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HERBAL PLANTS TARGETING OXIDATIVE STRESS IN HEPATOTOXICITY

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ABSTRACT

Hepatotoxicity, or liver damage due to drugs, chemical substances, toxins, infections and dietary factors, can be considered as a worldwide health issue. The liver is essential for metabolism, detoxification, and synthesis of key biomolecules; thus, it is particularly vulnerable to injury induced by oxidative stress. Overproduction of ROS could also lead to lipid peroxidation, mitochondrial dysfunction, and injuries to proteins and DNA, thus promoting liver disease formation. Herbal medicines have gained significant attention as potential hepatoprotective agents due to their antioxidant and therapeutic properties. Phytochemicals such as flavonoids, phenolics, alkaloids, and glycosides present in medicinal plants help reduce oxidative stress and protect liver cells from damage. Plants such as *Silybum marianum*, *Azadirachta indica*, *Camellia sinensis*, and *Ocimum sanctum* have shown promising hepatoprotective and antioxidant effects in experimental studies. This review highlights the role of oxidative stress in liver injury and discusses the therapeutic potential of herbal drugs in preventing and managing hepatotoxicity.

KEYWORDS: Hepatotoxicity; Oxidative stress; Reactive oxygen species (ROS); Herbal medicine; Hepatoprotective activity; Antioxidants; Phytochemicals; Liver diseases; *Silybum marianum*; *Azadirachta indica*; *Ocimum sanctum*; *Camellia sinensis*.

1. INTRODUCTION

Hepatotoxicity is medicinal, chemical, dietary, or herb-induced liver damage via hepato-toxins. Liver damage includes the following disorders: elevated liver enzymes, acute or chronic hepatitis, cholestasis, hepatic necrosis or fibrosis, cirrhosis, liver failure, and hepatic veno-occlusive disease.[1]

Liver is the main internal organ and gland amongst the most important and complex organs, representing about 2.5% of an adult body weight. It's formed from parenchymal cells (hepatocytes) and non-parenchymal cells (Sinusoidal endothelial cells, kupffer cells and hepatic stellate cells). It occupies the upper right part of the abdominal cavity and underneath the diaphragm. It is connected to hepatic artery and hepatic portal vein. In fact, during rest it receives about 25% of the cardiac output through hepatic artery and hepatic portal vein. The hepatic portal vein carries the absorbed blood containing nutrients, toxins, and other substances from the gastrointestinal tract (duodenum) to the liver. The liver filters this blood, after that sends it via the hepatic vein to the heart in order to pump it all over the body.[2]

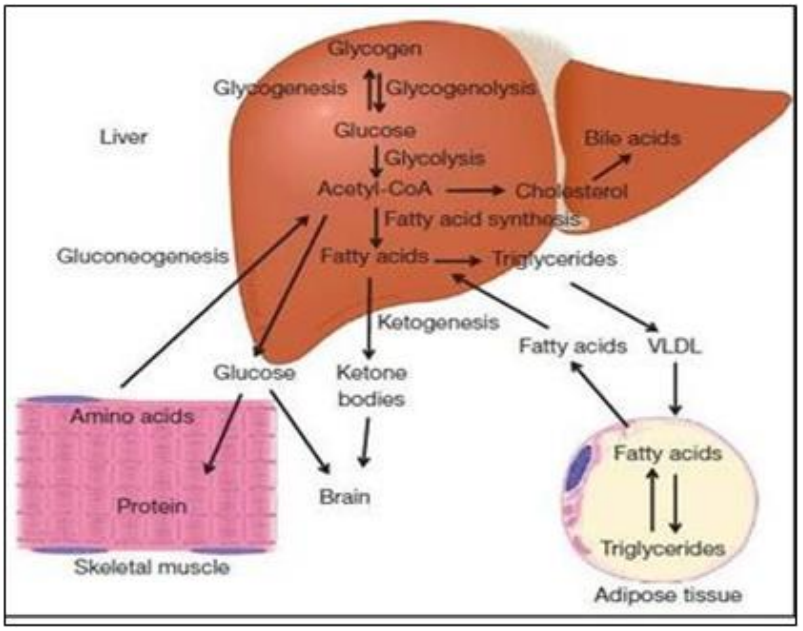

Fig. No. 1: Major metabolic functions of the liver.

