Systematic Review

Exploring the Therapeutic Potential of Phytochemicals in Autoimmune Diseases: A Systematic Literature Review

ABSTRACT

Autoimmune diseasesare a significant clinical challenge worldwide. Traditional treatments often have adverse effects, leading to a growing interest in alternative therapies. This systematic review attempts a qualitatively synthesize of current evidence on the therapeutic potential of phytochemicals in autoimmune diseases. The review includes randomized controlled trials (RCTs), clinical trials (CTs) and observational studies published between 2013 to 2023. Databases searched include PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). A total of 676 studies were retrieved from various databases. We followed the PICO framework to develop the review protocol and registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) with registration number INPLASY202460031.

In the context of rheumatoid arthritis, eight potential phytochemicals have been identified, including sinomenine, curcumin, flavonol quercetin, eichhornia crassipes, apocynin, β-sitosterol, tanshinone IIA, and 3′3-diindolylmethane (DIM). For multiple sclerosis, five phytochemicals - berberine, 23-Hydroxy Ursolic Acid (23-OH UA), forskolin, sulforaphane (SFN), and moringin - have shown effectiveness. Flavonol quercetin and portulaca oleracea exhibit potential for treating type 1 diabetes. Furthermore, curcumin and quercetin have demonstrated potential activity against oral lichen planus (OLP). Anatabine has shown effectiveness against Hashimoto's Thyroiditis, while thuja occidentalis is a potential option for the treatment of Inflammatory Bowel Disease (IBD). Additionally, agave tequilana shows potential efficacy against Systemic Lupus Erythematosus (SLE). These natural compounds offer promising alternative or adjunctive treatments with fewer adverse effects compared to conventional therapies. Nevertheless, rigorous clinical validation is necessary to translate these findings into clinical practice and establish standardized guidelines for their use in autoimmune disease management.

Keywords: Autoimmune diseases, Phytochemicals, Clinical trials. In vitro animal studies, Systematic review.

1. INTRODUCTION

Autoimmune diseases (AIDs) encompass a wide range of disorders characterized by an abnormal immune response against the body's own tissues, leading to persistent inflammation and tissue damage [1]. These conditions can affect individuals of all ages, with a higher prevalence in women. One of the key immune responses in these diseases is the production of autoantibodies, which serve as important biomarkers for the diagnosis, categorization, and monitoring of disease activity [2]. AIDs include but are not limited to, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes and psoriasis [3].

Despite the variation in their clinical manifestations, the underlying pathology of autoimmune diseases is largely driven by dysregulation of the immune system. This dysregulation often involves a complex

interplay of genetic, environmental, and immunological factors, leading to the development of autoimmunity and sustained inflammatory processes [2][4].

Conventional treatments for autoimmune diseases primarily involve the use of immunosuppressive drugs such as corticosteroids, methotrexate, and biologics [5]. While these treatments can effectively reduce disease activity and control symptoms, they are associated with significant adverse effects, including increased susceptibility to infections, liver toxicity, oxidative stress and cardiovascular complications [6-10]. In addition, not every patient responds in the same way to these medications, and some patients may develop resistance, over time. This highlights the need for alternative or adjunctive treatments that can deliver therapeutic benefits with fewer side effects [10].

In recent years, a significant number of studies have investigated the therapeutic properties of phytochemicals [11]. These bioactive compounds derived from plants, have attracted significant attention from researchers and the pharmaceutical industry because of their potential therapeutic applications in various chronic diseases, including AIDs [12][13]. For example, compounds such as curcumin from turmeric, resveratrol from grapes, and quercetin from onions and apples are well known for their anti-inflammatory, antioxidant, and immunomodulatory properties, which make them promising candidates for the treatment and management of AIDs [14]. The therapeutic potential of these phytochemicals in autoimmune diseases has been supported by a growing body of preclinical and clinical evidence [15]. However, their effectiveness and safety profile in the treatment of AIDs remain to be fully elucidated [16].

This systematic review qualitatively synthesizes current evidence on the therapeutic potential of phytochemicals in AIDs, with a focus on their efficacy and safety. The primary objectives of this review are to evaluate the efficacy of phytochemicals in improving disease activity, inflammatory markers, and quality of life in individuals with autoimmune diseases. Moreover, this review will compare the effectiveness of phytochemicals with that of conventional treatments and assess the safety profile of these bioactive compounds. The significance of this review lies in its potential to identify alternative therapeutic options for patients with autoimmune diseases.

