Chapter 9

Protective Effects of *Curcumin* on Gastric Inflammation and Liver Disease

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Abstract

Curcumin (diferuloylmethane), an anti-inflammatory and antioxidant compound, is isolated from the rhizomes of the plant *Curcuma longa Linn*. Most of the anti-inflammatory effects can be explained by the efficient inhibition of nuclear factor-κB–mediated and activation of PPARγ expression. These studies have been investigating the effects of curcumin on the gastric microcirculation, cytokine production after *Helicobacter pylori*–induced gastric inflammation, gastric cancer, drug-induced liver injury, and alcoholic liver disease (ALD). The results show that curcumin prevents indomethacin-induced gastropathy via decreased leukocyte-endothelium interaction at postcapillary venule, decreased ICAM-1 and TNF-α level, and improved gastric microcirculation. Curcumin attenuated gastric inflammation and gastric cancer via reduced NF-κB p65 expression, decreased vascular endothelial growth factor (VEGF) level, and macromolecular leakage in the gastric mucosa. Curcumin prevented liver injury through decreased oxidative stress, reduced liver inflammation, and restored GSH. Moreover, curcumin could decrease hepatocyte apoptosis and improved PPARγ protein expression in alcohol-induced liver injury.

Keywords: curcumin, gastric inflammation, gastric cancer, liver disease

1. Introduction

Curcumin (diferuloylmethane), the natural yellow pigment in tumeric, is isolated from the rhizomes of the plant *Curcuma longa* Linn. (*C. longa* L.). *C. longa* belongs to the Zingiberaceae family. It is a perennial herb that is distributed throughout tropical and subtropical regions of the world and is widely cultivated in Asian countries, such as India, Thailand, and China. The rhizomes are used as a traditional remedy in Nepal [1]. The powder form, called turmeric, is

bright yellow and has been used as a food-coloring agent in the United States. In India, it has been used as a spice, as a food preservative, and as therapeutic agent. The current Indian medicine claims the usage of tumeric is effective against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis [2].

In the nineteenth century, there has been considerable interest in the active compounds in tumeric called curcuminoids. Curcumin is the major curcuminoid compound that makes up approximately 90% of the curcuminoid content in tumeric, followed by demethoxycurcumin and bisdemethoxycurcumin [3]. The chemical structure of curcumin was determined by Roughley and Whiting (**Figure 1**) [4].

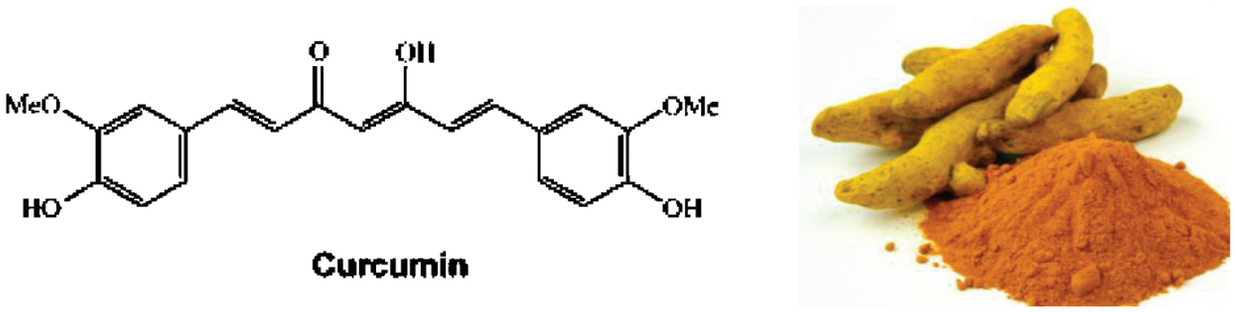

Figure 1. Chemical structure of curcumin (diferuloylmethane) [4].

Curcumin can be dissolved in organic solvents such as dimethylsulfoxide (DMSO), oil, alcohol, and petroleum agents. Interestingly, curcumin has been demonstrated to be safe for human and animals use. Human appeared to be able to tolerate high doses of curcumin without significant side-effects. A phase 1 study by Cheng et al. [5] found no adverse effects of curcumin ingestion for 3 months of dosage up to 8000 mg/day. Other human studies of curcumin included the following: a double-blinded, crossover trial in 18 patients with rheumatoid arthritis [6], a randomized, placebo-controlled trial with 45 postsurgical patients [7]. The doses of curcumin in these studies ranged from 1125 to 2500 mg/day. Only one postsurgical patient reported mild transient giddiness. No other serious adverse reactions were reported, including any changes in blood chemistry reports. Thus, curcumin appears to be safe in human even with ingestion at a high dosage.

