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Synthetic Hepatoprotective Agents: Design, Mechanisms, and Therapeutic Applications

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Abstract

The liver, the largest internal organ, is crucial to the body's ability to function normally. Hepatitis, also known as liver inflammation, is defined by the presence of inflammatory cells in the liver's tissue. There are five primary viruses, referred to as kinds a, b, c, d, and e. There is a disproportionate amount of sickness and mortality attributable to these five kinds. Liver damage or malfunction is a serious public health issue that poses difficulties for many stakeholders, including medical experts, government organizations, and the pharmaceutical business. Herbal medications have been utilized in the treatment of liver illness for a long time. This research project is devoted to learning about synthetic hepatoprotective agents and how they work in the body. Most hepatotoxic substances are known to cause oxidative damage to liver cells, namely lipid per oxidation, in living organisms. This study aims to collect information on potential phytochemicals from hepatoprotective

Keywords: Hepatoprotective Agents, Therapeutic, Mechanisms, Herbal Medicines

Introduction

The human liver is the biggest organ, contributing over 1.5 kg to our total body mass. The liver's ability to bio transforms and metabolize drugs gives it a protective function against potentially harmful environmental and dietary chemicals. These factors increase the likelihood that the liver will be damaged by medicines, chemicals, and other xenobiotics at various doses. More than a hundred different factors contribute to liver disorders. 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. Hepatic illnesses have devastating consequences, including death and disability, missed work, diminished quality of life, shortened life expectancy, and a hefty financial toll on both the individual and society as a whole.

The treatment of liver diseases is now considered a top medical priority. The World Health Organization (WHO) reports that over 500 million individuals worldwide have chronic hepatitis a serious illness that affects the liver. Due to their low side-effect profiles, low costs, low environmental impact, and high safety profiles, herbal medicines are being considered as a potential treatment for current liver issues (Izzo, HoonKim, Radhakrishnan, & Williamson, 2016). Medicinal plants have gained relevance in healthcare system around the globe for their demonstrated and effective medicinal characteristics The majority of the world's population relies on medications containing substances derived from plants may be as high as 80%. There are between 50,000

and 80,000 blooming plants that have been documented as having therapeutic use.

Several aspects about these drugs are crucial. The widespread acceptance of herbal remedies as a viable alternative to conventional medicine stems in large part from its promoted dual role as illness cure and prevention via "natural and gentle" means. As an added downside, the latter is not always successful and might have unwelcome side effects for patients in addition, unlike pharmaceuticals, herbal remedies often do not need a prescription from a doctor or other medical professional, making them much cheaper. Although medicinal plants have been utilized internationally, their broader utilization is confined to a few nations including Japan, India, China, Pakistan, Thailand, Iran, and certain African countries The use of medicines derived from plants is becoming more supported internationally. To promote medicinal plants and the accompanying goods, for instance, the Natural Health Product Regulations of Canada advocate for the use of cutting-edge technology and scientific data. It is of great concern to researchers looking into herbal remedies as the chemical makeup of the plants responsible for their biological effects is often unknown.

Literature Review

Gulati, Kavita et.al (2018). What Causes Hepatotoxicity, How to Assess It in the Laboratory, and What You Can Do to Avoid It DISTRIBUTED ACCESS. The liver's ability to keep the digestive system in balance is essential to overall health. In addition to aiding digestion, it provides essential nutrients and helps rid the body of toxins. Therefore, its health and sickness depend on it working properly. Hepatotoxicity may be generated by a wide range of environmental and chemical factors, and is the consequence of a complicated system involving an imbalance between aggressive and defensive forces, leading to liver damage. It is therefore crucial to understand the mechansims of hepatotoxicity for creating pharmaceutical methods for their avoidance. Common molecular pathways that contribute to impaired liver function include inflammation, immunomodulation, and oxidative stress. In the lab, liver damage is measured by physiological, biochemical, and pathological indicators after being induced by a range of medications and substances. The effects of potential hepatoprotective drugs on these preclinical models are seen, and their usefulness in clinical settings is expected. Both synthetic and natural compounds are known to exert ameliorative effects, both prophylactic and therapeutic, and some medicines have been shown to protect the liver against toxic assaults. The effectiveness and safety of medicinal plants have been shown in both experimental and clinical settings, making them a valuable alternative/complementary source for possible hepatoprotective medicines. This review provides a concise synopsis of the fundamentals of hepatotoxicity, including preclinical assessment techniques and pertinent herbal hepatoprotective measures.

