PLANT-DERIVED HEPATOPROTECTIVE DRUGS

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Plant-derived Hepatoprotective Drugs

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ISBN (Online): 978-981-5079-84-5

ISBN (Print): 978-981-5079-85-2

ISBN (Paperback): 978-981-5079-86-9

First published in 2023.

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PREFACE

Since the ancient period, plants have shown a pivotal role in leading a healthy life. In developing countries, plant based medicines have great importance to the people. Herbal medicines are used for the treatment of liver diseases for an extended time. The Liver, is the foremost organ for maintaining the human body's internal surroundings. Its major influence is on the flow of nutrients and controls the metabolism of carbohydrates, macromolecule and fats.

The book is an exclusive version of instructive matter in the aspect of Plant Derived Hepatoprotectives, a compilation of ten excellent review articles presenting the latest development in this field of natural product services. They cover a wide range of topics, all relevant to the evidence based therapeutic, protective and olfactory uses of common herbs.

The review by Ikbal *et al*. is focused on the anatomy, functions of the liver, types of liver injury, risk factors and various treatment strategies for liver diseases. Toxicology of the liver is a complex concept that entails either concurrent as well as sequential events. Drug-induced liver injury to the liver can match any form of acute or chronic liver injury. In the next review, the authors have highlighted the various hepatoprotective roles of medicinal plants. Details of Bioactive components and mode of action of hepatoprotective activity of the medicinal plant. With fewer side effects, herbal drugs have gained much attention in the mitigation of various liver disorders and in maintaining a healthy life. The author has provided a comprehensive chapter covering the scientific hepatoprotective agents that are often the treatment of choice to improve liver function and protect the liver from exposure to harmful compounds. Impressive studies have exposed that the health-promoting outcomes of bioactive constituents derivated from plants have often been applied to their antioxidant characteristics and raise cellular antioxidant protection system, scavenge free radicals, suppress lipid peroxidation, stimulate anti-inflammatory capacity, and assure the liver from destruction. These compounds are chlorogenic acid, curcumin, quercetin, hesperidin, rutin, betalains, apigenin, sylimarin, phyllanthin, mangiferin, α-mangostin, bellidifolin, ginsenosides, glycyrrhizin, lycopene, and andrographolide. Anishma*et al* has contributed a chapter on hepatoprotective effect of flavonoids. Many of the flavonoids have hepatoprotective activity and they are been used in traditional medicine to treat any kind of diseases like liver dysfunction and other damages caused by hepatoprotective. The next review by Jain NK and Singh N is also focused on various hepatoprotective plants and herbal formulations. Authors compile information on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models using cutting-edge scientific methods.

The next review by Jha *et al*. is also focused on the Regulatory affairs in herbal products. The review focused on various parameters/guidelines regulating the safety and efficacy of herbal pharmaceuticals, as well as their manufacturing and distribution, which have been strongly implemented by regulatory bodies. This chapter covers the importance of regulatory affairs to be used in the processing of herbs and herbal products and a comparative study of regulatory situations in different countries. Chakraborty R and Sen S have written a chapter on Hepatoprotective effects of edible plants and spices. The author focused on as part of the diet, edible plants could play an important role in protecting the liver from injury caused by oxidative stress, microorganism, or other exogenous substances This chapter highlighted edible plants with hepatoprotective activity. Koka SS *et al*. discuss the the role of terpenoids as hepatoprotective. Plants with a high level of terpenoids appear to have good hepatoprotective properties. Sweta S Koka *et al*. focused on the hepatoprotective effect of the tannin-rich compound. The tannin-containing drugs suppress or inhibit the formation of free

radicals generated due to the metabolism of hepato-toxins. Tannins are widely used in marketed formulations that are used in the treatment of hepato-toxicity. The next review by Sarkar BK presented a chapter on hepatoprotective phytochemicals: isolation and characterization from plant extracts. The author has presented the advances in phytochemistry. The authors have presented the advance in phytochemistry and the number of herbal and herbomineral preparations available in the Ayurveda, the traditional Indian Medicine which, have been investigated for its hepatoprotective potential to treat different types of liver disorders. The present review is focused on different herbal plants that have the potential to cure hepatotoxicity.

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CHAPTER 1

Hepatotoxicity

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Abstract: The largest organ in the human body is the liver which captures 2 to 3% of the human body weight, located on the right side of the anterior quadrant in the abdomen and below the anterior hemidiaphragm ribcage. It performs various important functions such as digestion of food, protein production, fluid production, detoxification of waste, *etc*. Liver injury known as liver trauma can be categorized into four types: hepatocellular, autoimmune, cholestatic and infiltrative. Drug-induced liver injury can match with any form of acute or chronic liver injury. Acute injury to the liver is mainly due to the action of cytochrome P450, which disintegrates drugs into electrophiles or free radicals; these reactive metabolites can covalently act on protein and unsaturated fatty acids for induction of lipid peroxidation which leads to calcium homeostasis or death. Toxicology of the liver is a complex concept that entails either concurrent as well as sequential events. These events determine the pathways, severity and effects of liver injury. Pharmacogenetics has made great progress in current years which indicates the creation of refined algorithms that take drug, host and environmental risk variables into account, allowing for the selection of better medicine based on accurate risk-benefit ratio calculations. In this chapter, we will discuss the anatomy, functions of the liver, types of liver injury, risk factors, and various treatment strategies for the treatment of liver diseases.

Keywords: Cytochrome P450, Hepatocellular, Injury, Liver, Risk factors.

INTRODUCTION

The liver occupies 2 to 3% of the average human body weight thus it is known as the largest organ. The word liver has its meaning rooted in Proto-Germanic “librn”, meaning secreting organ of the body (from the source of Old Norse life).

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It is found in the upper quadrant to the right side of the abdomen under the right hemidiaphragm ribcage that protects it by peritoneal reflection. The place from where it is protected is also known as ligamentous attachments. The ligaments are false and the avascular attachment is in connection with the capsule which is also known as the Glisson capsule [1]. The ligamentous attachment in connection with the umbilical fissure is connected with the falciparum ligament that comes around the umbilicus and extends to the ventral aspect of the liver [2]. There are two lobes present in the liver. The cone-shaped liver also supplies and acquires blood from the sources.

