Review article

Bioavailability of resveratrol: Possibilities for enhancement

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Abstract

Resveratrol is a naturally occurring polyphenol that has been shown to elicit a variety of beneficial effects *in vitro*. Translating these gains to *in vivo* and clinical settings has proven to be a major challenge, because of its poor oral bioavailability. This caveat was confirmed after reviewing clinical trials conducted on this investigational product over the past two years. This review provides alternative methods of administration of resveratrol which may enhance its bioavailability. However, these methods remain to be validated.

Keywords: Bioavailability; Clinical trials; Efficacy; Resveratrol

1 Introduction

It is increasingly recognised that grape products have various potential health benefits and possible applications in a clinical setting (Mukherjee et al., 2010; Vislocky and Fernandez, 2010; Artero et al., 2015). This is underscored by the French Paradox (Calabrese et al., 2010; Mukherjee et al., 2010; Artero et al., 2015), where the French population experiences less mortality due to coronary artery disease than other industrialised countries, despite a diet relatively high in saturated fats (Calabrese et al., 2010). This is also apparent in people who consume a Mediterranean diet. Cardiovascular health in the latter is partly attributed to moderate daily consumption of red wine (Calabrese, 2010; Calabrese et al., 2010; Artero et al., 2015; Giacosa et al., 2016).

Research has consequently focused on the potential health benefits of grape products, including grape seed extract (GSE) and red wine, and the underlying mechanisms thereof (Calabrese et al., 2010; Mukherjee et al., 2010; Vislocky and Fernandez, 2010; Smoliga et al., 2011; Park et al., 2012; Artero et al., 2015; Giacosa et al., 2016). Their possible beneficial properties have been shown in various pathologies which include cardiovascular (Chen et al., 2009; Crescente et al., 2009; Wong et al., 2013; Mulero et al., 2015; Riccioni et al., 2015; Tomayko et al., 2014; Bhullar and Udenigwe, 2016;), cancer (De Amicis et al., 2011; De Leo et al., 2011; Osmond et al., 2012; Zhu et al., 2012; Feng et al., 2016;), type 2 diabetes mellitus (T2DM) (Kang et al., 2010; Palsamy and Subramanian, 2010; Amiot et al., 2016) and neurodegenerative disorders (Jin et al., 2008; Zhang et al., 2013; Bastianetto et al., 2015).

These activities are largely ascribed to the polyphenol components of these products (Calabrese et al., 2010; Mukherjee et al., 2010; Fernández and Fraga, 2011; Artero et al., 2015; Giacosa et al., 2016). One such compound, which has received particular interest, is resveratrol, (*trans*-3,5,4′-trihydroxystilbene, RES). RES is a natural phytoalexin found in many plant species and produced in response to environmental stress (Mukherjee et al., 2010; Park et al., 2012). It was originally identified as the main active ingredient in *Polygonum cuspidatum* (Japanese knotweed), a plant widely used in Japanese and Chinese traditional medicine to treat fungal infections, inflammatory skin disorders, hepatotoxicity and cardiovascular disease (CVD) (Mukherjee et al., 2010). RES also displays anti-inflammatory and anti-oxidant properties which may be effective in the treatment of diseases with an inflammatory and oxidative aetiology such as chronic obstructive pulmonary disorder (COPD) (Fernández and Fraga, 2011; Barnes, 2013; Ma et al., 2015; Trotta et al., 2015, 2016; Banu et al., 2016). In addition RES has also displayed anti-inflammatory effects in a pre-clinical model of rheumatoid arthritis (Choo et al., 2014). RES exists as two isoforms, with the *trans*-resveratrol isoform being more biologically active than its *cis* counterpart (Fig. 1) (Calabrese et al., 2010; Mukherjee

et al., 2010; Artero et al., 2015).

