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Natural Alternatives and Therapeutic Approaches for Managing Cholestatic Pruritus: A Comprehensive Review

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ABSTRACT

Cholestatic pruritus is a debilitating condition commonly associated with liver diseases such as primary biliary cholangitis, primary sclerosing cholangitis, and cirrhosis. It significantly impacts the quality of life, and current treatments often offer limited efficacy and are associated with adverse side effects. This review explores natural alternatives for the management of cholestatic pruritus, focusing on medicinal plants and herbs with potential therapeutic effects. We specifically examine *Gardenia jasminoides*, *Citrus aurantium*, *Artemisia capillaris*, *Rehmannia glutinosa*,*Lycium barbarum*, *Andrographis paniculata*, *Picrorhiza kurroa*, *Rheum officinale*,*Glycyrrhiza glabra*, *Solanum nigrum*, *Radix Isatidis*, *Ziziphus jujube*, which have demonstrated anti-inflammatory, hepatoprotective, and pruritus-relieving properties. These plants contain a variety of bioactive compounds such as flavonoids, saponins, alkaloids, and terpenoids, which have been shown to modulate bile acid metabolism, reduce oxidative stress, and alleviate inflammation. Clinical and preclinical studies support the therapeutic potential of these plants, with many showing significant improvements in pruritus severity, liver function, and overall patient well-being. Moreover, these natural remedies offer an alternative to conventional therapies, often with fewer side effects. The review highlights the need for further research to understand the mechanisms of action of these plants, optimize their therapeutic efficacy, and establish standardized treatment protocols. The promising results from traditional medicine and phytotherapy open new avenues for the development of safer, more effective treatments for cholestatic pruritus.

Keywords: *Cholestatic pruritus, Natural alternatives, Therapeutic effects, Anti-inflammatory, Hepatoprotective.*

1. INTRODUCTION

Cholestatic Pruritus is a well-known and distressing symptom commonly associated with cholestatic liver diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), where it affects 20–70% and 38% of patients, respectively. In the large-scale TARGET-PBC observational study, 81% of the 211 PBC patients reported experiencing pruritus. Genetic cholestatic conditions, including Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), and benign recurrent intrahepatic cholestasis (BRIC), are also linked to pruritus. In Alagille syndrome, up to 88% of patients report pruritus, with 45% experiencing severe cases, while in PFIC, pruritus affects 76–80% of patients. In BRIC, most patients experience recurrent and sporadic itching episodes, although prevalence rates are less defined [1,2].

The TARGET-PBC study further highlighted the impact of pruritus on patient-reported outcomes (PROs) related to quality of life. Using assessments like the PBC-40, 5-D Itch, and PROMIS fatigue questionnaires, the study revealed that 30% of patients had a PBC-40 itch score greater than 7, indicating substantial effects on fatigue, cognition, social activities, sleep, and emotional well-being. Patients who completed the PROMIS fatigue assessment had a median score reflecting severe exhaustion and a need for significant recovery time after activities, suggesting that pruritus in these patients is as detrimental as chronic fatigue [3,4].

Despite its high prevalence and profound impact on quality of life, the underlying mechanisms of cholestatic pruritus remain poorly understood, and effective treatment options are limited. Current knowledge points to various pathways potentially involved in the pathogenesis of pruritus, including bile acids, autotaxin, lysophosphatidic acid, and endogenous opioids, but

a definitive mechanism is yet to be established. Consequently, treatment options are often inadequate. The TARGET-PBC study noted that only 52% of patients with pruritus received treatment for their symptoms, and many reported feeling that their itch was not adequately managed. This gap suggests that pruritus is often underdiagnosed and undertreated in clinical practice, leading to unnecessary suffering and reduced quality of life for affected patients [5].

Figure 1. Natural Alternatives for the Management of Cholestatic Pruritus

Given the limitations of current management strategies, there is a need for more precise diagnostic approaches and effective therapies for cholestatic pruritus. The lack of clear pathophysiological understanding has hindered the development of targeted therapies, leaving many patients to rely on skin-care measures and bile acid-binding resins, which provide inconsistent relief. Research on emerging treatments, such as ileal bile acid transporter (IBAT) inhibitors, is ongoing, but there remains an urgent need for further investigation into safe and effective therapies that can provide comprehensive relief for patients with cholestatic pruritus [6].

