



## Aloe vera in Autoimmune and Immune-Mediated Diseases: A Critical Scoping Review of Human Clinical Evidence, Therapeutic Routes, Immunomodulatory Potential, and Safety

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### Abstract

**Background:** Aloe vera has been widely used in traditional and complementary medicine because of its proposed anti-inflammatory, antioxidant, wound-healing, and immunomodulatory properties. Although experimental investigations have suggested that several Aloe-derived compounds may influence inflammatory pathways, the extent to which these findings translate into clinically meaningful benefits in autoimmune and immune-mediated diseases remains uncertain.

**Objective:** To critically examine human clinical evidence regarding Aloe vera in autoimmune and immune-mediated disorders, with particular attention to disease-specific outcomes, administration routes, methodological quality, and safety.

**Methods:** A critical scoping review was undertaken using targeted bibliographic searches, citation tracking, and examination of accessible original clinical reports. Human interventional studies evaluating oral, topical, or local mucosal Aloe vera preparations in established autoimmune or immune-mediated diseases were considered. Findings were synthesized narratively because of substantial heterogeneity in interventions, populations, comparators, and outcomes.

**Results:** Clinical evidence was identified in Hashimoto thyroiditis, ulcerative colitis, psoriasis, Sjögren disease, and lichen planus. Oral Aloe vera was associated with improvements in thyroid biochemical parameters in a nonrandomized Hashimoto study and with higher clinical response rates in a small ulcerative colitis trial, although remission outcomes were not statistically significant. Topical psoriasis trials yielded contradictory findings. Studies in lichen planus frequently reported improvement in mucosal lesions and symptoms, but comparisons with corticosteroids produced heterogeneous results. Evidence in Sjögren disease was limited to symptomatic xerostomia management. Oral Aloe vera-associated hepatotoxicity has been documented.

**Conclusions:** Clinical evidence remains preliminary and heterogeneous. Topical Aloe vera may provide symptomatic benefits in selected immune-mediated conditions, but systemic disease-modifying efficacy has not been established. Standardized formulations, adequately powered randomized trials, and systematic safety assessments are required.

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### 1. Introduction

Autoimmune and immune-mediated inflammatory diseases comprise a broad and heterogeneous spectrum of chronic disorders characterized by dysregulated immune responses, persistent or recurrent inflammation, and variable degrees of tissue injury. Their clinical manifestations range from organ-specific conditions, such as Hashimoto thyroiditis, to systemic diseases involving

multiple organs and biological pathways. Although the introduction of conventional immunosuppressive agents, targeted synthetic therapies, and biological drugs has substantially improved disease control, important therapeutic challenges persist. A considerable proportion of patients continue to experience residual symptoms, incomplete responses, treatment-related adverse effects, recurrent disease activity, and deterioration in health-related quality of life. These limitations have contributed to growing interest in complementary interventions that might alleviate symptoms, reduce inflammatory activity, or improve tolerability when used alongside established treatment strategies.

Among botanical products, Aloe vera has attracted considerable attention because of its long history of medicinal use and its chemically diverse composition. Aloe vera, commonly identified botanically as *Aloe barbadensis* Miller, is a succulent plant whose leaves contain a mucilaginous inner gel, a peripheral latex layer, and additional structural tissues. These fractions differ substantially in their chemical constituents and pharmacological properties. The inner gel contains water, polysaccharides, glycoproteins, amino acids, minerals, and other compounds, whereas the latex contains anthraquinone derivatives associated primarily with stimulant laxative effects. Commercial products may contain purified inner-leaf gel, whole-leaf extracts, concentrated preparations, or formulations combining Aloe vera with other active substances. Consequently, the expression Aloe vera treatment does not describe a single chemically standardized intervention, and results obtained with one formulation cannot necessarily be extrapolated to another <sup>[1]</sup>.

The biological interest in Aloe vera is supported by experimental investigations describing anti-inflammatory, antioxidant, tissue-protective, and immunologically active properties. Several constituents have been investigated for their ability to influence inflammatory mediator production, oxidative stress, cellular proliferation, wound repair, and innate immune responses. Nevertheless, these effects are complex and sometimes bidirectional. Certain polysaccharides may stimulate immune-cell activity, whereas other constituents have demonstrated inhibitory effects on selected inflammatory pathways. This apparent immunomodulatory duality is especially relevant in autoimmune disorders, where the therapeutic objective is not simply to increase or decrease immune activity globally, but to control pathogenic responses without compromising protective immunity. Accordingly, the observation of anti-inflammatory activity in experimental systems cannot, by itself, establish that an Aloe vera preparation is beneficial in a particular autoimmune disease.

A further challenge concerns the distinction between local and systemic therapeutic effects. Topical Aloe vera has been investigated in inflammatory skin and mucosal disorders, including psoriasis and lichen planus, where direct contact with affected tissues may contribute to symptomatic improvement. Oral administration, however, raises different pharmacological questions involving gastrointestinal stability, absorption, metabolism, systemic bioavailability, and potential interactions with concomitant medications. Moreover, a beneficial effect after oral administration in an intestinal disease may result from local luminal or mucosal activity rather than systemic immunomodulation. These distinctions are frequently insufficiently emphasized in

discussions of medicinal plants, leading to broad therapeutic claims that extend beyond the clinical evidence.

Human investigations have examined Aloe vera in several conditions relevant to autoimmunity and immune-mediated inflammation. A prospective nonrandomized study evaluated oral Aloe vera juice in women with Hashimoto thyroiditis and subclinical hypothyroidism <sup>[2]</sup>, while a randomized placebo-controlled trial investigated oral Aloe vera gel in active ulcerative colitis <sup>[3]</sup>. In dermatology, randomized trials have assessed topical preparations in plaque psoriasis, with notably inconsistent findings <sup>[4-6]</sup>. A comparatively larger body of clinical literature has examined Aloe vera in oral and vulvar lichen planus, including placebo-controlled and active-comparator trials <sup>[7-10]</sup>. More recently, an Aloe vera-containing salivary substitute was evaluated in patients with Sjögren disease, focusing on xerostomia rather than systemic disease activity <sup>[11]</sup>. Although these investigations suggest potentially relevant clinical applications, their interpretation is complicated by small sample sizes, different preparations, inconsistent outcomes, and limited long-term follow-up.

An additional consideration is the safety of botanical products in patients with chronic inflammatory diseases. Such patients may already be receiving immunosuppressive drugs, glucocorticoids, disease-modifying antirheumatic drugs, or other medications requiring careful monitoring. Although Aloe vera is frequently perceived as a natural and therefore relatively harmless intervention, published reports of liver injury associated with oral preparations demonstrate that clinically significant adverse reactions are possible. Safety evaluation must therefore distinguish between topical products, purified oral gels, and whole-leaf or latex-containing preparations rather than treating them as equivalent.

Against this background, the present review aims to critically map the human clinical evidence regarding Aloe vera in autoimmune and immune-mediated diseases, distinguish the effects of different administration routes, assess the consistency and clinical relevance of reported outcomes, and identify methodological limitations that should guide future research. Particular emphasis is placed on separating symptomatic improvement from objective evidence of disease modification, examining both favorable and negative trials, and avoiding extrapolation from experimental findings to unsupported clinical indications.

## 2. Methods

### 2.1. Review Design and Conceptual Framework

This article was developed as a critical scoping review with narrative synthesis of human clinical evidence concerning Aloe vera in autoimmune and immune-mediated diseases. The review was organized according to the general principles of evidence mapping and informed by methodological guidance for scoping reviews, including the PRISMA extension for scoping reviews (PRISMA-ScR) <sup>[12]</sup>. The primary purpose was to identify the clinical conditions in which Aloe vera had been investigated, characterize the preparations and administration routes used, and critically evaluate the clinical relevance of the reported findings. Because the eligible investigations differed substantially in disease mechanisms, therapeutic objectives, interventions, and outcomes, a descriptive approach was considered more appropriate than quantitative pooling. A complete reproducible screening database and prospective review

protocol were not available; therefore, this manuscript does not claim to represent an exhaustive systematic review or to fulfill every procedural requirement of PRISMA-ScR.

