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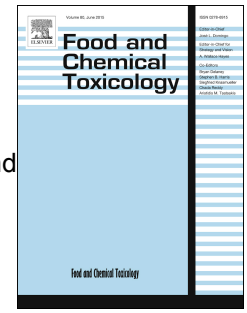

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Mechanistic insights of hepatoprotective effects of curcumin: Therapeutic updates and future prospects

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Abstract

The liver is the most essential organ of the body performing vital functions. Hepatic disorders affect the physiological and biochemical functions of the body. These disorders include hepatitis B, hepatitis C, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), liver cirrhosis, hepatic failure and hepatocellular carcinoma (HCC). Drugs related hepatotoxicity is one of the major challenges facing by clinicians as it is a leading cause of liver failure. During post-marketing surveillance studies, detection and reporting of drug-induced hepatotoxicity may lead to drug withdrawal or warnings. Several mechanisms are involved in hepatotoxicity such as cell membrane disruption, initiating an immune response, alteration of cellular pathways of drug metabolism, accumulation of reactive oxygen species (ROS), lipid peroxidation and cell death. Curcumin, the active ingredient of turmeric and exhibits therapeutic potential for the treatment of diabetes, cardiovascular disorders and various types of cancers. Curcumin is strong anti-oxidant and anti-inflammatory effects and thus it possesses hepatoprotective properties. Despite its low bioavailability, its hepatoprotective effects have been studied in various protocols of hepatotoxicity including acetaminophen, alcohol, lindane, carbon tetrachloride (CCL_4), diethylnitrosamine and heavy metals induced hepatotoxicities. This report reviews the hepatoprotective effects of curcumin with a focus on its mechanistic insights in various hepatotoxic protocols.

Keywords: Curcumin, hepatoprotective, mechanistic insights, therapeutic role, drug of future

1. Introduction

The liver is one the most vital organ in the body that performs various physiological functions. The main functions of liver are metabolism, secretion and storage. It has the capacity to detoxify of endogenous waste products and exogenous substances. Liver is the most essential site for metabolism of exogenous and endogenous substances. Metabolism of carbohydrates, proteins and fats takes place here. It is also involved in certain biochemical processes of growth, nutrients provision, energy supplying and reproduction. Any disorder of hepatic origin can affect physiological and biochemical functions of the liver (Giannini et al., 2005; Madrigal-Santillán et al., 2014). Hepatic disorders are highly prevalent and are the most common cause of illness and death worldwide. These disorders include hepatitis B, hepatitis C, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), liver cirrhosis, hepatic failure and hepatocellular carcinoma (HCC) (Wang et al., 2014).According to WHO, more than 2 billion people have been infected with HBV worldwide (Lavanchy, 2005). ALD, NAFLD and cirrhosis have prevalence of approximately 7.4%, 20-30% and 4.5-9.5% in general population respectively (Bellentani et al., 2010; Lim and Kim, 2008; Mandayam et al., 2004) and 564,000 people are infecting with hepatic cancer per year across the globe (Bosch et al., 2004). Prevalence of hepatitis B and hepatitis C in Pakistani general population is 3-5% and 6% respectively (Ali et al., 2011; Raja and Janjua, 2008). HCC affects males more than females as in Pakistan its incidence is 7.6/100,000 for males and 2.8 for females (Hafeez Bhatti et al., 2016).

The drugs related hepatic damage is one of the major challenges facing by clinicians as it is a leading cause of liver failure. During post marketing surveillance studies, detection and reporting of drug induced hepatotoxicity may lead to drug withdrawal or warnings. Bromfenac and troglitazone have been withdrawn from market because of hepatotoxicity while acetaminophen,

nevirapine, pyrazinamide, rifampin, valproic acid and zafirlukast have been labeled warning due to possibilities of serious hepatic damage (Kaplowitz, 2005; Lee, 2003). On the basis of biochemical analysis, DILI may be hepatocellular, cholestatic or mixed i.e. combination of both. Hepatocellular injury is characterized by ALT/ALP ratio of greater than 5 and cholestatic damage is characterized by ALT/ALP ratio of less than 2. ALT/ALP ratio of 2-5 makes a diagnosis of mixed hepatic damage(Fisher et al., 2015). Several mechanism are involved in hepatotoxicity such as cell membrane disruption, initiating immune response, alteration of cellular pathways of drug metabolism, accumulation of reactive oxygen species (ROS), lipid peroxidation and cell death (Navarro and Senior, 2006). Mitochondria are the primary target for xenobiotics in case of hepatotoxicity resulting in alteration of energy metabolism which along with oxidative stress and inflammatory cytokines induce hepatic damage. Alteration in activity of cytochrome P450 system enzymes also involve in drug induced hepatotoxicity as induction of CYP 2E1 promotes hepatocellular damage by inducing oxidative stress (Jaeschke et al., 2002).

Genetic factors variations can also predispose an individual to drug related hepatic damage. Decreased expression of CYP 2D6, deficiency of CYP 2C19, deficiency in acetylation capacity (inactive N-acetyl transferase type 2), sulfoxidation deficiency and deficiency in glutathione synthetase are some important risk factors for perhexiline, phenobarbital, sulfonamides, chlorpromazine and acetaminophen hepatotoxicity respectively (Larrey, 2002). Currently several therapeutic options are available for management of hepatic disorders and DILI. The antioxidant effects of α tocopherol, vitamin C and L-methionine have been successfully investigated in liver disorders (Patra et al., 2001). Other hepatoprotective agents available are vitamin A, carotenoids (β carotene), flavonoids (quercetin, esculetin, silymarin) and polyphenols (thyme, curcumin) (Vitaglione et al., 2005). Silymarin is extracted from *Silybummarianum*and is one of the most

common agents using for hepatoprotective like effect. Its primary mechanism is ameliorating oxidative stress by increasing activity of superoxide dismutase (SOD) and increasing serum level of glutathione and glutathione peroxidase as well as inhibiting toxin penetration into hepatic cells (Madrigal-Santillán et al., 2014; Wellington and Jarvis, 2001).

Curcumin is chemically a polyphenolic compound, known as diferuloylmethane (Priyadarsini, 2014). It is chemically known as 1,7-bis (4-hydroxy, 3-methoxyphenyl) 1,6-heptadiene-3,5-dione and was isolated for the first time in1815 by Vogel and Pelletier (Lampe and Milobedzka, 1913; Padhye et al., 2010). It is isolated from rhizome of *Curcuma longa*, commonly known as Turmeric or haldi in Hindi. Turmeric belongs to family Zingiberaceae (ginger family). It is perennial herb widely cultivated in tropical and subtropical areas such as Southeast Asia (Bao et al., 2010). Other sources of curcumin are *Curcuma aromatic, Curcuma phaeocaulis, Curcuma zedoaria* and *Curcuma caesia* (Lobo et al., 2009; Rajamma et al., 2012; Tohda et al., 2006). The use of curcumin in human diseases was published for the first time in 1937 (Oppenheimer, 1937). It has multiple targets and its use in management of various disorders have been reported so far (Zhou et al., 2011). The aim of the present paper is to review the pharmacological uses of curcumin, its antioxidant and anti-inflammatory activities and its potential role as hepatoprotective agent with clinical perspectives.

