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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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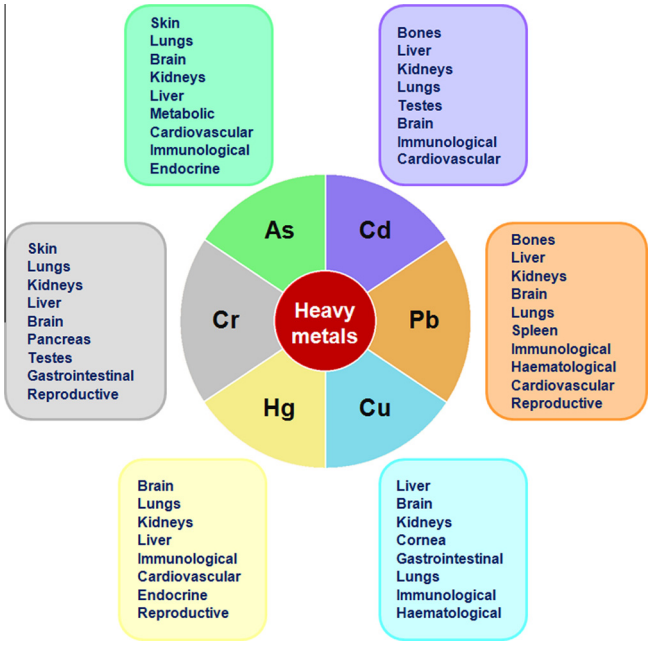

Fig. 1. Main organs and systems affected by environmental or occupational exposure to heavy metals.

(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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chronic anterior uveitis (Lal et al., 1999; Allegri et al., 2010), human immunodeficiency virus infection (James, 1994) and cystic fibrosis (Henke, 2008). Enhancing curcumin's bioavailability in the near future is will enable this promising natural product to be investigated as a therapeutic agent for treatment of human disease (Anand et al., 2007).

2.2. Antioxidant properties

Curcumin is a bis-α,β-unsaturated β-diketone and the β-diketo moiety undergoes keto-enol tautomerism (Fig. 2). Under acidic and neutral conditions, the bis-keto form predominates, whereas the enol form is found above pH 8 (Wang et al., 1997; Jovanovic et al., 1999). The enol form makes an ideal chelator of positively charged metals (Fig. 3), which are often found in the active sites of target proteins (Baum and Ng, 2004). Curcumin chelating potential of the type 1:1 and 1:2 have been reported for several metal cations (Gupta et al., 2011). The presence of the phenolic, β-diketone, as well as the methoxy groups contribute to the free-radical-scavenging activity of curcumin (Esatbeyoglu et al., 2012). Curcumin has demonstrated scavenging activity against a variety of ROS, including $O_2^{\cdot-}$, $HO^{\cdot}$, peroxyl radical ($ROO^{\cdot}$), nitrogen dioxide radical ($NO_2^{\cdot}$), 1,1-diphenyl-2-picryl-hydrazyl free radical ($DPPH^{\cdot}$), 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) and Q5 *N,N*-dimethyl-*p*-phenylenediamine dihydrochloride ($DMPD^{\cdot+}$) radical (Reddy and Lokesh, 1994; Fujisawa et al., 2004; Ak and Gülcin, 2008; Trujillo et al., 2013). On the other hand, curcumin may protect cells from oxidative stress indirectly by inducing Nrf2 (Fig. 4) (Tapia et al., 2012, 2013; Correa et al., 2013; González-Reyes et al., 2013). Nrf2 belongs to the CNC (cap 'n' collar) family of b-Zip transcription factors, together with p45 NF-E2, Nrf1 and Nrf3, and acts through the formation of a heterodimer with one of the small Maf proteins (Motohashi et al., 2002; Motohashi and Yamamoto, 2004). Nrf2 is a redox-sensitive transcription factor which, under basal conditions, is bound to its repressor Keap1 in the cytoplasm (Copple et al., 2008; Singh et al., 2010; Uruno and Motohashi, 2011; Buelna-Chontal and Zazueta, 2013). Keap1 serves as an adaptor protein between Nrf2 and the Cullin3-based E3-ligase ubiquitylation complex, with its N-terminal BTB leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome (Cullinan et al., 2004; Sinha et al., 2013). Curcumin contains two Michael reaction acceptor functionalities in its molecule that can modify the cysteine residues of Keap1 and promote a conformational change in the Nrf2-Keap1 complex by Michael addition to the thiols in Keap1 (Dinkova-Kostova et al., 2001; Balogun et al., 2003), thereby releasing Nrf2 and allowing it to translocate into the nucleus and bind as a heterodimer to ARE in DNA to initiate target gene expression and increase the expression of phase II enzymes (Dinkova-Kostova and Talalay, 1999, 2008; Hong et al., 2005). Dinkova-Kostova and Talalay, 1999 identified that the presence of keto-enol functionality and the aromatic ring system must be present to provide Nrf2 inducer activity to curcumin. In this way, curcumin upregulates genes that contain AREs in their promoters, including superoxide dismutase (SOD), catalase (CAT) (Shukla et al., 2003), glutathione peroxidase (GPx) (Piper et al., 1998), glutathione reductase (GR), glutathione-S-transferase (GST) (Oetari et al., 1996), heme oxygenase 1 (HO-1) (Balogun et al., 2003), NADPH:quinone oxidoreductase 1 (NQO1), glutamate

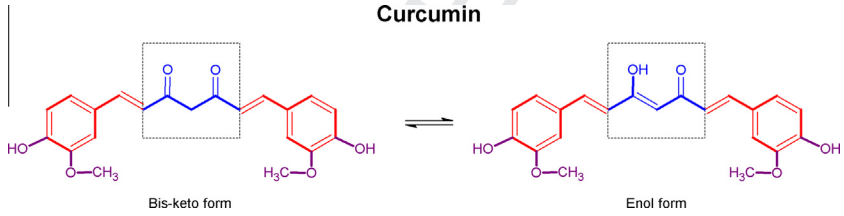

Fig. 2. Curcumin keto-enol tautomerism. The presence of the phenolic, β-diketone, as well as the methoxy groups contributes to the free-radical-scavenging activity of curcumin. The enol form makes an ideal chelator of positively charged metals. While the presence of keto-enol functionality and the aromatic ring system must be present to provide Nrf2 inducer activity to curcumin.

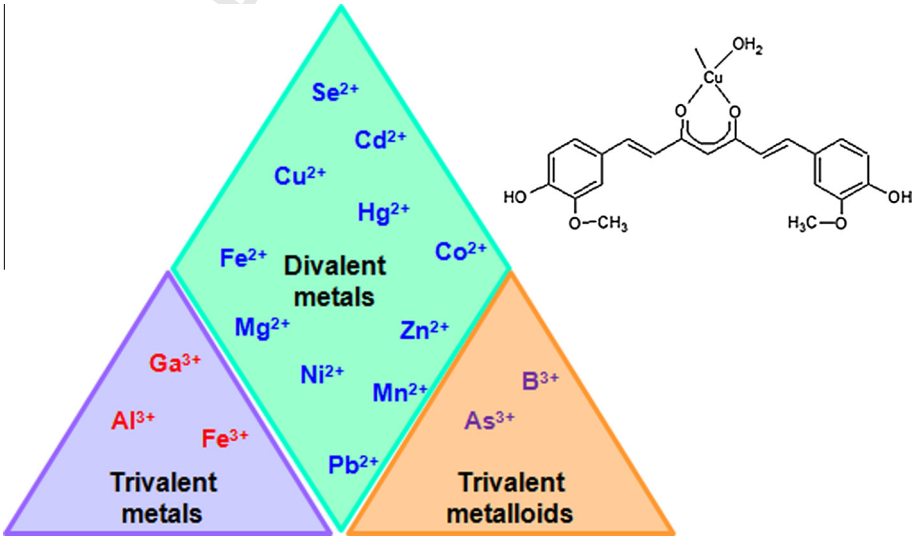

Fig. 3. Curcumin chelating potential for metallic and semi metalic cations.

