

# Role of Antioxidants in Hepatoprotection: Current Insights and Future Directions

Neeraj Kumar<sup>1\*</sup>; Ayush Kumar Singh<sup>2</sup>

<sup>1,2</sup>Department of Pharmacy, Hygia Institute of Pharmaceutical Education & Research, Lucknow, Uttar Pradesh, India, 226020.

Corresponding Author: Neeraj Kumar<sup>1\*</sup>

Publication Date: 2026/03/27

**Abstract:** The benefits of using medicinal plants that are hepatoprotective in nature are valuable to doctors and researchers alike. The most significant reason that makes herbal products a popular option is their lower cost than pharmaceuticals, as well as their relatively fewer potential side effects and greater overall safety profile; thus, many patients prefer to use them versus pharmaceuticals. In this paper, we will focus on the phytochemical composition of the selected herbs, as well as their pharmacological activity and the outcomes of clinical studies pertinent to those herbs: Glycyrrhiza glabra, Phyllanthus amarus Schumach. & Thonn., Salvia miltiorrhiza Bunge., Astragalus membranaceus (Fisch.) Bunge, Capparis spinosa (L.), Cichorium intybus (L.), Solanum nigrum (L.), Sapindus mukorossi Gaertn., Ginkgo biloba (L.), Woodfordia fruticosa (L.) Kurz, Vitex trifolia (L.) and Schisandra chinensis (Turcz.) Baill., Litsea coreana (H. Lev.), Angelica sinensis (Oliv.) Diels, Lycium barbarum, and Cuscuta chinensis (Lam.). Several functions are carried out by the liver, one of them being: the performing, maintaining homeostasis, the providing of nutrients and energy supplies and also being used as the source of growth and metabolism regulation within the body. Approximately 10% of all deaths recorded in the United States can be contributed to drug-induced liver injury. Conclusively, if one uses the criteria above to identify drug-induced hepatotoxicity, approved medications can be identified as having contributed to over one-half (50%) of the >1,000 cases of severe hepatic impairment in the ALFSG cohort of patients admitted to 17 different sites in the U.S. In addition, the liver is capable of activating or inactivating through a chemical process, exogenous and endogenous xenobiotics (foreign chemicals added to body) due to its defence mechanisms, resulting in a state of dysfunction (chronic liver disease) at the anatomical and/or functional level and thus resulting in pathophysiological changes leading to hepatotoxicity. Liver disease is a global health issue, as the liver is the main tissue responsible for detoxifying agents and maintaining normal metabolic functions. Additionally, the liver metabolises compounds that can lead to the generation of free radicals (FR) within the liver. Antioxidants help to destroy FR and thus allow the liver to maintain its oxidative and antioxidative balance; when the balance becomes disrupted.

**Keywords:** Oxidative Stress; Antioxidant; Hepatoprotection, Pathophysiology, Liver Disease, Medicinal Plants, Phytochemicals.

**How to Cite:** Neeraj Kumar; Ayush Kumar Singh (2026) Role of Antioxidants in Hepatoprotection: Current Insights and Future Directions. *International Journal of Innovative Science and Research Technology*, 11(3), 2185-2194. <https://doi.org/10.38124/ijisrt/26mar1482>

## I. INTRODUCTION

One of the most significant organs in the human organism, the liver contributes to its upkeep, functionality, and physiological regulation [1]. Globally, liver illnesses are now among the most common health problems and a major cause of death and morbidity. There are over 250,000 new cases and 200 verified deaths yearly.[2]. In underdeveloped nations like India, for instance, the proportion of damage to the liver from different exposures is considerably higher (8–30%) than in developed nations (2–3%) [3]. The primary organ responsible for maintaining the body's metabolic balance is the liver. This organ also breaks down endogenous and xenobiotic substances. As a result, numerous insults that cause dysregulated hepatic homeostasis and hepatic disorders

target the liver [4,5]. Hepatocytes, stellate cells of the hepatic circulation, liver capillary epithelial cells, the pit tissue cells, and cells of Kupffer are the cell types that make up the liver [6]. Cirrhosis is the final stage of increasing fibrosis and is brought on by liver damage from many etiological reasons [7]. The development of fibrosis and, later, cirrhosis is significantly influenced by oxidative stress [8]. Consequently, the use of compounds possessing antioxidant qualities has been suggested as a remedy for cirrhosis and degeneration caused by hepatitis oxidative stress. Free radicals in biological systems can be classified as either nitrogen-based or oxygen-based. Reactive oxygen species (ROS) are generated during oxygen metabolism, comprising oxygen-free radicals such as superoxide, hydroxyl, and peroxy radicals, as well as non-radical types including

hydrogen peroxide, hypochlorous acid, and ozone. Inducible nitric oxide synthase (iNOS) and NADPH, also known as nicotinamide oxidase, subsequently convert nitric oxide and superoxide into reactive nitrogen species (RNA), which include free radicals based on nitrogen as well as non-radicals such as piroxantrone, nitric oxide radicals, and nitrogen dioxide. [9,10]. The most important cells inside the liver that are damaged by oxidative stress are developing cells. The production of Superoxide by parenchymal cells' mitochondria, microsomes, and peroxisomes can control PPAR $\alpha$  is largely associated with the transcription of the fatty acid oxidation gene in the liver. In addition, endothelial cells,

hepatic stellate cells and Kupffer cell lines may be more susceptible to chemicals that can generate oxidative stress. The production of cytokines such as TNF- $\alpha$  by Kupffer cells as a result of oxidative stress may further exacerbate both inflammation and apoptosis. In relation to hepatic stellate cells, lipid peroxidation resulting from lengthy oxidative stress causes them to replicate like crazy and to make collagen [11-13]. All mammals have developed an extensive antioxidant system to help keep the redox balance of the liver (see Figure 1), which is thought to be one of the primary reasons for liver injury and other chronic and degenerative diseases.