In animals, the previous study demonstrated that curcumin is rapidly metabolized and poorly absorbed in Sprague-Dawley rats. Administrating curcumin orally was carried out by Wahlström and Blennow [8]. They demonstrated that this compound with a dose of 1–5 g/kg BW given to rats apparently did not cause any adverse effects and it was excreted about 75% in the feces, while traces found in the urine. In addition, measurements of blood plasma levels and biliary excretion showed that curcumin was poorly absorbed by the gastrointestinal (GI) tract. Curcumin could not be detected after 30 minutes when added to microsomes suspensions or hepatocyte suspensions. Furthermore, it was capable of disappearing from the blood after intravenous injection or after addition to the liver perfusion system. Moreover, oral LD_{50} was found to be 12.2 g/kg BW in rats [9]. In addition, a study in which rats were fed with curcumin

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1.8 g/kg BW per day for 90 days and monkeys were fed with curcumin 0.8 mg/kg BW per day for 90 days showed no adverse effects [10].

Curcumin has been tested to demonstrate pharmacoprotective effects in various gastrointestinal (GI) and liver diseases. We highlight studies on its potential mechanism of action classified into four categories: (i) Curcumin protects against *Helicobacter pylori* infection and gastric cancer, (ii) curcumin protects against nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer; (iii) curcumin protects against drug-induced liver injury; and (iv) curcumin protects against alcoholic liver disease (ALD).

2. Curcumin protects against *H. pylori* infection and gastric cancer

The discovery of *H. pylori* was first reported in 1984 by two Australian investigators, Barry Marshall and Robin Warren [11], who isolated the bacteria from mucosal biopsies of patients with chronic active gastritis. Its name was changed from *Campylobacter pyloridis*, *Campylobacter pylori*, and *Campylobacter*-like organism when the biochemical and genetic characterization has shown that it is in the genus *Helicobacter* [12].

H. pylori is a noninvasive, nonspore-forming, and spiral shaped gram-negative bacterium measuring approximately 3.5 × 0.5 μm. It has four to six sheathed flagella at one pole. These flagella and spiral shape of *H. pylori* help the bacterial movement into the mucus of stomach. It slowly grows in microaerophilic condition, 5% oxygen, 50% carbon dioxide at 37°C [13]. *H. pylori* is an unusual organism with a remarkably high level of genetic diversity [14], which means, it can survive in the human stomach and also multiply in high-acid environment of the stomach. When *H. pylori* infected human, it adheres on the gastric epithelial cells and induces chronic active gastritis, peptic ulcer, mucosal-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.

H. pylori is highly adapted to the stomach environment. To avoid the acidic environment of the stomach lumen, *H. pylori* uses its flagella to permit entry into the mucus. It adheres to the epithelial cells by producing adhesins for attachment to epithelial cells. *H. pylori* produces a potent urease enzyme. Urease generates carbon dioxide and ammonia, which potentially buffer the surrounding microenvironment and the bacterial cytosol [15]. In addition, urea is an important source of nitrogen for the bacteria.

Powerful flagella help the bacteria to swim through the viscous mucous layer covering the gastric epithelium, where bacterial adhesion proteins mediate a close interaction with the host cells [16]. *H. pylori* can bind tightly to epithelial cells by multiple bacterial surface components. The outer-membrane protein (Hop), such as BabA, binds to the fucosylated Lewis B blood-group antigen on the gastric epithelial cells [17]. Several Hop protein families also mediate adhesion to epithelial cells. When *H. pylori* adheres on gastric epithelial cells, it releases virulent factors to immune subversion. The host response to *H. pylori* participates in the induction of gastric epithelial damage and therefore has an integral role in *H. pylori* pathogenesis. *H. pylori* adheres on the gastric epithelial cells by bacterial adhesion proteins. Then, virulent factors are

delivered into host cells. Especially, cytotoxin-associated gene A (CagA) induces many pathological conditions. For example, activation of NF-κB that causes production of many inflammatory mediators inducing gastric inflammation [18].

