Antidotal effects of curcumin against neurotoxic agents: An updated review

Tahereh Farkhondeh1, Saeed Samarghandian2✉, Fariborz Samini3

1Department of Immunogenetics, BuAli Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran
2Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran
3Department of Neurosurgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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]. *Curcuma 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 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 ((1E,6E)-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 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 hexahydrocurscinol, tetrahydropcurcumin (THC), and hexahydrocurncin 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 neoplas (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 curcinoid 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 antioxidative 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].

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.

3. Protective effects of CUR against agents-induced neurotoxicity

3.1. D-galactosamine

D-galactose (GalN), causes oxidative stress leading to the damage to hippocampal neurons, modification in mitochondrial function, and reduction in protein content; hence, it is used to induce pathways involved in aging processes in animal models [40], CUR contribution in preventing GalN induced aging has been reported. It was observed that oral administration of CUR (50 mg/kg and 100 mg/kg) for 63 d improved the cognitive defect induced by GalN in rats. It was suggested that CUR improved GalN induced neurotoxicity by decreasing lipid peroxidation, protein oxidation (PO), and cleaved caspase-3 (CASP3) expression, as well as increasing antioxidant content in the neuronal mitochondria [36].

3.2. Fluoride (F)

F, the major inorganic ion, is well-recognized as a global problem that causes various diseases such as neurological failures and F-induced neurological diseases by disrupting neuronal cell bodies in selective brain areas [41]. F may penetrate into the brain, gather in hippocampus and induce process involved in the oxidative stress pathways [41]. The possible therapeutic aspects of CUR versus F-induced oxidative stress in hippocampal regions of mice have been reported. It was indicated that cotreatment of CUR (30 mg/kg) with F (120 ppm) for 30 d resulted in severe decrease in lipid peroxidation with a reduction in neurodegeneration in adult mice [42].

3.3. Formaldehyde (FA)

Formaldehyde is an aldehyde compound with highly toxic property for human and all animals [43], FA induces cellular DNA damage via rising the generation of ROS. It was seen that CUR (100 mg/kg) treatment for 15 d improved oxidative stress induced by FA in rat brain [43].

3.4. Rotenone (ROT)

ROT, crystalline isoflavone, used as an insecticide and pesticide that is mildly toxic to human and other animals [44]. It has reported that ROT injection into rats caused the development of signs resembling to those of Parkinson's disease (PD) [44]. PD is a disease in brain related to age that is connected with <70% of substantia nigra's neurons that release dopamine [44]. Oxidative damage and mitochondrial disorders are involved in the pathogenesis of PD. CUR has been showed to act as a neuroprotective on an animal model for induction of PD [44]. It was indicated that CUR ameliorated tyrosine hydroxylase (TH) and motor dysfunction levels in the substantia nigra of ROT-injured rats [44]. In addition, CUR decreased ROS and malondialdehyde (MDA) levels and also raised glutathione (GSH) content. Indeed, CUR ameliorated ROT-induced damage, through nuclear factor erythroid 2-related factor 2 (Nrf2) and the phosphorylation of Akt [44]. This study proposed that CUR ameliorated ROT-induced oxidative damage to the dopaminergic neurons in the Snap of animals through the Act/Nrf2 pathway [44].

3.5. Vincristine (VCR)

VCR is used as a chemotherapy agent to treat a number of types of cancer [45]. VCR may induce peripheral neuropathy through oxidative stress and inflammation in neurons and lead to discontinuation of chemotherapy [45]. The therapeutic effect of THC 40 mg/kg and 80 mg/kg against VCR induced neuropathy in animals has been observed. Hot plate, Randall–Selitto test, cold plate (thermal) test, formalin test and nociception indicated the preventive effect of THC in rats that received VCR. Total calcium, lipid peroxidation, nitric oxide (NO) and TNF-α levels in sciatic nerve tissue homogenate was improved in THC (80 mg/kg) treated group versus non-treated rats that received VCR. In addition, GSH activity and the levels of catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) increased in treated rats. Histopathological assessment on sciatic nerve also confirmed the therapeutic effect of THC versus the VCR. The neuroprotective effects of THC (80 mg/kg) may be on account of anti-inflammatory, anti-nociceptive, antioxidant and calcium inhibitory effects [46].

3.6. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

MPTP is a neurotoxin precursor to MPP+, which induces PD via inducing oxidative stress in the substantia nigra and destroying dopaminergic neurons [47]. The therapeutic effect of CNB-001, a novel pyrazole derivative of CUR, against MPTP in an experimental method of PD was reported. Application of CNB-001 (24 mg/kg) improved motor impairment and oxidative stress and decreased dopamine transporter, vesicular monoamine transporter 2 (VMAT2) and tyrosine hydroxylase (TH) expressions in mice exposed to MPTP. These data indicated the therapeutic effect of CNB-001 for treatment of PD [48].

