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Efficacy of nutraceuticals as adjunctive therapies in autoimmune diseases: A systematic review of clinical trials

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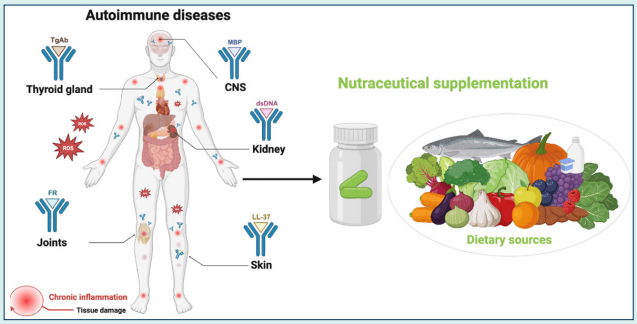
Abstract



Introduction: Autoimmune diseases are characterized by a dysregulation of the immune system, resulting in chronic inflammation and tissue damage. Although immunosuppressive therapies have advanced, their limited efficacy and the adverse effects associated with long-term use restrict their clinical utility, highlighting the need for alternative treatments. This study aimed to synthesize current evidence on the efficacy of nutraceutical interventions for these disorders.

Methods: A comprehensive search was conducted on PubMed, Embase, and ClinicalTrials.gov to identify studies published between 2010 and 2025 evaluating nutraceutical supplementation in patients with autoimmune diseases. Study selection and data extraction were performed according to predefined inclusion criteria.

Results: Thirty clinical trials involved 2,107 participants with rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, or Hashimoto's thyroiditis. Interventions included polyphenols, vitamins, minerals, omega-3 fatty acids, and probiotics, administered over 4 to 48 weeks, with sample sizes ranging from 24 to 351 participants. The studies demonstrated anti-inflammatory and immunoregulatory effects, as well as improvements in disease activity and clinical symptoms following supplementation with curcumin, probiotics, vitamin D, omega-3 fatty acids, baicalin, resveratrol, and quercetin. Additionally, reductions in autoantibody levels were observed after supplementation with curcumin, selenium, and genistein.

Conclusion: The available evidence suggests that these nutraceuticals are emerging as candidates with therapeutic potential for integration as adjunctive therapies in the management of autoimmune diseases.

Introduction

Autoimmune diseases are characterized by an enhanced and dysregulated immune system response against self-antigens, resulting in cellular and tissue damage.[1] They vary considerably in the organs they affect and in their clinical manifestations; some are confined to specific tissues, whereas others are systemic or widespread. Despite these differences, evidence indicates that they commonly progress through sequential phases of initiation, propagation, and resolution, which are associated with dysfunctions in the regulatory mechanisms of the immune response.[2] They constitute a growing public health problem, as they affect between 5% and 8% of the global population, and it is estimated that annual incidence has increased by 19.1% and prevalence by 12.5%.[3] In addition, a marked female predominance is observed, with women accounting for approximately 80% of diagnosed cases.[4] These disorders are associated with reduced life expectancy, impaired quality of life, and a substantial socioeconomic burden.[5-9] Accurate characterization of clinical symptomatology is essential for patient assessment and follow-up. Symptoms include pain, stiffness, fatigue, and impairments in quality of life, which can be quantified using validated scales that reflect disease severity.[10] Evaluation of therapeutic

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Review Highlights

What is the current knowledge?

- Immunosuppressive therapies have limited efficacy and are associated with adverse effects with long-term use.
- Diet has been linked to immune response and inflammatory processes.

What is new here?

- Patients with rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, and Hashimoto's thyroiditis show improvements in clinical outcomes following nutraceutical interventions.
- Polyphenols, vitamins, minerals, omega-3, and probiotics have been associated with modulation of clinical symptoms, inflammatory biomarkers, cytokines, autoantibodies, and T cell subpopulations.
- These findings suggest that nutraceuticals may have the potential to be considered as complementary therapies in the management of these diseases.

response focuses not only on improvements in clinical signs but also on the measurement of immunological biomarkers, such as T-cell subpopulations, cytokines, and autoantibodies, as well as inflammatory parameters, allowing for a comprehensive assessment of immune activity and the patient's inflammatory status.[10] Despite therapeutic advances achieved with conventional immunosuppressants, glucocorticoids, and biologics targeting key inflammatory mediators, clinical control remains limited in a considerable percentage of patients. For example, in rheumatoid arthritis, up to 64% of patients discontinue biologic therapies due to lack of efficacy, while in moderate to severe psoriasis, the dropout rate in the first year reaches 25% and in multiple sclerosis, 29% of patients discontinue treatment due to side effects and emotional burden.[11-13] Furthermore, these therapies have a nonspecific immunosuppressive effect associated with a higher risk of infections, malignancies, serious complications, and treatment discontinuation, compromising long-term adherence.[14-16] These limitations have driven the search for complementary strategies, among which diet represents a key determinant in the regulation of the immune system and the modulation of inflammatory processes.[17] Recent studies have shown that dietary components can influence the activation of inflammatory pathways and the progression of autoimmune diseases.[18-21] These effects are partly mediated by changes in the composition and functionality of the gut microbiota, which plays a central role in T-cell activation and differentiation, cytokine production, and maintenance of intestinal barrier integrity.[22] Disruption of this microbial balance leads to dysbiosis, characterized in autoimmune patients by a reduction in beneficial bacteria such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, along with an increase in proinflammatory species such as *Escherichia coli* and *Enterococcus gallinarum*.[22] This state promotes the expansion of T helper 17 cells (Th17) and the suppression of regulatory T cells (Treg), resulting in sustained secretion of inflammatory mediators and activation of signaling pathways including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT).[23] In this framework, bioactive food compounds have been identified as direct modulators of these immunological processes. Since the 1990s, clinical studies have evaluated the role of omega-3 fatty acids, vitamin D, selenium, probiotics, and polyphenols in patients with autoimmune diseases. Observational studies indicate that dietary patterns rich in these compounds may improve immune system function and contribute to the reduction of inflammation.[24,25] These findings have driven the development of nutraceuticals as an innovative therapeutic strategy, particularly in the context of pharmacological polytherapy, by enabling the controlled and safe administration of bioactive compounds with immunomodulatory effects.[26] Nevertheless, the available evidence remains limited and fragmented. Most studies have focused on a single nutraceutical or individual disease, making it difficult to draw comprehensive conclusions regarding clinical efficacy and underlying mechanisms. In this context, this systematic review aims to evaluate and synthesize the evidence on the efficacy of nutraceuticals as adjuvant therapies in autoimmune diseases, considering clinical symptomatology, immunological and inflammatory biomarkers, and the mechanisms that may explain their therapeutic effects.

