Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

PORTLAND PRESS

Review Article

CYP1B1 as a therapeutic target in cardio-oncology

Alexa N. Carrera[1,2,*], Marianne K.O. Grant[1,*] and Beshay N. Zordoky[1]

[1]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN, United States of America; [2]Augsburg University, Minnesota, Minneapolis, MN, United States of America

Correspondence: Beshay N. Zordoky (zordo001@umn.edu)

Cardiovascular complications have been frequently reported in cancer patients and survivors, mainly because of various cardiotoxic cancer treatments. Despite the known cardiovascular toxic effects of these treatments, they are still clinically used because of their effectiveness as anti-cancer agents. In this review, we discuss the growing body of evidence suggesting that inhibition of the cytochrome P450 1B1 enzyme (CYP1B1) can be a promising therapeutic strategy that has the potential to prevent cancer treatment-induced cardiovascular complications without reducing their anti-cancer effects. CYP1B1 is an extrahepatic enzyme that is expressed in cardiovascular tissues and overexpressed in different types of cancers. A growing body of evidence is demonstrating a detrimental role of CYP1B1 in both cardiovascular diseases and cancer, via perturbed metabolism of endogenous compounds, production of carcinogenic metabolites, DNA adduct formation, and generation of reactive oxygen species (ROS). Several chemotherapeutic agents have been shown to induce CYP1B1 in cardiovascular and cancer cells, possibly via activating the Aryl hydrocarbon Receptor (AhR), ROS generation, and inflammatory cytokines. Induction of CYP1B1 is detrimental in many ways. First, it can induce or exacerbate cancer treatment-induced cardiovascular complications. Second, it may lead to significant chemo/radio-resistance, undermining both the safety and effectiveness of cancer treatments. Therefore, numerous preclinical studies demonstrate that inhibition of CYP1B1 protects against chemotherapy-induced cardiotoxicity and prevents chemo- and radio-resistance. Most of these studies have utilized phytochemicals to inhibit CYP1B1. Since phytochemicals have multiple targets, future studies are needed to discern the specific contribution of CYP1B1 to the cardioprotective and chemo/radio-sensitizing effects of these phytochemicals.

Introduction

Cancer survivorship has significantly increased over the past two decades, thanks to advanced diagnosis and treatment of different types of cancers. Currently, there are more than 15 million cancer survivors in the United States and this number is expected to increase due to the continued improvement of diagnostics, therapeutics, and care models [1]. Although the increased survivorship is a cause for celebration, two-thirds of cancer survivors experience at least one late adverse effect [2]. Cardiovascular disease is the second highest cause of mortality in cancer survivors, after secondary malignancy. The cardiovascular toxicity of cancer treatments has been increasingly recognized as a critical issue in the care of cancer survivors. Therefore, cardio-oncology has emerged as a clinical subspecialty with an ultimate goal to mitigate cardiovascular complications in cancer patients and survivors [3,4]. Cardiovascular complications have been reported in cancer patients and survivors who received different types of cancer treatments including anthracyclines, monoclonal antibodies, alkylating agents, tyrosine kinase inhibitors, immune checkpoint inhibitors, proteasome inhibitors, and radiation, as reviewed in [5]. Despite the known cardiovascular toxic effects of these treatments, they are still clinically used because of their effectiveness as anti-cancer agents. Protection against cancer treatment-induced cardiotoxicity is challenging, because shared mechanistic pathways may contribute to both the tumor suppressive and the cardiotoxic effects

*These authors contributed equally to this work.

Received: 17 August 2020
Revised: 12 October 2020
Accepted: 28 October 2020

Version of Record published: 13 November 2020

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

of cancer treatments. For instance, anthracycline-induced apoptotic cell death is a shared pathway for the anti-cancer and cardiotoxic effects of anthracyclines [6]. Cardioprotective agents that have non-selective anti-apoptotic effects will likely inhibit the anti-cancer effects of anthracyclines. Likewise, novel immune checkpoint inhibitors activate the immune system to fight the cancer; however, this may lead to immune-mediated myocarditis [7]. In this scenario, indiscriminate immunosuppression may protect the heart, but will likely undermine the anti-cancer effects of these agents. Therefore, there is a critical need to identify therapeutic targets that have the potential to prevent cancer treatment-induced cardiovascular complications without reducing their anti-cancer effects.

Cytochrome P450 1B1 (CYP1B1) is a monooxygenase enzyme involved in the metabolism of a variety of xenobiotics and endogenous compounds [8]. In this review, we will discuss the growing body of evidence suggesting that CYP1B1 can be a promising therapeutic target in cardio-oncology. First, we will give a brief overview of the expression, regulation, and metabolic activity of CYP1B1. Second, we will briefly discuss the role of CYP1B1 in both cardiovascular diseases and cancer. Then, we will summarize the existing literature showing how CYP1B1 is involved in the cardiovascular toxicity of different cancer treatments and the potential cardiovascular protective effects of CYP1B1 inhibitors. In parallel, we will also discuss the role of CYP1B1 inhibitors in preventing resistance to cancer treatments to highlight that CYP1B1 inhibition may not only prevent cardiovascular toxicity, but also augment the anti-cancer effects of different cancer treatments. Importantly, we will discuss how CYP1B1-mediated signaling pathways may have divergent effects of the cardiovascular tissues and the cancer. At last, we will comment on the challenges that face clinically targeting CYP1B1 and highlight future research directions.

CYP1B1

CYP1B1 is a member of the CYP1 gene family which also includes CYP1A1 and CYP1A2. A novel cytochrome P450 enzyme (P450-EF) was first purified from 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)-treated mouse embryonic fibroblasts [9]. In 1994, P450-EF was identified and cloned as the mouse *Cyp1b1* [10]. In parallel, human *CYP1B1* was first cloned from TCDD-treated human epidermal keratinocytes [11]. *CYP1B1* showed approximately 40% homology with both *CYP1A1* and *CYP1A2* [12]. The human *CYP1B1* gene is located on chromosome 2 and contains three exons and two introns [13]. Mouse and rat orthologs of *CYP1B1* have also been cloned and characterized [12]. Although each of these orthologs has an mRNA of 5.2 kb and a predicted protein of 543 amino acids [12], they show significant species differences in their regulation, metabolic activity, and tissue-specific distribution [10,12–14].

Expression

Unlike most cytochrome P450 enzymes, CYP1B1 expression has not been detected in the human liver; however, it is expressed primarily in extrahepatic tissues [8]. Of importance in cardio-oncology, CYP1B1 has been shown to be expressed in cardiovascular tissues and overexpressed in malignant tumors. Indeed, CYP1B1 has been detected at the mRNA and protein levels in cardiovascular tissues of human and experimental animals [15]. CYP1B1 mRNA and protein have been detected in the rat and mouse heart and in the cardiac-derived H9c2 cells [16–19]. In addition to the myocardial tissues, CYP1B1 has been detected in the vasculature in both vascular smooth muscle cells and endothelial cells [20–25]. Intriguingly, CYP1B1 has been shown to be overexpressed in malignant tumor tissues [26], particularly in hormone-responsive tissues such as prostate [27], breast [28], and ovarian cancers [29,30]. Additional immunohistochemical studies showed that CYP1B1 protein expressions were detected in 53 out of 62 samples of the extrahepatic tissue. Among these 62 samples include human brain cortex tissues, kidney tissues, and lymphoid, prostate, cervix, uterus, oocytes, bone marrow, epithelial, smooth muscle cells, and ovary cells [22,31–33].

Regulation

The *CYP1B1* gene is transcriptionally induced by polycyclic aromatic hydrocarbons (e.g. TCDD) via the Aryl hydrocarbon Receptor (AhR) complex, which is a transcriptional factor that regulates CYP1A1 and CYP1B1 [11,12]. Xenobiotic-responsive elements (XREs) have been identified in the 5′ regulatory region of the *CYP1B1* gene [34]. Induction of the human, rat and mouse *CYP1B1* gene expression by AhR agonists has been well-documented in a variety of cell types [35–39]. In addition, the AhR is highly expressed in the heart [40], and activation of the AhR has been shown to induce CYP1B1 in cardiovascular tissues. For instance, concentrated ambient particles induce CYP1B1 mRNA in rat hearts [41]. Similarly, benzo(a)pyrene, a component of cigarette smoke, has been shown to induce CYP1B1 in the rat heart [42]. Conversely, AhR antagonists inhibit constitutive CYP1B1 expression [43]. Interestingly, CYP1B1 has been shown to be constitutively expressed in the hearts of both control and AhR-deficient mice, which implies the involvement of other pathways that regulate cardiac CYP1B1 [44].

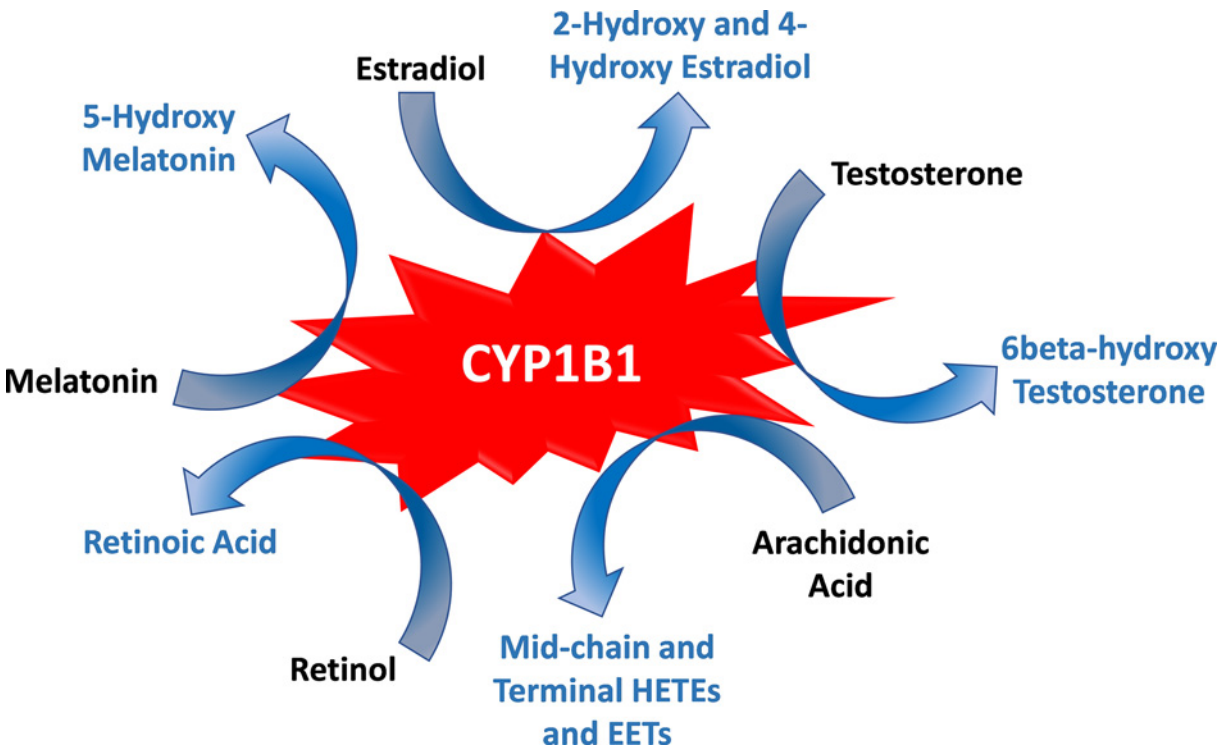

Figure 1. CYP1B1 is a central player in the metabolism of endogenous compounds

CYP1B1 metabolizes estradiol, testosterone, arachidonic acid, retinol, and melatonin to the biologically active metabolites: 2- and 4-hydroxyestradiol, 6β-hydroxytestosterone, mid-chain and terminal hydroxyeicosatetraenoic acids (HETEs), epoxyeicosatrienoic acids (EETs), retinoic acid, and 5-hydroxymelatonin, respectively.

AhR-independent up-regulation of CYP1B1 may be mediated by inflammation, estrogen signaling or other endogenous compounds. Inflammation has been shown to down-regulate most cytochrome P450 enzymes of the CYP1, CYP2, and CYP3 families [45,46]. In contrast, a few isoforms are up-regulated by inflammation such as CYP4F enzymes and CYP1B1 [46,47]. Specifically, the inflammatory cytokine interleukin-6 (IL-6) has been shown to induce CYP1B1 via miR27b in colorectal and breast cancer cells [48,49]. Tumor necrosis factor-α (TNF-α) has also been shown to up-regulate CYP1B1 via a p38-mediated mechanism in rat liver epithelial cells [32,50]. CYP1B1 is also up-regulated by 17β-estradiol through Estrogen Receptor α (ERα) [51]. G protein estrogen receptor (GPER) is also involved in CYP1B1 regulation [52]. Leptin and prostaglandin E2 have also been shown to up-regulate CYP1B1 expression through ligand-independent activation of the ERα pathway in MCF-7 breast cancer cells [53,54]. Other pathways that may play a role in CYP1B1 regulation include: the peroxisome proliferator-activated α (PPARα) in MCF-7 and HCT116 cells [55,56], the Wnt/β-catenin signaling pathway in endothelial cells and adreno-corticotropic hormone (ACTH) via cAMP in adrenal cells [36,57–59].

Metabolic activity

CYP1B1 has been shown to metabolize both endogenous (Figure 1) and exogenous compounds. CYP1B1 plays an important role in steroid metabolism, as reviewed in [60]. Estradiol is the preferred substrate for CYP1B1, followed by progesterone, then testosterone [61]. CYP1B1 metabolizes estradiol and estrone to their respective 4-hydroxy and 2-hydroxy metabolites [62–64]. Although at a lower activity, CYP1B1 has also been found to metabolize estradiol to 15α-, 6α-, 16α-, and 6β-hydroxy metabolites [61]. The 4-hydroxy-estradiol can be transformed to semiquinones and quinones that can form DNA adducts resulting in oncogenic effects [65,66] and undergo redox cycling to generate reactive oxygen species (ROS) [67]. Intriguingly, 4-hydroxyestradiol has been shown to up-regulate CYP1B1 in human mammary epithelial MCF-10A cells in a positive feedback loop [68]. Regarding androgen metabolism, CYP1B1 catalyzes the 6β-hydroxylation and 16α-hydroxylation of testosterone [61,63].

CYP1B1 is also involved in arachidonic acid metabolism. Arachidonic acid is metabolized by cytochrome P450 monooxygenases to different regioisomers of epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

(HETEs) [15,69,70]. Human and rat CYP1B1 orthologs have been reported to metabolize arachidonic acid primarily to mid-chain HETEs, while the main metabolites of the mouse ortholog were EETs [71,72]. CYP1B1-mediated production of mid-chain HETEs have been implicated in the pathogenesis of cardiac hypertrophy [72,73], and in doxorubicin (DOX)-induced cardiotoxicity [74]. In addition to steroid and arachidonic acid metabolism, both mouse and human CYP1B1 orthologs have been shown to oxidize retinol to retinal and retinal to retinoic acid [71,75]. Melatonin can also be metabolized to 6-hydroxymelatonin or converted back into N-acetylserotonin by CYP1B1 [76,77]. Regarding xenobiotic metabolism, CYP1B1 binds planar polyaromatic ring systems such as polyaromatic hydrocarbons to catalyze a monooxygenation step to produce carcinogenic metabolites [78,79]. CYP1B1 has also been shown to metabolize clinically relevant drugs such as theophylline, caffeine, and flutamide [80,81].

Role of CYP1B1 in cardiovascular diseases

We and others have demonstrated a significant role of CYP1B1 in the pathogenesis of cardiovascular diseases, most remarkably in cardiac hypertrophy and hypertension (Table 1). El-Kadi and colleagues demonstrated that cardiac CYP1B1 expression was up-regulated in different models of cardiac hypertrophy induced by isoproterenol [82–84], pressure overload [85,86], angiotensin II [73], and polycyclic aromatic hydrocarbons [42,87]. Additionally, heavy metal-induced cardiotoxicity has been associated with up-regulation of cardiac CYP1B1 [88–90]. The induction of CYP1B1 in these studies was associated with a perturbation in cardiac arachidonic acid metabolism with generation of more terminal and mid-chain HETEs. Importantly, inhibition of CYP1B1-mediated mid-chain HETEs production has been shown to prevent cardiac hypertrophy in male rats [73,86]. Confirming the causative role of CYP1B1 in developing cardiac hypertrophy, overexpression of CYP1B1 using CRISPR technology has been shown to induce cellular hypertrophy in the cardiac-derived RL-14 cells [72]. Inhibition of CYP1B1 has also been recently shown to prevent uremic toxins-induced cardiac hypertrophy [91]. Additionally, 2-methoxyestradiol, a specific CYP1B1 inhibitor, protected against pressure overload-induced cardiac hypertrophy via antioxidant and anti-inflammatory properties [86]. Similarly, Malik and colleagues have demonstrated an important role of CYP1B1 in hypertension and hypertension-associated pathophysiology [92]. Intriguingly, they have shown a sexually dimorphic role of CYP1B1 where CYP1B1 played a detrimental role in male rodents [93–95], while it had a protective effect in females [96,97]. The detrimental effects of CYP1B1 in male rodents have been attributed to CYP1B1-mediated production of 6β-hydroxytestosterone which was shown to exacerbate angiotensin II-induced hypertension [93], renal dysfunction [94], and vascular changes [95]. On the other hand, the protective effects of CYP1B1 in female rodents have been attributed to CYP1B1-mediated metabolism of estrogen to 2-methoxyestradiol [96,97]. Furthermore, CYP1B1 has been shown to contribute to the development of atherosclerosis, hypertension, and angiotensin II-induced aortic aneurysm in male apolipoprotein E-deficient mice [98,99]. *In vitro* studies have suggested the contribution of CYP1B1-mediated formation of genotoxic metabolites and DNA adducts in the development of atherosclerosis by polyaromatic hydrocarbons [100,101].

Several studies have reported the expression of other cytochrome P450 enzymes in cardiovascular tissues including human heart, aorta, and coronary arteries [16,102,103], as previously reviewed [15,104]. CYP2J2 is the most highly expressed cytochrome P450 enzyme in human cardiovascular tissues [103]. CYP2J2 metabolizes arachidonic acid to EETs which exhibit cardioprotective and anti-inflammatory properties [105,106]. Although overexpression of CYP2J2 has been shown to protect against anthracycline-induced cardiotoxicity in transgenic mice [107], CYP2J2-mediated EETs may promote tumor progression and metastasis [108,109]. Therefore, CYP2J2 may not be a reasonable therapeutic target in cardio-oncology. On the other hand, CYP1A1 has been shown to contribute to both anthracycline-induced cardiotoxicity [110–113] and tumor progression and survival of cancer cells [114,115]. Therefore, similar to CYP1B1, CYP1A1 may also be a reasonable therapeutic target in cardio-oncology. Taken together, isoform-specific targeting of cytochrome P450 enzymes is critical in cardio-oncology, since different isoforms may have opposing effects on the cancer or the cardiovascular system.

Role of CYP1B1 in cancer

The human CYP1B1 enzyme is overexpressed in numerous tumors compared with normal tissues [124]. For instance, immunohistochemistry reports showed high CYP1B1 mRNA and protein levels in prostate tumors, mammary tumors and peritumor benign tissues, and ovarian cancer tissues [30]. Similarly, CYP1B1 was shown to be expressed in eight different cell lines that represent four tumor tissues, with the highest expression levels manifested in HeLa, SKOV-3, and MDA-MB-231 cells, respectively [124]. CYP1B1 overexpression has been associated with the increase in cancer risk via pro-inflammatory cytokines, metastasis, and disturbance in the regulation of cell proliferation, migration, and differentiation [125–128]. Additionally, CYP1B1 overexpression is also associated with increased tumor size, a higher

Table 1 Role of CYP1B1 in cardiovascular diseases

Cardiovascular pathology	Model	Effect on CYP1B1 expression	Effect of CYP1B1 inhibition	References
Cardiac hypertrophy	Isoproterenol-induced cardiac hypertrophy in male SD rats	Up-regulation of CYP1B1 gene and protein expression in the heart	Not reported	[72,83]
	Isoproterenol-induced cellular hypertrophy in RL-14 cells	Induction of *CYP1B1* gene expression	Inhibition of CYP1B1 by TMS or siRNA ameliorated isoproterenol-induced cellular hypertrophy	[72]
	Abdominal aortic constriction in male SD rats	Increase in the protein expression of CYP1B1	2-ME inhibited left ventricular hypertrophy via antioxidant and anti-inflammatory mechanisms	[85,86]
	Angiotensin II-induced cellular hypertrophy in RL-14 and H9c2 cells	Induction of the protein expression of CYP1B1 and increased formation of its associated mid-chain HETEs	Inhibition of CYP1B1 by TMS, resveratrol, fluconazole or 19-HETE attenuated angiotensin II-induced cellular hypertrophy	[73,116–118]
	Angiotensin II-induced cardiac hypertrophy in male SD rats	Induction of CYP1B1 protein expression, but no effect on *CYP1B1* gene expression	Inhibition of CYP1B1 by TMS or 19-HETE ameliorated angiotensin II-induced cardiac hypertrophy	[73,118]
Hypertension	DOCA salt-induced hypertension in male Sprague–Dawley rats	No significant effect on CYP1B1 expression or activity	Inhibition of CYP1B1 by TMS reduced blood pressure, ameliorated cardiovascular and renal hypertrophy, and prevented vascular reactivity and endothelial dysfunction	[119]
	Male SHR rats	Higher CYP1B1 activity in the aorta, heart and kidney of SHRs as compared with control WKY rats	Inhibition of CYP1B1 by TMS reduced blood pressure, decreased vascular reactivity, cardiovascular hypertrophy, endothelial and renal dysfunction, and cardiac and renal fibrosis	[120]
	Angiotensin II-induced hypertension in intact male and OVX female mice	Not reported	Inhibition of CYP1b1 with 2-ME reduced blood pressure in ovariectomized female and intact male mice	[121]
	Angiotensin II-induced hypertension in male mice	Increased renal Cyp1b1 activity, increased 12-HETE and 20-HETE metabolites	*Cyp1b1* gene disruption reduced blood pressure and renal damage	[122]
	Angiotensin II-induced hypertension in female mice	Increased cardiac Cyp1b1 protein expression and catalytic activity	*Cyp1b1* gene disruption exacerbated hypertension and renal damage	[97,123]
	Angiotensin II-induced hypertension in male mice	Increased cardiac cytochrome P450 1B1 activity and plasma levels of 6β-hydroxytestosterone	*Cyp1b1* gene disruption mitigated angiotensin II-induced increase in systolic blood pressure and associated cardiac hypertrophy and fibrosis	[93]
Atherosclerosis	ApoE-deficient male mice on atherogenic diet	Increased cardiac Cyp1b1 activity	Cyp1b1 inhibition by TMS or gene disruption ameliorated atherosclerosis, and reduced blood pressure, endothelial dysfunction, oxidative stress and plasma lipids	[99]
Aortic aneurysm	Angiotensin II-induced aortic aneurysm in male ApoE-deficient mice	Not reported	Cyp1b1 inhibition by TMS or *Cyp1b1* gene disruption minimized aortic aneurysms via reduction in oxidative stress and inflammation	[98]
Heavy metal-induced cardiotoxicity	Acute arsenic toxicity in male C57Bl/6 mice	Induction of CYP1B1 gene expression	Not reported	[90]
	Acute mercury toxicity in male C57Bl/6 mice	Induction of cardiac *CYP1b1* gene expression	Not reported	[89]
	Cadmium-induced toxicity in newborn chicks	Increase in total CYP1B1 expression	Not reported	[88]

Abbreviations: ApoE, apolipoprotein E; DOCA, deoxycorticosterone acetate; SHR, spontaneously hypertensive rat; TMS, 2,4,3′,5′-tetramethoxystilbene; WKY, Wistar–Kyoto rat; 2-ME, 2-methoxyestradiol.

tumor grade, frequent lymph node metastasis, and lymphovascular invasion [125]. In cancer cells, CYP1B1 is thought to play a role in the bioactivation of xenobiotics, metabolism of steroid hormones, and the production of multiple pro-inflammatory and pro-angiogenic factors [26]. The detrimental effects of CYP1B1 have been demonstrated not only in cancer cells, but also in other cell types, including fibroblasts, endothelial cells, pericytes, and immune cells which constitute the tumor micro-environment, as reviewed in [26]. This is especially important, considering the crucial role of the tumor micro-environment in cancer progression and metastasis [26]. For instance, in endothelial cells, CYP1B1 was observed to promote endothelial nitric oxide synthase (eNOS) expression as well as nitric oxide levels, responsible for the many inflammatory and angiogenesis effects important for cancer progression [129,130].

The exact mechanisms of CYP1B1 overexpression in cancer cells and tumors are not fully elucidated. However, CYP1B1 is particularly overexpressed in hormone-related or estrogen-dependent cancers, such as breast, ovarian,

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

and prostate cancers [126,131]. This can be attributed to CYP1B1 involvement in the metabolism of estrogen, progesterone, testosterone, and other steroid-related hormones. CYP1B1-mediated metabolism of these hormones can result in the generation of genotoxic metabolites and oxidative damage [30,132]. Additionally, pro-inflammatory cytokines such as TNF-α and IL-6 have been especially known to induce the expression of CYP1B1 [49,133]. The mRNA and protein levels of the AhR and CYP1B1 are higher in inflammatory breast cancer tissues [126]. CYP1B1 role in carcinogenesis may be attributed to its ability to metabolize polycyclic aromatic hydrocarbons and activate pro-carcinogens into DNA-reactive metabolites [134]. Additionally, CYP1B1 converts melatonin into N-acetylserotonin which then activates tyrosine receptor kinase B (TrkB), eventually leading to breast cancer cell survival and migration [77]. WY-14643, a PPARα agonist, has been shown to increase the protein and mRNA levels of CYP1B1 in MCF-7 cells via PPARα-dependent mechanism, playing a critical role in the progression of human breast cancer [55]. Another way in which CYP1B1 has been shown to play a role in cancer development is by enhancing the invasion of MCF-7 and MCF-10A cells. CYP1B1 has been shown to induce epithelial–mesenchymal transition (EMT) and up-regulates several transcription factors involved in cell growth and metastasis via Sp1 induction [126]. A major metabolite generated by CYP1B1, 4-hydroxyestradiol, also mediates many oncogenic events in cells via the formation of DNA adducts [126,128]. Intriguingly, overexpression of CYP1B1 in tumors can also be attributed to its induction by chemotherapeutic agents and radiation therapy, as summarized in Table 2 and discussed in more detail in subsequent sections of the review.

