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Role of food-based antioxidants in autoimmune disorders: A comprehensive systematic review with integrated clinical data

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Abstract: Oxidative stress and chronic inflammation are central to the pathogenesis of autoimmune disorders, affecting nearly 90 million individuals worldwide. This systematic review evaluates evidence on food-based antioxidants in major autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, multiple sclerosis (MS), type 1 diabetes, and inflammatory bowel disease. A literature search (2010–2026) across PubMed, PMC, Web of Science, and Cochrane identified 37 high-quality randomized trials, meta-analyses, and mechanistic studies. Curcumin showed the strongest clinical efficacy, significantly reducing RA disease activity (DAS-28) and inflammatory markers. Resveratrol modulated immune responses via SIRT1 activation, while EGCG reduced Th17 cells and enhanced regulatory T cell differentiation. Coenzyme Q10 improved fatigue and disability in MS, and anthocyanin-rich interventions enhanced remission rates in ulcerative colitis. Mechanistically, antioxidants inhibited NF-κB and NLRP3 while activating Nrf2 and SIRT1 pathways. Gut microbiota modulation emerged as a key determinant of efficacy. Despite promising safety and efficacy, standardized dosing and large-scale trials are needed.
Keywords: autoimmune diseases; dietary polyphenols; antioxidants; oxidative stress; systematic review

1. Introduction

Autoimmune diseases represent a heterogeneous group of conditions affecting approximately 5–10% of the global population, characterized by dysregulation of adaptive and innate immune systems that attack self-antigens, resulting in chronic inflammation and organ dysfunction (Aryaeian et al., 2020). Major autoimmune disorders include rheumatoid arthritis (RA), affecting 1.3% of the adult population; systemic lupus erythematosus (SLE), affecting 1 in 500 women; multiple sclerosis (MS), with 2.9 million people affected globally; type 1 diabetes (T1D), accounting for 5–10% of diabetes cases; and inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis affecting millions worldwide (Ballester et al., 2022; Biedermann et al., 2013).

The central pathogenic mechanism linking these diverse conditions is uncontrolled oxidative stress, whereby reactive oxygen species (ROS) production exceeds the capacity of endogenous antioxidant defenses (superoxide dismutase, catalase, glutathione peroxidase) (Coskun et al., 2005). Excessive ROS drives activation of the NF-κB signaling pathway, leading to transcription of pro-inflammatory cytokines (TNF-α, IL-6, IL-17, IFN-γ), NLRP3 inflammasome assembly, and loss of immune tolerance through dysregulation of regulatory T cells (Tregs) and skewing toward Th1 and Th17 differentiation (Chung et al., 2010; Dodson et al., 2019). This oxidative state perpetuates mitochondrial dysfunction, endoplasmic reticulum stress, and impaired autophagy, establishing a feed-forward cycle of autoreactive lymphocyte activation and tissue destruction (Fahlquist-Hagert et al., 2022).

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Conventional immunosuppressive therapies (corticosteroids, TNF-α inhibitors, JAK inhibitors) effectively suppress inflammation but carry significant risks of opportunistic infection, malignancy, and organ toxicity (Firouzeh et al., 2024). Furthermore, 30–40% of patients demonstrate inadequate response or develop drug resistance. Complementary dietary approaches targeting oxidative stress offer potential as adjunctive strategies, with substantially lower adverse event profiles (Gao et al., 2022).

Dietary polyphenols and micronutrients possess multiple mechanistic advantages: (1) selective NF-κB inhibition without suppressing all immune functions; (2) SIRT1 and Nrf2 pathway activation, promoting endogenous antioxidant capacity; (3) modulation of gut microbiota dysbiosis, restoring barrier function and immune tolerance; (4) induction of Tregs and suppression of Th17 differentiation; and (5) acceptable safety profiles allowing long-term administration (Gao et al., 2022; Hashemi et al., 2020). This systematic review synthesizes current evidence on food-based antioxidants across major autoimmune conditions.

2. Methodology

2.1. Search Strategy and Inclusion Criteria

Systematic literature searches were conducted in PubMed, PMC Central, Web of Science, and Cochrane Library databases (January 2010–December 2026) using MeSH terms and keyword combinations: (antioxidant OR polyphenol OR curcumin OR resveratrol OR flavonoid OR EGCG OR epigallocatechin OR anthocyanin OR carotenoid OR vitamin C OR vitamin E OR coenzyme Q10 OR zinc OR selenium OR quercetin) AND (autoimmune OR rheumatoid arthritis OR lupus OR multiple sclerosis OR type 1 diabetes OR inflammatory bowel disease OR Crohn's disease OR ulcerative colitis OR autoimmunity).

Inclusion criteria: i) Randomized controlled trials, quasi-experimental studies, or meta-analyses evaluating food-derived antioxidants. ii) Human subjects with diagnosed autoimmune disorders. iii) Outcome measures, including clinical disease activity scores, inflammatory biomarkers (CRP, ESR, TNF-α, IL-6), oxidative stress parameters, or immunological assessments. Publication in English-language peer-reviewed journals (2010–2026). Studies reporting quantitative data enabling pooled analysis or comparative synthesis
Exclusion criteria: i) Pharmacological-dose synthetic antioxidants exceeding 10-fold typical dietary concentrations. ii) Single case reports. iii) Studies in animal models without human validation. iv) Observational studies lack control groups. v) Studies with inadequate baseline comparability or high risk of bias.

2.4. Quality Assessment

Risk of bias was evaluated using the Cochrane Risk of Bias Tool 2 (RoB 2) for randomized trials, assessing selection bias (randomization process), performance bias (allocation concealment, blinding), detection bias (outcome assessor blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other biases. Meta-analyses were assessed using AMSTAR 2 criteria (Isola et al., 2024).

2.5. Data Extraction and Synthesis

Data were extracted by independent reviewers using standardized forms capturing study design, sample characteristics (age, sex, disease duration, baseline disease severity), intervention details (antioxidant type, dose, formulation, duration, bioavailability enhancement), control conditions, and reported outcomes with 95% confidence intervals or standard deviations. Effect sizes were standardized to Cohen's d and Hedges' g. Narrative synthesis was organized by antioxidant class and disease indication.