Materials and Methods

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 guidelines for reporting systematic reviews.[27] This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with code CRD420261415948.

Search strategy and study selection

A comprehensive literature search was performed in PubMed, Embase, and ClinicalTrials.gov to identify clinical trials evaluating the use of nutraceuticals in autoimmune diseases. Studies published between 2010 and 2024 were considered. The final search date was March 20, 2025. Only articles published in English were included. No grey literature search was performed, as the focus was on peer-reviewed clinical trial evidence indexed in biomedical databases.

The complete search strategies, including MeSH and Emtree terms and keywords, are presented in Table 1.

All retrieved records were exported to Zotero, where duplicates were automatically removed and subsequently verified manually. Study selection was performed in two phases. First, titles and abstracts were screened for eligibility. Second, full-text articles were assessed according to predefined inclusion and exclusion criteria. The screening process was conducted independently by JCFI and LFML. Any discrepances between reviewers were resolved through discussion and consensus.

Table 1. Database and search strategies.

Database	Search strategy
PubMed	("Autoimmune Diseases"[Mesh] OR "Systemic Lupus Erythematosus"[Mesh] OR "Rheumatoid Arthritis"[Mesh] OR "Multiple Sclerosis"[Mesh] OR "Hashimoto Disease"[Mesh] OR "Psoriasis"[Mesh]) AND ("Curcumin"[Mesh] OR "Quercetin"[Mesh] OR "Resveratrol"[Mesh] OR "Genistein"[Mesh] OR "Baicalin"[All Fields] OR "Vitamin A"[Mesh] OR "Vitamin D"[Mesh] OR "Selenium"[Mesh] OR "Omega-3 Fatty Acids"[Mesh] OR "Probiotics"[Mesh]) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Randomized Clinical Trial"[All Fields]).
Embase	('autoimmune disease'/exp OR 'systemic lupus erythematosus'/exp OR 'rheumatoid arthritis'/exp OR 'multiple sclerosis'/exp OR 'hashimoto disease'/exp OR 'psoriasis'/exp) AND ('curcumin'/exp OR 'quercetin'/exp OR 'resveratrol'/exp OR 'genistein'/exp OR 'baicalin'/exp OR 'vitamin a'/exp OR 'vitamin d'/exp OR 'selenium'/exp OR 'omega 3 fatty acid'/exp OR 'probiotic agent'/exp) AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized clinical trial'/de).
ClinicalTrials.gov	Condition/disease: Autoimmune Diseases, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Multiple Sclerosis, Hashimoto Disease, Psoriasis; others terms: Clinical Trial, Randomized Controlled Trial, Randomized Clinical Trial; intervention/treatment: Curcumin, Quercetin, Resveratrol, Genistein, Baicalin, Vitamin A, Vitamin D, Selenium, Omega-3 Fatty Acids, Probiotics.

Inclusion and exclusion criteria

Eligible studies were clinical trials evaluating nutraceutical interventions in adult populations (≥ 18 years) of both sexes with a confirmed diagnosis of autoimmune disease. Diagnosis had to be established using validated international clinical criteria and supported, when available, by laboratory, histological, or imaging evidence.

Interventions included orally administered nutraceutical compounds such as vitamins, minerals, omega-3 fatty acids, probiotics, and polyphenols, with a minimum intervention duration of four weeks.

Comparator groups included placebo, standard care, or no intervention. Participants were required to have stable background therapy for at least two months prior to study initiation, without recent disease flares or relevant lifestyle changes that could influence treatment effects.

Outcomes of interest included changes in clinical symptomatology, autoantibody levels, inflammatory biomarkers, cytokines, and T cell subpopulations.

Studies were excluded if they involved pediatric populations, observational designs or preclinical models. Trials were also excluded when nutraceutical effects could not be clearly isolated due to combined or multi-component interventions, or when outcome data were insufficient. Additional exclusions included the use of non-validated outcome measures or self-reported non-standardized scales.

Data extraction and synthesis

Information from the included studies was independently collected by JFCI and LFML using a structured matrix to systematize the data. The following details were recorded: author and year of publication, country, sample size, diagnosis, intervention duration, type and dose of supplement, and reported outcomes. Any discrepancies were resolved by consensus between reviewers, and in cases of incomplete or ambiguous information, the corresponding authors were contacted directly.

Given the considerable heterogeneity among the clinical trials, a narrative synthesis approach was adopted. The extracted data were organized into tables and grouped into three predefined outcome domains following a hierarchical pathophysiological framework. This scheme reflects the relationship between the different biological levels, in which underlying immunological and molecular alterations are translated into observable changes in the clinical expression of the disease. The domains considered were clinical symptomatology, autoantibody levels, inflammatory biomarkers, cytokines, and immune cell subpopulations.

Assessment of the quality of studies

The methodological quality of the studies was evaluated using the Cochrane Collaboration's Risk of Bias 2 tool for clinical trials, considering the randomization process, deviations from intended interventions, completeness of outcome data, and the measurement and selection of reported outcomes.[28] The assessment was conducted independently by JCFI and LFML, with any discrepancies resolved by consensus. Based on these criteria, studies were classified as having a low risk of bias, a high risk of bias, or some concerns.

