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Anti-fibrotic Potential of *Moringa oleifera* in Hepatic Fibrosis: Molecular Mechanisms and Pharmacological Evidence

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Abstract

Aim: The current review aims to critically analyse the antifibrotic potential of *Moringa oleifera* and summarise the molecular effects of the phytoconstituents of this compound on the hepatic pathways in fibrosis. **Methods:** The pertinent scientific literature was gathered and examined in the large electronic databases such as PubMed, Google Scholar, ScienceDirect, and Web of Science. Experimental studies that investigate the pharmacological effects of *Moringa oleifera* in hepatic fibrosis were chosen from peer-reviewed articles. The *in vitro* and *in vivo* research articles were all analysed with a focus on the oxidative stress markers, inflammatory mediators, signal pathways, and hepatic stellate cell activation in relation to fibrogenesis. **Results:** The existing preclinical research indicates ongoing availability of studies that confirm that *Moringa oleifera* possesses significant anti-fibrotic, anti-oxidant and anti-inflammatory properties. Its bioactive components, flavonoids, phenolic compounds, and isothiocyanates decrease oxidative stress by reducing lipid peroxidation marker malondialdehyde and also reinstating endogenous antioxidant defence systems, superoxide dismutase, catalase and glutathione systems. *M. oleifera* downregulates key pro-fibrotic signalling pathways at the molecular level, including TGF-β/Smad, NF-κB, and p38-MAPK. All these effects prevent hepatic stellate cell activation and reduce α-smooth muscle actin expression and collagen deposition in the extracellular matrix. Moreover, cytokine regulation, such as TNF-α, IL-1β and IL-18, also promotes the inhibition of inflammatory reactions that cause fibrosis development. **Conclusion:** All in all, recent experimental data indicate that *M. oleifera* functions in several complementary ways to inhibit fibrogenic pathways and hepatic tissue protection. Despite its promising preclinical results that show its therapeutic benefits, these findings require further well-designed clinical studies to confirm its safety, pharmacokinetics and efficacy in the treatment of human liver fibrosis.

Major Findings: There is evidence of available experiments that *Moringa oleifera* suppresses hepatic fibrosis by lowering the oxidative stress and inflammatory cytokines, including TNF- α and IL-1β. Its bioactive compounds inhibit profibrotic signals such as TGF-β/Smad and p38-MAPK signalling and inhibit the activation of hepatic stellate cells and the deposition of collagen.

Keywords: Antifibrotic Mechanisms, Hepatic Fibrosis, Hepatic Stellate Cells (HSCs), *Moringa oleifera*, Oxidative Stress, TGF-β/Smad Signalling

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1. Introduction

One of the main signs of hepatic fibrosis is chronic liver damage, which presents an abnormal response to wound healing, defined by overproduction of Extracellular Matrix (ECM) and uncharacteristic hyperplasia of connective tissue[1–3]. Liver disease progression of fibrosis has a strong influence on the prognosis of liver disease and the odds of developing Hepatocellular Carcinoma (HCC), cirrhosis and liver failure[2,4,5]. Hepatic Stellate Cells (HSCs) and inflammatory reactions to hepatocyte injury make a significant

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contribution to the progression of fibrosis[4,6,7]. The causes of fibrosis in the liver include viral hepatitis, autoimmune hepatitis, alcoholism, non-alcoholic fatty liver disease (NASH), primary biliary cholangitis, and primary bile duct cirrhosis (both internal and external factors). Liver fibrosis is an illness that is associated with inflammation, cytotoxicity, hepatic damage, and excess accumulation of fats that may initiate the inflammatory response of the liver[8–10]. The importance of advanced liver disease in the world has been highlighted in a recent meta-analysis. The research was carried out by Zamani *et al.* (2025), who reviewed 46 eligible studies that included almost 8 million individuals and spanned 21 nations and discovered that the frequency of advanced fibrosis in the broader population was 3.3%, and cirrhosis made up 1.3% (Figure 1). The study also established a strong geographic heterogeneity and an upward trend after 2016, indicating that liver fibrosis and cirrhosis remain important health concerns in the world[1].

At present, transplantation of the liver represents the best and most efficacious therapy for cirrhosis; however, its clinical applicability is low because of a lack of donors and high fees[8]. There's no particular treatment for the management of liver fibrosis, and several hepatic anti-fibrotic medicines remain in the investigation and advancement stage[11]. Many studies have recently concentrated on natural substances derived from medicinal plants that may help treat medical disorders[12]. Hepatic fibrosis can be reduced by employing therapeutic plants, extracts derived from plants, and substances that are bioactive. Plant-derived

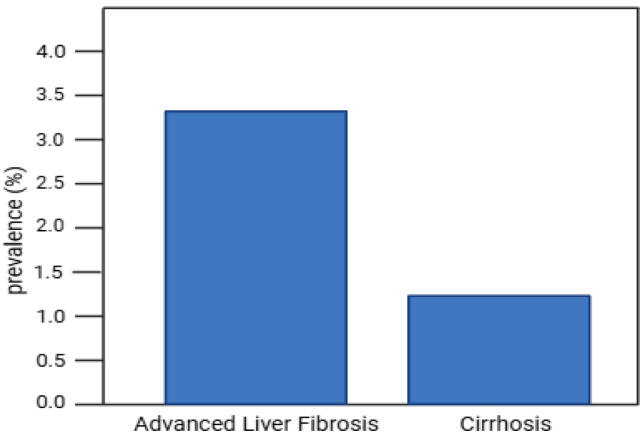


Figure 1. The global frequency of cirrhosis 1.3% and progressive fibrosis 3.3% in the general population.

compounds that prevent the activation of stellate cells and minimise ECM accumulation[13]. Extracts from herbs consist of a combination of bioactive compounds and a pharmacokinetic enhancer[14]. Therapeutic herbs and their phytochemicals can safeguard the liver via multiple mechanisms, such as the prevention of fibrogenesis, oxidative damage, and the growth of tumours[15]. These bioactive substances function through a variety of mechanisms, including the TGF-β/Smad signalling pathways, NF-κB, AMPK/mTOR, PI3K/AKT/mTOR, Wnt/β-catenin, hedgehog pathways, and other elements linked to liver fibrosis[6,13].