2. Pharmacology of Curcumin

Curcumin, the active ingredient of turmeric has been used for several medicinal uses thousands of years ago (Figure 1). As a folk remedy, it was used to treat eye infections, wounds dressing, bites, burns and skin disorders (Gupta et al., 2013). Certain phytochemicals including curcumin exhibits therapeutic potential for treatment of leading health disorders worldwide. These disorders include diabetes, cardiovascular disorders and various types of cancers (Borges et al.,

2017; Fetoni et al., 2015; Moghtaderi et al., 2017; Padhye et al., 2010). The polyphenolic curcumin targets various molecular signaling pathways causing either up regulation or down regulation of these pathways, which makes it an appropriate choice for management of various disorders including but not limited to cancers, disorders from neurologic, CVS, metabolic and infectious origin (Bonfanti et al., 2017; Gupta et al., 2012). The antiviral effect of the curcumin in prostate cancer (Fehl and Ahmed, 2017), seizure severity, depression like behavior, learning and memory deficit (Chang et al., 2016; Choudhary et al., 2013; Lopresti and Drummond, 2017; Motaghinejad et al., 2017), antifungal effect against Candida spp. (Andrade et al., 2013), antioxidative stress (Samarghandian et al., 2017) is also reported. Additionally, it's pharmacokinetic profile is already investigated (Mirzaei et al., 2017).

3. Curcumin as Hepatoprotective agent

Curcumin also known as yellow pigment of turmeric possesses anti-carcinogenic, anti-inflammatory, hepatoprotective and antioxidant properties (Bao et al., 2010). The protective effects of curcumin on liver mainly attributed to its antioxidant properties (Farombi et al., 2008). Curcumin consumption leads to decrease in structural alterations of liver and total bilirubin decrease in activities of ALT, AST, ALP, LDH, GGT and increase in serum proteins. It showed positive results in management of cholestasis, hepatic fibrosis and hepatic cancers (García-Niño and Pedraza-Chaverrí, 2014).

3.1. Antioxidant Potential

Oxidative stress is one of the most common mechanisms involved in organ injury. Oxygen is an essential molecule for all cells for production of ATP, but it may also have transformed into very toxic species i.e. Reactive oxygen species. During aerobic respiration, the production of free radicals can lead to aging and cell death. Oxygen molecules reduced by mitochondria to produce

superoxide ions or forms peroxide (H_2O_2). The superoxide and peroxide further react with metal ions and generate hydroxyl radicals, which reacts with cell components including DNA and proteins. The therapeutic potential of polyphenolic curcumin is mainly associated with its antioxidant properties (Jaeschke et al., 2012; Menon and Sudheer, 2007). The curcumin is found to be 10 times more antioxidant than vitamin E (Shishodia et al., 2005). Curcumin up regulates Nrf2 genes, which leads to rise in GSH concentration and activity of glutathione peroxidase and superoxide dismutase (SOD). The glutathione and glutathione peroxidase act synergistically to scavenge free radicals. SOD scavenges superoxide radicals by converting superoxide free radicals into H_2O_2 while preventing formation of OH radicals. H_2O_2 formed thus removed by action of catalase or glutathione peroxidase (Figure 2). Thus, it protects against free radical damage (Jagetia and Rajanikant, 2015).

3.2. Alteration in inflammatory mediators

Body responds initially to any injury through immune derived mediators known as proinflammatory and counter inflammatory components. Process of inflammation involves activation of signaling pathways at cellular level that can mobilize inflammatory cells and stimulates secretion of chemokines and cytokines at site of inflammation (Figure 3). The cytokines and chemokines involve in inflammatory cascade are interleukins [IL], interferon-α, interferon-γ and tumor necrosis factor-α [TNF-α], group of chemokine ligands [CCL] and different forms of CXCL (Namas et al., 2015). Broadly two types of receptors up-regulate in inflammatory responses that are CCR using for binding of CCL and CXCR using for binding for CXCL (D'Ambrosio et al., 2003). Alteration of genomic sequence of some genes (STAT genes, CREB and CCAAT/CEBP gene families, SOCS3 and IKBK genes) make an individual more vulnerable to inflammatory responses (Calvano et al., 2005).

Anti-inflammatory activities of various phytochemicals like flavonoids and curcumin have been extensively studied and investigated (Gupta et al., 2013; Minihane et al., 2015). Curcumin down regulates transcription factors responsible for inflammation such as activating transcription factor-3, activator protein-1, CREB binding protein, STAT proteins and NF-kB. Inflammatory mediators targeted directly by curcumin include C-reactive protein, interleukins, 5-lipooxygenase and macrophage inflammatory protein-1α (Gupta et al., 2012). It is documented that suppression of TNF-induced NF-kB activation is one of the most important anti-inflammatory mechanism of curcumin (Aggarwal et al., 2013).

3.3. Hepatoprotective effect in different models

3.3.1 Effect in Acetaminophen induced hepatotoxicity

Acetaminophen also known as Paracetamol is commonly used analgesic and antipyretic agent. Its chemical name is N-acety-p-aminophenol (APAP). Because of ADRs associated with NSAIDs and opioid analgesics, it is considered as first line analgesic in chronic liver disease (Hayward et al., 2016; McGarry et al., 2015). There are no serious adverse effects associated with acetaminophen use if taken in therapeutic doses. But still many cases are so far reported regarding severe drug related adverse event when acetaminophen taken in large doses. Hepatic injury is one of most common and severe adverse effect among them (Acheampong and Thomas, 2016). Most commonly acetaminophen causes hepatic necrosis which may leads to acute liver failure in case of supratherapeutic doses of acetaminophen. APAP causes hepatic toxicity in a dose dependent fashion. N-acetylcysteine (NAC), an antidote of APAP if given with 12 h after ingestion of hepatotoxic doses (i.e. doses greater than 4 g/day) of APAP can reverse hepatic damage. A delay of NAC therapy can result in greater rate of morbidity and mortality. However remains controversial but it is well documented that fasting and alcohol ingestion are two factors

that can enhance APAP related toxicity(Larson et al., 2005). APAP induced acute liver damage can be life threatening condition characterized by severe liver dysfunction, abnormal coagulation profile having INR of greater than 1.5 and hepatic encephalopathy. APAP normally metabolized by glucuronidation and sulfation but when taken in hepatotoxic doses, both the conjugation pathways become saturated while shunting metabolism of APAP to cytochrome P450 system. The metabolism through CYP 450 generates highly toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) (Khandelwal et al., 2011).

NAPQI reacts with hepatic proteins and glutathione leading to hepatic damage of N-acetyl P-benzoquinoneimine (NAPQI), leads to production of oxidative stress and depletion of glutathione stores which affects mitochondrial function. Among enzymes of CYP 450 system, CYP 2E1 is mainly involved in formation of reactive metabolite NAPQI through metabolism in case when glutathione stores get depleted. Alcohol intake induces CYP 2E1 and can enhance formation of NAPQI resulting in early hepatic damage. Other enzymes involved in generation of NAPQI including CYP 1A2, CYP 3A4 and CYP 2D6 (Harrelson et al., 2012; Jaeschke et al., 2012).Genetic polymorphisms in CYP 2E1 are more likely to pre-expose patient to APAP induced liver injury. Individuals with genotypes UGTIA-3 UTR, CD44 rs1467558 and CYP 3A5 rs776746 are at increased risk of liver damage secondary to APAP toxicity (Peter et al., 2013).Various parameters used to access APAP induced hepatic damage including liver enzymes (ALT, AST, and ALP), concentration of malondialdehyde and reduced GSH in liver tissue and estimation of proteins (Figure 4). ALT is currently most widely used biomarker among them(Girish et al., 2009).Serotonin has protective effects on APAP hepatotoxicity as it plays role in decreasing inflammation, oxidative stress, GSH depletion, peroxynitrite formation, hepatocyte apoptosis, ER stress and activation of 5-HT2B receptor. Its deficiency may exacerbate APAP

induced hepatic damage through abnormality of different markers mentioned above (Zhang et al., 2015). It is well documented that mitochondria are critical target for APAP toxicity through the formation of reactive metabolites. It leads to mitochondrial oxidative stress associated with alterations in calcium homeostasis and formation of peroxynitrite causing alterations in mitochondrial DNA and proteins. As a result, mitochondrial permeability transition (MPT) pores become open which further results in collapsing mitochondrial membrane potential and decreasing ability of mitochondria to synthesize ATP. Release of apoptosis inducing factor and endonuclease G and their role in DNA fragmentation is also a part of this cascade(Hinson et al., 2010; Jaeschke et al., 2012; Saito et al., 2010).

