

# The role of curcumin in liver diseases

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## Abstract

Chronic liver diseases are a major medical problem worldwide. Despite the availability of etiologic-specific treatments for several liver diseases, no drug or medication is available for the regression of hepatic fibrosis and cirrhosis. Curcumin is a natural compound extractable from turmeric. Several studies have uncovered its role in the modulation of biological mechanisms involved in liver injury. The best known biological effect of curcumin is the interaction with different pathways involved in the development of liver fibrosis, as shown in both *in vitro* and *in vivo* models of chronic liver injury. In pre-clinical studies, curcumin was also effective in decreasing alcohol-, glucose- and hepatitis C virus (HCV)-related liver injury, as well as HCV replication in hepatocytes. These data make curcumin a potential therapeutic agent for regression of fibrosis and cirrhosis, especially in the setting of HCV infection that can be easily eradicated thanks to the availability of several direct-acting antivirals.

**Key words:** curcumin, liver fibrosis, cirrhosis, hepatitis C virus, hepatocarcinoma.

## Introduction

Liver diseases are among the most important health problems worldwide. In developed countries, overnutrition and alcohol abuse represent the major causes of liver disease, whereas infectious diseases – especially from viruses and parasites – are the main cause in Africa and Asia. Moreover, mortality rates from liver diseases are increasing rather than declining worldwide [1]. About 2% of the world's population is chronically infected with hepatitis C virus (HCV) [2], while the prevalence of hepatitis B virus (HBV) in the global population is estimated to be 3.7% [3]; these viruses are the most common underlying agents in infection-related cirrhosis.

The availability of a new class of direct antiviral agents (DAA) against HCV is probably going to change the epidemiology of HCV infection. Results from randomized clinical trials (RCT) testing DAA showed a sustained viral response (SVR) rate up to 100% [2], thus making real-

izable the prospective of HCV global eradication [4]. However, little is known about the evolution of liver disease after viral eradication has been achieved; the complete regression of hepatic fibrosis is probably unachievable [5].

Liver fibrosis, and the subsequent cirrhosis, are the consequences of chronic liver injury due to several causes: viral cytotoxicity, oxidative stress, toxic stress (e.g. drugs, alcohol) and metabolic damage [6, 7].

Curcumin is the most important curcuminoid of turmeric, and it has been identified as the main factor responsible for its biological activities [8], including potent anti-oxidant and anti-inflammatory effects as well as the ability to modulate several signaling mechanisms [9–12]. Oxidative stress plays an important role in many chronic diseases and in carcinogenesis [13–15]. Several studies have shown that curcuminoid compounds can act as free-radical scavengers by reducing lipid peroxidation mediated by free radicals [16–18]. One of the most important discoveries in this field has been the curcumin-mediated suppression of nuclear factor  $\kappa$ B (NF- $\kappa$ B), which has a key role in triggering the inflammatory cascade in most chronic illnesses [19–21]. Importantly, NF- $\kappa$ B-dependent gene products also prevent apoptosis and promote cell proliferation, invasion and angiogenesis [22–26].

This review will focus on curcumin's role in preventing liver damage progression in different liver diseases, by interfering not only with inflammation and fibrosis, i.e. in non-alcoholic fatty liver disease (NAFLD), but also with HCV replication and other mechanisms involved in hepatocarcinoma (HCC) development in HCV-related chronic liver disease.

### Curcumin bioavailability

The interest in curcumin for chronic diseases has recently increased due to its anti-oxidant, anti-inflammatory and anti-tumoral properties [27]. However, the pharmacodynamic actions of curcumin described in pre-clinical trials are limited by its unfavorable pharmacokinetic profile. In fact, curcumin showed low absorption due to its poor solubility in water and fast liver and intestinal metabolism, which contribute to its rapid excretion [28]. Moreover, it is highly unstable and rapidly hydrolyzed at physiological pH [29], and undergoes intense hepatic biotransformation (by conjugation and CYP reduction enzymes with prevalent excretion through the bile) [30].

In order to overcome curcumin's unfavorable pharmacokinetic profile, several formulations have been proposed, including curcumin-loaded nanoparticles [31], complexes with phospholipids [32], microemulsifying [33] and association with

drug bioenhancers [34, 35]. Of particular interest is the delivery system of curcumin developed by Sasaki *et al.* [36] named Theracurmin, which consists of a highly absorptive formulation dispersed with colloidal nanoparticles. Oral administration of Theracurmin guaranteed a value of area under the curve (AUC) 40-fold higher compared with curcumin powder.

