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Antidotal or protective effects of *Curcuma longa* (turmeric) and its active ingredient, curcumin, against natural and chemical toxicities: A review

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ABSTRACT

Curcuma longa is a rhizomatous perennial herb that belongs to the family Zingiberaceae, native to South Asia and is commonly known as turmeric. It is used as herbal remedy due to the prevalent belief that the plant has medical properties. *C. longa* possesses different effects such as antioxidant, anti-tumor, antimicrobial, anti-inflammatory, wound healing, and gastroprotective activities. The recent studies have shown that *C. longa* and curcumin, its important active ingredient, have protective effects against toxic agents. In this review article, we collected in vitro and animal studies which are related to protective effects of turmeric and its active ingredient against natural and chemical toxic agents.

1. Introduction

Nowadays, herbal medicines are used in different diseases. The recent studies have shown some plants including black cumin [1], saffron [2], barberry [3] and green tea [4] have antidotal or protective effects against toxic agents in different tissues. *Curcuma longa* (turmeric), native to tropical South Asia, belongs to the *Zingiberaceae* family. There are about 133 species of *C. longa* in worldwide. Turmeric is used in food, cosmetic and pharmaceutical industries. More than 100 active compounds are found in this herb. The root is composed of volatile oil such as turmerone and coloring ingredient which is known to curcuminoids [5]. The d-α-phellandrene, cinol, d-sabinene borneol, sesquiterpenes and zingiberene are identified as volatile oil [6]. Curcumin, as curcuminoids, is an important compound in turmeric. It has different biological activities such as antioxidant [7], anti-carcinogenic [8,9] and anti-inflammatory activity [10,11]. The most of pharmacological effects of turmeric are related to the presence of curcumin which has antioxidant activity. In vivo and in vitro studies have shown that this herb has different pharmacological effects. In folk medicine, turmeric is used for respiratory diseases such as allergy, liver problems, sinusitis and anorexia [12]. Nowadays other effects have identified from this medicinal herb such as anticancer [13,14], cardioprotective [15], hepatoprotective [16,17], antiarthritic properties [18] and hypoglycemic [19]. Also it is applied in oral cancer, skin cancer [20], stomach cancer [21] and metabolic syndrome [22]. The studies have reported the protective effects of *C. longa* and its active components against toxic agents in different tissues such as liver [23], brain [24] and cardiovascular system [25].

2. Methods

In this review article, we collected different research projects in scientific databases such as MEDLINE, Scopus, Web of Science databases and local references, which study the protective or antidotal effects of *C. longa* and its major components against natural toxins and chemical-induced toxicity. Studies were identified through electronic databases from their inception up to Jun 2017. The keywords for the search were: *Curcuma longa*, turmeric, curcumin, natural toxin, antidote, chemical toxin and protective effects.

3. Natural toxins

According to recent studies, *C. longa* or curcumin has antidotal effects against some natural toxins in different organs.

3.1. Aflatoxin

3.1.1. Nephroprotective

Aflatoxins (AFs) as mycotoxin are produced by Aspergillus species. The four major forms of aflatoxin including B1, B2, G1, and G2 which aflatoxin B1 has more toxicity than other aflatoxins [26]. The toxicity of aflatoxins is appeared as hemorrhage, growth retardation, heart and kidney, damage to liver, and death [27,28]. Aflatoxin increased urea, Cr and uric acid while decreased total protein levels. It causes dilation

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Table 1
Nephroprotective effects of *C. longa* and curcumin against chemical or natural toxins.

Results	Constituents	In vitro/In vivo	Toxin	References
Extract decreased Cr, BUN, uric acid and necrosis of kidney	*C. longa*	mice	Acetaminophen	[47]
The level of CYP2E1, iNOSgene IL-1β and TNF-α decreased. The Antioxidant enzymes increased	Curcumin	rats	Acetaminophen	[49]
Reduced serum urea, creatinine and lipid peroxidation	Curcumin and curcumin nanoparticles	rats	Cisplatin	[56]
Curcumin increased the levels of NAMPT and SIRT proteins, decreased serum urea, MDA and kidney injury	Curcumin	rats	Cisplatin	[57]
Decreased MDA, serum urea and creatinine while increment of GSH, SOD and total protein	*C. onga*	rats	Acrylamid	[61]
Reduced urea, cr, uric acid, pro-apoptotic and pro-inflammatory gens. Increased antioxidant content	Curcumin	rats	Aflatoxin	[29]
Reduced BUN, urea, Cr and MDA	Curcumin	rats	Sodium fluoride	[66]
Decreased urea, Cr, lipid peroxidation. Increased the expression of Nrf2/HO-1 and Sirt1	Curcumin	rats	Gentamicin	[71–73]
Decreased MDA, elevated GSH,SOD and CAT	Curcumin	rats	Cadmium	[77]

Creatinin (Cr), Blood Urea Nitrogen (BUN), Catalase (CAT), Malondialdehyde (MDA), Super Oxide Dismutase (SOD), Glutathion (GSH), nuclear factor erythroid 2–related factor 2 (Nrf2), and sirtuin (Sirt).

of capillaries, enlargement of glomeruli and necrosis. It increased pro-apoptotic proteins such as bax and caspase3. Curcumin at dose of 200 mg/kg was administrated for 4 weeks orally. It decreased aflatoxin toxicity in kidney via reduction of serum urea, creatinine, uric acid, MDA and increasing of GSH, total protein levels. Curcumin also decreased histopathological changes, pro-apoptotic proteins and pro-inflammatory gen such as COX2 [29] (Table 1).

