# Exploring Herbal Remedies as Therapeutic Options for Hepatotoxicity Management

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***Abstract:*** **The liver is the organ with the most significant metabolic activities in nature; these include the metabolism of proteins, lipids, and carbohydrates. It also has bile secretion and detoxifying properties. It is highly organized, composed of lobes and lobules mostly generated by hepatocytes, as well as non-hepatocyte cells like Kupffer cells, and accounts for around 2.5 percent of body weight. Over millions of individuals worldwide suffer from liver disease, a serious medical ailment. Fatigue, stomach pain, and jaundice are typical symptoms. Congenital abnormalities, infections, toxic substances, or drugs are the main causes of liver illnesses. Liver illnesses come in more than 100 varieties. Some of the most prevalent forms are hepatitis, cirrhosis, and non-alcoholic fatty liver disease. Hepatotoxicity refers to liver damage brought on by medications or xenobiotic exposure. Increased liver enzymes are one of the most important diagnostic indicators for this type of injury, which can be classified as intrinsic, idiosyncratic, or immunoallergic. Natural remedies for liver disorders, such as milk thistle, curcumin, ginger, licorice, and dandelion, have shown encouraging results like anti-inflammatory, anti-fibrotic, and antioxidant properties , that makes them effective. Numerous cellular pathways are modulated by these medicinal drugs.**

***Keywords:*** **Hepatotoxicity, Haemochromatosis, Aspartate aminotransferase, alanine aminotransferase, Lipid peroxidation, Inflammation, Antioxidant, Glutathione, Hydroxycinnamic acids, Chlorogenic acid, Bilirubin, Hepatic stellate cells**

## 1. INTRODUCTION

The liver is the most important organ of the body, typically constitutes of approximately 2.5% of the total body weight which equates to roughly 1500 grams.[1] The liver is the largest organ, the largest gland and one of the most vital organs that functions as a centre for metabolism of nutrients and excretion of waste metabolites.[2] The main functions of liver are carbohydrates, protein and fat metabolism, detoxification, secretion of bile and storage of vitamins.[3]

### 1.1 Anatomy of Liver

The liver is almost a solid organ consisting of several lobes. Each lobe is made up of numerous lobules.[4] Under the microscope, each lobule is found to be composed of polygonal cells radiating from the centre. [5] Liver cells are arranged in the form of plates (hepatocytes), having a thickness of single-cell diameter, which provide a honeycomb or spongy like structure.[6] Throughout this structure, the cell plates are tunneled by a communicating system of cavities or lacunae. These lacunae contain hepatic sinusoids which are formed by endothelial cells and phagocyte cells of the Reticulo Endothelial system called kupffer cells (non hepatocytes).[7] Kupffer cells may contain phagocytosed substances and they are elongated structures having an irregular outline, crenated nucleus, few mitochondria and varying number of lysosomes. In the liver of an adult, hepatocytes occupy 78% of the tissue volume; non hepatocytes (Kupffer cells) account for 6.3% of the tissue volume and the remaining 15.7% is the extracellular space.[8]

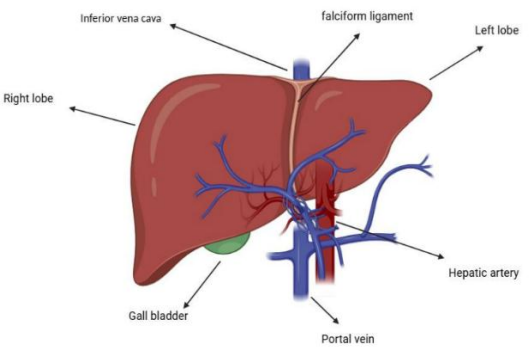


Figure 1: Anatomy of Liver.

