

The Therapeutic and Protective Role of Curcumin in Drugs and Chemicals Intoxication

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Abstract

Curcumin is considered one of the natural promising complementary or alternative medications. Curcumin has been approved as a safe herbal spice and coloring food additive wherein it is an active ingredient of turmeric. It has a wide spectrum of therapeutic influences besides its chemoprotection and cytoprotection effects because of its potency to scavenge the free radicals that are produced by endogenous and exogenous harmful stimuli. A number of studies investigated the protective and therapeutic role of curcumin in the intoxication management of drugs and other chemicals. The results of these studies concluded that curcumin has an eligibility to ameliorate the toxic manifestations of some drugs like anti-tuberculosis drugs, chemotherapeutic drugs, analgesics, psychiatric and anesthetic drugs besides the toxicity of some environmental and chemical pollutants such as heavy metals, insecticides, and other toxic agents such as nicotine, benzo-pyrene, alcohol, and aflatoxins.

Keywords: Antioxidant, Ameliorative, Protective

1. Introduction

Complementary or alternative medicine is considered the most suitable used term to describe the traditional therapies. Alternative medicine is the medical practice without the use of drugs or the use of other therapeutic agents as a substitute for drugs such as herbal medicine or acupuncture. Recently, research efforts have been focused on the safety and efficacy of some different types of alternative medicine such as herbal medicine because of the possibility of high risk during the use or the utilization chance in drug discovery¹.

Curcumin is one of the natural alternative medicines wherein it is an active ingredient of turmeric (*Curcuma longa*) that is a member of the ginger family. Curcumin has been approved as a safe herbal spice and coloring food additive by the Food and Drug Administration (FDA) in the USA, the Joint FAO/ WHO Expert Committee on Food Additives of the Food and Agriculture Organization/

World Health Organization, and the Natural Health Products Directorate of Canada². It is a yellow-orange dye and has a wide spectrum of therapeutic effects; it is considered antioxidant, anti-inflammatory, anticancer and antimicrobial beside its chemoprotection and cytoprotection effects because of its ability to scavenge the free radicals that are induced by endogenous and exogenous noxious stimuli³.

In the last years, a number of clinical trials studies proved the clinical efficacy of curcumin in the treatment of some human diseases wherein these studies indicated to its safety, tolerability, and nontoxicity even at high doses⁴. These researches also concluded to the proofs that curcumin has an ability to modify multiple cell signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, cyclooxygenase, endothelin-1, malondialdehyde, glutathione, prostaglandin, C- reactive protein, pepsinogen, phosphorylase kinase, transferrin receptor, triglyceride, total cholesterol, and transforming

growth factor. So, more attention was paid by some toxicologists to utilize the therapeutic efficacy of curcumin in the prevention and treatment of some intoxication cases based on its antioxidant effect⁵.

Therefore, this study will attempt to focus on the protective and therapeutic role of curcumin in the drugs and chemicals intoxication cases based on the available published data.

2. Drugs Intoxication

Drugs intoxication is a critical medical challenge faces physicians during their work in the hospital, especially for chronic disease patients. Searching for the drugs substitutes in many situations is difficult or impossible. Therefore, the use of alternative or adjuvant agents to prevent or protect the body against the adverse toxic effects of the used drugs becomes a novel trend in the recent medical researches.

In this context, the prolonged use of anti-tuberculosis drugs is considered one of these challenges. It is known that anti-tuberculosis drugs may lead to a liver dysfunction in a long grand wherein isoniazid, rifampicin, pyrazinamide, and ethambutol induce hepatotoxicity that represents a major problem for these patients. Adhvaryu *et al.*⁶ carried out a randomized controlled clinical trial to control hepatotoxic attacks in the tuberculosis patients by using curcumin wherein hepatotoxicity mechanism in these cases is attributed to the oxidative stress, the reduced glutathione level, and the activation of CYP2E1. Adhvaryu and his colleagues concluded that curcumin could play an effective role as a preventive agent in the cases of anti-tuberculosis drugs induced-hepatotoxicity.

It is also known that the toxic adverse effects of chemotherapeutic drugs represent a major problem for the oncologists in the treatment strategy of cancer in spite of chemotherapy is the cornerstone of the cancer therapy besides the radiotherapy. From this the point of view, the researchers' efforts were directed in the previous years to find a solution for this medical problem. Therefore, curcumin as one of the herbal medications was investigated as a modulator agent for the toxic effects of chemotherapeutic drugs in many studies. Etoposide emerges as one of these chemotherapeutic drugs which curcumin succeeds to overcome its adverse toxic effects wherein etoposide has potent anti-neoplastic activity able to treat the different types of cancer such as lung and testicular cancer

and lymphoma. Abdel-Fattah and his colleagues⁷ demonstrated that curcumin has the ability to reverse the toxic reproductive effects of etoposide; it can eliminate the harmful effects of etoposide on the spermatogenesis, serum testosterone level, and the oxidative stress as well as toxic histopathological changes. In addition, they clarified also that the protective effect of curcumin is based on its antioxidant, anti-inflammatory and antiapoptotic effect.

