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Mini Review

Herbal bioactivation, molecular targets and the toxicity relevance

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ABSTRACT

There have been increasing reports on the adverse reactions associated with herbal consumption. For many of these adverse reactions, the underlying biochemical mechanisms are unknown, but bioactivation of herbal compounds to generate reactive intermediates have been implicated. This minireview updates our knowledge on metabolic activation of herbal compounds, molecular targets and the toxicity relevance. A number of studies have documented that some herbal compounds can be converted to toxic or even carcinogenic metabolites by Phase I [e.g. cytochrome P450s (CYPs)] and less frequently by Phase II enzymes. For example, aristolochic acids (AAs) in *Aristolochia* spp, which undergo reduction of the nitro group by hepatic CYP1A1/2 or peroxidases in extrahepatic tissues to generate highly reactive cyclic nitrenium ions. The latter can react with macromolecules (DNA and protein), resulting in activation of *H-ras* and *myc* oncogenes and gene mutation in renal cells and finally carcinogenesis of the kidneys. Teucrin A and teuchamaedryn A, two diterpenoids found in germander (*Teuchrium chamaedrys*) used as an adjuvant to slimming herbal supplements that caused severe hepatotoxicity, are converted by CYP3A4 to reactive epoxide which reacts with proteins such as CYP3A and epoxide hydrolase and inactivate them. Some naturally occurring alkenylbenzenes (e.g. safrole, methyleugenol and estragole) and flavonoids (e.g. quercetin) can undergo bioactivation by sequential 1-hydroxylation and sulfation, resulting in reactive intermediates capable of forming DNA adducts. Extensive pulegone metabolism generated *p*-cresol that is a glutathione depletory. The hepatotoxicity of kava is possibly due to intracellular glutathione depletion and/or quinone formation. Moreover, several herbal compounds including capsaicin from chili peppers, dially sulfone in garlic, methysticin and dihydromethysticin in kava, oleuropein in olive oil, and resveratrol found in grape seeds are mechanism-based (suicide) inhibitors of various CYPs. Together with advances of proteomics, metabolomics and toxicogenomics, an integrated systems toxicological approach may provide deep insights into mechanistic aspects of herb-induced toxicities, and contribute to bridging the relationships between herbal bioactivation, protein/DNA adduct formation and the toxicological consequences.

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Contents

Abbreviations: AA, aristolochic acids; CYP, cytochrome P450; GSH, glutathione; GST, glutathione *S*-transferase; HPA, hydroxyphenylacetaldehyde; K_i, apparent inhibition constant; SULT, sulfotransferase; UGT, uridine diphosphate glucuronosyltransferase.

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1. Introduction

A number of clinical drugs can be metabolically activated *in vitro* and/or *in vivo* primarily through Phase I enzymes to chemically reactive and electrophilic metabolites [1–5]. The resulting electrophiles, if not quenched by low molecular weight endogenous nucleophiles such as glutathione (GSH), can result in covalent adducts to cellular proteins or DNA, potentially leading to enzyme inactivation, formation of immunogenic species, cell death, or oncogene activation. The toxicological consequences of exposure to reactive drug metabolites range from mild inflammation to organ failure, anaphylaxis, carcinogenesis, and death [1–4,6]. A well-known example is acetaminophen, a very commonly used over-the-counter analgesic and antipyretic agent, undergoing hepatic bioactivation at overdose to form excessive highly reactive and hepatotoxic intermediate *N*-acetyl-*p*-benzoquinoneimine [7,8]. *N*-Acetyl-*p*-benzoquinoneimine can covalently bind to a number of hepatic proteins and consequently induce oxidative stress, apoptosis, disruption of calcium homeostasis, activation of Kuppfer cells, and finally centrilobular hepatic necrosis [8].

