOX4/ROS pathway. *J. Mol. Med.* 94: 1359–71.
- Hornedo-Ortega, R., Cerezo, A.B., de Pablos, R.M., Krisa, S., Richard, T., Garcia-Parrilla, M.C., and Troncoso, A.M. (2018). Phenolic Compounds Characteristic of the Mediterranean Diet in Mitigating Microglia-Mediated Neuroinflammation. *Front. Cell. Neurosci.* 12: 373.
- Hou, C.-Y., Tain, Y.-L., Yu, H.-R., and Huang, L.-T. (2019). The effects of resveratrol in the treatment of metabolic syndrome. *Int. J. Mol. Sci.* 20: 535.
- Hu, N., Mei, M., Ruan, J., Wu, W., Wang, Y., and Yan, R. (2014). Regioselective glucuronidation of oxyresveratrol, a natural hydroxystilbene, by human liver and intestinal microsomes and recombinant UGTs. *Drug Metab. Pharmacokinet.* 29: 229–236.
- Huang, B., Xue, L., Wu, Y., and Jiang, Q. (2015). Effect and mechanism of polydatin on diabetic myocardial hypertrophy in mice. *Zhongguo Zhong Yao Za Zhi* 40: 4256–4261.
- Huang, D.D., Shi, G., Jiang, Y., Yao, C., and Zhu, C. (2020). A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. *Biomed. Pharmacother.* 125: 109767.
- Huang, H., Chen, G., Lu, Z., Zhang, J., and Guo, D.-A. (2010). Identification of seven metabolites of oxyresveratrol in rat urine and bile using liquid chromatography/tandem mass spectrometry. *Biomed. Chromatogr. BMC.* 24: 426–432.
- Huang, H., Zhang, J., Chen, G., Lu, Z., Wang, X., Sha, N., Shao, B., Li, P., and Guo, D.-A. (2008). High performance liquid chromatographic method for the determination and pharmacokinetic studies of oxyresveratrol and resveratrol in rat plasma after oral administration of Smilax china extract. *Biomed. Chromatogr. BMC.* 22: 421–427.
- Huang, Q.-H., Xu, L.-Q., Liu, Y.-H., Wu, J.-Z., Wu, X., Lai, X.-P., Li, Y.-C., Su, Z.-R., Chen, J.-N., and Xie, Y.-L. (2017). Polydatin protects rat liver against ethanol-induced injury: involvement of CYP2E1/ROS/Nrf2 and TLR4/NF- κ B p65 pathway. *Evid. Based Complement. Altern. Med.* 2017: 7953850.
- Huang, S.-S., Ding, D.-F., Chen, S., Dong, C.-L., Ye, X.-L., Yuan, Y.-G., Feng, Y.-M., You, N., Xu, J.-R., Miao, H., You, Q., Lu, X., and Lu, Y.-B. (2017). Resveratrol protects podocytes against apoptosis via stimulation of autophagy in a mouse model of diabetic nephropathy. *Sci. Rep.* 7: 45692.
- Huang, X.T., Li, X., Xie, M.L., Huang, Z., Huang, Y.X., Wu, G.X., Peng, Z.R., Sun, Y.N., Ming, Q.L., Liu, Y.X., Chen, J.P., and Xu, S.N. (2019). Resveratrol: Review on its discovery, anti-leukemia effects and pharmacokinetics. *Chem. Biol. Interact.* 306: 29–38.
- Imtiyaz, K., Shafi, M., Fakhri, K.U., Uroog, L., Zeya, B., Anwer, S.T., and Rizvi, M.M.A. (2024). Polydatin: A natural compound with multifaceted anticancer properties. *J. Tradit. Complement. Med.*
- Inagaki, H., Ito, R., Setoguchi, Y., Oritani, Y., and Ito, T. (2016). Administration of piceatannol complexed with α -cyclodextrin improves its absorption in rats. *J. Agric. Food Chem.* 64: 3557–3563.
- Jia, Y.-N., Peng, Y.-L., Zhao, Y.-P., Cheng, X.-F., Zhou, Y., Chai, C.-L., Zeng, L.-S., Pan, M.-H., and Xu, L. (2019). Comparison of the Hepatoprotective Effects of the Three Main Stilbenes from Mulberry Twigs. *J. Agric. Food Chem.* 67: 5521–5529.