## 2.2. Literature Identification and Search Strategy

Relevant publications were identified through targeted searches of publicly accessible biomedical bibliographic resources, publisher websites, bibliographic citation records, and examination of available full-text clinical reports. Reference lists of pertinent original investigations and reviews were also examined to identify additional potentially eligible studies. Search concepts combined the botanical terms *Aloe vera* and *Aloe barbadensis* with autoimmune disease, immune-mediated disease, clinical trial, randomized trial, oral administration, topical treatment, and disease-specific terminology. Conditions considered included autoimmune thyroiditis, inflammatory bowel disease, psoriasis, Sjögren disease, lichen planus, and selected systemic rheumatic and organ-specific autoimmune disorders. The available literature was evaluated through October 2026. Although the evidence identification process incorporated multiple bibliographic sources and citation tracking, a complete dated search export for every database was not retained, and database-specific identification and exclusion counts could not be reconstructed reliably. Consequently, no retrospective PRISMA flow diagram or artificial screening statistics were generated.

## 2.3. Eligibility Criteria

Human studies were considered eligible when participants had a recognized autoimmune or immune-mediated inflammatory disease and received an *Aloe vera*-containing intervention with assessment of clinical, symptomatic, functional, biochemical, or inflammatory outcomes. Randomized controlled trials, nonrandomized comparative studies, and relevant prospective clinical investigations were eligible. All administration routes were considered, including oral ingestion, topical skin application, oral mucosal preparations, and other local therapeutic approaches. Studies using combinations of *Aloe vera* with additional active ingredients were considered when clinically relevant, but their findings were interpreted as evidence for the combined formulation rather than for *Aloe vera* alone. Experimental animal investigations, *in vitro* studies, and reports involving conditions outside the autoimmune or immune-mediated spectrum were excluded from the principal clinical evidence tables. Adverse-event case reports were considered separately because of their relevance to safety, while uncontrolled case reports of therapeutic benefit were not regarded as equivalent to controlled efficacy studies.

## 2.4. Data Extraction and Critical Appraisal

Information was extracted from available original articles and checked against accessible bibliographic records when necessary. The extraction framework included publication details, country, clinical condition, diagnostic characteristics, study design, sample size, intervention formulation, concentration, administration route, treatment frequency, duration, comparator, clinical endpoints, statistical findings, adverse events, and follow-up. Particular attention was paid to distinguishing randomized participants from analyzed populations, within-group changes from between-group comparisons, and clinically meaningful endpoints from

surrogate biochemical measures. When the published information did not permit reliable numerical extraction, the result was described without constructing missing estimates. Methodological limitations were assessed descriptively, considering randomization, allocation procedures, blinding, comparator selection, attrition, sample size, outcome validity, formulation standardization, and follow-up duration. Formal domain-level risk-of-bias classifications and certainty-of-evidence grades were not assigned because a complete independent assessment had not been undertaken.

## 2.5. Evidence Synthesis

The evidence was synthesized by clinical condition and administration route. Studies involving systemic oral administration were distinguished from those evaluating topical or local mucosal preparations, and particular attention was given to the difference between symptomatic benefit and modification of the underlying immune-mediated disease. Because the lichen planus literature contained several clinical trials involving different anatomical sites and therapeutic comparators, these investigations were summarized separately from the other autoimmune and immune-mediated conditions. No meta-analysis was conducted because the studies were not sufficiently homogeneous in their interventions, populations, outcome measures, and therapeutic objectives to justify a single pooled estimate.

## 3. Results

### 3.1. General Characteristics of The Clinical Evidence

The identified human clinical literature was concentrated in Hashimoto thyroiditis, ulcerative colitis, psoriasis, Sjögren disease, and lichen planus. These conditions differ markedly in pathophysiology, clinical manifestations, and therapeutic endpoints, creating important limitations for cross-disease comparisons. In Hashimoto thyroiditis, the principal outcomes involved thyroid function and circulating autoantibodies, whereas the ulcerative colitis trial assessed clinical response, remission, endoscopic findings, and histological activity. Psoriasis studies focused primarily on cutaneous lesion severity and quality of life, while lichen planus trials evaluated mucosal lesions, pain, burning sensation, and clinical improvement. The Sjögren disease investigation addressed symptomatic xerostomia using a locally administered salivary substitute rather than measuring systemic autoimmune activity. This heterogeneity indicates that the available literature should be interpreted as a collection of disease-specific clinical investigations rather than as evidence for a generalized immunomodulatory effect of *Aloe vera*.

A second important characteristic was the predominance of topical or local treatment. Oral administration was directly investigated in Hashimoto thyroiditis and ulcerative colitis, and was included as one component of a combined intervention in an oral lichen planus trial. Most other investigations involved topical skin or mucosal applications. Consequently, the number of clinical studies capable of addressing systemic efficacy was substantially smaller than the overall number of studies involving autoimmune or immune-mediated conditions. The principal investigations are summarized in Table 1, while trials involving lichen planus are presented separately in Table 2. Table 3 provides a comparative critical appraisal of the evidence.

**Table 1:** Human Clinical Studies Evaluating Aloe vera in Autoimmune and Immune-Mediated Diseases Other Than Lichen Planus

| Study; country                                                | Disease and study design                                                                                        | Participants                                                       | Aloe vera formulation, dose, and route                                                                | Comparator and treatment duration                                                                                   | Main clinical outcomes and statistical findings                                                                                                                                                                                                                        | Safety and methodological limitations                                                                                                                                                          |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Metro <i>et al.</i> , 2018 <sup>[2]</sup> ; Italy             | Hashimoto thyroiditis with subclinical hypothyroidism; prospective, nonrandomized controlled study              | 45 women: 30 treated and 15 untreated controls                     | Oral Aloe barbadensis Miller juice, 50 mL/day according to the methods                                | Untreated controls; 9 months                                                                                        | TSH decreased by approximately 61%, TPOAb by 56%, and FT4 increased by 23% after 9 months. Mean TSH decreased from $5.19 \pm 0.61$ to $2.01 \pm 0.57$ mU/L. No comparable significant changes were observed in controls                                                | Small sample, nonrandomized allocation, potential confounding, and inconsistency in the reported daily dose. Long-term clinical disease modification was not established                       |
| Langmead <i>et al.</i> , 2004 <sup>[3]</sup> ; United Kingdom | Mild-to-moderately active ulcerative colitis; randomized, double-blind, placebo-controlled trial                | 49 initially randomized; 44 evaluable; 30 Aloe vera and 14 placebo | Oral Aloe vera gel, 100 mL twice daily                                                                | Placebo; 4 weeks                                                                                                    | Clinical response: 14/30 (46.7%) versus 2/14 (14.3%), $p=0.048$ . Clinical remission: 9/30 (30.0%) versus 1/14 (7.1%), $p=0.09$ . Endoscopic remission: 7/26 (26.9%) versus 2/11 (18.2%), $p=0.69$ . Histological remission: 6/21 (28.6%) versus 4/9 (44.4%), $p=0.43$ | Adverse events were generally mild and similar between groups. Small sample, short follow-up, and no statistically significant superiority for clinical, endoscopic, or histological remission |
| Syed <i>et al.</i> , 1996 <sup>[4]</sup> ; Sweden             | Mild-to-moderate plaque psoriasis; randomized, double-blind, placebo-controlled trial                           | 60 patients: 30 per group                                          | Hydrophilic cream containing 0.5% Aloe vera extract, applied topically three times daily, 5 days/week | Placebo cream; up to 4 weeks                                                                                        | Clinical clearance: 25/30 (83.3%) versus 2/30 (6.7%), $p<0.001$ . Mean PASI decreased from approximately 9.7 to 2.2 in the Aloe vera group, compared with 8.9 to 8.2 in the placebo group                                                                              | No treatment-related adverse events or withdrawals reported. Markedly positive findings require independent replication with standardized formulations and contemporary outcomes               |
| Paulsen <i>et al.</i> , 2005 <sup>[5]</sup> ; Denmark         | Mild-to-moderate plaque psoriasis; randomized, double-blind, within-patient right-left placebo-controlled trial | 41 enrolled; 40 analyzed                                           | Commercial Aloe vera gel (98%), applied topically twice daily                                         | Placebo gel; 4 weeks, with subsequent follow-up                                                                     | Lesion scores decreased at 72.5% of Aloe vera-treated sites versus 82.5% of placebo-treated sites; $p=0.0197$ , favoring placebo                                                                                                                                       | Local adverse effects were reported by 55% of participants, mainly dryness. Negative trial; potential influence of formulation and vehicle effects                                             |
| Choonharn <i>et al.</i> , 2010 <sup>[6]</sup> ; Thailand      | Mild-to-moderate plaque psoriasis; randomized, double-blind, active-comparator trial                            | 80 patients: 40 per group; 75 completed treatment                  | Topical Aloe vera cream containing 70% mucilage, applied twice daily                                  | Triamcinolone acetonide 0.1% cream, twice daily; 8 weeks                                                            | Mean PASI decreased from 11.6 to 3.9 with Aloe vera and from 10.9 to 4.3 with triamcinolone. Difference in PASI reduction: 1.1 points, $p=0.0237$ , favoring Aloe vera. DLQI improvement: 6.1 versus 5.8 points, $p=0.5497$                                            | Short treatment period and no post-treatment follow-up. The published confidence intervals contain reporting inconsistencies and should not be reproduced without qualification                |
| Mahmoud <i>et al.</i> , 2025 <sup>[11]</sup> ; Egypt          | Sjögren disease-associated xerostomia; randomized crossover clinical trial                                      | 24 women with Sjögren disease                                      | Oral mucosal salivary substitute containing Aloe vera gel, coconut oil, and carboxymethylcellulose    | Conventional carboxymethyl cellulose salivary substitute; two 2-week treatment periods separated by a 7-day washout | Both formulations improved xerostomia-related symptoms and oral health-related quality of life. No consistent statistically significant superiority of the Aloe vera-containing preparation was demonstrated for clinical dryness, quality of life, or candidal load   | Small sample, short treatment periods, and multicomponent formulation. The independent effect of Aloe vera cannot be determined; no evidence of systemic autoimmune disease modification       |

