



Integrative Management of Sjögren's Syndrome: Bridging Conventional Therapy and Medicinal Plants

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Abstract

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder primarily affecting the exocrine glands, leading to hallmark symptoms of xerostomia and xerophthalmia. The disease predominantly affects middle-aged women and may present with significant extraglandular manifestations, including musculoskeletal, pulmonary, renal, and neurological involvement, along with an increased risk of B-cell lymphoma. Its multifactorial pathogenesis involves genetic predisposition, environmental triggers, hormonal factors, and dysregulation of innate and adaptive immune responses, particularly B-cell hyperactivity, interferon signaling, and NF-κB-mediated inflammation. Current diagnostic approaches rely on clinical features, autoantibody detection, and histopathological evaluation, though delays in diagnosis remain common due to disease heterogeneity. Conventional management strategies are largely symptomatic, focusing on relief of sicca symptoms through topical agents and secretagogues, while immunosuppressive and biologic therapies are reserved for severe systemic involvement. However, these treatments show limited efficacy and may not adequately address disease progression or extraglandular complications. Growing interest in complementary and alternative medicine has highlighted the potential role of medicinal plants with immunomodulatory and anti-inflammatory properties. Traditional systems such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine employ herbs including ashwagandha, guduchi, liquorice root, rehmannia, astragalus, and slippery elm for symptom relief and immune regulation in SS. Emerging preclinical and limited clinical evidence suggests that these medicinal plants may improve glandular function, reduce inflammation,

and enhance patient quality of life. Integrating herbal therapies with conventional treatment may offer synergistic benefits, though concerns regarding safety, standardization, and herb-drug interactions persist. Further well-designed clinical trials and mechanistic studies are essential to validate the efficacy and safety of integrative therapeutic approaches for Sjögren's syndrome.

Key words: Sjögren's syndrome, Autoimmune disease, Medicinal plants, Immunomodulation, Complementary and alternative medicine, Integrative therapy.

I. INTRODUCTION:

The chronic autoimmune condition known as Sjögren's Syndrome (SS) mostly affects the exocrine glands and causes symptoms like xerostomia (dry mouth) and xerophthalmia (dry eyes) as a result of lymphocytic infiltration [1]. Mostly affecting middle-aged women, it can impair several organ systems [2]. Early stages of the disease exhibit signs of innate immunological hyperactivity, such as toll-like receptor activation, inflammatory cytokine release, and apoptosis [3]. Glands malfunction as a result of lymphocytic infiltration of the lacrimal and salivary glands [4]. In addition to being linked to the development of SS, the transcription factor NF-κB is essential for coordinating inflammatory responses [5]. Although there is no known cure for Sjögren's syndrome, there are therapies that can lessen its most prevalent symptoms, which include dry eyes, dry mouth, and damage to other mucous membranes. [6]. It is divided into two categories: primary SS, which develops on its own, and secondary SS, which is linked to additional autoimmune disorders [7]. Xerostomia and keratoconjunctivitis are the two main symptoms of the primary kind of SS. sicca,