### Curcumin and liver damage

#### Inflammation and fibrosis

Activation of hepatic stellate cells (HSCs) promotes liver fibrosis regardless of etiology. The mechanisms of HSC activation *in vivo* are often investigated with the fibrotic carbon tetrachloride (CCl<sub>4</sub>) in animal models. In these models, curcumin showed a major role as an inhibitor of HSC activation; it also seems to be able to reduce liver damage, as well as the  $\alpha$ -SMA and procollagen expression in the liver, when administered in CCl<sub>4</sub>-induced liver fibrosis models for 4–8 weeks. The recognized mechanism of action in those models included curcumin's ability to target multiple sites, such as platelet-derived growth factor-b receptor (PDGF-bR) [37], matrix metalloproteinases (MMPs) [37, 38], tissue growth factor b (TGFb) [39, 40], peroxisome proliferator-activated receptors (PPARc) [41], toll-like receptors (TLRs) [42], apoptotic pathway [43, 44], inflammatory cytokines [41, 42, 45, 46] and microRNAs [47, 48]. Recently, curcumin's capacity to increase cyclic adenosine monophosphate levels, which leads to an increase in the number of mitochondrial DNA duplicates, has been demonstrated [49].

A growing body of evidence has shown that leptin and its receptor (Ob-R) play an important role in activating HSCs and in the subsequent development of fibrosis. An *in vitro* study showed that curcumin is able to interrupt leptin signaling that would lead to HSC activation. It exerts this effect by inhibition of phosphorylation of Ob-R and suppression of Ob-R gene expression by stimulating PPARc activity and reducing oxidative stress [50].

Moreover, curcumin appears to be effective *in vitro* in inhibiting hyperglycemia-induced HSC activation [51]. It has been shown that curcumin suppression of membrane translocation and gene expression of glucose transporter-2 leads to a reduction of intracellular glucose level of HSCs [51]. The same authors reported that curcumin inhibits the insulin receptor substrates (IRS)/PI3K/AKT signaling pathway, which links leptin with the insulin pathway, preventing the translocation of glucose transporter-4. It suppresses the PKA activity while increasing the activity of AMP-activated protein kinase (AMPK), thus increasing the glucokinase activity and subsequently the conversion of glu-

cose to glucose-6-phosphate; the final effect is a reduction of glucose levels in HSCs [52].

Khan *et al.* [53] reported that curcumin also has anti-glycation properties: advanced glycation end-products (AGEs) are compounds formed by oxidative and non-oxidative reactions between proteins and/or lipids and carbohydrates [54] and their production is increased by hyperglycemia. Aging, chronic renal failure and diabetes facilitate the accumulation of AGEs in tissues and blood and lead to inflammation and liver fibrogenesis [55]. Amadori products are intermediates in the formation of AGEs; their conversion to AGEs is partially caused by oxidative reactions [56]; anti-oxidant agents may thus prevent the deposition of AGEs in tissues [57] which are involved in HSC activation. Several studies have shown the ability of curcumin to reduce HSC activation thanks to its anti-glycation properties [50, 58, 59]. However, there is no evidence for the role of curcumin in regulating gene expression of RAGE and AGE-R1 (which are the two categories of AGE receptors) *in vivo*. Lipid metabolism is implicated elsewhere in HSC activation, and curcumin appears to be also effective in inhibiting this pathway. In fact, *in vitro* studies have highlighted the effect of curcumin in increasing intracellular lipid accumulation in HSCs through the induction of lipogenesis-related genes, such as SREBP-1c, PPARc, and C/EBP  $\alpha$ , leading to inhibition of HSC activation [60]. In addition, different studies have also shown significant improvement in the lipid metabolism and delay in hepatic fibrosis progression in rats and mice with steatohepatitis treated with curcumin [61–63].

