

“Hepatoprotective Properties of Herbal Medicines: A Review on Natural Remedies for Liver Disorders”

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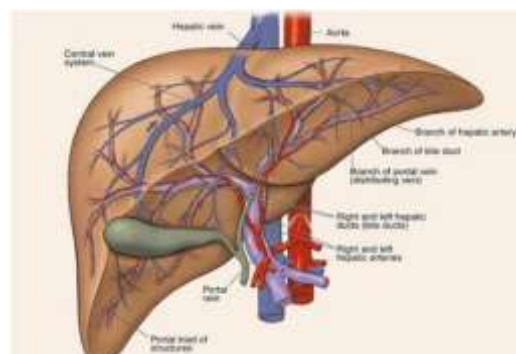
ABSTRACT: Liver toxicity is a major health issue that may be caused by many factors, such as oxidative stress, drug-induced liver injury, infection, and chronic exposure to toxic substances like alcohol, environmental toxins, and industrial chemicals. The liver has significant roles in detoxification, metabolism, and homeostasis; but hepatotoxic substance overexposure will initiate oxidative injury, inflammation, mitochondrial failure, and, consequently, liver disease including fibrosis, cirrhosis, and liver failure. In this review, mechanisms of liver toxicity were considered focusing on reactive oxygen species (Ros), lipid peroxidation, and inflammatory pathway contributions to cell injury in the liver. With the limitations and possible side effects of orthodox medicine in managing liver ailments, the use of herbal medicine as a natural alternative is increasingly gaining momentum. Medicinal herbs such as milk thistle (*Silybum marianum*), ginger (*Zingiber officinale*), green tea (*Camellia sinensis*), mandarin (*Citrus reticulata*), and liquorice (*Glycyrrhiza glabra*) have proven to possess extensive hepatoprotective qualities. These plants contain high levels of bioactive compounds including flavonoids, polyphenols, and saponins that have powerful antioxidant, anti-inflammatory, and hepatoregenerative activities. Research indicates that these herbal extracts can defend against liver cell injury by scavenging free radicals, inhibiting inflammation, and activating detoxifying pathways, preventing liver injury and facilitating liver regeneration. In addition, the review addresses various extraction techniques applied to separate active phytochemicals from the plants, such as solvent extraction, Soxhlet extraction, and ultrasound-assisted extraction. A comparative review of the above extraction methods highlights their effectiveness in achieving bioactive compounds with significant therapeutic potential. Moreover, the review provides a critical assessment

of the clinical efficacy and safety of the herbal drugs in treating liver toxicity. In general, the results are in favour of the integration of herbal medicine into mainstream treatment strategies for liver toxicity. Further clinical validation, standardization of dosages, and mechanistic studies should be the focus of future research to elucidate the therapeutic effects of herbal hepatoprotective agents.

KEYWORD: liver toxicity, oxidative stress, herbal medicine, liver detoxification, hepatic, reactive oxidative species.

I. INTRODUCTION

The liver is largest solid organ in the body, weighing about 1.5 kg in an adult (Fig.1) It lies in the right upper quadrant of the abdomen completely protected by the thoracic ribcage. The liver is connected to two large blood vessels, one called hepatic artery and the other called the portal vein. The hepatic artery carries blood from the aorta whereas the portal vein carries blood containing digested food from the small intestine. The basic functional unit of liver is the liver lobule, the human liver contains 50,000 to 100,000 individual lobules. (1)



(Figure.1) Diagrammatic overview of the liver anatomy.