One is the blood that flows from the hepatic artery that is oxygenated and the other is from the hepatic portal vein which is rich in nutrients. At any given point in time, the largest organ can carry blood supply up to one pint (13%) of the total body. The two lobes which are present among the small lobes have eight segments that comprise 1000 lobules. They form a common hepatic duct by linking up the lobules to a small duct that produces a connection to the larger duct.

The only organ that is developed in a vertebrate is the liver [3]. It digests the food we eat and helps in restoring energy and the excretion of toxic substances [4]. Nerves celiac ganglia and vagus nerve are also present in the liver. It is a multitasking organ – the liver is half-moon-shaped, straight and slightly tilted in the cavity of the body. The right portion lies at the initial portion of the small intestine and the left portion is above the stomach. The liver also is the only organ that can regenerate itself as it can replace its parts after 12 partial liver removal surgeries. It is a vascular organ: liver lobule has 3 structures. Each structure can be found in the respective corner of its portal vein, hexagon bile duct and hepatic artery. The blood flow is about 1500ml/min which is approximately about 25% of the cardiac output in which the amount is equivalent to a quarter of the blood that the heart pumps. When the liver tissue was observed under a microscope, it looked somewhat like a honeycomb that was organized beautifully.

FUNCTION

The liver is a vital organ [5]. It has many functions in which some of which are mentioned below:

1. Protein production: One of the important proteins that regulate fluids in the bloodstream and avoid sticking to the nearby tissues.

2. Hormones: It carries hormones throughout the body.

3. Fluid Production: Bile that is produced in the liver and stored in the gallbladder helps in digestion, and in the breakdown of fats into fatty acids, which in turn are taken into the body by the digestive tract.

4. Blood: There are a lot of toxins, by-products and harmful substances in a human body. The liver plays a role in filtering out all the blood that passes through the stomach and intestines.

5. Amino acids: Amino acids are responsible for several cellular metabolisms, the synthesis of nucleotides and lipids as well as detoxification reactions.

6. Blood clotting: Important blood clotting coagulants are created from vitamin K. The liver produces bile that helps in the absorption of vitamin K [6].

7. Vitamins and Minerals: The liver is the starting site for an abundant amount of vitamin A, D, E, K and B12. It also stores nutrients like iron and copper.

8. Glucose: In storing glycogen, the liver plays a major role as it removes the glucose from the bloodstream which is not needed.

9. Detoxification: It is an important role and the liver can excrete endogenous and exogenous waste. It also removes waste products such as bilirubin, ammonia and ketones. Afterwards, it converts them into recycling nutrients which can be excreted through feces or urine.

TYPES OF LIVER INJURY

A liver injury is sometimes referred to as liver trauma that can be defined as one form of damage in the liver that constitutes around 5% of all traumas, thus making it the most commonly found abdominal injury. In general, there are four major classes of liver injury which are cholestatic, hepatocellular, autoimmune and infiltrative. Drug-induced liver injury is relatively less common as compared to other disorders but it remains a challenging clinical trouble concerning both diagnosis and management [7].

A drug-induced liver injury is observed in 3-5% of patients who were referred to the hospitals with jaundice [8]. Therefore, it is regarded as the leading cause of acute liver failure in most Western nations, accounting for more than 50% of occurrences [9]. To date, there are no clear diagnostic standards for drug-induced liver injury while the most common procedures performed to determine the etiology of liver injury include liver biopsy and imaging as well as serologic indicators. Thus, direct or idiosyncratic drug-induced liver damage can be identified.

CHAPTER 2

Hepatoprotective Role of Medicinal Plants

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Abstract: With its ability to self-regenerate, the liver is considered an important gland in the human body, performing essential functions such as the production of vital proteins, lipids, lipoproteins, glucose homeostasis as well as the production and secretion of vitamin stores and bile acids. Therefore, any impairment of the organ can lead to serious problems in our bodies. There are various forms of disorders associated with an unhealthy liver, which affect the liver in different ways and can be detected by observing various general symptoms and some specific diagnostic tests. To treat and control these hazardous effects on our bodies, various medicines are available in the market that are mainly derived from plants and plant products. As they have fewer side effects, herbal medicines have attracted much attention for alleviating various liver diseases while maintaining a healthy lifestyle. Moreover, nanobased delivery of natural products shows higher hepatoprotective activity than crude extracts. In this chapter, various hepatoprotective functions of medicinal plants and their nano-based drug delivery have been highlighted.

Keywords: Liver, Homeostasis, Lipoprotein, Disorders, Tests, Herbal drugs, Mitigation.

INTRODUCTION

The liver is an important gland in the human body. Due to its essential role in the human body, our entire body function will be affected if our liver is impaired. The liver also has the ability to regenerate itself. It serves to provide biological mole-

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-cules and detoxify toxins. The essential functions of the liver include the production of vital proteins, lipids and lipoproteins, glucose homeostasis as well as the production and secretion of vitamin stores and bile acids [1]. Any damage to the liver can lead to severe consequences [2]. These include fibrosis, cell necrosis, decreased tissue glutathione levels and increased tissue lipid peroxidation. Furthermore, toxic chemicals, drugs, foods and infections, such as parasites, viruses, bacteria and fungi can lead to various liver dysfunctions or diseases such as jaundice, liver cancer, hepatitis and cirrhosis.

The liver also plays a central role in the production and secretion of bile juice which is used for the breakdown and digestion of fatty acids. It produces blood clotting factors *i.e.* prothrombin and fibrinogen. It also produces mucopolysaccharide sulphuric acid ester *i.e.* heparin, which prevents blood clotting in the blood vessels of the circulatory system. In the digestive system, it generates hundreds of enzymes and blood proteins for various bodily functions. Apart from that, the liver also produces urea, breaks down proteins, stores trace elements including copper, and iron along with vitamins A, B12, and D, and helps to neutralise drugs and toxins. It also filters our blood and eliminates harmful substances from the blood. Moreover, it helps in the elimination of excess hormones, and managing blood sugar by maintaining the optimal blood sugar level. The poorly functioning liver can lead to hypoglycaemia or diabetes. Besides, an impaired liver can cause an inability to fight infections as our liver has the ability to eliminate certain bacterial and general infections.