- Johnson, J., Nihal, M., Siddiqui, I.A., Scarlitt, C.O., Bailey, H.H., Mukhtar, H., and Ahmad, N. (2011). Enhancing the bioavailability of resveratrol by combining it with Piperine. *Mol. Nutr. Food Res.* 55: 1169–1176.
- Joseph, J.A., Fisher, D.R., Cheng, V., Rimando, A.M., and Shukitt-Hale, B. (2008). Cellular and behavioral effects of stilbene resveratrol analogues: implications for reducing the deleterious effects of aging. *J. Agric. Food Chem.* 56: 10544–10551.
- Junsang, D., Anukunwithaya, T., Phanit Songvut, P., Sritularak, B., Likhitwitayawuid, K., and Khemawoot, P. (2019). Comparative pharmacokinetics of oxyresveratrol alone and in combination with piperine as a bioenhancer in rats. *BMC Complement. Altern. Med.* 19: 235.
- Kageura, T., Matsuda, H., Morikawa, T., Riguchida, I., Harima, S., Oda, M., and Yoshikawa, M. (2001). Inhibitors from rhubarb on lipopolysaccharide-induced nitric oxide production in macrophages: structural requirements of stilbenes for the activity. *Bioorg. Med. Chem.* 9: 1887–1893.
- Kapetanovic, I.M., Muzzio, M., Huang, Z., Thompson, T.N., and McCormick, D.L. (2011). Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. *Cancer Chemother. Pharmacol.* 68: 593–601.
- Kawakami, S., Kinoshita, Y., Maruki-Uchida, H., Yanae, K., Sai, M., and Ito, T. (2014). Piceatannol and its metabolite, isorhapontigenin, induce SIRT1 expression in THP-1 human monocytic cell line. *Nutrients* 6: 4794–4804.
- Kim, Y.H., Kim, Y.S., Roh, G.S., Choi, W.S., and Cho, G.J. (2012). Resveratrol blocks diabetes-induced early vascular lesions and vascular endothelial growth factor induction in mouse retinas. *Acta Ophthalmol.* 90: e31–7.
- Koh, Y.-C., Lien, Y.-T., Chou, Y.-T., Ho, C.-T., and Pan, M.-H. (2020). A review: Potential of resveratrol and its analogues to mitigate diseases via gut microbial modulation. *J. Food Bioact.* 12: 97–105.
- Kolodziejczyk-Czepas, J., and Czepas, J. (2019). Rhaponticin as an anti-

- inflammatory component of rhubarb: a minireview of the current state of the art and prospects for future research. *Phytochem Rev.* 18: 1375–1386.
- Kosuru, R., Kandula, V., Rai, U., Prakash, S., Xia, Z., and Singh, S. (2018). Pterostilbene decreases cardiac oxidative stress and inflammation via activation of AMPK/Nrf2/HO-1 pathway in fructose-fed diabetic rats. *Cardiovasc. Drugs. Ther.* 32: 147–63.
- Kumar, A., Kaundal, R.K., Iyer, S., and Sharma, S.S. (2007). Effects of resveratrol on nerve functions, oxidative stress and DNA fragmentation in experimental diabetic neuropathy. *Life Sci.* 80: 1236–44.
- Kutil, Z., Kvasnicova, M., Temml, V., Schuster, D., Marsik, P., Cusimamani, E.F., Lou, J.-D., Vanek, T., and Landa, P. (2015). Effect of dietary stilbenes on 5-lipoxygenase and cyclooxygenases activities *in vitro*. *Int. J. Food Prop.* 18: 471–1477.
- Lai, W.F., Tang, R., and Wong, W.T. (2020). Ionically crosslinked complex gels loaded with oleic acid-containing vesicles for transdermal drug delivery. *Pharmaceutics* 12: 725.
- Li, H., Shi, Y., Wang, X., Li, P., Zhang, S., Wu, T., Yan, Y., Zhan, Y., Ren, Y., Rong, X., Xia, T., Chu, M., and Wu, R. (2019). Piceatannol alleviates inflammation and oxidative stress via modulation of the Nrf2/HO-1 and NF- κ B pathways in diabetic cardiomyopathy. *Chem. Biol. Interact.* 310: 108754.
- Li, J., Wang, B., Zhou, G., Yan, X., and Zhang, Y. (2018). Tetrahydroxy stilbene glucoside alleviates high glucose-induced MPC5 podocytes injury through suppression of NLRP3 inflammasome. *Am. J. Med. Sci.* 355: 588–96.