1.1 Functions of the Liver

1.1.1 Metabolic Detoxification The liver alters exogenous and endogenous chemicals (e.g. drugs), foreign molecules, and hormones to make them less toxic or less biologically active. This process, called metabolic detoxification, diminishes intestinal or renal tubular reabsorption of potentially toxic substances and facilitates their intestinal and renal excretion. In this way alcohol, barbiturates, amphetamines, steroids and hormones (including estrogen, aldosterone, antidiuretic hormone, and testosterone) are metabolized or detoxified, preventing excessive accumulation and adverse effects. (2)

1.1.2 Metabolism of Nutrients: Fats: Fat is synthesized from carbohydrate and protein,

primarily in the liver. Fat is absorbed by lacteals in the intestinal villi, and it enters the liver through the lymphatics, primarily as triglycerides. In the liver the triglycerides can be hydrolysed to glycerol and free fatty acids and used to produce metabolic energy adenosine triphosphate (ATP), or they can be released into the bloodstream as lipoprotein.

1.1.3 Bile production: It produces bile, which helps in digestion and absorption of fats.

1.1.4 Storage: It stores glycogen (energy), vitamins (A, D, B12), and minerals (Iron, copper)

1.1.5 Regulation of Blood Sugar: It helps maintain normal blood glucose levels by storing and releasing glucose as needed.

1.1.6 Immune Function: It helps fight infections by filtering bacteria and producing immune factors.

Table1: Functions of liver and their description:

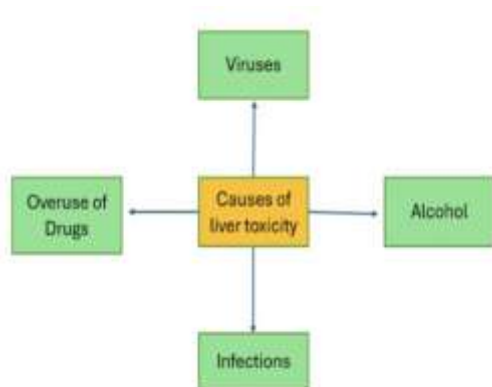
| Function | Description |
|-------------------------|--|
| Metabolism of nutrients | Converts nutrients from food into energy and stores it for later use. |
| Detoxification | Removes toxins and harmful substances from the blood. |
| Bile production | Produces bile that helps in digestion and absorption of fats. |
| Cholesterol regulation | Produces and regulates cholesterol levels in the body. |
| Immune function | Contains Kupffer cells that help fight infections and clear bacteria from the bloodstream. |

1.2 Various causes of Liver toxicity

Oxidative stress shows an imbalance between the systemic manifestation of reactive oxygen species and a biological system’s ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects by producing peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is generally indirect and caused by the reactive oxygen species (ROS) generated, e.g. O₂⁻ (superoxide radical), OH (hydroxyl radical) and H₂O₂ “hydrogen peroxide” (3)

Aspartame is widely consumed by humans who are diabetic and are under weight loss regime.

Aspartame also known as NutraSweet, after oral administration to humans and experimental animals, is rapidly and completely metabolized to 50% phenylalanine, 40% aspartic acid and 10% methanol. Methanol is being increasingly recognized as a substance that damages the liver cells, where it is oxidized to formaldehyde. (4) These processes are accompanied by elevation of NADH level and the formation of superoxide anion, which may be involved in lipid peroxidation. Some common causes of liver toxicity as shown in (Fig.2)

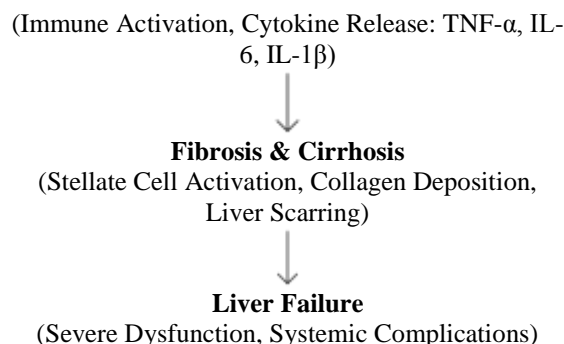
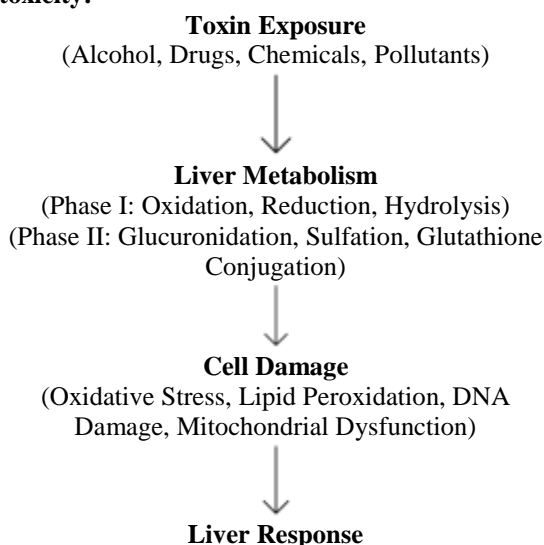


