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Role of Curcumin in Prevention of NAFLD Pathogenesis: Insights into Key Metabolic and Inflammatory Signaling Pathways

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ABSTRACT

Non-alcoholic Fatty Liver Disease (NAFLD), characterized by an elevated level of lipid accumulation in the liver, is the most widespread form of hepatic disorders, affecting 32% of the global population. In certain people, NAFLD may progress to the more advanced form, Non-alcoholic Steatohepatitis NASH (reversible), by developing inflammation and, in some cases, liver cirrhosis (irreversible). In turn, both NASH and cirrhotic livers have an increased chance of developing Hepatocellular Carcinoma (HCC) within the affected parenchyma. NAFLD, resulting from nutrient overload and a sedentary lifestyle, has a complex pathogenesis. This includes metabolic dysfunctions, such as insulin resistance, atherosclerosis, obesity, dyslipidemia, and hypertension. Resultantly, this leads towards oxidative stress, Endoplasmic Reticulum (ER) stress, and inflammatory response, consequently causing liver injury and inflammation. NAFLD is predicted to become the most common indication for liver transplantation by 2030. Currently, lifestyle modification strategies with few pharmacological options are available to control the progression of this disease. A few drugs resmetirom (FDA approved), statins, metformin, and fibrates, are currently in the market but they have notable side effects (osteoporosis and secondary infections). Hence, there is a dire need for a novel drug candidate with high efficiency and fewer side effects. This review focused on the therapeutic potential of curcumin, extracted from *Curcuma longa*, in preventing and modulating the key pathways involved in the pathogenesis of NAFLD as an innovative treatment candidate. The study conducted a comprehensive and collective analysis of the available literature to create a single document covering all the pathogenic aspects of NAFLD and explored the treatment strategies using curcumin. It should be noted that the current data on curcumin has been predominantly derived from preclinical sources, such as in-vitro, animal, and in-silico studies, with human trial evidences on curcumin remaining comparatively limited.

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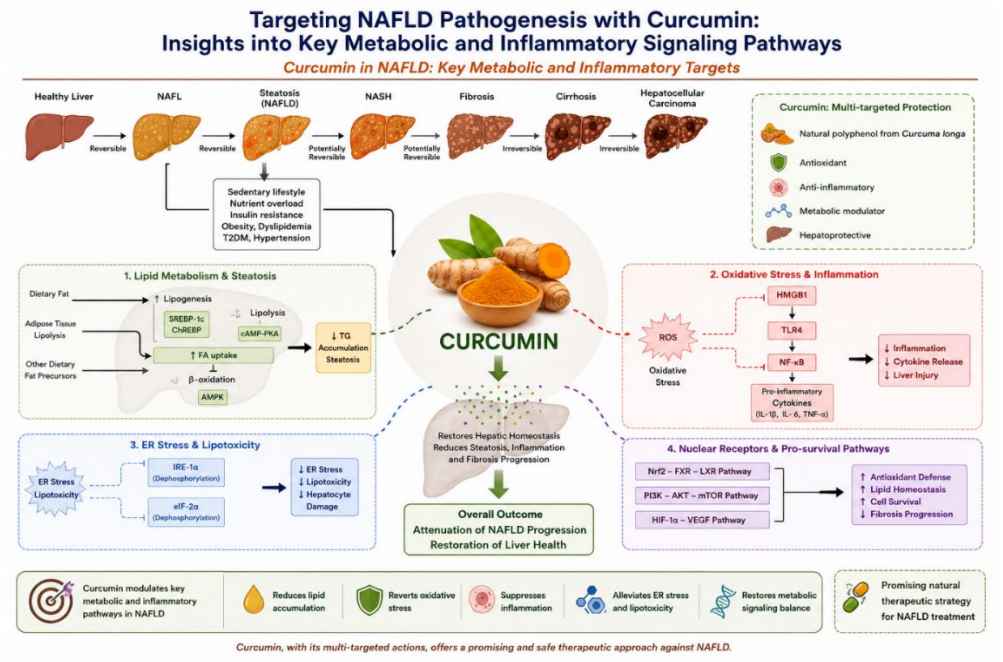
GRAPHICAL ABSTRACT



Keywords: curcumin, inflammation, liver, Non-alcoholic Fatty Liver Disease (NAFLD), treatment strategies

Highlights

- NAFLD affects 32% global population, with limited drugs may progress to cirrhosis.
- Review maps curcumin's effect on NAFLD's lipid, oxidative and ER stress pathways.
- Poor bioavailability and less human trials limits its clinical translation.

1.INTRODUCTION

Non-alcoholic Fatty Liver Disease (NAFLD) is one of the most prevalent chronic liver disorders caused by a sedentary lifestyle-induced accumulation of lipids and fatty acids in the hepatocytes [1,2]. The global prevalence of this chronic hepatic disease has been estimated at up to 32%, significantly increasing over time [3]. It is identified by the presence of large fat vesicles in ≥5% of liver cells having metabolic risk factors, such as

obesity and Type 2 Diabetes Mellitus (T2DM), without a secondary cause, for instance drugs or alcohol[4]. Based on histological findings, NAFLD is categorized as any case with steatosis and/or slight lobular inflammation called Non-alcoholic Fatty Liver (NAFL) or Non-alcoholic Steato-Hepatitis (NASH), distinguished by hepatocellular damage (ballooning degeneration in liver cells, fibrosis, and pervasive lobular inflammation) [5]. Since simple steatosis is identified as a benign illness, its combination with liver fibrosis can lead to cirrhosis and Hepatocellular Carcinoma (HCC) [6,7]. As a result, NAFLD is believed to play a significant role in regulating mortality from liver-related disorders. Usually, 20 to 30% of fatty liver patients develop NASH[8]. In the early 21st century, NASH was considered as a serious condition, mainly occurring in obese females suffering from T2DM. In contrast to cirrhosis and HCC, which have significant fatality rates, NAFLD and NASH are reversible liver illnesses[9]. Therefore, it is important to diagnose and treat this illness at the very early stage.

Furthermore, several factors are believed to be involved in the pathology of this disease. However, many studies showed that insulin resistance with or without obesity is behind its mechanism, classifying NAFLD as a metabolic syndrome. Currently, there is just one FDA-approved drug for NAFLD, resmetirom; however, it is suitable for moderate to advanced liver disorders, that is, fibrosis but not cirrhosis [8,10]. It has negative effects, such as it may develop signs and symptoms of hepatotoxicity involving fatigue, fever, nausea, vomiting, rash, and jaundice as well as stomachache and tenderness. Moreover, it has also been associated with gall bladder problems, such as cholelithiasis and cholecystitis [11]. Therefore, use of this notable drug is not suitable for everyone. It should be avoided in the patients who are taking blood-thinning drugs (clopidogrel), cholesterol-lowering drugs (gemfibrozil), statins, or immune system-suppressing drugs (cyclosporine) as well as the patients who have decompensated cirrhosis to avoid further risk of hepatotoxicity [12,13]. Diet and exercise are believed to be the primary treatments requiring lifestyle modification. However, people suffering from NAFLD usually have difficulty in maintaining an improved and healthier routine. As a result, more study into the pathophysiology of NAFLD is needed to find drugs that are both safe and efficient for prevention as well as treatment [14].

