JABET
Journal of Advanced Biotechnology and Experimental Therapeutics

REVIEW ARTICLE

J Adv Biotechnol Exp Ther. 2025 Jan; 8(1): 125-138
eISSN: 2616-4760, https://doi.org/10.5455/jabet.2025.11
Published by www.bsmiab.org

Pharmacological insights and therapeutic advances of mangiferin against various pathological conditions in liver diseases

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Academic editor
Md. Abdul Hannan, PhD
Bangladesh Agricultural University, Bangladesh

Article info
Received: 01 December 2024
Accepted: 16 January 2025
Published: 20 January 2025

Keywords
Apoptosis, Endoplasmic reticulum stress, Inflammation, Liver disease, Mangiferin, Oxidative stress

ABSTRACT

Currently, liver diseases have become a serious global health issue, and this situation occurs due to the exposure of the liver to different agents, such as chemicals, alcohol, viruses, and autoimmune diseases. Mangiferin is a natural bioactive xanthone C-glycoside compound and a potent antioxidant that is widely found in medicinal plants such as the leaves of *Mangifera indica L.* (*Anacardiaceae*). It possesses a wide range of biological properties, such as antidiabetic, hepatoprotective, anti-inflammatory, antioxidant, and anticarcinogenic activities. The purpose of this literature review was to delineate the hepatoprotective effects of mangiferin, a natural bioactive compound without side effects, and explain how it protects the liver via the suppression of pathological conditions involved in liver diseases. Relevant published research articles from peer-reviewed journals were searched in PubMed and Google Scholar to gain insights into the consequences of mangiferin in liver diseases. Several studies have suggested that pretreatment with mangiferin decreases hepatic inflammation, oxidative stress, apoptosis, fibrosis, endoplasmic reticulum (ER) stress, and hepatic dysfunction and concomitantly ameliorates the morphological structures of the liver. Therefore, mangiferin could be considered a multitarget therapeutic and promising drug candidate for the treatment of hepatic diseases, although a detailed mechanistic explanation needs to be provided. This literature review highlights the pathological conditions (inflammation, oxidative stress, apoptosis, ER stress) associated with liver diseases as well as the hepatoprotective and therapeutic effects of mangiferin in the liver.

INTRODUCTION

Liver disease is one of the most alarming concerns, and approximately 2 million people die of liver diseases and complications. Chronic liver diseases, including liver cirrhosis and liver cancers, are the 11th and 16th leading factors responsible for death worldwide and are characterized by various pathological conditions such as oxidative stress, ER stress, inflammation, apoptosis, and other pathologic conditions [1]. These conditions can be identified by examining any discrepancies with their respective markers. Nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are the most well-known liver diseases. Among them, fatty liver diseases are commonly caused by lipid accumulation in the liver, which aggravates inflammation and results in severe long-term effects on the liver [2, 3].

In addition, hepatocellular carcinoma is closely associated with multiple complications, including consequent inflammatory cascades along with insulin resistance, obesity, and iron deposition [4, 5].

Diabetes and obesity increase the levels of several proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [6]. In addition, these diseases are also associated with a reduction in adiponectin, which favors severe liver inflammation and, ultimately, hepatic steatosis [7, 8]. This condition is exacerbated by the upregulation of insulin-like growth factor-1 (IGF1), which promotes cellular proliferation within the liver, thereby leading to liver cancer. While annual global deaths due to liver disease are at their peak, the number of U.S. Food and Drug Administration (FDA)-approved drugs for the treatment of these diseases is low. Considering this situation, the exploration of all possible natural products and the determination of their therapeutic efficacy could be a treatment option without any side effects.

Eastern societies have long used natural products as liver disease remedies, which has attracted the attention of Western medical practitioners [9]. In addition, desirable outcomes are lacking with the available drugs, such as antihyperlipidemic or anti-inflammatory drugs, for treating liver diseases [10]. Therefore, more attention is being given to the efficacy of natural products as alternatives to restore liver function.

Mangiferin is used extensively against several lifestyle-associated disorders. It can be extracted from several parts of mango (*Mangifera indica*) fruits, including peels, kernels, and seeds, and it can possess diverse health-endorsing properties, including anti-inflammatory, antimicrobial, antidiabetic, antiallergic, antioxidant, anticancer, immunoregulatory and hypercholesterolemic properties. Mangiferin, a naturally occurring xanthone derivative with the chemical structure of 1,3,6,7-tetrahydroxyxanthone-C2-beta-D-glucoside (Figure 1), has been extensively studied for its wide range of pharmacological actions involving antioxidant properties. The antioxidant capability of mangiferin is associated primarily with its unique chemical structure, which facilitates the formation of stable complexes with metal ions, specifically ferric iron [Fe(III)] [11].

Researchers have demonstrated that mangiferin has a dual mechanism to protect against iron-induced oxidative damage. It successfully chelates Fe(III), preventing its reduction to Fe(II), a process that is important in the Fenton reaction and is likely to produce highly reactive hydroxyl radicals (•OH). With the maintenance of iron in its ferric state, mangiferin mitigates the availability of Fe(II) for redox cycling and the subsequent formation of reactive oxygen species (ROS). This chelation mechanism was confirmed through experiments showing that mangiferin significantly inhibits 2-deoxyribose degradation induced by Fe(III)–EDTA/citrate plus ascorbate, indicating that it forms a stable iron–mangiferin complex that reduces oxidative damage [12].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that controls antioxidant protein expression. Nrf2 is separated from its inhibitor, Kelch-like ECH-associated protein 1 (Keap1), under oxidative stress or in the presence of electrophiles and then translocates into the nucleus. Eventually, once in the nucleus, Nrf2 attaches to the antioxidant response element (ARE) in target gene promoter regions. In addition, phase II detoxifying enzymes such as NAD(P)H, oxidoreductase 1 (NQO1), and glutathione S-transferases (GSTs) are expressed.