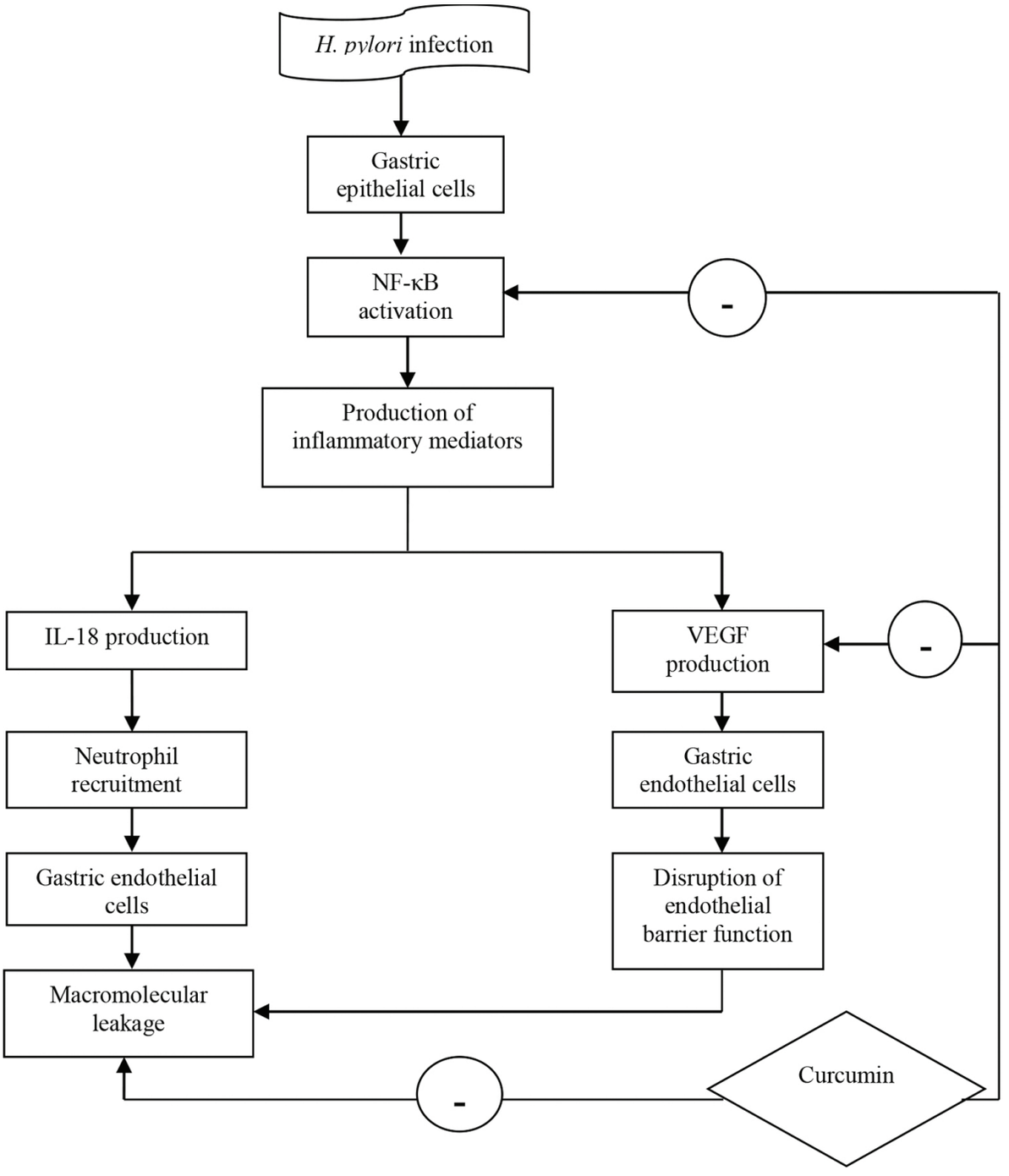

Figure 2. Protective mechanism of curcumin on *H. pylori* infection [19].

Effect of curcumin was examined by using rats [19]. The scheme of the effects was shown in **Figure 2**. Host inflammatory responses were measured by the following parameters: leakage

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of macromolecules from gastric postcapillary venules (PCVs), serum level of vascular endothelial growth factor (VEGF), and the expression of NF-κB subunit p65.

The successful inoculation of *H. pylori* was 85%. *H. pylori* infection led to the macromolecular leakage, the NF-κB-p65 expression, and increase of VEGF level compared with control group. Curcumin alone did not significantly change baseline of these parameters. There were