Maintaining a healthy liver is important to secure a healthy life. However, an unhealthy lifestyle and various other reasons can lead to liver dysfunction. There are various signs and symptoms which can help in the early detection of liver diseases or its dysfunction such as dark urine, discoloration, yellowish eyes, nail and skin, yellow, gray or pale stool, vomiting with or without blood, nausea, black or bloody stools, loss of appetite, unusually prolonged itching, weight fluctuation, mental confusion, sleep disturbance, abdominal pain, loss of stamina, fatigue and many more. There are other symptoms that may be experienced due to autointoxication thus indicating that our liver must be cleaned. This is a process in which our body, through improper digestion, elimination, *etc*., has poisoned the substances it produces on its own. These signs and symptoms include hair breakage, acne outbreaks, insomnia or bad dreams, flu-like feelings, exhaustion, an imbalance in blood sugar levels, and difficulty concentrating and thinking.

The most common liver diseases include hepatitis, jaundice, liver cancer and cirrhosis. Hepatitis is usually caused by viruses and it refers to the inflammation of the liver. Other reasons include chemicals, alcohol or other autoimmune hypersensitivity reactions. The most common hepatitis viruses are hepatitis A, B, C, D and E [3]. Jaundice, on the other hand, is the result of abnormal metabolism and retention of bilirubin. An early sign of jaundice is when our skin, nails, and

eyes have turned yellowish which indicates over circulation of bile. Jaundice can also cause itching on the body [3]. Cirrhosis is a chronic degenerative liver disease in which the parenchymal tissue degenerates while the lobules are interspersed with fats which leads to the formation of perilobular connective tissue. Severe cirrhosis can lead to hepatic coma, ammonia poisoning, renal failure or gastrointestinal bleeding [3].

Even in ancient times, plants played a central role in healthy living. In developing countries, herbal medicines have great importance to people. For the treatment of liver diseases, various herbal drugs have been studied and shown hepatoprotective effects and can be considered hepatoprotective agents. With that, various chemical constituents have been isolated which are responsible for the hepatoprotective effect [4].

For the treatment of liver disorders, a decoction consisting of numerous herbs with multiple properties individually is commonly used. Herbal decoction nourishes our whole body and focuses on treating the liver [5 - 7]. Herbal plants showing hepatoprotective nature include *Andographis paniculata, Embelia ribes, Zingiber officinale, Picrorhiza kurroa, Terminalia chebula, Cichorium intybus, Emblica officinalis (*amla fruit), *Terminalia arjuna, Berberis vulgaris, Phyllanthus niruri, Lawsonia inermis* (henna), and *Aloe barbadensis etc*.

The treatment of liver disorders in allopathic medicines is limited. Furthermore, allopathic drugs such as interferon and corticosteroids are too expensive and have a high risk of side effects and adverse effects [8]. Moreover, their efficacy and effectiveness are limited. Herbal medicines, on the other hand, are inexpensive and easily accessible. They are harmless substitutes for allopathic medicines as they occur naturally and are gentle. Over time, surveys have shown that 65% of hepatic patients have started taking herbal preparations.

Significance of Medicinal Plants in the Management of Liver Toxicity

Liver disorders are very common nowadays. There are various possible causes of liver toxicity. There are also medicines for various liver problems such as allopathic medicines and herbal medicines. Allopathic medicines may show adverse effects and they can be considered too expensive. They have limited effectiveness while herbal medicines are safe, and gentle and do not cause adverse effects. They are cost-effective in the long term. In Ayurveda, herbal substances are used to protect against liver damage by using various dietary agents and chemicals. Therefore, herbal medicines are considered safe and have the potential to cure liver diseases. Due to this, they have gained great popularity of late. Medicinal plants that have the potential to cure liver diseases are considered hepatoprotective drugs. The popularity of medicinal plants over Western

CHAPTER 3

Bioactive Compounds from Plants Having Hepatoprotective Activity

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Abstract: The liver plays an essential role in metabolic management, and detoxification associating the metabolisms of toxins, lipids, alcohols, carbohydrates and various drugs. It also plays a role in the immune response. However, some conditions, such as viral infections (hepatitis), inflammation, continuous liquor consumption, periodic use of antibiotic-related drugs, and non-alcoholic fatty liver illness, can produce free radicals and cytokines, enhance lipid peroxidation, and induce damage to hepatocytes. Hepatoprotective agents are often the treatment of choice to improve liver function and protect the liver from exposure to harmful compounds. Based on scientific reports, *Silybum marianum, Moringa oleifera, Garcinia mangostana, Glycyrrhiza glabra, Mangifera indica, Amaranthus spinosus, Andrographis paniculata, Phyllanthus species* (*amarus, niruri, emblica*), *Curcuma species* (*longa, xanthorrhiza, manga*), and *Citrus species* (aurantium, sinensis, unshiu, grandis) have been broadly administered for the liver ailments therapy through antioxidant-associated abilities. Impressive studies have exposed that the health-promoting outcomes of bioactive constituents derived from plants have often been applied to their antioxidant characteristics and raise the cellular antioxidant protection system, scavenge free radicals, suppress lipid peroxidation, stimulate anti-inflammatory capacity, and assure the liver from destruction. These compounds are chlorogenic acid, curcumin, quercetin, hesperidin, rutin, betalains, apigenin, silymarin, phyllanthin, mangiferin, α-mangostin, bellidifolin, ginsenosides, glycyrrhizin, lycopene, and andrographolide.

Keywords: Clinical study, Flavonoids, Hepatoprotective, Human & health, *In vitro*, *In vivo*, Lignan, Phenolics, Saponin, Terpenoid, Xanthone.

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INTRODUCTION

The liver is a central organ in the body's metabolism, and it is essential for survival in the form of protection, detoxification, and metabolism. It is the first organ after the digestive tract to be exposed to toxic materials, so it has the potential to be damaged and can lead to inflammation of liver cells and even cell death [1]. The prevalence of liver disease and its effects continue to increase. Liver disease is a world health problem, and more than 350 million people worldwide suffer from the disease [2]. Liver disease is commonly caused by infection and chemical compounds that enter the body through various mechanisms. One of the leading causes of the development of liver disease is an increase in stress which can be estimated as an imbalance between reactive oxygen species (ROS) production and antioxidant defense level [3].