In one study, mangiferin treatment increased the nuclear translocation of Nrf2 and increased the expression of NQO1 to provide protective effects against oxidative stress and DNA damage. Mangiferin also has antioxidant effects by directly binding to ferric iron, which neutralizes free radicals without depending on the Nrf2 pathway. Furthermore, it may increase the activity of other antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), through mechanisms involving

dissociation from Nrf2. Mangiferin also has anti-inflammatory properties, mitigating oxidative stress and DNA damage by suppressing proinflammatory cytokines and other inflammation-associated pathways independent of Nrf2 [13]. Recently, the renoprotective effects of mangiferin have been reviewed [14]. In addition, by blocking lipid peroxidation, it acts as a protective agent against a range of life-threatening cancers, including breast, colon, lung, and brain cancers. The enormous free-radical scavenging ability of mangiferin originates from the connection [15] of the polyhydroxy groups and the C-glucosyl linkages in mangiferin. The protective mechanism of the polyphenol mangiferin is associated with the suppression of nuclear factor kappa B (NF-κB) and the simultaneous activation of several transcription factors, such as Nrf-2 [16-18].

Oral administration of this polyphenol tends to convert mangiferin into active metabolites such as norathyriol, 1,7-dihydroxyxanthone, 1,3,6-trihydroxy-7-methoxyxanthone, 1,3,7-trihydroxyxanthone, and 1,3,6,7-tetrahydroxyxanthone [19]. Norathyriol ameliorates lipid metabolism by activating AMP-activated protein kinase (AMPK), sirtuin-1 (SIRT-1), and liver kinase B1, which together lead to protection against hepatic lipid metabolic disorders [20]. Clinical trials in different animal models and humans have shown significant improvements in carbohydrate metabolism, lipid metabolism, and protection against liver injury and fibrosis [21].

Therefore, the current review summarized the therapeutic or pharmacological potential of mangiferin against the pathologic conditions associated with liver diseases and explored its potential as a promising/novel drug candidate on the basis of its desirable properties. Furthermore, the study design incorporated the protective mechanisms of mangiferin against liver diseases with respect to clinical trials, doses, and molecular consequences.

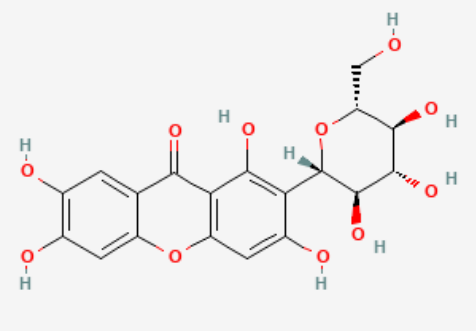

Figure 1. Chemical structure of mangiferin (C19H18O11) [19].

METHODS

The literature was collected from published online research databases (1999--2023), such as PubMed and Google Scholar, using the keywords 'mangiferin on liver diseases' and 'mangiferin on oxidative stress', 'mangiferin on inflammation' and 'mangiferin on apoptosis'. All figures were generated via Adobe Illustrator.

MANGIFERIN AGAINST PATHOLOGICAL CONDITIONS OF LIVER DISEASES

The pharmacological potential of mangiferin against several possible pathological conditions, including oxidative stress, inflammation, fibrosis, ER stress, and other pathologies related to liver disorders, is summarized and presented in Tables 1-3 and Figure 2.

