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Exploring The Therapeutic Potential Of Medicinal Plants With Spleen Protective Activity: A Comprehensive Review

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ABSTRACT

The spleen is a critical organ involved in immune response, blood filtration, and the destruction of old red blood cells. Spleen disorders, including splenomegaly, can lead to significant health issues. Traditional and herbal medicines have been used for centuries to treat various ailments, including spleen disorders. This review aims to provide a comprehensive overview of medicinal plants with spleen-protective activity, highlighting their potential mechanisms of action, active constituents, and therapeutic efficacy. Through an extensive literature survey, plants such as *Ipomoea digitata, Phyllanthus emblica, Andrographis paniculata, Curcuma longa and Tinospora cordifolia* have been identified for their significant spleen-protective properties. The pharmacological basis of these plants includes antioxidant, anti-inflammatory, and immunomodulatory activities. Special emphasis is given to *Ipomoea digitata,* a plant with promising but not yet fully proven spleen-protective effects. Understanding the traditional uses and scientific evidence supporting these medicinal plants can pave the way for developing novel therapeutic agents for spleen-related disorders. This review explores the social impact and potential benefits of integrating these herbal remedies into modern healthcare systems. This review underscores the significant role of medicinal plants in spleen protection and encourages further research to validate their clinical efficacy and safety. The integration of these herbal remedies into contemporary medicine could offer a promising avenue for managing spleen-related disorders and enhancing public health.

KEYWORDS

Splenomegaly, Spleen, Pathophysiology, Spleen protective activity

INTRODUCTION

Splenomegaly refers to the enlargement of the spleen, which can be determined by its weight or size. The spleen is crucial in blood formation and immune surveillance. Its primary functions include clearing out old and abnormal red blood cells, opsonized platelets and white blood cells, as well as removing microorganisms and antigens. As a secondary lymphoid organ, the spleen is also a site for the maturation and storage of T and B lymphocytes and plays a vital role in the production of immunoglobulin G (IgG) by mature B-lymphocytes in interaction with T-lymphocytes. Additionally, the spleen synthesizes immune system peptides such as properdin and tuftsin. Around one-third of the body's platelets are stored in the spleen. Normally, the spleen is located within the peritoneal cavity in the left upper quadrant, adjacent to ribs 9 through 12, and it borders the stomach, colon, and left kidney.

The size and weight of the spleen can vary based on an individual's weight, height, and sex, with men generally having larger spleens than women, and taller or heavier individuals having larger spleens. A spleen up to 12 cm in length is considered normal. A length between 12 cm and 20 cm suggests splenomegaly, while a length over 20 cm is indicative of massive splenomegaly. The normal weight range for an adult spleen is between 70 g and 200 g. Weights between 400 g and 500 g indicate splenomegaly, and weights over 1000 g confirm massive splenomegaly. Typically, a normal-sized spleen is not palpable in adults, but it might be felt due to variations in body build and chest wall structure. Splenomegaly can be diagnosed through clinical examination or imaging techniques like ultrasound, CT scans, or MRI. This condition may be transient, arising from an acute illness, or it could indicate a more serious underlying acute or chronic disease. (1)

ETIOLOGY

There are several potential causes of splenomegaly:

1. **Liver disease (cirrhosis, hepatitis):** Parenchymal liver disease can cause increased vascular pressure, leading to spleen enlargement.
2. **Hematologic malignancies (lymphomas, leukemias, myeloproliferative disorders):** Neoplastic cells infiltrate the spleen, resulting in splenomegaly.
3. **Venous thrombosis (portal or hepatic vein thrombosis):** This condition increases vascular pressure, causing the spleen to enlarge.
4. **Splenic congestion (venous thrombosis, portal hypertension, congestive heart failure):** Various conditions lead to congestion in the spleen.
5. **Cytopenias (autoimmune hemolytic anemia, immune-mediated neutropenia, Felty syndrome):** The immune-mediated destruction of blood cells causes functional splenomegaly.
6. **Splenic sequestration (pediatric sickle cell disease, hemolytic anemias, and thalassemias):** These conditions lead to the trapping of blood cells in the spleen.
7. **Acute or chronic infection (bacterial endocarditis, infectious mononucleosis, HIV, malaria, tuberculosis, histiocytosis, and abscess):** Infections can cause splenic enlargement.
8. **Connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, Adult-onset Still's disease, and some familial autoinflammatory syndromes):** These disorders can lead to splenomegaly.(2)
9. **Infiltrative disorders (sarcoidosis, amyloidosis, glycogen storage diseases):** These conditions cause the infiltration of abnormal substances into the spleen.
10. **Focal lesions (hemangiomas, abscess, cysts, and metastasis):** Localized lesions in the spleen can lead to its enlargement.