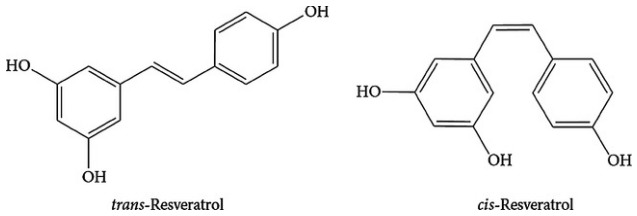

Fig. 1 Structures of *cis*- and *trans*-resveratrol.

alt-text: Fig. 1

RES has been studied extensively as a major contributor to the health benefits associated with the consumption of grape products. *In vitro* studies have clearly demonstrated the potential of resveratrol as a "therapeutic agent"; and yet animal and clinical trials have shown inconsistent, often less promising results. This is believed to be due to the notoriously low bioavailability of oral RES (in some instances as low as 0%) (Yiu et al., 2015; Sahebkar et al., 2015; Heebøll et al., 2016; Thazhath et al., 2016; Wong et al., 2016; Zortea et al., 2016) most likely due to its poor metabolic stability which is a result of its phase II metabolism (glucoronidation and sulfation) (Walle et al., 2004).

This overview provides recommendations concerning measures that may improve resveratrol's pharmacokinetics and therefore, bioavailability.

2 Methodology

A literature search was conducted between 2014 and 2016 by using the keywords: 'resveratrol and clinical trials'. A separate search was conducted on 'resveratrol and bioavailability' which was not confined to specific dates. The databases searched included: PubMed; Science Direct and Google Scholar.

3 Discussion

Results from clinical trials on RES and published between 2014 and 2016 (Table 1) indicate that resveratrol can cross the blood-brain-barrier (BBB) as it showed some efficacy in Alzheimer's disease (AD), Friedreich ataxia (FRDA), memory enhancement and an increase in cerebral blood flow (CBF) (Witte et al., 2014; Turner et al., 2015; Wightman et al., 2015; Yiu et al., 2015). RES's efficacy in ulcerative colitis (UC), indicates that orally administered RES can furnish concentrations in the gastrointestinal tract (GIT) sufficient to result in therapeutic benefits (Patel et al., 2010). This is thought to be due to RES's accumulation in epithelial cells lining the digestive tract (Almeida et al., 2009). RES was however found to be mostly ineffective in pathologies, such as CVD, T2DM and non-alcoholic fatty liver disease (NAFLD).

Table 1 Clinical trials conducted on resveratrol published between 2014 and 2016.

Aim	Treatment	Results
Determine the most efficacious dose of resveratrol to improve cerebral vasodilator responsiveness (CVR) in T2DM (Wong et al., 2016).	Synthetic *trans*-resveratrol once weekly (75 mg, 150 mg or 300 mg) versus placebo, for 4 weeks.	Significant enhancement in CVR compared to placebo. Maximum improvement was seen with the lowest dose.
[a]Evaluate effects of resveratrol treatment on glucagon-like peptide 1 (GLP-1) secretion, gastric emptying and glycaemic control in T2DM (Thazhath et al., 2016).	Resveratrol twice daily (500 mg) versus placebo, for 5 weeks.	No significant effect on GLP-1 secretion, gastric emptying or glycaemic control compared to placebo.
Evaluate the effect of a proprietary *trans*-resveratrol formulation on manifestations of diabetic foot syndrome (DFS) in patients with T2DM (Bashmakov et al., 2014).	*trans*-resveratrol twice daily (50 mg) versus placebo, for 60 days.	Resveratrol reduced foot ulcer size (in terms of both surface area and cumulative size) and plasma fibrinogen level compared to placebo.
Evaluate the effect of resveratrol on insulin resistance, glucose and lipid metabolism in non-alcoholic fatty liver disease (NAFLD) (Chen et al., 2015).	Resveratrol twice daily (150 mg) versus placebo, for 12 weeks.	Significant decrease in aspartate aminotransferase (AST), glucose, low-density lipoprotein (LDL) cholesterol, alanine aminotransferase (ALT), total cholesterol and homeostasis model assessment insulin resistance index (HOMA-IR) compared to placebo.
[a]Evaluate whether resveratrol alleviates NAFLD (Heebøll et al., 2016).	Resveratrol daily (1500 mg) versus placebo, for	No consistent therapeutic effect in alleviating clinical or histological NAFLD was