1.2 *Moringa oleifera*

Moringa is the only genus of flowering plants belonging to the Moringaceae family (Figure 2). Of its numerous species, *M. oleifera* Lam (*Moringa pterygosperma* G.) is mostly recognised and widely distributed, originating from India, Pakistan, Bangladesh, and Afghanistan. *M. oleifera* can thrive in any regions that are tropical or subtropical globally where temperatures range from 25 to 35°C[16] . In many countries, populations use their leaves, seed pods, and ripe seeds as vegetables[17,18]. It is also known as "drumstick tree" or "horseradish tree". Owing to its healing qualities, the plant was occasionally called "mother's best companion" or "miracle tree"[19]. Different formulations of *M. oleifera* are utilised for their anti-inflammatory, antihypertensive, diuretic, antimicrobial, antioxidant, antidiabetic, antihyperlipidemic, antineoplastic, antipyretic, and anti-ulcer properties, cardioprotective, antimicrobial, and liver-protecting effects[20]. It has been demonstrated that the protein content of *M. oleifera* leaves is comparable to that of milk and eggs[21]. It has been observed that more calcium than milk, more iron than spinach, more potassium than bananas, more vitamin C than oranges, and more vitamin A than carrots are all found in *M. oleifera*[22]. The plant is well-known in *Ayurvedic* medicine, and it has been claimed to have a range of pharmacological characteristics. Numerous recent studies have demonstrated the anti-inflammatory qualities of leaves, pods, seeds, flowers, roots, bark, and stems[17,22].

Extract from *Moringa oleifera* (MO) leaves exhibits anti-fibrotic effects by hindering the advancement of liver fibrosis via reduced production of collagen-1, TIMP-1, and α-SMA. A-SMA serves as a marker for



(a) (b)

Figure 2. **(a).** Leaf and **(b).** stem of *Moringa oleifera*.

HSCs and has a significant impact on the regulation of collagen production[23]. Leaves of the *M. oleifera* are the most effective source of extracts, particularly with water-based and alcoholic extraction techniques. They demonstrate cytotoxicity on cancer cell lines and offer protection in normal cell lines[24].

Due to their advantageous qualities, which include antioxidant, neuroprotective, hepatoprotective, antidepressant, anti-inflammatory, anticancer, wound-healing, blood glucose-lowering, antifungal and antibacterial activities, several bioactive metabolites found in *Moringa* species may be used to treat or prevent CDs. MO's versatile applications present a hopeful and long-lasting option for tackling chronic ailments, especially in circumstances with low resources[25].

1.2.1 Phytochemistry of Moringa oleifera

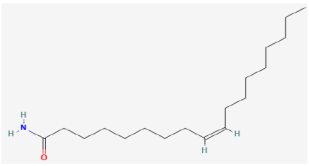
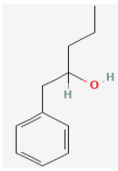
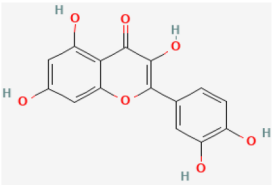
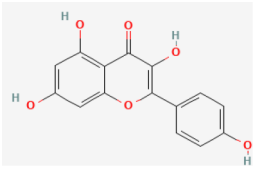
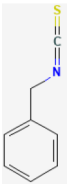
Moringa oleifera contains a lot of compounds, with key ones being carotenoids, tocopherols (α, γ, δ), polyunsaturated fatty acids, flavonoids, phenols, and numerous minerals[26,27]. Polyphenols (such as gallic acid) exhibit antidiabetic, anti-inflammatory, anti-obesity, and antioxidative properties. Chlorogenic acid (CGA) enhances antioxidant activity that is nonenzymatic. Ferulic acid serves as a powerful antioxidant that offers protection against lipid peroxidation, neutralises free radicals, and chelates Fe and Cu. Sinapic acid and p-coumaric acid have properties that are anti-inflammatory, antimicrobial, antimutagenic, antioxidant, antidiabetic, and antihyperlipidemic. Flavonoids such as quercetin have potent antioxidant characteristics, block different enzymes, reduce ROS generation, and bind to all metals involved in radical chain reactions[27] and is recognised as a potent hepatoprotective agent and is known to be an effective one (Table 2)[28]. MO contains isothiocyanates, which control signalling pathways and reduce the TNF-α and IL-1β level[17]. Nizazirin, which is present in MO seeds, is essential to their anti-inflammatory properties. MO seed extracts have flavonoids in them[29], phenolic acids, and glucosinolates[30], which help reduce protein denaturation. MIC-1, a type of glucosinolate, demonstrates potent anti-inflammatory qualities and possesses great bioavailability. Seed oil of *M. oleifera* has demonstrated a reduction in inflammatory markers associated with colitis, lung injury, and arthritis, indicating its potential to manage these disorders[31]. Several plant components, such as seeds, stems, bark, leaves, roots, flowers, and fruits, possess unique phytochemical profiles and possible therapeutic benefits (Table 1).

The entire *M. oleifera* plant has a lot of various vitamins and minerals[32–34]. Calcium is considered one of the most crucial minerals among the various minerals present in *M. oleifera* that are necessary to promote development and growth of humans. *M. oleifera* leaves that are fresh are believed to offer approximately 11,300 to 23,000 International Units of vitamin A. This

Table 1. *Moringa oleifera* phytoconstituents

Plant Part	Phytoconstituents	Biological Activity
Leaves	Quercetin, Kaempferol, Rutin, Chlorogenic acid, Oleamide, 1-Phenyl-2-pentanol	Antioxidant, Anti-fibrotic, Anti-inflammatory, Hepatoprotective[36,37]
Seeds	Moringin (benzyl isothiocyanate), Glucomoringin, Niazimicin, Seed oil (PUFAs)	Anti-fibrotic, Anticancer, Anti-inflammatory, Antioxidant[23,38]
Flowers	Flavonoids (quercetin derivatives), Alkaloids, Tannins	Antioxidant, Antimicrobial, Anti-inflammatory[26]
Pods/Fruits	Phenolic acids, Flavonoids, Saponins, Ascorbic acid	Antioxidant, Nutritional, Anti-inflammatory[39]
Roots	Alkaloids, Saponins, Terpenoids, Sterols	Analgesic, Anti-inflammatory, Antimicrobial[35]
Bark	Phenolic compounds, Sterols, Alkaloids	Antimicrobial, Antioxidant[35]

Table 2. Phytoconstituent from *Moringa oleifera* with their biological activities in liver fibrosis

Name of compound	Chemical Structure	Reported biological activity — significance to liver fibrosis
Oleamide (leaves)		prevents the phosphorylation of Smad2/3 caused by TGF-β1 in LX-2 HSCs → ↓ACTA2 (α-SMA), ↓COL1A1, ↓TIMP-1 and lowers pro-inflammatory cytokines (IL-6, IL-8). Direct anti-fibrotic activity[36,37].
1-Phenyl-2-pentanol (1-PHE) (leaves)		*in vitro* study on LX-2 cells shows inhibition of HSC activation markers (reduced α-SMA/COL1) and anti-fibrotic signalling modulation[38-40].
Quercetin (leaves)		Strongly supported anti-fibrotic actions in multiple studies: inhibits HSC activation, suppresses TGF-β1/Smad3 signalling, reduces ECM deposition and inflammation; antioxidant and anti-inflammatory — directly reduces fibrosis in CCl_4/BDL models. (Quercetin is a known major flavonoid in MO leaves)[41].
Kaempferol (leaves)		Inhibits HSC activation, reduces collagen deposition and profibrotic markers in CCl_4 models; anti-inflammatory (↓IL-6, ↓TNF-α), antioxidant — shown to attenuate liver fibrosis[42].
Moringin (benzyl isothocyanate) (Seeds)		Broad antioxidant, anti-inflammatory, chemoprotective activities; isothiocyanates modulate NF-κB, Nrf2 and other pathways — mechanistically relevant to preventing HSC activation and ECM deposition. Several *Moringa* extracts rich in these compounds show hepatoprotective/anti-fibrotic outcomes in preclinical studies[43].

vitamin is essential for various physiological functions, such as growth, development of the foetus, vision, immune system performance, division of the cell, cell growth, apoptosis, skin tissue preservation, and mental capacities[35].