The mechanisms underlying splenic enlargement vary depending on the cause. In acute infectious illnesses, the spleen increases its workload in clearing antigens and producing antibodies, leading to an increase in reticuloendothelial cells and potential splenic hyperplasia. In liver disease and congestion, increased venous pressure results in congestive splenomegaly. In myeloproliferative disorders, extramedullary hematopoiesis can cause infiltrative splenomegaly. (3)(4)

EPIDEMIOLOGY

Splenomegaly is a relatively uncommon condition, estimated to affect approximately 2% of the total population in the United States. There is no reported predilection for ethnicity, gender, or age among adults. In contrast, tropical splenomegaly is more prevalent in Asia and Africa. Older individuals are at higher risk of spleen rupture due to the thinning of the spleen capsule with age.

PATHOPHYSIOLOGY

Splenomegaly can be classified based on its underlying pathophysiological mechanisms:

- **Congestive:** Resulting from pooled blood, such as in portal hypertension.
- **Infiltrative:** Caused by the invasion of cells foreign to the spleen's normal environment, such as metastatic cancers, myeloid neoplasms, or lipid storage diseases.

- **Immune:** Stemming from increased immunological activity and subsequent hyperplasia, seen in conditions like endocarditis, sarcoidosis, and rheumatoid arthritis.
- **Neoplastic:** Arising when resident immune cells within the spleen develop into a neoplasm, as observed in lymphomas.

Various medicinal plants are known for their spleen-protective effects, attributed to bioactive compounds such as antioxidants and flavonoids. This review explores the traditional uses, phytochemical composition, and scientific evidence supporting these plants' efficacy in promoting spleen health. Integrating traditional wisdom with modern research offers insights into their potential role in contemporary healthcare.

MEDICINAL PLANTS WITH SPLEEN PROTECTIVE ACTIVITY

Ipomoea digitata Linn

Ipomoea digitata Linn. is a well-known medicinal plant used in Ayurveda for its healthpromoting effects in India and parts of South East Asia. *Ipomoea digitata*, a member of familyConvolvulaceae is known as *Ksheera-vidari* in Sanskrit, *palmodikka* in Malayalam and *milk yam* in English. Its synonyms are *Ipomoea paniculata, Convolvulus paniculata Linn, Ipomoeamauritiana Jacq* [5]. Flour of raw rhizome of this plant is given in enlargement of liver and spleen. But the effect on spleen is not yet completely proven. Ulcers, hemorrhoids, GI tract disorders and nagging coughs can be cured using the powder of tuberous root of *Ipomoea digitata*. Tubers contain Taroxerol, sitosterol, palmitic, stearic and oleic acid, linoleic and linolenic acids. It is a good anti-inflammatory agent thus helpingin pain and stiffness[6] .In Ayurveda, *Ipomoea digitate Linn* is used as an ingredient in Chyawanaprash due to its aphrodisiac, antioxidant, galactogogue, nervine tonic[7].