2. NATURAL ALTERNATIVES FOR THE MANAGEMENT OF CHOLESTATIC PRURITUS

Plants offer a promising natural approach for managing pruritus, particularly when associated with liver dysfunctions such as cholestatic liver diseases (Figure 1). Their inherent anti-inflammatory, antioxidant, and hepatoprotective properties address the underlying conditions that trigger pruritus. Several plants, including *Gardenia jasminoides*, *Citrus aurantium*, and *Artemisia capillaris*, reduce liver heat and inflammation, promote detoxification, and facilitate the elimination of excess bile acids, which are key contributors to pruritus. *Rehmannia glutinosa* nourish and support blood health, preventing skin dryness and enhancing hydration, while *Lycium barbarum*, rich in antioxidants like beta-carotene, strengthens liver function and immunity to alleviate pruritus systemically. Other plants, such as *Andrographis paniculata*, and *Picrorhiza kurroa*, contain bioactive compounds like saponins and terpenoids that directly relieve skin irritation through their anti-inflammatory effects. *Rheum officinale* and *Glycyrrhiza glabra* contribute to reducing oxidative stress within liver cells, preventing further damage and supporting overall liver health. Additionally, *Solanum nigrum*, *Radix Isatidis*, and *Ziziphus jujuba* improve bile flow and detoxification, mitigating the buildup of toxic compounds that exacerbate itchiness. These plants, rich in glycosides, flavonoids, and polysaccharides, act synergistically to protect liver function and enhance skin health, offering relief from pruritus while minimizing the need for conventional medications. Their natural mechanisms provide a safe, effective option for long-term management, reducing the risk of adverse side effects often associated with synthetic drugs [7-11].

Citrus aurantium

Citrus aurantium L., commonly known as bitter orange, has long been valued in traditional medicine for its diverse therapeutic properties. Its unripe fruit, Zhishi, is included in the Pharmacopoeia of China and has been used to regulate body balance and treat metabolic disorders. Ethnomedicinally, *C. aurantium* is employed to alleviate gastrointestinal issues, inflammation, and liver dysfunction. The peel extract is particularly significant in modern applications for managing conditions such as non-alcoholic fatty liver disease (NAFLD) and hepatotoxicity. Traditional uses emphasize its role in relieving indigestion, bloating, and improving liver health, demonstrating its longstanding importance in holistic medicine systems. The bioactive potential of *C. aurantium* arises from its rich phytochemical profile, including polymethoxyflavones like nobiletin, which constitutes over 27% of its peel extract, along with flavonoids, alkaloids, and essential oils. These compounds exhibit strong antioxidative, anti-inflammatory, and antiallergic properties, making the plant highly effective in addressing liver and metabolic disorders. Advanced metabolomics analyses have identified its ability to regulate liver metabolism and suppress cytochrome P450-mediated activation of toxic compounds, such as acetaminophen [12,13].

Pharmacological studies reveal that *C. aurantium* reduces lipid synthesis markers like peroxisome proliferator-activated receptor γ (PPAR-γ) and sterol regulatory element-binding protein 1c (SREBP-1c), lowers serum triglycerides and cholesterol, and suppresses pro-inflammatory cytokines. It also exhibits significant hepatoprotective activity by enhancing antioxidant defenses, mitigating apoptosis, and improving liver metabolism. The plant's ability to regulate bile acid metabolism and reduce liver heat makes it particularly valuable for managing pruritus associated with liver dysfunction. By addressing inflammation and supporting detoxification, *C. aurantium* offers a holistic approach to improving liver health [14-17].

Gardenia jasminoides

Gardenia jasminoides Ellis, a flowering plant of the Rubiaceae family commonly known as Cape jasmine, is native to East Asia and valued for its medicinal properties. Its fruit, has been a cornerstone of traditional remedies in Korea, China, and Japan, particularly for inflammatory conditions, jaundice, fever, edema, hepatic disorders, hypertension, headaches, and general discomfort. The plant contains a diverse range of bioactive compounds, including iridoids (notably geniposide and genipin), terpenoids, flavonoids, organic acids, and volatile oils, which vary depending on the plant part and processing. Geniposide, a major iridoid glycoside, is a critical marker for quality and contributes significantly to its pharmacological effects. However, potential adverse effects, such as hepatotoxicity and nephrotoxicity, necessitate cautious use. Extracts of *G. jasminoides* exhibit hepatoprotective, anti-inflammatory, antioxidant, antitumor, neuroprotective, anti-diabetic, and choleretic activities. Studies demonstrate its ability to reduce inflammation, oxidative stress, and matrix metalloproteinase expression in various models, underscoring its therapeutic versatility [18,19].

In liver health, *G. jasminoides* shows promise by attenuating liver fibrosis through inhibition of hepatic stellate cell activation and modulation of sonic hedgehog signaling. It also protects against acetaminophen-induced hepatotoxicity and cholestasis by inhibiting TLR4/NF-κB signaling, enhancing antioxidant enzyme activity, and reducing pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha. These findings highlight its potential as a therapeutic agent for liver disorders, though further research is required to elucidate mechanisms and ensure clinical safety [20-22].