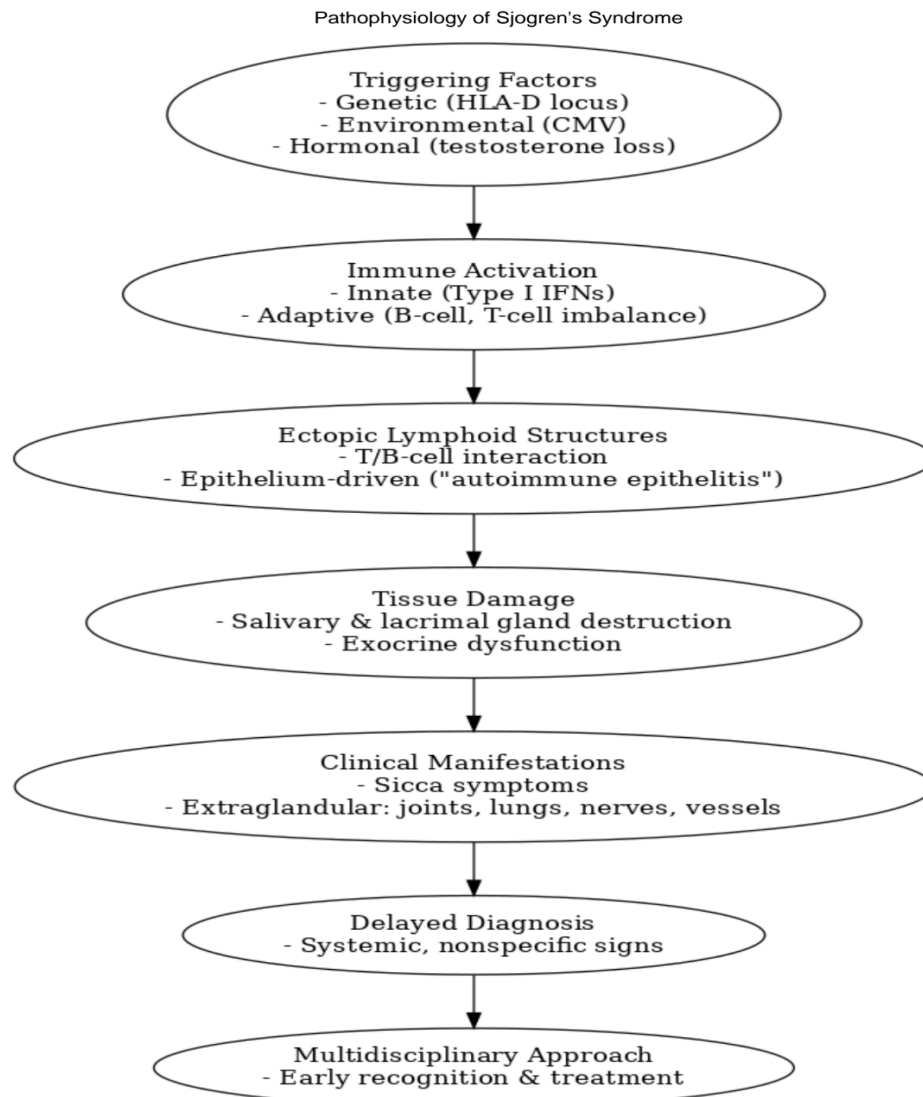


which could also include symptoms such joint discomfort, exhaustion, and involvement of the kidneys and lungs [8]. Systemic lupus erythematosus and rheumatoid arthritis are two autoimmune disorders that are primarily linked to secondary type SS. Symptoms resemble those of primary SS, but the primary disease may obscure or lessen them [9]. About 30–40% of patients have extraglandular sequelae, such as arthritis and a higher risk of B-cell lymphoma. [10] Histological analysis of the salivary gland and the detection of autoantibodies are usually required for diagnosis [11]. Environmental factors, genetic predisposition, and dysregulation of innate and adaptive immunity are all part of its pathogenesis [12]. Estimates of the prevalence of Sjögren's syndrome (SS) differ significantly between populations and studies. The prevalence was 0.065% in Madrid, Spain [13]. In older age groups and females, the prevalence is continuously higher [14]. With prevalences of 7% and 9%, respectively, primary SS seems to be less prevalent than secondary SS [15]. With female-to-male ratios ranging from 9.15 to 10.72, SS primarily affects women [16]. According to reports, there are 6.92 cases of primary SS for every 100,000 person-years [17].