The mechanism of liver disease begins with increased steatosis, and eventually, liver fibrosis can lead to death. Although the pathogenesis of fibrosis is unclear, ROS has a role in pathological changes in the liver, especially in liver disease problems caused by alcohol and toxins. Cell membranes have a significant role in countering the effects of ROS, the reaction process of peroxides into unsaturated fatty acids in the membrane can cause a decrease in membrane integrity and function, which implies quite severe pathological changes, as the natural protective mechanisms in the reduction of liver damage caused by peroxides. However, additional protective mechanisms through antioxidants are needed due to impaired protection or increasing oxygen species (OR). Many natural ingredients have antioxidant agents and are recommended to prevent and treat liver disease caused by free radicals [4].

Medicinal plants have been generally used to treat various types of liver diseases such as hepatitis, liver cirrhosis, jaundice, tumors or cancer, liver failure, cholangitis, leptospirosis, liver abscess, metabolic and degenerative lesions, and liver cell necrosis [5]. Medicinal plants have an essential contribution to human health that is promotive, therapeutic, and rehabilitative and it also contributes to disease prevention. The benefits of natural ingredients that have a role in traditional medicine have been generally developed. The use of natural or herbal ingredients has an essential role in treating cases of liver disease. Herbs can be assumed to have a hepatoprotective effect if they can maintain liver cell function and help accelerate healing. The use of herbs as hepatoprotective can be evaluated through antioxidant mechanisms. In Indonesia, some plants are believed to have efficacy as herbal plants. Therefore, Indonesia has an excellent opportunity to process medicinal plants into a product that provides hepatoprotection.

Hepatoprotector is a compound or substance that can protect cells and repair liver tissue disease by toxic effects. In its structure, hepatoprotective compounds include phenylpropanoids, coumarins, lignins, essential oils, terpenoids, saponins, flavonoids, lipid organic acids, alkaloids, and xanthines. Several natural antioxidant compounds such as flavonoids, terpenoids, and steroids have been studied pharmacologically for hepatoprotective activity [6]. This chapter hopes that scientific information can be obtained about herbal plants that have shown activity as hepatoprotection.

BIO MARKERS TO ASSESS THE LIVER DAMAGE AND HEPATOPROTECTIVE POTENCY

The Role of Antioxidant Enzymes in Liver Damage

Alcohol and some drugs can induce oxidative stress by increasing cellular oxidation, lipid peroxidation, and antioxidant depletion in the liver [7]. The body responds to chemical-induced damage by activating a set of endogenous antioxidant enzymes. Antioxidant enzymes provide protection by scavenging the ROS. Superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals ($\bullet O_2$) to hydrogen peroxide (H_2O_2) [10]. Although H_2O_2 is not radical, it is rapidly converted by the Fenton reaction to the highly reactive •OH radical. Glutathione peroxidase (GPx) detoxifies H_2O_2 by reaction with glutathione (GSH) to produce oxidized glutathione (GSSG). The oxidized glutathione is then reduced to GSH by glutathione reductase (GSR). Catalase (CAT) neutralizes H_2O_2 into H_2O, reducing free radicals [11]. Heme oxygenase 1 (HO-1) is an isozyme that is required in phase II detoxification and has an important role during oxidative stress resistance.

In excessive oxidation conditions, the activity of this antioxidant enzyme will be affected. Decreased GSH, SOD, GPx, CAT, GSR, and HO-1 in hepatocytes causes cells to be more susceptible to the dangers posed by free radicals. This means that measuring antioxidant enzyme activity is an indirect method commonly used to assess the status of antioxidant defenses against ROS damage [11]. A compound that has the potential to be hepatoprotective will show an increase in the level/activity of this antioxidant enzyme, and most of them are antioxidants. Antioxidant compounds can protect the liver by scavenging ROS and neutralizing lipid peroxides (LPO). The main product of LPO processes is lipid hydroperoxides (LOOH), and the secondary product formed during LPO is malondialdehyde (MDA). Increasing secondary oxidation products (including MDA) upon lipid peroxidation in hepatic tissue will cause cellular damage and cell membrane disruption and deplete endogenous antioxidant enzymes [11].

CHAPTER 4

Hepatoprotective Role of Herbs and Herbal Formulations

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Abstract: The liver is an important organ in the body's metabolism and excretory system. The prevalence of many forms of hepatic illnesses is on the rise, resulting in a major increase in morbidity and mortality worldwide. Viral hepatitis, alcoholic/non-alcoholic fatty liver disease, liver fibrosis, cirrhosis, hepatocellular cancer, and drug-induced liver injury are all important health concerns that take millions of lives each year throughout the world. Pharmaceutical medications are frequently linked to liver injury, and so have limited efficacy in the treatment of liver diseases. As a result, herbal drugs have grown in popularity and are widely used. For a long time, herbal remedies have been utilized to treat liver problems. There are a variety of herbal preparations on the market. Herbal medicine has been used to treat liver disorders for thousands of years. A large range of medicinal plants have been examined as hepatoprotective agents in preclinical and clinical investigations. However, more thorough research is needed to screen and evaluate the usage of herbal medicines in the treatment of diverse liver illnesses. The goal of this review is to compile information on promising medicinal plants that have been tested in hepatotoxicity models using cutting-edge scientific methods. The damage to liver cells caused by various toxic chemicals (antibiotics, chemotherapeutic agents, carbon tetrachloride (CCl_4), thioacetamide (TAA), and microbes have been well studied. In this scenario, the current synthetic medications to treat liver problems promote more liver damage. The purpose of this chapter is to examine various hepatoprotective plants and herbal formulations.

Keywords: Carbon tetrachloride, Hepatoprotective agents, Hepatitis, Liver, Liver Disorders, Phytochemicals, Thioacetamide.