	24 weeks.	observed.
[a]Evaluate the effects of resveratrol supplementation and lifestyle modifications on cardiovascular (CV) risk factors in patients with NAFLD (Faghihzadeh et al., 2015).	Resveratrol daily (500 mg) versus placebo, for 12 weeks.	No beneficial effect on anthropomorphic measurements, insulin resistance markers, lipid profile or blood pressure compared to placebo. Resveratrol did, however, significantly reduce ALT and hepatic steatosis compared to placebo.
[a]Evaluate the effects of resveratrol in patients with NAFLD, to assess whether it could be a potential therapeutic agent to alleviate symptoms (Chachay et al., 2014).	Resveratrol daily (3000 mg) versus placebo, for 8 weeks.	No significant improvement in insulin resistance, steatosis, or abdominal fat distribution when compared with placebo. However, the resveratrol group displayed an increase in liver enzymes.
Evaluate the effects of resveratrol supplementation as an anti-inflammatory and antioxidant agent on inflammation and quality of life (QOL) in patients with active ulcerative colitis (UC) (Samsami-kor et al., 2015).	Resveratrol daily (500 mg) versus placebo, for 6 weeks.	Improved QOL in patients with UC. The resveratrol group showed a significant reduction in inflammatory markers compared to placebo.
[a]Evaluate efficacy of two doses of resveratrol on peripheral blood mononuclear cell (PBMC) frataxin levels in individuals with Friedreich ataxia (FRDA) (Yiu et al., 2015).	Resveratrol daily (1000 mg or 5000 mg), for 12 weeks.	No significant effect on frataxin levels in patients with FRDA.
Evaluate safety and tolerability as well as the effect of resveratrol on plasma biomarkers, volumetric magnetic resonance imaging (MRI) outcomes and clinical outcomes of Alzheimer's disease (AD) (Turner et al., 2015).	Resveratrol (500 mg/day, with dose escalation of 500 mg increments every 13 weeks, ending with 1000 mg twice daily) versus placebo, for 52 weeks.	The study provided Class II evidence that resveratrol is safe for patients with AD, is well tolerated, and alters the trajectories of some AD biomarkers.
[a]Evaluate the effects of resveratrol on prostate size, prostate specific antigen (PSA) and sex steroid hormones in patients with benign prostate hyperplasia and metabolic syndrome (Kjær et al., 2015).	Resveratrol twice daily (75 mg or 500 mg) versus placebo, for 16 weeks.	No significant differences in terms of PSA concentration or prostate volume.
Evaluate the efficacy of resveratrol treatment on bone density in men with metabolic syndrome (Ornstrup et al., 2014).	Resveratrol daily (150 mg or 1000 mg) versus placebo, for 16 weeks.	High dose resveratrol positively affected bone, mainly by stimulating mineralisation.
[a]Evaluate efficacy of resveratrol on CV risk markers in overweight/slightly obese subjects (van der Made et al., 2015).	Resveratrol daily (150 mg) versus placebo, for 4 weeks.	No significant change in CV risk markers compared to placebo.
[a]Evaluate the efficacy of resveratrol supplementation on serum glucose and CV risk factors in patients with schizophrenia (SZ) (Zortea et al., 2016).	Resveratrol daily (200 mg) versus placebo, for 4 weeks.	No significant differences in body weight, waist circumference, glucose or total cholesterol compared to placebo.
Evaluate effects of chronic *trans*-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow (CBF) (Wightman et al., 2015).	Pure *trans*-resveratrol daily (500 mg) versus placebo, for 4 weeks.	Significant increase in blood flow in the frontal cortex compared to placebo. Extended supplementation revealed significantly reduced fatigue, as well as higher diastolic BP.
Evaluate whether resveratrol supplementation would enhance memory performance in older adults (Witte et al., 2014).	Resveratrol daily (200 mg) versus placebo, for 26 weeks.	Improved memory performance, glucose metabolism, and increased hippocampal functional connectivity (FC) compared to placebo.
Evaluate whether *trans*-resveratrol has beneficial effects on angiogenesis-related markers in peritoneal dialysis (PD) patients (Lin et al., 2016).	Trans-resveratrol daily (150 mg or 450 mg) versus placebo, for 12 weeks.	After 12 weeks, both the high- and low-dose resveratrol groups showed significant improvement in net ultrafiltration (UF) volume and rate, compared to placebo. The high-dose group showed significant reductions in angiogenesis-related markers compared to placebo.

[a] Trials where the desired study outcome was not achieved.