(Figure.2)

1.3 Mechanism of liver toxicity

Due to its unique metabolism and close relationship with the gastrointestinal tract, the liver is susceptible to injury from drugs and other substances. Around (75%) of blood coming to the liver arrives directly from gastrointestinal organs and then spleen via portal veins that bring drugs and xenobiotics in near-undiluted form. Several mechanisms are responsible for either inducing hepatic injury or worsening the damage process. Many chemicals damage mitochondria, an intracellular organelle. Its dysfunction releases excessive number of oxidants that, in turn, injure hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress, which results in liver damage. Injury to hepatocyte and bile duct cells leads to accumulation of bile acid inside the liver. This promotes further liver damage. (5)

1.3.1 Flow diagram showing mechanism of liver toxicity:



II. HERBAL PLANTS USED TO TREAT LIVER TOXICITY

2.1 History

The study of herbs dates back over 5000 years to the Sumerians, who described well-established medicinal uses for such plants as laurel, caraway and thyme. Ancient Egyptians of 1000 B.C. are known to have used garlic, opium, castor oil, coriander, mint, indigo, and other herbs as a medicine, and the old records also mentioned herb use and cultivation, including wheat, barley. Also, the use of herbal drugs can be traced back to 2100 B.C. in ancient China at the time of Xia dynasty and in India during the Vedic period. The first written report dates to 600 B.C. with the Charaka Samhita of India and the early notes of Eastern Zhou dynasty of China, which became systematized around 400 B.C. The age-old system of herbal medicine is being revived by day-to-day practice for its long-lasting curative effect, easy availability, natural way of healing, and less side effects. (6)

2.2 Plants used as medicine

Herbal medicines are gaining importance not only in India, but globally. Alternate system of medicine in India uses about 1200 plants for different ailments (7). Treatment options for common liver diseases are limited and therapy with modern medicine may lack in efficacy. The effectiveness of treatments such as those using corticosteroids and interferons is inconsistent, carries the risk of adverse events and is often very costly. So, there is a need for effective therapeutic agents with a low incidence of side effects. Plants potentially constitute such groups, which are traditionally used as hepatoprotective agents. The easy accessibility without the need of laborious pharmaceutical synthesis increased the attention toward the herbal medicines (8). Plant drugs are also known to play a major role in the management of liver diseases all over the world. There are many

plants and herbal extracts that have been shown to possess hepatoprotective activities in Indian, Chinese, and Korean system of medicine. The use of herbal resources for the treatment of liver diseases is an old approach of various traditional systems of medicine. These medicine systems conceptualize a general imbalance of the dichotomous energies that leads to the disease, and they focus on medicine that balances these energies and maintains good health. Phytomedicines are traditionally used in the treatment of liver disorders and are now included as complementary and alternative medicine for liver patients. (9)

III. SOME COMMONLY USED PLANTS

3.1 *Silybum marianum* (milk thistle)

Silybum marianum is currently the most well researched plant in the treatment of liver disease (with over 450 published review papers). The genus *Silybum* is a member of the daisy family (Compositae). The plant itself is a stout thistle, growing one to three meters tall in rocky soils, with large purple flowering heads (Fig .3). The leaves are characterized by distinct white “milky” veins that give the plant its common name. (10)