The liver is a key metabolic center as it masters many essential metabolic functions for example nutrient metabolism, synthesis of essential serum components, detoxification. All these vital hepatic functions should be adjusted to "a rhythmically changing systemic environment".

The liver, similar to other body organs, has a circadian clock which represents an internal

timing system works to adjust the physiological functions to their appropriate time of day. The liver utilizes this system to antedate recurrent general and ecological alterations and function.[3]

2. Role of oxidative stress in liver injury

Oxidative stress refers to elevated levels of reactive oxygen species (ROS) that react with lipids, proteins, and DNA. Oxidative stress is generally classified based on ROS intensity, ranging from physiological to pathological levels. When staying at physiological concentra tion, ROS plays an essential role in maintaining multiple physiological functions. When ROS increases to pathological levels, redox biology-related signaling will be activated.[1] ROS includes the superoxide anion (O2e), hydrogen peroxide (H2O2), and hydroxyl radicals (OH,).[4]

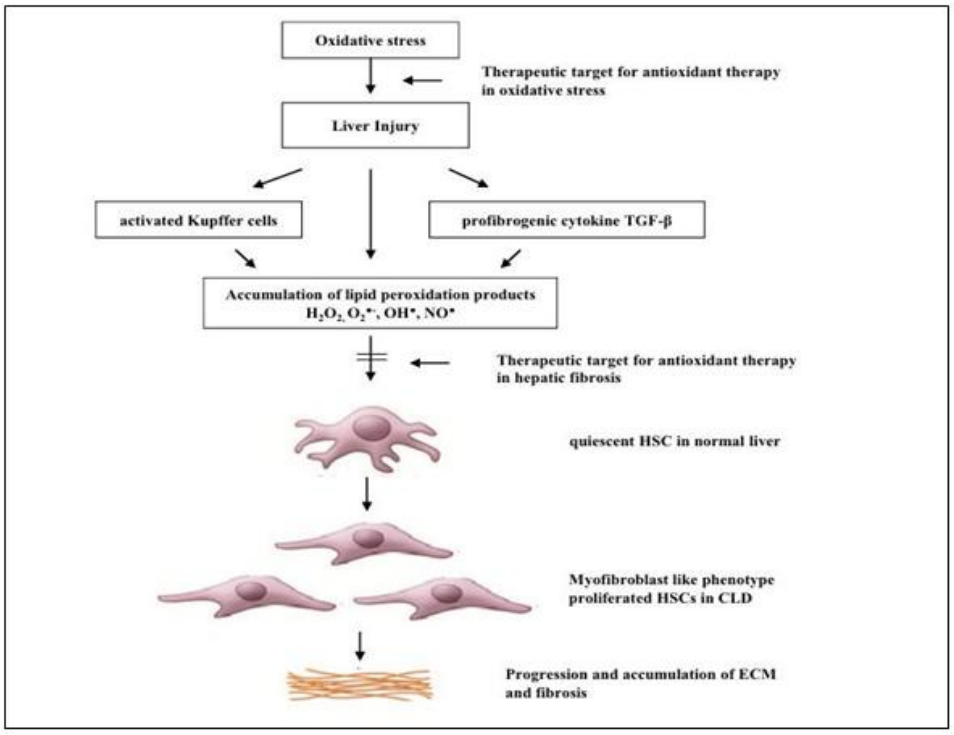

Fig. 2: Schematic representation of oxidative stress-induced chronic liver diseases.[5]

