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A Comprehensive Review on Physiological Effects of Curcumin

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ABSTRACT

Turmeric (*Curcuma longa* Linn) is an herbal medicine which is traditionally used as a spice, food colouring or flavouring agent and widely used for several diseases such as biliary disorders, cough, hepatic disorders, rheumatism, wound healing, sinusitis, diabetes, cardiac disorders and neurological disorder. It belongs to the *Zingiberaceae* family. Turmeric is a popular domicile remedy used in Indian food, is mainly a native of south-east Asia, is widely cultivated in India, Sri Lanka, Indonesia, China, Jamaica, Peru, Haiti and Taiwan and it is very less expensive. Curcumin is the main principle of turmeric. Curcumin has shown various biological properties pre-clinically and clinically. Curcumin is a highly pleiotropic molecule which can be modulators of various intracellular signalling pathways that maintain cell growth. It has been reported as anti-inflammatory, anti-angiogenic, antioxidant, wound healing, anti-cancer, anti-Alzheimer and anti-arthritis and possesses an excellent safety profile. All previous review articles on curcumin have collected the biological/pharmacological activities but this review article summarises the most interesting in vitro and in vivo studies of curcumin on most running diseases around the whole world.

ABBREVIATION

DMSO	Dimethyl sulfoxide
NSCLC	Non-Small Cell Lung Cancer
XIAP	X-Linked Inhibitor of Apoptosis
ROS	Reactivity Oxygen Species
SCLC	Small Cell Lung Cancer
FOXO1	Forkhead Box Protein O1
RAR β	Retinoic Acid Receptor Beta
MMPs	Metalloproteinases or Matrixins

NF- κ B	Nuclear Factor Kappa B
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
ATF-2	Activation of Transcription Factor-2
LDH	Lactate Dehydrogenase
CK	Creatine Kinase
ECM	Extracellular Matrix
AMPK	Adenosine Monophosphate Activated Protein Kinase
PPAR- γ	Peroxisome proliferator-activated receptor gamma

Introduction

Historically plants were used in India for medicinal purposes. Turmeric is an herbal medicine. It belongs to species of *Curcuma longa* Linn. It is a medicinal plant broadly employed in Ayurveda, Unani and Siddha system of medicine. It is also used as home remedy for various diseases [1]. Curcumin (diferuloylmethane) is the main constituent of the popular Indian spice turmeric, turmeric belongs to the ginger family (*Zingiberaceae*) [2]. The derivative of Curcumin is curcuminoids (Curcuminoids is a linear diarylheptanoid, polyphenolic molecules). The other two main forms of curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin and it is important for the yellow colour of turmeric [3]. Curcumin has two tautomeric compound form ketonic and enolic. The enolic group has more stability in the solid phase and solution. Curcumin is a bright yellow colour compound and it is applied as a food colouring agent [4]. Curcumin has been acquired a wide range of pharmacological and biological activities including anti-inflammatory, anti-cancer, anti-oxidant, wound healing, anti-microbial and many others biological properties [5, 6]. Turmeric was characterized as *C. Longa* Linn by Linnaeus, Liliopsida is the class of *C. longa* Linn, subclass is commelinids, order is zingiberaceous, and the family is *Zingiberaceae*, the genus is *Curcuma* and Species is *Curcuma longa*. The primitive turmeric is *C. aromatica* and the domiciliary species is called as *C. longa* Linn [3].

Physical and chemical properties of Curcumin

Curcumin is a brightly yellow color pigment compound with anti-oxidant and anti-tumor activities. Chemical name - diferuloylmethane, IUPAC name is 1, 7-bis (hydroxyl-3-methoxyphenyl)-1, 6-heptadiene 3,5-dione [7, 8]. The molecular formula is $C_{21}H_{20}O_6$, appearance-bright yellow-orange powder, melting point is 183 °C (361 °F; 456 K), molar mass-368.385 g mol⁻¹ and Curcumin solubility in DMSO (> 11 mg/mL) [9], Curcumin is rapidly soluble in organic solvents such as acetone, ethanol, DMSO, and dimethyl formamide [10]. The maximum oral dose of Curcumin is 8 g/day for 3 months (human) at this dose Curcumin has not caused any toxic and hazardous effects [11].