2. METHODS

This systematic review aims to explore the therapeutic potential of different phytochemicals against autoimmune diseases. We followed the PICO (population, intervention, comparison,outcome)framework to develop the review protocol. The protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) with registration number INPLASY202460031 [17][18].

2.1. Study characteristics

The experimental studies to be included were randomized controlled trials (RCTs), clinical trials (CTs), cohort studies, case–control studies, and observational studies published between 2013 and 2023. Only fully open-access studies with a detailed and scientific methodology to measure the therapeutic potential of phytochemicals are included.
The databases searched included PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL).

2.2. Quality assessment/Risk of bias analysis

The risk of bias was assessed via the Cochrane risk of bias tool for RCTs, the Newcastle–Ottawa Scale for observational studies and SYRCLE's risk of bias tool for animal studies. Two reviewers independently assessed the risk of bias, and disagreements were resolved by consensus.

3. RESULTS AND DISCUSSION

A total of 545 studies were retrieved from various databases, with an additional 131 studies sourced from references and other literature. After careful screening and eligibility assessment, 19 studies were found to be suitable for inclusion in the review. These selected studies encompassed four randomized control trials, fourteen in vitro animal studies, and one observational study (see Figure 1,which shows the PRISMA flow diagram of the study selection process (Tables 1, 2 and 3 summarize the studies selected).

A variety of phytochemicals have been evaluated for their therapeutic potential against several autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, oral lichen planus, inflammatory bowel disease, systemic lupus erythematosus, and Hashimoto's thyroiditis. The potential phytochemicals identified in this review include sinomenine, curcumin, flavonol quercetin, Eichhornia crassipes, apocynin, β-sitosterol, tanshinone IIA, 3′3-diindolylmethane (DIM), berberine, 23-hydroxy ursolic acid (23-OH UA), forskolin, sulforaphane (SFN), moringin, portulaca oleracea, anatabine, Thuja occidentalis and agave tequilana (see Table 4).

These findings indicate the promising role of phytochemicals in modulating immune responses, reducing inflammation, and potentially offering safer alternatives to conventional treatments.

Figure 1: PRISMA 2020 flow diagram for systematic reviews, which included searches of databases, registers and other sources