3. Herbal drugs

- Herbal medicines are naturally occurring, plant-derived substances that are used to treat illnesses within local or regional healing practices. These products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant.
- Herbal medicine, also known as herbalism or botanical medicine, is a medical system based on the use of plants or plant extracts that may be eaten or applied to the skin
- One of the greatest benefit associated with herbal medicine is the non existence of side

effects. Also, they tend to offer long lasting benefits in terms of overall wellness. there are a few risks associated with herbal medicine as well. In addition, a growing body of scientific research shows that herbal medicines can be highly effective for certain diseases and conditions. Moreover, as research in this area increases, the optimum doses for herbal medicines are known to ever greater accuracy.[6]

Causes of Hepatotoxicity

- **Viral Infections**:- Viral hepatitis infections that become chronic can cause chronic hepatitis, including hepatitis B and hepatitis C.
- **Alcohol-induced hepatitis**- Heavy alcohol use can cause acute or chronic hepatitis. If it goes on long enough, it can cause cirrhosis and liver failure.
- **Toxic hepatitis**- Chronic overexposure to toxins, such as industrial chemicals or drugs, can cause acute or chronic hepatitis.
- **Non-alcohol related fatty liver disease**- Metabolic conditions associated with obesity, high blood sugar and high blood lipids can cause excess fat storage in your liver, which can cause inflammation steatohepatitis).
- Biliary stasis:- Congenital (present at birth) conditions that obstruct or stall the flow of bile through your bile ducts can cause bile to build up and injure your liver, including biliary atresia and cystic fibrosis. Non- congenital causes include biliary structure and gallstones.
- **Autoimmune diseases**- Autoimmune conditions can cause chronjc inflammation and scarring in your liver or your bile ducts, including autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis.
- **Inherited metabolic disorders**- Conditions that affect blood flow to and from your liver- including Budd-Chiari syndrome, ischemia, arterial diseases and right-sided heart failure - can cause chronic liver damage.[7]

4. Types of liver injury

There are various types of liver disease such as Acute liver failure, Hepatitis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Alagille Syndrome, Alcohol Related Liver Disease, Fatty Liver, Alcoholic Hepatitis, Alcoholic Cirrhosis, Antitrypsin Deficiency, Budd-Chiari Syndrome, Gibber's Syndrome, Liver- Hemangioma, Non-alcoholic Steatohepatitis, Hepatic Encephalopathy, Cholestasis.

5. Test For Liver Diseases

A number of liver function test are available to test the proper function of the liver, (serum proteins, serum albumin, bilirubin (direct and indirect), ALT, AST, GGT, ALP, PT and PTT). Imaging tests such as transient elastography, ultrasound and magnetic resonance imaging can be used to examine the liver tissue and bile ducts.

Liver biopsy can be performed to examine liver tissue to distinguish between various conditions; tests such as elastography may reduce the need for biopsy in some situations.
Liver Biomarkers as well as the related in vitro diagnostic antibodies used for diagnosis being provided.[8]

6. Oxidative stress and Liver Injury

Free radicals are molecules that have an unpaired electron in their valence orbital. Free radicals and their related reactants are not equally toxic; the most reactive, and therefore damaging, products are assumed to be the oxygen-based hydroxyl radical and the nitrogen-based peroxynitrite anion. The generation of molecular oxygen in the form of reactive oxygen species (ROS) is a natural part of aerobic life that is responsible for the manifestation of cellular functions ranging from signal transduction pathways, defense against invading microorganisms and gene expression to the promotion of growth or death.[1] Redox signaling is of essential importance due to the abundance of oxygen in the Earth's atmosphere. Nevertheless, an excessive amount of ROS is highly toxic to cells. Oxidative stress affects the major cellular components: proteins, lipids and DNA.[9]

