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REVIEW ARTICLE

Role of Lifestyle Changes and Natural Herbs in the Management of Hepatic Health

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Abstract

Liver ailments are significant contributors to human illness and death globally. The prevalence of liver disorders is increasing owing to the widespread prevalence of hepatitis and alcohol addiction. These conditions can be triggered by infection, trauma, exposure to pharmaceuticals or hazardous substances, autoimmune disorders, or genetic abnormalities resulting in the accumulation of harmful substances. Despite advances in understanding the causes underlying hepatic dysfunction, no standard pharmaceutical therapy is available. The only currently advised option is to make lifestyle changes such as diet, intermittent fasting, and increased physical exercise. However, a lack of compliance continues to impede this strategy. As a result, there is an apparent need to characterize novel therapeutic alternatives. Current advances in the communication between the gut and hepatic tissue open new avenues for better explaining the molecular mechanisms behind the pathology of hepatic illness. Natural bioactive compound research has emerged as an appealing strategy for overcoming lifestyle change resistance. The current study aims to review some of the identified compounds and other herbal approaches with favourable characteristics to hepatic health. This review study discusses their protective properties, mode of action in ameliorating the major pathological events involved in liver disorders, and therapeutic applications.

Keywords: Hepatic Health, Intermittent Fasting, Lifestyle Changes, Multiorgan Failure, Natural Products

1. Introduction

The liver, the largest solid organ within the body, acts as a bridge connecting the vast reservoirs of nutrients, toxins, and hormones with the other constituents of the body[1]. The liver regularly encounters substances that can be harmful daily due to its function in processing, metabolism, and detoxing foreign substances. Chronic liver injury via metabolic, environmental, immunological, or bacterial causes leads to pathological alterations such as hyperplasia, infiltration of inflammatory cells and degeneration of liver cells[2].

The detection of liver abnormalities relies on the evaluation of multiple elements, including the examination of serum enzyme functions, serum bilirubin, protein levels, and serum albumin, along with serum ammonia, coagulation indicators, serum cholesterol, and urine urobilinogen levels. The primary and widely employed clinical marker for assessing liver function is Alanine Aminotransferase (ALT). When there is damage to liver cells, ALT is released into the bloodstream, making elevated ALT levels a significant indication of liver injury. Aspartate Aminotransferase (AST), found in the brain, cardiac cells, and skeletal muscle cells, is a less precise diagnostic marker for liver damage compared to ALT. The combined measurement of hepatic conjugated bilirubin and extrahepatic bilirubin is referred to as total bilirubin. However, total bilirubin alone lacks sensitivity in assessing liver well-being unless

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there is a blockage in the bile ducts. Another enzyme called Alkaline Phosphatase (ALP) exhibits elevated levels in cases of obstructive biliary disease[3]. Currently, there is a surging interest in investigating the advantages of adopting a vegetarian or vegan dietary approach in the prevention of various chronic ailments, encompassing several hepatic disorders such as cirrhosis, hepatic ulcerative syndrome, and fibrosis[4]. The utilization of herbal remedies continues to be a viable alternative to conventional treatment, offering a sense of therapeutic essence. In many cases, these treatments not only target the ailment but also present minimal undesirable side effects. Unlike synthetic medications commonly used for liver disorders, which have been found to possess strong pro-oxidant scavenging properties, herbal remedies have shown potential in mitigating inflammation and reducing the risk of cancer when used over the long term[5]. The efficacy of phytochemicals derived from plants in the management and prophylaxis of diverse life-threatening conditions is widely acknowledged. Extensive research has been carried out on plant phenolic compounds, including flavonoids, coumarins, lignans, tannins, and stilbenoids, to establish their scientific foundation for potential therapeutic applications in addressing a variety of human disorders[6,7].

Although Ayurvedic Medicine (AM) is widely utilized, there is a noticeable lack of literature addressing liver injury associated with its use[8]. An illustrative instance is Giloy, which has been linked to acute hepatitis exhibiting autoimmune characteristics and has the potential to unveil Autoimmune Hepatitis (AIH) in individuals with silent AIH-related Chronic Liver Disease (CLD)[9,10]. This review highlights several herbs known to impact hepatic well-being, while also discussing the beneficial and detrimental effects of various plant-derived compounds such as flavonoids and terpenoids.

2. Material and Methods

Using diverse keywords like hepatic health; natural products; and intermittent fasting, researchers study a wide range of reviews and research papers from a big collection of online resources. To cure liver problems, this study examines herbal modulation and its advantages. The literature study involves the review of numerous papers from various sources, including Google Scholar, Springer, Taylor and Francis, Elsevier, and Bentham.