INTRODUCTION

The liver is a key organ that aids in the maintenance of the body's different physiological processes. It plays a major role in metabolism, secretion, and storage, among other bodily functions. It is involved in the detoxification and

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excretion of a variety of foreign and endogenous chemicals. Proteins, glycogen, different vitamins, and metals are all stored in it. It also plays a role in blood volume regulation by moving blood from the portal to the systemic circulation and its reticuloendothelial system, as well as contributing to the immune system [1]. The liver controls the majority of chemical levels in the blood and excretes bile. This aids in the removal of waste materials from the liver. The liver filters all of the blood that leaves the stomach and intestines. The liver processes blood, breaking down, balancing, and creating nutrients, as well as metabolizing medications into forms that are easier to use or harmless for the rest of the body. The liver cells, often known as hepatocytes, perform a variety of functions. The liver is responsible for more than 500 important activities (Fig. **1**). The following are some of the more well-known functions:

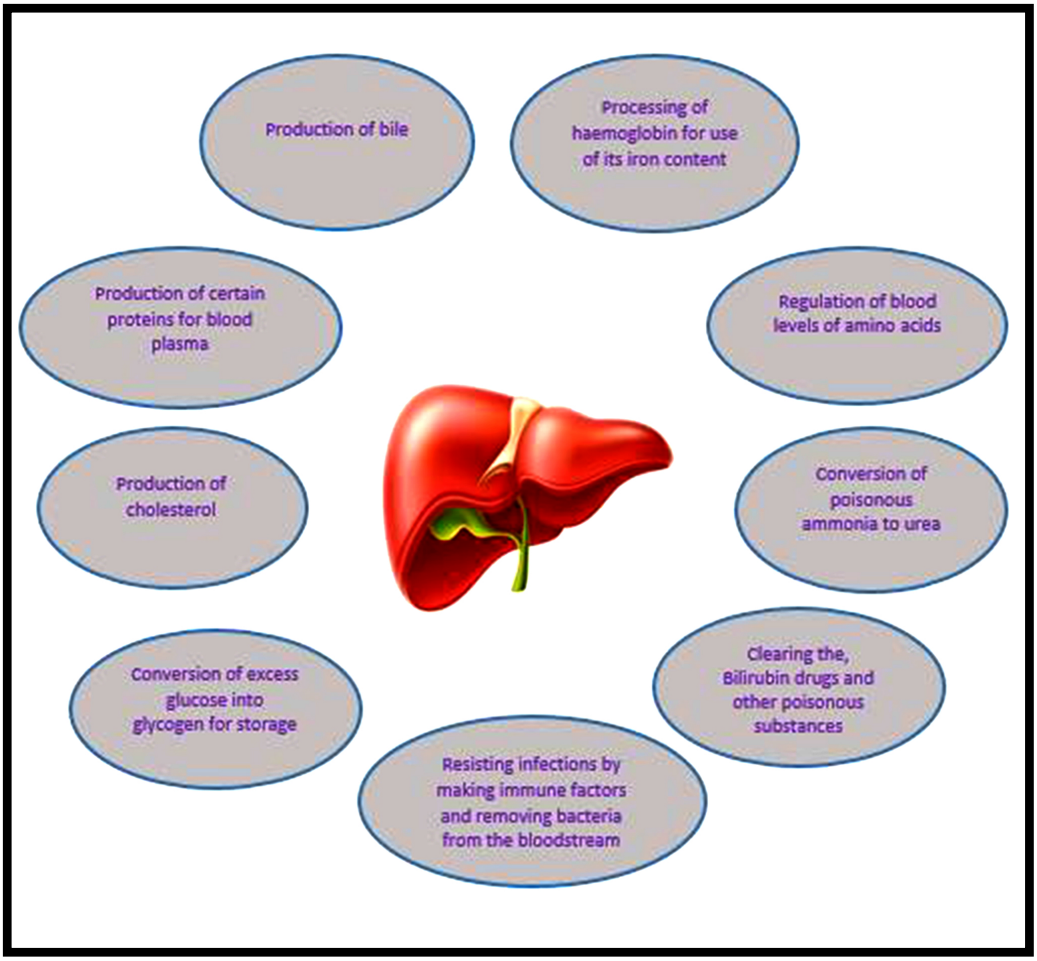

Fig. (1). Functions of the liver [8].

- Bile production aids in the removal of waste and the breakdown of fats in the small intestine during digestion [2].
- The manufacture of specific proteins for blood plasma [3].
- Cholesterol and specific proteins are produced to aid in the transport of fats throughout the body.
- Storage of excess glucose as glycogen (which can subsequently be converted back into glucose for energy), as well as balancing and producing glucose when needed [4].
- Controlling the amounts of amino acids in the blood, which are the building blocks of proteins [5].
- Haemoglobin processing for the usage of iron content (the liver stores iron).
- Clearing the blood from drugs and other harmful compounds by converting toxic ammonia into urea (urea is a by-product of protein synthesis and is eliminated in the urine).
- Making immune factors and eliminating pathogens from the bloodstream to fight illnesses [6].
- Bilirubin clearance [7].

Because of its essential function in chemical clearance and modification, the liver is vulnerable to drug-induced damage [9]. The liver is vulnerable to a variety of disorders due to its strategic position and multifaceted functions. Any damage to it or impairment of its function has serious health consequences for the individual who is affected. Due to food choices, alcohol consumption, poor cleanliness, uncontrolled drug use, and smoking, liver problems are the most common health concern in underdeveloped countries. Liver diseases are a prominent source of mortality all over the world [10]. According to studies, liver problems cause between 18000 and 20000 death of people worldwide each year [11, 12]. About 2-5 percent of hospital admissions in the United States are related to liver injury, with 10% of them resulting in acute liver failure [13, 14]. Globally, the crude incidence of liver disease is 14 per 100000 people per year, while the standard incidence is 8.1 per 100000 people per year [15]. Acute liver failure affects up to 13% of people in wealthy countries like the United States but only 5% of people in tropical countries like India [16]. Non-inflammatory, inflammatory, and degenerative liver illnesses are all possible. Due to hepatic insufficiency, elevated levels of plasma total cholesterol, Low-density lipoprotein Cholesterol (LDL-C), and triacylglycerols (TGs) are linked to an increased risk of atherosclerosis and cardiovascular disease [17, 18]. Hepatotoxicity is caused by a variety of toxins, including carbon tetrachloride (CCl_4), thioacetamide, and acute or chronic alcohol intake, as well as diseases such as hepatitis A, B, and C, and medications, the latter of which is the most common culprit. Alcohol consumption causes the formation of free radicals, which leads to the development of hepatitis and cirrhosis [19]. Although viral infection is one of the leading causes of hepatic