Several strategies are available for the management of APAP induced hepatotoxicity. N-acrtyl cysteine is the only clinical antidote available to date (Du et al., 2015). Resolvins are also studied for its protective affects against APAP induced hepatotoxicity which protect hepatocytes through inhibition of neutrophil infiltration (Patel et al., 2016). As search for novel drugs include testing plant extracts and other natural products. Curcumin is one of the most commonly used phytochemical reverses hepatic damage by affecting production of lipid peroxidation, oxidative stress and hepatocyte apoptosis (Jaeschke et al., 2011; Li et al., 2013). The curcumin is widely accepted for its anti-inflammatory activities among phytochemicals and thus recognized for its use in hepatitis. Curcumin intake results in significant decrease in serum level of transaminases and hepatic MDA while increasing in GSH concentration and improvement in liver histopathology (Somanawat et al., 2013).Curcumin protects against APAP induced hepatotoxicity through its antioxidant potential. It re-impairs antioxidant capacity of hepatic cells. The curcumin decreases the expression of matrix metallopeptidase-8 (MMP-8)and other cytokines including IL-1β, TNF-α and IL-8 initiating inflammatory cascade of body (Soliman et

al., 2014). It is documented that polyphenols like curcumin inhibits CYP2E1, thus inhibits the formation of toxic metabolites and preventing oxidative stress secondary to APAP toxicity. Curcumin prevent depletion of glutathione stores and induces formation of electrophilic radicals and thus prevents hepatic damage. Girish *et al* compared the hepatoprotective activity of four phytochemicals (picrolive, curcumin, ellagic acid and silymarin) using model of acetaminophen induced liver toxicity in mice. In an experiment, different parameter was used to access hepatoprotective activities of phytochemicals like serum levels as these parameters accessed after treatment with phytochemicals (picrolive, curcumin, ellagic acid and silymarin), there was significant decrease in level of ALT, AST, ALP, malondialdehyde and elevation in GSH concentration. Oral dose of 50 mg/kg and 100 mg/kg body weight were used in study. There was complete reversal of acetaminophen induced histopathological damage after treatment with Phytochemicals (Girish et al., 2009).

3.3.2. Effect in alcohol induced hepatotoxicity

Alcohol distributes throughout the body and its intoxication damage multiple organs in body mainly through oxidative stress, posttranslational alterations in proteins, altering lipid metabolism and signal transduction pathway (Souza-Smith et al., 2016). It puts an individual on high risk to infections by suppression host defense (D’ Souza El‐Guindy et al., 2010). ADH is the main enzyme involve in alcohol metabolism and thus alcohol detoxification using NAD^+ as cofactor. The cytochrome P450 system (CYP2E1) is also involve in alcohol metabolism and elimination (Plapp et al., 2015). As liver is primary site for alcohol metabolism so hepatic cells are more prone to alcohol related tissue damage and cause more severe problems of hepatic origin collectively called alcoholic liver disease. ALD includes fatty liver disease, fibrosis, steatosis, steatohepatitis and hepatocellular carcinoma (D’ Souza El‐Guindy et al., 2010;

Souza-Smith et al., 2016). Ethanol and some other substrates like CCL4, acetaminophen and N-nitrosdimethylamine are metabolized by CYP2E1 to more toxic metabolites. Oxidative stress is mainly involved in alcohol induced liver damage whereas oxidative stress is induced by CYP2E1, mitochondria and activated kupffer cells. CYP2E1 generates reactive products (acetaldehyde and 1-hydroxyethyl radical) and reactive oxygen species through oxidation of ethanol (Cederbaum, 2010). SOD and GSH-Px protects against oxidative stress by elimination ROS. Pathological conditions and some factors like ethanol leads to overproduction of ROS by activating proteins in caspase family and signaling molecules such as NF-kB and TNF-α.Activating inflammatory cascade further leads to cell damage (Liu et al., 2017).

The LPS is gut bacterial product and may enter blood circulation in cases of alcohol intoxication by causing structural changes in GI tract. By inducing inflammatory responses, LPS plays a very crucial role in causing serious hepatic problems including end stage liver disease. Alcohol also increases sensitivity of kupffer cells (site where LPS induced cytokine production occurs) to LPS as alcohol metabolite acetaldehyde produce malondialdehyde-acetaldehyde adduct (MMA) by interaction with malondialdehyde(Wang et al., 2012). The ALD involves proinflammatory factors such as NF-kB, TNF-α, IL-1β and profibrotic factors including TGF- β, Smad, MAPK and PAI-1.In short alcoholic hepatic injury is mediated by LPS/TLR4/MD-2/TNF-α-MAPK and TGF-β/Smad signaling(Boye et al., 2016). Hepatotoxicity as result of alcohol-acetaminophen interaction is also documented. Chronic alcohol intake causes induction of hepatic microsomal enzymes. CYP2E1 is important for oxidative metabolism of acetaminophen generating toxic metabolite NAPQI (Figure 5). Induction of CYP2E1 by chronic use of alcohol leads to increase rate of oxidative metabolism of acetaminophen and as result may leads to hepatotoxicity even at therapeutic dosages of acetaminophen (Prescott, 2000).

The hepatoprotective effects of curcumin in various studies investigated using model of alcohol induced hepatotoxicity. The pathogenesis of alcoholic liver disease is complex, but curcumin is currently highly effective hepatoprotective agent among Phytochemicals. Curcumin suppresses proinflammatory cytokines and thus inhibiting inflammatory cascade. It inhibit NF-kB (transcription factor) resulting in suppression of a number of proinflammatory molecules (Nanji et al., 2003). The curcumin also protects the liver against alcoholic damage by inducing expression of heme-oxygenase 1 (HO-1). HO-1 is enzyme that breaks down heme into CO, iron and bilirubin. In a study performed by Wei Bao *et al* it was investigated that curcumin induced the expression of HO-1, when administrated in advance at diverse doses of 5–50 μM before ethanol exposure, whose activity was depressed in alcohol treated rats. Curcumin also decreased plasma concentration of ethanol induced LDH, AST, MDA while increasing concentration of GSH (Bao et al., 2010).

3.3.3. Effect in lindane induced hepatotoxicity

Lindane is widely used organochlorine insecticide that has been used for decades(Tuduri et al., 2006).Lindane is also using in management of scabies and head lice. Because of its significant ADRs, it is now place as second line agent for treatment of scabies. ADRs associated with lindane use are mostly of neurologic origin, others include cardiac arrhythmias, suppressing liver function and altered menstruation (Nolan et al., 2012). Lindane causes tissue injury mostly through lipid peroxidation, causing oxidative stress and decreasing activity of GSH. It is also documented that risk of lindane induced hepatotoxicity further increases in hyperthyroid state. In such case toxicity is dependent on function of kupffer cells playing a role in generation of prooxidant and inflammatory mediators (Abdollahi et al., 2004; Simon-Giavarotti et al., 2002). Being lipophilic, lindane accumulates in adipose tissues surrounding visceral organs including

liver, muscles and heart. It causes alterations in hepatic lipid profile as it induces total serum cholesterol, LDL, VLDL, triglycerides while decreasing serum concentration of HDL (Padma et al., 2012).

It has been investigated that curcumin normalized all parameters reflecting hepatotoxicity induced by lindane. Curcumin use leads to decrease in lipid peroxidation while increase in activities of GSH, SOD, glutathione S-transferase, glutathione peroxidase, glutathione reductase and NADPH quinine reductase. Thus, curcumin protects against lindane induced hepatic damage through scavenging oxygen free radicals and ameliorating state of oxidative stress (Singh and Sharma, 2011). It also causes normalization of hepatic lipid profile. It was confirmed by a study in which positive effects of mixture containing curcumin, vitamin E, vitamin C on serum lipid profile and liver functions were successfully investigated in lindane induced hepatotoxicity and alterations in liver lipid profile. Curcumin, vitamin C and vitamin E (50 mg/kg body weight) were dissolved in dimethyl sulfoxide (DMSO) and were administered by gavaging (Sharma et al., 2010).

