

Review

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Review

Antiangiogenic Effects of Natural Compounds in Hepatic Inflammation

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Abstract: Alcoholic Liver Disease (ALD) and Non-Alcoholic Fatty Liver Disease (NAFLD) are the most common causes of chronic liver disease and are increasingly emerging as a global health problem. Such disorders can lead to liver damage, resulting in the release of pro-inflammatory cytokines and the activation of infiltrating immune cells. These are some of the common features of ALD progression in ASH (alcoholic steatohepatitis) and NAFLD to NASH (non-alcoholic steatohepatitis). Hepatic steatosis and subsequent fibrosis, whose continuous progression is accompanied by angiogenesis, lead to hypoxia, inducing the activation of vascular factors, which in turn triggers pathological angiogenesis and subsequent fibrosis, resulting in a vicious cycle. This condition further exacerbates liver injury and may contribute to the development of comorbidities, such as metabolic syndrome as well as hepatocellular carcinoma. Increasing evidence suggests that antiangiogenic therapy may have beneficial effects on these hepatic disorders and their exacerbation. Therefore, there is a great interest to deepen the knowledge of the molecular mechanisms of natural antiangiogenic products that could both prevent and control liver diseases. In this review, we focus on the role of major natural antiangiogenic compounds against steatohepatitis and determine their potential therapeutic benefits in the treatment of liver inflammation.

Keywords: liver disease; inflammation; steatosis; ALD; NAFLD; ASH; NASH; angiogenesis; hepatocellular carcinoma; natural compounds

1.1. The liver: function and diseases

Liver is an essential organ that plays a critical role in maintaining the metabolic and biochemical balance of the body. It is involved in nutrient metabolism, regulation of blood volume, storage of vitamins and minerals, support of the immune system, endocrine control of growth signaling pathways, lipid and cholesterol homeostasis, and degradation of xenobiotic compounds. In addition, its ability to oxidize lipids and package their excess for secretion and storage in other tissues makes it the major player in fat accumulation in various diseases [1,2].

The liver is composed of several cell types, mainly including hepatocytes, cholangiocytes, stellate cells, sinusoidal cells and Kupffer cells. Hepatocytes are the most abundant cells in the liver volume, and they perform many of the functions attributed to the liver; cholangiocytes are polarized cells that line the bile ducts within the liver and play a crucial role in the secretion and modification of bile, which is essential for digestion and absorption of fats in the small intestine, in addition to their immunological functions; hepatic stellate cells (HSCs) are a dynamic cell population that can exist in a quiescent state and can be activated when damage is induced to promote wound healing; sinusoidal endothelial cells are a specialized endothelial population that coat the hepatic sinusoids and allow the exchange of nutrients, hormones, and waste products between the blood and the liver

cells; finally, Kupffer cells are the resident macrophage population of the liver that help to remove foreign particles such as bacteria and viruses [3,4].

1.1.1. ALD and NAFLD

In the industrial city, increasing alcohol abuse and excessive eating are responsible for alcoholic liver disease (ALD) and non-alcoholic liver disease (NAFLD), respectively; both diseases have hepatic steatosis in common and range from a mild condition to more aggressive forms of the disease called alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH), where steatosis, hepatocyte apoptosis, inflammation and fibrogenesis coexist [5,6].

Hepatic steatosis represents the first step of these pathologies and is characterized by the accumulation of lipids, especially triglycerides, in the cytoplasm of hepatocytes, yet in the absence of inflammation, cell death or hepatic fibrosis. In this regard, two forms of steatosis can be distinguished: a macrovesicular form, where there is an arrangement of fat in a single large droplet that dislodges the nucleus in a peripheral location of the hepatocyte; and a microvesicular form, where fat collects in small droplets that do not dislodge the nucleus of the cells. These two aspects often reflect different stages of steatosis, and indeed clinical cases in which the two forms are associated are not uncommon [7,8].

Many hypotheses have been proposed to explain the pathogenetic mechanisms of ALD and NAFLD.

In ALD, as the liver is the main organ responsible for ethanol metabolism, ethanol and its metabolites (acetaldehyde-acetate, fatty acid ethanol esters (FAEE), ethanol-protein adducts) may exert a direct cytotoxic effect as hepatotoxins [9].

Hepatic ethanol metabolism involves oxidative and non-oxidative pathways. The main steps of the oxidative pathway are mediated by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH). ADH and ALDH convert ethanol to acetaldehyde and acetaldehyde to acetate, respectively [10]. The end products of these reactions are acetaldehyde, acetate, and high levels of NADH. Acetaldehyde injures the liver by directly inducing inflammation, extracellular matrix remodeling, and fibrogenesis [11]. In addition, it covalently binds to proteins and DNA, leading to lipid peroxidation and the subsequent production of toxic metabolites (e.g., malondialdehyde, 4-hydroxy-2,3-trans-nonenal), which are commonly analyzed under oxidative stress conditions [12,13]. Finally, acetaldehyde stimulates transforming growth factor (TGF)- β signaling in HSCs, which acquire a pro-fibrogenic and pro-inflammatory profile [14].

Changes in the NADH/NAD⁺ ratio can affect biochemical reactions in the mitochondria and gene expression in the nucleus. In particular, the re-oxidation of NADH requires additional oxygen in the mitochondria. To this end, hepatocytes absorb more than their normal share of oxygen from the arterial blood, but not enough to supply all regions of the liver adequately. Therefore, alcohol consumption causes significant hypoxia in perivenous hepatocytes, which are the first to show evidence of chronic alcohol-induced damage [15].

Cytochrome P450, in particular cytochrome P450 2E1 (CYP2E1), is upregulated in chronic alcohol abuse and assists ADH in the conversion of alcohol to acetaldehyde [16] (Figure 1). Reactive oxygen species (ROS), such as hydrogen peroxide and superoxide ions, generated by CYP2E1 are responsible for the pro-inflammatory profile of alcohol-induced liver injury by:

- (1) activation of redox-sensitive transcription factors (e.g., nuclear factor kappa B (NF- κ B), nuclear factor erythroid 2-related factor 2 (Nrf2), activating transcription factor 4 (ATF4), etc.) [17–19];
- (2) recruitment of neutrophils and other immune cells [20];
- (3) increasing levels of circulating inflammatory cytokines (e.g., tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β)) [21];
- (4) exacerbated lipid peroxidation associated with alcoholic liver injury [22].