1.2.2 Pathophysiology of Hepatic Fibrosis

1.2.2.1 Activation of Stellate Cells and Role of TNF-α and NF-κB Signalling in Fibrosis

Numerous hepatotoxic substances cause hepatocytes to become inflamed, converting quiescent stellate cells

(qHSC) into hepatocyte-derived stem cells (aHSC). Large numbers of extracellular matrix (ECM) proteins, primarily collagen types I and III, are produced as a result[44]. The secretion of pro-inflammatory cytokines like TNF-α is caused by macrophages in response to liver damage. These cytokines stimulate the IKK complex and start a pro-apoptotic pathway, which in turn causes inflammation via the NF-κB pathway. TNF-α stimulates HSC to become myofibroblasts, which accelerates the fibrosis process. Survival of hepatocytes, HSC, and the immunological response are all dependent on TNF-α[45].

1.2.2.2 p38-MAPK Pathway and HSC Proliferation

Certain intracellular pathways may be triggered by the cellular release of inflammatory cytokines. A significant pathway is mitogen-activated protein kinases-p38 (p38-MAPK)[46]. MAPK is essential for several disease advancements, including apoptosis, fibrosis, hypertrophy, and hepatitis[47]. Activation or phosphorylation of p38-MAPK can start the process of liver fibrosis. In addition to promoting myofibroblast differentiation, phosphorylation of p38-MAPK initiates HSC activation and proliferation. As a consequence, it could cause liver fibrosis to worsen. When an extracellular substance, such as cytokines, binds to particular receptors (TNF-αR, TGFBRI/II, and TLR), the p38-MAPK pathway is triggered[46]. G protein-coupled receptors then transmitted the signal to intracellular process activation[44].

1.2.2.3 TGF-β/Smad Pathway in Fibrogenesis

Transforming growth factor beta-1 (TGF-β1) is a fundamental mediator in several aspects, including the immunological reaction, matrix production, inflammation, cell proliferation, apoptosis and differentiation. An essential profibrotic factor is the TGF-β1 cytokine in hepatic fibrosis, and the TGF/Smad signalling pathway contributes greatly to the process of hepatic fibrosis[47,48]. MicroRNA-21 (miR-21) promotes the expression of collagen by phosphorylation of Smad2/3 and is repressed by Smad7 in this signalling pathway[49].

Excessive deposition of ECM is among the characteristics of hepatic fibrosis. Additionally, TGF-β stimulates the progression of fibrosis because it inhibits the degradation of the ECM. Besides affecting HSCs, TGF-β also contributes to immune cell homeostasis, which induces inflammatory responses to aggravate liver injury and fibrosis. Once attracted to the liver, these immune cells that contain lymphocytes and macrophages discharge pro-inflammatory cytokines that intensify fibrotic mechanisms and stimulate the HSC activation[37].

1.2.2.4 IL-1β and IL-18 Mediated Inflammation

IL-1β and IL-18 are considered potential targets associated with chronic inflammation and are believed to have a major impact on the fibrogenesis process in the liver. The NF-κβ signalling pathway is stimulated by pro-inflammatory cytokines IL-1β and IL-18, resulting in the target cell expressing certain pro-inflammatory genes. The NF-κβ transcription factor and nod-like receptor protein 3 (NLRP3) can trigger the IL-1β Profibrogenic Molecule, which significantly activates HCC. IL-18 is a cytokine that promotes inflammation and plays a role in the progression and recognition of host defence against pathogenic microbes. IL-18 can enhance the anti-inflammatory therapeutic strategy for chronic conditions. This occurs due to the natural opponents of IL-18 pro-inflammatory cytokines affected by autoimmune conditions[50].

1.2.2.5 Mitochondrial Dysfunction and ROS Accumulation

Mitochondrial impairment in MASH is caused by genetic and epigenetic influences. Overload of the FFAs exceeds the mitochondrial capacity, leading to the overproduction of ROS and oxidative stress. The additional ROS are generated through peroxisomal ω-oxidation and CYP2E1 activity. It is a dysfunction characterised by reduced mt DNA, loss of ATP, and leakage of lysosomal enzymes, which causes NF-κB and TNF-α–mediated pathways, resulting in the death of hepatocytes[51].

1.2.2.6 Oxidative Stress and Progression of Fibrosis

Another element that promotes fibrosis is oxidative stress, which participates in the advancement of hepatic fibrosis, primarily because of the overproduction of ROS, or reactive oxygen species and a diminished antioxidant capacity[52]. Proinflammatory mediators may be triggered by an unbalanced ratio of prooxidants to antioxidants caused by the continuous ROS generation. Significant oxidative stress brought on by elevated ROS ultimately results in fibrosis, HCC, NASH, and NAFLD