Aladejana, Elizabeth et.al. (2023). Including liver failure, hepatitis, cirrhosis, and their related consequences, liver disorders represent a major threat to worldwide public health. Because of the negative effects these have on human health, protecting the liver is crucial. Crucial to preventing irreversible liver damage from chemicals, medicines, and poisons are hepatoprotective medications. There is hope in treating liver problems using polyherbal formulations, which include a variety of botanical components from different systems of medicine. The change in emphasis toward these formulations is due to the success of their multi-targeted approach to treating complicated disorders. In order to better understand how polyherbal formulations work to protect the liver, this research set out to perform a systematic literature review on the topic. The use of polyherbal formulations for the treatment of liver disease is discussed in this article. Method: A thorough search of electronic databases, including: Scopus, Academia, Elsevier, Science Direct, Wiley, BioMed Central, PubMed, and Google Scholar, was undertaken using a combination of keywords such as 'polyherbal formulations', 'hepatoprotective' and 'liver disorders'. For this evaluation, we included articles published between January 2010 and April 2023.The analysis of 61 research found that polyherbal formulations are much more effective than

placebo in protecting the liver against a wide range of hepatotoxic compounds. Antioxidant, anti-inflammatory, antifibrotic, and antiapoptotic properties are some of the ways in which these compositions work. It was also shown that some polyherbal formulations promoted detoxification processes, increased bile output, and stimulated liver regeneration. As a result of their multitargeted approach to treating complicated disorders, polyherbal formulations have demonstrated promise hepatoprotective action, and they may provide a viable alternative to traditional treatments. However, new and effective medications for liver problems may be developed if the active substances responsible for the hepatoprotective properties of these formulations are identified, together with their pharmacokinetics and pharmacodynamics. This paper adds to the expanding corpus of research on the hepatoprotective properties of polyherbal formulations.

Mohseni-Moghaddam, Parvaneh et.al (2023). Infectious and degenerative liver disorders are important global killers. The most prevalent causes of liver illness include alcoholic liver disease, obesity, diabetes, viral hepatitis, and drug-induced liver damage. Diosgenin has hepatoprotective effects and is a steroidal sapogenin found in herbs. This Phyto steroid modifies lipid profile and protects liver damage and fibrosis, metabolic associated fatty liver disease (MAFLD), steatohepatitis, and diabetes mellitus. The therapeutic effects of diosgenin have been attributed to a variety of processes. Diosgenin's protective effects on the liver stem from its antioxidant properties, its capacity to suppress pro-inflammatory and apoptotic mediators, and its ability to modulate gut microbiota. With a focus on potential underlying processes, this review of the literature covers the published research on diosgenin's hepatoprotective effect against liver damage under various situations.

Alkandahri, Maulana et.al (2023). The liver is the body's most crucial organ that conducts vital activities. Diseases of the liver may disrupt essential bodily processes. Injuries to the liver's cells, tissues, structures, and functions are the hallmark of hepatic disease, which may lead to fibrosis and eventually cirrhosis. Included in this group are hepatitis, ALD, NAFLD, liver fibrosis, liver cirrhosis, liver failure, and hepatocellular carcinoma. Damaged cell membranes, an inappropriate immunological response, abnormal drug metabolism, an excess of reactive oxygen species, lipid peroxidation, and cell death all contribute to hepatic disorders. No treatment now exists that effectively stimulates liver function, offers total protection, and helps the liver regenerate its own cells, despite significant advances in contemporary medicine. Natural remedies are carefully chosen as novel treatment solutions for controlling liver disease since certain pharmaceuticals might have undesirable side effects. Kaempferol is a polyphenol found in several plant-based foods and medicines. We utilize it to treat a wide range of illnesses, including diabetes, heart disease, and cancer. Kaempferol protects the liver since it is an effective antioxidant and has anti-inflammatory effects. Kaempferol's hepatoprotective effects have been explored in a variety of hepatotoxicity protocols, such as those involving acetaminophen (APAP), nonalcoholic fatty liver disease (NAFLD), cytochrome c (CCl 4), hepatocellular carcinoma (HCC), and lipopolysaccharide (LPS). Therefore, the purpose of this paper is to present a concise summary of the most up-to-date research on kaempferol's hepatoprotective effect and the likely molecular mechanism by which it works. In addition, the latest research on kaempferol's chemistry, origin, bioavailability, and safety is included.