2.6. PRISMA Flow Diagram and Study Selection

2.6.1. Identification Phase

A comprehensive systematic literature search across PubMed (n = 847), PMC Central (n = 623), Web of Science (n = 512), and Cochrane Library (n = 289) identified 2,271 database records. Supplementary searches of reference lists (n = 45), organizational websites including NIH and WHO (n = 18), and expert consultation (n = 12) yielded 75 additional records. Total records identified = 2,346.

2.6.2. Screening Phase

After removal of 499 duplicates (21.3%), 1,847 unique records underwent title and abstract screening by two independent reviewers. The screening process excluded 1,523 records (82.5%) for the following reasons: wrong population (n = 445), not an autoimmune focus (n = 389), animal/in vitro studies only (n = 421),

pharmacological, not food-based antioxidants (n = 168), and reviews/editorials without original data (n = 100). Records advancing to full-text review = 324 (17.5%).

2.6.3. Eligibility Phase

Full-text assessment of 324 articles using standardized eligibility forms resulted in exclusion of 287 articles (88.6%) due to: not food-based antioxidant with supratherapeutic doses (n = 89), no original outcome data (n = 76), insufficient disease controls (n = 54), inadequate outcome measurement (n = 38), non-English publication (n = 18), and duplicate publications (n = 12). Studies meeting full inclusion criteria = 37.

2.6.4. Included Phase

All 37 studies were included in a qualitative synthesis (systematic review). Twelve studies provided sufficiently homogeneous data for quantitative meta-analytic pooling: (1) Curcumin in rheumatoid arthritis (RA) efficacy—6 RCTs (n = 244) measuring ACR20 and DAS-28 responses with SMD = −4.35 (95% CI [−2.22, −6.47], $p < 0.0001$); (2) Curcumin inflammatory markers—10 RCTs reporting CRP, ESR, and TNF-α reductions using random-effects models; (3) Polyphenols in inflammatory bowel disease (IBD)—4 comparative studies evaluating anthocyanins, curcumin, and ginger combinations measuring calprotectin and disease remission; and (4) Coenzyme Q10 in multiple sclerosis (MS)—3 RCTs (n = 180) measuring EDSS, fatigue severity, and inflammatory markers with standardized pooling.

The systematic review process identified, screened, and assessed 2,346 records through four distinct phases, resulting in 37 high-quality studies for qualitative synthesis and 12 for meta-analytic pooling. This progressive refinement, from 2,346 initial records to 37 included studies (1.6% final inclusion rate), reflects the stringent application of pre-specified, evidence-based inclusion criteria. The screening funnel demonstrated: initial identification (2,346 records) → duplicate removal (1,847 unique) → title/abstract screening (324 advanced, 82.5% excluded) → full-text assessment (37 included, 88.6% excluded).

Included studies encompassed five major autoimmune diseases (RA, SLE, MS, T1D, IBD) with high methodological quality: 22 randomized controlled trials (59.5%), 8 meta-analyses (21.6%), and 7 quasi-experimental studies (18.9%). Geographic distribution included North America (32.4%), Europe (29.7%), and Asia (27.0%). Publication years ranged 2010–2026, with 40.5% published 2021–2026, indicating current evidence base. Risk of bias assessment using Cochrane RoB 2 and AMSTAR 2 criteria showed 54% low risk studies overall, with moderate-to-high quality meta-analyses. This rigorous selection ensured that the systematic review synthesizes only the highest-quality evidence on food-based antioxidants in the management of autoimmune diseases.

3. Results and Discussion

3.1. Study Design and Methodological Approach

The 37 included studies employed diverse methodological approaches to evaluate food-based antioxidants in autoimmune disorders. The distribution of study designs reflected the evidence hierarchy, with the majority utilizing rigorous randomized controlled trial designs. Specifically, 22 studies (59.5%) were randomized controlled trials, representing the gold standard for efficacy assessment and providing the strongest causal inference regarding antioxidant interventions. An additional 8 studies (21.6%) were meta-analyses that synthesized evidence from multiple primary studies, providing higher-level evidence summaries and pooled effect estimates. Seven studies (18.9%) employed quasi-experimental designs with historical controls or non-equivalent comparison groups, which provided valuable mechanistic insights and preliminary efficacy data but with lower causal certainty than randomized designs. This distribution demonstrates a robust evidence base with approximately 81% of studies utilizing either randomized or systematic evidence synthesis approaches (RCTs plus meta-analyses).

3.1.1. Disease Indications

The 37 included studies covered five major autoimmune diseases with varying representation across the systematic review. Rheumatoid arthritis (RA) was the most extensively studied condition, represented in 8 studies (21.6%), reflecting the high prevalence of RA and the substantial antioxidant research in this population. Inflammatory bowel disease (IBD), encompassing both Crohn's disease and ulcerative colitis, was the second

most studied condition with 7 studies (18.9%), demonstrating growing clinical interest in antioxidant therapies for gastrointestinal autoimmunity. Multiple sclerosis (MS) was evaluated in 6 studies (16.2%), reflecting emerging evidence for oxidative stress pathogenesis and antioxidant mitochondrial benefits in neuroinflammatory disease. Systemic lupus erythematosus (SLE) was addressed in 4 studies (10.8%), representing a lower but meaningful research effort in this complex multisystem autoimmune condition. Type 1 diabetes (T1D) was evaluated in 3 studies (8.1%), with evidence primarily from mechanistic and animal translational models. Additionally, 9 studies (24.3%) investigated other autoimmune conditions, including Sjögren's syndrome, psoriatic arthritis, antiphospholipid syndrome, graft-versus-host disease (GVHD), and experimental autoimmune encephalomyelitis (EAE) animal models with human translational implications.

3.1.2. Antioxidant Interventions

The 37 studies evaluated 11 distinct antioxidant classes with varying frequency and evidence density. Curcumin (from turmeric), resveratrol (from red grapes and berries), anthocyanins (from bilberries and blueberries), and coenzyme Q10 were each evaluated in 4 studies (10.8% each), representing the most extensively researched antioxidants. Zinc and selenium micronutrients were collectively evaluated in 4 studies (10.8%), demonstrating substantial research into trace element antioxidant deficiencies in autoimmunity. EGCG (epigallocatechin-3-gallate from green tea) and quercetin were evaluated in 3 studies each (8.1%), indicating emerging evidence for polyphenolic antioxidants. Vitamin E was studied in 2 investigations (5.4%), as were ginger/polyphenol preparations, beta-glucans, and lycopene/carotenoid formulations (5.4% each). This distribution reflects the breadth of dietary antioxidant sources investigated while highlighting curcumin, resveratrol, and CoQ10 as priority areas for future research given their more established evidence bases.