It is important to consider the pharmacokinetic profile of a compound if it is intended to be used as a therapeutic agent. Currently, RES is only administered orally. Although RES is well absorbed it has low bioavailability, resulting in low plasma concentrations which gives rise to limited systemic distribution and concentrations that are not high enough at certain active sites to elicit significant pharmacological effects. This appears to be a reason for RES's failure compared to placebo treatment (Table 1). The expected beneficial effects of RES do not appear to be realised possibly due to bioavailability issues, which has prompted exploring and proposing different routes of RES administration.

3.1 Synergism with other phytochemicals

One aspect under research is the use of other phytochemicals in conjunction with RES, which is hoped will improve RES's bioavailability by protecting it from rapid metabolism (Johnson et al., 2011; Smoliga and Blanchard, 2014; Wightman et al., 2014). In mice, it has been found that piperine (10 mg/kg) combined with resveratrol (100 mg/kg) results in a 1544% increase in C_{max}; whereas the degree of exposure (i.e. area under the curve [AUC]) to RES was enhanced by 229% (Johnson et al., 2011).

The effect of piperine as an adjunct to RES treatment has been assessed for enhancement of cerebral blood flow and cognitive performance in healthy human volunteers (Wightman et al., 2014). The study concluded that co-supplemented piperine (20 mg three times daily) enhanced RES's (250 mg three times daily) bioefficacy. This, however, pertained to increased CBF, but not cognitive performance (Wightman et al., 2014). In the latter study, RES's bioavailability was not altered (Wightman et al., 2014) and therefore, it cannot be confirmed whether RES was responsible for these effects. It is possible that the CBF effects were due to piperine's action alone. It is recommended that further research be carried out on piperine co-supplementation where the mechanism of activity is elucidated.

3.2 Prodrugs

A potential avenue for maximising RES's bioavailability is the use of prodrugs (Smoliga and Blanchard, 2014). This approach aims to increase the amount of free *trans*-resveratrol by allowing the prodrug to generate RES within cells through enzymatic reactions, resulting in increased concentrations for enhanced biological activity at the target site (Smoliga and Blanchard, 2014). For a prodrug to be effective, three requirements should be met: the drug should be (I) metabolised leading to the generation of high plasma concentrations of the drug, (II) it should be absorbed into the tissue of interest and reach the target site where metabolism takes place, and (III) the prodrug itself should have desirable pharmacokinetics (Smoliga and Blanchard, 2014).

An example of a prodrug that has been under investigation is 3,5,4′-tri-*O*-acetylresveratrol (TARES) (Fig. 2) (Koide et al., 2011; Liang et al., 2013). A full pharmacokinetic analysis of RES and TARES has been performed in rats (Liang et al., 2013). It was shown that RES generated from TARES was eliminated at a much slower rate than RES in its free form. Furthermore, after administration the concentration of generated RES in the lungs was seven times higher than when RES was administered in its free form (Liang et al., 2013). The pharmacokinetic profile of generated RES was improved, albeit not significantly, as evidenced by a prolonged $t_{½}$ and an increased exposure after TARES administration (Table 2) (Liang et al., 2013).

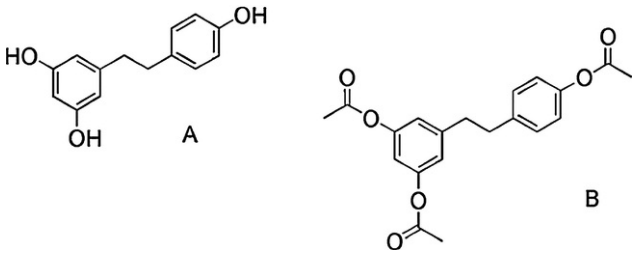

Fig. 2 Chemical Structures of resveratrol (A) and TARES (B).

Table 2 Exposure and half-life of TARES and resveratrol.