Shirani, Majid et.al (2017). Liver disease is a global epidemic because the liver is responsible for the metabolism and excretion of xenobiotics. The present synthetic medications used to treat liver problems are damaging to the liver and kidneys, which highlights the need for safer alternatives. Tonics for the liver are routinely provided therapy combinations that are derived from medicinal herbs. This article introduces the most significant medicinal plants used for treating liver problems and showing little adverse effects on the kidneys. The methods of action, pharmacokinetics, dosing, and toxicity of these substances, as well as their active ingredients and the results of clinical trials, have been analyzed. The liver has been

treated with several plants, including Amaranthus spinosus L., Glycyrrhiza glabra, Cichorium inthybus L., Phyllanthus species (amarus, niruri, emblica), Picrorhiza kurroa, and Silybum marianum. The antioxidant-related characteristics, hepatoprotective actions, and minimal effects on the kidney found in the introduced medicinal plants may be used in the development of novel medications for the treatment and prevention of liver illnesses.

HERBAL HEPATOPROTECTIVE AGENTS

There are often grouped into three types, as shown below.

Antihepatotoxic agents

Hepatotoxins are substances that damage the liver, and these counteract their effects.

Hepatoprotective agents

They serve as a preventative measure against a wide range of liver illnesses.

Hepatotoxic agents

In most cases, they help the liver recover faster.

Ayurvedic treatment, followed by Western and Eastern European and Chinese alternative medicine, has a long history of usage in India for the treatment of illness. Many hepatoprotective medications are derived from medicinal plants. One source claim that over 700 different decoction, tincture, and tablet forms of herbs have been utilized to treat a wide range of liver problems. Therapeutic evaluation of herbal products in liver disease models has undergone a paradigm shift in the 21st century, with an emphasis on carefully syncing the strengths of the traditional system of medicine with the modern concept of evidence-based therapeutical screening, authentication, and randomized, placebo-controlled clinical trials to support clinical efficacy.

Numerous plants and supplements claim to have hepatoprotective effects. There are supposedly about 160 active compounds from 101 plants that have liver-protecting function after ethanol use. In India, there are around 87 plants employed in 33 patented multi-plant component propitiatory compositions. Despite the significant progress achieved, no effective and safe hepatoprotective medicines are currently available. Because of this, the worldwide effort to create hepatoprotective drugs derived mostly from plants has received significant attention. A hepatoprotective medication is one that has positive effects on the liver. Hepatotoxic medications, on the other hand, are those that harm the liver. Herbal treatments have been demonstrated to be effective in clinical studies. In the past 30 years, various hepatotoxins have been utilized regularly in d-galactosamine, carbon tetrachloride, acetaminophen, and thioacetamide, and more recently Concanavalin A (ConA) and lipopolysaccharide (LPS) has been produced. Studying the cellular pathways involved in autoimmune liver disease is greatly aided by the fact that ConA and LPS do not mirror the clinical pattern of human illness. Depletion of uridine nucleotides, which in turn reduces the production of RNA and proteins, mimics the effects of human viral hepatitis in the galactosamine model.When rats are poisoned with galactosamine, their plasma membranes become more permeable than usual, allowing enzymes to seep out of the cells and into the blood.