As shown in *in vitro* models, another curcumin-mediated mechanism of inhibition of HSC activation is the elicitation of AMPK activity, which induces the expression of genes involved in lipid accumulation as well as in the increase of intracellular fatty acids and triglycerides levels [60]. In fact, the HSC activation is facilitated by reduction of lipid storage capacity and intracellular lipid droplets, as well as by suppression of PPARc, C/EBP $\alpha$ , SREBP 1 and other transcription factors [64, 65]. In detail, hepatic AMPK leads to a reduction in glucose output with a subsequent lowering of blood glucose; this effect is exerted by high AMP and low ATP concentrations [66]. AMPK is also believed to regulate lipogenesis and SREBP 1 activation [67]. Moreover, as reported in studies conducted by Kang *et al.* [68–70], curcumin exerts several effects that also reduce HSC activation: it suppresses the effects of specific protein-1, which is involved in attenuating the expression of SREBP-2, it reduces the gene expression of lectin-like oxidized LDL receptor-1 (LOX-1) and it suppresses the expression of LDL receptor.

Curcumin also has a role in other steps of fibrogenesis when increased extracellular proteins are deposited in the extracellular space of the liver. This deposition is regulated by the action of a group of enzymes called MMPs and their specific inhibitors, tissue inhibitors of metalloproteinases (TIMPs). When this balance is broken by hyperactivation of HSCs, fibrosis occurs. Available evidence showed that curcumin plays a role in downregulation of TIMP-1 and TIMP-2 *in vivo* [38, 71–73] and *in vitro* [74], while it upregulates MMP-2 [73], MMP-7 [72], MMP-9 [73] and MMP-13 [38, 72]. This leads to inhibition of HSC activation due to the degradation of one of the main components of the ECM, the fibrillar collagens. Furthermore, another crucial mechanism involved in liver fibrosis is the reduction of PPARc expression in HSCs: in fact, PPARc is highly expressed in inactive HSCs, while its activity is reduced when HSCs are activated both *in vivo* and *in vitro* [65, 75, 76]. Curcumin may thus interfere with liver fibrosis due to its role in induction of the expression of PPARc, which results in a reduction of vitamin A and lipid-droplet storing capability, deposition of ECM in the extracellular space and expression of  $\alpha$ -SMA and type I collagen- $\alpha$ 1, as well as in elicitation of cell proliferation and growth. Finally, the curcumin-mediated PPARc activation results in inhibition of trans-activating activity of NF- $\kappa$ B, while – when a specific PPARc antagonist is used – higher HSC proliferation is observed.

Considering that adipokines, such as leptin and adiponectin, have an important role in regulation adipocyte energy metabolism [77, 78], curcumin has anti-diabetic effects through the suppression of NF- $\kappa$ B in adipocytes and the reduction of NF- $\kappa$ B-regulated adipokines. So, curcumin has anti-diabetic effects that could be considered as valuable targets for diabetes mellitus [79].

With regard to clinical trials in humans, a randomized, double-blind, placebo-controlled trial [80] showed that a 12-week fermented turmeric powder (FTP) treatment was associated with a statistically significant decline in both ALT and AST levels in 30 subjects with mild elevated transaminases concentrations at baseline (with the possible speculation of a reduction of the hepatic cell damage by FTP therapy). One limitation of this study was the unknown etiology of the transaminase elevation in the enrolled patients. However, patients with chronic HCV and HBV infections, as well as those with abnormal transferrin saturation, were excluded before randomization (Table I).

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease, and it is associated with the classic clinical components

Table 1. Randomized clinical trials of curcumin treatment in subjects with different liver diseases

