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## Review Article

# Chemopreventive effect of natural dietary compounds on xenobiotic-induced toxicity



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## ABSTRACT

Contaminants (or pollutants) that affect human health have become an important issue, spawning a myriad of studies on how to prevent harmful contaminant-induced effects. Recently, a variety of biological functions of natural dietary compounds derived from consumed foods and plants have been demonstrated in a number of studies. Natural dietary compounds exhibited several beneficial effects for the prevention of disease and the inhibition of chemically-induced carcinogenesis. Contaminant-induced toxicity and carcinogenesis are mostly attributed to the mutagenic activity of reactive metabolites and the disruption of normal biological functions. Therefore, the metabolic regulation of hazardous chemicals is key to reducing contaminant-induced adverse health effects. Moreover, promoting contaminant excretion from the body through Phase I and II metabolizing enzymes is also a useful strategy for reducing contaminant-induced toxicity. This review focuses on summarizing the natural dietary compounds derived from common dietary foods and plants and their possible mechanisms of action in the prevention/suppression of contaminant-induced toxicity.

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## 1. Introduction

Industrial pollution and food contamination (partially derived from environmental contaminants) have become increasingly serious matters as these factors elevate the risk of chemical contaminant-induced adverse health effects. Foreign chemicals, or xenobiotics, are difficult to avoid given their ubiquity in our global society. For example, several varieties of common xenobiotics are encountered in daily life, including dioxin, polycyclic aromatic hydrocarbons (PAHs), nicotine, and aflatoxins. Long-term exposure to these xenobiotics can gradually and negatively affect human health through the induction of disease development via various exposure routes. Indeed, epidemiological and investigational studies have shown that daily and/or occupational exposure to PAHs through skin contact, inhalation, or ingestion can induce inflammation, metabolic syndrome, cardiovascular disease, and cancers [1–3]. Additionally, aflatoxins, a type of food contaminant present in cereal and groundnuts produced by *Aspergillus flavus* and *Aspergillus parasiticus*, have been demonstrated to be strong inducers of hepatocellular carcinogenesis, thereby causing hepatic fibrosis, cirrhosis, and cancer [4,5].

Xenobiotics that enter the human body undergo four stages: absorption, distribution, metabolism, and elimination [6]. The metabolism stage plays a central role in the bioactivation/detoxification of xenobiotics. These processes are performed by xenobiotics/drug-metabolizing enzymes (XMEs), including Phase I (oxidation, reduction, or hydrolysis reactions) and Phase II (conjugation reaction) enzyme systems. The terms “Phase I” and “Phase II” enzymes were first established by Williams [7] in 1959. XMEs are important enzyme families that are present in the liver and extrahepatic organs, including the skin, lung, kidney, intestine, and colon/rectum, that interact with endogenous and exogenous chemicals and xenobiotics [8]. A typical xenobiotic metabolism involves the continuous biotransformation steps of oxidation, reduction or hydrolysis of parent substances to introduce reactive or polar groups, such as  $-NH_2$ ,  $-COOH$ , and  $-OH$  groups (Phase I), followed by conjugated with hydrophilic molecules (Phase II), such as glutathione, glucuronic acid, and sulfate, to increase the hydrophilicity of the substances, thereby rendering the substances suitable for renal or intestinal excretion [9]. However, in some instances, xenobiotics are metabolized by Phase I enzymes, which can form reactive or mutagenic metabolites that may induce DNA mutation and carcinogenesis. For example, aflatoxin B<sub>1</sub> is metabolized to mutagenic aflatoxin-8,9-epoxide by CYP3A4 [10].

The majority of Phase I reactions are performed by cytochrome P450 (CYP) enzymes, particularly those in the CYP1, CYP2, and CYP3 families, which metabolize a vast range of xenobiotics [11]. It is well known that the CYP enzymes are regulated by farnesoid X receptor, liver X receptor, peroxisome proliferator activated receptor, constitutive androstane receptor, glucocorticoid receptor, pregnane X receptor, and aryl hydrocarbon receptor (AhR) [12,13].

Dietary chemoprevention is a potential strategy for preventing disease development and promoting health and is defined as the use of natural dietary compounds, also called phytochemicals [14–16]. Natural dietary compounds that are

found in our diet are obtained from widespread and commonly consumed fruits, vegetables, medicinal plants, and derivatives, such as nobiletin from citrus peel, quercetin from onions, curcumin from turmeric, and resveratrol from red wine [17,18]. A number of studies have suggested that numerous natural dietary compounds are able to prevent/reduce xenobiotic-induced harmful effects on human health modulated through regulated XMEs and related signaling pathways [19–21].

