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Hepatoprotective Effects of Curcumin from *Curcuma Longa* L.: A Comprehensive Account

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ABSTRACT

Since time immemorial, man has benefited from the active phytochemicals derived from plants. One such novel medicinal plant is *Curcuma longa,* or turmeric, which has a diverse usage from being a household spice to being a therapeutic gem. The medicinal value of the plant is due to curcumin, a polyphenol. It has remarkable pharmacological properties like antimicrobial, anti-inflammatory, antidiabetic, antimutagenic and hepatoprotective, among many others. In the present account, the hepatoprotective potential of the novel plant has been focused upon due to the increasing cases of various liver diseases in humans that lead to fatalities. The present work attempts to summarize the evidence of hepatoprotective effects of curcumin derived from *C. longa*, mostly in the last two decades, and thereby provide an insightful and comprehensive account. The enumeration of the evidence of curcumin's hepatoprotective properties will open many new avenues for further in-depth investigations.

Keywords: *Curcuma Longa; Curcumin; Hepatoprotective; Liver*

Introduction

Curcuma longa, commonly known as turmeric, is a significant member of the ginger family, Zingiberaceae. The plant, being a native of southeast Asia, is widely cultivated in India, Sri Lanka, China, Jamaica, Indonesia, and Taiwan. This perennial rhizomatous plant reaches a height of up to 1 meter with long, curved alternate leaves. The yellowish-orange rhizome is cylindrical and aromatic.

Taxonomic Position:

Division: Magnoliophyta

Class: Liliopsida

Subclass: Zingiberidae

Order: Zingiberales

Family: Zingiberaceae

Genus: *Curcuma*

Species: *C. longa*

Figure 1: Rhizome of *Curcuma longa* L.

C. longa is known to be a very significant member of the family for its wide spectrum pharmacological properties. Turmeric has been very well documented in Ayurveda for its therapeutic potential and described in Dashemani Lekhaniya (emaciating), Kusthagna (anti-dermatosis) and Visaghna (anti-poisonous), as presented by YT (1994) in the Charak Samhita of Agnivesh. In the traditional practice of medicine, it is documented to be useful for gastric and hepatic related issues, along with blood-related problems, the wound-healing process, and many dermatological infections (Aggarwal & Sung, 2009; Tung *et al*., 2019).

In Indian homes, this plant is being used in everyday practice for treating various ailments (Krup *et al*., 2013). It is also a household spice that has been used in almost all cuisines in many parts of India as well as other countries like Thailand, China, Iran, etc. for hundreds of years. It is also used cosmetically and in dermatologic diseases (Kocaadam & Şanlier, 2017).

For many centuries, this plant has been used as a potent cure for inflammation and infectious diseases. Among the diverse pharmacological activities like antimicrobial, antioxidant, anticarcinogenic, anti-inflammatory, and antidiabetic, this review is concentrated on the hepatoprotective potential of the novel plant. Since liver damage is lethal for living organisms, it is very important to provide as many possible ways of treatment as possible to prevent liver injury resulting from various causes. So, this review is an attempt to summarize the significant evidence where the role of curcumin derived from *C. longa* has proven to exhibit its protective action in the liver.

The therapeutic value of turmeric is due to the presence of curcuminoid, which is the major bioactive phenolic compound derived it. It is composed of curcumin (1,7-bis(4-hydroxy-3-methoxypheny1)-l,6-heptadiene-3,5-dione) and its derivatives bis-demethoxy-curcumin (BDMC) and dimethoxy-curcumin (DMC).

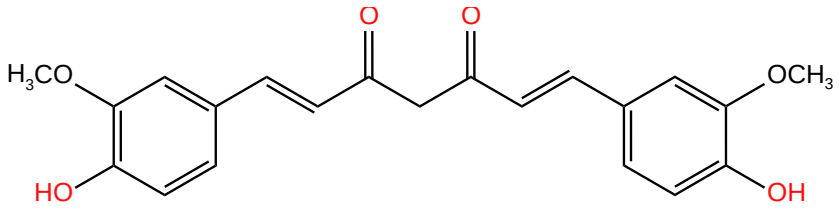

Figure 2: Structure of Curcumin

Extensive research is being done on the cellular, molecular, and biochemical mechanism of curcumin, to infer on the virtue of the active principle (Joe *et al*., 2004; Rivera & Muriel, 2009; Patel *et al*., 2020).

