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Review

Protective effect of curcumin against heavy metals-induced liver damage

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ABSTRACT

Occupational or environmental exposures to heavy metals produce several adverse health effects. The common mechanism determining their toxicity and carcinogenicity is the generation of oxidative stress that leads to hepatic damage. In addition, oxidative stress induced by metal exposure leads to the activation of the nuclear factor (erythroid-derived 2)-like 2/Kelch-like ECH-associated protein 1/antioxidant response elements (Nrf2/Keap1/ARE) pathway. Since antioxidant and chelating agents are generally used for the treatment of heavy metals poisoning, this review is focused on the protective role of curcumin against heavy metals liver injury. Curcumin has shown, in clinical and preclinical studies, numerous biological activities including therapeutic efficacy against various human diseases and anti-hepatotoxic effects against environmental or occupational toxins. Curcumin reduces the hepatotoxicity induced by arsenic, cadmium, chromium, copper, lead and mercury, prevents histological injury, lipid peroxidation and glutathione (GSH) depletion, maintains the liver antioxidant enzyme status and protects against mitochondrial dysfunction. The preventive effect of curcumin on the noxious effects induced by heavy metals has been attributed to its scavenging and chelating properties, and/or to the ability to induce the Nrf2/Keap1/ARE pathway. However, additional research is needed in order to propose curcumin as a potential protective agent against liver damage induced by heavy metals.

1. Introduction

Heavy metals are commonly defined as those metallic elements with high atomic weight such as arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb) and mercury (Hg) that may damage living organisms at low concentrations and that tend to accumulate in the food chain (IUPAC, 2002; Stummann et al., 2008). They enter to the human body by ingestion, inhalation or through the skin and their presence may cause serious toxicity (Jarup, 2003; Alissa and Ferns, 2011). Sources of exposure to these metals include occupational exposure and environmental contamination from industrial production with poor emission and disposal practices (Ahalya et al., 2003; CDC, 2009; Nobuntou et al., 2010; Martinez-Zamudio and Ha, 2011). The principal metal emission sources come from the following industries: petrochemical, extractive, metallurgic (foundry and metallurgy), mechanic (galvanic processes, painting), chemical (paints, plastic materials) and ceramic (Ziemacki et al., 1989). Exposure to compounds containing heavy metals is known to be toxic, mutagenic, teratogenic and carcinogenic to human beings and diverse animals (Fig. 1) (Jomova and Valko, 2011).

Toxic manifestations of these metals are attributed primarily to oxidative stress (Flora et al., 2008). Oxidative stress is defined as an imbalance between production of free radicals and reactive metabolites, so-called oxidants, and their elimination by antioxidant systems. This imbalance leads to damage of important biomolecules and organs with potential impact on the whole organism (Duracková, 2010). The associated DNA, protein, and lipid damage may underlie liver diseases as a key pathophysiological force. The above may also be related to chronic liver injury, hepatic inflammation, fibrosis and to hepatocellular carcinoma (Tanikawa and Torimura, 2006; Vera-Ramirez et al., 2013). The liver is an important organ to be considered when the effects of pollutants are investigated, since this organ plays a central role in the metabolism and detoxification of biological substances. Also, most of the substances absorbed by the intestine passes first through the liver where toxins and heavy metals may accumulate (Saïdi et al., 2013).

Chromium and copper undergo redox-cycling reactions, while the primary route for the toxicity of arsenic, cadmium, lead and mercury is the depletion of glutathione (GSH) and bonding to sulfhydryl groups of proteins. But the unifying factor in determining toxicity and carcinogenicity for all these metals is the generation of reactive oxygen species (ROS) such as the hydroxyl radical