Parameters	TARES (mg/kg)			Resveratrol (mg/kg)	P-value
	77.5	155	310	100	
$AUC_{0-\infty}$ (mg min/L)	272.7 ± 31.2	558.5 ± 58.9	1069.6 ± 115.7	320.0 ± 42.85	>0.05
$t_{½}$ (min)	370.1 ± 50.7	394.7 ± 43.6	419.7 ± 47.5	118.0 ± 20.31	>0.05

In vitro tests suggested no significant protective difference between TARES and free RES on γ-irradiation (Koide et al., 2011). In *in vivo* mice models, however, TARES with Cremephor EL as vehicle showed a better protective

activity than RES. This was attributed to its significantly improved stability against hydrolysis (Koide et al., 2011). TARES holds promise as an effective prodrug which increases the bioefficacy of RES by elevating the plasma level of free *trans*-resveratrol. Further testing, such as pre-clinical safety testing, is required to establish whether TARES could be used in a clinical setting.

3.3 Alternative routes of administration

Orally administered RES results in low bioavailability and the possibility exists that better efficacy will be observed if RES is administered via a different route. An administration route where first-pass metabolism is avoided, thereby allowing the drug to bypass the GIT will increase the bioavailability of RES, allowing for higher concentrations at active sites.

A novel inhalable spray-dried formulation of RES could be an effective future candidate in the treatment of COPD (Trotta et al., 2015). Trotta et al. (2015) developed a formulation that met all criteria (particular size, mass median aerodynamic diameter, geometric standard deviation, total recovery of loaded dose, sufficient aerosol performance, stability, absorption and rate of transport) for administration to the lung epithelium. By utilising the inhalable route of administration, the hope is that the concentration of RES will be maximised in the lungs, where it can elicit its biological effect. Bioavailability studies have not yet been performed, and it is suggested that this be pursued.

Oral transmucosal administration is another route being investigated (Ansari et al., 2011; Blanchard et al., 2014). A proof of concept study on the formulation of resveratrol-excipient lozenges investigated the solubility of the resveratrol-excipient matrices in water; and a bioavailability experiment with two healthy male participants was performed (Blanchard et al., 2014). The study demonstrated that the resveratrol-ribose lozenges had superior solubility compared to other resveratrol-excipient lozenges tested (Blanchard et al., 2014). This formulation achieved higher C_{max} values of RES and a quickened entry into the bloodstream compared to administration dependent on gastrointestinal absorption (Blanchard et al., 2014). No direct comparisons were made to RES in its free form, the study merely served as a proof of concept (Blanchard et al., 2014).

Increasing the solubility, stability and permeation of RES may be possible by complexing it with cyclodextrin-based nanosponges (NS) (Ansari et al., 2011). Resveratrol-loaded NS have shown more favourable release and stability profiles *in vitro* compared to RES alone (Ansari et al., 2011). An accumulation study in rabbit mucosa showed better accumulation with the NS than with the free RES (Ansari et al., 2011). A permeation study using pig skin revealed that the NS showed good permeation (Ansari et al., 2011). This method is proposed to be appropriate for buccal delivery, or as a topical application (Ansari et al., 2011). However, these methods require further testing in *in vivo* animal models before human trials can commence.

3.4 Nanotechnology

In recent years, interest in nanotechnology has grown considerably, and researchers have investigated its use in increasing the clinical efficacy of natural products, such as RES. Nanoparticles have been shown to increase the bioavailability of natural products, by improving the molecule of interest's stability within biological systems (Smoliga and Blanchard, 2014; Watkins et al., 2015). Furthermore, Nanoparticles have been found to increase the solubility and transport across membranes of these compounds (Neves et al., 2013; Watkins et al., 2015).

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been found to effectively increase the oral bioavailability of RES by protecting the incorporated RES from rapid metabolism, with the additional advantage of a more controlled release profile (Neves et al., 2013). This finding was supported for SLNs in another study on RES (Teskač and Kristl, 2010).

Phytochemicals conjugated to gold nanoparticles have been shown to have an enhanced bioavailability, cellular uptake and anti-cancer activity compared to the phytochemicals alone (Sanna et al., 2014). *In vitro* experiments with gold-conjugated RES nanoparticles (RES-AuNPs) versus RES alone, found RES-AuNPs to effectively inhibit MCF-7 cancer cell progression, with better anti-invasive activity than RES alone, without cytotoxicity (Park et al., 2016).