Finally, the last player in the inflammatory and fibrogenic phenomena is catalase, a peroxisomal enzyme involved in the regulation of non-oxidative alcohol metabolism, the product by which FAEE are responsible for alcoholic steatosis and useful as biomarkers of chronic alcohol consumption [16]

(Figure 1). Obesity, type 2 diabetes, hyperlipidemia and other conditions associated with insulin resistance are commonly present in patients with metabolic syndrome (MS). A large body of evidence suggests that NAFLD is associated with MS. The latter is a clinical entity characterized by a cluster of metabolic changes, including glucose intolerance, dyslipidemia, and hypertension [23–25]. Approximately 90% of NAFLD patients have one or more diagnostic criteria for MS, allowing NAFLD to be defined as the "hepatic representation" of MS [26].

We can distinguish two types of NAFLD: primary (associated with MS) and secondary (associated with other metabolic or iatrogenic conditions, distinct from MS). The pathophysiology of primary NAFLD is not fully understood.

Since 1998, the two-hit pathogenetic model of liver injury proposed by Day and James has been widely accepted [27]. The first hit leads to the initial accumulation of triglycerides within the hepatocyte, caused by increased hepatic lipid uptake. These metabolic imbalances correlate with insulin resistance, a characteristic feature of MS. Such an event is, among others, bidirectional to steatosis: on one hand, insulin resistance promotes the progression of NAFLD, but on the other hand, NAFLD triggers the development of insulin resistance [28]. Later, the condition of steatosis would thus predispose the liver to the second event (second hit), after which inflammation, fibrosis and liver damage would develop. The factors determining the second hit included several biomolecules capable of interfering with the insulin-induced signal transduction mechanism, including inflammatory cytokines (e.g., TNF- α , IL-6, IL-1 β , hormones produced by adipose tissue such as adipokines, leptins, and adiponectins), oxidative stress and lipid peroxidation markers, fatty acids, and even ceramides.

In fact, inhibition of ceramide synthesis relieves NAFLD and fibrosis. Moreover, increased hepatic steatosis is associated with ceramide-rich hepatic lipids [29,30].

In addition, insulin resistance results in increased hyperglycemia-induced endoplasmic reticulum (ER) stress, peripheral lipolysis, hepatic fatty acid (FA) uptake, and hepatic synthesis of de novo lipids [31–33]. Therefore, the oxidation and disposal of fatty acids results in a defect compared to their accumulation and neo-synthesis, leading to an accumulation of fats within hepatocytes with important consequences, such as dysregulated ketogenesis [34,35]. In addition, fatty acids negatively affect the intracellular insulin signaling mechanism and cause hepatic insulin resistance through multiple pathways mediating activation of protein kinase C (PKC-3), c-Jun N-terminal kinase (JNK), I-kappaB (I- κ B) kinase β , and NF- κ B [36–38].

Furthermore, insulin resistance has been found to be associated in increased mitochondrial fatty acid oxidation. This process, both mitochondrial and peroxisomal, can produce ROS which are hepatotoxic and contribute to the development of oxidative stress. In addition, fatty acids and their metabolites are ligands of PPAR α (peroxisomal proliferator-activated receptor- α), a transcription factor that regulates the expression of several genes encoding enzymes involved in fatty acid oxidation at the mitochondrial, peroxisomal and microsomal levels. In support of this, deletion of PPAR α in hepatocytes impaired fatty acid catabolism, resulting in hepatic lipid accumulation in steatosis models [39,40].

Regarding the role of inflammatory cytokines in the pathogenesis of NAFLD, they could cause hepatic and systemic insulin resistance, as well as promote liver injury, apoptosis, neutrophil chemotaxis, and HSC activation [41–43]. Studies have reported several cytokines involved in the development and progression of NAFLD, such as IL-1 β , IL-6, TNF- α , C-reactive protein (CRP), and NOD-like receptor protein 3 (NLRP3) inflammasome activation. Some of these inflammatory mediators can be used as biomarkers to assess the severity and prognosis of NAFLD [44,45] (Figure 1).

In addition, fatty acids accumulated in hepatocytes can stimulate cytokine production via the NF- κ B-dependent pathway [46]. An additional source of pro-inflammatory cytokines is the infiltrating macrophages in the adipose tissue of obese subjects; cytokines are increased in addition to promoting the onset of a state of insulin resistance. They appear to reduce the production of certain peptides produced by visceral adipose tissue, such as leptins, resistins and adiponectins, which are involved in the pathogenesis of NAFLD [47].

1.1.2. ASH and NASH

Alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) are two of the most common causes of chronic liver disease worldwide. ASH is caused by chronic alcohol consumption, while NASH is associated with poor dietary habits and obesity, and is associated with insulin resistance and type 2 diabetes [48]. Although ASH and NASH differ in their etiology, both diseases are characterized by excessive fat deposition and lipotoxicity, leading to inflammation, hepatocellular swelling, and fibrogenesis [49].

Between 90 and 100% of individuals who consume more than 40 g of alcohol per day will eventually develop alcoholic fatty liver. Approximately 10-35% of these individuals develop ASH, which is characterized by a severe inflammatory state of the liver, hepatocyte swelling, neutrophil infiltration, and/or hepatic fibrosis [50]. In approximately 8-20% of patients with ASH, the risk of developing hepatocellular carcinoma (HCC) increases by approximately 2% per year [51]. Factors involved in the pathophysiology of ASH include hepatic steatosis, oxidative stress, acetaldehyde-mediated toxicity, and cytokine- and chemokine-induced inflammation, but hepatic inflammation is the critical prerequisite for the development of liver fibrosis, cirrhosis, and HCC [52].

