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REVIEW ARTICLE

Curcumin: Reintroduced Therapeutic Agent from Traditional Medicine for Alcoholic Liver Disease

HAMID REZA RAHIMI[1], MAHMOUD REZA JAAFARI[2], AMIR HOOSHANG MOHAMMADPOUR[3], KHALIL ABNOUS[4], MAJID GHAYOUR-MOBARHAN[5], ELAHE RAMEZANZADEH[1], FATEME MOUSAVI[1], REZA KAZEMI OSKUEE[6,*]

[1] Student Research Committee, Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Nanotechnology Research Center, School of Pharmacy, Mashhad University of Medical Science, Mashhad, Iran
[3] Department of Clinical Pharmacy and Pharmaceutical Research Center, School of Pharmacy, Mashhad University of Medical Science, Mashhad, Iran
[4] Pharmaceutical Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[5] Biochemistry of Nutrition Research Center, and Department of New Sciences and Technology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[6] Neurogenic Inflammation Research Center, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Alcoholic liver disease (ALD) is the main cause of chronic liver disease across the world and can lead to fibrosis and cirrhosis. The etiopathogenesis of ALD is related to ethanol-induced oxidative stress, glutathione reduction, abnormal methionine metabolism, malnutrition, and production of endotoxins that activate Kupffer cells. Curcumin is an active ingredient of the rhizome of turmeric. The substance is shown to have minor adverse effects. As the substance possess low bioavailability in free formulation, different strategies has been conducted to improve its bioavailability which resulted in production of nanomiscels and nanoparticles. Curcumin can provide protection for the liver against toxic effects of alcohol use. Several studies showed curcumin blocks endotoxin-mediated activation of NF-κB and suppresses the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells. According to the molecular studies, curcumin inhibits NF-κB signaling pathway, regulates cytokines production and modulates immune response. It has been shown that curcumin can suppress gene expression, especially cytokines genes resulting in down-regulation of tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8, adhesion molecules (ICAM, VCAM) and C-reactive protein. Hence, curcumin can have therapeutic effects on the majority of chronic inflammatory diseases such as asthma, bronchitis, inflammatory bowel disease, rheumatoid arthritis, ALD, fatty liver, and allergy.

Keywords: Alcoholic Liver Diseases, Curcumin, Kupffer Cells, NF-kappa B

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INTRODUCTION

Alcohol is one of the major causes of end-stage liver disease across the world (1). Alcoholism is related to more than 60 diseases, and among them alcoholic liver disease (ALD) has the highest mortality rate (2).The second most popular cause for liver transplantation in the United States is ALD (1). ALD is a main cause of chronic liver disease globally and can lead to fibrosis and cirrhosis (3). ALD includes alcoholic steatosis, alcoholic hepatitis, alcoholic cirrhosis, and hepatocellular carcinoma (2-3). Almost 18 million people misuse alcohol and 10 million people suffer from ALD. It stays an important reason of liver failure and causes more than 20,000 deaths in the United States every year (4). The 12th cause of death in the United States in 2007 was liver cirrhosis, with a total of 29,925 deaths, 48% of which were alcohol related (3). There is a slow reduction in alcoholic cirrhosis-caused death in many countries (1).

Fatty liver progresses in about 90% of people who drink more than 60 g/day of alcohol but may also happen in people who drink less than this amount (5-7). Early work on the pathogenesis of the disease concentrated on ethanol metabolism–related oxidative stress and glutathione reduction, abnormal methionine metabolism, malnutrition, and production of endotoxins that activate Kupffer cells (3). Probable factors that influence the progression of liver injury include the dose of daily intake, the level of alcohol content in alcoholic beverage, duration, drinking patterns, sex, ethnicity, and associated risk factors such as obesity, iron overload, concomitant infection with hepatitis viruses, and genetic factors (3-8). ALD is an important complication of alcohol consumption and a prevalent liver disease in western countries. Oxidative stress has an important influence on progression of this disorder. Oxidative damage can be caused by alcohol alone or in combination with high fat diet (3,9) (Figure 1).