CHAPTER 5

Regulatory Affairs in Herbal Products

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Abstract: Various parameters/guidelines regulating the safety and efficacy of herbal pharmaceuticals, as well as their manufacturing and distribution, have been strongly implemented by regulatory bodies. To understand the pre-marketing requirements, the legislative status of herbal drugs/products was analyzed in this chapter for various countries in Southeast Asia, Africa, America, Europe, and Austria. Apart from the challenges of herb availability and conservation, it has been shown that there is a lack of harmony in the regulatory requirements for herbal products across the world. A critical evaluation was performed in order to detect the obstacles in the harmonization of herbal products. The worldwide trade and development of herbal products are being hampered by these issues. The herbal drug industry is inadequately regulated in most countries, and herbal medicines are often neither registered nor controlled. Quality compliance and assurance of the safety and efficacy of the marketed herbal drugs are major issues faced by developing as well as developed countries across the globe. The problem arises when herbal medication is utilized without legitimate permission, or in huge dosages, or in combination with other drugs for a longer period, or without discussion with a doctor, and produced properly. Taking these factors into account, the World Health Organization's International Drug Monitoring Program (WHO) has published standards for herbal assessment and quality control testing in order to improve the safety and efficacy of herbal-based therapeutics. This chapter covers the importance of regulatory affairs to be used in the processing of herbs and herbal products, and a comparative study of regulatory situations in different countries.

Keywords: Compliance, Harmonization, Legislative, Legitimate, Quality control, Regulatory affairs, Therapeutics.

1. INTRODUCTION

The World Health Organization's (WHO) International Drug Monitoring Program published certain recommendations for herbal drug evaluation and

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quality control analysis. The World Health Organization has made a series of efforts to improve the safety and efficacy of herbal medicines. Toxicity from herbal medicines occurs if they're used without appropriate indications, in large doses, or in combination with other medications, for extended periods of time without seeking medical advice [1].

Regulatory affairs are initiated from government affairs that include controlling the safety and efficacy of herbal products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics, and complementary medicines, for the protection of public health. It keeps track of the companies by establishing specialist departments of Regulatory Affairs professionals ensuring that they supply quality products to the public for their health and welfare. Because the production of herbal products takes time, from collection to manufacturing and packaging, Regulatory Affairs should be lead from the start to reduce the time required for the herbal product to reach the market, from developing effective regulatory strategies following the discovery of a new molecule to post-marketing planning, the Drug Regulatory Affairs (DRA) department or team a critical responsibility. Also, the cost-effective use of the company's resources has also increased by using regulatory affairs. Moreover, government authorities can easily rely upon scientifically knowledgeable company officials and hence, can work in cooperation with each other.

Scientists, regulators, industry, and, more recently, patient representatives and patient advocates have been brought together via research policies and alliances. In the near future, improved strategies for research-based corporate organizations, more integrated research tools dealing with appropriate translational requirements directed at clinical development, and proactive regulatory policies will be needed to accurately enhance the development of new technologies [2]. Depending on Ayurveda, a large no of companies are developing many products for therapeutic and supplementary uses. If we examine herbal products sold in India, we can easily find these don't bear product leaflet, which lacks usage instructions. When compared to allopathic medications, however, there is a significant difference. A pharmaceutical business invests a lot of money to prove its efficacy, which includes like bioavailability, toxicity, safety, clinical data, and so on. However, herbal products do not require this, and as a result, the majority of herbal products fail. If we look at the regulatory status of herbal products around the world, we can see how stringent other countries are when it comes to human safety [3].

The group of regulatory affairs is having a solid influential position that guarantees consistency with guidelines and empowers comprehension and understanding of a powerful regulation. Pharmaceutical, biologics, and medicine companies may be apprehensive if new products and processes are not thoroughly vetted and evaluated before they are published. However, failure to do so could

result in the organization ceasing to evaluate marketing submissions in a timely and correct manner.

The key functions of the global regulatory affairs group include:

- Leading and providing strategic regulatory guidance and delivering the global regulatory strategy for product development, manufacturing, and registration.
- Building and maintaining a credible relationship with regulatory authorities with effective written and verbal communication.
- Establishing an efficient repository and archive for correspondence compliant with regulatory standards for audits.
- Providing high-quality, complete user/reviewer-friendly documents electronically transmissible and reproducible.
- Developing and maintaining product information and label.
- Providing regulatory intelligence, from paying attention to the regulatory environment and changing landscape, to participating in external industry partnerships and developing policy with regulatory agencies.
- Ensuring published information and promotional/advertising materials meet regulatory requirements.
- Ensuring functional units comply with regulatory requirements and good regulatory practices.

This end goal drives the need for the regulatory team to:

- Deliver innovative, breakthrough regulatory strategies for product development and registration.
- Become more anticipatory of the company's success imperatives.
- Be proactive and forward-thinking, and provide timely, comprehensive, and robust global regulatory guidance.
- Understand the biopharmaceutical environment and regulatory actions on precedents and utilize such regulatory intelligence.
- Forge new standards to deliver more predictable outcomes.

TRADITIONAL MEDICINE PROGRAMME BY WHO

The World Health Assembly (WHA) has posted numerous resolutions in recognition of this fact, and the Alma-Ata Declaration urges that scientific consensus on herbal medicines should be included in national drug policies and regulatory measures. As presented in the Forty-fourth World Health Assembly, it stated that “WHO collaborated with its Member States in the review of national policies, legislation and decisions on the nature and extent of the use of traditional

CHAPTER 6

Hepatoprotective Effects of Edible Plants and Spices

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Abstract: Liver diseases are considered a major global public health problem that is always underestimated. Damage to hepatocytes caused by drugs, toxins, viruses, *etc*. is a major cause of hepatic disorders, including liver cancer. Oxidative stress is considered a primary underlying mechanism of liver disorders. Cytokine produced in response to ROS plays an important role in damaging the liver. Plants are also considered an important source of phytoconstituents with hepatoprotective activity. As part of the diet, edible plants could play an important role in protecting the liver from injury caused by oxidative stress, microorganisms, or other exogenous substances. Many vegetables, fruits, and spices have been investigated for their hepatoprotective activity in pre-clinical studies. Phytoconstituents like curcumin, catechin, rutin, myristicin, fumaric acid, silybin, picroside, kutkoside, glycyrrhizin, silymarin, and apigenin were found to exhibit hepatoprotective and antioxidant activity through diverse mechanisms including antioxidant activity, and anti-inflammatory activity. This chapter highlighted edible plants with hepatoprotective activity.