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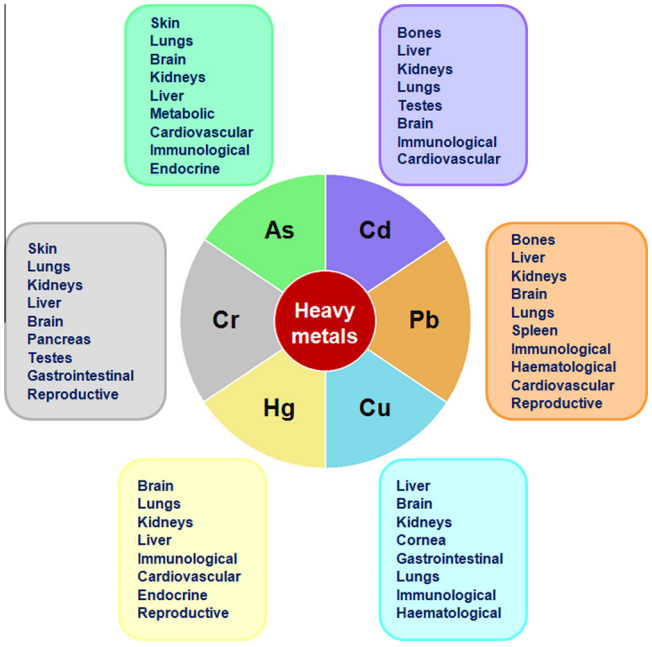

Fig. 1. Main organs and systems affected by environmental or occupational exposure to heavy metals.

(HO·), superoxide radical ($O_2^{\cdot-}$) or hydrogen peroxide (H_2O_2). The excessive ROS generation overwhelms the cell's capacity to maintain a reduced state (Ercal et al., 2001; Valko et al., 2005, 2006). Oxidative stress induced by metal exposure leads to the activation of the nuclear factor (erythroid-derived 2)-like 2/Kelch-like ECH-associated protein 1/antioxidant response elements (Nrf2/Keap1/ARE) pathway (Rubio et al., 2010), through the activation of numerous transducers such as mitogen-activated protein kinases (MAPK, ERK, p38), protein kinase C (PKC), and phosphatidylinositol 3 kinase (PI3K) which phosphorylate both Nrf2 and Keap1 (Kang et al., 2000; Yu et al., 2000; Kong et al., 2001; Huang et al., 2002). Also, reactive electrophiles directly attack the sulfhydryl-rich Keap1 protein, leading to conformational changes in their structure (Dinkova-Kostova et al., 2002). The cumulative impact of these events is the stabilization and activation of Nrf2 and transcriptional upregulation of antioxidant genes protecting cells from heavy metal toxicity and carcinogenesis from ROS and electrophiles (Kaspar et al., 2009; Kensler et al., 2007; Park and Seo, 2011; Simmons et al., 2011; Lau et al., 2013).

Hence application of an external source of antioxidants may offer some protection against oxidative stress. The term antioxidant refers to a wide spectrum of compounds, which are able to donate electrons and neutralize free radicals, resulting in the prevention of cell injuries (Lobo et al., 2010; Saeidnia and Abdollahi, 2013). In consequence, the search for effective, nontoxic, natural compounds with antioxidant activity has been intensified in recent years (Pérez-De la Cruz et al., 2006; Tapia et al., 2012; Negrette-Guzmán et al., 2013). In particular, curcumin (a dietary spice isolated from *Curcuma longa*) has become one of the most cited antioxidants due to the multitude of beneficial health effects that have been studied and established by the scientific community (Kumar and Maliakel, 2007). However, there is little information about the protective effects of curcumin against noxious effects caused by exposure to heavy metals in murine models, including those related to hepatic damage. Thus, the purpose of this paper is to review scientific evidence regarding oxidative stress, Nrf2, and hepatotoxicity induced by heavy metals, as well as the hepatoprotective effects of curcumin.