The majority of current treatments are symptomatic and have little effectiveness, especially when it comes to extraglandular symptoms. Clinical trials have typically failed because the great majority of patients who were included experienced pain, dryness, and weariness that did not significantly improve with the study medicine, even though they did not exhibit any extraglandular symptoms at the time of enrolment [18]. Herbal and plant-based therapies are becoming more popular as supplemental treatments for autoimmune diseases like Sjögren's syndrome [19]. Complementary and alternative medicine (CAM) is becoming more popular as a treatment for Sjögren's syndrome, according to recent studies. [20]. New biological agents, immunomodulatory/immunosuppressive drugs, and symptomatic treatments are among the current and potential drug-based therapies for Sjögren's syndrome. [21]. Managing Sjögren's Syndrome with the use of medicinal plants is the goal of this study. It examines scientific data as well as conventional wisdom.

II. PATHOPHYSIOLOGY:

- ❖ Both innate and adaptive immune responses are involved in the complicated autoimmune disease known as Sjögren's syndrome (SS). The pathophysiology of SS has been linked to abnormal B-cell and interferon responses, according to recent research [22]. One important characteristic is the development of ectopic lymphoid structures in the salivary glands, which involves imbalances between T-helper and T-regulatory cells as well as T/B-cell interactions [23]. The significance of type I interferon and B-cell pathways has been validated by genetic research [24]. The development of SS is facilitated by the activation of the innate immune system, namely the overexpression of genes regulated by interferon. Exocrine gland dysfunction may also be caused by non-immune causes, such as testosterone deprivation and malfunctioning autonomic nerve systems [25].
- ❖ The illness is characterised by exocrine gland lymphocytic infiltration, which impairs secretory function [26]. Although sicca symptoms are the feature of Sjögren's syndrome, the condition can also appear as neurological, musculoskeletal, vascular, and gastrointestinal problems [27]. The diagnosis of the disease is frequently delayed by extraglandular symptoms including interstitial pulmonary disease, Raynaud's phenomenon, or non-erosive polyarticular arthritis [28]. Primary care doctors and specialists must work together to prevent life-threatening consequences by early diagnosis [29]. A combination of environmental, genetic, and hormonal variables contribute to the multifactorial aetiology of SS [30].
- ❖ There are correlations between SS and particular HLA alleles, especially in the HLA-D locus, suggesting that genetic predisposition plays a major role [31]. SS is known as "autoimmune epithelitis" since it is thought that the epithelium controls the immune response [32]. Some scientists suggest that SS symptoms could result from tissue damage in the salivary and lacrimal glands caused by a prolonged CMV infection [33].



ROLE OF MEDICINAL PLANTS (complementary /Alternate medicine):

- In India, medicinal plants are used extensively to treat autoimmune diseases, such as Sjögren's syndrome. Many plants with immunomodulatory qualities, including ashwagandha, amalaki, guduchi, turmeric, liquorice root, and aloe vera, are used to treat autoimmune illnesses according to Ayurvedic principles [34].
- Ayurvedic principles such as vatadhikyavatrakta and udakvahasrotodushti are used to explain Sjögren's syndrome [35].
- The effectiveness of Chinese herbal medicines (CHM) in treating SS symptoms has been the subject of numerous investigations. CHM has been frequently given, especially those that moisten dryness and tonify yin, such as *Liriope platyphylla* and *Rehmaniaglutinosa* [36].
- According to meta-analyses, CHM can enhance salivary gland function and lower inflammatory indicators more successfully than Western medicine alone, either by itself or in conjunction with it [37].



FROM INDIA (AYURVEDA / SIDDHA / UNANI):



ASHWAGANDHA:

- A perennial shrub in the Solanaceae family, *Withania somnifera* is sometimes referred to as Indian ginseng or ashwagandha [38]. Traditional medical systems like Ayurveda and Unani have been using it for more than 3,000 years [39]. Numerous bioactive substances, including as withanolides, alkaloids, and glycosides, are found in the plant's roots and leaves [40].
- According to reports, it contains antioxidant, anti-inflammatory, anti-stress, and anticancer qualities [41]. It is particularly useful in the treatment of autoimmune diseases such as Sjögren's syndrome, which is typified by dry mouth and eyes brought on by malfunctioning exocrine glands [42]. The herb's immunostimulatory actions promote general health, while its adaptogenic qualities aid in the fight against stress and inflammation [43].