(Figure.3) milk thistle

3.1.1 Active Constituents

The active constituents of milk thistle are flavonolignans including silybin, silydianin, and silychristine, collectively known as silymarin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds. *Silybum* seeds also contain betaine (a proven hepatoprotector), and essential fatty acids, which may contribute to silymarin’s anti-inflammatory effect. Many studies have demonstrated the beneficial hepatoprotective effects of treatment with silymarin. In a Finnish military hospital study on consecutive patients with elevated serum liver enzymes (mostly due to ethanol ingestion), 420 mg/day silymarin was found to significantly lower liver enzymes –

aspartate aminotransferase (AST), alanine amino transferase (ALT) – after four weeks.

3.1.2 Mechanism of Action

Silymarin has been reported to protect liver cells from a wide variety of toxins, including acetaminophen, ethanol, carbon tetra chloride, and D-galactosamine (11-12). Silymarin has also been found to protect liver cells from ischemic injury, radiation, iron toxicity, and viral hepatitis (13). The mechanisms which provide silymarin’s hepatoprotective effects are many and varied, and include antioxidation, anti-lipid peroxidation, enhanced detoxification and protection against glutathione depletion.

Stimulation of Liver Regeneration:

Silymarin’s ability to stimulate liver regeneration is attributed to an increase in protein synthesis in damaged livers.

Anti-inflammatory Effects:

Silymarin has been shown to have significant anti-inflammatory effects on hepatic tissue. Several studies have demonstrated a variety of anti-inflammatory effects, including mast cell stabilization,³⁸ inhibition of neutrophil migration, Kupffer cell inhibition.

Antifibrotic Effects:

Hepatic stellate cells are crucial in liver fibrogenesis, transforming into myofibroblasts in response to fibrotic factors like chronic ethanol exposure and carbon tetrachloride, responsible for collagen fibre deposition in the liver. (14)

3.1.3 Dosage

The typical adult dosage for silymarin is 240 - 900 mg/day in two or three divided doses. At higher doses (>1500 mg/day) silymarin may produce a laxative effect due to increased bile flow and secretion. Mild allergic reactions have also been noted, but neither of these side effects was severe enough to discontinue the treatment. (15)

3.2 *Zingiber officinale* (ginger)

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) (Fig. 4) is widely used around the world in foods as a spice. For centuries, it has been an important ingredient in Chinese, Ayurvedic and Unani herbal medicines for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes. Among the pharmacological effects demonstrated are anti-platelets, antioxidant,

antitumor, anti-rhinoviral, anti-hepatotoxicity, anti-arthritic and anti-inflammatory. (16)



(Figure.4) ginger

3.2.1 Chemical constituents

Gingerol and other ginger constituents have been confirmed to have antioxidant activity, altering biochemical parameters, free radicals, antioxidant enzymes, and drug metabolizing enzymes in male rats' livers, and alleviating the toxicity of bromobenzene. (17)

3.2.2 Mechanism of action

Ginger's active component, curcumin, is an antioxidant and anti-inflammatory agent that protects endothelial cells from oxidative stress and inhibits reactive oxygen species (ROS), which can cause DNA damage and contribute to carcinogenesis and coronary heart disease. Ginger root extract may also protect against aspartame, which can cause hepatotoxicity and oxidative stress. It decreases liver function markers, serum total protein, albumin, total bilirubin levels, serum LDH activity, α -fetoprotein, and tumours necrosis factor (TNF), increases antioxidant enzyme levels, and reduces malondialdehyde levels. (18)

3.3 Green Tea (*Camellia sinensis*)

3.3.1 Description: (Fig.5) Green, black, and oolong teas are made from *Camellia sinensis* leaves, cultivated in China, India, Japan, and Indonesia. Green tea is made from unfermented leaves, while oolong tea is partially fermented. Black tea is fully fermented, with higher fermentation content resulting in lower polyphenol content and higher caffeine content. Black tea has 2-3 times the caffeine content of green tea. The plant originally grows as a large shrub or tree.