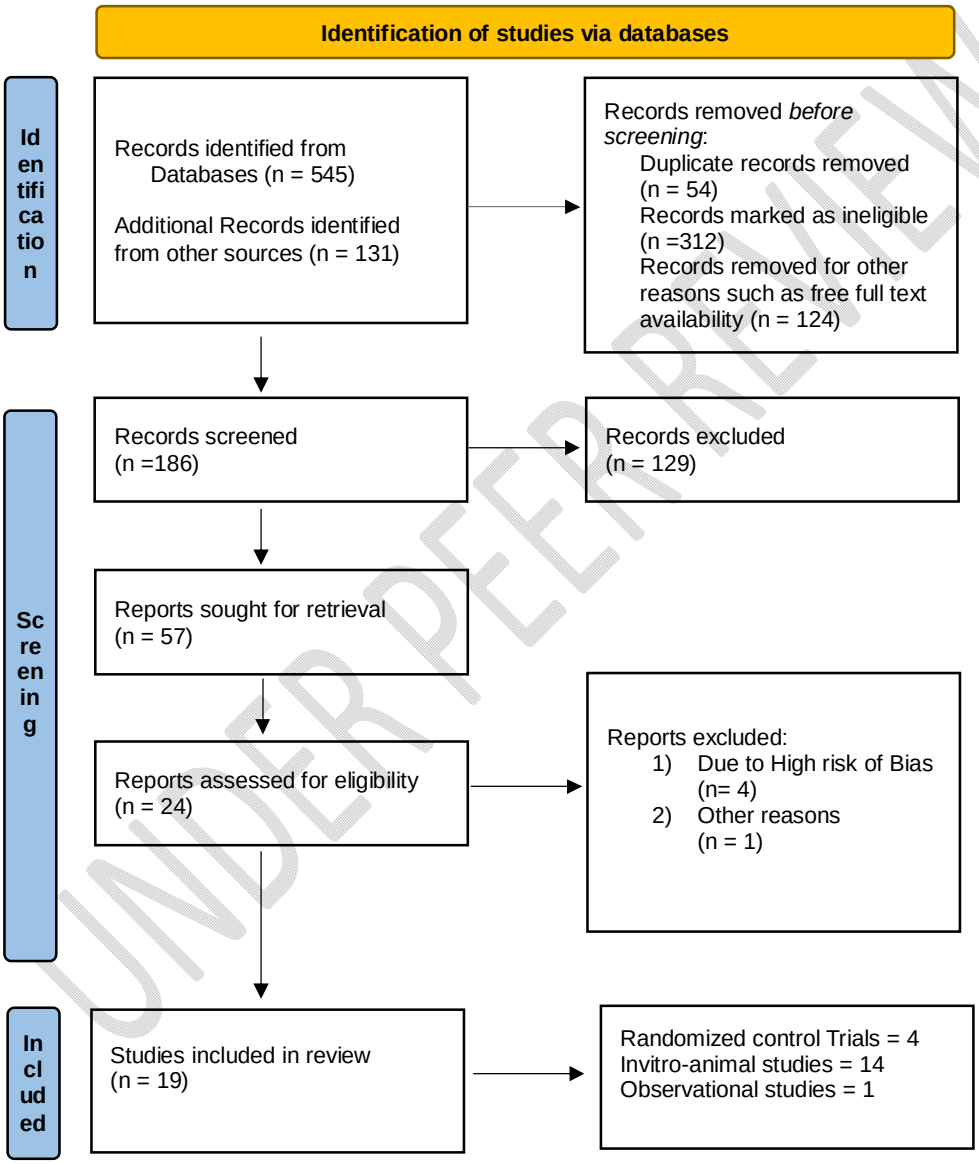

Table 1. Summary of selected randomized control trials for review.

First Author, Year	Autoimmune disease	Phytochemical	Type of comparator	Dosage	Route of administration	Findings
Li et al., 2018 [19]	Rheumatoid Arthritis (RA)	Sinomenine	methotrexate	10 to 50 µg/mL per day	~	Sinomenine regulated and reduced RA activity in clinical settings.
Khan et al., 2022 [20]	Rheumatoid Arthritis	Curcumin	~	180 mg/–day	Oral tablets	Curcumin was found to be more effective in patients with rheumatoid arthritis when given with strengthening exercises.
Kia et al., 2020 [21]	Oral lichen planus (OLP)	Curcumin	Prednisolone	80 mg/–day	Oral tablets	Oral Curcumin is an alternative therapy for OLP in patients with contraindicated Corticosteroids
Schmeltz et al., 2013 [22]	Hashimoto's thyroiditis	Anatabine	Placebo	0.17 to 0.25 mg/kg/day	Oral tablets	Anatabine-treated patients had a significant reduction in absolute serum thyroglobulin antibody levels from baseline by study end relative to those receiving placebo

Table 2: Summary of selected in vitro animal studies for review.

First Author, Year	Autoimmune disease	Animal Used for Experiment	Phytochemical	Type of comparator	Dosage (mg/kg/day)	Route of administration	Findings
Mosawy et al., 2014 [23]	Type 1 diabetes	C57BL/6 mice	Flavonol quercetin	Placebo (citrate buffer)	6	Intraperitoneal injection	Treatment with quercetin significantly reduced diabetes-induced platelet hyperaggregability in response to platelet agonist stimulation.
Tavaf et al., 2023 [24]	Experimental autoimmune encephalomyelitis (EAE) [Animal model of multiple sclerosis]	C57BL/6 mice	Berberine	~	10 -30	oral gavage	Berberine has a protective effect on disease development and alleviating disease status in EAE
Asmis et al., 2024 [25]	Experimental Autoimmune Encephalomyelitis (EAE) in a Murine Model of Multiple Sclerosis	C57BL/6 mice	23-Hydroxy ursolic acid (23-OH UA)	low-calorie maintenance diet	~	Oral	Dietary 23-OH represents an effective oral adjunct therapy for the prevention and treatment of relapsing-remitting Multiple Sclerosis.
Sattar et al., 2023 [26]	Rheumatoid arthritis	Sprague–Dawley rats	Eichhornia crassipes	piroxicam	100	Sub plantar injection	E. crassipes suppressed arthritis progression, reduced paw edema, and improved ankle joint histopathological and haematological analyses confirmed reduction of rheumatoid arthritis (RA).
Aman et al., 2023 [27]	Rheumatoid arthritis	Wistar rats	Apocynin gel	Diclofenac sodium gel	30	Topical Administration	Study proved the therapeutic activity of the APO-hybrid NPs-based gel formulation against Complete Freund's Adjuvant-induced rheumatoid arthritis (CFA-induced RA) in rats
Rakhshandeh et al., 2022 [28]	Type 1 diabetes	Wistar rats	Portulaca oleracea	~	100 -300	oral gavage	Portulaca oleracea extract significantly ameliorated streptozotocin-induced diabetes and other parameters that were