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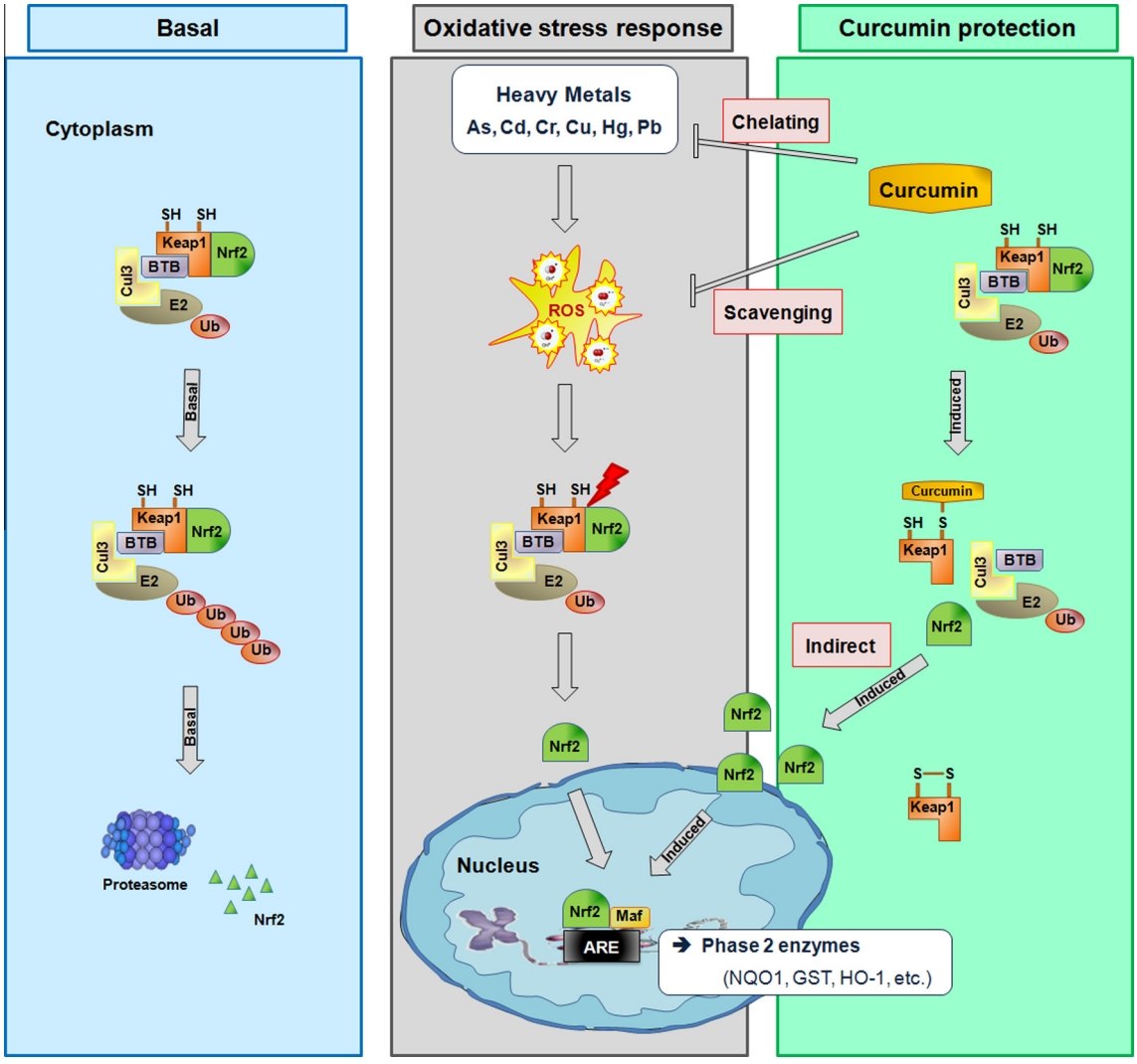

Fig. 4. General scheme for the induction of gene expression through Keap1/Nrf2/ARE pathway. Nrf2 is a redox-sensitive transcription factor which, under basal conditions, is bound to its repressor Keap1 in the cytoplasm. Keap1 serves as an adaptor protein between Nrf2 and the Cul3 complex, leading to ubiquitylation of Nrf2 and subsequent degradation by the 26S proteasome. Oxidative stress induced by heavy metals exposure leads to the activation of the Nrf2/Keap1/ARE pathway. Protective effects of curcumin were attributed to its ability to scavenge free radicals, to act as an chelating agent and/or its capacity to induce detoxifying enzymes by the up regulation of Keap1/Nrf2/ARE pathway. Reactive oxygen species (ROS), Kelch-like ECH-associated protein 1 (Keap1); nuclear factor (erythroid-derived 2)-like 2 (Nrf2); antioxidant responsive element (ARE); cullin-3 (Cul3); NADPH: quinone oxidoreductase 1 (NQO1); glutathione-*S*-transferase (GST); heme oxygenase-1 (HO-1).

cysteine ligase catalytic (GCLC) and regulatory (GCLM) subunits (Zhao et al., 2013) and aldose reductase (Kang et al., 2008).

Curcumin natural analogues from turmeric, other naturally-occurring analogues, synthetic analogues, and curcumin formulations exhibit different antioxidant activities in several in vitro and in vivo models (Anand et al., 2008). Curcumin was more potent than demethoxycurcumin and bisdemethoxycurcumin (Ahsan et al., 1999; Jeong et al., 2006). However tetrahydrocurcumin, one of the major metabolites of curcumin, exhibits greater antioxidant potential than curcumin in most models (Somparn et al., 2007; Wongeakin et al., 2009). On the other hand, the information about the antioxidant potential of curcumin in comparison with other naturally-occurring analogues is scarce; as a result, it is necessary to perform comparative studies about it. In this respect, caffeic acid, ferulic acid and capsaicin have shown a higher relative antioxidant potency than curcumin, but not eugenol or dehydrozyngerone in some models (Sharma, 1976; Joe and Lokesh, 1994; Rajakumar and Rao, 1994), indicating that an ortho-methoxylated phenolic chromophore is necessary for antioxidant activity. Finally, molecular design and synthesis of synthetic curcumin analogues have improved the antioxidant activity in contrast with curcumin in many experimental conditions (Wright, 2002; Selvam et al., 2005; Youssef et al., 2007).

2.3. Anti-hepatotoxic properties

The anti-hepatotoxic effects of curcumin against environmental or occupational toxins are well documented, and they have been attributed to its intrinsic antioxidant, anti-inflammatory, anti-cholestatic, anti-fibrogenic and anti-carcinogenic properties. Thus, curcumin has shown to protect the liver against injury and fibrogenesis by suppressing hepatic inflammation, attenuating hepatic oxidative stress (Mathuria and Verma, 2007), increasing expression of the xenobiotic detoxifying enzymes (Iqbal et al., 2003; Hemeida and Mohafez, 2008; Farghaly and Hussein, 2010), inhibiting hepatic stellate cells activation (Zheng et al., 2007; Priya and Sudhakaran, 2008) and supporting the mitochondrial function (Subudhi et al., 2008). In addition, curcumin has shown

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Table 1
Curcumin hepatoprotective properties.