The association between CYP1B1 polymorphisms and increased cancer risk has been extensively studied [30]. For instance, in 2015, Li and colleagues conducted a meta-analysis to carry a comprehensive and quantitative analysis on the role of CYP1B1 in cancer [127]. This analysis specifically focused on A453G and G119T, which are two critical polymorphisms that have been associated with the replacement of important amino acids that play a crucial role in catalytic activity. This extensive analysis found a significant association between G119T and A453G with prostate, lung, colorectal, endometrial, breast, bladder, and several other cancer risks [127]. Its polymorphisms, $Val^{432}Leu$, $Arg^{48}Gly$, $Ala^{119}Ser$, and $Asn^{453}Ser$ specifically, have been linked to increasing estrogen metabolism responsible for genotoxic metabolites that eventually result in hormone-induced cancers [30]. Additionally, a different meta-analysis focused on several other CYP1B1 polymorphisms. The analysis found that $Leu^{432}Val$ polymorphism is associated with ovarian, lung, and endometrial cancer risks. It also found that $Asn^{453}Ser$ and $Arg^{48}Gly$ are associated with endometrial cancer risks, and $Ala^{119}Ser$ is associated with breast cancer risk [135]. In contrast, another analysis found that the CYP1B1 polymorphisms $Arg^{48}Gly$, $Ala^{119}Ser$, and $Asn^{453}Ser$ are not associated with breast cancer risk [136]. The mechanisms by which CYP1B1 polymorphisms increase cancer risk include enhanced estrogen and progesterone receptor signaling, also known to influence cancer treatment response [30]. When studying the effect of polymorphisms on chemotherapeutic drug treatments, it was found that polymorphisms induce a slower response to anthracycline agents, whereas low polymorphism levels were shown to improve chemotherapy response [128]. Therefore, the presence of homozygous variant genotype (GG) and variant allele (G) of CYP1B1 4326C>G polymorphism of CYP1B1 was associated with lower response rates, shorter progression-free survival, and an overall decrease in patient survival among patients with triple-negative breast cancer [128]. This study shows the ability of CYP1B1 to interfere with cancer treatments. In an era of precision medicine, cancers with high-activity CYP1B1 variants may better respond to the beneficial effects of CYP1B1 inhibitors.

CYP1B1 inhibitors

The detrimental role of CYP1B1 in the pathogenesis of cancer and cardiovascular diseases, among other pathologies, has stimulated active research programs to identify and synthesize potent and selective CYP1B1 inhibitors. The medicinal chemistry, classification, and relative potency and selectivity of these inhibitors have been discussed in previously published excellent review articles [137–140]. Phytochemicals, which are chemicals derived from natural plants, have gained great popularity in the pharmaceutical and medicinal applications as potential cardioprotective and chemopreventive compounds due to their anti-inflammatory, antioxidant, anti-angiogenic, anti-mutagenic, and anti-proliferative properties [141–145]. Although not highly selective, phytochemicals have been the most common source for CYP1B1 inhibitors. Phytochemical groups that show strong inhibitory activity and relative selectivity toward CYP1B1 include stilbenes, flavonoids, coumarins, anthraquinones, and alkaloids [26,137]. More selective CYP1B1 inhibitors have been developed, including: 2,4,3′,5′-tetramethoxystilbene which is a highly potent and selective competitive inhibitor of CYP1B1 [146].

Phytochemicals are also of great interest as chemopreventive compounds due to their low toxicity, no apparent side effects, their regulatory role in cell signaling and gene expression, and high tolerance demonstrated in both *in vivo* and *in vitro* studies [142,147]. Flavonoids are among the most common phytochemicals, approximately 6000 different

Table 2 Effect of cancer treatments on CYP1B1 expression

Agent	Model	Dose/concentration	Effect on CYP1B1	References
Cyclophosphamide	HL-60S and HL-60R human promyelocytic leukemia sensitive (S) and resistant (R) cell lines	100 and 500 μg/ml 1, 2, 3 days	Concentration-dependent inhibition of gene expression	[175]
Doxorubicin (DOX)	Zebrafish	100 μM 40 h	Induction of gene and protein expression	[113]
	C57Bl/6 male and female mice	20 mg/kg single dose 1 day, 6 day	Induction of gene expression in the heart of male mice only	[19]
	Sprague–Dawley male rats	3 mg/kg × 5 doses (over 2-week-period) 1 day post	Induction of gene expression in the heart Increased mid-chain HETEs	[74]
	Sprague–Dawley male rats	2.5 mg/kg × 6 doses (over 2-week-period) 14 days post	Induction of gene expression in the liver and kidney	[168]
	Sprague–Dawley male rats	15 mg/kg single dose 1 day post	Induction of gene expression in the liver and kidney	[167]
	Sprague–Dawley male rats	15 mg/kg single dose 1 day post	Induction of gene and protein expression in the heart	[110]
	RL-14 human cardiac-derived cells	10 μM 12 h	Induction of gene and protein expression and catalytic activity	[74]
	RL-14 human cardiac-derived cells	10 μM 24 h	Induction gene and protein expression and catalytic activity	[176]
	H9c2 rat cardiac-derived cells	1–10 μM 2 h	Concentration-dependent induction of CYP1B1 gene expression	[111]
Daunorubicin	Sprague–Dawley male rats	5 mg/kg single dose 1 day post	No change in gene or protein expression in the heart	[169]
Dasatinib	H9c2 rat cardiac-derived cells	0–160 μM for 24 h	Induction of gene expression	[177]
Docetaxel	MDA 453 BT-20 MCF-7 (breast carcinoma)	8 ng/ml 4 h	Induction of gene expression in MDA-453 and BT-20 cells, No change in MCF-7	[178]
Sunitinib	Wistar albino male rats	25, 50, and 100 mg/kg daily for 4 weeks 1 day post	Dose-dependent induction of gene and protein expression in the liver and kidney	[179]
Radiation	Human skin	Ultraviolet B 0–4 minimal erythema doses for 0–48 h	Induction of gene and protein expression in skin biopsies	[180]
	Peripheral blood mononuclear cells	Solar radiation Measured in (W/m^2) 1 m above the ground for 24 h and given as daily duration (minutes) of the radiation effect exceeding 120 W/m^2	Significant correlation between solar radiation and CYP1B1 mRNA levels	[181]
	Zebrafish embryos	Ultraviolet B 8.9, 17.9, and 26.8 kJ/m^2 for 2, 4, and 6 h daily for two consecutive days	Induction of gene expression	[182]
	HaCaT human keratinocytes	Ultraviolet B Dose 20 mJ/cm^2 for 0–24 h	Induction of CYP1B1 gene transcript	[183]
	HaCaT human keratinocytes	Ultraviolet 0–6.6 mJ/cm^2 and cultured for 6 h before cell harvest	Induction of protein expression and DNA adduct formation	[184]

types existing today, found in fruits, vegetables, grains, teas, and wine as well as other beverages [142]. Flavonoids have been suggested for chemoprevention, which may be attributed to their ability to inhibit CYP1B1 expression and activity [26,142,148]. Aside from their potential chemopreventive role in cancer, flavonoids and polyphenolic compounds have also been shown to prevent various other diseases such as obesity, hypertension, and atherosclerosis, possibly via CYP1B1 inhibition [143,144,149]. For instance, a previous study focused on coronary heart disease found that flavonoids provide protective effects such as anti-inflammatory, antithrombotic, anti-ischemic, antioxidant, and vasorelaxant [150]. Moreover, flavonoids have been shown to decrease the risk of coronary heart disease through an improvement of coronary vasodilatation, a decrease in blood clotting in platelets, and a prevention of low-density lipoprotein (LDLs) oxidation [150,151].

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

Recent efforts have been exerted to discover the CYP1B1 inhibitory activity of commonly used drugs. Intriguingly, the anti-fungal drug fluconazole has been shown to inhibit CYP1B1 and protect against angiotensin II-induced cardiac hypertrophy [152]. Similarly, the clinically relevant β-blocker carvedilol has been found to inhibit CYP1B1 through a systematic drug repurposing approach [153]. Metformin, a medication usually given to treat diabetes, has also been shown to inhibit CYP1B1 expression, specifically in breast cancer cells [154]. Nevertheless, the mechanistic role of CYP1B1 inhibition in mediating the pharmacological effects of these agents is still poorly understood. In addition, almost all inhibitors of CYP1B1 have inhibitory activity toward other members of the CYP1 family, particularly CYP1A1 [155]. Although this lack of selectivity toward CYP1B1 may be undesirable from a mechanistic point of view, it may offer a therapeutic advantage since CYP1A1 is also a reasonable target in cardio-oncology as discussed earlier. Indeed, a number of studies have reported a protective effect of CYP1 inhibitors without discerning the protective effects to either CYP1A1 or CYP1B1 [112,113]. That being said, 2,4,3′,5′-tetramethoxystilbene (TMS) exhibited 50-fold selectivity for CYP1B1 over CYP1A1 and 500-fold selectivity for CYP1B1 over CYP1A2 [146]. Therefore, selective pharmacological inhibition of CYP1B1 can be achieved by using TMS in mechanistic studies. Genetic approaches using Cyp1b1 knockout mice may also be employed to mechanistically discern the exact role of Cyp1b1 [156].

Anthracycline-induced cardiotoxicity

Anthracyclines (e.g. DOX) are a group of chemotherapeutic agents used to treat hematologic malignancies and solid tumors in both pediatric and adult cancer patients. However, the clinical utility of anthracyclines is limited by a significant anthracycline-induced cardiotoxicity which may progress to end-stage heart failure [157,158]. Indeed, the cardiotoxic effects of anthracyclines were reported in cancer patients as early as the 1970s [159,160]. Anthracyclines have both acute and chronic cardiovascular toxic effects. Acute cardiotoxicity occurs in up to 11% of patients during or soon after the administration of anthracyclines and include various arrhythmias, hypotension, and acute heart failure [161,162]. On the other hand, chronic anthracycline-induced cardiotoxicity is dose-dependent and results in irreversible cardiomyopathic changes that affect approximately 2% of anthracycline-treated patients [163]. The precise mechanism of anthracycline-induced cardiotoxicity has not been fully elucidated yet, despite more than 40 years of research. There are different proposed mechanisms including: increased ROS, mitochondrial dysfunction, apoptotic cell death, altered molecular signaling, and perturbed myocardial energy metabolism [161,164–166].

Effect of anthracyclines on CYP1B1 expression

In vitro and *in vivo* studies have demonstrated the induction of CYP1B1 by DOX (Table 2). We first reported that DOX induced CYP1B1 gene expression in H9c2 cardiomyoblasts [111], an effect that was confirmed in RL-15 human cardiomyocytes at the gene, protein, and catalytic activity levels [74]. We were also the first to report that acute DOX administration induced CYP1B1 in the heart, liver, and kidney of male Sprague–Dawley rats [110,167]. Chronic DOX toxicity has also been shown to induce CYP1B1 in the heart, liver, and kidney [74,168]. Importantly, DOX-mediated induction of CYP1B1 was associated with a significant increase in mid-chain HETEs metabolites in the heart of male rats [74]. Intriguingly, we have recently demonstrated a sex-dependent induction of *Cyp1b1* gene expression by acute DOX administration in male C57Bl/6 mice, but not in female mice [19]. This male-specific induction of *Cyp1b1* was associated with a significant sexual dimorphism with male-specific cardiotoxicity [19]. While DOX has been shown to induce CYP1B1 expression *in vivo* and *in vitro*, a study using another anthracycline, daunorubicin, showed no changes in CYP1B1 gene or protein expression in the heart of male Sprague–Dawley rats [169].

Nevertheless, the aforementioned studies have not precisely defined the mechanism of CYP1B1 induction by DOX. Studying the general mechanisms of CYP1B1 induction, we can speculate that DOX may induce CYP1B1 via AhR activation, ROS generation, and/or inflammatory cytokines production (Figure 2). DOX has been shown to activate the AhR in hearts of C57Bl/6 mice, leading to an induction of Cyp1a1 [170]. Although the effect of DOX-induced AhR activation on Cyp1b1 expression was not reported in that study, it is inferred that DOX induced CYP1b1 since it is an AhR-dependent gene, similar to Cyp1a1. The authors have attributed the DOX-induced AhR activation to binding of DOX to the AhR due to its planar structure that resembles polyaromatic hydrocarbon receptors [170]. Counterintuitively, DOX-induced cardiotoxicity was exacerbated in AhR knock-out mice [170]. The cytoprotective effect of the AhR may be attributed to its intricate interplay with other signaling pathways in the heart, rather than its role in cytochrome P450 regulation. In contrast, DOX-induced apoptosis in H9c2 cardiomyoblasts was ameliorated by ginsenoside Rb1 via inhibition of the AhR pathway [171]. DOX has also been shown to generate a copious amount of ROS, particularly in the heart [172]. These ROS have been shown to induce CYP1B1 as well [173]. At last, DOX has been shown to provoke a strong inflammatory response which may lead to CYP1B1 induction, particularly through IL-6 and TNFα-mediated signaling [167,174]. Intriguingly, DOX-induced inflammation in the heart

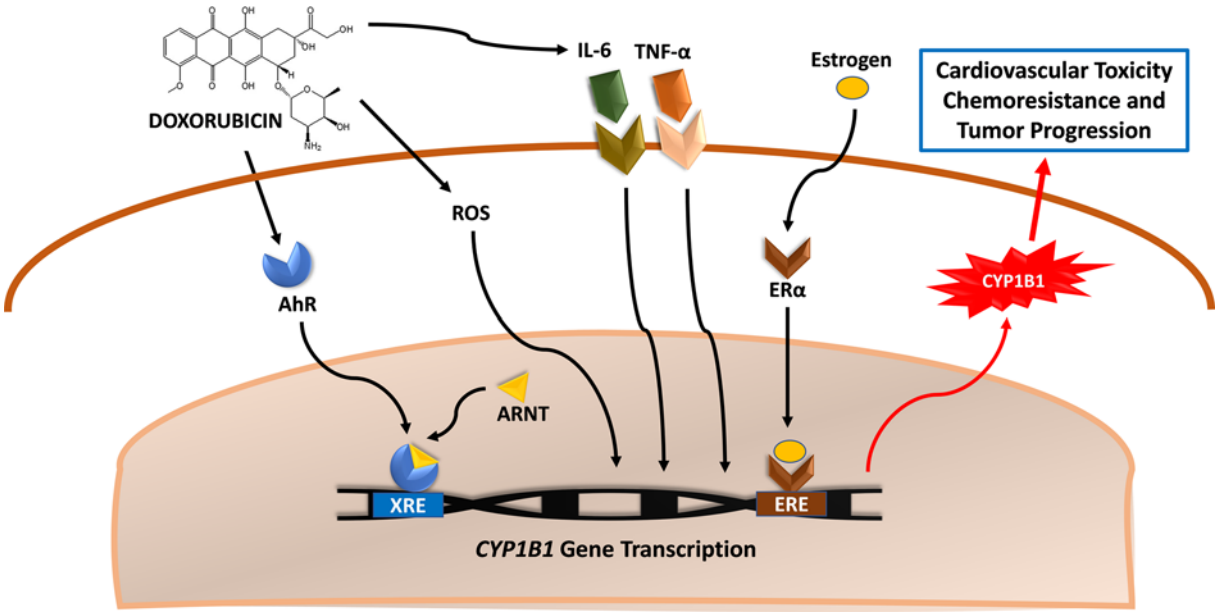

Figure 2. Possible mechanisms of DOX-mediated induction of CYP1B1

DOX may induce CYP1B1 via different mechanisms. First, DOX may directly or indirectly activate the AhR. Upon its nuclear translocation and binding to the AhR Nuclear Translocator (ARNT), the AhR–ARNT heterodimer activates the XRE to induce *CYP1B1* gene transcription. DOX may also induce CYP1B1 by generating ROS and eliciting an inflammatory response via IL-6 and TNF-α. Estrogen can also induce CYP1B1 gene expression via ERα; however, the role of DOX in this pathway is not known. Induction of CYP1B1 leads to both cardiovascular toxicity and increased chemoresistance.

of C57Bl/6 mice was sexually dimorphic with stronger inflammatory response in hearts of male mice [19]. This was associated with male-specific induction of *Cyp1b1* gene expression, strongly suggesting an important role of inflammation in DOX-mediated up-regulation of CYP1B1 [19].

Cardioprotective effects of CYP1B1 inhibitors

Protection from anthracycline-induced cardiotoxicity has been provided by several natural compounds with CYP1B1 inhibitory activity both *in vitro* and *in vivo* (Table 3). It is important to mention that these compounds are not selective inhibitors to CYP1B1 and they have multiple other targets that may mediate their cardioprotective effects. Nevertheless, the CYP1B1 selective inhibitor TMS has been shown to protect from chronic DOX-induced cardiotoxicity in male Sprague–Dawley rats *in vivo* and in RL-1 cardiomyocyte-like cells *in vitro* [74]. As summarized in Table 3, the cardioprotective effects of CYP1B1 inhibitors have been shown to be mediated by reduction in oxidative stress and apoptosis [185–188], improving mitochondrial function [189], reversing altered energy metabolism [190], protection from DOX-induced senescence in vascular smooth muscle cells [191], and reducing mid-chain HETEs concentration [74].

Chemosensitizing effects of CYP1B1 inhibitors

CYP1B1 inhibitors have also been shown to enhance the chemotherapeutic effects of DOX in several cancer cell lines including lung cancer [192–194], breast cancer [195–201], liver cancer [201–204], glioblastoma [205], prostate cancer [206], colorectal cancer [207,208], gastric cancer [209], and leukemia [210,211]. Importantly, several inhibitors have also been shown to overcome DOX resistance in DOX-resistant cancer cell lines [209,210,212–217]. Although all these compounds (Table 3) are known inhibitors of CYP1B1, the role of CYP1B1 in mediating the chemosensitizing effects of these compounds have not been determined in the summarized studies. The chemosensitizing effects of these compounds have been attributed to other mechanisms including: AMPK activation to promote cell apoptosis [192], regulating miR-520b/ATG7 axis [204], miR-101/Nrf2 pathway [218], FZD7/β-catenin pathway [202], down-regulating P-glycoprotein (P-gp) expression [200], and the PTEN/Akt pathway [197]. Inhibition of CYP1B1 may interplay with these pathways leading to the chemo-sensitizing effects.

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

Table 3 Cardioprotective and chemosensitizing effects of CYP1B1 inhibitors toward anthracyclines

Inhibitor	Inhibition IC_{50} (nM)	Cardioprotective effects	Chemosensitizing effects
Acacetin	7–14 [219–221]	Not reported	Enhances the chemotherapeutic effect of DOX in non-small-cell lung carcinoma cells [194]
Isorhamnetin	17 [219]	Protection from chronic DOX-induced cardiotoxicity *in vivo* in rats and *in vitro* in H9c2 cells [201]	Potentiates DOX-induced toxicity in MCF-7, HepG2, and Hep2 cancer cells [201]
Chrysin	24–270 [219,220]	Protection from acute and chronic DOX-induced cardiotoxicity *in vivo* in rats [222,223]	Enhanced cytotoxicity of DOX in a spheroid culture model of human lung squamous cell carcinoma [224], BEL-7402/ADM [225], lung cancer A549 cells [192], and human non-small-cell lung cancer cell lines [193]
Apigenin	25 [219]	Attenuated chronic DOX-induced cardiotoxicity in *in vivo* in rats and *in vitro* in rat cardiomyocytes [186–188]	Augmented the cytotoxic effect of DOX against HepG2 cells [203], and DOX-resistant hepatocellular carcinoma cell line BEL-7402/ADM [204,218,226] Reverse chemo-resistance to DOX in DOX–resistant breast cancer cells (MCF–7/ADR) [198]
Kaempferol	47 [219]	Protected from chronic DOX-induced cardiotoxicity *in vivo* in rats and *in vitro* in H9c2 cells [227]	Potentiated the cytotoxic effect of DOX in glioblastoma cells [205]
Quercetin	77 [219]	Protected rat and human cardiomyocytes and H9c2 cells from DOX-induced toxicity *in vitro* [176,188,189,199,228]. Protected from chronic DOX in rats [190,229] and mice [185] *in vivo*. Augmented the cardioprotective effect of losartan against chronic DOX cardiotoxicity [230]	Enhanced DOX anti-cancer effects in xenografts of leukemia P388 cells [185], liver cancer cells [231], 4T1 breast cancer cells [232,233] Reversed chemoresistance to DOX in hepatocellular carcinoma cells [202], breast cancer cells [200,212], prostate cancer cells [206], multidrug-resistant leukemia K562 cells [210] Enhanced chemotherapeutic effect of DOX against human breast cancer cells [195–197,199,234], human colorectal HT29 cancer cell line [208], neuroblastoma cells [235]
Luteolin	79 [219]	Protected against DOX-induced cardiomyocyte toxicity *in vitro* [188] Attenuated acute DOX-induced myocardial lipid peroxidation *in vivo* [236]	Luteolin (10 μM) attenuated the cytotoxic effects of DOX in breast cancer cells MCF-7 cells [237] Luteolin (5 μM) sensitized oxaliplatin-resistant colorectal cancer cell lines HCT116 and SW620 [207] and human lung carcinoma A549 cells [238] to DOX
Genistein	IC_{50} = 2100 nm [239] Ki = 1900 nm [240] Induced CYP1B1 gene expression [241,242]	Protected from chronic DOX-induced cardiotoxicity *in vivo* [243,244] Protected from DOX-induced senescence in vascular smooth muscle cells [191]	Potentiated the cytotoxic effect of DOX in MCF-7, MCF-7/ADR cells, MDA-MB-231 (breast), PC-3 (prostate), H460 (lung), and BxPC-3 (pancreas) cancer cells [213,245–247] Attenuated DOX-induced cytotoxicity in MCF-7 breast cancer cells in one study [248] Sensitized diffuse large cell lymphoma to CHOP (cyclophosphamide, DOX, vincristine, prednisone) chemotherapy in SCID tumor-bearing mice *in vivo* [249]
Resveratrol, reviewed in [250]	1400–40000 [251,252]	Protection from DOX-induced cardiomyocyte toxicity in H9c2 cells [253–258], rat primary cardiomyocytes [259–261], and human cardiac progenitor cells [262] *in vitro*. Protection from acute DOX-induced cardiotoxicity [255,263–267] and chronic DOX-induced cardiotoxicity *in vivo* [258,259,262,268–276]	Potentiated DOX-induced cytotoxicity in U373MG glioblastoma, MCF-7 breast cancer cells, LNCaP prostate carcinoma, Reh B-cell leukemia cells, Human ovarian cancer cells OVCAR-3 and uterine (Ishikawa) cells, Human hepatocellular carcinoma cell line (HepG2), Cervical cancer cell line (HeLa), MDA-MB-231 cells, HT-29 human colon carcinoma cells, Hela and Caski cells, HCT 116 and HT-29, Lymphoblastic leukemia cell line (MOLT-4), Human multiple myeloma cell line (U266B1), Burkitt's lymphoma cell line (Raji cell), canine hemangiosarcoma cells [259,277–286] Reversed chemoresistance in DOX-resistant MCF-7 [214–217], DOX-resistant gastric cancer cells (SGC7901/DOX) [209] Augmented the chemotherapeutic effect of DOX tumor-bearing mice *in vivo* [209,215,217,285,287].
Berberine	Ki = 44, IC_{50} = 90–190 [288,289] Induced CYP1B1 gene expression [290]	Protection from acute DOX-induced cardiotoxicity [291–294] and chronic DOX-induced cardiotoxicity [295] *in vivo* Protection from DOX-induced toxicity in H9c2 cells [291,296] and primary rat cardiomyocytes [294] *in vitro*	Enhanced sensitivity to DOX in Jurkat, HeLa, and lung cancer cells *in vitro* and in leukemia mouse model *in vivo* [211,297,298]. Reversed DOX resistance in resistant human breast cancer MCF-7/MDR cell *in vitro* and *in vivo* [299]. Berberine in combination with DOX suppresses growth of murine melanoma B16F10 cells in culture and xenograft [300]
2,4,3′,5′-tetramethoxy-stilbene	IC_{50} = 6 [146]	Protection from chronic DOX-induced cardiotoxicity in rats *in vivo* and in RL-14 cardiomyocyte-like cells *in vitro* via decreasing the formation of cardiac mid-chain HETEs [74]	Not reported

Radiation therapy

Radiation therapy is a highly effective treatment for many types of cancers including lymphoma, breast, lung, neck, and head cancers [5,301]. However, radiation-based cancer treatments can also result in serious cardiotoxic side effects, including pericardial fibrosis, pericardial effusion, and diffuse myocardial fibrosis, all of which can lead to heart failure [302]. Restrictive cardiomyopathy, valvular abnormalities, coronary disease, peripheral vascular disease, and arrhythmias can also occur following radiation therapy [303]. It has been clearly shown that the risk of heart failure following radiation therapy for various cancers is dose-dependent [304]. In fact, several studies showed a correlation between an increase in radiation dose with an increase in incidence of major coronary events, associating these with cardiac mortality [305,306]. The cardiotoxic effects of radiation therapy may be exhibited 5–30 years following treatment [5,302]. These late-onset cardiac effects are especially observed in patients that have been treated for breast carcinoma, Hodgkin's lymphoma, lung carcinoma, and other thoracic malignancies, likely due to the incidental irradiation of the heart [304].

Effect of radiation on CYP1B1 expression

Although there is limited evidence regarding the effect of radiation therapy on CYP1B1 expression, exposure to ultraviolet (UV) and solar radiation have been shown to induce CYP1B1 (Table 2). In a longitudinal study, levels of CYP1B1 mRNA isolated from human peripheral blood mononuclear cells were compared with yearly solar radiation records, and a significant correlation was found [181]. However, this study had several limitations including small sample size and lack of individual radiation exposure levels. Exposure to UV and UV-B radiation induces CYP1B1 mRNA in human keratinocytes, HaCaT cells, zebrafish, and human skin biopsies (Table 2).

