REVIEW

Effects of resveratrol on drug- and carcinogen-metabolizing enzymes, implications for cancer prevention

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Abstract

Resveratrol is a polyphenol found in grape skins and peanuts that has demonstrated many health benefits including protection against aging, cardiovascular and metabolic disease, neurological decline, and cancer. The anticancer properties of resveratrol have been attributed to a variety of mechanisms, including its general inhibition of phase I metabolism and induction of phase II metabolism. The effects of resveratrol on these enzymes, however, are still unclear, as in vitro evidence often contrasts with animal studies and clinical trials. Reasons for these variances could include the low bioavailability of resveratrol and the effects of resveratrol metabolites. Due to resveratrol's interactions with drug-metabolizing enzymes and drug transporters, individuals concurrently taking pharmacological doses of resveratrol with other supplements or medications could potentially experience nutrient-drug interactions. This review summarizes the known effects of resveratrol and its main metabolites on drug metabolism in order to help characterize which populations might benefit from resveratrol for the prevention of cancer, as well as those that may need to avoid supplementation due to potential drug interactions.

Abbreviations

ABCATP, -binding cassette; AHR, aryl hydrocarbon receptor; AUC, area under the curve; B[a], Pbenzo-*a*-pyrene; BCRP, breast cancer resistance protein; BROD, 7-benzoxy resorufin *O*-deethylation; CDNB, 1-chloro-2,4-dinitrobenzene; COX-2, cyclooxygenase-2; CYP, cytochrome P450; DBF, *O*-benzylfluorescein benzyl ester; DMBA, dimethylbenz[*a*]anthracene; EROD, ethoxyresorufin-*O*-deethylase; GST, glutathione-*S*-transferase; HED, human equivalent dose; MRP3, multidrug resistance protein 3; NQO1, NAD(P)H dehydrogenase, quinone 1; NQO2, NAD(P)H dehydrogenase, quinone 2; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; PNPH, p-nitrophenol hydroxylase; R34S, resveratrol-3-O-4′-O-disulfate; R3G, resveratrol-3-*O*-glucuronide; R3S, resveratrol-3-*O*-sulfate; R4S, resveratrol- 4′-*O*-sulfate; ROS, reactive oxygen species; TCDD, 2,37,8-tetrachloro-dibenzo-p-dioxin; TMS, 2,3,3′5′-tetramethoxystilbene; UGT, Uridine diphosphate-glucuronosyl transferase; XRE, xenobiotic response element.

Introduction

Resveratrol (3, 4′,5-trihydroxy-*trans*-stilbene; see Fig. 1) is a polyphenol found in grapes and peanuts that has demonstrated anticancer, antiaging, and anti-inflammatory properties in preclinical models (Zordoky et al. 2015). Evidence supporting the clinical benefit of resveratrol supplementation is mixed, but recent reviews examine the evidence for resveratrol as an agent to prevent and/or treat obesity (de Ligt et al. 2015), cardiovascular disease (Zordoky et al. 2015), diabetes (Szkudelski and Szkudelska 2015), neurological disease (Bastianetto et al. 2015), aging (Ramis et al. 2015), and cancer (Patel et al. 2013; Carter et al. 2014). Many questions remain regarding the dose and duration of resveratrol supplementation for either prevention or as a therapeutic and
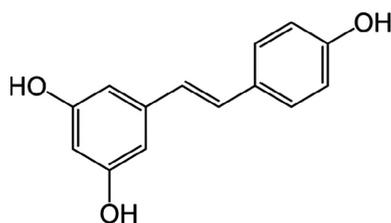
Figure 1. Structure of transresveratrol, a trihydroxystilbene naturally found in red wine and peanuts.

for which conditions. To determine who might benefit from resveratrol for cancer prevention, it is imperative to understand the ideal dose, the activity of resveratrol metabolites, and pharmacological targets.

Resveratrol Dosing

Resveratrol is available over the counter with single capsules containing between 20 to 500 mg pure resveratrol (Chachay et al. 2011). With pharmaceutical doses (i.e. doses attainable only through supplementation and not by a balanced diet alone) being not only achievable but also easily accessible, questions of toxicity and safety have emerged. Detailed reviews of the bioavailability, metabolism, and toxicity of resveratrol are available (Wenzel and Somoza 2005; Cottart et al. 2014). Based on clinical trials (Brown et al. 2010; Chow et al. 2010; Kalash et al. 2014) and on human equivalent dose (HED) calculations from animal models (Crowell et al. 2004), the majority of the available evidence supports an upper limit of 1 g daily for most individuals. However, in one study, doses as high as 2 g daily were safe and well-tolerated in older adults with Alzheimer disease when starting with a dose of 500 mg daily and increasing by an additional 500 mg every 13 weeks (Turner et al. 2015). It is possible that the higher tolerable upper limit in this trial could be due to the gradual dose escalation schedule, or could be population dependent.

The ideal dose for resveratrol supplementation, however, may be less. Metabolic disturbance is a risk factor for multiple cancer types (Uzunlulu et al. 2016) and reversal of metabolic disturbances by low-dose resveratrol may reduce cancer risk as well as improve cancer outcomes (Fay et al. 2009; Seyfried and Shelton 2010). In recent clinical trials, 5–250 mg doses of resveratrol showed a positive effect on metabolic parameters [e.g. glycemic control, insulin sensitivity, the Homeostasis Model Assessment (HOMA) index, and oxidative stress] in diabetics (Brasnyó et al. 2011; Bhatt et al. 2012) as well as healthy obese adults (Timmers et al. 2011; Witte et al. 2014). However, in a recent, randomized, controlled cross-over trial with diet-controlled diabetics, 1 g daily resveratrol had no effect on glycemic control or other metabolic parameters (Thazhath et al. 2016). Similarly, doses ranging from 1 to 2 g daily resveratrol had little

or no benefit in older adults with glucose intolerance (Crandall et al. 2012) or healthy obese males (Dash et al. 2013; Poulsen et al. 2013). While the specific metabolic parameters measured are study dependent, taken together, these clinical trials suggest higher efficacy of resveratrol on metabolic control at a lower dose. Conversely, one small, randomized clinical trial in individuals with metabolic syndrome showed that 1.5 g resveratrol daily improved AUC of insulin and insulinogenic index compared to placebo (Méndez-del Villar et al. 2014). Only one animal study has investigated differential dosing of resveratrol; in mice fed a high fat diet, 5 mg resveratrol (HED of 28 mg for a 70 kg human) reduced intestinal adenoma number and volume more potently than a 1 g dose, this efficacy was correlated with activation of adenosine monophosphate-activated protein kinase (AMPK), a central regulator of metabolic control (Cai et al. 2015). One explanation for this nonlinear dose response is that lower doses of antioxidants allow for low levels of reactive oxygen species (ROS) to activate natural cellular defense mechanisms (Cai et al. 2015). It is also possible that higher doses of resveratrol compete with other polyphenols for transporters, reducing their uptake and potential synergistic effects.