Artemisia capillaris

Artemisia capillaris Thunb, commonly known as wormwood or Yin-Chen in Chinese, belongs to the Artemisia genus, which comprises over 500 species within the Anthemideae tribe of the Asteraceae family. This plant has been widely used as a traditional medicinal herb for centuries to address pyrexia, pain, hepatotoxicity, inflammation, cholestasis, and jaundice. Traditional Chinese medicine (TCM) has utilized *A. capillaris* to treat conditions ranging from liver inflammation to severe cirrhosis and hepatocarcinogenesis [23]. Several bioactive constituents, such as p-hydroxyacetophenone, β-sitosterol, scoparone, cirsimaritin, quercetin, capillarisin, and chlorogenic acid, have been identified in *A. capillaris*, demonstrating diverse therapeutic properties, including hepatoprotective, anti-inflammatory, antioxidant, antiviral, and antifibrotic effects. The pharmacological benefits of *A. capillaris* largely depend on the species, plant part, and harvest timing [24]. For example, *A. capillaris* and *A. scoparia* share similar uses in TCM, but the former is richer in chlorogenic acid, while the latter contains higher levels of scoparone. The bioactive compound levels also vary across plant parts and harvest seasons, influencing therapeutic efficacy and potential toxicity. For instance, the scoparone content peaks in *A. capillaris* leaves in July and in the capitulum by early September. This variability underscores the importance of optimizing harvest time to balance efficacy and safety. Despite its established use in treating liver diseases, recent pharmacological investigations suggest that *A. capillaris* may also benefit conditions like metabolic syndrome, psoriasis, and fibrosis. However, challenges such as limited knowledge of pharmacokinetics, potential herb-drug interactions, and the absence of a defined therapeutic window complicate its clinical applications. Recent studies highlight the need for comprehensive pharmacokinetic analyses to guide dosing strategies and broaden the potential uses of *A. capillaris*. This review consolidates existing knowledge of its pharmacological effects and bioactive components, aiming to expand the understanding of its therapeutic potential [25-27].

Rheum officinale

Rheum officinale Baillon, also known as Chinese rhubarb or Dahuang, is an herbaceous perennial in the Polygonaceae family. Its roots, stems, and leaves have been integral to Asian traditional medicine, widely used to address ailments like constipation, jaundice, gastrointestinal bleeding, and ulcers. Beyond its traditional applications, recent studies have spotlighted various *Rheum* species, including *R. emodi*, *R. undulatum*, and *R. palmatum*, for their potential in modern therapeutic contexts due to their antioxidant, anti-inflammatory, antibacterial, anticancer, and anti-allergic properties. In particular, *Rheum officinale* Baillon has gained attention for its diverse pharmacological benefits, which may support food and dietary supplement applications aimed at promoting health and mitigating oxidative stress [28].

The bioactivity of *Rheum officinale* is primarily attributed to hydroxyanthraquinones, including anthraquinone derivatives such as emodin, aloe-emodin, rhein, chrysophanol, and physcion. Emodin, a prominent anthraquinone in *R. officinale*, is well-studied and exhibits anti-inflammatory, immunosuppressive, hepatoprotective, and antitumor activities. These compounds have demonstrated potential in inhibiting enzymes like monoamine oxidase, suggesting applications for neurological health. Other constituents like bianthrone derivatives, catechins, and stilbenes contribute to its broad-spectrum pharmacological effects, making *R. officinale* a valuable source of bioactive compounds [29].

Rheum officinale has shown diverse pharmacological effects, spanning multiple health areas. Traditionally used as a laxative, antiphlogistic, and hemostatic agent, *R. officinale* is applied to treat gastrointestinal disorders, jaundice, and indigestion. It is also a component of many traditional Chinese formulations prescribed to cancer patients. In vitro and in vivo studies indicate its anti-inflammatory and immunosuppressive effects, and it has shown anti-viral and vasorelaxative properties that could benefit cardiovascular health. Emodin, in particular, has been shown to inhibit cancer cell proliferation, enhance TGF-β1 gene expression, and promote cellular repair mechanisms, which are valuable for conditions like pancreatitis. Anthraquinone derivatives in *R. officinale*, such as emodin and rhein, exhibit antioxidant properties that help mitigate oxidative stress—a critical factor in liver damage. By inhibiting lipid oxidation, *R. officinale* protects hepatocytes from damage due to toxic agents. The antioxidant capacity of these compounds not only supports liver health but also aligns with the consumer demand for natural antioxidants in functional foods. Moreover, emodin's hepatoprotective effects extend to reducing inflammation, promoting hepatocellular proliferation, and regulating metabolic enzymes, underscoring its potential in addressing chronic liver conditions [30-34].