Pharmacokinetics properties of Curcumin

Curcumin pharmacokinetics and bioavailability studies have been indicated low intestinal absorption. Oral administration of 400 mg of Curcumin shows absorption rate of 60–66% [12] and rapid clearance from the body. Curcumin clinical use is limited largely because it has low solubility and fast metabolism that leads to low bioavailability [10]. It is permeable across blood-brain barrier [4, 12, 13].

Pharmacological properties of Curcumin

Curcumin possess so many properties like anti-oxidant, anti-inflammatory, anti-viral and anti-fungal actions. Some investigators proved that Curcumin has not been shown any toxic effect in humans. Curcumin prevents the growth of *Helicobacter pylori* which induces gastric ulcers [13]. Curcumin shows anti-inflammatory activity by inhibition of molecules that play an important role in inflammatory disorder [14]. Turmeric is effective in preventing post-surgical inflammation and exerts anti-osteoporotic activity. Curcumin can bind with heavy metals such as cadmium and lead which can reduces the toxic effect of these heavy metals [15]. Curcumin

inhibits the pathway of cyclooxygenase, 5-lipoxygenase and glutathione S-transferase. Curcumin prevents atherosclerosis by reducing the formation of blood clumps [4]. Curcumin has potential for scavenging superoxide radicals, hydrogen peroxide and nitric oxide (NO) from activated macrophages, reduces the iron complex and lipid peroxidation both in vitro and in vivo [16, 17].

Role of Curcumin in Alzheimer disease

Curcumin has shown its beneficial action by binding the copper, lowering the cholesterol level, inhibiting the enzyme acetylcholinesterase, modifying the insulin signalling pathway, suppressing the tau and by enhancing the phagocytosis of A β by microglia/macrophages [18–22].

Effect of Curcumin on respiratory disorder (lungs cancer)

Curcumin inhibit the apoptosis through modulation of the miRNA pathways which is important for inhibition of caspase-3, and which to prevent the PI3K/Akt pathway (implicated in growth factor-mediated cell survival) [23], and also inhibit the XIAP. Curcumin has cytotoxic properties of NSCLC and SCLC, which are mediated by an increase of ROS and apoptosis. Curcumin inhibited lung cancer cell proliferation via the JAK/STAT3 pathway which is incriminated in tumor recurrence and drug resistance [24, 25]. This inhibition leads to the prevention of abnormal cell growth and suppressed the proliferation, migration, invasion and angiogenesis of SCLC cells. Another mechanism by which Curcumin reduces the proliferation of SCLC cells is the induction of FOXO1, a transcription factor that regulates cell proliferation, differentiation and DNA damage repair. Curcumin's induction of FOXO1 upregulates p21 and p27 gene codes and down regulates cyclin D, inducing cycle arrest and apoptosis [26]. Inhibition of cell proliferation by Curcumin also appears from epigenetic effects by reactivation of silenced tumor cells suppressor genes. In NSCLC cells, Curcumin decreases the RAR β (retinoic acid receptor beta) promoter methylation [27], which induces the expression of RAR β and leads to prevent the tumor cells growth. The antineoplastic role of Curcumin is also mediated by the decrease the cancer cell migration. In patients of NSCLC Curcumin downregulates early growth response protein 1 (EGR-1) and enhancement of cell-cell adhesion [28]. Furthermore, Curcumin prevents the production and activity of MMPs (Metalloproteinases or matrixins) by several mechanisms [29]. In NSCLC patients Curcumin inhibits phosphokinase A, with preventing the NADPH oxidase-2 and reduces ROS production. ROS is important for activation of transcription factor-2 (ATF-2), induces MMP-9 production. Another mechanism is reducing the Rac1/PAK1 pathway [30], which leads to the downregulation of MMP-2 and MMP-9 and reducing cell migration. Curcumin helps in downregulation of adiponectin, a cytokine produced by adipose tissue and implicated in lung cancer. This downregulation prevents the NF- κ B and reduces the production of MMPs which causes the reduction in the migration and invasion capability of these cells. Curcumin decreases the expression of DNA repair proteins and enhances p53 levels, inducing apoptosis of cells [28, 31, 32].