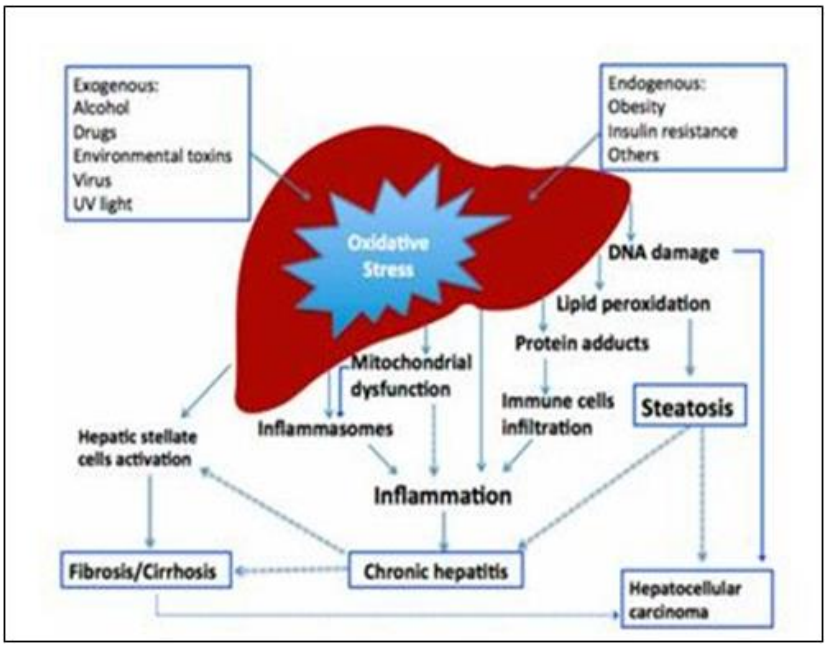

Fig. No. 3: The general mechanism scheme of oxidative stress induced by various factors on liver disease.[10]

Hepatocytes are important sites of ROS production, especially in mitochondria, and are also sensitive to ROS-mediated injury. Each hepatocyte contains 1000 to 2000 mitochondria occupying about 20% of the cell volume. ROS-mediated damage of lipids and particularly, PUFAs, can alter cell membrane fluidity and permeability. Mitochondrial lipid peroxidation negatively affects the electron transport chain, aggravating ROS production and oxidative stress. Mitochondrial dysfunction in hepatocytes has been linked to the development and progression of chronic liver disorders. For instance, patients with non-alcoholic steatohepatitis (NASH) exhibit hepatic oxidative stress due to impaired mitochondrial respiratory capacity and proton leakage. In a mouse model of fatty liver disease, pharmacological improvement of mitochondrial redox homeostasis with the flavonoid dihydromyricetin was shown to be hepatoprotective.[11]

7. Role of Herbal Drugs in Targeting Oxidative Stress

Treating liver diseases with botanical drugs has a long tradition, but evidence for efficacy is sparse. Moreover, there are concerns about the quality of studies testing herbal remedies. In spite of these limitations, a number of herbals show promising effects, either experimentally in cell culture, in animal studies, or even in clinical trials.[12]

Compounds with different structures but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of various diseases. Several

phytomolecules including flavonoids, alkaloids, glycosides and saponins obtained from various plant sources have been reported as potent hepatoprotective agents.

Plant tissues contain a wide variety of compounds with antioxidant activity. Phenolic compounds (flavonoids and phenolic acids), nitrogen compounds (alkaloids, chlorophyll derivatives, amino acids and amines), carotenoids, lignans, and terpenes were reported to possess antioxidative activity in suppressing the initiation or propagation of the chain reactions.

Flavonoids and phenolic compounds are the main antioxidative compounds of herbal drugs. The phenolic compounds exhibit considerable free radical scavenging activities, through their reactivity as hydrogen- or electron-donating agents, and metal ion chelating properties.

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described. They may have beneficial health effects because of their antioxidant properties and their inhibitory role in various stages of tumor development. Some potent herbs with established hepatoprotective activity are described, where as some investigational lead molecules with significant hepatoprotective effects are mentioned.[13]

7.1. Silymarin

Silybum marianum is currently the most well-researched plant in the treatment of liver disease. 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. The leaves are characterized by distinct white “milky” veins that give the plant its common name.