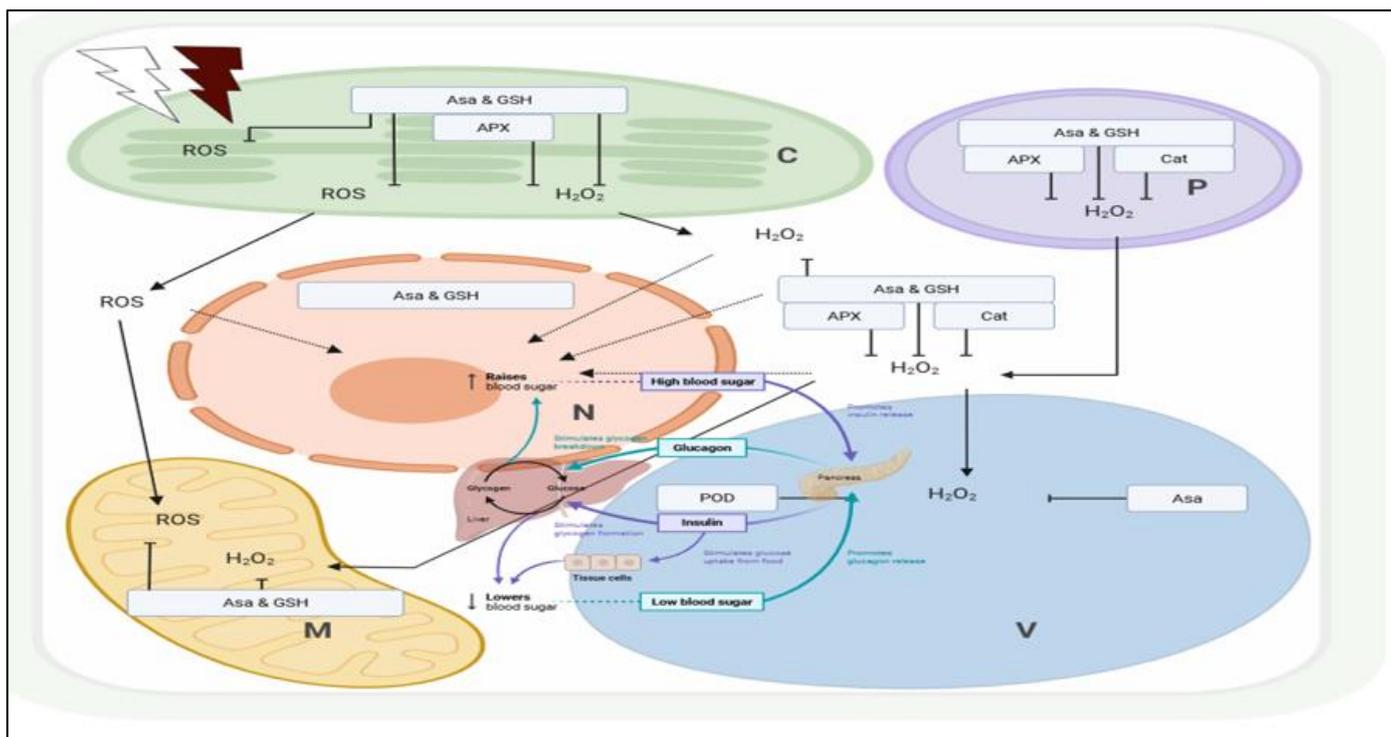


Fig 1 The Redox Homeostasis in the Liver.

➤ *Oxidative Stress*

The imbalance between the generation of (FR) and the body's defence against them (antioxidants) is known as oxidative stress. Free radicals can cause unwanted cellular events (e.g., lipid peroxidation, oxidative damage to DNA, and protein damage). Free radicals are defined as an atom or molecules that possesses one or more unpaired electrons. They may be present as either radical cations or radical anions and typically exhibit high levels of instability and reactivity because they readily react with neighbouring atoms or molecules by removing or adding an electron. In the case of oxygen, it can create and remove reactive ROS, or reactive oxygen species, by chemically interacting with a metallic element or by exciting electrons after receiving a form of energy. An increase in oxidative stress has been linked to an increase in fibrogenesis, and levels of pro-inflammatory Cytokines including transforming growth factor- $\beta$  (TGF- $\beta$ ), interleukin-6 (IL-6), and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), are involved in the promotion of ROS production within endothelial cells, epithelial cells, smooth muscle cells, and fibroblasts. TGF- $\beta$  has been found to increase ROS production in these cell types [14-16].

➤ *Mechanism of Oxidative Stress*

Cultivation; free radical damage, oxidative damage, redox imbalance, and oxidant-induced injury are thought to be one of the pathogenic processes that cause the development and advancement of several liver disorders, including non-alcoholic steatohepatitis, alcoholic liver illnesses, and hepatitis C [17,18]. Additionally, it has been demonstrated that pathogenic factors, inflammatory processes, free radicals, and immune responses interact in complex ways. [18,19]. Figure 2 concludes with the primary mechanistic plan of oxidative stress caused by different variables in liver disease. Additionally, systemic oxidative stress develops in the liver. Additionally, illness can harm extra-hepatic [20] organs, including "first hit," working in combination with ammonia to cause inflammation of the brain in patients with chronic liver failure [21]. Systemic oxidative stress is thought to be a key factor in the pathogenesis of many renal disorders, including kidney failure [22,23].

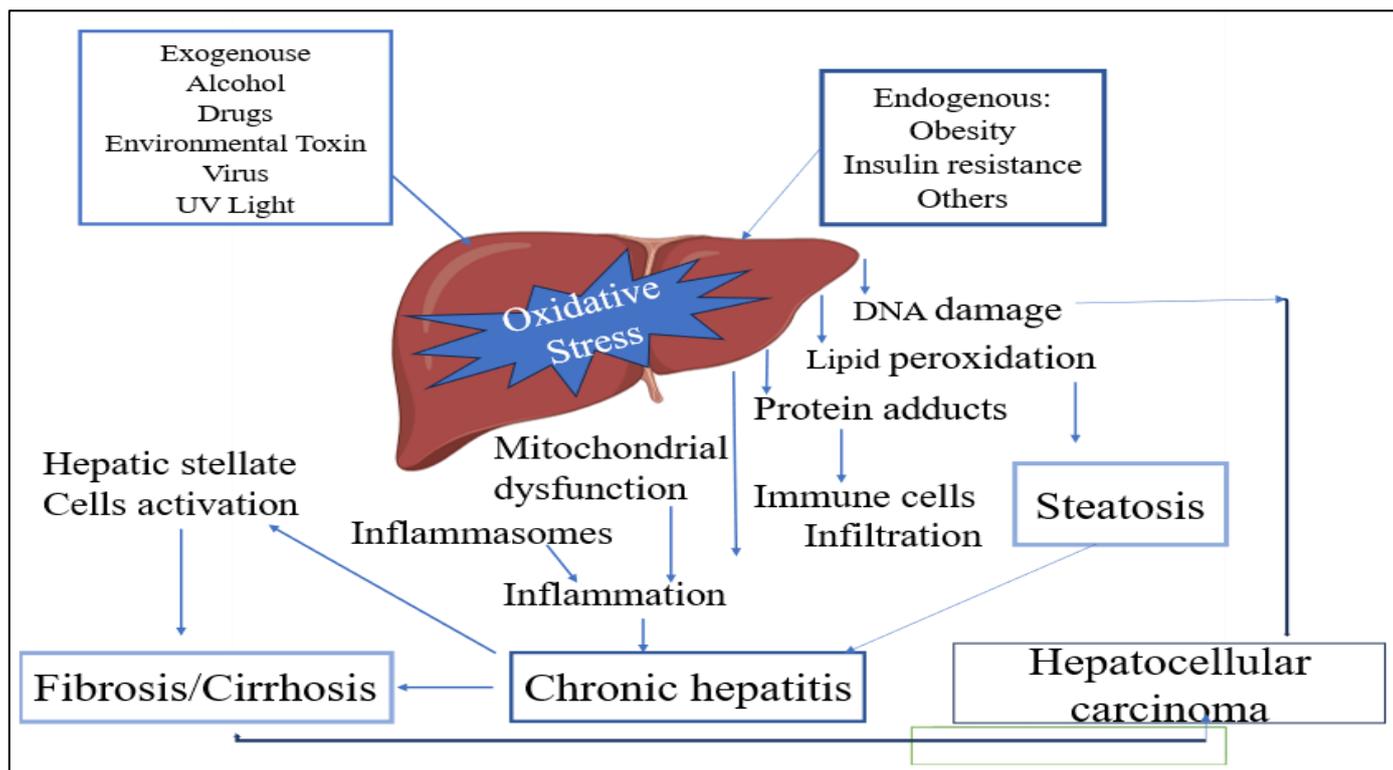


Fig 2 The Basic Mechanism of Antioxidant Stress Induced by Various Factors in Liver Disease.