Girish and Pradhan (2008) While studying the efficacy of herbal drugs for treating liver diseases, I have thoroughly focused on the effects of curcumin. They reported that curcumin proved to be very efficient in treating hepatotoxicity that was induced by various toxic drugs, plant toxins and viral agents. Though it has to be also noted that the efficacy of curcumin could be lower due to temperature and light sensitivity and poor bioavailability.

Literature Review

Different Hepatoprotective Activities of *C. Longa*:

Several studies and experimental trials have found that curcumin is successful in attenuating liver damage that is induced by ethanol, carbon tetrachloride (CCl_4) intoxication, thioacetamide, iron overdose, etc. The following discussion accounts for some of the significant reports and findings on the hepatoprotective properties of curcumin from *C. longa*.

Hepatoprotective Activities against Carbon Tetrachloride (Ccl_4)-Induced Liver Damage:

Acute liver damage can be induced in wide varieties of laboratory animals by a well-known hepatotoxic drug, carbon tetrachloride (CCl_4). The liver damage is caused by the generation of reactive oxygen species that cause oxidative stress and eventually cellular damage. It hampers the integrity of the hepatocytes and thereby leads to the release of liver enzymes into the blood serum. Several studies have reported the hepatoprotective effects of curcumin on CCl_4-induced liver damage in many experiments on animal models (Park *et al.*, 2000; Chattopadhyay *et al.*, 2004; Fu *et al*., 2008).

Kang *et al*., (2002) assessed the effect of curcumin on the process of collagen synthesis in rat livers injured by CCl_4 induction. Curcumin was observed to have an inhibitory effect on the collagen synthesis and activation of the hepatic stellate cells in both in vivo and in vitro conditions of induced rat liver injury. and thereby, can be used as an anti-fibrogenic agent.

Similarly, in 2004, Gaedeke *et al.*, It was found that curcumin could block the expression of many mediators that were induced by TGF-β in renals cells and thereby exhibiting antifibrotic property.

In a study carried out by Kamalakkannan *et al*., (2005), CCl_4 was given to rats for three months at a dosage of 3 ml/kg/week. There are certain enzymes like aspartate transaminase (AST), alkaline phosphatase (ALP), and γ-glutamyl transferase (GGT), that act as markers, and their concentrations increased. The levels of thiobarbituric acid reactive substances (TBARS) and hydroperoxides in the liver and kidney also increased with a sharp decrease in the activities of enzymic antioxidants like superoxide dismutase (SOD), catalase, etc. Curcumin and its synthetic analogue of bisdemethoxy curcumin (BDMC-A), when orally administered to CCl_4 exposed- rats for three months, were capable of increasing the activities of tissue enzymic antioxidants and glutathione concentration. The levels of marker enzymes and the plasma TBARS also were seen to have increased. This study revealed that BDMC-A had more potential effect than curcumin.

The concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) drastically increase in CCl_4-administered rats, that result in inflammation and damage of liver. This effect was observed to be negated by the administration of curcumin, which prevents liver damage by its antioxidant property and by inhibiting the activation of NF-κB. These observations of the prevention of the production of proinflammatory cytokines were made by Reyes-Gordillo *et al*., in 2007.

In a similar study by Elaziz *et al*., (2010), The effect of *C. longa* extract was observed against the acute hepatotoxicity of CCl_4 which decreased protein content, immunoglobulins, the activity of superoxide dismutase (SOD) and glutathione level. Production of nitric oxide (NO) production, levels of γ glutamyl transferase (γGT), glutamate oxaloacetate transaminase and glutamate pyruvate transaminase were also increased by the effect of carbon tetrachloride. The oral dose of 80 mg per Kg of the powder of *C. longa* for four weeks daily before the carbon tetrachloride injection allowed the activity of superoxide dismutase and glutathione level to elevate, along with prevention of nitric oxide production, and the levels of γ glutamyl transferase, glutamate oxaloacetate transaminase and glutamate pyruvate transaminase also coming to normal ranges. The curcumin of *C. longa* could reduce the effects of CCl_4 of lowering the red blood cells, white blood cells and haemoglobin content. All these findings and parameters well established the protective action of *C. longa* against hepatotoxicity caused by CCl_4.