Resveratrol Metabolites

The benefits of oral resveratrol could also be derived from its metabolites, which have demonstrated more potent activity than resveratrol against multiple cancer types in some preclinical models (Aires et al. 2013; Ruotolo et al. 2013). Resveratrol has high oral absorption (up to 70%) (Walle et al. 2004) but is rapidly metabolized by sulfotransferases (Miksits et al. 2005) and UDP-glucuronosyltransferases (Brill et al. 2006). Emerging evidence also indicates a role for the gut microbiome in resveratrol metabolism (Qiao et al. 2014; Cai et al. 2015).

The primary metabolite in humans is the sulfated metabolite resveratrol-3-*O*-sulfate (R3S). Other sulfated metabolites include resveratrol-4′-*O*-sulfate (R4S) and resveratrol-3-*O*-4′-*O*-disulfate (R34S) (Miksits et al. 2005). Glucuronidated metabolites include resveratrol-3-*O*-glucuronide (R3G) and resveratrol-4′-*O*-glucuronide (R4G). A glucuronide-sulfate metabolite has also been detected in humans after resveratrol administration (Chow et al. 2010). Piceatannol (3,4,3′,5′-tetrahydroxy-*trans*-stilbene) is a minor metabolite which results from metabolism of resveratrol by cytochrome P450 enzymes (CYPs) (Chang et al. 2007). Figure 2 illustrates the structures of these main metabolites of resveratrol, including piceatannol. In addition, 3,4′-dihydroxy-*trans*-stilbene, 3,4′-dihydroxybibenzyl (lunularin), and dihydroresveratrol have been identified as human gut microbial metabolites (Bode et al. 2013).
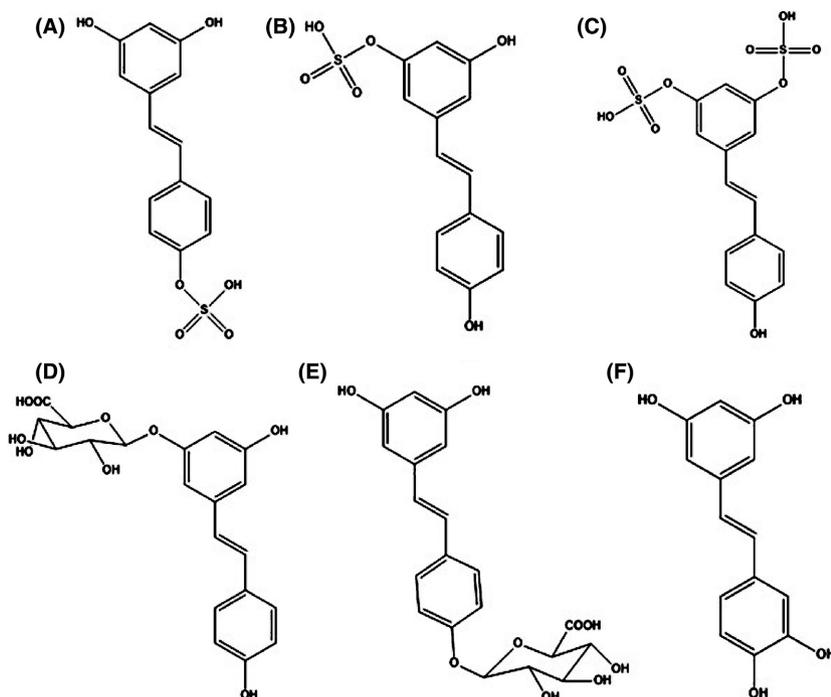
Figure 2. Structures of resveratrol's main metabolites. (A) transresveratrol-4′-O-sulfate (main metabolite found in mice) (B) transresveratrol-3-O-sulfate (main metabolite found in humans) (C) transresveratrol-3-O-4′-O-disulfate (D) transresveratrol-3-O-glucuronide (major glucuronide product) (E) transresveratrol-4′-O-glucuronide, (F) piceatannol (a minor resveratrol metabolite that is quickly metabolized by phase II enzymes).

Resveratrol and Chemoprevention

Resveratrol has been shown to act as a calorie-restriction mimetic, antioxidant, and anti-inflammatory agent, supporting an anticancer environment (Kulkarni and Cantó 2014; Bitterman and Chung 2015). Less attention has been given to another mechanism by which resveratrol may prevent carcinogenesis, namely, through the inhibition of procarcinogen-activating enzymes (phase I metabolism, or CYPs) and induction of conjugation enzymes (phase II metabolism). While some of resveratrol's interactions with CYP enzymes have been summarized in an existing review (Detampel et al. 2012), we will present the updated evidence and include a discussion of resveratrol's effects on phase II metabolism, focusing on implications for cancer prevention. Figure 3 illustrates the systemic actions of resveratrol based on the available evidence. We will also discuss the anticancer activities of resveratrol's main glucuronide and sulfate metabolites when evidence is available.

Resveratrol and Phase I Metabolism

Phase I metabolism of pharmaceutical drugs, phytochemicals, environmental pollutants, and other endogenous and exogenous compounds is accomplished mainly by the CYP enzymes. CYPs catalyze oxidation, reduction, hydrolysis, deamination, and other reactions that add or expose polar substituents to a compound (Omiecinski et al. 2011). This increased polarity may facilitate the elimination of these compounds, or perhaps create a bioactive metabolite. Altering the activity of these enzymes could result in reduced efficacy or increased toxicity of treatment regimens. The effects of resveratrol on isolated isozymes and in microsomes are summarized in Table 1. Table 2 summarizes the effects of resveratrol on drug- and carcinogen-metabolizing enzymes in clinical studies and animal models.

Cyp3a4

CYP3A enzymes, particularly CYP3A4, are among the most important and investigated components of xenobiotic metabolism. CYP3A4 plays a role in the metabolism of 60% known drugs (Zhou et al. 2005) and metabolizes the majority of anticancer medicines, including imatinib, docetaxel, and irinotecan (Tian and Hu 2014). Therefore, when considering resveratrol supplementation it is necessary to predict potential interactions with CYP3A4 to ensure the safety of patients receiving chemotherapeutics.