Glycyrrhiza glabra

Glycyrrhiza glabra has been an integral part of traditional medicine for thousands of years. Known for its wide array of therapeutic effects, the primary active compound, glycyrrhizin, undergoes hydrolysis in vivo to form glycyrrhetinic acid, which is responsible for much of licorice's pharmacological properties. Historically, licorice has been used to treat a range of conditions, including liver diseases, respiratory issues, gastrointestinal disorders, and inflammatory conditions. Glycyrrhizin, the key sweet-tasting saponin found in licorice, is particularly recognized for its hepatoprotective, anti-inflammatory, and antiviral properties. Glycyrrhizin, a triterpene glycoside, has a variety of pharmacological activities, including anti-inflammatory, anti-viral, antioxidative, and hepatoprotective effects [35-37].

In traditional Chinese medicine, licorice has been used to treat conditions such as hepatitis, chronic bronchitis, gastritis, and tumor growth. Additionally, glycyrrhizin has shown protective effects in conditions like biliary atresia and liver damage caused by viral infections. In the case of hepatitis C virus (HCV) infections, glycyrrhizin inhibits the replication of the virus and has been shown to enhance the efficacy of antiviral drugs like interferon. Its hepatoprotective action is believed to be mediated by its antioxidant properties, which help mitigate oxidative stress, and its ability to regulate proinflammatory mediators and induce heme oxygenase-1[38,39]. Licorice is most commonly used for its hepatoprotective benefits, particularly in preventing liver damage induced by toxic agents such as carbon tetrachloride (CCl_4). Studies have demonstrated that glycyrrhizin protects against hepatic steatosis and oxidative stress caused by viral proteins and iron overload. Furthermore, glycyrrhizin has been shown to have a synergistic effect with omega-3 fatty acids, enhancing the liver's defense against toxins and improving liver function. This combination exhibits potent anti-inflammatory, antioxidant, and anti-fibrotic effects, further supporting the potential of glycyrrhizin in treating liver diseases.

In addition to its liver benefits, glycyrrhizin has been investigated for its anticancer potential. It has been shown to inhibit the growth of liver cancer cells and reduce inflammation in the liver, making it a promising adjunct therapy for liver cancer treatment. The immunomodulatory effects of glycyrrhizin also contribute to its ability to enhance immune responses, potentially improving the body's ability to fight infections and tumors [40-43].

Solanum nigrum

Solanum nigrum, commonly known as black nightshade, is a herbaceous perennial plant in the Solanaceae family, native to Eurasia and introduced to regions like North America and Australia. It has long been used in traditional medicine across various cultures for its wide range of therapeutic properties. The plant is valued for its antioxidant, anti-ulcerogenic, anti-inflammatory, and antitumorigenic characteristics. The primary bioactive compounds in *S. nigrum* include alkaloids such as solamargine and solasonine, which produce solasodine a bioactive compound that holds significant pharmaceutical value [44-45]. The therapeutic potential of this plant has been explored in a variety of contexts, with particular interest in its

protective effects against liver damage and other conditions associated with oxidative stress. *S. nigrum* contains a variety of bioactive compounds, including flavonoids and steroidal glycoalkaloids, which are largely responsible for its medicinal effects. Among the most notable alkaloids are solamargine, solasonine, solasodine, and solanine. These steroidal glycoalkaloids possess several pharmacological properties, including antioxidant, anti-inflammatory, and hepatoprotective activities. Previous studies have identified these compounds as key contributors to the plant's ability to protect against liver damage caused by toxins and oxidative stress. The plant's flavonoid content also plays a role in its antioxidant capacity, further enhancing its protective effects. The pharmacological profile of *S. nigrum* includes a broad range of beneficial effects. The plant has demonstrated significant anti-inflammatory, antioxidant, hepatoprotective, antipyretic, and anticancer properties [46-48]. Its ability to reduce inflammation and combat oxidative stress makes it a valuable therapeutic agent for conditions involving chronic inflammation and free radical damage. Additionally, its antimicrobial and diuretic effects contribute to its use in treating infections and promoting urinary health. The plant's flavonoids and glycoalkaloids work synergistically to provide these pharmacological benefits, with much of the research focusing on their role in preventing and treating liver diseases, including alcohol-induced liver damage and hepatic fibrosis [49-51].