### 1.3 Signs and symptoms

- Jaundice or yellowing of the skin
- Darkened urine [9]
- Nausea
- Loss of appetite
- Unusual weight loss or weight gain [10]
- Vomiting
- Diarrhea
- Light-colored stools
- Abdominal pain in the upper right part of the stomach

- Malaise or a vague feeling of illness
- Generalized itching
- Varicose veins (enlarged blood vessels)[11]
- Fatigue
- Hypoglycemia (low blood sugar)
- Low grade fever

1.4 Causes of liver diseases

Liver diseases can be caused by variety of factors which includes

- Congenital birth defects or abnormalities of the liver present at birth
- Metabolic disorders or defects in basic body processes[12]
- Viral or bacterial infections
- Alcohol or poisoning by toxins
- Certain medications those are toxic to the liver
- Nutritional deficiencies
- Trauma or injury

1.5 Types of liver disease

There are more than 100 different forms of liver diseases that affect human being. Some of the most common forms of liver diseases are as follows:

- Hepatitis: Inflammation of liver which is caused by variety of viruses and also by auto immunity.[14]
- Jaundice: Characterized by increase in the level of bilirubin in blood leads to deposition of a brownish-yellow pigment in the skin, sclera and mucous membrane.[15]
- Non alcoholic fatty liver disease: Characterized by fat accumulation associated with obesity and sometimes it may produce steatohepatiits like hepatitis.[16]
- Cirrhosis: Fibrous tissue formation in liver caused by viral hepatitis, alcoholism or by other toxic substances.[17]
- Fatty liver: An excessive accumulation of fat inside the liver cells.[18]
- Fibrosis: Gradual destruction of liver tissue.[19]
- Haemochromatosis: A hereditary disorder caused by accumulation of iron leads to damage of liver.[20]
- Tumor: A typical mass of tissue that form when cells begin to multiply at a rapid rate. The liver can develop benign (noncancerous) and malignant (cancerous) tumors.[21]
- Wilson disease: A hereditary disease caused by copper accumulation.[22]
- Primary sclerosing cholangitis: An inflammatory disorder.[23]
- Primary biliary cirrhosis: An auto immune disease.[24]
- Gilbert's disease: Bilirubin metabolic disorder.[25]

1.6 Prevalence

Liver diseases accounted for about two million deaths each year, including cirrhosis, viral hepatitis, and liver cancers. That is a mere 4% of all global deaths, which translates into one death per 25 deaths caused by liver disease. Liver cancers contributed approximately between 600,000 and 900,000 of these deaths. Around a third of those who die from liver-related diseases are female, which again reflects the far-reaching extent of these diseases [26]. Liver diseases stand as the 11th leading cause of death, yet the true number of deaths, as estimated, could be much higher [27]. Cirrhosis has been designated as the tenth leading cause of death in Africa (up from thirteenth in 2015), the ninth leading cause in Southeast Asia and Europe, and the fifth leading cause in the Eastern Mediterranean [28]. Hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD) have been documented as the commonest risk factors for the ensuing chronic liver disease. NAFLD accounted for 60% confidentiality in terms of cases attributed to these chronic diseases, followed by HBV at 29%, HCV at 9%, and ALD at 2% [29]. Alcoholism has been declared a foremost *cause* of death from cirrhosis, marking 34.3% of cases. Hepatitis B, the other notable chronic liver disease (CLD), was in minority with an average 60% prevalence among all chronic liver disease, including non-cirrhotic liver disease as well as the predominant cause of hepatocellular carcinoma (HCC) [30]. Drug-induced liver injury (DILI) is another immense player contributing to hepatotoxicity. Drug classes most often associated with hepatotoxicity include antibiotics, anti-epileptic, or central nervous system drugs, and nonsteroidal anti-inflammatory drugs. Studies have shown that anti-tubercular drugs accounted for a mortality rate averaging 17.3%-21.5%, with anti-tubercular drugs making up 58% of DILI cases and antiepileptic drugs accounting for 11.2%. DILI also seems to be related to a higher mortality rate when jaundice is present [31]. About 50% of all cases of acute liver failure have been attributed to hepatotoxic drugs including acetaminophen, isoniazid, and erythromycin. [32]

