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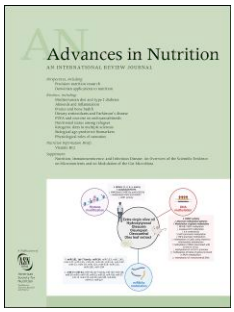

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Dietary and Nutritional Factors in Systemic Lupus Erythematosus Pathophysiology: A Scoping Review of the Evidence from In-Vitro, In-Vivo and Human Studies

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Abbreviations

AA: arachidonic acid

AHEI: Alternative Healthy Eating Index

ALA: alpha-linolenic acid

aMed: Alternative Mediterranean Diet Score

ANA: antinuclear antibodies

BMDC: bone marrow-derived dendritic cells

CRP: C-reactive protein

cSiO2: crystalline silica

DASH: Dietary Approach to Stop Hypertension

DAQ: dietary antioxidant quality scores

dsDNA: double-stranded DNA

DHA: docosahexaenoic acid

EDIP: Empirical Dietary Inflammatory Pattern

EPA: eicosapentaenoic acid

EVOO: extra virgin olive oil

FDC: follicular dendritic cells

HLIS: Healthy Lifestyle Index Score

HSD: high-sodium diet

IL-6: interleukin-6

IL-10: interleukin-10

LA: linoleic acid

LPS: lipopolysaccharide

MUFA: monounsaturated fatty acids

NHS: Nurses' Health Study

NRI: Nutritional Risk Index

PGA: Physician Global Assessment

PROMIS: Patient-Reported Outcomes Measurement Information System

PUFA: polyunsaturated fatty acids

PNI: Prognostic Nutritional Index

RA: rheumatoid arthritis

SCF: stem cell factor

SGK1: glucocorticoid-inducible serine/threonine protein kinase 1

SLAQ: Systemic Lupus Activity Questionnaire

SLE: Systemic Lupus Erythematosus

SM: anti-smith antibodies

SPMs: specialized pro-resolving mediators

VDR: vitamin D receptors

VOO: virgin olive oil

Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease whose pathogenesis involves interplay between genetic predisposition and environmental factors, including diet. This scoping review maps and synthesizes current evidence from human and animal studies on the relationships between dietary factors and lupus pathophysiology. Following PRISMA guidelines, we identified 139 relevant studies from Scopus, PubMed, and EBSCO published between 2012-2023. Our analysis reveals that specific dietary components significantly influence lupus risk and disease activity. Diets high in sugar, carbohydrates, and sodium were associated with increased inflammation and exacerbated disease severity. Conversely, several factors demonstrated protective effects. Higher intake of omega-3 polyunsaturated fatty acids (PUFAs) was consistently linked to reduced inflammatory markers and improved patient-reported outcomes, while a higher omega-6 to omega-3 ratio correlated with worsened disease activity. Moderate alcohol consumption, particularly wine, was associated with a reduced risk of SLE incidence. Adequate vitamin D levels were connected to attenuated disease progression and immunomodulation. Furthermore, natural products like olive oil phenolic compounds and curcumin showed promise in reducing oxidative stress and inflammatory pathways in murine models. The evidence underscores that dietary modification presents a viable strategy for modulating immune function and inflammation in SLE. Integrating nutritional guidance with conventional therapies could improve disease management. Future large-scale randomized controlled trials are essential to establish precise dietary recommendations and elucidate the mechanisms underlying diet-lupus interactions.

Statement of Significance

This scoping review offers a comprehensive synthesis of the evidence linking dietary and nutritional factors in Systemic Lupus Erythematosus (SLE) pathophysiology.

Keywords: Systematic Lupus Erythematosus; autoimmune disease; dietary factors; nutrition; scoping review.