In this review, we will discuss the regulative effects of natural dietary compounds on XMEs and provide a literature overview of natural dietary compounds as chemopreventive agents for preventing xenobiotic-induced toxicity.

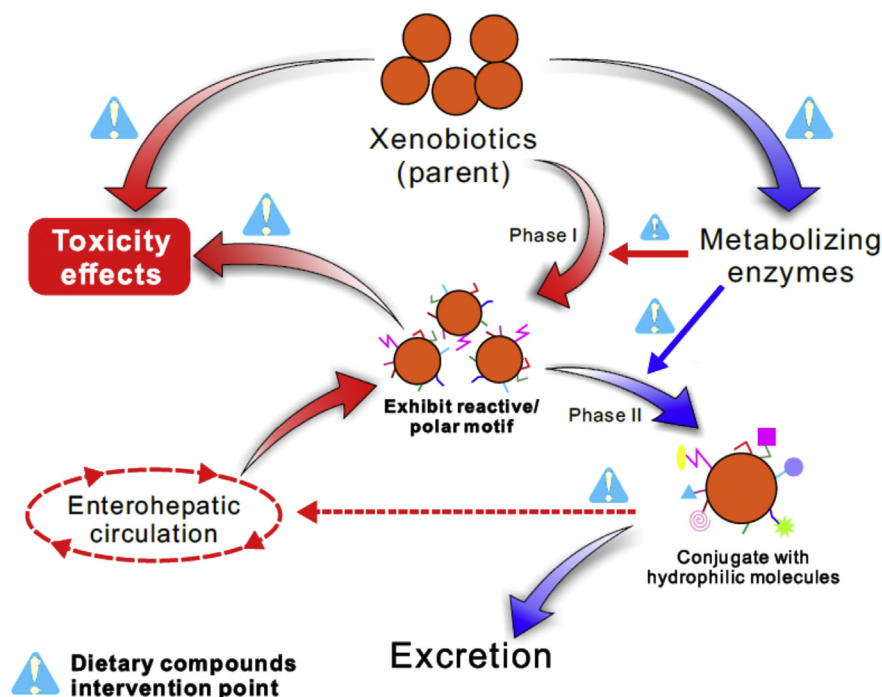
## 2. Potential strategies for reduced xenobiotics-induced toxicity effects by natural dietary compounds (Figure 1)

Xenobiotics enter our body through metabolism and excretion. Nevertheless, the stage of xenobiotic metabolism contributes to the conversion of the parent substances for either metabolic bioactivation or detoxification [22]. The key enzymes for xenobiotic bioactivation are CYPs (Phase I), which catalyze the xenobiotics to generate reactive metabolites, such as a molecular ions, quinone, and epoxide. This is a necessary step and is followed by Phase II conjugation reaction [23]. Therefore, the principal strategy for the repression of xenobiotic bioactivation by natural dietary compounds is the modulation of the type and expression level of CYPs—although not complete inhibition—through the suppression of xenobiotic-induced receptor activation and related signaling transduction pathways, such as the AhR signaling pathway. Moreover, the use of natural dietary compounds as CYP inhibitors against CYP enzymatic activity is also a means of suppressing xenobiotic bioactivation. In contrast, Phase II enzymes, including glutathione S-transferases (GSTs), UDP-glucuronosyl-transferase (UGTs), sulfotransferases, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH):quinone acceptor oxidoreductase 1, and quinone reductase, have been associated with xenobiotic detoxification and, ultimately, excretion [8]. Phase II enzymes induced by natural dietary compounds act as a detoxification strategy through the detoxification of reactive xenobiotic metabolites and the promotion of xenobiotic excretion.

Furthermore, several studies have suggested the existence of a link between xenobiotics/reactive metabolites and the induction of inflammation and tumorigenesis mechanisms, such as inducing inflammatory cytokines expression, promoting cell proliferation and enhancing metastasis [24,25]. Hence, the ability of natural dietary compounds to suppress adverse mechanisms correlates with the effectiveness of these compounds at preventing/inhibiting xenobiotic-induced toxicity (Figure 2).

## 3. Natural dietary compounds suppressed xenobiotics-induced toxicity

Most existing studies of natural dietary compounds that suppress xenobiotic-induced toxicity have been focused on



**Figure 1 – Schematic representation of potential strategies for reduced xenobiotics-induced toxicity effects by natural dietary compounds.**

two major contaminants, PAHs and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Indeed, TCDD is the most studied and toxic of all the dioxins. Several studies have also found that natural dietary compounds prevent less common xenobiotic-induced toxicity, such as 1,2-dimethylhydrazine (DMH), *N*-nitrosodiethylamine, 3-methylcholanthrene, and ferric nitrilotriacetate.

