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Review Article

Evaluation of Combined Curcumin and *Cassia fistula* Therapy in the Management of Hepatotoxicity and Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Hepatotoxicity is a major cause of liver dysfunction resulting from exposure to drugs, chemicals, and xenobiotics, often leading to oxidative stress and inflammatory damage. Curcumin from Curcuma longa possesses strong antioxidant and anti-inflammatory properties that protect hepatocytes by reducing lipid peroxidation and modulating key signaling pathways. Cassia fistula, rich in flavonoids and phenolic compounds, enhances hepatic antioxidant defenses and stabilizes liver cell membranes. The combined use of curcumin and Cassia fistula provides synergistic hepatoprotection by reducing oxidative stress, suppressing inflammation, improving liver enzyme levels (ALT, AST, ALP), and preserving hepatic architecture. This combination represents a promising natural approach for the prevention and management of hepatotoxicity.

INTRODUCTION

HEPATOTOXICITY

Hepatotoxicity describes liver dysfunction or structural damage that occurs following exposure to excessive amounts of drugs or other foreign substances (xenobiotics) [1]. Substances capable of inducing such injury are referred to as hepatotoxins or hepatotoxicants. These agents are clinically significant and include overdosed pharmaceutical drugs, industrial chemicals, naturally occurring toxins such as microcystins, as well as certain herbal medicines and dietary supplements [2,3]. Notably, liver injury may also occur with some medications even when they are used within recommended therapeutic dose limits.

Liver damage can arise not only from the direct toxic effects of the parent compound but also through the generation of reactive metabolites or immune-mediated mechanisms that target hepatocytes, biliary epithelial cells, and the hepatic vasculature [4,5]. In recent years, concerns

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surrounding drug-induced liver injury have intensified, particularly after the U.S. Food and Drug Administration (FDA) withdrew two medications from the market due to severe hepatotoxicity that was not fully identified during pre-approval clinical testing. Such events often heighten public apprehension regarding drug safety and regulatory oversight.

Drug-induced liver injury (DILI) remains the leading cause for post-marketing drug withdrawal and is responsible for more than half of all acute liver failure cases in the United States. Alarmingly, over 75% of idiosyncratic drug-induced liver reactions result in liver transplantation or death [6,7]. Recognizing this burden, both the National Institutes of Health (NIH) and the FDA have launched initiatives aimed at improving the prediction, detection, and clinical management of hepatotoxic events [8,9]. Despite these efforts, hepatotoxicity continues to pose major clinical and regulatory challenges as new therapeutic agents enter the market. Ongoing multicenter and collaborative research programs are expected to further clarify the mechanisms underlying drug-associated liver injury [10].

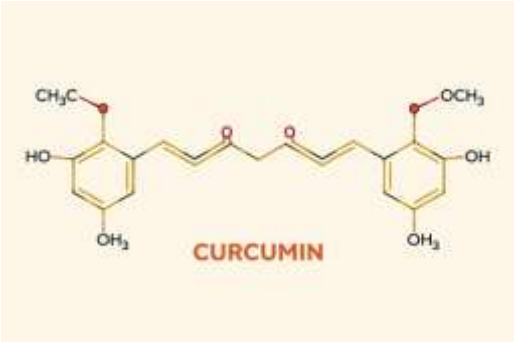
Beyond hepatocytes, hepatic non-parenchymal cells play a pivotal role in the development and progression of liver injury. These include Kupffer cells, sinusoidal endothelial cells, and hepatic stellate (Ito) cells, along with infiltrating immune cells such as monocytes and neutrophils. Kupffer cells and neutrophils are key contributors to inflammatory signaling, releasing pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species that intensify oxidative stress during toxicant-induced injury and ischemia-reperfusion events.

Additionally, Kupffer cells are central mediators of liver damage associated with chronic alcohol exposure. Sinusoidal endothelial cells, distinguished by their fenestrated architecture, are particularly susceptible to injury during cold ischemia-reperfusion, contributing to graft dysfunction following liver transplantation. These cells are also sensitive to certain chemotherapeutic agents, which can lead to veno-occlusive disease. Meanwhile, activation of hepatic stellate cells results in excessive collagen deposition, driving hepatic fibrosis and, ultimately, the development of cirrhosis [11].