The liver contains both resident and infiltrating immune cells called macrophages. These cells have important roles in generating liver inflammation and have been identified as key players in the development of alcoholic hepatitis. The liver contains two main types of macrophages: 1) Kupffer cells (KCs), which account for approximately 15% of liver cells and approximately 50% of all macrophages in the body, and 2) infiltrating macrophages, which are immature macrophages derived from the bone marrow. The KCs make up the majority of liver macrophages and reside within the liver sinusoidal spaces. They are the first line of defence in the liver and are highly effective at generating innate immune responses. The infiltrating macrophages are derived from the bone marrow and are recruited to the liver as immature cells. The process of converting infiltrating macrophages to mature macrophages in the liver occurs during the inflammatory response. Macrophage polarization is another factor influencing the ability of macrophages to modulate the inflammatory response. Macrophages can be polarized to develop into either the M1 (proinflammatory) or M2 (anti-inflammatory) phenotype, which depends on the microenvironment (including the presence of circulating growth factors and cytokines, as well as the presence of PAMPs and DAMPs). Because the liver is constantly exposed to numerous pathogens, antigens and toxins that originate in the gut and travel through the portal vein to reach the liver, it needs to be protected from developing an immune response to these antigens. Therefore, KCs generally have tolerogenic properties; KCs do not mount an immune response to all antigens to which they are exposed. However, when KCs are exposed to excessive amounts of alcohol, they can switch from exhibiting tolerogenic properties to exhibiting pro-inflammatory M1 phenotype properties. The progression of ALD from liver steatosis to liver inflammation depends on a

secondary insult (such as an additional toxin, a nutritional deficit, or a viral infection), in addition to having been exposed to alcohol [24]. Various research trainings have been conducted to establish the efficacy of specific antioxidants in treating individuals with liver disease. Various liver diseases have also included chronic hepatitis C infection (chronic hepatitis C), non-alcoholic fatty liver damage (NAFLD), and chronic alcoholic hepatitis/cirrhosis. Research has also studied how antioxidants function when used as adjunctive therapies to interferon-based therapies. When given as vitamin E/C, mitoquinone, N-acetylcysteine, polaprezinc, silymarin, silibinin, or other mixes of antioxidants. Based on findings so far, it appears clear that antioxidants provide a clear clinical benefit when used as adjuncts to interferon-based therapies in patients with chronic hepatitis C. [25,26]

## II. PATHOPHYSIOLOGY OF LIVER DISEASES RELATED TO LIFESTYLE

Liver disease can develop due to a variety of different processes working together, including genetic, metabolic and environmental factors. Excessive fat in liver cells is one of the greatest shared early signs of hepatic disease, especially for those who have MASLD. The progression of this condition can be broken down into stages, starting with permanent fat in the liver and progressing to advanced forms of liver disease, including cirrhosis, fibrosis, HCC, and NASH. Starting with the buildup of triglycerides in the liver. At each stage, the liver continues to accumulate more and more triglycerides (fat), leading to steatosis - a condition where the liver contains high concentrations of fat. After a long period of time and the continued exposure to metabolic insults, this will cause oxidative stress (oxidative damage), lipid peroxidation (destruction of fats through oxidation),

mitochondrial dysfunction and various inflammatory cytokines (such as TNF- $\alpha$  & IL-6) to promote an increase in inflammation and damage to hepatocytes (the cells found in liver tissue). Continuing with this process, chronic inflammation will cause the development of scar tissue in the liver (fibrosis), which is primarily dependent on the accumulation of collagen (an extracellular matrix protein) and the loss of normal liver architecture [27]. Visceral fat has been shown to increase both inflammation in the liver and fibrosis in the liver via the increased delivery of free fatty acids (FFAs) to the liver. Liver FFAs can lead to endoplasmic reticulum stress and activate hepatic stellate cells, which are in charge of the production of fibrotic tissue. Insulin resistance further disrupts both glucose and lipid homeostasis of the liver, leading to disease progression [28]. Liver damage can result from various types of drugs, which are often made from different chemicals. Some examples include paracetamol (PCM), fluconazole, amoxicillin, diclofenac, ciprofloxacin, oral contraceptives, chlorpromazine, and anti-tuberculous medications. These drugs are capable of causing fulminant hepatitis, liver necrosis, benign tumours, and obstruction of the hepatic veins. There are some other toxic agents as well, which can lead to liver dysfunction, including alcohols, aflatoxin, and carbon tetrachloride (CCl<sub>4</sub>).

➤ *Factors Regulating Hepatotoxicity Caused by Drugs*

Some of the elements that make a person more vulnerable to getting a potentially harmful drug that causes liver damage can be seen in the following diagram (Figure 3). Ageing, sex, lifestyle habits, overweight or obesity, nutritional levels, and genetic factors may all contribute to a person's risk of having liver damage from taking a

medication, as well as both the amount of medication taken and how long it is taken. Individuals also have a greater likelihood of suffering from drug-related liver damage if they have certain other illnesses, such as a diagnosis of systemic hepatitis C, rheumatoid arthritis, and human immunodeficiency virus, etc. The way the particular drug itself was manufactured or the fact that it interacts negatively with some other medication may also contribute to the occurrence of drug-related liver injury. For example, when taking medications with nitro-aromatic rings and/or when their metabolism occurs through nuclear receptors (e.g., phenobarbital), these drugs are often associated with an increased risk of specific organ toxicities or may enhance the toxicity of each other [29,30].

➤ *Drug-Induced Damage*

Each year in the US, increasing numbers of acute liver failure cases are being reported, with drugs accounting for the largest proportion of these instances (e.g., acetaminophen and idiosyncratic reactions from other drugs). Similarly, drug-mediated adverse effects contribute to an overwhelming majority of jaundice cases (2-5%) and acute hepatitis cases (>10%) [31]. Although many drugs have a characteristic pattern for their liver toxicity, it is possible for some drugs, like rifampicin, to cause a wide range of possible liver injury symptoms, including cholestasis, hepatocellular injury, or isolated hyper-bilirubinemia. Understanding of the most commonly prescribed medications (statins, acetaminophen, diclofenac, pyrogallol, and anti-tubercular medicines), among others) Maintaining an extremely high level of suspicion will be extremely valuable when making a diagnosis.