Resveratrol has been shown to attenuate pregnane X receptor (PXR)-induced expression of Cyp3a11, a
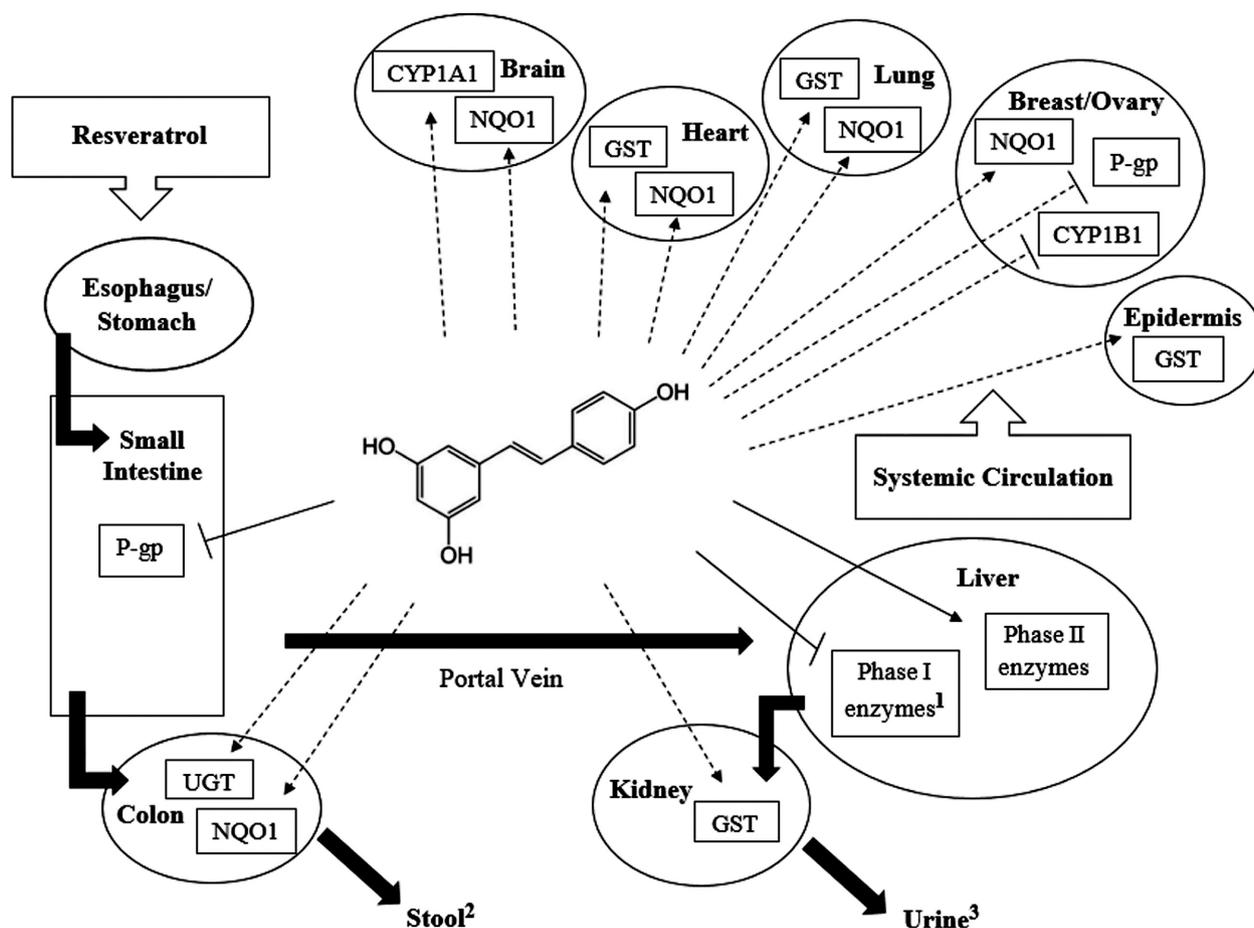
Figure 3. Systemic effects of resveratrol on drug- and carcinogen-metabolizing enzymes. Solid lines within the figure refer to effects that have been demonstrated in both preclinical and clinical models. Dotted lines indicate effects that have only been demonstrated in cell culture and/or animal studies. 1 Denotes the exception of CYP1A2, which was induced by resveratrol in a clinical study (Chow et al. 2010).2 Concentration of resveratrol in stool ranges from 0 to 23 μg resveratrol/g dry weight feces, with the concentration of metabolites <1% (Boocock et al., 2007). 3 77% of all urinary species excreted within 4 h post consumption, likely due to enterohepatic recirculation (Boocock et al., 2007).CYP, cytochrome P450; GST, glutathione S-transferase; NQO1, NAD(P)H dehydrogenase, quinone 1; P-gp, P-glycoprotein; UGT, Uridine diphosphate.

homolog of CYP3A4, in mouse hepatocytes (Deng et al. 2014). It also irreversibly inactivates CYP3A4 by undergoing metabolism by the enzyme, then forming an irreversible complex by means of a reactive intermediate (Chan and Delucchi 2000). Resveratrol has inhibited CYP3A4 at IC_{50} values of 4.0 μmol/L in human liver microsomes (Piver et al. 2001) and in heterologously expressed isozymes at IC_{50} values ranging from 1.1 to 15.8 μmol/L (Piver et al. 2001; Yu et al. 2003; Wang et al. 2015; Zhan et al. 2015). Injection of mice with 50 mg/kg resveratrol (HED of 284 mg for a 70 kg human) resulted in an approximately 61% loss of hepatic Cyp3a activity (Canistro et al. 2009).

Consistent with the in vitro data, CYP3A4 is one of the few CYP enzymes with data directly showing resveratrol-drug interactions in animal models and humans. Rats treated with as little as 2.5 mg/kg resveratrol (HED

of 28 mg for a 70 kg human) experienced increased plasma levels of calcium channel blockers, nicardipine (Choi et al. 2009) and diltiazem (Hong et al. 2008), substrates of CYP3A4. In a clinical trial with healthy volunteers, 500 mg/day resveratrol for 10 days significantly decreased the metabolite to parent ratio of carbamazepine (an anticonvulsant) and increased the AUC of carbamazepine by 1.5-fold, indicating inhibition of CYP3A4 (Bedada and Nearati 2015). In another clinical study, 1 g daily resveratrol significantly inhibited CYP3A4 activity among participants with a high baseline activity, as measured from a 33% geometric mean change in the AUC of buspirone, a CYP3A4 probe drug (Chow et al. 2010). Because of ethical concerns, it is not possible to design a study to determine whether this inhibition of CYP3A4 by resveratrol translates to reduced clearance and subsequent toxicity from other CYP3A4 substrates in

Table 1. Inhibitory effect of resveratrol in liver microsomes and heterologously expressed isozymes (only studies that measured enzyme activity are included).