Active Constituents

The active constituents of milk thistle are flavonolignans, including silybin, silydianin, and silychristine, collectively known as silymarin. Silybin is the component with the greatest degree of biological activity, and milk thistle extracts are usually standardized to contain 70-80 percent silybin. Silymarin is found in the entire plant but is concentrated in the fruit and seeds. Silybum seeds also contain betaine and essential fatty acids, which may contribute to silymarin’s anti-inflammatory effect.

Fig. No. 4: Silybum marianum.

Silymarin has been reported to protect liver cells from a wide variety of toxins, in cluding acetaminophen, ethanol, carbon tetra chloride, and D-galactosamine.

Silymarin has also been found to protect liver cells from ischemic injury, radiation, iron toxicity, and viral hepatitis. The mechanisms which provide silymarin's hepatoprotective effects are many and varied, and include antioxidation, anti-lipid peroxidation, enhanced detoxi fication, and protection against glutathione depletion.

Silymarin has been found to inhibit the formation of leukotrienes from poly unsaturated fatty acids in the liver, via its inhibition of the enzyme lipoxygenase. These leukotrienes are known to be some of the most damaging chemicals found in man.

Studies also demonstrated that silymarin increased hepatocyte protein synthesis, decreased the activity of tumor promoters, stabilized mast cells,38 modulated im mune functions,39,40 and was anti-inflammatoryand antifibrotic.[14]

7.2. Berberine

Berberine (BBR, C20H18NO4) is an isoquinoline alkaloid of the protoberberine type, which presents in an array of plants, including Hydrastis canadensis, Coptis chinensis, Berberis aquifolium, Berberis vulgaris, and Berberis aristata among others.

The isoquinoline alkaloid drug belongs to the structural class of protoberber ines which includes a quaternary base. There are many derivates and analogues available, such as berberinehydrochloride, berberine sulfate, and berberine citrate or phosphate, contributing to its multiple pharmacological and biochemical effects.

BBR is traditionally used as an antimicrobial and antiprotozoal drug, the antimicrobial activity against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and chlamydia, which have been applied in Chinese medicine for many decades. Recent researches have revealed novel pharmacological properties and multiple therapeutic applications, mainly concerning metabolic diseases, such as obesity and type 2 diabetes.

Kinetic study shows that BBR metabolites are widely distributed into various tissues, including liver, heart, kidney, spleen, lung, and even brain, with the liver being the most predominant organ, and average concentration of BBR in liver is approximately 70 fold greater than that inplasma.

Other dosing routes, such as femoral vein administration also identified the disposition of BBR in blood, liver, and bile fluid. Additionally, BBR has longer half-life in liver than other tissues, suggesting liver as the main target organ of BBR.[15]