Keywords: Antioxidant, Edible plant, Hepatoprotective activity, Phytochemicals.

INTRODUCTION

The liver is the largest organ of the human body that plays a central role in the metabolism of exogenous substances and eliminating toxins. The liver consists of almost 2–5% of the adult body weight and approximately 10% of the blood flowing through the liver [1, 2]. The liver also assists in converting essential micronutrients into usable forms required by the human body and accomplishes more than 500 different functions. Damage to hepatic cells is a significant problem and is responsible for a broad spectrum of liver diseases. Endogenous

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substances like drugs, toxins, viruses, *etc* are a major cause of hepatic disorders [1].

Different liver diseases are considered a major global public health problem that is always underestimated. A global survey almost eight years ago estimated that 844 million people suffer from chronic liver diseases (CLDs), with more than 2 million deaths/year. Complications of cirrhosis, viral hepatitis and hepatocellular carcinoma are considered a major cause of death associated with liver diseases. A recent rise in the number of non-alcoholic steatohepatitis (NASH) was also reported [3, 4]. Alcohol-associated liver disease (AALD) is considered the main reason for liver disease. Alcohol usually causes liver injury and coexists with viral hepatitis and other infections. While non-alcoholic fatty liver diseases like non-alcoholic fatty liver (*i.e*. steatosis or steatosis) and NASH (*i.e* fibrosis, cirrhosis, carcinoma) are also responsible for wide range of complications [4]. Hepatocellular carcinoma (HCC) is the most frequent primary liver malignancy associated with a large number of deaths and is considered the foremost reason for global cancer-related death. CLDs and liver cirrhosis continue as leading reasons for the development of HCC. Many factors like viral hepatitis and excessive alcohol intake are considered major underlying causes associated with such conditions [5]. The consumption of excessive alcohol is associated with a spectrum of liver injury. Excessive alcohol intake enhances NADH levels that alter the cellular redox potential and increase the synthesis of lipids. Alcohol consumption is also associated with enhanced generation of free radicals and increases the expression of lipogenic enzymes and cytokines. Sterol regulatory element binding protein-1c (SREBP-1c) and early growth response-1 (Egr-1) are linked and play an important role in such conditions. Regular and excessive intake of alcohol results in different hepatic lesions associated with steatosis, fibrosis, hepatitis, and cirrhosis. Inflammation, destruction of parenchyma, and free radical generation lead to fibrosis and cirrhosis [6]. Viral hepatitis is closely linked with the pathogenesis of chronic liver disease. It was estimated that approximately 400 million people are affected by either hepatitis B and C infection [2].

Good food always boosts health, and bioactive components present in the food always play a vital role in preserving and maintaining health. Through diet, we receive an adequate amount of nutrients, antioxidants, and other bioactive molecules that are in synergy, and promote health. Bioactive molecules present in food besides the protein, fat, carbohydrates, vitamins, and minerals play an important role in maintaining health [7]. Oxidative stress is considered a situation caused by the increase in the generation of ROS/RNS or depletion of antioxidant defence. ROS may cause major damage to the liver. Parenchymal cells are the principal target of ROS and linked with liver injury. Cytokines produced in response to ROS are also important in the pathogenesis of different liver diseases

[8]. Food contains diverse phytochemicals including antioxidant molecules that may play an important role in preserving the liver from oxidative stress-induced diseases. The consumption of antioxidant-rich foods may help enhance the antioxidant capacity of the body and would therefore reduce the risk of liver damage or may induce healing quickly [9]. A number of phytochemicals like naringenin, quercetin, curcumin, resveratrol, silymarin, carotenoids (*i.e*. lycopene, lutein, β-carotene, β-cryptoxanthin) present in edible plants also exhibit potent ROS scavenging effect. Further, pre-clinical/clinical studies indicated that these phytochemicals act via different mechanisms like reducing lipid accumulation, reducing insulin resistance, maintaining oxidative stress, and decreasing inflammatory cytokine generation and exhibit their beneficial effect in different liver disorders [8 - 10]. This chapter mainly focused on the beneficial effect of edible plants in liver disorders.

HEPATOPROTECTIVE VALUE OF EDIBLE PLANTS

Edible plants are also considered an important source of phytoconstituents with hepatoprotective activity. Plants are an important source of hepatoprotective activity and among them, edible plants could play an important role in protecting the liver from injury caused by oxidative stress, microorganisms, or other exogenous substances. A number of investigations reported the beneficial effects of edible plants or plant parts in liver diseases. Many vegetables, fruits, and spices have been investigated for their hepatoprotective activity in pre-clinical studies (Table **1**). A study on experimental animals showed that the plants/plant parts positively ameliorated liver enzymes like SGPT, SGPOT and other parameters. Further, these extracts enhanced the level of endogenous antioxidants and inhibited lipid peroxidation [11 - 19].

Table 1. Edible plants with hepatoprotective activity

Common Name	Plant name & Family	Edible Part	Model used	Parameter screened	Image
Pomelo / Grape Fruit	*Citrus paradisi* (Rutaceae)	Fruit	dimethylnitrosamine (DMN)-induced hepatic damage	ALAT, ASAT, ALP, and bilirubin, albumin, MDA	

CHAPTER 7

Hepatoprotective Phytochemicals: Isolation and Characterization from Plant Extracts

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Abstract: The liver is the body's primary organ responsible for metabolism and excretion. Oxidation, reduction, hydration, condensation, hydrolysis, conjugation, and isomerization are some of the metabolic routes used by the human liver to metabolise chemicals. Any of the aforementioned processes can be disrupted, resulting in liver cell damage or hepatotoxicity, which can lead to a variety of disorders. These disorders are linked to increased death rates over the world. Medicines, chemicals, dietary changes, and herb-induced liver injury via hepatotoxins can all cause hepatotoxicity. A number of herbal and herbomineral preparations are available in Ayurveda, the traditional Indian Medicine, which has been investigated for their hepatoprotective potential to treat different types of liver disorders. The present review is focused on different herbal plants that have the potential to cure hepatotoxicity.