*Correspondence to: Reza Kazemi Oskuee; PharmD, PhD. Department of Medical Biotechnology, School of Medicine, Azadi Square, Pardis Campus, Mashhad, Iran.
Tel: +98 51 3800 2301, Fax: +98 51 3800 2287, E-mail: oskueekr@mums.ac.ir
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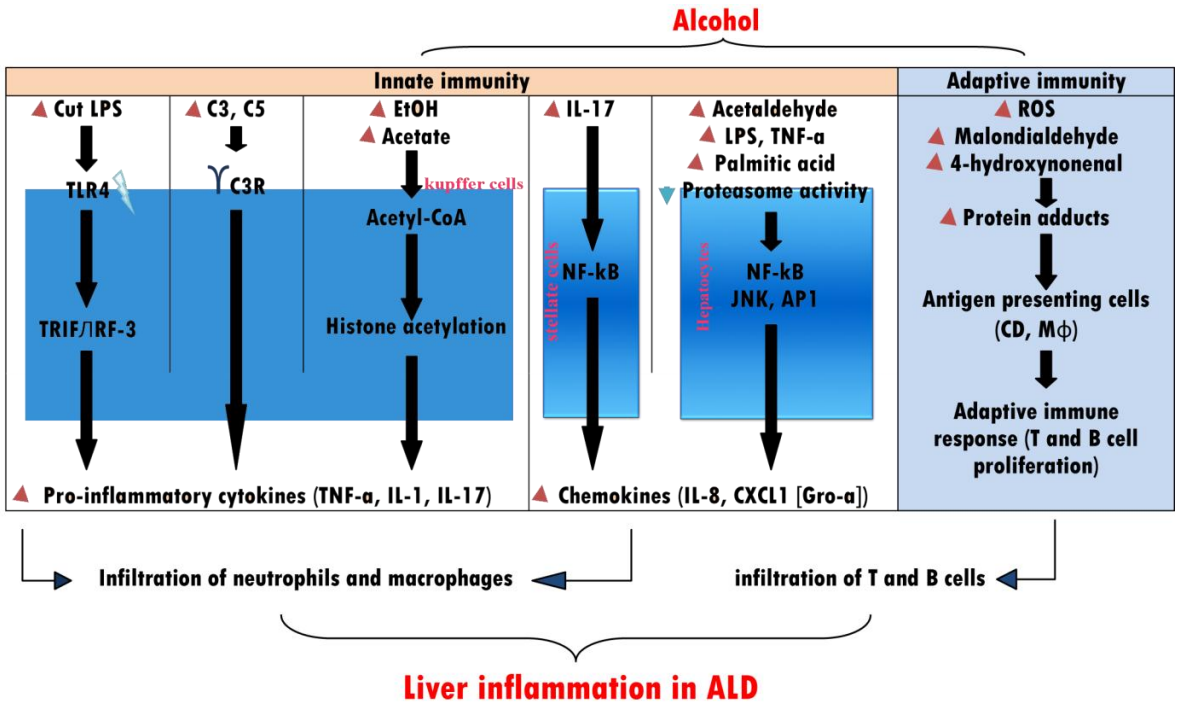

Figure 1. Mechanisms underlying inflammation in ALD: (1) Activation of non-specific immunity. Parenchymal migration of neutrophils and macrophages is an important characteristic of ALD and is probably due to ethanol-mediated activation of non-specific immunity and subsequent induction of pro-inflammatory cytokines and chemokines. Alcohol use or abuse up-regulates a diversity of factors that activate Kupffer cells, stellate cells, and hepatocytes, leading to the production of cytokines and chemokines. Alcohol disposal also reduces proteasome activity and increase IL-8 expression in hepatocytes. (2) Activation of adaptive immunity. ALD is associated with infiltration of CD4+ and CD8+ T cells in the liver. Alcohol use induces reactive oxygen species (ROS) and causes the expression of many protein adducts that might serve as antigens in the adaptive immune response, leading to the accumulation of T and B cells in the liver (quotation from Szabo et al. (8)).
- LPS: Lipopolysaccharides, TLR4: Toll-like receptor 4, TRIF: TIR-domain-containing adapter-inducing interferon-β, C: Complement protein, EtOH: Ethanol, IL: Interleukin, NF-κB: Nuclear factor-kappa B, JNK: c-Jun NH2-terminal kinase, AP1: activator protein-1, CXCL1: Chemokine (C-X-C motif) ligand 1, ROS: Reactive oxygen species

Research has shown that treatment with antioxidants, such as curcumin, silymarin, green tea, and vitamins C and E, can protect DNA from damage and regulate liver pathogenesis-related cascades by reducing reactive oxygen species (9). In this narrative review, the therapeutic effects, safety and bioavailability of curcumin in the treatment of ALD and inflammatory diseases are presented and discussed.

Evidence acquisition

Bibliographical search was performed in Medline, Scopus, OVID, Google Scholar databases up to September 2014 using the following keywords in all fields: "alcoholic liver disease" OR "ALD" AND [(Curcumin) OR (Turmeric) OR (Inflammation)] OR (Safety of Curcumin) OR (Bioavailability of Curcumin).

