INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

A Review On Herbal Plants And Bio Active Chemicals For Their Hepatoprotective Activity

V. Moni Prashanth , V. V. Rajesham *, T. Rama Rao

CMR College of Pharmacy, Kandlakoya (V), Medchal Road, Hyderabad- 501401, Telangana, India.

ARTICLE INFO

Received: 22 Aug 2024
Accepted: 26 Aug 2024
Published: 01 Sep 2024
Keywords:
Liver, Paracetamol, Tetracycline, Antitubercular drugs, Chemotherapeutic agents, Hepatoprotective activity
DOI:
10.5281/zenodo.13625577

ABSTRACT

Liver, the largest gland functioning as an organ of storage, manufacturing and biotransformation is a vulnerable target for injury. Chronic alcohol consumption, exposure to toxic chemicals and certain drugs like paracetamol, tetracycline, antitubercular drugs, chemotherapeutic agents, NSAIDS, damage the liver cells (hepatocytes) in long run. Drug induced liver injury is a major health problem, the manifestations of which are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant liver failure. Modern medicine has provided us many drugs that alleviate liver diseases but compared to it herbal medicine is preferred because the latter is cost effective and considered to be a safe approach for treatment with minimal side effects. Through the decades many scientists, researchers have reported hepatoprotective activity of many medicinal plants mostly in the form of plant extracts. The present review is aimed at compiling data on different medicinal plants with hepatoprotective activity on various models of hepatotoxicity.

INTRODUCTION

The liver, largest organ in human body, contributes 2% of our body weight, weighing almost 1.5 kg in a fully grown adult. The liver is the site for drug metabolism and biotransformation, thereby having defensive role in the body against toxic foreign chemical agents. Due to these, the liver is exposed to drugs, chemicals, and other xenobiotics in different concentrations which finally results in liver injury. There are over hundreds of etiologies causing hepatic diseases. The most profound causes of hepatic disease consist of microbes (hepatitis virus A, B, C, Cytomegalovirus, Epstein-Barr virus, and yellow fever virus); disease related to metabolic syndrome (fatty liver disease caused by obesity, hemochromatosis, and Wilson's disease); xenobiotics (alcohol, drugs, and chemicals); hereditary-related hepatic diseases; autoimmune diseases (biliary cirrhosis, hepatitis, and sclerosing cholangitis); and liver malignancies. End result of

***Corresponding Author:** V. V. Rajesham
Address: *CMR College of Pharmacy, Kandlakoya (V), Medchal Road, Hyderabad- 501401, Telangana, India.*
Email : vvrajesham@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

hepatic diseases is disturbance and loss of workdays, compensation in quality of personal life, squeezing in expected life span, and financial burden to the individual as well as to the society, subsequently resulting in mortality and morbidity (Pandey, Egyptian Liver Journal). Around the globe, near to 2 million people are fading away each year because of hepatic complexities among which 1 million are due to complication of cirrhosis and another half are cognated to liver carcinoma and viral hepatitis. At present, the most prevalent cause of death is cirrhosis ranking 11 (1.16 million deaths) and liver cancer which ranks 16 (788,000 deaths) for death complication, and in combination, they account for 3.5% of all deaths worldwide. High intake of alcoholic product is the major factor for liver disease in global context. A report published by the World Health Organization showed that among the total alcohol consumer worldwide which is predicted to be around 2 billion, slightly less than half, i.e., 75 million, are diagnosed with disorders related to the alcohol use specifically to several alcohol-associated liver disease. In 2015, more people died with viral hepatitis-related disease (1.34 million deaths) than by human immunodeficiency virus (HIV) (1.06 million deaths) or malaria (0.44 million deaths) and similar to the number caused by tuberculosis (1.37 million) []. Among the morbidity cause by viral hepatitis, total of 96% is accounted for hepatitis B virus (66%) and hepatitis C virus (30%) which is mainly due to the cirrhosis complication and profusion of liver cancer (Pandey, Egyptian Liver Journal) Drug-induced liver injury (DILI) is one of the major problems associated with the treatment for several acute and chronic disease conditions. Research studies revealed that antitubercular drug (isoniazid), antipsychotic (chlorpromazine), penicillin antibiotic (amoxicillin), and histamine antagonist (cimetidine), analgesic and antipyretic (acetaminophen), and HMG-CoA reductase inhibitors (statins) are major drugs causing DILI [. In West region of the globe, amoxicillin/clavulanic acid-induced liver injury occurs in 1 in 2350, whereas combined antitubercular drug-induced liver injury is more profound in the east region Among them, India and Nigeria have highest burden of DILI followed by China and South Korea having herbal and alternative medicine-induced liver injury, WHO. Globally, antimicrobial agents are considered as the major cause of idiosyncratic DILI]. The above latest figures depict that the worldwide liver disease burden has increased with growing time showing massive influence on the public life around the globe WHO (Ahmad A, (2014)) Traditional medicine is prevalent all over the world which plays important role for preventive and curative purpose for people in developing countries]. According to the definition given by the WHO, “Traditional medicine is regarded as diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicine, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness”. (Al-Asmari AK, 2014:1-22)Hepatic problems are one of the highly pronounced reason for mortality and morbidity in human Liver damage is usually related to cell necrosis, diminution, and increase of liver biomarkers such as aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), an increase in tissue lipid per oxidation, and oxidative damage . Traditional medicine from the natural sources has significant effect in the management of the hepatic diseases. Many natural phytoconstituents have been demonstrated to be effective hepatoprotective agents, while many more are claimed to have hepatoprotective and hepatocurative activity. Natural product-based phytoconstituents are