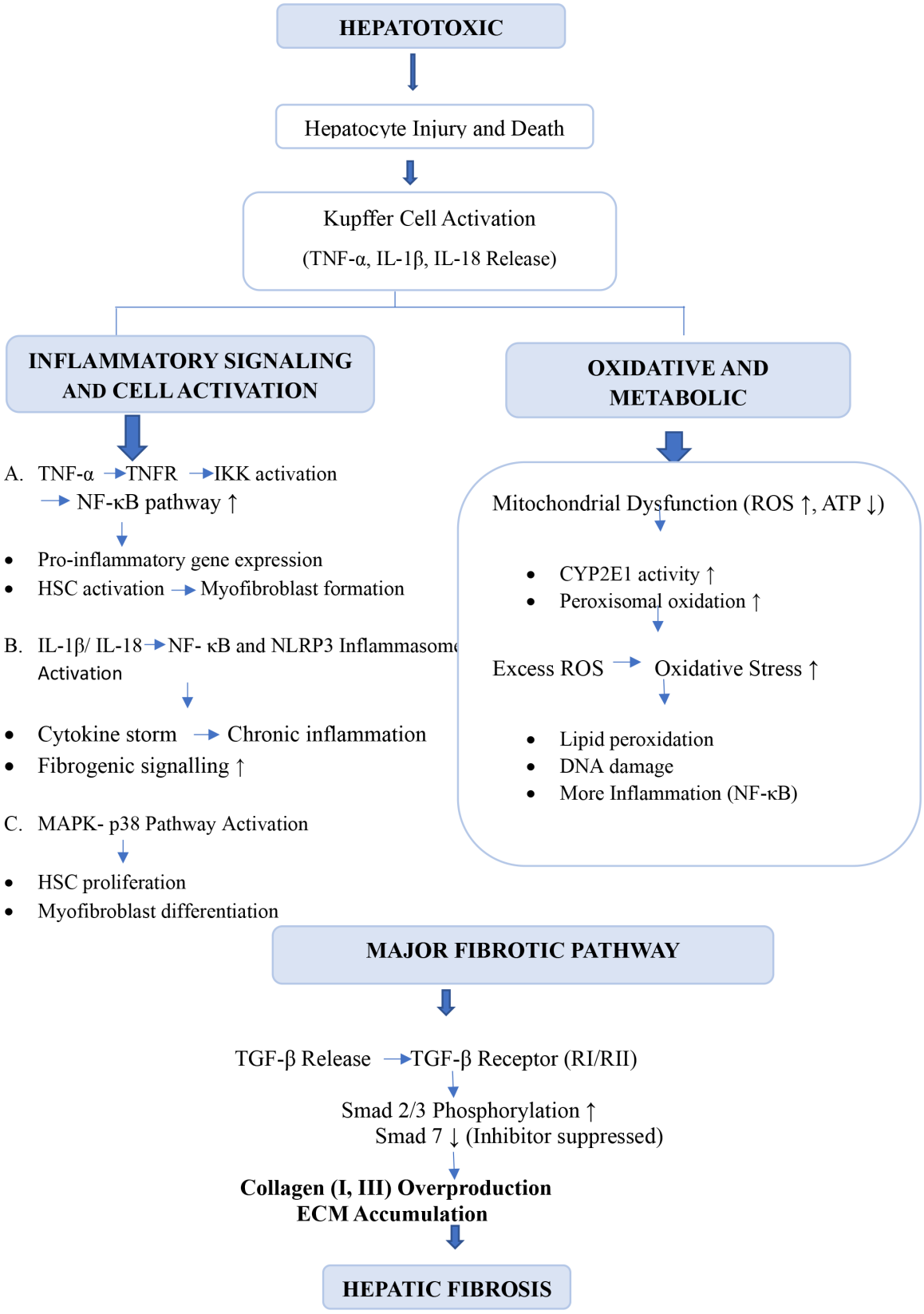


Figure 3. Liver fibrosis caused by hepatotoxicity with hepatocyte injury-mediated Kupffer cell activation, inflammatory and oxidative cell signatures, fibrogenic pathway (TGF-β1/Smad) activation, overproduction of extracellular matrix, and development of hepatic fibrosis.

in the end. External antioxidants, including flavonoids, vitamins C and E, and provitamin A, are needed to combat this illness by neutralising or lowering ROS levels (Figure 3)[53].

A. TNF-α TNFR IKK activation
NF-κB pathway ↑
- Pro-inflammatory gene expression
- HSC activation Myofibroblast formation

B. IL-1β/ IL-18 NF- κB and NLRP3 Inflammasome Activation
- Cytokine storm Chronic inflammation
- Fibrogenic signalling ↑

C. MAPK- p38 Pathway Activation
- HSC proliferation
- Myofibroblast differentiation

1.2.3 Pharmacological Evidence of Moringa oleifera

1.2.3.1 Antioxidant Activity

Oxidative stress can result due to an imbalance in Reactive Oxygen Species (ROS) and the antioxidants of a biological system, potentially resulting in various health conditions[20,23,54]. Antioxidants might assist in avoiding the previously mentioned illnesses by efficiently counteracting free radicals. Although the synthetic antioxidants are highly active, one should not