Curcumin and its therapeutic properties

Curcumin or diferuloylmethane [(1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl)- 1, 6-heptadiene-3, 5-dione] is an active ingredient of the rhizome of turmeric (10-13). Curcumin has protective effects against oxidative stress by decreasing the lipid oxidation and developing antioxidant status, thus can be considered as an efficient antioxidant (14). Curcumin has therapeutic effects on the majority of chronic and inflammatory diseases such as fatty liver, metabolic syndrome, atherosclerosis plaque stabilizing, diabetes mellitus, obesity, asthma, bronchitis, inflammatory bowel disease, rheumatoid arthritis, depression, cancer, allergy, Parkinson's disease and it also has a therapeutic effect on wound healing without any significant adverse effect (11,15-17).

Nuclear factor κB (NF-κB) signaling pathway is one of the most important pathways in the cellular and molecular inflammation. In this cellular signaling pathway, cytokines and adhesion molecules are secreted (15,16). According to the molecular studies, curcumin inhibits NF-κB signaling pathway, regulates cytokines production and modulates immune response. It has been shown that curcumin can suppress gene expression, especially cytokines genes resulting in down-regulation of tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8, adhesion molecules (ICAM, VCAM) and C-reactive protein (11,18,19).

Modern science has demonstrated that curcumin exerts its effects by modulation of several major molecular targets, including transcription factors (e.g., AP-1, Egr-1, β-catenin, and PPAR-γ), enzymes (e.g., COX2, 5-LOX, iNOS, and hemeoxygenase-1), cell cycle proteins (e.g., cyclin D1 and p21), receptors (e.g., EGFR and HER_2), and cell surface adhesion molecules (20). Curcumin attaches to different kinds of proteins and prevents the activity of various kinases. Hence, it can be considered as an anti-proliferative,

anti-invasive, and antiangiogenic agent (15).

Curcumin as new therapeutic agent for ALD and other liver diseases

Some studies have revealed that curcumin can improve ethanol-induced oxidative stress in hepatocytes (21,22). Rong et al administered 2.4 g/kg/day ethanol for 4 weeks and 4 g/kg/day for another 2 weeks to Balb/c mice which were simultaneously treated with curcumin for all the 6 weeks. They showed that curcumin could improve ethanol-induced hepatocytes oxidative stress in vitro (21). Curcumin reduces ethanol-induced histopathological changes of the liver and improves cell recovery and stops the release of cellular alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The relief of oxidative damage by curcumin can also prevent chronic ALD (21). Long-term treatment with curcumin can ameliorate the serum level of ALT and AST (23). Curcumin is able to provide protection for the liver against toxic effects of alcohol use. Oral curcuminoids supplementation (1g/day) was found to be efficient in decreasing oxidative stress load (24,25). Curcumin has also an impressive chemopreventive effect on hepatocellular cancer (26). Ethanol exposure results in a sustained malondialdehyde elevation, glutathione depletion and evident release of cellular lactate dehydrogenase and AST, which can be significantly ameliorated by curcumin pretreatment. It should be noted that dose- and time-dependent induction of hemeoxygenase-1 was involved in such hepatoprotective effects by curcumin (22).

In a study by Nanji et al on four groups of rats (6 rats per group), the effects of intragastric infusion of curcumin on preventing ethanol-induced fatty liver was investigated (27). One group was given fish oil plus ethanol (FE); the second group was given fish oil plus dextrose (FD); and the third and fourth groups were given FE or FD supplemented with 75 mg/kg/day of curcumin. Liver samples were analyzed for histopathology, lipid peroxidation, NF-κB binding, TNF-α, IL-12, monocyte chemotactic protein-1, macrophage inflammatory protein-2, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nitrotyrosine. They found that the rats receiving FE developed fatty liver, necrosis, and inflammation. This was accompanied by activation of NF-κB and the induction of cytokines; chemokines, COX-2, iNOS, and nitro tyrosine formation (Figure 2). Curcumin therapy (FE-curcumin diet) inhibited both the pathological and biochemical changes induced by alcohol (27). In addition, no histological or biochemical evidence of liver injury was detected in rats receiving FD or FD-curcumin. The results of the study by Nanji et al study showed that both endotoxin and the Kupffer cells are implicated in the pathogenesis of ALD, and that curcumin represses the stimulatory effects of endotoxin in isolated Kupffer cells (27). Tu et al correspondingly revealed that curcumin blocks endotoxin-mediated activation of NF-κB and suppresses the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells (28). Thus, it can be said that curcumin prevents ALD, in part by repressing induction