3. Hepatic Health and its Impact on Adjacent Organs

The liver, an essential metabolic organ, is tasked with overseeing the regulation of body energy metabolism and upholding metabolic equilibrium. Moreover, it plays a crucial role in the purification of medications and toxins. Hepatocytes possess various enzyme systems that metabolize numerous foreign substances (xenobiotics), converting them into more soluble metabolites that can be excreted through urine or bile. Disruption of hepatic signalling and metabolism can result in metabolic liver conditions such as Nonalcoholic Fatty Liver Disease (NAFLD) or type 2 diabetes. While various sites in the body, such as the gastrointestinal mucosa, lungs, kidneys, and circulating enzymes in plasma, contribute to drug metabolism, the liver stands out as the primary and most significant site, both quantitatively and qualitatively as mentioned in Figure 1. Notably, the consumption of alcohol in large quantities can hinder drug metabolism by competing with the drug for the same group of metabolizing enzymes[11]. Alcohol stands as a prevalent factor behind liver diseases on a global scale, contributing to a diverse range of direct liver damage encompassing, cirrhosis, steatosis, alcoholic hepatitis, and hepatocellular carcinoma. Notably, liver cancer has now emerged as the third most prominent cause of cancer-related mortality worldwide[12]. Individuals diagnosed with cirrhosis and portal hypertension face an elevated susceptibility to the emergence of circulatory impairment, which carries the potential for multiple organ failure. Besides impacting the liver, this condition can affect various other organ systems. As the disease advances, the circulatory system undergoes a hyperdynamic state, leading to the manifestation of pulmonary, cardiac, and renal dysfunction, ultimately resulting in diminished survival rates. Infections and a modified cardiac function referred to as cirrhotic cardiomyopathy can serve as triggers for the onset of additional complications, including hepatorenal syndrome[13]. Hepatocyte programmed cell death plays a significant role in the deterioration of metabolic function observed in individuals experiencing both acute and chronic liver injuries. The progression of cirrhosis begins when the liver is exposed to detrimental agents such as pharmaceuticals, alcohol, and the hepatitis B or C virus. Concurrently, regenerative nodules form and hepatocyte functionality progressively deteriorates. Notably, essential bioactive molecules with hemodynamic implications, including aldosterone, renin, substance P, angiotensin II, and vasopressin are also metabolized in the liver[14].

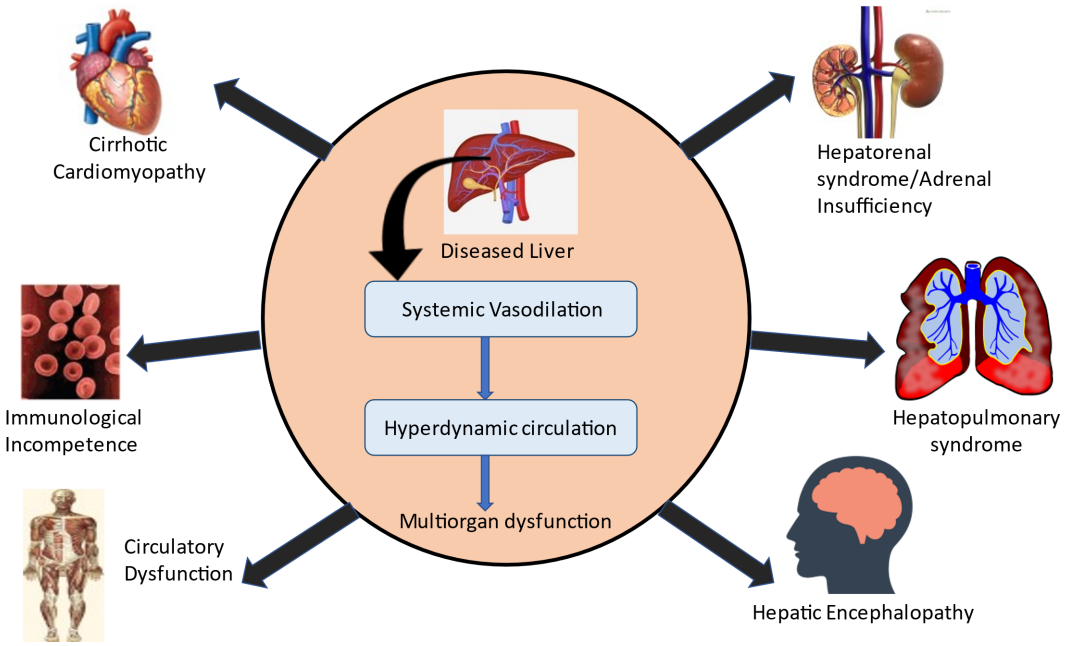

Figure 1. Multiorgan dysfunction due to liver injury.

Cirrhosis often leads to atypical functioning of the autonomic nervous system, characterized by impaired regulation of heart rate, the heightened activity of the sympathetic nervous system, and reduced sensitivity of the baroreflex (BRS). Individuals with cirrhosis, when subjected to normal physiological or drug-induced stress, have trouble increasing their heart rate. Moreover, when faced with sympathetic nervous system stimulation, their heart rates demonstrate a lesser increase compared to healthy individuals[15]. Presently, Hepatic Encephalopathy (HE) is defined by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) as a cognitive impairment arising from hepatic injury. In a small-scale study involving individuals suffering from alcoholic cirrhosis and grade I-II Hepatic Encephalopathy (HE), it was noted that the capacity for distributing (11) C-flumazenil, as well as the ratio of glutamate/glutamine to creatinine, were elevated, while the choline to creatinine ratio was reduced among cirrhosis patients with, HE. Magnetic Resonance Imaging (MRI) scans conducted on individuals with underlying hepatic encephalopathy unveiled increased signals in the putamen, caudate nucleus, subthalamic nucleus, globus pallidus, tectum, substantia nigra, and red nucleus in T1-weighted images. Nevertheless, MRI results in HE patients might return to normal following liver transplantation. A recent study indicated that individuals with alcoholic cirrhosis exhibited greater brain oedema, cortical impairment, and reduced brain capacity in comparison to non-alcoholic patients[16]. Individuals experiencing liver damage demonstrate an increased incidence of immune-related pulmonary disorders, including pneumonia, and lifestyle-related conditions like chronic obstructive pulmonary disease. Within the realm of liver disease, a distinct pulmonary impairment arises, characterized by diffusion irregularities and the emergence of Hepatopulmonary Syndrome (HPS) and Portopulmonary Hypertension (PoPH). The distinguishing characteristic of HPS in terms of pathophysiology is the expansion of capillaries near the alveoli. The occurrence of HPS can be attributed solely to the presence of liver disease, whereas PoPH arises from the combination of liver disease and portal hypertension[17].