Protective effects of CYP1B1 inhibitors against radiation-induced toxicity

There is a paucity of research showing the protective effects of CYP1B1 inhibitors against radiation therapy-induced cardiovascular toxicity. However, inhibition of CYP1B1 has been shown to protect from other radiation-induced toxicities in non-cardiovascular tissues and organs, including: protection from macromolecular damage, hemorrhage, and fibrosis in HaCaT cells and ovarian tissues by isorhamnetin [219,307], protection against follicular loss and destruction of ovarian histoarchitecture in ovarian tissues by chrysin [308], protection against nuclear DNA damage in HaCaT cells by apigenin [309]. Similarly, resveratrol has been shown to protect experimental animals from radiation-induced erectile dysfunction, immune-suppression, intestinal injury, hepatotoxicity, and ovarian toxicity [310–312]. Berberine has also been shown to reduce the incidence and severity of acute intestinal symptoms in patients receiving pelvic radiation [313]. *In vivo* studies in mice showed the protective effects of berberine against radiation-induced intestinal injury by decreasing inflammation markers, lipid peroxidation, and mucosal injury in the intestinal tissue [314,315]. Moreover, berberine decreased markers of endothelial dysfunction and reduced the incidence of lung injury induced by radiation therapy in patients with non-small cell lung cancer [316]. Several phytochemicals, such as isorhamnetin, chrysin, apigenin, luteolin, berberine, and luteolin have all been shown to protect human keratinocytes from radiation-induced damage through reduction in ROS production [309,317–319].

Radiosensitizing effects of CYP1B1 inhibitors

While there is limited evidence of the cardiovascular protective effects of CYP1B1 inhibitor against radiation-induced cardiovascular toxicity, there is a plethora of preclinical studies showing the radiosensitizing effects of phytochemicals with CYP1B1 inhibitory activity. While these phytochemicals have been shown to target multiple pathways, they exhibit strong inhibitory activity toward CYP1B1, with IC_{50} values in the nanomolar to micromolar range (Table 3). When combined with radiation therapy, resveratrol has been shown to augment the anti-cancer effects of radiation in both *in vitro* and *in vivo* studies [320–324], as reviewed in [250]. For instance, resveratrol has proven in the past to offer radiosensitizing effects in nasopharyngeal cancer cells via inhibition of E2F transcription factor, colony-forming activities, and the induction of G_1 phase cell cycle arrest [325]. Apigenin has been shown to enhance the apoptotic effects of radiation in SQ-5 human lung carcinoma cells by increasing the protein expression of WAF1/p21 while decreasing protein levels of Bcl-2 [326]. Moreover, apigenin alongside genistein and quercetin enhanced radiation-induced cell death by decreasing DNA damage renewal and cell repopulation, demonstrating higher antitumor activities [327]. Additional *in vivo* studies also demonstrated the radiosensitizing effects of apigenin in Ehrlich carcinoma-bearing mice exposed to whole body γ irradiation via the down-regulation of angiogenic regulators such as vascular endothelial growth factor-C (VEGF-C), down-regulation of matrix metalloproteinase-2 (MMP2), and the enhancement of apoptosis [328]. The radiosensitizing effects of quercetin have also been demonstrated in DLD-1 human colorectal cancer xenograft model *in vivo* and in HeLa and MCF-7 cells *in vitro* [329,330].

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

Similarly, berberine has been shown to radiosensitize human esophageal cancer cells (ESCC) at doses lower that 15 μM [331] through down-regulation of RAD51, an important factor whose down-regulation is crucial, as it is found in excessive amounts in ESCCs [331]. Berberine has also been demonstrated to radiosensitize human colon cancer cells via induction of AMPK activation, a protein responsible for the regulation of tumor progression and metastasis and also via decreasing migration of SW480 and HCT 116 cells [332]. Berberine has been shown to radiosensitize human liver cancer cell lines SMMC-7221 exposed to radiation, in which decreased cell viability and tumor growth inhibition were observed in nude mice xenograft [315]. At last, nasopharyngeal carcinoma cells CNE-2, hepatocellular HCC cells, and non-small cell lung cancer cell LLC and A549 are some other cell lines in which berberine has shown to enhance radiosensitivity effects through reduction in proliferation and viability, induction of apoptosis and cell cycle arrest in G_0 and G_1 phases, decrease in protein expressions of Sp1, and inhibition of growth factor transforming growth factor-beta (TGF-B) and vimentin proteins [333–335].

Other cardiotoxic cancer treatments

Cisplatin

Cisplatin is a chemotherapeutic alkylating agent mostly used to treat ovarian, testicular, lung, and bladder cancers [336,337]. The two most common adverse effects of cisplatin are nephrotoxicity and ototoxicity; nevertheless, cisplatin treatment may also result in severe cardiotoxicic effects including electrocardiographic changes in the heart, acute coronary ischemia [338], arrythmias, myocarditis, cardiomyopathy, and congestive heart failure [339]. The protective effects of CYP1B1 inhibitors against cisplatin-induced cardiovascular damage are not well-studied. However, protection from other cisplatin-induced toxicities have been reported. For instance, chrysin offers protection against cisplatin-induced hepatotoxicity and colon toxicity [340]. Luteolin, kaempferol, chrysin, and quercetin also prevent ototoxicity and nephrotoxicity damage induced by cisplatin [340–345]. Resveratrol offered protection against cisplatin-induced epididymal toxicity, testicular toxicity, and toxicity in ovarian and cavity cancer cells [346,347]. At last, berberine has been shown to reverse the nephrotoxic and hepatotoxic effects caused by cisplatin [348].

Not only do these phytochemicals offer protection against cisplatin-induced toxicity, but they also augment the chemotherapeutic effects of cisplatin by enhancing cell death via induction of apoptosis and/or necroptosis [340,348–356]. For instance, apigenin, specifically targets mTOR/PI3K/Akt signaling pathways to promote the cytotoxic effect of cisplatin by increasing the inhibitory effects on cell migration [354]. Berberine also has the potential to down-regulate the overexpressed genes in squamous cell carcinoma [357]. Isorhamnetin has been shown to trigger microtubule distortion and depolymerization and inhibit cancer cell migration [349]. Since these phytochemicals have multiple molecular targets, the evidence of CYP1B1 involvement in these effects is anecdotal. However, other studies have offered more direct evidence of CYP1B1 in chemoresistance to cisplatin therapy. Immunohistochemistry showed CYP1B1 to be up-regulated in non-small cell lung cancer tissues of cisplatin-resistant patients, and CYP1B1 silencing significantly decreased CXCR4 expression levels and overall cisplatin resistance [358]. To further support these findings, a study using human HEK293 kidney cells found that two potent CYP1B1 inhibitors, 7k (DMU2105) and 6j (DMU2139) with IC_{50} values of 10 and 9 nM, were shown to overcome cisplatin resistance in CYP1B1-overexpressing lines [359]. A third study using *Glycyrrhiza glabra* extract and quercetin, both showing CYP1B1 inhibitory activity, reversed cisplatin resistance in triple-negative MDA-MB-468 breast cancer cells via inhibition of cytochrome P450 1B1 enzyme (CYP1B1) [358,360].

Cyclophosphamide

Cyclophosphamide is another alkylating chemotherapeutic agent used to treat a variety of cancers. At high doses, cyclophosphamide has been reported to cause cardiotoxic effects [361] that are usually manifested in the forms of myocyte damage, edema, and hemorrhagic necrotic perimyocarditis [362,363]. In contrast with other chemotherapeutic agents, cyclophosphamide has been shown to inhibit CYP1B1 gene expression in HL-6 human acute promyelocytic leukemia cell line [175]. Studies using the flavonoids chrysin and resveratrol proved their ability to exhibit ameliorative effects against brain, heart, liver, testis, kidney, and hepatorenal toxicities induced by cyclophospamide [364,365]. Similarly, apigenin exhibits great inhibitory effects on genotoxicity of antitumor agents. Moreover, cardiotoxicity, hepatotoxicity, gentotoxicity, urotoxicity, and ovarian toxicity effects all seemed to be reduced by quercetin, berberine, and genestein treatment, generally through antioxidant and anti-inflammatory activities [366–368].

Carfilzomib

Carfilzomib is a chemotherapeutic agent used primarily for the treatment of multiple myeloma [369]. Carfilzomib has been shown to cause cardiotoxic effects such as congestive heart failure, hypertension, coronary artery disease,

ischemic heart disease, arrhythmia, and cardiorespiratory arrest [370–372]. Currently, there is no published research that shows the effect of carfilzomib on CYP1B1 expression. There is also a paucity of research describing the cardioprotective effects by CYP1B1 inhibitors. However, there is one study that reported the anti-cancer effect of carfilzomib when used in combination with resveratrol. Resveratrol enhanced the effects of carfilzomib in multiple myeloma cell lines showing higher anti-proliferative and apoptotic effects in a dose-dependent manner [373].

Dasatinib

Dasatinib, an orally administered chemotherapeutic drug, is an inhibitor of many tyrosine kinases, and is an effective agent for treating chronic myeloid leukaemia [374]. Dasatinib has been shown to induce several adverse effects including pulmonary and cardiovascular toxicities. Dasatinib-induced cardiovascular toxicity may lead to heart failure, pericardial effusion, left ventricular dysfunction, pulmonary artery disease, myocardial ishcemia–reperfusion injury, and pulmonary artery disease [375,376]. Intriguingly, dasatinib has been shown to induce CYP1B1 expression in H9c2 cells, an effect that was associated with an induction of cardiac hypertrophy markers such as B-type natriuretic peptide (BNP) and β-MHC [177]. However, co-treatment with resveratrol did not ameliorate dasatinib-induced expression of these hypertrophic markers [177].

Sunitinib

Sunitinib is a tyrosine kinase inhibitor commonly used to treat stromal tumors, renal carcinoma, and pancreatic neuroendocrine tumors [377]. Sunitinib-induced cardiotoxic effects have been reported in patients including hypertension, left ventricular systolic dysfunction, and congestive heart failure [378,379]. The mRNA and protein expression levels of CYP1B1 in rat renal and hepatic tissues were induced by sunitinib [179]. Sunitinib has also been shown to activate the AhR/CYP1A1 pathway in rat heart and the cardiac-derived H9c2 cells [380]. Similar to CYP1A1, CYP1B1 is an AhR-regulated gene, so it is expected that CYP1B1 is also induced by sunitinib, although the effect of sunitinib on CYP1B1 was not reported in this particular study. Importantly, resveratrol has been shown to protect from sunitinib-induced cardiac hypertrophy in rats [380]. In contrast with the presumably protective effect of phytochemical inhibitors of CYP1B1, genistein, the most prevalent phytoestrogen in soy, increased sunitinib-induced apoptosis in neonatal rat ventricular myocytes and exacerbated sunitinib-induced lethality in mice [381]. The detrimental effect of phystoestrogens in sunitinib-induced cardiotoxicity can be attributed to the fact that estrogen exacerbates sunitnib-induced cardiotoxicity in female mice [382], in contrast with DOX-induced cardiotoxicity which preferentially affect male mice, as reviewed in [383].

Immunotherapy

Cancer immunotherapy has emerged as a novel and effective approach to combat incurable cancers by activating the host's immune system to recognize and destroy the tumor cells [384,385]. Expectedly, activation of the immune system leads to several immune-related adverse effects, including cardiovascular toxicity [386]. Immunotherapy-induced cardiovascular toxicity is mostly inflammatory in nature and includes myocarditis, pericarditis, and vasculitis [387]. Although there are no published reports describing the effect of cancer immunotherapy on CYP1B1 expression, immunotherapy-induced inflammatory reaction is expected to up-regulate CYP1B1. Likewise, there are no published studies reporting the potential protective effects of CYP1B1 inhibitors on immunotherapy-induced cardiovascular toxicity. Nevetheless, natural comounds with CYP1B1 inhibitory activity have demonstrated immunomodulatory functions *in vitro* and *in vivo*, which may contribute to their anti-cancer effects, as recently reviewed [388,389]. Therefore, more research is needed to understand the potential interplay between CYP1B1 inhibitors and cancer immunotherapy in the context of cardio-oncology.

Conclusions

CYP1B1 has been described as "a unique gene with unique characteristics" because it is implicated in a wide variety of pathological conditions [390]. CYP1B1 plays a central role in the metabolism of several biologically active endogenous compounds (Figure 1). It is also capable of generating carcinogenic metabolites leading to DNA adduct formation, in addition to its role in generating ROS. Therefore, the biological significance of CYP1B1 has been the focus of scientific research of several research groups all over the world. The detrimental role of CYP1B1 in the four phases of carcinogenesis, the initiation, promotion, progression, and metastasis, has been recognized for almost two decades [391,392]. More recently, the contribution of CYP1B1 to the pathogenesis of cardiometabolic diseases has also been increasingly appreciated [8,92,393]. Since we first reported the induction of CYP1B1 by DOX, the most cardiotoxic chemotherapeutic drug [111], a growing body of evidence has strongly suggested the contribution of

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

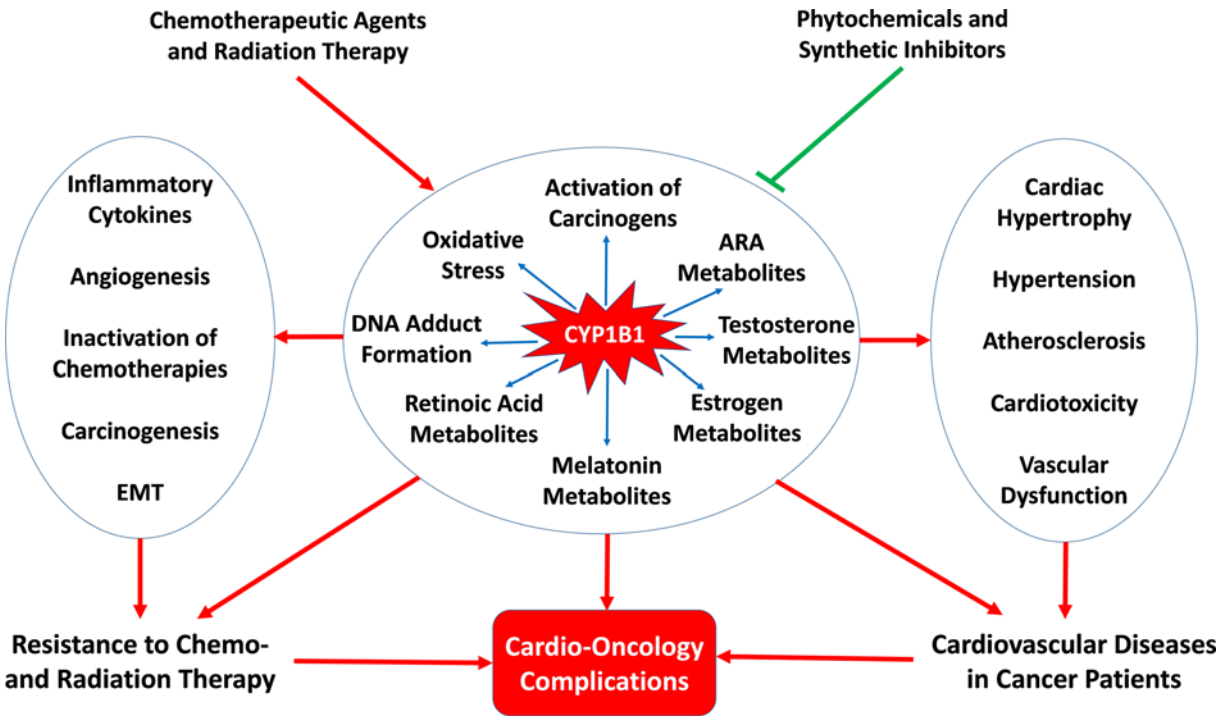

Figure 3. The potential role of CYP1B1 in cardio-oncology

Chemo- and radiation therapy induce CYP1B1, leading to perturbation in the metabolism of arachidonic acid (ARA), steroids, melatonin, and retinol, and activation of pro-carcinogens, production of oxidative stress, and DNA adduct formation. Induction of CYP1B1 induces and/or exacerbates therapy-induced cardiovascular toxicity and increases resistance to chemo- and radiation therapy. These detrimental effects can be potentially mitigated by phytochemical and synthetic CYP1B1 inhibitors.

CYP1B1 to chemotherapy-induced cardiovascular toxicity. All the studied cardiotoxic chemotherapies, with the notable exception of cyclophosphamide, have been shown to induce CYP1B1 in different experimental conditions (Table 2). Induction of CYP1B1 can be detrimental in many ways. First, it can induce or exacerbate therapy-induced cardiovascular complications. Second, it can also lead to significant chemo- and radio-resistance, undermining both the safety and effectiveness of cancer treatment.

It is intriguing that the same enzyme may have divergent effects on the cardiovascular system and the malignant tumors (Figure 3). Several CYP1B1-mediated signaling pathways may lead to these divergent effects. For instance, while mid-chain and terminal HETEs are detrimental to the cardiovascular system [72,73], they enhance survival, proliferation, and metastasis of cancer cells [394–398]. Likewise, CYP1B1-mediated formation of genotoxic metabolites and DNA adducts lead to atherosclerosis and cardiovascular disease [100,101], and may also contribute to CYP1B1-mediated carcinogenesis [134]. CYP1B1 has also been shown to induce EMT which is involved in cardiac fibrosis [399,400] and in cancer progression [126,401]. CYP1B1-mediated inflammation, which has deleterious effects on the cardiovascular system [19,85,86], can also contribute to carcinogenesis and tumor progression [126,402]. Therefore, inhibitors of CYP1B1 are poised to optimize the benefit and reduce the cardiovascular risk of cancer treatments by interfering with these divergent signaling pathways. Nevertheless, there are no studies that systemically compare these divergent effects within the same model. Indeed, the use of tumor-bearing animal models is strongly needed to discern these divergent signaling pathways underpinning the cardioprotective and the chemo/radio-sensitizing effects of CYP1B1 inhibitors in the same animal model. A plethora of phytochemicals have demonstrated significant CYP1B1 inhibitory activity with varying degrees of potency and selectivity. Although these phytochemicals have shown promising cardioprotective, chemosensitizing, and radiosensitizing properties in preclinical studies, as reviewed in [250,403,404]; the specific role of CYP1B1 inhibition in these effects has been rarely investigated. Since phytochemicals have multiple targets, the identification of a specific molecular mechanism that mediate their effects is very challenging. Therefore, future studies need to discern the role of CYP1B1 by using more selective inhibitors, such as 2,4,3′,5′-tetramethoxystilbene, in addition to CYP1b1 knockout mouse models.

The translation of these promising preclinical findings to the care of cardio-oncology patients is another challenge. A large number of phytochemicals with CYP1B1 inhibitory activity have been tested in clinical trials in healthy individuals, cancer patients, and patients with cardiovascular diseases. The results of these clinical trials are generally mixed and do not provide a strong evidence of a clear clinical benefit. A clinical trial of resveratrol in 20 patients with colorectal cancer has shown a promising anti-cancer effect. Eight doses of 0.5 or 1.0 gram of resveratrol given before surgical resection was well-tolerated and resulted in 5% reduction in tumor proliferation [405]. Likewise, the recurrence rate of neoplasia after colon cancer resection was 7% in patients treated with a flavonoid mixture and 47% in the control [406]. Oral genistein given 14–21 days before urothelial bladder cancer surgery was well-tolerated and reduced bladder cancer tissue phosphorylated-epidermal growth factor receptor (EGFR), which contributes to the proliferation and survival of cancer cells [407]. Although these studies, among others, have shown that these phytochemicals are well-tolerated by cancer patients, a Phase II clinical trial of bortezomib with and without high-dose resveratrol (5 grams daily) in multiple myeloma patients was terminated early due to unexpected renal toxicity in the resveratrol arm [408]. Although this safety concern may be specific to multiple myeloma patients who are at an increased risk for renal failure, these results hindered the advancement of resveratrol and probably other phytochemicals to more clinical trials in cancer patients.

In addition, since several agents which had shown promising cardioprotective effects in preclinical studies failed in subsequent clinical trials (e.g. vitamin E and N-acetyl cysteine [409,410]), the clinical community has become more critical of translating preclinical findings to patient care. Indeed, oncologists are usually very concerned about the possibility that cardioprotective agents may undermine the anti-cancer effects of chemotherapy and/or lead to increased incidence of secondary malignancy. This concern is heightened in case of phytochemicals which have multiple targets and exhibit a high probability of significant drug interactions [411–413]. In addition, there has been a concern that phytochemicals with antioxidant properties may scavenge ROS and negatively impact the outcome of ROS-dependent cancer treatments, as reviewed in [414]. Therefore, elucidating the molecular mechanism of the cardioprotective and chemo/radio-sensitizing properties of phytochemicals is pivotal to the design of specific therapeutic agents that are both safe and effective. As discussed in this review, there is growing evidence that CYP1B1 is an attractive target wherein its inhibition may offer protection against cancer treatment-induced cardiovascular toxicity and prevent chemo/radio-resistance at the same time.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

This work was supported by the National Heart, Lung, and Blood Institute [grant number 1R01HL151740 (to B.N.Z.)]; the St. Baldrick's Foundation for Childhood Cancer [grant number 638335 (to B.N.Z.)]; and the National Institutes of Health's National Center for Advancing Translational Sciences [grant number UL1TR002494 (to B.N.Z. and A.N.C.)]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funders had no role in in the writing of the manuscript, or in the decision to publish.

Open Access

Open access for this article was enabled by the participation of University of Minnesota in an all-inclusive *Read & Publish* pilot with Portland Press and the Biochemical Society.

Abbreviations

AhR, Aryl hydrocarbon receptor; CYP1B1, cytochrome P450 1B1; DOX, doxorubicin; EET, epoxyeicosatrienoic acid; EMT, epithelial–mesenchymal transition; ERα, estrogen receptor α; ESCC, esophageal cancer cell; HETE, hydroxyeicosatetraenoic acid; IL-6, interleukin-6; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TMS, 2,4,3′,5′-tetramethoxystilbene; UV, ultraviolet.

References

1 (2019) Study cancer survivors. *Nature* **568**, 143, https://doi.org/10.1038/d41586-019-01095-9
2 Ponisch, W. and Niederwieser, D. (2006) Late effects after chemotherapy. *Internist (Berl.)* **47**, 266–268
3 Tajiri, K., Aonuma, K. and Sekine, I. (2017) Cardio-oncology: a multidisciplinary approach for detection, prevention and management of cardiac dysfunction in cancer patients. *Jpn. J. Clin. Oncol.* **47**, 678–682, https://doi.org/10.1093/jjco/hyx068
4 Coviello, J.S. (2018) Cardio-oncology: a subspecialty in its infancy. *J. Adv. Pract. Oncol.* **9**, 154–155