3.3.4. Effect in CCl_4 induced hepatotoxicity

The CCl_4 is a causative agent of several disorders through its potential of inducing oxidative stress and inflammatory. CCl_4 metabolize through enzymes of CYP 450 system generating hepatotoxic metabolites trichloromethyl radicals and trichloroperoxyl radicals. Both of these metabolites lead to hepatotoxicity through induction of lipid peroxidation which in turn gives MDA products leading to hepatic injury (Oyinloye et al., 2017; Shah et al., 2017). CCl_4 exposure causes alteration of several biomarkers reflecting its hepatotoxic effects such as increase in aminotransferases (ALT, AST), ALP and γ-GT. It also induces dyslipidemia such as increasing TC, triglycerides and LDL levels while decreasing HDL concentration (Khan et al., 2012). The

hepatotoxic metabolites of CCl_4 bind with antioxidant enzymes and results in decreasing activity of CAT, SOD, GST, GSH-Px, GSR and GSH and inducing oxidative stress(Khan et al., 2012; Yoshioka et al., 2017). CCl_4 induced oxidative stress can regulates several transcription factors including NF-kB, activator protein 1 (AP-1) and early growth response 1 (EGR-1). Activation of NF-kB up regulates the inflammatory cascade by stimulating release of proinflammatory cytokines(Go et al., 2016). Blood flow likely to be increased along with accumulation of inflammatory cytokines in hepatocytes which results in hepatic tissue inflammation (Al-Seeni et al., 2016).

The alteration in expression of IL-6/STAT3 pathway genes by CCl_4 also contributes to hepatic inflammation with CCl_4. Collagen synthesis and accumulation leading to hepatic fibrosis with CCl_4 use is also reported as it increases tissue inhibitors of metalloproteinases (TIMP-1)(Hafez et al., 2015). CCl_4 exposure induced activation of transforming growth factor (TGF)-β and inhibition of nitric oxide formation leads to hepatic steatosis, fibrosis and cirrhosis. Activation of TGF-β up regulates the expression of tissue inhibitor of metaloproteinases (TIMP) which results in suppression of matrix metalloproteinases (MMP) and increased expression of extracellular matrix (ECM). Accumulation of ECM is a key feature of hepatic fibrosis(Hafez et al., 2017). Transformation of hepatic stellate cells from quiescent vitamin A storing cells into proliferative and fibrogenic myofibroblastic cells is a major source of accumulation of ECM(Attia et al., 2016). The deficiency of indoleamine 2,3 dioxygenase (IDO) further increases the risk for CCl_4 related hepatotoxicity as deficiency of IDO induces expression of proinflammatory cytokines (Ogiso et al., 2016). It is documented that CCl_4 related toxicity varies over 24 hour's period. This is because formation of circulating acetone increases in fasting conditions which induces CYP 2E1 generating hepatotoxic metabolites of CCl_4 (Bruckner et al., 2002).

Although remains controversial, sympathetic nervous system (SNS) plays an important role in hepatotoxicity caused by CCl_4 through induction of inflammatory responses. SNS is likely to be involve in over expression of ILs, monocyte chemoattractant protein-1 (MCP-1/CCL2) and TNF-α while these proinflammatory cytokines have central role in CCl_4 induced hepatotoxicity (Lin et al., 2015). As investigated using animal's model, the diabetic patients are more prone to CCl_4 induced hepatotoxicity. This is because of induced biotransformation of CCl_4 in diabetic individuals. Oxidative stress and lipid peroxidation also increases in diabetic patients, thus increasing risk of CCl_4 related hepatotoxicity(Sawant et al., 2004). A study suggests that hypercalcemia as a result of vitamin D3 administration also increasing risk for CCl_4 related hepatotoxicity through induction of oxidative stress (Yoshioka et al., 2017). Increased gene expression of paraoxonases (PON1, PON2, and PON3) protects against CCl_4 induced hepatic damage through its antioxidant properties. PON1 and PON3 expressed in liver while PON2 is widely distributed in body (Hafez et al., 2014). Nuclear factor-erythroid 2-related factor 2 (Nrf2) is transcription factor which regulates Nrf2 target genes in hepatocytes encoding enzymes for detoxification of CCl_4 and its metabolites including glutathione S-transferase (GST), NADH quinine dehydrogenase 1 (NQO1) and glutamate-cysteine ligase catalytic subunit (GCLC). Thus up regulation of Nrf2 can protect against CCl_4 related hepatic damage (Chen et al., 2013).

The curcumin protects against CCl_4 induced hepatic damage because of its antioxidant properties. Use if curcumin can restore all biomarkers reflecting hepatic damage i.e. decreasing level of aminotransferases (ALT and AST), suppressing lipid peroxidation, reduction in MDA, improving GSH/GSSG ratio, recovery of redox balance and increasing level of reduced GSH. Curcumin also up regulates Nrf2 proteins thus protects against CCl_4 inducing damage as Nrf2 regulates Nrf2 target genes which helps in detoxification of CCl_4 and its metabolites (Lee et al.,

2017a; Lee et al., 2016). Because of antioxidant potential, curcumin also inhibits lipid storage in hepatocytes and neutralize lipid dysmetabolism. Thus, it is possible alternative choice in management of hepatic dyslipidemia(Lee et al., 2017b). The curcumin has low bioavailability and thus, not much effective against systemic diseases as documented. Its liposomal and nanoparticulated formulations increases its bioavailability and as a result increases its efficacy against hepatic toxicity induced by chemicals including CCl_4 (Choudhury et al., 2016).

3.3.5. Effect in diethylnitrosamine induced hepatotoxicity

Diethylnitrosamine (DEN) is a well-known hepatic carcinogen and mutagen and is used most widely in animal models to initiate hepatocarcinogenesis. It is present in different concentration in tobacco smoke, water, cheddar cheese, cosmetics, agriculture chemicals and pharmaceuticals (Sun et al., 2012). Biotransformation of DEN through CYP isoenzymes (CYP 1A2 and CYP 2E1) results in formation of reactive electrophilic species that are responsible for causing chromosomal aberrations (Bishayee et al., 2011). Exposure to DEN results in oxidative stress because of accumulation reactive oxygen species leading to DNA damage and in turn results in hepatocarcinogenesis. DEN induced oxidative stress can disturb several metabolism pathways such as alanine, aspartate, glutamate metabolism, valine, leucine, isoleucine biosynthesis and TCA cycle. Expression of antioxidant genes may dysregulate with the initiation of carcinogenesis and thus weakens defense of hepatic cells against prooxidant species (Zeng et al., 2015). Exposure to the chronic stress can further exacerbate the oxidative stress and increase risk for DEN induced oxidative potential and carcinogenesis(Bilal et al., 2017). It is reported that deficiency of transcription coactivator peroxisome proliferator-activated receptor-binding protein (PBP/MED1) can protects against DEN related HCC. The reason is defective metabolism of DEN in PBP/MED1 deficient hepatocytes (Matsumoto et al., 2009).