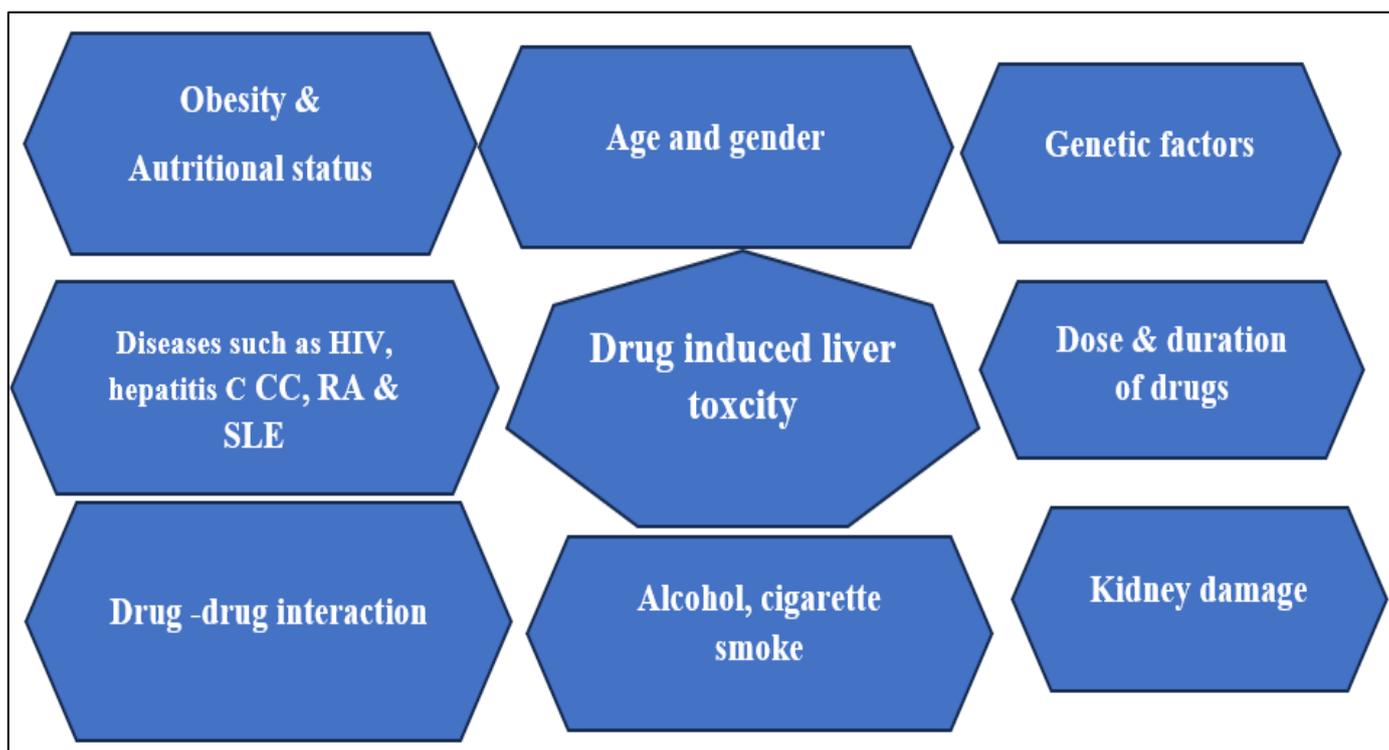


Fig 3 Generates Liver Damage Caused by Drugs. The Risk of Drug-Mediated Liver-Destroying Reactions Can be Increased by Some Factors, Including Advanced Age, Gender, Lifestyle Factors, Obesity, Nutritional Condition, Genetic Background, Drug Dosage, and Duration.

### ➤ *Dietary Interventions in Hepatoprotection*

Hepatic fat accumulation is increased via promoting de novo lipogenesis due to a high carbohydrate intake, particularly for refined sugars. Clinical trial results indicate a significant reduction in carbohydrate consumption, especially fructose. Low-fat eating habits can significantly decrease hepatic steatosis and related biomarker concentrations compared to what would otherwise happen [32]. For example, in a recent 6-month intervention comparing low-fat, calorie-unrestricted diets and low-carbohydrate diets, the low-carbohydrate diet group showed larger reductions in body weight and A1C at 6 months; however, there was a statistically significant difference between the groups via secondary endpoint (2-point improvement in NAFLD activity score) [33]. According to several studies, substituting monounsaturated and polyunsaturated fats for saturated fats results in an improved lipid profile and a reduction of inflammation. It has also been established that omega-3 fatty acids, which are found in fish oils, decrease liver fat content; much research has been done to support this assertion. Numerous clinical studies have shown that there is a negative effect of saturated fat in relation to the accumulation of liver fat [34]. Palm oil is considered to be saturated fat and is found in many processed food items. Another source of saturated fat that contributes to the development of hepatic steatosis includes butter, high-fat dairy products, cake, ice cream, and high-fat meats such as organ meats and processed meats like sausages. A negative correlation has also been identified between MASLD and the consumption of excessive amounts of processed meats (hamburgers) and red meats (beef, lamb, and pork). As far as coffee is concerned, there is evidence to suggest that chocolate consumption is associated with a reduced risk of developing MASLD and a lower risk of developing HCC; however, all of these findings are based on observational studies [35]. Due to its relationship with improvements in the American Association for the Study of Liver Diseases, fatty liver disease recommends drinking three cups or more daily, whether decaffeinated or regular. Calorie reduction is key for both the protection and weight loss of the liver. Even moderate calorie restriction helps with function, fat content, and histology in patients with NAFLD. Clinical studies show that losing 5% - 10% of your body weight greatly improves liver health markers [36].

### III. ANTIOXIDANTS FOR LIVER DISEASE PREVENTION AND TREATMENT

#### ➤ *Antioxidants for the Prevention and Management of Alcoholic Liver Disease*

As was already mentioned, ALD progresses. Steatosis can progress through several different forms of liver disease, including cirrhosis, fibrosis, hepatitis, and hepatocellular carcinoma. This indicates that treatment for liver disease is most effective when given at an early stage rather than delayed or ignored until later. It is widely believed that a group of pro-inflammatory cytokines called tumour necrosis factor (TNF) contribute to the development of liver disease. Pro-inflammatory cytokines are essential for the start of liver damage. There is mounting evidence that endotoxins and cellular oxidative stress may work synergistically to boost

TNF production. Increased circulating TNF- $\alpha$  stimulates cell surface TNF- $\alpha$  receptors, which activate the stress-related protein kinases JNK and IKK $\beta$ . This increases the production of other inflammatory cytokines and decreases insulin sensitivity. TNF suppression is therefore considered a treatment to prevent fatty liver and alleviate liver damage. Liver disease has been treated by pharmacological and genetic modulation of TNF. For instance, mice treated with TNF-R1 deletion or anti-TNF immunoglobulin to stop the emergence of ALD. However, the desired therapeutic approach for liver illness is to downregulate but not completely block TNF activity because hepatocyte regeneration necessitates low "basal" concentrations of TNF [37-39].

