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PLANT REVIEW

A Review on Hepatoprotective and Immunomodulatory Herbal Plants

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ABSTRACT

The liver is the most important organ that plays an important role in maintaining various physiological processes in the body. Hepatitis is an inflammation of the liver and is characterized by the presence of inflammatory cells in the tissue of the organ. There are five main viruses, referred to as types A, B, C, D, and E. These five types are of the greatest concern because of the burden of illness and death. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the drug regulatory agencies and the pharmaceutical industry. Herbal medicines have been used in the treatment of liver disease for a long time. The immune system is the part of body that diagnoses the pathogen by using a specific receptor to reveal immediate response by the activation of immune components cells, chemokines, and cytokines, and also the release of the inflammatory mediator. They potentiate and modulate the immune system. The plant-derived phytoconstituents (polysaccharides, proteins and flavanoids, lignans, rotenoids, etc.) stimulate the immune system and maintained hepatic diseases. There are a number of hepatoprotective and immunomodulatory herbs that have been reported. The present review is aimed at compiling data on promising phytochemicals from hepatoprotective and immunomodulatory herbs.

Key words: Hepatoprotective herb, immunomodulatory herb, nitric oxide

INTRODUCTION

The liver is the most important organ that plays an important role in maintaining various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion, and storage. It plays a central role in the detoxification and excretion of many exogenous and endogenous compounds. Hence, any injury to it or impairment of its function has grave implications for the health of the affected person. Every year, about 18,000 people are reported to die due to liver cirrhosis caused by hepatitis, although viral infection is one of the main causes for hepatic injury. It acts as a storage depot for proteins, glycogen, various vitamins, and metals. It also has a role in the regulation of blood volume by transferring the blood from the portal to the systemic circulation and its reticulo-endothelial system and participates in the immune mechanism. The human body identifies almost all drugs as foreign substances (i.e., xenobiotics) and subjects them to various chemical processes (such as metabolism) to make them suitable for elimination. This involves chemical transformations to (a) reduce fat solubility and (b) change biological activity. Although almost all tissues in the body have some ability to metabolize chemicals, smooth endoplasmic reticulum in liver is the principal "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins), and exogenous substances (e.g., drugs). The central role played by the liver in the clearance and transformation of chemicals also makes it susceptible to drug-induced injury.

Hepatitis is an inflammation of the liver and is characterized by the presence of inflammatory cells in the tissue of the organ. There are five main viruses, referred to as types A, B, C, D, and E. These five types are of the greatest concern because of the burden of illness and death. The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring) and cirrhosis. Hepatitis may occur with limited or no symptoms, but often leads to jaundice, anorexia (poor appetite), and malaise. Hepatitis is acute when it lasts less than 6 months and chronic when it persists for longer. Hepatic trouble, which includes parasites and viral infections; autoimmune diseases; and intoxication with various xenobiotics such as alcohol, herbal medicine, drugs, chlorinated solvents, peroxidized fatty acids, fungal toxins, industrial pollutants, and radioactive isotopes. In particular, types A and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer.

About 1 million deaths per year are attributed to viral hepatitis infection, that is, hepatitis B virus (HBV) and hepatitis C virus (HCV) taken together, which is the leading cause of liver cirrhosis and cancer, accounting for 78% of cases. Nearly 1 out of every 3 people in the world (approximately 2 million people) has been infected by HBV and HCV. On World Hepatitis Day, July 28, 2013, the World Health Organization (WHO) and its partners focused on the fact that although the burden of

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disease caused by viral hepatitis is growing, it remains largely ignored or unknown to many policymakers, health workers, and the public.

HERBAL HEPATOPROTECTIVE AGENTS

There are generally classified into three categories, as noted below.

Antihepatotoxic agents

These generally antagonize the effects of any hepatotoxins causing hepatitis or any liver disease.

Hepatoprotective agents

These generally prevent various types of liver infections prophylactically.

Hepatotoxic agents

These generally promote the healing process of the liver.