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by extensive dysfunction of both the adaptive and innate immune systems (1). SLE can manifest clinically in various organs, including the skin (cutaneous lupus erythematosus), kidneys (lupus nephritis), joints, lungs, cardiovascular system and central nervous system (2). In SLE, autoreactive T cells and B cells produce a variety of autoantibodies, including antinuclear antibodies (ANA), anti-smith antibodies (SM), and antibodies against double-stranded DNA (dsDNA), which can form immune complexes that are deposited in various organ tissues (3,4). However, antibody deposition is not the only complication involving the immune system in SLE. For example, dysregulation in the complement system has also been documented, leading to an amplified inflammatory response that exacerbates tissue damage (5,6). As a result, the management of lupus often involves multi-target therapies using immunosuppressive agents and corticosteroids (7).

The exact causes of SLE are not fully understood, but it is believed to involve both genetic and environmental factors (8,9). The role of environmental factors is highlighted by the significantly higher SLE incidence in African Americans compared to West Africans, despite their shared genetic background (10). The mechanisms underlying this disparity remains unclear, but dietary factors may play a role. Indeed, dietary and lifestyle components can modulate immune responses and the inflammatory processes that underlie lupus pathogenesis.

For example, micronutrients such as vitamin D and zinc have emerged as key regulators of immune function, oxidative stress, and inflammation (11–13). Additionally, dietary plant secondary metabolites such as polyphenols have shown promise in modulating immune

responses, gut microbiome, and mitigating inflammatory processes implicated in lupus pathogenesis (14).

We hypothesized that specific dietary and nutritional factors are linked to lupus risk and disease activity, with some being protective and others harmful. Given growing evidence connecting diet, micronutrients, and immune modulation, this review aims to synthesize findings from observational studies, in vitro, animal models, and human clinical data on diet-SLE interactions.

Unlike prior reviews that focus on single nutrients, this study offers several contributions. First, it integrates evidence from human studies and animal models to provide mechanistic insight alongside epidemiological data. Second, it organizes the literature into key categories such as macronutrients, essential fatty acids, vitamin D, sodium, alcohol, and natural products and therefore allowing comparison of protective and harmful factors. Third, it includes emerging evidence on bioactive compounds such as olive oil phenolics and curcumin, which have received limited attention. Overall, this approach provides a more holistic view of how dietary patterns, rather than single nutrients, influence lupus pathogenesis.

Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15). The four-phase flow PRISMA methodology was followed, as seen in **Figure 1** (16). The search for peer-reviewed manuscripts published between 1 January 2012 up to July 2023 was conducted by four authors independently (F.Z., N.P., M.P., J.J). The Scopus, Pubmed, and EBSCO databases were queried between 1

January 2012 and 9 July 2023. The search terms that were used were: lupus and ((food) or (diet) or (nutrition*) or (nutrient*)).

Studies were included if they met the following criteria: (1) primary research articles (observational studies, clinical trials, *in vivo* animal studies, *in vitro* mechanistic studies); (2) investigation of an association between dietary/nutritional factors and SLE outcomes (incidence, disease activity, biomarkers, organ involvement); (3) published in peer-reviewed journals; (4) English language; (5) published between January 2012 and July 2023. Dietary factors were defined as any nutritional component consumed orally, including macronutrients (carbohydrates, proteins, fats), micronutrients (vitamins, minerals), bioactive compounds (polyphenols, flavonoids), whole foods, dietary patterns, and nutritional supplements. Exclusion criteria included narrative reviews, systematic reviews, meta-analyses, commentaries, conference abstracts, editorials, and studies not specifically addressing SLE.

The included studies were documented in Mendeley, and duplicate records were eliminated. Studies were evaluated by comprehensive examination of titles, keywords, abstracts, and full texts. Articles that did not align with the guiding statement and the predetermined criteria were subsequently excluded. In the event of disagreement regarding eligibility of a specific article, resolution was achieved through discussion with all authors involved in the initial search; the study was included only if all authors agreed. Summaries of included studies were collected and organized in Microsoft Excel. Finally, the authors classified studies into distinct thematic categories: macronutrients, ultra-processed foods and general dietary factors, alcohol consumption, iodine intake, vitamin D, essential fatty acids, and natural products. In this review, "general dietary factors" encompasses overall dietary patterns, macronutrient

96 composition, ultra-processed food consumption, and lifestyle factors that influence nutritional
97 status (e.g., meal patterns, dietary quality indices, eating behaviors).