Liver damage, particularly from alcohol abuse, is a widespread issue that can lead to the development of conditions such as alcoholic liver disease, cirrhosis, and hepatocellular carcinoma. Oxidative stress plays a central role in the progression of these diseases by increasing the production of reactive oxygen species and free radicals, which overwhelm the liver's antioxidant defenses. *S. nigrum* has shown promise as a hepatoprotective agent due to its ability to mitigate oxidative stress and reduce liver damage. The steroidal glycoalkaloids, especially solamargine and solasonine, have been shown to protect the liver from damage caused by toxic agents such as carbon tetrachloride (CCl_4) and D-galactosamine (D-GalN), an agent used to induce liver fibrosis in experimental models. The plant's ability to reduce inflammation, protect liver cells from oxidative damage, and support liver function makes it a potential candidate for the prevention and treatment of liver diseases [52,53].

Picrorhiza kurroa

Picrorhiza kurroa Royle ex Benth, commonly known as Kutki, is a small perennial herb belonging to the *Plantaginaceae* family. It has been used for centuries in traditional Ayurvedic medicine, as documented in ancient texts like the *Charaka Samhita*. Its therapeutic applications continue to be valued in contemporary Asian medicine, and in recent years, the herb has gained significant attention from biomedical researchers, particularly for its pharmacological potential. Notably, *P. kurroa* has demonstrated hepatoprotective activity in various experimental and clinical studies, leading to further research into its bioactive compounds and their associated therapeutic effects. Additionally, the herb has been investigated for its potential in treating SARS-CoV-2 through in-silico studies, and its clinical applications, particularly in combination with other herbs for COVID-19, have been explored. However, *P. kurroa* faces the threat of overharvesting due to increased demand, and it has been listed as an endangered species in some regions. To mitigate this, plant tissue culture and genetic engineering techniques are being explored to ensure sustainable production [54].

The primary bioactive compounds in *P. kurroa* are iridoid glycosides, including kutkins, kutkosides, and picrosides, as well as cucurbitacins, triterpenes, and simple phenols like apocynin. These compounds are responsible for the plant's diverse pharmacological activities. The most extensively studied bioactive compounds include picroside II, androsin, and 4-hydroxy-3-methoxyacetophenone, which exhibit hepatoprotective, anti-inflammatory, anti-arthritic, anti-diabetic, and anti-asthmatic properties. These compounds also possess collagen synthesis-promoting, collagenase inhibitory, hyaluronidase inhibitory, anti-fibrotic, antioxidant, immunomodulatory, anti-carcinogenic, antimicrobial, and anti-leishmanial activities, highlighting the plant's therapeutic potential across a range of clinical conditions [55,56].

The pharmacological properties of *P. kurroa* are extensive, including hepatoprotective, anti-inflammatory, anti-arthritic, anti-diabetic, anti-asthmatic, anti-fibrotic, antioxidant, immunomodulatory, and anti-carcinogenic effects. Its hepatoprotective activity is particularly notable, with compounds like picroside II and androsin playing key roles in protecting liver cells from damage induced by toxic agents. Studies have shown that *P. kurroa* can reduce oxidative stress, inflammation, and fibrosis in the liver, making it an effective treatment for liver disorders such as hepatitis and cirrhosis. In addition to its liver-protective effects, *P. kurroa* exhibits strong anti-inflammatory and antioxidant properties, which make it a promising candidate for treating conditions like rheumatoid arthritis and asthma. Its anti-carcinogenic properties have also been explored in cancer research, while its antimicrobial and anti-leishmanial activities add to its value in treating infections [57-60].

P. kurroa has demonstrated substantial hepatoprotective effects, especially in liver injury induced by agents like D-galactosamine and lipopolysaccharide. Key bioactive compounds, including picroside II, androsin, and 4-hydroxy-3-methoxyacetophenone, protect liver cells by reducing inflammation, oxidative stress, and fibrosis. These compounds have been shown to inhibit the cytotoxic effects of TNF-α in liver cells and prevent hepatocyte damage in experimental models. The mechanisms of hepatoprotection involve modulation of inflammatory pathways and enhancement of antioxidant defenses, contributing to the plant's ability to mitigate liver damage and support liver regeneration. Given these effects, *P. kurroa* holds significant potential as a therapeutic agent for liver diseases [61-66].