Reporting bias assessments

The risk of bias due to missing results at the synthesis level, consistent with publication bias, was considered. However, due to clinical and methodological heterogeneity of the included studies and the absence of a quantitative synthesis, formal statistical methods could not be applied. Instead, potential publication bias was addressed qualitatively through a descriptive assessment of outcome patterns across the included studies, considering the direction and statistical significance of reported effects, the presence or absence of null or negative findings, and study characteristics such as sample size. This assessment was conducted independently by JCFI and LFML, and any disagreements were resolved through discussion.

Results

Included studies

The search initially identified 1,096 records across databases. After removal of duplicates, 855 articles were screened by title and abstract, with 711 excluded. Full-text assessment was performed for 144 articles, of which 13 could not be retrieved. Of the remaining 131 reports, 101 were excluded for predefined reasons, mainly combined interventions, pediatric populations, and insufficient or irrelevant outcomes. A total of 30 clinical trials met the inclusion criteria and were included in the systematic review (Fig. 1).

Characteristics of the included studies

Thirty clinical trials encompassed a total of 2,107 patients with autoimmune diseases, including rheumatoid arthritis (n = 13),[29-41] psoriasis (n = 5),[42-46] multiple sclerosis (n = 5),[47-51] Hashimoto's thyroiditis (n = 4)[52-55] and lupus (n = 3).[56-58] The nutraceuticals examined were curcumin, omega-3 fatty acids, probiotics, selenium, vitamin D, genistein, quercetin, resveratrol, baicalin, and vitamin A. Intervention durations ranged from 4 to 48 weeks, with sample sizes per trial varying between 24 and 351 participants. The interventions were primarily delivered in capsule or tablet form. Some formulations were specifically designed to enhance bioavailability using nanoparticles or nanomicelles, particularly for curcumin, while others were conventional preparations. Supplements were generally taken on a regular schedule and, when necessary, with food to support absorption and tolerability. Probiotic studies employed both mono- and multi-strain formulations, such as *Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus fermentum* and *Bifidobacterium bifidum*.[40,42,44,48] In most studies, supplements were administered alongside standard therapies, including disease-modifying antirheumatic drugs, glucocorticoids, immunomodulators, biologics, retinoids, levothyroxine, and topical treatments for patients with psoriasis. In some trials, a prior drug washout or exclusion of specific medications was required to prevent interactions and isolate the effect of the supplements.[34,41,43,47,52,55] Overall, they demonstrated good safety and tolerability. Adverse events were infrequent, mild, and comparable to placebo, with no consistent reports of serious events or clinically relevant alterations. Individual study results are presented in Tables 2–4.

Quality and risk of bias assessment

The studies demonstrated adequate methodological quality for inclusion in the review. Most trials showed a low risk of bias in domains related to deviations from planned interventions, availability of outcome data, and selection of reported outcomes. The main sources of bias were associated with limitations in the description of the randomization process and in outcome measurement, with a relevant number of studies classified as high risk. Overall, more than half of the trials were considered to have a low risk of bias, while a smaller proportion presented some concerns or a high risk. The distribution of risk bias by domain and the overall assessment of the included studies are presented in Fig. 2 and Table 5.

Reporting biases

In the qualitative assessment, most of the included studies reported favorable effects of the evaluated interventions, whereas null or negative findings were less frequent. Additionally, several studies had small sample sizes.

Discussion

The results of this systematic review suggest potential improvements in clinical disease activity across patients with rheumatoid arthritis, psoriasis, lupus, multiple sclerosis, and Hashimoto's thyroiditis, as well as favorable

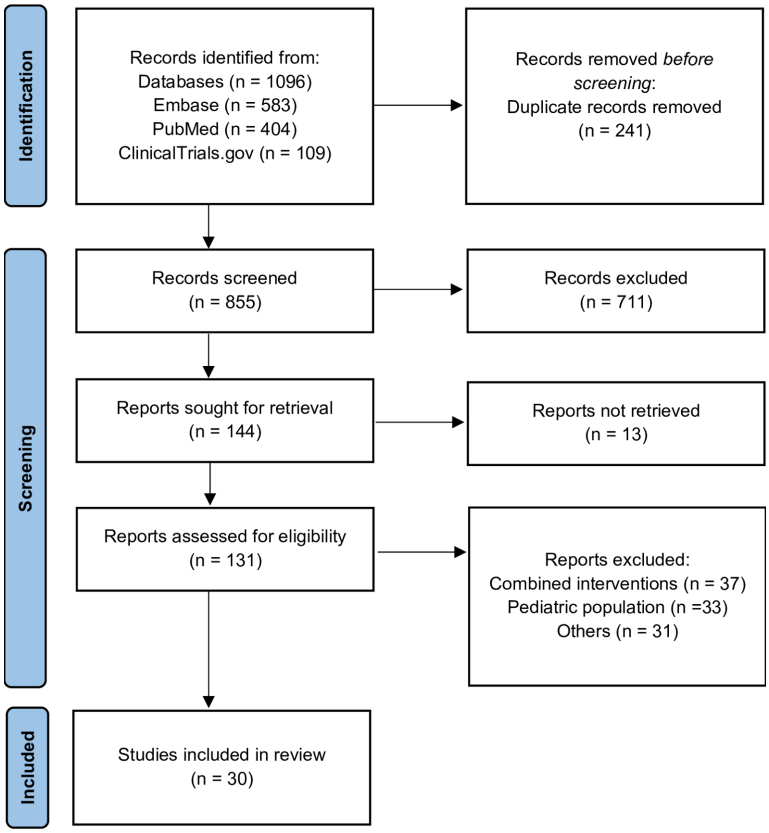

Fig. 1. PRISMA flow diagram of literature search and selection process.