Adding to this, years of research and experimentation have identified abnormal expression and function of the proteins and genes (SREBP-1c, ChREBP, ACC, FAS, PPARα, PERK, ATF6, IRE1, SREBP2, ATF4, CHOP, etc.) as crucial factors in the development and progression of liver steatosis [15,16]. Several nutraceuticals are under research and experimentation to investigate if they modulate protein as well as gene expression [17,18]. A nutraceutical compound, curcumin, has gained immense popularity as a potential drug against metabolic disorders. Curcumin, isolated from *Curcuma longa*, is a beneficial, bioactive-polyphenolic compound having several pharmacological properties [19]. In-vivo experiments have shown that curcumin has a favorable impact on the prevention and control of NAFLD by lowering fat accumulation and inflammation [20]. Moreover, curcumin also plays a significant role in slowing the progression of NAFLD to NASH and decreases the risk of liver cancer [21]. The current study used the keywords "NAFLD", “hepatic steatosis", "curcumin", and "nutraceuticals" to search the PubMed database for relevant publications of recent years. As this study did not follow a predefined search data range, a systematic screening protocol, or formal inclusion/exclusion criteria for study selection, it was presented as a narrative rather than a systematic review. Accordingly, the literature discussed herein signified a representative, expert guided synthesis of mechanistic and preclinical evidence on curcumin in NAFLD, rather than an exhaustive, PRISMA-based appraisal of all available studies on the topic.

2.PATHOLOGY OF NAFLD

NAFLD begins with simple steatosis resulting from fat accumulation in hepatic cells and progresses to NASH, being different from simple steatosis by causing inflammation and ballooning in liver cells. The inflammation in the liver may ultimately progress to fibrosis and cirrhosis, eventually causing liver cancer [9]. Adding to this, the pathogenesis of hepatic steatosis is characterized by the structural and functional changes in hepatic tissues due to the complex interactions among metabolic disorders, hereditary predispositions, and environmental factors[14]. This section of the review would give a brief description of the pathogenesis and pathophysiology of NAFLD for the better understanding of the functional alterations caused by this illness (Figure 1) [6].

NAFLD is an example of abnormal lipid accumulation, leading to excess triglyceride (TG) synthesis in hepatocytes and hence increasing the

risk of hepatic steatosis [14]. The development of NAFLD involves several factors, mainly beginning from fat deposition in the liver and Insulin Resistance (IR). This step is known as the 'first hit' of the disease. The primary substrates for TG production are white adipose tissue WAT (60%), de-novo lipogenesis (DNL) (26%), and high-fat or high-sugar diets (15%) [21]. Normally, the lipid droplets of WAT store fatty acids in the form of TGs. These stored TGs act as energy storage houses, releasing them at the time of need [22]. Due to IR, the anti-lipolytic ability of the insulin decreases, causing abnormal behavior of WAT, leading to excessive release of TGs in the body. The overly-released TGs cause lipid deposition in regions other than adipose tissue, such as the liver, resulting in NAFLD [7]. Moreover, DNL, one of the crucial lipid accumulation pathways, is intimately linked with IR. It has been reported in the literature that the sterol regulatory element binding protein-1c (SREBP-1c), as well as the carbohydrate-response element binding protein (ChREBP), are responsible for the modulation of the DNL pathway. Actually, SREBP-1c is a type of regulatory protein that is activated by IR to promote DNL in liver cells. Additionally, ChREBP is activated by increased glucose concentration, regulating the production of acetyl Co-A carboxylase (ACC) and fatty acid synthase (FAS), hence promoting DNL in the liver cells. Usually, DNL is meant for converting carbohydrates into fatty acids, which are esterified into triglycerides (TGs) and then stored in hepatocytes. During energy deficit conditions, these TGs undergo β-oxidation to fulfill the body's energy demand. Excessive release of FFAs in hepatocytes damages β-oxidation, leading to dysfunctional mitochondria. This series of damages causes inflammation in the liver, resulting in oxidative stress [23].

The elevated levels of FFAs increase DNL, reducing lipolysis with lowered β-oxidation and fewer very low-density lipoproteins (VLDL), leading to TG secretion and oxidative stress. All these series of physiological changes set off cascade reactions, overwhelming the liver's antioxidant defenses [23,24]. Concurrently, ER stress occurs, exacerbating cellular dysfunction [25]. The accumulative effects of oxidative and ER stress result in Lipotoxicity, hepatocyte injury, inflammation, and apoptosis. This is known as the 'second hit' of this disease. The cross talk between several complex factors (extrinsic factors and endotoxins), parenchymal and non-parenchymal hepatocytes (hepatic stellate cells HSCs, endothelial cells, and Kupffer cells KCs), inflammatory responses, reactive oxygen

species (ROS), and intrahepatic FFAs leads to cell damage and ultimately NASH [26].

Furthermore, amid the obesity pandemic, dietary factors have emerged as critical in the progression of NAFLD[27]. According to studies, fructose exacerbates the situation by upregulating the gene expression connected to liver fibrosis, inflammation, ER stress, and adipocyte apoptosis. While, a high-fat diet (HFD) itself can cause obesity, IR, and moderate fatty liver [28]. Both animal and human research showed that fructose selectively metabolizes in the liver, triggering hepatic stress responses, such as the activation of c-Jun N-terminal kinase (JNK) and IR. This promotes fat storage in the liver, increases lipogenesis, and hinders fatty acid oxidation (FAO). This eventually leads towards hepatic inflammation and fibrosis, recognizing fructose as a key risk factor in the progression of NAFLD to more severe forms, such as NASH [29].

Moreover, highly expressed peroxisome proliferator-activated receptor α (PPARα) plays an important role in the liver's lipid metabolism by regulating transport, delivery, and movement of FFAs involved in oxidation of mitochondria. It has been observed that the accumulation of FFAs and TGs in patients having a fatty or inflamed liver shows a reduced expression of PPARα. It affects hepatic homeostasis by causing Lipotoxicity, thus inciting overly-expressed inflammatory responses, resultantly contributing to the progression of NAFLD [30].