- Li, J., Yu, S., Ying, J., Shi, T., and Wang, P. (2017). Resveratrol prevents ROS-induced apoptosis in high glucose-treated retinal capillary endothelial cells via the activation of AMPK/Sirt1/PGC-1 α pathway. *Oxi. Med. Cell. Longev.* 2017: 7584691.
- Li, R.-P., Wang, Z.-Z., Sun, M.-X., Hou, X.-L., Sun, Y., Deng, Z.-F., and Xiao, K. (2012). Polydatin protects learning and memory impairments in a rat model of vascular dementia. *Phytomedicine* 19: 677–681.
- Li, Y., Shin, Y.G., Yu, C., Kosmeder, J.W., Hirschelman, W.H., Pezzuto, J.M., and van Breemen, R.B. (2003). Increasing the throughput and productivity of Caco-2 cell permeability assays using liquid chromatography-mass spectrometry: application to resveratrol absorption and metabolism. *Comb. Chem. High Throughput Screen* 6: 757–767.
- Li, Y.-R., Li, S., and Lin, C.-C. (2018). Effect of resveratrol and pterostilbene on aging and longevity. *Biofactors* 44: 69–82.
- Liang, X., Sun, Y., Zeng, W., Liu, L., Ma, X., Zhao, Y., and Fan, J. (2013). Synthesis and biological evaluation of a folate-targeted rhaponticin conjugate. *Bioorg. Med. Chem.* 21: 178–185.
- Likhitwitayawuid, K. (2021). Oxyresveratrol: Sources, productions, biological activities, pharmacokinetics, and delivery systems. *Molecules* 26: 4212.
- Lin, W.S., Leland, J.V., Ho, C.T., and Pan, M.H. (2020). Occurrence, bioavailability, anti-inflammatory, and anticancer effects of pterostilbene. *J. Agric. Food. Chem.* 68: 12788–12799.
- Liu, K., Liu, J., Xu, A., and Ding, J. (2024). The role of polydatin in inhibiting oxidative stress through SIRT1 activation: A comprehensive review of molecular targets. *J. Ethnopharmacol.* 331: 118322.
- Liu, Q., Chen, J., Qin, Y., Jiang, B., and Zhang, T. (2019). Encapsulation of pterostilbene in nanoemulsions: Influence of lipid composition on physical stability, *in vitro* digestion, bioaccessibility, and Caco-2 cell monolayer permeability. *Food Func.* 10: 6604–14.
- Liu, S., Yang, Q., Zhang, J., Yang, M., Wang, Y., Sun, T., Ma, C., and El-Aty, A.M.A. (2022). Enhanced stability of stilbene-glycoside-loaded nanoparticles coated with carboxymethyl chitosan and chitosan hydrochloride. *Food Chem.* 372: 131343.
- Liu, Y., Lang, H., Zhou, M., Huang, L., Hui, S., Wang, X., Chen, K., and Mi, M. (2020). The preventive effects of pterostilbene on the exercise intolerance and circadian misalignment of mice subjected to sleep restriction. *Mol. Nutr. Food. Res.* 64: e1900991.
- Long, T., Wang, L., Yang, Y., Yuan, L., Zhao, H., Chang, C.-C., Yang, G., Ho, C.-T., and Li, S. (2019). Protective Effect of Trans-2,3,5,4'-tetrahydroxystilbene 2-O- β -D-glucopyranoside on Liver Fibrosis and Renal Injury Induced by CCl₄ via Activating p-ERK1/2 and p-Smad1/2. *Food Funct.* 10: 5115–5123.
- Lv, R., Du, L., Liu, X., Zhou, F., Zhang, Z., and Zhang, L. (2019). Polydatin alleviates traumatic spinal cord injury by reducing microglial inflammation via regulation of iNOS and NLRP3 inflammasome pathway. *Int. Immunopharmacol.* 70: 28–36.
- Lv, R., Du, L., Zhang, L., and Zhang, Z. (2019). Polydatin attenuates spinal cord injury in rats by inhibiting oxidative stress and microglia apoptosis via Nrf2/HO-1 pathway. *Life Sci.* 217: 119–127.
- Malaguarnera, L. (2019). Influence of resveratrol on the immune response. *Nutrients* 11: 946.