regarded as the best and most validated source for developing novel therapeutic agents, but poor absorption, distribution, metabolism, and elimination followed by few toxicological properties still restrain the wide utilization of them for therapeutic purpose. In the last couple of decades, researcher and scientist are more encouraged for finding out more promising hepatoprotective agents from plant source to develop novel modern medicine for different liver aliments. (Pandey, Egyptian Liver Journal) In view of these facts, this review is effort to evaluate the available proven scientific data on the following:

1. (i) Recently developed modern medicines for liver disorder
2. (ii) Major phytoconstituents from the natural sources with their hepatoprotective activity
3. (iii) Promising hepatoprotective agents from the natural sources with its mechanism of action
4. (iv) Clinical trial data of some promising hepatoprotective leads in patients with different liver diseases
5. (v) Common mechanism of action of natural product-based leads for the protection against different liver diseases (Ahmad A, (2014))

HEPATOTOXICITY

Toxic liver disease, or drug-induced liver injury (DILI), is damage to your liver. It's also called hepatotoxicity or toxic hepatitis. It can cause serious symptoms or liver damage if you don't get help. Medications, herbal supplements, chemicals, solvents, and alcohol are all possible causes of hepatotoxicity Hepatotoxins and their mechanism of hepatotoxicity: In this review, the authors mainly concentrated on hepatotoxins like Carbon tetrachloride, Paracetamol, D-Galactosamine and Thioacetamide. (A, 2016)

1. Carbon tetrachloride:

The hepatotoxicity ofCCl4 is due to the formation of the highly reactive trichloromethyl free radical in the body which attacks the polyunsaturated fatty acids of the membrane of endoplasmic reticulum. Carbon tetrachloride poisoning leads rapidly to cessation of movement of large quantities of triglycerides from the liver to the plasma leading to fatty liver. If the damage is severe it leads to an abnormal increase in liver enzymes followed by hepatocellular necrosis. There is an influx of monocytes into the liver during acute and chronic CCl4 induced hepatotoxicity causing an increase of Reactive Oxygen Species (ROS)production and a rise in Kupffer cell leukotriene production in the liver leading to imbalance between cytoprotective and cytotoxic prostanoids (Ashok, 2001)

2. Paracetamol:

Paracetamol is metabolically activated by cytochrome P450 to a reactive metabolite that covalently binds to protein8. The reactive metabolite responsible for hepatotoxicity is N-acetyl-p-benzoquinone- imine which reacts with N-acetyl cysteine (Mujahid, 2019) . Although considered safe at therapeutic doses, in overdose, it produces a centrilobular hepatic necrosis that can be fatal. Various mechanisms leading to paracetamol toxicity includes (andey, 2023)

a Increased formation of superoxide anions which cause lipid peroxidation (oxidative stress) via hydrogen peroxide formation.
b Decreased glutathione concentrations in centrilobular cells.

3. D-galactosamine:

Galactosamine administration induces an inflammatory response in liver that biochemically and histologically resembles viral hepatitis. A single administration causes hepatocellular necrosis and fatty liver. It causes appearance of specific lesions in liver cells, characterized by inhibition of nuclear RNA and protein synthesis.

4. Thioacetamide:

Thioacetamide, originally used as a fungicide is a potent hepatotoxic and is bioactivated by CYP450

and/or flavin- containing monooxygenase (FMO) systems to sulfine (sulfoxide) and sulfene (sulfone) metabolites, which causes centrilobular necrosis. This metabolite causes liver fibrosis. Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. In the present study, the authors have reviewed the hepatoprotective activity of medicinal plants evaluated in carbon tetrachloride, paracetamol, D- galactosamine and thioacetamide induced hepato- toxicity. (A, 2016)

HERBAL MEDICINE

Herbal medicine, also called botanical medicine or phytomedicine, refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use outside conventional medicine. It is becoming more mainstream as improvements in analysis and quality control, along with advances in clinical research, show the value of herbal medicine in treating and preventing disease. (AW, 2018) Plants have been used for medicinal purposes long before recorded history. Ancient Chinese and Egyptian papyrus writings describe medicinal uses for plants as early as 3,000 BC. Indigenous cultures (such as African and Native American) used herbs in their healing rituals, while others developed traditional medical systems (such as Ayurveda and Traditional Chinese Medicine) in which herbal therapies were used. Researchers found that people in different parts of the world tended to use the same or similar plants for the same purposes. In the early 19th century, when chemical analysis first became available, scientists began to extract and modify the active ingredients from plants. Later, chemists began making their own version of plant compounds and, over time, the use of herbal medicines declined in favor of drugs. Almost one fourth of pharmaceutical drugs are derived from botanicals. (Ahmad A, (2014)) Recently, the World Health Organization estimated that 80% of people worldwide rely on herbal medicines for some part of their primary health care. In Germany, about 600 to 700 plant-based medicines are available and are prescribed by some 70% of German physicians. In the past 20 years in the United States, public dissatisfaction with the cost of prescription medications, combined with an interest in returning to natural or organic remedies, has led to an increase in herbal medicine use. (A, 2016)