Table 2. Evidence on the effect of nutraceuticals on clinical symptomatology.

Authors	Country	Sample size (I/C)	Diagnosis	Duration (weeks)	Intervention	Dose	Outcomes (*P* value ≤ 0.05)
Gilli et al[42]	Brazil	35 (18/17)	Psoriasis	9	Probiotic	5×10^9 CFU	↓ PASI, BSA, DLQI
Khan et al[30]	Pakistan	90 (45/45)	Rheumatoid arthritis	32	Curcumin	180 mg	↓ DAS-28
Bocheńska et al[43]	Poland	34 (24/10)	Psoriasis	8	Genistein	75 mg	↓ PGA
Moludi et al[44]	Iran	50 (25/25)	Psoriasis	8	Probiotic	1.8×10^9 CFU/g	↓ PASI
El-Banna & Gado[32]	Egypt	70 (40/30)	Rheumatoid arthritis	12	Vitamin D	50,000 UI	↓ DAS-28
Dolati et al[47]	Iran	50 (25/25)	Multiple sclerosis	24	Curcumin	80 mg	↓ EDSS
Javadi et al[33]	Iran	49 (24/25)	Rheumatoid arthritis	12	Curcumin	120 mg	↓ DAS-28
Jacob et al[34]	India	24 (16/8)	Rheumatoid arthritis	12	Curcumin	250 mg	↓ DAS-28, ACR
Hang et al[35]	China	351 (175/176)	Rheumatoid arthritis	12	Baicalin	500 mg	↓ EULAR
Bilia et al[45]	Italy	30 (15/15)	Psoriasis	12	Curcumin	3000 mg	↓ PASI
Khojah et al[36]	Egypt	100 (50/50)	Rheumatoid arthritis	12	Resveratrol	1000 mg	↓ DAS-28
Javadi et al[37]	Iran	50 (25/25)	Rheumatoid arthritis	8	Quercetin	500 mg	↓ DAS-28, MS
Amalraj et al[38]	India	36 (24/12)	Rheumatoid arthritis	12	Curcumin	500 mg	↓ DAS-28, ACR
Kouchaki et al[48]	Iran	60 (30/30)	Multiple sclerosis	12	Probiotics	2×10^9 CFU/g	↓ EDSS
Rajaei et al[39]	Iran	60 (30/30)	Rheumatoid arthritis	12	Omega-3	1800 mg EPA 2100 mg DHA	↓ DAS-28, MS
Antiga et al[46]	Italy	63 (31/32)	Psoriasis	12	Curcumin	500 mg	↓ PASI
Vaghef-Mehrabany et al[40]	Iran	46 (22/24)	Rheumatoid arthritis	8	Probiotic	1×10^8 CFU	↓ DAS-28
Chandran & Goel[41]	India	45 (30/15)	Rheumatoid arthritis	8	Curcumin	1000 mg	↓ DAS-28

ACR: American College of Rheumatology, BSA: Body Surface Area, C: control, DAS-28: Disease Activity Score 28, DHA: docosahexaenoic acid, DLQI: Dermatology Life Quality Index, EDSS: Expanded Disability Status Scale, MS: morning stiffness, EPA: eicosapentaenoic acid, EULAR: European League Against Rheumatism, I: intervention, mg: milligrams, PASI: Psoriasis Area and Severity Index, PGA: Physician Global Assessment, CFU: colony forming units, IU: international units.

Table 3. Evidence on the effect of nutraceuticals on autoantibody levels

Authors	Country	Sample size (I/C)	Diagnosis	Duration (weeks)	Intervention	Dose	Outcomes (*P* value ≤ 0.05)
Sedighi et al[56]	Iran	70 (30/32)	Systemic lupus erythematosus	10	Curcumin	1000 mg	↓ Anti-dsDNA
Khan et al[30]	Pakistan	90 (45/45)	Rheumatoid arthritis	32	Curcumin	180 mg	↓ RF
Hu et al[53]	China	90 (43/47)	Hashimoto's thyroiditis	24	Selenium	200 µg	↓ TPOAb, TgAb
Tian et al[54]	China	52 (32/20)	Hashimoto's thyroiditis	12	Selenium	200 µg	↓ TPOAb
Jacob et al[34]	India	24 (16/8)	Rheumatoid arthritis	12	Curcumin	250 mg	↓ RF
Zhang et al[55]	China	278 (135/143)	Hashimoto's thyroiditis	4	Genistein	600 mg	↓ TPOAb, TgAb
Amalraj et al[38]	India	36 (24/12)	Rheumatoid arthritis	12	Curcumin	500 mg	↓ RF

Anti-dsDNA: anti-double-stranded DNA antibodies, C: control, RF: rheumatoid factor, I: intervention, mg: milligrams, TgAb: anti-thyroglobulin antibodies, TPOAb: anti-thyroid peroxidase antibodies, µg: micrograms.

changes in symptoms, functional capacity, autoantibodies, and inflammatory biomarkers. However, these effects should be interpreted as context-dependent patterns derived from preliminary and heterogenous evidence rather than uniform or generalized responses across autoimmune diseases.