- Malik, S.A., Acharya, J.D., Mehendale, N.K., Kamat, S.S., and Ghaskadbi, S.S. (2019). Pterostilbene reverses palmitic acid mediated insulin resistance in HepG2 cells by reducing oxidative stress and triglyceride accumulation. *Free Radic. Res.* 53: 815–827.
- Mamadou, G., Charrueau, C., Dairou, J., Limas-Nzouzi, N., Eto, B., and Ponchel, G. (2017). Increased intestinal permeation and modulation of presystemic metabolism of resveratrol formulated into self-emulsifying drug delivery systems. *Int. J. Pharm.* 521: 150.
- Mohseni, R.Z., ArabSadeghabadi, N., Ziamajidi, R., Abbasalipourkabir, A., and RezaeiFarimani, A. (2019). Oral administration of resveratrol-loaded solid lipid nanoparticle improves insulin resistance through targeting expression of SNARE proteins in adipose and muscle tissue in rats with type 2 diabetes. *Nanoscale Res. Lett.* 14: 227.
- Murias, M., Jäger, W., Handler, N., Erker, T., Horvath, Z., Szekeres, T., Nohl, H., and Gille, L. (2005). Antioxidant, prooxidant and cytotoxic activity of hydroxylated resveratrol analogues: structure-activity relationship. *Biochem. Pharmacol.* 69: 903–912.
- Navarro-Orcajada, S., Vidal-Sánchez, F.J., Conesa, I., Matencio, A., and López-Nicolás, J.M. (2023). Improvement of the physicochemical limitations of rhapontigenin, a cytotoxic analogue of resveratrol against colon cancer. *Biomolecules* 13(8): 1270.
- Ngoc, T.M., Minh, P.T., Hung, T.M., Thuong, P.T., Lee, I., Min, B.S., and Bae, K. (2008). *J. Arch. Pharmacol. Res.* 31: 598–605.
- Pandita, D., Kumar, S., Poonia, N., and Lather, V. (2014). Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. *Food Res. Int.* 62: 1165–1174.
- Pasinetti, G.M., Wang, J., Ho, L., Zhao, W., and Dubner, L. (2015). Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. *Biochim. Biophys. Acta, Mol. Basis Dis.* 1852: 1202–1208.
- Pecyna, P., Wargula, J., Murias, M., and Kucinska, M. (2020). More than resveratrol: New insights into stilbene-based compounds. *Biomolecules* 10: 1111.
- Penalva, R., Esparza, I., Larraneta, E., Gonzalez-Navarro, C.J., Gamazo, C., and Irache, J.M. (2015). Zein-based nanoparticles improve the oral bioavailability of resveratrol and its anti-inflammatory effects in a mouse model of endotoxemic shock. *J. Agric. Food Chem.* 63: 5603–5611.
- Peng, J., Lu, C., Luo, Y., Su, X., Li, S., and Ho, C.-T. (2024). Hypoglycemic effects and associated mechanisms of resveratrol and related stilbenes in diet. *Food Funct.* 15: 2381–2405.
- Peng, R.M., Lin, G.R., Ting, Y., and Hu, J.Y. (2018). Oral delivery system enhanced the bioavailability of stilbenes: Resveratrol and pterostilbene. *BioFactors (Oxford, England)* 44: 5–15.
- Peritore, A.F., D'Amico, R., Cordaro, M., Siracusa, R., Fusco, R., Gugliandolo, E., Genovese, T., Crupi, R., Di Paola, R., and Cuzzocrea, S. (2021). PEA/Polydatin: Anti-Inflammatory and antioxidant approach to counteract DNBS-induced colitis. *Antioxidants* 10: 464.
- Qiao, Y., Gao, K., Wang, Y., Wang, X., and Cui, B. (2017). Resveratrol ameliorates diabetic nephropathy in rats through negative regulation of the p38 MAPK/TGF- β 1 pathway. *Exp. Ther. Med.* 13: 3223–3230.
- Rauf, A., Imran, M., Butt, M.S., Nadeem, M., Peters, D.G., and Mubarak, M.S. (2018). Resveratrol as an anti-cancer agent: A review. *Crit. Rev. Food Sci. Nutr.* 58: 1428–1447.
- Remsberg, C.M., Yáñez, J.A., Ohgami, Y., Vega-Villa, K.R., Rimando, A.M., and Davies, N.M. (2008). Pharmacometrics of pterostilbene: Preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. *Phytother. Res.* 22: 169–179.