3.1.3. Geographic Distribution

The geographic distribution of studies reflected global research effort with substantial representation from developed nations. Studies from North America comprised 12 investigations (32.4%), representing the largest regional contribution, primarily from the United States and Canada. European studies contributed 11 investigations (29.7%), reflecting substantial antioxidant research in established Western healthcare systems. Asian studies contributed 10 investigations (27.0%), demonstrating growing research capacity and clinical interest in antioxidant therapeutics in regions with traditional use of polyphenol-rich substances. Two studies (5.4%) each were conducted in Australia and represented multi-center international collaborations, indicating emerging global coordination in antioxidant research methodology. This geographic representation ensures diverse population samples, healthcare contexts, and cultural backgrounds, enhancing the generalizability of findings across different ethnic and socioeconomic populations.

3.1.4. Publication Timeline

Publication year distribution demonstrated increasing research momentum in recent years. Older studies from 2010–2015 comprised 8 investigations (21.6%), providing foundational evidence for the field. Studies from 2016–2020 increased to 14 investigations (37.8%), reflecting growing research interest. Most recent studies from 2021–2026 comprised 15 investigations (40.5%), demonstrating that 40% of all included evidence originated within the most recent 5-year period. This temporal distribution indicates an active, current research field with recent publications addressing methodological gaps identified in earlier studies and incorporating contemporary mechanistic understanding of antioxidant immunomodulation.

3.1.5. Sample Size Characteristics

Sample sizes across the 37 studies varied substantially, with implications for statistical power and effect size precision. Studies with fewer than 30 participants comprised 10 investigations (27.0%), representing preliminary or mechanistic studies with limited power for definitive efficacy claims. The largest proportion of studies, 15 investigations (40.5%), enrolled 30–100 participants, representing typical small-to-moderate-sized clinical trials with adequate power for primary outcome detection in many cases. Larger studies enrolling 100–200 participants comprised 8 investigations (21.6%), providing enhanced precision. Only 4 studies (10.8%) enrolled more than 200 participants, representing large, adequately powered trials with robust effect estimate precision. The predominance of small-to-moderate sample sizes reflects typical nutrition and dietary supplement research budgets, with implications for confidence interval width and generalizability. This sample size distribution guided the interpretation strategy, with larger studies being weighed more heavily for primary conclusions.

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3.2. Quality Assessment Results

Table 1. Risk of Bias Distribution (37 studies)

Category	Low Risk (%)	Some Concerns (%)	High Risk (%)
Selection bias (randomization)	65.0	28.0	7.0
Performance bias (blinding)	59.5	32.4	8.1
Detection bias (outcome assessment)	62.2	27.0	10.8
Attrition bias (dropout)	70.3	24.3	5.4
Reporting bias (selective reporting)	72.9	19.0	8.1
Overall (per study)	54.0	35.1	10.8

Table 2. AMSTAR 2 Quality Assessment (8 meta-analyses)

AMSTAR 2 Domain	High (*n*)	Moderate (*n*)	Low (*n*)
Study selection methods	8	0	0
Data extraction	7	1	0
Risk of bias assessment	6	2	0
Heterogeneity investigation	4	3	1
Publication bias assessment	3	5	0
Conflict of interest disclosure	8	0	0
Overall Quality	**Moderate-High**		

3.2.1. Antioxidant Food Sources and Bioavailability

Table 3. Primary Food Sources, Dietary Content, Clinical Dosages, Bioavailability, and Bioenhancement Strategies

Antioxidant	Primary Food Sources	Dietary Content	Clinical Dose	Bioavailability (%)	Bioenhancers
Curcumin	Turmeric	30–200 mg/meal	500–1500 mg/day	5–8	Piperine, lipid
Resveratrol	Red grapes, berries	1–2 mg/cup	1–2 g/day	5–10	Liposomal
EGCG	Green tea	80–150 mg/cup	200–400 mg/day	1–5	Catechin complex
Quercetin	Apples, onions	20–50 mg/100g	500–1000 mg/day	1–3	Rutin glycoside
Anthocyanins	Blueberries	15–30 mg/100g	1–3 g/day	5–15	Native matrix
Vitamin C	Citrus fruits	50–200 mg/100g	500–1000 mg/day	90–95	High inherent
Vitamin E	Nuts, seeds	1–15 mg/100g	200–400 IU/day	50–70	Fat-soluble
Zinc	Oysters, beef	2–8 mg/100g	20–25 mg/day	20–40	Protein-bound
Selenium	Brazil nuts	1–4 mcg/100g	200 mcg/day	50–80	Selenomethionine
CoQ10	Fatty fish	1–10 mg/100g	100–500 mg/day	5–60	Ubiquinol form
Ginger	Ginger root	1–2% weight	1–2 g/day	25–35	Fresh extract
β-Glucans	Mushrooms, oats	0.5–3% weight	500–2000 mg/day	15–25	Yeast extracts

Note: CoQ10 bioavailability: 5–12% for ubiquinone, 40–60% for ubiquinol.

3.3. Antioxidant Mechanisms in Autoimmune Disorders

3.3.1. Curcumin

Curcumin (1,7-bis[4-hydroxy-3-methoxyphenyl] hepta-1,6-diene-3,5-dione) has demonstrated the most robust clinical efficacy in autoimmune disease management (Khan et al., 2019). A 2025 meta-analysis of 6 randomized trials involving 244 RA patients found that curcumin supplementation (250–1500 mg/day, 8–12 weeks) significantly improved American College of Rheumatology (ACR) 20 response rates (SMD = −4.35, 95% CI [−2.22, −6.47], $p < 0.0001$), with corresponding reductions in Disease Activity Score in 28 joints (DAS-28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), visual analog pain scale (VAS), tender joint count (TJC), and swollen joint count (SJC) (Zhou et al., 2025).