98 **Discussion**

99 ***Macronutrients and general dietary factors***

100 Macronutrients and general dietary factors have been extensively studied in relation to
101 systemic lupus erythematosus (SLE), offering insights into the role of diet in disease activity and
102 risk. Correa-Rodríguez et al. (2020) explored the association between dietary sugar intake and
103 cardiovascular risk markers in patients with SLE (17). The study included 193 patients and
104 examined clinical and metabolic factors like disease activity, obesity, diabetes, hypertension, and
105 lipid levels. It found that higher intake of free sugars was linked to greater disease activity and
106 complications, including dyslipidemia(17). This suggests that elevated sugar consumption may
107 exacerbate disease progression and cardiovascular risk in SLE patients.

108 Additionally, the composition of macronutrients in the diet has been examined for its
109 potential influence on SLE risk. Castro-Webb et al. (2021) analyzed data from the Black
110 Women's Health Study and found that higher intakes of monounsaturated fats (MUFAs),
111 saturated fats, and trans fats were linked to a decreased risk of developing SLE (18).
112 Interestingly, a diet high in carbohydrates, particularly from sugar-sweetened beverages and
113 fruits, and low in fats, was associated with an increased risk of SLE. These findings suggest that
114 a balanced intake of fats, particularly MUFAs and saturated fats, may offer some protective
115 effects against SLE onset (18).

116 Julià et al. (2021) added further evidence to the role of sugar intake in SLE by showing
117 that patients with SLE consumed higher levels of sweets compared to healthy controls,

118 highlighting a possible dietary pattern that could influence disease activity (19). Similarly, Petrić
119 et al. (2020) investigated the dietary habits of 76 SLE patients in clinical remission and
120 discovered associations between low-quality proteins, calorie-rich foods, and reduced levels of
121 complement proteins C3 and C4 (20). These proteins are crucial in immune regulation, and their
122 decreased levels could signal potential disease activation, suggesting that diets high in fast food
123 and fried foods may contribute to disease flares (20).

124 On a broader scale, lifestyle factors also play a significant role in SLE risk. Choi et al.
125 (2022) conducted an extensive analysis of 185,962 women over 4,649,477 person-years from the
126 Nurses' Health Study (NHS) and NHSII cohorts, examining the relationship between a Healthy
127 Lifestyle Index Score (HLIS) and SLE incidence (21). They found that adopting healthy lifestyle
128 practices, such as maintaining a balanced diet, regular physical activity, and a healthy body
129 weight, could halve the risk of developing SLE, despite the known genetic predisposition to the
130 disease (21). These findings reinforce the importance of modifiable lifestyle factors in mitigating
131 disease risk.

132 Nutritional status itself has also been linked to disease severity in SLE patients. Correa-
133 Rodríguez et al. (2019) highlighted that poor immune-nutritional status, as measured by the
134 Prognostic Nutritional Index (PNI) and Nutritional Risk Index (NRI), correlated with heightened
135 disease activity and organ damage in SLE patients (22). Behiry et al. (2019) reported that over
136 three-quarters of the SLE patients in their study were either overweight or obese, with their
137 dietary patterns characterized by reduced intake of fruits, vegetables, and dairy products, and
138 elevated consumption of fats and oils. This unhealthy dietary pattern was associated with
139 increased BMI, body weight, and disease duration, indicating a direct link between poor dietary
140 choices and disease progression (23).

Contradictory evidence regarding the role of diet in SLE risk has also emerged. Tedeschi et al. (2020) examined the relationship between dietary quality and SLE risk in the NHS and NHSII cohorts and found no significant association between prudent or Western dietary patterns and SLE incidence (24). Similarly, Barbhaiya et al. (2021) evaluated the impact of four dietary quality scores; namely the Alternative Healthy Eating Index (AHEI-2010), Alternative Mediterranean Diet Score (aMed), Dietary Approach to Stop Hypertension (DASH), and Empirical Dietary Inflammatory Pattern (EDIP), and found that long-term adherence to these dietary patterns did not significantly influence SLE risk (25).