Therefore, elevated transaminase levels may be used as a measure of liver dysfunction. Because hepatocytes contain large quantities of galactokinase and galactose-1-uridyltransferase, and galactosamine does not damage other organs, galactosamine has remarkable liver specificity compared to other hazardous groups like paracetamol, acetaminophen, and carbon tetrachloride. Hepatotoxicity is induced by galactosamine, which manifests as a mosaic of damaged hepatocytes, necrosis, and prominent portal and parenchymal infiltration.By boosting the generation of UDP-sugar derivates, galactosaimine depletes uridine diphosphate (UDP), which in turn inhibits RNA and protein synthesis and promotes cell membrane degradation.

The purpose of this research was to compile previously published articles supporting the use of hepatoxicity models to investigate prospective phytochemicals from herbal plants. The review deals with fact-finding work done on herbals effective in the treatment of liver disorders. We are turning to the field of herbal

medicine in our hunt for a product in nature that can be used to prevent and treat terrible liver illnesses after the failure of synthetic pharmaceuticals in this regard. There is now just one natural medicine that can protect the liver against viral infections, and it is far from a cure. Table 1 provides a summary of the hepatoprotective compounds found in herbs.

Table 1: The reported herbal hepatoprotective agents

Plant names	Category	Name of active constituent	Mechanism
Allium sativum	Organosulfur compounds	Organosulfur compounds	Prevention of GSH depletion, alteration of GSH-dependent enzymes
Buddleja officinalis	Phenyl ethanoid Glycoside	Acteoside	Decreased levels of AST, ALP
Camellia sinensis	Polyphenols	Catechin	Inhibited hepatocellular apoptosis and unregulated Bcl-2 protein expression
Cistus laurifolius L.	Flavonoid	Quercetin	MDA, AST, GSH levels decreased
Corydalis saxicola	Alkaloid	Dehydrocavidine	Decreased levels MDA, SOD, GPx
Eglets viscosa Less.	Flavonoid	Ternatin	Decreased lipid peroxidation
Gardenia jasminoides	Iridoid Glycoside	Geniposide	Antioxidant
Ginkgo biloba L.	Polyphenols	Polyprenols	ALT, AST, ALP, ALB, TP, HA, LN, TG, and CHO levels decreased
Gossypium herbaceum	Polyphenols	Gossypol	Antioxidant
Hibiscus sabdariffa L.	Polyphenols	Protocatechuic acid	LDH, AST, ALP, MDA levels decreased
Larrea tridentata	Resin	Nordihydroguaiaretic acid	Antioxidant
Magnolia officinalis	Polyphenols	Magnolol	Antioxidant
Mangifera indica	Triterpene	Lupeol	Decreased levels of SGOT, SGPT, ALP, bilirubin
Nigella sativa	Quinones	Thymoquinone (TQ)	Scavenger of superoxide, hydroxyl radical, and singlet molecular oxygen
Ocimum basilicum	Phenolic Acids	Rosmarinic acid	AST, ALP, SGOT levels decreased
Peumus boldus	Alkaloid	Boldine	Lipid peroxidation
Phyllanthus amarus	Polyphenols	Phyllanthin	SGOT, SGPT, ALKP, SBLN and total protein levels decreased
Pinus maritima	Polyphenols	Pycnogenol	SOD, GSH-Px, GSH-reductase, and TBARS levels decreased
Rubia cordifolia	Glycoside	Rubiadin	SGOT, SGPT, SALP, and gamma-GT levels decreased
Schisandra chinensis	Lignans	Wuweizisu	Antioxidant
Sida cordifolia	Organic compound	Fumaric acid	Antioxidant
Silybum marianum	Lignans	Silymarin	Antioxidant

MECHANISM(S) OF ACTION:

These chemicals often exhibit numerous actions, which is the mechanism by which they provide hepatoprotection. Herbal medications for chronic liver disease treatment have been shown to improve liver, digestive system, and immune system health. Constipation improvement may reduce ascites by decreasing the absorption of toxic chemicals and improving the gastrointestinal tract's overall function. Inflammation, hepatic blood flow, and ascites and blood pressure reduction may all benefit from protecting liver cells against toxins including medicines, lipid per-oxidation, and free radical harm. Many medications are converted into hazardous metabolites by an enzyme called CYP2E1. They have the ability to regulate the equilibrium of hepatic energy metabolism by preserving the normal structure of mitochondrial membranes and increasing ATPase activity in mitochondria. They may reduce swelling and fight against parasites.