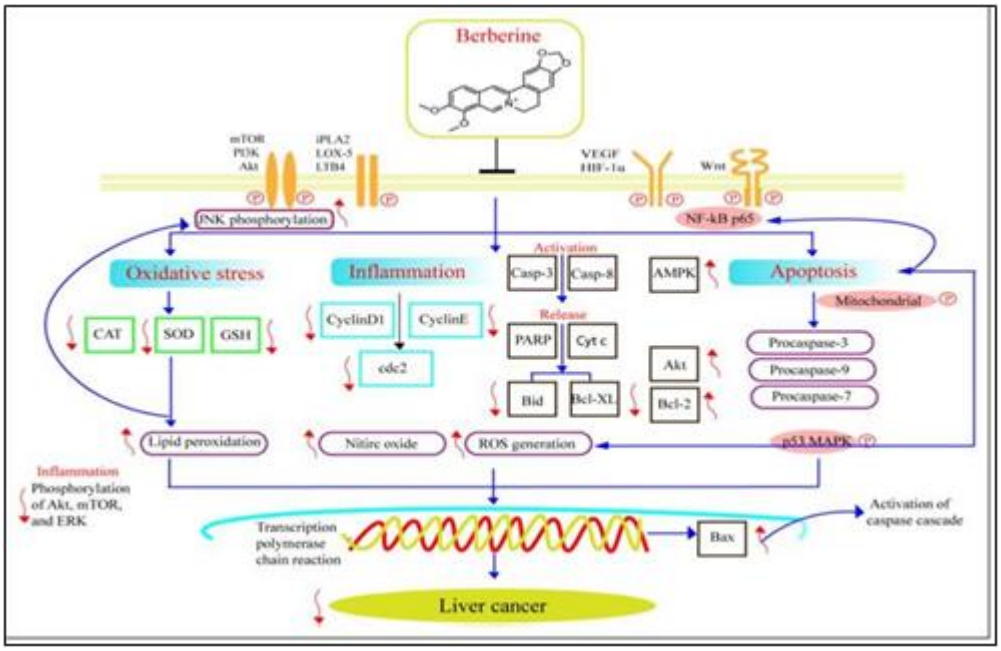

Fig. No. 5: Pathophysiology of Liver.

BBR regulates oxidative stress through the promotion of reactive oxygen species (ROSs), and lipid per oxidation alongside the down-regulation of the actions of gluta thione (GSH), catalase (CAT), and superoxide dismutase (SOD) expressions via the JUK signaling pathway.[16]

7.3. Neem

Neem is now widely used in medicine, and its extract includes a variety of chemical

components, the two most sought-after of which are nimbinine, and nimbendiol, Azadirachta indica, the neem tree's botanical name, is a resilient, evergreen plant native to tropical and subtropical regions that grow quickly. Neem's impact on the skin is one of its main benefits2. Because they are antibacterial, the tree's oils are used as a general antiseptic because they are antibacterial. Neem, also known as Azadirachta indica, is a plant that belongs to the Meliaceae family and has long been valued for its therapeutic benefits3. The seeds, leaves, blossoms, and bark of this tree, which is found in tropical and semitropical regions of the world, areused for a variety of things. Since ancient times, neem tree extracts have been widely employed in health management because they possess a number of health-promoting qualities.[17]

The findings imply that leaf, blossom, and stem bark extracts have significant antioxidant activity. In a different investigation, it was shown that ethanolic extracts of flowers and seed oil had superior free radical scavenging abilities. Additionally, it was shown in a comparative investigation that the bark had more complex phenolic contents than the leaves and had stronger antioxidant activity. The evaluation of the methanolic extract of the roots' roots for the estimate of various flavonoids and their capacity to scavenge free radicals has also been conducted.[18]

Fig. No. 6: Neem.

7.4. Camellia sinensis (Green Tea)

Tea is one of the most widely consumed beverages in the world. Tea plant Camellia sinensis (family-Theaceae) has been originated from Southeast China, gradually expanded to India, Sri Lanka and further into many tropical and sub-tropical countries. The tea plant is grown in about 30 countries Worldwide. It grows best in tropical and subtropical areas with adequate rainfall, good drainage and slightly acidic soil.[19]

Fig. No. 7: Camellia sinesis.

- Black tea is abundant in antioxidants, such as flavonoids, demonstrated to prevent the oxidation of LDL cholesterol, preventing damage in both the bloodstream and at artery walls, and lowering the risk of heart disease.
- It also helps to prevent tooth decay, can lower cholesterol, act as an arthritis soother, and may help folks burn fat. Antioxidants have a vital role in maintaining healthy life.
- Tea contains high amount of antioxidants. Antioxidants are widely used as ingredients in dietary supplement and have been investigated for the prevention of diseases such as cancer and coronary heart diseases. Antioxidants have vital function in food as preservatives.
- Amount of antioxidants in tea depend upon tea origin and processing technology. Black tea consumed throughout the world is a popular beverage and ensures that an antioxidative agent available in everyday life.
- luercetin, luteolin, rutin, apigenin, and kaempferol . These compounds have been shown to increase PPARα (Ppara) gene expression and suppress Srebp1c in mouse liver. Furthermore, holy basil parts have shown anti-cancer, antioxidative, anti-inflammatory, and antidiabetic effects in vitro. Holy basil has the potential to be developed into medications or supplements aimed at preventing metabolic diseases. However, previous studies primarily focused on the bioactivities of holy basil leaves, while their flower by-products may contain potent bioactivities that have not been explored.[20]