PAHs are one of the most common contaminants derived from environmental and food contamination, and recent epidemiological studies have established that the dietary intake of PAHs is the major route of daily human exposure [26,27]. Benzo[*a*]pyrene (BaP), a toxicological representative for carcinogenic PAHs, is formed by the incomplete combustion of organic materials, cigarette smoke, and process of roasting foods. The mutagenic activity of BaP has been correlated with CYP1s catalyzed by BaP that generate reactive diol epoxide and quinone metabolites, which were shown to initiate tumor development through the induction DNA adduct formation and the production of reactive oxygen species (ROS) generation. Furthermore, there is increasing recognition that CYP1B1 acts a PAH bioactivator, which may be attributed to the fact that the catalytic activity for the generation of BaP-diol epoxide was higher than CYP1A1. Furthermore, several studies have shown that the abolishment of CYP1B1 expression, but not CYP1A1, caused a reduction of the BaP-induced DNA adduct formation and mitochondrial dysfunction [28–30].

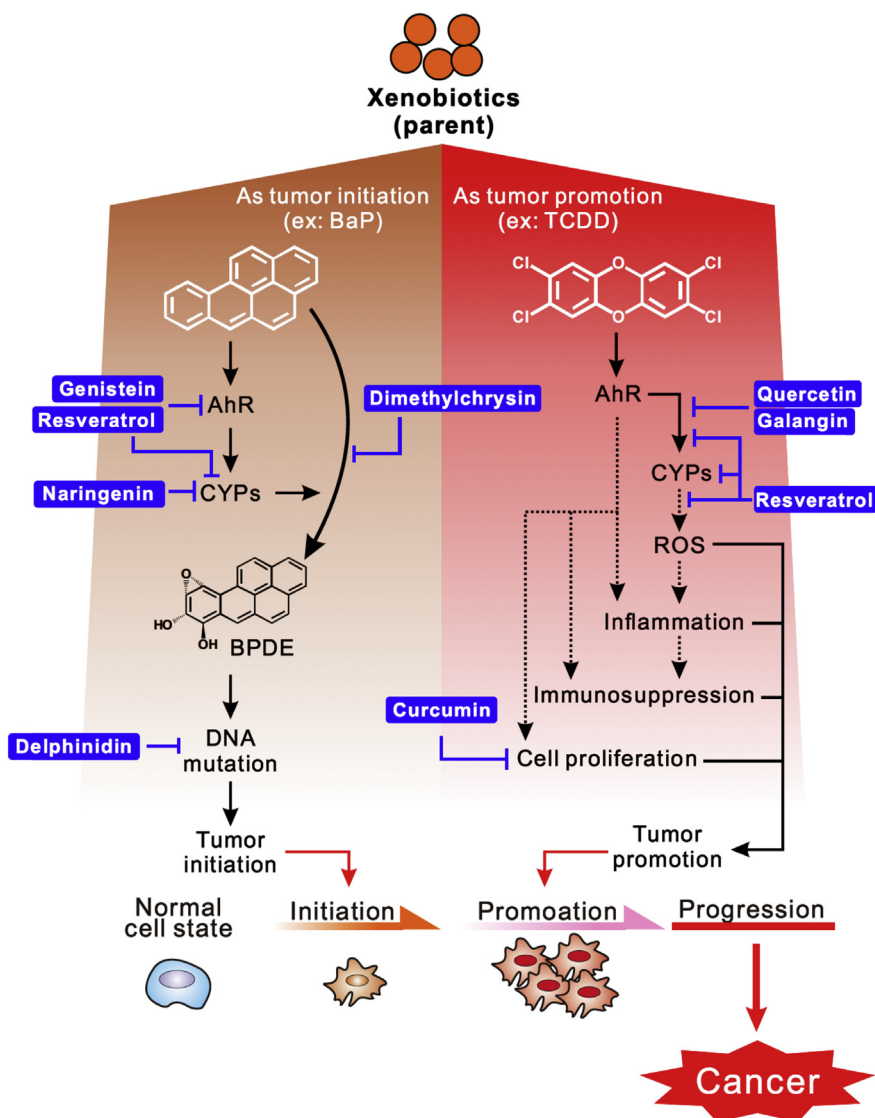
TCDD, a prototype of a group of highly toxic environmental pollutants, is formed as an unintended by-product of incomplete combustion and appear as persistent pollutants in the environment, foods, and milk [31]. Pitot et al. [32] documented

that TCDD behaves as a nongenotoxic tumor promoter because TCDD was not able to interact with DNA and failed to reveal mutagenic activity in the Ames test [33]. TCDD is recognized a tumor promoter that is attributed to the blockage of normal cell regeneration, inhibition of damage cell leading to apoptotic cell death, suppression of cell contact inhibition, and induction of inflammation through direct activation of AhR, epidermal growth factor receptor, and nuclear factor- $\kappa$ B signaling pathways [34–36].