Properties	Outcome	References
Antihepatotoxic	↓ Structural alterations ↓ Activities of ALT, AST, ALP, ACP, LDH and γ-GT ↓ Total bilirubin ↑ Serum proteins	Kaur et al. (2006), Dattani et al. (2010), Nayak and Sashidhar (2010), Naik et al. (2011)
Antioxidant	↓ Lipid and protein oxidation ↓ ROS y RNS ↑ Expression and activities of SOD, CAT, GPx, GR, GST, HO-1, NQO1 and GCL ↑ GSH ↑ Induction of Nrf2 ↑ Activity of cytochrome P450 ↑ Mitochondrial function ↑ Activities of SDH and ATPase	Sugiyama et al. (2006), Wei et al. (2006), Farombi et al. (2008); Srinivasan et al. (2008), Ramirez-Tortosa et al. (2009), Bao et al. (2010), El-Agamy (2010), Yousef et al. (2010), Guangwei et al. (2010), Subudhi and Chainy (2010), Tokaç et al. (2013)
Anti-cholestatic	↑ Serum cholesterol ↑ Bile acids ↑ Direct and/or total bilirubin	Ahmed and Mannaa (2004), Said and El-Agamy (2009)
Antifibrotic	↓ Activation of HSC ↑ Activation of PPAR-γ ↓ Expression of PDGF, EGF, TGF-β and their receptors ↓ Collagen αI(I), fibronectin, TIMP-1 and α-SMA	Fu et al. (2008), Lin and Chen (2008) Pinlaor et al. (2010) Vizzutti et al. (2010)
Anti-inflammatory	↓ Activation of NF-κB ↓ Expression of TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IFN-γ, MCP-1 and ICAM-1 ↓ Expression of COX-2, iNOS ↓ Expression of TLR2 and TLR4	Nanji et al. (2003), Leclercq et al. (2004), Reyes-Gordillo et al. (2007), Tu et al. (2012)
Antihepatocarcinogenic	↑ Apoptosis ↓ Expression of p53 and $p21^{ras}$ ↓ Expression of PCNA, $p34^{cdc2}$ and cyclin E	Chuang et al. (2000a,b), Cao et al. (2007), Qian et al. (2011), Wang et al. (2011)

Alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP); acid phosphatase (ACP); lactate dehydrogenase (LDH); γ-glutamyl transferase (γ-GT); reactive oxygen species (ROS); reactive nitrogen species (RNS); superoxide dismutase (SOD); catalase (CAT); glutathione peroxidase (GPx); glutathione reductase (GR), glutathione-*S*-transferase (GST); heme oxygenase-1 (HO-1); NADPH:quinone oxidoreductase 1 (NQO1); glutamate–cysteine ligase (GCL); glutathione (GSH); nuclear factor (erythroid-derived 2)-like 2 (Nrf2); succinate dehydrogenase (SDH); adenosine triphosphatase (ATPase); hepatic stellate cells (HSC); peroxisome proliferator-activated receptor-γ (PPAR-γ); platelet-derived growth factor (PDGF); epidermal growth factor (EGF); transforming growth factor-β (TGF-β); tissue inhibitor of metalloproteinase-1 (TIMP-1); α-smooth muscle actin (α-SMA); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); tumor necrosis factor-α (TNF-α); interleukin-1β, -6, -12 (IL-1β, IL-6, IL-12); interferon-γ (IFN-γ); monocyte chemotactic protein (MCP-1); intercellular adhesion molecule-1 (ICAM-1); cyclooxygenase-2 (COX-2); inducible nitric oxiden synthase (iNOS); Toll like receptor-2, -4 (TLR2, TLR4); proliferating cell nuclear antigen (PCNA).

protective effects against liver injury by upregulating the Keap1/Nrf2/ARE pathway (Garg et al., 2008). These properties make curcumin a potential protective agent against heavy metal-induced liver injury (Table 1).

3. Arsenic hepatotoxicity

Epidemiological studies have clearly indicated an association between chronic arsenic exposure and abnormal liver function, hepatomegaly, hepatoportal sclerosis, ascites, liver fibrosis and cirrhosis (Nevens et al., 1990; Li et al., 2006; Flora et al., 2007; Liu and Waalkes, 2008), from exposure to arsenic in the drinking water (Santra et al., 1999; Guha Mazumder, 2005; Das et al., 2012), environmental exposure to arsenic through burning high-arsenic coal in interior stoves (Lu et al., 2001; Liu et al., 2002), or when it is used as a therapeutic agent in the treatment of leukemia (Hao et al., 2013; Wang et al., 2013a,b). The mechanisms by which arsenic causes hepatotoxicity are not fully elucidated, however, emerging evidence supports the role of oxidative stress and inflammation in the pathogenesis of arsenic-induced organ damage (Dong, 2002; Fouad et al., 2012). It has been shown that arsenite and other arsenicals induce in liver the following alterations: hepatocellular damage, hepatomegaly, oxidative stress (Guha Mazumder, 2005; Nandi et al., 2005; Bashir et al., 2006; Xu et al., 2013a,b), oxidative stress in liver mitochondria, inappropriate mitochondrial permeability transition (Santra et al., 2007; Hosseini et al., 2013), apoptosis (Zhang et al., 2013), hepatic steatosis, inflammation, necrosis and fibrosis associated with hepatic stellate cells (HSCs), NADPH oxidase and TGF-β/SMAD activation (Ghatak et al., 2011; Pan et al., 2011) and liver carcinogenesis (Liu et al., 2006; Waalkes et al., 2006; Xie et al., 2007).

3.1. Mechanism of action and Nrf2 induction

Evidence of oxidative stress has been detected in almost all the experimental conditions of arsenic toxicity (Das et al., 2005; Jomova et al., 2011). Arsenic may cause an increase in production of ROS such as $O_2^{\cdot -}$, H_2O_2, ROO·, singlet oxygen ($^1O_2$), nitric oxide (NO·), dimethylarsinic peroxyl radical [$(CH_3)_2AsOO\cdot$] and the dimethylarsinic radical [$(CH_3)_2As\cdot$] (Valko et al., 2006). It has been suggested that mitochondria are the main target for arsenic-containing compounds with a deflection of electrons from the respiratory chain to generate ROS, inhibitory effects on cellular respiration, disruption of oxidative phosphorylation and concomitant decrease in the cellular levels of adenosine triphosphate (ATP) (Fluharty and Sanadi, 1962; Chen et al., 1986). ROS might also be produced by cytosolic enzymes with peroxidase activity or during the oxidation of As(III) to As(V) (Henkler et al., 2010). ROS production by arsenic may result in an attack, not only against antioxidant defenses and DNA, but also against membrane phospholipids, which are very sensitive to oxidation, producing ROO· and then malondialdehyde (MDA) (Escobar et al., 2010). On the other hand, arsenic may also generate its toxic effects via bonding to sulfhydryl groups of proteins and depletion of GSH (Hossain et al., 2000; Jomova and Valko, 2011).

Nrf2 activation by arsenic induced-cell damage has been reported in osteoblasts (Aono et al., 2003), human keratinocytes

(Pi et al., 2003; Endo et al., 2008; Zhao et al., 2011), embryonic fibroblasts (He et al., 2006), human breast adenocarcinoma and human urothelial cells (Wang et al., 2008), pancreatic β-cells (Yang et al., 2012), endothelial cells (Wang et al., 2012) and skin lesions in people exposed to inorganic arsenic-contaminated water (Cordova et al., 2013). Aono et al. (2003) reported for the first time that inorganic arsenic activates the transcription factor Nrf2 and Pi et al. (2003) indicated that H_2O_2 is the mediator of arsenic-induced nuclear Nrf2 accumulation. On the other hand, Jiang et al. (2009) presented evidence that Nrf2 protects against liver and bladder injury in mice treated with arsenic ameliorating the pathological changes, DNA hypomethylation, oxidative DNA damage and apoptotic cell death. Abiko et al. (2010) observed in human hepatocarcinoma cells (HepG2) a reduction of arsenic-induced cytotoxicity through Nrf2/HO-1 signaling. Li et al. (2011) and Liu et al. (2013a,b) demonstrated that sodium arsenite exposure in Chang human hepatocytes increased Nrf2 protein levels, HO-1, NQO1 and GSH, as an adaptive cell defense mechanism against hepatotoxicity. Recently, Anwar-Mohamed et al. (2013) showed that methylated pentavalent arsenic metabolites are bifunctional inducers as they increase cytochrome P450 1A1 (CYP1A1) through activating the aryl hydrocarbon receptor (AhR) and NQO1 through activating the Nrf2/Keap1/ARE signaling pathway in HepG2 cells.