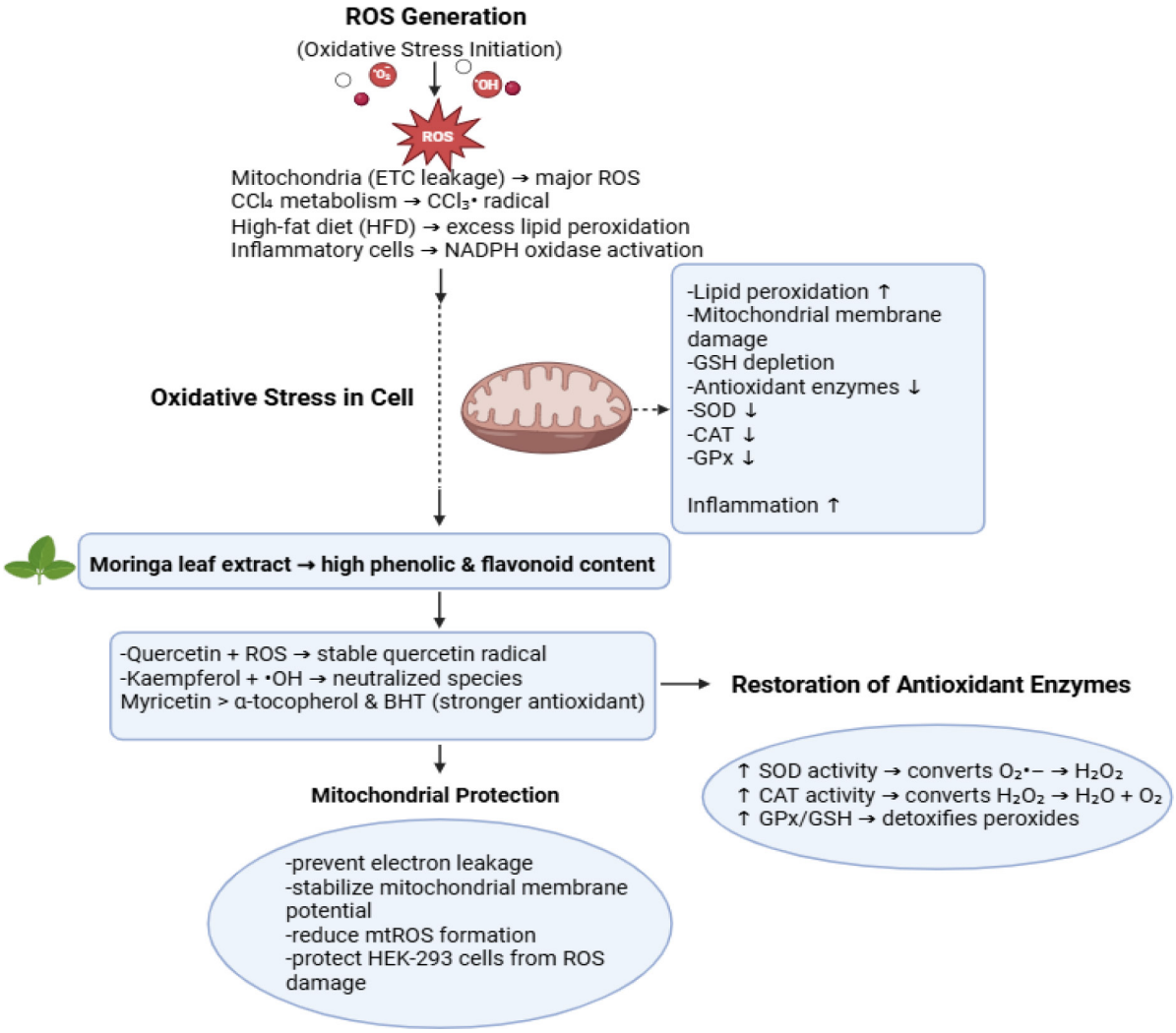


Figure 4. Mitochondrial damage by oxidative stress and mitigation by *Moringa oleifera*. The diagram shows that there is too much ROS generation that results in lipid peroxidation, endogenous antioxidant depletion, mitochondrial dysfunction, and inflammation. The antioxidant property of *M. oleifera* is high in phenolic and flavonoid, which scavenges free radicals, restores the antioxidant activity (SOD, CAT and GPx), stabilises the mitochondria membrane potential and prevents oxidative damage to cells.

ignore their possible side effects, which can be harmful. Therefore, the search for natural antioxidants has grown dramatically over the last few years[54]. Both compound phenolic acids and flavonoids have been shown to have anti-photoaging, anti-oxygen radical and anti-cancer effects. Nevertheless, the strong scavenging ability of MO that greatly enhances its overall hepatoprotective, anti-inflammatory, and antioxidant qualities is largely caused by the elevated concentration of phenolic acid[55].

The main phenolic constituents of *M. oleifera* leaves are flavonoids (apigenin, quercetin, luteolin, kaempferol and myricetin), lignans (secoisolariciresinol, medioresinol, isolariciresinol and epipinoresinol glycosides), and phenolcarboxylic acids, as well as derivatives of them (coumaroylquinic, caffeoylquinic, and feruloylquinic acids). Hydroxyl groups bring about the antioxidant activity[56–58].

The *M. oleifera* leaf ethanolic extract had a strong anti-lipid peroxidation effect and antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH) on the rat model of CCl - hepatotoxicity, which justified its activity as a hepatoprotective and antioxidant (Figure 4)[59]. In additional research, the leaf extracts of *M. oleifera* that were prepared using deep eutectic solvent (DES) possess a high activity that scavenges free radicals, which was primarily because of the high levels of quercetin and kaempferol glycosides[57]. In addition, *M. oleifera* leaf powder, when incorporated into high-fat diet models, resulted in a significant improvement of the bioactivity of antioxidant enzymes and oxidative stress indicators were also reduced, which also contributes to encouraging the use of this nutraceutical in the prevention of liver injury due to ROS[56]. Alpha-tocopherol and butylated hydroxytoluene (BHT) do not match myricetin, which is extracted from the *Moringa* seeds, regarding antioxidant properties. *M. oleifera* food grade extract and its components, i.e. astragalin, isoquercetin and cryptochlorogenic acid, can diminish the ROS in HEK- 293 cells[34].

One of the studies analysed the antioxidant property and the phenolic composition of leaves from *M. oleifera* growing in a non-traditional environment of a temperate climate. They discovered that the leaves also still have significant nutraceutical properties, and consequently, *M. oleifera* can be a viable source of natural antioxidants outside the tropics. Specifically, the most significant amount of the phenolic compounds was obtained in the methanol extract, which had the strongest antioxidant activity[60].

1.2.3.2 Anti-inflammatory Activity

The inflammatory process is critical to the incidence and progression of liver fibrosis since it triggers the release of cytokines and triggers the activation of hepatic stellate cells (HSCs) activation[61,62]. Potential anti-inflammatory properties of *M. oleifera* extracts imply that they may be used as natural resources to create plant-based medications that reduce inflammation or supplements, which are becoming more and more popular because they are less likely to cause adverse effects than synthetic substitutes[63]. *M. oleifera* has been extensively researched for its anti-inflammatory effects in both *in vitro* and *in vivo* investigations. Rat liver damage caused by thioacetamide was significantly reduced by an *M. oleifera* ethanolic leaf extract by suppressing the production of inflammatory biomarkers like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), as well as reducing serum transaminases and lipid peroxidation levels[64]. Methanolic extracts given to diabetic rats over 42 days reduced cytokines that promote hepatic inflammation, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), while also enhancing antioxidant enzyme activities[65].

MO's anti-inflammatory properties are mediated at the molecular level via the downregulation of important pathways. In a model of liver fibrosis induced by CCl_4, ethanolic extract (150–600 mg/kg) dramatically reduced hepatic expression of TNF-α and phosphorylated p38-MAPK, two important mediators of inflammation and fibrogenesis[66]. Additionally, it has been demonstrated that bioactive substances like *Moringa*-derived isothiocyanates and flavonoids (quercetin, kaempferol) prevent NF-κB signalling from being activated, which lowers the transcription of pro-inflammatory genes (IL-1β, IL-18, COX-2, and TNF-α) (Figure 5)[17].

Together, these investigations offer compelling pharmacological proof that *M. oleifera* inhibits inflammatory reactions at the molecular and cellular levels, suggesting that it may be used as a natural remedy to prevent and lessen liver fibrosis.

