Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Review Article

Chemopreventive effect of natural dietary compounds on xenobiotic-induced toxicity

Jia-Ching Wu [a], *Ching-Shu Lai* [b], *Mei-Ling Tsai* [b], *Chi-Tang Ho* [c], *Ying-Jan Wang* [a,d,e,*], *Min-Hsiung Pan* [e,f,g,*]

[a] *Department of Environmental and Occupational Health, National Cheng Kung University Medical College, Tainan, Taiwan*
[b] *Department of Seafood Science, National Kaohsiung Marine University, Kaohsiung, Taiwan*
[c] *Department of Food Science, Rutgers University, New Brunswick, NJ, USA*
[d] *Department of Biomedical Informatics, Asia University, Taichung, Taiwan*
[e] *Graduate Institute of Clinical Medicine, Taipei Medical University, Taipei, Taiwan*
[f] *Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan*
[g] *Institute of Food Science and Technology, National Taiwan University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Received 18 September 2016
Received in revised form
20 October 2016
Accepted 21 October 2016
Available online 7 December 2016

Keywords:
chemoprevention
environmental pollutants
metabolism
phytochemicals
xenobiotics

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.

* *Corresponding authors*. Department of Environmental and Occupational Health, National Cheng Kung University Medical College, 138 Sheng-Li Road, Tainan 70428, Taiwan (Y.-J. Wang); Institute of Food Science and Technology, National Taiwan University, Number 1, Section 4, Roosevelt Road, Taipei 10617, Taiwan (M.-H. Pan).
E-mail addresses: yjwang@mail.ncku.edu.tw (Y.-J. Wang), mhpan@ntu.edu.tw (M.-H. Pan).
http://dx.doi.org/10.1016/j.jfda.2016.10.019

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_1 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