Effect of Curcumin in Osteoarthritis (inflammatory disorder)

Osteoarthritis is a chronic joint disorder of the liftable joints affecting the older-age population worldwide. It is estimated by loss of cartilage, remodelling of adjacent bone and bony overgrowth [33]. Mechanism-based antiarthritic potential of Curcumin includes chondrocyte regeneration and apoptosis, inflammation, and oxidative stress. Curcumin inhibits inflammation in osteoarthritis by intraperitoneal administration of curcumin at 50 mM (► Fig. 1) [34].

Effect of Curcumin on cardiac disorder

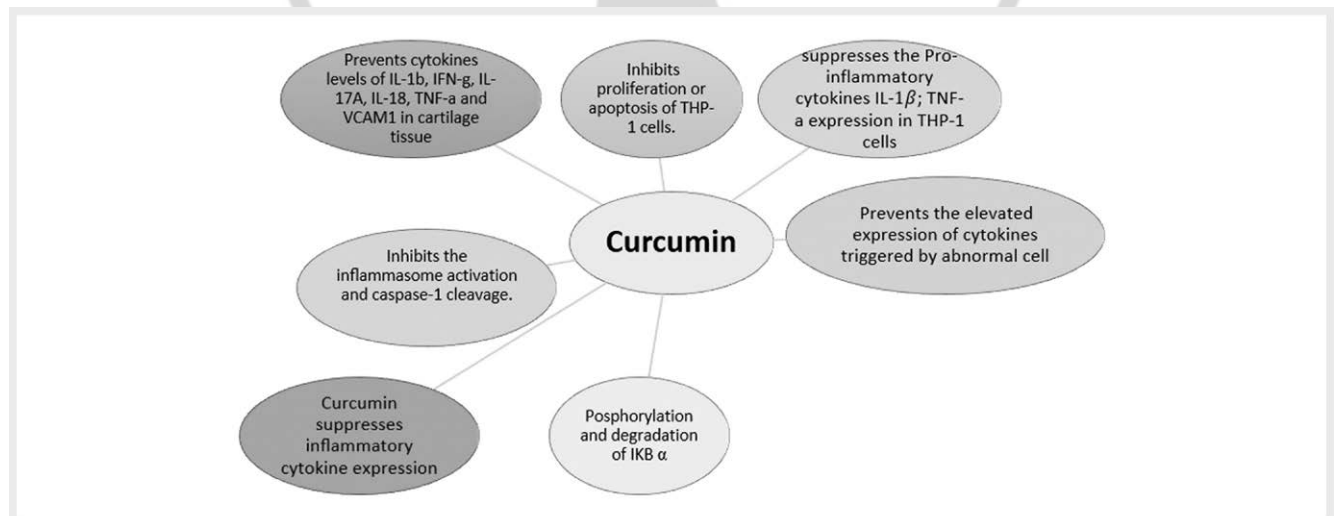
Curcumin has anti-inflammatory and antioxidant properties thereby this compound reduces cardiovascular complications, such as unstable angina, CHF and arrhythmia [35]. Curcumin has an antioxidant property which inhibits the oxidative stress. Inhibits the apoptosis and also have anti-inflammatory properties. This compound exerts cardioprotective role on myocardial ischemia [35]. It reduces the release of cardiac LDH and CK and increases the post-ischemic cardiac function. Curcumin also plays a protective role in cardiomyocyte structure, attenuating extracellular matrix (ECM) remodelling and promotes cardiac contraction [36]. Oxidative stress is an important factor contributing to ischemic myocardial injury (IMI). Curcumin reduces the isoproterenol-induced myocardial ischemia by improving the levels of SOD catalase, glutathione, suppressing the production of thiobarbituric acid reactive substances and the leakage of lactate dehydrogenase (LDH) [37]. Wang et al. Study proved that Curcumin reduces the mitochondrial hydrogen peroxide activity [38]. This compound also suppresses the malondialdehyde levels [39]. Curcumin by improving the anti-apoptotic protein Bcl-2 level favour a protective effect against cerebral ischemia/reperfusion injury (IRI) by the activation of JAK2/STAT3 signaling pathway [40, 41]. It also recovers post-ischemic cardiac function, myocardial infarct size and lactate dehydrogenase release in the coronary flow. This compound reduces the myocardial IRI by preventing inflammation, which may be a critical pathway of myo-

cardial ischemia. Curcumin has been shown lowering the upregulation of IL-1, IL-6, IL8 and TNF α (► Fig. 2) [42]. Curcumin releases the cytoplasmic inflammatory cytokine NF- κ B. This compound also inhibits TLR2, reduces infarct size, and myocardial injury [43, 44]. Some studies have been proved that inactivation of TLR2 reduces the myocardial IRI [34]. Curcumin ameliorates the heat stress and enhances the stabilization of the cytoskeletal structures, it increases the level of mitochondrial energy production to ensure sufficient energy supply and also improves cardiac contractility [45].