Reference	Number of patients	Type of patients	Outcome measures	Study design	Curcumin formulation, treatment schedule and duration	Results
Kim <i>et al.</i> [84]	48	Subjects $\geq 20$ years with ALT level between 40 and 200 U/l	AST, ALT, GGT, total bilirubin, lipid profile	(Randomized) placebo-controlled	Fermented turmeric powder 3 g QD for 12 weeks	Significant reduction of ALT levels in the treatment group ( $p = 0.02$ )
Panahi <i>et al.</i> [94]	102	Patients with NAFLD (grades 1–3 according to liver sonography)	Anthropometric measures, lipid profile, glucose, insulin, glycated hemoglobin, uric acid concentrations	(Randomized) placebo-controlled	Curcumin 500 mg BID for 8 weeks	Reduction in serum levels of total cholesterol ( $p < 0.001$ ), low-density lipoprotein cholesterol ( $p < 0.001$ ), triglycerides ( $p < 0.001$ ), non-high-density lipoprotein cholesterol ( $p < 0.001$ ), and uric acid ( $p < 0.001$ )
Rahmani <i>et al.</i> [95]	80	Patients with ultrasonographic evidence of NAFLD	Liver fat content and severity of NAFLD, anthropometric measures, lipid profile AST, ALT, glycated hemoglobin, fasting glucose concentrations	(Randomized) placebo-controlled	Curcumin 500 mg/day of an amorphous dispersion preparation comprising 70-mg curcuminoids for 8 weeks	Reduction in NAFLD severity ( $p < 0.001$ ). Reductions in body mass index ( $p = 0.002$ ) and serum levels of total cholesterol ( $p < 0.001$ ), low-density lipoprotein cholesterol ( $p < 0.001$ ), triglycerides ( $p = 0.001$ ), AST ( $p = 0.002$ ), ALT ( $p = 0.001$ ), glucose ( $p = 0.048$ ), and glycated hemoglobin ( $p < 0.05$ )
Panahi <i>et al.</i> [86]	87	Patients with NAFLD (grades 1–3 according to liver sonography)	Anthropometric measurements, hepatic enzymes, and liver ultrasonography	(Randomized) placebo-controlled	Curcumin 500 mg BID for 8 weeks	Reduction in body mass index ( $p < 0.05$ ) and waist circumference ( $p < 0.05$ ); ultrasonographic findings were improved in 75.0% of subjects in the curcumin group, while the rate of improvement in the control group was 4.7% ( $p < 0.001$ ). Serum levels of AST and ALT were reduced in the curcumin group ( $p < 0.001$ )

AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT –  $\gamma$ -glutamyl transpeptidase, NAFLD – non-alcoholic fat liver disease, QD – *quaque die* (once a day), BID – *bis in die* (twice a day).

of the metabolic syndrome: obesity, diabetes, dyslipidemia, insulin resistance [81]. These predisposing conditions are highly prevalent in the western countries; hence NAFLD has become a public health concern with an estimated prevalence of 6–35% among adults worldwide [82]. Liver steatosis is recognized as a decisive “first hit” in the pathogenesis of the disease and it is defined by the presence of cytoplasmic triglyceride (TG) droplets in > 5% of hepatocytes in the absence of significant alcohol consumption [83]. Therefore, modifications in dietary and lifestyle habits represent the first therapeutic target to prevent NAFLD or its progression to non-alcoholic steatohepatitis (NASH)/cirrhosis [84]. However, as in other conditions requiring considerable changes in dietary habits, most patients fail to comply with effective lifestyle modifications. The NAFLD is demonstrated to evolve in severe liver fibrosis and cirrhosis. To date, there is no specific drug available on the market able to effectively reverse liver steatosis or slow NAFLD progression. Therefore, there is a growing interest to find effective and safe treatments for this important clinical problem. Natural products have been the subject of increasing attention owing to their multi-target action and overall safety in several conditions [85–88]. Due to the possible protective action that curcumin exerts on the liver, and the beneficial effect shown on the associated conditions of NAFLD, including obesity [89], dyslipidemia [90], and impaired fasting glucose [91], this compound has been considered as a potential therapeutic agent in NAFLD. In recent years, curcumin (and its derivatives) has been tested in animal models of NAFLD with results elucidating possible mechanisms of action and paving the way to possible clinical use. In a methionine choline deficient (MCD)-diet-induced NAFLD mouse model, bisdemethoxycurcumin (BDMC), a close curcumin analogue, was investigated for its potential hepatoprotective effect. To this aim, a control group (normal diet), a NAFLD group (MCD diet), and a MCD + BDMC group were studied after a 4-week treatment. Convincing results showed that BDMC was associated with significantly lower circulating aspartate aminotransferase (AST), alanine aminotransferase (ALT) and inflammatory markers (IL-6 and TNF- $\alpha$ ) compared to MCD mice. Moreover, TG levels, expressed as mg/total liver tissue, were very similar to the ones measured in the control group. In this study, the BDMC also showed an inhibitory effect on liver lipogenesis by reducing the expression of genes related to fatty acid synthesis, which are generally found upregulated in NAFLD. In a subsequent study, male Sprague–Dawley rats were fed with a high-fat and high-sugar diet for 8 weeks (NAFLD group), then randomly assigned to curcumin by oral gavage (80 mg/kg/day) or