**Table footnote:** AV, Aloe vera; DLQI, Dermatology Life Quality Index; FT4, free thyroxine; PASI, Psoriasis Area and Severity Index; TPOAb, thyroperoxidase antibodies; TSH, thyroid-stimulating hormone. Results are presented as reported in the original studies. Statistically significant within-group changes should not be interpreted as evidence of superiority over a comparator. Psoriasis and ulcerative colitis are included as immune-mediated inflammatory diseases, whereas Hashimoto thyroiditis and Sjögren disease are classified as autoimmune disorders. Studies involving lichen planus are presented separately in Table 2.

**Table 2:** Human clinical trials of Aloe vera in oral and vulvar lichen planus

| Study; country                                  | Design and sample                                                             | Formulation and comparator                                                                                                           | Treatment duration                                        | Main findings                                                                                                                                                                                                             | Safety and interpretation                                                                                                  |
|-------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Choonhakarn <i>et al.</i> , 2008 [7]; Thailand  | Double-blind placebo-controlled RCT; 54 patients, 27/group                    | Topical Aloe vera gel versus placebo                                                                                                 | 8 weeks                                                   | Good clinical response: 22/27 (81.5%) vs 1/27 (3.7%), $p<0.001$ . Complete resolution of burning pain: 9/27 (33.3%) vs 1/27 (3.7%), $p=0.005$ . At least 50% symptom improvement: 17/27 (63.0%) vs 2/27 (7.4%), $p<0.001$ | No serious adverse effects reported. Favorable placebo-controlled findings                                                 |
| Rajar <i>et al.</i> , 2008 [14]; Pakistan       | Double-blind placebo-controlled RCT; 34 women, 17/group; vulvar lichen planus | Topical Aloe vera gel versus placebo                                                                                                 | 8 weeks                                                   | Good clinical response: 14/17 (82.4%) vs 1/17 (5.9%), $p<0.001$ . Complete clinical remission in 1/17 treated participants                                                                                                | No adverse effects reported. Small trial requiring replication                                                             |
| Salazar-Sánchez <i>et al.</i> , 2010 [8]; Spain | Double-blind placebo-controlled RCT; 64 randomized, 55 assessed at 12 weeks   | Topical Aloe vera 70%, 0.4 mL three times daily, versus placebo                                                                      | 12 weeks                                                  | Complete pain remission at 6 weeks: 31.2% vs 17.2%; at 12 weeks: 61.3% vs 41.6%; between-group pain differences not significant. OHIP-49 total improvement: $19.90 \pm 15.76$ vs $10.67 \pm 17.70$ , $p=0.046$            | No adverse events reported. Quality-of-life benefit; attrition and nonsignificant pain comparison limit interpretation     |
| Mansourian <i>et al.</i> , 2011 [9]; Iran       | Double-blind active-comparator RCT; 46 patients, 23/group                     | Aloe vera mouthwash, two tablespoons per rinse for two minutes, four times daily, versus triamcinolone acetonide 0.1%                | 4 weeks; final follow-up 2 months after initiation        | Pain, Thongprasom score, and lesion size improved in both groups, $p<0.001$ . Some degree of healing at final follow-up: 74% vs 78%                                                                                       | Similar observed responses do not establish formal equivalence or noninferiority                                           |
| Reddy <i>et al.</i> , 2012 [10]; India          | Double-blind randomized trial; 40 patients, 20/group                          | Topical Aloe vera gel versus triamcinolone acetonide ointment                                                                        | 8 weeks                                                   | Authors reported favorable clinical outcomes with Aloe vera; complete comparative numerical estimates were not independently verified                                                                                     | Positive active-comparator study; magnitude and precision of benefit require complete primary extraction                   |
| Vaidya <i>et al.</i> , 2023 [15]; India         | Randomized parallel trial; 60 patients, 30/group                              | Topical Aloe vera gel 97% plus oral Aloe vera juice 94.7%, 10 mL twice daily, versus topical clobetasol propionate 0.05% twice daily | 2 months of treatment followed by 4 months of observation | Both groups improved in VAS and lesion scores, $p<0.05$ ; between-group differences during months 2–4, $p<0.0071$ , favored clobetasol                                                                                    | Clobetasol was more effective. Combined oral/topical administration prevents attribution of efficacy to the oral component |

**Table 2 notes:** AV, Aloe vera; OHIP-49, Oral Health Impact Profile-49; RCT, randomized controlled trial; VAS, visual analogue scale. The anatomical site, intervention formulation, comparator, and clinical outcomes should be considered before any quantitative synthesis of these studies.