Recent studies indicate that 5-20% of patients with NAFLD develop NASH during their clinical course, 10-20% develop higher grade fibrosis and <5% progress to cirrhosis [53]. Thus, ASH and NASH share a common pathogenesis and are mediated by different mechanisms [54]. The "two-hit" theory suggests that oxidative stress and cytokines lead to the progression of necroinflammation and ultimately to fibrosis and cirrhosis [55]. Indeed, hepatic macrophages and Kupffer cells are able to activate HSCs through the production of IL-6 and TNF- β , while HSCs in turn produce pro-inflammatory cytokines, such as TNF- α and IL-8 [56]. Fat-derived products can also cause inflammation and injury in the liver by activating the inflammasome and inducing the production of IL-1 and IL-18. Fat products can also cause inflammation and injury in the liver by activating the NLRP3 inflammasome, which induces the production of IL-1 β and IL-18; evidence for the critical role of NLRP3 activation is the marked protection from disease in knockout mice following acute or chronic alcohol administration [57]. In addition, oxidative stress strains antioxidant defenses, which become inadequate. This results in liver injury through direct cellular damage and NF- κ B-mediated cellular signaling [58]. Several studies also show that oxidative stress and the increase in ER stress-mediated Nrf2 are induced, which appears to be some common features of ASH and NASH (Figure 1); accordingly, altered markers of ER stress are recorded in numerous experimental preclinical models whose diets are administered alcohol or HFD [59].

As previously reported, the mechanisms that drive disease progression also induce steatosis. Therefore, steatosis could be considered as an "adaptive" response of the liver to stress, and continuous insult leads to ASH and NASH, in which we find not only steatosis but also inflammation and fibrosis [61,62].

In addition to oxidative stress and cytokines production, insulin resistance and hyperglycemia are active players in the progression of the pathology by directly inducing fibrosis or by regulating connective tissue synthesis [63,64].

Unfortunately, although significant progress has been made in identifying the key players that mediate the transition from steatosis to steatohepatitis, treatment options for ASH and NASH are limited [65]. Exercise and dietary interventions remain the main recommendations for patients with NAFLD and NASH. However, it is difficult for patients to adhere to such lifestyle changes for a variety of social, psychological, physical, genetic and epigenetic reasons; therefore, pharmacotherapy is essential [66,67].

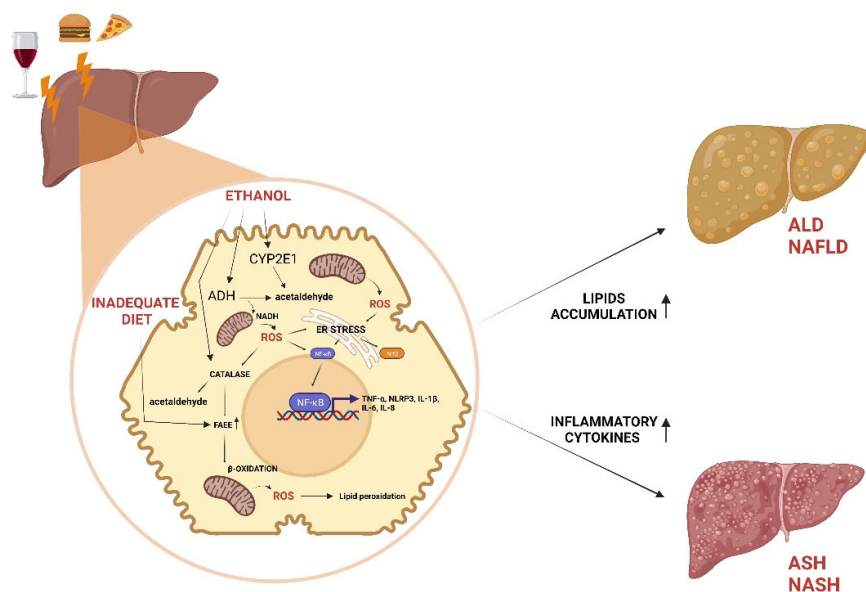


Figure 1. Role of alcohol consumption and inadequate diet on liver disease.

ADH, catalase and CYP2E1 contribute to oxidative metabolism of ethanol to generate acetaldehyde. Alcohol metabolism, high fat and high carbohydrate diet induce NAFLD and ALD by FFAE accumulating in lipid droplets. Accumulation of ROS resulting from ethanol or β -oxidation leads to formation of lipid peroxides and ER stress, which induce NF- κ B activation and consequent inflammatory state at the base of ASH and NASH.

2.1. Angiogenesis and hepatic inflammation

In this review, we focus on the role of the main natural compounds with health beneficial properties, including their role in angiogenesis within the pathophysiology of liver fibrosis.

Angiogenesis is a widely described and studied composite process that leads to the development of new vessels from pre-existing vasculature [68,69]. The angiogenic phenomenon occurs physiologically during normal tissue growth and wound healing, but also in pathological contexts such as liver disease and tumorigenesis [70,71].

In the liver, angiogenesis proceeds with molecular mechanisms similar to those demonstrated in other parts of the body. However, several differences in this organ make angiogenesis more complex, such as a more complex parenchyma with two distinct microvascular structures (portal vein and hepatic sinusoids), the presence of liver-derived angiopoietin-like peptide 3 (ANGPTL3), and the activity of HSCs, which play an active role in liver fibrosis by proliferating and becoming myofibroblasts that can modulate angiogenesis [72–75].

Multiple factors trigger angiogenesis in liver disease, including tissue inflammation and fibrosis. These lead to progressive tissue hypoxia, which in turn causes capillarization of sinusoids and initiation of the angiogenic process that leads to progression of NAFLD and ALD to NASH and ASH, respectively. Hypoxia activates angiogenesis through signaling mediated by transcription factors called hypoxia-inducible factors (HIFs), such as HIF-1 (Figure 2), which, among other things, stimulates inflammation via the NF- κ B pathway [76].

All this occurs because the intrahepatic vascular remodeling, which causes the deposition of fibrillar collagen (type I) instead of sinusoidal collagen (type IV), generates a continuous capillarization of the sinusoids and the development of intrahepatic shunts, leading to decreased effective hepatocyte perfusion and consequent loss of specific endothelial fenestrations. This process, together with the accumulation of fibrotic tissue, creates vascular resistance and decreases oxygen

transport to liver parenchyma, resulting in the upregulation of pro-angiogenic mechanisms via hypoxia, establishing a vicious cycle [77–79].