Andrographis paniculata

Andrographis paniculata, also known as Kalmegh, is a medicinal herb native to Southeast Asia, including regions like India, China, Taiwan, and Sri Lanka. It is widely recognized for its bitter taste, which is linked to its pharmacological properties, including antimicrobial, antiviral, anti-inflammatory, immunostimulatory, anti-cancer, anti-HIV, anti-allergic, and hypoglycemic effects. The therapeutic activities of *A. paniculata* are attributed to bioactive compounds such as lactones and flavonoids. One of its most significant applications is its hepatoprotective effect, especially in liver diseases caused by alcohol, toxins, and drugs. As the liver plays a vital role in metabolism, detoxification, and biosynthesis, it is vulnerable to conditions like hepatitis, cirrhosis, and liver failure [67,68].

The primary active compound, andrographolide, contributes to *A. paniculata* hepatoprotective properties, which makes it a promising herbal remedy for liver dysfunctions. The chemical composition of *A. paniculata* includes diterpenes, lactones, flavonoids, alkenes, ketones, aldehydes, and phytosteroids. Andrographolide, the key bioactive compound, is present in high concentrations in the leaves and is responsible for the plant's bitter taste. Other notable compounds include neoandrographolide, andrographiside, andropanoside, and flavonoids like quercetin, kaempferol, and apigenin. Additionally, phytosteroids such as β-sitosterol and stigmasterol exhibit antioxidant properties. These compounds contribute to the plant's diverse therapeutic effects, including its antioxidant, anti-inflammatory, hepatoprotective, antimicrobial, and anticancer activities. Techniques such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) can help identify and standardize these active compounds. *A. paniculata* has demonstrated significant hepatoprotective effects, particularly against liver damage induced by paracetamol and carbon tetrachloride (CCl4). Studies show that andrographolide reduces liver inflammation, oxidative stress, and fibrosis, while promoting liver regeneration. Furthermore, *A. paniculata* enhances the body's antioxidant defense mechanisms, protecting liver cells from damage. These properties make *A. paniculata* a promising natural treatment for liver diseases, including hepatitis, cirrhosis, and fatty liver disease. This research aims to further evaluate *A. paniculata* hepatoprotective effects and explore the mechanisms behind its protective activity in paracetamol-induced hepatotoxicity in mice [69-73].

Lycium barbarum

Lycium barbarum, commonly known as goji or wolfberry, has been a significant component of traditional Chinese medicine, especially for liver and eye health. Due to its perceived health benefits, goji has recently gained popularity worldwide as a "superfood." Traditionally, it has been consumed in various forms, including infusions and extracts, which are valued for their nutritive and antioxidant properties. Contemporary studies reinforce the therapeutic potential of *L. barbarum* extracts, particularly the polysaccharides, which have shown broad biological activities including antioxidant, anti-aging, immunomodulatory, neuroprotective, and anti-cancer effects [74].

The active compounds in *Lycium barbarum* include a complex of bioactive polysaccharides known as *L. barbarum*, which are major contributors to its antioxidant, anti-inflammatory, and immunomodulatory effects. *L. barbarum* fruit contains flavonoids, zeaxanthin, and zeaxanthin dipalmitate, which have been associated with protective activities against liver toxicity and oxidative damage. Additionally, certain cerebrosides in *L. barbarum* show hepatoprotective effects, particularly in bioactivity-guided studies where these compounds displayed liver cell protection under chemical stress [75,76].

Research over the past decade has highlighted multiple pharmacological actions of *L. barbarum*, as potent antioxidants, *L. barbarum* help elevate antioxidant biomarkers in human serum, thus protecting against oxidative stress-related damage. *L. barbarum* have demonstrated neuroprotective and anti-aging properties, validated through in vitro and in vivo studies. Additionally, in cancer cell models, *L. barbarum* treatment has been shown to inhibit proliferation, induce cell cycle arrest in the S phase, and trigger apoptosis by disrupting calcium balance. The potential of *L. barbarum* in managing metabolic health is also significant, with effects on glucose control and increased endurance, which can help in conditions related to insulin resistance and metabolic syndrome. The liver-protective effects of *L. barbarum* extracts are among the most studied properties. *L. barbarum* have shown efficacy in mitigating alcohol-induced liver injury by reducing lipid accumulation and oxidative stress, key factors in liver toxicity. In various studies, *L. barbarum* were found to protect liver cells from chemical and oxidative stress-related damage, partially due to their free radical scavenging ability. Zeaxanthin dipalmitate, a carotenoid found in *L. barbarum*, has been shown to reduce hepatic fibrosis in experimental models, while certain extracts offer protection against hepatotoxins like CCl4 and galactosamine [77].

The prevalence of non-alcoholic fatty liver disease (NAFLD) has prompted further studies into *L. barbarum* for its potential to mitigate fatty liver progression. NAFLD is increasingly common, linked to obesity and metabolic syndrome, and can progress to nonalcoholic steatohepatitis (NASH), which carries a risk for liver fibrosis and cirrhosis. Although research is ongoing, the hepatoprotective properties of *Lycium barbarum* and its ability to modulate oxidative stress and lipid metabolism hold promise as complementary strategies for managing liver health in chronic conditions like NAFLD and alcohol-related liver disease [78].

