



Therapeutic Potentials of Herbal Extracts in Autoimmune Diseases A Systematic Literature Review

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Abstract

There has been a noticeable increase in the occurrence of autoimmune diseases over the years, and this trend cannot be solved due to the failure of finding new treatment strategies. Despite the availability of established protocols for managing autoimmune infections, the protocols of oncology, metabolic diseases, and transplantation are often employed as paradigms for handling autoimmune diseases (AD). Glucocorticoids, widely prescribed drugs for autoimmune conditions, exhibit rapid and extensive effects on immune cells. Nevertheless, the long-term use of glucocorticoids has been associated with specific toxicities. Therefore, this review emphasizes the exploration of natural anti-inflammatory steroid alternatives that draw upon the traditional utilization of medicinal plants and herbal products. Consequently, investigating medicinal plants as a valuable source of potent anti-inflammatory agents holds significant importance and warrants further exploration in novel drug design.

Keywords:

Autoimmune diseases, Herbal extracts, Medicinal plants, Natural active compounds, Natural anti-inflammatory sources

INTRODUCTION

Extensive research and observations have highlighted significant distinctions in Autoimmune diseases (AD), such as their diverse manifestations, unique causative factors, distinct pathogenic processes, and dynamic nature. These factors collectively contribute to the existing limitations of treatment strategies, resulting in the inability to achieve the anticipated complete remission in AD cases.

Autoimmune diseases exhibit diversity in their presentation and origin. The precise mechanism underlying this self-intolerance remains incompletely understood. Therefore, the exploration of autoimmune mechanisms and the development of innovative treatment strategies remain active areas of research (Ngo et al., 2014).

Currently, more than 80 identified autoimmune disorders can be categorized as either organ-specific, such as type 1 diabetes affecting the pancreas, or systemic, like systemic lupus erythematosus impacting the skin, joints, kidneys, and CNS. Autoimmunity is commonly associated with a breakdown in B cell or T cell tolerance, and there is often a genetic link between the human leukocyte antigen (HLA) locus and increased susceptibility to autoimmune diseases. Therefore, a key challenge in treating autoimmune disorders lies in the development of targeted and personalized therapeutic approaches. New research in treatment options can highlight the necessity for personalized medications that minimize side effects along with the adoption of patient-centric treatment strategies which improve prognosis (Fugger et al., 2020).

Autoimmune disorders are commonly treated with strong conventional medications such as steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs). However, the continuous use of these medications poses significant risks and can lead to serious side effects. As a result, there is a pressing need for alternative treatments that are equally effective but less expensive. Herbal extracts have emerged as a potential option over steroid drugs, as they have shown promise in modulating the immune system and reducing inflammation, which are key factors in autoimmune diseases. Natural compounds found in herbs like turmeric, *Boswellia serrata*, and green tea possess anti-inflammatory properties and can influence immune cell activity,

potentially restoring immune balance. Although further research is required to fully understand their mechanisms of action, determine optimal dosages, and ensure long-term safety, these herbal extracts offer alternative or complementary approaches to conventional treatments for autoimmune illnesses (M.C. Recio et al., 2012; Verma et al., 2022).

Phytochemical compounds can modulate immune cell function by interacting with inflammation-related pathways. Phytochemicals like curcumin, artemisinin, and astaxanthin have shown diverse effects on immune-associated inflammation. Consuming these natural substances provides precision nutritional support and offers a potentially safer alternative to drugs targeting immune cell signaling pathways (Bland, 2021).

Traditional medicines are an essential part of alternative healthcare systems, and India, in particular, possesses a vast wealth of traditional medicines. With its rich heritage and knowledge in this field, India has the potential to rise to the challenge of meeting the global demand for traditional medicines. The global acceptance and reinforcement of traditional medicine would greatly benefit from evidence-based validation of ethnopharmacological claims. The identification of conserved biomarkers across species offers an innovative pathway for drug discovery and development. India's extensive traditional medicine resources position it well to contribute to meeting the global demand for traditional medicines (Mukherjee et al., 2017).

This review aims to evaluate the potential of medicinal plants and herbal extracts as natural alternatives to steroids for the treatment of autoimmune diseases. It seeks to address the limitations of current treatment strategies and explore the use of herbal sources as potent anti-inflammatory agents. The focus is on personalized treatment approaches that minimize side effects and provide alternative or complementary options to conventional medications for improved management of autoimmune diseases.