Enzyme	Substrate	Model	IC$_{50}$ (μmol/L)	K$_i$ (μmol/L)	Reference
CYP3A4	Testosterone	Human liver microsome	4.0		Piver et al. 2001
		Rat liver microsome	20		Piver et al. 2001
		Recombinant isozyme	10		Piver et al. 2001
		Recombinant isozyme	15		Piver et al. 2003
		Human liver microsome		25	Piver et al. 2003
		Recombinant isozyme	1.1		Yu et al. 2003;
CYP3A11	Aripiprazole	Recombinant isozyme	6.8		Zhan et al. 2015
(homolog)	Nifedipine	Mouse liver microsome	15.8		Wang et al. 2015
CYP1A1	EROD	Human HepG2 microsome	1.0	0.42	Ciolino and Yeh 1999
		Human HepG2 cell	1.0		Ciolino and Yeh 1999
		Human MCF-7 cell	0.5		Ciolino and Yeh 1999
		Recombinant isozyme		1.2	Chang et al. 2001
		Recombinant isozyme	40		Piver et al. 2001
		Recombinant isozyme	30		Piver et al. 2003;
CYP1A2	EROD	Recombinant isozyme		15.5	Chang et al. 2001
		Recombinant isozyme	30		Piver et al. 2001
		Human liver microsome		25	Piver et al. 2003
	Phenacetin	Mouse liver microsome	127.3		Wang et al. 2015
CYP1B1	EROD	Recombinant isozyme		0.8	Chang et al. 2001
		Recombinant isozyme	40		Piver et al. 2003
CYP2B1	EFC	Rat liver microsome[1]			Huynh and Teel 2002
CYP2B6	BROD	Recombinant isozyme	>50		Piver et al. 2003
		Recombinant isozyme	100		Piver et al. 2003
		Human liver microsome		100	Piver et al. 2003
CYP2D6	Bufuralol	Human liver microsome	> 50		Yu et al. 2003
	Aripiprazole	Recombinant isozyme	87.9		Zhan et al. 2015
CYP2E1	Chlorzoxazone	Human liver microsome	150		Piver et al. 2001
		Recombinant isozyme	50		Piver et al. 2003;
		Human liver microsome	74.3	50	Piver et al. 2003
		Mouse liver microsome			Wang et al. 2015
	PNPH	Rat liver microsome	18.5		Mikstacka et al. 2002
CYP2C9	Diclofenac	Human liver microsome	>50		Yu et al. 2003
CYP 2C19	DBF	Human liver microsome	22.5		Orsini et al. 2016

BROD, 7-benzoxy resorufin; EFC, 7-ethoxy-4-trifluormethyl courmarin; EROD, 7-ethoxyresorufin; DBF, *O*-benzylfluorescein benzyl ester; PNPH, *p*-nitrophenol hydroxylase.
[1]$P < 0.05$ for percent inhibition.

humans; however, these studies strongly suggest that individuals receiving CYP3A4 substrates should avoid supplementation with resveratrol due to potential toxicity related to reduced clearance.

CYP1A1 and CYP1A2

CYP1A1 (mainly extrahepatic) and 1A2 (exclusively hepatic) help metabolize a range of medications, including anticancer drugs such as tegafur (solid tumors), flutamide (prostate), and dacarbazine (skin) (Zhou et al. 2010). CYP1A enzymes also activate procarcinogens such as benzo[*a*]pyrene (B[a]P), a polycyclic aromatic hydrocarbon found in cigarette smoke (Ding et al. 2014) and grilled/smoked food products (Rose et al. 2015) and 2,37,8-tetrachloro-dibenzo-*p*-dioxin (TCDD), a contaminant in

chlorophenoxy herbicides (Saberi Hosnijeh et al. 2012). Resveratrol has been shown to inhibit both the expression and activity of CYP1A enzymes (Detampel et al. 2012). Theoretically, inhibition of CYP1A through resveratrol supplementation would result in less activation of procarcinogens, making resveratrol a viable cancer prevention strategy for those with exposure to procarcinogens such as B[a]P. This relationship has prompted multiple preclinical studies to study the extent and mechanism of resveratrol's inhibition of CYP1A and the subsequent development of derivatives to enhance this observed inhibition (Orsini et al. 2016).

In preclinical models, resveratrol inhibits CYP1A gene expression by blocking transcription through the aryl hydrocarbon receptor (AHR) pathway. CYP1A gene expression is induced by the binding of a ligand (e.g.

Table 2. Effect of resveratrol on drug- and carcinogen-metabolizing enzymes in clinical trials and animal studies (only studies which measured enzymatic activity are included).

Enzyme	Substrate	Species	Dose per day (HED)	Administration	Effect	Reference
CYP3A4	Diltiazem	Rat	2.5 mg/kg (28 mg)[2]	Oral	Inhibition[W]	Hong et al. 2008
	Nicardipine		0.5 mg/kg (6 mg)[2] 2.5 mg/kg (28 mg)[2]	Oral	Inhibition[W]	Choi et al. 2009
	Buspirone	Human	1.0 g[1]	Oral	Inhibition[M]**	Choi et al. 2009
	Carbamazepine	Human	0.5 g[2]	Oral	Inhibition[W]*	Chow et al. 2010
CYP3A11 (homolog)	Nifedipine	Mice	2.5 mg/kg (14 mg)[2]	Oral	Inhibition[W] Inhibition**	Bedada and Nearati 2015 Wang et al. 2015
CYP3A1/2	Testosterone	Mice	50 mg/kg (284 mg)[2]	Intraperitoneal	Inhibition***	Canistro et al. 2009
CYP1A2	Caffeine	Human	1.0 g[1]	Oral	Induction*	Chow et al. 2010
		Mice	10 mg/kg (56 mg)[2]	Oral	Inhibition**	Wang et al. 2015
CYP2B1/2	Testosterone	Mice	50 mg/kg (284 mg)[2]	Intraperitoneal	Inhibition**	Canistro et al. 2009
CYP2D6	Dextromethorphan	Human	1.0 g[1]	Oral	Inhibition*	Chow et al. 2010
CYP2E1	Chlorzoxazone	Mice	5 mg/kg (28 mg)[2]	Oral	Inhibition***	Wang et al. 2015
CYP2C9	Losartan	Human	1.0 g[1]	Oral	Inhibition*	Chow et al. 2010
GST	CDNB	Mice	25 mg/kg (142 mg)[2]	Intraperitoneal	Inhibition**	Canistro et al. 2009
		Human	1.0 g[1]	Oral	Induction[NS]	Chow et al. 2010
		Mice	Low dose[3]	Oral	Induction*	Liu et al. 2015
		Mice	16.7 mg/kg (95 mg)[2]	Oral	Induction*	Tung et al. 2015
		Rat	10 mg/kg (114 mg)[2]	Oral	Induction*	Ali et al. 2015
		Rat	20 mg/kg (227 mg)[2]	Oral	Induction*	Sadi et al. 2015
	Measured directly	Rat	~2.5 mg (28 mg)[2]	Oral	Induction*	Javkhedkar et al. 2015
NQO1	2.6-dicholorophenol-indophenol	Mice	16.7 mg/kg (95 mg)[2]	Oral	Induction*	Tung et al. 2013
	2.6-dicholorophenol-indophenol	Mice	16.7 mg/kg (95 mg)[2]	Oral	Induction *	Tung et al. 2015
UGT	1-naphthol	Mice	25 mg/kg (142 mg)[2]	Intraperitoneal	Induction**	Canistro et al. 2009
	Bilirubin as indirect measure	Human	1.0 g[2]	Oral	Induction[NS]	Chow et al. 2010
P-gp (transporter)	Nicardipine	Rat	0.5 mg/kg (6 mg)[2]	Oral	Inhibition[W]	Choi et al. 2009
			2.5 mg/kg (28 mg)[2]	Oral	Inhibition[M]**	Choi et al. 2009
	Fexofenadine	Human	500 mg	Oral	Inhibition[W]*	Bedada et al. 2014

CDNB, 1-chloro-2,4-dinitrobenzene; HED, human equivalent dose (based on 70 kg human); PROD, pentoxyresorufin dealkylase.
[1]Blood concentrations averaged 72.7 ng/mL (0.32 μmol/L).
[2]Blood concentration not given.
[3]5.7 μg/mL resveratrol mixed with drinking water three times weekly.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; [NS]Not significant; [W]Weak (1.25- to 2-fold change in AUC); [M]Moderate (2- to 5-fold change in AUC).