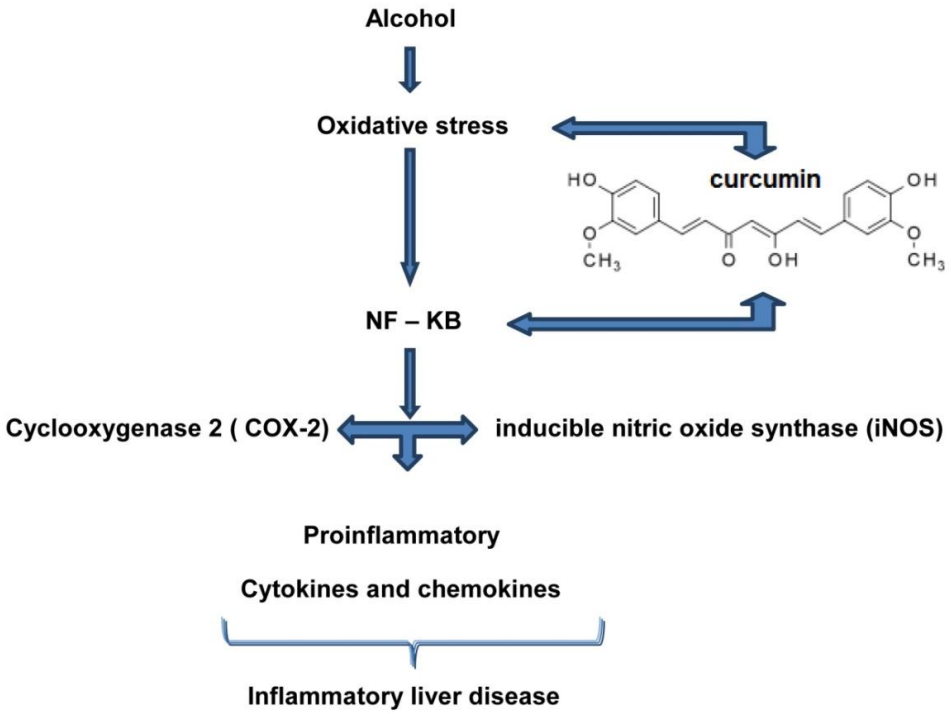

Figure 2. Suggested mechanism of curcumin against ALD. Alcohol consumption increases the levels of endotoxin in the portal circulation and oxidative stress. This results, in turn, in the activation of multiple NF-κB-responsive genes including pro-inflammatory cytokines, chemokines, COX-2, and iNOS. Curcumin, a phenolic antioxidant, prevents lipid peroxidation and the activation of NF-κB-responsive genes, thereby protecting against ALD (quotation from Nanji et al (27)).

of NF-κB-dependent genes (27). In this respect, Samuhasaneeto et al showed that curcumin can cure liver histopathology in early stage of ethanol-induced liver injury by decrease of oxidative stress and blockade of NF-κB activation in rats treated with ethanol and curcumin via an intragastric tube for 4 weeks (30).

Nonetheless, it has been suggested that curcumin may have dual effects on alcoholic liver injury depending on its concentration. Zhao et al injected 5% ethanol and/or curcumin (1×10^{-3} or 1×10^{-4} mol/L) intravenously to mice (29). They found that 1×10^{-3} mol/L curcumin accelerated liver injury and liver cellular edema during only 5% ethanol-induced liver injury evolution, whereas 1×10^{-4} mol/L curcumin did not lead to (or protected) ALD. Similarly, Lee et al ascertained that the low-doses of curcumin are protective against alcohol-induced liver damage which this occurs by modulation of the alcohol metabolic pathway, cytochrome P4502E1 and AMPK protein (31).

Besides ALD, curcumin has shown to possess high therapeutic capacity for treating other hepatic disorders (32). It has been found to be effective on hepatitis B and C, nonalcoholic fatty liver disease, drug-induced hepatotoxicity, biliary cirrhosis and primary sclerosing cholangitis (32,33). Therefore, in general, curcumin (especially in lower doses) can be considered as a promising natural therapeutic agent against liver diseases.