Study design

For the present review, a systemic literature search was undertaken across online databases such as PubMed, MEDLINE, Google Scholar, and ScienceDirect using the relevant keyword: "Autoimmune diseases", "Herbal alternatives", "Natural remedies", "Drug mechanisms" and, Drug design. Journals were reviewed and relevant articles were selected with high precision.

Cyclooxygenase (Cox) and auto-immune mechanisms

To develop target treatments for immune system disorders, such as autoimmune diseases, it is crucial to understand the COX-mediated immunological mechanism. Modifying COX activity and prostaglandin synthesis can be able to control immunological reactions and inflammation, opening up possibilities for the development of new medicinal therapies. COX enzymes catalyze the conversion of arachidonic acid into prostaglandins, which are bioactive lipid molecules involved in various physiological processes, including immune regulation. Two isoforms of the enzyme, COX-1, and COX-2, are largely involved in COX-mediated immunological responses. COX-2 is absent under normal circumstances and is an inducible isoform that is quickly synthesized in response to inflammatory stimuli, cytokines, and growth hormones. Pro-inflammatory prostaglandins, such as PGE₂ (prostaglandin E₂), are synthesized through the action of COX-2 and play a crucial role in promoting inflammation by increasing vascular permeability, enhancing immune cell migration, and inducing pain and fever. These prostaglandins can amplify the immune response and facilitate the recruitment of immune cells to the site of inflammation (Korbecki et al., 2014).

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and ibuprofen, are commonly used medications that target COX enzymes to alleviate pain and inflammation. Traditional NSAIDs inhibit both COX-1 and COX-2 enzymes, leading to the reduction of both pro-inflammatory and anti-inflammatory prostaglandin production but they carry potential risks and side effects. Some of the complications associated with NSAIDs include Gastrointestinal irritation, ulcers, bleeding, perforations, increased risk of cardiovascular events, such as heart attack and stroke, kidney damage, and impaired kidney function Extensive research has revealed numerous medicinal plants that possess active compounds with therapeutic properties which can be implemented in the treatment of autoimmune diseases like Rheumatoid arthritis(RA). These antiarthritic plants contain a diverse range of chemical constituents, including phenols, coumarins, essential oils, monoterpenes, catechins, quinones, carotenoids, flavonoids, alkaloids, anthocyanins, and xanthines (Davis & Robson, 2016).

Phytochemicals: Promising Therapeutic Potential and Evidence-Based Validation

Autoimmune diseases are a group of complex disorders characterized by an abnormal immune response, where the body's immune system mistakenly attacks its healthy cells and tissues. In recent years, there has been growing interest in exploring herbal alternatives as complementary or alternative therapies for autoimmune diseases.

There is a growing need for evidence-based validation of ethnopharmacological claims regarding traditional medicine (TM) in order to strengthen and globalize its usage. One innovative approach to achieve this is by identifying biomarkers that are highly conserved across different species. This approach can provide a foundation for biomarker-driven drug discovery and development.

Traditional systems that use natural plant products, including traditional Chinese medicine and Indian Ayurvedic medicine, provide a wide and potential resource in this area. Drugs that are made from plants are an important and potential source for the creation of entirely novel therapies for rheumatoid arthritis (RA) and other inflammatory diseases. Practitioners of traditional medicine frequently favor the use of herbal extracts, either alone or looking for purified herbal components that have superior bioactivity than the original herbal extract when it comes to the drug discovery process. Purified components are prioritized to mimic and improve the bioactivity seen in the source herbal extract (Bland 2021).

Huo-Luo-Xiao-Ling Dan – is a traditional Chinese medicine commonly used for inflammatory disorders. An experimental study was conducted by Hongmei *et al.*, (2010). Huo-Luo-Xiao-Ling Dan, gives us valuable insights into their potential pharmacological activities. COX-1 selective inhibitors, such as acetyl-11-keto- β -boswellic acid, acetyl- α -boswellic acid, acetyl- β -boswellic acid, betulinic acid, and COX-2 selective inhibitors like senkyunolide O and cryptotanshinone, show promising specificity for targeting specific COX isoforms. Furthermore, compounds like roburic acid and phenethyl-trans-ferulate exhibit non-selective inhibition of both COX-1 and COX-2. The discovery of these natural product ligands and their inhibitory effects on COX enzymes provide a foundation for further research and the potential development of novel therapeutic agents for inflammatory conditions and related diseases (cao *et al.*,2010).