Promising results have been reported for cationic chitosan- and anionic alginate-coated poly(D,L-lactide-coglycolide) nanoparticles, allowing for controlled release of RES and protection from light-exposure degradation (Sanna et al., 2012). These nanoparticles have been found suitable for the encapsulation and administration of RES, due to increased stability of RES, improved drug loading and a controlled release mechanism (Sanna et al., 2012). The authors of the study report that these nanoparticles have the potential to effectively prevent or suppress cancers via i.v. or topical administration (Sanna et al., 2012). This is yet to be tested in animal studies.

A review on the utilisation of nanotechnology for the delivery of natural products concluded that nanotechnology may be a superior method for chemoprevention and chemotherapy compared to currently available treatments (Siddiqui and Sanna, 2016). Unfortunately, very few clinical trials have been conducted to test such formulations. Nanotechnology is not without its drawbacks. These include: potential toxicity, possibility of crossing biological membranes such as the blood-brain-barrier, possible changes that could occur to the nanoparticles in the body, targeting issues and their shortened half-life due to the immune macrophage system in the liver and spleen (Watkins et al., 2015). Considering the potential that nanotechnology holds in treatment, research should be focussed on these issues.

3.5 Metabolites

There is some controversy surrounding the idea that it may be the metabolites of RES that contribute to the biological effects that are observed, rather than RES itself (Smoliga and Blanchard, 2014). Sulfate metabolites of RES have been shown to result in biologically active concentrations of resveratrol intracellularly (Patel et al., 2013). The current thought is that RES monosulfates can deliver RES to target tissues more effectively *in vivo,* as it is more stable in its conjugated form (Patel et al., 2013). RES monosulfates have been found to regenerate RES in mice maintaining physiological concentrations in plasma and tissues (Patel et al., 2013). Also, an *in vitro* study conducted on colorectal cell lines showed that sulfate metabolites serve as an intracellular reservoir of RES (Patel et al., 2013). This *in vivo* method of resveratrol generation may prove to be more effective in obtaining therapeutic benefits (Patel et al., 2013). Further comparative studies would be of value, to ascertain whether the administration of RES metabolites is more beneficial than traditional RES administration.

3.6 Novel formulations

The synthesis of a novel product consisting of red grape cells (RGC) has been carried out (Azachi et al., 2014). The main polyphenol in RGC is RES with one hexose moiety (Azachi et al., 2014). The human pharmacokinetic analysis of RGC-resveratrol revealed a relatively high bioavailability compared to RES alone (Azachi et al., 2014). The glycosylated structure of RGC-resveratrol provided more stability and resistance to enzymatic degradation (Azachi et al., 2014). Furthermore, the RGC has a higher water solubility than RES (Azachi et al., 2014). This stability and probable higher solubility in bodily fluids, combined with the rapid gastrointestinal absorption that was observed, means that RGC-resveratrol could serve as an effective alternative to pure *trans*-resveratrol in a clinical setting (Azachi et al., 2014). Clinical studies need to be performed to investigate this further.

3.7 Dose-manipulation

Another strategy that has been investigated to enhance RES's oral bioavailability is dose-manipulation by saturating the enzymes responsible for its metabolism. Since RES is known to have poor metabolic stability owing to extensive phase II metabolism, it has been hypothesised that dose-escalation could result in the saturation of metabolic enzymes in the GIT, resulting in increased oral bioavailability of the compound.

However, studies have shown that this does not seem to be the case. A study by Chen et al. (2016) on Sprague-Dawley rats was performed with the intention of characterising the pharmacokinetic profile of oxyresveratrol (OXY), a RES analogue. A comparison was made between Sprague-Dawley rats receiving OXY and those receiving RES, both i.v. and orally. It was found that the oral bioavailability of RES displayed linear pharmacokinetics, even at high doses (200 and 400 μmol/kg) (Chen et al., 2016). This is uncharacteristic of what would be seen had the metabolic enzymes in the GIT been saturated.

Furthermore, Das et al. (2008) performed a dose-escalation study where 15, 25 and 50 mg/kg of RES was administered to Sprague-Dawley rats. None of the dosages showed a significant difference in bioavailability, with RES displaying linear pharmacokinetics, even at dosages as high as 50 mg/kg (Das et al., 2008).

3.8 Naturally occurring resveratrol analogues

Some naturally occurring resveratrol analogues possess a stronger pharmacological potency and have a more favourable pharmacokinetic profile than RES itself.