Sengupta *et al*. (2011) also studied the effect of curcumin in carbon tetrachloride-intoxicated mice, in terms of liver damage. The aqueous extract of turmeric has been found to reduce the levels of SGOT, SGPT and bilirubin, which increase in the serum due to the intoxication of CCl_4, thereby giving a protection from liver damage.

Curcumin was effective in elevating the levels of total antioxidant status (TAS) while reducing the levels of total oxidant status (TOS) and malondialdehyde (MDA) in serum and liver extracts in CCl_4 -induced liver damage. CCl_4 also causes necrosis, fibrosis, along with steatosis and degeneration of hepatocytes. The mitotic activity and cirrhosis in liver also increases due to its effect. Treating the rat models with curcumin showed alleviation of inflammation and steatosis (Hismiogullari *et al*., 2014). Similar reports were put forward by

Fu *et al.,* (2008) where it was reported that curcumin successfully reduced the pathological indexes for hepatocytic death caused by CCl_4 in rat models.

Lee *et al.* (2016) also documented the hepatoprotective activities of curcumin and turmeric extract, from the results of their experiment in CCl_4-induced liver damage in animal model. The peroxidated lipids and the oxygen species produced cause hepatocyte necrosis, inflammation and hepatic fibrosis. Lipid accumulation also occurred in the hepatic damage process. The elevated levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were restored after curcumin treatment. The lipid accumulation was also found to be attenuated.

Recently, Ibrahim *et al*. (2020) has reported that the treatment of crude extracts of *C. longa* and curcuminoid could increase the levels of superoxide dismutase (SOD), catalase and GPx activities, which decrease significantly in CCl_4-induced hepatotoxic rats. As mention ed earlier, the increase in the levels and activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the serum shows the histochemical alteration of the liver. It was also specifically reported that the curcuminoids and silymarin could restore the activities of AST to its normal levels. Histopathological observations also confirmed the protective effect of curcuminoids against histological distortion of the liver in such rats.

Hepatoprotective Activities in Alcoholic Liver Disease (ALD):

Ethanol oxidation generates free radicals and induces the production of toxic metabolites. Oxidative stress leads to the pathogenesis of alcoholic liver disease (ALD). Curcumin, through its antioxidant and anti-inflammatory effects, along with its ability to scavenge free radicals and antifibrotic activity, can exhibit its hepatoprotective nature. (Baliga *et al*., 2018).

An experimental study was carried out by Nanji *et al.,* (2003) in alcohol-induced liver male Wistar rats, where curcumin is reported to inhibit the expression of NF-κB-dependent genes like Tumour Necrosis Factor-α (TNF- α), interleukin 12 (IL-12), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2) and nitric oxide synthase (iNOS). The lipid peroxidation leading to liver damage could be prevented by the treatment of curcumin. Curcumin was also observed to have a significant effect on the accumulation of fat on liver. This was found to be due to the inhibition of TNF-α leading to the reduction of fat storage in liver. The antioxidant mechanism also aided in the reduction of the fatty liver condition in the rats that were treated with curcumin. It was also reported for the first time that curcumin would successfully prevent alcoholic liver disease. The study emphasized on the further clinical trials with curcumin treatment on humans with similar liver disease conditions, to establish its therapeutic usage.

Samuhasaneeto *et al*., (2009) studied liver pathology in the early stages of ethanolic liver damage and the effect of curcumin on it. It was concluded that curcumin improved the histopathological status of the liver by reducing oxidative stress and inhibiting NF-kB activation in female Sprague-Dawley rats.

Curcumin treatment for six weeks in mice that were exposed to ethanol for six weeks in specific dosages, could reverse the effects of liver damage. In this experiment conducted by Rong *et al*., (2012), curcumin was shown to lower reactive oxygen species (ROS) production and enhance antioxidative defense mechanism.

Uchio *et al.* (2017) reported about the inhibition of hepatic oxidative stress and inflammatory cytokine production in mice, suppressing its acute ethanol-induced liver injury by the application of hot water extract of turmeric.