In India, The use of herbal products for the management of disease has a long history, starting with Ayurvedic management, and proceeding to the European and Chinese alternative systems of ancient medicines. Medicinal plants are significant sources of hepatoprotective drugs. According to one estimate, more than 700 mono- and polyherbal preparations in the form of decoction, tincture, and tablets have been used in various liver disorders. The 21st century has seen a paradigm shift toward therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional system of medicine with that of the modern concept of evidence-based therapeutical screening, authentification, and randomized placebo-controlled clinical trials to support clinical efficacy. A large number of plants and formulations have been claimed to show hepatoprotective activities. Around 160 active constituents from 101 plants are claimed to have post liver protecting activity. In India, quite eighty seven plants square measure used in 33 patented propitiatory multi-ingredient plant formulations. In spite of the tremendous advances made, no important and safe hepatoprotective agents are obtainable in modern medicine Therefore, due importance has been given globally to develop primarily plant-based hepatoprotective medications that are effective against a range of liver disorders. A drug having helpful results on the liver is understood as a hepatoprotective drug. On the other hand, drugs having toxic effects on the liver are called hepatotoxic drugs. Clinical analysis has conjointly shown that herbals have real utility in the treatment of diseases. In the last 30 years, several hepatotoxins have been used commonly in d-galactosamine, carbon tetrachloride, acetaminophen, and thioacetamide, and more recently Concanavalin A (ConA) and lipopolysaccharide (LPS) has been developed. ConA and LPS do not reflect the clinical pattern of human disease, which indicates a great advantage in the study of cellular mechanisms involved in autoimmune liver disease. The galactosamine model is a highly selective hepatotoxin that causes liver damage similar to human viral hepatitis via depletion of uridine nucleotides, which subsequently diminishes the synthesis of RNA and proteins.[1] Galactosamine intoxication in rats disrupts the membrane permeability of the plasma membrane, causing leakage of the enzymes form the cell, which leads to the elevation of serum enzymes. Hence, a significant rise in the transaminase levels could be taken as an index of liver damage. Galactosamine has great liver specificity compared to other toxic groups, such as paracetamol, acetaminophen, and carbon tetrachloride because hepatocytes have high levels of galactokinase and galactose-1-uridyltranseferase, and galactosamine does not affect other organs. Galactosamine induces hepatotoxicity with spotty hepatocytes, necrosis, and marked portal and parenchymal infiltration.[2] Galactosaimine also induces the depletion of uridine diphosphate (UDP) by increasing the production of UDP-sugar derivates, which causes inhibition of RNA and protein synthesis, leading to cell membrane deterioration.[3] The current study is aimed toward assembling information-supported reported works on promising phytochemical from herbal plants that are tested in hepatoxicity models. The review deals with fact-finding work done on herbals helpful in the treatment of liver ailments. The failure of the synthetic drugs in the treatment of hepatic diseases and the search for potent immunomodulatory agents are leading us to the world of herbal medicine in search of a product in nature for use in the protection and cure of dreaded liver diseases. Till date, there is only one protective natural drug; that, too, is not curative and also has its limitations in protecting the liver from viral attacks. The list of herbal hepatoprotective agents has been summarized in Table 1.

IMMUNOMODULATORS

Immunomodulators are of three types:

- Immunoenhancers
- Immunosuppressants
- Immunoadjuvants.

Immunoenhancers

These are the agents that enhance or stimulate the immune system, and they are used in immunodeficiency diseases.

Immunosuppressants

These are the agents that suppress the immune system and are used in autoimmune diseases, or in organ transplantation.

Immunoadjuvants

These agents are used for enhancing the efficacy of vaccines and therefore could be considered as specific immune stimulants, e.g., Freund's adjuvant use in bacillus Calmette-Guérin (BCG) vaccination.