There is a tight relationship between the liver and the heart. Cardiovascular function may be hampered by hepatic disease, and vice versa. Non-Alcoholic Fatty Liver Disease (NAFLD) is a condition marked by the buildup of liver fat when less than 10g of alcohol is consumed each day. NAFLD increases the risk of cardiomyopathy, valvular calcification, arrhythmia, and certain conduction abnormalities while promoting the development of coronary atherosclerosis. Cardiac failure can manifest in

the early phase (within the first 30 days) or later stages (beyond 30 days) following liver transplantation, and it is accompanied by a significant risk of mortality. The occurrence of heart failure in the early stages following liver transplantation is indicative of the cardiovascular stress associated with the surgical procedure, while late-onset heart failure suggests the presence of coronary atherosclerosis. Employing various imaging techniques such as echocardiography, CT, and CMR, along with the timely implementation of heart failure therapies, holds significant importance in effectively managing individuals who are candidates for liver transplantation[18]. The prevalence of kidney failure in cases of Acute Liver Failure (ALF) ranges from 40% to 85%. This can be attributed to the fact that individuals with cirrhosis often exhibit inaccurately low levels of serum creatinine, primarily caused by reduced hepatic synthesis of creatinine and diminished skeletal muscle mass. Among hospitalized patients with cirrhosis who experience acute upper gastrointestinal haemorrhage, the occurrence of acute renal failure serves as an autonomous prognostic indicator for mortality. As liver disease advances, there is a notable constriction of the renal vascular bed, making the kidneys vulnerable to the development of Hepatorenal Syndrome (HRS). While individuals with Acute Liver Failure (ALF) may also encounter portal hypertension, its severity tends to be less pronounced compared to those with cirrhosis[19].

Cirrhosis has been associated with a condition known as hepatoadrenal syndrome, wherein there is a decline in adrenal function because of the suppression of Adrenocorticotropic Hormone (ACTH) and Corticotropin-Releasing Hormone (CRH) due to elevated levels of pro-inflammatory cytokines[20].

4. Hepatic Toxicity and HPA Axis

The stimulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis plays a pivotal role in the physiological response to stress by promoting the production of glucocorticoids, such as cortisol in humans and corticosterone in rodents. These hormones are essential for enabling the body to adapt to variations in environmental factors (such as temperature, exposure to harmful substances, and infections) as well as internal circumstances (including inflammation and tissue damage)[21]. The study of dysfunctions within the Hypothalamus-Pituitary-Adrenal (HPA) axis has predominantly focused on conditions such as depression, Chronic Fatigue Syndrome (CFS), and Fibromyalgia (FM), while investigations into hepatic cholestasis, cirrhosis, and other liver diseases have been comparatively limited[4]. This discrepancy arises from the fact that symptoms such as fatigue, asthenia, and muscular weakness, which are commonly experienced in depression, CFS, and FM, tend to worsen during periods of stress. Interestingly, patients with cholestatic liver disease and Primary Biliary Cirrhosis (PBC) often exhibit various systemic symptoms, including fatigue and depression, the underlying causes of which remain poorly understood but may involve disruptions in the functioning of the HPA axis[22].

The Central Nervous System (CNS) receives sensory inputs from both internal and external sources, and in turn, communicates signals to all organs to maintain a state of metabolic and physiological balance known as homeostasis. The initiation of positive feedback pathways begins in the hypothalamus, where Corticotropin-Releasing Hormone (CRH) is secreted, subsequently stimulating the anterior pituitary gland to release Adrenocorticotropic Hormone (ACTH). ACTH then triggers the adrenal glands to release glucocorticoids (GC). These adrenal steroids travel to vital organs, including the liver, where they bind to specific receptors with transcriptional functions[22,23]. Glucocorticoids (GC) have a high affinity for Glucocorticoid Receptors (GR), which are abundant in the liver. Through their interaction with these receptors, GC plays a regulatory role in the expression of numerous genes associated with energy production, homeostasis, growth, and inflammation. The primary regulation of liver function occurs through the Hypothalamic-Pituitary-Adrenal (HPA) axis, although there are interconnected signalling pathways between the HPA axis and other hypothalamus-dependent pathways. While GC stimulates downstream signalling cascades, they also initiate a negative feedback mechanism that inhibits the production of Corticotropin-Releasing Hormone (CRH) in the hypothalamus and Adrenocorticotropic Hormone (ACTH) in the pituitary gland[24]. The HPA axis plays a crucial role in regulating hepatic functions and includes molecular mechanisms that modulate HPA axis activity based on the body's requirements[25]. Effective clearance of active glucocorticoids (such as cortisol and corticosterone) is crucial because impaired glucocorticoid clearance is linked to metabolic disturbances (such as glucose intolerance and hepatic steatosis) as well as suppression of the HPA axis[26] as shown in Figure 2.