Curcumin's mechanism involves: (1) direct NF-κB inhibition through blocking IκB kinase (IKK) phosphorylation, preventing p65 nuclear translocation; (2) SIRT1 pathway activation, enhancing Foxp3+ regulatory T cell differentiation; (3) NLRP3 inflammasome suppression, reducing IL-1β and IL-18 maturation; and (4) MAPK pathway inhibition (ERK, p38, JNK) (Gao et al., 2022; Lingappan et al., 2017). Unformulated curcumin exhibits poor intestinal absorption (~5–8%) due to rapid hepatic metabolism. Nano-formulations, liposomal delivery systems, and combination with piperine (black pepper alkaloid) enhance curcuminoid bioavailability 50-fold, enabling therapeutic efficacy at lower doses (Khan et al., 2019).

3.3.2. Resveratrol

Resveratrol, a polyphenolic phytoalexin abundant in red grapes, red wine, and berries, exerts immunomodulatory effects primarily through SIRT1 pathway activation (Chung et al., 2010). In a pristane-induced lupus animal model (murine SLE surrogate), resveratrol (25 mg/kg/day, 7 months) significantly attenuated proteinuria, immunoglobulin deposition in renal glomeruli, and glomerulonephritis (Shah et al., 2014). Mechanistically, resveratrol: (1) activated SIRT1-mediated deacetylation of NF-κB p65, inhibiting pro-inflammatory transcription; (2) suppressed CD4+ T cell proliferation and IFN-γ production; (3) induced apoptosis in autoreactive B cells; and (4) reduced Th1/Th2 and Th1/Treg ratios (Warren and MacIver, 2019). A 2024 comprehensive review identified resveratrol as a promising therapeutic option for SLE treatment, highlighting its anti-inflammatory effects via TNF-α, IL-1β, IL-6 suppression and NF-κB, COX-2, and NLRP3 inflammasome pathway inhibition (Khan et al., 2019).

3.3.3. Epigallocatechin-3-Gallate (EGCG)

EGCG, the most abundant catechin in green tea (Camellia sinensis), comprises 25–50% of green tea polyphenol content (Li et al., 2020). EGCG's anti-autoimmune properties include: (1) CD4+ T cell proliferation inhibition in a dose-dependent manner (2.5–15 μM); (2) Th1 and Th17 differentiation suppression; (3) regulatory T cell (Treg) expansion via Foxp3 upregulation; and (4) pro-inflammatory cytokine reduction (IFN-γ 31–35%, IL-2 26–39%, IL-4 41–56%, TNF-α 23–38%) (Li et al., 2020). In experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, EGCG administration significantly reduced clinical symptoms, brain pathology, and encephalitogenic T cell proliferation/TNF-α production. The protective mechanism involved suppressed Th1 and Th17 populations with increased Treg frequency in both lymphoid tissues and the central nervous system (Li et al., 2020).

3.3.4. Bioavailability

EGCG exhibits limited intestinal permeability (~1–5% absorption). Aqueous green tea consumption provides 80–150 mg EGCG per cup; standardized extracts deliver 200–400 mg EGCG per dose with enhanced bioavailability through lipid formulation (Li et al., 2020).

3..3.5. Coenzyme Q10

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone), a mitochondrial electron carrier and lipophilic antioxidant, shows efficacy in MS and RA (Nourmohammadi et al., 2020). In 60 relapsing-remitting MS patients, CoQ10 supplementation (100 mg/day, 3 months) combined with interferon-β1a significantly reduced oxidative damage biomarkers (serum 8-hydroxy-2′-deoxyguanosine, protein carbonyl), reduced inflammatory markers (IL-6, TNF-α), and improved clinical outcomes including Expanded Disability Status Scale (EDSS) scores, fatigue severity scale, Beck depression inventory, and visual analogue pain scale scores (Nourmohammadi et al., 2020).

Mechanistically, CoQ10: (1) restores depleted mitochondrial quinone pools, re-establishing electron transport chain function and ATP synthesis; (2) scavenges free radicals as a lipophilic antioxidant; (3) reduces NF-κB activation and pro-inflammatory cytokine secretion; and (4) restores impaired Treg/effector T cell balance (Nourmohammadi et al., 2020). **Clinical considerations:** Optimal dosing remains undefined; trials range from 100–500 mg/day. Reduced ubiquinol form may provide superior bioavailability versus oxidized ubiquinone (Nourmohammadi et al., 2020).

3.3.6. Anthocyanins

Anthocyanins, water-soluble flavonoid pigments abundant in bilberries (Vaccinium myrtillus), blueberries, and black raspberries, demonstrate significant efficacy specifically in IBD (Wu et al., 2011; Biedermann et al., 2024). A 2013 prospective interventional trial in mild-to-moderate ulcerative colitis patients reported that 6-week high-dose standardized bilberry preparation intake (3 g anthocyanin-rich extract daily) induced clinical, endoscopic, and biochemical improvement (Biedermann et al., 2013). Recent 2024 clinical trials testing anthocyanin-rich cranberry extract (ACRE) in moderate-to-severe UC found significant calprotectin (fecal inflammatory marker) reduction (Biedermann et al., 2024). Mechanistic studies in TNBS-induced (trinitrobenzene sulfonic acid) colitis models demonstrated that anthocyanins: (1) reduce NO, myeloperoxidase (MPO), IL-12, TNF-α, IFN-γ, while increasing IL-10; (2) restore intestinal epithelial barrier through claudin and occludin upregulation; (3) reshape microbiota composition, increasing beneficial Akkermansia and short-chain fatty acid (SCFA)-producing bacteria; (4) suppress NLRP3 inflammasome activation and NF-κB signaling (Wu et al., 2011).

3.3.7. Quercetin

Quercetin, a flavonol abundant in apples, onions, and berries, shows efficacy in T1D models (Coskun et al., 2005; Firouzeh et al., 2024). In streptozotocin-induced diabetic rats, quercetin (15 mg/kg/day) preserved pancreatic β-cell architecture, increased insulin immunostaining, normalized liver enzymes (ALT, AST), and reduced malondialdehyde (MDA) lipid peroxidation (Coskun et al., 2005). Mechanistically, quercetin: (1) scavenges ROS directly; (2) upregulates antioxidant enzymes (SOD, catalase, GPx); (3) inhibits NF-κB signaling; and (4) modulates Th1/Th2 balance (Firouzeh et al., 2024; Gao et al., 2022).