Expression of epidermal growth factor (EGF) is also a risk factor of causing cirrhosis and HCC. Polymorphism in human EGF gene can results in increase expression of EGF which could be associated with progression of cirrhosis. Exposure to DEN also increase expression of EGF and put an individual at risk to cirrhosis and HCC (Fuchs et al., 2014). Inducible nitric oxide synthase (iNOS) increase formation of NO during inflammation which plays a critical role in carcinogenesis of various origins. iNOS is reported to be up regulated in various malignant cancers like breast, lung, prostate, bladder, colon, gastric and malignant melanoma. NO activates MMP and cause induction of vascular permeability and pro-angiogenic factors which contribute to angiogenesis, cell migration and invasion. DEN also up regulates expression of iNOS enzyme and increasing serum NO levels making a road way to HCC (Fathy and Nikaido, 2013). Increased activity of hepatic NrF2 proteins can protects against DENA induced HCC as it regulates the expression of antioxidant and detoxifying enzymes including NQO1, GST-alpha2, GST-alpha5 and GST-m1 (Bishayee et al., 2011). L-carnitine is naturally occurring compound present in mitochondria. It exhibits protective effects against mitochondrial toxic agents and has potential to protect against DEN induced HCC. Carnitine transporter (OCTN-2) regulates the levels of carnitine in hepatocytes which may be destroyed in presence of oxidative stress created by DEN. Carnitine deficiency put an individual at high risk to HCC when exposed to DEN (Al-Rejaie et al., 2009).

Several biomarkers may be used by reflecting DEN-induced hepatic damage including alteration in level of aminotransferases (ALT, AST), ALP, LPO, SOD, GSH, GST and GSR. Through increase in LPO and decrease in SOD and glutathione dependent enzymes DEN induces oxidative stress (Shaarawy et al., 2009). N linked glycoprotein is another biomarker that can be used to monitor the progression of hepatic cancers. Only liver and B lymphocytes are responsible

for synthesis of N-glycans, therefore any alteration of serum level of N-glycans reflects disorder of hepatic or B lymphocytes origin. The exact mechanism that linked alteration in N-glycosylation with hepatic disease is still unknown (Fang et al., 2010). Potential of curcumin in prevention and management of DEN induced hepatic damage is studied and reported. Curcumin Increases the expression of HO-1 via activation of Nrf2 signaling by curcumin results in protection against oxidative stress and thus prevents DEN induced hepatic damage (Farombi et al., 2008).

3.3.6. Effect in heavy metals induced hepatotoxicity

Any metal having toxic effects termed as heavy metals irrespective of their atomic masses and density. These include a list of metals from common transition metals such as copper, lead, zinc, mercury, arsenic, silver and nickel (Singh et al., 2011). Heavy metals are mostly originated from natural sources like earth crust. Human activities i.e. mining and smelting operations, industrial productions and agricultural use of metallic compounds are main sources of environmental contamination with heavy metals. Other sources of environmental contamination include volcanic eruptions, metal corrosion, soil erosion of metals and metals leaching (Tchounwou et al., 2012). Some metals are essential for normal physiologic processes like zinc, iron and copper necessary for catalytic activities of various enzymes. Toxic effects of heavy metals are also documented where oxidative stress is main mechanism involve in toxicity (Abdel-Monem et al., 2013). Exposure to heavy metals generate ROS i.e. hydroxyl radical and superoxide radical which cause lesions of DNA, proteins and lipids and leads to cellular dysfunction (Ercal et al., 2001). Some metals like Fe, Cu and Cr undergoes redox cycling while Cd, Hg and Ni promote ROS synthesis by depleting glutathione. As discussed earlier, lipid peroxidation also increases in presence of oxidative stress (Stohs and Bagchi, 1995).

The hepatotoxicity due to heavy metals' exposure alters various biomarkers in liver including enzymes essential for normal physiologic processes of liver. These include elevation in ALT, AST, ALP, LDH and MDA levels. MDA production increases because of inhibition of free radical scavenging enzymes. Decrease in SOD, catalase, glutathione peroxidase, glutathione reductase and glutathione S-transferase occur in case of liver toxicities with heavy metals. (Rajamanickam, 2008; Sunitha et al., 2001). Exposure to heavy metals also promotes apoptosis of hepatic cells. As studied, exposure to silver nanoparticles induces p21 gene in hepatocytes, which promotes p53-dependent apoptosis (figure 6). Ag also induces pro-apoptotic Bcl-2 family genes i.e. Bax and Noxa. Both of these genes are pro-apoptotic and helps in Ag induced apoptosis of hepatic cells (Choi et al., 2010). Methionine is reported to protect against heavy metals damage. By reaction with oxidant forming methionine sulfoxide, it plays an important role in reducing oxidative stress. It also acts as precursor for synthesis of glutathione, thus protecting hepatic cells from oxidative damage (Patra et al., 2001).

Among Phytochemicals, phenolic compounds are best known for their antioxidant activities. In case of heavy metals, their antioxidant activities also relate to their high tendency of chelating heavy metals (Michalak, 2006). Having antioxidant and anti-inflammatory properties, curcumin has potential to protect against heavy metals induced hepatotoxicity. It can binds with lead to form a complex thus protecting against lead related toxicity especially neurotoxicity and nephrotoxicity (Gupta et al., 2015). Curcumin prevents structural damage, decreasing lipid peroxidation and preventing glutathione depletion while improving the activity of SOD, CAT, GPx, GR, GST and NQO1. It induces detoxifying enzymes by up regulating Keap1/Nrf2/ARE pathway. Curcumin also decrease activation of NF-kB and expression of proinflammatory

cytokines. All these mechanisms collectively lead to hepatoprotective like effect by curcumin against heavy metals intoxication (García-Niño and Pedraza-Chaverrí, 2014).

4. Low bioavailability of curcumin

Bioavailability of curcumin is low, which could limit its health benefits despite of wide range of biological effects (Bell, 2002). The main reasons for its low plasma and tissue concentration are its poor absorption, rapid metabolism and rapid systemic elimination (Anand et al., 2007). This has been observed experimentally in bleomycin-induced injured animals (Smith et al., 2010). The oral treatment had no effect in mice however, intraperitoneal treatment with curcumin caused significant attenuation of inflammation as well as collagen deposition (Prasad et al., 2014). Similar problem was encounter in a Phase II clinical trial with curcumin treatment for patients with advanced pancreatic cancer. It was found with the oral dose of curcumin 8 grams per day, that only 22–41 ng/ml of curcumin was detected in plasma (Dhillon et al., 2008).

5. Latest advancement in curcumin research

Several formulation techniques are available to improve the plasma and tissue concentration of curcumin including liposomal techniques, curcumin nanopaticles and curcumin phospholipd complex (Anand et al., 2007). Onoue *et al* in 2010 reported that nanocrystal dispersion amorphous solid dispersion and nanoemulsion results in improving pharmacokinetic properties of curcumin (Onoue et al., 2010). Use of piperine as adjuvant also enhances the serum concentrations, extent of absorption and bioavailability of curcumin in both animals and humans ($Shoba_1$ et al., 1998). Solubilized curcumin has caused better therapeutic effects in rats for antiarthritis effects (Khayyal et al., 2018). Similarly, encapsulated curcumin in the form of nanoparticles exhibited marked bioavailability as compared to simple curcumin when evaluated both in vitro and in vivo (Liu et al., 2018).

In addition to this, recently different formulations have been reported with 100-fold better bioavailability than the simple curcumin when studied in human for the purpose of clinical trials (Jamwal, 2018). The products such as NovaSol and CurcuWin are the most prominent of them (Jamwal, 2018; Ullah et al., 2017). Thus, the applications of modern technologies have greatly resolved the issue of curcumin bioavailability.

6. Concluding remarks

Curcumin is polyphenolic phytochemical with notable pharmacological effects and promising therapeutic potential. It possesses antioxidant and anti-inflammatory properties which make it a suitable choice in management of various diseases like disorders of neoplastic, metabolic, cardiovascular, neurological, arthritic and infectious origin. Its antioxidant and anti-inflammatory properties make it a safe hepatoprotective agent having favorable ADRs profile. Hepatoprotective effects of curcumin have been reported using different hepatotoxic models including acetaminophen, alcohol, lindane, CCl_4, diethylnitrosamine and heavy metals induced hepatotoxicity. The obstacle to its use for systemic disorders is its low bioavailability. Several formulation techniques are available to improve its bioavailability. In addition to affecting anti-oxidant, pro-oxidant and inflammatory mediators it also alters gene expression at molecular level. Although there is extensive research of curcumin related hepatoprotectivity using *In vitro* and animal studies, data of hepatoprotectivity by curcumin in human population is limited. Having multiple targeting potential, future trials of curcumin as hepatoprotective agent with improved bioavailability should be highly encouraged.