Many natural dietary compounds in fruits, vegetables, medicinal plants, and derivatives have been isolated and exhibit health-promoting properties. Natural dietary compounds acting as chemopreventive agents for disease have been characterized by a large number of investigational studies. Since CYPs were first discovered by Klingenberg [37] in 1958, the importance and functions of XMEs for biotransformation of xenobiotics and drugs have gradually become appreciated. Several studies also found that natural dietary compounds not only exhibited disease prevention activity but also displayed the ability to prevent and suppress xenobiotic-induced toxicity through regulated various XEMs and related signaling pathways [19–21,38]. The chemopreventive effects and molecular targets of selected natural dietary compounds in xenobiotic-induced toxicity are described below.

### 3.1. Flavonoids (Figure 3)

Flavonoids are a large family of natural polyphenolic compounds ubiquitous in fruits, vegetables, and medicinal plants. Predicated upon structural differences, flavonoids can be classified into seven groups: flavones, flavanones, flavonols,

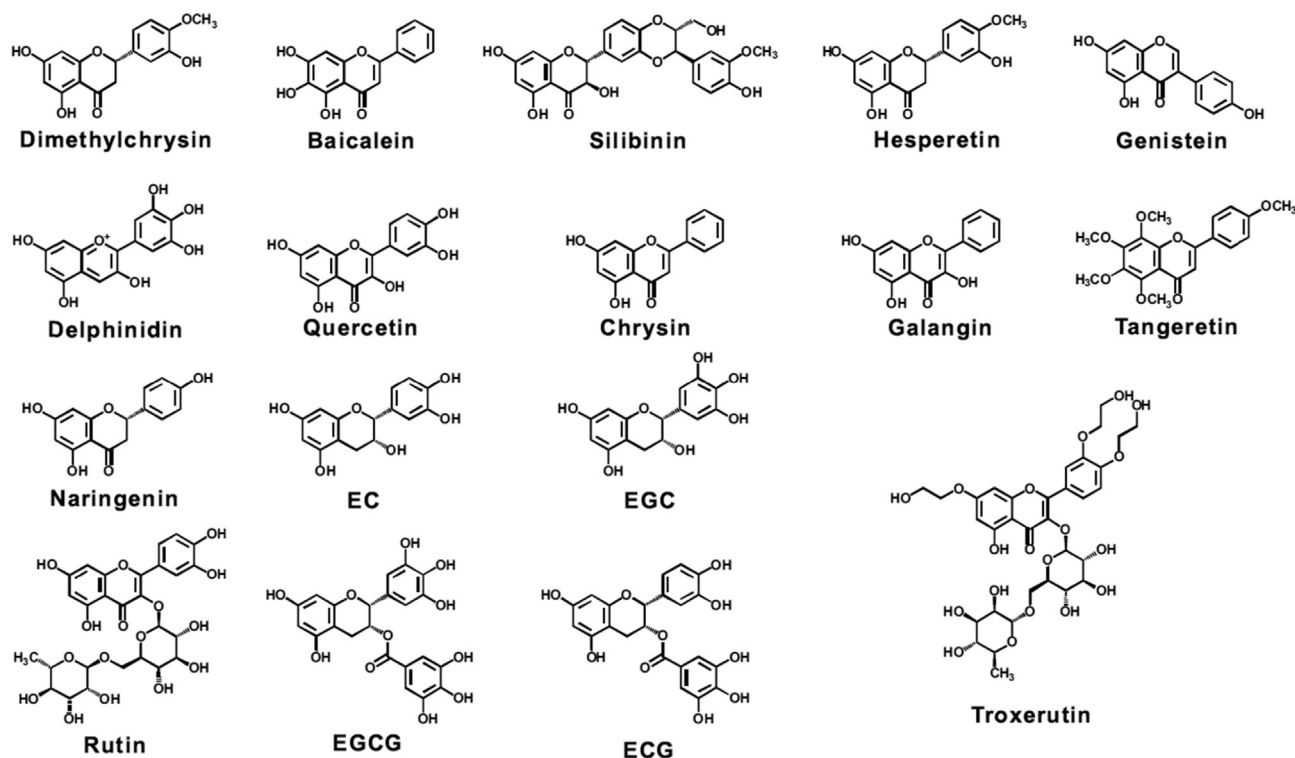


**Figure 2 – Schematic mechanism of xenobiotics-induced carcinogenesis was suppressed by natural dietary compounds. AhR = aryl hydrocarbon receptor; BaP = benzo[a]pyrene; BPDE = benzo[a]pyrene diol epoxide; CYP = cytochrome P450; ROS = reactive oxygen species; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin.**

flavanonols, isoflavones, flavanols, and anthocyanidins [39]. Previous studies suggested that flavonoids possess many beneficial human health effects, such as antioxidation, anti-inflammation and anticarcinogenesis [39].