an equal volume of cellulose and compared with a control group (normal diet). Biohumoral markers, including ALT, TG, total cholesterol (TC) and HOMA index, as well as liver histology parameters, were consistent with a significant recovery of the clinical features of the NAFLD in curcumin-fed rats. In this study, a specific pathophysiologic effect has been proposed: by measuring adiponectin precursor (ADIPOQ) mRNA, protein expressions and DNA methylation status and by analyzing the correlations between these and changes in TC, TG, ALT and HOMA-I, DNA methylation of ADIPOQ was found to be one of the mechanisms by which curcumin executes its hepatoprotective function in NAFLD [92]. This first study testing curcumin in humans with NAFLD (grades 1–3 in ascending severity, according to liver ultrasonography definition) evaluated the metabolic effects in subjects randomly assigned to a curcumin (1000 mg/day in 2 divided doses) ( $n = 44$ ) or control ( $n = 43$ ) group for a period of 8 weeks. Serum levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, non-high-density lipoprotein cholesterol and also uric acid significantly decreased in the curcumin group [93]. The highest quality trial testing curcumin compounds in subjects with NAFLD was published in 2016 by Rahmani *et al.* [94] and added a placebo-controlled design and an ultrasound end-point. In this study, 80 subjects of both sexes, selected as in the study presented above, were 1 : 1 randomly assigned to curcumin (500 mg/day of an amorphous dispersion preparation comprising 70-mg curcuminoids) or placebo supplementation for 8 weeks. Most anthropometric and biohumoral parameters (total cholesterol, LDL-C, HDL-C, triglycerides, BMI, body weight, ALT, AST, HbA<sub>1c</sub>) were found significantly improved after the supplementation in the curcumin group compared with placebo. Similarly, a comparison of liver ultrasonographic findings (severity of liver steatosis on a scale from 1 to 3) at baseline and after 8 weeks revealed a significant improvement in almost 80% of subjects in the curcumin versus 27% in the placebo group. Interestingly, the effect of curcumin in reducing US evidence of liver fat remained significant after adjustment for possible confounding factors, including baseline levels of TG, HbA<sub>1c</sub>, ALT and changes in body weight.

Although direct comparison between the two human studies available in the literature are limited by the different curcumin posology employed, there are striking similarities in the overall beneficial effect on the metabolic profile in treated subjects. Findings of this randomized controlled trial are also summarized in Table I.

Moreover, a more recent randomized placebo-control trial of 87 subjects confirmed these data [95]. After 8 weeks of curcumin (phytosomal form, at daily dose of 1 g), a reduction in body mass in-

**Table II.** Ongoing or future randomized clinical trials of curcumin in metabolic syndrome, non-alcoholic fatty liver disease and other liver diseases (from clinicaltrials.gov)

Name	ClinicalTrials.gov Identifier	Number of patients estimated	Type of patients	Purpose	Study design	Curcumin formulation, treatment schedule and duration
Effects of Short-term Curcumin and Multi-polyphenol Supplementation on the Anti-inflammatory Properties of HDL (PSI)	NCT02998918	20	> 18 and < 60 years old healthy, non-smoker patients	VCAM-1 and ICAM-1 expression in whole plasma and in HDL at baseline, after 1 h and after 1 week of supplementation	(Randomized) cross-over, single blind	PolyResveratol 500 mg (100 mg curcumin phytosome, 100 mg quercetin phytosome, 100 mg green tea phytosome, 100 mg trans-resveratrol, 100 mg trans-pterostilbene) BID for a week versus curcumin phytosome 1 g QD for a week
Effect of Oral Supplementation With Curcumin in Patients With Proteinuric Diabetic Kidney Disease	NCT01831193	100	> 18 and < 80, diabetic patients with moderate chronic kidney disease (glomerular filtration rate between 15–60 ml/min/1.73 m <sup>2</sup> )	Proteinuria, HbA <sub>1c</sub> , AST, ALT	(Randomized) double-blind, placebo-controlled	1.67 g of curcumin (7 capsules of 231 mg) divided into 3 doses daily for 6 months
Curcumin Supplement in Nonalcoholic Fatty Liver Patients With Type 2 Diabetes	NCT02908152	50	> 30 and < 65 diabetic patients and CAP score > 263	Hepatic steatosis measured by CAP score using Fibroscan, glucose, HbA <sub>1c</sub> , AST, ALT	(Randomized), quadruple blind placebo-controlled	Curcumin 1500 mg for 12 weeks QD
Effects of Curcumin Supplementation on Lipid Profile and Inflammatory Markers of Patients With Type 2 Diabetes	(NCT02529969)	50	> 40 and < 65, diabetic non-insulin dependent patients, BMI < 30	Triglyceride and C-reactive protein	(Randomized) double blind, placebo-controlled	Curcumin 500 mg for 12 weeks QD
A Study Evaluating the Safety and Efficacy of Curcumin in Patients With Primary Sclerosing Cholangitis	NCT02978339	15	> 18 and < 75, diagnosis of primary sclerosing cholangitis (PSC)	ALP, AST, ALT, GGT, bilirubin, CRP, albumin, Mayo PSC risk score, quality of life	Open-label study	One 750 mg softgel by mouth BID for 12 weeks. Each 750 mg CuraMed softgel supplies 500 mg of highly bioavailable BCM-95 curcumin
Effects of Curcumin Supplementation on Glycemic Control, Oxidative Stress, Lipid Profile and Inflammatory Markers of Patients With Type 2 Diabetes	NCT02529982	50	Non-insulin dependent diabetic patients	Fasting blood glucose, total capacity antioxidant	(Randomized) double blind placebo-control	500 mg curcumin for 12 weeks