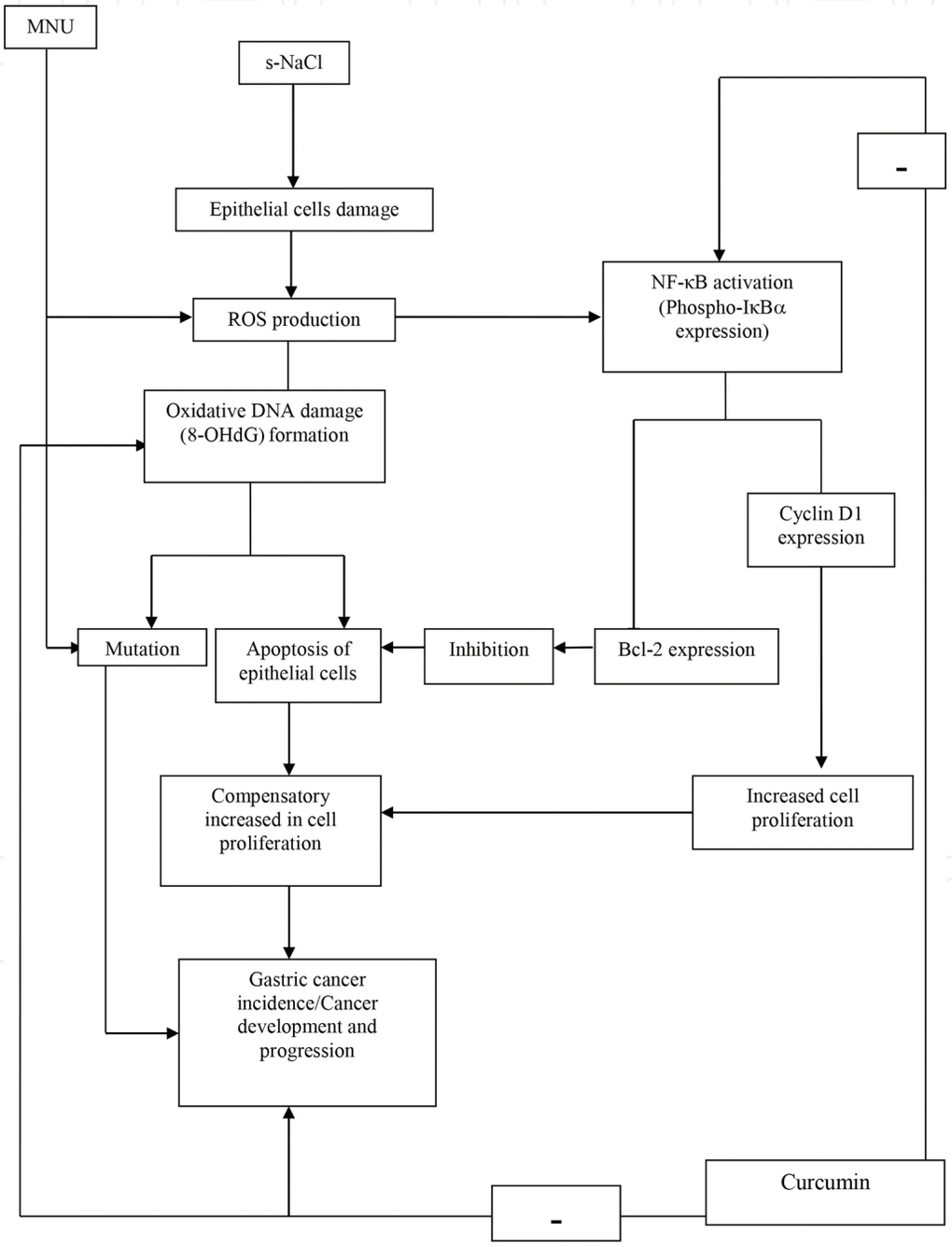

Figure 3. Protective mechanism of curcumin on N-methyl-N-nitrosourea (MNU) and saturated sodium chloride (s-NaCl)-induced gastric cancer [20].

significant decrease of macromolecular leakage and NF-κB-p65 expression ($p \leq 0.05$) in the curcumin-treated groups (curcumin 200 mg/kg and 600 mg/kg BW) compared with *H. pylori*-infected group, respectively. These results could be concluded that *H. pylori* infection increased macromolecular leakage, NF-κB-p65 expression, and serum VEGF level. Curcumin can reduce macromolecular leakage, decrease serum VEGF level, and NF-κB-p65 expression. It is implied that curcumin may have an anti-inflammatory effect on *H. pylori* infection [19].

In addition, the present study to examine the protective effect of curcumin on gastric cancer induced by N-methyl-N-nitrosourea (MNU) and saturated sodium chloride (s-NaCl) administration [20]. The scheme of the results was shown in **Figure 3**. Gastric cancer can generate in any part of the stomach. Cancers were found in the forestomach of all rats induced by MNU and s-NaCl. Curcumin supplementations showed 40–50% reduction of cancer incidence. Expressions of 8-OHdG, cyclin D1, and Bcl-2 significantly increased in rat with MNU and s-NaCl administration compared with control group. The phospho-IκBα expression had a tendency to increase in MNU and s-NaCl group compared with control group. Immunoreactive cells of 8-OHdG in curcumin supplementation significantly decreased when compared with MNU and s-NaCl group. The relative intensity of phospho-IκBα in curcumin group tended to reduce when compared with MNU and s-NaCl group. Curcumin can attenuate cancer via a reduction of phospho-IκBα and 8-OHdG expressions, which may play a promising role in gastric carcinogenesis [20].