3.7. Tetrachlorobenzoquinone (TCBQ)

Tetrachlorobenzoquinone is a combined substance of two constant pollutants, pentachlorophenol and hexachlorobenzene [49]. Hexachlorobenzene is used as a fungicide and produced as the generation of industrial interactions [49]. Pentachlorophenol is used as an anti-microbial, anti-sapstain, pesticide, biocide defoliant, wood preservative, and disinfectant agent [50]. It was observed that TCBQ caused the cytotoxicity in PC12 cells by induction oxidative stress and inflammatory cytokines release. TCBQ activates nuclear factor-kappa B (NF-kB) signaling and leads to increase in mRNA and protein expressions of mediators, and inflammatory cytokines such as cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), TNF-α, inducible nitric oxide synthases (iNOS), the production of NO, interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). CUR could prevent the neurotoxic effect of TCBQ by reducing inflammatory responses and oxidative stress in PC12 cells [51].

3.8. Pentylentetrazole (PTZ)

PTZ is an effective drug for circulatory and respiratory stimulant, and depression; however, prevention of its side effects such as
seizures is difficult [52]. PTZ is commonly used in animal models to induce seizures [53]. The therapeutic effect of CUR against PTZ induced oxidative stress, mitochondrial dysfunctions, and cognitive defects in a rat model of epilepsy were indicated. CUR (100 mg/kg, p.o.) injection ameliorated cognitive deficits in PTZ rats. The current research proposed that CUR treatment could be able to control cognitive functions via ameliorating mitochondrial functions and oxidative stress (decreased ROS generation, PO, lipid peroxidation, and increased GSH activities) [54]. The effect of CUR on the development of kindling in PTZ kindled rats and its role in apoptosis and neuronal damage has been also indicated. CUR (300 mg/kg) elevated the latency to clonic seizures, myoclonic jerks, generalized tonic-clonic seizures, and reduced the number of myoclonic jerks and ameliorated the seizure score. CUR reversed PTZ kindling by apoptosis and ameliorating oxidative stress [54].

3.9. Sevoflurane (SEVO)

SEVO is a highly fluorinated methyl isopropyl ether, nonflammable, sweet-smelling applied as an inhalational anesthetic for maintenance and induction of general anesthesia that is able to cause neurological dysfunctions in the brain and leads to neuronal damage later in life [50]. It was reported that CUR prevented the SEVO anesthesia-induced cognitive defects in mice. CUR improved early memory-related proteins, inflammation, apoptosis, oxidative-nitrosative stress, and later cognitive dysfunction in animal exposed to SEVO. This study indicated that CUR prevented the SEVO exposure-induced cognitive defects later in life via controlling oxidative nitrosative stress, inflammation, and apoptosis in mice brain [50].

3.10. Sodium nitroprusside (SNP)

SNP, an inorganic compound, is used as a vasodilator drug to reduce blood pressure by releasing NO [55]. However, many adverse effects such as brain damage may occur during treatment with SNP [55]. The therapeutic effects of Theracurmin (®), and CUR, versus SNP-induced oxidative damage in cerebrum, has been indicated [56]. Oral treatment of Theracurmin (®) (1 g/kg and 3 g/kg) mainly ameliorated brain damage and motor impairment induced by SNP. However, CUR (300 mg/kg, orally) has no protective effect against motor dysfunction induced by SNP. This study indicated that CUR and Theracurmin (®) improved brain damage and motor impairment via inhibiting oxidative stress. However, Oral administration of Theracurmin (®), was more effective than CUR due to its high bioavailability [56].

3.11. Acrylamide (ACR)

ACR with the chemical formula C3H3NO, a vinyl monomer, is a chemical agent that used in several industrial processes, including preparing dyes, paper, and plastics, caulk, food packaging, and some adhesives and in treating drinking water and wastewater [57]. ACR is seen in cigarette smoke. ACR formation may occur during food processing with high-temperature cooking, such as roasting, frying and baking [57]. In this situation, the interaction between sugars and an amino acid results in acrylamide formation [57]. ACR is a highly toxic agent that is easily absorbed by the skin and distributed throughout the body organs. The neurotoxicity of ACR has also been observed in exposed human and animals [57].

The ameliorative effect of CUR versus ACR-induced oxidative stress in the neuronal cell of Drosophila was reported. CUR decreased the incidence of ACR-induced mortality, and ameliorated the activities of oxidative stress markers, mitochondrial function in the fly head region. In addition, CUR reduced acetylcholinesterase and dopamine levels in fly head region [58]. The efficacy of CUR against ACR-induced mitochondrial dysfunction, neurotoxicity and oxidative stress in an experimental model has been indicated. CUR (50 mg/kg) significantly ameliorated ACR-induced oxidative stress (reduced levels of ROS, MDA and NO) and restored the GSH activities and the levels of brain regions (cortex – Ct, cerebellum –Cb) and anti-oxidant enzymes in sciatic nerve (SN). CUR decreased ACR-induced increase in cytosolic calcium activities in cerebellum and sciatic. In addition, CUR ameliorated acetylcholinesterase activity and dopamine level in brain regions. Taken together these indicated that CUR may be therapeutic as effective agents in the management neuropathy problem induced by ACR [59].