5 Lenneman, C.G. and Sawyer, D.B. (2016) Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circ. Res.* **118**, 1008–1020, https://doi.org/10.1161/CIRCRESAHA.115.303633
6 Ma, W., Wei, S., Zhang, B. and Li, W. (2020) Molecular mechanisms of cardiomyocyte death in drug-induced cardiotoxicity. *Front. Cell Dev. Biol.* **8**, 434, https://doi.org/10.3389/fcell.2020.00434
7 Bonaca, M.P., Olenchock, B.A., Salem, J.E., Wiviott, S.D., Ederhy, S., Cohen, A. et al. (2019) Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation* **140**, 80–91, https://doi.org/10.1161/CIRCULATIONAHA.118.034497
8 Li, F., Zhu, W. and Gonzalez, F.J. (2017) Potential role of CYP1B1 in the development and treatment of metabolic diseases. *Pharmacol. Ther.* **178**, 18–30, https://doi.org/10.1016/j.pharmthera.2017.03.007
9 Pottenger, L.H., Christou, M. and Jefcoate, C.R. (1991) Purification and immunological characterization of a novel cytochrome P450 from C3H/10T1/2 cells. *Arch. Biochem. Biophys.* **286**, 488–497, https://doi.org/10.1016/0003-9861(91)90070-Y
10 Savas, U., Bhattacharyya, K.K., Christou, M., Alexander, D.L. and Jefcoate, C.R. (1994) Mouse cytochrome P-450EF, representative of a new 1B subfamily of cytochrome P-450s. Cloning, sequence determination, and tissue expression. *J. Biol. Chem.* **269**, 14905–14911
11 Sutter, T.R., Tang, Y.M., Hayes, C.L., Wo, Y.Y., Jabs, E.W., Li, X. et al. (1994) Complete cDNA sequence of a human dioxin-inducible mRNA identifies a new gene subfamily of cytochrome P450 that maps to chromosome 2. *J. Biol. Chem.* **269**, 13092–13099
12 Murray, G.I., Melvin, W.T., Greenlee, W.F. and Burke, M.D. (2001) Regulation, function, and tissue-specific expression of cytochrome P450 CYP1B1. *Annu. Rev. Pharmacol. Toxicol.* **41**, 297–316, https://doi.org/10.1146/annurev.pharmtox.41.1.297
13 Tang, Y.M., Wo, Y.Y., Stewart, J., Hawkins, A.L., Griffin, C.A., Sutter, T.R. et al. (1996) Isolation and characterization of the human cytochrome P450 CYP1B1 gene. *J. Biol. Chem.* **271**, 28324–28330, https://doi.org/10.1074/jbc.271.45.28324
14 Bhattacharyya, K.K., Brake, P.B., Eltom, S.E., Otto, S.A. and Jefcoate, C.R. (1995) Identification of a rat adrenal cytochrome P450 active in polycyclic hydrocarbon metabolism as rat CYP1B1. Demonstration of a unique tissue-specific pattern of hormonal and aryl hydrocarbon receptor-linked regulation. *J. Biol. Chem.* **270**, 11595–11602, https://doi.org/10.1074/jbc.270.19.11595
15 Zordoky, B.N. and El-Kadi, A.O. (2010) Effect of cytochrome P450 polymorphism on arachidonic acid metabolism and their impact on cardiovascular diseases. *Pharmacol. Ther.* **125**, 446–463, https://doi.org/10.1016/j.pharmthera.2009.12.002
16 Thum, T. and Borlak, J. (2000) Gene expression in distinct regions of the heart. *Lancet* **355**, 979–983, https://doi.org/10.1016/S0140-6736(00)99016-0
17 Zordoky, B.N. and El-Kadi, A.O. (2007) H9c2 cell line is a valuable in vitro model to study the drug metabolizing enzymes in the heart. *J. Pharmacol. Toxicol. Methods* **56**, 317–322, https://doi.org/10.1016/j.vascn.2007.06.001
18 Zordoky, B.N., Anwar-Mohamed, A., Aboutabl, M.E. and El-Kadi, A.O. (2009) Acute doxorubicin cardiotoxicity alters cardiac cytochrome P450 expression and arachidonic acid metabolism in rats. *Toxicol. Appl. Pharmacol.* **242**, 38–46, https://doi.org/10.1016/j.taap.2009.09.012
19 Grant, M.K., Seelig, D.M., Sharkey, L.C. and Zordoky, B.N. (2017) Sex-dependent alteration of cardiac cytochrome P450 gene expression by doxorubicin in C57Bl/6 mice. *Biol. Sex Differ.* **8**, 1, https://doi.org/10.1186/s13293-016-0124-4
20 Bertrand-Thiebault, C., Ferrari, L., Boutherin-Falson, O., Kockx, M., Desquand-Billiald, S., Fichelle, J.M. et al. (2004) Cytochromes P450 are differently expressed in normal and varicose human saphenous veins: linkage with varicosis. *Clin. Exp. Pharmacol. Physiol.* **31**, 295–301, https://doi.org/10.1111/j.1440-1681.2004.03996.x
21 Conway, D.E., Sakurai, Y., Weiss, D., Vega, J.D., Taylor, W.R., Jo, H. et al. (2009) Expression of CYP1A1 and CYP1B1 in human endothelial cells: regulation by fluid shear stress. *Cardiovasc. Res.* **81**, 669–677, https://doi.org/10.1093/cvr/cvn360
22 Kerzee, J.K. and Ramos, K.S. (2001) Constitutive and inducible expression of Cyp1a1 and Cyp1b1 in vascular smooth muscle cells: role of the Ahr bHLH/PAS transcription factor. *Circ. Res.* **89**, 573–582, https://doi.org/10.1161/hh1901.097083
23 Tang, Y., Scheef, E.A., Wang, S., Sorenson, C.M., Marcus, C.B., Jefcoate, C.R. et al. (2009) CYP1B1 expression promotes the proangiogenic phenotype of endothelium through decreased intracellular oxidative stress and thrombospondin-2 expression. *Blood* **113**, 744–754, https://doi.org/10.1182/blood-2008-03-145219
24 De Caterina, R. and Madonna, R. (2009) Cytochromes CYP1A1 and CYP1B1: new pieces in the puzzle to understand the biomechanical paradigm of atherosclerosis. *Cardiovasc. Res.* **81**, 629–632, https://doi.org/10.1093/cvr/cvp013
25 Dubey, R.K., Jackson, E.K., Gillespie, D.G., Rosselli, M., Barchiesi, F., Krust, A. et al. (2005) Cytochromes 1A1/1B1- and catechol-O-methyltransferase-derived metabolites mediate estradiol-induced antimitogenesis in human cardiac fibroblast. *J. Clin. Endocrinol. Metab.* **90**, 247–255, https://doi.org/10.1210/jc.2003-032154
26 D'Uva, G., Baci, D., Albini, A. and Noonan, D.M. (2018) Cancer chemoprevention revisited: cytochrome P450 family 1B1 as a target in the tumor and the microenvironment. *Cancer Treat. Rev.* **63**, 1–18, https://doi.org/10.1016/j.ctrv.2017.10.013
27 Tokizane, T., Shiina, H., Igawa, M., Enokida, H., Urakami, S., Kawakami, T. et al. (2005) Cytochrome P450 1B1 is overexpressed and regulated by hypomethylation in prostate cancer. *Clin. Cancer Res.* **11**, 5793–5801, https://doi.org/10.1158/1078-0432.CCR-04-2545
28 Vaclavikova, R., Hubackova, M., Stribrna-Sarmanova, J., Kodet, R., Mrhalova, M., Novotny, J. et al. (2007) RNA expression of cytochrome P450 in breast cancer patients. *Anticancer Res.* **27**, 4443–4450
29 McFadyen, M.C., Cruickshank, M.E., Miller, I.D., McLeod, H.L., Melvin, W.T., Haites, N.E. et al. (2001) Cytochrome P450 CYP1B1 over-expression in primary and metastatic ovarian cancer. *Br. J. Cancer* **85**, 242–246, https://doi.org/10.1054/bjoc.2001.1907
30 Gajjar, K., Martin-Hirsch, P.L. and Martin, F.L. (2012) CYP1B1 and hormone-induced cancer. *Cancer Lett.* **324**, 13–30, https://doi.org/10.1016/j.canlet.2012.04.021
31 Muskhelishvili, L., Thompson, P.A., Kusewitt, D.F., Wang, C. and Kadlubar, F.F. (2001) In situ hybridization and immunohistochemical analysis of cytochrome P450 1B1 expression in human normal tissues. *J. Histochem. Cytochem.* **49**, 229–236, https://doi.org/10.1177/002215540104900210

32 Umannova, L., Machala, M., Topinka, J., Novakova, Z., Milcova, A., Kozubik, A. et al. (2008) Tumor necrosis factor-alpha potentiates genotoxic effects of benzo[a]pyrene in rat liver epithelial cells through upregulation of cytochrome P450 1B1 expression. *Mutat. Res.* **640**, 162–169, https://doi.org/10.1016/j.mrfmmm.2008.02.001
33 Heidel, S.M., Holston, K., Buters, J.T., Gonzalez, F.J., Jefcoate, C.R. and Czupyrynski, C.J. (1999) Bone marrow stromal cell cytochrome P4501B1 is required for pre-B cell apoptosis induced by 7,12-dimethylbenz[a]anthracene. *Mol. Pharmacol.* **56**, 1317–1323, https://doi.org/10.1124/mol.56.6.1317
34 Wo, Y.Y., Stewart, J. and Greenlee, W.F. (1997) Functional analysis of the promoter for the human CYP1B1 gene. *J. Biol. Chem.* **272**, 26702–26707, https://doi.org/10.1074/jbc.272.42.26702
35 Alexander, D.L., Eltom, S.E. and Jefcoate, C.R. (1997) Ah receptor regulation of CYP1B1 expression in primary mouse embryo-derived cells. *Cancer Res.* **57**, 4498–4506
36 Brake, P.B. and Jefcoate, C.R. (1995) Regulation of cytochrome P4501B1 in cultured rat adrenocortical cells by cyclic adenosine 3′,5′-monophosphate and 2,3,7,8- tetrachlorodibenzo-p-dioxin. *Endocrinology* **136**, 5034–5041, https://doi.org/10.1210/endo.136.11.7588239
37 Terashima, J., Jimma, Y., Jimma, K., Hakata, S., Yachi, M., Habano, W. et al. (2018) The regulation mechanism of AhR activated by benzo[a]pyrene for CYP expression are different between 2D and 3D culture of human lung cancer cells. *Drug Metab. Pharmacokinet.* **33**, 211–214, https://doi.org/10.1016/j.dmpk.2018.04.002
38 Ociepa-Zawal, M., Rubis, B., Lacinski, M. and Trzeciak, W.H. (2007) The effect of indole-3-carbinol on the expression of CYP1A1, CYP1B1 and AhR genes and proliferation of MCF-7 cells. *Acta Biochim. Pol.* **54**, 113–117, https://doi.org/10.18388/abp.2007˙3276
39 Hankinson, O. (2016) The role of AHR-inducible cytochrome P450s in metabolism of polyunsaturated fatty acids. *Drug Metab. Rev.* **48**, 342–350, https://doi.org/10.1080/03602532.2016.1197240
40 Korashy, H.M. and El-Kadi, A.O. (2006) The role of aryl hydrocarbon receptor in the pathogenesis of cardiovascular diseases. *Drug Metab. Rev.* **38**, 411–450, https://doi.org/10.1080/03602530600632063
41 Ito, T., Suzuki, T., Tamura, K., Nezu, T., Honda, K. and Kobayashi, T. (2008) Examination of mRNA expression in rat hearts and lungs for analysis of effects of exposure to concentrated ambient particles on cardiovascular function. *Toxicology* **243**, 271–283, https://doi.org/10.1016/j.tox.2007.10.013
42 Aboutabl, M.E., Zordoky, B.N. and El-Kadi, A.O. (2009) 3-methylcholanthrene and benzo(a)pyrene modulate cardiac cytochrome P450 gene expression and arachidonic acid metabolism in male Sprague Dawley rats. *Br. J. Pharmacol.* **158**, 1808–1819, https://doi.org/10.1111/j.1476-5381.2009.00461.x
43 Roblin, S., Okey, A.B. and Harper, P.A. (2004) AH receptor antagonist inhibits constitutive CYP1A1 and CYP1B1 expression in rat BP8 cells. *Biochem. Biophys. Res. Commun.* **317**, 142–148, https://doi.org/10.1016/j.bbrc.2004.03.016
44 Shimada, T., Sugie, A., Shindo, M., Nakajima, T., Azuma, E., Hashimoto, M. et al. (2003) Tissue-specific induction of cytochromes P450 1A1 and 1B1 by polycyclic aromatic hydrocarbons and polychlorinated biphenyls in engineered C57BL/6J mice of arylhydrocarbon receptor gene. *Toxicol. Appl. Pharmacol.* **187**, 1–10, https://doi.org/10.1016/S0041-008X(02)00035-2
45 Zordoky, B.N. and El-Kadi, A.O. (2009) Role of NF-kappaB in the regulation of cytochrome P450 enzymes. *Curr. Drug Metab.* **10**, 164–178, https://doi.org/10.2174/138920009787522151
46 Theken, K.N., Deng, Y., Kannon, M.A., Miller, T.M., Poloyac, S.M. and Lee, C.R. (2011) Activation of the acute inflammatory response alters cytochrome P450 expression and eicosanoid metabolism. *Drug Metab. Dispos.* **39**, 22–29, https://doi.org/10.1124/dmd.110.035287
47 Anwar-mohamed, A., Zordoky, B.N., Aboutabl, M.E. and El-Kadi, A.O. (2010) Alteration of cardiac cytochrome P450-mediated arachidonic acid metabolism in response to lipopolysaccharide-induced acute systemic inflammation. *Pharmacol. Res.* **61**, 410–418, https://doi.org/10.1016/j.phrs.2009.12.015
48 Malik, D.E., David, R.M. and Gooderham, N.J. (2019) Interleukin-6 selectively induces drug metabolism to potentiate the genotoxicity of dietary carcinogens in mammary cells. *Arch. Toxicol.* **93**, 3005–3020, https://doi.org/10.1007/s00204-019-02558-8
49 Patel, S.A., Bhambra, U., Charalambous, M.P., David, R.M., Edwards, R.J., Lightfoot, T. et al. (2014) Interleukin-6 mediated upregulation of CYP1B1 and CYP2E1 in colorectal cancer involves DNA methylation, miR27b and STAT3. *Br. J. Cancer* **111**, 2287–2296, https://doi.org/10.1038/bjc.2014.540
50 Smerdova, L., Smerdova, J., Kabatkova, M., Kohoutek, J., Blazek, D., Machala, M. et al. (2014) Upregulation of CYP1B1 expression by inflammatory cytokines is mediated by the p38 MAP kinase signal transduction pathway. *Carcinogenesis* **35**, 2534–2543, https://doi.org/10.1093/carcin/bgu190
51 Tsuchiya, Y., Nakajima, M., Kyo, S., Kanaya, T., Inoue, M. and Yokoi, T. (2004) Human CYP1B1 is regulated by estradiol via estrogen receptor. *Cancer Res.* **64**, 3119–3125, https://doi.org/10.1158/0008-5472.CAN-04-0166
52 Cirillo, F., Pellegrino, M., Malivindi, R., Rago, V., Avino, S., Muto, L. et al. (2017) GPER is involved in the regulation of the estrogen-metabolizing CYP1B1 enzyme in breast cancer. *Oncotarget* **8**, 106608–24, https://doi.org/10.18632/oncotarget.22541
53 Khanal, T., Kim, H.G., Do, M.T., Choi, J.H., Won, S.S., Kang, W. et al. (2014) Leptin induces CYP1B1 expression in MCF-7 cells through ligand-independent activation of the ERalpha pathway. *Toxicol. Appl. Pharmacol.* **277**, 39–48, https://doi.org/10.1016/j.taap.2014.03.003
54 Han, E.H., Kim, H.G., Hwang, Y.P., Song, G.Y. and Jeong, H.G. (2010) Prostaglandin E2 induces CYP1B1 expression via ligand-independent activation of the ERalpha pathway in human breast cancer cells. *Toxicol. Sci.* **114**, 204–216, https://doi.org/10.1093/toxsci/kfq013
55 Hwang, Y.P., Won, S.S., Jin, S.W., Lee, G.H., Pham, T.H., Choi, J.H. et al. (2019) WY-14643 regulates CYP1B1 expression through peroxisome proliferator-activated receptor alpha-mediated signaling in human breast cancer cells. *Int. J. Mol. Sci.* **20**, 5928, https://doi.org/10.3390/ijms20235928
56 Khor, C.Y. and Khoo, B.Y. (2020) PPARalpha plays an important role in the migration activity, and the expression of CYP2S1 and CYP1B1 in chrysin-treated HCT116 cells. *Biotechnol. Lett.* **42**, 1581–1595, https://doi.org/10.1007/s10529-020-02904-2
57 Ziegler, N., Awwad, K., Fisslthaler, B., Reis, M., Devraj, K., Corada, M. et al. (2016) beta-Catenin is required for endothelial Cyp1b1 regulation influencing metabolic barrier function. *J. Neurosci.* **36**, 8921–8935, https://doi.org/10.1523/JNEUROSCI.0148-16.2016

58 Zheng, W., Brake, P.B., Bhattacharyya, K.K., Zhang, L., Zhao, D. and Jefcoate, C.R. (2003) Cell selective cAMP induction of rat CYP1B1 in adrenal and testis cells. Identification of a novel cAMP-responsive far upstream enhancer and a second Ah receptor-dependent mechanism. *Arch. Biochem. Biophys.* **416**, 53–67, https://doi.org/10.1016/S0003-9861(03)00282-0

59 Zheng, W. and Jefcoate, C.R. (2005) Steroidogenic factor-1 interacts with cAMP response element-binding protein to mediate cAMP stimulation of CYP1B1 via a far upstream enhancer. *Mol. Pharmacol.* **67**, 499–512, https://doi.org/10.1124/mol.104.005504

60 Niwa, T., Murayama, N., Imagawa, Y. and Yamazaki, H. (2015) Regioselective hydroxylation of steroid hormones by human cytochromes P450. *Drug Metab. Rev.* **47**, 89–110, https://doi.org/10.3109/03602532.2015.1011658

61 Jansson, I., Stoilov, I., Sarfarazi, M. and Schenkman, J.B. (2001) Effect of two mutations of human CYP1B1, G61E and R469W, on stability and endogenous steroid substrate metabolism. *Pharmacogenetics* **11**, 793–801, https://doi.org/10.1097/00008571-200112000-00007

62 Hayes, C.L., Spink, D.C., Spink, B.C., Cao, J.Q., Walker, N.J. and Sutter, T.R. (1996) 17 beta-estradiol hydroxylation catalyzed by human cytochrome P450 1B1. *Proc. Natl. Acad. Sci. U.S.A.* **93**, 9776–9781, https://doi.org/10.1073/pnas.93.18.9776

63 Shimada, T., Watanabe, J., Kawajiri, K., Sutter, T.R., Guengerich, F.P., Gillam, E.M. et al. (1999) Catalytic properties of polymorphic human cytochrome P450 1B1 variants. *Carcinogenesis* **20**, 1607–1613, https://doi.org/10.1093/carcin/20.8.1607

64 Lee, A.J., Cai, M.X., Thomas, P.E., Conney, A.H. and Zhu, B.T. (2003) Characterization of the oxidative metabolites of 17beta-estradiol and estrone formed by 15 selectively expressed human cytochrome p450 isoforms. *Endocrinology* **144**, 3382–3398, https://doi.org/10.1210/en.2003-0192

65 Markushin, Y., Zhong, W., Cavalieri, E.L., Rogan, E.G., Small, G.J., Yeung, E.S. et al. (2003) Spectral characterization of catechol estrogen quinone (CEQ)-derived DNA adducts and their identification in human breast tissue extract. *Chem. Res. Toxicol.* **16**, 1107–1117, https://doi.org/10.1021/tx0340854

66 Embrechts, J., Lemiere, F., Van Dongen, W., Esmans, E.L., Buytaert, P., Van Marck, E. et al. (2003) Detection of estrogen DNA-adducts in human breast tumor tissue and healthy tissue by combined nano LC-nano ES tandem mass spectrometry. *J. Am. Soc. Mass Spectrom.* **14**, 482–491, https://doi.org/10.1016/S1044-0305(03)00130-2

67 Chen, Z.H., Hurh, Y.J., Na, H.K., Kim, J.H., Chun, Y.J., Kim, D.H. et al. (2004) Resveratrol inhibits TCDD-induced expression of CYP1A1 and CYP1B1 and catechol estrogen-mediated oxidative DNA damage in cultured human mammary epithelial cells. *Carcinogenesis* **25**, 2005–2013, https://doi.org/10.1093/carcin/bgh183

68 Lanxiang, W., Bin, W., Ge, X., Yutang, H., Chunjie, W. and Honghao, Z. (2019) Long-term exposure of 4-hydroxyestradiol induces the cancer cell characteristics via upregulating CYP1B1 in MCF-10A cells. *Toxicol. Mech. Methods* **29**, 686–692, https://doi.org/10.1080/15376516.2019.1650146

69 Capdevila, J.H. and Falck, J.R. (2001) The CYP P450 arachidonic acid monooxygenases: from cell signaling to blood pressure regulation. *Biochem. Biophys. Res. Commun.* **285**, 571–576, https://doi.org/10.1006/bbrc.2001.5167

70 El-Sherbeni, A.A., Aboutabl, M.E., Zordoky, B.N., Anwar-Mohamed, A. and El-Kadi, A.O. (2013) Determination of the dominant arachidonic acid cytochrome p450 monooxygenases in rat heart, lung, kidney, and liver: protein expression and metabolite kinetics. *AAPS J.* **15**, 112–122, https://doi.org/10.1208/s12248-012-9425-7

71 Choudhary, D., Jansson, I., Stoilov, I., Sarfarazi, M. and Schenkman, J.B. (2004) Metabolism of retinoids and arachidonic acid by human and mouse cytochrome P450 1b1. *Drug Metab. Dispos.* **32**, 840–847, https://doi.org/10.1124/dmd.32.8.840

72 Maayah, Z.H., Althurwi, H.N., El-Sherbeni, A.A., Abdelhamid, G., Siraki, A.G. and El-Kadi, A.O. (2017) The role of cytochrome P450 1B1 and its associated mid-chain hydroxyeicosatetraenoic acid metabolites in the development of cardiac hypertrophy induced by isoproterenol. *Mol. Cell. Biochem.* **429**, 151–165, https://doi.org/10.1007/s11010-017-2943-y

73 Elkhatali, S., Maayah, Z.H., El-Sherbeni, A.A., Elshenawy, O.H., Abdelhamid, G., Shoieb, S.M. et al. (2017) Inhibition of mid-chain HETEs protects against angiotensin II-induced cardiac hypertrophy. *J. Cardiovasc. Pharmacol.* **70**, 16–24, https://doi.org/10.1097/FJC.0000000000000494

74 Maayah, Z.H., Althurwi, H.N., Abdelhamid, G., Lesyk, G., Jurasz, P. and El-Kadi, A.O. (2016) CYP1B1 inhibition attenuates doxorubicin-induced cardiotoxicity through a mid-chain HETEs-dependent mechanism. *Pharmacol. Res.* **105**, 28–43, https://doi.org/10.1016/j.phrs.2015.12.016

75 Zhang, Q.Y., Dunbar, D. and Kaminsky, L. (2000) Human cytochrome P-450 metabolism of retinals to retinoic acids. *Drug Metab. Dispos.* **28**, 292–297

76 Ma, X., Idle, J.R., Krausz, K.W. and Gonzalez, F.J. (2005) Metabolism of melatonin by human cytochromes p450. *Drug Metab. Dispos.* **33**, 489–494, https://doi.org/10.1124/dmd.104.002410

77 Anderson, G. (2019) Breast cancer: Occluded role of mitochondria N-acetylserotonin/melatonin ratio in co-ordinating pathophysiology. *Biochem. Pharmacol.* **168**, 259–268, https://doi.org/10.1016/j.bcp.2019.07.014

78 Wang, A., Savas, U., Stout, C.D. and Johnson, E.F. (2011) Structural characterization of the complex between alpha-naphthoflavone and human cytochrome P450 1B1. *J. Biol. Chem.* **286**, 5736–5743, https://doi.org/10.1074/jbc.M110.204420

79 Shiizaki, K., Kawanishi, M. and Yagi, T. (2017) Modulation of benzo[a]pyrene-DNA adduct formation by CYP1 inducer and inhibitor. *Genes Environ.* **39**, 14, https://doi.org/10.1186/s41021-017-0076-x

80 Shimada, T., Gillam, E.M., Sutter, T.R., Strickland, P.T., Guengerich, F.P. and Yamazaki, H. (1997) Oxidation of xenobiotics by recombinant human cytochrome P450 1B1. *Drug Metab. Dispos.* **25**, 617–622

81 Rochat, B., Morsman, J.M., Murray, G.I., Figg, W.D. and McLeod, H.L. (2001) Human CYP1B1 and anticancer agent metabolism: mechanism for tumor-specific drug inactivation? *J. Pharmacol. Exp. Ther.* **296**, 537–541

82 Zordoky, B.N., Aboutabl, M.E. and El-Kadi, A.O. (2008) Modulation of cytochrome P450 gene expression and arachidonic acid metabolism during isoproterenol-induced cardiac hypertrophy in rats. *Drug Metab. Dispos.* **36**, 2277–2286, https://doi.org/10.1124/dmd.108.023077

83 Althurwi, H.N., Tse, M.M., Abdelhamid, G., Zordoky, B.N., Hammock, B.D. and El-Kadi, A.O. (2013) Soluble epoxide hydrolase inhibitor, TUPS, protects against isoprenaline-induced cardiac hypertrophy. *Br. J. Pharmacol.* **168**, 1794–1807, https://doi.org/10.1111/bph.12066