As proposed in previous chemopreventive strategies for the suppression of xenobiotic-induced toxicity, several flavonoids exhibited the ability to downregulate CYPs expression and activity towards the decreased formation of mutagenic metabolites. For instance, dimethylchrysin (5,7-dimethoxyflavone) reduced BaP-DNA binding activity through the inhibition of CYP1A1 activity and decreased the formation of reactive metabolites [40,41]. Baicalein, silymarin, and quercetin suppressed BaP-induced toxicity by inhibiting CYPs expression and activity and increasing Phase II enzyme expression, which promotes detoxification and elimination [42–44]. Furthermore, Liu *et al.* [44] found a synergistic effect of the combination quercetin and

curcumin treatment, which suppressed BaP-induced lung carcinogenesis through the regulation of Phase I and Phase II enzymes. However, hesperetin and naringenin were demonstrated to suppress DMH-induced colorectal carcinogenesis and *N*-nitrosodiethylamine-induced hepatocarcinogenesis, respectively, attributed to the inhibition of CYPs activity and induction of GST and UGT expression [45,46]. In particular, metabolized xenobiotics are often conjugated with glucuronic acid in the liver by UGTs and returned to the intestine by biliary excretion. Glucuronide-conjugated xenobiotics excreted in the intestine can be cleaved by gut microbial  $\beta$ -glucuronidase and placed into enterohepatic recirculation, re-exposing organs to reactive metabolites and affecting xenobiotic detoxification and excretion [47–49]. Vinothkumar *et al.* [50] detected that oral administration of troxerutin significantly inhibited DMH-induced fecal microbiota  $\beta$ -glucuronidase and facilitated DMH



**Figure 3 – Chemical structure of potential flavonoids for preventing/suppressing xenobiotic-induced toxicity. EC = (–)-epicatechin; ECG = (–)-epicatechin gallate; EGC = (–)-epigallocatechin; EGCG = epigallocatechin-3-gallate.**

excretion from feces. Moreover, several studies investigated the inhibition mechanism of CYPs enzymatic activity. For example, genistein exhibited as mixed-type CYP1A1 inhibition and competitive inhibition of CYP1B1 [51]. Muto *et al.* [52] suggested that epigallocatechin-3-gallate (EGCG) significantly inhibited CYP1A1 activity by mixed-type inhibition and as CYP3A4 activity by noncompetitive inhibition. Interestingly, only a few studies have discussed the ability of nobiletin and tangeretin, the most abundant flavonoids in citrus fruits, to regulate XMEs expression and activity [53–55]. Nobiletin and tangeretin have exhibited prevention/suppression of xenobiotic- or chemically-induced carcinogenesis through tumor promotion regulation; whereas those compounds that regulate XMEs are defective.

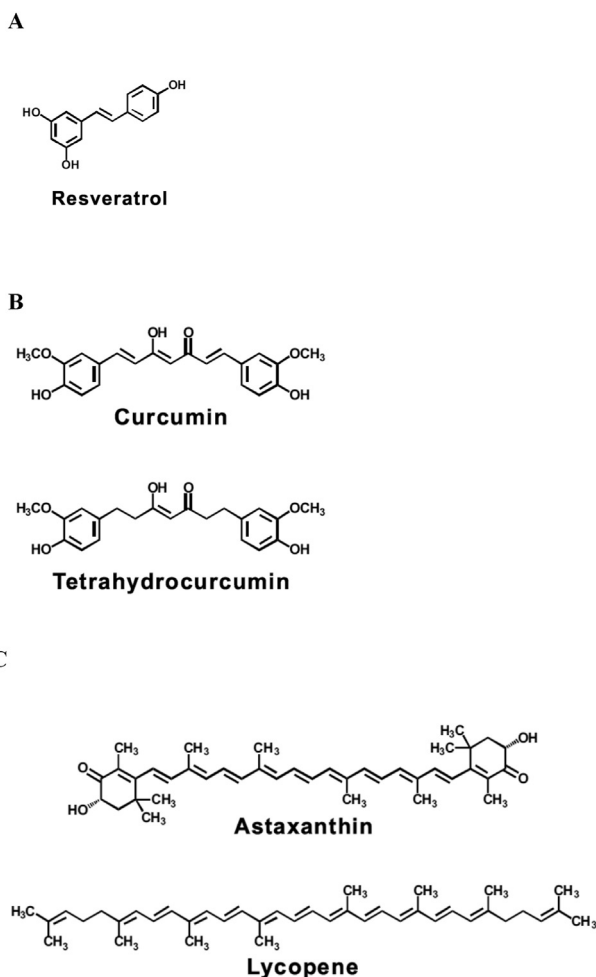
### 3.2. Stilbenes (Figure 4A)