Hepatotoxic drugs can produce either predictableor idiosyncratic liver toxicities. Host factors influence the severity of hepatotoxicity, leading to acute liver failure, chronic liver disease, or cirrhosis. [33] Hepatotoxicity is most commonly associated with drugs such as acetaminophen, anti-tubercular drugs, anti-epileptic drugs, dapsone, steroid hormones, ferrous sulfate overdose, antiretroviral drugs, and some chemicals used in chemotherapy. Acetaminophen is known to treat acute liver failure, intrinsic DILI, fever, and other pathologies including osteoarthritis and cardiovascular, renal, and gastrointestinal disorders in children and adults . [34]

## 2. HEPATOTOXICITY

According to the history of the liver, adverse effects caused by accumulation of something like drugs within the body of a person or in foreign object in human (xenobiotic) ingestion are hepatotoxicity.[35] Chemicals that typically cause injury to the liver are referred to as either hepatotoxins or hepatotoxicants.[36] Among their exogenous mixtures that are clinically important, hepatotoxicants might involve overdoses of some specific chemistries, synthetic chemicals, natural venoms like microcystins, herbal remedies, and dietary supplements[36-37]. Hepatotoxicity may arise from either the direct poisoning by the primary metabolite or from a reactive metabolite or immunologically mediated response affecting hepatocytes, biliary epithelial cells, and/or liver vasculature.[37-38] Generally, hepatotoxicity is mentioned and diagnosed by the presence of elevated levels of liver function marker proteins such as aspartate aminotransferase(AST), alanine aminotransferase(ALT), alkaline phosphatase(APT), or total bilirubin.[39] Treatment should discontinue to consider a changed or mandatory authority if ALT interests exceed three times the upper limit of normal(ULN) symptoms in the presence of hepatitis symptoms and/or hostility or five times compared to ULN without symptoms.[40] The increase in serum ALT is more specific to hepatocellular injury, whereas also the increase in AST may denote muscle, heart, or feather abnormalities.[39] Hepatotoxicity classifies into two-the natural and idiosyncratic.[41] Natural reactions are cure-dependent, and they are predict able-theyre're less common; on the-the other hand-idiosyncratic reactions are cure-independent, unchangeable, and more common.[42] In addition, hepatic injury can be distributed as mentioned-hepatocellular, cholestatic, or mixed, based on the type of enzyme elevation.[43.

### 2.1 Mechanism involved in Hepatotoxicity

At celluar level:

1. Oxidative Stress: Damage to liver cells may result from the buildup of reactive oxygen species (ROS). DNA damage, protein oxidation, and lipid peroxidation can result from ROS's reaction with biological macromolecules.[44]
2. Inflammation: When immune cells like Kupffer cells and natural killer cells are activated, pro-inflammatory cytokines are released, which can harm the liver.[45]
3. Apoptosis: Liver damage may result from the liver cells' planned demise. Numerous things, such as oxidative stress, inflammation, and DNA damage, can cause apoptosis.[46]
4. Necrosis: Liver damage may result from the unchecked death of liver cells. Ischemia, poisons, and infections are some of the causes of necrosis.[47]

Hepatotoxic Molecular Mechanisms

1. CYP450 Enzymes: The metabolism of xenobiotics depends heavily on the cytochrome P450 (CYP450) enzymes. Nevertheless, some xenobiotics can also be bioactivated by the CYP450 enzymes, resulting in the production of reactive compounds that may harm the liver.[48]
2. Mitochondrial malfunction: Damage to liver cells may result from the buildup of ROS brought on by mitochondrial malfunction.[49]
3. DNA Damage: Apoptosis can result from DNA damage because it can trigger the activation of several signaling pathways, such as the p53 pathway.[50]
4. Inflammatory Signaling Pathways: Pro-inflammatory cytokines, which can harm the liver, can be released when inflammatory signaling pathways, such the NF-κB pathway, are activated.[51]