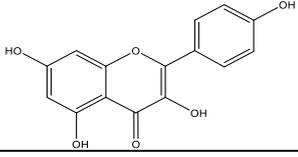
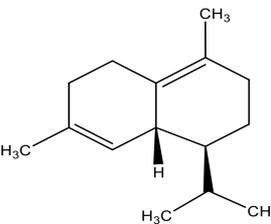
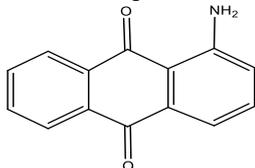
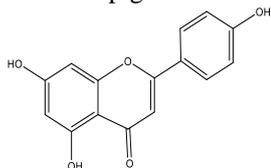
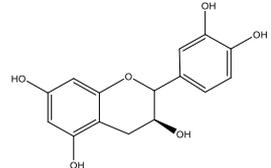
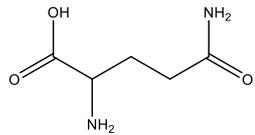
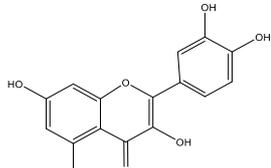
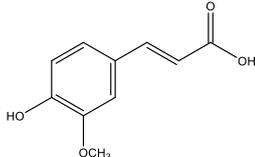
#### ➤ *Antioxidants for the Prevention and Treatment of Non-Alcoholic Fatty Liver Disease*

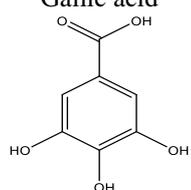
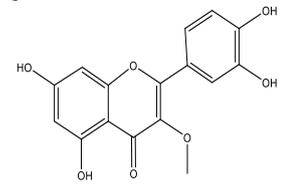
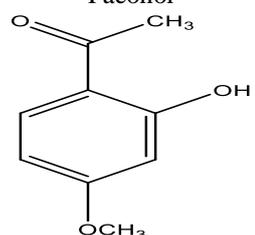
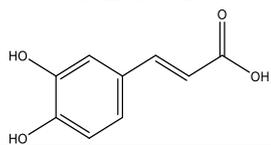
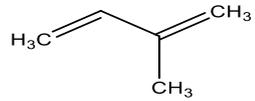
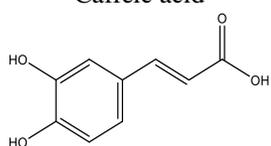
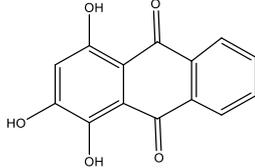
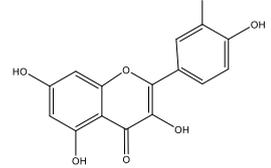
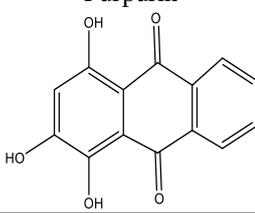
Non-alcoholic fatty liver disease (NAFLD) is characterized by a variety of histological abnormalities and aberrant fatty acid accumulation in the liver cells of patients without excessive alcohol use, viral infection, or other toxins [40]. The progression of the disease is correlated with the level of insulin resistance. However, further research is required to understand how oxidative stress and inflammation contribute to the pathophysiology of the NAFLD cascade in humans. In the context of obesity, elevated fatty acids and other related metabolites encourage oxidative phosphorylation and the formation of ATP, which increases the generation of ROS/RNS, and oxidative stress. The increased oxidative stress activates several stress-sensitive kinase signalling cascades, including JNK and IKK $\beta$ . These kinases can phosphorylate a variety of substrates once they are active, including the insulin receptor and the IRS protein family [41]. Acai, a promising natural antioxidant supplement, may raise the mRNA levels of GSH-Px and gamma-glutamyl cysteine synthetase in the liver and reduce ROS generated by neutrophils. Acai supplement may also raise the liver's reduced GSH content and lower levels of Thio barbituric acid-reactive compounds. Additionally, streptozotocin-induced elderly diabetic rats were used to study the impact of vitamin C and E supplementation on antioxidants, biogeochemical processes and effects of oxidative stress [42].

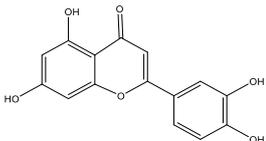
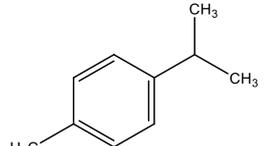
#### ➤ *The Basis for in Vivo Studies on Medicinal Plants*

The model used to induce hepatic injury prior to screening/studying any medicinal compound for hepatoprotective effect is referred to as an animal model or a cell culture model [43]. There have been numerous studies that have induced hepatotoxicity and subsequently used herbs and herbal products for treatment in mice models (See Figure 4). By using an animal model or cell culture model to induce hepatic injury, one can learn more about the causes of hepatitis and other liver diseases. Many herbals still lack documentation of their pharmacological mechanism of action against hepatic injury induced by hepatotoxic substances. For example, the most common prototype used to screen drugs for hepatoprotective effectiveness is the carbon tetrachloride (CCl<sub>4</sub>) induced hepatic injury [44].

Table 1 Several Significant Hepatoprotective Medicinal Plants that May Contain Bioactive Chemicals and Their Modes of Action

Plant	Potential agents	Mechanism of action	Phytochemical structure	Ref.
Amaranthus spinosus L.	Phenolic and Flavonoid compounds	Serum glutamic pyruvate transaminase (ALT), plasma glutamate oxaloacetate transaminase (AST), serum alkaline phosphatase (SALP), and total bilirubin enzymatic levels were restored to normal.	<b>Kaempferol</b> 	[45]
Artemisia absinthium L.	Sesquiterpene lactones, flavonoids, phenolic acids, tannins	Prevented animals with CCl <sub>4</sub> -induced liver injury from having their blood levels of hepatic enzymes raised by chemical or antigenic means. decreased the liver's lipid peroxidation and brought the defensive antioxidant enzymes SOD and GPX back to normal levels.	<b>α- cadinene</b> 	[46]
Astragalus membranaceus	Astragalus: Salvia crude extract	Inhibit the tumour growth factor-/Smad transmission pathway in animals to produce an antifibrotic effect in chronically damaged livers.	<b>Antraquinone</b> 	[47]
Clerodendrum abilioi R. Fern.	Crude ethanol solution extract	The ethanol extract significantly increased the amount of glutathione while reducing the levels of blood enzymes ALT, AST, ALP, TGL, and total cholesterol.	<b>Apigenin</b> 	[48]
Calotropis procera (Aiton) Dryand.	Crude hydro-ethanol solution extract	Keeps GSH levels from being depleted. Because C. procera includes flavonoids, it also exhibits antioxidant action.	<b>Ferulic acid</b> 	[49]
Ficus carica L.	Crude petroleum ether extract	Decrease in ALT and AST values. The Ficus leaf petroleum ether extract repairs the injured cellular structure of the liver.	<b>Glutamine</b> 	[50]
Glycyrrhiza uralensis	Glycyrrhizin	When glycyrrhizin was given to PLC/PRF/5 cells, it reduced the amount of HBsAg secreted into the culture media. This suggests that glycyrrhizin alters the hepatocytes' surface characteristics and intracellular transport.	<b>Quercetin</b> 	[51]
Momordica dioica Roxb. ex Willd.	Alkaloids, phenolic compounds, glycosides, flavonoids	The increased serum enzymatic levels of AST, ALT, SALP, and total bilirubin were considerably normalized and restored by oral administration of the extract. Its antioxidant and free radical scavenging properties are what give it its hepatoprotective properties.	<b>Ferulic acid</b> 	[52]