In addition to this, endoplasmic reticulum stress, aka ER stress, is a defense mechanism for the restoration of protein homeostasis by initiating the unfolded protein response (UPR) [31]. Whereas, if UPR fails to maintain cell viability, it activates the cell death pathway, that is, the pro-apoptotic pathway [32]. The complex sphingolipids and cholesterol of the ER membrane play a vital role in protein transport and lipogenesis. Therefore, lipid synthesis is directly impacted by ER stress and hence linked with the pathogenesis of NAFLD, ultimately causing progression into NASH [33]. When inactive, ER stress sensors PERK, ATF6, and IRE1, coupled with glucose-regulated protein (GRP) 78, mediate UPR. In case of ER stress, all these sensors are activated, causing several downstream reactions [34]. Lipid accumulation in the liver is regulated by these pathways where IRE1-XBP1 as well as PERK and pelF2 boost up the process of adipo-genesis. On the contrary, ATF6, SREBP2, and HDAC1 inhibit adipo-genesis. If ER stress remains unresolved, upregulation of lipid input may occur, increasing

hepatic steatosis resultantly [35]. Moreover, it is also reported to downregulate the lipid outflow. Adding to this, apoptosis is also promoted by ER stress by the activation of ATF6, PERK, and IRE1 [36]. The PERK mediates the phosphorylation of elf2, leading to the upregulation of ATF4. The activated ATF4 produces CHOP (an apoptosis protein), a substrate for ATF6. The ATF6-led activation of XBP1 causes inflammation through the JNK pathway. Moreover, IRE1 is meant for the activation of the JNK pathway and TRAF2, hence promoting apoptotic cell death as well as inflammation. As far as regulation of adaptive UPR is concerned, XBP1 splicing and the activation of IRE1 play a significant role, indicating the role of ER stress in the development and progression of NAFLD to NASH [37].

Another factor that plays a crucial role in the pathogenesis of NAFLD is Lipotoxicity. It refers to the toxic effect of prolonged high concentrations of lipids and their metabolites accumulated in non-adipose tissues. This prolonged deposition leads to tissue damage. It is worth noticing that not all lipids are toxic in nature. For instance, TGs and FFAs with unsaturated double bonds can protect the liver from any injury or damage. Whereas saturated fatty acids, that is, palmitic acid, stearic acid, etc., ceramides, free cholesterol, and bile acids have detrimental effects on liver health. As far as ceramides are concerned, they promote IR and inflammation; however, bile acids damage cell membranes [26]. Due to Lipotoxicity, increased FFAs overpower hepatocytes, ultimately causing mitochondrial damage, ROS production, ER stress, oxidative stress, and liver inflammation. All these lipotoxic effects lead to eventual progression of NAFLD into NASH [22].

Additionally, Lipotoxicity affects several cell types in the liver, causing apoptosis, inflammation, and ultimately hepatic fibrosis. Furthermore, hepatic stellate cells (HSCs) and Kupffer cells (KCs) also play a significant role in NAFLD pathogenesis. HSCs cause fibro-genesis in hepatic cells and activation of TLR4, aka lipotoxic chemicals, boosting inflammatory responses and fibrotic signaling. Normally, KCs are meant for the regulation of inflammatory pathways. They contribute to the progression of hepatic diseases by releasing pro-inflammatory cytokines and oxidized LDL, leading to worsening inflammation in NASH patients [14].

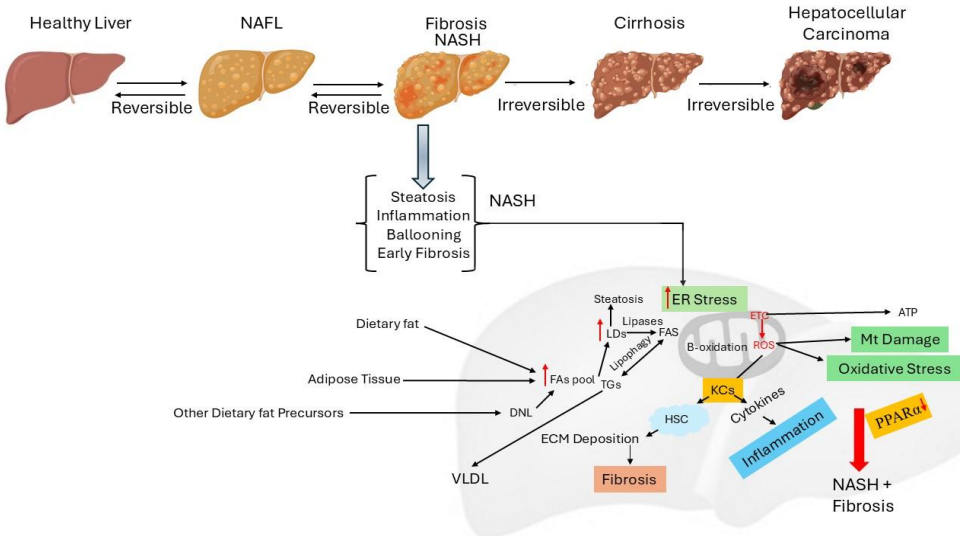


Figure 1. Progression Stages of NAFLD

The primary symptom of NAFL, which first develops in healthy livers, is hepatic steatosis caused by nutrient overload and a sedentary lifestyle. Hepatic steatosis causes Lipotoxicity in the liver cells characterized by oxidative stress, reduced PPARα expression, and ER stress as well as mitochondrial dysfunction accompanied by Kupffer cell activation. If NAFL is not timely treated, it may lead to a severe version of NASH, characterized by fibrosis and inflammation. As NASH worsens, it may lead to cirrhosis and liver cancer (HCC) [6].

3.TREATMENT STRATEGIES OF NAFLD

NAFLD is believed to be associated with several metabolic disorders, such as obesity, diabetes, high blood pressure, dyslipidemia, and other metabolic diseases in terms of the “metabolic syndrome” [38]. To describe the pathophysiology of NAFLD in a better way, an international consensus agreed to rename it "metabolic-associated fatty liver disease" (MAFLD) in 2020. Several strategies have been tried to discover the cure for this disease, such as diet and lifestyle changes termed non-drug treatments. Whereas, the complex pathology of NAFLD requires drug therapies, classified as medical treatments (Figure 2) [39]. The prevalence of this serious liver disease has increased, yet there has been a lack of FDA-approved treatments until now. In March 2024, the FDA approved a drug called “resmetirom” sold under the brand name Rezdiffra™ for the treatment of moderate to advanced

forms of NASH. Resmetirom is suggested for the person with NASH without severe scarring on their liver. It is strictly advised to administer it in conjunction with a nutritious diet and healthy lifestyle. It has certain side effects, such as nausea and diarrhea. Adding to this, the medicine comes with precautions and warnings against drug-induced liver damage and gallbladder-related side effects [12]. Therefore, there is a dire need for a drug with minimal side effects and maximum results.