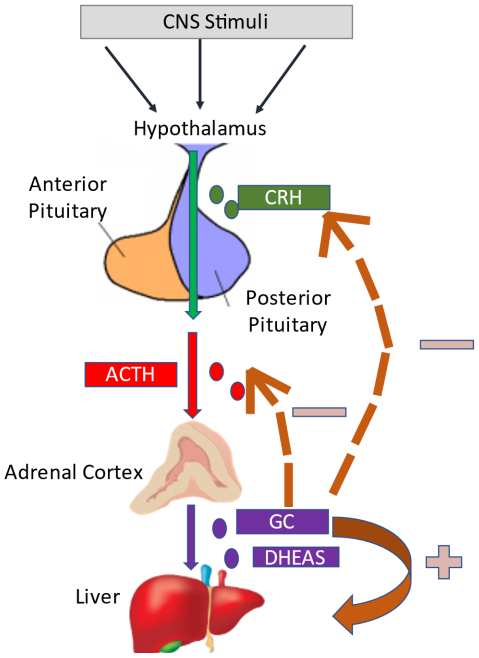

Figure 2. HPA axis and hepatic functions.

Iinsufficient levels of cortisol, a marker for an HPA axis malfunction, have been noticed in individuals with chronic liver disease and have been linked to the development of hepatic cholestasis and cirrhosis[27,28]. In research conducted on the adrenal functionality in individuals suffering from advanced liver disease and awaiting a transplant, in comparison to a group of healthy individuals, it was observed that the patients with liver disease exhibited a significant decline of over 60% in their plasma cortisol levels when subjected to indirect adrenal stimulation through hypoglycemia induced by insulin. Furthermore, when ACTH was administered to stimulate cortisol production, these patients experienced a decrease of approximately 39% in cortisol production[29]. The Hypothalamic-Pituitary-Adrenal (HPA) axis and the liver exhibit a symbiotic relationship, working in conjunction to maintain the equilibrium of numerous metabolic processes. Instances of excessive production of glucocorticoids, which are clinical conditions associated with the overabundance of these hormones, have also been linked to the occurrence of hepatic disorders[30,31]. An investigation provides evidence that cholestasis is correlated with a noteworthy inhibition of the Hypothalamic-Pituitary-Adrenal (HPA) axis' capacity to react to stress, attributed to suboptimal levels of Corticotropin-Releasing Hormone (CRH) in the hypothalamus and Adrenocorticotropic Hormone (ACTH) in the bloodstream within animals experiencing cholestasis. The assessment of HPA activity, as reflected by the concentrations of CRH and ACTH in various tissues, along with corticosterone and cortisol in circulation, exhibited a substantial suppression of HPA axis functionality across all examined models[32].

5. Lifestyle Changes for Management of Hepatic Health

It is highly advisable to implement lifestyle adjustments for individuals diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD), Hepatitis C Virus (HCV), and those who have undergone liver transplantation. One such change one can make is by introducing Intermittent fasting to daily routine[27].

5.1 Utilization of Intermittent Fasting for the Treatment of Hepatic Disorders

Intermittent Fasting (IF) refers to specific eating patterns that restrict the intake of food for a predetermined duration, enabling the body to undergo a fasting period[33]. Typically, this entails abstaining from both food and beverages for a span of 12 to 16 hours each day, sustained over a month[34]. It is postulated that IF might confer metabolic advantages to the liver, distinct from calorie reduction and weight reduction, which could potentially enhance the histological state of NAFLD[33]. Most of the research investigating the effects of intermittent fasting on NAFLD has been conducted during the religious observance of Ramadan, primarily examining Time-Restricted Feeding (TRF) practices. During this period, individuals fast from daylight for approximately 12-14 hours each day over a span of around 30 days. The results from these studies have predominantly yielded favourable results, indicating that following the 30-day duration, daily Time-Restricted Feeding (TRF) significantly improved non-invasive markers of fatty liver disease (such as the BARD Score, NAFLD Fibrosis Score, and Fibrosis-4 Index score) while concurrently reducing insulin resistance[35,36].

C57BL/6 mice were divided into two groups: one group underwent intermittent fasting while the other group was provided food ad libitum as controls. It was observed that subjecting the mice to 12 hours of intermittent fasting each day for a duration of 30 days led to a significant decrease in their overall food intake compared to the mice

with unrestricted feeding. The fasting regimen resulted in a noteworthy reduction in liver mass, although it had only a minimal impact on body weight. Additionally, when the mice were subsequently allowed to eat freely for 30 days, the effects on the liver caused by the 30-day fasting period were not reversed. Consequently, the study concluded that implementing a daily 12-hour intermittent fasting routine for one month notably decreased liver weight in mice, indicating an enhancement in liver metabolism[37].