Our findings are consistent with previous reviews and meta-analyses that evaluated specific nutraceuticals in individual autoimmune diseases. For example, Long et al[59] reported improvements in the Disease Activity Score 28 (DAS-28), C-reactive protein (CRP), and erythrocyte sedimentation rate following polyphenol supplementation in rheumatoid arthritis. Similarly, Zeng et al[60] documented changes in the Systemic Lupus Erythematosus Disease Activity Index 2000, DAS-28, Psoriasis Area and Severity Index, and Expanded Disability Status Scale, as well as reductions in interleukin 6 (IL-6) and CRP, in patients with lupus, rheumatoid arthritis, psoriasis, and multiple sclerosis who received probiotics. Xu et al[61] reported changes in DAS-28, tender joint count, and the Health Assessment Questionnaire (HAQ) following omega-3 fatty acid supplementation in rheumatoid arthritis, with no relevant effects on swollen joints, the Physician Global Assessment, or the Visual Analogue Scale; in contrast, vitamin D supplementation showed an effect only on HQA. In turn, Zhang et al[62] observed reductions in anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies following selenium supplementation in Hashimoto's thyroiditis. Unlike previous studies that focused on a single nutraceutical and a specific disease using quantitative analyses, our review integrated multiple nutraceuticals and autoimmune diseases using a structured data extraction

Table 4. Evidence on the effect of nutraceuticals on inflammatory biomarkers, cytokines, and T cell subpopulations.

Authors	Country	Sample size (I/C)	Diagnosis	Duration (weeks)	Intervention	Dose	Outcomes (*P* value ≤ 0.05)
Sedighi et al[56]	Iran	70 (30/32)	Systemic lupus erythematosus	10	Curcumin	1000 mg	↓ IL-6
Zamani et al[29]	Iran	59 (30/29)	Rheumatoid arthritis	12	Selenium	200 µg	↓ CRP
Chahardoli et al[52]	Iran	42 (21/21)	Hashimoto's thyroiditis	12	Vitamin D	50,000 UI	↑ TGF-β ↓ IL-17
Khan et al[30]	Pakistan	90 (45/45)	Rheumatoid arthritis	32	Curcumin	180 mg	↓ CRP, ESR
Pourhabibi-Zarandi et al[31]	Iran	48 (24/24)	Rheumatoid arthritis	8	Curcumin	500 mg	↓ CRP, ESR
Hu et al[53]	China	90 (43/47)	Hashimoto's thyroiditis	24	Selenium	200 µg	↑ Treg
Moludi et al[44]	Iran	50 (25/25)	Psoriasis	8	Probiotic	1.8×10^9 CFU/g	↓ CRP, IL-6
El-Banna & Gado[32]	Egypt	70 (40/30)	Rheumatoid arthritis	12	Vitamin D	50,000 UI	↑ Treg
Dolati et al[47]	Iran	50 (25/25)	Multiple sclerosis	24	Curcumin	80 mg	↑ Treg, FoxP3 ↑ TGF-β, IL-10
Jacob et al[34]	India	24 (16/8)	Rheumatoid arthritis	12	Curcumin	250 mg	↓ CRP, ESR
Khojah et al[36]	Egypt	100 (50/50)	Rheumatoid arthritis	12	Resveratrol	1000 mg	↓ CRP, ESR ↓ TNF-α, IL-6
Hang et al[35]	China	351 (175/176)	Rheumatoid arthritis	12	Baicalin	500 mg	↓ CRP
Amalraj et al[38]	India	36 (24/12)	Rheumatoid arthritis	12	Curcumin	500 mg	↓ CRP, ESR
Kouchaki et al[48]	Iran	60 (30/30)	Multiple sclerosis	12	Probiotics	2×10^9 CFU/g	↓ CRP
Javadi et al[37]	Iran	50 (25/25)	Rheumatoid arthritis	8	Quercetin	500 mg	↓ TNF-α
Curado Borges et al[57]	Brazil	49 (22/27)	Systemic lupus erythematosus	12	Omega-3	1080 mg EPA 200 mg DHA	↓ CRP
Zhang et al[55]	China	278 (135/143)	Hashimoto's thyroiditis	4	Genistein	600 mg	↑ IFN-γ ↓ IL-2
Sotirchos et al[49]	United States	40 (19/21)	Multiple sclerosis	24	Vitamin D	10,400 UI	↓ $CD4^+$ $IL\text{-}17^+$ T lymphocytes
Rajaei et al[39]	Iran	60 (30/30)	Rheumatoid arthritis	12	Omega-3	1800 mg EPA 2100 mg DHA	↓ CRP, ESR
Saboor-Yaraghi et al[50]	Iran	36 (19/17)	Multiple sclerosis	24	Vitamin A	25,000 UI	↑ FoxP3 ↑ TGF-β
Arriens et al[58]	United States	50 (25/25)	Systemic lupus erythematosus	24	Omega-3	2250 mg EPA 2250 mg DHA	↑ IL-23 ↓ ESR
Antiga et al[46]	Italy	63 (31/32)	Psoriasis	12	Curcumin	500 mg	↓ IL-22
Vaghef-Mehrabany et al[40]	Iran	46 (22/24)	Rheumatoid arthritis	8	Probiotic	1×10^8 FCU	↑ IL-10 ↓ TNF-α, IL-12
Ramirez-Ramirez et al[51]	Mexico	50 (25/25)	Multiple sclerosis	48	Omega-3	800 mg EPA 1600 mg DHA	↓ TNF-α, IL-1β, IL-6
Chandran & Goel[41]	India	45 (30/15)	Rheumatoid arthritis	8	Curcumin	1000 mg	↓ CRP

C: control, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, FoxP3: forkhead box P3, I: intervention, IFN-γ: interferon gamma, IL-1β: interleukin 1 beta, IL-2: interleukin 2, IL-6: interleukin 6, IL-10: interleukin 10, IL-12: interleukin 12, IL-22: interleukin 22, IL-23: interleukin 23, mg: milligrams, CRP: C-reactive protein, TGF-β: transforming growth factor beta, TNF-α: tumor necrosis factor alpha, Treg: regulatory T cells, CFU: colony forming units, IU: international units, ESR: erythrocyte sedimentation rate