GUDUCHI:



- Guduchi, or *Tinospora cordifolia*, is a perennial climber shrub that is frequently utilised in Ayurvedic medicine [44]. Alkaloids, diterpenoid lactones, glycosides, steroids, and polysaccharides are among its many chemical components [45]. Guduchi
- has many therapeutic benefits, including hepatoprotective, anti-inflammatory, anti-arthritis, antioxidant, and immunomodulatory activities [46].
- By inhibiting Ama, which is linked to free radicals in the body, guduchi



functions as an immunomodulator and has been demonstrated to be successful in treating autoimmune diseases [47]. In Ayurvedic medicine, it is a

beneficial Rasayana due to its revitalising and adaptogenic qualities [48].

LICORICE ROOT:



- Since ancient times, licorice root, which comes from the *Glycyrrhiza* species, has been used medicinally [49]. With different metabolite profiles, *G. glabra*, *G. uralensis*, and *G. inflata* are the primary commercial species [50].
- Because of their close evolutionary relationship, the roots and rhizomes of five different species of *Glycyrrhiza* (*G. glabra*, *G. uralensis*, *G. echinata*, *G. inflata*, and *G. lepidota*) exhibit similarities under the microscope, but they differ in traits such as cork thickness, medullary ray size, and vascular properties [51].
- The main ingredient in licorice root, glycyrrhizin, has been shown to alter ACE2 and HMGB1 levels in healthy people, which may have uses in respiratory conditions like COVID-19 [52].

- The oral cavity's local glucocorticoid system has been linked to autoimmune and inflammatory diseases; licorice derivatives such as glycyrrhetic acid raise local cortisol levels by inhibiting 11 β -hydroxysteroid dehydrogenase type 2 [53].

FROM OTHER COUNTRIES (Traditional Chinese medicine and Western herbalism):

Sjögren's syndrome (SS) can be treated using Chinese herbal medicine (CHM). Traditional Chinese medicine uses syndrome differentiation to identify a number of patterns, such as dryness heat and yin deficiency. *Liriope platyphylla*, *Rehmaniaglutinosa*, and *Scrophulariabuergeriana* are common herbs used for SS because they tonify yin and relieve dryness. [54]



ASTRAGALUS



- Astragalus membranaceus has demonstrated encouraging results in a number of autoimmune conditions. It affected the development of Th17 cells during pregnancy in systemic lupus erythematosus [55].
- A significant component of astragalus, astragaloside, has shown anti-inflammatory and immune-boosting qualities, possibly through modulating T-cell balance and increasing CD45 phosphatase activity [56].
- Additionally, by altering cytokine levels such as IL-4, IFN- γ , TGF- β 1, and IL-5, Astragalus improved renal pathology, decreased haematuria and albuminuria, and altered Th1/Th2 balance in a rat model of IgA nephropathy [57].
- These results imply that by regulating immune responses and lowering inflammation, astragalus may have therapeutic potential in a number of autoimmune diseases, especially those that impact the kidneys.

REHMANNIA ROOT:



- Traditional Chinese medicine states that Rehmannia root is important in the treatment of Sjögren's syndrome (SS). According to studies, Rehmanniaglutinosa is the main herb used to help SS patients with their dryness, engender fluid, and tonify their yin [58].



- By increasing salivary flow rates, decreasing lymphocytic infiltration, and modifying T and B cell interactions, Catalpol, an active component of *Rehmanniae Radix*, has demonstrated therapeutic benefits in the treatment of SS [59].
- Sheng-Di-Huang, or raw *Rehmanniaglutinosa*, is a component of the core prescription pattern for the treatment of SS, according to extensive population research conducted in Taiwan [60]. These results demonstrate how crucial *Rehmannia* root is to the management of SS symptoms in traditional Chinese medicine.