When the duration of food intake is restricted to 14 hours or more, it depletes the body's glycogen stores, triggering the breakdown of triglycerides into Free Fatty Acids (FFAs) and glycerol in adipocytes, a process known as lipolysis. In the liver, FFAs are converted into ketone bodies, initiating the activation of potent transcription factors called Peroxisome Proliferator-Activated Receptor Alpha (PPAR-α) and Activating Transcription Factor 4 (ATF4). These transcription factors stimulate the release of fibroblast growth factor 21 (FGF21), a protein with diverse effects on the body. Notably, FGF21 contributes to increasing insulin resistance and inhibiting the synthesis of fats in the liver, as depicted in Figure 3. Additionally, during fasting, a decline in circulating amino acids suppresses the activity of the mammalian Target of Rapamycin (mTOR), which in turn hinders further anabolic processes and promotes autophagy. Autophagy facilitates the elimination of excess lipids from the liver[38].

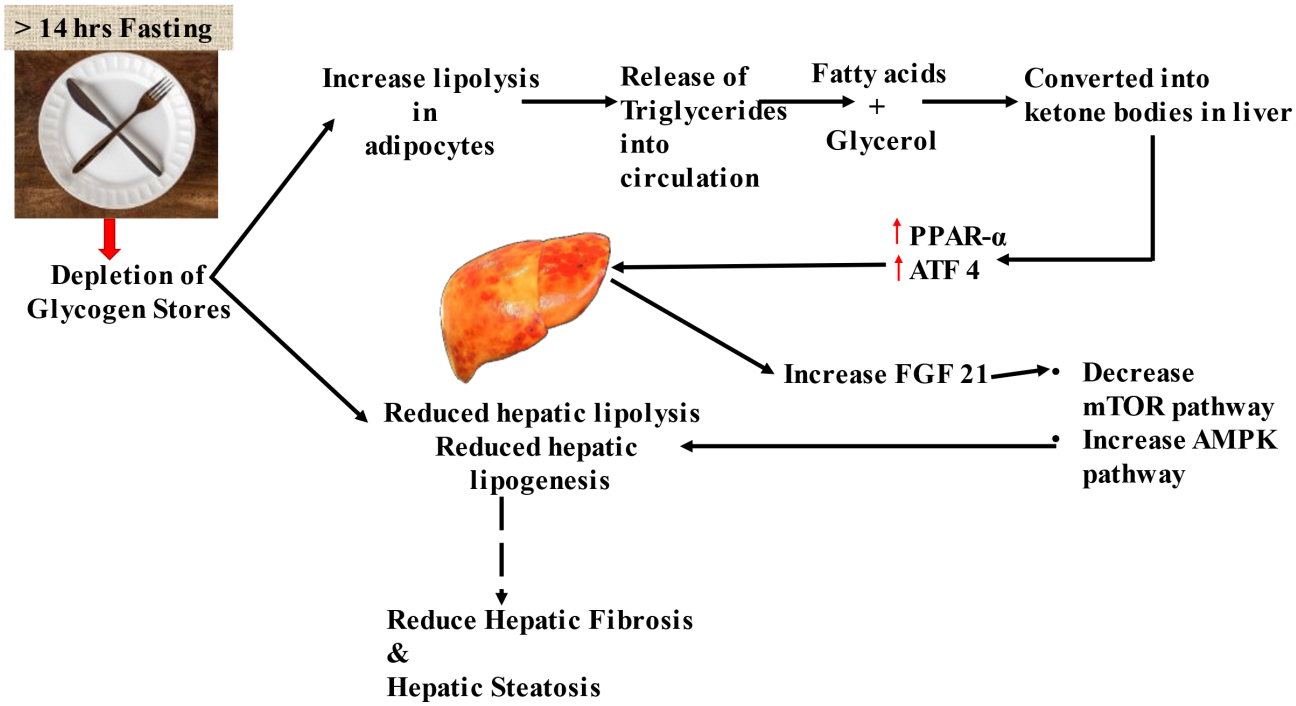

Figure 3. Proposed metabolic benefits of fasting.

A randomized controlled trial was carried out to compare the efficacy of Alternate-Day Fasting (ADF) with daily Time-Restricted Feeding (TRF) in individuals diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD). The trial involved 97 participants who followed the TRF diet for 12 weeks and 95 participants who followed the ADF diet. The findings revealed that ADF resulted in a more significant reduction in overall fat mass (-3.48 kg) and total cholesterol (-14.6%) compared to TRF (-2.62 kg) and the control group (-1.05 kg). However, there were no notable differences between the two fasting approaches concerning fat-free mass, body weight, other lipid levels, fasting insulin, or liver stiffness (assessed using vibration-controlled transient elastography). These results suggest that extended periods of fasting may not be necessary to observe metabolic benefits for the liver[39].

While Intermittent Fasting (IF) offers potential benefits, it is crucial to acknowledge that this approach may not be appropriate for every patient or population. Firstly, although there is emerging research on the effects of fasting during pregnancy on both mothers and their children, the results are inconsistent, and the long-term

implications remain uncertain. Therefore, it is advisable to discourage the practice of IF during pregnancy until more substantial evidence is obtained. Secondly, although IF seems to be safe for individuals with type 2 diabetes[40], caution should be exercised for those who are taking glucose-lowering medications. Studies on IF have reported various side effects, including decreased energy levels, sensations of coldness, headaches, reduced concentration, halitosis, irritability, constipation, and excessive preoccupation with food[41].