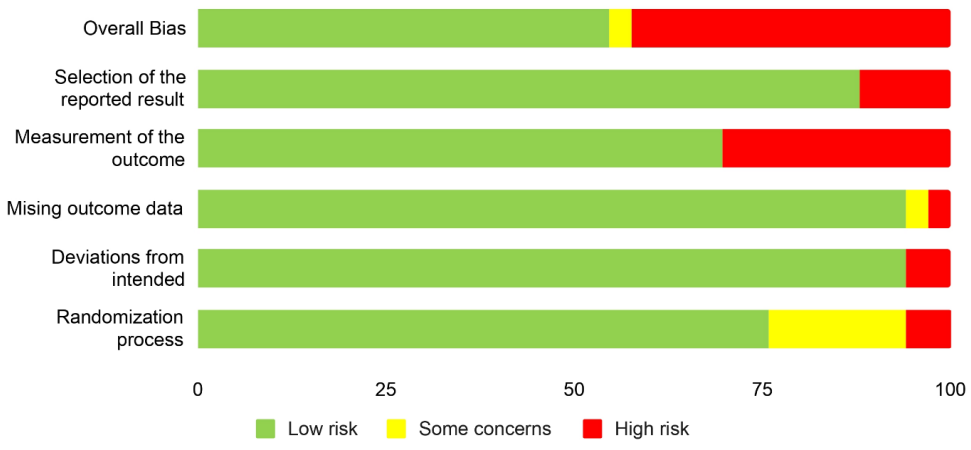

Fig. 2. Risk of bias chart based on the Rob2 tool.

Table 5. Risk of Bias in the included studies

Study	D1	D2	D3	D4	D5	Overall
Sedighi et al[56]	+	+	+	+	+	+
Zamani et al[29]	+	+	+	+	+	+
Chahardoli et al[52]	+	+	+	+	-	-
Gilli et al[42]	+	+	+	+	+	+
Khan et al[30]	!	+	+	-	-	-
Pourhabibi-Zarandi et al[31]	+	+	+	+	-	-
Bochenska et al[43]	!	-	+	+	-	-
Hu et al[53]	!	-	+	-	+	-
Moludi et al[44]	+	+	+	+	+	+
Tian et al[54]	!	+	+	-	+	-
El-Banna & Gado[32]	-	+	+	-	+	-
Dolati et al[47]	+	+	+	+	+	+
Javadi et al[33]	+	+	+	+	+	+
Jacob et al[34]	+	+	+	+	+	+
Bilia et al[45]	+	+	+	+	+	+
Khojah et al[36]	-	+	+	-	+	-
Hang et al[35]	+	+	+	+	+	+
Amalraj et al[38]	+	+	+	+	+	+
Kouchaki et al[48]	+	+	+	+	+	+
Javadi et al[37]	+	+	+	+	+	+
Curado Borges et al[57]	+	+	-	+	+	-
Zhang et al[55]	+	+	+	+	+	+
Sotirchos et al[49]	+	+	+	+	+	+
Rajaei et al[39]	+	+	+	+	+	+
Saboor Yaraghi et al[50]	+	+	+	+	+	+
Arriens et al[58]	+	+	+	-	+	-
Antiga et al[46]	+	+	+	+	+	+
Vaghef-Mehrabany et al[40]	+	+	+	+	+	+
Ramirez-Ramirez et al[51]	+	+	!	+	+	!
Chandran & Goel[41]	+	+	+	-	+	-

D1: Randomization process, D2: Deviations from the planned intervention, D3: Lack of outcome data, D4: Outcome measurement, D5: Selection of the expected outcome, Green cells: Low risk, Yellow cells: Some concerns, Red cells: High-risk.

matrix and a narrative synthesis.[28] The evidence was organized into tables and grouped into predefined outcome domains, including clinical symptomatology, autoantibody levels, and immunological outcomes. This approach allowed the identification of recurring patterns of improvement; however, it does not quantify effect size or statistical heterogeneity, which limits inferential strength compared with meta-analyses.[63] Nevertheless, the application of strict criteria regarding treatment stability, adherence, and control of confounding factors increased the reliability of the findings, revealing overall trends that suggest the potential of nutraceuticals to modulate immune and inflammatory responses rather than providing definitive quantitative evidence.[63]

Growing evidence suggests that nutraceuticals play a relevant role in the management of autoimmune diseases. Although this review focuses on human clinical evidence, mechanistic insights derived primarily from preclinical studies provide biological plausibility for the observed clinical effects. These bioactive compounds may modulate the immune response through multiple mechanisms, including regulation of the gut microbiota, activation and differentiation of T cells, and suppression of pro-inflammatory cytokines.

Polyphenols, including curcumin, resveratrol, and quercetin, regulate key inflammatory pathways such as NF-κB, MAPK, and JAK/STAT, leading to reduced levels of IL-6, tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and cyclooxygenase-2 (COX-2), while promoting anti-inflammatory mediators such as interleukin 10 (IL-10) and transforming growth factor beta (TGF-β).[64, 65] These compounds suppress T helper 1 (Th1) and Th17 responses while enhancing Treg cell differentiation, contributing to restoration of immune balance.[66] Additional mechanisms include inhibition of macrophage activation and NLRP3 inflammasome signaling, as well as downregulation of interferon gamma (IFN-γ), interleukin 2 (IL-2), and interleukin 17 (IL-17), alongside enhancement of antioxidant defenses.[67-69] Beyond immune signaling, polyphenols influence gut microbiota composition by promoting beneficial taxa, including short-chain fatty acid producing bacteria such as *Roseburia*, *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii*, while reducing pathogenic species, thereby increasing butyrate production, strengthening intestinal barrier integrity, and reducing systemic inflammation.[70,71] These effects are also associated with increased expression of tight junction proteins such as zonula occludens-1 and occludin.[69] In addition, genistein and baicalin affect inflammatory cytokine expression, inhibit STAT3 and NF-κB signaling, promote Th17/Treg balance, and modulate gut microbiota composition and short-chain fatty acid production, favoring taxa such as *Eubacterium* spp., *Subdoligranulum* spp. and *Butyricimonas* spp.[72-76] Among micronutrients, vitamin D modulates monocytes, macrophages, and T cells; inhibits IL-2, IFN-γ, IL-6, and TNF-α; and promotes IL-10 production, while also enhancing FoxP3$^+$ Treg cell responses, suppressing Th17 differentiation and IL-17 production, and contributing to improved microbial diversity and reduced disease incidence.[77-79] Vitamin A promotes the expansion of FoxP3$^+$ Treg cells while regulating gut microbiota and limiting the growth of pro-inflammatory bacteria, supporting immune tolerance.[80,81] Selenium, through its selenoproteins, modulates the activation, proliferation, and differentiation of immune cells, inhibits NF-κB signaling, and reduces IL-6 and TNF-α levels.[82] It also influences CD4$^+$ T-cell polarization, decreasing Th1, T helper 2 (Th2), and Th17 responses, while increasing CD4$^+$CD25$^+$FoxP3$^+$ Treg cells and immunosuppressive cytokines.[83] Furthermore, it affects gut microbiota composition and diversity.[84] Omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, regulate inflammatory processes and immune responses by reducing innate and adaptive immune activation, decreasing Th1 and Th2 responses, increasing IL-10 levels, promoting Treg cells, and reducing