A. hirtifolium

A. hirtifolium from Alliaceae family, commonly known as Persian shallot (moosir in Persian) is endemic to Iran. Based on available pharmaceutical investigations, antioxidant and hepatoprotective effects of A. hirtifolium have been also demonstrated. In addition, A. hirtifolium extracts had antioxidant properties comparable to or slightly higher than garlic extracts. The commonly known phytochemical compounds identified in A. hirtifolium are saponins, sapogenins, sulphur containing compounds (e.g. thiosulfinates) and flavonoids including shallomin, quercetin and kaempferol. Alliin, alliinase, allicin, s-allyl-cysteine, diallyl disulphide, diallyltrisulphide, and methylallyltrisulphide are the most important biological secondary metabolites of A. hirtifolium. Disulphide and trisulfide compounds are among

the most important compounds existing in A. hirtifolium. Researches have shown that both the corn and the flower of shallot contain a high density of glycosidic flavanols. Linolenic, linoleic, palmitic, palmitoleic, stearic, and oleic acids have been identified in A. hirtifolium oil, as well. Treating rats with hydroalcoholic extract of A. hirtifolium could protect liver cells against oxidant effects of alloxan, and consequently caused a significant reduction in serum concentration of alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST). Biochemical results have confirmed the usefulness of A. hirtifolium extract in decreasing the destructive effects of alloxan on liver tissue, and consequently decreasing the enzymes' leakage into cytosol, which is possibly achieved by herbal antioxidant compounds including flavonoids. It was also reported that consumption of A. hirtifolium caused a reduction in AST level compared to the group with a hypercholesterolemic diet. A research on the effect of hydroalcoholic A. hirtifolium extract on the level of liver enzymes in streptozotocin-induced diabetic rats indicated that hydroalcoholic extract of A. hirtifolium could significantly decrease serum levels of liver enzymes [AST, ALT, ALP and (lactate dehydrogenase) LDH] in a dose-dependent manner. Antioxidant micronutrients in the extract of A. hirtifolium may also restore liver damages. Shallomin and other active constituents of A. hirtifolium did not produce any adverse effect on the organs such as liver and kidney.

B. vulgaris

B. vulgaris (barberry), a well-known medicinal plant in Iran and also a food, belongs to Berberidaceae family. As a shrub with 1 to 3 meters in height, B. vulgaris grows in many regions of the world, including Iran (especially Khorasan). Fruit, leaves, and stem have medical usages including hepatoprotection. B. vulgaris fruit extract contains various flavonoids that act as antioxidant. Berberine, oxyacanthine, and other alkaloids such as berbamine, palmatine, columbamine, malic acid, jatrorrhizine, and berberrubine comprise some other compounds. Stigmasterol, terpenoids lupeol, oleanolic acid, stigmasterol glucoside and polyphenols were also identified in this plant. Berberine, an isoquinoline alkaloid with a long medicinal history, exists in roots, rhizomes, and stem bark of the plant. Berberine inhibits potassium and calcium currents in isolated rat hepatocytes. It has hepatoprotective effects, both preventive and curative, on CC14-induced liver injury through scavenging the peroxidative products. CC14 significantly increased the serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels in rats. Treatment with the methanolic extract of B. vulgaris fruit significantly helped these changes reach to an almost normal level. In addition, the extract could prevent CC14-induced liver oxidative damage in rats. Domitrović's study was indicative of berberine's effect on protecting the liver from CC14-induced injury. The hepatoprotective mechanisms of berberine could be attributed to the free radical scavenging, decline in oxidative/nitrosative stress, and the inhibition of inflammatory response in the liver. In addition, B. vulgaris extract/β-cyclodextrin exhibited better hepatoprotective effects than free extract on oral administration possibly due to greater bioavailability. Formulated extract could be used as an economical phytotherapeutical supplement that is helpful for chronic or acute conditions or a support for routine

therapies of serious hepatic disorders. In Hermenean's study, pre-treatment with formulated or non-formulated extract prevented the increase in ALT, AST, and malondialdehyde (MDA) levels, and helped the level of antioxidant enzymes return to normal values. According to histopathological and electron-microscopic examination, in both pre-treated groups, more moderate damage in liver was observed with a more pronounced protective effect after administration of the formulated extract