3. Curcumin protects against NSAID-induced ulcer

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs worldwide. It is well-known that NSAIDs cause gastric mucosal damage ranging from nonspecific dyspepsia to ulceration, upper gastrointestinal (GI) bleeding, and death. These can summarize by the term "NSAIDs gastropathy." NSAIDs caused topical damage from "ion trapping" effect [21], the reduction of the hydrophobicity of the gastric mucosal surface, and uncoupling of oxidative phosphorylation [22, 23]. The systemic effect caused by inhibiting cyclo-oxygenases (COX). NSAIDs block the formation not only of proinflammatory cytokines but also of gastroprotective prostaglandins those maintain gastric mucosal blood flow and bicarbonate production [24]. The enhanced synthesis of leukotrienes may occur by shunting the arachidonic acid metabolism towards the 5-lipoxygenase pathway [25–27]. COX inhibition, enhanced synthesis of leukotrienes, contributing to gastric mucosal injury by promoting tissue ischemia and inflammation [28–31].

Mechanism of NSAID-induced gastric ulceration is a neutrophil-dependent process. NSAIDs induced neutrophil adherence to vascular endothelium [32]. Neutrophils play an important role by releasing a variety of inflammatory mediators, including neutrophil elastase and ROS caused gastric mucosal injury. Furthermore, adhesion molecules expressed on activated neutrophils, such as CD11b and CD18, play an important role in neutrophil-induced tissue injury [33–35].

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Protective effects of curcumin on NSAIDs were examined [36]. The scheme of the effects was shown in **Figure 4**. The study demonstrates effects of curcumin on gastric microcirculation, tumor necrosis factor (TNF)-α, and intercellular adhesion molecule (ICAM)-1 levels on rat with NSAID-induced gastric injury. The stomach histopathology in NSAIDs group showed multiple erosions with mild to moderate inflammation. Serum of ICAM-1, TNF-α levels, and leukocyte-endothelium interaction increased significantly when compared with control group. Pretreatment with curcumin group resulted in decreasing the elevation serum of ICAM-1, TNF-α levels, and leukocyte-endothelium interaction. The stomach histopathology was improved in curcumin administration group. Therefore, curcumin accomplishes the protective effect on NSAID-induced gastric mucosal injury on improving gastric microcirculation and reducing inflammatory cytokines [36].