							elevated.
Kapoor et al., 2022 [29]	Multiple sclerosis	Wistar rats	Forskolin	Fingolimod (FNG), Simvastatin (SIM), Donepezil (DON), and Memantine (MEM)	40	orally	FSK therapy restored brain mitochondrial-ETC complex enzymes and neurotransmitter levels while decreasing inflammatory cytokines and oxidative stress markers. The Luxol fast blue (LFB) stain results further indicate FSK's neuroprotective potential in preventing oligodendrocyte death.
Zhang et al., 2020 [30]	Rheumatoid arthritis	Wistar rats	β-sitosterol solid lipid nanoparticles	Indomethacin	2.5 and 25	orally	β-sitosterol solid lipid nanoparticles showed the antiarthritic effect via suppression of NF-kB and activation of HO-1/Nrf-2 pathway.
Du et al., 2020 [31]	Rheumatoid arthritis	C57BL/6 mice	Tanshinone IIA	sodium carboxylmethyl cellulose	300	oral gavage	The effects of Tan IIA on RA can be attributed to its influence on different signalling pathways, including MAPK, AKT/mTOR, HIF-1, and NF-kB. The compound Tan IIA has great therapeutic potential for RA treatment.
Stan et al., 2019 [32]	Inflammatory bowel disease	CD1 mice	Thuja occidentalis	Ethanol	5, 25 and 50	oral gavage	Study proved that administration of 25 or 50 mg Thuja occidentalis inhibited the inflammatory process induced by TNBS in the intestine
Du et al., 2019 [33]	Rheumatoid arthritis	C57BL/6 mice	3′3-Diindolylmethane (DIM)	Sodium carboxylmethyl cellulose suspension	10	oral gavage	DIM inhibited proliferation, migration and invasion of RA-FLSs and reduce proinflammatory factors induced by TNF-α in vitro by blocking MAPK and AKT/mTOR pathway and prevent inflammation and knee joint destruction in vivo, which suggests that DIM might have therapeutic potential for RA.
Yoo et al., 2019 [34]	Experimental Autoimmune Encephalomyelitis (EAE) in a Murine Model of Multiple Sclerosis	C57BL/6 mice	Sulforaphane (SFN)	phosphate-buffered saline	50	oral	The SFN treatment showed anti-inflammatory and antioxidative effects in the EAE mice. SFN has neuroprotective effects via anti-inflammatory processing, so it could be a new therapeutic or nutritional supplement for MS.
Gutiérrez Nava et al., 2017 [35]	Systemic lupus erythematosus	BALB/c mice	Agave tequilana	Methotrexate and prednisone	10	oral	A. tequilana contains active compounds with the capacity to modify the evolution of the systemic autoimmunity type-SLE on a murine model.
Giacoppo et al., 2016 [36]	Experimental Autoimmune Encephalomyelitis (EAE) in a Murine Model of Multiple Sclerosis	C57BL/6 mice	Moringin	~	10	Intraperitoneal injection	Study has found that Moringin can reduce apoptosis by decreasing the expression of the Fas ligand and cleaved caspase 9. At the same time, it increases the expression of antioxidant Nrf2 in EAE mice. These results provide an interesting discovery, identifying Moringin as a modulator of the Wnt–β-catenin signalling cascade and a potential new therapeutic target for the treatment of MS.

Table 3: Summary of the selected observational studies for review.

First Author, Year	Autoimmune disease	Phytochemical	Type of comparator	Dosage	Route of administration	Findings
Zhao et al., 2022 [37]	Oral lichen planus	Quercetin		40 μM	~	In vitro experiments revealed that quercetin affects the Th1/Th2 balance by targeting IL-6 and IFN-γ to regulate the immune system for treating OLP. Quercetin significantly impacts the apoptosis and migration of T lymphocytes in OLP patients.