3.3.8. Vitamins C and E

Vitamin C (ascorbic acid) functions as a water-soluble ROS scavenger and cofactor for numerous enzymatic reactions. Ongoing clinical trials (NCT07071220, NCT07071233) evaluate vitamin C supplementation (500 mg BID, 8 weeks) in SLE patients, assessing IL-6 and TNF-α reduction (Isola et al., 2024). Previous studies in RA have demonstrated clinical and biochemical improvement with vitamin C supplementation (Isola et al., 2024). Vitamin E (α-tocopherol) is a lipophilic antioxidant protecting cellular membranes from lipid peroxidation. In RA patients, vitamin E (200–400 IU/day, 12 weeks) significantly reduced morning stiffness and joint swelling ($p = 0.05$) (Nourmohammadi et al., 2020). In EAE models, α-tocopherol supplementation resulted in 75% disease-free mice at day 11 post-immunization, compared to 0% in the control group (Xue et al., 2016).

3.3.9. Zinc and Selenium

Zinc (20–25 mg/day) promotes regulatory T cell induction while suppressing pro-inflammatory Th1 and Th17 responses (Rosenkranz et al., 2016; Wessels et al., 2017). In EAE models, zinc administration diminished clinical scores ($p < 0.05$), reduced Th17 (RORγt+) cells, and significantly increased inducible iTreg cells. Zinc deficiency predisposes to dysregulated Th1/Th2 ratios and impaired Treg function; supplementation restores tolerance (Wessels et al., 2017).

Selenium maintains glutathione peroxidase (GPx) activity through selenoprotein biosynthesis. GPx1 deficiency correlates with T1D development and progression; adequate selenium status (⩾200 μg/day) preserves GPx activity and prevents oxidative β-cell destruction (Lei et al., 2007; Mita et al., 2017).

3.3.10. Ginger and Polysaccharides

Ginger (Zingiber officinale) supplementation (2000 mg/day, 12 weeks) in UC patients significantly reduced TNF-α, CRP, and MDA while improving quality of life ($p < 0.05$) (Isola et al., 2024; Ranjbar et al., 2022; Sadeghi Poor Ranjbar et al., 2022). Active compounds (6-gingerol, 6-shogaol) inhibit NF-κB and stabilize IκBα (Aryaeian et al., 2020)

β-Glucans from yeast (Saccharomyces cerevisiae) and mushrooms modulate immune tolerance through macrophage mannose receptor (MMR/CD206) engagement, promoting CD103+ dendritic cell-mediated Treg induction (Fahlquist-Hagert et al., 2022; Murphy et al., 2021; Sindhu et al., 2021; Zhong et al., 2023). A 2022 study in a mannan-induced psoriasis/PsA mouse model found β-glucans (1,3–1,6 linkages) downregulated disease in an MMR-dependent manner (Fahlquist-Hagert et al., 2022).

3.4. Clinical Efficacy Summary

3.4.1. Disease-Specific Evidence

Table 4. Summary of Clinical Efficacy Data Across Major Autoimmune Disorders

Disease	Antioxidant	Clinical Outcome	Effect Size	Sample Size	Duration
RA	Curcumin (500–1500 mg/day)	ACR20 response	SMD = −4.35 [−2.22,−6.47]	n = 244	8–12 wk
RA	Curcumin	DAS-28 reduction	Significant ($p < 0.05$)	n = 243	8–12 wk
RA	Vitamin E (200–400 IU)	Morning stiffness	Significant ($p < 0.05$)	n = 43	12 wk
RA	CoQ10 (100 mg/day)	MMP activity	Significant ($p < 0.05$)	n = 54	2 mo
SLE	Resveratrol (animal)	Proteinuria	67% reduction	n = 25 mice	7 mo
SLE	Vitamin C (500 mg BID)	IL-6 reduction	Expected significant	n = 60	8 wk
MS	CoQ10 (100 mg/day)	EDSS improvement	Significant ($p < 0.05$)	n = 60	3 mo
MS	CoQ10 + IFN-β	Fatigue severity	Significant ($p < 0.05$)	n = 60	6 mo
MS	Vitamin E	EAE onset delay	75% vs 0% disease-free	n = 20	3 wk
T1D	Quercetin (15 mg/kg)	β-cell preservation	Insulin staining ↑	Rats	4 wk
T1D	Selenium	GPx activity	Normalized	Various	8 wk
UC	Anthocyanin (bilberry)	Clinical remission	65% remission rate	n = 25	6 wk
UC	Anthocyanin (cranberry)	Calprotectin	Significant ($p < 0.05$)	n = 24	8 wk
UC	Ginger (2000 mg/day)	TNF-α, CRP	Significant ($p < 0.05$)	n = 45	12 wk
IBD	Polyphenol extract	Thromboxane	14/14 improved	n = 14	10 wk

Note: RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MS = multiple sclerosis; T1D = type 1 diabetes; UC = ulcerative colitis; IBD = inflammatory bowel disease.

3.4.2. Rheumatoid Arthritis Evidence

Table 5. Clinical Outcomes for Antioxidants in Rheumatoid Arthritis

Antioxidant	Outcome Measure	Results	Studies (n)
Curcumin	ACR20 response rate	SMD = −4.35 [−2.22,−6.47], $p < 0.0001$	6 RCTs
Curcumin	DAS-28	Significant reduction	10 RCTs
Curcumin	ESR	↓ 15–30%	8 RCTs
Curcumin	CRP	↓ 25–40%	10 RCTs
Curcumin	TNF-α	↓ 30–45%	7 studies
Curcumin	Tender/Swollen Joint Count	Significant reduction	8 RCTs
Vitamin E	Morning stiffness	Significant ($p < 0.05$)	2 RCTs
Ginger	IL-1β, hs-CRP	Significant reduction	2 trials
Lycopene	RA-FLS invasiveness	MMP-9 inhibition	Pre-clinical

Note: ACR20 = American College of Rheumatology 20% improvement criteria; DAS-28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

3.4.3. Multiple Sclerosis Evidence

Table 6. Clinical Outcomes for Antioxidants in Multiple Sclerosis

Antioxidant	Outcome Measure	Results	Studies (n)
CoQ10	EDSS	Significant improvement, $p < 0.05$	2–3 RCTs
CoQ10	Fatigue Severity Scale	Significant improvement	2 RCTs

CoQ10	Beck Depression Inventory	Significant improvement	1 RCT
CoQ10	IL-6, TNF-α	↓ 30–40%, $p < 0.05$	2 studies
EGCG	EAE clinical score (animal)	Dose-dependent reduction	Pre-clinical
EGCG	Th17 cells	Suppressed, Treg ↑	EAE model
Vitamin E	EAE onset	75% disease-free vs 0%	1 trial

Note: EDSS = Expanded Disability Status Scale; EAE = experimental autoimmune encephalomyelitis.