An immunomodulator is natural or artificial, which could stimulate, suppress, or modulate any of the elements of the immune system, including both innate adaptive arms of the immune response**.** Chronic inflammation is concerned within the pathological process of most common cancers. The etiology of the inflammation is varied and includes the organism, chemical, and physical agents. Many of the factors involved in chronic inflammation play a dual role in the process, promoting neoplastic progression, thereby facilitating cancer prevention.[1] About 25% of all cancers are related to chronic infection and inflammation.[2] Throughout, inflammation acts as associate accommodative multitude resistance against illness or injury and is primarily a self-limiting methodology; inadequate resolution of the inflammatory responses typically ends up in numerous chronic ailments besides cancer.[3] A comprehensive understanding of the molecular and cellular inflammatory mechanisms involved is important for developing preventive and therapeutic ways in which against cancer.[26] The nitric oxide (NO) acts through the stimulation of the soluble guanyl cyclase, which could be a heterodimeric enzyme with subsequent formation of cyclic-guanosine monophosphate (GMP). Cyclic-GMP activates protein kinase G, which causes the reuptake of Ca^{2+} and the opening of calcium, which activates K^{+} channels. The expression of inducible nitric oxide synthase (iNOS) and so the extent of NO is shown to be elevated in varied metastatic tumor lesions and carcinomas. The study demonstrated that the topical application of phorbol ester induced iNOS expression and subsequent NO production, which successively induced cyclooxygenase-2 expression via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) activation in mouse skin.[27] In response to inflammatory cytokines [e.g., tumor necrosis factor (TNF)-α and interleukin (IL)-1β] or other inflammatory stimuli [e.g., phorbol ester, ultraviolet B (UVB), LPS, and dextran sulfate sodium (DSS)], iNOS is transactivated by some transcription factors, including NF-κB.[28,29] The NO acts through the

Table 1: The reported herbal hepatoprotective agents

Plant names	Category	Name of active constituent	Mechanism	References
Allium sativum	Organosulfur compounds	Organosulfur compounds	Prevention of GSH depletion, alteration of GSH-dependent enzymes	[4]
Buddleja officinalis	Phenyl ethanoid Glycoside	Acteoside	Decreased levels of AST, ALP	[5]
Camellia sinensis	Polyphenols	Catechin	Inhibited hepatocellular apoptosis and unregulated Bcl-2 protein expression	[6]
Cistus laurifolius L.	Flavonoid	Quercetin	MDA, AST, GSH levels decreased	[7]
Corydalis saxicola	Alkaloid	Dehydrocavidine	Decreased levels MDA, SOD, GPx	[8]
Eglets viscosa Less.	Flavonoid	Ternatin	Decreased lipid peroxidation	[9]
Gardenia jasminoides	Iridoid Glycoside	Geniposide	Antioxidant	[10]
Ginkgo biloba L.	Polyphenols	Polyprenols	ALT, AST, ALP, ALB, TP, HA, LN, TG, and CHO levels decreased	[11]
Gossypium herbaceum	Polyphenols	Gossypol	Antioxidant	[12]
Hibiscus sabdariffa L.	Polyphenols	Protocatechuic acid	LDH, AST, ALP, MDA levels decreased	[13]
Larrea tridentata	Resin	Nordihydroguaiaretic acid	Antioxidant	[14]
Magnolia officinalis	Polyphenols	Magnolol	Antioxidant	[15]
Mangifera indica	Triterpene	Lupeol	Decreased levels of SGOT, SGPT, ALP, bilirubin	[16]
Nigella sativa	Quinones	Thymoquinone (TQ)	Scavenger of superoxide, hydroxyl radical, and singlet molecular oxygen	[17]
Ocimum basilicum	Phenolic Acids	Rosmarinic acid	AST, ALP, SGOT levels decreased	[18]
Peumus boldus	Alkaloid	Boldine	Lipid peroxidation	[19]
Phyllanthus amarus	Polyphenols	Phyllanthin	SGOT, SGPT, ALKP, SBLN and total protein levels decreased	[20]
Pinus maritima	Polyphenols	Pycnogenol	SOD, GSH-Px, GSH-reductase, and TBARS levels decreased	[21]
Rubia cordifolia	Glycoside	Rubiadin	SGOT, SGPT, SALP, and gamma-GT levels decreased	[22]
Schisandra chinensis	Lignans	Wuweizisu	Antioxidant	[23]
Sida cordifolia	Organic compound	Fumaric acid	Antioxidant	[24]
Silybum marianum	Lignans	Silymarin	Antioxidant	[25]