In the same context, curcumin proved its efficacy as a chemopreventive agent against another anticancer toxicity such as cisplatin that is considered one of the most efficient and commonly used antineoplastic agents in the testicular tumors treatment. Tousson *et al.*⁸ discovered that curcumin can counteract cisplatin-induced testicular dysfunction through ameliorating the oxidative stress and improving the antioxidant defense system preventing all cisplatin toxic effect by recovering the abnormality of sperm and the plasma testosterone level.

Every day and with the research development, curcumin prove its credentials as a preventive agent against the toxicity of more chemotherapeutic drugs such as doxorubicin that lead to debilitating consequences in the heart, liver, kidneys, brain and reproductive organs. The study of Jain and Rani⁹ suggested that curcumin could exert a positive impact on doxorubicin-induced cardiotoxicity while the study of Mohajeri and Sahebkar¹⁰ reported that the ability of curcumin to abrogate the toxic effect of doxorubicin on the different body organs especially the heart has pertained to antioxidant, autophagy, apoptosis and mitochondrial permeability.

In the related context, Moghadam *et al.*¹¹ used the protective effect of curcumin to prevent the hepatotoxicity of another chemotherapeutic drug that is methotrexate. According to this study, Curcumin can significantly attenuate all toxic biochemical and histopathological changes in the liver that are induced by methotrexate through its antioxidant and anti-inflammatory effects. Furthermore, Avci *et al.*¹² showed that the natural curcumin antioxidant also has protective effects against cyclophosphamide-induced oxidative stress and cardiotoxicity normalizing the toxic biochemical, histopathological and immunohistochemical changes.

On the other hand, some researchers used curcumin as a neuroprotective agent based on the scientific facts that were concluded in the previous studies. These facts indicated to the ability of curcumin to exert a neuropro-

tection in the cerebral ischemia and against excitotoxicity in the cerebral cortical neurons and retinal cultures^{13,14}. Matteucci and his colleagues¹⁵ indicated that over-activation of NMDA receptors may induce an excitotoxicity that is relevant in the pathophysiology of CNS insult. Moreover, they also confirmed the preventive role of curcumin against NMDA-induced excitotoxicity modifying the activity of NMDA receptors.

In addition, more researches focused on the role of curcumin in attenuating the toxic effects of some psychiatric and anesthetic drugs on the different body organs. For example, not limited to, Shaterpour *et al.*¹⁶ reported that curcumin may be co-treatment with lithium in the various psychiatric diseases as a safe additive agent without any drug interaction to prevent lithium-induced nephrotoxicity. Curcumin can react with the reactive species and up-regulation of many cytoprotective and antioxidant proteins leading to an improvement in the renal histopathological and biochemical changes.

Furthermore, Sakr *et al.*¹⁷ conducted their study on the testicular toxicity of fluoxetine that is commonly prescribed for the treatment of depression and anxiety wherein it is a selective serotonin reuptake inhibitor. The results of this study concluded that the concurrent use of curcumin and fluoxetine could ameliorate the testicular abnormalities through a decrease in the number of Bax-positive cells, an increase in testosterone, LH and GSH levels, and a decrease in the lipid peroxidation depending on the antioxidant properties of curcumin.

Another study carried out on one of the commonly used anesthetic drugs in pediatric that is Ketamine; it is a noncompetitive N-methyl-D-aspartic acid receptor antagonist. Ketamine causes thymocytes toxicity through the apoptotic pathway via the oxidative stress induction, mitochondrial dysfunction, and the mitochondrial cell death. In this study, Pavlovic and his colleagues indicated that the high concentration of curcumin can decrease the ketamine-induced toxicity in thymocytes associated with a decrease in the apoptosis rate and caspase-3 activity by a reduction in ROS production and prevention of mitochondrial dysfunction¹⁸.

Sheweita *et al.*¹⁹ also showed that pretreatment with curcumin prior to the administration of tramadol can alleviate cardiac, liver and kidney toxicity that is caused by tramadol via the augmentation of the antioxidant defense mechanism, scavenging the ROS, and the oxidative stress suppression. As a result of this, a large number

of patients can utilize tramadol as an analgesic medication in chronic pain conditions for a prolonged period without its toxicity risk. Therefore, Sheweita and his colleagues recommended that these patients should use curcumin to alleviate the probable toxicity of tramadol.