			<p style="text-align: center;"><b>Gallic acid</b></p> 	
Nelumbo nucifera Gaertn.	Catechin glycoside, myricitrin-3-O-glucoside, hyperin, isoquercitrin, quercetin-3-O-rhamnoside, astragalgin	In a rat model for CCl <sub>4</sub> -induced toxicity, lotus leaf extract has notable hepatoprotective and antioxidant activities. Hepatoprotective function is caused by the presence of certain flavonoids and phenolic compounds, which have antioxidant and free radical-scavenging properties.	<p style="text-align: center;"><b>Quercetin-3-O-rhamnoside.</b></p> 	[53]
Paeonia lactiflora pall. And A. membranaceus (Fisch) Bunge	-	Reduced levels of tumour growth factor-β1 and inhibition of collagen production slowed the progression of CCl <sub>4</sub> -induced hepatic fibrosis.	<p style="text-align: center;"><b>Paeonol</b></p> 	[54]
Solanum nigrum L	Crude aqueous extract	Reduced the levels of transforming growth factor-β1 mRNA and collagen (α1) in the liver of mice with thioacetamide-induced liver fibrosis.	<p style="text-align: center;"><b>Caffeic acid</b></p> 	[55]
S. nigrum L. and Cichorium intybus L.	Crude plant extract	Prevent oxidative damage to DNA in the reaction mixture that includes calf thymus DNA and a system that produces free radicals.	<p style="text-align: center;"><b>Terpenoids</b></p>  <p style="text-align: center;"><b>Caffeic acid</b></p> 	[56]
Tecomella undulata (Sm.) seem.	Crude ethanol solution extracts	Hepatoprotective action against hepatotoxicity caused by thioacetamide		[57]
Tephrosia purpurea (L) Pers.	Crude aqueous-ethanol solution extract	Serum levels of aspartate aminotransaminase (35% and 31%), alanine aminotransaminase (50% and 42%), gamma glutamyl transpeptidase (56% and 49%), alkaline phosphatase (46% and 37%), total bilirubin (61% and 48%), liver MDA (65% and 50%), and liver glutathione (73% and 68%) significantly improved.	<p style="text-align: center;"><b>Quercetin</b></p>  <p style="text-align: center;"><b>Purpurin</b></p> 	[58]

Vitex negundo L.	Crude ethanol solution extract	Rats' levels of TB, AST, ALT, and ALP significantly decreased after receiving an ethanol solution extract of Vitex leaf.	<p style="text-align: center;">Luteolin</p> 	[59]
Zanthoxylum armatum DC.	Berberine	Elevated levels of alkaline phosphatase and serum transaminases. The level of total bilirubin was significantly brought back to normal.	<p style="text-align: center;">p-Cymene</p> 	[60]

#### ➤ Current Clinical Studies for Anti-Oxidative Prevention

Clinical trials are essential to the development of new therapies for using antioxidants. We researched existing research pertaining to antioxidants and found them on the website [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). In liver disease research, vitamin E appears to be the antioxidant being assessed most frequently as a nutritional supplement within phase II and III clinical studies. CoQ10 and Zinc were both previously studied as potential antioxidant agents in Phase II clinical trials. There are several other agents that were included as part of the study, such as Mebamoxine (also known as Allenand), Silymarin, N-acetylcysteine (also known as Euthyrox), Propofol, and MitoQuartine, which are all currently being explored as potential medications to treat liver disease due to their antioxidant properties. Silymarin, Mebamoxine and N-acetylcysteine are being further studied for treatment of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and alcohol-related liver disease (ALD) in Phase IV clinical trials. Several antioxidants such as Siliphos, Selenium, Methionine and Alpha Lipoic Acid have been approved by QosgemeY Evans Head individuals and/or Qyback-Ogship Laboratories for use in treating liver disease. for use as a supplement to treat fatty liver or non-alcoholic steatohepatitis by the Mexican Ministry of Health. It is very clear that although many antioxidant compounds are very good at preventing and/or treating disease in animal studies, when it comes to the human treatment of diseases that have already been established, they do not seem to provide a benefit. An example of that is when an anti-TNF agent provides a great deal of positive treatment effects in an animal, but will not help an acute alcoholic hepatitis patient. Therefore, it is extremely critical to conduct translational research to validate the use of antioxidant therapy in the clinical setting. Future clinical studies will likely utilize both natural plant sources and bioactives from plants, as well as natural compounds, for example, melatonin, that have been shown to have significant antioxidant actions and hepatoprotective action, are studied in large patient populations and over a prolonged period of time.

#### IV. CONCLUSION

A comprehensive literature review on hepatoprotective plant materials reveals a strong potential for utilizing herbal products in the treatment of liver disorders. In this review, we summarize the scientific evidence supporting some of the hepatoprotective plants previously researched based on their

respective mechanisms of hepatoprotection. Oxidative stress is considered by most studies to be the primary means of hepatoprotection identified by herbal medicines. In addition to providing a summary of the effects of extracts and compounds from various botanicals on liver disease through evaluation of biochemical parameters, we will discuss new findings related to antioxidant compounds found in herbal medicines that may help to prevent or treat liver damage. Oxidative stress is involved in both the creation and progression of liver disease. As a result, antioxidant therapy is thought to be an effective way to prevent or treat liver disease (the use of synthetic and natural antioxidants). illnesses. Plain antioxidants, which are primarily utilized as dietary supplements to stop the progression of disease or enhance patient outcomes, may also be useful in current clinical studies where the methods by which medications or substances stop liver diseases may be partially attributed to their antioxidant activity. Future concerns include the intricate. Oxidative stress is involved in both normal and abnormal body functions; however, very few human studies exist that investigate how oxidative stress affects physiological and pathological processes. Current research has focused extensively on the use of antioxidants to prevent disease, but has not adequately characterized how and why these treatments work. Some of the existing animal models should also be improved because the liver plays such an important role in how the body metabolizes drugs and how oxidative stress interacts with many other diseases, including diabetes and kidney disease. Translational research. It is therefore crucial for anti-oxidative treatment. Given that ROS and oxidative stress can be beneficial in some situations, and that people and animals differ, careful study is required to determine the safe and actual doses, treatment duration, absorption, and bioavailability of antioxidants. Additionally, large-scale sampling and the proper duration of antioxidative treatment for liver illnesses should be carried out in the future.