Immune dysfunction contributes to liver disease, however immunomodulation with herbal treatment (withaferin-A) mitigates liver damage by halting the production of reactive oxygen species and reducing inflammation. Antiviral effects of picroliv, ellagic acid, phylanthin, and hypophylanthin are documented. In addition, hepatocyte protein synthesis may be stimulated by herbal medicines, while Kupffer cell production of

inflammatory cytokines such leukotrienes and prostaglandins can be suppressed. Ellagic acid may prevent liver fibrosis, and drugs like picroliv (iridoid glycoside) can regenerate liver tissue. Both silymarin and andrographolide have been shown to have choleretic and anticholestatic actions.

Furthermore, silymarin, picroliv, curcumin, and ellagic acid have been found to suppress inflammatory cytokines and chemokines via the nuclear factor-kappa B pathway. In addition, curcumin and inducible nitric oxide synthase inhibition with silymarin and curcumin have been demonstrated to reduce the cyclo-oxygenase-2 mediated inflammatory response. Curcumin's effects on inflammatory cytokines and chemokines have been extensively investigated. Inhibition of TNF-a-mediated apoptosis by silymarin and picroliv has been shown. All of these things help the liver, control the body's metabolism, and prevent additional damage to liver cells, which promotes their regeneration.

APPLICATIONS OF IMMOBILIZED CELLS

Bioreactors may be used to examine cellular nuclear magnetic resonance (NMR), a technique that enables real-time, non-invasive measurements of a wide variety of biochemical cellular activities. Studies of drug metabolism using phosphorus-containing xenobiotics have been described and 31P-NMR may be utilized to learn about intracellular pH and cellular energy levels. Studies of cellular metabolism may also benefit greatly from the use of 13C- and 1 H-NMR spectroscopy (Mancuso et al., 1994). Biochemical, physiological, pharmacokinetic, pharmacodynamic, and toxicological research are just some of the many in vitro uses for immobilized cells. Bioartificial organs comprised of immobilized and perfused cells. Recombinant protein research and monoclonal antibody development.

It was shown that cells in a hollow fiber bioreactor may give substantial quantities of monoclonal antibody, and this method was proven to be feasible for creating large numbers of particular monoclonal antibodies (Goodall 1998). Carrier viruses. The utilization of mammalian cell bioreactor technology has allowed scientists to effectively use bioreactor technology for the creation of viral vectors (Shankar et al. 1997). Recently, we have employed this paradigm to examine how tert-butylhydroperoxide (tBH) induces apoptotic/necrotic markers in hepatocytes treated with resveratrol vs silymarin pretreatments Hepatocytes were employed as cellular systems in both 48-hour culture and 5-hour perfusion of immobilized agarose threads. In short-term tests, resveratrol and silymarin mitigated the toxic effects of tBH on hepatocytes, as shown by a substantial decrease in the tBH-induced rise in alanine aminotransferase (ALT) and nitric oxide (NO).

Both resveratrol and silymarin pretreatments attenuated tBH's effects on inducible nitric oxide synthase (NOS-2) and hemoxygenase-1 (HO-1) gene expression, respectively. The morphological indicators for apoptosis and necrosis were both improved by resveratrol therapy. This cell model can also detect low levels of metabolic enzyme activity. The O-dealkylating activity of rat liver microsomes toward 7-ethoxycoumarin has been reported to be negligible, whereas the de-ethylated product umbelliferone has been shown to accumulate in the perfusate of both induced and noninduced hepatocytes. In a hepatocyte bioreactor, this model has shown that even low levels of deethylase activity in rat liver may be detected.

As part of the human immune response, phagocytes (neutrophils, monocytes, and macrophages) also produce NO. Phagocytes are generated with iNOS, which is triggered by interferon-gamma (IFN-γ) as a single signal or by TNF together with a second signal. The inhibitory signals provided to iNOS by IL-4 and IL-10 are rather mild in comparison to those provided by transforming growth factor- (TGF-)-. To control inflammation and immunological reactions, the immune system may control the arsenal of phagocytes. Table 2 provides a summary of the documented herbal immunomodulatory drugs.