Keywords: Herbal plants, Hepatotoxicity, Liver diseases, Herbal drugs, Indian Herb, Phytochemical.

INTRODUCTION

The liver is one of the body's most important organs. Its activity is linked to several critical activities, such as metabolism, secretion, and storage space, and it plays an important role in controlling various physiological processes. Many researchers have studied its ability to detoxify endogenous (waste metabolites) and/or exogenous (toxic chemicals) substances of organisms, as well as manufacture beneficial agents, since the 1970s [1 - 4].

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The liver has a role in all biochemical activities, such as in growth, reproduction, delivering nutrition, and supplying energy to the body's organs. It also helps in the metabolism of carbohydrates and lipids, the production of bile, and the storage of vitamins [5]. Hepatic illnesses continue to be one of the most serious dangers to public health, and they are a concern all over the world [4, 6]. Hepatic disease is a term that refers to an injury to the cells, tissues, structure, or function of the liver. It can be caused by biological factors (bacteria, viruses, and parasites), autoimmune diseases (immune hepatitis, primary biliary cirrhosis), or the action of different chemicals (some drugs), toxic chemicals [carbon tetrachloride (CCl4), thioacetamide, dimethylnitrosamine (DMN), D-galactosamine/lipopolysaccharide (GalN/LPS)], and, without a doubt, excessive alcohol intake [7 - 9]. Despite tremendous developments in contemporary medicine, no fully effective medications exist that stimulate hepatic activity, provide total organ protection, or help in the regeneration of hepatic cells [10, 11]. Furthermore, certain medicines might cause side effects. As a result, alternative medications for the treatment of hepatic illnesses must be identified, with the goal of making these drugs more effective and less harmful. The usage of some plants and the consumption of various fruits have played important roles in human health care. Around 80% of the world's population relies on traditional medicine for treatment [4, 9], which is mostly based on plant components. Various scientific investigations of medicinal plants and the consumption of fruits have revealed that the properties responsible for their beneficial effects can be attributed to the presence of biologically active chemical compounds or substances called phytochemicals, which are supplementary nutrients for life. In conclusion, research that has looked at the impact that various phytochemicals have on health may be found. The following are some of the most often mentioned examples: (1) The vinca alkaloids (vincristine, vinblastine, and vindesine); (2) The betalain pigments (betanin and indicaxanthine); (3) Anthocyanins (cranberries); and (4) Resveratrol; all of these have been studied for their cancer-fighting potential [4, 12 - 14]. All therapeutic plants, as well as the consumption of certain fruits, have different impacts on biological systems. Although a few studies have looked at their hepatoprotective properties, the vast bulk of research has focused on their sedative, analgesic, antipyretic, cardioprotective, antibacterial, antiviral, antiprotozoal, and anticarcinogenic properties [15]. In addition to these studies, there is a long history of experiential confirmation on the use of natural remedies for the treatment of hepatic diseases, and this field has emerged as an innovative field of research, with the primary goal of analysing the consumption of traditional fruits and medicinal plants by a large number of people, as well as the various phytochemicals extracted from these foods. Chemical substances found in liver-protective fruits and plants include phenols, coumarins, lignans, essential oils, monoterpenes, glycosides, alkaloids, carotenoids, flavonoids, organic acids, and

xanthenes [16]. The goal was to compile data from studies on some fruits and plants that are commonly consumed by humans and have been shown to have hepatoprotective properties, as well as an analysis of a resin and some phytochemicals extracted from fruits, plants, yeasts, and algae that have been tested in various hepatotoxicity models [17 - 20]. When it comes to detoxifying the many poisons found in food, beverages, drugs, and the environment, the liver can take the most abuse. Pre-existing liver illness, age, female sex, and heredity are only a few of the risk factors that might lead to hepatic drug harm. The liver, as the primary site of metabolism, plays a critical role in the detoxification of many toxins consumed and/or created during food absorption [1 - 3]. To prevent toxins from accessing other bodily systems, the liver filters all blood from the digestive tract before passing it on to the rest of the body [4]. It controls practically all of the body's processes by utilising several metabolic pathways for energy generation, metabolism, and reproduction [5]. The liver also produces a variety of complement systems and proteins that aid the immune system [6]. As a result, a functioning liver is essential for a healthy person.

Causes of Liver Diseases

Due to food choices, alcohol use, poor cleanliness, uncontrolled drug use, and smoking, liver problems are the most common health concern in underdeveloped nations. Non-inflammatory, inflammatory, and degenerative liver illnesses are all possible. Because of hepatic insufficiency, high levels of plasma total cholesterol (LDL-C) and triacylglycerols (TGs) are linked to an increased risk of atherosclerosis and cardiovascular disease [7, 8]. Hepatotoxicity is caused by a variety of toxins such as carbon tetrachloride (CCl4), thioacetamide, acute or chronic alcohol intake, various illnesses such as hepatitis A, B, and C, and medications, the latter of which is the most commonly reported. Free radical generations with alcohol use result in the development of hepatitis, leading to cirrhosis [21].

Role of Medicinal Plants in Hepatotoxicity

Plant materials have been employed in Ayurveda to protecting the liver from various poisons and dietary factors. As a result, herbal treatments have grown in popularity in recent years due to their safety and potential to cure ailments. These drugs are also incredibly cost-effective when used for a long time. Many medicinal plants found in various areas of India have been identified as hepatoprotective medications and are widely utilised to treat liver diseases. Hepatoprotective action may be found in a variety of plants and polyherbal preparations. Hepatoprotective action has been claimed for around 160 phytoconstituents and other phytochemicals [10]. Over 87 plants are utilised in

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Shiv Shankar Shukla

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