Radix Isatidis

Radix Isatidis, (family Brassicaceae), is a traditional Chinese medicinal herb renowned for its therapeutic properties. Commonly known as "Ban-Lan-Gen" in Chinese, it has been utilized for centuries to treat ailments such as influenza, fever,

hepatitis, encephalitis, and colds. Its traditional use also includes cooling the blood and addressing viral infections. Modern pharmacological studies have validated its role in combating infections, modulating the immune system, and reducing inflammation [79, 80].

R. Isatidis contains over 70 bioactive compounds, including alkaloids, lignans, ceramides, flavonoids, and sulfur-containing metabolites. Polysaccharides, a major component, exhibit diverse pharmacological activities, particularly antiviral and immunomodulatory effects. Syringic acid, isolated from the root, has shown potent anti-inflammatory properties by inhibiting endotoxin shock induced by lipopolysaccharides (LPS). Methanolic extracts of *Radix Isatidis* significantly suppress the release of inflammatory mediators such as nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokines from macrophages, contributing to its anti-inflammatory and immune-modulating effects [81].

Radix Isatidis exhibits broad-spectrum antimicrobial activity, effectively suppressing the growth of pathogens like Escherichia coli and Helicobacter pylori. It also enhances the phagocytic activity of neutrophils against Staphylococcus aureus. Clinically, *Radix Isatidis* has demonstrated efficacy against various subtypes and strains of influenza viruses, including Severe Acute Respiratory Syndrome (SARS). Additionally, polysaccharides isolated from *Radix Isatidis* display antiviral effects, particularly against type II herpes simplex virus (HSV-2) and influenza A virus (IAV). Recent studies indicate that these polysaccharides can function as adjuvants, boosting both humoral and cell-mediated immune responses when used alongside vaccines like H1N1 influenza and hepatitis B surface antigen [82].

Radix Isatidis has gained attention for its hepatoprotective effects, particularly in viral hepatitis and liver-related conditions. Polysaccharides extracted from the root inhibit oxidative stress, reduce inflammation, and provide antiviral defense. Studies in vitro have shown these polysaccharides to possess potential anti-hepatitis B virus (HBV) activity, demonstrating inhibitory effects on viral replication in the HepG2.2.15 cell line. By modulating immune responses and protecting hepatocytes, *R. Isatidis* offers a promising avenue for the development of novel therapeutic agents for liver diseases [83,84].

Jujubae Fructus

Jujube commonly known as *Jujubae Fructus*, is the fruit of *Ziziphus jujuba*, a species in the Rhamnaceae family. With a history of over 4,000 years of cultivation, particularly in Asia, Europe, and Australia, jujube is highly regarded as both a food and medicinal plant. In traditional practices, *J. fructus* is valued for its ability to strengthen the stomach, tonify the spleen, nourish the blood, and provide overall vitality. The fruit is recognized for its sweet taste and warm nature, aligning with its therapeutic effects on the spleen, stomach, and heart meridians. Modern scientific research supports many of its traditional uses, revealing a broad range of health benefits. *J. fructus* contains a variety of bioactive compounds, many of which contribute to its medicinal properties. Over 278 compounds have been identified, including triterpenoid acids, saponins, cyclopeptide alkaloids, flavonoids, and neo-lignans. Among the key bioactive constituents are cyclic AMP, phenolic compounds, flavonoids, triterpenic acids, and polysaccharides. These components are responsible for the fruit's diverse pharmacological activities. Triterpenoid acids and flavonoids are primarily linked to anti-inflammatory, antioxidant, and anticancer effects, while polysaccharides play a significant role in regulating metabolic processes like insulin resistance and lipid metabolism. Scientific studies have confirmed the broad pharmacological effects of *J. Fructus*. In vivo and in vitro research demonstrate its potential as an anti-inflammatory, antioxidant, antimicrobial, gastrointestinal protective, cardiovascular, neuroprotective, sedative-hypnotic, and anxiolytic agent. Jujube's anti-inflammatory effects are particularly notable, with the fruit exhibiting the ability to reduce inflammation in various disease models. It has also shown antimicrobial activity, inhibiting pathogens such as *Staphylococcus aureus*, *Escherichia coli*, and *Helicobacter pylori*. Moreover, the fruit's neuroprotective effects make it useful in managing conditions like insomnia and anxiety. Studies have found that compounds in jujube, including saponins and flavonoids, contribute to its sedative-hypnotic effects, helping to calm the nervous system [85-88].