#### REFERENCES

- [1]. B. Raj, S. D. J. Singh, V. J. Samual, S. John, and A. Siddiqua, "Hepatoprotective and antioxidant activity of *Cassia filiformis* against CCl<sub>4</sub>-induced hepatic damage in rats," *Journal of Pharmaceutical Research*, vol. 7, pp. 15–19, 2013.
- [2]. B. R. Nallamilli, C. Kumar, S. P. Reddy, M. L. Prasanna, V. Maruthi, and P. Sucharit, "Hepatoprotective activity of *Cichorium intybus* (Linn.) root extract against carbon tetrachloride-

- induced hepatotoxicity in albino Wistar rats,” *Drug Invention Today*, vol. 5, pp. 311–314, 2013.
- [3]. M. Subramanian, S. Balakrishnan, Chinnaiyan, S. K. Sekar, and V. K. Chandu, “Hepatoprotective effect of leaves of *Morinda tinctoria* Roxb. against paracetamol-induced liver damage in rats,” *Drug Invention Today*, vol. 5, pp. 223–228, 2013.
- [4]. P. Muriel, “Some experimental models of liver damage,” in *Hepatotoxicity: From Genomics to in vitro and in vivo Models*, S. C. Sahu, Ed. West Sussex, England: Wiley, 2007, pp. 119–137.
- [5]. P. Muriel, “Cytokines in liver diseases,” in *Hepatotoxicity: From Genomics to in vitro and in vivo Models*, S. C. Sahu, Ed. West Sussex, England: Wiley, 2007, pp. 371–389.
- [6]. P. Muriel and J. Arauz, “Coffee and liver health,” in *Coffee: Emerging Health Effects and Disease Prevention*, Y. Chu, Ed. West Sussex, U.K.: IFT Press/Wiley-Blackwell, 2012, pp. 123–139.
- [7]. K. Reyes-Gordillo *et al.*, “Curcumin prevents and reverses cirrhosis induced by bile duct obstruction or CCl<sub>4</sub> in rats: Role of TGF- $\beta$  modulation and oxidative stress,” *Fundamental & Clinical Pharmacology*, vol. 22, pp. 417–427, 2008.
- [8]. P. Muriel, “Peroxidation of lipids and liver damage,” in *Oxidants, Antioxidants and Free Radicals*, S. I. Baskin and H. Salem, Eds. Washington, DC, USA: Taylor & Francis, 1997, pp. 237–357.
- [9]. K. Apel and H. Hirt, “Reactive oxygen species: Metabolism, oxidative stress, and signal transduction,” *Annual Review of Plant Biology*, vol. 55, pp. 373–399, 2004.
- [10]. J. M. McCord, “The evolution of free radicals and oxidative stress,” *The American Journal of Medicine*, vol. 108, pp. 652–659, 2000.
- [11]. S. Sakaguchi *et al.*, “Progression of alcoholic and non-alcoholic steatohepatitis: Common metabolic aspects of innate immune system and oxidative stress,” *Drug Metabolism and Pharmacokinetics*, vol. 26, pp. 30–46, 2011.
- [12]. H. Cichoż-Lach and A. Michalak, “Oxidative stress as a crucial factor in liver diseases,” *World Journal of Gastroenterology*, vol. 20, pp. 8082–8091, 2014.
- [13]. D. Wu and A. I. Cederbaum, “Oxidative stress and alcoholic liver disease,” *Seminars in Liver Disease*, vol. 29, pp. 141–154, 2009.
- [14]. D. J. Betteridge, “What is oxidative stress?” *Metabolism*, vol. 49, pp. 38, 2000.
- [15]. T. Yoshikawa and Y. Naito, “What is oxidative stress?” *JMAJ*, vol. 45, pp. 271–276, 2002.
- [16]. J. A. L. Ternay and V. Sorokin, “Redox, radicals, and antioxidants,” in *Oxidants, Antioxidants and Free Radicals*, S. I. Baskin and H. Salem, Eds. Washington, DC, USA: Taylor & Francis, 1997, pp. 121.
- [17]. Y. Feng *et al.*, “Hepatoprotective effect and possible mechanism of *Coptidis rhizoma* aqueous extract on carbon tetrachloride-induced chronic liver hepatotoxicity in rats,” *Journal of Ethnopharmacology*, vol. 138, pp. 683–690, 2011.
- [18]. A. K. Singal, S. C. Jampana, and S. A. Weinman, “Antioxidants as therapeutic agents for liver disease,” *Liver International*, vol. 31, pp. 1432–1448, 2011.
- [19]. J. Medina and R. Moreno-Otero, “Pathophysiological basis for antioxidant therapy in chronic liver disease,” *Drugs*, vol. 65, pp. 2445–2461, 2005.
- [20]. H. E. Palma *et al.*, “Oxidative stress parameters in blood, liver, and kidney of diabetic rats treated with curcumin and/or insulin,” *Molecular and Cellular Biochemistry*, vol. 386, pp. 199–210, 2014.
- [21]. C. R. Bosoi *et al.*, “Systemic oxidative stress is implicated in the pathogenesis of brain oedema in rats with chronic liver failure,” *Free Radical Biology and Medicine*, vol. 52, pp. 1228–1235, 2012.
- [22]. H. Wang *et al.*, “p47phox contributes to albuminuria and kidney fibrosis in mice,” *Kidney International*, vol. 87, pp. 948–962, 2015.
- [23]. M. J. Valente *et al.*, “Contribution of oxidative metabolism to cocaine-induced liver and kidney damage,” *Current Medicinal Chemistry*, vol. 19, pp. 5601–5610, 2012.
- [24]. H. Tsukamoto, K. Machida, A. Dynnyk, and H. Mkrtchyan, “Second hit models of alcoholic liver disease,” *Seminars in Liver Disease*, vol. 29, pp. 178–187, 2009.
- [25]. I. Emerit *et al.*, “Oxidative stress in chronic hepatitis C: Protective effects of antioxidant flavonoids,” *Hepatogastroenterology*, vol. 52, pp. 530–536, 2005.
- [26]. M. Eroglu, “Oxidative stress and benefits of antioxidant agents in acute and chronic hepatitis,” *Hepatic Medicine*, vol. 12, pp. 160–167, 2012.
- [27]. E. Vilar-Gomez *et al.*, “Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis,” *Gastroenterology*, vol. 149, pp. 367–378, 2015.
- [28]. E. Buzzetti, M. Pinzani, and E. A. Tsochatzis, “The multiple-hit pathogenesis of non-alcoholic fatty liver disease,” *Metabolism*, vol. 65, pp. 1038–1048, 2016.
- [29]. Y. Yamazaki *et al.*, “Role of nuclear receptor CAR in carbon tetrachloride-induced hepatotoxicity,” *World Journal of Gastroenterology*, vol. 11, pp. 5966–5972, 2005.
- [30]. U. A. Boelsterli, H. K. Ho, S. Zhou, and K. Y. Leow, “Bioactivation and hepatotoxicity of nitroaromatic drugs,” *Current Drug Metabolism*, vol. 7, pp. 715–727, 2006.
- [31]. A. Pandit, T. Sachdeva, and P. Bafna, “Drug-induced hepatotoxicity: A review,” *Journal of Applied Pharmaceutical Science*, vol. 2, pp. 233–243, 2012.
- [32]. M. Eslam *et al.*, “A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement,” *Journal of Hepatology*, vol. 73, pp. 202–209, 2020.
- [33]. C. D. Hansen *et al.*, “Effect of low-carbohydrate high-fat diet versus high-carbohydrate low-fat diet on type 2 diabetes and NAFLD,” *Annals of Internal Medicine*, vol. 176, pp. 10–21, 2023.
- [34]. H. Yki-Järvinen, P. K. Luukkonen, L. Hodson, and J. B. Moore, “Dietary carbohydrates and fats in nonalcoholic fatty liver disease,” *Nature Reviews*