Stilbenes, such as resveratrol and pterostilbene, are natural nonflavonoid phenolic compounds present in grapevine organs, berries, and a number of plants [56,57]. It has been suggested that resveratrol displays several beneficial human health properties, including anti-high-fat diet-induced senescence, protective mycotoxin-induced cytotoxicity, reduced carbon monoxide-induced cardiotoxicity, and suppressed xenobiotic-induced toxicity through the regulation of xenobiotic-induced AhR activation [57–62]. Recently, studies have demonstrated that resveratrol acts a chemoprotective agent against a wide range of PAH-induced toxicities, including BaP, 7,12-dimethylbenz[a]anthracene, and dibenzo[a,l]pyrene, which is mediated through reduced production of

reactive metabolites and DNA-adduct formation by specifically inhibiting CYP1A1 and 1B1 activation [40,63–65]. Additionally, resveratrol opposed PAH-induced oxidative stress through activation of the nuclear factor E2-related factor 2 (Nrf2) signaling pathway to produce antioxidation molecules, such as superoxide dismutase, glutathione, glutathione reductase, and catalase [63,65,66]. With respect to the chemoprevention of TCDD-induced toxicity, previous studies found that resveratrol exhibited as a chemopreventive agent for resisting TCDD triggered harmful effects by directly inhibiting CYP1As activity (half maximal inhibitory concentration = 1.46  $\mu$ M) and suppressed recruitment of active AhR and RNA polymerase II on promoter regions of the CYPs gene [59,61]. However, resveratrol also enabled the modulation of hepatotoxicity markers, XMEs, and oxidative stress induced by pyrogallol, which is used clinically as an anti-psoriasis treatment [67]. Based on the observation that resveratrol exhibited the ability to inhibit CYPs activity, Aldawsari *et al.* [68] and Mikstacka *et al.* [69] showed that resveratrol is a potential backbone structure for the synthesis high efficacy CYPs inhibitors. This structural insight may provide an opportunity to discovery useful chemicals for the inhibition of xenobiotics that have been converted to carcinogenic metabolites by suppressing CYPs activity.

### 3.3. Diarylheptanoids (Figure 4B)

The chemical structure of diarylheptanoids, a small class of plant secondary metabolites, consist of two aromatic rings



**Figure 4 – Chemical structure of potential (A) stilbene, (B) diarylheptanoids, and (C) carotenoids for preventing/suppressing xenobiotic-induced toxicity.**

and one seven-carbon chain. These compounds are mainly present in zingiberaceous plants, including *Curcuma longa* Linn and *Curcuma comosa* Roxb [70]. Well-known diarylheptanoids are curcumin and its major metabolite, tetrahydrocurcumin. TCDD- and PAH-enhanced AhR activation and recruitment of xenobiotic response element are well-

established mechanisms that contribute to increased CYPs expression. Choi *et al.* [71] demonstrated that curcumin not only affected TCDD-induced AhR activated and xenobiotic response element binding but also increased proteasomal degradation of AhR and Ah receptor nuclear translocator through an induction of the ROS-dependent pathway. Previous studies suggested that curcumin and tetrahydrocurcumin may have a beneficial potential for the remediation of xenobiotic-induced harmful effects through modulated CYPs expression [44,65,72,73].

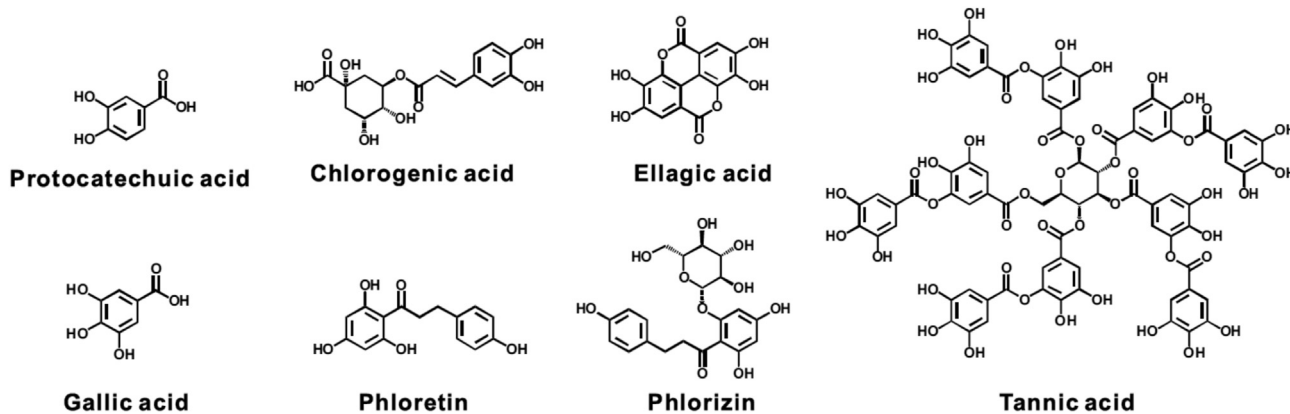
### 3.4. Carotenoids (Figure 4C)