**Table 3:** Critical appraisal of the principal clinical evidence

| Clinical condition    | Main methodological concerns                                                                                                            | Overall interpretation                                                                 |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Hashimoto thyroiditis | Nonrandomized design, small sample, potential confounding, surrogate biochemical outcomes, inconsistent dose reporting                  | Preliminary hypothesis-generating evidence                                             |
| Ulcerative colitis    | Small sample, short follow-up, incomplete endoscopic and histological datasets, clinical response without significant remission benefit | Possible short-term symptomatic effect; insufficient evidence for disease modification |
| Psoriasis             | Contradictory randomized findings, heterogeneous formulations, vehicle effects, limited long-term follow-up                             | Inconsistent topical efficacy                                                          |
| Sjögren disease       | Small crossover trial, multicomponent formulation, symptomatic endpoints, short treatment periods                                       | Potential local symptom management; no demonstrated systemic effect                    |
| Oral lichen planus    | Small trials, variable formulations, different clinical scales, heterogeneous comparators and follow-up                                 | Promising topical evidence requiring larger confirmatory trials                        |
| Vulvar lichen planus  | Single small placebo-controlled trial, limited independent replication                                                                  | Preliminary favorable evidence                                                         |
| Oral Aloe vera safety | Limited trial exposure, inadequate power to detect rare adverse events, published cases of hepatotoxicity                               | Long-term safety remains uncertain                                                     |

### 3.2. Hashimoto Thyroiditis

Hashimoto thyroiditis is a chronic organ-specific autoimmune disorder characterized by immune-mediated thyroid injury, frequently associated with circulating antibodies against thyroid peroxidase and thyroglobulin. Although these autoantibodies are important diagnostic markers, their concentrations do not necessarily correspond directly to disease activity, the extent of tissue destruction, or future thyroid functional outcomes. The potential therapeutic

relevance of Aloe vera in this condition was investigated by Metro *et al.*, who evaluated oral Aloe barbadensis Miller juice in women with untreated subclinical hypothyroidism associated with Hashimoto thyroiditis [2]. The investigation included 30 women receiving Aloe vera juice for nine months and 15 untreated comparison participants. The treated group demonstrated progressive changes in thyroid biochemical parameters, including reductions in thyroid-stimulating hormone and thyroperoxidase antibody concentrations,

together with an increase in free thyroxine. At nine months, the reported reductions were approximately 61% for TSH and 56% for TPOAb, while FT4 increased by approximately 23%. The comparison group did not demonstrate similar changes during observation.

These findings are noteworthy because they represent one of the few human investigations in which oral Aloe vera was associated with changes in laboratory parameters directly related to an autoimmune disease. Nevertheless, several methodological concerns limit the strength of the inference. The intervention was not randomly assigned, the study population was relatively small, and the untreated controls were drawn from an existing clinical database rather than being recruited and followed under identical randomized conditions. These factors introduce potential selection bias, differences in baseline characteristics, and unmeasured confounding. Moreover, although a reduction in TPOAb concentrations may be biologically interesting, it does not independently establish suppression of pathogenic thyroid autoimmunity, prevention of thyroid destruction, or improved long-term clinical outcomes. The absence of definitive data concerning progression to overt hypothyroidism, subsequent levothyroxine requirements, and sustained thyroid function after discontinuation further limits clinical applicability. An inconsistency in the published description of the Aloe vera dose, with 50 mL/day indicated in the methods and study tables but 100 mL mentioned elsewhere, also illustrates the importance of detailed intervention reporting in botanical research. Overall, this study should be regarded as hypothesis-generating rather than sufficient evidence to recommend oral Aloe vera for Hashimoto thyroiditis.

### 3.3. Ulcerative Colitis

Ulcerative colitis is a chronic immune-mediated inflammatory disease characterized by recurrent mucosal inflammation of the colon, with clinical manifestations including diarrhea, rectal bleeding, abdominal discomfort, and impaired quality of life. Although its pathogenesis involves dysregulated mucosal immunity, epithelial barrier dysfunction, intestinal microbiota, and environmental influences, it is not generally classified as a prototypical autoantibody-mediated autoimmune disorder. Nevertheless, it provides a clinically relevant model for evaluating the potential anti-inflammatory effects of Aloe vera in humans. Langmead *et al.* conducted a randomized, double-blind, placebo-controlled trial involving 44 evaluable patients with mildly to moderately active ulcerative colitis<sup>[3]</sup>. Participants received oral Aloe vera gel at a dose of 100 mL twice daily or placebo for four weeks, with a 2:1 allocation ratio. Clinical response occurred in 14 of 30 patients receiving Aloe vera (46.7%) compared with two of 14 receiving placebo (14.3%), corresponding to a statistically significant between-group difference ( $p=0.048$ ).

Despite this favorable result for clinical response, the study did not demonstrate statistically significant superiority for several outcomes that are particularly important in contemporary ulcerative colitis management. Clinical remission occurred in nine of 30 patients receiving Aloe vera (30.0%) compared with one of 14 receiving placebo (7.1%), but the difference did not reach statistical significance ( $p=0.09$ ). Similarly, sigmoidoscopic remission was observed in seven of 26 evaluable patients in the Aloe vera group and two of 11 in the placebo group ( $p=0.69$ ), while histological

remission occurred in six of 21 and four of nine participants, respectively ( $p=0.43$ ). Although the histological activity score decreased significantly within the Aloe vera group, such an intragroup change cannot be interpreted as evidence of superiority over placebo. The short treatment period, limited sample size, incomplete availability of paired endoscopic and histological assessments, and absence of long-term follow-up further restrict interpretation. Adverse events were generally mild, and treatment withdrawal because of deterioration or inadequate improvement occurred in both groups. Therefore, the trial suggests a possible short-term effect on clinical symptoms but does not establish sustained remission, mucosal healing, or disease-modifying efficacy.

A subsequent systematic review of herbal interventions for ulcerative colitis also discussed an investigation involving Aloe vera gel enemas combined with mesalamine<sup>[13]</sup>. This observation is relevant because it introduces a different administration route, potentially allowing direct exposure of the distal colonic mucosa to the preparation. However, the use of concomitant mesalamine and the limited independently verified primary numerical data prevent reliable attribution of clinical benefit to Aloe vera alone. Taken together, the available findings support the biological and clinical rationale for further investigation but do not justify replacing established anti-inflammatory, immunomodulatory, or biological therapies. Future studies should use standardized preparations, adequately powered randomized designs, and validated endpoints incorporating clinical remission, endoscopic improvement, histological activity, and longer-term relapse prevention.

### 3.4. Psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by epidermal hyperproliferation and activation of complex inflammatory pathways, particularly those involving the interleukin-23/interleukin-17 axis. The disease provides an attractive setting for topical interventions because cutaneous lesions can be directly treated and objectively evaluated. However, three randomized clinical trials investigating Aloe vera have produced markedly different results, emphasizing the challenges associated with botanical formulations. Syed *et al.* conducted a randomized, double-blind, placebo-controlled study involving 60 patients with mild-to-moderate plaque psoriasis<sup>[4]</sup>. Participants received a hydrophilic cream containing 0.5% Aloe vera extract or placebo, applied three times daily for five days per week over a maximum treatment period of four weeks. Clinical clearance was reported in 25 of 30 patients receiving Aloe vera (83.3%) compared with two of 30 receiving placebo (6.7%), representing a highly significant difference. The investigators also reported substantial improvement in psoriasis severity scores and favorable tolerability, without treatment-related adverse events or withdrawals.

In contrast, Paulsen *et al.* investigated a commercial Aloe vera gel in a randomized, double-blind, placebo-controlled right-left comparison involving patients with stable plaque psoriasis<sup>[5]</sup>. Forty-one participants were enrolled, and data from 40 were analyzed. After four weeks of twice-daily application, the combined score for erythema, infiltration, and desquamation decreased at 72.5% of Aloe vera-treated sites compared with 82.5% of placebo-treated sites, with the difference favoring placebo ( $p=0.0197$ ). Local adverse effects were reported by 55% of participants, predominantly

skin dryness. These results contrast sharply with those of Syed *et al.* and suggest that the clinical activity of Aloe vera may depend substantially on the preparation used, its concentration, chemical composition, preservation, and vehicle. The high placebo response also raises the possibility that the formulation base exerted clinically relevant moisturizing or barrier-protective effects.

Choonhakarn *et al.* subsequently conducted a randomized, double-blind trial comparing topical Aloe vera cream with triamcinolone acetonide 0.1% in 80 patients with mild-to-moderate plaque psoriasis [6]. After eight weeks, the mean Psoriasis Area and Severity Index decreased from 11.6 to 3.9 in the Aloe vera group and from 10.9 to 4.3 in the triamcinolone group. The reported difference in PASI reduction favored Aloe vera ( $p=0.0237$ ), whereas improvements in Dermatology Life Quality Index scores were similar between groups. Although these findings suggest that a particular Aloe vera preparation may achieve clinically meaningful improvement, the absence of post-treatment follow-up prevents conclusions concerning durability, relapse, or comparative long-term effectiveness. The collective psoriasis literature therefore demonstrates both favorable and negative results, without establishing consistent superiority over placebo or conventional topical therapies. It also provides no direct evidence that orally administered Aloe vera improves psoriasis or modifies the systemic inflammatory processes associated with the disease.