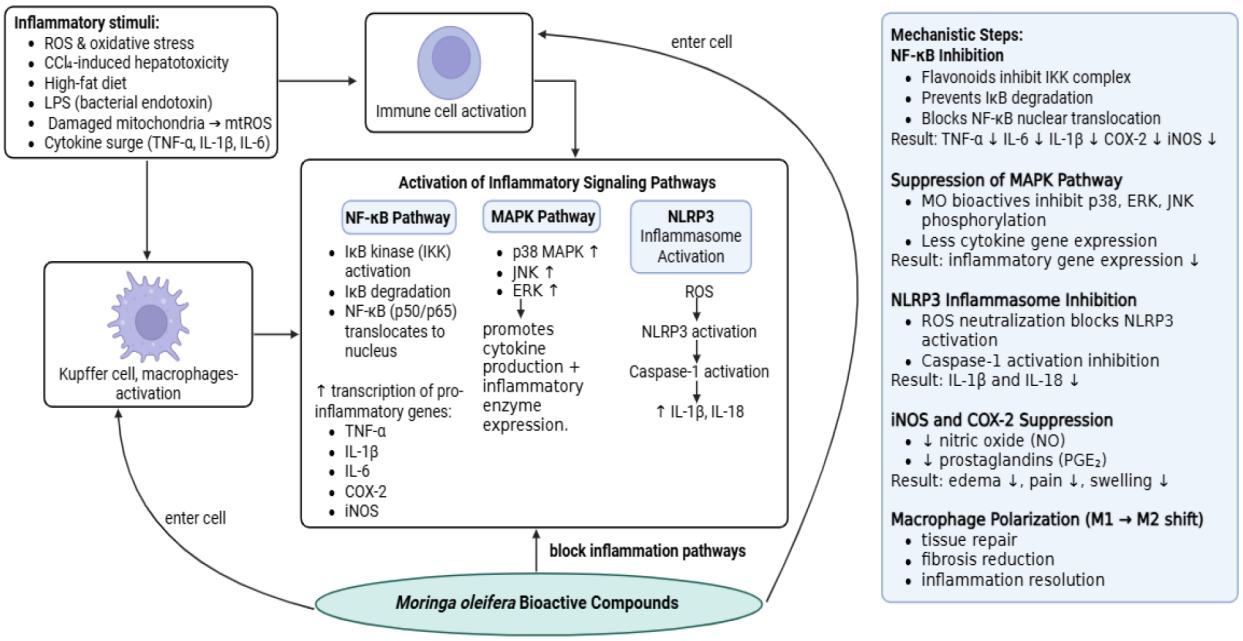


Figure 5. Kupffer cells and immune cells are stimulated by hepatotoxic and inflammatory stimuli through NF-κB, MAPK, and NLRP3 inflammasome signalling by releasing more pro-inflammatory cytokines like TNF-α, IL-1 β and IL-18. These routes induce oxidative stress and inflammatory gene expression, which cause liver damage. Anti-inflammatory action of *Moringa oleifera* bioactive compounds inhibits the major inflammatory pathways, cytokine-induced synthesis, and inflammatory-mediated liver injury.

1.2.3.3 Hepatoprotective Activity

As the main organ for metabolising and excreting foreign chemicals, the liver is located between absorption and systemic circulation and plays an important function in drug metabolism. The liver is also more vulnerable to drug poisoning because of these roles. Hepatotoxicity is a common ailment that can cause major problems and even death in both people and animals[67].

It has been demonstrated that MO works well to reduce inflammation, fight infections, boost antioxidant activity, stop the growth of cancer, and support liver health (Table 3)[68].

The *in vivo* investigation confirms the ability of *Moringa oleifera* leaf extract to protect the liver from BPA-induced hepatotoxicity via a twofold mechanism. It acts as an anti-inflammatory agent by dramatically downregulating pro-inflammatory cytokines such as TNF-α and IL-6 and as a potent antioxidant by reducing oxidative stress indicators (such as MDA). Through the reduction of inflammation and oxidative stress, *M. oleifera* effectively enhances liver function and histology (Figure 6)[69]. Another *in vivo* study confirms hepatoprotective effects and potential as an oral medication leaf extract from *M. oleifera*. Its therapeutic importance for protecting the liver was validated when it was shown to effectively reduce biomarkers of liver damage and improve liver function[70].

Using *M. oleifera* leaves, the green manufacturing of zinc oxide nanoparticles (ZnO-NPs) was successfully carried out. The experiment revealed that the ZnO-NPs produced by *M. oleifera* had significant effects on liver functionality and reduced liver injury biomarkers, which verified the function of the nanoparticles (hepatoprotective effects) in eliminating CCl_4 induced hepatic injury[71].

Taken altogether, these results make *M. oleifera* a highly strong natural hepatoprotective agent that manifests itself by means of antioxidant defence restoration, inhibition of the fibrosis-related markers, and the signaling pathways regulation: Nrf2/HO-1 and TGF-β/Smad.

2. Summary and Future Perspective

Moringa oleifera (MO) has demonstrated anti-fibrotic properties in hepatic fibrosis models, although its application in clinical settings has not yet been thoroughly investigated. In patients with hepatic fibrosis