B[a]P or TCDD) to the AHR, its translocation to the nucleus, and binding of the complex to the xenobiotic response element (XRE) (Zanger and Schwab 2013). The exact target of resveratrol's inhibition along this AHR pathway is still an active area of research; the proposed mechanisms are illustrated in Figure 4. Early work in human HepG2 cells suggested that 10 μmol/L resveratrol may act on a binding region separate from the AHR
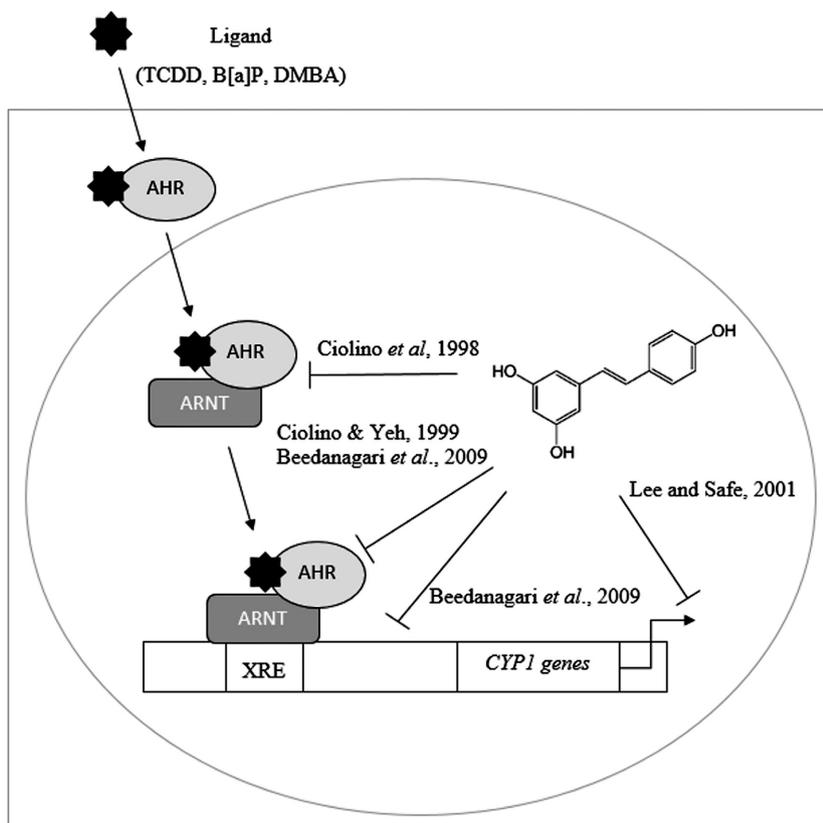
Figure 4. Proposed mechanisms for resveratrol's suppression of CYP1 induction. An early model showed that resveratrol inhibited the transformation of the AHR to its nuclear form by forming a complex with the ARNT. Resveratrol has also been shown to act later in the pathway, inhibiting the binding of the nuclear AHR complex to the XRE or inhibiting the recruitment of RNA polymerase II to the DNA. These mechanisms block the transcription of CYP1A1 and CYP1B1. Still, others have proposed that CYP1 inhibition occurs posttranscriptionally. AHR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; CYP, cytochrome P450; XRE, xenobiotic response element.

binding site (Ciolino et al. 1998). Subsequent studies with similar doses in B[a]P- and 7,12-dimethylbenz[a]anthracene (DMBA)-induced HepG2 and MCF-7 cells suggested that resveratrol affects binding to the XRE and recruitment of RNA polymerase II (Ciolino and Yeh 1999; Beedanagari et al. 2009). A posttranscriptional mechanism of inhibition has also been proposed based on evidence that 10 μmol/L resveratrol increased the rate of CYP1A1 mRNA degradation in T47D breast cancer cells (Lee and Safe 2001). Conversely, high levels of resveratrol (50 μmol/L) weakly induced CYP1A2 mRNA expression in HepG2 cells (Koe et al. 2014). Resveratrol's effect on the AHR pathway and subsequent expression of CYP1A enzymes may depend on the dose, carcinogen, and model used.

Resveratrol has also demonstrated mechanism-based inactivation of CYP1A2 in a microsomal assay; however, a requirement of NADPH for this inhibition indicated that a resveratrol metabolite was likely responsible for the observed inhibitory activity (Chang et al. 2001). Although a subsequent study found that RS3 did not significantly inhibit CYP1A2 in cell cultures containing the recombinant human isozyme (Yu et al. 2003), piceatannol has been shown to inhibit CYP1A activity to an extent similar to that of resveratrol in rat hepatic microsomes (Chang et al. 2007) and could affect its interactions with CYP1A enzymes.

While evidence from in vitro models demonstrated inhibition of CYP1A1 and CYP1A2 by resveratrol, there are no clinical studies to corroborate this effect. In an early phase clinical study, resveratrol-induced CYP1A2 activity. When participants were given 100 mg caffeine after treatment with 1 g daily resveratrol for four weeks, the metabolic ratio of caffeine/paraxanthine decreased significantly compared to baseline measurements (indicative of CYP1A2 induction) (Chow et al. 2010). The observed difference between this clinical observation and previous in vitro studies could be attributed to the indirect assessment of CYP1A2 activity, or to resveratrol metabolism. The effects of resveratrol on CYP1A enzymes could also be model-dependent. Addition of 50 μmol/L resveratrol to human medullablastoma cells resulted in upregulation of CYP1A1 as well as increased cell differentiation and apoptosis (Liu et al. 2004).

Cyp1b1

CYP1B1 is an extrahepatic enzyme overexpressed in breast, prostate, endometrial, and ovarian cancers (Gajjar et al. 2012). It has been shown to biotransform anticancer agents in vitro and may contribute to drug therapy resistance (Rochat et al. 2001). Furthermore, CYP1B1 is involved in the metabolism of 17β-estradiol and the formation of a toxicologically active metabolite, 4-hydroxyestradiol (Tsuchiya et al. 2004). Therefore, inhibition of CYP1B1 is an attractive target for hormonally driven cancers such as breast (Gajjar et al. 2012). Tamoxifen, a selective estrogen receptor modulator, is approved for breast cancer prevention in high-risk women; however, its metabolites have been shown to upregulate the CYP1B1 gene, a mechanism that may explain the association between long-term tamoxifen use and a small increased risk of endometrial cancer (Tsuchiya et al. 2004; Williams-Brown et al. 2011).