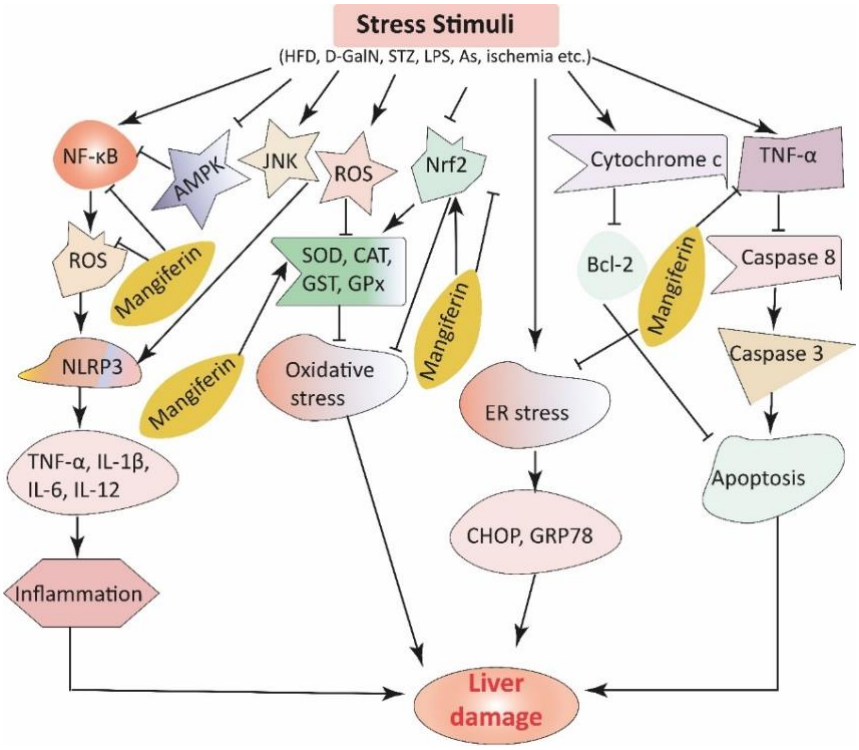

Figure 2. Summary of the protective mechanisms of mangiferin against liver disease. Stress stimuli such as HFD, D-GalN, STZ, LPS, As, and ischemia trigger the generation of ROS, which reduce the levels of several antioxidant enzymes (SOD, CAT, GST, GPx) and hence cause oxidative stress, ultimately resulting in liver diseases. Mangiferin intercepts oxidative stress by increasing the level of antioxidant enzymes. In addition, these stimuli also trigger inflammatory cascades via the activation of the NF-κB pathway. Nevertheless, mangiferin blocks inflammatory cascades via the suppression of ROS and the NF-κB pathway. The production of cytochrome C decreases the expression of Bcl-2, thus decreasing apoptosis. Mangiferin also inhibits ER stress by suppressing CHOP and GRP78. Furthermore, after the activation of TNF-α, it helps to activate caspase compounds, resulting in apoptosis, and mangiferin inhibits this apoptosis in the liver.

Table 1. Pharmacological effects of pretreated mangiferin in vivo.

Animals	Toxins	MGF Dose	Duration	Molecular Results	Ref.
Swiss albino mice	$CdCl_2$	2.5 mg/kg; i.p.	30 d	Antioxidants (GSH, GST, SOD, CAT)↑	[22]
Male BALB/c mice	LPS	1–200 mg/kg	1 h	Inflammation (TNF-α)↓ Oxidative stress (ROS)↓	[23]
Male C57BL/6 mice	Acetaminophen	12.5–50 mg/kg; i.p.	1 h	Antioxidants (GSH, SOD)↑ Oxidative stress (ROS)↓ AMPK activation ↑ Inflammation (TNF-α, MCP-1, CXCL-1, JNK, CXCL-2, IL-1β, IL-6)↓	[24]
Male Wistar rats	IR	20 mg/kg; i.p.	3 d	Apoptosis (Caspase-3↓, Bcl-2)↑ Inflammation (NF-κB-p65, IL-1β, IL-6)↓ Antioxidants (GST)↑ Oxidative stress (MDA)↓	[25]
Female Wistar rats	Iron-dextran	40 mg/kg; orally	7 d	Antioxidants (GPx, GSH, SOD)↑	[26]
Male albino rats	CCl_4	30 and 60 mg/kg; p.o.	7 d	Antioxidants (GSH, GPx, GST, GRD, TBARS, SOD, CAT)↑	[27]
Male and female albino rats	CCl_4	60 mg/kg; p.o.	7 d	Antioxidants (GSH, SOD, CAT)↑	[28]
Male BALB/c mice	LPS (50 lg/kg) and D-GalN (800 mg/kg).	5, 10 and 20 mg/kg; (intragastric)	8 h	ER stress (CHOP, GRP78) ↓ miR-20a/miR-101a↓ Nrf2↑	[29]

AMPK; AMP-activated protein kinase, Bcl-2; B-cell lymphoma 2, caspases; cysteine aspartases, CAT; catalase, CCl4; carbon tetrachloride, CdCl2; cadmium chloride, CXCL; chemokine (C-X-C motif) ligand, D-GalN; D-galactosamine, GPx; glutathione peroxidase, GRD; glutathione reductase, GRP78; glucose-regulated protein 78, GSH; glutathione, GST; glutathione S-transferase, i.e.; intragastric, i.p.; intraperitoneal, ILs; interleukin, IR; ischemia-reperfusion, LPS; lipopolysaccharide, MCP-1; monocyte chemoattractant protein-1, MDA; malondialdehyde, NFκB; nuclear factor kappa β, Nrf2; nuclear erythroid 2–related factor 2, ROS; reactive oxygen species; SOD; superoxide dismutase, STZ; streptozotocin, TBARS; thiobarbituric acid reactive substances, TNF; tumor necrosis factor.

Table 2. Pharmacological effects of posttreatment with mangiferin in vivo.