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Table 1. Hepatoprotective properties of curcumin

S.No	Hepatotoxic agent	Hepatotoxic mechanism	Hepatoprotective mechanism of curcumin	References
01	Acetaminophen	Formation of toxic metabolite NAPQI by CYP 2E1	Inhibits CYP 2E1	(Harrelson et al., 2012; Jaeschke et al., 2012; Zhang et al., 2015)
			Preventing depletion of glutathione	
02	Alcohol	Oxidation of alcohol by CYP 2E1 generating ROS	Inhibits CYP 2E1	(Bao et al., 2010; Liu et al., 2017; Wang et al., 2012; Zhang et al., 2015)
		Decreasing activity of HO-1	Increasing expression of HO-1	
		Activating inflammatory cascade through NF-kB and TNF-α	Inhibiting inflammatory cascade/inhibiting NF-kB	
03	Lindane	oxidative stress, lipid peroxidation, decreasing activity of GSH	Decrease lipid peroxidation, Increasing activity of GSH, SOD, GST, GSH-Px, GSR	(Abdollahi et al., 2004; Oyinloye et al., 2017; Padma et al., 2012; Sharma et al., 2010)
		Alteration in hepatic lipid profile	Normalizing hepatic lipid profile	
04	CCL4	Decreasing activity of CAT, SOD, GSH, GST, GSH-Px, GSR	Up regulating Nrf2 proteins and detoxifying CCL4 and its metabolites	(Go et al., 2016; Hafez et al., 2015; Hafez et al., 2017; Lee et al., 2017a)
		Up regulating NF-kB and EGR-1		
		Alteration in expression of IL-6/STAT 3		
		Up regulating TIMP-1, TGF- β		
		Inhibit NO formation		
05	Diethylnitrosamine	Oxidative stress	Increasing expression of HO-1 and decreasing oxidative stress	(Farombi et al., 2008; Fathy and Nikaido, 2013; Fuchs et al., 2014; Zeng et al., 2015)
		Dysregulating expression of antioxidant genes	Activating Nrf2 signaling	
		Increasing expression of EGF		

		Up regulating expression of iNOS		
06	Heavy metals	Oxidative stress	Heavy metals chelation	(Ercal et al., 2001; García-Niño and Pedraza-Chaverrí, 2014; Michalak, 2006; Stohs and Bagchi, 1995)
		Depleting glutathione stores	Decreasing lipid peroxidation and preventing glutathione depletion	
		Decreasing activity of CAT, SOD, GSH, GST, GSH-Px, GSR	Increasing activity of CAT, SOD, GSH, GST, GSH-Px, GSR, NQO1	
			Up regulating Keap/Nrf2/ARE pathway	
			Decreasing activity of Nf-kB	

Legends of Figures

Figure 1. Pharmacological properties of Curcumin

Figure 2. Hepatoprotective effect of curcumin through its antioxidant actions. NQO1=quinone oxidoreductase 1; SOD= superoxide dismutase; GPx=glutathione peroxidase; GR=glutathione reductase; GST=glutathione S-transferase; HO=Heme oxygenase-1; CAT= catalase.

Figure 3. Hepatoprotective mechanism of curcumin through its antiinflammatory actions. IFNγ=Interferon gamma; NF-κB (nuclear factor kappa-light-chain-enhancer; TNF- α= Tumor necrosis factor; IL-12= Interleukin 12.

Figure 4. Hepatoprotective mechanism of curcumin through its antihepatotoxic actions. ALT=alanine aminotransferase; γ-GT=Gamma Glutamyl Transferase; ALP=Alkaline phosphatase; Aspartate transaminase (AST).

Figure 5. Hepatoprotective mechanism of curcumin through its antifibrotic actions. PDGF= Platelet-derived growth factor; PPAR-γ or PPARG= Peroxisome proliferator-activated receptor gamma; HSC=hepatic stellate cells; TGFβ= Transforming growth factor beta; Collagen α 1cI=Collagen, type I, alpha 1.

Figure 6. Hepatoprotective mechanism of curcumin through its antihepatocarcinogenic actions. ROS= reactive oxygen species; p53 = Tumor protein or phosphoprotein; p21=a gene found on chromosome 6 at 6p21.2 that played an important in cell cycle regulation.