Similar hepatoprotective effect of curcumin in liver damage caused by alcohol in mice was observed by Wang *et al*. (2019). They concluded that curcumin inhibited the endoplasmic reticulum stress and regulated the mitochondrial dysfunction.

Salehi *et al*. (2021) reported the crucial role played by curcumin in inducing the biogenesis of mitochondria, by which the intrinsic and extrinsic apoptotic pathways in alcohol-affected hepatic cells are activated. In this way, curcumin prevents liver cells' degeneration from alcoholic induction.

Very recently, a study done by Chen *et al*. (2023) revealed that curcumin/cyclodextrin polymer complex (CUR/CDP) can inhibited or down regulated the expression of proteins related to DNA damage, and thereby attenuate liver injury caused by ethanol.

Hepatoprotective Activities in Non-Alcoholic Fatty Liver Disease (NAFLD):

Non-alcoholic Fatty Liver Disease (NAFLD) is one of the most prevalently occurring liver disorder which encounters excessive fat accumulation in the liver, without any significant alcohol consumption. An amorphous formulation of curcumin was subjected to patients with NAFLD for 8 weeks to assess its efficacy, in a trial done by Rahmani *et al*. (2016). The fat content of liver of the patients was observed to reduce, along with the total body mass content, cholesterol, glucose and triglycerides.

Mansour-Ghanaei *et al*. (2019) examined that curcumin treatment in a dose-dependent manner could reduce the levels of the liver enzymes like alanine aminotransferase and aspartate aminotransferase.

It has been reported through a detailed investigation by Ahsan *et al.* (2020) that curcumin could prevent the progression of fibrosis, preventing the oxidative stress in liver induced by 8-OH-deoxyguanosine.

Lee *et al*. (2022) recently had validated a quantification method for curcumin and all its derivatives. They also reaffirmed the protective ability of curcumin against NAFLD.

Hepatoprotective Activities in Thioacetamide-Induced Liver Damage:

Thioacetamide (TAA) is a hepatocarcinogenic agent that has a necrotic effect on the liver cells. This necrotic effect was modified into apoptosis, which is caused through the release of cytochrome from mitochondria, followed by the activation of caspases.

Shapiro *et al.* (2006) reported that curcumin directly played a role in improving the survival status of rats by lowering oxidative stress, liver necroinflammation which occurred due to thioacetamide induction.

Thioacetamide-induced liver cirrhosis in rats was examined and found to be prevented by curcumin. Curcumin could prevent liver damage through its anti-inflammatory activity. Hydroxyproline levels and the weight of the spleen were found to be lower, along with reduced oxidative stress, when treated with curcumin (Bruck *et al*., 2007).

Infection due to virus or bacteria, or any toxic chemical damage the hepatocytes. These hepatocytes start an inflammatory response which activate the production of collagen by hepatic stellate cells. It was reported by Wang *et al.* (2012) that curcumin inhibited the activation of hepatic stellate cells, suppressed the inflammatory activity, and also induced apoptosis of hepatocytes, already damaged by thioacetamide. Thereby, curcumin was established its role in inhibition of the thioacetamide-induced hepatic fibrosis as studied in the BALB/c mice.

The ethanolic extract of the rhizome of *C. longa* exhibited hepatoprotective properties on thioacetamide-induced liver cirrhosis of 8 weeks in rats, in an experiment conducted by Salama *et al*. (2013). They showed hepatoprotective effects at oral doses of 250 mg per kg and 500 mg per kg. It worked by inhibiting the proliferation of hepatocytes. The extract could also rise the levels of glutathione and help in hepatic detoxification.

Farjam *et al.* (2014) examined the effect of curcumin treatment in thioacetamide-induced hepatic encephalopathy. This study was done in male Sprague Dawley rats, which showed inflammation and necrotic hepatic tissue after thioacetamide induction. Both the inflammation and necrosis were significantly reduced along with lowering of the levels of ammonia, ALP, ALT and AST, by the treatment of curcumin, in a dose dependent manner.

Hepatoprotective Activities Against Iron and Heavy Metals Toxicity:

A very common effect of toxicity in liver is due to excessive iron deposition in hepatocytes, that produces fibrosis and cirrhosis. In a study done by Reddy and Lokesh (1996), it was inferred that curcumin could prevent the serum levels of AST and ALT, which are important parameters to assess liver damage. The lipid peroxidation levels induced by iron administration in wistar rats, were remarkably reduced by a dosage of curcumin of 30 mg per Kg of body weight for 10 days.