Curcumin potential in hepatic disorder (liver disease)

Hepatic disorders covers all the problems that cause hepatic damage to perform its functions [46]. Abuse drug is the most common cause of hepatic disease. Toxic Drug effects on hepatic cells cause hepatic cell damage and hepatic inflammation. Accumulation of fats occurs in hepatic cells which affects their function in chronic alcohol abuse [47, 48]. Curcumin lowers the level of PGI₂, LDL and increases the HDL [49].

- a) **Effect of Curcumin in non-alcoholic liver disease** Curcumin in the dose of 200 mg/kg/day (orally) for 3 weeks prevent the inflammation of non-alcoholic liver male Wistar-Albino rat [50]. Curcumin prevents the development and progression of fibrosis. Reduces the tissue inhibitor metalloproteinase-1 (TIMP-1) secretion and prevents 8-OH-deoxyguanosine-mediated liver oxidative stress. Curcumin inhibits the inflammation of non-alcoholic liver, by preventing the proinflammatory cytokines, lipid peroxidation products, PI3K/Akt and hepatic stellate cells activation. It ameliorates non-alcoholic steatohepatitis (NASH) via lipid reduction, increase insulin resistance, improved anti-inflammatory and antioxidant effects which possibly related to activation of Nrf2 [51, 52]. Curcumin inhibits the NF- κ B pathway which is responsible for the transcription of DNA and protein [53].
- b) **Effect of Curcumin in alcoholic hepatic Disease** Curcumin acts in AMPK (adenosine monophosphate activated protein kinase)



► Fig. 1 Effect of Curcumin in osteoarthritis (inflammatory disease).

to reduce the liver fat and serum alanine transaminase (ALT). Curcumin prevents the impairment in lipid metabolism and it can prevent fatty acid biosynthesis [54]. Curcumin decreases the elevated biomarker AST, ALT, LDH, ALP and reduces the damaged liver cell in animal (► **Fig. 3**) [55].

- c) **Effect of Curcumin in oxidative stress in liver** ROS is the main principle for oxidative stress, generation of free radicals and cellular abnormality. Curcumin inhibits initiation of styrene oxidation and reduces chronic disorders and prevents bacterial cell growth in the liver [15].
- d) **Effect of Curcumin in liver injury** Single dose at 100 mg/kg of Curcumin given by intraperitoneal route is responsible for the inhibition of lipid peroxidation, free radical formation and DNA abnormal function. Curcumin inhibits the D-galactosamine, protects the impacted nitric oxide synthase-2 (NOS-2) down-regulation and reduces the level of NO in the liver (► **Fig. 3**) [56].

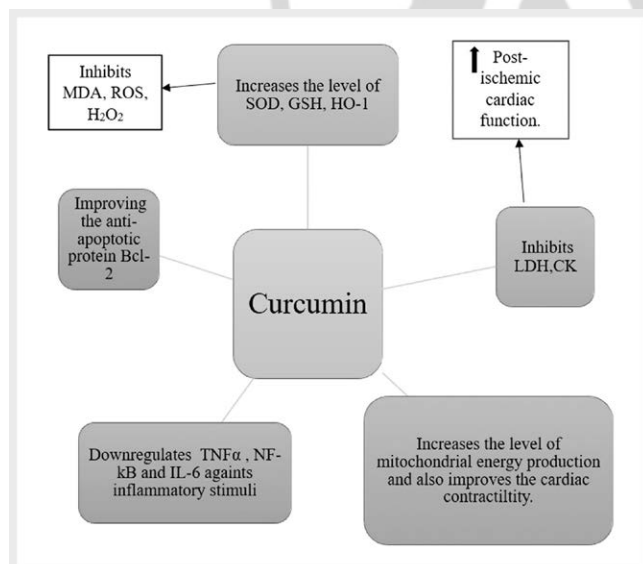
Effect of Curcumin on glucose level and pancreatic B cell (diabetes mellitus)