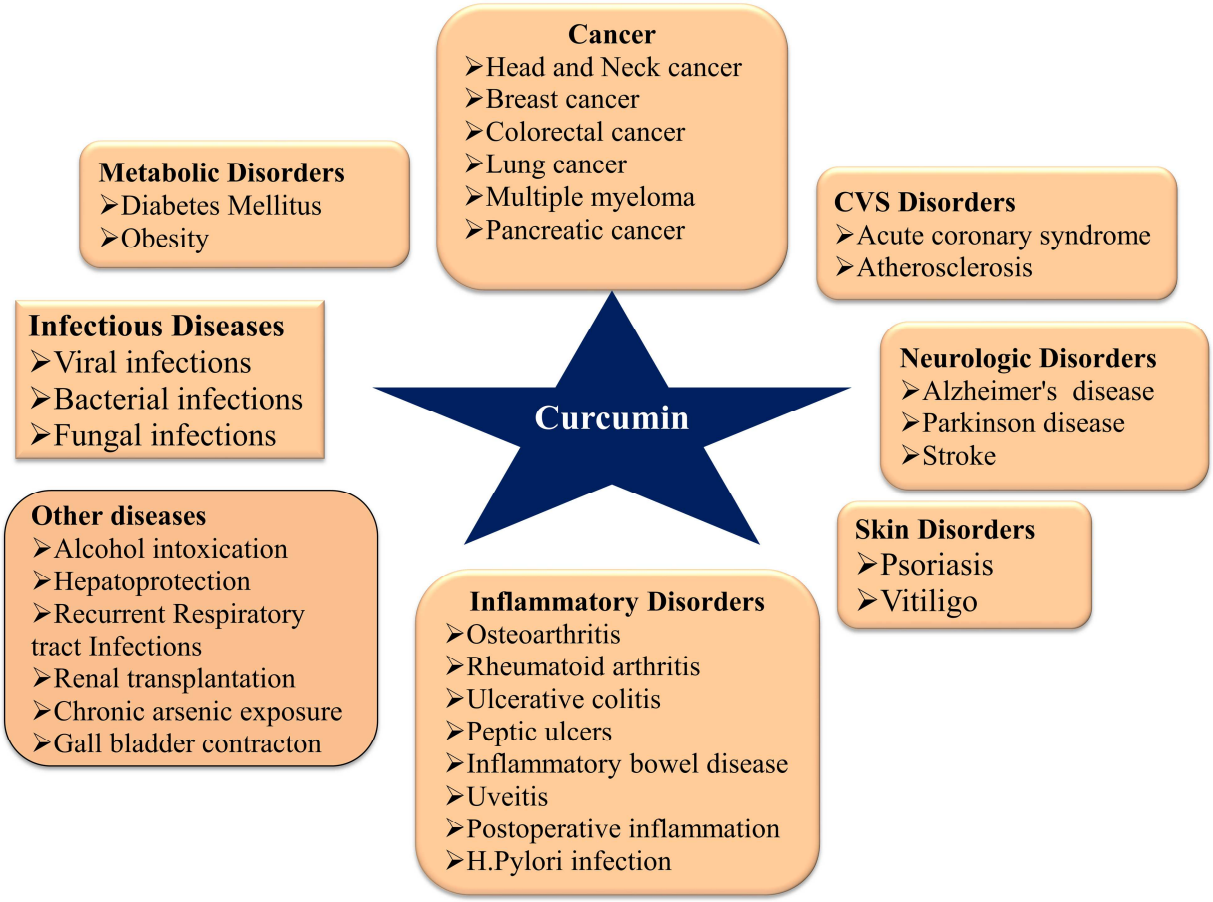

Figure 1. Cancer: Head and Neck cancer (Aggarwal et al., 2004), breast cancer (Kakarala et al., 2010), colorectal cancer (Li et al., 2007), lung cancer (Chen et al., 2008), multiple myeloma (Bharti et al., 2003), pancreatic cancer (Dhillon et al., 2008); CVS disorders: Acute coronary syndrome (Shamsara et al., 2009), atherosclerosis (Olszanecki et al., 2005); Neurologic disorders: Alzheimer's disease (Baum et al., 2008), Parkinson's disease (B Mythri and M Srinivas Bharath, 2012), stroke (Kalani et al., 2015); Skin disorders: Psoriasis (Sun et al., 2013), vitiligo (Becatti et al., 2010); Inflammatory disorders: Osteoarthritis (Volpe, 2018), Rheumatoid arthritis (Chandran and Goel, 2012), ulcerative colitis (Lang et al., 2015), peptic ulcers (Khonche et al., 2016), inflammatory bowel disease (Holt et al., 2005), uveitis (Allegri et al., 2010), postoperative inflammation (Jurenka, 2009), H. Pylori infection (Di Mario et al., 2007); Metabolic disorders: Diabetes (Meng et al., 2013), obesity (Shehzad et al., 2011); Infectious diseases: Viral infections (Chen et al., 2010), bacterial infections (Rudrappa and Bais, 2008), fungal infections (Martins et al., 2008); Other diseases: Alcohol intoxication(Lee et al., 2013), hepatoprotection (Lee et al., 2013), recurrent respiratory tract infections (Zuccotti et al., 2009), renal transplantation (Shoskes et al., 2005), chronic arsenic exposure (Biswas et al., 2010), gall bladder contraction (Rasyid et al., 2002).

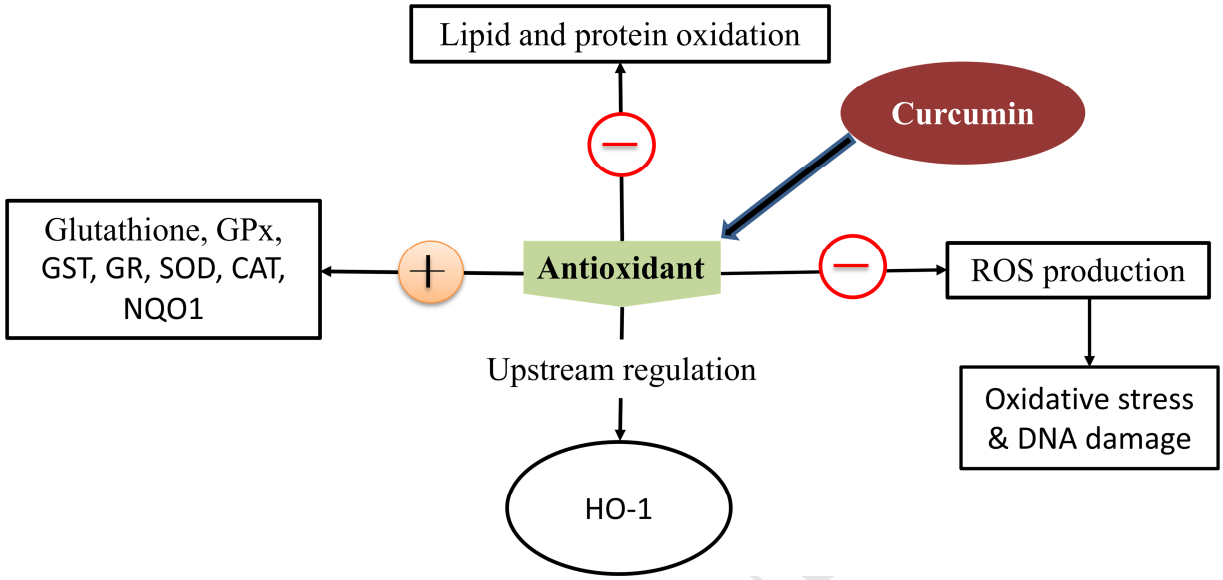

Figure 2. Curcumin decreases ROS inhibits lipid and protein oxidation and up regulates GSH, NQO1, GST, GR, GPx, CAT, SOD and HO-1 expression.

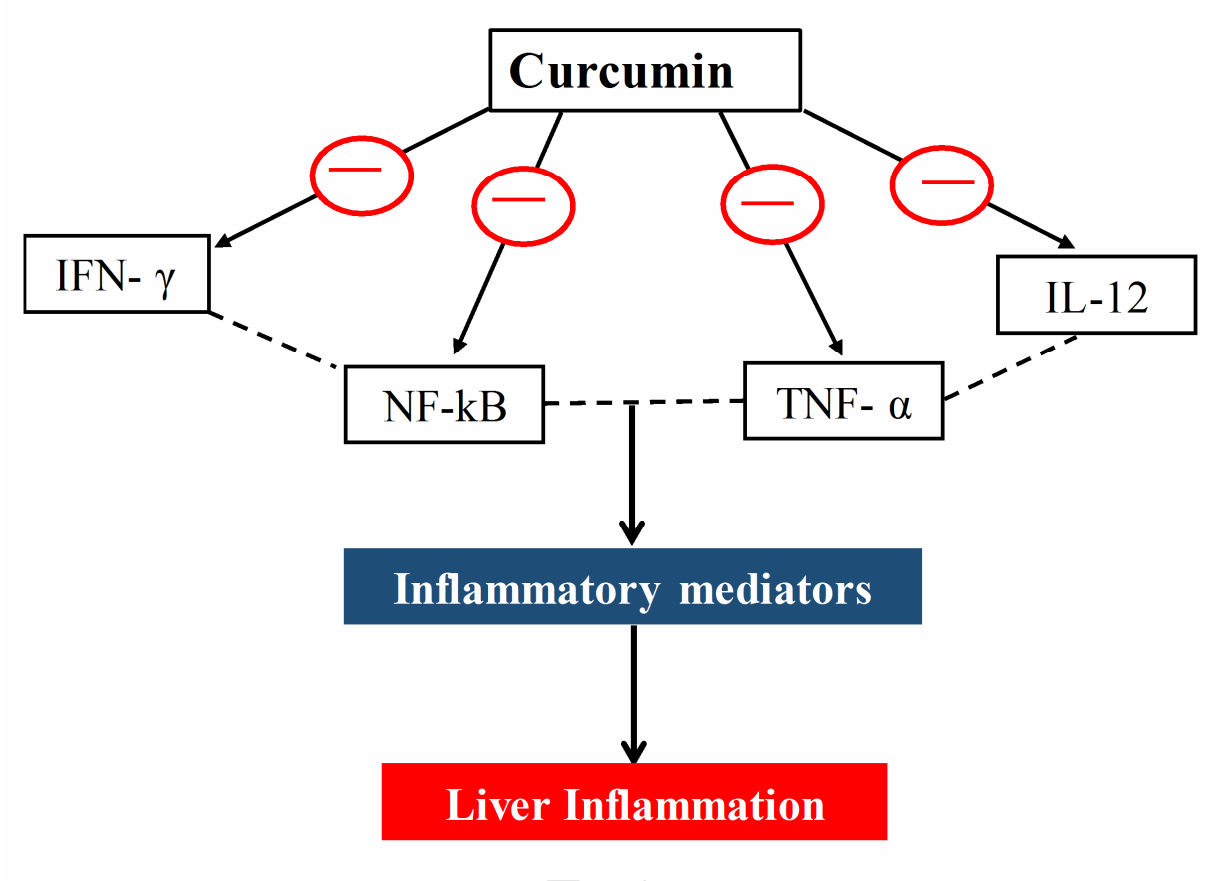

Figure 3. Curcumin causes negative regulation of IFN- γ, NF-kB, TNF- α, IL-12 leads to decrease in concentration of inflammatory mediators.