84 Tse, M.M., Aboutabl, M.E., Althurwi, H.N., Elshenawy, O.H., Abdelhamid, G. and El-Kadi, A.O. (2013) Cytochrome P450 epoxygenase metabolite, 14,15-EET, protects against isoproterenol-induced cellular hypertrophy in H9c2 rat cell line. *Vascul. Pharmacol.* **58**, 363–373, https://doi.org/10.1016/j.vph.2013.02.004
85 El-Sherbeni, A.A. and El-Kadi, A.O. (2014) Alterations in cytochrome P450-derived arachidonic acid metabolism during pressure overload-induced cardiac hypertrophy. *Biochem. Pharmacol.* **87**, 456–466, https://doi.org/10.1016/j.bcp.2013.11.015
86 Maayah, Z.H., Levasseur, J., Siva Piragasam, R., Abdelhamid, G., Dyck, J.R.B., Fahlman, R.P. et al. (2018) 2-Methoxyestradiol protects against pressure overload-induced left ventricular hypertrophy. *Sci. Rep.* **8**, 2780, https://doi.org/10.1038/s41598-018-20613-9
87 Zordoky, B.N. and El-Kadi, A.O. (2010) 2,3,7,8-Tetrachlorodibenzo-p-dioxin and beta-naphthoflavone induce cellular hypertrophy in H9c2 cells by an aryl hydrocarbon receptor-dependant mechanism. *Toxicol. In Vitro* **24**, 863–871, https://doi.org/10.1016/j.tiv.2009.12.002
88 Guo, K., Ge, J., Zhang, C., Lv, M.W., Zhang, Q., Talukder, M. et al. (2020) Cadmium induced cardiac inflammation in chicken (Gallus gallus) via modulating cytochrome P450 systems and Nrf2 mediated antioxidant defense. *Chemosphere* **249**, 125858, https://doi.org/10.1016/j.chemosphere.2020.125858
89 Amara, I.E., Elshenawy, O.H., Abdelrady, M. and El-Kadi, A.O. (2014) Acute mercury toxicity modulates cytochrome P450, soluble epoxide hydrolase and their associated arachidonic acid metabolites in C57Bl/6 mouse heart. *Toxicol. Lett.* **226**, 53–62, https://doi.org/10.1016/j.toxlet.2014.01.025
90 Anwar-Mohamed, A., El-Sherbeni, A.A., Kim, S.H., Althurwi, H.N., Zordoky, B.N. and El-Kadi, A.O. (2012) Acute arsenic toxicity alters cytochrome P450 and soluble epoxide hydrolase and their associated arachidonic acid metabolism in C57Bl/6 mouse heart. *Xenobiotica* **42**, 1235–1247, https://doi.org/10.3109/00498254.2012.693971
91 Zhang, Y., Wang, S., Huang, Y., Yang, K., Liu, Y., Bi, X. et al. (2020) Inhibition of CYP1B1 ameliorates cardiac hypertrophy induced by uremic toxin. *Mol. Med. Rep.* **21**, 393–404
92 Malik, K.U., Jennings, B.L., Yaghini, F.A., Sahan-Firat, S., Song, C.Y., Estes, A.M. et al. (2012) Contribution of cytochrome P450 1B1 to hypertension and associated pathophysiology: a novel target for antihypertensive agents. *Prostaglandins Other Lipid Mediat.* **98**, 69–74, https://doi.org/10.1016/j.prostaglandins.2011.12.003
93 Pingili, A.K., Kara, M., Khan, N.S., Estes, A.M., Lin, Z., Li, W. et al. (2015) 6beta-hydroxytestosterone, a cytochrome P450 1B1 metabolite of testosterone, contributes to angiotensin II-induced hypertension and its pathogenesis in male mice. *Hypertension* **65**, 1279–1287, https://doi.org/10.1161/HYPERTENSIONAHA.115.05396
94 Pingili, A.K., Thirunavukkarasu, S., Kara, M., Brand, D.D., Katsurada, A., Majid, D.S. et al. (2016) 6beta-Hydroxytestosterone, a cytochrome P450 1B1-testosterone-metabolite, mediates angiotensin II-induced renal dysfunction in male mice. *Hypertension* **67**, 916–926, https://doi.org/10.1161/HYPERTENSIONAHA.115.06936
95 Pingili, A.K., Jennings, B.L., Mukherjee, K., Akroush, W., Gonzalez, F.J. and Malik, K.U. (2020) 6beta-Hydroxytestosterone, a metabolite of testosterone generated by CYP1B1, contributes to vascular changes in angiotensin II-induced hypertension in male mice. *Biol. Sex Differ.* **11**, 4, https://doi.org/10.1186/s13293-019-0280-4
96 Singh, P., Song, C.Y., Dutta, S.R., Gonzalez, F.J. and Malik, K.U. (2020) Central CYP1B1 (cytochrome P450 1B1)-estradiol metabolite 2-methoxyestradiol protects from hypertension and neuroinflammation in female mice. *Hypertension* **75**, 1054–1062, https://doi.org/10.1161/HYPERTENSIONAHA.119.14548
97 Jennings, B.L., Moore, J.A., Pingili, A.K., Estes, A.M., Fang, X.R., Kanu, A. et al. (2015) Disruption of the cytochrome P-450 1B1 gene exacerbates renal dysfunction and damage associated with angiotensin II-induced hypertension in female mice. *Am. J. Physiol. Renal Physiol.* **308**, F981–F992, https://doi.org/10.1152/ajprenal.00597.2014
98 Thirunavukkarasu, S., Khan, N.S., Song, C.Y., Ghafoor, H.U., Brand, D.D., Gonzalez, F.J. et al. (2016) Cytochrome P450 1B1 contributes to the development of angiotensin II-induced aortic aneurysm in male Apoe(-/-) mice. *Am. J. Pathol.* **186**, 2204–2219, https://doi.org/10.1016/j.ajpath.2016.04.005
99 Song, C.Y., Ghafoor, K., Ghafoor, H.U., Khan, N.S., Thirunavukkarasu, S., Jennings, B.L. et al. (2016) Cytochrome P450 1B1 contributes to the development of atherosclerosis and hypertension in apolipoprotein E-deficient mice. *Hypertension* **67**, 206–213, https://doi.org/10.1161/HYPERTENSIONAHA.115.06427
100 Moorthy, B., Miller, K.P., Jiang, W., Williams, E.S., Kondraganti, S.R. and Ramos, K.S. (2003) Role of cytochrome P4501B1 in benzo[a]pyrene bioactivation to DNA-binding metabolites in mouse vascular smooth muscle cells: evidence from 32P-postlabeling for formation of 3-hydroxybenzo[a]pyrene and benzo[a]pyrene-3,6-quinone as major proximate genotoxic intermediates. *J. Pharmacol. Exp. Ther.* **305**, 394–401
101 Moorthy, B., Miller, K.P., Jiang, W. and Ramos, K.S. (2002) The atherogen 3-methylcholanthrene induces multiple DNA adducts in mouse aortic smooth muscle cells: role of cytochrome P4501B1. *Cardiovasc. Res.* **53**, 1002–1009, https://doi.org/10.1016/S0008-6363(01)00536-3
102 Michaud, V., Frappier, M., Dumas, M.C. and Turgeon, J. (2010) Metabolic activity and mRNA levels of human cardiac CYP450s involved in drug metabolism. *PLoS ONE* **5**, e15666, https://doi.org/10.1371/journal.pone.0015666
103 Delozier, T.C., Kissling, G.E., Coulter, S.J., Dai, D., Foley, J.F., Bradbury, J.A. et al. (2007) Detection of human CYP2C8, CYP2C9, and CYP2J2 in cardiovascular tissues. *Drug Metab. Dispos.* **35**, 682–688, https://doi.org/10.1124/dmd.106.012823
104 Zordoky, B.N. and El-Kadi, A.O. (2008) Modulation of cardiac and hepatic cytochrome P450 enzymes during heart failure. *Curr. Drug Metab.* **9**, 122–128
105 Deng, Y., Theken, K.N. and Lee, C.R. (2010) Cytochrome P450 epoxygenases, soluble epoxide hydrolase, and the regulation of cardiovascular inflammation. *J. Mol. Cell Cardiol.* **48**, 331–341, https://doi.org/10.1016/j.yjmcc.2009.10.022
106 Evangelista, E.A., Lemaitre, R.N., Sotoodehnia, N., Gharib, S.A. and Totah, R.A. (2018) CYP2J2 expression in adult ventricular myocytes protects against reactive oxygen species toxicity. *Drug Metab. Dispos.* **46**, 380–386, https://doi.org/10.1124/dmd.117.078840
107 Zhang, Y., El-Sikhry, H., Chaudhary, K.R., Batchu, S.N., Shayeganpour, A., Jukar, T.O. et al. (2009) Overexpression of CYP2J2 provides protection against doxorubicin-induced cardiotoxicity. *Am. J. Physiol. Heart Circ. Physiol.* **297**, H37–H46, https://doi.org/10.1152/ajpheart.00983.2008

108 Jiang, J.G., Ning, Y.G., Chen, C., Ma, D., Liu, Z.J., Yang, S. et al. (2007) Cytochrome p450 epoxygenase promotes human cancer metastasis. *Cancer Res.* **67**, 6665–6674, https://doi.org/10.1158/0008-5472.CAN-06-3643
109 Panigrahy, D., Edin, M.L., Lee, C.R., Huang, S., Bielenberg, D.R., Butterfield, C.E. et al. (2012) Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J. Clin. Invest.* **122**, 178–191, https://doi.org/10.1172/JCI58128
110 Zordoky, B.N., Anwar-Mohamed, A., Aboutabl, M.E. and El-Kadi, A.O. (2010) Acute doxorubicin cardiotoxicity alters cardiac cytochrome P450 expression and arachidonic acid metabolism in rats. *Toxicol. Appl. Pharmacol.* **242**, 38–46, https://doi.org/10.1016/j.taap.2009.09.012
111 Zordoky, B.N. and El-Kadi, A.O. (2008) Induction of several cytochrome P450 genes by doxorubicin in H9c2 cells. *Vascul. Pharmacol.* **49**, 166–172, https://doi.org/10.1016/j.vph.2008.07.004
112 Lam, P.Y., Kutchukian, P., Anand, R., Imbriglio, J., Andrews, C., Padilla, H. et al. (2020) Cyp1 inhibition prevents doxorubicin-induced cardiomyopathy in a Zebrafish heart-failure model. *ChemBioChem* **21**, 1905–1910, https://doi.org/10.1002/cbic.201900741
113 Asnani, A., Zheng, B., Liu, Y., Wang, Y., Chen, H.H., Vohra, A. et al. (2018) Highly potent visnagin derivatives inhibit Cyp1 and prevent doxorubicin cardiotoxicity. *JCI Insight* **3**, https://doi.org/10.1172/jci.insight.e96753
114 Al-Dhfyan, A., Alhoshani, A. and Korashy, H.M. (2017) Aryl hydrocarbon receptor/cytochrome P450 1A1 pathway mediates breast cancer stem cells expansion through PTEN inhibition and beta-Catenin and Akt activation. *Mol. Cancer* **16**, 14, https://doi.org/10.1186/s12943-016-0570-y
115 Rodriguez, M. and Potter, D.A. (2013) CYP1A1 regulates breast cancer proliferation and survival. *Mol. Cancer Res.* **11**, 780–792, https://doi.org/10.1158/1541-7786.MCR-12-0675
116 Shoieb, S.M. and El-Kadi, A.O.S. (2020) Resveratrol attenuates angiotensin II-induced cellular hypertrophy through the inhibition of CYP1B1 and the cardiotoxic mid-chain HETE metabolites. *Mol. Cell. Biochem.* **471**, 165–176, https://doi.org/10.1007/s11010-020-03777-9
117 Shoieb, S.M. and El-Kadi, A.O.S. (2018) S-Enantiomer of 19-Hydroxyeicosatetraenoic acid preferentially protects against angiotensin II-induced cardiac hypertrophy. *Drug Metab. Dispos.* **46**, 1157–1168, https://doi.org/10.1124/dmd.118.082073
118 Elkhatali, S., El-Sherbeni, A.A., Elshenawy, O.H., Abdelhamid, G. and El-Kadi, A.O. (2015) 19-Hydroxyeicosatetraenoic acid and isoniazid protect against angiotensin II-induced cardiac hypertrophy. *Toxicol. Appl. Pharmacol.* **289**, 550–559, https://doi.org/10.1016/j.taap.2015.10.003
119 Sahan-Firat, S., Jennings, B.L., Yaghini, F.A., Song, C.Y., Estes, A.M., Fang, X.R. et al. (2010) 2,3′,4,5′-Tetramethoxystilbene prevents deoxycorticosterone-salt-induced hypertension: contribution of cytochrome P-450 1B1. *Am. J. Physiol. Heart Circ. Physiol.* **299**, H1891–H1901, https://doi.org/10.1152/ajpheart.00655.2010
120 Jennings, B.L., Montanez, D.E., May, Jr, M.E., Estes, A.M., Fang, X.R., Yaghini, F.A. et al. (2014) Cytochrome P450 1B1 contributes to increased blood pressure and cardiovascular and renal dysfunction in spontaneously hypertensive rats. *Cardiovasc. Drugs Ther.* **28**, 145–161, https://doi.org/10.1007/s10557-014-6510-4
121 Pingili, A.K., Davidge, K.N., Thirunavukkarasu, S., Khan, N.S., Katsurada, A., Majid, D.S.A. et al. (2017) 2-Methoxyestradiol reduces angiotensin II-induced hypertension and renal dysfunction in ovariectomized female and intact male mice. *Hypertension* **69**, 1104–1112, https://doi.org/10.1161/HYPERTENSIONAHA.117.09175
122 Jennings, B.L., Anderson, L.J., Estes, A.M., Yaghini, F.A., Fang, X.R., Porter, J. et al. (2012) Cytochrome P450 1B1 contributes to renal dysfunction and damage caused by angiotensin II in mice. *Hypertension* **59**, 348–354, https://doi.org/10.1161/HYPERTENSIONAHA.111.183301
123 Jennings, B.L., George, L.W., Pingili, A.K., Khan, N.S., Estes, A.M., Fang, X.R. et al. (2014) Estrogen metabolism by cytochrome P450 1B1 modulates the hypertensive effect of angiotensin II in female mice. *Hypertension* **64**, 134–140, https://doi.org/10.1161/HYPERTENSIONAHA.114.03275
124 Piotrowska, H., Kucinska, M. and Murias, M. (2013) Expression of CYP1A1, CYP1B1 and MnSOD in a panel of human cancer cell lines. *Mol. Cell. Biochem.* **383**, 95–102, https://doi.org/10.1007/s11010-013-1758-8
125 Mohamed, H.T., Gadalla, R., El-Husseiny, N., Hassan, H., Wang, Z., Ibrahim, S.A. et al. (2019) Inflammatory breast cancer: activation of the aryl hydrocarbon receptor and its target CYP1B1 correlates closely with Wnt5a/b-beta-catenin signalling, the stem cell phenotype and disease progression. *J. Adv. Res.* **16**, 75–86, https://doi.org/10.1016/j.jare.2018.11.006
126 Kwon, Y.J., Baek, H.S., Ye, D.J., Shin, S., Kim, D. and Chun, Y.J. (2016) CYP1B1 enhances cell proliferation and metastasis through induction of EMT and activation of Wnt/beta-catenin signaling via Sp1 upregulation. *PLoS ONE* **11**, e0151598, https://doi.org/10.1371/journal.pone.0151598
127 Li, C., Long, B., Qin, X., Li, W. and Zhou, Y. (2015) Cytochrome P1B1 (CYP1B1) polymorphisms and cancer risk: a meta-analysis of 52 studies. *Toxicology* **327**, 77–86, https://doi.org/10.1016/j.tox.2014.11.007
128 Abdul Aziz, A.A., Md Salleh, M.S., Mohamad, I., Krishna Bhavaraju, V.M., Mazuwin Yahya, M., Zakaria, A.D. et al. (2018) Single-nucleotide polymorphisms and mRNA expression of CYP1B1 influence treatment response in triple negative breast cancer patients undergoing chemotherapy. *J. Genet.* **97**, 1185–1194, https://doi.org/10.1007/s12041-018-1013-x
129 Tang, Y., Scheef, E.A., Gurel, Z., Sorenson, C.M., Jefcoate, C.R. and Sheibani, N. (2010) CYP1B1 and endothelial nitric oxide synthase combine to sustain proangiogenic functions of endothelial cells under hyperoxic stress. *Am. J. Physiol. Cell Physiol.* **298**, C665–C678, https://doi.org/10.1152/ajpcell.00153.2009
130 Melincovici, C.S., Bosca, A.B., Susman, S., Marginean, M., Mihu, C., Istrate, M. et al. (2018) Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom. J. Morphol. Embryol.* **59**, 455–467
131 Baek, H.S., Kwon, Y.J., Ye, D.J., Cho, E., Kwon, T.U. and Chun, Y.J. (2019) CYP1B1 prevents proteasome-mediated XIAP degradation by inducing PKCepsilon activation and phosphorylation of XIAP. *Biochim. Biophys. Acta Mol. Cell Res.* **1866**, 118553, https://doi.org/10.1016/j.bbamcr.2019.118553
132 Nebert, D.W. and Russell, D.W. (2002) Clinical importance of the cytochromes P450. *Lancet* **360**, 1155–1162, https://doi.org/10.1016/S0140-6736(02)11203-7
133 Salama, S.A., Kamel, M.W., Diaz-Arrastia, C.R., Xu, X., Veenstra, T.D., Salih, S. et al. (2009) Effect of tumor necrosis factor-alpha on estrogen metabolism and endometrial cells: potential physiological and pathological relevance. *J. Clin. Endocrinol. Metab.* **94**, 285–293, https://doi.org/10.1210/jc.2008-1389

134 Roos, P.H. and Bolt, H.M. (2005) Cytochrome P450 interactions in human cancers: new aspects considering CYP1B1. *Expert Opin. Drug Metab. Toxicol.* **1**, 187–202, https://doi.org/10.1517/17425255.1.2.187
135 Liu, J.Y., Yang, Y., Liu, Z.Z., Xie, J.J., Du, Y.P. and Wang, W. (2015) Association between the CYP1B1 polymorphisms and risk of cancer: a meta-analysis. *Mol. Genet. Genomics* **290**, 739–765, https://doi.org/10.1007/s00438-014-0946-x
136 Economopoulos, K.P. and Sergentanis, T.N. (2010) Three polymorphisms in cytochrome P450 1B1 (CYP1B1) gene and breast cancer risk: a meta-analysis. *Breast Cancer Res. Treat.* **122**, 545–551, https://doi.org/10.1007/s10549-009-0728-z
137 Dutour, R. and Poirier, D. (2017) Inhibitors of cytochrome P450 (CYP) 1B1. *Eur. J. Med. Chem.* **135**, 296–306, https://doi.org/10.1016/j.ejmech.2017.04.042
138 Chun, Y.J. and Kim, S. (2003) Discovery of cytochrome P450 1B1 inhibitors as new promising anti-cancer agents. *Med. Res. Rev.* **23**, 657–668, https://doi.org/10.1002/med.10050
139 Cui, J. and Li, S. (2014) Inhibitors and prodrugs targeting CYP1: a novel approach in cancer prevention and therapy. *Curr. Med. Chem.* **21**, 519–552, https://doi.org/10.2174/09298673113206660277
140 Dong, J., Zhang, Q., Cui, Q., Huang, G., Pan, X. and Li, S. (2016) Flavonoids and naphthoflavonoids: wider roles in the modulation of cytochrome P450 family 1 enzymes. *ChemMedChem* **11**, 2102–2118, https://doi.org/10.1002/cmdc.201600316
141 Zhu, F., Du, B. and Xu, B. (2018) Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review. *Crit. Rev. Food Sci. Nutr.* **58**, 1260–1270, https://doi.org/10.1080/10408398.2016.1251390
142 Panche, A.N., Diwan, A.D. and Chandra, S.R. (2016) Flavonoids: an overview. *J. Nutr. Sci.* **5**, e47, https://doi.org/10.1017/jns.2016.41
143 Dyck, G.J.B., Raj, P., Zieroth, S., Dyck, J.R.B. and Ezekowitz, J.A. (2019) The effects of resveratrol in patients with cardiovascular disease and heart failure: a narrative review. *Int. J. Mol. Sci.* **20**, 904, https://doi.org/10.3390/ijms20040904
144 Zordoky, B.N., Robertson, I.M. and Dyck, J.R. (2015) Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases. *Biochim. Biophys. Acta* **1852**, 1155–1177, https://doi.org/10.1016/j.bbadis.2014.10.016
145 Toma, L., Sanda, G.M., Niculescu, L.S., Deleanu, M., Sima, A.V. and Stancu, C.S. (2020) Phenolic compounds exerting lipid-regulatory, anti-inflammatory and epigenetic effects as complementary treatments in cardiovascular diseases. *Biomolecules* **10**, 641, https://doi.org/10.3390/biom10040641
146 Chun, Y.J., Kim, S., Kim, D., Lee, S.K. and Guengerich, F.P. (2001) A new selective and potent inhibitor of human cytochrome P450 1B1 and its application to antimutagenesis. *Cancer Res.* **61**, 8164–8170
147 Thilakarathna, S.H. and Rupasinghe, H.P. (2013) Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients* **5**, 3367–3387, https://doi.org/10.3390/nu5093367
148 George, V.C., Dellaire, G. and Rupasinghe, H.P.V. (2017) Plant flavonoids in cancer chemoprevention: role in genome stability. *J. Nutr. Biochem.* **45**, 1–14
149 Matsumura, N., Takahara, S., Maayah, Z.H., Parajuli, N., Byrne, N.J., Shoieb, S.M. et al. (2018) Resveratrol improves cardiac function and exercise performance in MI-induced heart failure through the inhibition of cardiotoxic HETE metabolites. *J. Mol. Cell Cardiol.* **125**, 162–173
150 Chirumbolo, S. (2015) Flavonoids in coronary heart disease. *Thromb. Res.* **135**, 1040–1041
151 Benavente-Garcia, O. and Castillo, J. (2008) Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. *J. Agric. Food Chem.* **56**, 6185–6205, https://doi.org/10.1021/jf8006568
152 Alammari, A.H., Shoieb, S.M., Maayah, Z.H. and El-Kadi, A.O.S. (2020) Fluconazole represses cytochrome P450 1B1 and its associated arachidonic acid metabolites in the heart and protects against angiotensin II-induced cardiac hypertrophy. *J. Pharm. Sci.* **109**, 2321–2335, https://doi.org/10.1016/j.xphs.2020.03.016
153 Wang, Y., He, X., Li, C., Ma, Y., Xue, W., Hu, B. et al. (2020) Carvedilol serves as a novel CYP1B1 inhibitor, a systematic drug repurposing approach through structure-based virtual screening and experimental verification. *Eur. J. Med. Chem.* **193**, 112235, https://doi.org/10.1016/j.ejmech.2020.112235
154 Do, M.T., Kim, H.G., Tran, T.T., Khanal, T., Choi, J.H., Chung, Y.C. et al. (2014) Metformin suppresses CYP1A1 and CYP1B1 expression in breast cancer cells by down-regulating aryl hydrocarbon receptor expression. *Toxicol. Appl. Pharmacol.* **280**, 138–148, https://doi.org/10.1016/j.taap.2014.07.021
155 Mohd Siddique, M.U., Barbhuiya, T.K., Sinha, B.N. and Jayaprakash, V. (2019) Phytoestrogens and their synthetic analogues as substrate mimic inhibitors of CYP1B1. *Eur. J. Med. Chem.* **163**, 28–36, https://doi.org/10.1016/j.ejmech.2018.11.039
156 Buters, J.T., Doehmer, J. and Gonzalez, F.J. (1999) Cytochrome P450-null mice. *Drug Metab. Rev.* **31**, 437–447, https://doi.org/10.1081/DMR-100101929
157 Christiansen, S. and Autschbach, R. (2006) Doxorubicin in experimental and clinical heart failure. *Eur. J. Cardiothorac. Surg.* **30**, 611–616, https://doi.org/10.1016/j.ejcts.2006.06.024
158 Outomuro, D., Grana, D.R., Azzato, F. and Milei, J. (2007) Adriamycin-induced myocardial toxicity: new solutions for an old problem? *Int. J. Cardiol.* **117**, 6–15, https://doi.org/10.1016/j.ijcard.2006.05.005
159 Lefrak, E.A., Pitha, J., Rosenheim, S. and Gottlieb, J.A. (1973) A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer* **32**, 302–314, https://doi.org/10.1002/1097-0142(197308)32:2%3c302::AID-CNCR2820320205%3e3.0.CO;2-2
160 Gilladoga, A.C., Manuel, C., Tan, C.T., Wollner, N., Sternberg, S.S. and Murphy, M.L. (1976) The cardiotoxicity of adriamycin and daunomycin in children. *Cancer* **37**, 1070–1078, https://doi.org/10.1002/1097-0142(197602)37:2+%3c1070::AID-CNCR2820370814%3e3.0.CO;2-6
161 Takemura, G. and Fujiwara, H. (2007) Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. *Prog. Cardiovasc. Dis.* **49**, 330–352, https://doi.org/10.1016/j.pcad.2006.10.002
162 Zhang, Y.W., Shi, J., Li, Y.J. and Wei, L. (2009) Cardiomyocyte death in doxorubicin-induced cardiotoxicity. *Arch. Immunol. Ther. Exp. (Warsz.)* **57**, 435–445, https://doi.org/10.1007/s00005-009-0051-8

163 Von Hoff, D.D., Layard, M.W., Basa, P., Davis, Jr, H.L., Von Hoff, A.L., Rozencweig, M. et al. (1979) Risk factors for doxorubicin-induced congestive heart failure. *Ann. Intern. Med.* **91**, 710–717, https://doi.org/10.7326/0003-4819-91-5-710

164 Nakamura, T., Ueda, Y., Juan, Y., Katsuda, S., Takahashi, H. and Koh, E. (2000) Fas-mediated apoptosis in adriamycin-induced cardiomyopathy in rats: in vivo study. *Circulation* **102**, 572–578, https://doi.org/10.1161/01.CIR.102.5.572

165 Ueno, M., Kakinuma, Y., Yuhki, K., Murakoshi, N., Iemitsu, M., Miyauchi, T. et al. (2006) Doxorubicin induces apoptosis by activation of caspase-3 in cultured cardiomyocytes in vitro and rat cardiac ventricles in vivo. *J. Pharmacol. Sci.* **101**, 151–158, https://doi.org/10.1254/jphs.FP0050980

166 Ferreira, A., Cunha-Oliveira, T., Simoes, R.F., Carvalho, F.S., Burgeiro, A., Nordgren, K. et al. (2017) Altered mitochondrial epigenetics associated with subchronic doxorubicin cardiotoxicity. *Toxicology* **390**, 63–73, https://doi.org/10.1016/j.tox.2017.08.011

167 Zordoky, B.N., Anwar-Mohamed, A., Aboutabl, M.E. and El-Kadi, A.O. (2011) Acute doxorubicin toxicity differentially alters cytochrome P450 expression and arachidonic acid metabolism in rat kidney and liver. *Drug Metab. Dispos.* **39**, 1440–1450, https://doi.org/10.1124/dmd.111.039123

168 Alsaad, A.M., Zordoky, B.N., El-Sherbeni, A.A. and El-Kadi, A.O. (2012) Chronic doxorubicin cardiotoxicity modulates cardiac cytochrome P450-mediated arachidonic acid metabolism in rats. *Drug Metab. Dispos.* **40**, 2126–2135, https://doi.org/10.1124/dmd.112.046631

169 Maayah, Z.H., Abdelhamid, G., Elshenawy, O.H., El-Sherbeni, A.A., Althurwi, H.N., McGinn, E. et al. (2018) The role of soluble epoxide hydrolase enzyme on daunorubicin-mediated cardiotoxicity. *Cardiovasc. Toxicol.* **18**, 268–283, https://doi.org/10.1007/s12012-017-9437-8

170 Volkova, M., Palmeri, M., Russell, K.S. and Russell, R.R. (2011) Activation of the aryl hydrocarbon receptor by doxorubicin mediates cytoprotective effects in the heart. *Cardiovasc. Res.* **90**, 305–314, https://doi.org/10.1093/cvr/cvr007

171 Zhang, Y., Wang, Y., Ma, Z., Liang, Q., Tang, X., Tan, H. et al. (2017) Ginsenoside Rb1 inhibits doxorubicin-triggered H9C2 cell apoptosis via aryl hydrocarbon receptor. *Biomol. Ther. (Seoul)* **25**, 202–212, https://doi.org/10.4062/biomolther.2016.066

172 Wei, S., Ma, W., Li, X., Jiang, C., Sun, T., Li, Y. et al. (2020) Involvement of ROS/NLRP3 inflammasome signaling pathway in doxorubicin-induced cardiotoxicity. *Cardiovasc. Toxicol.* **20**, 507–519, https://doi.org/10.1007/s12012-020-09576-4

173 Pei, J., Juni, R., Harakalova, M., Duncker, D.J., Asselbergs, F.W., Koolwijk, P. et al. (2019) Indoxyl sulfate stimulates angiogenesis by regulating reactive oxygen species production via CYP1B1. *Toxins (Basel)* **11**, 454, https://doi.org/10.3390/toxins11080454

174 Grant, M.K.O., Abdelgawad, I.Y., Lewis, C.A. and Zordoky, B.N. (2020) Sexual dimorphism in doxorubicin-induced systemic inflammation: implications for hepatic cytochrome P450 regulation. *Int. J. Mol. Sci.* **21**, 1279, https://doi.org/10.3390/ijms21041279

175 Xie, H.J., Lundgren, S., Broberg, U., Finnstrom, N., Rane, A. and Hassan, M. (2002) Effect of cyclophosphamide on gene expression of cytochromes p450 and beta-actin in the HL-60 cell line. *Eur. J. Pharmacol.* **449**, 197–205, https://doi.org/10.1016/S0014-2999(02)01995-7