Animal studies suggest modes of action of how general dietary factors may affect the pathophysiology of lupus

In TLR7-dependent mouse model, western-style diet appears to be linked to the incidence of lupus through changes in the microbiota composition (26). In TLR8-deficient mice, a high-fat diet worsens lupus through TLR7 signaling. This leads to stronger immune responses, more anti-DNA antibodies, increased IgG/IgM deposits in the kidney, and greater kidney damage. (27). Table 1 summarizes the effect of macronutrients, ultra-processed foods, and general dietary factors on lupus incidence and severity.

Essential fatty acids

Essential fatty acids, specifically omega-3 and omega-6 fatty acids, are critical components of the human diet, as they cannot be synthesized by the body. These polyunsaturated fatty acids (PUFAs) play significant roles in modulating immune responses, which has drawn substantial attention for their influence on the pathogenesis and progression of autoimmune diseases, including SLE (28,29). Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and

docosahexaenoic acid (DHA), are metabolized into eicosanoids,lipid-based signaling molecules that participate in immune responses. Unlike eicosanoids derived from omega-6 fatty acids, those from omega-3 are generally less inflammatory, contributing to a more balanced immune response (30). Moreover, EPA and DHA are precursors to specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins, which actively resolve inflammation, promote tissue repair, and aid in microbial clearance (31).

On the other hand, omega-6 fatty acids, with linoleic acid (LA) as a primary example, are converted into arachidonic acid (AA), which serves as a precursor for eicosanoids like prostaglandins, thromboxanes, and leukotrienes (29). These eicosanoids are typically pro-inflammatory and play essential roles in initiating and promoting inflammatory responses necessary for combating infections and repairing tissue damage (32,33). However, when inflammation becomes chronic, these pro-inflammatory eicosanoids can contribute to autoimmune disease development. The balance between omega-3 and omega-6 fatty acids is therefore crucial for maintaining immune homeostasis (34). Research has shown that this balance is particularly important in autoimmune conditions such as lupus, where dietary interventions involving omega fatty acids have demonstrated potential benefits in disease management (35,36).

Several clinical studies have explored the impact of omega-3 supplementation in SLE patients. Arriens et al. (2015) conducted a randomized placebo-controlled trial in which 50 SLE patients received daily fish oil supplementation containing 2.25 g of EPA and 2.25 g of DHA for six months (37). The omega-3 supplemented group showed significant improvements in quality of life, as assessed by the RAND Short Form-36, and reductions in disease severity, based on the Physician Global Assessment (PGA). Additionally, circulating inflammatory markers were

reduced in the treatment group (37). Similarly, Borges et al. (2017) found that after 12 weeks of daily supplementation with 1080 mg EPA and 200 mg DHA, SLE patients exhibited a reduction in C-reactive protein (CRP), an inflammatory marker, though no significant changes were observed in interleukin-6 (IL-6), interleukin-10 (IL-10), leptin, or adiponectin levels (38).

Further studies have examined the relationship between PUFA profiles and inflammation in SLE patients. Vordenbäumen et al. (2020) conducted a cross-sectional study of the erythrocyte membrane PUFA profiles of 68 adult SLE patients (36). They observed that higher levels of omega-6 PUFAs and a higher ratio of LA to alpha-linolenic acid (ALA) were associated with increased CRP levels. Conversely, a higher percentage of omega-3 PUFAs was inversely correlated with CRP levels, indicating a potential anti-inflammatory effect of omega-3s. Moreover, increased intake of omega-3-rich foods, such as fish, was associated with an improved omega-3 status and a reduction in self-reported disease damage, as measured by the Brief Index of Lupus Damage (36). Similar findings were reported by Charoenwoodhipong et al. (2020) in a cohort of 456 SLE patients from the Michigan Lupus Epidemiology and Surveillance cohort (35). They found that for every unit increase in the omega-6 ratio, the Systemic Lupus Activity Questionnaire (SLAQ) score increased by 0.3 points (higher SLAQ scores indicate greater disease activity and symptom severity). Additionally, each gram increase in omega-3 PUFA consumption per 1,000 kilocalories was associated with a decrease in lupus activity and fewer sleep disturbances, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) (35).