Animals	Toxins	MGF Dose	Duration	Molecular Results	Ref.
Male Wistar rats	STZ	20 mg/kg; i.p.	28 d	Inflammation (TNFα)↓	[30]
Male albino Wistar rats	STZ	40 mg/kg; orally	30 d	Antioxidants (GSH, CAT, SOD, GPx)↑	[31]
Male Swiss albino rats	D-GalN	5, 10, 20 and 25 mg/kg; i.p.	14 d	Oxidative stress (ROS) ↓ Antioxidants (GSH)↑ Inflammation (TNFα, NF-κB, IFN-γ, IL1β, IL6, IL12, IL18)↓	[32]
Albino Wistar rats	Ethanol	50 mg/kg; orally	8 weeks	Antioxidants (SOD, CAT)↑	[33]
Male SD rats	STZ	0.12 g/kg; orally	28 d	Inflammation (NF-kB)↓	[34]
SD rats	SM	30, 60 and 120 mg/kg	7 d	Antioxidants (GSH)↑	[35]
Male SD rats	HFD	300 mg/kg; orally	13 weeks	Antioxidants (GSH)↑ Lipid accumulation (TG, TC)↓	[36]
Male golden Syrian hamsters	HFD	150 mg/kg; orally	8 weeks	Lipid accumulation (TG)↓	[37]
Male ZDF rats	Water extracted from the root	100 mg/kg; orally	6 weeks	Inflammation (NF-κB)↓ Lipid accumulation (TG, TC)↓	[38]
Male Wistar rats	$NaAsO_2$	40 mg/kg;	6 weeks	Antioxidants (GSH, GSSG)↑ Oxidative stress (ROS)↓ Inflammation (TNFα)↓ Apoptosis (cytochrome c, Bax, Caspase 3, Caspase 9, Caspase 12)↓	[39]
Male SD rats	Alcohol	50-100 mg/kg/d; i.g.	12 weeks	Antioxidants (SOD, GSH-PX, CAT)↑ Inflammation (NF-κB p65, NLRP3, IL-1, IL-8, IL-1β)↓ Oxidative stress (ROS, MDA)↓	[40]
Male weanling Wistar rats	Cafeteria diet	250, 40 mg/kg	8 d	Inflammation (NF-κB)↓ Antioxidants (SOD)↑ Oxidative stress (MDA)↓	[41]
Male Kunming mice	HFD	15, 30, and 60 mg/kg; i.p.	12 weeks	Inflammation (NF-κB, JNK)↓ Lipid accumulation (TG, TC)↓	[42]
Male albino rats	STZ	50 and 100 mg/kg; orally	15 d	Antioxidants (GSH, SOD, CAT)↑	[43]
Male BALB/c mice	LPS and D-GalN	5, 10 and 20 mg/kg; i.p.	1 h	Inflammation (IL-1β, NLRP3, TNF-α, MCP-1)↓ Oxidative stress (MDA, ROS)↓ Apoptosis (Caspase-1)↓ Nrf2↑	[44]
Male SD rats	STZ	40 mg/kg	28 d	Antioxidants (Catalase, SOD, GPx, GST, and GSH)↑ Oxidative stress (MDA)↓	[45]
Wistar albino rats	STZ	20 mg/kg; orally	20 d	Lipid accumulation (TG, TC)↑ Oxidative stress (MDA)↓ Antioxidants (SOD, GSH, CAT)↑	[46]
Male albino mice	$Pb(NO_3)_2$	100 mg/kg; orally	6 d	Oxidative stress (MDA, ROS)↓ Antioxidants (CAT, SOD, GST, GPX, GRD)↑ Inflammation (NF-κB)↓ Apoptosis (Bax↓, Bcl-2↑) Anti-apoptotic proteins (Bcl-2)↑	[47]
Male Sprague Dawley rats	Iron dextran	50, 100, or 200 mg/kg; orally	4 weeks	Antioxidants (SOD)↑	[48]
Male C57BL/6J mice	HFD	25, 50 and 100 mg/kg/d; i.g.	12 weeks	Inflammation (NLRP3, NF-κB, IL-1β)↓	[49]

Bax; BCL2 Associated X, Bcl-2; B-cell lymphoma 2, Caspases; Cysteine aspartases, CAT; catalase, D-GalN; D-galactosamine, GPx; glutathione peroxidase, GRD; glutathione reductase, GSH; glutathione, GSSG; Glutathione disulfide, GST; glutathione S-transferase, HFD; high-fat diet, i.g., intragastric, i.p.; intraperitoneal, IL; Interleukin, JNK; c-Jun N-terminal kinase, LPS; SM; Sulfar mustard, MCP-1; Monocyte chemoattractant protein-1, MDA; malondialdehyde, NaAsO2; Sodium Arsenite, NLRP3; NLR family pyrin domain containing 3, Nrf2; Nuclear erythroid 2–related factor 2, Pb(NO3)2; Lead(II) nitrate, SD; Sprague Dawley, SOD; superoxide dismutase, STZ; Streptozotocin, TC; Total cholesterol, TG; Triglyceride, TNF; Tumor Necrosis Factor, ZDF; Zucker diabetic fatty.

Table 3. Pharmacological effects of mangiferin in vitro.

Cell lines	Model drug (Toxins)	MGF dose	Treatment duration	Results	Ref
HepG2 cells	AGE-HSA	10 μM	2 h	Inflammation (NF-κB)↓	[50]
HepG2 cells	$NaAsO_2$	0 - 50 μM		Inflammation (TNF-α)↓	[39]
HepG2 cells		10, 20, 40, and 80 μM	24 h	Antioxidants (Catalase, SOD, GPx, GST, GSH)↑ Oxidative stress (MDA)↓	[45]
HepG2 cells	NAFLD	400 μM	24 h	Inflammasome (NLRP3)↓	[49]
Primary hepatocytes	GalN	100 nM	12 h	Oxidative stress (ROS)↓ Apoptosis (Caspase 3)↓ Nrf2↑	[32]
SCRHs	TA3	10-200 μg/ml	2 h	Oxidative stress (ROS) ↓	[51]
Primary hepatocytes	LPS	12.5, 25 and 50 μM	1 h	Inflammation TNF-α and IL-1β ↓	[44]
Primary hepatocytes	$Pb(NO_3)_2$	30, 40, 50, 60, 70 and 80 μg/ml	2 h	Antioxidants (GPx, GST, CAT, SOD)↑ Inflammation (NF-κB)↓ Apoptosis (Bcl-2↑, Bax↓)	[47]
Rat liver mitochondria	Fe^{2+}- citrate	10 μM	20 min	Antioxidants (SOD, CAT)↑ Oxidative stress (MDA, ROS)↓	[11]
Primary hepatocytes	LPS	-	24 h	ER stress (CHOP, GRP78) ↓ miR-20a/miR-101a↓ Nrf2↑	[52]