2. Curcumin

Curcumin or diferuloylmethane (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is a hydrophobic polyphenol compound naturally concentrated in the rhizome of the herb *Curcuma longa*, commonly known as turmeric (Altenburg et al., 2011). Traditionally, turmeric has been used in therapeutic preparations against biliary disorders, anorexia, coryza, herpes zoster, acne, cough, urinary tract diseases, diabetic wounds, hepatic disorder, rheumatism and sinusitis (Ammon and Wahl, 1991; Chainani-Wu, 2003; Chattopadhyay et al., 2004). At present, turmeric is used as a dietary spice, and by the food industry as additive, flavoring, preservative and as coloring agent in foods and textiles (FAO, 2004; Aggarwal et al., 2007; Basnet and Skalko-Basnet, 2011). Curcumin is a major component of turmeric and it has been shown to exhibit several activities including antioxidant (Iqbal et al., 2003; Surh, 2003; Dairam et al., 2008; Al-Jassabi et al., 2012), antimicrobial (Çıkrıkçı et al., 2008; Tajbakhsh et al., 2008), anti-inflammatory (Jurenka, 2009; Bereswill et al., 2010), antiviral (Barthelemy et al., 1998; Kutluay et al., 2008) and anticarcinogenic (Aggarwal et al., 2003, 2006; Wang et al., 2009; Youns et al., 2010; Das and Vinayak, 2012; Huang et al., 2013).

Curcumin and turmeric products have been characterized as safe by the Food and Drug Administration (FDA) in the USA, the Natural Health Products Directorate of Canada and the Joint FAO/WHO Expert Committee on Food Additives of the Food and Agriculture Organization/World Health Organization (NCI, 1996). Over 2400 metric tons of turmeric are imported into the USA (Sharma et al., 2005). The average intake of turmeric in the Indian diet is approximately 2–2.5 g for a 60 kg individual, which corresponds to a daily intake of approximately 60–100 mg of curcumin (Shah et al., 1999; Lao et al., 2006; Tayyem et al., 2006). In addition, curcumin has entered scientific clinical trials at the phase I, II and III levels for its therapeutic efficacy, even at doses as high as 12 g/day during 3 months (Cheng et al., 2001; Hsu and Cheng, 2007; NIH, 2007; Dhillon et al., 2008). However, curcumin exhibits poor bioavailability and the hydrophobic nature of curcumin is one of the main reasons for this poor water-solubility/suspension capacity (Anand et al., 2008; Kidd, 2009). To improve the solubility, bioavailability and bioactivity of curcumin, numerous approaches have been undertaken. These include (1) curcumin analogues: natural analogues from turmeric such as demethoxycurcumin, bisdemethoxycurcumin or tetrahydrocurcumin (Grynkiewicz and Ślifirski, 2012; Lin et al., 2012; Bhullar et al., 2013), natural analogues occurring in nature, like cassumunins or dehydrozyngerone (Nagano et al., 1997; Yogosawa et al., 2012) and synthetic analogues (Al-Hujaily et al., 2011; Chen et al., 2011; Yadav et al., 2012b), and (2) curcumin formulations: adjuvants (Sehgal et al., 2011; Banji et al., 2013), nanoparticles (Gangwar et al., 2012; Liu et al., 2012), liposomes (Taylor et al., 2011; Dhule et al., 2012), micelles (Gong et al., 2013; Liu et al., 2013a,b) and phospholipid complexes (Lin et al., 2009).

2.1. Therapeutic potential

Despite its low bioavailability, numerous clinical studies have suggested that curcumin has therapeutic efficacy against various human diseases (Gupta et al., 2013), including cancer (Garcea et al., 2004, 2005), diabetes (Balasubramanyam et al., 2003), Alzheimer's disease (Ringman et al., 2012), familial adenomatous polyposis (Cruz-Correa et al., 2006), inflammatory bowel disease (Holt et al., 2005), rheumatoid arthritis (Deodhar et al., 1980; Chandran and Goel, 2012), hypercholesterolemia (Soni and Kuttan, 1992), liver injury (Kim et al., 2013), atopic asthma (Kim et al., 2011), psoriasis (Kurd et al., 2008), osteoarthritis (Belcaro et al., 2010), neurological diseases (Sanmukhani et al., 2013),

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