6. Natural Herbs in the Management of Hepatic Health

Hepatoprotective agents encompass a category of therapeutic substances comprising both synthetic and natural compounds, employed to safeguard the liver from harm caused by diverse toxins. In the pursuit of novel pharmaceutical compounds, natural sources such as plants are consistently explored and harnessed. Ethnomedical practices, along with traditional Indian systems of medicine, extensively employ numerous medicinal plants and their preparations for the management of liver disorders[42]. Studies have documented that the presence of flavonoids in plants accounts for their hepatoprotective effects, attributable to their potent antioxidant characteristics.

6.1 Examples of Some Natural Herbs

By a research investigation, the ethanolic extract of *Symplocos racemosa* (EESR) bark exhibited notable hepatoprotective properties in the face of carbon tetrachloride (CCl4)-induced hepatic injury, thereby showcasing promising prospects for clinical utilization in liver disease treatment. The liver specimens obtained from the control group exhibited the presence of healthy hepatic parenchyma; however, upon CCl4 administration, severe degenerative alterations, centrilobular necrosis, and fatty infiltration were observed, indicating substantial impairment to the structural integrity of the liver. The administration of EESR demonstrated favourable outcomes, including a reduction in fatty infiltration, centrilobular necrosis and amelioration of hepatic protection, as evidenced by improvements in histopathological alterations[43].

Likewise, the principal bioactive compound present in turmeric, called curcumin, exhibits antifibrotic, anti-inflammatory, and antioxidative properties, which may contribute to its efficacy in addressing conditions such as cholestasis, Hepatocellular Carcinoma (HCC), hepatic fibrosis, and drug-induced liver injury[44]. In rats with NAFLD induced by a High-Fat Diet (HFD), the administration of curcumin was observed to alleviate the accumulation of ectopic fat in the liver, while also mitigating metabolic endotoxemia and intestinal inflammation. In experimental models of NAFLD induced by HFD, curcumin has demonstrated advantageous effects on the interaction between the gut and the liver, targeting both the integrity of the intestinal barrier and various stages of the inflammatory signalling pathway triggered by lipopolysaccharide (LPS)[45]. Recently, there has been growing interest in the use of *Camellia oleifera* seeds for the prevention of liver diseases. The defatted seeds of *C. oleifera* possess hepatoprotective properties against CCl4-induced hepatotoxicity in rats, as evidenced by the mitigation of hepatitis and fibrosis, reduction in body fat accumulation and liver steatosis, and regulation of adipokine levels[46]. Furthermore, the impact of *C. oleifera* seeds on the interaction between the gut and the liver has been reported for the first time. The extract derived from *C. oleifera* seeds has demonstrated inhibitory effects on the expression of the endotoxin receptor TLR4 and its downstream factors, including MyD88 and TRIF, which could potentially hinder the activation of NF-κB[47].

Histopathological investigations provided compelling evidence of the therapeutic effectiveness of the aqueous extract derived from *Aloe indica* in counteracting liver damage induced by carbon tetrachloride (CCl4). The findings revealed a reversal of centrilobular necrosis, macrovascular fatty alterations, and the presence of scattered lymphomononuclear cell infiltration within the hepatic parenchyma. Furthermore, the extract exhibited a capacity to enhance bile flow and increase bile solids, indicating a potential stimulation of liver cell secretory activity. The hepatoprotective action was also attributed to the extract's ability to preserve the liver's metabolic enzymes through its antioxidant properties[48]. Scientists investigated to explore the hepatoprotective properties of *Acacia catechu* and its potential mechanisms against acetaminophen (APAP)-induced liver damage, utilizing a female Wistar rat model. Hepatotoxicity was induced by administering acetaminophen orally. The groups treated with the seed extract (400 mg/kg body weight) and bark extract (400 mg/kg body weight) demonstrated significant hepatoprotective effects, comparable to the well-established clinical antidote, N-acetylcysteine.

Consequently, the *Acacia catechu* seed extract emerged as a more promising candidate for safeguarding the liver against APAP-induced hepatotoxicity[49].

An additional research study provided evidence that *Sanguisorba officinalis* exhibited a remarkable reduction in the levels of ALT and AST, indicating its hepatoprotective properties. In clinical settings, elevated levels of ALP frequently signify cholestasis resulting from liver injury. Total Bilirubin (TBIL) serves as a sensitive indicator of bilirubin metabolic abnormalities and is often elevated during acute liver injury. Treatment with *Sanguisorba officinalis* resulted in a significant decrease in TBIL levels compared to the control group. Serum Triglyceride (TG) serves as an additional indicator of liver impairment and tends to increase when the liver is damaged. However, in the group treated with *Sanguisorba officinalis*, TG levels exhibited a significant reduction compared to the model group. This reduction further emphasizes the hepatoprotective effects of *Sanguisorba officinalis*. The presence of phytochemical compounds such as gallic acid and catechin in *Sanguisorba officinalis* has been recognized for their potent antioxidant properties, which can bestow health benefits and likely contribute to the hepatoprotective activity of the plant[50].