C. officinalis

C. officinalis (marigold), from Asteraceae family, is a medicinal plant and cosmetic herb popularly known in Europe and the USA. The dried flower heads or the dried ligulate flowers of this plant are used for pharmaceutical and/or cosmetic purposes. Antibacterial, anti-inflammatory, antiviral, and antioxidant activities have been already noted for C. officinalis. It has been taken in order to treat fevers and jaundice and to promote menstruation. Extracts, tinctures, balms, and salves of C. officinalis have been applied directly to heal wounds and soothe inflamed and injured skin. C. officinalis compounds, which are potentially active chemical constituents, are monoterpenes, such as α-thujene and T-muurolol, sesquiterpene and flavanol glycosides, triterpene alcohols, triterpenoid saponins, flavonoids, carotenoides, xanthophylls, phenolic acids, mucilage, bitters, phytosterols, tocophrrols, calendulin, resin, and volatile oil. The anti-inflammatory features of C. officinalis flowers, according to in vivo pharmacological tests, have been associated with the triterpenoid fatty acid esters. In Singh's study, 80% effect of methanolic extract of leaves (500 mg/kg orally, four doses at 12 hours interval) of C. officinalis was investigated against acetaminophen-induced hepatic damage in albino rats. The potential hepatoprotective effects of C. officinalis extracts against CC14-induced oxidative stress and cytotoxicity in isolated primary rat hepatocytes were detected. confirmed by significant improvement in cell viability and enzymes leakages (ALT, AST, and LDH). Also, the reduction of hepatocytolysis and steatosis, and return to normal values of various enzymes activity could be attributed to hepatoprotective effects. C. officinalis plant extracts significantly improved cell survival, contributing greatly to preserving the cellular membranes integrity against CC14. Moreover, plant extracts of C. officinalis protect the intracellular antioxidant defense system, indicated by preserving GST and inhibiting LPO. Protective role of the flower extract of C. officinalis against CC14- induced acute hepatotoxicity and cisplatin-induced nephrotoxicity has been shown. Possible mechanism of action of the flower extract may be due to its antioxidant activity and reduction of oxygen radicals.

A. sativum

A. sativum (garlic) is one of the world's most known medicines that have been used for flavoring and as a medical herb mainly due to its prophylactic and therapeutic capacities. Garlic

from Alliaceae family has known nutritional properties, particularly for its bioactive components, and is used as antidiabetic, anti-inflammatory, antihypertension, antimicrobial, anti-atherosclerotic, and hepatoprotective in different diet-oriented therapeutical regimes to heal various lifestyle-associated disorders. Garlic and its supplements are taken in many cultures for their hypolipidemic, antiplatelet, and procirculatory effects. In Iran, it is known for being useful for gastrointestinal disorders. In addition, some garlic combinations may be immune-enhancing and chemo preventive. Some combinations could be antioxidative while others may stimulate oxidation. Sapogenins, saponins, sulphuric compounds, and flavonoids have been detected in different species of Allium genus. Additional biological effects attributed to garlic extract may be due to S-allylcysteine, S-allylmercaptocysteine, and N (alpha)-fructosyl arginine that are formed throughout the extraction. Most garlic's beneficial effects are due to organosulphate molecule allicin. The hepatoprotective effect of garlic extracts on Cd-induced oxidative damage in rats has been reported. A. sativum extract decreased hepatic activities of ALT, AST, and alkaline phosphatase and simultaneously increased the plasma activities of ALT and AST. Cd-induced oxidative damage in rat liver is predisposed to decreasing by moderate dose of A. sativum extracts probably through reduced LPO and improved antioxidant defense system that could not prevent and protect Cd-induced hepatotoxicity. A. sativum chemical compounds have curative effects on iron liver excess. In another study, the hepatoprotective effects by A. sativum, ginger (Zingiber officinale), and vitamin E against CC14-induced liver damage were examined in male Wistar albino rats. Serum alanine amino transferase, aspartate amino transferase, and alkaline phosphatase levels decreased significantly 24 h after CC14 administration in rats pretreated with garlic, ginger, vitamin E, and various mixtures of garlic and ginger compared to the rats treated with only CC14. LPO expressed by serum MDA was assayed to assess the severity of liver damage by CC14, including the extent of hepatoprotection by garlic, ginger, and vitamin E. MDA concentration was significantly decreased in rats pretreated with garlic, ginger, vitamin E, and various mixtures of garlic and ginger compared to the rats administered by CC14 alone. Histological examination of the liver was indicative of severe infiltration of inflammatory cells in rats treated with CC14 alone although the change in the normal architecture of the hepatic cells decreased considerably in pre-treated rats. The hepatoprotective activity of A. sativum extract at a dose of 300 mg/kg body weight, administered intraperitoneally for 14 d before the induction of D-galactosamine and lipopolysaccharide (DGalN/LPS) was investigated against DGalN/LPS-induced hepatitis in rats. Pretreatment with aqueous A. sativum extract helped the altered parameters (ALT , AST, ALP, LDH, gamma glutamyl transferase, bilirubin, LPO, tumor necrosis factor, and myeloperoxidase activity level, total cholesterol, triglycerides, free fatty acids, and antioxidant enzyme activities) reach to nearly normal control values. Aqueous A. sativum extract could afford a significant protection in the DGalN/LPS-induced hepatic damage easing. An investigation of chemopreventive effects of A. sativum extract and silymarin on N-nitrosodiethylamine and CC14-induced hepatotoxicity in male albino rats indicated synergistic effect of silymarin and A. sativum, and their hepatoprotective features against hepatotoxicity.