AGE-HSA; Advanced glycation end products-Human serum albumin, CCl4; Carbon tetrachloride, D-GalN; D-galactosamine, FFA(II) nitrate, Bcl-2; B-cell lymphoma 2, GPx; glutathione peroxidase, GSH; glutathione, GST; glutathione S-transferase, LPS; lipopolysaccharide, MDA; malondialdehyde, NaAsO2; Sodium arsenite, NAFLD; Nonalcoholic fatty liver disease, NFκB; Nuclear factor kappa B, NLRP3; NLR family pyrin domain containing 3, ROI; Reactive oxygen intermediates, ROS; Reactive oxygen species, SCRHs; sandwich configuration of cultured rat hepatocytes, SOD; superoxide dismutase, TG; Triglyceride, TNF; Tumor Necrosis Factor, TPA; 12-O-tetradecanoylphorbol-13-acetate.

Liver inflammation

Hepatic inflammation is a complex process that occurs in response to different stress conditions and is associated with most acute and chronic liver disorders. Depending on different types of factors, inflammation can be beneficial or harmful to the liver. A mild inflammatory response induces hepatoprotective effects, tissue repair, and homeostasis mechanisms, whereas excessive inflammation triggers the loss of hepatocytes and liver disorders [53, 54]. This phenomenon damages hepatocytes and instigates inflammatory responses, thus causing inflammation and cell death [55]. D-galactosamine (D-GalN) is recognized as a hepatotoxin generally used to induce liver inflammation via NF-κB-dependent iNOS overexpression and other proinflammatory cytokines, such as TNF-α, interleukin-1-beta (IL-1β) and IL-6 [32, 44]. High-fat diets (HFDs) and lipopolysaccharides (LPSs) also stimulate the production of different inflammatory mediators [41, 44]. Studies have shown that the majority of proinflammatory cytokine- and inflammatory enzyme-encoding genes are regulated predominantly by NF-κB, which is the key inflammatory protein [24, 32]. NLR family pyrin domain containing 3 (NLRP3) is a Nod-like receptor that forms an inflammasome along with its adaptor proteins, and its activation is caused by ROS [49]. The NLRP3 inflammasome is also associated with the pathogenesis of liver damage. After the activation of NLRP3, it engages the adaptor apoptosis-associated speck-like protein containing a CARD ASC, which further recruits procaspase-1, which ultimately contributes to the maturation of the inflammatory mediator IL-1β [44]. NLRP3 activation activates caspase-1; thus, the proinflammatory cytokines pro-IL-1β and pro-IL-18 are activated and trigger the release of mature inflammatory mediators, leading to an inflammatory cascade [49]. In addition, saturated fatty acid and adipose tissue disturbances lead to an inflammatory response along with the generation of inflammatory chemokines and cytokines in the liver. The inflammatory pathways, which include the NF-κB and c-Jun N-terminal

protein kinase (JNK) pathways, are associated with hepatic inflammation and the pathogenesis of inflammatory liver injury [42]. Lead is a hazardous metal that causes hepatic damage. Moreover, nitrate [$Pb(NO_3)_2$] and N-acetyl-q-benzoquinone imine (NAQPI), the reactive intermediate compounds from lead [Pb(II)] and acetaminophen, respectively, instigate the generation of ROS and JNK activation; thus, ROS trigger inflammation [24, 31, 47].

However, mangiferin plays an important role in protecting the liver from various inflammatory modulators. One study revealed that 5-25 mg/kg mangiferin treatment for 14 d minimized the expression of proinflammatory cytokines (TNF-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, and IL-10) in male Swiss albino rats. This hepatoprotective role of mangiferin occurred because of the reduction in inflammation caused by the inhibition of NF-kB [32]. Doses of 5, 10, 20, and 25 mg/kg mangiferin reduce the expression of inflammatory cytokines in D-GalN-induced rats [32]. In male Zucker diabetic fatty (ZDF) rats, treatment with 100 mg/kg mangiferin for 6 weeks reduced liver inflammation through the suppression of NF-κB [38]. Furthermore, the administration of 250 mg/kg leaf extract and 40 mg/kg mangiferin to male weanling Wistar rats fed streptozotocin (STZ) for 8 d suppressed NF-kB protein expression and protected the liver against inflammation, as it has anti-inflammatory activity [41]. Another study showed that in male Kunming HFD-fed mice, 15, 30, and 60 mg/kg mangiferin for 12 weeks alleviated the liver by inhibiting the inflammatory responses of the cytokines NF-κB and JNK [42]. The administration of 100 mg/kg mangiferin for 6 d in $Pb(NO_3)_2$-treated male albino mice minimized the level of NF-κB [47]. Because of its anti-inflammatory mechanism, mangiferin alleviated LPS/D-GalN-induced NLRP3 inflammasome expression. In D-GalN-induced male BALB/c mice, the administration of 5, 10, or 20 mg/kg mangiferin for 1 h reduced the expression of IL-1β, NLRP3, TNF-α, and MCP-1 [44]. In addition, after treatment with 12.5−50 mg/kg mangiferin for 12 h in acetaminophen-induced male C57BL/6 mice, the mRNA levels of TNF-α, MCP-1, IL-1β, IL-6, NF-κB, CXC chemokine ligand-1 and CXC chemokine ligand-2 (CXCL-1 and CXCL-2) were decreased [24]. Moreover, treatment with 25, 50, or 100 mg/kg mangiferin in HFD-fed male C57BL/6J mice for 12 weeks alleviated the expression of NLRP3, NF-κB, and IL-1β, thus mitigating liver inflammation. In addition, treatment with 12.5, 25, or 50 μM mangiferin for 1 h reduced inflammation by reducing the levels of TNF-α and IL-1β in primary hepatocytes [44]. Treatment with mangiferin at 100 mg/kg/d and 100 μM reduced the activity of the NLRP3 inflammasome in NAFLD model mice and HepG2 cells, respectively [49].