An agent-like resveratrol that has high favorability among the general population could potentially serve as an alternative chemoprevention option. As little as 5 μmol/L resveratrol was able to reduce the catechol estrogen formation by through inhibition of CYP1B1 in human mammary epithelial cells (Chen et al. 2004). In overweight and obese postmenopausal women, 1 g daily resveratrol for 12 weeks also had a favorable effect on estrogen metabolism (Chow et al. 2014); however, the effect on CYP1B1 was not determined. While resveratrol may be an attractive chemoprevention option, combination treatments should be avoided, particularly among breast cancer patients (see continued discussion of tamoxifen under "CYP2D6").

Preclinical studies have also demonstrated CYP1B1 inhibition by resveratrol. In baculovirus-infected insect cell microsomes, the apparent K_i of heterologously expressed human CYP1B1 was found to be 0.8 μmol/L, similar to the apparent K_i of 1.2 μmol/L for CYP1A1 (Chang et al. 2001). Considering that transcription of CYP1B1 is also mediated by the AHR pathway (Go et al. 2015), inhibition by resveratrol likely occurs at the transcription level (see Fig. 4). Indeed, treatment of human MCF-7 breast cancer cells with 10 μmol/L resveratrol inhibited TCDD-induced expression of CYP1B1 (Beedanagari et al. 2009). In human lymphoblast microsomes, 200 μmol/L resveratrol was metabolized by CYP1B1 and produced the anticancer compound, piceatannol (Potter et al. 2002). Given that resveratrol's metabolites have a greater potential to reach mammary and other endocrine tissues, it may be more beneficial to investigate their effects on CYP1B1 than the parent compound.

Cyp2b6

CYP2B6 is a major hepatic enzyme involved in the activation of cyclophosphamide, an anticancer prodrug (Zanger and Schwab 2013) as well as bupropion, a drug used for smoking cessation and depression (Pekthong et al. 2012). Expression of CYP2B6 is regulated by xenosensing nuclear receptors, constitutive androstane receptor (CAR), and PXR (Zanger and Schwab 2013). Because resveratrol has been shown to inhibit PXR-induced expression of CYP3A4 (Deng et al. 2014), it has also been suggested that the polyphenol may inhibit PXR-induced expression of CYP2B6 (Smutny and Pavek 2014). Consistent with this hypothesis, liver microsomes from 6- to 12-month-old male rats incubated with high micromolar concentrations (100–250 μmol/L) resveratrol had significantly inhibited Cyp2b1, which shares a high sequence identity with human CYP2B6 (Huynh and Teel 2002). Resveratrol likewise demonstrated inhibition of CYP2B6 in human liver microsomes, but also at supraphysiological concentrations (IC$_{50}$ of 100 μmol/L) (Piver et al. 2003).

There is also evidence, however, to suggest that resveratrol activates CAR and subsequently CYP2B6. In transfected HepG2 cells, 5 μmol/L resveratrol activated CAR as detected by CYP2B6 reporter activity (Yao et al. 2011). Consistent with CAR activation, multiple injections with 50 mg/kg (HED of 284 mg for a 70 kg human) resveratrol in mice induced testosterone metabolism by hepatic Cyp2b1/2 (Canistro et al. 2009). Differences in resveratrol's effect on CYP2B6 may be related to the fact that microsomal experiments tend to only observe inhibitory effects. It is also possible that CYP2B6 induction is caused by resveratrol metabolites. The effect of resveratrol on this enzyme should be elucidated in order to determine how concurrent supplementation may alter the efficacy of drugs metabolized by CYP2B6.

Cyp2e1

CYP2E1 is involved in the metabolism of various carcinogens, including volatile organic solvents like toluene and nitrosamines (Piver et al. 2001). Common carcinogens like alcohol, nicotine, and tobacco smoke increase the expression of this enzyme (Jiménez-Garza et al. 2015) and inhibition of CYP2E1 could serve as a way to prevent carcinogenesis among those highly exposed to such compounds. For example, in rats with chemically induced hepatic cancer, 60 mg/kg resveratrol (HED of 681 mg for a 70 kg human) reduced Cyp2e1 expression and suppressed carcinogenesis (Wu et al. 2013). While expression of CYP2E1 is highest in the liver, it has also been detected in extrahepatic tissues including the brain, adrenal cortex, ovaries, testes, gastrointestinal tract, and cardiac tissue

(Zanger and Schwab 2013), suggesting a potential for resveratrol to protect against cancer in multiple organs.

Resveratrol has inhibited microsomal CYP2E1, however, this mechanism is still unclear. In human and rat microsomes, 100 μmol/L resveratrol acted as a reversible, noncompetitive inhibitor of CYP2E1, as determined by kinetic studies (Piver et al. 2001). As little as 5.0 μmol/L was found to inhibit enzymatic activity in murine liver microsomes (Wang et al. 2015). Preincubation of murine liver microsomes with NADPH resulted in irreversible inhibition of CYP2E1 by similarly low doses of resveratrol (IC$_{50}$ value of 18.5 μmol/L) (Mikstacka et al. 2002). The requirement of NADPH in this study suggests that resveratrol itself is metabolized by CYP2E1 and a reactive intermediate is responsible for inactivation. Mechanistic differences regarding resveratrol's inhibition of CYP2E1 could be due to differences in dose and substrate, or could be a result of the enzyme's multiple active sites (Liu et al. 2013). Nevertheless, an understanding of resveratrol's effect on this enzyme would provide additional insight regarding its anticancer properties due to the expression of CYP2E1 in multiple tissues, as well as its involvement in the metabolism of carcinogens.

Cyp2d6

CYP2D6 is found mainly in the liver, but has also been expressed in the gastrointestinal tract and brain (Zanger and Schwab 2013) and metabolizes approximately 25% of prescribed medications (Ingelman-Sundberg 2005). CYP2D6 converts tamoxifen, a drug used for both treatment and prevention of breast cancer, to its active metabolite endoxifen (Jin et al. 2005).

In cell culture, inhibition of CYP2D6 by resveratrol and its main metabolite, R3S, was rather insignificant, with IC$_{50}$ values of 87.9 μmol/L for resveratrol (Zhan et al. 2015) and > 50 μmol/L for R3S (Yu et al. 2003). In humans administered 1 g/day resveratrol for 4 weeks, however, CYP2D6 activity was decreased by 1.7-fold, as measured by a dextromethorphan/dextrorphan molar ratio (Chow et al. 2010). While evidence is limited, these clinical results suggest that supplementation with resveratrol may significantly inhibit activation of tamoxifen, and combined treatment is likely not beneficial for breast cancer prevention and treatment.