Moreover, the study of Tung *et al.*²⁰ demonstrated that curcumin has a protective effect against paracetamol-induced hepatotoxicity via an increase in the activities of antioxidant enzymes in hepatic tissues such as catalase, glutathione peroxidase, and superoxide dismutase associated with a decrease in the lipid peroxidation. Likewise, Elshama *et al.*²¹ proposed curcumin as a protective antioxidant agent against the toxicity of another drug that is atorvastatin wherein they reported that concurrent administration of curcumin with subchronic use of atorvastatin can modulate the histopathological, ultra-structural and biochemical manifestations of myotoxicity in the different types of the muscles.

3. Chemicals Intoxication

Recently, the environmental and chemical pollutants represent another major challenge because of its health hazards on humans. The toxicologists have voiced concern that the possible intoxication mechanism of the most environmental and chemical pollutants is the oxidative stress. It is known that the excessive production of reactive oxygen species (ROS) causes an imbalance between oxidants and antioxidant systems wherein ROS are high reactive to lipids, protein, membrane, and DNA leading to a lipid peroxidation enhancement and a rapid cellular damage.

In last years, many researches provide new insights into the beneficial usages of curcumin in protection or treatment the toxicity of the environmental and chemical pollutants. Heavy metals toxicity is considered one of the serious environmental and industrial intoxicants wherein lead, mercury and arsenic are believed to be the most toxic elements that cause oxidative stress and toxicity. According to the study of Sudjarwo *et al.*²² lead may induce the testicular toxicity based on the oxidative stress mechanism, so the use of curcumin can improve the toxic testicular histopathological changes, increase the count, motility, and viability of the sperm, and also increase the antioxidant enzymes activities besides a decrease of testicular malondialdehyde (MDA). From the results of another study that was conducted on the lead toxicity,

Baxla and his colleagues²³ concluded that the curcumin also could have a promising protective role against lead-induced hepatotoxicity.

Arsenic is one of the above-mentioned serious toxic elements wherein it is considered carcinogen. At the same time, arsenic may induce apoptosis in the cancer cells, so it is used to treat acute promyelocytic leukemia. Therefore, a renewed attention towards arsenic is paid because of its double roles as a toxic and therapeutic agent. Furthermore, the drinking of the contaminated groundwater by arsenic represents a major health problem affecting a large number of population in many developing countries²⁴. According to Karim *et al.*²⁵ curcumin succeeded to protect the body against the biochemical disorders that are caused by arsenic toxicity while Mathews and his colleagues²⁶ confirmed that curcumin has hepatoprotective effect against the liver toxicity which is also induced by arsenic.

Mercury is ranked as a third element of the most serious toxic elements on the earth by the US government agency. Mercury was increased almost triple times in the atmosphere by the human civilization activities and then its burden on human health is rising wherein it remains in the circulation system for several years. Thus, it is believed to be a more potent neurotoxin, besides it is considered hepatotoxic and nephrotoxic agent²⁷. Agarwal and Saxena²⁸ investigated the role of curcumin in the treatment of mercury intoxication; they suggested that curcumin could enhance the mercury elimination and reduce the mercury accumulation in the body besides its ability to improve hepatic and renal functions via regulating their biomarkers.

Cadmium is also one of the toxic heavy metals wherein human exposure for its hazards is increasing nowadays because there is an increase in its level in the environment because of industrial activities. It is accumulated in the different body organs such as the kidney, liver, pancreas, and testis. Cadmium induced-renal toxicity is considered a major trouble in comparison to its impact on other organs wherein cadmium has a preferential uptake via the receptor-mediated endocytosis in the renal proximal tubule generating the reactive oxygen species and activating the cell death pathways²⁹. Akinyemi *et al.*³⁰ revealed that curcumin can inhibit the activities of renal adenosine deaminase and arginase that are involved in cadmium induced renal toxicity besides to the ability of curcumin to increase the activity of non-enzymatic antioxidant as well as increasing the endothelial nitric oxide with a concomitant decrease in the levels of malondialdehyde and

renal biomarkers. Moreover, curcumin can also prevent the cadmium accumulation in the renal tissues because of its chelating ability. Therefore, curcumin is considered a renoprotective agent.

Selenium is one of the essential trace elements that play an important role in the redox management of the body wherein it is necessary for the anti-oxidative enzymes activities such as glutathione peroxidase. It is also known that the high concentrations of selenium may be toxic to the body because it acts as a pro-oxidant which generates the free radicals³¹. Selenium toxicity may affect the liver leading to a significant decrease in the levels of hepatic succinate dehydrogenase, malate dehydrogenase, and lactate dehydrogenase. According to Padmaja and Raju³², the administration of curcumin as an antioxidant causes a less decrease in the levels of these enzymes preventing the oxidative damage that is mediated by selenium and then it protects the liver against its toxicity.