## 3. HEPATOTOXICITY TYPES

1. Intrinsic Hepatotoxicity: When a xenobiotic is directly harmful to liver cells, this is known as intrinsic hepatotoxicity.[52]
2. Idiosyncratic Hepatotoxicity: This type of hepatotoxicity happens when a xenobiotic damages the liver of a limited percentage of people.[53]

3. Immunoallergic Hepatotoxicity: This condition happens when a xenobiotic causes an immunological reaction that damages the liver.[54]

## 4. HERBAL REMEDIES AND THEIR MECHANISMS OF ACTION

### 4.1 Milk Thistle (Silybum marianum)

Often referred to as "milk thistle," Silybum marianum (Family: Asteraceae/Compositae) is one of the oldest and most extensively studied plants for the treatment of liver disorders.[55] The plant itself produces big purple flower heads and thrives as a robust thistle in rocky soils. The plant gets its name because of the milky veins that outline its leaves. The dried seeds of the milk thistle plant are used to extract silymarin because they contain higher levels of the compound than other plant parts.[56] Four flavonolignan isomers—silybin, isosilybin, silydianin, and silychristin—combine to generate silymarin, which has the empirical formula C25H22O10.[57] 4.2 Antioxidant properties: Lipid peroxide radicals, hydrogen peroxide (H2 O2), superoxide radicals, and hydroxyl radicals (.OH) are among the free radicals that have been linked to liver diseases. Both increased exposure to xenobiotics and regular metabolic processes in the body result in the production of these reactive oxygen species (ROS).[58] ROS-induced peroxidation of polyunsaturated fatty acids in the cell membrane bilayer is one mechanism of free radical damage. This leads to a series of lipid peroxidations that damage the cellular membrane and further oxidize membrane lipids and proteins. Cell contents, such as DNA, RNA, and other biological constituents, harmed.[59]

4.3 Anti-inflammatory properties: One of silymarin's key pharmacological characteristics is its inhibitory action on the 5-lipoxygenase pathway, which inhibits the formation of leukotrienes.[60] At greater silibinin5 concentrations, prostaglandin (E2) synthesis was unaffected but leukotriene (B4) synthesis was decreased.[61]

4.4 Antifibrotic properties: Hepatic insufficiency, portal hypertension, and hepatic encephalopathy can arise from the modification of the liver architecture caused by liver fibrosis.[62] The primary process in fibrogenesis is thought to be the transformation of hepatic stellate cells (HSC) into myofibroblasts. Silymarin delays HSC activation and suppresses NF-B. It may also interfere with intracellular signaling pathways and inhibit protein kinases and other kinases involvel in signal transduction.[63]

### 4.5 Curcumin

The Zingiberaceae family includes turmeric (Curcuma longa Linn), which is grown in tropical and subtropical climates worldwide. It comes from Indonesia, India, and Southeast Asia.[64] Rhizomes are used to treat leprosy, hypertension, cholera, syphilis, spleen diseases, and as an expectorant, cosmeceuticals, antiseptic, anthelmintic, blood purifier, pesticide, and spasmolytic. cold, cough, bronchitis, and rheumatism.[65]

4.6 Anti oxidant properties: One of the most prevalent processes causing organ damage is oxidative stress. Although oxygen is a necessary molecule for all cells to produce ATP, it may also change into extremely harmful species called reactive oxygen species.[66] Cell damage and aging can result from the generation of free radicals during aerobic respiration. Peroxide (H2O2) or superoxide ions are created when mitochondria reduce oxygen molecules.[67] Superoxide and peroxide also combine with metal ions to produce hydroxyl radicals, which then react with proteins and DNA in cells. Polyphenolic curcumin's antioxidant qualities are primarily linked to its medicinal potential. It has been discovered that curcumin is ten times more antioxidant than vitamins.[68]Curcumin upregulates Nrf2 genes to lead to increased activities of glutathione peroxidase and superoxide dismutase (SOD). By combining action with glutathione, such action scavenges free radicals. Glutathione peroxidase catalyzes superoxide free radical transformations into H2O2 while inhibiting any subsequent hydroxyl radical formations, hence scavenging the superoxide radicals.[69] That leaves H2O2 to be acted on by either glutathione peroxidase or catalase. [70]