MATERIAL AND METHOD

CURCUMIN

Turmeric (Curcuma longa L.) is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. It is native to tropical South Asia but is now widely cultivated in the tropical and subtropical regions of the world. The deep orange-yellow powder known as turmeric is prepared from boiled and dried rhizomes of the plant. It has been commonly used as spice and medicine (Rhizome Curcumae Longae), particularly in Asia. In Ayurveda medicine, turmeric is primarily used as a treatment for inflammatory conditions and in traditional Chinese medicine, it is used as stimulant, aspirant, carminative, cordeal, emenagogue, astringent, detergent, diuretic and martirnet [12-14].



In India and China, wild turmeric (C. aromaticaSalisb., commonly called as Kasthuri

manjal or yujin) is sometimes used as turmeric production [15]. This species is known as C. wenyujin Y.H. Chen et C. Ling in China. It was also occasionally used to substitute Rhizome Curcumae Longae but recently it has been separated as Rhizoma Wenyujin Concisum in the 2005 version of the Pharmacopoeia of People's Republic of China [16]. In Thailand and some other countries, C. domestica Val. is also used as the scientific name of turmeric [17-19] although it is recognized as a synonym of C. longa [20].



(Figure 1)

The image depicts fresh turmeric rhizomes alongside powdered turmeric, highlighting their characteristic bright yellow-orange colour.

It represents the natural source of curcumin, widely recognized for its antioxidant, anti-inflammatory, and hepatoprotective properties.

TAXONOMICAL CLASSIFICATION [20]

(Table 1).

Taxonomic Rank	Classification
Kingdom	Plantae
Subkingdom	Tracheobionta
Super Division	Spermatophyta
Division	Magnoliophyta
Class	Liliopsida
Subclass	Commelinidae
Order	Zingiberales
Family	Zingiberaceae
Genus	*Curcuma*
Species	*Curcuma longa*

Curcuma longa contains bioactive curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) that exhibit strong antioxidant, anti-inflammatory, and hepatoprotective effects. Volatile oils, sesquiterpenes, phytosterols, and phenolic acids act synergistically to enhance its immunomodulatory and tissue-protective properties.

Phytochemical Constituent	Chemical Class	Major Properties
Curcumin	Diarylheptanoid (Polyphenol)	Potent antioxidant, anti-inflammatory, hepatoprotective, anticancer, antimicrobial, neuroprotective
Demethoxycurcumin	Curcuminoid	Antioxidant, anti-inflammatory, anti-tumor, hepatoprotective
Bisdemethoxycurcumin	Curcuminoid	Free radical scavenging, anti-inflammatory, chemopreventive
Turmerone (α-turmerone)	Sesquiterpene	Anti-inflammatory, neuroprotective, antimicrobial
β-Turmerone	Sesquiterpene	Anti-proliferative, antioxidant, anti-inflammatory
Ar-turmerone	Sesquiterpene	Anti-tumor, immunomodulatory, anti-inflammatory
Zingiberene	Sesquiterpene hydrocarbon	Antioxidant, antimicrobial
Curlone	Sesquiterpene ketone	Anti-inflammatory, analgesic
Curcumol	Sesquiterpenoid	Anticancer, hepatoprotective, anti-fibrotic
Curdione	Sesquiterpenoid	Anti-inflammatory, hepatoprotective
Bisabolene	Terpene	Antimicrobial, antioxidant
Stigmasterol	Phytosterol	Anti-inflammatory, cholesterol-lowering

β-Sitosterol	Phytosterol	Immunomodulatory, anti-inflammatory, antioxidant
Vanillic acid	Phenolic acid	Antioxidant, hepatoprotective
Ferulic acid	Phenolic compound	Antioxidant, anti-inflammatory, hepatoprotective

CASSIA FISTULA

Cassia fistula is a moderate sized deciduous plant 10 m tall, flowers yellow, leaves alternate, pinnate, 30-40 cm long, with 4-8 pairs of ovate leaflets, 7.5-15 cm long, and 2-5 cm broad. Fruits pendulous, cylindrical, brown, septate, 25-50 cm long, 1.5-3 cm in diameter, with 25-100 seeds. Seeds lenticular, light brown, lustrous [21]. It is a deciduous tree with greenish gray bark, compound leaves, leaflets are each 5-12 cm long pairs. A semi-wild tree known for its beautiful bunches of yellow flowers and also used in traditional medicine for several indications. A fruit is cylindrical pod and seeds many in black, sweet pulp separated by transverse partitions. The long pods which are green, when unripe, turn black on ripening after flowers shed [22]. The pulp is dark brown in color, sticky, sweet and mucilaginous, odor characteristic, and somewhat disagreeable [23].