Curcumin acts as an antidiabetic in some experimental diabetes models. The structural and functional fault in the deficiency of insulin-producing and insulin-responsive tissues in the body have been shown some complicated pathogenesis of T2DM. Wojcik et al. showed that Curcumin acts at multiple molecular targets and pathways which shown effective role in diabetic patients [57]. Jeenger et al declared that Curcumin improves various microvascular diabetic complications such as retinopathies, nephropathies, cardiomyopathies and neurological disorders which are eventually

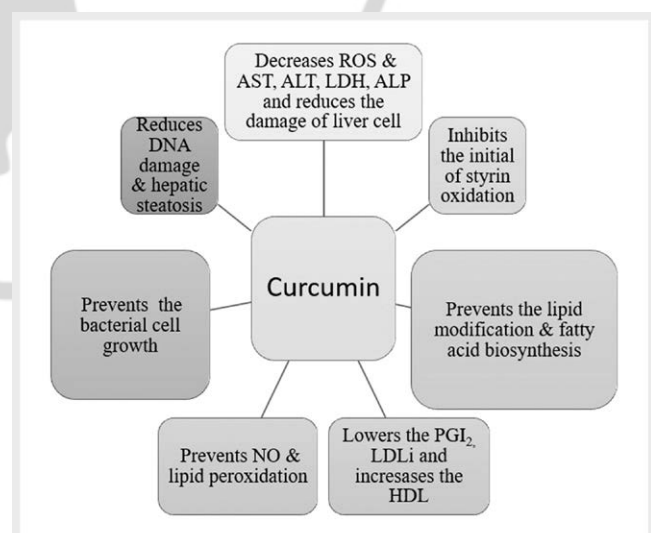
linked to diabetes induced oxidative stress and inflammatory disorders [58]. Curcumin demonstrated its effect in diabetes by lowering blood glucose level, enhancing carbohydrate metabolism and restoring the activities of multiple antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, catalase and glutathione-S transferase. Curcumin also inhibits the lipid peroxidation [59]. Curcumin can modulate the functions of multiple cell signaling and it inhibits the level of thiobarbituric acid reactive substances (TBARS) and reduces the sorbitol dehydrogenase (SDH). Curcumin activates the liver enzyme connected with gluconeogenesis, glycolysis and lipid metabolic pathways. It activates the function of nuclear factor erythroid-2-related factor-2 (NRF2) [60]. It can also induce the peroxisome proliferator-activated receptor gamma (PPAR- γ) activation. Curcumin can also increase the levels of plasma insulin and lipoprotein lipase (LPL) activity [61]. Curcumin prevents the IL-6, TNF- α , maintained the extracellular matrix proteins, vasoactive factors and a key transcriptional co-activator (p300) in cultured human retinal microvascular endothelial cells (HRECS) and dermal-derived human microvascular endothelial cells (HMVECS) in hyperglycemic tissues [62]. Curcumin inhibits poly ADP-ribose polymerase-1 activation and prevents cytokine (TNF- α , IL-1 β , etc.) Induced NF- κ B translocation which enhance islet neogenesis and prevents the level of reactive oxygen species (ROS) production within the islet (► **Fig. 4**) [63].