These findings collectively highlight the importance of the omega-6 to omega-3 ratio in modulating inflammation and disease outcomes in SLE. A higher ratio of omega-6 to omega-3 PUFAs appears to correlate with increased inflammation and disease activity, while increasing

omega-3 intake is associated with improved clinical outcomes and reduced inflammatory markers. Thus, balancing omega-3 and omega-6 fatty acids through dietary modifications may be a valuable strategy in managing autoimmune diseases like lupus.

Animal studies suggest modes of action behind the potential protective effect of omega-3 PUFAs in lupus

In lupus mouse models induced by crystalline silica (cSiO2), supplementation with docosahexaenoic acid (DHA) has been shown to significantly inhibit the proliferation of immune cells such as B-cells, T-cells, follicular dendritic cells (FDC), and IgG-positive plasma cells within the lungs (39). This supplementation also reduced levels of anti-dsDNA IgG in both bronchial lavage fluid and plasma. Additionally, DHA attenuated the development of glomerulonephritis, alongside a reduction in B-cell accumulation in the renal cortex (39). Furthermore, a diet high in DHA mitigated the upregulation of genes associated with inflammation, immune responses (both innate and adaptive), interferon signaling, chemokines, and antigen processing in lupus models (40). Dietary DHA intake in lupus-prone mice also inhibited the expression of mRNA signatures commonly linked to the formation of ectopic lymphoid tissues, systemic autoimmunity, and glomerulonephritis (40).

In the lupus mouse model induced by cSiO2, there was a marked autoantibody response, particularly IgG, IgM, and to a lesser extent, IgA. However, DHA supplementation dose-dependently reduced these autoantibody levels, which were inversely correlated with omega-3 fatty acid levels in tissue phospholipids (41). This negative correlation extended to the activation of interferon-regulated genes, production of pro-inflammatory cytokines, leukocyte infiltration, ectopic lymphoid structure formation in the lungs, systemic autoantibody production, and glomerulonephritis development (42).

Additionally, Pestka et al. (2014) compared the effects of omega-3, omega-6, and omega-9-rich diets in lupus-prone mice (43). Mice fed omega-6 or omega-9 diets exhibited elevated levels of plasma autoantibodies, proteinuria, and glomerulonephritis. In contrast, mice on an omega-3-rich diet showed significantly lower levels of these symptoms. This suppression of autoimmune responses by omega-3 was linked to the downregulation of CD4+ T cell-related genes, including CD80, CTLA-4, IL-10, IL-18, CCL-5, CXCR3, IL-6, TNF-α, and osteopontin in kidney and spleen tissues, relative to the omega-6 and omega-9 diets (43).These genes are involved in inflammatory responses, antigen presentation, T-cell activation, B-cell activation and differentiation, and leukocyte recruitment.

Table 2 provides a summary of the relationships between essential fatty acids and the incidence and severity of lupus, highlighting the potential therapeutic role of omega-3 in modulating immune and inflammatory responses in lupus-prone models.

Alcohol consumption

Moderate alcohol consumption has been observed to have a protective effect against lupus. In a study by Barbhaiya et al. (2017), 125 new cases of SLE were identified in the Nurses' Health Study (NHS) and 119 in the NHSII cohort (44). When comparing individuals who consumed alcohol to those who did not, a meta-analyzed multivariable hazard ratio (HR) for a cumulative alcohol consumption of ≥5 grams/day was found to be 0.61 (95% Confidence Interval [CI] 0.41–0.89), indicating a reduced risk of SLE. Notably, the protective effect was still evident when alcohol consumption occurred more than four years prior to diagnosis, with a similar HR of 0.61 (95% CI 0.41–0.91). Women who regularly consumed wine, in particular, demonstrated a significant reduction in SLE risk compared to non-drinkers, suggesting a potential correlation between moderate alcohol intake (≥5 grams or approximately 0.5 standard

drinks per day) and a reduced risk of SLE (44).This finding raises the possibility that polyphenols in wine, rather than alcohol alone, may play a crucial role in this protective effect.