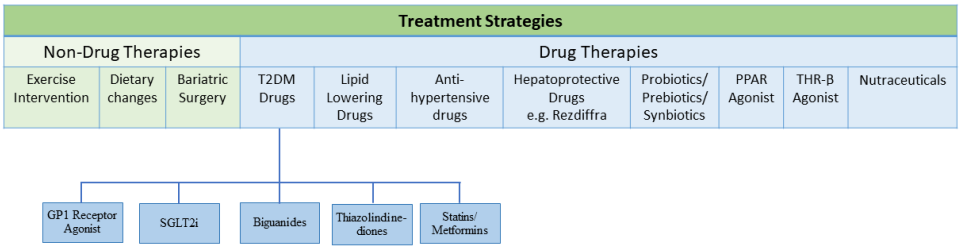


Figure 2. Treatment Strategies of NAFLD

The above flowchart shows the current treatment strategies for NAFLD, that is, non-drug treatments and drug therapies. The diagram shows a structured view of the several interventions that have been used to manage NAFLD [40].

4.CURCUMIN: A POTENTIAL NUTRACEUTICAL FOR NAFLD TREATMENT

Given the huge gap in the availability of an effective drug against NAFLD, researchers are increasingly exploring nutraceutical compounds as alternative therapeutic options. Therapeutic effects of curcumin have a very long history. Marco Polo was the first man who recognized its medical importance in the 12th century [41]. Later, Arab traders introduced turmeric (curcumin) in Europe in the 13th century, followed by the medicinal use of curry powder turmeric in the subcontinent during British rule [42]. Moreover, China has been utilizing curcumin to improve blood circulation for centuries. Modern studies have reported a great variety of pharmacological effects of curcumin, being an antioxidant, anti-inflammatory, anticancer, and an immune system regulator. *Curcuma longa L.*, the principal botanical source of curcumin belongs to the family *Zingiberaceae*. However, the genus *Curcuma* have several medicinally important species including *C. zedoaria, C. xanthorrhiza, C. aromatica.,*

and *C. caesia*. These species are reported to contain diverse phytochemicals, such as curcuminoids, sesquiterpenes, essential oils, and other phenolic compounds playing antioxidant, anti-inflammatory, hepatoprotective, antimicrobial, metabolic, and neuroprotective roles. A comprehensive review of *Curcuma* species reported approximately 427 compounds. This highlights pharmacological evidences for both the *C. longa* and *C. zedoaria*, including hepatoprotective, anti-inflammatory, antioxidant, antifungal, antihypertensive, and neuroprotective activities [43]. Furthermore, the experimental studies have investigated the traditional medicinal applications and pharmacological activities of *C. zedoaria* (white turmeric), including potential effects against inflammatory, gastrointestinal, oncogenic, and hepatic disorders [44]. Also, recent clinical evidences have extended these observations to NAFLD. A randomized clinical (single blind controlled) trial published in 2025 evaluated *C. zedoaria* in patients with grade 1-2 NAFLD, comparing 500 mg twice daily for 60 days with vitamin E. This study provided the direct clinical evidence that a *Curcuma* specie other than *C. longa* has been investigated as a potential intervention for NAFLD [45].

Importantly, a randomized double-blind placebo-controlled trial involving 64 NAFLD patients, administered with turmeric *(C. longa)* rhizome powder at 2 g/day for 8 weeks significantly reduced ALT, AST, GGT, together with YGs, LDL, HDL, and malondialdehyde. Although sonographic NAFLD grade and total cholesterol did not significantly change [46]. Another randomized placebo-controlled study reported improvement in hepatic fat content and several metabolic parameters following an 8 week curcumin intervention in patients with NAFLD [47]. However, clinical findings have not been uniformly positive. A 12-week randomized placebo-controlled trial found that the curcumin supplementation reduced hepatic fibrosis and NF-kB activity compared with baseline. However, the overall improvement in inflammatory and hepatic parameters, was not significantly greater than lifestyle modification alone [48].

Beyond NAFLD, human clinical research has investigated curcumin in several disease categories. A clinical trials experiment identified 389 eligible citations with metabolic disorders and musculoskeletal disorders representing major areas of investigation, followed by neurocognitive, gastrointestinal, and cancer-related conditions. Most of the included trials

were randomized and placebo-controlled, although the strength of evidence varied considerably between conditions [49]. Similarly, a systematic review and meta-analysis of 103 randomized controlled trials involving 7216 patients found evidence of beneficial effects of curcumin supplementation for several metabolic, inflammatory, and oxidative stress-related outcomes while emphasizing the need for larger, long-term, and well-designed trials [50]. All these therapeutic effects of curcumin make it a potential candidate for the treatment of cancer, neurodegenerative diseases, cardiovascular diseases, and hepatic disorders. However, low solubility and poor assimilation have been causing hindrance, which can be overcome by using curcumin combined with drugs with other chemicals as well as complexes [51,52]. The pathogenesis of NAFLD as described earlier in this review involves lipogenesis, ROS generation, ER stress, and Lipotoxicity causing mild to severe liver disorder is speculated to be cured by utilizing curcumin due to its relatable and effective metabolism in the body of human beings. Several bioinformatics' evidences showed the potential use of curcumin against NAFLD and NAFLD related disorders (Table 1).

Table 1. Bioinformatics-based Evidences of Curcumin Against Several Diseases

Disorders	In-silico approach	Key Targets/Findings
NAFLD	Molecular docking screening	Curcumin showed consistently high binding affinity across liver diseases targets with strongest binding to TNF [53].
NAFLD	STITCH database, gene data scoring	High confidence curcumin interaction against GSTA1 NAFLD specific target [54].
Liver Fibrosis (NAFLD-associated Stage)	Molecular docking	Curcumin mediated proteins PDFG, PDGFRB, TIMP-1, TLR-9; disrupts PDGF–receptor binding, hence inhibited fibrosis [55].
Hepatic Fibrosis (NAFLD-associated Stage)	Network pharmacology + molecular docking	Curcumin and demethoxy-curcumin strongly bound MAPK1, EGFR, SRC [56].
NAFLD	Network pharmacology + molecular docking +	Proteins AKT1, TNF, and IFNAR1 were mediated by curcumin, hence

Disorders	In-silico approach	Key Targets/Findings
	pharmacophore modeling + MD simulations	modulated hepatic proliferative and inflammatory pathways [57].
T2DM (shared insulin resistance pathways)	Network pharmacology + molecular docking	Curcumin's flavonoids display antidiabetic activity by interacting with MAPK and PI3K-AKT signaling pathways, altering Ras-GTPase activity and enhancing the expression of GLUT4 [58].
T2DM (shared insulin resistance pathways)	Network pharmacology + quantum-polarized ligand docking + MD simulation	Curcumin binds strongly to key hub targets—AKT1, TNF-α, EGFR, and STAT3—with significant binding free energy, highlighting its therapeutic potential against diabetic complications [59].
T2D, (shared insulin resistance pathways)	Network pharmacology + Molecular docking + MD simulation	Curcuminoids profiled against diabetic-related proteins with binding/interaction energy predictions [60].
T2DM (shared insulin resistance pathways)	Virtual screening + Molecular docking + MD simulation	Curcumin among 17 top ligands with binding affinities superior to standard antidiabetic drugs [61].
T2DM (shared insulin resistance pathways)	Network pharmacology + Molecular docking	Curcumin's role targeting TGR5 investigated in bile-acid-dependent modulation (linked to hepatic fat content) [62].
Inflammation (LPS-induced having sharing inflammatory targets))	Network pharmacology + Molecular docking + MD simulations, in-vitro validated	135 targets identified, strong binding affinities of curcumin having stable complexes with core targets, such as IL-6, TNF, IL-1β, AKT1, and STAT3 [63].