3.2. Curcumin hepatoprotection

Curcumin has shown beneficial effects in clinical trials in patients with arsenic-induced genotoxicity (Biswas et al., 2010b; Roy et al., 2011) and arsenic-induced Bowen's disease (Cheng et al., 2001). Also, in studies in rodents and in in vitro models, curcumin has shown protective effect against arsenic-induced genotoxicity (Mukherjee et al., 2007; Roy et al., 2008; Biswas et al., 2010a; Tiwari and Rao, 2010), angiogenesis (Pantazis et al., 2010), skin disorders (Zhao et al., 2013), reproductive toxicity (Reddy et al., 2012; Khan et al., 2013), neurotoxicity (Yadav et al., 2009, 2010, 2011), immunotoxicity (Khan et al., 2012; Sankar et al., 2013c), nephrotoxicity (Sankar et al., 2013b) and hepatotoxicity. Yousef et al. (2008) and El-Demerdash et al. (2009) treated rats with sodium arsenite (5 mg/kg) and curcumin (15 mg/kg) and they found that curcumin ameliorates arsenic-induced liver damage preventing hepatomegaly and loss of body weight. Curcumin treatment also preserved the structural integrity of the hepatocellular membrane, prevented lipid peroxidation and the decrease in the content of GSH and total proteins and changes in the liver activity of the antioxidant enzymes GST, SOD and CAT. This protective effect of curcumin was attributed to its ability to scavenge free radicals (Ak and Gülcin, 2008), to induce detoxifying enzymes (Dinkova-Kostova and Talalay, 1999; Messarah et al., 2013) and to block thiol depletion (Donatus et al., 1990).

In contrast, Gao et al. (2013) demonstrated in female Kunming mice exposed to sodium arsenite (10, 50, 100 mg/L) in drinking water that the co-treatment with curcumin (200 mg/kg), reduced the arsenic-induced hepatic injuries by supporting arsenic methylation and accelerating its urinary excretion, as a detoxification process. Notably, these authors observed that treatment with curcumin antagonized arsenic-induced hepatic oxidative stress by the upregulation of Nrf2 and the induction of NQO1 and HO-1 proteins, two typically recognized Nrf2 downstream targets. Similarly, curcumin led to nuclear accumulation of Nrf2 protein and increased the expression of ARE regulated genes in keratinocytes (HaCaT) treated with sodium arsenite, augmenting the viability and survival of cells upregulating *NQO1*, *HO-1*, *GCL*, and *GCLM* genes expression (Zhao et al., 2013). Previously, Farombi et al. (2008) had found that liver protection by curcumin is mediated by Nrf2 activation.

In order to increase curcumin's bioavailability, Yadav et al. (2012a,b) prepared encapsulated curcumin chitosan nanoparticles (nanocurcumin) and they treated rats with sodium arsenite (2 mg/kg) plus curcumin (15 mg/kg) or nanocurcumin (1.5 and 15 mg/kg). Co-administration of curcumin or nanocurcumin ameliorated changes in hepatic oxidative stress parameters and re-established the activity of SOD and CAT. Remarkably, nanocurcumin (15 mg/kg) chelates arsenic more effectively than curcumin from blood, liver, brain and kidneys and retained its ability as an antioxidant. Nanocurcumin increases the efficacy and bioavailability of curcumin and reduces the dose required to exert protective effect against arsenic toxicity. Recently, Sankar et al. (2013a) described that nanoparticle-encapsulated curcumin in poly(lactic-co-glycolic acid) (PLGA) showed hepatoprotective effects against sodium arsenite-induced oxidative damage. Rats were treated with sodium arsenite (25 ppm) plus curcumin (100 mg/kg) or curcumin-nanoparticles (100 mg/kg). In this case, curcumin and nano-encapsulated curcumin protected against arsenic-induced hepatotoxicity by reducing lipid peroxidation, supporting GSH levels and SOD, CAT, GPx and GR activities. However, curcumin-nanoparticles showed higher protection than free curcumin. Sankar et al. (2013b) have demonstrated that curcumin-nanoparticles show immunomodulatory effects in arsenic-exposed rats.

On the other hand, Mathews et al. (2012) induced oxidative stress by treating rats with arsenic trioxide (4 mg/kg) and curcumin (15 mg/kg). In this model, curcumin prevents the arsenic trioxide-induced hepatic dysfunction and oxidative stress by maintaining the liver antioxidant enzyme status. Thus, curcumin protects against arsenic-induced hepatic damage scavenging free radicals, chelating arsenicals compounds or activating Nrf2/Keap1/ARE pathway.

4. Cadmium hepatotoxicity

The liver is critically damaged by acute or chronic exposure to cadmium (Souza et al., 1996; Yamano et al., 1999; Casalino et al., 2006). Acute cadmium exposure has been related to the elevation in the levels of serum liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (Kang et al., 2013), hepatic necroinflammation, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), fibroplasias and liver-related mortality (Chang et al., 2012; Hyder et al., 2013). A critical determining factor in cadmium-induced liver injury is the hepatic concentration of metallothionein (MT) (Kuester et al., 2002). MT is a low molecular weight, cysteine-rich, intracellular protein with high affinity for both essential and non-essential metals (Park et al., 2001). MT forms a complex with cadmium and reduces its free concentration within the cell, thus reducing the hepatotoxic potential of cadmium (McKenna et al., 1996; Klaassen et al., 2009). As the binding capacity of MT becomes saturated, the increased availability of unbound cadmium initiates a series of events resulting in cell injury or death (Goering et al., 1993; Shaikh et al., 1999). Cadmium hepatotoxicity also involves the binding of Cd^{2+} to sulfhydryl groups on critical molecules, thiol group inactivation, oxidative stress (Bucio et al., 1995; Casalino et al., 2002), mitochondrial permeability transition (Li et al., 2003), mitochondrial dysfunction (Al-Nasser, 2000), mitochondrial fragmentation (Xu et al., 2013a,b) and apoptosis (Habeebu et al., 1998). Secondary injury from acute cadmium exposure occurs from the activation of Kupffer cells and neutrophil infiltration; pro-inflammatory cytokines and chemokines have also been implicated in the toxic process (Sauer et al., 1997; Rikans and Yamano, 2000).

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4.1. Mechanism of action and Nrf2 induction

Cadmium competes with essential metals, that have well-defined homeostatic uptake and efflux pathways, for the same transport systems to enter into the cells, disrupting the intracellular balance of the essential metals and producing toxic effects (Souza et al., 1997; Ohrvik et al., 2007). Metals susceptible to the mimetic action of cadmium include calcium, zinc, magnesium and iron (Martelli et al., 2006). ROS are often implicated in cadmium-induced deleterious health effects and $HO^{\cdot}$, O_2^{-} and H_2O_2 have been detected *in vivo*, which are often accompanied by activation of redox sensitive transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activating protein-1 (AP-1) and Nrf2, and alteration in the expression of ROS related genes (Patra et al., 2011; Wu et al., 2012). Thus, cadmium induces tissue injury through oxidative stress, increase in lipid peroxidation, alterations in the antioxidant defense system (Jurczuk et al., 2006; Thijssen et al., 2007), epigenetic changes in DNA expression, inhibition of heme synthesis, depletion of GSH and distortion of proteins due to cadmium binding to sulfhydryl groups (Bernhoft, 2013), disruption of calcium homeostasis (Leffler et al., 2000; Yuan et al., 2013), impairment of mitochondrial function (Chávez et al., 1985; Takaki et al., 2004; Cannino et al., 2009) and apoptosis (Kim et al., 2000).

Activation of Nrf2 by cadmium has been described in rat kidney cells (Chen and Shaikh, 2009), rat heart (Ferramola et al., 2011), mouse macrophages (Ishii et al., 2000) and mouse embryonic fibroblasts (He et al., 2008). Stewart et al. (2003) identified that treatment of mouse hepatoma (Hepa 1c1c7) cells with cadmium chloride increased the half-life of Nrf2 by delaying the rate of Nrf2 degradation. Wu et al. (2012) investigated the role of Nrf2 in cadmium-induced hepatotoxicity in a murine model. Nrf2-null mice, wild-type mice, Keap1-knockdown mice with enhanced Nrf2, and Keap1-hepatocyte knockout mice with maximum Nrf2 activation were treated with cadmium chloride. These authors found that Nrf2 activation prevents cadmium-induced oxidative stress and liver injury by inducing genes involved in antioxidant defense rather than genes that scavenge cadmium. Similarly, Casalino et al. (2006, 2007) showed that in the liver of acutely cadmium-intoxicated rats, the activation of the Nrf2 factor was significantly increased, as well as the ARE-mediated gene expression and activity of NQO1 and α-GST. This probably occurs through activating protein kinases that promote the phosphorylation of Nrf2, or by the interaction of heavy metals with sulfhydryl groups of Keap1 altering the structure of this inhibitor, removing the association between Nrf2 with Keap1 and consequently activating ARE-mediated gene expression.