In a study conducted on autoimmune encephalomyelitis induced in mice models, ginseng and its compounds such as ginsenosides and polysaccharides have shown promising preventive and therapeutic effects. The immune regulatory activity of red ginseng extract on immune-related myelin degeneration and its prognosis suggest the therapeutic potential of herbal extract in Autoimmune treatment. Several studies are going on to improvise the results and augment the efficiency of these natural derivatives (Lee *et al.*,2016).

In a study conducted by Venkadesha *et al.*, (2016) therapeutic effects of three herbal extracts, namely Huoluo-xiao-ling dan (HLXL), Celastrus, and Green tea, as well as a purified compound called Celestrol, which is derived from Celastrus were analyzed. These herbal products were evaluated using a rat adjuvant-induced arthritis (AA) model mimicking rheumatoid arthritis (RA). In addition, they examined the impact of these herbal interventions on various immunological, biochemical, and molecular parameters associated with the disease process in RA (Venkadesha *et al.*,2016)

The "thunder god" vine, scientifically known as *Tripterygium wilfordii* Hook F (TWHf), is a plant, native to southern China and has been traditionally used to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. TWHf, belonging to the Celastraceae family, exhibits inhibitory effects on mitogen-stimulated lymphoproliferation. Furthermore, its active derivatives have shown the ability to inhibit the production of proinflammatory cytokines by monocytes and lymphocytes. Additionally, TWHf has been found to suppress the production of PGE2 through the cyclooxygenase pathway. These properties make TWHf a promising natural remedy for managing autoimmune diseases (Coo *et al.*,2016).

Traditional herbal remedies (Indian Ayurvedic, or Chinese) and their formulations are well-known for having the best prognosis and the fewest negative effects. 80% of people worldwide actively use polyherbal formulations of some kind for health, according to the WHO (WHO 2016, Global Report on Psoriasis).

According to a study conducted by Sivapalan *et al.*, (2020) under the title-“Phytochemical analysis, anti-inflammatory, antioxidant activity” demonstrates the anti-inflammatory and antioxidant properties of *Calotropis gigantea* extracts, it highlights the potential of herbal alternatives as a potent drug. The findings of this investigation indicate that the *C. gigantea* aqueous, methanol and petroleum ether extracts exhibited anti-inflammatory and antioxidant properties in a dose-dependent manner. This study highlights the potential of herbal alternatives as a valuable therapeutic option (Sivapalan *et al.*,2020).

Potency and bioavailability of Herbal extracts

Herbal extracted molecules face challenges of low bioavailability upon oral administration, primarily due to poor permeation across the gastrointestinal (GI) epithelia. Herbal extracts are often complex mixtures of various compounds, including active ingredients, several strategies can be employed to address this issue: Standardization of extracts, Formulation optimization, Phytochemical modification, Co-administration of absorption enhancers, Encapsulation in liposomes or nanoparticles, Combination with other bio-enhancers like permeation inducers (Breedveld *et al.*,2006).

It has been difficult to develop herbal remedies for autoimmune diseases because of issues with efficacy, toxicity, poor water solubility, and low bioavailability due to elevated systemic clearance. Utilizing different innovative colloidal carriers, including NLCs (nanostructured lipid carriers), SLNs (solid lipid nanoparticles), liposomes, niosomes, and transferosomes, has emerged as a promising strategy to solve these difficulties. These colloidal carriers provide possible answers for the efficient and secure delivery of medications used to treat autoimmune diseases that are made from plant extracts (Aslam *et al.*,2016).

According to a study conducted by Maheshwari *et al.*,(2023) on psoriasis, several phytochemical compounds with promising therapeutic potential were extracted. The lifelong repercussions of psoriasis, a chronic autoimmune inflammatory skin disease, include the emergence of comorbid ailments such as psoriatic arthropathy, psychiatric disorders, cardiovascular problems, and hepatic abnormalities.

The World Health Organisation recognized psoriasis as a serious non-communicable disease in 2014, highlighting the suffering brought on by misdiagnosis, inadequate therapy, and the related societal stigma. Systemic medications, which include methotrexate, acitretin, and cyclosporine in combination with phototherapy, are frequently used to treat patients with severe psoriasis.