4.1. Anti-lipolytic Effects of Curcumin

Adipose tissues are a major site for fat storage; the lipolysis of this stored fat leads to the release of FFAs in the bloodstream. These FFAs, taken up by the liver, contribute to the accumulation of fats in the liver,

causing NAFLD [24]. Furthermore, this excessive fat in the hepatic cells makes them insulin resistant, a hallmark of metabolic dysfunction. This leads towards the progression of NAFLD to the more severe form, that is, NASH [25]. Curcumin, a natural polyphenolic compound, helps in inhibiting lipolysis by causing blockage of the cAMP/PKA signaling pathway via upregulation of AMPK. An oral administration of curcumin reduces the CD36 level and ultimately reduces the release of FFAs in the bloodstream. Moreover, curcumin suppresses the expression of the regulatory factors of DNL, that is, SREBP-1c and ChREBP, consequently downregulating the expression of FAS, preventing fatty acid synthesis. Hence, curcumin plays an effective role in lowering the substrate availability for hepatocellular lipogenesis, aiding in the prevention of fat accumulation in liver cells, a key factor in NAFLD (Figure 3) [64].

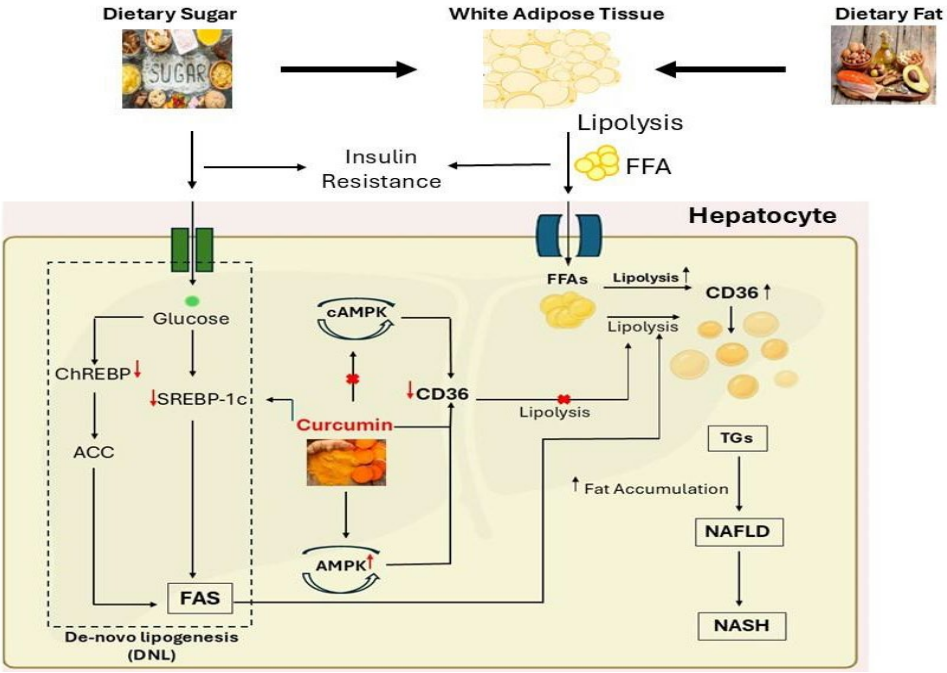


Figure 3. Anti-lipolytic Effects of Curcumin

Curcumin, a classic polyphenolic substance, inhibits lipolysis and plays an important role in preventing NAFLD. Typically, higher absorption of FFAs in the liver leads towards increased expression of CD36, which increases lipolysis. This enhanced lipolysis leads towards fat accumulation in the liver, known as NAFLD. As a result, it disrupts the AMPK and

cAMPK pathways. Curcumin inhibits the cAMPK pathway, which leads towards increased AMPK pathway activity. The increased AMPK pathway lowers CD36 expression, which inhibits lipolysis and hence prevents NAFLD. Additionally, SREBP-1c and ChREBP are regulatory factors for DNL. ChREBP activates ACC. ACC promotes FAS upregulation, which leads towards lipolysis and the production of TGs. This TG accumulates in the liver, creating NAFLD, which progresses to NASH. SREBP-1c, likewise, activates FAS and has a similar impact in NAFLD as ChREBP. Curcumin suppresses the expression of SREBP-1c and ChREBP, thus preventing NAFLD development. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black symbols (↓↑×) show the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × is for inhibition) [64].

4.2. Prevention of Insulin Resistance (IR)

Insulin plays an important role in the regulation of glucose production by reducing its level in the hepatic cells. Whereas, insulin resistance is affected by hepatic cells, leading to excessive fat accumulation and intensifying liver damage. Curcumin reduces the di-acylglycerol (DAG) build-up as well as translocation of the protein kinase C epsilon (PKCε), both of which are involved in the disruption of hepatic insulin signaling. Therefore, curcumin plays a significant role in balancing the liver metabolism. These findings make curcumin a potential candidate for the therapeutic intervention in NAFLD management [64,65].

4.3. As an Antioxidant

The most common mechanism responsible for the organ damage is oxidative stress. Generally, oxygen is an important precursor of ATP but it may also involve the production of very lethal species known as ROS, causing aging and cell death [66]. Mitochondria reduce these ROS into superoxide or peroxide ions that ultimately react with metal ions to form hydroxyl ions. These hydroxyl ions damage DNA, proteins, lipids, and other vital organs. The conversion of toxic ROS species into less toxic hydroxyl ions is called an antioxidant property. The polyphenolic compound curcumin, having ten times greater antioxidant potential as compared to vitamin E, is responsible for reversing this damage by upregulating Nrf2 genes [67]. This upregulation of Nrf2 is responsible for the expression of glutathione peroxidase and superoxide dismutase (SOD).

These GSH and SOD scavenge free radicals and convert OH free ions into H_2O_2. This newly formed H_2O_2 is then removed by the action of catalase and glutathione peroxidase (Figure 9). Hence, curcumin protects against liver damage (Figure 4) [68].