Liver oxidative stress

Oxidative stress is a key factor in a wide range of liver disorders [39, 56]. Cellular and molecular investigations revealed that the increase in oxidative stress is due to the overproduction of ROS and the depletion of antioxidants [22, 32, 39]. Furthermore, the functions of modified antioxidant enzymes, such as SOD, CAT, glutathione peroxidase (GPx), and glutathione (GSH) metabolism, cause an imbalance in the action of oxidant or antioxidant defense systems, thus contributing to the overproduction of ROS [31]. Chronic hyperglycemia and the cytotoxic action of STZ trigger ROS production, which results in oxidative tissue damage. In living organisms, antioxidant enzymes and nonenzymatic antioxidants act as the first line of defense against ROS-induced oxidative stress [31]. Nrf2 affects genes encoding antioxidant proteins. Nrf2 responds to oxidative stress from the cytosol and translocates toward the nucleus, where the cytoprotective response is produced after the sequential binding of Nrf2 to the ARE.

Thus, this increases the level of antioxidant enzymes and reduces the degree of oxidative stress damage [32, 57].

In the cafeteria, diet-fed male weanling Wistar rats treated with 250 mg/kg leaf extract and 40 mg/kg mangiferin for 8 d presented increased SOD and decreased malondialdehyde (MDA) contents [41]. In STZ-induced male albino Wistar rats, 40 mg/kg mangiferin for 30 d increased the expression levels of antioxidants (GSH, CAT, SOD, GPx) [31]. The administration of 50 mg/kg mangiferin in ethanol-treated Albino Wistar rats for 8 weeks upregulated the levels of SOD and CAT antioxidants [33]. In Sprague-Dawley (SD) rats treated with SM, 30, 60, or 120 mg/kg mangiferin for 7 d, the expression of the antioxidant GSH increased [35]. The use of 300 mg/kg mangiferin for 13 weeks mitigated oxidative stress by increasing GSH levels in HFD-fed male SD rats [36]. After treatment with 1-200 mg/kg mangiferin for 1 h or for 7 d in LPS-triggered male BALB/c mice, oxidative stress was reduced through the suppression of excess ROS [23]. In alcohol-treated male SD rats, 50–100 mg/kg mangiferin upregulated the levels of antioxidants (SOD, GSH-PX, and CAT) and decreased oxidative stress by mitigating the levels of ROS and MDA [17, 20]. In male albino rats induced with STZ, the administration of mangiferin (50 and 100 mg/kg) orally for 15 d increased the contents of GSH, SOD, and CAT [43]. Treatment with 100 mg/kg mangiferin in Pb(NO3)2-induced male albino mice for 6 d inhibited oxidative stress via a reduction in the contents of MDA and ROS and increased the levels of the antioxidants CAT, SOD, GST, GPX, and glutathione reductase (GRD) [47]. Doses of 20 mg/kg mangiferin for 3 d in IR-induced male Wistar rats for 3 d increased the GST content and decreased the content of MDA, thus mitigating oxidative stress [25]. In iron-dextran-treated female Wistar rats treated with 40 mg/kg mangiferin for 7 d, the liver antioxidant enzymes GPx, GSH, and SOD were upregulated [26]. The levels of liver antioxidants (CAT, SOD, GPx, GST, and GSH) were alleviated, and the MDA level was reduced by treatment with 40 mg/kg mangiferin for 28 d in STZ-treated male SD rats [45]. In a previous study, oxidative stress was decreased in STZ-treated Wistar albino rats treated with 20 mg/kg mangiferin for 20 d through downregulation of MDA and upregulation of antioxidants (SOD, GSH, and CAT) [46]. With the administration of 30 and 60 mg/kg mangiferin for 7 d in CCl4-treated male albino rats, liver antioxidants such as GSH, GPx, GST, GRD, thiobarbituric acid reactive substances (TBARS), SOD, and CAT are increased [27]. In CCl4-treated male and female albino rats, treatment with 60 mg/kg mangiferin for 7 d upregulated the levels of the antioxidants GSH, SOD, and CAT in the liver [28]. In TA3-induced male SD rats, 10-200 μg/ml mangiferin for 2 hours minimizes oxidative stress through the suppression of the overproduction of ROS in the liver in the sandwich configuration of cultured rat hepatocytes (SCRHs) [51]. In addition, treatment with 100 nM mangiferin for 12 h reduces oxidative damage by alleviating the expression level of the transcription factor Nrf2 in hepatocytes [32]. The administration of mangiferin (10 μM) for 20 minutes in Fe2+- citrate-treated rats facilitated the expression of SOD and CAT and alleviated the levels of MDA and ROS, hence reducing oxidative damage in rat liver mitochondria [11]. In the liver, oxidative stress was mitigated by increasing the SOD content via treatment with 50, 100, or 200 mg/kg mangiferin for 4 weeks in iron dextran-treated male SD rats [48].