Further insights into the relationship between alcohol consumption and SLE were provided by Hahn et al. (2020), who discovered that stem cell factor (SCF) levels decreased significantly with each gram of cumulative alcohol intake per day (45). Women consuming more than 5 grams of alcohol daily exhibited stem cell factor levels that were 7% lower than those of non-drinkers. Although no significant associations were found between alcohol intake and other cytokines, the reduction in stem cell factor levels offers a potential mechanism through which alcohol could reduce the risk of SLE. Interestingly, this effect was independent of autoantibody status, further supporting the idea that alcohol, particularly when consumed in moderation, may play a role in reducing the incidence of lupus by lowering circulating SCF levels (45).

An inverse relationship between alcohol intake and SLE risk is biologically plausible. Previous research has shown that alcohol can diminish cellular responses to immunogens and reduce the production of pro-inflammatory cytokines, including TNF, IL-8, and IL-6, in immune cells such as alveolar macrophages and peripheral blood monocytes (46). In addition, wine contains polyphenolic compounds such as resveratrol, which have demonstrated antioxidant and anti-inflammatory properties (47), including modulation of IFN-γ (48) and reductions in serum levels of IL-1β and IL-18 in animal models (49), although the relevance of these findings to typical dietary intake in humans remains uncertain.

However, the potential benefits of moderate alcohol intake should be viewed in the context of its established health risks, including liver toxicity and increased risk of certain cancers (50). Furthermore, J- or U-shaped associations between alcohol intake and adverse health outcomes, including rheumatoid arthritis (RA), cardiovascular diseases, and all-cause-

mortality have been reported (51–53). Moderate alcohol intake (5–9.9 g/day) has been associated with the lowest levels of inflammatory biomarkers among women with pre-clinical RA (54). Notably, Barbhaiya et al. (2017) reported that the inverse association between alcohol intake and SLE risk became slightly stronger after excluding heavy drinkers (individuals consuming >30 g/day), suggesting a similar non-linear relationship (44).

Table 3 summarizes the potential impact of alcohol consumption on lupus incidence and disease severity, highlighting the nuanced role that moderate alcohol intake, particularly wine, may have in influencing SLE risk.

Sodium Intake

High sodium intake worsens lupus symptoms. Animal studies show that a high-sodium diet speeds up disease progression and makes lupus nephritis more severe, reducing survival in MRL/lpr mice. This is linked to increased Th1 and Th17 immune cells. Using SGK1 (glucocorticoid inducible serine/threonine protein kinase 1) inhibitors helped reduce these harmful effects. (55). Moreover, HSD was shown to enhance the maturation and activation of bone marrow-derived dendritic cells (BMDCs) through the p38 MAPK-STAT1 pathway, both in vitro and in vivo (56). Another study in NZBWF1 mice found that a high-sodium diet increased anti-dsDNA antibodies but did not change blood pressure or kidney damage. Urinary ET-1 increased, while some kidney markers (renal endothelin A receptor and IL-2) decreased, suggesting that long-term high sodium may not worsen heart and kidney problems in SLE. (57).

Conversely, a clinical trial examining the effects of a low-sodium diet on patients with SLE and rheumatoid arthritis (RA) found that reducing sodium intake lowered pro-inflammatory Th17 cell counts, increased Treg cell counts, and decreased serum IL-9 levels. These effects were

reversible upon returning to a regular sodium diet (58). This finding aligns with earlier animal studies that suggested high sodium diets amplify systemic inflammation, while low sodium diets mitigate it, particularly by affecting cytokine production and inflammation (55). Notably, no significant changes in apoptotic human peripheral blood mononuclear cells (PBMCs) or factors modulating proliferation were observed during the trial, indicating that the diet specifically influenced inflammatory pathways without altering cell survival (58).