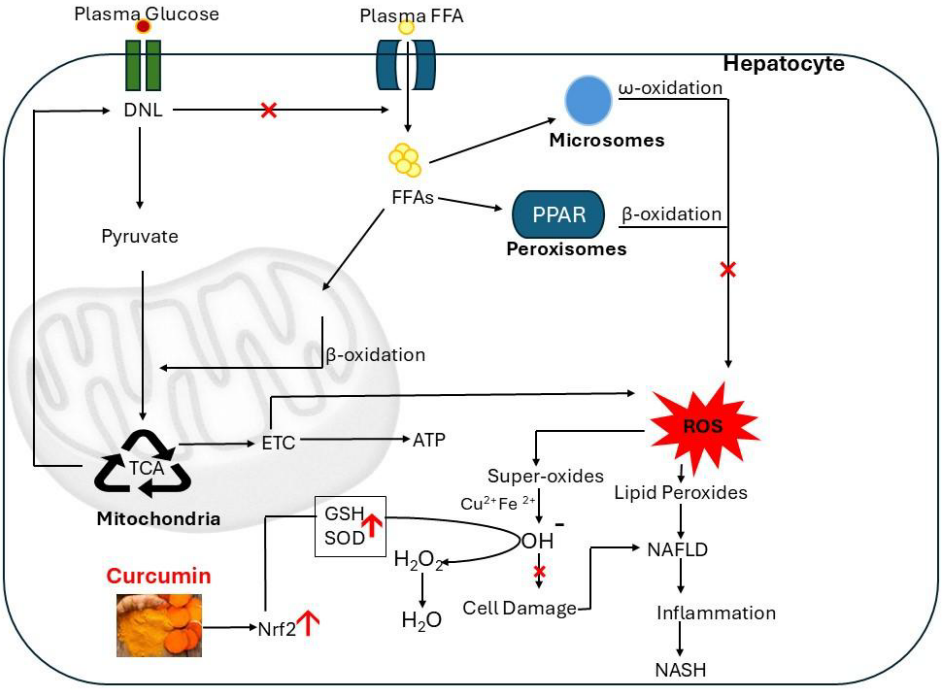


Figure 4. Curcumin as an Antioxidant

Overload of fatty acids in the liver causes the release of ROS, also known as oxidative stress. This stress response aggravates liver damage, causing inflammation, the second stage of fatty liver disease, NASH. The ROS are generated by oxygen released from ETC. The mitochondrial reduction of this lethal oxygen species into superoxide, which, on reaction with metal ions, forms hydroxyl ions. The hydroxyl ions cause organ damage, DNA damage, and ultimately inflammation. Curcumin reverses this damage by activating Nrf2. The activation of Nrf2 upregulates the release of dismutase and peroxidases. These peroxidases and dismutase act as a scavenger of free OH ions and convert them into H_2O_2. The newly generated H_2O_2 is then released in the form of water. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black symbols (↓↑×) show

the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × is for inhibition) [68].

4.4. As an Anti-inflammatory Agent

As already mentioned, NAFLD is a spectrum of hepatic disorders starting with the deposition of fats in the liver. If it remains untreated and progresses, it may lead towards a more severe form known as NASH, involving hepatic inflammation and damage. This inflammation response is accompanied by the activation of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and chemokines [69]. Curcumin inhibits inflammation by increasing M2-like macrophages in white adipose tissues, promoting the synthesis of anti-inflammatory cytokines. It has been reported that oral administration of curcumin is very helpful in controlling the progression of high-fat diet-induced NASH by changing metabolism and the accumulation of $CD4^+$ in hepatic cells [70]. Adding to this, HMGB1 interacts with TLR4, inducing the translocation of the activated NF-κB in the nucleus. This translocation results in the release of pro-inflammatory cytokines. Curcumin helps to reduce this HMGB1-led NF-κB translocation, hence preventing the release of pro-inflammatory cytokines [71]. Furthermore, the hepatoprotective ability of curcumin inhibits TRPM2 channels, reducing Ca^{2+} levels, ultimately reducing the risk of NASH (Figure 5) [72].

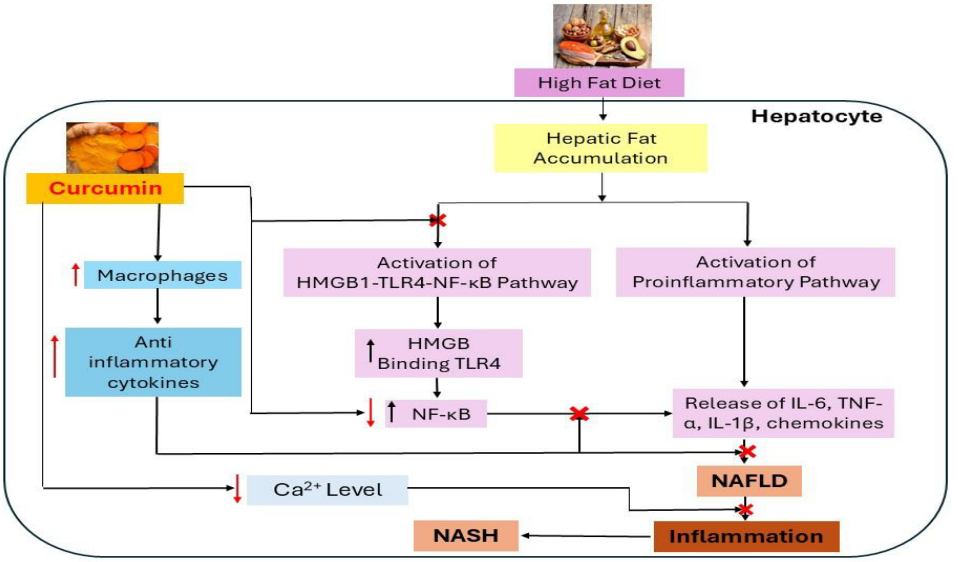


Figure 5. Anti-inflammatory Effects of Curcumin

The diagram depicts the development and progression of NAFLD because of inflammatory pathways. Curcumin either downregulates or inhibits these pathways by synthesizing anti-inflammatory cytokines via upregulation of M2 macrophages in adipose tissues. Moreover, it inhibits HMGB1-TLR4-NF-κB, suppressing the release of pro-inflammatory cytokines and mitigating liver inflammation. Also, curcumin acts as an inhibitor of TRPM2 channels to reduce the release of Ca^{2+}, promoting a hepatoprotective effect against NASH. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black symbols (↓↑×) show the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × for inhibition) [71,72].

4.5. As Suppressor of ER Stress

Lipids are a major component of the endoplasmic reticulum (ER) membrane. Any disruption in lipid homeostasis triggers an ER stress response. It has been reported that palmitic acid-induced ER stress in the mouse adipose tissues increases the phosphorylation of inositol-requiring enzyme 1α (IRE-1α) and eukaryotic initiation factor 2α (eIF-2α), main ER stress markers. It was evident that curcumin, in a dose-dependent manner (0.1-10 μM), dephosphorylated these stress markers and played a significant role in the suppression of ER stress. In the same manner, mice subjected to a short time of HFD, increased the phosphorylation of IRE-1α and eIF-2α proteins. However, when the same mouse was administered curcumin orally (50 mg/kg), the attenuation of these stress markers was observed. These results were also cross-validated by treatment with a well-established and known inhibitor of ER stress, TUDCA, which showed similar results (Figure 6) [64].