J. fructus has demonstrated significant liver-protective properties, particularly against damage induced by harmful substances such as CCl_4 (carbon tetrachloride). Research indicates that jujube helps protect the liver by neutralizing free radicals, thereby reducing oxidative stress, which is a key factor in liver injury. Polysaccharides and triterpenic acids found in the fruit are thought to play a crucial role in these protective effects. Additionally, *J. fructus* has been shown to modulate inflammatory responses, further supporting its ability to safeguard liver health. By reducing liver inflammation and oxidative damage, jujube not only helps maintain liver function but also supports the regeneration of liver cells [88]. Jujube's therapeutic effects on the liver, along with its anti-inflammatory, antioxidant, and metabolic benefits, make it a valuable plant in both traditional and modern medicine, especially for conditions related to liver damage and metabolic disorders [89].

Rehmannia glutinosa

Rehmannia glutinosa Libosch, commonly known as Chinese foxglove, is a traditional herbal medicine from the Scrophulariaceae family with over 2,000 years of documented use in Eastern Asia. Highly regarded in traditional Oriental medicine, *R. glutinosa* roots are processed in three forms for medicinal use: fresh root (Saeng-Ji-Whang), dried root (Gun-Ji-Whang), and steamed root (Sook-Ji-Whang). Each form has unique therapeutic applications; dried and steamed roots, in particular, are utilized to modulate immune responses and serve as haemostatic, cardiotonic, and diuretic agents. Recent

studies confirm its antibacterial and anti-inflammatory activities, reinforcing its standing as a valuable component of traditional medicine [90].

The bioactive compounds in *R. glutinosa* include a range of constituents isolated from both the root (*Rehmanniae Radix*) and the fresh plant. The primary compounds are β-sitosterol and mannitol, alongside smaller quantities of stigmasterol, campesterol, catalpol, rehmannin, and vitamin A. Notably, catalpol, a major iridoid found in *R. glutinosa*, is recognized for its diverse biological functions, including anti-inflammatory, liver-protective, blood sugar-reducing, and neuroprotective properties. In addition to iridoids, *R. glutinosa* also contains saccharides, amino acids, inorganic ions, and trace elements, which contribute to its broad medicinal applications. *R. glutinosa* exerts various pharmacological effects on multiple bodily systems, including the blood, immune, endocrine, cardiovascular, and nervous systems. Studies have shown that *R. glutinosa* extracts can inhibit the release of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) from mouse astrocytes, two cytokines crucial in bone metabolism regulation and bone resorption processes. This cytokine modulation suggests that *R. glutinosa* may play a beneficial role in bone health, particularly in the context of osteoporosis prevention. Beyond bone health, its therapeutic effects extend to immunomodulation, antioxidant, anti-tumor, anti-aging, and endocrine-regulating properties, highlighting its versatility as a medicinal herb [91,92].

R. glutinosa has shown significant potential in protecting liver health, attributed mainly to its anti-inflammatory and antioxidant properties. Catalpol, a key iridoid constituent, is known to offer substantial liver protection by reducing inflammation and oxidative stress, which are critical in preventing liver cell damage. This herb also assists in regulating metabolic pathways associated with liver function, including lipid and carbohydrate metabolism, further enhancing its liver-protective capacity. By mitigating liver inflammation and supporting detoxification, *R. glutinosa* promotes liver regeneration and resilience, underscoring its therapeutic value for liver-related disorders. *R. glutinosa* is a comprehensive and potent herbal medicine whose applications span from immune support to liver health, cardiovascular protection, and more [93,95].

3. CONCLUSION

Cholestatic pruritus remains a challenging condition with limited effective treatments, underscoring the need for alternative therapeutic options. Medicinal plants such as *Gardenia jasminoides*, *Citrus aurantium*, *Artemisia capillaris*, and others offer promising potential due to their anti-inflammatory, hepatoprotective, and pruritus-relieving properties. The bioactive compounds within these plants, including flavonoids, saponins, and alkaloids, demonstrate the ability to modulate bile acid metabolism, reduce oxidative stress, and alleviate inflammation. Preclinical and clinical studies provide encouraging evidence of their efficacy in improving pruritus and liver function with fewer side effects than conventional therapies. However, further research is crucial to elucidate their mechanisms of action, optimize dosing strategies, and establish standardized treatment protocols. By integrating these natural remedies into therapeutic approaches, safer and more effective treatments for cholestatic pruritus may be developed, ultimately enhancing patient quality of life.

CONFLICTS OF INTEREST

The authors report no financial of interest in this work.

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