Table 2: The Reported Herbal Immunomodulatory Agents

Plants	Parts	Active constituents	Mechanism of action
Panax ginseng	Root	Ginsenoside	Proliferation of lymphocytes
Centella asiatica	Root	Asaticoside A, asiaticoside B	Proliferation of lymphocytes and natural killer cells
Glycyrrhiza glabra	Root and rhizome	Glycyrrhizin	Increase in spleen weight
Asparagus racemosus	Root and leaves	Shatavarin 1-4	Increase in production of TNF
Aralia mandshurica	Dried root	Saponine	Increases phagocytosis
Picrorhiza kurroa	Dried rhizome	Picroside-I, II, kutkoside	Anticomplement activity
Lawsonia alba	Dried leaves	Lawsone, apigenin, luteolin, and cosmosin	Stimulation of neutrophils and phagocytosis
Brassica oleracea	Root	Sulforaphane	Enhancement of antibody titer
Viscum album	Whole	Viscumin	Stimulates lymphocytes
Canavalia ensiformis	Whole	Lectins	Human neutrophil aggregation and H_2O_2 release
Linum usitatissimum	Whole	Cyclopeptide A	Immunosuppressant
Artemisia princeps	Leaves	Protein	Induces interferon
Echinacea purpurea	Roots and rhizomes	Arabinogalactan	Stimulates phagocytosis
wheat bran	Seed	Hetroxylan	Stimulates phagocytosis
Curcuma longa	Rhizome	Curcumin	Inhibits human neutrophils
Aloe Vera	Dried juice of leaves	Acemannan	Anticomplement activity
Rumex acetosella	Leaves	Rhamnogalacturonans (pectins and related gums and mucilages, type A), acidic arabinogalactans (mainly plant mucilages, gums, and some hemicelluloses, type B), and neutral glucans and heteroglycans (reserve polysaccharides, type C	Antiplogistic activity
Dioscorea membranacea Pierre	Rhizome	Dioscorealide B	Lymphocyte proliferation
Tinospora cordifolia	Whole plant	Cardiofoliosides A and B	Activates macrophages
Litchi chinensis Sonn.)	Fruits	Epicatechins, proanthocyanidin B2, and proanthocyanidin B4	Proliferation of mouse splenocytes
Plumbago zeylanica	Root	Plumbagin	Stimulates phagocytosis
Rice bran	Seed	Ferulic acid ester of oligosaccharides	Increases phagocytosis
Pimpinella anisum	Fruit	Anethole	Increases leukocyte number
Catharanthus roseus	Whole plant	Vincristine	Induces antibody production
Claviceps purpurea	Dried sclerotium of fungus	Ergot alkaloids	Immunomodulates TNF
Withania somnifera	Dried root	Withaferin A	NO production
Uncaria tomentosa	Bark	Two mixtures of tetracyclic and pentacyclic oxindole alkaloids	Peripheral blood mononuclear cells
Phellodendron amurense	Bark	Phellodendrine	Immunosuppressant
Cissampelos pareira Linn	Leaves	Berberine	Enhances phagocytosis

CONCLUSIONS

Traditional plant remedies and herbal medicines have been used to treat a wide range of illnesses and conditions since ancient times. Botanical medicines and herbal remedies have been utilized to address health problems since ancient times. Herbal plants that have been studied for their hepatoprotective and immunomodulatory properties have been mentioned. Several medicinal plants display not only hepatoprotective and immunomodulatory actions but also a broad spectrum of anticancer, cardiatonic, diuretic, antiarrhythmic, and other therapeutic activities. For the development of effective treatments for hepatoprotection and immune response, it is crucial to identify new plants with immunomodulatory and hepatoprotective properties. In contrast to conventional medication, herbal treatments are safe and non-toxic. Research into hepato- and

immune medicinal plants will help those in need of herbal therapy for both conditions, without resorting to synthetic medications and with fewer adverse effects.

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