176 Alrushaid, S., Zhao, Y., Sayre, C.L., Maayah, Z.H., Forrest, M.L., Senadheera, S.N. et al. (2017) Mechanistically elucidating the in vitro safety and efficacy of a novel doxorubicin derivative. *Drug Deliv. Transl. Res* **7**, 582–597, https://doi.org/10.1007/s13346-017-0379-2

177 Alsaad, A.M.S. (2018) Dasatinib induces gene expression of CYP1A1, CYP1B1, and cardiac hypertrophy markers (BNP, beta-MHC) in rat cardiomyocyte H9c2 cells. *Toxicol. Mech. Methods* **28**, 678–684, https://doi.org/10.1080/15376516.2018.1497746

178 Martinez, V.G., O'Connor, R., Liang, Y. and Clynes, M. (2008) CYP1B1 expression is induced by docetaxel: effect on cell viability and drug resistance. *Br. J. Cancer* **98**, 564–570, https://doi.org/10.1038/sj.bjc.6604195

179 Korashy, H.M., Ansari, M.A., Maayah, Z.H., Imam, F., Raish, M., Attafi, I.M. et al. (2016) Differential effects of sunitinib on the expression profiles of xenobiotic-metabolizing enzymes and transporters in rat liver and kidneys. *Basic Clin. Pharmacol. Toxicol.* **119**, 173–183, https://doi.org/10.1111/bcpt.12555

180 Katiyar, S.K., Matsui, M.S. and Mukhtar, H. (2000) Ultraviolet-B exposure of human skin induces cytochromes P450 1A1 and 1B1. *J. Invest. Dermatol.* **114**, 328–333, https://doi.org/10.1046/j.1523-1747.2000.00876.x

181 Tuominen, R., Warholm, M., Moller, L. and Rannug, A. (2003) Constitutive CYP1B1 mRNA expression in human blood mononuclear cells in relation to gender, genotype, and environmental factors. *Environ. Res.* **93**, 138–148, https://doi.org/10.1016/S0013-9351(03)00090-2

182 Behrendt, L., Jonsson, M.E., Goldstone, J.V. and Stegeman, J.J. (2010) Induction of cytochrome P450 1 genes and stress response genes in developing zebrafish exposed to ultraviolet radiation. *Aquat. Toxicol.* **98**, 74–82, https://doi.org/10.1016/j.aquatox.2010.01.008

183 Villard, P.H., Sampol, E., Elkaim, J.L., Puyoou, F., Casanova, D., Seree, E. et al. (2002) Increase of CYP1B1 transcription in human keratinocytes and HaCaT cells after UV-B exposure. *Toxicol. Appl. Pharmacol.* **178**, 137–143, https://doi.org/10.1006/taap.2001.9335

184 Nair, S., Kekatpure, V.D., Judson, B.L., Rifkind, A.B., Granstein, R.D., Boyle, J.O. et al. (2009) UVR exposure sensitizes keratinocytes to DNA adduct formation. *Cancer Prev. Res. (Phila.)* **2**, 895–902, https://doi.org/10.1158/1940-6207.CAPR-09-0125

185 Han, Y., Yu, H., Wang, J., Ren, Y., Su, X. and Shi, Y. (2015) Quercetin alleviates myocyte toxic and sensitizes anti-leukemic effect of adriamycin. *Hematology* **20**, 276–283, https://doi.org/10.1179/1607845414Y.0000000198

186 Zare, M.F.R., Rakhshan, K., Aboutaleb, N., Nikbakht, F., Naderi, N., Bakhshesh, M. et al. (2019) Apigenin attenuates doxorubicin-induced cardiotoxicity via reducing oxidative stress and apoptosis in male rats. *Life Sci.* **232**, 116623, https://doi.org/10.1016/j.lfs.2019.116623

187 Sahu, R., Dua, T.K., Das, S., De Feo, V. and Dewanjee, S. (2019) Wheat phenolics suppress doxorubicin-induced cardiotoxicity via inhibition of oxidative stress, MAP kinase activation, NF-kappaB pathway, PI3K/Akt/mTOR impairment, and cardiac apoptosis. *Food Chem. Toxicol.* **125**, 503–519, https://doi.org/10.1016/j.fct.2019.01.034

188 Psotova, J., Chlopcikova, S., Miketova, P., Hrbac, J. and Simanek, V. (2004) Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part III. Apigenin, baicalelin, kaempherol, luteolin and quercetin. *Phytother. Res.* **18**, 516–521, https://doi.org/10.1002/ptr.1462

189 Chen, X., Peng, X., Luo, Y., You, J., Yin, D., Xu, Q. et al. (2019) Quercetin protects cardiomyocytes against doxorubicin-induced toxicity by suppressing oxidative stress and improving mitochondrial function via 14-3-3gamma. *Toxicol. Mech. Methods* **29**, 344–354, https://doi.org/10.1080/15376516.2018.1564948

190 Zakaria, N., Khalil, S.R., Awad, A. and Khairy, G.M. (2018) Quercetin reverses altered energy metabolism in the heart of rats receiving adriamycin chemotherapy. *Cardiovasc. Toxicol.* **18**, 109–119, https://doi.org/10.1007/s12012-017-9420-4

191 Lee, K.Y., Kim, J.R. and Choi, H.C. (2016) Genistein-induced LKB1-AMPK activation inhibits senescence of VSMC through autophagy induction. *Vascul. Pharmacol.* **81**, 75–82, https://doi.org/10.1016/j.vph.2016.02.007
192 Shao, J.J., Zhang, A.P., Qin, W., Zheng, L., Zhu, Y.F. and Chen, X. (2012) AMP-activated protein kinase (AMPK) activation is involved in chrysin-induced growth inhibition and apoptosis in cultured A549 lung cancer cells. *Biochem. Biophys. Res. Commun.* **423**, 448–453, https://doi.org/10.1016/j.bbrc.2012.05.123
193 Brechbuhl, H.M., Kachadourian, R., Min, E., Chan, D. and Day, B.J. (2012) Chrysin enhances doxorubicin-induced cytotoxicity in human lung epithelial cancer cell lines: the role of glutathione. *Toxicol. Appl. Pharmacol.* **258**, 1–9, https://doi.org/10.1016/j.taap.2011.08.004
194 Punia, R., Raina, K., Agarwal, R. and Singh, R.P. (2017) Acacetin enhances the therapeutic efficacy of doxorubicin in non-small-cell lung carcinoma cells. *PLoS ONE* **12**, e0182870, https://doi.org/10.1371/journal.pone.0182870
195 Li, S.Z., Li, K., Zhang, J.H. and Dong, Z. (2013) The effect of quercetin on doxorubicin cytotoxicity in human breast cancer cells. *Anticancer Agents Med. Chem.* **13**, 352–355, https://doi.org/10.2174/1871520611313020020
196 Staedler, D., Idrizi, E., Kenzaoui, B.H. and Juillerat-Jeanneret, L. (2011) Drug combinations with quercetin: doxorubicin plus quercetin in human breast cancer cells. *Cancer Chemother. Pharmacol.* **68**, 1161–1172, https://doi.org/10.1007/s00280-011-1596-x
197 Li, S.Z., Qiao, S.F., Zhang, J.H. and Li, K. (2015) Quercetin increase the chemosensitivity of breast cancer cells to doxorubicin via PTEN/Akt pathway. *Anticancer Agents Med. Chem.* **15**, 1185–1189, https://doi.org/10.2174/1871520615999150121121708
198 Seo, H.S., Ku, J.M., Choi, H.S., Woo, J.K., Lee, B.H., Kim, D.S. et al. (2017) Apigenin overcomes drug resistance by blocking the signal transducer and activator of transcription 3 signaling in breast cancer cells. *Oncol. Rep.* **38**, 715–724, https://doi.org/10.3892/or.2017.5752
199 Li, S., Yuan, S., Zhao, Q., Wang, B., Wang, X. and Li, K. (2018) Quercetin enhances chemotherapeutic effect of doxorubicin against human breast cancer cells while reducing toxic side effects of it. *Biomed. Pharmacother.* **100**, 441–447, https://doi.org/10.1016/j.biopha.2018.02.055
200 Li, S., Zhao, Q., Wang, B., Yuan, S., Wang, X. and Li, K. (2018) Quercetin reversed MDR in breast cancer cells through down-regulating P-gp expression and eliminating cancer stem cells mediated by YB-1 nuclear translocation. *Phytother. Res.* **32**, 1530–1536, https://doi.org/10.1002/ptr.6081
201 Sun, J., Sun, G., Meng, X., Wang, H., Luo, Y., Qin, M. et al. (2013) Isorhamnetin protects against doxorubicin-induced cardiotoxicity in vivo and in vitro. *PLoS ONE* **8**, e64526, https://doi.org/10.1371/journal.pone.0064526
202 Chen, Z., Huang, C., Ma, T., Jiang, L., Tang, L., Shi, T. et al. (2018) Reversal effect of quercetin on multidrug resistance via FZD7/beta-catenin pathway in hepatocellular carcinoma cells. *Phytomedicine* **43**, 37–45, https://doi.org/10.1016/j.phymed.2018.03.040
203 Korga, A., Ostrowska, M., Jozefczyk, A., Iwan, M., Wojcik, R., Zgorka, G. et al. (2019) Apigenin and hesperidin augment the toxic effect of doxorubicin against HepG2 cells. *BMC Pharmacol. Toxicol.* **20**, 22, https://doi.org/10.1186/s40360-019-0301-2
204 Gao, A.M., Zhang, X.Y., Hu, J.N. and Ke, Z.P. (2018) Apigenin sensitizes hepatocellular carcinoma cells to doxorubic through regulating miR-520b/ATG7 axis. *Chem. Biol. Interact.* **280**, 45–50, https://doi.org/10.1016/j.cbi.2017.11.020
205 Sharma, V., Joseph, C., Ghosh, S., Agarwal, A., Mishra, M.K. and Sen, E. (2007) Kaempferol induces apoptosis in glioblastoma cells through oxidative stress. *Mol. Cancer Ther.* **6**, 2544–2553, https://doi.org/10.1158/1535-7163.MCT-06-0788
206 Shu, Y., Xie, B., Liang, Z. and Chen, J. (2018) Quercetin reverses the doxorubicin resistance of prostate cancer cells by downregulating the expression of c-met. *Oncol. Lett.* **15**, 2252–2258
207 Chian, S., Li, Y.Y., Wang, X.J. and Tang, X.W. (2014) Luteolin sensitizes two oxaliplatin-resistant colorectal cancer cell lines to chemotherapeutic drugs via inhibition of the Nrf2 pathway. *Asian Pac. J. Cancer Prev.* **15**, 2911–2916, https://doi.org/10.7314/APJCP.2014.15.6.2911
208 Atashpour, S., Fouladdel, S., Movahhed, T.K., Barzegar, E., Ghahremani, M.H., Ostad, S.N. et al. (2015) Quercetin induces cell cycle arrest and apoptosis in CD133(+) cancer stem cells of human colorectal HT29 cancer cell line and enhances anticancer effects of doxorubicin. *Iran J. Basic Med. Sci.* **18**, 635–643
209 Xu, J., Liu, D., Niu, H., Zhu, G., Xu, Y., Ye, D. et al. (2017) Resveratrol reverses doxorubicin resistance by inhibiting epithelial-mesenchymal transition (EMT) through modulating PTEN/Akt signaling pathway in gastric cancer. *J. Exp. Clin. Cancer Res.* **36**, 19, https://doi.org/10.1186/s13046-016-0487-8
210 Chen, F.Y., Cao, L.F., Wan, H.X., Zhang, M.Y., Cai, J.Y., Shen, L.J. et al. (2015) Quercetin enhances adriamycin cytotoxicity through induction of apoptosis and regulation of mitogen-activated protein kinase/extracellular signal-regulated kinase/c-Jun N-terminal kinase signaling in multidrug-resistant leukemia K562 cells. *Mol. Med. Rep.* **11**, 341–348, https://doi.org/10.3892/mmr.2014.2734
211 Liu, J., Zhu, Z., Liu, Y., Wei, L., Li, B., Mao, F. et al. (2020) MDM2 inhibition-mediated autophagy contributes to the pro-apoptotic effect of berberine in p53-null leukemic cells. *Life Sci.* **242**, 117228, https://doi.org/10.1016/j.lfs.2019.117228
212 Scambia, G., Ranelletti, F.O., Panici, P.B., De Vincenzo, R., Bonanno, G., Ferrandina, G. et al. (1994) Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF-7 human breast-cancer cell line: P-glycoprotein as a possible target. *Cancer Chemother. Pharmacol.* **34**, 459–464, https://doi.org/10.1007/BF00685655
213 Xue, J.P., Wang, G., Zhao, Z.B., Wang, Q. and Shi, Y. (2014) Synergistic cytotoxic effect of genistein and doxorubicin on drug-resistant human breast cancer MCF-7/Adr cells. *Oncol. Rep.* **32**, 1647–1653, https://doi.org/10.3892/or.2014.3365
214 Diaz-Chavez, J., Fonseca-Sanchez, M.A., Arechaga-Ocampo, E., Flores-Perez, A., Palacios-Rodriguez, Y., Dominguez-Gomez, G. et al. (2013) Proteomic profiling reveals that resveratrol inhibits HSP27 expression and sensitizes breast cancer cells to doxorubicin therapy. *PLoS ONE* **8**, e64378, https://doi.org/10.1371/journal.pone.0064378
215 Kim, T.H., Shin, Y.J., Won, A.J., Lee, B.M., Choi, W.S., Jung, J.H. et al. (2014) Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of DOX. *Biochim. Biophys. Acta* **1840**, 615–625, https://doi.org/10.1016/j.bbagen.2013.10.023
216 Huang, F., Wu, X.N., Chen, J., Wang, W.X. and Lu, Z.F. (2014) Resveratrol reverses multidrug resistance in human breast cancer doxorubicin-resistant cells. *Exp. Ther. Med.* **7**, 1611–1616, https://doi.org/10.3892/etm.2014.1662

Clinical Science (2020) **134** 2897–2927
https://doi.org/10.1042/CS20200310

217 Chen, J.M., Bai, J.Y. and Yang, K.X. (2018) Effect of resveratrol on doxorubicin resistance in breast neoplasm cells by modulating PI3K/Akt signaling pathway. *IUBMB Life* **70**, 491–500, https://doi.org/10.1002/iub.1749
218 Gao, A.M., Zhang, X.Y. and Ke, Z.P. (2017) Apigenin sensitizes BEL-7402/ADM cells to doxorubicin through inhibiting miR-101/Nrf2 pathway. *Oncotarget* **8**, 82085–82091, https://doi.org/10.18632/oncotarget.18294
219 Takemura, H., Itoh, T., Yamamoto, K., Sakakibara, H. and Shimoi, K. (2010) Selective inhibition of methoxyflavonoids on human CYP1B1 activity. *Bioorg. Med. Chem.* **18**, 6310–6315, https://doi.org/10.1016/j.bmc.2010.07.020
220 Shimada, T., Tanaka, K., Takenaka, S., Murayama, N., Martin, M.V., Foroozesh, M.K. et al. (2010) Structure-function relationships of inhibition of human cytochromes P450 1A1, 1A2, 1B1, 2C9, and 3A4 by 33 flavonoid derivatives. *Chem. Res. Toxicol.* **23**, 1921–1935, https://doi.org/10.1021/tx100286d
221 Doostdar, H., Burke, M.D. and Mayer, R.T. (2000) Bioflavonoids: selective substrates and inhibitors for cytochrome P450 CYP1A and CYP1B1. *Toxicology* **144**, 31–38, https://doi.org/10.1016/S0300-483X(99)00215-2
222 Mantawy, E.M., Esmat, A., El-Bakly, W.M., Salah ElDin, R.A. and El-Demerdash, E. (2017) Mechanistic clues to the protective effect of chrysin against doxorubicin-induced cardiomyopathy: plausible roles of p53, MAPK and AKT pathways. *Sci. Rep.* **7**, 4795, https://doi.org/10.1038/s41598-017-05005-9
223 Mantawy, E.M., El-Bakly, W.M., Esmat, A., Badr, A.M. and El-Demerdash, E. (2014) Chrysin alleviates acute doxorubicin cardiotoxicity in rats via suppression of oxidative stress, inflammation and apoptosis. *Eur. J. Pharmacol.* **728**, 107–118, https://doi.org/10.1016/j.ejphar.2014.01.065
224 Maruhashi, R., Eguchi, H., Akizuki, R., Hamada, S., Furuta, T., Matsunaga, T. et al. (2019) Chrysin enhances anticancer drug-induced toxicity mediated by the reduction of claudin-1 and 11 expression in a spheroid culture model of lung squamous cell carcinoma cells. *Sci. Rep.* **9**, 13753, https://doi.org/10.1038/s41598-019-50276-z
225 Gao, A.M., Ke, Z.P., Shi, F., Sun, G.C. and Chen, H. (2013) Chrysin enhances sensitivity of BEL-7402/ADM cells to doxorubicin by suppressing PI3K/Akt/Nrf2 and ERK/Nrf2 pathway. *Chem. Biol. Interact.* **206**, 100–108, https://doi.org/10.1016/j.cbi.2013.08.008
226 Gao, A.M., Ke, Z.P., Wang, J.N., Yang, J.Y., Chen, S.Y. and Chen, H. (2013) Apigenin sensitizes doxorubicin-resistant hepatocellular carcinoma BEL-7402/ADM cells to doxorubicin via inhibiting PI3K/Akt/Nrf2 pathway. *Carcinogenesis* **34**, 1806–1814, https://doi.org/10.1093/carcin/bgt108
227 Xiao, J., Sun, G.B., Sun, B., Wu, Y., He, L., Wang, X. et al. (2012) Kaempferol protects against doxorubicin-induced cardiotoxicity in vivo and in vitro. *Toxicology* **292**, 53–62, https://doi.org/10.1016/j.tox.2011.11.018
228 Dong, Q., Chen, L., Lu, Q., Sharma, S., Li, L., Morimoto, S. et al. (2014) Quercetin attenuates doxorubicin cardiotoxicity by modulating Bmi-1 expression. *Br. J. Pharmacol.* **171**, 4440–4454, https://doi.org/10.1111/bph.12795
229 Bartekova, M., Simoncikova, P., Fogarassyova, M., Ivanova, M., Okruhlicova, L., Tribulova, N. et al. (2015) Quercetin improves postischemic recovery of heart function in doxorubicin-treated rats and prevents doxorubicin-induced matrix metalloproteinase-2 activation and apoptosis induction. *Int. J. Mol. Sci.* **16**, 8168–8185, https://doi.org/10.3390/ijms16048168
230 Matouk, A.I., Taye, A., Heeba, G.H. and El-Moselhy, M.A. (2013) Quercetin augments the protective effect of losartan against chronic doxorubicin cardiotoxicity in rats. *Environ. Toxicol. Pharmacol.* **36**, 443–450, https://doi.org/10.1016/j.etap.2013.05.006
231 Wang, G., Zhang, J., Liu, L., Sharma, S. and Dong, Q. (2012) Quercetin potentiates doxorubicin mediated antitumor effects against liver cancer through p53/Bcl-xl. *PLoS ONE* **7**, e51764, https://doi.org/10.1371/journal.pone.0051764
232 Du, G., Lin, H., Yang, Y., Zhang, S., Wu, X., Wang, M. et al. (2010) Dietary quercetin combining intratumoral doxorubicin injection synergistically induces rejection of established breast cancer in mice. *Int. Immunopharmacol.* **10**, 819–826, https://doi.org/10.1016/j.intimp.2010.04.018
233 Du, G., Lin, H., Wang, M., Zhang, S., Wu, X., Lu, L. et al. (2010) Quercetin greatly improved therapeutic index of doxorubicin against 4T1 breast cancer by its opposing effects on HIF-1alpha in tumor and normal cells. *Cancer Chemother. Pharmacol.* **65**, 277–287, https://doi.org/10.1007/s00280-009-1032-7
234 Scambia, G., Ranelletti, F.O., Benedetti Panici, P., Piantelli, M., Bonanno, G., De Vincenzo, R. et al. (1991) Quercetin inhibits the growth of a multidrug-resistant estrogen-receptor-negative MCF-7 human breast-cancer cell line expressing type II estrogen-binding sites. *Cancer Chemother. Pharmacol.* **28**, 255–258, https://doi.org/10.1007/BF00685531
235 Zanini, C., Giribaldi, G., Mandili, G., Carta, F., Crescenzio, N., Bisaro, B. et al. (2007) Inhibition of heat shock proteins (HSP) expression by quercetin and differential doxorubicin sensitization in neuroblastoma and Ewing's sarcoma cell lines. *J. Neurochem.* **103**, 1344–1354, https://doi.org/10.1111/j.1471-4159.2007.04835.x
236 Sadzuka, Y., Sugiyama, T., Shimoi, K., Kinae, N. and Hirota, S. (1997) Protective effect of flavonoids on doxorubicin-induced cardiotoxicity. *Toxicol. Lett.* **92**, 1–7, https://doi.org/10.1016/S0378-4274(97)00028-3
237 Sato, Y., Sasaki, N., Saito, M., Endo, N., Kugawa, F. and Ueno, A. (2015) Luteolin attenuates doxorubicin-induced cytotoxicity to MCF-7 human breast cancer cells. *Biol. Pharm. Bull.* **38**, 703–709, https://doi.org/10.1248/bpb.b14-00780
238 Tang, X., Wang, H., Fan, L., Wu, X., Xin, A., Ren, H. et al. (2011) Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung carcinoma A549 cells to therapeutic drugs. *Free Radic. Biol. Med.* **50**, 1599–1609, https://doi.org/10.1016/j.freeradbiomed.2011.03.008
239 Scott, L.M., Durant, P., Leone-Kabler, S., Wood, C.E., Register, T.C., Townsend, A. et al. (2008) Effects of prior oral contraceptive use and soy isoflavonoids on estrogen-metabolizing cytochrome P450 enzymes. *J. Steroid Biochem. Mol. Biol.* **112**, 179–185, https://doi.org/10.1016/j.jsbmb.2008.10.001
240 Roberts, D.W., Doerge, D.R., Churchwell, M.I., Gamboa da Costa, G., Marques, M.M. and Tolleson, W.H. (2004) Inhibition of extrahepatic human cytochromes P450 1A1 and 1B1 by metabolism of isoflavones found in Trifolium pratense (red clover). *J. Agric. Food Chem.* **52**, 6623–6632, https://doi.org/10.1021/jf049418x