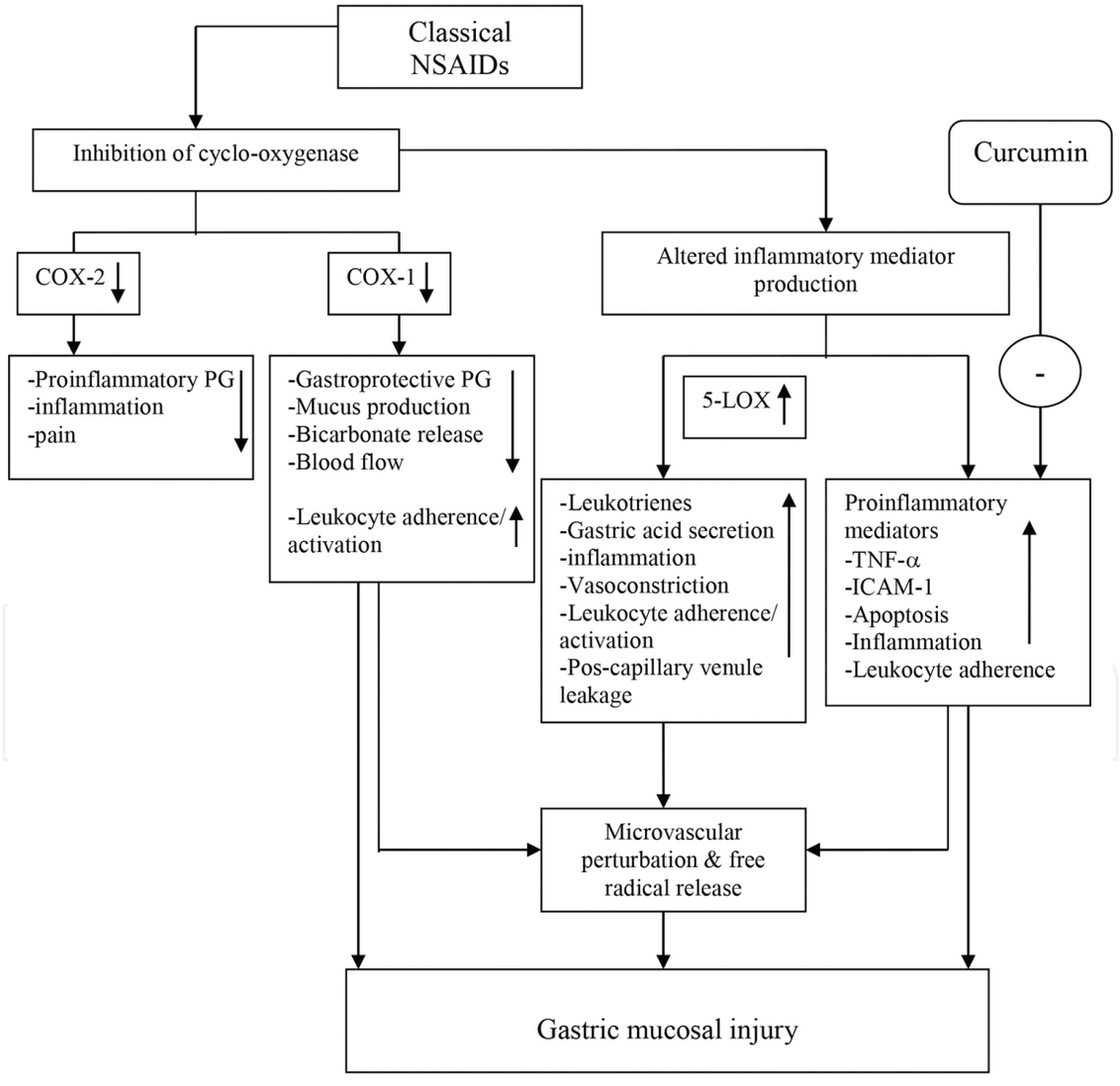

Figure 4. Protective mechanism of curcumin on NSAID-induced gastric mucosal injury [36].

4. Curcumin protects against drug-induced liver injury

N-acetyl-P-aminophenol (APAP) or paracetamol is a widely used analgesic and antipyretic drugs [37, 38]. APAP toxicity is one of the most common drug-induced liver damages worldwide, where major liver major complication is caused due to APAP overdose. APAP metabolites produced in the liver and other organs are the main contributors for the mechanism of its toxicity [39, 40].

The scheme of liver injury by drug was shown in **Figure 5**. In therapeutic doses, APAP is mainly metabolized via glucuronidation and sulfation and in conjugated forms are excreted from the body. Besides, APAP partly is metabolized by cytochrome P450 (CYP 450), to some metabolites, mainly N-acetyl-*p*-benzoquinone imine (NAPQI), which are dramatically increased in high APAP concentrations. These metabolites of APAP are detoxified by glutathione (GSH) and removed from the body. Then, in APAP overdose causes increasing of toxic metabolites. These metabolites interact with a range of cellular proteins via covalent binding, which disrupting hepatocyte function causing necrosis, apoptosis, and liver injury occurs [41, 42].