Table II. Cont.

Name	ClinicalTrials.gov Identifier	Number of patients estimated	Type of patients	Purpose	Study design	Curcumin formulation, treatment schedule and duration
Micellar Curcumin and Metabolic Syndrome Biomarkers	NCT01925547	42	> 18 years metabolic syndrome	C-reactive protein, AST, ALT, GGT, TNF- $\alpha$ , IL-6, insulin, plasma albumin, serum total cholesterol, triglyceride, cholesterol, blood pressure, body weight	(Randomized) crossover double blind	80 mg micellar curcumin (oral) TID for 6 weeks
Curcumin Therapy in Patients With Impaired Glucose Tolerance and Insulin Resistance	NCT01052025	200	Patients aged 35 years or older with an abnormal fasting plasma glucose (100–125 mg/dl) or with insulin resistance (140–199 mg/dl) by using 75 mg of glucose OGTT	Reduction of blood sugar level, lipid profile, insulin resistance status and oxidative stress status	(Randomized) single blind placebo-control	Curcumin capsule contains 250 mg curcuminoids, 3 capsules per time, 2 times a day before meal for 12 months

AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT –  $\gamma$ -glutamyl transpeptidase, NAFLD – non-alcoholic fat liver disease, QD – quaque die (once a day), BID – bis in die (twice a day), TID – tris in die (three times a day).

dex and waist circumference and an improvement in ultrasonographic liver findings were observed, with a significant reduction of ALT and AST.

In a previous randomized double-blind placebo-control trial of the same group, 117 subjects with metabolic syndrome were randomly assigned to curcuminoids or placebo [96]. After 8 weeks of follow up, supplementation with curcuminoid (at a daily dose of 1 g) and piperine (at a daily dose of 10 mg) combination significantly improved the oxidative and inflammatory status of patients. In particular, there was observed an improvement in serum superoxide dismutase activities and a reduction in concentration malondialdehyde and C-reactive protein. These results are in line with previous studies [97].

Of note, the important role of curcumin in a clinical setting was recently reviewed by an International Lipid Panel expert [98]. In this work, the authors concluded that an evidence-based approach to the use of lipid-lowering nutraceuticals could improve the quality of the treatment, including therapy adherence, and achievement of the LDL-C goal in clinical practice, an important endpoint in cardiovascular disease [99–102]. Moreover, in Table II, ongoing or future trials registered at clinicaltrials.gov to be performed with curcumin in metabolic and hepatic diseases are listed.

### Curcumin and HCV replication

Kim *et al.* demonstrated that the induction of heme-oxygenase 1 (HO-1) and the inhibition of PI3K-AKT partially promote HCV replication. HO-1 is a curcumin-induced gene and it is a potential therapeutic protein for the regulation of homeostasis in several diseases [103]. Furthermore, HO-1 inhibits the replication of HCV [104]. In fact, its knock-down partially reverses the curcumin-mediated inhibition of HCV replication and since HO-1 is induced by ROS, HO-1 and ROS may have a role in inhibiting HCV replication [105, 106]. Kim *et al.* also showed that curcumin may have a role in the suppression of HCV replication by blocking the AKT-SREBP-1 pathway [107]. A recent study showed different mechanisms in curcumin-mediated HCV replication inhibition. First of all, they demonstrated that the main metabolized form of curcumin (THC), derived from the lack of  $\alpha$ 1 $\beta$  unsaturated ketone groups, is not active in inhibiting HCV replication. Therefore, they postulated that the key structures involved in this HCV inhibition process were the ketone groups; moreover, they discovered that curcumin was able to affect the entry pathway and had no activity against replication or assembly/release of infectious particles. Curcumin seemed to exert its activity directly impairing the ability of the virus to enter the target cells, and the proposed mechanism of action was