3.1.2. Hepatoprotective

Aflatoxin B1 is common mycotoxin which produced by *Aspergillus flavus* and *A. parasiticus* [30]. AFB1 causes mutagenicity, genotoxicity, immunosuppression and hepatocellular carcinoma (HCC) in humans and animals [31,32]. AFB1 is bioactivated by the cytochrome P450 and produced the AFB1-exo-8, 9-epoxide which lead to reactive oxygen species (ROS) generation [33]. Curcumin at doses of 100 or 200 mg/kg decreased ALT, AST, uric acid, creatinine and urea levels [34] (Table 2).

3.2. Lipopolysaccharide (LPS)

3.2.1. Cardioprotective

LPS induces the secretion of inflammatory mediators such as TNF-α, IL-6, synthesis of nitric oxide and cyclooxygenase 2 [35]. Also, it plays a role in diseases including neurodegenerative, acute respiratory distress syndrome, vascular diseases and periodontal diseases [36]. The LPS toxicity is related to ROS production and the formation of PGE2 and NO [37]. Also LPS leads to cardiac hypertrophy via increasing of histone acetylation in myocardium. Histones play a role in response to stress stimulation in cardiac toxicity [38]. Also p300-HAT is responsible for LPS-induced cardiac hypertrophy. Curcumin (100 μg/kg) reduced LPS toxicity in cardiac tissues via remodeling of chromatin, especially histone acetylation and inhibition of p300 p300-HAT activity [39].

3.2.2. Lung protective

LPS plays a role in the pathogenesis of recurrent airway obstruction which is inflammation problem in horses [40]. LPS is used for inflammatory induction in experimental models. It increases the counts of LPS neutrophil, IL-6, TNF-α, myeloperoxidase and elastase. A lysine salt of curcumin with name NDS27 reduced LPS-induced inflammation via decreasing of IL-6, TNF-α, myeloperoxidase and elastase. The observed effects of curcumin are related to antioxidant activity [41].

3.2.3. Neuroprotective

3.2.3.1. Nitropropionic acid (3-NPA). 3-nitropropionic acid as a toxic agent is produced by fungi. It is toxic for humans and lead to disturbance of mitochondrial function. The signs of Huntington's disease are appeared with this agent [42]. 3-NPA altered the level of MDA, nitrite (NO2), GSH and neuroinflammatory factors. Curcumin at doses of 25 and 50 mg/kg improved the signs of toxicity with 3-NPA via

Table 2
Hepatoprotective effects of *C. longa* and curcumin against chemical or natural toxins.

Toxin	In vitro/In vivo	Constituents	Results	References
CCl_4	rats	*C.longa*	Elevated the level of nuclear translocated Nrf2, reduced AST, ALT and MDA	[79,80]
Aflatoxin B1	rats	Curcumin nanoparticle	Decreased AST, ALT and MDA	[34]
Thioacetamide	rats	*C. longa*	Decreased MDA, nitrotyrosine, urinary 8-OH-dG, TGF-β and TNF-α. Increased antioxidant enzymes	[83]
Lead acetate	rats	*C. longa*	Decreased liver enzymes and increased antioxidant content	[90]
Lead acetate	mice	Curcumin or nanocurcumin	Decreased liver enzymes and increased antioxidant content	[91]
Cadmium	rats	*C. longa*	Reduced HSC activity, liver fibrosis and hepatic enzymes	[94]
Cadmium	rats	Curcumin	Increased antioxidants, scavenge of ROS	[95]
Mercury	rats	Curcumin	Changed metallothionein mRNA, increased antioxidant content and chelated mercury	[178]
Arsenic	rats	Curcumin	Scavenging free radicals, chelating arsenicals compounds, reduction of lipid peroxidation	[102]
Propanil	rats	Curcumin	Reduction of ROS, lipid peroxidation and hepatic enzymes	[104]
Cisplatin	rats	Curcumin	Improved hepatic enzymes, liver histopathology, NADPH expression	[106]
Nicotine	mice	Curcumin	Reduction of oxidative stress and inflammatory cytokines such as TNF-a and IL-1, increased liver weight	[111]
Chromium	rats	Curcumin	Improved hepatic structural, enzymes and antioxidant content	[119]
Copper	rats	Curcumin	Reduced lipid peroxidation, restored the GSH and antioxidant enzyme levels	[122]
Diazinon	rats	Combination of curcumin and vitamin E	Elevation of catalase, glutathione peroxidase and glutathione-*S*-transferase	[129]

Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Reactive Oxygen Species (ROS).