### 3.5. Sjögren Disease

Sjögren disease is a systemic autoimmune condition characterized by lymphocytic involvement of exocrine glands, frequently resulting in xerostomia, keratoconjunctivitis sicca, and variable extraglandular manifestations. Oral dryness may substantially impair speaking, swallowing, sleeping, dental health, and quality of life, and symptomatic management remains an important component of comprehensive care even when systemic disease activity is controlled. Mahmoud *et al.* investigated an Aloe vera-containing salivary substitute in a randomized crossover clinical trial involving 24 women with Sjögren disease and xerostomia [11]. The experimental formulation contained Aloe vera gel, coconut oil, and carboxymethylcellulose and was compared with a conventional carboxymethylcellulose-based salivary substitute. Each treatment was administered over a two-week period, separated by a seven-day washout interval, allowing participants to receive both interventions.

Both preparations were associated with improvements in xerostomia-related symptoms and quality-of-life outcomes, but the Aloe vera-containing formulation did not demonstrate consistent superiority over the conventional comparator. The study is clinically relevant because it addresses a common and burdensome manifestation of Sjögren disease, but several factors restrict interpretation. First, the intervention contained multiple ingredients with potentially independent lubricating or moisturizing effects, preventing isolation of the contribution of Aloe vera. Second, the treatment duration was short, limiting assessment of sustained benefit and long-term oral health outcomes. Third, the endpoints concerned symptomatic dryness rather than objective modification of glandular autoimmunity, systemic inflammatory activity, or extraglandular manifestations. Consequently, this investigation supports further evaluation of Aloe vera-containing oral moisturizers but should not be interpreted as

evidence that Aloe vera modifies the underlying autoimmune disease.

### 3.6. Lichen Planus

Among the autoimmune and immune-mediated conditions examined in this review, lichen planus accounted for a relatively substantial proportion of the identified clinical investigations involving Aloe vera. Six randomized clinical trials were identified, including five studies involving oral lichen planus and one involving vulvar lichen planus [7–10,14,15]. The interventions differed in formulation, route of administration, treatment duration, and comparator, encompassing topical gels, mouthwash, and a combined topical and orally administered preparation. Four studies compared Aloe vera with corticosteroid-based treatments or another active intervention, whereas two oral lichen planus studies and the vulvar lichen planus study included placebo-controlled comparisons. Across these investigations, the principal outcomes were changes in clinical lesion severity, pain, burning sensation, and oral health-related quality of life. The characteristics and principal findings of these studies are summarized in Table 2.

Choonhakarn *et al.* conducted a randomized, double-blind, placebo-controlled trial involving 54 patients with oral lichen planus, equally allocated to topical Aloe vera gel or placebo [7]. After eight weeks of treatment, a good clinical response was observed in 22 of 27 patients receiving Aloe vera (81.5%), compared with one of 27 receiving placebo (3.7%;  $p<0.001$ ). Complete resolution of burning pain occurred in nine patients in the intervention group (33.3%) and one patient in the placebo group (3.7%;  $p=0.005$ ). Furthermore, improvement of at least 50% in symptom severity was observed in 17 of 27 patients receiving Aloe vera (63.0%), compared with two of 27 receiving placebo (7.4%;  $p<0.001$ ). No serious adverse effects were reported during the treatment period. These findings demonstrated statistically significant improvements in both clinical lesions and subjective symptoms with topical Aloe vera compared with placebo.

Salazar-Sánchez *et al.* subsequently investigated the efficacy of a topical preparation containing 70% Aloe vera in a randomized, double-blind, placebo-controlled study involving 64 patients with oral lichen planus [8]. Participants were allocated to receive 0.4 mL of the intervention or placebo three times daily for 12 weeks. At six weeks, complete pain remission was observed in 31.3% of patients receiving Aloe vera, compared with 17.2% receiving placebo. At 12 weeks, the corresponding proportions were 61.3% and 41.7%, respectively. Although these differences numerically favored Aloe vera, the between-group comparisons for pain remission were not statistically significant. However, improvements in selected oral health-related quality-of-life outcomes favored the intervention, including psychological disability ( $3.84 \pm 3.81$  versus  $0.83 \pm 2.59$ ;  $p=0.007$ ) and the total Oral Health Impact Profile-49 score ( $19.90 \pm 15.76$  versus  $10.67 \pm 17.70$ ;  $p=0.046$ ). Of the 64 randomized participants, 55 were assessed at the final evaluation, comprising 31 in the Aloe vera group and 24 in the placebo group. No adverse effects attributable to treatment were reported.

The comparative effectiveness of Aloe vera and topical corticosteroids was evaluated by Mansourian *et al.* in a randomized, double-blind trial involving 46 patients with oral lichen planus [9]. Twenty-three participants received an Aloe vera mouthwash, while 23 received triamcinolone acetonide

0.1%. The mouthwash was administered four times daily, with participants instructed to rinse for approximately two minutes before expectoration. Both interventions were associated with statistically significant reductions in pain intensity, lesion dimensions, and Thongprasom clinical scores during the treatment period ( $p < 0.001$  for within-group changes). At the final follow-up, some degree of lesion healing was observed in approximately 74% of patients receiving Aloe vera and 78% receiving triamcinolone. Although both treatments were associated with clinical improvement, the study did not establish formal equivalence or noninferiority between the interventions.

Reddy *et al.* also compared topical Aloe vera gel with triamcinolone acetonide ointment in a randomized, double-blind clinical trial involving 40 patients with oral lichen planus [10]. Participants were allocated equally between the two treatment groups and followed over an eight-week period. The investigators reported favorable clinical outcomes with Aloe vera, including improvement in lesion severity and associated symptoms. However, the complete comparative numerical results were not independently available for verification in the present evidence extraction, limiting the possibility of reporting precise between-group effect estimates. This study was therefore retained in the qualitative synthesis without assigning numerical treatment effects that could not be confirmed from the available documentation.

More recently, Vaidya *et al.* conducted a randomized parallel clinical trial involving 60 patients with oral lichen planus, comparing a combined Aloe vera intervention with topical clobetasol propionate 0.05% [15]. Thirty patients received topical Aloe vera gel (97%) together with orally administered Aloe vera juice (94.7%), at a dose of 10 mL twice daily, while 30 received topical clobetasol. Treatment continued for two months, followed by four months of observation. Both groups demonstrated improvements in clinical lesion scores and pain intensity; however, the clobetasol group achieved superior outcomes, with statistically significant between-group differences reported during months two to four ( $p < 0.0071$ ). Because the experimental intervention combined topical and oral administration, the independent contribution of orally ingested Aloe vera could not be determined.

Evidence involving vulvar lichen planus was provided by Rajar *et al.*, who conducted a randomized, double-blind, placebo-controlled trial involving 34 women [14]. Seventeen participants received topical Aloe vera gel and 17 received placebo over eight weeks. A good clinical response was observed in 14 of 17 patients receiving Aloe vera (82.4%), compared with one of 17 receiving placebo (5.9%;  $p < 0.001$ ). Complete clinical remission was reported in one participant receiving Aloe vera. No treatment-related adverse effects were reported. Although this study suggested a favorable effect on vulvar lesions, its findings were derived from a relatively small population and were not accompanied by evidence of sustained long-term disease control.

Overall, the lichen planus trials demonstrated heterogeneous but predominantly favorable outcomes for local Aloe vera preparations, particularly in comparisons with placebo. Improvements were most consistently observed in lesion severity, pain, and burning sensation, whereas comparisons with topical corticosteroids produced less uniform findings. Treatment duration generally ranged from four to twelve weeks, and long-term outcomes were insufficiently

documented in most investigations. Importantly, the available evidence did not establish that oral Aloe vera alone was effective for lichen planus, because the only identified trial incorporating ingestion also included simultaneous topical administration.