Carotenoids are a class of natural hydrophilic colorful plant pigments present in animals, fruits, vegetables, and algae, such as lycopene,  $\beta$ -carotene, astaxanthin, and lutein. Several studies reported that lycopene and astaxanthin induced protein antioxidation and Phase II enzyme expression via the activation of the Nrf2 signaling pathway, which contributes to the suppression of 7,12-dimethylbenz[a]anthracene-induced carcinoma development and homocysteine-induced oxidative stress, respectively [74,75].

### 3.5. Phenolics (Figure 5)

Phenolics are a variety of chemicals that include mono-phenolic, diphenolic, and polyphenolic compounds. Indeed, most phenolics display antioxidant activity. The biological activity of these chemicals is not necessarily dependent on simple or complex structure. For instance, gallic acid (3,4,5-trihydroxybenzoic acid), a simple mono-phenolic phytochemical, is found in gallnuts, apple peel, grapes, and lemons. Giftson Senapathy *et al.* [76]. were reported that gallic acid significantly suppressed DMH-induced colorectal carcinogenesis through reduced CYPs expression and raised the expression level of GST, DT-diaphorase and  $\gamma$ -glutamyl transpeptidase in the liver and colonic mucosa. However, the detailed mechanisms of several natural phenolic dietary compounds that prevent/suppress xenobiotic-induced toxicity, and the harmful effects have not been clarified [74,77,78].

Despite this, these investigational research efforts may allow us to consider how to apply these commonly-found daily dietary phytochemicals for chemoprevention.



**Figure 5 – Chemical structure of potential phenolics for preventing/suppressing xenobiotic-induced toxicity.**

**Table 1 – Potential modulated targets of xenobiotics metabolized by natural dietary compounds. Natural dietary compounds regulated enzyme increased (▲) or decreased (▼) expression of mRNA/protein or enzyme activity.**