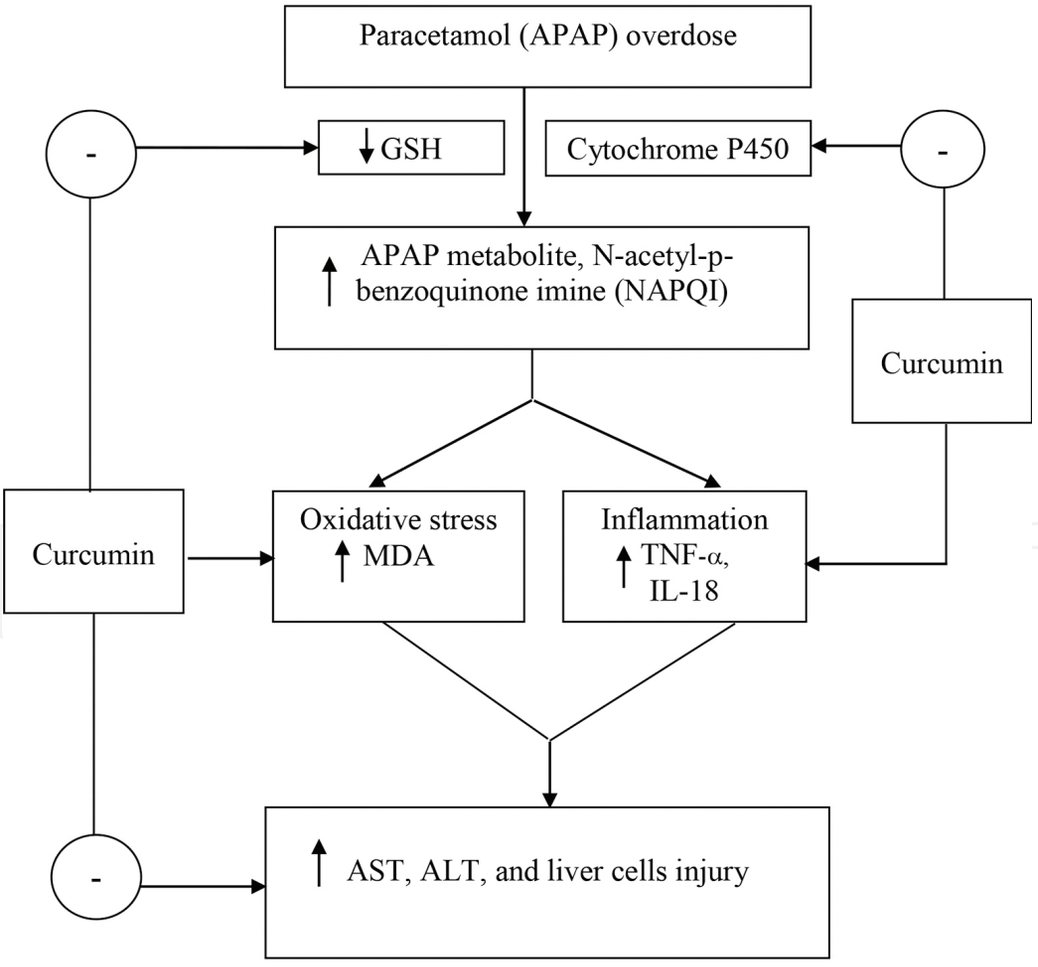

Figure 5. Protective mechanism of curcumin on paracetamol overdose-induced hepatitis [43].

The protective effects of curcumin on paracetamol overdose-induced hepatitis in mice were studied. The effect was shown in **Figure 5**. The results showed that serum transaminases, Hepatic malondialdehyde (MDA), and inflammatory cytokines (TNF-α and IL18) were increased significantly in the 400 mg/kg of APAP group compared with the control group. Curcumin treatment groups (curcumin 200 mg/kg and 600 mg/kg) were significantly decreased these parameters compared with the APAP group. The level of GSH decreased significantly in the APAP compared with the control group. Curcumin treatment groups (curcumin 200 mg/kg and 600 mg/kg) were significantly increased GSH level compared with the APAP group. The histological appearance of the liver in the control group showed normal. In the APAP group, the liver showed damage with extensive hemorrhagic hepatic necrosis at all zones. Curcumin treatment groups (curcumin 200 mg/kg and 600 mg/kg) improved the liver histopathology. In curcumin 200 mg/kg group, the liver showed mild focal necrosis and the normal architecture was well preserved in curcumin 600 mg/kg group. The results indicated that curcumin prevented APAP-induced hepatitis through decreased oxidative stress, reduced liver inflammation, and restored GSH, which caused the improvement of liver histopathology [43]

5. Curcumin protects against alcoholic liver disease

Alcoholic liver disease (ALD) represents a spectrum of clinical illness and morphological changes that range from fatty liver, hepatic inflammation, and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis) [44]. Ethanol oxidation generates toxic products such as acetaldehyde, and reactive oxygen species resulted in oxidative stress that initiates apoptosis and cell injury [45–48]. More than 80–90% of heavy drinkers develop fatty liver, but only up to 20–40% of this population develops more severe forms of alcoholic liver disease (ALD), including fibrosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [49].

Pathogenic mechanisms of alcoholic liver disease were proposed. Ethanol promotes the translocation of lipopolysaccharide from the gastrointestinal lumen to the portal vein. In Kupffer cells, lipopolysaccharide binds to CD14, which combines with Toll-like receptor 4 (TLR4) which is responsible for activating the innate immune system. The increase on inflammatory cytokine production in conjunction with a decrease in signal transducer and activator of transcription (STAT) factors' expression reduces liver regeneration. Long-term alcohol consumption alters the intracellular balance of antioxidants with subsequent decrease in the release of mitochondrial cytochrome c and expression of Fas ligand, leading to hepatic apoptosis. Activated Kupffer cells and hepatocytes are suggested to be sources of free radicals (especially ROS), which are responsible for lipid peroxidation and further apoptotic damage. Activation of hepatic stellate cells also contributes to the production of cytokines, ROS and TGF-β exacerbating liver fibrosis [49].