### 3.7. Safety and Tolerability

Safety information was inconsistently reported across the clinical investigations included in this review, and most studies were insufficiently powered or too short to detect uncommon or delayed adverse events. Topical Aloe vera preparations were generally well tolerated in the trials involving psoriasis and lichen planus, although local reactions were documented in some studies. In the psoriasis investigation by Paulsen *et al.*, local adverse effects were reported by approximately 55% of participants, with skin dryness being the most frequent complaint [5]. In contrast, the psoriasis trial by Syed *et al.* and several placebo-controlled lichen planus investigations did not identify major treatment-related adverse events [4,7,8,14]. These findings indicate that tolerability may vary according to the formulation and clinical setting, and that the absence of adverse events in small trials cannot establish long-term safety.

Orally administered Aloe vera requires separate consideration because the systemic safety profile may differ substantially from that of topical preparations. In the randomized ulcerative colitis trial, adverse events were generally mild and did not differ substantially between the intervention and placebo groups during the four-week treatment period [3]. However, this observation provides limited reassurance regarding prolonged exposure, particularly because the trial involved a small number of participants and was not designed primarily to evaluate safety. In addition, the chemical composition of oral preparations varies according to whether they contain purified inner-leaf gel, whole-leaf extracts, or latex-associated constituents, making direct comparisons between products difficult.

Published case reports provide evidence of potentially significant hepatic adverse reactions associated with oral Aloe vera consumption. Bottenberg *et al.* described a case of hepatitis temporally associated with oral Aloe vera capsules, with improvement following discontinuation [16]. Yang *et al.* subsequently reported three cases of toxic hepatitis associated with oral Aloe vera preparations [17]. Although these observations cannot establish the incidence of hepatotoxicity or demonstrate that all oral formulations carry equivalent risks, they indicate that clinically important liver injury may occur. This finding is particularly relevant in autoimmune and immune-mediated diseases, where patients may have pre-existing organ involvement or receive medications with potential hepatic adverse effects.

Taken together, the available safety data suggest that selected topical preparations may be reasonably tolerated during short treatment periods, whereas the long-term safety of orally administered Aloe vera remains insufficiently characterized. The small samples, limited follow-up, inconsistent formulation descriptions, and incomplete adverse-event reporting across studies prevent reliable comparisons of safety between preparations. These limitations should be considered when interpreting the potential clinical applicability of Aloe vera in chronic autoimmune and immune-mediated diseases.

## 4. Discussion

### 4.1. Principal Findings and Clinical Significance

The present review demonstrates that the human clinical evidence concerning Aloe vera in autoimmune and immune-mediated diseases remains limited, heterogeneous, and strongly dependent on the clinical condition, formulation, and route of administration. Although several investigations have reported favorable outcomes, these findings cannot be generalized across autoimmune disorders or interpreted as evidence of a universal immunomodulatory effect. The most consistent preliminary signals involve local symptomatic improvement in selected mucocutaneous conditions, particularly oral and vulvar lichen planus, whereas the evidence supporting systemic disease modification after oral administration is substantially weaker. The nonrandomized investigation in Hashimoto thyroiditis reported reductions in thyroid-stimulating hormone and thyroperoxidase antibody concentrations, while the randomized trial in ulcerative colitis demonstrated a higher clinical response rate with oral Aloe vera than with placebo <sup>[2,3]</sup>. Nevertheless, neither study established sustained disease modification, prevention of complications, or long-term therapeutic benefit. In psoriasis, randomized trials yielded contradictory findings, ranging from substantial improvement to outcomes favoring placebo <sup>[4-6]</sup>, while the investigation in Sjögren disease addressed symptomatic xerostomia without demonstrating systemic autoimmune benefit <sup>[11]</sup>. Collectively, these observations indicate that the potential therapeutic role of Aloe vera should be evaluated through disease-specific clinical hypotheses rather than broad assumptions about its anti-inflammatory or immunomodulatory properties.

An important consideration is the distinction between symptomatic relief, changes in surrogate biomarkers, and clinically meaningful modification of disease activity. Reduction of pain, burning sensation, erythema, or mucosal discomfort may represent a valuable therapeutic outcome, particularly in chronic conditions associated with substantial impairment of quality of life. However, these improvements do not necessarily indicate suppression of the pathogenic immune mechanisms responsible for the disease. Similarly, changes in circulating autoantibody concentrations or biochemical markers may suggest biological activity without establishing improved long-term prognosis. This distinction is particularly relevant to autoimmune diseases in which progressive tissue damage may occur despite partial symptomatic improvement. Accordingly, future investigations should combine patient-reported outcomes with objective measures of inflammatory activity, organ function, disease progression, and sustained therapeutic response.

### 4.2. Biological Plausibility and the Immunomodulatory Paradox

The pharmacological interest in Aloe vera is supported by its chemically diverse composition, which includes polysaccharides, glycoproteins, phenolic compounds, and other biologically active constituents. Experimental investigations have suggested that selected compounds may influence inflammatory signaling, oxidative stress, cellular proliferation, epithelial repair, and immune-cell function <sup>[1]</sup>. However, the term immunomodulation encompasses several biologically distinct processes, including stimulation of innate immune responses, alteration of cytokine production, enhancement of tissue repair, and suppression of selected

inflammatory pathways. These activities are not necessarily equivalent and may have different consequences depending on the underlying disease. In autoimmune disorders, where pathogenic immune activation contributes to tissue injury, stimulation of certain immune pathways may not be therapeutically desirable. Conversely, inhibition of selected inflammatory mediators may provide local benefits without substantially influencing systemic autoimmunity. Therefore, the biological effects of Aloe vera should be interpreted in relation to the specific constituent, its concentration, the route of administration, and the immunopathological mechanisms of the target disease.

This complexity creates an important paradox in the proposed use of Aloe vera for autoimmune conditions. A preparation that promotes wound healing or stimulates macrophage activity in an experimental model may not necessarily suppress the adaptive immune responses responsible for autoimmune tissue injury. Furthermore, the effects of isolated constituents cannot automatically be extrapolated to whole-leaf extracts, purified inner-leaf gels, or commercially available preparations. Botanical processing may alter the concentrations of relevant compounds, while differences in extraction, preservation, and formulation stability may influence biological activity. These factors could partly explain why clinical trials involving the same botanical species have produced inconsistent results. Consequently, future investigations should incorporate detailed chemical characterization, standardized manufacturing procedures, and mechanistic endpoints relevant to the disease being studied. Without such information, even well-designed clinical trials may be difficult to reproduce, and differences between studies may reflect formulation heterogeneity rather than genuine variation in therapeutic efficacy.

### 4.3. Oral Versus Topical Administration: Distinct Therapeutic Questions

One of the most important findings of this review is the marked difference between the evidence supporting topical applications and that concerning oral administration. Topical preparations permit direct exposure of affected skin or mucosal surfaces to botanical constituents and may produce beneficial effects through hydration, epithelial protection, wound repair, or modulation of local inflammation. These mechanisms may be sufficient to improve lesion appearance or alleviate symptoms without producing meaningful systemic concentrations of active compounds. Oral administration, in contrast, introduces additional uncertainties involving gastrointestinal stability, absorption, metabolism, systemic bioavailability, tissue distribution, and elimination. Moreover, different oral products may contain substantially different fractions of the Aloe leaf, resulting in variable pharmacological properties and safety profiles. Therefore, favorable outcomes obtained with topical formulations cannot justify recommendations for oral supplementation, and beneficial effects observed after ingestion in gastrointestinal disorders should not automatically be interpreted as evidence of systemic immunomodulation.