4.7 Anti inflammatory properties Modifications in the mediators who have flamed up the inflamed body thus have proinflammatory and counter-inflammatory components that the immune system uses in the first line against any injury. The activation of cellular signaling pathways which would induce chemokine and cytokine production as well as mobilization of inflammatory cells at the site of damage would evoke inflammation.[71]The group of chemokine ligands [CCL], various forms of CXCL, interleukins [IL], interferon-α, interferon-γ, and tumor necrosis factor-α [TNF-α] are the cytokines and chemokines involved

in the inflammatory cascade.[72] In general, two receptor types—CCR, which binds CCL, and CXCR, which binds CXCL—are up-regulated in inflammatory responses. An individual is more susceptible to inflammation if the genomic sequence of certain genes (STAT genes, CREB and CCAAT/CEBP gene families, SOCS3 and IKBK genes) is altered.[73] Curcumin inhibits the transcription factors that cause inflammation, including NF-kB, activator protein-1, CREB binding protein, STAT proteins, and activating transcription factor-3. Curcumin directly targets inflammatory mediators such as interleukins, C-reactive protein, 5-lipooxygenase, and macrophage inflammatory protein-1α.[74] It has been shown that inhibiting TNF-induced NF-kB activation is. one of the most important mechanism of curcumin longa.[75]

4.8 Ginger

Abutilon indicum, which is one of the really important—to this country-medicinal herbs, has been identified with a whole number of therapeutic or pharmacological activities like anti-inflammatory, antibacterial, and antioxidant actions.[76] These are the conditions for which it is presumed to act for the management of liver damage due to toxicity from medicines or otherwise from other pollutants.[77] Therapeutic efficacy is expected to be due to very rich phytochemical constructs, such as terpenoids, flavonoids, and saponin. Traditional uses Ginger is a carminative, pungent stimulant and popularly used for indigestion, stomach complaints, malaria, and in fevers.[78] Of these conditions, it primarily acts for those caused by alterations of Kapha and Vata. Ginger with lime juice and rock salt increases appetite and secretes gastric juices.[79] It is well-known for different ailments such as abdominal pain, anorexia, arthritis, atonic dyspepsia, haemorrhage, cancer, congestion in the chest, chicken pox, cholera, chronic bronchitis, cold extremities, colic, colitis, common cold, cough, cystic fibrosis, diarrhoea, dyspnea, dropsy, febrile, flatulence, indigestion, gallbladder disorders, hyperacidity, hypercholesterolemia, hyperglycemia, indigestion, morning sickness, nausea, rheumatism, sore throat, throat ache, stomach ache, and vomiting.[80] Ginger forms an important constituent in many pharmacopoeial Ayurvedic formulations.

4.9 Anti ulcer properties: Ginger is known to prevent the development of ulcer-like diseases in the stomach.[81]

The effect of ginger and 6-gingerol was assessed against experimentally induced gastric ulceration in rats. Fresh ginger decocted in water produced symptomatic improvement in 10 patients suffering from peptic ulcer.[82]

4.10 Anti-inflammatory property

Ginger has shown to inhibit paw swelling caused by carrageenan as well as equally active with aspirin. Chronic adjuvant arthritis induction in rats has been reduced by topical application of essential ginger oil.[83] Ginger and its pungents exhibit dual action as inhibitors, acting against both cyclooxygenase (prostaglandin synthetase) and lipoxygenase in the respective biosynthetic pathways of prostaglandins and leukotrienes during the metabolism of arachiodonic acid.[84]