SLIPPERY ELM:



- The North American tree known as the slippery elm (*Ulmus rubra*) is prized for its therapeutic qualities, especially its inner bark. Dietary fibres and mucilage are the main ingredients of slippery elm, which has long been used to treat a variety of conditions, such as inflammation, sore throats, and digestive problems. [61].
- Although there is little scientific proof of its effectiveness, it is becoming more and more well-liked as a supplemental treatment for inflammatory disorders of the upper airways [62].

CONVENTIONAL MEDICAL MANAGEMENT:

1. SYMPTOMATIC TREATMENT:

- ✓ The main goal of symptomatic treatment for Sjögren's syndrome is to control

symptoms of sicca. Topical cyclosporine A, artificial tears, and eye protection products are advised for dry eyes [63].

- ✓ Muscarinic agonists, such as pilocarpine and cevimeline, are used to treat oral symptoms by increasing salivary flow [64]. Mild immunomodulatory drugs are recommended for systemic signs, whereas corticosteroids, immunosuppressants, or biological agents such as anti-CD20 antibodies may be necessary in more severe cases [65].
- ✓ Ongoing research attempts to create more selective medications based on illness pathophysiology, even if existing treatments are still primarily symptomatic [66].

2. IMMUNOSUPPRESSIVE AGENTS:

- ✓ Using systemic immunosuppressants for severe organ manifestations is common, as is the case with other connective-tissue disorders [67].
- ✓ Similar to the actions of androgens, certain medications, such as cyclophosphamide, have shown promise in lowering inflammation of the salivary and lacrimal glands in animal models [68].

3. BIOLOGIC THERAPY:

- ✓ Primary Sjögren's syndrome (PSS) may benefit from biologic treatments, especially when it comes to addressing extraglandular symptoms and other autoimmune diseases. The most studied anti-CD20 monoclonal antibody is rituximab, which is presently undergoing randomised controlled trials [69].
- ✓ B-cell modulators like epratuzumab and belimumab, T-cell inhibitors like alefacept and abatacept, and molecules involved in the interleukin-6, interferon, and Toll-like receptor pathways are additional possible biologic targets [70].
- ✓ Biologics provide a more focused strategy to address disease aetiology, whereas traditional treatments concentrate on immunosuppression and symptomatic alleviation [71].



4. LIMITATIONS OF CONVENTIONAL DRUGS:

- ✓ The effectiveness of traditional therapies for Sjögren's syndrome (SS) is low, especially when it comes to ocular dryness. Oral secretagogues, topical anti-inflammatories, and artificial tears are examples of current treatments [72]. However, the underlying autoimmune disease and extraglandular symptoms are frequently ignored by these treatments [73].
- ✓ Despite being often recommended, conventional DMARDs are not very efficient in treating ocular problems [74]. Lack of standardised outcome measures and problems with patient selection have plagued clinical trials [75].

INTEGRATING MEDICAL DRUGS AND MEDICINAL DRUGS:

SYNERGISTIC POTENTIAL:

Combining traditional medications with medicinal plants has encouraging synergistic potential for Sjögren's syndrome. Combination treatments can increase therapeutic scope, decrease toxicity, and improve efficacy by taking use of the complimentary interactions between synthetic medications and plant-based substances. [76]

SAFETY AND CAUTION:

- When taken with corticosteroids, liquorice, a prevalent element in TCM, might block corticosteroid 11 β -dehydrogenase in the kidney and liver, which may result in drug-herb interactions [77].
- Concerns regarding possible interactions were raised by a Taiwanese study that revealed 1.495% of patients took systemic corticosteroids and licorice-containing TCM remedies at the same time [78].
- In individuals with Sjögren's disease, dehydroepiandrosterone (DHEA) supplementation has been demonstrated to restore sex steroid concentrations and may improve certain symptoms, especially dry mouth [79]. Herbal compositions should require quality assurance.