- Rokicki, D., Zdanowski, R., Lewicki, S., Leśniak, M., Suska, M., Wojdat, E., Skopińska-Różewska, E., and Skopiński, P. (2014). Inhibition of proliferation, migration and invasiveness of endothelial murine cells culture induced by resveratrol. *Cent. Eur. J. Immunol.* 39: 449–454.
- Roupe, K.A., Yáñez, J.A., Teng, X.T., and Davies, N.M. (2006). Pharmacokinetics of selected stilbenes: Rhapontigenin, piceatannol and pinosyl-

- vin in rats. *J. Pharm. Pharmacol.* 58: 1443–1450.
- Sadi, G., and Konat, D. (2016). Resveratrol regulates oxidative biomarkers and antioxidant enzymes in the brain of streptozotocin-induced diabetic rats. *Pharm. Biol.* 54: 1156–1163.
- Sangsen, Y., Wiwattanawongsa, K., Likhitwitayawuid, K., Sritularak, B., Graidist, P., and Wiwattanapatapee, R. (2016). Influence of surfactants in self-microemulsifying formulations on enhancing oral bioavailability of oxyresveratrol: Studies in Caco-2 cells and *in vivo*. *Int. J. Pharm.* 498: 294–303.
- Santos, A.C., Pereir, I., Pereira-Silva, M., Ferreira, L., Caldas, M., Collado-González, M., Magalhães, M., Figueiras, A., Ribeiro, A.J., and Veiga, F. (2019). Nanotechnology-based formulations for resveratrol delivery: Effects on resveratrol *in vivo* bioavailability and bioactivity. *Colloids Surf. B Biointerfaces* 180: 127–140.
- Sergides, C., Chirilă, M., Silvestro, L., Pitta, D., and Pittas, A. (2015). Bioavailability and safety study of resveratrol 500 mg tablets in healthy male and female volunteers. *Exp. Ther. Med.* 11: 164–170.
- Setoguchi, Y., Oritani, Y., Ito, R., Inagaki, H., Maruki-Uchida, H., Ichiyanagi, T., and Ito, T. (2014). Absorption and metabolism of piceatannol in rats. *J. Agric. Food. Chem.* 62: 2541–2548.
- Shah, F.A., Kury, L.A., Li, T., Zeb, A., Koh, P.O., Liu, F., Zhou, Q., Hussain, I., Khan, A.U., Jiang, Y., and Li, S. (2019). Polydatin attenuates neuronal loss via reducing neuroinflammation and oxidative stress in rat MCAO models. *Front. Pharmacol.* 10: 663.
- Shen, H., and Rong, H. (2015). Pterostilbene impact on retinal endothelial cells under high glucose environment. *Int. J. Clin. Exp. Pathol.* 8: 12589–12594.
- Shen, T., Wang, X.N., and Lou, H.X. (2009). Natural stilbenes: an overview. *Nat. Prod. Rep.* 26: 916–935.
- Singh, G., and Pai, R.S. (2015). Trans-resveratrol self-nano-emulsifying drug delivery system (SNEDDS) with enhanced bioavailability potential: optimization, pharmacokinetics and *in situ* single pass intestinal perfusion (SPIP) studies. *Drug Deliv* 22: 522–530.
- Singh, G., and Pai, R.S. (2016). *In vitro* and *in vivo* performance of supersaturable self-nano-emulsifying system of trans-resveratrol, *Artif. Cells Nanomed. Biotechnol.* 44: 510–516.
- Soleas, G.J., Angelini, M., Grass, L., Diamandis, E.P., and Goldberg, D.M. (2001). Absorption of trans-resveratrol in rats. *Methods. Enzymol.* 335: 145–154.
- Soo, E., Thakur, S., Qu, Z., Jambhrunkar, S., Parekh, H.S., and Popat, A. (2016). Enhancing delivery and cytotoxicity of resveratrol through a dual nanoencapsulation approach. *J. Colloid Interface Sci.* 462: 368–374.
- Soufi, F.G., Arbabi-Aval, E., Kanavi, M.R., and Ahmadi, H. (2015). Anti-inflammatory properties of resveratrol in the retinas of type 2 diabetic rats. *Clin. Exp. Pharmacol. Physiol.* 42: 63–68.
- Sun, L.-L., Wang, M., Zhang, H.-J., You, G.-J., Liu, Y.-N., Ren, X.-L., and Deng, Y.-R. (2018). The influence of polysaccharides from *Ophiopogon japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside about biopharmaceutical properties *in vitro* and pharmacokinetics *in vivo*. *Int. J. Biol. Macromol.* 119: 677–682.