4.2. Curcumin hepatoprotection

In several studies in rodents and in vitro models, curcumin has been shown to have the potential to protect against cadmium nephrotoxicity (Tarasub et al., 2011; Deevika et al., 2012), immunotoxicity (Pathak and Khandelwal, 2008; Alghasham et al., 2013), lung diseases (Rennolds et al., 2012), reproductive toxicity (Souza et al., 1996; Salama and El-Bahr, 2007; Oguzturk et al., 2012; Singh et al., 2012), neurotoxicity (Daniel et al., 2004), colon toxicity (Singh et al., 2011) and hepatotoxicity. In this context, Eybl et al. (2004) investigated the preventive effect of curcumin on cadmium-induced liver damage in rats and mice. Animals were treated with curcumin (50 mg/kg) and cadmium chloride (rats 25 μmol/kg and mice 30 μmol/kg). Curcumin ameliorated the cadmium-induced hepatic lipid peroxidation. However, curcumin treatment did not exert any change on GSH levels, probably because of the relatively low dose of the antioxidant and the short duration of treatment (3 days). Moreover, they evaluated the trace element concentrations in the liver and their results suggested that curcumin could regulate the status of essential metals involved in cadmium toxicity, like zinc and iron. In a second study, Eybl et al. (2006b) examined the capacity of curcumin and manganese (Mn) complex of curcumin (Mn–curcumin) to protect against cadmium-induced oxidative damage. Manganese was incorporated in the curcumin structure in order to exert SOD activity and to potentiate the radical scavenging ability (Vajragupta et al., 2006). Mice were pre-treated with curcumin or Mn–curcumin (0.14 mmol/kg) and intoxicated with cadmium chloride (33 μmol/kg). Curcumin and Mn–curcumin effectively prevented the increase of hepatic lipid peroxidation and attenuated the cadmium-induced decrease in hepatic GSH levels. The activity of GPx or CAT in liver was unchanged in cadmium-treated mice. On the other hand, the authors did not find any differences in cadmium distribution in tissues; neither curcumin nor Mn–curcumin corrected the changes in the balance of essential elements caused by cadmium. They also demonstrated that incorporating manganese into the curcumin molecule does not potentiate the antioxidant action of curcumin. Later, Eybl et al. (2006a) designed a comparative study of natural antioxidants against cadmium-induced oxidative damage in mice. Animals were treated with cadmium chloride (7 mg/kg) and curcumin (50 mg/kg), resveratrol (20 mg/kg) or melatonin (12 mg/kg). All antioxidants prevented hepatic lipid peroxidation but only curcumin and melatonin ameliorated the decrease in GSH in cadmium-exposed mice. The antioxidants completely prevented the cadmium-induced decrease in hepatic GPx activity, and CAT activity was maintained only by resveratrol. The accumulation of cadmium was measured in liver, brain, kidneys and testes and was not affected by antioxidants pre-treatment. In this case, curcumin acts as a scavenger rather than as a chelating agent.

In 2008, Tarasub et al. treated rats with cadmium acetate (200 mg/kg) and co treated with curcumin (250 mg/kg). They found that curcumin was unable to prevent against cadmium-induced oxidative damage. But recently, Tarasub et al. (2012) have reported that curcumin (200 and 400 mg/kg) in combination with vitamin C (100 mg/kg) can prevent the cadmium-induced oxidative damage, MT expression and liver structural lesions at dose of 5 mg/kg. According to the authors, the combined treatment was more effective than with either antioxidant alone as a consequence of the antioxidant/anti-radical properties of curcumin and vitamin C. Thus, curcumin protects against cadmium-induced hepatic injury scavenging free radicals. Nevertheless, in these models it was not determined whether curcumin could act as an indirect antioxidant and activate the Nrf2/Keap1/ARE pathway and it remains to be determined if curcumin prevents the decreased activity of antioxidant enzymes and GSH by activating this pathway or by acting as a direct antioxidant. Daniel et al. (2004) demonstrated the chelating capacity of curcumin against cadmium in rat brain. So it is important to determine whether curcumin has the same activity in the liver.

5. Chromium hepatotoxicity

Several studies have demonstrated that liver is an organ capable of being injured by Cr(VI) (Wood et al., 1990) and histopathological changes such as parenchymatous degeneration, steatosis of hepatocytes and necrosis have been observed (Woźniak et al., 1991; Kurosaki et al., 1995; Acharya et al., 2001). Cr(VI) hepatotoxicity is associated with increased ROS levels (Wang et al., 2006; Patlolla et al., 2009), lipid peroxidation (Bagchi et al., 1995a, 1995b), DNA damage (Yuann et al., 1999), inhibition of DNA, RNA and protein synthesis (Gunaratnam and Grant, 2008), reduction of the activity of the antioxidant enzymes (Ueno et al., 1989;

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Anand, 2005; Soudani et al., 2013), mitochondrial damage (Pourahmad et al., 2001, 2005) including impaired mitochondrial bioenergetics (Ryberg and Alexander, 1984; Fernandes et al., 2002), cell growth arrest (Xiao et al., 2012) and apoptosis (Kalayarasan et al., 2008).

5.1. Mechanism of action and Nrf2 induction

Cr(III) is poorly transported across membranes, while the chromate ion $(CrO_4)^{-2}$, the dominant form of Cr(VI) in neutral, aqueous solutions and structurally similar to phosphate and sulfate, can be transported into cells by the anion carrier in cellular membranes (Alexander and Aaseth, 1995). Inside cells, Cr(VI) is reduced through reactive intermediates Cr(V), Cr (IV) and to the more stable Cr(III) by cellular reducers such as GSH, cysteine, ascorbic acid and riboflavin and NADPH-dependent flavoenzymes, cytochrome P450 reductases and the mitochondrial electron transport chain (Jannetto et al., 2001; Pourahmad and O'Brien, 2001; Ueno et al., 2001). The redox couples Cr(VI)/(V), Cr(V)/(IV), Cr(IV)/Cr(III) and Cr(III)/(II) have been shown to serve as cyclical electron donors in a Fenton-like reaction, which generates ROS such as $O_2^{\cdot-}$, H_2O_2, $OH^{\cdot}$, thiyl radicals and carbon-based radicals (Stohs and Bagchi, 1995; Liu and Shi, 2001), leading to genomic DNA damage (Henkler et al., 2010), oxidative deterioration of lipids and proteins (Kalahasthi et al., 2006; Myers et al., 2008, 2011), activation of NF-κB and tumor suppressor protein p53 (Ye et al., 1999; Son et al., 2010), cell cycle arrest, tyrosine phosphorylation (Bagchi et al., 2001; Ding and Shi, 2002); mitochondrial damage (Ryberg and Alexander, 1990; Rudolf et al., 2005; Myers et al., 2010) and apoptosis (Pritchard et al., 2000, 2001; Quinteros et al., 2008). Cr(III) produces damage to cellular proteins, DNA and organelles (Stearns et al., 2002; Raja and Nair, 2008) and can be lethal to organisms and their offspring (Bailey et al., 2006).

He et al. (2007) demonstrated in Hepa 1c1c7 and mouse embryonic fibroblasts cells that Nrf2 protects cells against both apoptosis and ROS production induced by Cr(VI) by the activation of Keap1/Nrf2/ARE. They showed that Nrf2 and Keap1 were ubiquitinated in the cytoplasm and translocated into the nucleus in association with each other. But, both proteins were deubiquitinated upon nuclear translocation. Finally, treatment with Cr(VI) disrupted the Nrf2/Keap1 association in the nucleus, Nrf2 was recruited to the ARE inducing the cytoprotective genes HO-1 and NQO1 expression. Keap1 is shuttled back to the cytoplasm assisting a new round of Nrf2 ubiquitination and activation. It is noteworthy to mention that O'Hara et al. (2006) suggested that Cr(VI) silences induction of ARE-driven genes required for protection from secondary insults in human bronchial epithelial cells. On other side, Kalayarasan et al. (2008) found that potassium dichromate induces a slight activation of Nrf2 in the hepatocytes of Wistar rats.