Conclusion

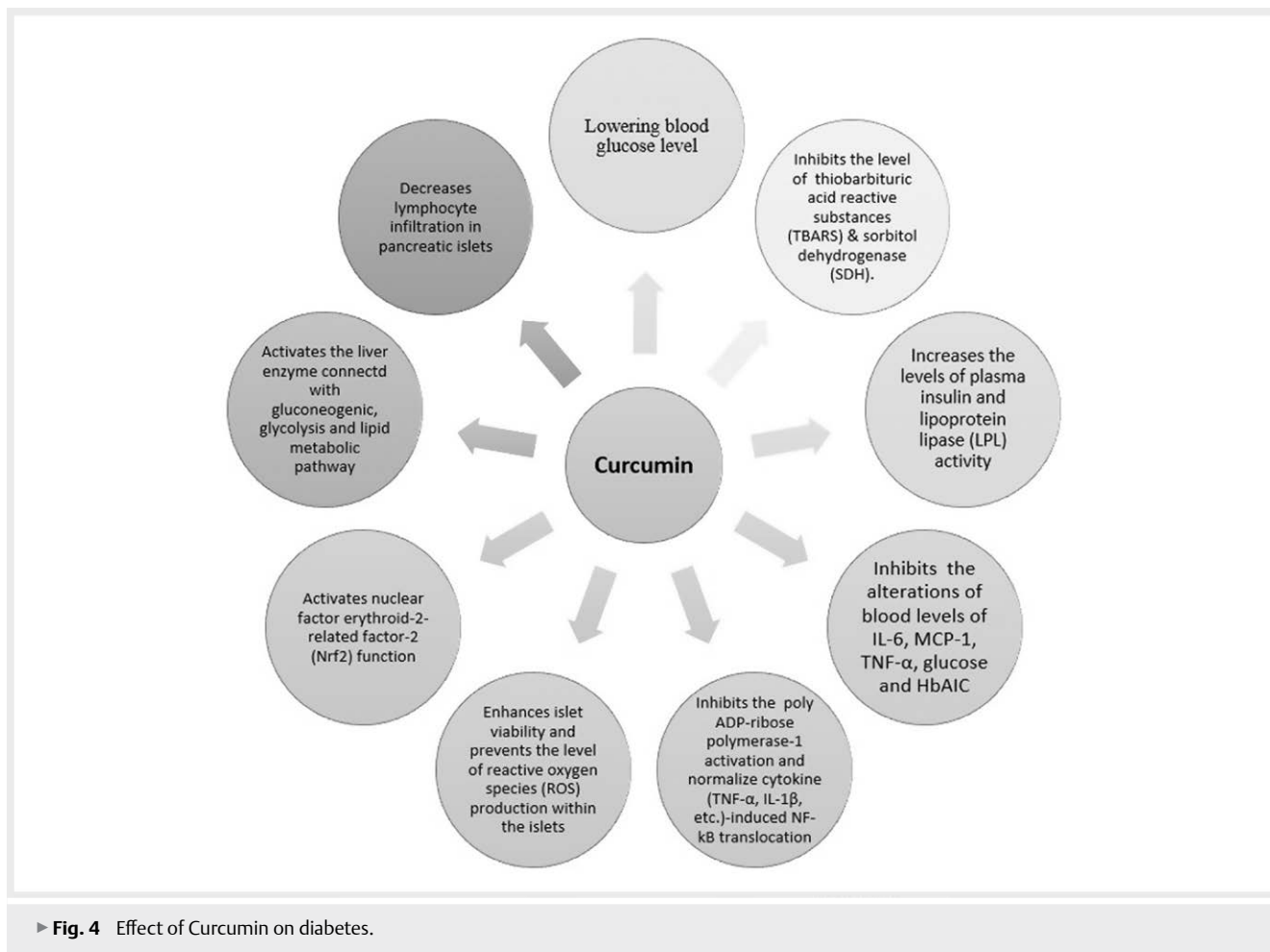
Turmeric is a popular household remedy used in Indian food. Curcumin is a principal constituent of turmeric. Although Curcumin has been found effective in patients with rheumatoid arthritis, inflammatory eye diseases, inflammatory bowel disease, chronic pancreatitis, psoriasis, hyperlipidemia, post-operative inflammation and cancers in preliminary studies but well-controlled clinical trials are still needed. Further, Keeping in view the biological safety, efficacy, cost effectiveness and easier availability well controlled clinical studies are advocated to confirm its efficacy in various other



► **Fig. 2** Curcumin increases the level of SOD, GSH, HO-1 (Heme oxygenase) and reduces the level of MDA, ROS, H₂O₂, inhibits lactate dehydrogenase, creatine kinase, enhance post ischemic cardiac function, Curcumin improves the anti-apoptotic protein Bcl-2, downregulates TNF α , NF- κ B and IL-6 against inflammatory stimuli and also increases the level of mitochondrial energy production and improves the cardiac contractility.



► **Fig. 3** Effect of Curcumin in liver disease.



most running disorders such as diabetes, Alzheimer, cardiovascular, liver injury and osteoarthritis as sufficient in vitro and preclinical data is available to support for conducting clinical studies in these areas.

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Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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