In pathological liver angiogenesis, there is a strong dialogue between different cell populations: indeed, wound healing generates an increase in the expression of some cytokines and factors with pro-angiogenic and inflammatory actions. Kupffer cells may contribute to angiogenesis by releasing ROS and inducing new vessel formation by stimulating the expression of TNF- α , HIF-1 and VEGF (vascular endothelial growth factor) [80]. Upon liver injury, these cells further produce TGF- β , the major regulator in chronic liver disease, contributing to all stages of disease progression from initial insult, through inflammation and fibrosis, to cirrhosis and HCC [81] (Figure 2). HSCs express several chemokines capable of stimulating angiogenesis and respond to hypoxia in a HIF-1 α -related pathway through the production of IL-8 and the increase of VEGF, Ang-1 (angiopoietin-1) and their corresponding receptors VEGFR-2 and Tie-2 [82,83] (Figure 2). In addition, other cells not present in the liver are activated: leukocytes and mast cells are involved in the regulation of angiogenesis by releasing histamine, heparin, cytokines and other angiogenic factors (Ang-2, EGF (epidermal growth factor), PlGF (placental growth factor), TGF- β 1, VEGF, etc.) [84,85].

Therefore, angiogenesis represents a key stage of inflammation and fibrosis [86] in liver disease. For these reasons, several antiangiogenic molecules (e.g., the anti-vascular endothelial growth factor (VEGF) monoclonal antibodies bevacizumab, brivanib, dovitinib, nintedanib, etc.) are currently used in the treatment of various cancers, including HCC, suggesting that angiogenesis is a promising therapeutic target [87–89]. Therefore, it is of great importance to determine the potential therapeutic benefits of various natural compounds in the prevention and treatment of liver inflammation. In this scenario, there are several natural compounds active in this field.

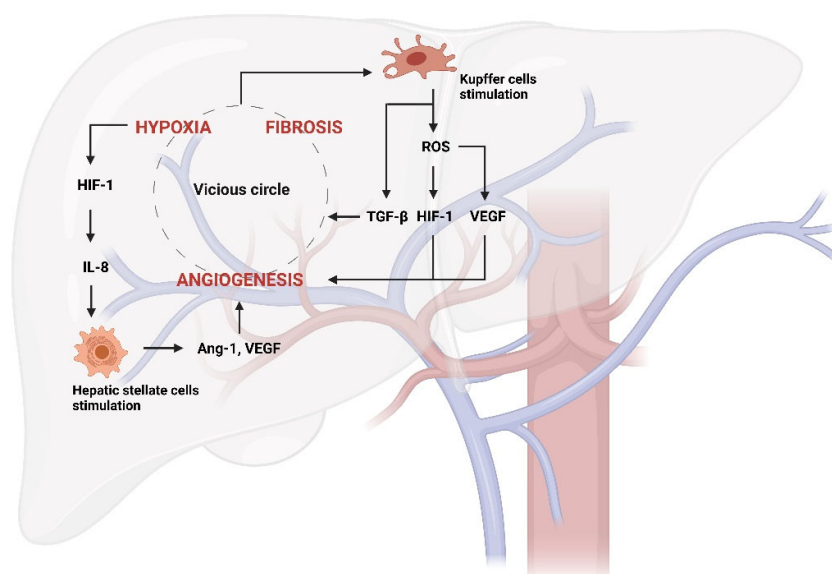


Figure 2. Vicious circle generated from hypoxia, fibrosis, and angiogenesis in liver disease.

Hypoxia activates hypoxia-inducible factors (HIFs), such as HIF-1, which among other things stimulates hepatic stellate cells (HSCs) activation via IL-8 production. They consequently produce angiogenic factors, such as Ang-1 (Angiopoietin-1) and VEGF (Vascular Endothelial Growth Factor). The stimulation of Kupffer cells by the vicious circle further aggravates this pathological process through TGF- β release. Furthermore, Kupffer cells can produce ROS inducing new vessel formation by the stimulation of HIF-1 and VEGF.

3.1. Phytochemicals to counteract the stages of liver disease via angiogenesis inhibition

3.1.1. Quercetin

Quercetin is a flavonoid found in fruits such as apples, red grapes, citrus fruits, tomatoes, onions, and other green leafy vegetables. Quercetin possesses various biological and pharmacological activities, including antioxidant, antiviral, anti-inflammatory, antiproliferative, and antifibrotic effects [90,91]. In recent studies, quercetin inhibited hepatic inflammation and fibrosis in mice by downregulating the HMGB1-TLR2/4-NF- κ B signaling pathway [92]. Moreover, it also limited hepatic fibrosis by inhibiting HSCs activation and reducing autophagy by regulating crosstalk between TGF- β 1/Smads and PI3K/Akt pathways [93].

Nevertheless, recent data have shown that macrophages play a complex role in liver fibrogenesis and are directly involved in the progression and resolution of liver fibrosis [94,95]. Indeed, inflammatory cytokines released by macrophages perpetuate inflammation and activate HSCs; quercetin showed direct effects by reducing the number of hepatic macrophages and ameliorating liver fibrosis after treatment of mice with CCl₄ [96] (Table 1). In conclusion, quercetin is a flavonoid with numerous beneficial biological and since its anti-inflammatory and antifibrotic effects it may hold promise as a potential therapeutic agent for liver fibrosis.

3.1.2. Silybin

Silybin is a flavonolignan that exists as a mixture of two diastereomers, silybin A and silybin B, in a roughly equimolar ratio [97]. It is usually extracted together with other compounds from milk thistle (*Silybum marianum*) in a mixture called silymarin, consisting of 50-60% silybin and the rest of silydianin, silycristin, taxifolin and other polyphenolic components [98]; known compounds with antioxidant activity [99]. Several pharmacological actions of silybin have been identified, including antioxidant and anti-inflammatory properties, antifibrotic effects, and modulation of insulin resistance. Specifically, in chronic inflammation, it underlies liver fibrosis and the development of cirrhosis [100].

The common mechanism underlying the initiation and progression of liver inflammation is oxidative stress [101]. NF- κ B is a key transcriptional regulator of the inflammatory response and plays an essential role in the regulation of inflammatory signaling pathways in the liver [102]. Furthermore, NF- κ B is activated in virtually all chronic liver diseases, including ALD, NAFLD, viral hepatitis, and biliary liver disease [103–105]. There is increasing evidence for a general inhibition of inflammatory mediators such as NF- κ B and inflammatory metabolites (e.g. prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄)) by silymarin [106].

In isolated rat Kupffer cells, silymarin weakly inhibited the formation of PGE₂ but strongly blocked the biosynthesis of LTB₄ [107]. This selective inhibition of LTB₄ formation by Kupffer cells and possibly other cell types may explain its anti-inflammatory potential.

In addition, it can reduce or normalize liver function parameters, such as transaminase levels, and improve ultrasound parameters of liver anatomy [108]. Therefore, silymarin (formulation derived from Eurosil 85®) has been investigated as a therapeutic option for NAFLD and NASH (Table 1).