Herbal products are widely used by patients in place of novel drug delivery systems for traditional medicines since they are generally considered to be safer and have advantages over other traditional therapies in terms of accessibility, affordability, patient compliance, and side effect minimization. Additionally, natural compounds have a wide range of molecular structures and multiple mechanisms of action for treating disease. Therefore, as an alternative to synthetic medications for the treatment of inflammatory autoimmune disorders, researchers display interest in new herbal alternatives.

The review article of Musumeci *et al.*,(2023) highlights the heterogeneity of some clinical studies examining the effects of Citrus flavonoids in managing autoimmune diseases. While some studies indicate potential benefits, others caution against their use. Thus, the current evidence is inconclusive, and further large-scale clinical studies are warranted to elucidate the precise role of Citrus flavonoids in the management of autoimmune diseases. Future research should focus on standardizing study protocols, assessing long-term safety and efficacy, and exploring potential interactions with conventional medications. Clarifying the therapeutic potential of Citrus flavonoids could offer new insights into the development of natural remedies for autoimmune diseases (Musumeci *et al.*, 2023).

Ayurvedic medicine is highlighted as a holistic approach to treating RA, focusing on balancing the body, mind, and consciousness. There are various herbs with anti-RA properties, including their secondary metabolites such as phenolic chemicals, tannins, flavonoids, and alkaloids. These herbal remedies show promise in reducing RA symptoms and preventing the condition (Patel *et al.*, 2023).

Chronic urticaria is characterized by the prolonged presence of wheals, angioedema, or both, resulting from mast cell activation and degranulation. Antihistamines are the standard pharmacological intervention, but long-term users often seek alternatives. Phytomedicine utilizes whole plants, plant components, or extracted active compounds to develop formulations for various disorders. Numerous herbs commonly found in herbal formulations exhibit anti-inflammatory and anti-allergic properties, as well as antioxidant effects. Exogenous antioxidants have shown the potential in ameliorating autoimmune disorders (Gammeri *et al.*, 2023).

The ginger extract could be a promising therapeutic approach to inhibit adhesion formation and may have potential as an anti-inflammatory and antifibrosis herbal medicine in clinical trials. The study highlights the importance of phytochemicals, such as the active component gingerol found in ginger, in providing potential therapeutic benefits for treating adhesive diseases and underscores the need for further clinical studies to confirm its effectiveness (Yahyazadeh 2023).

Scientific name	Family name	Common name	Active constituent
Aloe barbadensis miller (Surjushe <i>et al.</i> ,2008)	Liliaceae	Aloe vera	Lignin
Azadiracta indica (Alzohairy, 2016)	Meliaceae	Neem	Azadirachtin
Curcuma longa (Jukic, <i>et al.</i> , 2007).	Zingiberaceae	Turmeric	Curcumin
Nigella sativa Linn (Palaniswamy <i>et al.</i> , 2012)	Ranunculaceae	Black Cumin	Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol.

Common herbs and their anti-inflammatory compounds - table1.0

Summary

In conclusion, this review highlights the significant potential of herbal extracts in the management of autoimmune diseases. The immunomodulatory properties of these natural remedies, coupled with their anti-inflammatory effects, make them valuable as complementary or alternative treatments. Unlike traditional nonsteroidal anti-inflammatory drugs, herbal extracts offer the advantage of fewer adverse effects, enhancing their safety profile. The diverse array of bioactive compounds present in herbal extracts, such as phenols, flavonoids, and alkaloids, contribute to their therapeutic properties. Promising herbal products like Huo-Luo-Xiao-Ling Dan and Tripterygium wilfordii Hook F have shown inhibitory effects on cyclooxygenase enzymes and the potential to mitigate autoimmune responses. However, further research, including well-designed clinical trials, is necessary to establish their safety, efficacy, and optimal usage in autoimmune disease management. Overall, the findings of this review suggest that herbal extracts hold great promise as valuable additions to the therapeutic armamentarium for autoimmune diseases, offering immunomodulatory effects and symptom relief.

Abbreviation

AD - Autoimmune diseases

AA - Adjuvant-induced arthritis

COX - Cyclooxygenase

ROS - Reactive oxygen species

NSAIDs - Nonsteroidal anti-inflammatory drugs

GI - Gastrointestinal

RA - Rheumatoid arthritis

WHO - World Health Organization

CNS - Central nervous system

NLCs - Nanostructured lipid carriers

HLA - Human leukocyte antigen

SLNs - Solid lipid nanoparticles

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Conflict of interest

There is no conflict of interest.

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