a modulation of the fluidity of the viral membrane with no effect on the integrity of viral particles. Moreover, curcumin seems to be able to interfere with the cell-to-cell HCV spreading mechanism, and this capability may be correlated with its hydrophobicity by which curcumin could insert among lipids of the viral envelope, thereby increasing its rigidity and thus inhibiting its fusion capabilities.

### Curcumin and hepatocellular carcinoma (HCC)

One of the earliest papers presenting evidence about the role of curcumin in prevention of HCC was published by Soni *et al.* in 1997 [108]. They showed that turmeric and curcumin inhibit the aflatoxin B1-induced mutagenesis in hepatic murine cells, reducing the genesis of gammaglutamyl-transpeptidase-positive foci. Furthermore, in 1998, Lin *et al.* [109] showed that curcumin decreases migration and invasion of a highly aggressive human HCC cell line through dose-dependent inhibition of MMP-9 secretion. In a N-diethylnitrosamine (DEN)-induced model of hepatocarcinogenesis conducted in C3H/NeH rats, Chuang *et al.* [110] found that administration of curcumin significantly decreases both incidence and multiplicity of HCC; similar results were achieved in subsequent studies conducted by different authors in female Wistar rats [111–113]: they all showed

the protective role of curcumin in *in vivo* models of DEN-induced HCC. In these studies the suppressive effects of curcumin in the DENA-initiated alteration of hepatic foci in rats was accompanied by the restoration of normal levels of several hepatic metabolic enzymes. Busquets *et al.* [114] evaluated the effects of curcumin in a xenograft model of hepatocarcinogenesis; they demonstrated that the administration of curcumin can decrease the growth rate of HCC in Yoshida ascites hepatoma in rats, even with no influence on the tumor volume reduction, thus excluding a possible effect of curcumin on cell apoptosis. The effects of curcumin in combination with standard chemotherapeutic agents have also been investigated *in vitro*. In an interesting study, Notarbartolo *et al.* [115] showed that the combination of curcumin with cisplatin and doxorubicin results in synergistic cell growth inhibition in HA22T/VGH cells. Despite the reported positive evidence in some preclinical models, several studies have documented the failure of curcumin in protecting against chemical hepatocarcinogenesis in rodents. Curcumin failed to prevent HCC in rats treated with different chemical tumor inducers including *N*-ethyl-*N*-hydroxyethylnitrosamine, 3, 2'-methyl-4-aminobiphenyl [116] 3, 2'-methyl-4-aminobiphenyl, DENA/2-amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline [117, 118], and 3,3',4,4'-tetrachlorobiphenyl [119]. Curcumin also failed to protect against copper-in-