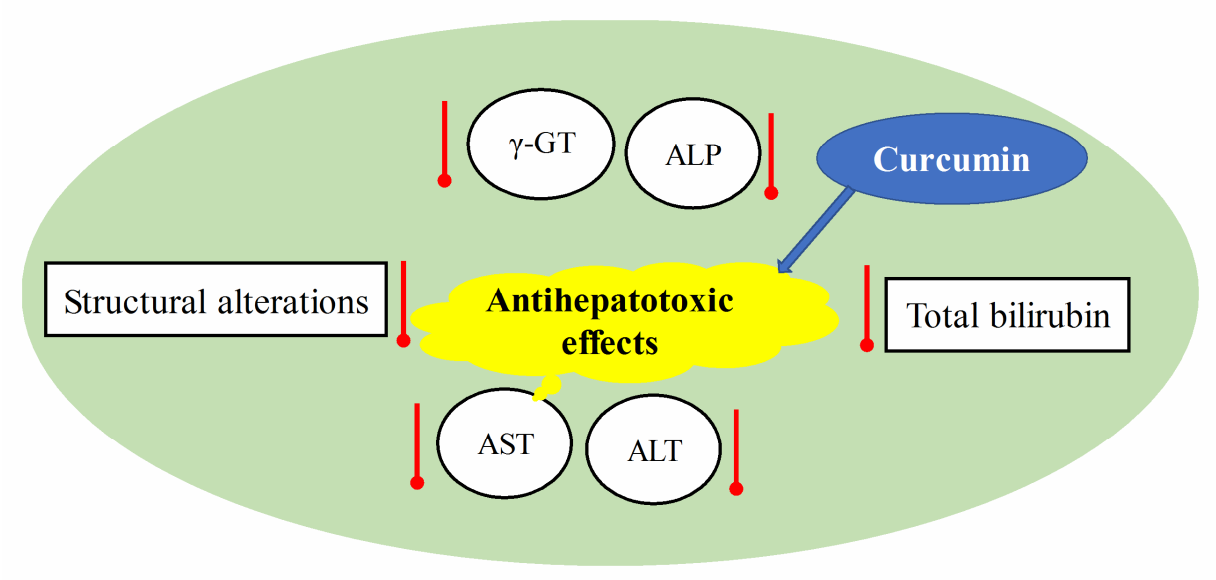

Figure 4. Curcumin decreases total bilirubin, structural alterations and hepatotoxic markers including γ-GT, ALP, AST and ALT.

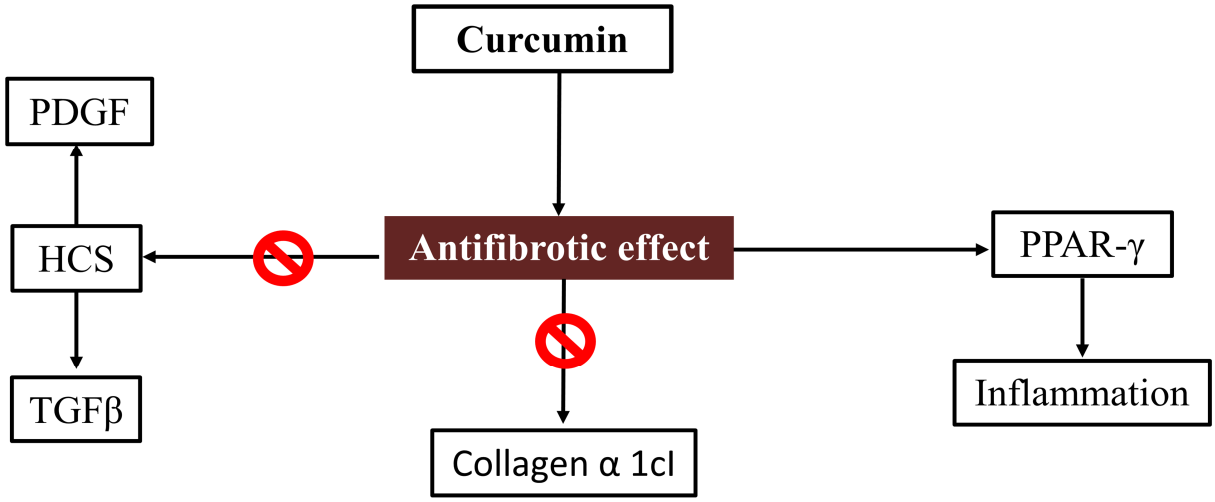

Figure 5. Curcumin down regulates HCS, Collagen α 1cI while up regulates PPAR-γ.

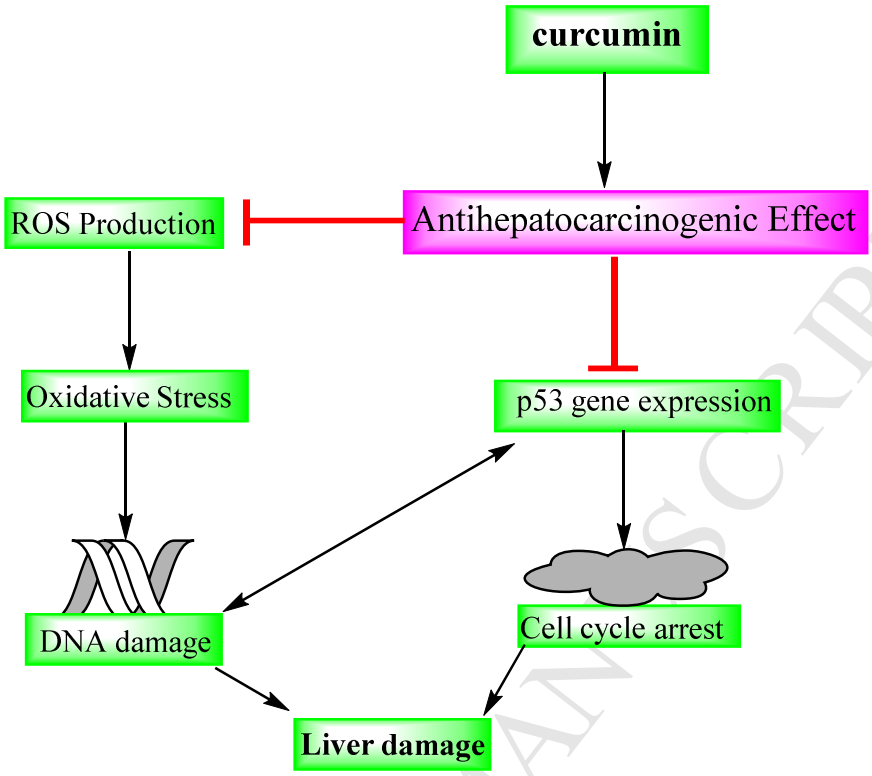

Figure 6. Curcumin possesses antihepatocarcinogenic effects by decreasing ROS production and downregulating p53 and p21 genes.

Highlights

Hepatoxicity caused morbidity and mortality in millions of people around the world.

Drug resistance and sensitivity with the classical treatments is a great challenge need to be address

Natural compound, curcumin has shown versatile hepatoprotective effects in different in vitro and in vivo models.

Based on documented data, it could be the drug of future as a potent hepatoprotective agent after clinical confirmation.