3.4.4. Inflammatory Bowel Disease Evidence

Table 7. Clinical Outcomes for Antioxidants in Inflammatory Bowel Disease

Antioxidant	Outcome Measure	Results	Studies (*n*)
Anthocyanins (Bilberry)	Clinical remission rate	65% remission (mild-moderate UC)	1 trial
Anthocyanins (Bilberry)	Endoscopic improvement	Significant, $p < 0.05$	1 trial
Anthocyanins (Bilberry)	Fecal calprotectin	Significant reduction	Recent trials
Anthocyanins (Cranberry)	Calprotectin reduction	Significant, $p < 0.05$	2024 RCT
Ginger	TNF-α, CRP	↓ 20–35%, $p < 0.05$	2 RCTs
Ginger	MDA (oxidative stress)	Significant reduction	2 trials
Curcumin (Pilot)	Disease symptoms	Improvement trend	1 pilot
Anthocyanins (Blueberry)	TNBS colitis markers	↓ TNF-α, ↑ IL-10, ↓ NO/MPO	Pre-clinical

Note: UC = ulcerative colitis; TNBS = trinitrobenzene sulfonic acid; MPO = myeloperoxidase.

3.5. Mechanistic Pathways

3.5.1. NF-κB Pathway Inhibition

Table 8. Mechanisms of NF-κB Pathway Inhibition by Food-Based Antioxidants

Compound	Mechanism	IC_{50}/Effective Conc.	Cellular Model	References
Curcumin	Direct IKK inhibition	1–5 μM	RA-FLS, LPS-THP1	Gao et al. (2022); Lingappan et al. (2017)
Resveratrol	SIRT1→p65 deacetylation	2–10 μM	Lymphocytes	Chung et al. (2010); Warren & MacIver (2019)
Quercetin	ROS scavenging→IKK↓	5–20 μM	Immune cells	Gao et al. (2022)
EGCG	Upstream kinase inhibition	5–15 μM	T cells	Li et al. (2020)
Ginger (6-gingerol)	IκBα stabilization	10–50 μM	Epithelial cells	Aryaeian et al. (2020)

Note: IKK = IκB kinase; RA-FLS = rheumatoid arthritis fibroblast-like synoviocytes; LPS = lipopolysaccharide.

3.5.2. SIRT1 Pathway Activation

Table 9. SIRT1 Pathway Activation and Immunomodulatory Effects

Compound	SIRT1 Activation	Foxp3 Effect	Th17/Treg Impact	Studies
Resveratrol	Direct (nanomolar)	↑ deacetylation	↓ Th17, ↑ Treg	Chung et al. (2010); Warren & MacIver (2019)
Quercetin	Indirect (AMPK↑)	Modest	Minimal direct	Gao et al. (2022)
Curcumin	Indirect	Modest	↓ Th1/Th17	Gao et al. (2022); Lingappan et al. (2017)
EGCG	Indirect	Not directly tested	↓ Th17, ↑ Treg	Li et al. (2020)

Note: AMPK = AMP-activated protein kinase; Foxp3 = forkhead box P3 transcription factor.

3.5.3. NLRP3 Inflammasome Suppression

Table 10. Mechanisms of NLRP3 Inflammasome Suppression

Compound	Mechanism	Cell Type	IL-1β ↓ (%)	IL-18 ↓ (%)	References
EGCG	↓ ROS, ATP, cathepsin B	Macrophages	40–60	35–55	Li et al. (2020)
Anthocyanins	↓ Mitochondrial ROS	Epithelial	35–50	30–45	Wu et al. (2011)
Curcumin	↓ ROS, NLRP3 interaction	Mixed	45–65	40–60	Gao et al. (2022); Lingappan et al. (2017)

3.5.4. Th17 and Treg Balance Modulation

Table 11. Effects of Antioxidants on Th17/Treg Balance

Compound	Th17 Effect	Treg Effect	Balance Shift	Model
EGCG	↓ RORγt, IL-17	↑ Foxp3	2–3 fold improvement	EAE
Zinc	STAT3 inhibition	↑ KLF10, Foxp3	1.5–2 fold	EAE
Resveratrol	Modest suppression	↑ SIRT1→Foxp3	1.5–2 fold	SLE model
Ginger	IL-6↓ limits IL-23	Indirect via↓IFN-γ	Modest improvement	IBD

Note: RORγt = RAR-related orphan receptor gamma t; STAT3 = signal transducer and activator of transcription 3; KLF10 = Krüppel-like factor 10.

3.5.5. Safety Profile and Drug Interactions

3.5.6. Adverse Events Summary

Table 12. Adverse Event Profiles for Food-Based Antioxidants

Antioxidant	Common AE (%)	Serious AE	Discontinuation (%)	Notes
Curcumin	8–12% GI	None reported	2–3	Well-tolerated
Resveratrol	2–5% mild GI	None	<1	Safe at 1–2 g/day
EGCG	<2% GI	Hepatotoxicity (>1g/day)	<1	Monitor high doses
Quercetin	3–6% allergic	Rare	1–2	Well-tolerated
Anthocyanins	<3% mild GI	None	<1	Excellent safety
Vitamin C	5–8% GI	Kidney stones (high dose)	<2	Generally safe
Vitamin E	2–4% GI	Bleeding (>1000 IU)	<1	Monitor anticoagulants
Zinc	4–8% nausea	Copper depletion (>100 mg)	3–4	Monitor long-term
Selenium	2–5% nail/hair	None (typical doses)	<1	Safe at 200 µg/day
CoQ10	2–3% insomnia, GI	None	<1	Excellent safety

Note: GI = gastrointestinal.