5.2. Curcumin hepatoprotection

Curcumin has demonstrated protective effects against Cr(VI)-induced toxicity in male reproductive system (Chandra et al., 2007; Devi et al., 2012), kidney (Molina-Jijón et al., 2011) and liver of rodents. Recently, we studied the hepatoprotective effects of curcumin against chromium-induced damage (García-Niño et al., 2013). In rats, we administered curcumin (400 mg/kg) and potassium dichromate (15 mg/kg) and we found that curcumin successfully prevented the Cr(VI)-induced liver injury by reducing hepatocyte damage and the histological alterations, ameliorating lipid and protein oxidation, maintaining the activity of SOD, CAT, GPx, GR and GST, protecting against mitochondrial dysfunction and avoiding the membrane permeability transition pore opening. Apparently, these protective effects of curcumin against chromium-induced liver injury are a consequence of its scavenging activity. Previously, Molina-Jijón et al. (2011) demonstrated that curcumin did not chelate chromium using an *in vitro* system.

6. Copper hepatotoxicity

The liver accounts for approximately 8% of the total amount of copper in the body and represents the tissue with the highest copper concentration (Luza and Speisky, 1996). In this context too low concentrations of copper in tissues induce anemia and too high concentrations induce hepatic damage, however, copper levels in tissues are normally well regulated in healthy animals (Hogstad, 1996). Copper contained in food is absorbed into the portal vein and then loaded into hepatocytes. There, the Cu^{2+} transporting beta polypeptide ATPase (ATP7B) mediates the secretion on one side into the bile and on the other into the bloodstream after linkage to ceruloplasmin, a protein responsible for organized delivery into all tissues (Dijkstra et al., 1996; Tao and Gitlin, 2003; Zhang et al., 2011; Fieten et al., 2012). Chronic copper accumulation in the liver causes hepatitis leading to hepatic failure, pericentral hepatic necrosis, cholestasis, cirrhosis and ultimately death (Chuttani et al., 1965; Hébert et al., 1993; Giuliodori et al., 1997). The hepatocyte cytotoxic mechanisms for copper involve ROS formation, GSH oxidation, lipid peroxidation (Stacey and Klaassen, 1981; Sokol et al., 1994) and mitochondrial dysfunction (Nakatani et al., 1994; Pourahmad and O'Brien, 2000).

6.1. Mechanism of action and Nrf2 induction

The common oxidation states for copper are Cu(I) and Cu(II) and the easy exchange between these two oxidation states endows copper with redox properties that may be of an essential or deleterious nature in biological systems (Peña et al., 1999). The major functions of copper-biological molecules involve oxidation–reduction reactions in which they react directly with molecular oxygen to produce $HO^{\cdot}$ from H_2O_2 and $O_2^{\cdot-}$ via the Fenton and Haber–Weiss reactions which may cause oxidative damage (Gaetke, 2003; Tisato et al., 2010). Copper-induced ROS are important contributing factors in cellular damage that includes lipid peroxidation in membranes, direct oxidation of proteins, and cleavage of DNA and RNA molecules (Peña et al., 1999). Besides, excess cellular copper can disrupt normal cell metabolism by displacing other ions at their metal binding sites or through non-specific binding to enzymes, DNA, and other biomolecules (Alt et al., 1990). Also, copper ions participate in the auto-oxidation of sulfhydryl groups and in the depletion of GSH (Hultberg et al., 1998). Mitochondria are particularly sensitive to oxidative damage because of the excess copper and the resulting oxyradicals may overwhelm cellular defensive mechanisms, compromising respiratory function and further impairing cellular health and survival (Collins et al., 2010).

The induction of Nrf2 mediated by copper has been described in human peripheral blood monocyte-derived macrophages and murine macrophages (RAW264.7) (Calay et al., 2010), human mammary ARE-reporter cell line (AREc32) (Wang et al., 2010), and fetal lung human diploid fibroblasts (Wi-38) (Boilan et al., 2013). Muller et al. (2007) identified genes that provide insight into the adaptive transcriptional response to copper overload-induced oxidative stress in HepG2 cells. They detected increased expression of genes involved in the formation of GSH, GCLM and GCLC, and HO-1 via the transcription factor Nrf2. Korashy and El-Kadi (2006), observed that Cu^{2+} inhibited the constitutive and inducible expression of NQO1 and GST Ya in Hepa 1c1c7 cells, however Cu^{2+} treatment did not alter Nrf2 levels. On the other hand, Piret et al. (2012) studied the toxic effects of copper(II) oxide nanoparticles in HepG2

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cells. Transcriptomic data, siRNA knockdown and DNA binding activities suggested that nanoparticles induced activation Nrf2.

6.2. Curcumin hepatoprotection

Protective effects of curcumin against copper-induced toxicity have been studied for genotoxicity (Urbina-Cano et al., 2006; Corona-Rivera et al., 2007), neurotoxicity (Baum and Ng, 2004; Zhao et al., 2010) and liver damage. Wan et al. (2007), in a Wilson disease model, an autosomal recessive disorder of copper metabolism with neuropsychiatric and hepatic symptoms, explored the protective effects of curcumin in copper-overloaded rats. Animals were fed with forage containing copper sulfate (1 g/kg) and in drinking water (0.185%), they were also co-administered curcumin (50 or 200 mg/kg). They observed that in relation to copper-overloaded rats, treatment with curcumin ameliorated lipid peroxidation, recovered the GSH and SOD levels, decreased apoptosis, down-regulated the expression and content of proinflammatory cytokines TNF-α and IL-8 and improved the histological changes induced by copper in liver. This protective effect was explained by the antioxidant and anti-apoptotic properties, in a similar way as has been described in the model of iron overload (Thephinlap et al., 2009; Messner et al., 2010; Qian et al., 2012).

Wan and Luo (2007) demonstrated that curcumin prevented the oxidative damage and the apoptosis induction in Buffalo rat liver cells (BRL) treated with 100 μmol/L of copper sulfate by reducing ROS and inhibiting c-Jun N-terminal protein kinases (JNK) expression. JNK and p38 are kinases strongly activated by extra- or intracellular stress and inflammatory cytokines that promote the inhibition of cell growth or promotion of cell death (Guo et al., 1998), and curcumin can modulate p38- and JNK-MAPK pathways (Yu et al., 2010; Fan et al., 2012; Topcu-Tarladacalisir et al., 2013). Kou et al. (2013) also recognized the protective effect of curcumin against copper-mediated LDL oxidation because of the upregulation of HO-1, GCLM and CD36 expression in undifferentiated THP-1 cells, suggesting the possible involvement of Keap1/Nrf2/ARE pathway. Thus, curcumin protects against copper-induced hepatic damage by scavenging free radicals, and upregulating the Nrf2/Keap1/ARE pathway. It remains to be determined if there is a possible chelating activity of curcumin against copper hepatotoxicity, as has been previously suggested by Baum and Ng (2004) for copper neurotoxicity.

7. Lead hepatotoxicity

The histopathological alterations that have been described after chronic lead exposure are anisokaryosis, nuclear vesiculation, binucleation, cytoplasmic inclusions and swelling, hydropic degeneration, reduction in glycogen content (Jarrar and Taib, 2012), portal inflammatory cell infiltration (El-Neweshy and El-Sayed, 2011), steatosis, apoptosis and mild fibrosis (Shalan et al., 2005), biliary hyperplasia, edema, congestion and apoptotic and necrotic cells (Mehana et al., 2012).