Endoplasmic reticulum stress in the liver

ER stress is characterized by the accumulation of misfolded proteins within the lumen of the ER [58]. It is commonly instigated during the development of solid tumors and stage progression [59]. Various factors, such as nutrient deficiencies, hypoxia, and breakdown of calcium, can affect the homeostasis of this compartment, thereby causing

ER stress and triggering unfolded protein response (UPR) activation. The UPR is a complex signaling network that is mediated by three ER transmembrane stress sensors: inositol-requiring enzyme 1α (IRE1α), pancreatic endoplasmic reticulum kinase (PERK), and transcription factor 6 activation (ATF6) in mammalian cells [59-63].

ER stress has been demonstrated to occur during acute liver injury induced by LPS and D-GalN. Extensive ER stress instigates liver damage through cell apoptosis, steatosis, or an inflammatory response [29, 52]. ER homeostasis is associated with lipid metabolism [64, 65]. ER stress and the UPR are involved in the pathogenesis of human diseases such as liver disease [64]. NAFLD is currently the leading cause of liver abnormalities in the United States and Western countries. ALD and NAFLD are diseases linked with triglyceride accumulation in hepatocytes and involve hepatic steatosis to progressive nonalcoholic steatohepatitis (NASH), leading to progressive liver damage, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [64, 66, 67]. Alcohol-related ROS accumulation increases hepatic CYP2E1 (CYP2E1) expression, decreases the S-adenosylmethionine/S-adenosylhomocysteine ratio, elevates homocysteine levels in the blood, and epigenetic regulation is the only factor that might cause ER stress. Eventually, ER stress and UPR pathway activation are observed in the livers of chronic ALD patients as well as in a variety of experimental ALD models [64, 65, 68]. Peroxisomes are small organelles located in the cytoplasm of cells. Peroxisome deficiency triggers lipid metabolism disruption, such as fatty acid oxidation, in human patients and animal models of peroxisomal biogenesis disorders [69, 70]. In both the presence and absence of an HFD, ER stress regulates peroxisomal redox imbalance-induced hepatic steatosis and NAFLD in catalase mutant mice [69].

MicroRNAs (miRNAs), such as miR-144-3p, directly target Nrf2 to modify cisplatin resistance in lung cancer, and miR-340-5p may act as a direct mediator of Nrf2 in the postexercise skeletal muscle of mice, indicating that miRNAs may regulate Nrf2 expression [29, 71]. Several studies have shown that mangiferin reduces LPS/DGalN-induced acute liver injury via activation of the miR-20a/miR-101a-Nrf2 axis pathway [44].

Recently, mangiferin was shown to protect against ER stress by regulating the miR-20a/miR-101a-Nrf2 axis and restoring hepatic function in mice [29]. Furthermore, mangiferin attenuated the ER stress-related NLRP3 inflammasome by controlling AMPK activity in perivascular adipose tissue in rats [72].

Other pathologies in the liver

The peroxisome proliferator-activated receptor PPAR-α is known as a nuclear receptor that conserves the homeostasis of lipid metabolism, and mangiferin has an important role in activating PPAR-α [38]. NAFLD decreases the autophagy pathway that controls autophagy as well as lipid metabolism by mitigating the AMPK/mechanistic target of the rapamycin (mTOR) signaling pathway [42]. AMPK acts as a major mediator of energy metabolic homeostasis and assists in the protection of mitochondria. The phosphorylation of AMPK inhibits NF-κB signaling and, hence, inflammation via the activation of sirtuin-1, the forkhead box O family, and peroxisome proliferator-activated receptor γ coactivator 1α. Mangiferin improved AMPK activation [24]. Akt is a pluripotent molecule and another kinase, ERK1/2 that plays a key role in preventing hepatotoxicity and is dwindled in the arsenic-administered liver, and mangiferin ameliorated the expression levels of Akt and ERK1/2 due to its anti-apoptotic activity [39].

Administration of 1, 5, 10, or 20 mg/kg mangiferin for 1 hour reduced apoptosis in LPS- and D-GalN-treated male BALB/c mice [44]. Supplementation with 100 mg/kg mangiferin for 6 d prevented Pb(II)-induced apoptotic death and protected hepatocytes in male albino mice via the inhibition of BCL2 Associated X (Bax) and the upregulation of the anti-apoptotic marker Bcl-2 [47]. Mangiferin at 100 mg/kg and 150 mg/kg prevented lipid accumulation through the suppression of plasma triglyceride (TG) and total cholesterol (TC) levels in male ZDF rats and golden Syrian hamsters, respectively [37]. In response to mangiferin supplementation, the expression of TNF-α was mitigated concomitantly with decreased expression of downstream extramitochondrial apoptotic cascades, such as TNF-α, cytochrome c, Bax, caspase 3, caspase 9, caspase 12, TRADD, and caspase 8, in $NaAsO_2$-treated male Wistar rats treated with 40 mg/kg mangiferin for 6 weeks because of the anti-apoptotic activities of mangiferin [39]. Pretreatment with 20 mg/kg mangiferin enhanced Bcl-2 and downregulated caspase 3 due to its anti-apoptotic effect on IR-induced male Wistar rats [25]. In addition, 100 nM mangiferin treatment for 12 hours in D-GalN-treated hepatocytes protected the liver by inhibiting the expression of caspase 3 and reducing apoptosis [32].