3.5.7. Drug-Nutrient Interaction Matrix

Table 13. Potential Drug-Nutrient Interactions Between Antioxidants and Common Autoimmune Therapies

Antioxidant	Warfarin	NSAIDs	Steroids	TNF-α Inhibitors	Methotrexate	JAK Inhibitors
Curcumin	↑ anticoagulation	Minor	Synergy	Synergy	No interaction	Possible
Resveratrol	↑ anticoagulation	No	Synergy	Synergy	No interaction	Possible

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EGCG	Minor	No	Synergy	Synergy	No interaction	No interaction
Quercetin	Minor	Minor	Synergy	Synergy	No interaction	No interaction
Vitamin E	↑ bleeding risk	No	Synergy	Synergy	No interaction	No interaction
Vitamin C	No	No	Synergy	Synergy	No interaction	No interaction
Zinc	No	No	↓ absorption	No interaction	No interaction	No interaction
Selenium	No	No	Synergy	No interaction	No interaction	No interaction

Note: NSAIDs = non-steroidal anti-inflammatory drugs; TNF-α = tumor necrosis factor alpha; JAK = Janus kinase.

3.6. Bioavailability and Microbiota Modulation

3.6.1. Bioavailability Determinants

A critical limitation in clinical antioxidant translation is poor oral bioavailability. Curcumin exhibits ~5% absorption in native form; resveratrol similarly shows modest intestinal permeability (5–10%); EGCG undergoes minimal systemic absorption (<1% reaches circulation intact) (Khan et al., 2019; Li et al., 2020). Strategies enhancing bioavailability include:

1. **Lipid formulation:** Liposomal, micellar, and nanoemulsion delivery systems increase lipophilic polyphenol solubility, reducing first-pass metabolism
2. **Piperine co-administration:** Black pepper alkaloid inhibits UGT1A1 glucuronidation, increasing curcumin serum levels 20-fold
3. **Structural modification:** Nano-curcumin and phospholipid complexes (phytosome formulations) improve bioavailability 2–10 fold
4. **Gut microbiota metabolism:** Colonic bacteria metabolize polyphenols to phenolic acids with enhanced absorption and biological activity (e.g., curcumin→dihydroferulic acid)

3.6.2. Microbiota Modulation and Immune Tolerance

Emerging evidence reveals that food-based antioxidant efficacy depends substantially on gut microbiota composition (Mousa et al., 2022). Dysbiosis—characterized by reduced alpha-diversity and pathogenic bloom of pro-inflammatory taxa—drives multiple autoimmune diseases through: (1) molecular mimicry (bacterial epitopes cross-reactive with self-antigens); (2) lipopolysaccharide (LPS) translocation across compromised intestinal barriers; and (3) suppression of short-chain fatty acid (SCFA)-producing bacteria that generate butyrate—a key histone deacetylase (HDAC) inhibitor promoting Treg differentiation (Mousa et al., 2022; Rosenkranz et al., 2016).

Polyphenol-induced microbiota shifts include enrichment of beneficial taxa: Faecalibacterium prausnitzii (butyrate producer, NF-κB antagonist), Roseburia species, Akkermansia muciniphila (mucus layer restoration), and Prevotella histicola (CD103+ dendritic cell induction, Treg promotion) (Mousa et al., 2022). This prebiotic mechanism represents a missing link explaining polyphenol efficacy: direct immune modulation is supplemented by sustained microbiota rebalancing, perpetuating tolerance and reducing disease flare risk.

3.7. Clinical Integration Framework

3.7.1. Evidence-Based Integration Strategy

Evidence supports adjunctive antioxidant therapy rather than monotherapy replacement (Khan et al., 2019; Nourmohammadi et al., 2020; Zhou et al., 2025). Curcumin, resveratrol, and CoQ10 demonstrate additive or synergistic effects when combined with conventional agents (TNF-α inhibitors, JAK inhibitors, corticosteroids) (Khan et al., 2019; Nourmohammadi et al., 2020). In MS patients, CoQ10 (100 mg/day) combined with interferon-β proved superior to interferon-β monotherapy for oxidative stress reduction and clinical outcomes

(Nourmohammadi et al., 2020). In RA, polyphenol combinations including curcumin, quercetin, and ginger demonstrated superior efficacy versus single polyphenol supplementation (Zhou et al., 2025).

3.7.2. Clinical Integration Framework

A tiered clinical integration framework can be applied to guide the adjunctive use of antioxidant and polyphenol-based interventions alongside standard immunosuppressive therapies. Tier 1 interventions, supported by the strongest clinical evidence, include curcumin for rheumatoid arthritis, anthocyanin-rich preparations for ulcerative colitis, and CoQ10 for multiple sclerosis, all of which demonstrate consistent benefits when used as adjuncts to conventional treatment. Tier 2 interventions, supported by moderate but growing evidence, include resveratrol for systemic lupus erythematosus, epigallocatechin gallate (EGCG) for multiple sclerosis and rheumatoid arthritis, and vitamin E for multiple sclerosis, particularly when combined with established immunomodulatory agents. Tier 3 interventions represent emerging or preclinical evidence and include quercetin for type 1 diabetes, zinc supplementation based on autoimmune encephalitis models, selenium for the prevention of type 1 diabetes–related complications, and vitamin C for rheumatoid arthritis and systemic lupus erythematosus, warranting further validation in large-scale human trials before routine clinical implementation.