Bioavailability of Curcumin

Several studies have demonstrated poor bioavailability of curcumin (12,34-36), which in part can be due to chemical structure of curcumin as a polyphenolic compound, poorly soluble in water. This substance has low absorption, fast metabolism, and fast systemic elimination (34). A study showed that oral administration of curcumin at high doses of 2 g/kg to rats and healthy human volunteers results in a moderate serum concentration of 1.35 ± 0.23 μg/mL (37). Hence, several scientists have focused on the improvement of curcumin bioavailability with different strategies. Some of these strategies are: use of piperine that inhibits glucuronidation of curcumin (37); use of nano-micelles such as curcumin phytosome preparation (Meriva®) or SinaCurcumin® (32,36); and use of curcumin nanoparticles which increases oral absorption of curcumin (36).

Curcumin plus piperine: Sehgal et al demonstrated neuroprotective potential of curcumin plus piperine was remarkably higher compared to curcumin alone against benzo(a)pyrene induced DNA damage (38). Piperine was shown to enhance the bioavailability of curcumin up to 154% in rat (34), and also by around 2000% in human following oral consumption of curcumin 2 g/day plus piperine (20 mg/kg) (37). Nevertheless, inhibition of glucuronidation by piperine is a great problem as it may influence the metabolism of other medications; and thus, causes drug interaction and limitations (39).

Nanocurumin: In vivo pharmacokinetic studies have shown that curcumin-entrapped nanoparticles can at least produce 9-fold increase in oral bioavailability when contrasted to curcumin administered with piperine (as absorption enhancer) (40). In addition, while free, unencapsulated curcumin is rapidly metabolized and excreted, only nanocurcumin has shown to have sustainable plasma levels (41). Recently, a curcumin nanoformulation introduced as dendrosomal curcumin, which is curcumin encapsulated in nontoxic nanocarrier termed "dendrosome", has been developed as an effective formula against glioblastoma cells with greater bioavailability (42).

Curcumin-phosphatidylcholine (Lecithin) formulation is a patented product (Meriva®) that provides a better serum concentration of curcumin compared to free (unformulated) curcumin after oral administration (43). This formulation can also produce higher liver levels of curcumin (43). The oral bioavailability of curcumin by Meriva has been increased through physiological pathway of fat digestion. In the intestinal enterocytes, absorbed fats are packaged into large and extremely low-density lipoprotein particles called chylomicrons which are too big to pass directly into blood vessels. Therefore, they are transported into the circulation via the lymph, which eventually drains into the blood via the thoracic duct. The advantage to this route is that the first pass effect is by-passed and the bioavailability of curcumin increases (34).

Nanomicelles Curcumin: Nanomicelle containing curcumin is a registered curcumin product (SinaCurcumin®) for oral use which has been developed in Nanotechnology Research Center of Mashhad University of Medical Science and marketed by Exir Nano Sina Company in Tehran-Iran (IRC:1228225765). Each soft gel of SinaCurcumin® contains 80 mg of curcumin in the form of nano-micelle (44). These nano-micelles are prepared from GRAS (generally recognized as safe) pharmaceutical excipients and C3-complex form of curcumin. The percent of encapsulation of curcumin in this nano-micelle is near to 100% and the sizes are around 10 nm. SinaCurcumin® has a significantly higher bioavailability after oral use compared to simple powder of curcumin. This is due to the fact that a confronting barrier for lipophilic molecules (such as curcumin) known as unstirred water layer, which coats on the surface of intestinal epithelial cells, blocks the absorption of free curcumin (45). However, soft gels of SinaCurcumin®, after oral intake, open in the stomach in less than 15 minutes and will be diffused to the small intestine (11). After reaching the small intestine, nanomicelles can be solved in unstirred water layer. In fact, curcumin, which is insoluble in water, becomes water-soluble by preparation in the form of nanomicelles. Moreover, in nanomicelle formulation, the absorption of curcumin is enhanced by bile salts. In point of fact, bile salts largely facilitate absorption of fat-soluble substances such as lipophilic vitamins, lipids, fatty acids, cholesterol and SinaCurcumin® as nanomicelle (46).

Safety of Curcumin

Turmeric is considered as a GRAS agent in food by the United States Food and Drug Administration (47). Safety of curcumin has been shown in experimental studies on different animals (32,35). In rats, oral administration of curcumin at 13.6 mmol/kg body weight has shown no adverse effect (48). In humans, oral doses of 0.5 to 8 g/day of curcumin for 3 months create no toxicity. In addition, it has been shown that consumption of 12g/day of curcumin is also safe for humans (12,25,34).

CONCLUSION

Curcumin has antioxidant, anti-inflammatory, chemopreventive, and chemotherapeutic activity without major adverse effects. Chronic inflammatory diseases such as asthma, bronchitis, inflammatory bowel disease, rheumatoid arthritis, ALD, fatty liver, and allergy can be therapeutic targets of curcumin.

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