7.5. Ocimum sanctum

- Ocimum sanctum L., commonly known as Tulsi or Holy Basil, is an important herb in various traditional medicine systems, including Ayurveda, Unani, Siddha, Chinese, Roman, and Greek medicine. It is known to have hepatoprotective qualities and is known

to offer a range of therapeutic benefits, including analgesia, hepatoprotection, hypolipidemia, and immunomodulation, anti-diabetic, anti-inflammatory, antipyretic, antineoplastic, and anti-stress effects. These activities are explained by the existence of various potent phytochemicals. Additionally, Research has indicated that a combination of Tulsi and silymarin can enhance its hepatoprotective activity, demonstrating a synergistic effect in Liver therapy.

- Holy basil (Ocimum sanctum L.) is an herb in the family Lamiaceae found ubiquitously in Southeast Asia and worldwide. Basil contains phenolic compounds such as chlorogenic acid, caffeic acid, and vanillic acid, as well as flavonoids such as

Fig. No. 8: Ocimum Sanctum.

- Holy basil extracts have demonstrated the ability to reduce hepatic fat content and lower liver lipid peroxidation in a rodent model of hypercholesterolemia, possibly by acting through the SREBP1 pathway. Due to the crosstalk between choline metabolism and the regulation of lipogenesis via mTOR/SREBP1, the choline pathway may mediate the effects of holy basil extracts on MASLD. This study aimed to investigate whether Ocimum sanctum L. flower extracts (OSLY) altered choline metabolites and one- carbon metabolism gene expression in rats, the changes in choline metabolism were correlated with changesinmetabolic markers, and choline metabolites mediated the effects of OSLY on metabolic markers. This study contributes to the field of plant science by characterizing the metabolites in the holy basil flower, a lesser-studied part of this common plant. Our research enhances the understanding of holy basil's ecological contributions and highlights its potential as a source of active compounds for treating MASLD.[21]

8. Advantages of Herbal drugs

Popularity of herbal is increasing globally and at least one quarter of patients with liver diseases

use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting vigorous preclinical studies followed by clinical trial, to unravel the mysteries hidden in the plants. This approach will help exploring the real therapeutic value of these natural pharmacotherapeutic agents and standardized the dosage regimen on evidence based findings to become more than a fashionable trend.

Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental hepatotoxicity models in laboratory or higher animals, several herbals exerted hepatoprotective/curative effects that warrants their clinical testing. Due to lack of scientific based pharmacological data, most for the herbal formulations cannot be recommended for the treatment of liver diseases.[22]

9. Future scope

There is no doubt that certain herbal products contain chemically defined components that can protect the liver from oxidative injury, promote virus elimination, block fibrogenesis, or inhibit tumor growth. Although additive effects may be lost, the active molecules must be isolated and tested in suitable culture and animal experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. Biologically active molecules derived from herbal extracts can serve as suitable primary compounds for effective and targeted hepatotropic drugs.[23]

10. The Challenges in Liver Disease

Diagnosis Liver disease is a multifaceted health challenge, marked by diverse conditions, each with its distinct etiology and clinical manifestations. The primary challenge lies in the accurate and timely identification of these conditions. The clinical presentation of liver diseases varies from subtle symptoms in the early stages to severe complications as the disease progresses. Complicating the matter, these symptoms can often overlap with those of other medical conditions, further emphasizing the need for precise diagnostic tools. Liver disease not only encompasses hepatic manifestations but can also involve extrahepatic symptoms, such as fatigue, jaundice, and cognitive impairment, making the diagnosis even more intricate.[24]

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