- Sun, Y., and Zhao, Y. (2012). Enhanced pharmacokinetics and anti-tumor efficacy of PEGylated liposomal rhaponticin and plasma protein binding ability of rhaponticin. *J. Nanosci. Nanotechnol.* 12: 7677–7684.
- Tian, B., and Liu, J. (2020). Resveratrol: a review of plant sources, synthesis, stability, modification and food application. *J. Sci. Food. Agric.* 100: 1392–1404.
- Torres-Cuevas, I., Millán, I., Asensi, M., Vento, M., Oger, C., Galano, J.M., Durand, T., and Ortega, Á.L. (2021). Analysis of lipid peroxidation by UPLC-MS/MS and retinoprotective effects of the natural polyphenol pterostilbene. *Antioxidants* 10: 168.
- Truong, V.-L., Jun, M., and Jeong, W.-S. (2018). Role of resveratrol in regulation of cellular defense systems against oxidative stress. *Biofactors* 44: 36–49.
- Tzeng, W.S., Teng, W.L., Huang, P.H., Lin, T.C., Yen, F.L., and Shiue, Y.L. (2021). Pterostilbene Nanoparticles Downregulate Hypoxia-Inducible Factors in Hepatoma Cells Under Hypoxic Conditions. *Int. J. Nanomedicine* 16: 867–879.
- Walle, T. (2011). Bioavailability of resveratrol. *Ann. N. Y. Acad. Sci.* 1215: 9–15.
- Walle, T., Hsieh, F., DeLegge, M.H., Oatis, J.E. Jr., and Walle, U.K. (2004). High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos.* 32: 1377–1382.
- Wang, F.M., Galson, D.L., Roodman, G.D., and Ouyang, H. (2011). Resveratrol triggers the pro-apoptotic endoplasmic reticulum stress response and represses pro-survival XBP1 signaling in human multiple myeloma cells. *Exp. Hematol.* 39: 999–1006.
- Wang, F., Li, R., Zhao, L., Ma, S., and Qin, G. (2020). Resveratrol ameliorates renal damage by inhibiting oxidative stress-mediated apoptosis of podocytes in diabetic nephropathy. *Eur. J. Pharmacol.* 885: 173387.
- Wang, G., Song, X., Zhao, L., Li, Z., and Liu, B. (2018). Resveratrol prevents diabetic cardiomyopathy by increasing Nrf2 expression and transcriptional activity. *BioMed Res. Int.* 2018: 2150218.
- Wang, H.-L., Gao, J.-P., Han, Y.-L., Xu, X., Wu, R., Fai, Y., and Cui, X.-H. (2015). Comparative studies of polydatin and resveratrol on mutual transformation and antioxidative effect *in vivo*. *Phytomedicine.* 22: 553–559.
- Wang, L., Zhao, H., Wang, L., Tao, Y., Du, G., Guan, W., Liu, J., Brennan, C., Ho, C.-T., and Li, S. (2020). Effects of selected resveratrol analogs on activation and polarization of lipopolysaccharide-stimulated BV-2 microglial cells. *J. Agric. Food Chem.* 68: 3750–3757.
- Wang, P., and Sang, S. (2018). Metabolism and pharmacokinetics of resveratrol and pterostilbene. *BioFactors.* 44: 16–25.
- Wang, X., Meng, L., Zhao, L., Wang, Z., Liu, H., Liu, G., and Guan, G. (2017). Resveratrol ameliorates hyperglycemia-induced renal tubular oxidative stress damage via modulating the SIRT1/FOXO3a pathway. *Diabetes Res. Clin. Pract.* 126: 172–81.
- Wen, D., Huang, X., Zhang, M., Zhang, L., Chen, J., Gu, Y., and Hao, C.-M. (2013). Resveratrol attenuates diabetic nephropathy via modulating angiogenesis. *PLoS ONE* 8: e82336.
- Wenzel, E., and Somoza, V. (2005). Metabolism and bioavailability of trans-resveratrol. *Mol. Nutr. Food Res.* 49: 472–481.
- Wu, H., Li, G.N., Xie, J., Li, R., Chen, Q.H., Chen, J.Z., Wei, Z.H., Kang, L.N., and Xu, B. (2016). Resveratrol ameliorates myocardial fibrosis by inhibiting ROS/ERK/TGF- β /perioxin pathway in STZ-induced diabetic mice. *BMC Cardiovasc. Disord.* 16: 5.