Cyp2c9

CYP2C9 metabolizes several common drugs, including nonsteroidal anti-inflammatory drugs, which target COX-2 and may protect against the development of certain cancers (Ghosh et al. 2010). It also metabolizes drugs with narrow therapeutic indices, such as the anticoagulant (S)-warfarin. Mice fed a diet containing 0.5% weight per weight resveratrol for 12 weeks experienced enhanced anticoagulant activity by warfarin, suggesting inhibition of Cyp2c9 (Chiba et al. 2016). In humans, a dose of 1 g daily resveratrol for 4 weeks was shown to inhibit CYP2C9 by 2.71-fold using losartan as a probe drug. Blood concentrations of resveratrol reached an average of 72.7 ng/mL (0.32 μmol/L) in this study (Chow et al. 2010). One study found that R3S was not able to inhibit the recombinant CYP2C9 isozyme (Yu et al. 2003). Given the role that CYP2C9 plays in the metabolism of drugs with narrow therapeutic indices, even minor interactions could potentially impact the efficacy of these drugs.

Cyp2c19

CYP2C19, a mainly hepatic enzyme, plays a major role in the metabolism of proton pump inhibitors such as omeprazole and pantoprazole, antidepressants like citalopram, and endogenous compounds like progesterone (Zanger and Schwab 2013). Resveratrol has demonstrated moderate inhibition of CYP2C19 in microsomes containing the heterologously expressed isoform (IC$_{50}$ of 11.6 μmol/L) (Yu et al. 2003) and the human recombinant form (IC$_{50}$ of 22.5 μmol/L) (Orsini et al. 2016). Additionally, a naturally occurring trimer of resveratrol, α-viniferin, potently inhibited CYP2C19 activity in human liver microsomes at an IC$_{50}$ of 0.93 μmol/L (Sim et al. 2014). Evidence is limited regarding resveratrol's effect on CYP2C19 and whether such interactions have implications for cancer prevention.

Resveratrol and Phase II Metabolism

In phase II metabolism, xenobiotics and endogenous compounds are primed for elimination via bile or urine. The conjugating enzymes involved in this process typically act as transferases, adding large polar groups to their substrates (Jancova et al. 2010). Such enzymes include glutathione S-transferase, NAD(P)H hydrogenase, quinone 1, UDP-glucuronosyl transferase, and catechol-O-methyl transferase. By inducing phase II enzymes, resveratrol may facilitate the removal of carcinogens from the body. The effects of resveratrol in vivo and in vitro are summarized in Tables 1 and 2, respectively.

Glutathione S-transferase

Glutathione *S*-transferase (GST) facilitates the transfer reaction between the thiol moiety of glutathione and substrates intended for elimination (Jancova et al. 2010). GST protects against exposure to oxidative stress and carcinogens, such as nitrosamines and polycyclic aromatic

hydrocarbons (Pool-Zobel et al. 2005). GST inactivates estrogen quinones, protecting against estrogen-induced cancers (Yager 2015). GST activation may also reduce the risk of colorectal (Klusek et al. 2014) and hepatic (Shen et al. 2014) cancers as well as protect against tobacco-induced esophageal (Zendehdel et al. 2009) and prostate carcinomas (Kidd et al. 2003). Thus, induction of GST is considered a potential strategy for cancer prevention.

A growing body of evidence strongly supports an induction effect of resveratrol on GST. In rats with nonalcoholic fatty liver disease, 10 mg/kg resveratrol (HED of 114 mg for a 70 kg human) induced total Gst activity by 84% (Ali et al. 2015). It also induced Gst activity by 63% in mouse epidermis at a topical dose of 16 μmol/L in 0.2 mL acetone, and by 20% in human keratinocyte cells (20 μmol/L) (Cichocki et al. 2014). In aged mice, administration of 16.67 mg/kg resveratrol (95 mg for a 70 kg human) for 6 months increased heart and liver Gst levels (Tung et al. 2015). Resveratrol treatment also restored overall Gst activity in spontaneously hypertensive rats (Javkhedkar et al. 2015), streptozotocin-induced diabetic rats (Sadi et al. 2015), rats with gentamicin-induced renal damage (Silan et al. 2007), and in mice with B[a]P-induced lung carcinogenesis (Liu et al. 2015). Furthermore, 10 mg/kg resveratrol restored both the expression and catalytic activity of Gst after pyrogallol-induced reduction in mouse livers (Upadhyay et al., 2008). In humans, 1 g daily dose of resveratrol for 4 weeks induced GST activity among individuals with low baseline expression, although the overall effect was not significant (Chow et al. 2010). Given the association between GST induction and reduced cancer risk (McIlwain et al. 2006), induction of this enzyme could be a significant mechanism by which resveratrol provides protection against cancer.

NAD(P)H dehydrogenase, quinone 1 and 2 (NQO1 and NQO2)

NAD(P)H dehydrogenase, quinone 1 (NQO1) plays an important role in chemoprevention due to its ability to catalyze the reduction in quinones to catechols (Lu et al. 2008). This reduction is thought to decrease quinone-induced oxidative stress and therefore protect the cell (Zhang et al. 2012). Conversely, its homolog, NQO2, does not appear to share such benefits, as Nqo2 knockout mice demonstrated increased antioxidant and detoxifying enzyme expression (Buryanovskyy et al. 2004).

In mouse hepatoma cells, 21 μmol/L resveratrol doubled Nqo1 activity (Mayhoub et al. 2012). Furthermore, 2.0 μmol/L resveratrol induced NQO1 mRNA expression by 4-fold in normal human bronchial epithelial cells (Tan et al. 2012). Resveratrol also inhibited NQO2 in K562 cells (Buryanovskyy et al. 2004), which is doubly

favorable in terms of chemoprevention. Furthermore, R3S induced NQO1 more potently than resveratrol in murine hepatoma cells, with only 2.6 μmol/L needed to double the concentration of NQO1 (Hoshino et al. 2010).

The induction of NQO1 by resveratrol could have significant implications for breast cancer prevention. Estrogens can be metabolized into catechols and further oxidized into ortho-quinones, which react with DNA to form adducts (Cavalieri and Rogan 2014). By inducing NQO1, resveratrol may facilitate the reduction in semiquinones to catechols and subsequent inactivation by catechol-O-methyl transferase (Cavalieri and Rogan 2014; Yager 2015). Rats cotreated with 3 mg estradiol daily and 50 mg resveratrol every other month for 8 months had increased tumor latency and reduced estradiol-induced tumor development, as well as upregulation of the Nqo1 gene in mammary tissue (Singh et al. 2014), demonstrating resveratrol's potential to protect against breast cancer.