Figure 6 shows that curcumin alleviates NAFLD by downregulating ER stress. It causes dephosphorylation of the key ER stress markers IRE-1α and eIF-2α, resultantly suppressing ER stress response. The cellular stress response also decreases, hence reducing inflammation in liver cells, consequently preventing NAFLD. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black symbols (↓↑×) show the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × is for inhibition) [64].

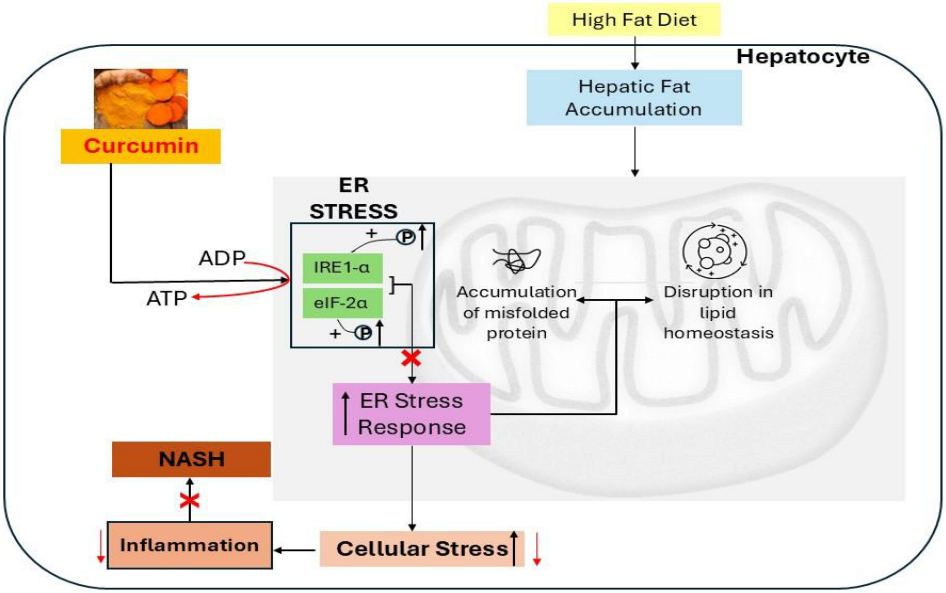


Figure 6. Curcumin and ER Stress

4.6. Nrf2-FXR LXR Pathway Modulation

One of the most widespread hepatic disorders, NAFLD, is characterized by the lipid accumulation in the liver. Usually, lipid and cholesterol balance in the body is maintained by liver X-receptor α (LXR-α) by the formation of heterodimers with retinoid X receptor (RXR). The core mechanism behind this fat buildup is the upregulation of lipogenesis by LXR-α and its target gene, that is, sterol regulatory element binding protein-1c (SREBP-1c), which regulates the activation of ACC and FAS genes, hence contributing to the development of NAFLD. In addition, because of fatty liver, cytochromes CYP3A and CYP7A are also downregulated, affecting the metabolism and detoxification of drugs and cholesterol, respectively, causing liver damage. Research has shown that curcumin apparently played a profound and vital role in the attenuation of liver steatosis. In an experimental setup, steatosis was induced in the C57BL/6 mice with a high-fat, high-fructose diet. It was observed that curcumin significantly helped in the downregulation of CYP3A and CYP7A cytochromes, restoring the health and functioning of the liver. Meanwhile, curcumin also controlled the fat buildup by evidently affecting the expression of CD36, FAS, and SREBP-1c. Additionally, Nrf2 (marker for ROS) and FXR levels dropped

undoubtedly, causing upregulation of LXR-α on the other side. This study showed the synergistic regulation of the Nrf2-LXR-α and FXR pathways, opening ways for the treatment strategies of NAFLD (Figure 7) [73].

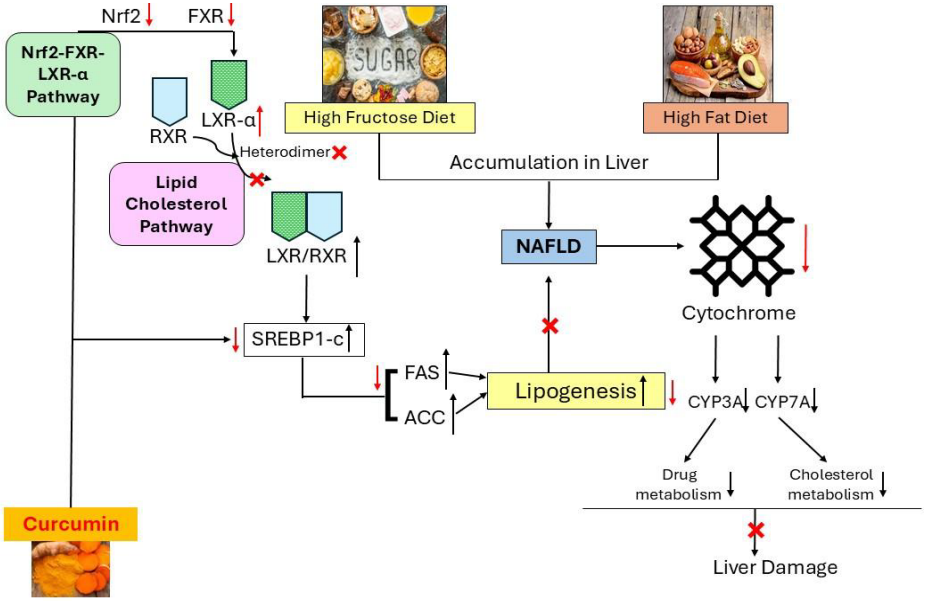


Figure 7. Curcumin's Role in Attenuating NAFLD through Multiple Pathways

Curcumin plays a significant role in alleviating NAFLD. Curcumin inhibits the hetero-dimerization of RXR and LXR-α by mediating the Nrf2-FXR-LXR-α pathway. It restores metabolism of lipids by downregulating the SREBP-1c/LXR pathway, suppressing lipogenesis, and consequently upregulating CYP3A and CYP7A expression. Hence, it prevents the liver damage, suggesting a promising therapeutic approach against NAFLD. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black symbols (↓↑×) show the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × is for inhibition) [73].