CHALLENGES AND RESEARCH GAPS:

- Its diverse appearance and resemblance to various illnesses make diagnosis difficult,

particularly in the elderly [80]. Systemic involvement can be treated with immunosuppressants, however there is no proof of their effectiveness [81].

- Frequent monitoring is essential for managing the elevated risk of lymphoma and preventing complications [82].
- Malignant, viral, and metabolic disorders are examples of both local and systemic causes that are included in differential diagnosis [83].
- Although keratoconjunctivitis sicca and SS may not differ much in clinical or laboratory testing, impression cytology has shown notable differences in epithelial and goblet cells, making it a useful tool for differential diagnosis [84].

EVIDENCE FROM SCIENTIFIC STUDIES:

PRECLINICAL EVIDENCE AND CLINICAL EVIDENCE:

- ❖ Preclinical research on Sjögren's syndrome (SS) has yielded important information on possible biomarkers and disease processes. The role of immune cells, especially B lymphocytes, in SS pathogenesis has been better understood thanks to mouse models [85].
- ❖ It is suggested that both innate and adaptive immune cells play a part in the progressive development of the disease, and that a type I interferon signature aids in the spread of the disease [86].
- ❖ Although autoantibodies, especially anti-Ro and anti-La, can be found years before symptoms appear, they are not enough to identify people who are at risk of advancement [87].
- ❖ Ro60 peptide immunisation has been shown in animal models to induce various stages of preclinical autoimmune, with genetic variables impacting glandular malfunction, lymphocyte infiltration, and epitope dissemination [88].
- ❖ Vaccination with 60 kD in a model of Sjögren's syndrome, Ro peptide causes various stages of preclinical autoimmunity in several strains of inbred mice [89].



- ❖ These models offer useful resources for researching preclinical stages and possible treatment targets by shedding light on the gradual onset of SS-like sickness and the genetic regulation of disease progression[90].
- ❖ Results and a review of the epidemiology literature indicate that mercury exposure does not induce autoantibodies in Colombian artisanal gold mining settings[91].
- ❖ The goal of recent advancements in clinical practice guidelines and categorisation criteria is to enhance patient care and diagnosis [92].
- ❖ The symptom-relieving benefits of herbal formulations, especially for dryness and exhaustion, are supported by a small number of clinical trials and case studies [93].

III. FUTURE PERSPECTIVES:

- Recent studies on Sjögren's syndrome (SS) demonstrate important developments in diagnosis, treatment, and prognosis for the future. Ultrasonography of the salivary glands is becoming a more viable diagnostic method that could either replace or supplement histology [94].
- To enhance patient selection for clinical trials, new grouping criteria and verified outcome measures are being developed. Results from therapeutic studies using novel biotechnology agents have been inconsistent, perhaps as a result of irreparable damage in recruited patients and illness heterogeneity [95].
- Future therapies might concentrate on B-cell depletion and target particular biochemical pathways that underlie the symptoms of each patient [96]. In order to maximise therapeutic approaches, ongoing research attempts to provide improved activity scores, prognostic indicators, and patient classification techniques [97].

IV. CONCLUSION:

Sjögren's syndrome's complicated origin and wide range of symptoms make treatment difficult. Conventional therapies can alleviate

symptoms, but they are still ineffective in controlling systemic involvement. Traditional medical systems' medicinal plants have promise anti-inflammatory and immunomodulatory properties that may help with glandular and extraglandular symptoms. In preclinical and restricted clinical settings, herbal treatments such as rehmannia, liquorice root, ashwagandha, and guduchi have had positive effects. Although safety, dosage standardisation, and possible drug interactions need to be carefully considered, their integration with conventional pharmaceutical treatments may have synergistic effects.. More thorough clinical trials and mechanistic research are desperately needed to confirm the effectiveness and safety of these herbal treatments. In order to provide comprehensive, individualised treatment for those impacted by SS, this study emphasises the significance of integrating traditional knowledge with contemporary evidence.

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