pro-inflammatory cytokines such as IL-6 and IL-17, thereby attenuating tissue inflammation and improving disease severity.[85,86] They also influence gut microbiota composition, contributing to the reversal of dysbiosis and improvement in metabolic alterations.[87] Probiotics strains exert modulatory effects through interactions with the gut microbiota and Treg cells. Tryptophan-derived metabolites, such as indole-3-aldehyde and indoleacetic acid, activate the aryl hydrocarbon receptor, contributing to immune regulation and maintenance of intestinal barrier integrity.[88] These effects are associated with reduced inflammation, enhanced $CD4^{+}CD25^{+}FoxP3^{+}$ Treg cells responses, increased IL-10 and TGF-β1 levels, and attenuation of Th1 and Th17-mediated responses, along with maintenance of short-chain fatty acid production[89,90] (Fig. 3).

Despite this biological plausibility, the available clinical evidence has several limitations, including risk of bias, small sample sizes, short intervention durations, heterogeneity in dosage and formulations, and limited geographic diversity, which precluded the performance of meta-analyses or robust subgroup analyses.[63,91] Additionally, restricting the search to selected databases and English-language literature may have resulted in the exclusion of relevant evidence.[92] Although the strict study selection criteria strengthened methodological rigor, they may also have limited data representativeness. Furthermore, data extraction involved an unavoidable degree of subjectivity, despite the use of predefined criteria and independent peer review. The presence of publication bias in this review cannot be ruled out. This is supported by the predominance of studies reporting favorable results and the limited representation of null or negative outcomes, which likely reflects a greater tendency for positive results to be published. The exclusion of gray literature may have further increased this risk. The