This study demonstrated effects of curcumin attenuated inflammation and liver pathology in rats with alcoholic liver disease. The effect was shown in **Figure 6**. The results showed that the liver histopathology in ethanol group revealed moderate steatosis and necroinflammation. In

ethanol group, hepatic MDA, hepatocyte apoptosis, and NF-κB activation have increased significantly when compared with control. The 400 mg/kg BW of curcumin treatment revealed the decreased of hepatocyte apoptosis, hepatic MDA, NF-κB activation. The peroxisome proliferator-activated receptor gamma (PPARγ) protein expression increased in the curcumin groups. Therefore, curcumin improved liver damage in ethanol-induced hepatitis by reduction of oxidative stress, inhibition of NF-κB activation, and restoration of PPARγ [50].

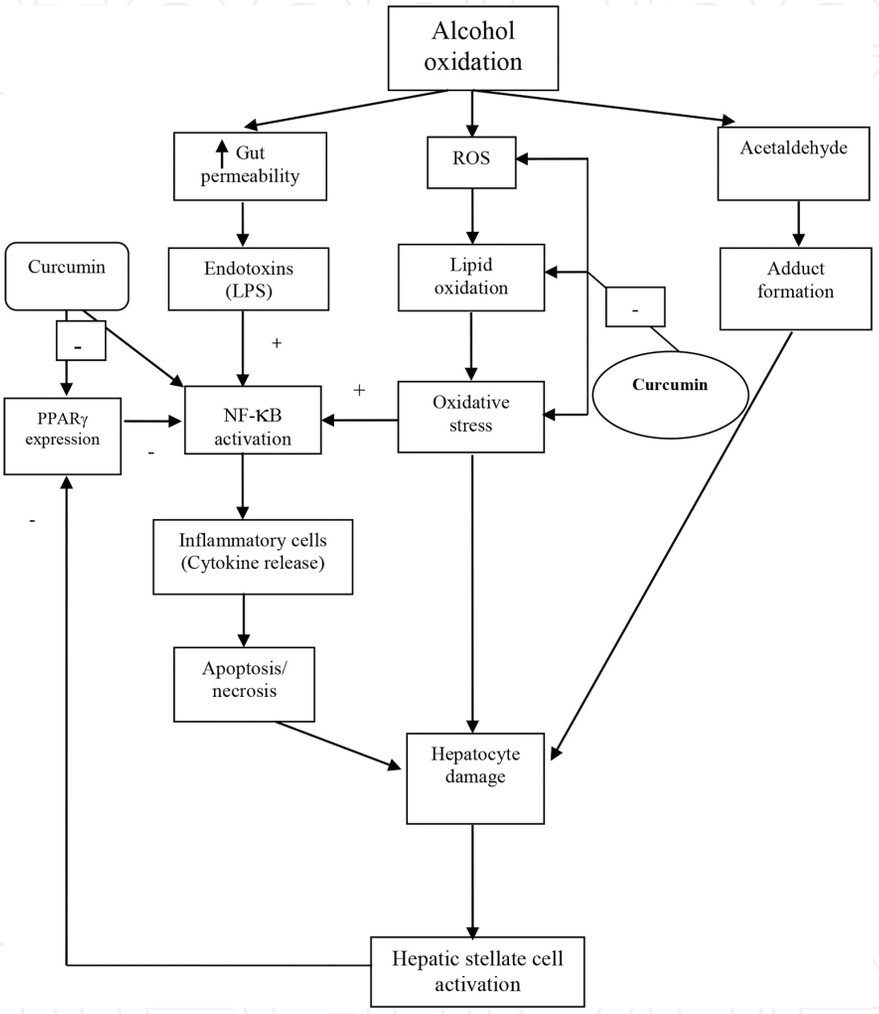

Figure 6. Protective mechanism of curcumin on changes of PPARγ expression, NF-κB activation and oxidative stress in rats with alcoholic hepatitis [50].

6. Conclusion

Curcumin prevents indomethacin-induced gastropathy by decreasing ICAM-1, TNF-α levels, and leukocyte-endothelium interaction. Curcumin reduces *H. pylori*-induced gastric inflammation and gastric cancer by reducing macromolecular leakage, decreasing serum VEGF level, and NF-κB-p65 expression. Curcumin improves liver damage caused by APAP overdose by

decreasing hepatic MDA, TNF-α and IL18, and restoring GSH. Moreover, curcumin attenuates alcohol-induced liver injury by decreasing the elevation of hepatic MDA, inhibition of NF-κB activation and improving of liver pathology. Overall, the major mechanisms of curcumin are associated with reduction of oxidative stress, restoration of glutathione and PPARγ expression, inhibition the activation of NF-κB, attenuation of inflammation, and the improvement of histopathology. Therefore, these features make curcumin a very promising new therapeutic option for the treatment of gastrointestinal and liver diseases.

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