Acute lead exposure in rodents and in vitro models involves a decrease in hepatic CYP450 content (Degawa et al., 1994; Korashy and El-Kadi, 2012), inhibition of heme synthetic pathway (Lake and Gerschenson, 1978; Jaffe et al., 2001), alterations in hepatic cholesterol metabolism (Kojima et al., 2004; Ademuyiwa et al., 2009), ROS generation, lipid peroxidation (Sandhir and Gill, 1995; Pandya et al., 2010), suppression of activity of antioxidant enzymes and decrease in GSH levels (Daggett et al., 1997, 1998; Korashy and El-Kadi, 2006; Liu et al., 2011), mitochondrial dysfunction (Wielgus-Serafińska et al., 1980; Bragadin et al., 1998, 2007; Pal et al., 2013), oxidative DNA damage (Hernández-Franco et al., 2011; Narayana and Al-Bader, 2011) and apoptosis (Pagliara et al., 2003; Mukherjee et al., 2013).

7.1. Mechanism of action and Nrf2 induction

Lead causes oxidative stress by inducing the generation of ROS, like $HO^{\bullet}$, $O_2^{\bullet -}$, H_2O_2, $^1O_2$, hydroperoxides ($HO_2^{\bullet}$) and lipid peroxides ($LPO^{\bullet}$) (Valverde et al., 2001; Flora et al., 2004), by reducing the antioxidant defense system of cells via depleting GSH, inhibiting sulfhydryl dependent enzymes or activity of antioxidant enzymes (Gurer and Ercal, 2000; Patil et al., 2006; Patrick, 2006) and/or increasing susceptibility of cells to oxidative attack by altering membrane integrity and fatty acid composition. Another mechanism of free radical generation and adduct formation may involve aminolevulinic acid (ALA), the heme precursor whose levels are elevated by lead exposure through feedback inhibition of the enzyme δ-aminolevulinic acid dehydrogenase (ALAD). As lead, ALA has the tendency to bind to sulfhydryl groups and thus results in overproduction of ROS (Rahman and Sultana, 2006; Gillis et al., 2012). Moreover, lead is able to substitute for other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+}, Zn^{2+} and monovalent cations like Na^{+}, affecting various fundamental biological processes like intra- and intercellular signaling, cell adhesion, protein folding and maturation, apoptosis, ionic transportation, enzyme regulation or release of neurotransmitters (Aboul-Soud et al., 2011; Flora et al., 2012).

Korashy and El-Kadi (2006) were the first to identify that Pb^{2+} and Hg^{2+} regulate the expression of *Nqo1* and *Gstya* genes through Nrf2-ARE-dependent transcriptional mechanisms, inducing the expression of NQO1 and GST Ya mRNAs in a time-dependent manner in Hepa 1c1c7 cells. Recently, Wang et al. (2013a,b) showed evidence supporting the up-regulation of Nrf2 and MRP1 in response to lead-induced oxidative and electrophilic stress in rat testes. MRP1 is a plasma membrane glycoprotein that can confer multidrug resistance by increased export of drugs from the cell resulting in a decreased intracellular drug concentration (Zaman et al., 1995).

7.2. Curcumin hepatoprotection

Curcumin has shown protective effects in rodents against lead neurotoxicity (Shukla et al., 2003; Daniel et al., 2004; Dairam et al., 2007), cardiotoxicity (Asali et al., 2011; Roshan et al., 2011a, 2012), nephrotoxicity (Farzanegi et al., 2012; Ghoniem et al., 2012; Sangartit et al., 2012), immunotoxicity (El-Sherbiny et al., 2010), bone disease (Roshan et al., 2011b) and hepatotoxicity. El-Ashmawy et al. (2006) studied the hepatoprotective potential of turmeric powder against lead-induced liver toxicity by feeding mice with a diet supplemented with lead acetate (0.5%) and turmeric (1% or 5%). Turmeric co-treatment prevented the decrease in the GST activity and ameliorated lipid peroxidation, but the level of GSH was slightly decreased in liver. Due to its content of polyphenolic compounds, like curcumin, two possible mechanisms were proposed by which turmeric could protect liver, by scavenging ROS and chelating this toxic metal. Also, turmeric protects against lead-induced genotoxicity in bone marrow chromosomes.

On the other hand, Memarmoghaddam et al. (2011) determined the effect of exercise training and curcumin supplementation on lead-induced oxidative damage in liver. Mice performed progressive running training sessions and they received curcumin solution (30 mg/kg) and lead acetate (20 mg/kg). In this way, curcumin, endurance training and the combination reduce the heat shock protein levels and lipid peroxidation generated by lead exposure. These authors suggested that aerobic exercise and anti-oxidant supplements might have beneficial effects for health. Recently, Flora et al. (2013) evaluated the protective efficacy of curcumin and nanocurcumin against lead-induced toxicity in blood, liver, kidney and brain. Mice were co-administered lead acetate (25 mg/kg) and curcumin (15 mg/kg) or nanocurcumin (15 mg/

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kg). In liver, curcumin and nanocurcumin showed beneficial effects by protecting against lipid peroxidation, protein oxidation and restoring altered ROS levels, GSH and glutathione disulfide (GSSG). Interestingly, the hepatoprotection by curcumin and nanocurcumin was similar. In contrast, lead concentration was determined in liver tissue and it was found that curcumin and nanocurcumin both reduced lead content, but that nanocurcumin showed a greater chelating effect than curcumin. It is worth mentioning that in blood, curcumin and nanocurcumin re-established ALAD activity and the protective effects in kidney and brain were similar, nanocurcumin being more effective than curcumin. Thus, the scavenging and chelating properties of curcumin seems to be mainly responsible for the protective effect against lead-induced hepatotoxicity. It has also been demonstrated that increasing curcumin's bioavailability will make a more effective hepatoprotective agent. However, it remains unclear whether curcumin can activate Nrf2/Keap1/ARE pathway in models of hepatotoxicity caused by lead poisoning.

8. Mercury hepatotoxicity

Hepatocellular effects described for mercury are elevated serum ALT, ornithine carbamyltransferase and serum bilirubin levels,