Figure 2. Long cylindrical seed pods of Cassia fistula (L.)

Table 2. Phytochemical profile of Cassia fistula with associated pharmacological effects

Phytochemical Class	Major Constituents Identified	Plant Part	Pharmacological Purpose / Biological Activity
Anthraquinones	Rhein, Emodin, Chrysophanol, Physcion	Pod pulp, bark, leaves	Hepatoprotective, antioxidant, anti-inflammatory, mild laxative, detoxification
Flavonoids	Quercetin, Kaempferol, Luteolin, Apigenin	Leaves, flowers	Strong antioxidant, free-radical scavenging, anti-inflammatory, anti-steatotic
Phenolic compounds	Gallic acid, Ferulic acid, Caffeic acid	Leaves, bark	Reduction of oxidative stress, lipid peroxidation inhibition, hepatocyte protection
Tannins	Catechin, Epicatechin, Proanthocyanidins	Bark, leaves	Astringent, antioxidant, liver cell membrane stabilization
Saponins	Triterpenoid saponins	Leaves, seeds	Hypolipidemic, anti-inflammatory, improves lipid metabolism (useful in NAFLD)
Glycosides	Anthraquinone glycosides	Pods, leaves	Detoxification, bile secretion enhancement
Terpenoids	β-Sitosterol, Lupeol	Leaves, bark	Anti-inflammatory, hepatoprotective, cholesterol-lowering
Alkaloids	Trace alkaloids	Leaves	Anti-inflammatory, antioxidant support
Polysaccharides	Mucilage, complex carbohydrates	Pod pulp	Anti-oxidant, gut–liver axis modulation
Proteins & Amino acids	Essential amino acids	Seeds	Tissue repair, liver regeneration

TAXONOMICAL CLASSIFICATION [24,25]

Taxonomic Rank	Classification

Kingdom	Plantae
Subkingdom	Tracheobionta
Super Division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Fabales
Family	Fabaceae
Genus	*Cassia*
Species	*Cassia fistula*

COMBINATION THERAPY:

Curcumin and *Cassia fistula* for Hepatoprotection

The combination of curcumin and *Cassia fistula* offers a promising hepatoprotective strategy through complementary and synergistic mechanisms. Curcumin exerts potent antioxidant and anti-inflammatory effects by scavenging reactive oxygen species, inhibiting lipid peroxidation, and modulating key signaling pathways such as NF-κB and Nrf2, thereby protecting hepatocytes from chemical- and drug-induced injury. In parallel, *Cassia fistula*, rich in flavonoids, anthraquinones, and phenolic compounds, enhances hepatic antioxidant defenses, stabilizes cellular membranes, and supports liver enzyme normalization.

When used in combination, these phytoconstituents act synergistically to reduce oxidative stress, suppress inflammatory cytokine release, prevent hepatocellular necrosis, and promote liver regeneration. The dual action on oxidative damage and inflammatory pathways results in improved biochemical markers (ALT, AST, ALP) and preservation of hepatic architecture, suggesting that curcumin–*Cassia fistula* combination therapy may provide superior protection against hepatotoxicity compared to either agent alone.

CONCLUSION

Hepatotoxicity remains a major clinical and regulatory concern due to its association with drug withdrawal and acute liver failure. The complex involvement of hepatocytes and non-parenchymal liver cells in oxidative stress, inflammation, and fibrotic progression underscores the need for effective and safer hepatoprotective interventions. Natural products with multi-targeted mechanisms offer a promising approach to address these challenges.

Curcumin, derived from *Curcuma longa*, exhibits potent antioxidant, anti-inflammatory, and hepatoprotective activities through modulation of oxidative stress and key molecular pathways such as NF-κB and Nrf2. Similarly, *Cassia fistula* possesses significant hepatoprotective potential owing to its rich content of flavonoids, phenolic compounds, and anthraquinones, which contribute to membrane stabilization, antioxidant defense enhancement, and normalization of liver enzymes.

The combined use of curcumin and *Cassia fistula* demonstrates a synergistic hepatoprotective effect by concurrently targeting oxidative damage, inflammatory responses, and hepatocellular injury. This combination therapy results in improved biochemical markers and preservation of liver architecture, suggesting superior efficacy compared to individual treatments. Overall, the findings support the potential of curcumin–*Cassia fistula* combination therapy as a safe and effective natural strategy for the prevention and management of hepatotoxicity, warranting further experimental and clinical investigations.

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