- Gastroenterology & Hepatology*, vol. 18, pp. 770–786, 2021.
- [35]. U. Hayat *et al.*, “The effect of coffee consumption on non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis,” *Annals of Hepatology*, vol. 20, p. 100254, 2021.
- [36]. M. E. Rinella *et al.*, “AASLD practice guidance on clinical assessment and management of nonalcoholic fatty liver disease,” *Hepatology*, vol. 77, pp. 1797–1835, 2023.
- [37]. L. A. Feagins *et al.*, “Nonalcoholic fatty liver disease: A potential consequence of tumour necrosis factor-inhibitor therapy,” *European Journal of Gastroenterology & Hepatology*, vol. 27, pp. 1154–1160, 2015.
- [38]. C. S. Coffin *et al.*, “Liver diseases associated with anti-TNF- $\alpha$  therapy for inflammatory bowel disease,” *Inflammatory Bowel Diseases*, vol. 17, pp. 479–484, 2011.
- [39]. T. H. Frazier *et al.*, “Treatment of alcoholic liver disease,” *Therapeutic Advances in Gastroenterology*, vol. 4, pp. 63–81, 2011.
- [40]. Lirussi, F.; Azzalini, L.; Orlando, S.; Orlando, R.; Angelico, F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Database Syst. Rev. 2007, 24, CD004996.
- [41]. C. Carter-Kent, N. N. Zein, and A. E. Feldstein, “Cytokines in the pathogenesis of fatty liver and progression to steatohepatitis,” *The American Journal of Gastroenterology*, vol. 103, pp. 1036–1042, 2008.
- [42]. M. Naziroglu, P. J. Butterworth, and T. T. Sonmez, “Dietary vitamin C and E modulate antioxidant levels in diabetic aged rats,” *International Journal for Vitamin and Nutrition Research*, vol. 81, pp. 347–357, 2011.
- [43]. M. Salehi, H. Karegar-Borzi, M. Karimi, and R. Rahimi, “Medicinal plants for management of gastroesophageal reflux disease: A review of animal and human studies,” *J. Altern. Complement. Med.*, vol. 23, no. 2, pp. 82–95, 2016.
- [44]. N. Rodrigues, A. Almeida, H. Silva, D. Pinto, A. Seca, and M. Pereira, “Potential anti-inflammatory effects of *Artemisia gorgonum* on rat liver injury induced by CCl<sub>4</sub> – Erratum,” *Microsc. Microanal.*, pp. 1–2, 2016.
- [45]. N. Takada, S. Takase, A. Takada, and T. Date, “Differences in the hepatitis C virus genotypes in different countries,” *J. Hepatol.*, vol. 17, no. 3, pp. 277–283, 1993.
- [46]. N. Amat, H. Upur, and B. Blažeković, “In vivo hepatoprotective activity of the aqueous extract of *Artemisia absinthium* L. against chemically and immunologically induced liver injuries in mice,” *J. Ethnopharmacol.*, vol. 131, no. 2, pp. 478–484, 2010.
- [47]. G. M. Dusheiko, “Summary: Antiviral treatment of hepatitis C virus,” *Antiviral Res.*, vol. 29, no. 1, pp. 77–82, 1996.
- [48]. R. W. Chamberlain, N. Adams, A. A. Saeed, P. Simmonds, and R. M. Elliott, “Complete nucleotide sequence of a type 4 hepatitis C virus variant, the predominant genotype in the Middle East,” *J. Gen. Virol.*, vol. 78, no. 6, pp. 1341–1347, 1997.
- [49]. F. McOmish *et al.*, “Geographical distribution of hepatitis C virus genotypes in blood donors: An international collaborative survey,” *J. Clin. Microbiol.*, vol. 32, no. 4, pp. 884–892, 1994.
- [50]. N. Y. Gond and S. S. Khadabadi, “Hepatoprotective activity of *Ficus carica* leaf extract on rifampicin-induced hepatic damage in rats,” *Indian J. Pharm. Sci.*, vol. 70, no. 3, pp. 364–366, 2008.
- [51]. H. Sato *et al.*, “Therapeutic basis of glycyrrhizin on chronic hepatitis B,” *Antiviral Res.*, vol. 30, nos. 2–3, pp. 171–177, 1996.
- [52]. P. F. Surai, “Silymarin as a natural antioxidant: An overview of the current evidence and perspectives,” *Antioxidants*, vol. 4, no. 1, pp. 204–247, 2015.
- [53]. The Plant List, “The Plant List Version 1.1,” 2013. [Online]. Available: <http://www.theplantlist.org>
- [54]. W. Y. Sun, W. Wei, L. Wu, S. Y. Gui, and H. Wang, “Effects and mechanisms of extract from *Paeonia lactiflora* and *Astragalus membranaceus* on liver fibrosis induced by carbon tetrachloride in rats,” *J. Ethnopharmacol.*, vol. 112, no. 3, pp. 514–523, 2007.
- [55]. C. C. Hsieh, H. L. Fang, and W. C. Lina, “Inhibitory effect of *Solanum nigrum* on thioacetamide-induced liver fibrosis in mice,” *J. Ethnopharmacol.*, vol. 119, no. 1, pp. 117–121, 2008.
- [56]. S. Sultana, S. Perwaiz, M. Iqbal, and M. Athar, “Crude extracts of hepatoprotective plants, *Solanum nigrum* and *Cichorium intybus*, inhibit free radical-mediated DNA damage,” *J. Ethnopharmacol.*, vol. 45, no. 3, pp. 189–192, 1995.
- [57]. A. Khatri, A. Garg, and S. S. Agrawal, “Evaluation of hepatoprotective activity of aerial parts of *Tephrosia purpurea* L. and stem bark of *Tecomella undulata*,” *J. Ethnopharmacol.*, vol. 122, no. 1, pp. 1–5, 2009.
- [58]. H. Hosseinzadeh and M. Nassiri-Asl, “Pharmacological effects of *Glycyrrhiza* spp. and its bioactive constituents: Update and review,” *Phytother. Res.*, vol. 29, no. 12, pp. 1868–1886, 2015.
- [59]. A. S. Abdulkarim *et al.*, “Hepatitis C virus genotypes and hepatitis G virus in hemodialysis patients from Syria: Identification of two novel hepatitis C virus subtypes,” *Am. J. Trop. Med. Hyg.*, vol. 59, no. 4, pp. 571–576, 1998.
- [60]. T. A. Cha *et al.*, “Use of a signature nucleotide sequence of the hepatitis C virus for detection of viral RNA in human serum and plasma,” *J. Clin. Microbiol.*, vol. 29, no. 11, pp. 2528–2534, 1991.