García-Niño *et al*. (2014) investigated the protective action of curcumin on the liver against heavy metals like arsenic, cadmium, chromium, copper, lead, and mercury. It was observed that curcumin could reduce the hepatotoxicity caused by the heavy metals, could prevent histological damage induced by them, and prevent histological injury along with lipid peroxidation and glutathione depletion. The liver's antioxidant enzymes status was also seen to be maintained.

Effect of Curcumin Against Paracetamol, Concanavalin A, and Nicotine:

Oxidative stress often leads to hepatotoxic conditions in liver disorders. Such hepatotoxity was induced by the administration of 500mg/kg of paracetamol in mice, due to which there was a noticeable upgradation in the activities of certain marker enzymes like alanine transaminase, etc. and decreased activity of reduced glutathione and catalase levels. When the mice were pre-treated with curcumin, along with picroliv and ellagic, at doses of 50 mg per Kg and 100 mg per kg administered orally, the levels of these enzymes changed to normal ranges, supporting their hepatoprotective property. This study put forward the suggestion of using these phytochemicals in treating liver ailments (Girish *et al*., 2009).

Concanavalin A is a potent polyclonal mitogen that damages the liver parenchyma through a gradual activation of T lymphocytes, followed by cytokine secretion. Li *et al.* (2014) presented reports of curcuma oil exhibiting hepatoprotective properties in such Con A-induced injury and also chemotherapeutic effect against inoculated hepatoma in mice. They observed that curcuma oil had anti-inflammatory, anti-oxidative and antitumor properties along with several advantages of addressing multiple targets and with minimum side effects.

Curcumin was reported by Salahshoor *et al*., (2016), to increase the liver weight, decrease the levels of nitric oxide in nicotine-treated male mice, thereby posing to be hepatoprotective in nature against nicotine-toxicity.

A widely used pesticide, Carbofuran, exerts harmful effects on the liver of humans along with other animals. The toxic effect of the chemical on blood and liver can be ameliorated by the usage of turmeric extract (Hossen *et al*., 2017).

Some other Significant Hepatoprotective Activities:

Colpitts *et al.* (2014) documented that curcumin of turmeric was able to inhibit the entry of hepatitis C virus of all genotypes into the liver cells of humans, by disrupting virus binding through regulation of membrane fluidity.

Taebi *et al.* (2020) reported that the extract of *C. longa* and curcumin could positively lower the proliferation of human hepatocellular carcinoma cell line (HepG2), in a concentration-dependent manner. They were also observed to increase fatty acid oxidation and reduce the lipid synthesis gene expression.

Discussion

Among many different diseases, those that lead to liver damage are the most deleterious. Since liver diseases due to diverse causes are responsible for many of the human deaths worldwide (Farzaei *et al*., 2018), it is very essential to provide as many ways of treating or preventing liver damage as possible in both modern and traditional medicine. Curcumin derived from *C. longa* has been documented to exhibit hepatoprotective properties against alcoholic as well as non-alcoholic liver disease. It is also reported by many workers to be potent against the damaging effects of the hepatotoxic drug - carbon tetrachloride and also against thioacetamide, paracetamol, concanavalin A, nicotine, iron, heavy metals like arsenic, cadmium, chromium, copper, lead, mercury, etc.

Conclusion

The therapeutic power of turmeric is receiving a considerable amount of attention for its manifold benefits in treating various diseases. Various investigations have concluded that curcumin, the phytochemical from *C. longa*, has the ability to modulate the functions of several signal transductions, which ultimately can attenuate acute or chronic diseases. In regard to medicinal usage, *C. longa* has been the focus of investigation, where, several preclinical and clinical studies proved the virtue of curcumin as a hepatoprotectant, with long-term health benefits. This account enumerates the findings to assert that curcumin has significant protective effect on liver-related diseases through many cellular and molecular mechanisms. This review would provide an impetus for further investigative trials and new drug discoveries utilizing the novel phytochemical, curcumin of *Curcuma longa* L.

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