Artemisia annua L

Artemisia annua L. (A. annua), a traditional Chinese medicine, has been used for centuries to treat a variety of ailments, including intermittent fevers from malaria, bone steaming and heat/fever due to exhaustion, tuberculosis, lice, wounds, scabies, and dysentery. The discovery of artemisinin and its potent anti-malarial properties has brought significant attention to A. annua (8). Recently, it has been found to have inhibitory effects against a range of parasites (such as Plasmodium, Toxoplasma gondii, Leishmania, Acanthamoeba, Schistosoma), viruses (including hepatitis A virus, herpes simplex viruses 1 and 2, and human immunodeficiency virus), fungi (Candida, Malassezia, Saccharomyces spp.), and bacteria (Enterococcus, Streptococcus, Staphylococcus, Bacillus, Listeria, Haemophilus, Escherichia, Pseudomonas, Klebsiella, Acinetobacter, Salmonella, Yersinia spp.). Additionally, A. annua has demonstrated anti-inflammatory and anti-cancer properties and has been used to treat osteoarthritis, leukemia, colon cancer, renal cell carcinoma, breast cancer, non-small cell lung cancer, prostate cancer, and hepatoma. Oral administration of n-hexane fractions derived from Artemisia annua leaves and seeds to infected mice over a ten-day period can significantly reduce the parasite load in the liver and spleen. This treatment also decreases spleen weight by activating Th1-based protective cell-mediated immunity and generating memory cells (9).

Andrographis paniculata

Green Chiretta (GC), also known as Andrographis paniculata or the “King of Bitters” and kalmegh, has been traditionally used to treat various conditions such as abdominal discomfort, respiratory infections, inflammation, dysentery, intermittent fevers, malaria, and pyrexia.(10) Studies have shown that GC possesses a range of beneficial properties, including antioxidant, antimicrobial, anti-hepatitis, antimalarial, antidiarrheal, anti-HIV, and antihyperglycemic effects. Recent in-vitro research indicates that GC has anti-inflammatory and antioxidant properties by inhibiting albumin protein denaturation and scavenging DPPH radicals. Another study in human lung epithelial cells (Calu-3) demonstrated the anti-SARS-CoV-2 efficacy of GC extract and its main constituent, andrographolide, suggesting potential therapeutic applications. Additionally, an 80% ethanol leaf extract of GC and andrographolide significantly reduced swelling, uric acid levels, and the expression of IL-1α, IL-1β, IL-6, and TNF-α in the synovial fluid of gout-induced rats, showing an anti-gout effect. GC leaf extract has also been reported to alleviate hind limb weight-bearing loss, cartilage injury, and inflammation in osteoarthritis-induced rats, and to reduce pro-inflammatory

cytokines, matrix metalloproteinases, pain responses, and inflammatory markers in vitro, indicating its potential against osteoarthritis. The pharmacological efficacy of crude leaf extracts highlights the importance of evaluating their biological activities to identify the therapeutic effects of individual phytochemical components. (11) In the present study, the aqueous leaf extract of Green Chiretta (GC) appears as a promising natural therapeutic agent for protecting against cardiac and spleen toxicity caused by methotrexate (MTX) exposure.

Phyllanthus amarus

Phyllanthus amarus (family: Euphorbiaceae) is of immense interest due to its wide spectrum of biological activities, such as anti-inflammatory, antimicrobial, antiviral (against Hepatitis B), antimutagenic, anticarcinogenic, hepatoprotective, nephroprotective, cardio protective, and hypoglycemic(12).It has been demonstrated that the medicinal properties were due to the phytochemicals possessed by *P. amarus*, including alkaloids, polyphenols, flavonoids, lignans, ellagitannins, triterpenes, sterols, and volatile oil(13).Recent research activities have well established the immunomodulatory properties of *P. amarus*, which provides a source for the development of agents for suppression of normal or exaggerated immune response. The study's data indicated that the extract of P. amarus effectively inhibited the production of IL-2, IFN-γ, and IL-4. This inhibition of cytokines from Th1 and Th2 cells may underlie the observed decrease in T and B lymphocyte proliferation, demonstrating the extract's potential inhibitory effect on T-cell mediated inflammation. This inhibition of T and B lymphocytes could be beneficial in treating certain immune-mediated conditions, such as autoimmune disorders and asthma. The findings suggest that P. amarus extract was more effective than the standard immunosuppressive drug cyclophosphamide, particularly in terms of its lower toxicity and its effect on reducing spleen weight gain.