In a cross-sectional study on the Mexican-Mestizo population, a link was found between excessive weight (BMI > 25) and sodium consumption (59). Overweight individuals showed significant reductions in several micronutrients and macronutrients, hinting at poor dietary choices. Overweight SLE patients consuming fewer calories than their normal-weight counterparts could benefit from reduced sodium intake, but may also suffer from deficiencies in essential micronutrients that regulate immune function, such as vitamins B and C, zinc, and selenium (59). Additionally, these patients frequently had low-quality diets, as indicated by their dietary antioxidant quality scores (DAQs) and elevated serum hsCRP levels, although these metrics were not significantly correlated (22). Instead, the mineral content of their diets, particularly sodium and potassium levels, appeared to influence hsCRP levels in SLE patients. High sodium or low potassium intake was linked to increased inflammation (22). Furthermore, sodium intake was associated with elevated anti-dsDNA levels and reduced C4 complement protein levels, while potassium intake correlated with C3 complement protein levels (60). However, another observational study found that higher sodium intake was inversely related to C3 and C4 levels in inactive SLE patients. In this study, gut health was also explored, revealing a rise in *Megamonas funiformis* and plasma zonulin, both indicators of increased gut permeability (61).

Sodium intake influences both innate and adaptive immunity. In the innate immune system, prolonged high-sodium diets are thought to promote inflammation, driven mainly by macrophages and dendritic cells. While this heightened inflammation may offer protection against systemic infections, it can be detrimental in autoimmune diseases like SLE. In adaptive immunity, HSD suppresses Treg cells and activates Th17 cells, leading to increased inflammation and worsening autoimmune conditions (62). Overall, the evidence suggests that high sodium intake significantly contributes to the worsening of SLE in both murine and human models, primarily by enhancing systemic inflammation through various mechanisms. Table 4 summarizes the impact of excessive sodium intake on lupus incidence and severity.

Vitamin D

Vitamin D, primarily recognized for its vital roles in calcium regulation, is also an important immune function regulator. Both the innate and adaptive arms of the immune system possess vitamin D receptors (VDR) (63,64). For example, upon pathogenic infection, innate immune cells, like macrophages, convert inactive vitamin D into its active form, calcitriol, which subsequently induces the production of antimicrobial peptides such as cathelicidin (65). In addition, vitamin D also modulates the inflammatory cascade such as by inhibiting pro-inflammatory cytokines like IL-6 and TNF-alpha, while upregulating anti-inflammatory mediators if overexpression of inflammation occurs (66). In terms of the adaptive immunity, vitamin D has been found to regulate T helper 1 (Th1) and Th17 cell responses, both implicated in autoimmunity and inflammation, and modulate the regulatory T-cell (Treg) functions in order to preserve immune tolerance (67–69). B cell differentiation and antibody production are also regulated by vitamin D, further exemplifying its roles in immune response (70). Clinical evidence suggests that vitamin D deficiency is linked to increased susceptibility to infections

346 such as Covid-19, influenza, and tuberculosis (71–74). Given the importance of vitamin D in
347 immune function regulation, it is not surprising if vitamin D has a vital role in autoimmune
348 disorders including lupus.

349 Lupus patients have been consistently shown to have vitamin D deficiency. Cutillas-
350 Marco et al. (2014) investigated a relatively small group of CLE patients and found that the CLE
351 patients had higher odds of having vitamin D deficiency (75). Similar observation was also
352 reported by García-Carrasco et al. (2017) (76). They found that 126 out of 137 patients with SLE
353 had either vitamin D insufficiency or deficiency, where insufficiency was defined as serum 25-
354 hydroxyvitamin D <30 ng/ml and deficiency as <10 ng/ml (76). Furthermore, a systematic
355 review and meta-analysis carried out by Islam et al. (2019) analyzed 34 case-control studies
356 comprising 2265 SLE patients and 1846 healthy controls, found that inadequate level of vitamin
357 D was prominent in SLE patients when compared to healthy controls (11).