Major bioactive phytochemicals with hepatoprotective activity

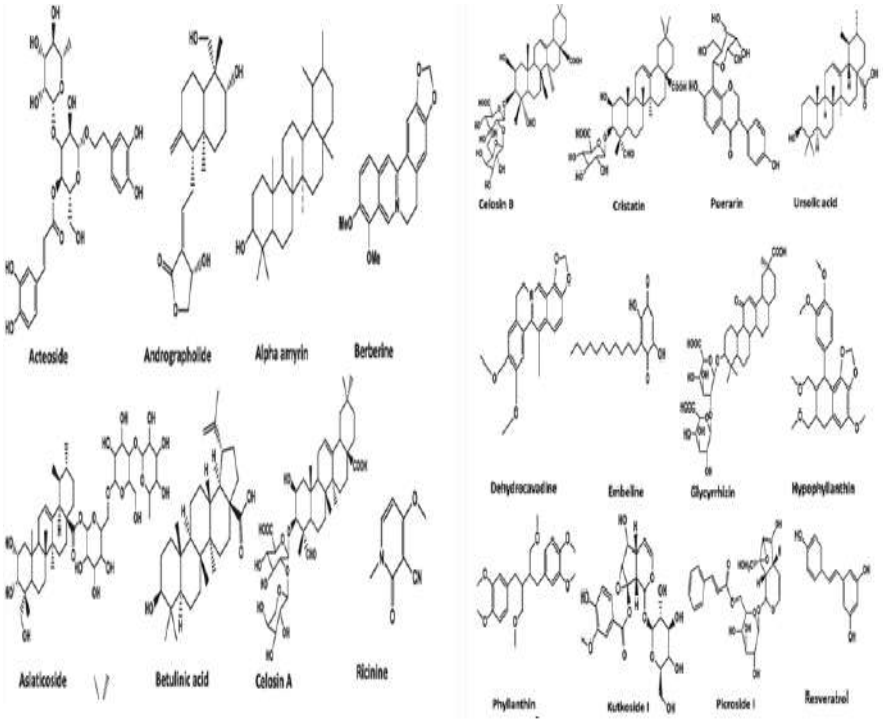

Figure 1: Bioactive Phytochemicals

1.Silymarin (family: Asteraceae)

Silymarin, an active compound of Silybum marianum (L.) Gaertn., commonly known as "milk thistle," is one of the oldest plants which has been commonly utilized for the treatment of liver diseases. Dried seeds are major sources of active phytoconstituents, which contain four flavonolignans isomer, i.e., silybin, isosilybin, silydianin, and silychristin. The complex mixture of these four flavonolignans isomer is known as silymarin. Silymarin shows hepatoprotection via various underlying mechanisms of which most common are modulation of enzymatic and nonenzymatic liver biochemical markers and induction of nuclear factor-erythroid 2-related factor 2 (Nrf2) expression. In addition, anti-inflammatory properties of silymarin have been proved in several models of liver damage. In rats, with alcoholic fatty liver model, silymarin acted by downregulating the expression of nuclear factor kappa B (NF-κB), interleukin-6 (IL-6), mission mode project-2 (MMP-2), mission mode project-13 (MMP-13), transforming growth factor beta-1 (TGF-β1), tumor-suppressor Krueppel-like factor, collagen α1 expression, and platelet-derived growth factor (PDGF) signaling when tested in hepatotoxic damage animal models. Likewise, silymarin could inhibit cells infected by HCV via TNF-α-induced activation of NF-κB and its nuclear translocation. Silymarin is well tolerated by patients with good safety profile. Poor water solubility of silymarin is being overcame by silymarin-loaded solid nanoparticles which enhance its antioxidant and hepatoprotective activity in comparison with crude silymarin.

2.Glycyrrhizin (family: Leguminacae)

Glycyrrhizin, a triterpenoid glycoside isolated from the root of Glycyrrhiza glabra L. commonly known as liquorice root, has been used in traditional medicine system of Nepal, India, China, and other countries for the treatment of jaundice. It is a mixture of potassium and calcium salt of glycyrrhizinic acid, and other phytoconstituents involved are glycyrrhetinic acid, beta-sitosterol, hydroxycoumarins, and flavonoids. Glycyrrhizin shows hepatoprotective effect via various mechanisms such as increasing antioxidant defense in hepatic cell and as anti-