Therefore, silybin has antioxidant and anti-inflammatory properties and may inhibit NF- κ B and inflammatory metabolites, having potential as a therapy for NAFLD and NASH, since it improves liver function and multiple ultrasound parameters used in liver ultrasonography. Silybin holds promise as a therapeutic agent for liver inflammation and fibrosis.

3.1.3. Breviscapine

Breviscapine is a crude mixture of several flavonoids from the traditional Chinese herb *Erigeron breviscapus*. It consists of more than 90% scutellarin and also contains baicalein, naringenin, scopoletin, kaempferol, apigenin, scutellarin, luteolin, caffeic acid, and protocatechuic acid [109]. It has multiple pharmacological activities, including anti-inflammatory, antioxidant, antiapoptotic,

vasorelaxant, antiplatelet, anticoagulant, and myocardial protective activities [110,111]. Recent studies show that breviscapine protects against CCl₄-induced liver injury by reducing proinflammatory cytokine secretion and oxidative stress [112]. In addition, scutellarin, the main component of breviscapine, has been shown to regulate lipid metabolism and reduce oxidative stress in NAFLD [113].

Further studies show that in mice fed a high-fat diet (HFD), high-fat/high-cholesterol diet (HFHC), or methionine- and choline-deficient diet (MCD), breviscapine attenuates hepatic lipid accumulation, inflammation, and fibrosis by mediating effects via direct inhibition of TGF- β -activated kinase 1 (TAK1) MAPKKK (mitogen-activated protein kinase kinase kinase).

In addition to being an upstream protein kinase of MAPK signaling, TAK1 also activates NF- κ B during NAFLD progression [114]. Because of the pivotal role of TAK1 in many physiological processes, such as inflammation, cell differentiation, and apoptosis, inhibition of metabolic stress-induced TAK1 activation may provide a potent hepatoprotective effect [115]. Indeed, recent studies have highlighted the important role of TAK1 in regulating hepatocyte lipid metabolism and reducing hepatocyte inflammation in NAFLD and NASH [116,117] (Table 1).

3.1.4. ALS-L1023

ALS-L1023 is an extract isolated from *Melissa officinalis*, known in natural medicine as an antiangiogenic agent [118–121]. ALS-L1023 modulated the mRNA expression of angiogenic factors (VEGF-A and fibroblast growth factor 2 (FGF-2)), metalloproteinases (MMPs) MMP-2 and MMP-9, and their inhibitors (TIMP-1, TIMP-2, and thrombospondin (TSP-1)) [122,123]. It also reduces visceral adipose tissue (VAT) production in mice with HFD-induced NAFLD by suppressing lipid synthesis and steatosis, inflammatory cell infiltration, and collagen accumulation in the liver; thus, supporting the idea that ALS-L1023 may have a great contribution to regulate the development and progression of NAFLD and consequent NASH [124,125]. In addition, this extract reduced inflammation in diet-induced NAFLD in female ovariectomized mice and rescued from oxidative stress through Akt activation. For these reasons, ALS-L1023 is in a Phase IIa clinical trial in patients with NAFLD. Recent studies are also evaluating whether ALS-L1023 could alleviate liver fibrosis, as anti-fibrotic effects are essential properties of NASH drugs. In this regard, biochemical analysis showed that the ALS-L1023 mouse group had significantly decreased alanine transaminase and aspartate transaminase. In addition, the area of fibrosis was significantly reduced after administration of ALS-L1023, and its anti-fibrotic effect was greater than that of the reference compound OCA (obeticholic acid) [126] (Table 1). ALS-L1023 has antiangiogenic and anti-inflammatory properties, reduces VAT production and inflammation in NAFLD as well as to alleviate liver fibrosis, with a significative antifibrotic effect.

3.1.5. Curcumin

Curcumin, along with demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin, is the major phenylpropanoid compound found in the roots of the perennial plant *Curcuma longa*. It is unclear whether all four analogs have the same activity. Although curcumin was found to be the most potent in most systems [127–130], bisdemethoxycurcumin and cyclocurcumin were found to have higher activity in some studies [131,132]. There is also evidence that the mixture of all three is more potent than just one [132]. Curcumin has shown anti-angiogenic and other beneficial properties in several experimental models of liver injury by inhibiting the NF- κ B pathway [133]. It prevents aflatoxin-induced liver injury [134] and regresses cirrhosis [135].

In acute CCl₄ intoxication, oxidative stress and expression of pro-inflammatory cytokines, such as TNF- α , IL-1 β and IL-6, and NF- κ B activation are associated with some increases in several markers of liver injury and distortion of hepatic microscopic structure; pretreatment with curcumin prevented oxidative stress, NF- κ B activation, and liver injury. Similarly, in biliary cirrhosis, curcumin showed anti-fibrogenic properties associated with downregulation of the cytokine TGF- β [136] (Table 1).

NAFLD induced in methionine and choline-deficient (MCD) mice significantly upregulates the hexosamine biosynthetic pathway and O-GlcNAc transferase via ER stress. This model has been

shown to be a useful experimental model for NASH. Curcumin treatment alleviates the severity of hepatic steatosis by blocking the NF- κ B signaling pathway through inhibition of O-GlcNAcylation and enhancing antioxidant systems, including SOD1 (superoxide dismutase 1), GPx (glutathione peroxidase), and CAT (catalase) [137] (Table 1).

3.1.6. Sulforaphane

Sulforaphane (SFN) is an organosulfur compound in the isothiocyanate group that is found in high concentrations in cruciferous vegetables such as broccoli and cauliflower [138]. It has been reported to exert a variety of bioactive effects, including antioxidant, anti-inflammatory, cytotoxic, and cytoprotective effects [139]. In tumor angiogenesis, SFN inhibits NF- κ B-regulated VEGF expression in human prostate cancer cells [140]; Peng liu et al. have shown that SFN interferes with the proliferation, migration and tube formation of endothelial cells, but it is also capable of inhibiting the pro-angiogenic effect of HepG2 cells both in vitro, ex vivo and in vivo. SFN significantly inhibited the viability and migration of HUVECs (human umbilical vein endothelial cells), consistent with previous findings [141].