3.3.2 History:

Tea has been used as both a drink and as a medicine in the last 5000 years in China. Historical uses of tea include as a stimulant, an astringent for clearing phlegm, and as a digestive aid.

3.3.3 Active Constituents:

Tea contains a wide assortment of bioactive constituents, most of which are contained in two groups, alkaloids and polyphenols. Examples of alkaloids found in tea include caffeine, theobromine, and theophylline. (19) These alkaloids provide the stimulant effects of tea and figure prominently in the experience of tea drinking, although they are not thought to be central to tea's medicinal effects. The polyphenols found in all tea give it its astringent, somewhat bitter flavour. The hepatoprotective and other health effects of green tea are believed to be chiefly dependent on the polyphenol content. (20) The polyphenols contained in teas are classified as catechins, which are bioflavonoids, which in turn is a subcategory of the larger group of polyphenols. Green tea contains six primary catechin compounds: (+) catechin, Gallo catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate. Epigallocatechin gallate (also known as EGCG) is the most active component and is the best researched of the green tea polyphenols (GTP).



(Figure.5) (*Camellia sinensis*)

3.3.4 Mechanism:

Green tea exhibits antioxidant and free radical scavenger properties. The green tea extract alongside its main catechin polyphenols have medicinal value in the prevention and therapeutics of the several diseases (21). The green tea exerts improvement in liver function by preventing the production of reactive oxygen species (ROS) and

enhancing the antioxidant defence system capacity. Thus, green tea extract has protective effects against ethanol toxicity. Catechins have been discovered to be powerful antioxidants, which is thought to be at least in part responsible for green tea's hepatoprotective activity. In 2-nitropropane poisoning, epigallocatechin gallate administration lowered hepatic lipid peroxide levels 100 percent at six hours and 30 percent at 15 hours.

3.3.5 Toxicity and dosage:

Green tea is safe at any dose, with no toxicity observed in animal studies or human experience. Single doses of decaffeinated green tea solids, equivalent to 45 cups of tea, have been well tolerated. (22)

3.4 Citrus reticulata (mandarin)

(Citrus reticulata) also known as the mandarin, (Fig.6) is a citrus fruit with a similar appearance to oranges, rich in vitamin C, flavonoids, acids, and volatile oils, making it a nutritionally significant fruit.



Figure.6 (Citrus reticulata)

3.4.1 Chemical constituents

Flavonoids, particularly polymethoxyflavones and flavanones like hesperidin, rutin, and naringin, are found in citrus pulp and peel, with rutin being a glycoside of quercetin. (23)

3.4.2 Mechanism of action

Rutin is a medication used for blood vessel protection and is a key ingredient in multivitamin preparations and herbal remedies. It can combine with cations to supply nutrients to plant cells. In humans, it is a potent antioxidant, the strongest among citrus peel-based antioxidants like quercetin, acacetin, morin, hispidulin, hesperidin, and naringin. Hesperidin, a flavanone glycoside

found in citrus fruits, is believed to play a role in plant defense and antioxidant effects. In human nutrition, it contributes to blood vessel integrity and has anti-inflammatory effects. Hesperidin also has biological effects, including anti-inflammatory, antimicrobial, anticarcinogenic, antioxidant, and decreasing capillary fragility. It also protects against DNA damage and doxorubicin-induced hepatotoxicity by improving liver enzyme activities and reducing levels of total bilirubin, albumin, and sialic acid. Rutin and hesperidin significantly increased liver glutathione levels, peroxidase, glutathione-S-transferase, and peroxidase activities, and reduced lipid peroxidation levels. Pretreatment with these compounds may protect the liver from the hepatotoxic effect of doxorubicin, which attaches to iron ions and prevents hydrogen peroxide binding, preventing cell damage. (24)