4.11 Licorice: Traditional Chinese medicine has been a promising flavoring agent for licorice because of its broad applications in various disease conditions. It has been endowed with biological capabilities including detoxication, antioxidation, and anti-infection activites.[85]

4.12 Anti inflammatory properties

Licorice has been anti-inflammatory due to lowering PGE2, MMPs, TNF, and free radicals as corroborated by traditional applications such as diuresis, relieving coughs, "lifting" mucous, stimulating digestive activity, and relieving pain among others.[86] Licorice processed DGN products greatly ameliorated symptoms of RA in CIA rats. Licorice processed DGN products regulated matrix metalloproteinases, inflammatory cytokines, and vascular endothelial growth factors in blood and cell supernatants.[87] Licorice processed DGN products revealed anti-inflammatory effects through the TLR4/NF-κβ/NLRP3 signaling pathway on CIA rats and LPS-induced RAW264.7 cells, and regulated the metabolic profile in managing RA.[88] This was the conclusion of the study. In vivo anti-inflammatory activities were shown by total flavonoids isolated from licorice extracts and licorice by suppressing COX-2 gene, iNOS, and signals of MAPK.

4.13 Dandelion

Dandelion-Taraxacum officinale-is a common herbal remedy found in the treatment of many ailments including liver diseases from historical past generations.[89] Its roots, leaves, and flowers are supplied with bioactive components like taraxasterol,

taraxacoside, and flavonoids, which play a role in antioxidant and anti-inflammatory action.[90] Dandelion is said to aid the liver, facilitate digestion, treat liver disorders.[91] It achieves that effect by reducing liver injury and inflammation, promoting regeneration and restoration of liver function. The dandelion plant is a great source of nutrients like potassium, vitamins, inulin, phytosterols, and amino acids.[92] Moreover, there are phenolic chemicals, phytosterols, triterpenes, and sesquiters.[93] It also contains oligofructans, chicoric acid, hydroxycinnamic acids, chlorogenic acid, triterpenoids, lupane etc. [94]

4.14 Anti oxidant properties: The antioxidant effect of dandelion is due to its ability to scavenge reactive oxygen species (ROS) and inhibit lipid peroxidation.[95] Quercetin and kaempferol flavonoids particularly exert inhibitory effects on pro-inflammatory cytokines and enzymes and subsequently reduce liver inflammation.[96]

4.15 Anti inflammatory properties: Dandelion suppresses nuclear factor-kappa B (NF-κB) and that leads to the downregulation of pro-inflammatory gene expression.[97] Besides, sesquiterpenes such as taraxasterol from the plant have been shown to inhibit activation of hepatic stellate cells implicated in liver fibrosis.[98]

4.16 Anti-fibrotic properties: Dandelion arises as the plant suppresses extracellular matrix protein accumulation while stimulating transforming growth factor-beta (TGF-β), which modulates the liver fibrogenic response.[99] Hepatic stellate cells are deactivated with dandelion and also activate the hepatic regeneration capacities.[100]

## CONCLUSION

The liver is an important organ performing various metabolic functions, including detoxifying the body, secreting bile, and metabolizing proteins, fats, and carbohydrates. Liver diseases are said to be one of the diseases that afflict millions of people across the globe and can result in serious health problems. For example, symptoms of liver diseases include jaundice, pain in the abdomen, and great fatigue .Liver diseases can cause medicines, toxic agents, infectious agents, or inherited defects. While there are more than 100 types of liver disease, the most common include hepatitis, cirrhosis, and non alcoholic fatty liver disease. Milk thistle, curcumin, ginger, licorice, and dandelion are some of nature's medicines that have bright hopes in liver disease therapy on account of their anti-inflammatory, anti-fibrotic and antioxidant effects. In this context, it becomes pertinent to learn various hepatotoxic mechanisms, types of liver injury, and significance of herbal measures in managing liver disease.

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