inflammatory agent, High-mobility group protein box (HMGB1) is either diminished or interrupted for binding to glutathione S-transferase omega-1 (GSTO1) promoter region by glycyrrhizin to show anti-inflammatory effect. Not only glycyrrhizin, its metabolite, and glycyrrhetinic acid inhibited collagen αI(I) gene expression in liver fibrosis caused by CCl4 [. Glycyrrhetinic acid also helps in liver cell growth through the mechanism of epithelial growth factor receptor (EGFR) binding, stimulating DNA synthesis in liver cells by extracellular signal-regulated kinases (ERK2)-mediated pathway, which helps in liver regeneration. During interferon alpha (IFN-α)-based therapy failure, glycyrrhizin administered through intravenous route dramatically lowered the serum alanine transaminase level after 12 weeks of therapy and improved liver fibrosis and necrosis caused by inflammation after 52-week treatment in patients with hepatic disease. Moreover, it is also effective in prevention of HCV-related liver cirrhosis in older patients. In a study using in vitro cell model and in vivo animal models with hepatic injury, it was revealed that 18β-glycyrrhetinic acid reduces oxidative stress and expression of inflammatory markers which were predicted as a result of the downregulation of NF-κB and upregulation of Nrf2 target genes.

Andrographolide and neoandrographolide (family: Acanthaceae)

Andrographolide and neoandrographolide are the active chemical constituents of herbaceous plant of Andrographis paniculata Nees. commonly known as “king of bitters” due to its extremely bitter taste and is well-known for liver diseases. The main active chemical constituent is diterpene lactone class which is obtained from the leaves, i.e., neoandrographolide, 14-deoxy-11-dehydroandrographolide, 14-deoxy-11-oxoandrographolide and deoxy-andrographolide, andrographolide, andrographine, panicoline, paniculide-A, paniculide-B, and paniculide-C. Andrographolide inhibits inflammation, angiogenesis, and fibrosis in chemically induced liver injury animal model via antioxidant and anti-inflammatory mechanisms. Oxidative stress-inducible gene such as hypoxia-inducible factor-1 alpha, superoxide dismutase (SOD-1), heme oxygenase-1 (HO-1), and glutathione S-transferase (GST1) which uprise nuclear Nrf2 content and its DNA-binding activity and other upregulated protein and gene are balanced by andrographolide. It also helps in upregulation of HO-1 via the p38 mitogen-activated protein kinase, MAPK/Nrf2 pathway shows anti-HCV activity. Additionally, andrographolide helps in downregulation of hypoxia-inducible genes such as vascular endothelial growth factor (VEGF) and also diminishes TNF-α and cycloxygenase-2 (COX-2) expression and finally reduces liver hypoxia and attenuates hepatic apoptosis and fibrosis in rats. The compound decreases serum levels of TNF-α and interleukin-1 beta (IL-1β) and hepatic expression of TGF-β, cannabinoid receptor type 1 (CBR1), and Bax. The predicted mechanism for the decrement of serum levels of TNF-α and IL-1β is through the downregulation of JNK and ERK phosphorylation. A study in high-fat diet (HFD) fed mice administering andrographolide showed that cellular lipid accumulation is diminished.

Picroside I and kutkoside (family: Scrophulariaceae)

Picroside and kutkoside are the active chemical constituents of roots and rhizomes of Picrorhiza kurroa Royle, commonly known as “Kutki” or “Kutaki,” and have been used to treat hepatic disorder since long. The major active constituents are kurkoside, apocynin, drosin, cucurbitacin glycoside, and the iridoid glycoside such as picroside 1, 2, and 3. Kutkin is formed when picroside I and kutkoside are mixed in the ratio of 1:2, Picroside-I and kutkoside show hepatoprotective effect via membrane stabilizing,

hypolipidemic and antioxidant properties, and finally liver regenerative effect in rats via stimulation of nucleic acid and protein synthesis. Picroside-I and kutkoside are free radical scavengers (superoxide anion O2•) and inhibit lipid peroxidation in liver tissue. It also showed restoration of bilirubin and activity of serum liver biomarkers level of AST, ALT, ALP, and LDH against acetaminophen-induced liver toxicity animal model by protecting injury hepatocyte proving its hepatoprotective effect [. Moreover, picroside also reduces the lipid peroxidation, normalizes glutathione metabolism, and inhibits hepatocarcinogenesis caused by N-nitrosodiethylamine in rats by increasing the life span of tumor bearing rats. It acts against less expression of LDL receptor on cell surface caused by paracetamol and uprises the conjugated dienes in liver cells as well as maintain of oxidation–reduction balance for healthy liver.

Curcumin (family: Zingiberaceae)

