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Antidotal effects of curcumin against neurotoxic agents: An updated review

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ABSTRACT

Curcumin (CUR), the main phenolic composition in turmeric, shows preventive effects in various diseases. CUR is commonly found in the *Curcuma* species and historically applied in herbal medicine. Numerous studies have indicated that CUR possesses protective effects against toxic agents in the various animal tissues including the brain. This study found that CUR may be effective in nervous system problems induced by neurotoxic agents. However, due to the lack of information on human, more investigations are needed to determine the efficacy of CUR as an antidote matter. The current study aimed to critically review the recent literature data from 2014 to 2016 that regarding the therapeutic aspects of CUR versus neurotoxic agents-induced brain damage and its involved mechanisms.

1. Introduction

1.1. General knowledge

Flavonoids are the main compound of plant's ingredients with extensive vital abilities selected for treatment of diseases [1,2]. The investigation on flavonoids has been continuing with developing concern as they do by a lot of signaling lines interfered in different medical disorders [3]. Flavonoids are also the main polyphenolic ingredients that express a variety of biological activities, such as anti-microbial, anti-inflammatory, anti-thrombotic, antioxidant, anti-allergic, anti-microbial, analgesic, and vasodilatory effects [4].

Curcumin (diferuloylmethane) (CUR), famous flavonoids, with the chemical formula of 1,7-bis(4-hydroxy-3 methoxyphenyl)-1,6-heptadiene-3,5-dione, has been separated from the ground rhizome of the *Curcuma* species [5]. *Curcumae longae*, prevalently named as turmeric, is connected with the Zingiberaceae's family and a native of south and southeastern Asia, particularly India [6]. Turmeric is usually applied as a flavoring, natural yellow agent, perfume ingredient and food additive [7]. The prominent chemical ingredient of turmeric is a polyphenolic ingredient named curcuminoids, including bisdemethoxycurcumin, demethoxycurcumin, and CUR [8]. Curcuminoids were first studied by Vogel and Pelletier, and indicated to be diferuloylmethane (C21H20O6) in 1910 [8,9]. Among the three components, CUR as a most active component of turmeric has the highest concentration in the total spice [9]. Turmeric and its ingredients have been applied in historical medicine for treatment of several disorders and current physiological studies have been investigating its fruitful effects [10]. According to the cultured cells, animal models, and human clinical trials findings, turmeric and CUR may be effective treatment for immunosystem disorders [11], neurodegenerative disorders [12], coronary artery diseases [13], respiratory failures [14], gastrointestinal diseases [15], urinary system failures [16], parasitic infections [17], joint pain, inflammation [18], and dental problems [19]. Turmeric and its main ingredients have also been elucidated to control anticancer [20] anti-microbial [21], and anti-genotoxic effects [22]. The health effects of turmeric may stem from its main ingredients such as CUR. The antioxidant, anti-apoptotic, anti-inflammatory and immunomodulatory activity of CUR lead to the control of reverse destructive processes [23].

Furthermore, it has also been illustrated to have the protective effects and diseases management against toxic agents-induced toxicity through various mechanisms [24]. The neuroprotective

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effect of CUR has been reported to have the effects against some toxic materials [24]. However, different from the flavonoids, the fruitful effects of CUR in the act of toxin materials remain nascent in current literature. Therefore, this review aimed to provide an updated overview of studies on the therapeutic aspect of CUR versus neurotoxicity produced by neurotoxic agents.

1.2. Chemistry and structural characterization of CUR

CUR [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane, 1] (Figure 1) belongs to a class of chemicals called flavonoids which induces turmeric's yellow color [25]. Turmeric consists of 2–5% CUR. For the first time, CUR was purified from turmeric, and the chemical formula was found as diferuloylmethane [25]. Recent study shows that CUR's samples include nearly 4% bisdemethoxycurcumin, 20% demethoxycurcumin, and 76% diferuloylmethane [26]. According to these structures, CUR has a seven carbon linker and three major functional groups including an alpha, beta-unsaturated beta-diketone moiety and an aromatic o-methoxy phenolic group [26]. The antioxidant activity of CUR is related to the o-methoxyphenol group and methylenic hydrogen and it also contributes an electron/hydrogen atom to free radicals. The alpha, beta-unsaturated beta-diketone moiety strongly via Michael reaction acts with protein thiols [26]. CUR acts as a chelator of heavy metals via interaction of beta-diketo group with transition metals, thereby decreasing metal toxicity [27]. CUR is a hydrophobic compound and mostly dissolvable in acetone, oils, ethanol, and, dimethylsulfoxide. In acidic condition, the dye of turmeric/CUR changes from amber to dark red [26]. Among three analogs, CUR exhibits most potent activity in some systems [28]. CUR is metabolized into curcumin sulfonate and curcumin glucuronide after orally prescription and metabolized into hexahydrocurcuminol, tetrahydrocurcumin (THC), and hexahydrocurcumin after *i.p.* injection [28]. THC has been activated in some circumstance; however, the biological activity of CUR is not known [28].