SFN has been shown to inhibit STAT3 (signal transducer and activator of transcription 3), and this is consistent with reduced expression of HIF-1 α and VEGF in HepG2, suggesting that STAT3/HIF-1 α /VEGF may be responsible for the anti-angiogenic effects of SFN. This latter also inhibits TGF- β -induced epithelial-mesenchymal transition of HCC via ROS-dependent pathway [142]. SFN-induced Nrf2 activation was indeed confirmed by mRNA upregulation of redox genes such as HO-1 (heme oxygenase-1), MRP2 (multidrug resistance-associated protein 2), and NQO1 (NAD(P)H quinone dehydrogenase 1) in several cell lines [143,144] (Table 1). Essentially, SFN is a bioactive compound with a range of beneficial effects, including antioxidant, anti-inflammatory, cytotoxic, and cytoprotective effects, which has been shown to inhibit angiogenesis in human prostate and liver cancer cells by inhibiting NF- κ B-regulated VEGF expression, and through inhibiting the STAT3/HIF-1 α /VEGF pathway. SFN also induces Nrf2 activation, which may contribute to its antitumor effects.

3.1.7. Cordycepin

Cordycepin is an adenosine derivative, antimetabolite and antibiotic from the fungus *Cordyceps militaris* [145]. Cordycepin has a broad spectrum of biological activities, including anti-inflammatory, antioxidant, antifibrotic, antiadipogenic and antitumor activities [146,147]. Guo Z. et al. have shown that it suppresses the migration and invasion of human liver cancer cells by downregulating CXCR4 [148]. A hallmark of NASH pathogenesis is the inflammatory response, which initially triggers the release of numerous types of proinflammatory cytokines. Cordycepin suppresses the production of proinflammatory cytokines in LPS-stimulated macrophages and exerts anti-inflammatory effects by suppressing NLRP3 activity, an important regulator of the inflammatory process in macrophages [149]. Furthermore, NLRP3 deficiency in HCC cells enhances the activity of natural killer cells to delay tumor development in the xenograft mouse model [150].

Tian Lan et al. also demonstrate in their study how cordycepin attenuates metabolic stress-induced NASH by preventing steatosis, inflammation, and fibrosis. Specifically, cordycepin inhibited the activation of the NF- κ B signaling pathway and attenuated the secretion of proinflammatory cytokines in hepatocytes under metabolic stress. This is due to an increase in AMPK phosphorylation through an interaction with the α -subunit of AMPK. The latter acts in mice treated with NASH-inducing diets as a central regulator of fatty acid, cholesterol and glucose homeostasis through phosphorylation of enzymes that regulate metabolism, including ACC α (acetyl-CoA carboxylase), glycogen synthase, glucose transporter 4, HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase [151] (Table 1). In conclusion, cordycepin, an adenosine derivative, has been shown to exhibit various biological activities, including anti-inflammatory, antioxidant, antifibrotic, anti-adipogenic, and antitumor effects. Cordycepin also enhances natural killer cell activity to delay tumor development in xenograft mice models. These findings suggest that cordycepin may have potential therapeutic applications in the treatment of liver diseases, including NASH and liver cancer.

3.1.7. Methoxyeugenol

Methoxyeugenol has been identified in Brazilian red propolis, produced by bees of the species *Apis mellifera*, and the therapeutic effects of propolis have been known in folk medicine for centuries and have been used to treat infections, gastric disorders and to improve wound healing [152,153]. Another source of methoxyeugenol is nutmeg (*Myristica fragrans* Houtt.), which is used as a spice and whose use in folk medicine is reported mainly for the treatment of gastrointestinal disorders [154]. However, studies support its use in the treatment of nonalcoholic hepatic steatosis [155], as it appears to promote lipid metabolism regulation and exert anti-inflammatory effects. Bruno de Souza Basso et al. have shown that methoxyeugenol promotes HSC deactivation without evidence of cell death, suggesting a reduction in proliferative rate [156]. In addition, the cytokine TGF- β , a growth factor that plays an important role in the development of liver fibrosis, particularly by activating quiescent HSCs, is reduced in the same cells treated with methoxyeugenol.

The maintenance of lipid metabolism is mediated by nuclear receptors of the PPAR family, mainly PPAR α/γ , and several studies have shown that PPAR γ activation can inhibit macrophage activation and NF- κ B-mediated inflammatory pathways [157,158]. In light of this, PPAR γ activation may enhance phenotypic modulation of activated HSCs by restoring lipid metabolism and inhibiting inflammatory signaling. In this regard, methoxyeugenol increases PPAR γ mRNA expression. In vivo studies on the use of methoxyeugenol, administered in the CCl₄-induced liver fibrosis model, attenuate the inflammatory process and fibrosis, reducing intralobular inflammation by decreasing the gene expression of TNF- α , IL-6 and IL-8, as well as NF- κ B protein expression [156] (Table 1). Overall, methoxyeugenol shows promising potential as a natural compound for the treatment of liver diseases.

3.1.8. Naringenin

Naringenin is a flavone found in various plants and is particularly abundant in citrus fruits [159]. Several studies show that it exerts multiple biological effects, including anti-inflammatory, antioxidant, hypolipidemic effects: protective factors for NAFLD [160,161].

The study by Wang et al. showed that the mRNA expression levels of NF- κ B, IL-1 β , IL-18 and NLRP3 were improved in mice fed an MCD diet. In vivo experiments showed that naringenin significantly reduced the mRNA and protein levels of these factors. In addition, hepatic triglyceride levels were not further reduced in NLRP3^{-/-} mice fed an MCD diet treated with naringenin. For further confirmation, primary hepatocytes from wild-type and NLRP3^{-/-} mice were isolated and NLRP3^{-/-} cells were stimulated with LPS and oleic acid. It was found that naringenin is highly effective in preventing lipid deposition in WT primary hepatocytes, but much less effective in NLRP3^{-/-} primary hepatocytes, demonstrating that this flavonoid acts precisely by reducing the levels of the NLRP3 inflammasome [162] (Table 1).

3.1.9. Ferulic acid

Ferulic acid (FA) is a phenolic acid widely found in grains, vegetables, and plants such as *Angelica sinensis*. FA exhibits several biological activities, including antioxidant, anticancer, antidiabetic, and immune function-enhancing effects [163,164].