Ocimum sanctum Linn

Ocimum sanctum Linn (Labiatae), known as holy basil, is a commonly used home remedy and has been advocated for various ailments like cold, fever, dysentery, hemorrhage and dyspepsia, glucoma, cataract, chronic conjunctivitis, and other painful eye diseases, as well as gastric and hepatic disorders in indigenous system of medicine . The plant is endowed with a variety of pharmacological properties including antistress, antifertility, immunoregulatory, hypoglycemic, antibacterial, antifungal, antiinflammatory, anti-carcinogenic, antioxidant, and cyclooxygenase inhibitory(14)The present study was to investigate the acute and subacute toxicity of a 50% ethanolic leaves extract of Ocimum sanctum Linn (OSE) when administered orally. For the acute toxicity assessment, four groups of mice (n = 6/group/sex) were given doses of 200, 600, and 2000 mg/kg orally, with general behavior, adverse effects, and mortality being monitored for up to 14 days. In the subacute toxicity study, rats were administered OSE via gavage at doses of 200, 400, and 800 mg/kg/day (n = 6/group/sex) for a period of 28 days. Biochemical, hematological, and histopathological changes in various tissues (liver, kidney, spleen, heart, and testis/ovary) were evaluated. The results indicated that OSE did not cause any hazardous symptoms, death, or central and autonomic nervous system toxicities in the acute toxicity test. During the subacute treatment, no significant changes were observed in body weight, food and water consumption, or hematological and biochemical profiles. Additionally, there were no notable macroscopic or microscopic changes in the vital organs of the rats. These findings suggest that Ocimum sanctum extract may be safe for human use.

Tinospora cordifolia

Tinospora cordifolia, a climbing shrub from the family Menispermaceae, is commonly found throughout the Indian subcontinent and China. Both the stem and root of this plant are used therapeutically, primarily due to their immunomodulatory properties as well as their antimalarial and antileprotic effects. The aqueous extract of Tinospora cordifolia contains various chemical constituents, including alkaloids, steroids, glycosides, and polysaccharides. In Ayurveda, an Indian traditional system of medicine, a decoction made from the stem of Tinospora cordifolia combined with Piper longum is commonly prescribed to treat malarial fever and is also effective in reducing splenomegaly. Additionally, the alcoholic extract of Tinospora cordifolia is used in both Ayurveda and modern medicine as an immune enhancer (15). The findings of this study offer a new perspective on treating hyper-reactive malarious splenomegaly

Phyllanthus niruri

Phyllanthus niruri, a member of the Euphorbiaceae family, is renowned worldwide for its diverse applications in traditional medicine across many Asian, African, and South American countries. Numerous preclinical and clinical studies have highlighted the beneficial pharmacological and therapeutic effects of P. niruri extracts. Among its most notable medicinal properties are its anti-hepatotoxic, anti-lithic, anti-tumor, anti-HIV, and anti-hepatitis B activities. Additionally, extracts of Phyllanthus niruri have been shown to enhance both specific and non-specific immune responses to infections and are generally considered advantageous in treating immunodeficiency conditions. Traditionally, decoctions made from the whole aerial parts of the plant, using water or a water-alcohol mixture, are consumed for various ailments. (16). the study evaluated the immunomodulatory effects and impact of the extract on body weight, relative lymphoid organ weight, splenic cellularity, and peripheral blood hematologic parameters. Ingesting the extract led to a significant increase ($P< 0.01$) in body weight, the weight and cell count of the spleen and lymph nodes, and the number of RBCs, WBCs, and platelets. The extract of Phyllanthus niruri also significantly increased ($P< 0.01$) hemoglobin concentration in a non-dose-dependent manner.