3.12. Streptozotocin (STZ)

Streptozotocin (2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose)) is produced by Streptomyces achromogenes and that intracerebro-ventricular (ICV) STZ injection made Alzheimer's model [60]. Neuroprotective effects of CUR in ICV injection STZ-induced Alzheimer's model in rodents have been observed. It was indicated that CUR prevented oxidative stress and extrinsic apoptosis in ICV-STZ-injected rats. CUR treatment decreased the hippocampal β-amylloid storage and ameliorated cognitive disorder in passive avoidance tasks and Morris water maze. Therefore, ICV-STZ-induced Alzheimer's dementia induces apoptosis in hippocampus, which could be decreased by treatment of CUR [60].

3.13. Arsenic (As)

As, a natural ingredient of the earth's crust, is greatly divided in the whole of the environment and it belongs to the heavy metal group [55]. Its inorganic form is highly toxic. Human faced to high amount of As occurred via smoking tobacco, industrial processes, food, drinking contaminated water, and irrigation [55]. As exposure causes oxidative damage in the tissues including brain [55]. The protective effects of nanoparticles-encapsulated CUR (CUR-NP) and CUR versus sodium AS-induced neuronal oxidative damage in rat has been indicated. Treatment with CUR and CUR-NP ameliorated increased lipid peroxidation, GPx, GSH content and the levels of SOD, CAT, and glutathione reductase (GR) in the brain of rat exposed to As. The histopathological evaluation also confirmed therapeutic effects of CUR-NP and CUR. However, CUR-NP acts more effective than CUR on As-induced oxidative damage brain tissue [61].

3.14. 3-Nitropropionic acid (3-NPA)

3-nitropropionic acid (C3H7NO3) is a mycotoxin that is generated by a number of fungi and seen in some food and traditional Chinese medicines [62]. It is a potent mitochondrial
inhibitor and toxic to humans. 3-NPA is also applied for causing signs of Huntington's disease. CUR has been shown to have therapeutic activity by reducing oxidative stress. The neuroprotective effect of CUR versus 3-NPA induced neurotoxicity in rats has been indicated. Injection of 3-NPA (10 mg/kg for 21 d) illustrated the biochemical changes (lipid peroxidation, nitrite (NO₂), and GSH level), reduction in body weight and neuroinflammatory factors (TNF-α and IL-1β level), and declination of motor function and neurochemical (DA, NE, 5-HT, DOPAC, 5-HIAA and HVA). CUR (25 mg/kg and 50 mg/kg) administration once daily for 21 d ameliorated these modifications. This study indicated the therapeutic effect of CUR versus 3-NPA-induced neurotoxicity.

### 3.15. Oxaliplatin (Oxa)

Oxa is a chemotherapy agent and used to treat metastatic colorectal cancer. However, a serious dose-limiting side effect such peripheral neurotoxicity is the major concern about oxaliplatin use in the cure of cancer tissues. It is observed that its neurotoxicity caused by oxidative stress limits its therapeutic application in long-term use. The neuroprotective effects of CUR on respiratory chain complexes in the brain and Oxa-induced mitochondrial oxidative stress of rats have been reported. Pretreatment with CUR significantly improved protein carbonyl content induced by Oxa and the mitochondrial lipid peroxidation levels. CUR improved modified enzymatic antioxidants and non-enzymatic and also complex enzymes of mitochondria. It was suggested that CUR reduced Oxa-induced side effects in the brain by ameliorating oxidative stress as document by mitochondrial disorder. Table 1 showed the protective effects of CUR against agents-induced neurotoxicity.

### 4. Conclusions

In this study, several animal studies from 2014 to 2015 were summarized to find the protective effects of CUR against toxicities agents. According to the results of different studies, CUR acts as an antidote in neurotoxicity induced by toxic agents. GalN, F, FA, ROT, MPTP, TCBQ, ACR, STZ, As, 3-NPA, and Oxa are some examples of chemical agents that CUR could protect the brain against their toxicity. It is also confirmed CUR with excessive therapeutic effects, showed protective effects against some chemical drugs such as VCR, PTZ, SEVO, STNP which have organ toxicities, particularly in overdose. Different mechanisms such as inhibition of oxidative stress, inflammation and apoptosis are mentioned in CUR antidotal effects. In conclusion, CUR has protective effects against toxicities induced by toxic agents. However, more studies were needed to verify the antidotal effects of CUR in human intoxications.

### Conflict of interest statement

We declare that we have no conflict of interest.

### References