Several recent studies have demonstrated the hepatoprotective effects of FA [165]. Indeed, its administration improves lipid metabolism and liver inflammation in apolipoprotein E-deficient mice fed a HFD by upregulating AMPK α and downregulating lipogenic genes [166]. In addition, FA showed beneficial effects against oxidative stress and liver damage by activating Nrf2/HO-1 and PPAR γ pathways [167].

Jianzhi Wu et al. reported FA as an agent capable of preventing all histological changes of CCl₄-induced liver fibrosis in mice by suppressing hepatic oxidative stress, inflammatory response, macrophage activation, and HSCs activation through phosphorylation of AMPK by direct binding and consequent inhibition of PTP1B (protein tyrosine phosphatase 1B) [168]. Therefore, activated AMPK in hepatocytes not only suppressed apoptosis and NOX2 (NADPH oxidase 2)-derived ROS

production, but also inhibited the production of endothelial pro-inflammatory cytokines [169]. FA is also able to prevent the nuclear translocation of NF- κ B. All this makes FA a good player in the treatment of liver fibrosis and its advanced complications (Table 1).

3.1.10. Betaine

Betaine is an essential biochemical modulator of the methionine/homocysteine cycle that is originally extracted from the juice of sugar beet (*Beta vulgaris*) [170] and is also found in various microorganisms, plants, and animals [171]. Aqueous extracts of betaine are used in traditional Eastern medicine to treat liver disease [172]. Recent studies show that betaine suppresses inflammation through activation of NF- κ B during aging [173]. Eui-Yeun Yi et al. found that betaine suppressed angiogenesis in the in vivo Matrigel plug assay, in addition to in vitro inhibition in tube formation, migration, and invasion assays performed on HUVECs. Betaine also inhibits NF- κ B and Akt activation [174].

VEGF and FGF-2 are known to be key stimuli for angiogenesis [175,176]. When investigating the involvement of betaine in the expression of key angiogenic factors, it was found that the mRNA expression of FGF-2 was significantly reduced. Betaine also shows beneficial effects by downregulating the expression of MMP-2 and MMP-9, key regulators of extracellular matrix turnover through the degradation of a variety of extracellular matrix proteins. Extracellular proteolytic activity is important in the process of endothelial cell migration and invasion, focal events in angiogenesis [177,178] (Table 1). Therefore, betain suppresses inflammation and angiogenesis by inhibiting NF- κ B and Akt activation, reducing the expression of key angiogenic factors and regulating the extracellular matrix turnover.

3.1.11. Catechins

Catechins are a group of flavanols that are abundant in plant fruits, vegetables, and beverages. Fruits such as grapes, apple, cocoa, and green tea are considered the major sources of catechins, which represent some promising candidates in the field of biomedicine [179–182]. Green tea is one of the most popular beverages in the world and has been studied for its health-promoting properties in several diseases such as cancer, obesity, diabetes, and cardiovascular disease [183]. Many of the biological effects of green tea are mediated by its polyphenolic catechins, particularly (-)-epigallocatechin-3-gallate (EGCG), which accounts for 50–85% of total catechins. Several studies show how green tea in animals restores gene and protein levels of proinflammatory cytokines in galactosamine-induced hepatitis [184]. Similar observations have indeed been reported in CCl₄-induced liver injury in rodents [185], where mRNA expression levels of TNF- α , COX-2, iNOS, smooth muscle actin, TGF-1, procollagen-I, MMP-2, MMP-9, and TIMPs are increased along with an increase in NF- κ B activity. Treatment with green tea extract significantly reduced liver damage, oxidative stress, inflammatory response, and expression of all pro-fibrogenic markers analyzed except TIMP-2 and MMP-9. Other studies show that treatment with such extract inhibits the levels of IL-1, IL-6, TNF- α [186]. Furthermore, vascular endothelial (VE) cadherin and Akt, known downstream proteins in the VEGFR-2-mediated cascade, are other target proteins by which EGCG inhibits angiogenesis [187]. It has also been observed that pentameric procyanidins isolated from cocoa inhibit gene expression of the tyrosine kinase ErbB2, thereby slowing down in vitro angiogenesis of human aortic endothelial cells [188] (Table 1).

3.1.12. Puerarin

Puerarin, a natural compound extracted from *Pueraria lobata*, has antioxidant and anti-inflammatory effects [189]. Various studies show that puerarin may regulate leptin signaling through the Janus kinase 2 (JAK2)/STAT3 pathway, thereby ameliorating hepatic steatosis [190]. Jingxuan Zhou et al. showed that in a rat model of HFD-induced NAFLD, puerarin administration reduced the abdominal fat coefficient [191]. In addition, puerarin significantly reduces inflammation caused by lipid accumulation. This induces ROS overproduction and consequent activation of the NF- κ B

pathway, as well as a variety of inflammatory factors, such as interleukins (IL-1 β and IL-18) and TNF- α [192]. In addition, puerarin decreased thiobarbituric acid reactive substances and protein carbonyl content in the liver of CCl₄-treated mice by regulating the expression of phosphorylated JNK, phosphorylated c-Jun protein, and cholesterol 7 α hydroxylase (CYP7A1) in the liver [193] (Table 1).

3.1.13. Resveratrol

Resveratrol (RSV) is a stilbene found in grape skins, blueberries, raspberries, mulberries, and peanuts, and its high concentration in red wine partly explains the relatively low incidence of cardiovascular disease despite the prevalence of HFD in populations using it [194]. Resveratrol has antioxidant activity in a wide range of liver diseases [194,195]. In particular, its effect is mainly exerted through ROS reduction and enhancement of endogenous antioxidant enzyme activity (e.g., SOD, CAT). In addition, RSV promotes the synthesis of antioxidant molecules and the expression of related genes involved in mitochondrial energy biogenesis, particularly through the AMPK/SIRT1/Nrf2, ERK/p38 (extracellular signal-regulated kinase), and PTEN/Akt (phosphatase and tensin homologue/protein kinase B) signaling pathways [196]. Resveratrol acts as an antioxidant by inhibiting the ubiquitination of Nrf2, thereby preserving its critical function. Nrf2, in turn, translocates to the nucleus and induces the transcription of various antioxidant genes, such as SOD and CAT, thereby enhancing antioxidant defense [197].