Regarding the efficacy of curcumin that was proved in the treatment of various types of toxicities, the researchers started to direct towards another field to investigate the ability of curcumin to detoxify other chemical compounds intoxication such as insecticides that produce oxidative stress generating the free radicals affecting many body organs.

Pyrethroid is considered one of the neurotoxic insecticides that show a high toxicity and oxidative damage in the brain tissue according to the World Health Organization (WHO)³³. Abdel-Rheim and his colleagues³⁴ reported that the high and medium dose of curcumin can act as an effective antioxidant in the toxicity cases of pyrethroid via reducing the oxidative stress burden and the histological damage. A second study was conducted on another insecticide toxicity (carbofuran) that is an acetylcholinesterase inhibitor and then it is capable of the nerve impulses inhibition. Purushothaman and Kuttan³⁵ confirmed the same previous result wherein the administration of curcumin as an antioxidant can significantly ameliorate the carbofuran toxicity and improve the carbofuran-induced neurobehavioral difficulties. Moreover, Curcumin can also restore the reduced mitochondrial enzymes in the hepatic tissues and increase hepatic carbohydrate metabolizing enzyme hexokinase and glucose 6-phosphate dehydrogenase.

In another context, curcumin as a food additive is used to overcome the neurotoxicity of another food additive that is monosodium glutamate wherein curcumin is known that it has a neuroprotective effect against the different neurotoxic insults. Khalila and Khedrb³⁶ sug-

gested that curcumin as a complementary supplement with monosodium glutamate can protect the neural cell via decreasing mGLUR5 and NMDA2B receptor expression, and TNF α level.

Furthermore, the study of Mathuria and Verma³⁷ suggested co-administration of curcumin as a complementary agent with the contaminated food by aflatoxins that are toxic fungal metabolites produced by *Aspergillus flavus*. They showed that curcumin could ameliorate aflatoxins toxicity via improving the biochemical markers disorders such as serum creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In the related context, curcumin can modulate another aspect of aflatoxins intoxication wherein it can restore the morphologic features of sperm and improves its viability and motility³⁸.

In addition, there are many trials, which were carried out by the researchers to use the beneficial effects of curcumin in alleviating other chemicals toxicities. The toxicity of chemical components of cigarette smoke is considered one of the common chemical intoxications wherein it is toxic and carcinogenic mixture according to WHO. Cigarette smoke contains an estimated 5000 chemicals such as nicotine and benzopyrene that are responsible for the development of cardiovascular diseases and lung cancer³⁹.

Sinha and Maiti⁴⁰ indicated to the possibility of curcumin use to ameliorate the harmful effects of nicotine. It may be used in the diet as a potential blocker of nicotine to protect the health of population while Kalpana and his colleagues⁴¹ suggested that curcumin may be a promising agent in the treatment of hyperlipidemia and atherosclerosis wherein it has an anti-hyperlipidemic effect against nicotine-induced toxicity.

In the related context, the study of Abou-El-Naga⁴² indicated to the role of curcumin in amelioration the toxic effect of benzopyrene on some organs of adult and newborn wherein benzopyrene is a carcinogenic polycyclic hydrocarbon and one of the components of cigarette smoke. Likewise, in the toxicity cases of benzopyrene, the use of curcumin can recover the histological view of ovaries and uterus associated with an improvement in the neonatal growth retardation, and a reduction in the malformation rate and the skeletal development retardation.

Finally, curcumin proved its efficacy as a protective agent against a number of hepatotoxins. For example, but not limited to, curcumin can provide an effective protection against the liver toxicity and the oxidative damage that is induced by thioacetamide. Curcumin can attenuate

the lipid peroxidation and oxidative stress in the tissues improving the liver functions tests based on enhancing the enzymatic antioxidant defense mechanism⁴³. In the same way, curcumin exhibit an inhibitory action against alcohol intoxication that manifests by the reduced acetaldehyde concentration in the blood. Curcumin can also prevent alcohol-induced hepatotoxicity by alleviating the oxidative stress via ERK/p38/Nrf2-mediated antioxidant signaling pathways⁴⁴.

4. Conclusion

Curcumin is one of the natural alternative medicines. Its protective and therapeutic efficacy was utilized by a large number of researchers in the management of intoxicated cases. Curcumin has a great potential for usage by the toxicologists to prevent or cure the toxic manifestations of common toxic agents whatever drugs or chemicals. Many studies revealed that its excellent efficacy is attributed to exerting an antioxidant effect against the oxidative stress mechanism inducing toxicity.

5. Recommendation

In the future, further clinical trials should be carried out to assay the preventive and therapeutic effects of curcumin in human intoxicated cases considering its potential beneficial effects as an alternative or complementary medication.

6. Conflict of Interest Statement

There are no conflicts of interest.

7. References

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