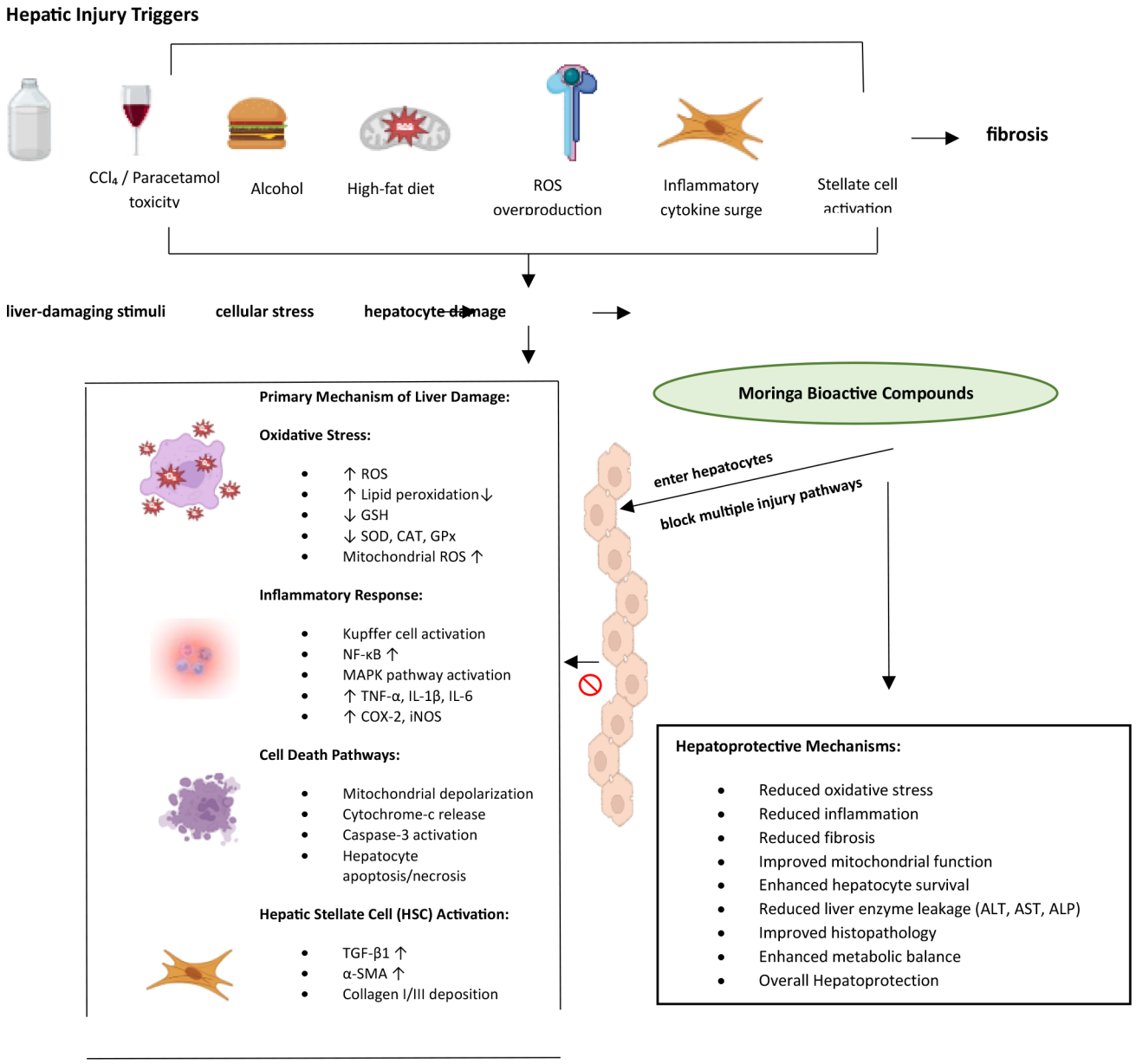


Figure 6. Toxic and metabolic-induced hepatic injury results in oxidative stress, inflammatory signalling, mitochondrial dysfunction, and hepatocyte damage, which is followed by hepatic stellate cell-activation and fibrosis. *Moringa oleifera* bioactive compounds gain entry to hepatocytes and obstruct various injury pathways through reducing oxidative stress, suppressing inflammatory mediators, enhancing mitochondria, inhibiting stellate cell activation, and normalising liver enzymes, which provide hepatoprotection in general.

or early cirrhosis, it is crucial to start well-planned Phase I/II clinical trials with an emphasis on safety, tolerability, pharmacokinetics, dose optimisation, and early indicators of success[79]. The extensive *in vitro* and animal evidence cannot be accurately extrapolated to human disease without such clinical confirmation.

The low bioavailability and restricted hepatic targeting of MO's active phytochemicals are one of the main translational obstacles. Advanced formulation techniques, including targeted liposomal vehicles, pro-drug systems, and nanoparticle delivery, need to be further developed and evaluated *in vivo* in order to overcome this. In hepatic stellate cell models, for example, a recent study demonstrated that Aloe vera-loaded nanoparticles and extracts of *M. oleifera* dramatically increased gene-modulation associated

Table 3. Bioactive constituents and anti-fibrotic potential of *Moringa oleifera*: *in vitro* and *in vivo* research evidence

Plant Part/ Source	Experimental Model	Model of Study (*In vitro*/*In vivo*)	Dosage	Treatment Duration	Extract	Therapeutic Characteristics
leaf powder	The study evaluated the antioxidant activity of the *Moringa oleifera* leaf powder on the fibrosis of hepatocellular carcinoma-related liver injury.	*In vivo* (mice)	1 µL/g body weight (intra-peritonel)	6 weeks (with CCl_4 induction)	Leaf powder extract (MOLP)	Reduced inflammation, oxidative stress; attenuated apoptosis; mitigated fibrosis via TLR4/NF-κB signalling down-regulation; improved histopathology[66].
leaf	The study examined the therapeutic impact of the ethanolic leaf extract of *Moringa oleifera* in an experimental model of liver fibrosis on the reversal of fibrotic alteration and liver damage.	*In vivo* (rats)	600 mg/kg	3, 6, and 10 weeks (after 11 weeks of CCl_4 induction)	Ethanolic extract MO leaves	Reduced METAVIR fibrosis scores (from F3-F4 to F1 in treatment groups); ameliorated liver fibrosis histologically; curative effect[4].
leaf	The study investigated whether sodium nitrate induces hepatic fibrosis in rats fed on the leaves of *Moringa oleifera* to determine how the plant diet prevents hepatic fibrosis.	*In vivo* (rats)	10% leaf powder mixed in diet; $NaNO_3$ 500 mg/L in drinking water	6 weeks (simultaneous/ after $NaNO_3$)	Leaf powder (MOLP)	↓ TGF-β1 expression; ↓ α-SMA; reduced collagen deposition; reduced apoptosis (caspase-3); reduced DNA fragmentation; overall ameliorated hepatic fibrosis[72].
Leaf	The study has investigated the anti-fibrotic properties of 1-phenyl-2-pentanol, which has been extracted in hepatic stellate cells using an *in-vitro* model.	*In vitro* (LX-2 human hepatic stellate cells stimulated with TGF-β1)	1-phenyl-2-pentanol up to 80 µg/mL	48 hours	Crude MO leaf extract + isolated compound 1-phenyl-2-pentanol	Downregulation of COL1A1, COL4A1, SMAD2/3, MMP-2; reduced MMP-9 secretion; inhibition of HSC activation; modulation of Wnt/β-catenin signalling[40].
Seeds (Seed Oil)	The study evaluated the impact of the seed oil of *Moringa oleifera* on the IL-18 and IL-1β gene expression in the liver fibrosis model of mice in order to determine its anti-inflammatory property.	*In vivo* (CCl_4-induced liver fibrosis in mice)	Different ratios of MOSEIL: CCl_4 (P1 1:1, P2 1:2, P3 1:4, P4 1:8)	2 months (1-month CCl_4 induction + MOSEIL treatment phase)	Seed Oil (MOSEIL)	Suppressed IL-18 and IL-1β gene expression; improved liver histopathology; prevented fibrosis progression and body weight loss[50].
leaves	The study investigated the preventive effects of the *Moringa oleifera* extract in the production of TNF-alpha and TGF-beta in the chemically induced liver fibrosis in rats by acetaminophen.	*In vivo* (albino rats)	300 mg/kg (oral)	2 weeks	Ethanolic extract of MO leaves	Decreased ALT, AST, ALP; ↓ TNF-α and TGF-β levels; improved histopathology; reduced fibrosis markers[73].

Table 3. Continued...