1.3. Safety study of CUR

Safety of CUR has been indicated for many years; however, its innocuousness is not clear as pharmaceutical formulations at high doses in the dietary matrix. Animal studies indicated safety of this compound. US National Cancer Institute (NCI) indicated that CUR administration in monkeys, dogs, and rats at doses of up to 3.5 g/kg for up to 3 months has not any adverse effects [29]. Various studies indicated that dietary CUR administration at 2% of the diet in rats and mice has no toxicity. Human studies also confirmed that dietary administration of turmeric (1.5 g/d, equating to 150 mg/d), was safe for human [30]. Administration of 0.55 g and 1.65 g CUR per day to person with inflammatory bowel for 28 d had no any adverse effects [31]. Patients with rheumatoid arthritis who received 1.2–2.1 g of oral CUR daily for 2–6 weeks had no clinical manifestations of toxicity [32]. Adverse effects were not seen in patients with high-risk premalignant conditions or pre-invasive malignant that received 8 g of oral CUR per day for 3 months [33]. Cheng *et al.* 2001 indicated that oral administration of a dose of CUR from 500 to 8000 mg/d for 3 months had not any toxic effect in patients with Bowens disease, oral leukoplakia, resected bladder cancer, stomach metaplasian, and cervical intraepithelial neoplasm (CIN) [33]. Toxicity was not observed in patients with advanced colorectal cancer that used a dose of 440–2200 mg/d extract of *Curcuma*, equivalent to 36–180 mg CUR, for up to 4 months [34]. Until one month of treatment, neither CUR nor its metabolites were found in the urine and plasma but both curcumin sulfate and CUR were observed in feces. Toxicity was not found after administration of CUR ranging from 500 to 12000 mg in healthy human volunteers [35]. Low concentrations of CUR were observed only in the serum of patient that consumed 10000 or 12000 mg/d of CUR [36]. Even histological examination showed that CUR treatment improved precancerous lesions in some cases, including two patients with intestinal metaplasia of the stomach, 2 patients with Bowens disease, one patient with bladder cancer, and one patient with CIN could be promoted into a drug for the treatment and prevention of disorders including cancer. Because of its weak bioavailability, oral consumption of CUR at low levels are not performed outside the gastrointestinal tract [35]. Therefore, the oral consumption of CUR does not cause cytotoxic concentrations outside the gastrointestinal tract. However, few studies indicated adverse effects of CUR and curcuminoids in some situation. *In vivo* study indicated that CUR acted as an iron chelator and induced iron deficiency anemia in mice fed with diets poor in iron [37]. This proposes that CUR deteriorates iron metabolism, especially in people with iron deficiency. CUR has also been found to disturb the activity of the drug-metabolizing enzymes including glutathione-S-transferase, cytochrome P450, and UDP-glucuronosyltransferase [37]. The inhibition of these enzymes may increase the plasma levels of some chemicals and it may causes toxicity [37]. These toxic effects of CUR may be also induced by reactive oxygen species (ROS) [38]. Animal experiments have indicated that, despite the fact that a low concentration of CUR has antioxidant effects, higher levels of CUR induce the ROS levels [38]. The low clinical efficiency of CUR treatment in the cancer diseases has been discussed recently [39]. However, the some adverse effects were observed in patient with cancer. In this context, developed diarrhea was observed in patients with developed gastrointestinal cancer, after CUR treatment for up to 4 months [39]. According to the present preclinical data, CUR administration should be prescribed cautiously in patients with certain conditions [39]. However, the concentration of CUR applied in different investigations is not clear due to its various content in the various type of turmeric [39]. Although there is study concentrated on the adverse effects of CUR, it is significant to have a document indicating that CUR has therapeutical effects and acts as an antidote agent against toxic materials [39].

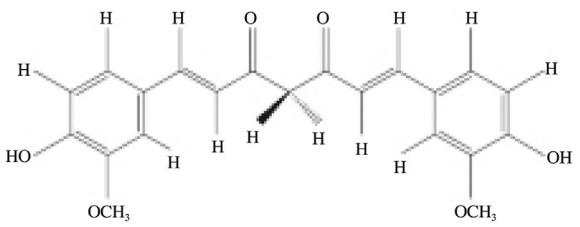

Figure 1. Chemical structure of curcumin.

2. Methods

Online papers were considered through various search websites including PubMed, Iran Medex, Medline, Google Scholar, and Scopus from 2014 to 2016 to find reviews, editorials, and articles about antidotal effects of CUR against neurotoxic agents. Key words were CUR, neurotoxicity, and neurotoxic agents.

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