241 Lepri, S.R., Sartori, D., Semprebon, S.C., Baranoski, A., Coatti, G.C. and Mantovani, M.S. (2018) Genistein affects expression of cytochrome P450 (CYP450) genes in hepatocellular carcinoma (HEPG2/C3A) cell line. *Drug Metab. Lett.* **12**, 138–144, https://doi.org/10.2174/1872312812666180709150440
242 Wei, Y.K., Gamra, I., Davenport, A., Lester, R., Zhao, L. and Wei, Y. (2015) Genistein induces cytochrome P450 1B1 gene expression and cell proliferation in human breast cancer MCF-7 cells. *J. Environ. Pathol. Toxicol. Oncol.* **34**, 153–159, https://doi.org/10.1615/JEnvironPatholToxicolOncol.2015013315
243 Chen, M., Samuel, V.P., Wu, Y., Dang, M., Lin, Y., Sriramaneni, R. et al. (2019) Nrf2/HO-1 mediated protective activity of genistein against doxorubicin-induced cardiac toxicity. *J. Environ. Pathol. Toxicol. Oncol.* **38**, 143–152, https://doi.org/10.1615/JEnvironPatholToxicolOncol.2019029341
244 Bai, Z. and Wang, Z. (2019) Genistein protects against doxorubicin-induced cardiotoxicity through Nrf-2/HO-1 signaling in mice model. *Environ. Toxicol.* **34**, 645–651, https://doi.org/10.1002/tox.22730
245 Li, Y., Ahmed, F., Ali, S., Philip, P.A., Kucuk, O. and Sarkar, F.H. (2005) Inactivation of nuclear factor kappaB by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. *Cancer Res.* **65**, 6934–6942, https://doi.org/10.1158/0008-5472.CAN-04-4604
246 Satoh, H., Nishikawa, K., Suzuki, K., Asano, R., Virgona, N., Ichikawa, T. et al. (2003) Genistein, a soy isoflavone, enhances necrotic-like cell death in a breast cancer cell treated with a chemotherapeutic agent. *Res. Commun. Mol. Pathol. Pharmacol.* **113-114**, 149–158
247 Monti, E. and Sinha, B.K. (1994) Antiproliferative effect of genistein and adriamycin against estrogen-dependent and -independent human breast carcinoma cell lines. *Anticancer Res.* **14**, 1221–1226
248 Rigalli, J.P., Tocchetti, G.N., Arana, M.R., Villanueva, S.S., Catania, V.A., Theile, D. et al. (2016) The phytoestrogen genistein enhances multidrug resistance in breast cancer cell lines by translational regulation of ABC transporters. *Cancer Lett.* **376**, 165–172, https://doi.org/10.1016/j.canlet.2016.03.040
249 Mohammad, R.M., Al-Katib, A., Aboukameel, A., Doerge, D.R., Sarkar, F. and Kucuk, O. (2003) Genistein sensitizes diffuse large cell lymphoma to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. *Mol. Cancer Ther.* **2**, 1361–1368
250 Abdelgawad, I.Y., Grant, M.K.O. and Zordoky, B.N. (2019) Leveraging the cardio-protective and anticancer properties of resveratrol in cardio-oncology. *Nutrients* **11**, 627, https://doi.org/10.3390/nu11030627
251 Chang, T.K., Lee, W.B. and Ko, H.H. (2000) Trans-resveratrol modulates the catalytic activity and mRNA expression of the procarcinogen-activating human cytochrome P450 1B1. *Can. J. Physiol. Pharmacol.* **78**, 874–881, https://doi.org/10.1139/y00-067
252 Piver, B., Berthou, F., Dreano, Y. and Lucas, D. (2003) Differential inhibition of human cytochrome P450 enzymes by epsilon-viniferin, the dimer of resveratrol: comparison with resveratrol and polyphenols from alcoholized beverages. *Life Sci.* **73**, 1199–1213, https://doi.org/10.1016/S0024-3205(03)00420-X
253 Cao, Z. and Li, Y. (2004) Potent induction of cellular antioxidants and phase 2 enzymes by resveratrol in cardiomyocytes: protection against oxidative and electrophilic injury. *Eur. J. Pharmacol.* **489**, 39–48, https://doi.org/10.1016/j.ejphar.2004.02.031
254 Lou, Y., Wang, Z., Xu, Y., Zhou, P., Cao, J., Li, Y. et al. (2015) Resveratrol prevents doxorubicin-induced cardiotoxicity in H9c2 cells through the inhibition of endoplasmic reticulum stress and the activation of the Sirt1 pathway. *Int. J. Mol. Med.* **36**, 873–880, https://doi.org/10.3892/ijmm.2015.2291
255 Gu, J., Hu, W., Song, Z.P., Chen, Y.G., Zhang, D.D. and Wang, C.Q. (2016) Resveratrol-induced autophagy promotes survival and attenuates doxorubicin-induced cardiotoxicity. *Int. Immunopharmacol.* **32**, 1–7, https://doi.org/10.1016/j.intimp.2016.01.002
256 Liu, M.H., Lin, X.L., Guo, D.M., Zhang, Y., Yuan, C., Tan, T.P. et al. (2016) Resveratrol protects cardiomyocytes from doxorubicin-induced apoptosis through the AMPK/P53 pathway. *Mol. Med. Rep.* **13**, 1281–1286, https://doi.org/10.3892/mmr.2015.4665
257 Liu, M.H., Shan, J., Li, J., Zhang, Y. and Lin, X.L. (2016) Resveratrol inhibits doxorubicin-induced cardiotoxicity via sirtuin 1 activation in H9c2 cardiomyocytes. *Exp. Ther. Med.* **12**, 1113–1118, https://doi.org/10.3892/etm.2016.3437
258 Gu, J., Fan, Y.Q., Zhang, H.L., Pan, J.A., Yu, J.Y., Zhang, J.F. et al. (2018) Resveratrol suppresses doxorubicin-induced cardiotoxicity by disrupting E2F1 mediated autophagy inhibition and apoptosis promotion. *Biochem. Pharmacol.* **150**, 202–213, https://doi.org/10.1016/j.bcp.2018.02.025
259 Rezk, Y.A., Balulad, S.S., Keller, R.S. and Bennett, J.A. (2006) Use of resveratrol to improve the effectiveness of cisplatin and doxorubicin: study in human gynecologic cancer cell lines and in rodent heart. *Am. J. Obstet. Gynecol.* **194**, e23–e26, https://doi.org/10.1016/j.ajog.2005.11.030
260 Danz, E.D., Skramsted, J., Henry, N., Bennett, J.A. and Keller, R.S. (2009) Resveratrol prevents doxorubicin cardiotoxicity through mitochondrial stabilization and the Sirt1 pathway. *Free Radic. Biol. Med.* **46**, 1589–1597, https://doi.org/10.1016/j.freeradbiomed.2009.03.011
261 Xu, X., Chen, K., Kobayashi, S., Timm, D. and Liang, Q. (2012) Resveratrol attenuates doxorubicin-induced cardiomyocyte death via inhibition of p70 S6 kinase 1-mediated autophagy. *J. Pharmacol. Exp. Ther.* **341**, 183–195, https://doi.org/10.1124/jpet.111.189589
262 De Angelis, A., Piegari, E., Cappetta, D., Russo, R., Esposito, G., Ciuffreda, L.P. et al. (2015) SIRT1 activation rescues doxorubicin-induced loss of functional competence of human cardiac progenitor cells. *Int. J. Cardiol.* **189**, 30–44, https://doi.org/10.1016/j.ijcard.2015.03.438
263 Wang, G.Y., Wang, Y.M., Zhang, L.N., Li, Q., Yue, H., Song, C.M. et al. (2007) Effect of resveratrol on heart function of rats with adriamycin-induced heart failure. *Zhongguo Zhong Yao Za Zhi* **32**, 1563–1565
264 Osman, A.M., Al-Harthi, S.E., AlArabi, O.M., Elshal, M.F., Ramadan, W.S., Alaama, M.N. et al. (2013) Chemosensetizing and cardioprotective effects of resveratrol in doxorubicin-treated animals. *Cancer Cell Int.* **13**, 52, https://doi.org/10.1186/1475-2867-13-52
265 Al-Harthi, S.E., Alarabi, O.M., Ramadan, W.S., Alaama, M.N., Al-Kreathy, H.M., Damanhouri, Z.A. et al. (2014) Amelioration of doxorubicin-induced cardiotoxicity by resveratrol. *Mol. Med. Rep.* **10**, 1455–1460, https://doi.org/10.3892/mmr.2014.2384
266 Ruan, Y., Dong, C., Patel, J., Duan, C., Wang, X., Wu, X. et al. (2015) SIRT1 suppresses doxorubicin-induced cardiotoxicity by regulating the oxidative stress and p38MAPK pathways. *Cell. Physiol. Biochem.* **35**, 1116–1124, https://doi.org/10.1159/000373937

267 Sin, T.K., Tam, B.T., Yung, B.Y., Yip, S.P., Chan, L.W., Wong, C.S. et al. (2015) Resveratrol protects against doxorubicin-induced cardiotoxicity in aged hearts through the SIRT1-USP7 axis. *J. Physiol.* **593**, 1887–1899, https://doi.org/10.1113/jphysiol.2014.270101
268 Tatlidede, E., Sehirli, O., Velioglu-Ogunc, A., Cetinel, S., Yegen, B.C., Yarat, A. et al. (2009) Resveratrol treatment protects against doxorubicin-induced cardiotoxicity by alleviating oxidative damage. *Free Radic. Res.* **43**, 195–205, https://doi.org/10.1080/10715760802673008
269 Zhang, C., Feng, Y., Qu, S., Wei, X., Zhu, H., Luo, Q. et al. (2011) Resveratrol attenuates doxorubicin-induced cardiomyocyte apoptosis in mice through SIRT1-mediated deacetylation of p53. *Cardiovasc. Res.* **90**, 538–545, https://doi.org/10.1093/cvr/cvr022
270 Gu, J., Song, Z.P., Gui, D.M., Hu, W., Chen, Y.G. and Zhang, D.D. (2012) Resveratrol attenuates doxorubicin-induced cardiomyocyte apoptosis in lymphoma nude mice by heme oxygenase-1 induction. *Cardiovasc. Toxicol.* **12**, 341–349, https://doi.org/10.1007/s12012-012-9178-7
271 Dudka, J., Gieroba, R., Korga, A., Burdan, F., Matysiak, W., Jodlowska-Jedrych, B. et al. (2012) Different effects of resveratrol on dose-related doxorubicin-induced heart and liver toxicity. *Evid. Based Complement. Alternat. Med.* **2012**, 606183, https://doi.org/10.1155/2012/606183
272 Dolinsky, V.W., Rogan, K.J., Sung, M.M., Zordoky, B.N., Haykowsky, M.J., Young, M.E. et al. (2013) Both aerobic exercise and resveratrol supplementation attenuate doxorubicin-induced cardiac injury in mice. *Am. J. Physiol. Endocrinol. Metab.* **305**, E243–F253, https://doi.org/10.1152/ajpendo.00044.2013
273 Arafa, M.H., Mohammad, N.S., Atteia, H.H. and Abd-Elaziz, H.R. (2014) Protective effect of resveratrol against doxorubicin-induced cardiac toxicity and fibrosis in male experimental rats. *J. Physiol. Biochem.* **70**, 701–711, https://doi.org/10.1007/s13105-014-0339-y
274 Cappetta, D., Esposito, G., Piegari, E., Russo, R., Ciuffreda, L.P., Rivellino, A. et al. (2016) SIRT1 activation attenuates diastolic dysfunction by reducing cardiac fibrosis in a model of anthracycline cardiomyopathy. *Int. J. Cardiol.* **205**, 99–110, https://doi.org/10.1016/j.ijcard.2015.12.008
275 Shoukry, H.S., Ammar, H.I., Rashed, L.A., Zikri, M.B., Shamaa, A.A., Abou Elfadl, S.G. et al. (2017) Prophylactic supplementation of resveratrol is more effective than its therapeutic use against doxorubicin induced cardiotoxicity. *PLoS ONE* **12**, e0181535, https://doi.org/10.1371/journal.pone.0181535
276 Matsumura, N., Zordoky, B.N., Robertson, I.M., Hamza, S.M., Parajuli, N., Soltys, C.M. et al. (2018) Co-administration of resveratrol with doxorubicin in young mice attenuates detrimental late-occurring cardiovascular changes. *Cardiovasc. Res.* **114**, 1350–1359, https://doi.org/10.1093/cvr/cvy064
277 Fulda, S. and Debatin, K.M. (2004) Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol. *Oncogene* **23**, 6702–6711, https://doi.org/10.1038/sj.onc.1207630
278 Al-Abd, A.M., Mahmoud, A.M., El-Sherbiny, G.A., El-Moselhy, M.A., Nofal, S.M., El-Latif, H.A. et al. (2011) Resveratrol enhances the cytotoxic profile of docetaxel and doxorubicin in solid tumour cell lines in vitro. *Cell Prolif.* **44**, 591–601, https://doi.org/10.1111/j.1365-2184.2011.00783.x
279 Osman, A.M., Bayoumi, H.M., Al-Harthi, S.E., Damanhouri, Z.A. and Elshal, M.F. (2012) Modulation of doxorubicin cytotoxicity by resveratrol in a human breast cancer cell line. *Cancer Cell Int.* **12**, 47, https://doi.org/10.1186/1475-2867-12-47
280 Schroeter, A. and Marko, D. (2014) Resveratrol modulates the topoisomerase inhibitory potential of doxorubicin in human colon carcinoma cells. *Molecules* **19**, 20054–20072, https://doi.org/10.3390/molecules191220054
281 Tomoaia, G., Horovitz, O., Mocanu, A., Nita, A., Avram, A., Racz, C.P. et al. (2015) Effects of doxorubicin mediated by gold nanoparticles and resveratrol in two human cervical tumor cell lines. *Colloids Surf. B Biointerfaces* **135**, 726–734, https://doi.org/10.1016/j.colsurfb.2015.08.036
282 Sheu, M.T., Jhan, H.J., Hsieh, C.M., Wang, C.J. and Ho, H.O. (2015) Efficacy of antioxidants as a Complementary and Alternative Medicine (CAM) in combination with the chemotherapeutic agent doxorubicin. *Integr. Cancer Ther.* **14**, 184–195, https://doi.org/10.1177/1534735414564425
283 Khaleel, S.A., Al-Abd, A.M., Ali, A.A. and Abdel-Naim, A.B. (2016) Didox and resveratrol sensitize colorectal cancer cells to doxorubicin via activating apoptosis and ameliorating P-glycoprotein activity. *Sci. Rep.* **6**, 36855, https://doi.org/10.1038/srep36855
284 Hashemzaei, M., Karami, S.P., Delaramifar, A., Sheidary, A., Tabrizian, K., Rezaee, R. et al. (2016) Anticancer effects of co-administration of daunorubicin and resveratrol in Molt-4, U266 B1 and Raji cell lines. *Farmacia* **64**, 36–42
285 Rai, G., Mishra, S., Suman, S. and Shukla, Y. (2016) Resveratrol improves the anticancer effects of doxorubicin in vitro and in vivo models: a mechanistic insight. *Phytomedicine* **23**, 233–242, https://doi.org/10.1016/j.phymed.2015.12.020
286 Carlson, A., Alderete, K.S., Grant, M.K.O., Seelig, D.M., Sharkey, L.C. and Zordoky, B.N.M. (2018) Anticancer effects of resveratrol in canine hemangiosarcoma cell lines. *Vet. Comp. Oncol.* **16**, 253–261, https://doi.org/10.1111/vco.12375
287 Hallajian, F., Ghasmi, M., Abedi, S.M., Behzadi, R., Hayati, E., Sadeghzadeh, N. et al. (2018) Evaluation of the effect of resveratrol and doxorubicin on (99m)Tc-MIBI uptake in breast cancer cell xenografts in mice. *Cancer Biother. Radiopharm.* **33**, 403–410, https://doi.org/10.1089/cbr.2018.2523
288 Lo, S.N., Chang, Y.P., Tsai, K.C., Chang, C.Y., Wu, T.S. and Ueng, Y.F. (2013) Inhibition of CYP1 by berberine, palmatine, and jatrorrhizine: selectivity, kinetic characterization, and molecular modeling. *Toxicol. Appl. Pharmacol.* **272**, 671–680, https://doi.org/10.1016/j.taap.2013.07.005
289 Lo, S.N., Shen, C.C., Chang, C.Y., Tsai, K.C., Huang, C.C., Wu, T.S. et al. (2015) The effect of oxidation on berberine-mediated CYP1 inhibition: oxidation behavior and metabolite-mediated inhibition. *Drug Metab. Dispos.* **43**, 1100–1107, https://doi.org/10.1124/dmd.115.063966
290 Wen, C.J., Wu, L.X., Fu, L.J., Shen, D.Y., Zhang, X., Zhang, Y.W. et al. (2014) Preferential induction of CYP1A1 over CYP1B1 in human breast cancer MCF-7 cells after exposure to berberine. *Asian Pac. J. Cancer Prev.* **15**, 495–499, https://doi.org/10.7314/APJCP.2014.15.1.495
291 Wu, Y.Z., Zhang, L., Wu, Z.X., Shan, T.T. and Xiong, C. (2019) Berberine ameliorates doxorubicin-induced cardiotoxicity via a SIRT1/p66Shc-mediated pathway. *Oxid. Med. Cell Longev.* **2019**, 2150394, https://doi.org/10.1155/2019/2150394
292 Xiong, C., Wu, Y.Z., Zhang, Y., Wu, Z.X., Chen, X.Y., Jiang, P. et al. (2018) Protective effect of berberine on acute cardiomyopathy associated with doxorubicin treatment. *Oncol. Lett.* **15**, 5721–5729
293 Hao, G., Yu, Y., Gu, B., Xing, Y. and Xue, M. (2015) Protective effects of berberine against doxorubicin-induced cardiotoxicity in rats by inhibiting metabolism of doxorubicin. *Xenobiotica* **45**, 1024–1029, https://doi.org/10.3109/00498254.2015.1034223
294 Lv, X., Yu, X., Wang, Y., Wang, F., Li, H., Wang, Y. et al. (2012) Berberine inhibits doxorubicin-triggered cardiomyocyte apoptosis via attenuating mitochondrial dysfunction and increasing Bcl-2 expression. *PLoS ONE* **7**, e47351, https://doi.org/10.1371/journal.pone.0047351
295 Zhao, X., Zhang, J., Tong, N., Liao, X., Wang, E., Li, Z. et al. (2011) Berberine attenuates doxorubicin-induced cardiotoxicity in mice. *J. Int. Med. Res.* **39**, 1720–1727, https://doi.org/10.1177/147323001103900514

296 Coelho, A.R., Martins, T.R., Couto, R., Deus, C., Pereira, C.V., Simoes, R.F. et al. (2017) Berberine-induced cardioprotection and Sirt3 modulation in doxorubicin-treated H9c2 cardiomyoblasts. *Biochim. Biophys. Acta Mol. Basis Dis.* **1863**, 2904–2923, https://doi.org/10.1016/j.bbadis.2017.07.030
297 Zhu, T., Li, L.L., Xiao, G.F., Luo, Q.Z., Liu, Q.Z., Yao, K.T. et al. (2015) Berberine increases doxorubicin sensitivity by suppressing STAT3 in lung cancer. *Am. J. Chin. Med.* **43**, 1487–1502, https://doi.org/10.1142/S0192415X15500846
298 Tong, N., Zhang, J., Chen, Y., Li, Z., Luo, Y., Zuo, H. et al. (2012) Berberine sensitizes mutliple human cancer cells to the anticancer effects of doxorubicin in vitro. *Oncol. Lett.* **3**, 1263–1267, https://doi.org/10.3892/ol.2012.644
299 Pan, Y., Zhang, F., Zhao, Y., Shao, D., Zheng, X., Chen, Y. et al. (2017) Berberine enhances chemosensitivity and induces apoptosis through dose-orchestrated AMPK signaling in breast cancer. *J. Cancer* **8**, 1679–1689, https://doi.org/10.7150/jca.19106
300 Mittal, A., Tabasum, S. and Singh, R.P. (2014) Berberine in combination with doxorubicin suppresses growth of murine melanoma B16F10 cells in culture and xenograft. *Phytomedicine* **21**, 340–347, https://doi.org/10.1016/j.phymed.2013.09.002
301 FitzGerald, T.J., Bishop-Jodoin, M., Laurie, F., Lukez, A., O'Loughlin, L. and Sacher, A. (2019) Treatment toxicity: radiation. *Hematol. Oncol. Clin. North Am.* **33**, 1027–1039, https://doi.org/10.1016/j.hoc.2019.08.010
302 Armanious, M.A., Mohammadi, H., Khodor, S., Oliver, D.E., Johnstone, P.A. and Fradley, M.G. (2018) Cardiovascular effects of radiation therapy. *Curr. Probl. Cancer* **42**, 433–442, https://doi.org/10.1016/j.currproblcancer.2018.05.008
303 Gagliardi, G., Constine, L.S., Moiseenko, V., Correa, C., Pierce, L.J., Allen, A.M. et al. (2010) Radiation dose-volume effects in the heart. *Int. J. Radiat. Oncol. Biol. Phys.* **76**, S77–S85, https://doi.org/10.1016/j.ijrobp.2009.04.093
304 Mrotzek, S.M., Rassaf, T. and Totzeck, M. (2020) Cardiovascular damage associated with chest irradiation. *Front. Cardiovasc. Med.* **7**, 41, https://doi.org/10.3389/fcvm.2020.00041
305 Darby, S.C., Ewertz, M., McGale, P., Bennet, A.M., Blom-Goldman, U., Bronnum, D. et al. (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N. Engl. J. Med.* **368**, 987–998, https://doi.org/10.1056/NEJMoa1209825
306 van den Bogaard, V.A., Ta, B.D., van der Schaaf, A., Bouma, A.B., Middag, A.M., Bantema-Joppe, E.J. et al. (2017) Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J. Clin. Oncol.* **35**, 1171–1178, https://doi.org/10.1200/JCO.2016.69.8480
307 Mueller, M.M., Peter, W., Mappes, M., Huelsen, A., Steinbauer, H., Boukamp, P. et al. (2001) Tumor progression of skin carcinoma cells in vivo promoted by clonal selection, mutagenesis, and autocrine growth regulation by granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. *Am. J. Pathol.* **159**, 1567–1579, https://doi.org/10.1016/S0002-9440(10)62541-2
308 Mantawy, E.M., Said, R.S. and Abdel-Aziz, A.K. (2019) Mechanistic approach of the inhibitory effect of chrysin on inflammatory and apoptotic events implicated in radiation-induced premature ovarian failure: emphasis on TGF-beta/MAPKs signaling pathway. *Biomed. Pharmacother.* **109**, 293–303, https://doi.org/10.1016/j.biopha.2018.10.092
309 Das, S., Das, J., Paul, A., Samadder, A. and Khuda-Bukhsh, A.R. (2013) Apigenin, a bioactive flavonoid from Lycopodium clavatum, stimulates nucleotide excision repair genes to protect skin keratinocytes from ultraviolet B-induced reactive oxygen species and DNA damage. *J. Acupunct. Meridian Stud.* **6**, 252–262, https://doi.org/10.1016/j.jams.2013.07.002
310 Panganiban, R.A., Mungunsukh, O. and Day, R.M. (2013) X-irradiation induces ER stress, apoptosis, and senescence in pulmonary artery endothelial cells. *Int. J. Radiat. Biol.* **89**, 656–667, https://doi.org/10.3109/09553002.2012.711502
311 Zhang, H., Yan, H., Zhou, X., Wang, H., Yang, Y., Zhang, J. et al. (2017) The protective effects of Resveratrol against radiation-induced intestinal injury. *BMC Complement. Altern. Med.* **17**, 410, https://doi.org/10.1186/s12906-017-1915-9
312 Velioglu-Ogunc, A., Sehirli, O., Toklu, H.Z., Ozyurt, H., Mayadagli, A., Eksioglu-Demiralp, E. et al. (2009) Resveratrol protects against irradiation-induced hepatic and ileal damage via its anti-oxidative activity. *Free Radic. Res.* **43**, 1060–1071, https://doi.org/10.1080/10715760903171100
313 Li, G.H., Wang, D.L., Hu, Y.D., Pu, P., Li, D.Z., Wang, W.D. et al. (2010) Berberine inhibits acute radiation intestinal syndrome in human with abdomen radiotherapy. *Med. Oncol.* **27**, 919–925, https://doi.org/10.1007/s12032-009-9307-8
314 Li, G.H., Zhang, Y.P., Tang, J.L., Chen, Z.T., Hu, Y.D., Wei, H. et al. (2010) Effects of berberine against radiation-induced intestinal injury in mice. *Int. J. Radiat. Oncol. Biol. Phys.* **77**, 1536–1544, https://doi.org/10.1016/j.ijrobp.2010.02.062
315 Li, X.D., Wang, Z., Wang, X.R., Shao, D., Zhang, X., Li, L. et al. (2019) Berberine-loaded Janus gold mesoporous silica nanocarriers for chemo/radio/photothermal therapy of liver cancer and radiation-induced injury inhibition. *Int. J. Nanomedicine* **14**, 3967–3982, https://doi.org/10.2147/IJN.S206044
316 Liu, Y., Yu, H., Zhang, C., Cheng, Y., Hu, L., Meng, X. et al. (2008) Protective effects of berberine on radiation-induced lung injury via intercellular adhesion molecular-1 and transforming growth factor-beta-1 in patients with lung cancer. *Eur. J. Cancer* **44**, 2425–2432, https://doi.org/10.1016/j.ejca.2008.07.040
317 Han, X., Piao, M.J., Kim, K.C., Madduma Hewage, S.R., Yoo, E.S., Koh, Y.S. et al. (2015) Isorhamnetin protects human keratinocytes against ultraviolet B-induced cell damage. *Biomol. Ther. (Seoul)* **23**, 357–366, https://doi.org/10.4062/biomolther.2015.005
318 Wu, N.L., Fang, J.Y., Chen, M., Wu, C.J., Huang, C.C. and Hung, C.F. (2011) Chrysin protects epidermal keratinocytes from UVA- and UVB-induced damage. *J. Agric. Food Chem.* **59**, 8391–8400, https://doi.org/10.1021/jf200931t
319 Wolfle, U., Heinemann, A., Esser, P.R., Haarhaus, B., Martin, S.F. and Schempp, C.M. (2012) Luteolin prevents solar radiation-induced matrix metalloproteinase-1 activation in human fibroblasts: a role for p38 mitogen-activated protein kinase and interleukin-20 released from keratinocytes. *Rejuvenation Res.* **15**, 466–475, https://doi.org/10.1089/rej.2011.1309
320 Zoberi, I., Bradbury, C.M., Curry, H.A., Bisht, K.S., Goswami, P.C., Roti Roti, J.L. et al. (2002) Radiosensitizing and anti-proliferative effects of resveratrol in two human cervical tumor cell lines. *Cancer Lett.* **175**, 165–173, https://doi.org/10.1016/S0304-3835(01)00719-4
321 Lu, K.H., Chen, Y.W., Tsai, P.H., Tsai, M.L., Lee, Y.Y., Chiang, C.Y. et al. (2009) Evaluation of radiotherapy effect in resveratrol-treated medulloblastoma cancer stem-like cells. *Childs Nerv. Syst.* **25**, 543–550, https://doi.org/10.1007/s00381-009-0826-6