In NAFLD, RSV seems to play an interesting role in regulating the deposition of *de novo* fibrogenesis by acting on several key pathways. Indeed, RSV administration reduces portal pressure, HSC activation and improves hepatic endothelial function in cirrhotic rats, with an overall beneficial effect on cirrhosis and portal hypertension [198,199]. Again, it is well known that RSV administration in hepatocytes causes inhibition of mRNA expression of inflammatory mediators, including TNF- α , IL-1 β , as well as TNF- α and IL-6 in cultured hepatocyte cells, and reduces the number of Kupffer CD68(+) cells recruited to the liver [200,201] (Table 1).

3.1.14. Fucoidan

Fucoidan, a sulfated polysaccharide containing substantial amounts of L-fucose and sulfate ester groups, is readily present in edible brown seaweeds, which are widely consumed in Asian countries due to their extensive health benefits [202,203]. An *ex vivo* angiogenesis assay showed that fucoidan caused a significant reduction in microvessel outgrowth and significantly reduced the expression of the angiogenesis factor VEGF-A [204]. Fucoidan was also evaluated for its activity in combination with sorafenib and bevacizumab in HCC. In vitro, on Huh-7 cells, fucoidan showed a potent synergistic effect with anti-angiogenic drugs and significantly reduced HCC cell line viability in a dose-dependent manner via inhibition of pro-angiogenic PI3K/AKT/mTOR and KRAS/BRAF/MAPK pathways [205] (Table 1).

3.1.15. Carnosol and Carnosic Acid

Carnosol and carnosic acid are two major components of rosemary extracts that contribute to the chemopreventive, anti-inflammatory, antitumor, and antimetastatic activities of *Rosmarinus officinalis* [206,207]. Lopez-Jimenez et al. demonstrate for the first time how these diterpenes modulate different relevant steps of the angiogenic process, inhibiting cytokine-induced adhesion molecule expression, monocyte adhesion to endothelial cells through a mechanism related to NF- κ B, and capillary tube formation by endothelial cells, in addition to inducing apoptosis in endothelial and tumor cells in vitro. These results suggest their potential use in the treatment of angiogenesis-related malignancies [208] (Table 1).

Table 1. Antiangiogenic effects of natural compounds and their molecular mechanism.

PHYTOCHEMICALS	MAIN DIETARY SOURCES	DESIGNED STUDY	ANTIANGIOGENIC EFFECTS	REF.
Quercetin	apples, red grapes, citrus fruits, tomatoes, onions and green leafy vegetables	Mice	HMGB1/TLR2/4-NF-κB signaling pathway downregulation; TGF-β1/Smads and PI3K/Akt crosstalk regulation	92; 93
Silybin	<i>Silybum marianum</i>	Rats	NF-κB, PGE 2 and LTB 4 inhibition	102; 106
Breviscapine	<i>Erigeron breviscapus</i>	Mice	TGF-β-activated kinase 1 (TAK1)/ NF-κB signaling pathway Inhibition	114
ALS-L1023	<i>Melissa officinalis</i>	Mice	mRNA modulation of VEGF-A, FGF-2, MMP-2, MMP-9 TIMP-1, TIMP-2, TSP-1	122; 123
Curcumin	<i>Curcuma longa</i>	Mice	NF-κB inhibition; TGF-β downregulation	133; 136
Sulforaphane	Broccoli, cauliflowers	Hep G2 and HUVEC cells	NF-κB/VEGF, STAT3/HIF-1α/VEGF signaling pathway inhibition; HO-1, NQO1, MRP2 genes upregulation	140; 142-144
Cordycepin	<i>Cordyceps militaris</i>	HCC cells	CXCR4 downregulation; NLRP3 suppression; NF-κB inhibition	148-150
Methoxyeugenol	Brazilian red propolis	Mice	mRNA up-regulation of PPARγ; TNF-α, IL-6 e IL-8 genes downregulation	156
Naringenin	citrus fruits	Mice	mRNA downregulation of NF-κB, IL-1β, IL-18 NLRP3	162
Ferulic acid	cereals, vegetables, and plants such as <i>Angelica sinensis</i>	Mice	AMPKα up-regulation; lipogenic genes downregulation; Nrf2/HO-1 and PPARγ pathways activation; nuclear translocation block of NF-κB; PTP1B inhibition	166-169
Betaine	<i>Beta vulgaris</i>	HUVEC cells	NF-κB and Akt inhibition; FGF-2 MMP-2 MMP- downregulation	174; 177; 178
Catechins	grapes, apple and cocoa	Haec cells; Mice	IL-1, IL-6, TNF-α inhibition; ErbB2 gene downregulation	186; 188
Puerarin	<i>Pueraria lobata</i>	Rats	(JAK2)/STAT3 signaling pathway regulation; JNK activity regulation,	190; 193
Resveratrol	grape skins, blueberries,	Primary hepatocyte;	Nrf2 ubiquitination	197; 200; 201

	raspberries, mulberries, and peanuts	Mice	inhibition; TNF- α , IL-1 β , IL-6 mRNA inhibition	
Fucoidan	edible brown seaweeds	HCC; Huh-7 cells	VEGF-A gene downregulation	204; 205
Carnosol and Carnosic Acid	<i>Rosmarinus officinalis</i>	BAECs and HUVEC cells	NF- κ B inhibition	208

4.1. Conclusions and Perspectives

Angiogenesis plays an important role in the development of liver disease, contributing to the progression of fibrosis and remodeling leading to capillarization of the sinusoids with the formation of intrahepatic shunts. As a result, vascular resistance increases and hepatocyte perfusion decreases, leading to hypoxia.

Many anti-angiogenic drugs, mainly tyrosine kinase inhibitors and humanized monoclonal antibodies, are currently used, but they are often expensive or toxic, limiting their use in many cases. Therefore, it is useful to identify less toxic, inexpensive, novel and effective anti-angiogenic compounds. In this regard, several natural plant products have shown prominent anti-angiogenic effects. However, the bioavailability of natural products is a critical issue since many of them have poor aqueous solubility and low absorption rate.

On the positive side, a large number of natural anti-angiogenic substances are being discovered and the study of their complex mechanisms has not yet been fully investigated.

Therefore, it is of great interest to study natural compounds and their derivatives to gain new insights into the biochemical mechanisms involved in signaling pathways in liver diseases. Accordingly, research on new natural products with anti-angiogenic effects seems very promising and may lead to the discovery of new drugs, which would be a significant achievement in this field. Furthermore, this sets the stage has the potential to identify new targets for more selective and effective synthetic anti-angiogenic agents.

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