Curcumin is the principle curcuminoid found in rhizome of Curcuma longa commonly known as "turmeric." Traditional use of turmeric for the treatment of bilirubin-related liver disease such as jaundice and several other hepatic complications is being documented since long. Structurally, similar phenolic compounds found in the rhizomes of turmeric are known as curcuminoids in their mixed form. Three major curcuminoids present in rhizomes of turmeric are curcumin, dimethoxy curcumin, and bisdemethoxycurcumin. Chemically, curcumin is a diferuloylmethane which consists of diferulic acid moiety fused with methylene moiety or other carbon group and exists mainly in keto-enol form. Hepatoprotection mechanism of the curcumin may be due to its antioxidant activity and activation of the phase 2 detoxifying/antioxidant enzymes such as HO-1 and NADPH quinone oxidoreductase-1 (NQO1) and Nrf2/Kelch-like ECH-associated protein 1 (Keap1)/antioxidant-responsive element (ARE) pathway .In addition, its administration in diet reduces oxidative stress, decreases Cytochrome P450 2E1 (CYP2E1) and paired-related homeobox 1 (Prx1) expression, while upregulates paired-related homeobox 6 (Prx6) expression .Oxidative stress caused by hepatotoxins is closely associated with activation of some inflammatory mediators such as MAPKs, NF-κB, and signal transducer and activator of transcription-3 (STAT3) via different pathways .Research reported that curcumin can inhibit the expression of toll-like receptor-2 (TLR2), toll-like receptor-4 (TLR4), and HMGB1 in rat suffered with fibrogenesis expression of ligand molecules. Concanavalin A-induced hepatitis in mice via T-cell-mediated pathway become less severe when administered with curcumin which is mainly due to the inhibition of liver inflammation. Likewise, curcumin could diminish liver toxicity cause by lipopolysaccharide (LPS)/D-galactosamine (D-GalN) through inhibition of hepatic mRNA levels of Sirtuin (silent mating type information regulation 2 homolog)-1 (SIRT1). It also suppresses expression of gene for receptors which are involved in final product of advanced glycation in hepatic stellate cells (HSCs) by uprising the peroxisome proliferator-activated receptor-gamma (PPARγ) activity and subsiding oxidative stress. Moreover, curcumin could protect against paracetamol-induced hepatocyte apoptosis by reducing the availability of proapoptotic genes Bax and caspase-3 while improving antiapoptotic genes. However, curcumin is able to downregulate Bcl-2 mRNA expression and upregulates p53 protein expression in thioacetamide-induced cytotoxicity, facilitating apoptosis in damaged cells which reduces hepatic inflammatory gene and fibrogenesis. Additionally, antioxidant and anti-inflammatory effect of curcumin could protect mice against human cytomegalovirus infection. (Ashok, 2001)

Phyllanthin and hypophyllanthin (family: Euphorbiaceae)

Phyllanthin is a potent hepatoprotective lignans found in Phyllanthus niruri Linn., commonly known as "gale of the wind," is a long-established herbal remedy for jaundice and other hepatic diseases. The main active chemical constituents include alkaloids, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, phyllanthusiin D gallocatechins, geraniin, hypophylanthis, lignans, nirutin, phyllanthin, and phyllanthenol. Chemically, phyllanthin and hypophyllanthin are lignans isolated from the hexane extract and have been established as the hepatoprotective agents. Phyllanthus niruri is effective against infective hepatitis and other liver. Ethanolic extract of this plant possesses potent hepatoprotective activity both in vitro and in vivo. In India, it was used to treat jaundice in children because of its liver-protective and detoxifying action. A study in the UK revealed that Phyllanthus extract could be effective for treatment of both acute and chronic hepatitis in children. Phyllanthin and hypophyllanthin both can protect rat liver from toxicity induced by carbon tetrachloride and cytotoxicity induced by galactosamine. These lignans also protect against liver damage induced by alcohol and normalize a "fatty liver" condition. The hepatoprotective effects of phyllanthus lignin are achieved with the mechanism of inhibition of superoxide and hydroxyl radicals and lipid peroxidation.

Berberine (family: Berberidaceae)

Berberine is an isoquinoline alkaloid which could be isolated from roots, rhizomes, and stem bark of Berberis aristata DC, commonly known as "barberry" and has been used as tonic remedy for liver since long ago. The major active chemical constituents present in Berberis aristata are berberine, oxyberberine, berbamine, aromoline, karachine, and oxycanthine. Berberine is experimentally proved hepatoprotective phytoconstituent. Berberine shows antioxidant activity which could suppress oxidative stress and attenuates apoptosis through the increment of ratio of Bcl-2/Bax in ischemia-/reperfusion-injured rat liver inhibiting caspase-3 cleavage in the liver [.Its mechanism of action is upregulation of Akt and inhibition of mTOR expression .Furthermore, hepatocyte nuclear factor-4 alpha and PPARα/peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) could be restored with berberine showing hepatoprotective effect in liver ischemia. Experiment in mice with steatosis induced by ethanol showed that berberine protects the liver from ethanol-induced oxidative stress .Berberine even reduces the expression of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9), a cholesterol homeostasis regulator, and decreases IFN-γ, TNF-α, IL-1α and 8-isoprostane levels in LPS-induced hepatoxicity mouse model .Carbon tetrachloride-induced liver injury is attenuated by berberine via suppression of TNF-α, COX-2, and iNOS expression and oxidative stress .Berberine could diminish liver fibrosis through the activation of AMPK and decreasing the expression of NOX4 and phosphorylated Akt .