3.5 Glycyrrhiza glabra (licorice)

3.5.1 Description: Glycyrrhiza glabra as shown in (Fig.7) originating in the Mediterranean and Middle East, has been used medicinally since at least 500 BC. Cultivated in Europe since the 16th century, it was one of the most prescribed herbs at the time and is sometimes referred to as "the grandfather of herbs."(25)



Figure.7 liquorice

3.5.2 History

Glycyrrhiza, a traditional herb from Western and Eastern traditions, is used for treating peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, and infections, with medicinal properties including demulcent, expectorant, antitussive, and mild laxative activity. (26)

3.5.3 Active Constituents: Glycyrrhiza, a plant used to treat hepatic disorders, contains the triterpene glycoside glycyrrhizin, also known as glycyrrhizic acid or glycyrrhetic acid. It contains flavonoids, isoflavonoids, chalcones, coumarins, triterpenoids, and phytosterols. Glycyrrhiza's

concentration ranges from 6-14 percent and is 50 times sweeter than sucrose, making it often used in combination with other medications.

3.5.4 Mechanism of action

Glycyrrhizin suppresses 11-beta hydroxysteroid dehydrogenase, the enzyme responsible for inactivating cortisol and progesterone in humans. It doesn't have a significant mineralocorticoid effect in adrenalectomized animals or severe adrenocorticoid insufficiency, indicating the need for endogenous cortisol. (27)

Hepatoprotective Activity: Glycyrrhiza flavonoids have been found to have a direct hepatoprotective effect, protecting hepatocytes from carbon tetrachloride and galactosamine exposure. This is attributed to their anti-lipid peroxidation effect. (28)

3.5.5 Dosage

Daily doses of liquorice root extract (3,138 or 6,276 mg/kg b.w., orally) or glycyrrhizin (240 or 480 mg/kg b.w. orally) are recommended.

IV. METHODS OF EXTRACTION OF PLANT CONSTITUENTS

4.1 Milk Thistle (Silymarin)

Extraction by Enzyme-Mediated Solvent: In a 1000 mL conical flask, weigh 100 g of milk thistle seed powder and mix with 300ml of solution (n-hexane: ethanol, 2:1, v/v). The added cellulase measuring 3.06mg/mL reacts under appropriate conditions, and the samples were extracted by shaking at 25 C for 2 h. After filtering twice, the mixture was rotary evaporated at 45 C until no solvent flowed out, and the oil was then flushed with nitrogen to eliminate the residue hexane. (29)

4.2 Ginger (Zingiber officinale Roscoe)

Fresh Zingiber officinale Roscoe rhizomes were collected and dried in a laboratory. The samples were ground in a blender and stored in plastic bags for extraction. Soxhlet extraction was performed using 5g of biomass and 150mL of solvent, lasting 6 hours at different temperatures. The extractions were conducted at each solvent's boiling point, ensuring the biomass was thoroughly dried and ground before use. The solvents used were ethyl acetate, ethanol, hexane, and water and, in each case, the procedure was repeated three times. A rotary vacuum evaporator was used to concentrate the Soxhlet extracts, and they were

then dried in an air circulation oven at 40 C for about 24 h. The extraction yields were calculated. (30)

4.3 Extraction of Antioxidant Polyphenols from Green Tea (Camellia sinensis)

The study focuses on the extraction of tea polyphenols from selenium-enriched green tea. The tea was ground into a fine powder and stored at 4 C. The components of DES were mixed with a molar ratio of ChCl/HBD and then heated at 60C to form a homogeneous solution. The initial weight of the green tea powder was mixed with 10 ml of DES solution. The UAE (ultrasound-assisted extraction) process was conducted using an ultrasonic processor, with initial ultrasonication conditions of 325 W and 10 min. The sample was kept on ice to avoid high temperature effects. The experiments were carried out in triplicate. For UAE-DES or UAE with ethanol extraction, the green tea powder and DES or ethanol were mixed in a 50 mL centrifuge tube. For ethanol extraction, the green tea powder and ethanol were mixed in a 50 mL centrifuge tube, and the extraction was carried out at room temperature for 24 hours. For hot water extraction, the green tea powder and 85 C water were mixed in a 50 mL centrifuge tube, and the extraction was carried out at room temperature for a specific time. (31)