Recently, there has been a steady increase in the market sales and research activities of herbal medicines. They are commonly used in a hope of promoting health and treating various diseases such as colds, inflammation, insomnia, depression, heart diseases, diabetes, cancer, acquired immunodeficiency syndrome, and liver diseases [9]. The 2002 National Health Interview Survey of the United States ($n = 5456$) indicates that 19% of American adults used herbal supplements within the past year [10]. In a study including 61,587 individuals aged 50–76 years in the United States, one third of the population claimed that they used an herbal product [11]. Much research has been made to the biochemical, pharmacological and toxicological profiling of commonly used herbal medicines. Market-driven information on natural products is widespread and has further fostered their use in daily life. However, there is no universal regulatory system that insures the safety and activity of herbal medicines in most countries and evidence-based verification of the efficacy and safety of herbal medicines is still lacking [12,13].

In contrast to synthetic drugs, herbal medicines have often been claimed to be non-toxic or generally regarded as safe, because of their natural origin and traditional use in folk medicines. However, safety concerns arise due to organ toxicity, adulteration, contamination, contents of heavy metals, herb–drug interactions, or poor quality control [12,14–16]. Administration of herbal medicines has been associated with toxicities of the heart, liver, blood, kidney, central nervous system, and skin and less frequently carcinogenesis [12,14,15]. Adverse reactions and poisoning events associated with the use of herbal medicines have been increasingly reported. Furthermore, adulteration of herbal remedies by surreptitious addition of synthetic drugs and other potentially toxic compounds has been documented [14,15]. Moreover, co-administration of herbal medicines with conventional drugs, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin), gives rise to the potential of harmful herb–drug interactions which may cause altered drug response and toxicity [17–21]. Like synthetic drugs, herbal constituents often undergo Phase I and Phase II reactions to form nontoxic metabolites which are excreted into the feces and urine [6,22,23], but the formation of reactive and potentially toxic metabolites is possible and this has important toxicological implications. The current paper updates our knowledge on herbal bioactivation, molecular targets and the toxicity relevance.

2. Herbal compounds undergoing bioactivation associated with clinical toxicity

2.1. Aristolochic acids

Aristolochic acids (AAs) are a group of structurally related nitrophenanthrene carboxylic acids present in several commonly used Chinese herbal medicines including *Aristolochia fangchi* (Guang Fang Ji or Fang Ji), *A. debilis*, *A. sinarum* or *A. contorta* (Ma Dou Ling, Qing Mu Xiang, or Tian Xuan Teng), *A. manshuriensis* (Mu Tong), and *Asarum sieboldii* (Xi Xin). The predominant AAs are AAI (8-methoxy-6-nitro-phenanthro-(3,4-*d*)-1,3-dioxolo-5-carboxylic acid) and its 8-demethoxylated form AAII (6-nitro-phenanthro-(3,4-*d*)-1,3-dioxolo-5-carboxylic acid). AAs present in the herbal supplement are responsible for AA nephropathy (AAN) first reported in young Belgian women that is characterized by unique proximal tubule atrophy and tubulointerstitial fibrosis and development of urothelial cancer in about half of these patients [24–27]. The first symptom of AAN is the excretion of low-molecular-weight proteins in urine followed by a rapidly progressive renal deterioration, while chronic AAN is characterized by extensive interstitial fibrosis with atrophy and loss of renal tubules [25]. The lesions of chronic AAN are mainly located in the cortex involving proximal tubular epithelial cells, whereas glomeruli are relatively spared with minimal inflammation. Approximately 200 cases of AAN have been reported worldwide, with many of them developing renal failure and needing renal transplant [24]. AAs in *A. clematitis* grown in the wheat fields in the endemic region are also responsible for Balkan endemic nephropathy, occurring exclusively in residents of farming villages in the Danube river basin [28]. The nephrotoxic and carcinogenic effects of AAs have been established in animal models and similar toxicities were observed in AAN patients [24,26]. A recent case-control study involving 4594 case patients in Taiwan has demonstrated that intake of a total (accumulated) dose of AAs greater than 150 mg from AA-containing herbal medicines (equivalent to >60 g Mu Tong belonging to the *Akebia* species) during a period of at least 4 years is independently associated with an increased risk for occurrence of urinary tract cancer with an odds ratio (OR) of 1.6 [29]. When the accumulated dose of AAs was >500 mg, the OR was 2.0.