3.7.3. Disease-Specific Clinical Recommendations

Adjunctive antioxidant and polyphenol-based therapies show disease-specific benefits across several autoimmune and inflammatory disorders. In rheumatoid arthritis, curcumin at 500–1000 mg/day—preferably formulated with piperine or as a nano-preparation—used alongside standard DMARD therapy may reduce disease activity and inflammatory markers, while ginger (2000 mg/day) and vitamin E (200–400 IU/day) provide additional anti-inflammatory support; treatment duration should be individualized, with 8–12 weeks commonly used as a trial period (Zhou et al., 2025; Isola et al., 2024; Nourmohammadi et al., 2020). In systemic lupus erythematosus, resveratrol at 1–2 g/day shows promise, particularly in lupus nephritis and systemic disease activity, although large-scale human trials are ongoing; vitamin C supplementation at 500 mg twice daily may attenuate oxidative damage and autoantibody production, and curcumin may be considered as adjunct therapy in treatment-resistant cases (Shah et al., 2014; Warren and MacIver, 2019; Isola et al., 2024; Khan et al., 2019). For multiple sclerosis, CoQ10 supplementation at 100–500 mg/day in combination with interferon-β or natalizumab has been shown to significantly reduce oxidative stress markers and improve fatigue and depression scores, while EGCG from green tea (200–400 mg/day) demonstrates strong preclinical neuroprotective effects and vitamin E (200–400 IU/day) provides adjunctive antioxidant support (Nourmohammadi et al., 2020; Li et al., 2020; Xue et al., 2016). In type 1 diabetes, quercetin (500–1000 mg/day) may help preserve pancreatic β-cell function and reduce oxidative injury, zinc supplementation (20–25 mg/day) supports regulatory T-cell function and immune tolerance in genetically susceptible individuals, and selenium intake of at least 200 µg/day is required to sustain glutathione peroxidase activity and protect β-cells from oxidative destruction, although further human trials are needed (Coskun et al., 2005; Rosenkranz et al., 2016; Wessels et al., 2017; Lei et al., 2007; Mita et al., 2017; Firouzeh et al., 2024). In inflammatory bowel disease, particularly ulcerative colitis, anthocyanin-rich preparations such as bilberry or blueberry extracts at approximately 3 g/day have demonstrated clinical remission in preliminary studies, while ginger (2000 mg/day) and curcumin (500 mg/day) reduce pro-inflammatory cytokine production and improve clinical symptoms; combination polyphenol therapies appear to confer synergistic benefits superior to monotherapy, especially in mild-to-moderate disease (Biedermann et al., 2013; Biedermann et al., 2024; Isola et al., 2024; Ranjbar et al., 2022; Sadeghi Poor Ranjbar et al., 2022; Martin and Bolling, 2015).

3.8. Limitations and Research Gaps

Current evidence supporting antioxidant and polyphenol-based interventions in autoimmune diseases is constrained by several important limitations. Significant heterogeneity exists across trials with respect to antioxidant dose, formulation (native extracts versus bioavailability-enhanced preparations), intervention duration, and patient populations, which limits direct comparability and quantitative synthesis; accordingly, meta-analyses frequently report substantial statistical heterogeneity, with I^2 values often exceeding 70%. Most studies are further limited by small sample sizes, typically enrolling only 20–60 participants, and adequately powered randomized controlled trials ($n > 200$) are scarce for most antioxidants, with curcumin in rheumatoid arthritis being a notable exception (Zhou et al., 2025). In addition, follow-up periods are generally short, commonly restricted to 8–12 weeks, leaving long-term efficacy, safety, and adherence—critical considerations

for chronic autoimmune diseases requiring sustained remission—poorly characterized beyond six months or multiple years. Publication bias also remains a concern, as studies reporting positive outcomes are more likely to be published than those with null or negative findings, potentially inflating estimated treatment effects. Finally, translation of mechanistic insights into clinical trials is limited, as most human studies prioritize clinical endpoints and non-specific inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate, while parallel assessment of mechanistic biomarkers—including NF-κB transcriptional activity, Th17/Treg balance, and gut microbiota composition before and after intervention—is rarely incorporated.
Standardized protocols establishing optimal doses, formulations, and co-administration strategies for each antioxidant in each disease context. Longitudinal assessments of microbiota composition, SCFA levels, tight junction protein expression, and parallel immune phenotyping (Mousa et al., 2022). Next-generation trials should include ROS measurement, NF-κB and Nrf2 transcriptional activity, Th17/Treg flow cytometry, cytokine panels, and epigenetic profiling (Dodson et al., 2019; Gao et al., 2022; Tonelli et al., 2022). Genomic, epigenomic, and immune profiling to identify disease subtypes most responsive to specific antioxidants. Multi-year prospective studies evaluating sustained remission rates, hospitalization reduction, and safety profiles. Systematic investigation of antioxidant combinations (polyphenol cocktails) vs. monotherapy (Martin and Bolling, 2015).

4. Conclusions

Food-based antioxidants represent a promising adjunctive therapeutic class for autoimmune disease management, offering mechanisms complementary to conventional immunosuppression, with substantially superior safety profiles enabling long-term administration. Curcumin, resveratrol, EGCG, anthocyanins, and CoQ10 provide the strongest current evidence, with mechanistic pluripotency—targeting NF-κB, SIRT1, Nrf2, and microbiota dysbiosis simultaneously. However, clinical translation is limited by heterogeneous trial designs, small sample sizes, and insufficient long-term follow-up.

Future investigation should prioritize: (1) large, adequately powered trials with standardized protocols; (2) mechanistic biomarker integration alongside clinical outcomes; (3) microbiota-immune axis characterization; (4) precision medicine approaches identifying responder phenotypes; and (5) optimal formulation and dosing strategies. When rigorously integrated with conventional immunosuppressive therapy, food-based antioxidants hold substantial potential to reduce disease burden, inflammatory complications, and medication side effects in the 90 million individuals with autoimmune disease globally.

Authors' contribution

Deepika Sharma was involved in the conceptualization of the study, conducted the literature search, performed data extraction, and prepared the original draft of the manuscript along with tables and figures. Hissay Choden Bhutia contributed through literature search, quality assessment, data extraction, and critical review and editing of the manuscript. Gana Maya Rai was responsible for quality assessment, risk of bias evaluation, data synthesis, and manuscript review. Swastika Sharma assisted with data extraction, mechanistic pathway analysis, and manuscript review and editing. Debasrita Banerjee led conceptualization and methodology design, supervised the study, contributed to manuscript review and editing, provided final approval, and handled corresponding author responsibilities. Ravi Yadav contributed by developing the clinical integration framework, reviewing the manuscript, and offering expert consultation. All authors have read and approved the final manuscript.

Competing Interest

The authors declared no conflict of interest.

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AI Declaration

Artificial intelligence tools (ChatGPT OpenAI) were used to support language editing, improve sentence clarity, and assist with structural refinement during manuscript revision. The authors reviewed and verified all content and take full responsibility for the accuracy, originality, and integrity of the work, including ensuring that all statements and citations are appropriate and scientifically sound.

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