V. PLANTS, CONSTITUENTS AND THEIR USES IN LIVER TOXICITY. (AS SHOWN IN TABLE 2)

5.1 Milk Thistle is commonly noted for its ability to protect the liver due to its active ingredient silymarin which is made up of silibinin, silydianin, and silychristin. Silymarin is also known to be a very powerful antioxidant as it reduces inflammation and oxidative stress within the liver. It also aids in cellular detoxification from substances like alcohol and heavy metals, helps in liver cell healing, and protects liver cells. It is very often used to treat cirrhosis, hepatitis, and fatty liver disease. (32)

5.2. Ginger Gingerol, shogaol, and zingerone found in ginger are considered bioactive and their antioxidant and anti-inflammatory properties make these compounds very helpful. These compounds also help reduce inflammation of the liver, protect the liver from oxidative stress, improve liver enzyme levels, and protect the liver from damage. Ginger has also been shown to reduce lipid build up in the liver cells and therefore prevent fatty liver disease. (33)

5.3 Mandarin oranges contain flavonoids such as hesperidin, naringenin, and limonene that have hepatoprotective properties. These inhibit fat storage in the liver, decrease fibrosis, and decrease inflammation. Hesperidin and naringenin also increase the detoxification function of the liver and are thus useful in the prevention of liver disease brought on by toxins. (34)

5.4 Liquorice root is rich in glycyrrhizin, flavonoids, and saponins, which have strong liver-protective effects. Glycyrrhizin specifically is most effective in treating liver fibrosis and inflammation, thus being a valuable treatment option for diseases like hepatitis and NAFLD. Liquorice also increases

the liver's efficiency in detoxifying toxins. One must, however, avoid consuming too much liquorice because it has been observed to have possible impacts on blood pressure. (35)

5.5 Green tea is a strong liver-protective drink, primarily because of its high epigallocatechin gallate (EGCG), catechins, and theanine content. EGCG is a strong antioxidant that can decrease oxidative stress, inhibit liver steatosis (fat accumulation), and enhance liver detoxification. Green tea has been researched to reduce liver enzyme levels and inhibit alcohol and toxin-induced liver damage. (36)

Table2: Summary of plant names, chemical constituents and their uses in liver toxicity.

| Plant Name | Chemical Constituents | Uses in Liver Toxicity |
|---------------------------------|---|--|
| Milk Thistle (Silybum marianum) | Silymarin (Silibinin, Silydianin, Silychristin) | Antioxidants, hepatoprotective, enhance liver regeneration, reduce oxidative stress. |
| Ginger (Zingiber officinale) | Gingerol, Shogaol, Zingerone | Reduces liver inflammation, protects against oxidative damage, improves liver enzyme levels. |
| Mandarin (Citrus reticulata) | Hesperidin, Naringenin, Limonene | Prevents fat accumulation in the liver, reduces fibrosis, and has anti-inflammatory effects. |
| Liquorice (Glycyrrhiza glabra) | Glycyrrhizin, Saponins, Flavonoids, | Protects against drug-induced liver injury, reduces liver fibrosis, enhances detoxification. |

VI. CONCLUSION:

The liver toxicity is a major health concern, often caused by oxidative stress, drugs and toxins. The incidents of the liver toxicity are rising day by day. Many traditional as well as modern approaches are being followed for its treatment. Traditional approaches like use of herbal medicines are being more preferred due to their less side effects, safety and natural origins. Herbal medicines like Milk Thistle, Ginger, Green Tea, Mandarin and Liquorice offer promising hepatoprotective benefits through antioxidants and anti-inflammatory effects. Their bioactive compounds support liver health and detoxification. While these remedies show potential, further research is needed to ensure their efficacy and safety for their clinical use.

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