A recent meta-analysis has revealed a potential association between *Panax ginseng* consumption and a decreased risk of liver cancer incidence, as well as improved prognosis following cancer chemotherapy[51]. Among the primary bioactive constituents found in ginseng, extensive research has been conducted to investigate the pharmacological mechanisms of ginsenoside IVa, rare ginsenoside 20(R)-Rg3, ginsenoside F2, ginsenoside Mc and particularly ginsenoside Rg1 on liver health[52]. Research findings have indicated that ginsenoside Rg1 exhibits notable inhibitory effects on the mRNA expression of hepatic Lipopolysaccharide (LPS) receptors, including TLR4 and CD14, while also suppressing NF-κB activation. Consequently, this leads to the suppression of proinflammatory mediator production and the alleviation of liver inflammation in both animal and cellular models[53]. Furthermore, ginseng saponins have displayed the potential in influencing the interaction between the gut and the liver, thereby exerting protective effects on the liver through their impact on the intestinal biological barrier and mitigating lipopolysaccharide-induced liver inflammation[54].

Berries, a widely consumed fruit in our daily lives, are renowned for their rich content of polyphenols and plant cell wall polysaccharides[55]. Among the various berries, blueberries have gained recognition for their substantial health benefits in mitigating liver fibrosis, primarily through their impact on the interaction between the gut and the liver[56]. Extracts containing anthocyanins, distinctive polyphenols found in blueberries and cranberries, have demonstrated significant reductions in body weight gain, total plasma cholesterol, and total liver lipids in mice fed a high-fat diet. These effects are likely attributed to the reduction in plasma Lipopolysaccharide (LPS) concentration and the decreased relative abundance of *Rikenella* and *Rikenellaceae* in the gut microbiota[57]. These findings suggest that berries possess the capacity to modulate the gut-liver axis, thus offering the potential for the prevention of liver diseases[58]. Additionally, studies have indicated that blueberries possess the ability to rectify imbalances in gut microbiota, augment the production of intestinal tight junction proteins, and inhibit the expression of pivotal pro-inflammatory factors such as TLR4 and NF-κBp65, which are involved in the LPS/TLR4 inflammatory pathway. These effects contribute to the maintenance of intestinal epithelial barrier equilibrium and the alleviation of the consequent inflammatory response in the liver[59].

Additional herbal remedies such *as Dendrobii officinalis, Amomum villosum*, loquat fruit, and Semen Hoveniae[60] have demonstrated their ability to target both the intestinal mucosal barriers and hepatic inflammation triggered by endotoxins in models of liver disease. As a result, they effectively inhibit the origin and progression of inflammation[61,62]. However, it is important to highlight that these observations originate from a restricted set of recent investigations, the majority of which concentrate on a solitary model of liver disease and employ extracts derived from combinations of plant sources.

7. Natural Products for the Treatment of Hepatic/Liver Dysfunction

The utilization of Ayurvedic Herbal Medicines (AHM) has a long history, dating back to ancient times, with a legacy spanning over 3000 years. These products are extensively marketed and endorsed as natural remedies, leading to a perception of safety few are mentioned in Table 1. However, in India, there is a scarcity of comprehensive studies or significant series focusing on the hepatotoxic effects of AHM, aside from anecdotal case reports[63].

Table 1. List of natural products showing hepatoprotective effects

Natural Product	Source	Mechanism	Limitations
Phenols			
Resveratrol[64,65]	*Veratrum nigrum*	-The downregulated expression of collagen-1, TGF-β, and NF-κB mRNA, protein expression of desmin and α-SMA. -Attenuated hepatic accumulation of triglycerides. -Induces cell death in human S-HEP-1 hepatic cancer cells by suppressing the expression of antioxidant proteins and reducing ROS levels.	-No protection against liver injury induced by aflatoxin B1. -In NAFLD, lead to symptoms such as nausea, vomiting, diarrhoea, and impaired liver function. -At high doses, triggers apoptosis in normal cells.
Chlorogenic acid[66,67]	*Lonicera japonica*	-Via the TGFb1/Smad7 signaling pathway regulated by miR-21.	At a high dose of 7 mg/kg, enhances leukocyte adhesion in rats, leading to peroxide generation in the venule wall and albumin leakage in mesenteric venules.
Tea polyphenols	*Camellia sinensis*	By inhibiting the TLR4/MyD88-mediated NF-κB signal pathway, it reduces liver inflammation and promotes overall oxidant clearance while decreasing endotoxin levels.	Hepatotoxicity at high doses.
Curcumin[68]	*Curcuma longa*	Inhibits the activation of Hepatic Stellate Cells and induces their apoptosis.	Headache, Yellow stool, Diarrhea, and rash.
Salvianolic acid[69]	*Salvia miltiorrhiza*	Suppresses the activation and proliferation of HSCs, inhibiting the production of type I collagen and α-SMA.	No Potential side effects.
Terpenoids			
Sweroside[70,71]	*Swertia bimaculata*	-Activation of PPARα stimulates fatty acid oxidation and regulates liver fat metabolism. -Prevents the activation of the NLRP3 inflammasome, which promotes fibrosis, in macrophages and liver tissues.	No Potential side effects.
Paeoniflorin[72,73]	*Paeonia albiflora*	-Regulates the insulin signalling pathway IRS/Akt/GSK3β. -Activating the LKB1/AMPK signalling pathway inhibits lipogenesis, insulin resistance, and hepatic steatosis. -Inhibits the ROCK/NF-κB signalling pathway, exerting an anti-inflammatory effect.	Excessive bleeding, Diarrhoea. Digestive upset.
β-Patchoulene[74,75]	*Pogostemon cablin*	Activate CD36/AMPK signalling pathway	Irritative to sensitive skin.
Acanthoic Acid[76]	*Eleutherococcus senticosus*	-Prevents the buildup of lipids and the synthesis of fatty acids, leading to the activation of the FXR and LXR signalling pathways, resulting in increased expression of the AMPK-SIRT1 signalling pathway.	No Potential side effects.