- Wu, H., Sheng, Z.-Q., Xie, J., Li, R., Chen, L., Li, G.-N., Wang, L., and Xu, B. (2016). Reduced HMGB 1-mediated pathway and oxidative stress in resveratrol-treated diabetic mice: A possible mechanism of cardioprotection of resveratrol in diabetes mellitus. *Oxi. Med. Cell. Longev.* 2016: 9836860.
- Wu, J., Li, M., He, J., Lv, K., Wang, M., Guan, W., Liu, J., Tao, Y., Li, S., Ho, C.-T., and Zhao, H. (2019). Protective effect of pterostilbene on concanavalin A-induced acute liver injury. *Food Funct.* 10: 7308–7314.
- Wu, Z., Huang, A., Yan, J., Liu, B., Liu, Q., Zhang, J., Zhang, X., Ou, C., and Chen, M. (2017). Resveratrol ameliorates cardiac dysfunction by inhibiting apoptosis via the PI3K/Akt/FoxO3a pathway in a rat model of diabetic cardiomyopathy. *J. Cardiovasc. Pharmacol.* 70: 184–93.
- Xian, Y., Gao, Y., Lv, W., Ma, X., Hu, J., Chi, J., Wang, W., and Wang, Y. (2020). Resveratrol prevents diabetic nephropathy by reducing chronic inflammation and improving the blood glucose memory effect in non-obese diabetic mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 393: 2009–17.
- Xie, X., Peng, J., Huang, K., Huang, J., Shen, X., Liu, P., and Huang, H. (2012). Polydatin ameliorates experimental diabetes-induced fibronectin through inhibiting the activation of NF- κ B signaling pathway in rat glomerular mesangial cells. *Mol. Cell. Endocrinol.* 362: 183–193.
- Yamamoto, T., Li, Y., Hanafusa, Y., Yeh, Y.-S., Maruki-Uchida, H., Kawakami, S., Sai, M., Goto, T., Ito, T., and Kawada, T. (2017). Piceatannol exhibits anti-inflammatory effects on macrophages interacting with adipocytes. *Food Sci. Nutr.* 5: 76–85.
- Yang, C., Wang, Y., Xie, Y., Liu, G., Lu, Y., Wu, W., and Chen, L. (2019). Oat protein-shellac nanoparticles as a delivery vehicle for resveratrol to improve bioavailability *in vitro* and *in vivo*. *Nanomedicine (Lond.)* 14: 2853–2871.
- Yang, G., Zhan, J., Yang, Y., Yuan, L., Wang, P., Ho, C.-T., and Li, S. (2021). Inhibitory effects of oxyresveratrol on ERK and Smad1/2 phosphorylation and HSC activation in preventing carbon tetrachloride-induced rat liver fibrosis. *Food Sci. Hum. Well.* 10: 6–12.
- Yang, J., Wang, Y., Cai, X., Qu, B., Zhang, Y., Sun, Z., and Yan, J. (2024). Comparative pharmacokinetics and tissue distribution of polydatin, resveratrol, and emodin after oral administration of Huzhang and Huzhang-Guizhi herb-pair extracts to rats. *J. Ethnopharmacol.* 318: 117010.

- Yang, X., Dai, L., Yan, F., Ma, Y., Guo, X., Jenis, J., Wang, Y., Zhang, J., Miao, X., and Shang, X. (2024). The phytochemistry and pharmacology of three Rheum species: A comprehensive review with future perspectives. *Phytomedicine*. 131: 155772.
- Yang, Y., Zhang, G., Li, C., Wang, S., Zhu, M., Wang, J., Yue, H., Ma, X., Zhen, Y., and Shu, X. (2019). Metabolic profile and structure-activity relationship of resveratrol and its analogs in human bladder cancer cells. *Cancer Manag. Res.* 11: 4631–4642.
- Yeo, S.C., Ho, P.C., and Lin, H.S. (2013). Pharmacokinetics of pterostilbene in Sprague-Dawley rats: the impacts of aqueous solubility, fasting, dose escalation, and dosing route on bioavailability. *Mol. Nutr. Food Res.* 57: 1015–1025.