Table 4: List of autoimmune diseases and potential phytochemicals identified as having therapeutic effects

Autoimmune Disease	Potential Phytochemical
Rheumatoid Arthritis (RA)	Sinomenine Curcumin Flavonol Quercetin Eichhornia Crassipes Apocynin β-Sitosterol Tanshinone IIA 3′3-Diindolylmethane (DIM)
Multiple Sclerosis (MS)	Berberine 23-Hydroxy Ursolic Acid (23-OH UA) Forskolin Sulforaphane (SFN) Moringin
Type 1 Diabetes	Flavonol Quercetin Portulaca Oleracea
Oral Lichen Planus (OLP)	Curcumin Quercetin
Hashimoto's Thyroiditis	Anatabine
Inflammatory Bowel Disease (IBD)	Thuja Occidentalis
Systemic Lupus Erythematosus (SLE)	Agave Tequilana

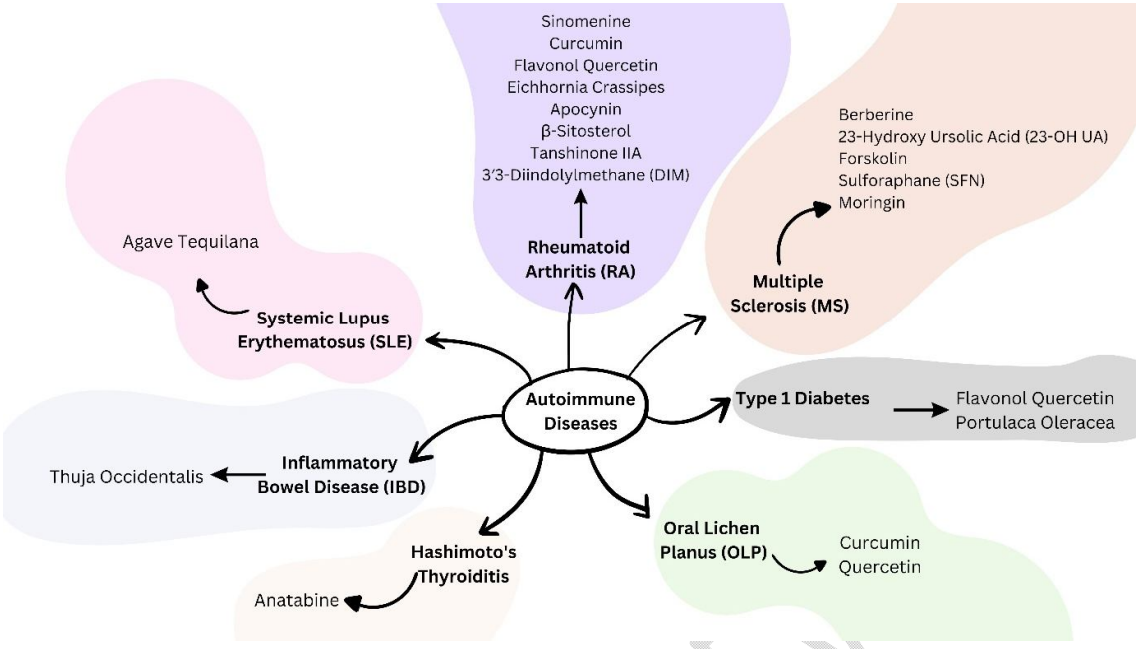

Figure 2: Illustration of Autoimmune diseases identified and potential phytochemicals for their treatment.

4. CONCLUSION

This systematic review provides compelling evidence supporting the utilization of phytochemicals in the management of autoimmune diseases. In the context of rheumatoid arthritis, eight potential phytochemicals have been identified, including sinomenine, curcumin, flavonol quercetin, Eichhornia crassipes, apocynin, β-sitosterol, tanshinone IIA, and 3′3-diindolylmethane (DIM). Five phytochemicals, namely, berberine, 23-hydroxyursolic acid (23-OH UA), forskolin, SFN (SFN), and moringin, have been shown to be effective against multiple sclerosis. The flavonols quercetin and Portulaca oleracea have potential for the treatment of type 1 diabetes.

Additionally, curcumin and quercetin have demonstrated potential activity against oral lichen planus (OLP). Anatabine has been shown to be effective against Hashimoto's thyroiditis, and Thuja occidentalis is a potential option for the treatment of inflammatory bowel disease (IBD). Furthermore, Agave Tequilana is another phytochemical with potential efficacy against systemic lupus erythematosus (SLE). Compared with conventional therapies, these natural compounds offer promising alternative or adjunctive treatments with fewer adverse effects.

However, rigorous clinical validation is necessary to translate these findings into clinical practice and establish standardized guidelines for their use in autoimmune disease management.

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