leaf	The study investigated that *Moringa oleifera* leaf extract suppresses CCl 4-induced hepatic inflammatory and apoptosis by regulating oxidative stress and TLR4/NF-κB.	*In vivo* (mice)	200 and 400 mg/kg (two doses)	6 weeks (after CCl_4 induction)	Leaf extract (aqueous/ethanolic)	Reduced hepatic inflammation and apoptosis; lowered oxidative stress; downregulated TLR4/NF-κB pathway; improved histopathology[61].
leaves	The study stated that *Moringa oleifera* leaves contain oleamide that has an anti-fibrotic effect through the inhibition of the Smad2/3 signaling by TGF-β1.	*In vitro* (LX-2 human hepatic stellate cells activated with TGF-β1)	5 and 10 µg/mL (MO crude extract and Oleamide)	48 hours	Crude MO leaf extract + Oleamide (OLA)	Suppressed activation of HSCs: ↓ ACTA2, COL4A1, COL1A1, TIMP-1, MMP-9, MMP-2; ↓ SMAD2/3/4; ↓ IL-6, IL-8, MMP-9 secretion; inhibited TGF-β/SMAD-mediated fibrotic signalling[37].
leaves	The study examined that *Moringa oleifera* can suppress the development of liver fibrosis by inhibiting the expression of collagen-1, TIMP -1 and α- smooth muscle actin in a rat model.	*In vivo* (rats; CCl_4-induced liver fibrosis)	150, 300, 600 mg/kg (oral gavage)	14 weeks	Ethanol extract of MO leaves	↓ METAVIR fibrosis scores; ↓ Collagen-1 expression; ↓ α-SMA + TIMP-1 expressions; improved histopathology[23].
Seed	The research investigated the *Moringa oleifera* seed extract ability to alleviate hepatic fibrosis in rats, which means that the extract is protective against fibrotic damage.	Rats (CCl_4-induced liver fibrosis)	1 g/kg (seed extract, oral, daily)	8 weeks (with extract given simultaneously with CCl_4)	Seed extract (crude)	↓ Elevated serum aminotransferases and globulin; ↓ hepatic hydroxyproline and myeloperoxidase; fewer α-SMA positive cells; ↓ Collagen I and III accumulation; antioxidant activity (↑ SOD, ↓ MDA and protein carbonyl)[74].
leaf powder	The study assessed the anti-fibrogenic effects of the leaf powder of *Moringa oleifera* on hepatocellular carcinoma progression showing it to inhibit fibrogenesis.	*In vivo* (BALB/c mice; with CCl_4 + MOLP)	1 µL/g body weight (intraperitoneal)	6 weeks	Leaf powder (green material)	↓ TGF-β expression inhibited fibrogenesis progression in early liver damage → inflammation/fibrosis stage; potential preventative effect[75].
Seed (Seed Oil)	The experiment revealed that *Moringa oleifera* seed oil suppresses the expression of CTGF in a mouse liver fibrosis model, which means that it suppresses fibrotic signalling.	*In vivo* (CCl_4-induced liver fibrosis in mice)	Ratios MOSEIL: CCl_4 - P1 1:1, P2 1:2, P3 1:4, P4 1:8	2 months	Seed oil (MOSEIL)	Reduced expression of CTGF; attenuation of liver fibrosis progression; improved liver morphology[76].

Table 3. Continued...

leaves	The research tested the anti-inflammatory and anti-fibrotic actions of *Moringa oleifera* ethanolic leaf extract in an *in vivo* fibrosis model by regulating TNF-α and p38-MAPK.	*In vivo* (Wistar rats, with CCl_4-induced liver fibrosis)	150, 300, 600 mg/kg (oral gavage)	14 weeks (during CCl_4 induction)	Ethanol extract of MO leaves	↓ TNF-α and ↓ p38-MAPK expression; exhibited both anti-inflammatory and anti-fibrotic effects vs control; dose-dependent response[45].
leaves	The study results indicated that *Moringa oleifera* inhibits CCl_4-induced liver fibrosis (*in vivo* study in rats) by suppressing the activation of hepatic stellate cells.	*In vivo* (rats; CCl_4-induced liver fibrosis)	300 mg/kg (oral)	8 weeks	Ethanol extract of leaves	HSC activation inhibition; collagen deposition reduction; enhanced liver function tests and histopathology; decreased fibrosis markers[77].
Seeds	The research compared MRI-based texture analysis as a method of measuring the protective effect of induced liver fibrosis in rats.	Wistar rats, CCl_4-induced liver fibrosis	0.5 g/kg (intragastric, daily)	8 weeks (concomitant with CCl_4)	Ethanolic seed extract	↓ AST and ALT; ↓ collagen-I deposition (fibrosis index reduced to 5.23% vs 12.73% in fibrotic group); histopathology and MRI-texture analysis confirmed hepatoprotection[78].

with TGF-β and COL1A1, surpassing free chemicals[80]. The growing application of MO-derived nanoparticles for enhanced solubility, cellular absorption, and bio-stability is highlighted by complementary reviews[81] .

Beyond the classic TGF-β/Smad axis, mechanistic studies must explore metabolic cross-talk (e.g., SIRT1/AMPK), miRNA networks, inflammasome/NLRP3-driven pathways, and epigenetic regulation. The necessity to map the entire range of anti-fibrotic pathways *in vivo* is highlighted by early *in vitro* findings on MO-derived oleamide, which show reduction of Smad2/3 signalling in LX-2 cells[37]. Furthermore, multi-ligand docking studies have demonstrated the synergistic impacts of MO phytochemicals, which point to the possibility of combination treatments and necessitate validation in fibrosis models[82].

There is a dearth of thorough evaluation of standard pharmacokinetic profiling, chronic dosage toxicity, herb-drug interaction potential, and long-term safety. These data are essential for translation into humans, especially individuals with hepatic impairment and polypharmacy. The hepatoprotective and antioxidant potential of MO-mediated selenium nanoparticles was demonstrated in diabetic rats in a recent study[83]. However, the consequences for fibrosis and human dosage are still unknown.

Furthermore, *Moringa oleifera* leaf nanoparticles show enhanced hepatoprotective and antioxidant effects in pre-clinical models. Optimising their design, dosing, and safety could strengthen combination therapy strategies for hepatic fibrosis[84].

3. Conclusion

In preclinical models of hepatic fibrosis, *Moringa oleifera* (MO) exhibits potent anti-fibrotic, hepatoprotective, anti-inflammatory and antioxidant characteristics. Its biologically active phytochemicals, like oleamide, quercetin, kaempferol, and moringin, prevent the activation of hepatic stellate cells (HSCs) and reduce the extracellular matrix accumulation, and lessen oxidative damage and inflammation through a variety of pathways, such as TGF-β/Smad, NF-κB, p38-MAPK, and inflammasome/NLRP3 signalling. Clinical translation is still restricted despite strong *in vitro* and *in vivo* data because of issues with bioavailability, liver targeting, pharmacokinetics, and long-term safety. Nanoparticle-based formulations and combination

therapies with other bioactive compounds or lifestyle interventions present promising avenues to overcome these barriers. Well-designed Phase I/II clinical investigations, standardised extract formulations, and biomarker-based monitoring validation are necessary for MO's effectiveness and safety in humans. Overall, MO represents a versatile, natural, and potentially cost-effective approach for liver fibrosis prevention and treatment, particularly in resource-limited settings, but rigorous clinical validation is urgently needed.

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Author Contribution

Madhurani: Manuscript preparation and collection of data. Pooja Negi: Guidance throughout the preparation of the manuscript. Digvijay Singh and Alfisha assisted in the literature review and manuscript editing. Sweta Kumari and Shoyab Ali helped in compiling the data and helped with the referencing part of the manuscript. All authors have read and agreed to the published version of the manuscript.