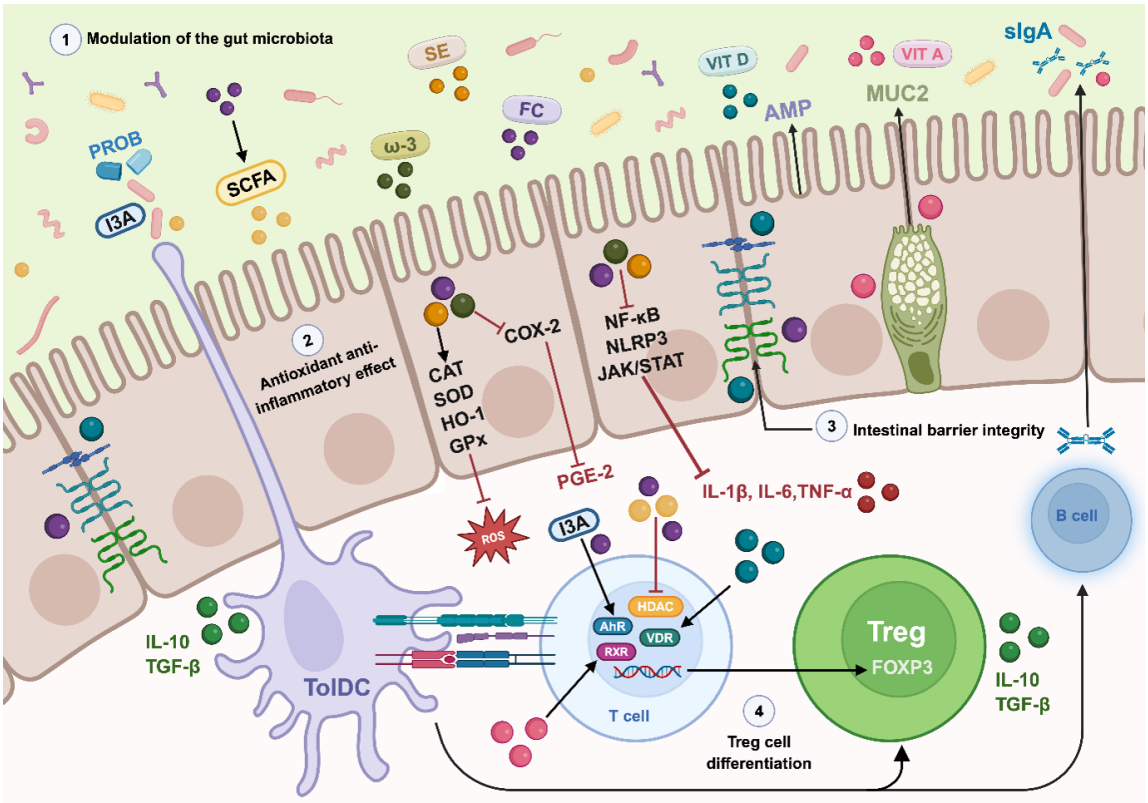

Fig. 3. Molecular mechanisms associated with the effects of nutraceuticals on autoimmune diseases. 1) Modulation of the gut microbiota. Polyphenols and probiotics increase butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Akkermansia muciniphila*. Butyrate promotes microbial diversity, induces a tolerogenic phenotype in dendritic cells, and enhances FoxP3 expression, facilitating Treg differentiation. Tryptophan-derived metabolites produced by probiotics, such as I3A, act as ligands for the AhR, contributing to immune regulation and the maintenance of intestinal barrier integrity. 2) Modulation of inflammatory pathways and oxidative stress. Polyphenols inhibit NF-κB, NLRP3, and JAK/STAT, reduce IL-1β, IL-6, TNF-α, and increase CAT, GPx, SOD, and HO-1. Omega-3 fatty acids decrease COX-2 activity and PGE2 production, promoting an immunoregulatory profile with increased IL-10 and TGF-β. Selenium limits oxidative damage through selenoproteins and reduces immune hyperreactivity. 3) Strengthening of the intestinal barrier. Vitamin A stimulates secretory IgA production by B cells, a key immunoglobulin in mucosal immunity that neutralizes pathogens and toxins in the lumen and prevents epithelial translocation. Vitamin D, through the VDR, promotes tight junctions proteins and antimicrobial peptides. Polyphenols and probiotics enhance these effects by increasing butyrate production and supporting bacteria involved in epithelial repair. 4) Induction of Treg cells. Butyrate exerts epigenetic effects by inhibiting HDACs and upregulating FoxP3 expression. Polyphenol and probiotics generate AhR ligands that reinforce this regulatory pathway. Vitamins A and D, via RXR and VDR, cooperate with TGF-β in driving naïve T cell differentiation toward a Treg phenotype. Omega-3 fatty acids and selenium further support this environment by increasing IL-10 and TGF-β production. **Abbreviations**. SCFAs: short-chain fatty acids, AhR: aryl hydrocarbon receptor, AMP: antimicrobial peptides, CAT: catalase, FC: phenolic compounds, COX-2: cyclooxygenase-2, FoxP3: forkhead box P3, GPx: glutathione peroxidase, HDAC: histone deacetylase, HO-1: heme oxygenase-1, I3A: indole-3-acetic acid, IL-1β: interleukin 1 beta, IL-6: interleukin 6, IL-10: interleukin 10, JAK/STAT: Janus kinase/signal transducer and activator of transcription, MUC2: mucin 2, NF-κB: nuclear factor kappa B, NLRP3: NLRP3 inflammasome, PGE2: prostaglandin E2, PROB: probiotics, ROS: reactive oxygen species, RXR: retinoid X receptor, SE: selenium, SOD: superoxide dismutase, TGF-β: transforming growth factor beta, TolDC: tolerogenic dendritic cells, TNF-α: tumor necrosis factor alpha, Treg: regulatory T cells, VDR: vitamin D, VIT A: vitamin A, VIT D: vitamin D, W-3: omega-3 fatty acids, sIgA: secretory immunoglobulin A.

findings should therefore be interpreted with caution, as the available evidence remains preliminary and constrained by methodological limitations and heterogeneity across studies. The absence of a formal certainty-of-evidence framework was also considered a methodological limitation of this review. Considering these limitations, nutraceuticals may represent promising adjunctive interventions, although the current evidence is of limited certainty. Further well-designed randomized controlled trials are required to confirm their efficacy and clarify their clinical applicability. In this context, their complementary use alongside pharmacological treatments could help reduce symptom burden and contribute to the prevention of associated complications.[93] From a health policy and healthcare management perspective, the integration of nutraceuticals may optimize resource allocation, reduce costs associated with more intensive interventions, and support low-risk preventive or adjunctive strategies.[94]

Conclusion

The current evidence suggests that nutraceutical interventions may be associated with improvements in clinical outcomes and inflammatory and immunological markers in autoimmune diseases, including rheumatoid arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, and Hashimoto's thyroiditis. Compounds such as curcumin, probiotics, omega-3 fatty acids, baicalin, resveratrol, quercetin, and vitamins A and D have been reported to modulate inflammatory and immunological pathways, while curcumin, selenium, and genistein may contribute to reduce autoantibody levels. Although these findings are promising, the available evidence is limited by substantial heterogeneity in study design, small sample sizes, variability in interventions and outcome measures, and the moderate to high risk of bias observed in several trials. In addition, the absence of quantitative synthesis limits the strength of inference and precludes firm conclusions regarding effect size or comparative efficacy. Therefore, while nutraceuticals may hold promise as adjunctive strategies in the management of autoimmune diseases, the overall body of evidence appears to be of limited-to-moderate certainty based on methodological limitations, including risk of bias, heterogeneity, and imprecision across studies. Their clinical use should therefore be considered exploratory rather than established. Further large-scale, high-quality randomized controlled trials with standardized methodologies are required to confirm these preliminary findings and define their therapeutic role within conventional treatments frameworks.

Authors' Contribution

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Investigation: Jennifer Carolina Flores Iglesias, Luis Fernando Méndez López.
Methodology: Jennifer Carolina Flores Iglesias.
Project administration: Luis Fernando Méndez López.
Validation: Jennifer Carolina Flores Iglesias, Luis Fernando Méndez López.
Visualization: Jennifer Carolina Flores Iglesias, Luis Fernando Méndez López.
Writing–original draft: Jennifer Carolina Flores Iglesias.
Writing–review & editing: Jennifer Carolina Flores Iglesias, Luis Fernando Méndez López.

Competing Interests

The authors declared that there was no conflict of interest in this study.

Declaration of AI-Assisted Tools in the Writing Procedure

The authors used Grammarly to assist in improving the clarity and English language of the manuscript.

Ethical Approval

Not applicable.

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