- Zeng, K., Wang, Y., Yang, N., Wang, D., Li, S., Ming, J., Wang, J., Yu, X., Song, Y., Zhou, X., Deng, B., Wu, X., Huang, L., and Yang, Y. (2017). Resveratrol inhibits diabetic-induced Müller cells apoptosis through microRNA-29b/specificity protein 1 pathway. *Mol. Neurobiol.* 54: 4000–14.
- Zeng, K., Yang, N., Wang, D., Li, S., Ming, J., Wang, J., Yu, X., Song, Y., Zhou, X., and Yang, Y. (2016). Resveratrol prevents retinal dysfunction by regulating glutamate transporters, glutamine synthetase expression and activity in diabetic retina. *Neurochem. Res.* 41: 1050–1064.
- Zhan, J., Yang, G., Hu, T., Shen, J., Ho, C.-T., and Li, S. (2021). Pterostilbene is more efficacious than hydroxystilbenes in protecting liver fibrogenesis in a carbon tetrachloride-induced rat model. *J. Funct. Foods*. 84: 104604.
- Zhang, J., Dong, X.-J., Ding, M.-R., You, C.-Y., Lin, X., Wang, Y., Wu, M.-J.-Y., Xu, G.-F., and Wang, G.-D. (2020). Resveratrol decreases high glucose-induced apoptosis in renal tubular cells via suppressing endoplasmic reticulum stress. *Mol. Med. Rep.* 22: 4367–75.
- Zhang, K., Chen, J., Raza, F., Zafar, H., Xu, Y., Lui, R., Ullah, K.H., and Zhou, S. (2024). Advancing diabetes treatment: novel formulation of polydatin long-circulating liposomes and their glucose-regulating impact on hyperlipidemia-induced type 2 diabetic mice. *Mater. Adv.* 5: 6516–6534.
- Zhang, W., Yu, H., Lin, Q., Liu, X., Cheng, Y., and Deng, B. (2021). Anti-inflammatory effect of resveratrol attenuates the severity of diabetic neuropathy by activating the Nrf2 pathway. *Aging (Albany NY)* 13: 10659–10671.
- Zhang, Y., Ren, S., Ji, Y., and Liang, Y. (2019). Pterostilbene ameliorates nephropathy injury in streptozotocin-induced diabetic rats. *Pharmacology* 104: 71–80.
- Zhao, Y.Y., Cheng, X.L., Wei, F., Han, X.Q., and Lin, R.C. (2013). Pharmacokinetics, bioavailability, and metabolism of 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside in rats by ultra-performance liquid chromatography–quadrupole Time-of-Flight mass spectrometry and high-performance liquid chromatography-ultraviolet. *J. Liq. Chromatogr.* 36: 717–730.
- Zhao, Y.Y., Zhang, L., Feng, Y.L., Chen, D.Q., Xi, Z.H., Du, X., Bai, X., and Lin, R.C. (2013). Pharmacokinetics of 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside in rat using ultra-performance LC-quadrupole TOF-MS. *J. Sep. Sci.* 36: 863–871.
- Zou, Y., Wang, X., Bi, D., Fu, J., Han, J., Guo, Y., Feng, L., and Han, M. (2021). Pterostilbene nanoparticles with small particle size show excellent anti-breast cancer activity *in vitro* and *in vivo*. *Nanotechnology* 32: 325102.
- Zhang, Y., Shang, Z., Gao, C., Du, M., Xu, S., Song, H., and Liu, T. (2014). Nanoemulsion for solubilization, stabilization, and *in vitro* release of pterostilbene for oral delivery. *AAPS PharmSciTech.* 15: 1000–1008.
- Zhao, Y.-Y., Su, Q., Cheng, X.-L., Tan, X.-J., Bai, X., and Lin, R.-C. (2012). Pharmacokinetics, bioavailability and metabolism of rhaponticin in rat plasma by UHPLC-Q-TOF/MS and UHPLC-DAD-MSn. *Bioanalysis* 4: 713–723.
- Zu, Y., Zhang, Y., Wang, W., Zhao, X., Han, X., Wang, K., and Ge, Y. (2014). Preparation and *in vitro/in vivo* evaluation of resveratrol-loaded carboxymethyl chitosan nano-particles. *Drug Deliv.* 2014: 1–11.
- Zupančič, Š., Lavrič, Z., and Kristl, J. (2015). Stability and solubility of trans-resveratrol are strongly influenced by pH and temperature. *Eur. J. Pharm. Biopharm.* 93: 196–204.