These protective benefits, however, may be age- or tissue-dependent. When mice of varying ages were given 16.67 mg/kg resveratrol daily (HED of 95 mg for a 70 kg human) for 6 months, Nqo1 activity increased in young (2-month-old) and aged (18-month-old) mice but decreased in mature (12-month-old) mice (Tung et al. 2013). Older mice given the same resveratrol treatment as described above had increased Nqo1 activity in the brain and liver, but decreased activity in the heart (Tung et al. 2015).

Clinical evidence also supports an inhibitory effect on NQO1. In patients with nonalcoholic fatty liver disease, 3 g daily resveratrol for 8 weeks decreased NQO1 expression in peripheral blood mononuclear cells (Chachay et al. 2014). Cancer patients receiving 5 mg resveratrol had higher levels of NQO1 in colorectal mucosa than those receiving 1 g resveratrol (Cai et al. 2015), suggesting a dose-dependent response. Resveratrol's varied effects on NQO1 further underscore the need to determine which populations may benefit from supplementation and at what dose.

Uridine diphosphate- glucuronosyl transferase

UDP-glucuronosyl transferases (UGTs) are detoxifying enzymes that facilitate the elimination of xenobiotics, such as carcinogens and pollutants, and endogenous substances, such as bile acids and hormones, through glucuronidation (Jancova et al. 2010). Increased expression of UGTs has been associated with reduced risk of various cancer types (Guillemette et al. 2014). In Caco-2 intestinal cancer cells, 20 μmol/L resveratrol significantly induced UGT1A1 expression (Iwuchukwu et al. 2011). Hepatic Ugt activity was increased 83% in mice injected with 25 mg/kg (HED of 142 mg for a 70 kg human) (Canistro

et al. 2009). In a clinical trial, 1 g daily resveratrol for 4 weeks significantly increased bilirubin clearance among subjects with low baseline UGT1A1 activity; however, the resveratrol intervention had a minimal effect on overall bilirubin clearance (Chow et al. 2010). Lack of UGT induction in this study could be due to resveratrol's low bioavailability, as resveratrol may not reach adequate concentrations in the liver to significantly induce bilirubin-UGT.

Transport Proteins

Transport proteins play a major role in drug elimination. These transporters work in tandem with phase I and II metabolism, as various drugs are oxidized or conjugated to form substrates for these transporters (Chan et al. 2004). Transporters include ATP-binding cassette (ABC) transport proteins like breast cancer resistance protein (BCRP, ABCG2) and multidrug resistance protein 3 (MRP3, ABCC3). They also include solute carrier transporters, such as organic anion transporting polypeptides (OATPs).

ABC transport proteins are present in the apical membrane of the small intestine, liver, and kidney, facilitating the elimination of xenobiotics by active efflux (Chan et al. 2004). Interactions with these transporters, therefore, could alter the bioavailability of xenobiotics. Supplemental doses of resveratrol (500 mg/day) have been shown to inhibit P-glycoprotein (P-gp, ABCB1), an ABC transporter (Bedada et al. 2014), as well as increase the bioavailability of P-gp substrates such as doxorubicin, a first-line breast cancer drug (Kim et al. 2014). In doxorubicin-resistant human breast cancer cells, 12 μmol/L resveratrol was able to increase cytotoxicity and reverse doxorubicin resistance by downregulating the expression of P-gp (Huang et al. 2014). While enhancement of P-gp substrate bioavailability may be beneficial for cancer treatment, identifying the extent of resveratrol's activity is necessary to prevent toxicity.

Resveratrol and its metabolites are substrates for BCRP, which is responsible for their active efflux at the enterocyte and subsequent fecal excretion. In fact, efflux of glucuronidated and sulfated resveratrol metabolites was inhibited by 70% and 95%, respectively, in Bcrp knockout mice compared to wild-type mice (Alfaras et al. 2010). MRP3 has a greater preference for glucuronidated metabolites, transporting these conjugated metabolites out of the cell for circulation and subsequent urinary excretion (van de Wetering et al. 2009). Evidence regarding interactions resveratrol and drug metabolism through these transporters, however, is lacking.

Additionally, resveratrol and its major sulfate metabolite, R3S, have been shown to interact with OATPs in hamster ovary and breast cancer cells, allowing for their uptake into enterocytes and hepatocytes (Riha et al. 2014). Competition for these transporters could result in significant interactions with drugs, including anticancer drugs like docetaxel and imatinib (Kalliokoski and Niemi 2009), or with flavonoids and other polyphenols that could potentially confer protection against cancer.

Conclusions and Future Directions

Resveratrol has received a great amount of attention over the past two decades due to its ability to inhibit cancer initiation, promotion, and progression in preclinical models (Singh et al. 2015). While these chemoprevention properties have been attributed multiple mechanisms, we have presented the available evidence describing resveratrol's effects on xenobiotic metabolism and drug transporters. Resveratrol has been shown to inhibit several important CYP enzymes, many of which are responsible for the bioactivation of carcinogens. Furthermore, resveratrol induces conjugating enzymes, facilitating the elimination of toxic substances. Since supraphysiological doses of resveratrol used in preclinical studies are not achievable in humans due to low bioavailability, it cannot be concluded that resveratrol's interaction with these enzymes is the sole mechanism by which it affords chemoprotection. However, evidence of nutrient-drug interactions suggests that this mechanism may still contribute to resveratrol's overall anticancer properties. This evidence also suggests that resveratrol's interactions with drug metabolism are significant enough to warrant further investigation before it can be recommended clinically.

While in vitro studies provide a controlled environment for precise quantification of resveratrol's effect on phase I and II metabolism, such studies fail to capture the activity of resveratrol metabolites, which may have important clinical effects. With the limited evidence available, we have attempted to consider the activity of resveratrol's sulfated and glucuronidated metabolites to evaluate the translatability of certain animal models to humans. Future studies should investigate the anticancer and drug interaction activity of resveratrol metabolites, particularly those found in extrahepatic tissues, as they are more likely to reach these sites. Enzymes with minimal evidence available, such as CYP2C9, CYP2C19, and UGT, should perhaps receive particular attention.

Another priority for future studies should include identifying the ideal dose of resveratrol supplementation for cancer prevention. The vast majority of preclinical and clinical studies utilize very high doses. While a growing body of evidence supports higher efficacy of lower dose resveratrol for disease prevention (Cai et al. 2015; Posadino et al. 2015), lower doses could also mitigate nutrient-drug interactions.

Caution should be taken when using supplemental doses of resveratrol for health benefits such as chemoprevention. This polyphenol has demonstrated significant interactions with phase I and II enzymes both in vitro and in vivo. While these interactions may be beneficial in terms of reduced activation and higher clearance of carcinogens, they could also result in nutrient-drug interactions. Individuals taking drugs such as tamoxifen or warfarin, whose efficacy is highly dependent on specific CYP enzymes, could be particularly affected. Additional research is needed before recommendations can be made supporting resveratrol supplementation above dietary levels for prevention or therapeutic purposes.

Disclosure

None declared.

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