Resveratrol trimethyl ether (*trans*-3,5,4′-trimethoxystilbene, RTE) is a polyphenonic compound and natural analogue of RES. RTE has been found to have better metabolic stability than RES, as its clearance is 8–9 fold slower (Lin and Ho, 2011). Furthermore, RTE's plasma exposure after oral and i.v. administration was much greater than that of RES. This improved metabolic stability of RTE is attributed to the complete methoxylation of the compound's hydroxyl groups (Lin and Ho, 2011). The authors determined that the major determinant of RTE's oral absorption was aqueous solubility; which they showed could be improved by drug delivery systems such as randomly methylated-β-cyclodextrin (RM-β-CD) (Lin and Ho, 2011). RTE has a more favourable pharmacokinetic profile than RES, and the possibility exists of enhancing its oral bioavailability further through the use of drug delivery systems., Ffurther investigation is warranted for the use of RTE as a therapeutic agent.

Pterostilbene (*trans*-3,5-dimethoxy-4′-hydroxystilbene, PTS) is another RES analogue shown to be a suitable candidate for further development. PTS has been shown to possess a more favourable pharmacokinetic profile than RES, due to a much slower clearance, longer mean transition time and a more abundant plasma exposure (Yeo et al., 2013). This has been ascribed to PTS having less hydroxyl groups than RES, making it less susceptible to conjugation metabolism. The favourable pharmacokinetics of PTS has been confirmed by Choo et al. (2014), where PTS showed superior anti-inflammatory activity compared to RES *in vitro*. In addition, *in vivo* PTS was found to distribute extensively to major drug target organs, such as the kidneys, liver, heart, brain and lungs (Choo et al., 2014). With these considerations, PTS could be a viable option as a therapeutic agent, especially for anti-inflammatory purposes.

Oxyresveratrol (trans-3,5,2′,4′-tetrahydroxystilbene, OXY), yet another RES analogue, has an additional hydroxyl group on the aromatic ring which results in it having better water solubility than RES. Chen et al. (2016) examined the pharmacokinetic profile of OXY and RES in Sprague-Dawley rats. The AUC and mean transit time of OXY was found comparable to that of RES (Chen et al., 2016). OXY was found to be orally bioavailable and was absorbed much faster and cleared much slower than RES. Owing to the favourable pharmacokinetics, further studies on the efficacy of OXY as a therapeutic agent is warranted.

The methoxylated analogue of RES, isorhapontigenin (trans-3,5,4′-trihydroxy-3′-methoxystilbene, ISO) has been found to be approximately 50% more orally bioavailable than RES and possess rapid absorption and abundant

plasma exposure (Yeo et al., 2017). In terms of efficacy, with regards to anti-inflammatory activity, ISO was found to be superior to RES (Yeo et al., 2017). Of great interest, was ISO's suppression of the PI3K/Akt pathway, which is insensitive to corticosteroids. ISO's superior pharmacokinetics and anti-inflammatory activity when compared to RES suggests that it may be more worthwhile to develop further than RES.

The RES analogue *trans*-4-4′-dihydrostilbene (DHS) has shown promising anti-cancer activity in pre-clinical studies (Chen et al., 2015). Similar to RTE, the major barrier to DHS's oral absorption was found to be its aqueous solubility. This was overcome by solubilising DHS with hydroxypropyl-β-cyclodextrin, which yielded a pharmacokinetic profile that was superior to that of RES. The studies by Lin and Ho (2011) and Chen et al. (2015) shed light on the possible benefit of cyclodextrins in improving the pharmacokinetic profiles of analogues of RES, and warrants further investigation.

4 Conclusion

From current literature, it is clear that orally administered resveratrol has low bioavailability *in vivo.* A variety of methods that could overcome the inherent issues with resveratrol bioavailability have been proposed, however these need to be further validated in order to determine which are safe, effective and superior to traditional oral administration of resveratrol before clinical evaluation can take place.

Declaration of interest

The authors state no conflict of interest.

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Highlights

- Resveratrol has a variety of beneficial effects *in vitro*.
- Orally administered resveratrol has low bioavailability *in vivo*.
- Methods are proposed for enhancing bioavailability.