322 Kao, C.L., Huang, P.I., Tsai, P.H., Tsai, M.L., Lo, J.F., Lee, Y.Y. et al. (2009) Resveratrol-induced apoptosis and increased radiosensitivity in CD133-positive cells derived from atypical teratoid/rhabdoid tumor. *Int. J. Radiat. Oncol. Biol. Phys.* **74**, 219–228, https://doi.org/10.1016/j.ijrobp.2008.12.035
323 Chen, Y.A., Lien, H.M., Kao, M.C., Lo, U.G., Lin, L.C., Lin, C.J. et al. (2017) Sensitization of radioresistant prostate cancer cells by resveratrol isolated from Arachis hypogaea stems. *PLoS ONE* **12**, e0169204, https://doi.org/10.1371/journal.pone.0169204
324 Voellger, B., Waldt, N., Rupa, R., Kirches, E., Melhem, O., Ochel, H.J. et al. (2018) Combined effects of resveratrol and radiation in GH3 and TtT/GF pituitary adenoma cells. *J. Neuro Oncol.* **139**, 573–582, https://doi.org/10.1007/s11060-018-2918-1
325 Tan, Y., Wei, X., Zhang, W., Wang, X., Wang, K., Du, B. et al. (2017) Resveratrol enhances the radiosensitivity of nasopharyngeal carcinoma cells by downregulating E2F1. *Oncol. Rep.* **37**, 1833–1841, https://doi.org/10.3892/or.2017.5413
326 Watanabe, N., Hirayama, R. and Kubota, N. (2007) The chemopreventive flavonoid apigenin confers radiosensitizing effect in human tumor cells grown as monolayers and spheroids. *J. Radiat. Res.* **48**, 45–50, https://doi.org/10.1269/jrr.0635
327 van Rijn, J. and van den Berg, J. (1997) Flavonoids as enhancers of x-ray-induced cell damage in hepatoma cells. *Clin. Cancer Res.* **3**, 1775–1779
328 Medhat, A.M., Azab, K.S., Said, M.M., El Fatih, N.M. and El Bakary, N.M. (2017) Antitumor and radiosensitizing synergistic effects of apigenin and cryptotanshinone against solid Ehrlich carcinoma in female mice. *Tumour Biol.* **39**, 1010428317728480, https://doi.org/10.1177/1010428317728480
329 Li, Y., Wang, Z., Jin, J., Zhu, S.X., He, G.Q., Li, S.H. et al. (2020) Quercetin pretreatment enhances the radiosensitivity of colon cancer cells by targeting Notch-1 pathway. *Biochem. Biophys. Res. Commun.* **523**, 947–953, https://doi.org/10.1016/j.bbrc.2020.01.048
330 Lin, C., Yu, Y., Zhao, H.G., Yang, A., Yan, H. and Cui, Y. (2012) Combination of quercetin with radiotherapy enhances tumor radiosensitivity in vitro and in vivo. *Radiother. Oncol.* **104**, 395–400, https://doi.org/10.1016/j.radonc.2011.10.023
331 Liu, Q., Jiang, H., Liu, Z., Wang, Y., Zhao, M., Hao, C. et al. (2011) Berberine radiosensitizes human esophageal cancer cells by downregulating homologous recombination repair protein RAD51. *PLoS ONE* **6**, e23427, https://doi.org/10.1371/journal.pone.0023427
332 Park, J.J., Seo, S.M., Kim, E.J., Lee, Y.J., Ko, Y.G., Ha, J. et al. (2012) Berberine inhibits human colon cancer cell migration via AMP-activated protein kinase-mediated downregulation of integrin beta1 signaling. *Biochem. Biophys. Res. Commun.* **426**, 461–467, https://doi.org/10.1016/j.bbrc.2012.08.091
333 Wang, J., Kang, M., Wen, Q., Qin, Y.T., Wei, Z.X., Xiao, J.J. et al. (2017) Berberine sensitizes nasopharyngeal carcinoma cells to radiation through inhibition of Sp1 and EMT. *Oncol. Rep.* **37**, 2425–2432, https://doi.org/10.3892/or.2017.5499
334 You, X., Cao, X. and Lin, Y. (2019) Berberine enhances the radiosensitivity of hepatoma cells by Nrf2 pathway. *Front. Biosci. (Landmark Ed.)* **24**, 1190–1202
335 Peng, P.L., Kuo, W.H., Tseng, H.C. and Chou, F.P. (2008) Synergistic tumor-killing effect of radiation and berberine combined treatment in lung cancer: the contribution of autophagic cell death. *Int. J. Radiat. Oncol. Biol. Phys.* **70**, 529–542, https://doi.org/10.1016/j.ijrobp.2007.08.034
336 Wheate, N.J., Walker, S., Craig, G.E. and Oun, R. (2010) The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Trans.* **39**, 8113–8127, https://doi.org/10.1039/c0dt00292e
337 Hu, Z., Yu, J., Gui, G., Chen, Y., Huang, R., Jiang, L. et al. (2016) Cisplatin for testicular germ cell tumors: a rapid review. *J. Evid. Based Med.* **9**, 144–151, https://doi.org/10.1111/jebm.12210
338 Berliner, S., Rahima, M., Sidi, Y., Teplitsky, Y., Zohar, Y., Nussbaum, B. et al. (1990) Acute coronary events following cisplatin-based chemotherapy. *Cancer Invest.* **8**, 583–586, https://doi.org/10.3109/07357909009018924
339 Pai, V.B. and Nahata, M.C. (2000) Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf.* **22**, 263–302, https://doi.org/10.2165/00002018-200022040-00002
340 Li, X., Huang, J.M., Wang, J.N., Xiong, X.K., Yang, X.F. and Zou, F. (2015) Combination of chrysin and cisplatin promotes the apoptosis of Hep G2 cells by up-regulating p53. *Chem. Biol. Interact.* **232**, 12–20, https://doi.org/10.1016/j.cbi.2015.03.003
341 Li, X., Guo, S., Xiong, X.K., Peng, B.Y., Huang, J.M., Chen, M.F. et al. (2019) Combination of quercetin and cisplatin enhances apoptosis in OSCC cells by downregulating xIAP through the NF-kappaB pathway. *J. Cancer* **10**, 4509–4521, https://doi.org/10.7150/jca.31045
342 Wang, Z., Sun, W., Sun, X., Wang, Y. and Zhou, M. (2020) Kaempferol ameliorates Cisplatin induced nephrotoxicity by modulating oxidative stress, inflammation and apoptosis via ERK and NF-kappaB pathways. *AMB Express* **10**, 58, https://doi.org/10.1186/s13568-020-00993-w
343 Gundogdu, R., Erkan, M., Aydin, M., Sonmez, M.F., Vural, A., Kokoglu, K. et al. (2019) Assessment of the effectiveness of quercetin on cisplatin-induced ototoxicity in rats. *J. Int. Adv. Otol.* **15**, 229–236, https://doi.org/10.5152/iao.2019.5902
344 Wang, H., Luo, Y., Qiao, T., Wu, Z. and Huang, Z. (2018) Luteolin sensitizes the antitumor effect of cisplatin in drug-resistant ovarian cancer via induction of apoptosis and inhibition of cell migration and invasion. *J. Ovarian Res.* **11**, 93, https://doi.org/10.1186/s13048-018-0468-y
345 Kang, K.P., Park, S.K., Kim, D.H., Sung, M.J., Jung, Y.J., Lee, A.S. et al. (2011) Luteolin ameliorates cisplatin-induced acute kidney injury in mice by regulation of p53-dependent renal tubular apoptosis. *Nephrol. Dial. Transplant.* **26**, 814–822, https://doi.org/10.1093/ndt/gfq528
346 Chang, C.H., Lee, C.Y., Lu, C.C., Tsai, F.J., Hsu, Y.M., Tsao, J.W. et al. (2017) Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: A key role of AMPK and Akt/mTOR signaling. *Int. J. Oncol.* **50**, 873–882, https://doi.org/10.3892/ijo.2017.3866
347 Reddy, K.P., Madhu, P. and Reddy, P.S. (2016) Protective effects of resveratrol against cisplatin-induced testicular and epididymal toxicity in rats. *Food Chem. Toxicol.* **91**, 65–72, https://doi.org/10.1016/j.fct.2016.02.017
348 Liu, L., Fan, J., Ai, G., Liu, J., Luo, N., Li, C. et al. (2019) Berberine in combination with cisplatin induces necroptosis and apoptosis in ovarian cancer cells. *Biol. Res.* **52**, 37, https://doi.org/10.1186/s40659-019-0243-6
349 Zhang, B.Y., Wang, Y.M., Gong, H., Zhao, H., Lv, X.Y., Yuan, G.H. et al. (2015) Isorhamnetin flavonoid synergistically enhances the anticancer activity and apoptosis induction by cis-platin and carboplatin in non-small cell lung carcinoma (NSCLC). *Int. J. Clin. Exp. Pathol.* **8**, 25–37
350 Jia, W.Z., Zhao, J.C., Sun, X.L., Yao, Z.G., Wu, H.L. and Xi, Z.Q. (2015) Additive anticancer effects of chrysin and low dose cisplatin in human malignant glioma cell (U87) proliferation and evaluation of the mechanistic pathway. *J. BUON* **20**, 1327–1336

351 Khan, R., Khan, A.Q., Qamar, W., Lateef, A., Tahir, M., Rehman, M.U. et al. (2012) Chrysin protects against cisplatin-induced colon. toxicity via amelioration of oxidative stress and apoptosis: probable role of p38MAPK and p53. *Toxicol. Appl. Pharmacol.* **258**, 315–329, https://doi.org/10.1016/j.taap.2011.11.013
352 Chen, X., Xu, H., Yu, X., Wang, X., Zhu, X. and Xu, X. (2019) Apigenin inhibits in vitro and in vivo tumorigenesis in cisplatin-resistant colon cancer cells by inducing autophagy, programmed cell death and targeting m-TOR/PI3K/Akt signalling pathway. *J. BUON* **24**, 488–493
353 Liu, R., Ji, P., Liu, B., Qiao, H., Wang, X., Zhou, L. et al. (2017) Apigenin enhances the cisplatin cytotoxic effect through p53-modulated apoptosis. *Oncol. Lett.* **13**, 1024–1030, https://doi.org/10.3892/ol.2016.5495
354 Erdogan, S., Turkekul, K., Serttas, R. and Erdogan, Z. (2017) The natural flavonoid apigenin sensitizes human CD44(+) prostate cancer stem cells to cisplatin therapy. *Biomed. Pharmacother.* **88**, 210–217, https://doi.org/10.1016/j.biopha.2017.01.056
355 Luo, H., Daddysman, M.K., Rankin, G.O., Jiang, B.H. and Chen, Y.C. (2010) Kaempferol enhances cisplatin's effect on ovarian cancer cells through promoting apoptosis caused by down regulation of cMyc. *Cancer Cell Int.* **10**, 16, https://doi.org/10.1186/1475-2867-10-16
356 Sung, M.J., Kim, D.H., Jung, Y.J., Kang, K.P., Lee, A.S., Lee, S. et al. (2008) Genistein protects the kidney from cisplatin-induced injury. *Kidney Int.* **74**, 1538–1547, https://doi.org/10.1038/ki.2008.409
357 Palmieri, A., Iapichino, A., Cura, F., Scapoli, L., Carinci, F., Mandrone, M. et al. (2018) Pre-treatment with berberine enhances effect of 5-fluorouracil and cisplatin in HEP2 laryngeal cancer cell line. *J. Biol. Regul. Homeost. Agents* **32**, 167–177
358 Sharma, R., Gatchie, L., Williams, I.S., Jain, S.K., Vishwakarma, R.A., Chaudhuri, B. et al. (2017) Glycyrrhiza glabra extract and quercetin reverses cisplatin resistance in triple-negative MDA-MB-468 breast cancer cells via inhibition of cytochrome P450 1B1 enzyme. *Bioorg. Med. Chem. Lett.* **27**, 5400–5403, https://doi.org/10.1016/j.bmcl.2017.11.013
359 Horley, N.J., Beresford, K.J., Chawla, T., McCann, G.J., Ruparelia, K.C., Gatchie, L. et al. (2017) Discovery and characterization of novel CYP1B1 inhibitors based on heterocyclic chalcones: overcoming cisplatin resistance in CYP1B1-overexpressing lines. *Eur. J. Med. Chem.* **129**, 159–174, https://doi.org/10.1016/j.ejmech.2017.02.016
360 Xie, S., Tu, Z., Xiong, J., Kang, G., Zhao, L., Hu, W. et al. (2017) CXCR4 promotes cisplatin-resistance of non-small cell lung cancer in a CYP1B1-dependent manner. *Oncol. Rep.* **37**, 921–928, https://doi.org/10.3892/or.2016.5289
361 Kim, J. and Chan, J.J. (2017) Cyclophosphamide in dermatology. *Australas. J. Dermatol.* **58**, 5–17, https://doi.org/10.1111/ajd.12406
362 Nishikawa, T., Miyahara, E., Kurauchi, K., Watanabe, E., Ikawa, K., Asaba, K. et al. (2015) Mechanisms of fatal cardiotoxicity following high-dose cyclophosphamide therapy and a method for its prevention. *PLoS ONE* **10**, e0131394, https://doi.org/10.1371/journal.pone.0131394
363 Kurauchi, K., Nishikawa, T., Miyahara, E., Okamoto, Y. and Kawano, Y. (2017) Role of metabolites of cyclophosphamide in cardiotoxicity. *BMC Res. Notes* **10**, 406, https://doi.org/10.1186/s13104-017-2726-2
364 Taslimi, P., Kandemir, F.M., Demir, Y., Ileriturk, M., Temel, Y., Caglayan, C. et al. (2019) The antidiabetic and anticholinergic effects of chrysin on cyclophosphamide-induced multiple organ toxicity in rats: pharmacological evaluation of some metabolic enzyme activities. *J. Biochem. Mol. Toxicol.* **33**, e22313, https://doi.org/10.1002/jbt.22313
365 El-Sheikh, A.A., Morsy, M.A. and Okasha, A.M. (2017) Inhibition of NF-kappaB/TNF-alpha pathway may be involved in the protective effect of resveratrol against cyclophosphamide-induced multi-organ toxicity. *Immunopharmacol. Immunotoxicol.* **39**, 180–187, https://doi.org/10.1080/08923973.2017.1318913
366 Mansour, D.F., Saleh, D.O. and Mostafa, R.E. (2017) Genistein ameliorates cyclophosphamide - induced hepatotoxicity by modulation of oxidative stress and inflammatory mediators. *Open Access Maced J. Med. Sci.* **5**, 836–843, https://doi.org/10.3889/oamjms.2017.093
367 Saleh, D.O. and Mansour, D.F. (2016) Ovario-protective effects of genistein against cyclophosphamide toxicity in rats: role of anti-mullerian hormone and oestradiol. *Eur. J. Pharmacol.* **789**, 163–171, https://doi.org/10.1016/j.ejphar.2016.07.026
368 Germoush, M.O. and Mahmoud, A.M. (2014) Berberine mitigates cyclophosphamide-induced hepatotoxicity by modulating antioxidant status and inflammatory cytokines. *J. Cancer Res. Clin. Oncol.* **140**, 1103–1109, https://doi.org/10.1007/s00432-014-1665-8
369 Engelhardt, M., Szymaniak-Vits, M., Ajayi, S., Dold, S.M., Muller, S.J., Scheubeck, S. et al. (2018) Carfilzomib. *Recent Results Cancer Res.* **212**, 265–283, https://doi.org/10.1007/978-3-319-91439-8˙13
370 Moreau, P., Mateos, M.V., Berenson, J.R., Weisel, K., Lazzaro, A., Song, K. et al. (2018) Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. *Lancet Oncol.* **19**, 953–964, https://doi.org/10.1016/S1470-2045(18)30354-1
371 Groen, K., van de Donk, N., Stege, C., Zweegman, S. and Nijhof, I.S. (2019) Carfilzomib for relapsed and refractory multiple myeloma. *Cancer Manag. Res.* **11**, 2663–2675, https://doi.org/10.2147/CMAR.S150653
372 Shah, C., Bishnoi, R., Jain, A., Bejjanki, H., Xiong, S., Wang, Y. et al. (2018) Cardiotoxicity associated with carfilzomib: systematic review and meta-analysis. *Leuk. Lymphoma* **59**, 2557–2569, https://doi.org/10.1080/10428194.2018.1437269
373 Li, Q., Yue, Y., Chen, L., Xu, C., Wang, Y., Du, L. et al. (2018) Resveratrol sensitizes carfilzomib-induced apoptosis via promoting oxidative stress in multiple myeloma cells. *Front. Pharmacol.* **9**, 334, https://doi.org/10.3389/fphar.2018.00334
374 Keating, G.M. (2017) Dasatinib: a review in chronic myeloid leukaemia and Ph+ acute lymphoblastic leukaemia. *Drugs* **77**, 85–96, https://doi.org/10.1007/s40265-016-0677-x
375 Ozgur Yurttas, N. and Eskazan, A.E. (2018) Dasatinib-induced pulmonary arterial hypertension. *Br. J. Clin. Pharmacol.* **84**, 835–845, https://doi.org/10.1111/bcp.13508
376 Gillieron, M., Bolens, M. and Friedli, B. (1979) Conduction of disorders after total correction of Fallot's tetralogy. Electrocardiographic and electrophysiological study. *Arch. Mal. Coeur. Vaiss.* **72**, 55–61
377 Ferrari, S.M., Centanni, M., Virili, C., Miccoli, M., Ferrari, P., Ruffilli, I. et al. (2019) Sunitinib in the treatment of thyroid cancer. *Curr. Med. Chem.* **26**, 963–972, https://doi.org/10.2174/0929867324666171006165942

378 Mueller, E.W., Rockey, M.L. and Rashkin, M.C. (2008) Sunitinib-related fulminant hepatic failure: case report and review of the literature. *Pharmacotherapy* **28**, 1066–1070, https://doi.org/10.1592/phco.28.8.1066
379 Di Lorenzo, G., Autorino, R., Bruni, G., Carteni, G., Ricevuto, E., Tudini, M. et al. (2009) Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. *Ann. Oncol.* **20**, 1535–1542, https://doi.org/10.1093/annonc/mdp025
380 Maayah, Z.H., Ansari, M.A., El Gendy, M.A., Al-Arifi, M.N. and Korashy, H.M. (2014) Development of cardiac hypertrophy by sunitinib in vivo and in vitro rat cardiomyocytes is influenced by the aryl hydrocarbon receptor signaling pathway. *Arch. Toxicol.* **88**, 725–738
381 Harvey, P.A. and Leinwand, L.A. (2015) Dietary phytoestrogens present in soy dramatically increase cardiotoxicity in male mice receiving a chemotherapeutic tyrosine kinase inhibitor. *Mol. Cell. Endocrinol.* **399**, 330–335, https://doi.org/10.1016/j.mce.2014.10.011
382 Harvey, P.A. and Leinwand, L.A. (2015) Oestrogen enhances cardiotoxicity induced by Sunitinib by regulation of drug transport and metabolism. *Cardiovasc. Res.* **107**, 66–77, https://doi.org/10.1093/cvr/cvv152
383 Meiners, B., Shenoy, C. and Zordoky, B.N. (2018) Clinical and preclinical evidence of sex-related differences in anthracycline-induced cardiotoxicity. *Biol. Sex Differ.* **9**, 38, https://doi.org/10.1186/s13293-018-0198-2
384 Wei, S.C., Duffy, C.R. and Allison, J.P. (2018) Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov.* **8**, 1069–1086, https://doi.org/10.1158/2159-8290.CD-18-0367
385 Yang, Y. (2015) Cancer immunotherapy: harnessing the immune system to battle cancer. *J. Clin. Invest.* **125**, 3335–3337, https://doi.org/10.1172/JCI83871
386 Postow, M.A., Sidlow, R. and Hellmann, M.D. (2018) Immune-related adverse events associated with immune checkpoint blockade. *N. Engl. J. Med.* **378**, 158–168, https://doi.org/10.1056/NEJMra1703481
387 Khunger, A., Battel, L., Wadhawan, A., More, A., Kapoor, A. and Agrawal, N. (2020) New insights into mechanisms of immune checkpoint inhibitor-induced cardiovascular toxicity. *Curr. Oncol. Rep.* **22**, 65, https://doi.org/10.1007/s11912-020-00925-8
388 Moody, R., Wilson, K., Jaworowski, A. and Plebanski, M. (2020) Natural compounds with potential to modulate cancer therapies and self-reactive immune cells. *Cancers (Basel)* **12**, 673, https://doi.org/10.3390/cancers12030673
389 Deng, L.J., Qi, M., Li, N., Lei, Y.H., Zhang, D.M. and Chen, J.X. (2020) Natural products and their derivatives: promising modulators of tumor immunotherapy. *J. Leukoc. Biol.* **108**, 493–508, https://doi.org/10.1002/JLB.3MR0320-444R
390 Faiq, M.A., Dada, R., Sharma, R., Saluja, D. and Dada, T. (2014) CYP1B1: a unique gene with unique characteristics. *Curr. Drug Metab.* **15**, 893–914, https://doi.org/10.2174/1389200216666150206130058
391 Nebert, D.W. and Dalton, T.P. (2006) The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. *Nat. Rev. Cancer* **6**, 947–960, https://doi.org/10.1038/nrc2015
392 Murray, G.I. (2000) The role of cytochrome P450 in tumour development and progression and its potential in therapy. *J. Pathol.* **192**, 419–426, https://doi.org/10.1002/1096-9896(2000)9999:9999%3c::AID-PATH750%3e3.0.CO;2-0
393 Anderson, G. and Mazzoccoli, G. (2019) Left ventricular hypertrophy: roles of mitochondria CYP1B1 and melatonergic pathways in co-ordinating wider pathophysiology. *Int. J. Mol. Sci.* **20**, 4068, https://doi.org/10.3390/ijms20164068
394 Cardenas, S., Colombero, C., Panelo, L., Dakarapu, R., Falck, J.R., Costas, M.A. et al. (2020) GPR75 receptor mediates 20-HETE-signaling and metastatic features of androgen-insensitive prostate cancer cells. *Biochim. Biophys. Acta. Mol. Cell Biol. Lipids* **1865**, 158573, https://doi.org/10.1016/j.bbalip.2019.158573
395 Borin, T.F., Shankar, A., Angara, K., Rashid, M.H., Jain, M., Iskander, A. et al. (2017) HET0016 decreases lung metastasis from breast cancer in immune-competent mouse model. *PLoS ONE* **12**, e0178830, https://doi.org/10.1371/journal.pone.0178830
396 Liu, Q., Tan, W., Che, J., Yuan, D., Zhang, L., Sun, Y. et al. (2018) 12-HETE facilitates cell survival by activating the integrin-linked kinase/NF-kappaB pathway in ovarian cancer. *Cancer Manag. Res.* **10**, 5825–5838, https://doi.org/10.2147/CMAR.S180334
397 Nguyen, C.H., Brenner, S., Huttary, N., Atanasov, A.G., Dirsch, V.M., Chatuphonprasert, W. et al. (2016) AHR/CYP1A1 interplay triggers lymphatic barrier breaching in breast cancer spheroids by inducing 12(S)-HETE synthesis. *Hum. Mol. Genet.* **25**, 5006–5016
398 Yang, L., Ma, C., Zhang, L., Zhang, M., Li, F., Zhang, C. et al. (2018) 15-Lipoxygenase-2/15(S)-hydroxyeicosatetraenoic acid regulates cell proliferation and metastasis via the STAT3 pathway in lung adenocarcinoma. *Prostaglandins Other Lipid Mediat.* **138**, 31–40, https://doi.org/10.1016/j.prostaglandins.2018.07.003
399 Zeng, J., Li, D., Li, Z., Zhang, J. and Zhao, X. (2020) Dendrobium officinale attenuates myocardial fibrosis via inhibiting EMT signaling pathway in HFD/STZ-induced diabetic mice. *Biol. Pharm. Bull.* **43**, 864–872, https://doi.org/10.1248/bpb.b19-01073
400 Kovacic, J.C., Mercader, N., Torres, M., Boehm, M. and Fuster, V. (2012) Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease. *Circulation* **125**, 1795–1808, https://doi.org/10.1161/CIRCULATIONAHA.111.040352
401 Moretti, S., Nucci, N., Menicali, E., Morelli, S., Bini, V., Colella, R. et al. (2020) The aryl hydrocarbon receptor is expressed in thyroid carcinoma and appears to mediate epithelial-mesenchymal-transition. *Cancers (Basel)* **12**, https://doi.org/10.3390/cancers12010145
402 Scobie, M.R., Houke, H.R. and Rice, C.D. (2019) Modulation of glioma-inflammation crosstalk profiles in human glioblastoma cells by indirubin-3′-(2,3 dihydroxypropyl)-oximether (E804) and 7-bromoindirubin-3′-oxime (7BIO). *Chem. Biol. Interact.* **312**, 108816, https://doi.org/10.1016/j.cbi.2019.108816
403 Liu, C., Ma, X., Zhuang, J., Liu, L. and Sun, C. (2020) Cardiotoxicity of doxorubicin-based cancer treatment: what is the protective cognition that phytochemicals provide us? *Pharmacol. Res.* **160**, 105062, https://doi.org/10.1016/j.phrs.2020.105062
404 Tiwari, P. and Mishra, K.P. (2020) Flavonoids sensitize tumor cells to radiation: molecular mechanisms and relevance to cancer radiotherapy. *Int. J. Radiat. Biol.* **96**, 360–369, https://doi.org/10.1080/09553002.2020.1694193
405 Patel, K.R., Brown, V.A., Jones, D.J., Britton, R.G., Hemingway, D., Miller, A.S. et al. (2010) Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer Res.* **70**, 7392–7399, https://doi.org/10.1158/0008-5472.CAN-10-2027

406 Hoensch, H., Groh, B., Edler, L. and Kirch, W. (2008) Prospective cohort comparison of flavonoid treatment in patients with resected colorectal cancer to prevent recurrence. *World J. Gastroenterol.* **14**, 2187–2193, https://doi.org/10.3748/wjg.14.2187

407 Messing, E., Gee, J.R., Saltzstein, D.R., Kim, K., diSant'Agnese, A., Kolesar, J. et al. (2012) A phase 2 cancer chemoprevention biomarker trial of isoflavone G-2535 (genistein) in presurgical bladder cancer patients. *Cancer Prev. Res. (Phila.)* **5**, 621–630, https://doi.org/10.1158/1940-6207.CAPR-11-0455

408 Popat, R., Plesner, T., Davies, F., Cook, G., Cook, M., Elliott, P. et al. (2013) A phase 2 study of SRT501 (resveratrol) with bortezomib for patients with relapsed and or refractory multiple myeloma. *Br. J. Haematol.* **160**, 714–717, https://doi.org/10.1111/bjh.12154

409 Whittaker, J.A. and Al-Ismail, S.A. (1984) Effect of digoxin and vitamin E in preventing cardiac damage caused by doxorubicin in acute myeloid leukaemia. *Br. Med. J. (Clin. Res. Ed.)* **288**, 283–284, https://doi.org/10.1136/bmj.288.6413.283-a

410 Dresdale, A.R., Barr, L.H., Bonow, R.O., Mathisen, D.J., Myers, C.E., Schwartz, D.E. et al. (1982) Prospective randomized study of the role of N-acetyl cysteine in reversing doxorubicin-induced cardiomyopathy. *Am. J. Clin. Oncol.* **5**, 657–663, https://doi.org/10.1097/00000421-198212000-00015

411 Hao, D.C. and Xiao, P.G. (2019) Impact of drug metabolism/pharmacokinetics and their relevance upon traditional medicine-based cardiovascular drug research. *Curr. Drug Metab.* **20**, 556–574, https://doi.org/10.2174/1389200220666190618101526

412 Li, Y., Revalde, J. and Paxton, J.W. (2017) The effects of dietary and herbal phytochemicals on drug transporters. *Adv. Drug Deliv. Rev.* **116**, 45–62, https://doi.org/10.1016/j.addr.2016.09.004

413 Cho, H.J. and Yoon, I.S. (2015) Pharmacokinetic interactions of herbs with cytochrome p450 and p-glycoprotein. *Evid. Based Complement. Alternat. Med.* **2015**, 736431, https://doi.org/10.1155/2015/736431

414 Fernando, W., Rupasinghe, H.P.V. and Hoskin, D.W. (2019) Dietary phytochemicals with anti-oxidant and pro-oxidant activities: a double-edged sword in relation to adjuvant chemotherapy and radiotherapy? *Cancer Lett.* **452**, 168–177, https://doi.org/10.1016/j.canlet.2019.03.022