4.7. PI3K/AKT/mTOR and HIF-1/VEGF Cascade

Since metabolic factors are involved in the pathogenesis of NAFLD, researchers recently reclassified and renamed NAFLD as MAFLD [74]. Synergistic effects of curcumin in combination with resveratrol (Cur + Res) were studied on palmitic acid-induced NAFLD. It was observed that the

level of lipid in hepatic cells was reduced. The results were further validated in the diabetic GK rats. The results showed the reduced lipid levels in the bloodstream as well as attenuating liver steatosis. In addition, in-vivo studies showed that PI3K/AKT/mTOR and HIF-1/VEGF signaling pathways are upregulated, causing lipogenesis and inflammation specifically under stress environments, that is, in MAFLD. On treatment with the Cur + Res combination, stress conditions were normalized by downregulating these cascade pathways, giving a promising therapeutic hint against MAFLD (Figure 8) [75].

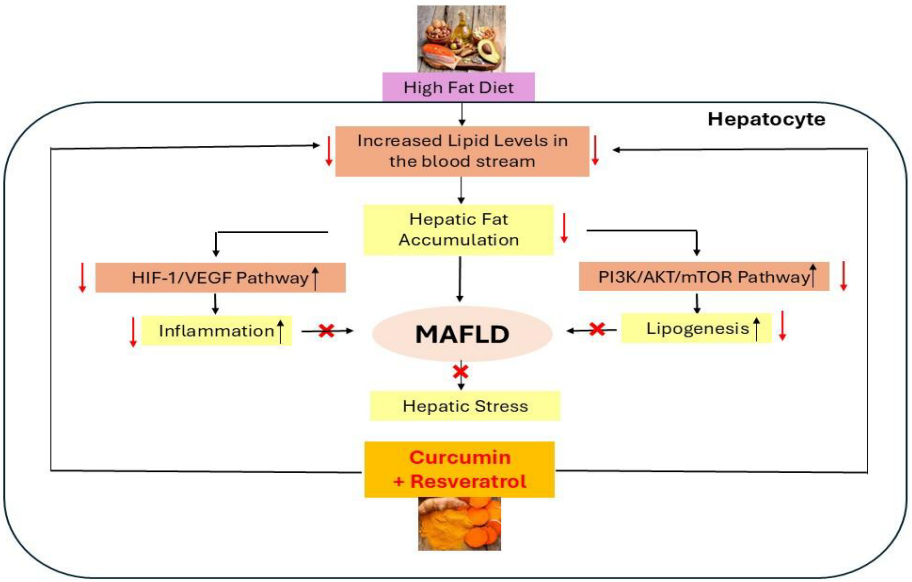


Figure 8. Curcumin and Resveratrol Effectively control MAFLD Pathogenesis

Usually, metabolic factors are responsible for the development of fatty liver disease by initiating cascade pathways. A high-fat diet leads towards the accumulation of lipids in the bloodstream and liver cells, triggering the activation of PI3K/AKT/mTOR as well as HIF-1/VEGF pathways. This causes lipogenesis and inflammation in hepatocytes, respectively. This inflammation results in liver stress known as MAFLD. Curcumin and resveratrol in combination help in the downregulation of PI3K/AKT/mTOR and HIF-1/VEGF pathways, consequently mitigating MAFLD [75,76]. Red symbols (↓↑×) show the preventive effect of curcumin, whereas black

symbols (↓↑×) show the pathogenic effect of respective factors (↑ for upregulation, ↓ for downregulation, and × is for inhibition).

5. CONCLUSION

NAFLD, which has been affecting almost one-third of the population worldwide, is emerging as a prominent cause of chronic hepatic disease. Its advancement to more severe stages of the disease, such as NASH, fibrosis, or cirrhosis, poses a serious and substantial public health concern, especially given the lack of specific, FDA-approved pharmaceutical drugs and therapies. On the basis of this context, curcumin, a natural chemical derived from *Curcuma longa*, due to its pleiotropic bioactivities, is proposed as an exciting therapeutic agent against NAFLD. The current study attempted to meticulously analyze the key pathophysiological mechanisms, such as insulin resistance, dyslipidemia, oxidative stress, ER stress, and Lipotoxicity. This indicates the multifaceted interaction of metabolic dysfunctions contributing to liver damage. The literature review stated that the preclinical data evidently supports curcumin's efficacy in lowering Lipotoxicity and oxidative stress by upregulating Nrf2 as well as counteracting inflammation by modulation of the cytokine profiles. Moreover, it lowers ER stress, influencing main molecular pathways, such as AMPK, NF-κB, ER stress pathway, modifying Nrf2-FXR-LXR, and PI3K/AKT/mTOR/HIF-1/VGF regulatory pathways. Adding to this, curcumin's ability to influence lipid metabolism while improving insulin sensitivity makes it a potential drug in slowing the progression of NAFLD and reverting the healthy state of hepatic cells. The above-mentioned multifaceted activities provide convincing evidence favoring curcumin's potential as a NAFLD drug. Nevertheless, turning this preclinical evidence into clinical trials demands more research. There is a need to conduct rigorous and large-scale human clinical trials to confirm its safety and efficacy, optimal dosages, and formulations. Nonetheless, a large amount of preclinical evidence recommends that curcumin is a good candidate for generating effective and well-tolerated adjunctive therapy in the fight against NAFLD. This makes it a key area of future research for high-impact clinical trials.

5.1.Limitations and Future Prospects

Moreover, curcumin's natural origin and exceptional safety profile enhance its appeal as a sustained treatment for NAFLD. In contrast to

synthetic medications, curcumin aligns with the growing patient demand for harmless, plant-based therapy. However, hurdles, such as its restricted bioavailability continue to prevent widespread clinical usage. Innovative delivery technologies, such as nano-formulations, lipid-based carriers, and co-encapsulation strategies, show significant promise in overcoming this barrier and improving both systemic absorption and therapeutic efficacy. Continued improvements in these technologies are required to fully realize curcumin's clinical implications.

Since the global prevalence of NAFLD has been rising, this review would be helpful in emphasizing the medicinal potential of curcumin. Yet, robust and effective clinical trials are direly needed for the validation of these experimental findings, analysis of the best dosages, and evaluation of the long-term effects. In addition, exploring the therapeutic potential of curcumin in combination with current pharmacological therapies as well as lifestyle modifications may reveal combinatorial advantages, opening gates for the development of personalized and integrated therapeutic approaches.

Moreover, understanding the individual diversity in genetic predisposition, food, and microbiota could further help in the optimization of its application in a variety of patient populations. In a nutshell, curcumin evidently provides a paradigm shift in the management of NAFLD together with its safety, efficacy, and adaptability to combat this silent epidemic. Adding to this, curcumin has great potential to reduce the global health burden of NAFLD by targeting several molecular pathways and disease progression mechanisms as well as integrating seamlessly into both the preventive and therapeutic strategies. With continued innovative research and rigorous clinical validation, curcumin may become a keystone of modern hepatic sciences, providing hope to millions at risk of liver complications.

Author Contribution

Tayyaba Naseem: conceptualization, writing – original draft, visualization, writing – review & editing. **Aghna Maryam:** writing – review & editing.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data availability is not applicable as no new data was created

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