Category	Chemicals	Xenobiotics	Effect metabolizing targets	Reference no.	
Flavonoids	Dimethylchrysin	BaP	CYP1A1▼	[40,41]	
	Baicalein	BaP	CYPs, b5, CYPs▼; GST, UGT, QR▲	[42]	
	Silibinin, hesperetin	DMH	CYPs, b5, 2E1, CYPs, b5R▼; GST, UGT▲	[46,84]	
	Genistein	DMBA	CYP1A1, 1B1▼	[51]	
	Delphinidin	DBP	CYP1A1, 1A2, 1B1▼	[63]	
	Quercetin	BaP	CYPs, CYP b5▼; GST▲	[44]	
	Quercetin, rutin, chrysin	TCDD	CYP1A1▼	[61,85]	
	Galangin, tangeretin	TCDD	CYP1A1, 1A2▼	[86]	
	Troloxerutin	DMH	CYPs, CYPs, b5R▼; GST, UGT▲; β-glucuronidase, β-glucosidase (gut)▼	[50]	
	Naringenin	NDEA	CYPs▼; GST▲	[45]	
	Naringenin	DMBA	CYP1B1▼	[87]	
	EC, ECG, ECG, EGCG	BaP, PhIP, AFB <sub>1</sub>	CYPs▼	[52]	
	EGCG	Paracetamol	CYP2E1, 3A4▼; GST▲	[88]	
	Stilbene	Resveratrol	BaP	CYPs, CYP b5▼; GST▲	[40,65]
		Resveratrol	BaP, DMBA	CYP1A1/1A2, 1B1, 2B▼; NQO1▲	[78]
Resveratrol		DMBA	CYP1A1, 1B1, UGT1A1▼	[64]	
Resveratrol		DBP	CYP1A1, 1A2, 1B1▼	[63]	
Resveratrol		TCDD	CYP1A1, 1A2, 1B1▼	[59,61,89]	
Resveratrol		Pyrogallol	CYP1A2, 2E1▼; GST-ya, -yc▲	[67]	
Diarylheptanoids	Curcumin	BaP	CYPs, CYP b5▼; GST▲	[44,65]	
	Curcumin	TCDD	CYP1A1, 1B1▼	[71]	
	Curcumin, tetrahydrocurcumin	Fe-NTA	GST, NQO1▲	[73]	
Carotenoids	Astaxanthin	DMBA	CYP1A1, 1B1▼; NQO1, GST▲	[74]	
	Lycopene	Homocysteine	PON1, NQO1▲	[75]	
Phenolics	Protocatechuic acid, chlorogenic acid, tannic acid	BaP, DMBA	CYP1A1/1A2, 1B1, 2B▼	[78]	
	Protocatechuic acid	3-MC	CYP2E1▼	[77]	
	Ellagic acid	DMBA	CYP1A1, 1B1▼; NQO1, GST▲	[74]	
	Gallic acid	DMH	CYPs, b5▼; GST, DTD, GGT▲	[76]	
	Phloretin, phlorizin	TCDD	CYP1A1▼	[85]	
Crude extract	Black tea extract	DMBA	CYP b5, 1A1, 1A2, 2B▼	[90,91]	
	Red wine extract	Homocysteine	NQO1▲	[92]	
	Green/white tea extract	BaP	CYP1A1, 1B1▼; GST, QR▲	[93]	
	Green tea extract, Kava extract	TCDD	CYP1A1▼	[61]	
	Blueberry extract	DMBA	CYP1A1, 1B1▼; NQO1, GST▲	[74]	
	Chokeberry extract	NDEA	CYP1A1/1A2, 2B1, 2E1▼	[94]	
	Apple juice extract	TCDD	CYP1A1▼	[85]	
	Purple rice bran extract	Aflatoxin B1	CYP1A1, 1A2, 3A▼; GST, UGT▲	[82]	
	Black soybean seed coat Extract	BaP	CYP1A1▼; GSTs▲	[95]	
	Seaweed extract	TCDD	CYP1A1 activity▼	[83]	

3-MC = 3-methylcholanthrene; AFB<sub>1</sub> = aflatoxin B<sub>1</sub>; BaP = benzo[a]pyrene; CYP = cytochrome P450; DBP = dibenzo[a,l]pyrene; DMBA = 7,12-dimethylbenz[a]anthracene; DMH = 1,2-dimethylhydrazine; EC = (-)-epicatechin; ECG = (-)-epicatechin gallate; EGC = (-)-epigallocatechin; EGCG = epigallocatechin-3-gallate; Fe-NTA = ferric nitrotriacetate; GSTs = glutathione S-transferases; LXR = liver X receptor; NDEA = N-nitrosodiethylamine; QR = quinone reductase; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; UGTs = UDP-glucuronosyl-transferase.

### 3.6. Crude extracts

Beneficial phytochemicals can be purified from fruits, vegetables, medicinal plants and crude extracts (complex composition) from the same sources. Moreover, a number of studies have shown that when two or more phytochemicals are combined as chemopreventive agents, such as curcumin combined with silymarin and EGCG combined with cranberry proanthocyanidins, a synergistic effect is observed that enhances the biological activity or preventive effect [79,80]. Sandur *et al.* [81] found that natural curcuminoid extracts from *Curcuma longa* exhibited more anti-inflammatory and antiproliferative activities than pure curcumin, curcumin derivatives and reconstituted curcuminoids. Recently, Suwanakul *et al.* [82] and Ilavarasi *et al.* [83] reported that extracts of purple rice bran and seaweed had the ability to attenuate the AFB1-induced initiation stage of hepatocarcinogenesis through alteration of XMEs and blockage of TCDD-induced toxicity, respectively.

## 4. Conclusion

Industrial pollution and food contamination have become increasingly serious due to adverse human health effects. This review article discusses the chemopreventive activity of various natural dietary compounds to prevent/suppress xenobiotics-induced toxicity (Table 1). These natural dietary compounds exhibited various biological functions for the regulation of xenobiotics metabolism, xenobiotic-induced harmful effects, and injury. Metabolism of xenobiotics and the regulation of xenobiotic-related signaling pathways are key factors for the activation of xenobiotic toxicity. Metabolism of xenobiotics and the first-pass effect are not only carried out in the liver but also in the intestines by gut mucosa and microbiota. The chemopreventive effects of natural dietary compounds discussed in this article are purported to occur by the regulation of XMEs expression and activity, reduction in the level of reactive metabolites and inhibition of xenobiotic-induced multiple signaling pathways.

## Conflicts of interest

All authors have no conflicts of interest to declare.

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