Picrorhiza kurroa

Picrorhiza kurroa is a significant alpine herb native to the Himalayan region, thriving at altitudes between 3000-5000 meters in temperate zones. In the Indian system of medicine, it is known as "Kutki" and is one of the 2000 essential drugs derived from plant sources. The rhizomes are characterized by their bitter and acrid taste and are known for their cooling, laxative, carminative, digestive, stomachic, anthelmintic, anti-inflammatory, depurative, cardiotonic, galactopurifying, expectorant, antipyretic, anti-periodic, and purgative properties in larger doses. They are also beneficial for treating gastropathy, flatulence, colic, hypotension, cough, asthma, bronchitis, hiccoughs, fever, diabetes, jaundice, hemorrhoids, breast milk impurities, and general debility (17). Cyclophosphamide, used during chemotherapy, can cause hepatic damage and urotoxicity due to its cytotoxic nature, affecting internal organs. Significant improvements were observed in the relative organ weights of the kidney, liver, and spleen, suggesting that Picrorhiza kurroa could be recommended for drug-induced immunopathy in these organs.

Punica granatum L.

Various parts of the Punica granatum L. tree, commonly known as pomegranate, including the peel, seeds, and bark, have been used for centuries in traditional medicine to treat a variety of diseases. Research has demonstrated that pomegranate peel extract (PPE) possesses antibacterial, antifungal, antiprotozoal, antihelminthic, and antioxidant properties. Recently, it has been reported that pomegranate peel has a protective effect against hepatic injury induced by murine malaria. Therefore, the current study aimed to investigate the impact of P. granatum treatment on splenic damage, apoptosis, and oxidative stress caused by murine malaria (18). The findings demonstrated the potential antimalarial, antioxidant, and anti-inflammatory properties of pomegranate. Pomegranate peel extracts significantly lowered parasitemia and the spleen index in treated mice compared to the untreated group. Additionally, spleen histology scores indicated better improvement in the pomegranate-treated mice. The untreated mice showed clear evidence of splenomegaly through increased spleen capsule thickness, whereas pomegranate peel extract had a notable restorative effect on the spleen capsules of treated mice. The extract also significantly decreased the levels of proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, as well as inducible nitric oxide synthase (iNOS). Furthermore, the study revealed that pomegranate extract significantly reduced oxidative stress by lowering levels of nitric oxide (NO) and malondialdehyde (MDA).(19)

Silybum marianum

Extracts from the flowers and leaves of Silybum marianum (St. Mary's thistle, milk thistle) have been used for centuries to treat disorders of the liver, spleen, and gallbladder (Rainone, 2005). In the 1960s, the biologically active compounds in the seed and fruit extracts were studied, and their chemical structures were identified. Sonnenbichler et al. (1999) isolated a mixture called silymarin, which is composed of flavonolignans and has been the focus of most clinical studies. The main constituents of silymarin are

silibinin, isosilibinin, silicristin, and silidianin. Importantly, S. marianum is considered a safe herbal product, as no health hazards or side effects are associated with the proper administration of therapeutic doses. (20)

CONCLUSION

The exploration of medicinal plants with spleen-protective activity reveals a rich diversity of phytochemicals with significant therapeutic potential. Plants such as Ipomoea digitata, Tinospora cordifolia, Phyllanthus niruri, Picrorhiza kurroa, Punica granatum, and Silybum marianum have been studied extensively for their spleen-protective properties and other health benefits. These plants contain a variety of bioactive compounds, including alkaloids, glycosides, flavonolignans, and antioxidants, which contribute to their therapeutic effects.

Research has demonstrated that these plants can mitigate spleen-related disorders through various mechanisms such as immunomodulation, anti-inflammatory action, antioxidant activity, and cytoprotection. For instance, Ipomoea digitata shows potential in treating splenomegaly, while Tinospora cordifolia and Phyllanthus niruri enhance immune responses and protect against infections. Picrorhiza kurroa has shown efficacy in alleviating drug-induced immunopathy in vital organs, and Punica granatum has proven to be effective against malarial-induced splenic damage. Silybum marianum, with its well-documented hepatoprotective and splenic benefits, stands out as a safe and effective herbal remedy.

Overall, the findings underscore the importance of these medicinal plants in traditional and modern medicine for spleen health. Further research and clinical trials are necessary to fully understand their mechanisms of action and optimize their therapeutic applications. The integration of these natural remedies into contemporary medical practices could offer promising alternatives for managing spleen-related conditions, enhancing patient care, and promoting overall health.

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