Table 1 continued...

Natural Product	Source	Mechanism	Limitations
Asiatic Acid[77,78,79]	*Centella asiatica*	By inhibiting the NFkB signalling pathway, it effectively alleviates hepatocyte injury, hepatic steatosis, and hepatocyte apoptosis, thereby relieving oxidative stress and inflammation.	-Skin allergy and burning sensations (with external use), stomach upset, headache, nausea, extreme drowsiness dizziness
Flavonoids			
Silibinin[80]	*Silybum marianum*	-↓ neoplastic cell proliferation, -↓ neoplastic cell apoptosis -↓ glutathione and superoxide dismutase levels, membrane stabilization -Membrane stabilizing, hepatoprotective, anti-fibrotic, antioxidant, free radical scavenging activity.	-Worsens the tumour-promoting effects of ethanol.
Hesperetin[81]	*Citrus reticulata*	-Inhibits TGF-β1/Smad pathway-mediated extracellular matrix progression and apoptosis	-Stomach pain and upset, diarrhoea, headache.
Isoflavone[82,83,84]	Legumes	-Directly targeted cyclooxygenase-1 activity as well as its downstream TXA2 biosynthesis/AMPK Activation	-Nausea, constipation. bloating, diarrhoea - Sheep that consume red clover and captive cheetahs fed diets containing soy experience reproductive abnormalities, leading to infertility.
Anthocyanidin[85,86,87,88]	Petals Leaves Rhizomes	Induced endotoxemia and associated liver inflammation Nrf2/ARE Signaling Pathway/ Hyperglycemia, insulin resistance, hyperlipidemia, and NAFLD in diabetic rats were alleviated.	-Exhibits low stability -Susceptible to factors such as temperature, pH, relative humidity, light, sugars, vitamin C, oxygen levels, sulfur dioxide or sulfites, enzymes, and metal ions.
Polysaccharides			
Seabuckthorn berry polysaccharide[89]	The berries of seabuckthorn (*Hippophae rhamnoides* L)	Inhibits ROS and apoptosis by Nrf2/HO1/ SOD signalling in Drug-Induced Liver Injury	Care in patients with high blood pressure, palpitations headache, swelling, and dizziness.
Walnut green husk polysaccharides[90]	Walnut green husk	Improves gut microbiota and short-chain fatty acids in NAFLD	Stomach upset
Pinus koraiensis pine nut polysaccharide[91,92]	Pine nut	Inhibits inflammation and ROS by Nrf2 signalling in alcoholic liver disease and drug-induced liver injury	Pine mouth syndrome manifests as a taste disturbance, bitter or metallic sensation, occurring 1 to 3 days after consuming contaminated pine nuts.
Mussel polysaccharide α-D-glucan[93]	*Mytilus coruscus*	-Inhibits inflammation. -Increase short-chain fatty acids. -Inhibit PPAR signalling in NAFLD	No potential side effects

8. Conclusion

As the biggest solid organ in the body, the liver acts as an important connector between different nutrients, poisons, and hormones in the body. Due to its function in digesting and detoxifying foreign molecules, it is continually exposed to hazardous toxins. Chronic liver damage can cause pathological changes in the liver, such as cell ageing and inflammatory cell infiltration. Analysing several aspects, such as enzyme activity, bilirubin levels, and coagulation markers, is necessary to evaluate liver function. While ALP denotes obstructive biliary illness, ALT is a major marker for liver damage. The potential advantages of a vegetarian or vegan diet in reducing liver illnesses are gaining more and more attention. As they provide therapeutic advantages with few side effects, herbal therapies are also being investigated as alternatives to conventional treatments. Plant-based phytochemicals including flavonoids and tannins have demonstrated potential for decreasing inflammation and cancer risk. The heart, lungs, kidneys, and immune system are just a few of the other organs that liver problems can have a significant impact. Multiple organ failure may result from complications such as cirrhotic cardiomyopathy and hepatorenal syndrome. Other common repercussions of liver illnesses include hepatic encephalopathy, immune-related pulmonary ailments, and cardiovascular issues. The HPA axis, which controls the stress response, is essential for maintaining the health of the liver. Liver conditions including cirrhosis and cholestasis have been linked to HPA axis dysfunctions. The HPA axis releases hormones called glucocorticoids, which control gene expression and liver function. Hepatic diseases can be exacerbated by high amounts of glucocorticoid production and low cortisol levels. Botanical therapies have become more important in supporting liver health. Flavonoids found in medicinal plants have hepatoprotective effects. Different plant-based remedies are used in traditional medical systems like Ayurveda to treat liver diseases. In general, improving liver health and preventing liver disorders and related consequences need an understanding of the function of the liver, measuring liver health, and investigating herbal therapies.

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