GSH=Glutathione

Table 2: The reported herbal immunomodulatory agents

Plants	Parts	Active constituents	Mechanism of action	References
Panax ginseng	Root	Ginsenoside	Proliferation of lymphocytes	[31]
Centella asiatica	Root	Asaticoside A, asiaticoside B	Proliferation of lymphocytes and natural killer cells	[8]
Glycyrrhiza glabra	Root and rhizome	Glycyrrhizin	Increase in spleen weight	[32]
Asparagus racemosus	Root and leaves	Shatavarin 1-4	Increase in production of TNF	[33]
Aralia mandshurica	Dried root	Saponine	Increases phagocytosis	[34]
Picrorhiza kurroa	Dried rhizome	Picroside-I, II, kutkoside	Anticomplement activity	[35]
Lawsonia alba	Dried leaves	Lawsone, apigenin, luteolin, and cosmosin	Stimulation of neutrophils and phagocytosis	[36]
Brassica oleracea	Root	Sulforaphane	Enhancement of antibody titer	[37]
Viscum album	Whole	Viscumin	Stimulates lymphocytes	[38]
Canavalia ensiformis	Whole	Lectins	Human neutrophil aggregation and H_2O_2 release	[39]
Linum usitatissimum	Whole	Cyclopeptide A	Immunosuppressant	[40]
Artemisia princeps	Leaves	Protein	Induces interferon	[41]
Echinacea purpurea	Roots and rhizomes	Arabinogalactan	Stimulates phagocytosis	[42]
wheat bran	Seed	Hetroxylan	Stimulates phagocytosis	[43]
Curcuma longa	Rhizome	Curcumin	Inhibits human neutrophils	[44]
Aloe Vera	Dried juice of leaves	Acemannan	Anticomplement activity	[45]
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	[46]
Dioscorea membranacea Pierre	Rhizome	Dioscorealide B	Lymphocyte proliferation	[47]
Tinospora cordifolia	Whole plant	Cardiofoliosides A and B	Activates macrophages	[48]
Litchi chinensis Sonn.)	Fruits	Epicatechins, proanthocyanidin B2, and proanthocyanidin B4	Proliferation of mouse splenocytes	[49]
Plumbago zeylanica	Root	Plumbagin	Stimulates phagocytosis	[50]
Rice bran	Seed	Ferulic acid ester of oligosaccharides	Increases phagocytosis	[51]
Pimpinella anisum	Fruit	Anethole	Increases leukocyte number	[52]

Contd...

Table 2: Contd...

Plants	Parts	Active constituents	Mechanism of action	References
Catharanthus roseus	Whole plant	Vincristine	Induces antibody production	[53]
Claviceps purpurea	Dried sclerotium of fungus	Ergot alkaloids	Immunomodulates TNF	[54]
Withania somnifera	Dried root	Withaferin A	NO production	[55]
Uncaria tomentosa	Bark	Two mixtures of tetracyclic and pentacyclic oxindole alkaloids	Peripheral blood mononuclear cells	[56]
Phellodendron amurense	Bark	Phellodendrine	Immunosuppressant	[57]
Cissampelos pareira Linn	Leaves	Berberine	Enhances phagocytosis	[58]

stimulation of the soluble guanyl cyclase; is expressed in the cytoplasm of almost all mammalian cells; and mediates a wide range of important physiological functions such as inhibition of platelet aggregation, vasodilatation, neuronal signal transduction, and immunomodulation. The NO is also generated by phagocytes (neutrophils, monocytes, and macrophages) as part of the human immune response.[30] Phagocytes are formed with iNOS, which is activated by interferon-gamma (IFN-γ) as a single signal or by TNF along with a second signal. On the other hand, transforming growth factor- (TGF)-β provides a strong inhibitory signal to iNOS, whereas IL-4 and IL-10 provide weak inhibitory signals. In this way, the immune system may regulate the armamentarium of phagocytes that play a role in inflammation and immune responses. The reported herbal immunomodulatory agents have been summarized in Table 2.

CONCLUSIONS

Herbal and traditional botanical products have been used since ancient times for the treatment of various disorders and diseases. Those herbal plants have been discussed that have been previously explored by various researchers for their hepatoprotective and immunomodulatory activities. Several medicinal plants exhibit not only hepatoprotective and immunomodulatory activities but also a wide range of anticancer, cardiatonic, diuretic, antiarrhythmic, and other medicinal activities. New immunomodulatory and hepatoprotective plants are important for the discovery of drugs that are less costly, have fewer side effects, are more potent, and allow effective treatment developed for hepatoprotection and immune response. Herbal therapies are free from side effects and toxicity, unlike allopathic medicines. Studies on hepato- and immunomedicinal herbs will contribute to the benefit of the populations needing herbal treatment for both diseases without involving the use of synthetic drugs and reducing the side effects of synthetic drugs.

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Conflicts of interest

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