PHARMACOLOGICAL ADVANCES IN MANGIFERIN IN LIVER DISEASES

Mangiferin reportedly ameliorates alcohol-induced liver injuries. Although the exact molecular mechanism is unclear, mangiferin restores PDE3B stability, consequently reducing fatty acid release by activating AMPK/TBK1 signaling and diminishing noncanonical NF-κB activation, which leads to a reduction in ethanol-induced liver injury. PDE3B is a family member of the PDE family that is found mostly in energy metabolism tissues, such as adipose 9, and may play a role in inhibiting catecholamine-induced lipolysis [29]. Mangiferin has been empirically determined to have several other pharmacological effects, including antitumor, cardioprotective, antidiabetic, neurogenerative, antipyretic, anti-inflammatory, and cytotoxic effects [17]. Although mangiferin is a natural constituent with limited adverse effects, it has not been used clinically for several reasons, such as disparaging solubility, poor oral absorption, and low bioavailability [73]. The development and modification of mangiferin-based derivatives have become current research hotspots for improving mangiferin solubility and establishing mangiferin as a clinical drug. Various mangiferin adjuvants, including incorporated nanoparticles and mangiferin, have been developed, and their efficacy has been determined in many animal studies. Soft nanoparticles of mangiferin complexed with self-assembled phospholipids were designed. These nanoparticles improved the oral solubility, bioavailability, and overall efficacy of mangiferin [28]. Mangiferin calcium salt (MCS) was developed, and its oral absorption effects were analyzed in type 2 diabetes and NAFLD rats. MCS was found to improve the condition of type 2 diabetes and NAFLD rats more effectively than mangiferin by regulating glucose and lipid metabolism [74]. In addition to its pharmacological effects on liver, kidney, and heart disease, it can be used to counteract skin infections. In a vesicular system, plurethosomes for mangiferin based on the block copolymer pluronic and phosphatidylcholine were designed for application in skin orders induced by environmental pollutants such as ozone [75]. Mangiferin-alginate-grafted N-succinylated chitosan (NSC) nanoconjugate was also developed to test its effectiveness in reducing TC, blood glucose, TG, and hyperlipidemia [76]. The pharmacological effects of mangiferin with adjuvants are summarized and represented in Table 4.

Table 4. The pharmacological effect of mangiferin with adjuvants.

Animals	MGF adjuvants	Dose	Duration	Results	Ref
Albino Wistar rats	Phospholipon® 90H, Soft nanoparticles	60 mg/kg; p.o.	7 days	Oral bioavailability ↑ Antioxidant (SOD, CAT, GSH) ↑ Oxidative stress (LPO) ↓	[28]
SD rats	Calcium salt	60, 240, and 960 mg/kg; gavage	7 days	Oral bioavailability ↑ Lipid Accumulation (TG, TC) ↓	[74]
Wistar rats	N-succinylated chitosan	10 mg/kg; orally	28 days	Lipid Accumulation (TG, TC) ↓	[76]

CAT; catalase, GSH; glutathione, LPO; lipid peroxidase, SD; Sprague Dawley, SOD; superoxide dismutase, TC; total cholesterol, TG; triglyceride.

CONCLUSIONS AND FUTURE PROSPECTS

The accumulation of different kinds of toxic compounds is associated with reduced liver function, hence triggering liver diseases. Thus, proper treatment might ameliorate the liver condition and function of the liver. Although many medications are used for the treatment of liver diseases, their use is restricted and limited due to their side effects. Therefore, the role of a natural polyphenol compound with fewer side effects has been investigated. This review suggests that mangiferin protects the liver and enhances liver function through the suppression of various host cellular factors, such as proinflammatory cytokines, oxidative markers, ER stress, and apoptotic and fibrotic factors, and reduces various comorbidities that are likely to cause liver diseases, including diabetes, ALD, NAFLD, and liver cirrhosis. The therapeutic effects of this study will be further researched in the future to determine the importance of pharmacological medications involving the use of natural compounds to treat liver diseases.

Mangiferin also has an indirect negative effect on the development of endothelial dysfunction. Mangiferin induces the secretion of exosomes by perivascular adipose tissue (PVAT), which reverses the effects of inflammation-induced endothelial dysfunction following palmitic acid (PA) treatment. Mangiferin-induced exosome production also decreases NF-ƙB signaling in endothelial cells and reduces endothelial dysfunction [77]. Mangiferin has an overall high potential as a clinical drug for various diseases, although its oral solubility limits its application. Although there should be a number of ongoing investigations, more investigations are needed for mangiferin to establish an approved clinical drug.

AUTHOR CONTRIBUTIONS

This work involved collaboration among all the authors. MJU and AM designed the outline of the manuscript. TZS, SA, MF, and MRU wrote the initial draft of the manuscript. MJU, AM, MGH, and WS reviewed the scientific contents described in the manuscript. All the authors have read and approved the final submitted version of the manuscript.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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