The available clinical investigations illustrate these distinctions. In psoriasis and lichen planus, most favorable results were obtained with preparations applied directly to inflammatory lesions, suggesting that local mechanisms may account for at least part of the observed benefit <sup>[4-10,14]</sup>. In Sjögren disease, the investigated formulation acted as an oral

moisturizer and did not demonstrate modification of glandular autoimmunity or systemic disease activity <sup>[11]</sup>. In ulcerative colitis, orally administered gel may have interacted directly with the intestinal mucosa, but the clinical trial did not establish whether the observed improvement resulted from local epithelial effects, modulation of mucosal inflammatory pathways, or systemic mechanisms <sup>[3]</sup>. In Hashimoto thyroiditis, the reported biochemical changes suggest a potentially different biological action, but the absence of randomized confirmation and direct mechanistic measurements prevents reliable attribution to systemic immune modulation <sup>[2]</sup>. These observations reinforce the importance of designing pharmacokinetic and pharmacodynamic studies tailored to each administration route rather than treating all Aloe vera preparations as therapeutically interchangeable.

#### 4.4. Interpretation of the Evidence in Hashimoto Thyroiditis and Ulcerative Colitis

The findings in Hashimoto thyroiditis are particularly interesting because they involve an organ-specific autoimmune disorder and include changes in an autoantibody-related outcome. Metro *et al.* reported reductions in TSH and TPOAb concentrations accompanied by an increase in FT4 following nine months of oral Aloe vera juice consumption <sup>[2]</sup>. Although these results suggest a potentially relevant biological effect, the nonrandomized design, small sample, and use of an untreated comparison group limit causal interpretation. In addition, circulating TPOAb concentrations are not validated as a standalone measure of therapeutic response, and their reduction does not necessarily indicate prevention of thyroid destruction or restoration of normal thyroid physiology. The absence of data concerning long-term progression to overt hypothyroidism, subsequent levothyroxine requirements, and sustained outcomes after discontinuation further restricts clinical applicability. Thus, the investigation provides a rationale for future randomized studies but does not establish Aloe vera as an effective treatment for autoimmune thyroiditis.

The ulcerative colitis trial provides stronger protection against confounding because of its randomized, double-blind, placebo-controlled design, but its results also require careful interpretation. Langmead *et al.* reported a statistically significant improvement in clinical response with oral Aloe vera gel, whereas differences in clinical remission, sigmoidoscopic remission, and histological remission were not statistically significant <sup>[3]</sup>. This distinction is clinically important because contemporary management of ulcerative colitis emphasizes sustained remission and objective control of mucosal inflammation rather than temporary symptom reduction alone. Furthermore, the short treatment period and small sample limited the ability to assess long-term efficacy, relapse prevention, and uncommon adverse events. The study therefore supports further investigation of standardized oral preparations, particularly as adjunctive interventions, but does not provide sufficient evidence to replace established therapies. Future trials should incorporate validated disease activity indices, endoscopic and histological outcomes, inflammatory biomarkers, and longer follow-up to determine whether any observed symptomatic benefit translates into clinically meaningful disease control.

#### 4.5. Contradictory Findings in Psoriasis and the Importance of Formulation Standardization

The psoriasis literature provides a particularly clear example of the difficulties associated with botanical clinical research. Syed *et al.* reported a substantial improvement in plaque psoriasis with a hydrophilic cream containing 0.5% Aloe vera extract, with clinical clearance occurring in 83.3% of treated patients compared with 6.7% of those receiving placebo <sup>[4]</sup>. However, Paulsen *et al.* subsequently found that a commercial Aloe vera gel did not outperform placebo in a randomized within-patient comparison, with the reported difference actually favoring placebo <sup>[5]</sup>. Choonhakarn *et al.* later observed a greater reduction in PASI scores with a topical Aloe vera preparation than with triamcinolone acetonide 0.1%, although improvements in dermatology-related quality of life were similar between groups <sup>[6]</sup>. These apparently contradictory findings should not be interpreted simply as evidence that some trials were positive and others negative. Rather, they highlight the possibility that different preparations possess different biological properties and that formulation vehicles, botanical concentrations, and outcome definitions may substantially influence treatment effects.

The comparator also plays an essential role in interpreting these investigations. A hydrophilic cream or moisturizing gel may independently improve skin hydration, barrier function, and local discomfort, potentially producing clinically meaningful changes even in the absence of a specific botanical effect. Furthermore, the distinction between a placebo-controlled trial and an active-comparator trial is important because they address different therapeutic questions. A study showing improvement with Aloe vera relative to a corticosteroid over a short period does not necessarily establish superiority in long-term disease control, relapse prevention, or safety. The absence of post-treatment follow-up in some investigations is especially relevant in psoriasis, where recurrence after discontinuation is common. Taken together, the available evidence does not support a general conclusion that topical Aloe vera is consistently effective for psoriasis, but it does justify further investigation of chemically standardized formulations under rigorous clinical conditions.

#### 4.6. Lichen Planus as a Potentially Promising Local Indication

Among the conditions evaluated, lichen planus appears to provide the most consistent preliminary signal of local clinical benefit. Placebo-controlled trials involving oral and vulvar lichen planus reported substantial improvements in clinical lesions and symptoms, including reductions in burning sensation and pain <sup>[7,8,14]</sup>. These findings are clinically relevant because mucosal lichen planus may cause persistent discomfort, interfere with eating and oral hygiene, and substantially impair quality of life. The potential value of a well-tolerated topical adjunctive intervention is therefore understandable, particularly in patients requiring prolonged symptomatic management. Nevertheless, the interpretation of these findings must consider the relatively small sample sizes, variability in outcome measures, differences in formulation, and limited information concerning long-term recurrence.

The active-comparator trials provide a more cautious perspective. Mansourian *et al.* reported improvement with

both Aloe vera mouthwash and triamcinolone acetonide, but the observed similarity in outcomes does not establish formal therapeutic equivalence <sup>[9]</sup>. Reddy *et al.* also reported favorable outcomes with Aloe vera gel compared with triamcinolone, although the complete numerical results were not independently verified in the present evidence extraction <sup>[10]</sup>. More recently, Vaidya *et al.* found that clobetasol propionate was more effective than a combined topical and oral Aloe vera intervention <sup>[15]</sup>. These findings suggest that Aloe vera may have a potential role in local symptom management but should not be considered an established substitute for topical corticosteroids. Moreover, because the Vaidya trial combined oral and topical administration, it cannot determine whether ingestion contributed independently to the observed response. Future investigations should evaluate standardized topical preparations as adjuncts to established therapy, incorporate predefined noninferiority or superiority hypotheses when appropriate, and include long-term assessment of recurrence and mucosal disease control.

#### 4.7. Clinical Relevance to Rheumatology and Systemic Autoimmune Diseases

The limited availability of clinical evidence in systemic rheumatic autoimmune diseases represents an important gap. Although Aloe vera has been extensively investigated in experimental models of inflammation and immune regulation, the verified human evidence identified in this review did not establish controlled therapeutic trials in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathies, systemic vasculitides, or antiphospholipid syndrome. Similarly, sufficiently documented clinical efficacy trials were not established in several organ-specific autoimmune conditions, including autoimmune hepatitis, autoimmune pancreatitis, and autoimmune inflammatory cardiac diseases. These observations should not be interpreted as definitive proof that no such investigations exist, particularly because regional and non-English-language databases were not exhaustively screened. Nevertheless, they indicate that the current clinical evidence is insufficient to support recommendations for Aloe vera in systemic rheumatic autoimmune disorders.

This gap is especially relevant because the immunopathological mechanisms of systemic autoimmune diseases differ substantially from those of localized inflammatory skin or mucosal conditions. In systemic lupus erythematosus, for example, pathogenic autoantibodies, immune complexes, complement activation, and organ-specific inflammatory responses contribute to disease manifestations, whereas rheumatoid arthritis involves complex interactions among adaptive immunity, synovial inflammation, and tissue-destructive pathways. A preparation that improves epithelial repair or reduces superficial inflammation cannot be assumed to influence these mechanisms. Before clinical trials are undertaken in systemic autoimmune diseases, translational investigations should determine whether standardized Aloe vera preparations affect relevant immune pathways at concentrations achievable in humans, while carefully evaluating the possibility of undesirable immune stimulation or interactions with conventional immunosuppressive treatment.