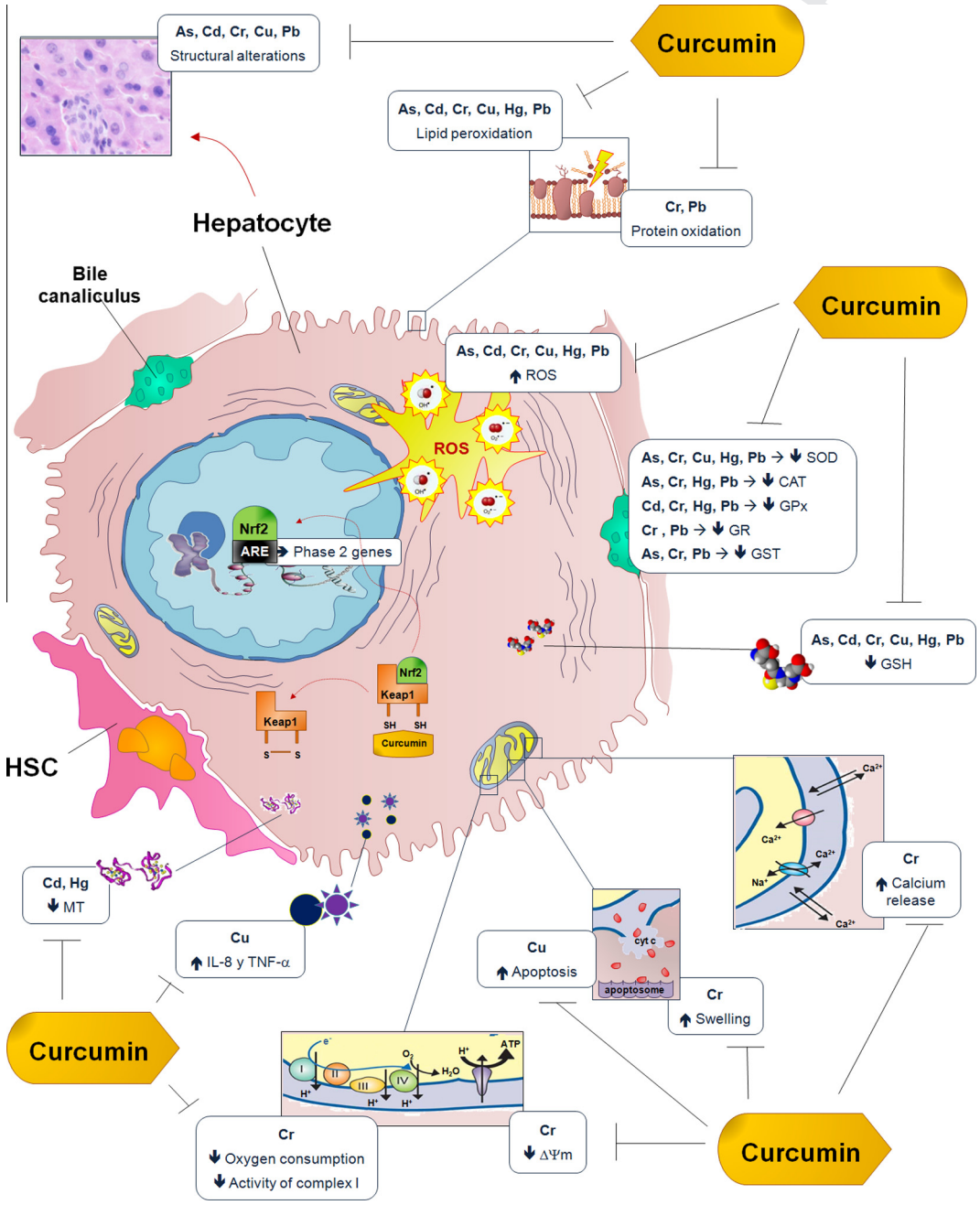

Fig. 5. Protective effect of curcumin against heavy-metals induced-hepatic damage. Arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), lead (Pb), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-*S*-transferase (GST), glutathione (GSH), reactive oxygen species (ROS), nuclear factor (erythroid-derived 2)-like 2 (Nrf2), antioxidant responsive element (ARE), Kelch-like ECH-associated protein 1 (Keap1), hepatic stellate cells (HSC), mitochondrial membrane potential ($\Delta\Psi m$), metallothionein (MT), tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8).

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hepatomegaly and centrilobular hepatic steatosis, decrease in the synthesis of hepatic coagulation factors (Kanluen and Gottlieb, 1991; Ashour et al., 1993; Joshi et al., 2011, 2012; Cao et al., 2012), decreased activity of metabolic enzymes (Chang et al., 1973), increase in lipid peroxidation products (Stacey and Kappus, 1982; Benov et al., 1990; Huang et al., 1996; Lin et al., 1996), mitochondrial dysfunction (Belyaeva et al., 2011), proliferation of the endoplasmic reticulum, floccular degeneration of the hepatic mitochondria with extrusion of degenerated hepatic organelles and cytoplasmic debris into the sinusoidal space and engulfed by Kupffer cells and vacuolar degeneration of the mitochondria in the Kupffer cells (Chang and Yamaguchi, 1974; Desnoyers and Chang, 1975a,b).

8.1. Mechanism of action and Nrf2 induction

Exposure to mercury compounds induces oxidative stress (Atchison and Hare, 1994; Mahboob et al., 2001; Gutierrez et al., 2006; Al-azzawie et al., 2013; Farina et al., 2013). Mercury induces the formation of H_2O_2, $ROO^{\cdot}$ and $HO^{\cdot}$ that may cause cell membrane damage and cell death (Miller et al., 1991; Hussain et al., 1999), inhibition of the activity of antioxidant enzymes such as CAT, SOD and GPx (Benov et al., 1990; Sener et al., 2007; Franco et al., 2009; Pal and Ghosh, 2012), depletion of GSH, decrease of the sulfhydryl groups of proteins (Hultberg et al., 1998, 2001; Farina et al., 2011; Bridges et al., 2012), interference with enzyme functions and disturbance in both protein synthesis and energy production (Zahir et al., 2006; Castro-González and Méndez-Armenta, 2008; Ragunathan et al., 2010; Amara and El-Kadi, 2011). The mitochondrion is a primary target of mercury-induced injury and the mitochondrial electron transport chain is the most likely site where excess ROS are generated to induce oxidative stress in mercury toxicity (Yee and Choi, 1996). Mitochondrial effects of mercury *in vivo* and *in vitro*, include mitochondrial dysfunction (Chávez and Holguín, 1988; Chávez et al., 1989; Hare and Atchison, 1992; Dreiem et al., 2005; Hernández-Esquivel et al., 2011), membrane permeability transition pore opening (Limke and Atchison, 2002; Polunas et al., 2011) and apoptosis (Shenker et al., 1999; Kim and Sharma, 2004; Humphrey et al., 2005).

In contrast with Cu^{2+} treatment, it has been described that mercury increases Nrf2 levels in human monocytes (Wataha et al., 2008). Korashy and El-Kadi (2006) identified that Hg^{2+} and Pb^{2+} regulate the expression of *Nqo1* and *Gstya* genes through Nrf2/Keap1/ARE pathway in Hepa 1c1c7 cells. Later, Amara and El-Kadi (2011) examined the effect of Hg^{2+} on the expression of NQO1 in HepG2 cells. In this case, Hg^{2+} treatment increased activity, protein, and mRNA of NQO1, which was associated with increased nuclear accumulation of Nrf2 protein and ARE activation.

8.2. Curcumin hepatoprotection

Despite the fact that curcumin has the potential to prevent or protect against noxious effects induced by heavy metals, its potentially protective role against mercury toxicity has been poorly studied. Agarwal et al. (2010) demonstrated that curcumin (80 mg/kg) pretreatment and post-treatment had a protective effect on mercury-induced oxidative stress in the liver, kidneys and brain of rats treated with mercuric chloride (12 μmol/kg). Moreover, curcumin reestablished the antioxidant enzyme activities, reversed mercury-induced liver and kidney injury markers and modified the expression of metallothionein mRNA. Also, curcumin chelates mercury in this model by reducing its concentration in these tissues. However, mercury-induced histological alterations were not prevented by curcumin treatment. Apparently, curcumin protects against mercury-induced hepatic damage by scavenging free radicals and chelating this metal. Furthermore, it is important to evaluate the participation of Nrf2/Keap1/ARE pathway as a protective mechanism induced by curcumin.

9. Summary and conclusions

Heavy metals are persistent and widespread pollutants that affect the structure and function of several organs by generating oxidative stress. Liver is a sensitive organ affected by arsenic, cadmium, chromium, copper, lead and mercury exposure. However, the antioxidant, anti-inflammatory, anti-fibrogenic and anti-carcinogenic activities of curcumin may confer therapeutic efficacy against different environmental or occupational hepatic toxins. In this manner, curcumin can protect against the toxic effects of heavy metals on the liver by reducing the structural damage, preventing lipid peroxidation, avoiding GSH depletion, maintaining the activity of SOD, CAT, GPx, GR, GST and NQO1 and protecting against the following liver mitochondrial alterations: oxidative phosphorylation-disruption, decrease in the cellular ATP levels, mitochondrial permeability transition, calcium homeostasis disruption and apoptosis (Fig. 5). These protective effects of curcumin were attributed to its ability to scavenge free radicals, to act as a chelating agent and/or its capacity to induce detoxifying enzymes by upregulation of the Keap1/Nrf2/ARE pathway (Fig. 4). In addition, curcumin down-regulated NF-κB as well as the expression and content of proinflammatory cytokines preventing noxious effects induced by heavy metals in the liver. In addition, the development of new strategies or technologies that improves curcumin's bioavailability could result in greater protection against liver damage caused by these agents. Another field that has not been studied in depth is related to the role of curcumin as a protective agent against mitochondrial dysfunction induced directly or indirectly by the oxidative stress generated by heavy metals. Despite the great potential of curcumin to prevent heavy metals-induced hepatotoxicity, the number of studies is still limited. As a result, additional research about physiological, cellular and molecular mechanisms involved in curcumin hepatoprotection are needed, in order to propose it as a potential therapeutic agent against oxidative damage generated by exposure to heavy metals.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Transparency Document

The Transparency document associated with this article can be found in the online version.

10. Uncited reference

Tarasub et al. (2008). Q7

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