Embelin (family: Myrsinaceae)

Embelin, chemically known as "2,5-dihydroxy-3-undecyl-1,4-benzoquinone," is an active chemical constituent of leaves of Embelia ribes Burm.f. commonly known as "false black pepper" and is known for free radical scavenging and liver protective function. The active constituents are embelin, christembine, quercitol, and resin. Embelin shows its hepatoprotective effect mainly through its free radical scavenging and lipid peroxidation pathway. Embelin can control the liver biomarkers: AST, ALT, ALP, LDH, bilirubin γ-glutamyl transpeptidase, and total protein levels in carbon tetrachloride-treated rats. Study in mitochondria of rat liver showed that embelin could inhibit lipid peroxidation, and impaired

superoxide dismutase level was restored with embelin administration. Furthermore, to extra plot mechanism and rate of reactions of embelin with hydroxyl, way of oxidizing single electron and radical called "organo haloperoxyl" with the technique known as nanosecond pulse radiolysis was studied. Its redox potential was also evaluated, and the study depicted that embelin is a potent-free radical scavenger in physiological conditions.

Resveratrol

Resveratrol chemically known as "trans-3,5,4′-trihydroxystilbene" is a naturally occurring polyphenol compound present in Vitis labrusca commonly known as "grapes," Vaccinium myrtillus L. commonly known as "blueberries" and Rubus idaeus L. commonly known as "raspberries" with potent antioxidant properties. Resveratrol, a phytoalexin, is generated in plants when bacteria and fungi attacked it. Resveratrol shows liver protection via reduction of oxidative stress during hepatocyte injury by modifying the expression of nuclear transcription factors Nrf2 and NF-κB and downregulating HO-1 and iONS gene expression .This enhances the free radical scavenging properties as well as phase 2 enzymes .Furthermore, it even inhibits proinflammatory cytokines such as IL-2, IL-6, and TNF-α in concanavalin A-induced autoimmune hepatitis .In liver injury cause by high cholesterol, resveratrol shows protective effect which is mediated by the enhancement of autophagy and downregulation of proapoptotic proteins such as Bax and caspase-3 and caspase-8 .Followingly, hepatotoxicity caused by isoniazid and rifampicin is ameliorated by resveratrol by modulating the expression of SIRT1 mRNA hepatic cells of mice, which finally minimize hepatic oxidative stress in the liver, production of cytokine, and expression of gene called PPARγ .Moreover, resveratrol also prevents hepatotoxicity resulted from higher consumption of acetaminophen by upregulating expression of SIRT1 and downregulating p53 signaling, enhancing the expression of cell nuclear antigen, promoting hepatic cell proliferation, enhancing liver regeneration and inducing uprising the level of cyclin D1 and Cdk4 . (Pandey, Egyptian Liver Journal)

CONCLUSION:

From this study, it is clear that many medicinal plants process significant hepatoprotective activity. Our review will help researchers to choose different herbs and blend it to a formulation which could be an effective treatment for various liver diseases.

REFERENCES

1. A, T. M. (2016). Liver regeneration and ibrosis after inflammation. Inflammation and Regeneration. 1-6.
2. Ahmad A, A. R. ((2014)). Resveratrol mitigate structural changes and hepatic stellate cell activation in N'-nitrosodimethylamine-induced liver fibrosis via restraining oxidative damage. Chem Biol Interact 221:1–12, 8.
3. Al-Asmari AK, A.-E. A.-A. (2014:1-22). A review of hepatoprotective plants used in Saudi traditional medicine. Ev-Based Complement Altern Med .
4. andey, B. B. (2023). Promising hepatoprotective agents from the natural sources: a study of scientific evidence. Egypt Liver Journal , 7.
5. Ashok, S. K. (2001). Hepatoprotective effect of Ginkgo biloba against carbon tetrachloride induced hepatic injury in rat. Indian Journal of Pharmacology, 33, 260-266., 25.
6. AW, F. A. (2018). uidance molecules in vascular smooth muscle. Frontiers in Physiology, 9-15.
7. Baiocchini A, M. C. (2016). Extracellular matrix molecular remodelling in Human liver fibrosis evolution. . PLOS One, 33.

8. H U. Mythily *, S. S. (2020). Molecular docking studies on phytochemicals of solanam nigrum fruit. IJPR.
9. Mujahid, .. M. (2019). Hepatoprotective activity of Adenanthera Pavonina and Erythrina Indica in Anti Tubercular Drug Induced Hepatotoxicity in Rats. Hepatoprotective activity of Adenanthera Pavonina and Erythrina Indica in Anti Tubercular Drug Induced Hepatotoxicity in Rats.
10. Mythily U, S. S. (2020). Molecular docking studies on phytochemicals of Solanum nigrum fruits for itshepatoprotective activity. IJPSR , 10.
11. PAMKAJ, S. (2013). Studies On The Antioxident And Hepatoprotective Properties Of Some Medicinal Plants. INFLIBNET.
12. Pandey, B. B. (Egyptian Liver Journal). Promising hepatoprotective agents from the natural sources: a study of scientific evidence. Egypt Liver Journal 13, 14 . 2023, 7.

HOW TO CITE: V. Moni Prashanth , V. V. Rajesham , T. Rama Rao , A Review On Herbal Plants And Bio Active Chemicals For Their Hepatoprotective Activity, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 9, 25-37. https://doi.org/10.5281/zenodo.13625577