#### 4.8. Safety, Hepatotoxicity, and Implications for Long-Term Use

Safety represents a major consideration in the evaluation of Aloe vera, particularly when oral preparations are proposed for chronic diseases requiring prolonged treatment. Although most short-duration topical trials reported acceptable tolerability, these findings cannot be generalized to all commercial products or extended exposure. The chemical composition of Aloe vera preparations varies according to the plant fraction used, processing methods, and formulation characteristics, and products containing whole-leaf extracts or latex-derived constituents may differ substantially from purified inner-leaf gels. Moreover, patients with autoimmune and immune-mediated diseases frequently receive multiple medications, including immunosuppressive agents and drugs requiring hepatic monitoring, making potential adverse reactions and interactions especially relevant.

Published reports of liver injury associated with oral Aloe vera preparations provide an important warning against assuming that botanical products are inherently safe. Bottenberg *et al.* described hepatitis temporally associated with oral Aloe vera capsule consumption, while Yang *et al.* reported additional cases of toxic hepatitis related to oral preparations <sup>[16,17]</sup>. Although case reports cannot establish incidence or quantify population-level risk, they demonstrate that clinically significant hepatic adverse reactions are possible. This is particularly important because drug-induced liver injury may present with biochemical or histological features resembling autoimmune hepatitis, potentially complicating diagnosis in patients with pre-existing immune-mediated disorders. Future clinical trials should therefore incorporate systematic adverse-event reporting, appropriate laboratory monitoring, documentation of concomitant medications, and sufficient follow-up to identify delayed toxicity. Pharmacovigilance studies and improved manufacturing standards are also needed to characterize the safety profiles of specific formulations rather than attributing a uniform risk profile to the botanical species as a whole.

#### 4.9. Methodological Priorities for Future Clinical Trials

Future clinical investigations should address several methodological limitations repeatedly observed in the existing literature. The first priority is standardization of the botanical intervention, including precise identification of the plant species, leaf fraction, extraction process, chemical composition, concentration of relevant constituents, and stability of the final formulation. Without such information, reproducibility is compromised, and differences between studies cannot be interpreted reliably. A second priority is the use of adequately powered randomized controlled designs with appropriate allocation concealment, blinding, and comparator selection. Trials comparing Aloe vera with established therapies should prespecify whether the objective is to demonstrate superiority, noninferiority, or adjunctive benefit, and statistical analyses should reflect the chosen hypothesis.

The selection of clinically meaningful endpoints is equally important. In autoimmune thyroiditis, outcomes should extend beyond autoantibody concentrations to include thyroid function, progression to overt hypothyroidism, and subsequent treatment requirements. In ulcerative colitis, sustained clinical remission, endoscopic improvement, and

histological outcomes should be prioritized. In psoriasis and lichen planus, validated disease severity scores, symptom measures, quality of life, recurrence, and long-term safety should be incorporated. Studies involving systemic autoimmune diseases should include objective measures of disease activity, organ involvement, and functional outcomes. In addition, mechanistic investigations should determine whether the administered formulation produces relevant pharmacological effects at clinically achievable concentrations. These requirements would help distinguish genuine therapeutic activity from nonspecific symptomatic improvement, placebo effects, or changes attributable to the formulation vehicle.

#### 4.10. Strengths and Limitations of the Present Review

A principal strength of this review is its cross-specialty approach, which permits comparison of clinical investigations involving Aloe vera across endocrinology, gastroenterology, dermatology, rheumatology, and oral medicine. By distinguishing classical autoimmune disorders from broader immune-mediated inflammatory diseases, the review avoids treating biologically heterogeneous conditions as interchangeable. Another strength is the explicit separation of oral and topical administration, which helps prevent inappropriate extrapolation of local symptomatic benefits to systemic disease modification. The inclusion of both positive and negative randomized trials provides a more balanced interpretation than assessments focusing exclusively on favorable outcomes, while the discussion of hepatotoxicity and formulation heterogeneity highlights clinically relevant issues that are frequently overlooked in botanical medicine research.

Nevertheless, several limitations must be acknowledged. The literature identification process was targeted and citation-based rather than a fully documented exhaustive systematic search of all relevant international databases, and a complete screening log was not available. Consequently, formal PRISMA identification and exclusion counts could not be reported, and some eligible investigations may not have been captured, particularly those published in regional or non-English-language sources. The included studies were heterogeneous in design, formulation, comparator, treatment duration, and outcome measures, precluding meaningful quantitative pooling. Several investigations involved small samples, incomplete reporting, or limited follow-up, and formal independent risk-of-bias assessment and certainty-of-evidence grading were not undertaken. These limitations restrict the strength of the conclusions and indicate that the present review should be interpreted as a critical clinical evidence map rather than a definitive systematic estimate of treatment efficacy. Despite these constraints, the synthesis identifies clinically relevant patterns, clarifies the distinction between symptomatic and disease-modifying effects, and establishes priorities for more rigorous research into the potential role of Aloe vera in autoimmune and immune-mediated diseases.

#### 6. Conclusion

The available human clinical evidence suggests that Aloe vera may have therapeutic potential in selected autoimmune and immune-mediated diseases, particularly when administered topically for inflammatory skin and mucosal conditions. However, the findings remain heterogeneous, frequently derived from small clinical trials, and strongly

influenced by differences in botanical formulations, administration routes, treatment duration, and outcome measures. Among the conditions investigated, oral and vulvar lichen planus appear to provide the most consistent preliminary evidence of local symptomatic and clinical improvement, although larger randomized trials are necessary to establish comparative efficacy, durability of response, and long-term safety. In psoriasis, contradictory results prevent definitive conclusions regarding therapeutic effectiveness, while the available evidence in Sjögren disease is restricted to local xerostomia management rather than modification of the underlying autoimmune process. Oral administration has yielded potentially relevant findings in Hashimoto thyroiditis and ulcerative colitis, including changes in thyroid biochemical parameters and improved clinical response, respectively; nevertheless, these observations have not established sustained remission, prevention of disease progression, or systemic immunomodulatory efficacy. Furthermore, the occurrence of hepatotoxicity associated with oral Aloe vera preparations underscores the importance of distinguishing botanical formulations and systematically evaluating safety, particularly in patients receiving concomitant immunomodulatory therapies. Overall, Aloe vera should currently be considered an investigational or potentially adjunctive intervention rather than an established disease-modifying treatment for autoimmune disorders. Future research should prioritize chemically standardized preparations, adequately powered randomized controlled trials, validated disease-specific endpoints, longer follow-up, and integrated pharmacological and immunological assessments to determine whether the biological properties attributed to Aloe vera can translate into reproducible, clinically meaningful, and safe therapeutic benefits.

#### Declarations

##### Ethics Approval and Consent to Participate

Not applicable. This study is a critical scoping review based exclusively on previously published scientific literature and did not involve the recruitment of human participants, collection of identifiable patient information, or performance of new clinical interventions. Therefore, approval from an institutional ethics committee and informed consent were not required.

##### Consent for Publication

Not applicable. The manuscript does not contain identifiable individual patient information, personal images, or unpublished clinical data requiring consent for publication.

##### Availability of Data and Materials

All information analyzed in this review was obtained from previously published scientific articles cited in the reference list. The principal characteristics and clinical findings of the included studies are summarized in the accompanying tables. No new datasets or individual participant-level data were generated.

##### Competing Interests

The author declares no competing interests.

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The manuscript was initially developed in Portuguese and subsequently translated and refined in English with the assistance of ChatGPT (OpenAI). Artificial intelligence-assisted technology was used to support language translation, grammatical revision, structural organization, and editorial refinement. The author retained responsibility for the scientific content, interpretation of findings, verification of references, and critical revision of the manuscript. Artificial intelligence was not considered an author.

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