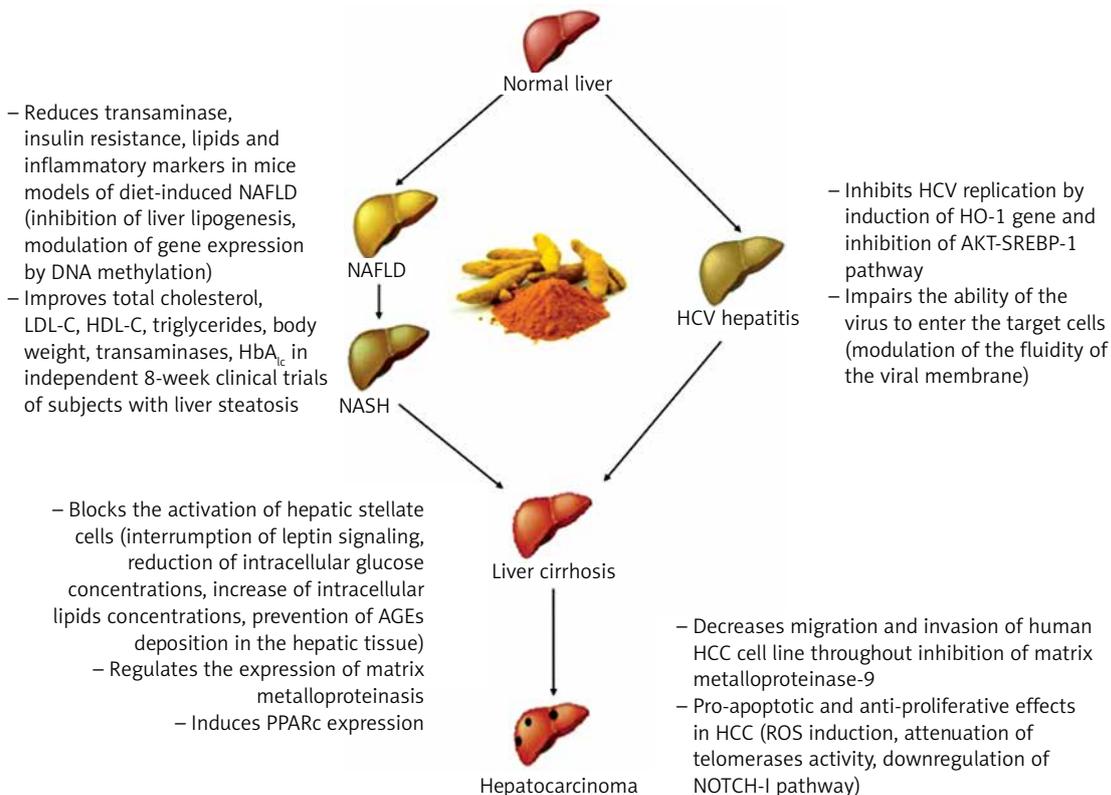


Figure 1. Curcumin main effects on sequential stages of liver pathology

duced HCC in rats [120]. In the aforementioned studies, curcumin was administered in a relatively low dose, which probably prevented the occurrence of its pro-oxidants effects. In a very recent *in vitro* study, Cao *et al.* [121] evaluated the concomitant administration of sorafenib and curcumin; the authors assembled sorafenib and curcumin codelivered nanoparticles (SCN) and then measured their antiproliferative effects, in comparison with free sorafenib, curcumin and a physical mixture of sorafenib and curcumin (Sora + Cur). The coassembled SCN presented significantly enhanced antiproliferative effects compared to sorafenib, curcumin (6.0 and 1.5-fold higher reduction of tumor growth rate, respectively), and their physical mixture. In the same study, *in vivo* antiproliferative and antiangiogenic activities of SCN were determined by immunohistochemistry measurements. The captured images showed that the neovasculature was detected in the tumor sections from control, sorafenib, curcumin, and Sora + Cur groups, but was barely detected in the SCN-treated group, which implicated the higher antiangiogenic capability of SCN over other chemotherapy regimens. This evidence verified the enhanced therapeutic efficacy on *in vivo* antiproliferative and antiangiogenic activities by SCN.

## Conclusions

There are numerous etiological factors able to elicit chronic liver inflammation that could lead to hepatic fibrosis and cirrhosis, including metabolic, infectious and autoimmune diseases. Despite the availability of etiologic-specific treatments for several liver diseases, no drugs or medications are currently approved for the regression of hepatic fibrosis and cirrhosis, which represent the final consequences of chronic liver injury. The interest in anti-fibrotic therapeutic or preventive agents has recently risen due to the availability of a new class of DAA against HCV. Whereas the clinical efficacy of these brand new medications has been widely demonstrated in eradicating HCV infection [2, 122–128], little is known about their effects on liver fibrosis and a significant histological improvement of cirrhosis with antiviral agents is probably unfeasible.

Curcumin is a natural compound easily extractable from turmeric and is widely used in middle-eastern diets. Several studies have uncovered its role in the modulation of many biological mechanisms involved in liver injury, and they are summarized in Figure 1.

The available data make curcumin a promising phytotherapy in chronic hepatitis and a potential therapeutic agent for regression of liver fibrosis and cirrhosis, especially in the setting of HCV infection, which could be easily eradicated with many

direct-acting antivirals. Even though results from studies conducted so far are encouraging, several critical issues still must be overcome before curcumin may become available in clinical practice. The above-mentioned poor bioavailability of curcumin is a critical limiting factor which affects the drug pharmacodynamics, and then the use of a novel drug delivery system for curcumin must be considered when testing its clinical effects.

## Conflict of interest

All authors declare no conflict of interest.

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