358 In addition, a small group of patients with CLE and vitamin D insufficiency (serum 25-
359 hydroxyvitamin D levels <30ng/ml) or deficiency (levels <10ng/ml) were found to have
360 improved disease severity when treated with an oral vitamin D supplementation schedule. They
361 received 1400 IU of cholecalciferol and 1250 mg of calcium carbonate daily for 40 days. This
362 was followed by two tablets daily, each containing a fixed combination of 1250 mg of calcium
363 carbonate and 400 IU of cholecalciferol, for one year (75). On the other hand, Hayashi et al.
364 reported that vitamin D appeared to have no beneficial effect on SLE patients (77). However,
365 there were some significant limitations in this particular study. There was no information with
366 regards to the doses of vitamin D administered and length of treatment. Other confounding
367 factors such as other therapeutics such as immunosuppressants which definitely played a factor
368 also could not be excluded (77).

The therapeutic benefits of vitamin D relate to the immune function modulation, particularly in the inflammation-related pathways. In the lupus-prone NZB/W F1 mice, the correction of vitamin D level attenuated lupus pathology progression, delayed the onset of proteinuria, and reduced the concentrations of anti-double-stranded DNA autoantibodies (78). In addition, vitamin D promotes the adoption of a regulatory phenotype in lymphocytes and consequently increased the expression of IL-10, regulatory $CD4^+$ T cells, and IL-10-expressing B-cells (78). Vitamin D also ameliorates the impairment of endothelium-dependent vasorelaxation and the shift towards the expression of interferon-stimulated genes (ISGs) in lupus patients (79).

Piantoni et al. (2015) carried out a two-year prospective study 34 patients diagnosed with SLE (80). During the first year, an intensive cholecalciferol regimen was given to 16 patients, involving a 300,000 IU initial dose and a monthly maintenance dose of 50,000 IU, amounting to 850,000 IU for the year. On the other hand, 18 patients received a standard dose of 25,000 IU of cholecalciferol every month, amounting to 300,000 IU annually. In the following year, the treatment plans were swapped between the groups. They observed an increase in the total count of CD4+CD45RA+CCR7− T-cells, while noting a significant decrease in CD8+CD28− T-cells. The analysis of peripheral blood mononuclear cells (PBMCs) from eight patients after undergoing the intensive regimen also showed a reduction in the IFN-γ/IL-4 ratio in CD8+ T-cells over the 12-month period. These results suggested that vitamin D supplementation modified the phenotype of T-cells in the SLE patients (80). Furthermore, Franco et al. (2017) carried out a systematic review and meta-analysis and found that vitamin D supplementation appeared to be beneficial in SLE patients by reducing anti-dsDNA positivity (81). Table 5 summarizes the beneficial effects of vitamin D on lupus incidence and severity.

Natural products

Conventional treatments for SLE, such as antimalarials, corticosteroids and immunosuppressants, target the symptoms and underlying inflammation but can come with significant side effects (82). Given the complexity of SLE and the potential adverse effects of standard therapies, there has been growing interest in the use of natural products as complementary or alternative treatments. These products, often derived from plants, herbs, animals, and other natural sources, have been used for centuries in traditional medicine systems worldwide. **Table 6** summarizes the effects of natural products on lupus incidence and severity.

Olive oil

Virgin olive oil (VOO) and extra virgin olive oil (EVOO) are both essential components of the Mediterranean diet. Olive oils are well-recognized for their anti-inflammatory and immunomodulatory properties, which are attributable to its diverse range of bioactive (83). The health benefits of olive oils are traditionally ascribed to its major component (monounsaturated fatty acids, mainly oleic acid) (84). However, more recent evidence indicates that minor components of olive oils, which include polyphenol fractions (constituting up to 2% of total content), also contribute to its health-beneficial properties (85). This growing understanding fuels the interest in integrating olive oil into daily diets as an adjunct therapy in managing autoimmune diseases.

Cells of the innate immune system, including macrophages and monocytes, play a crucial role in initiating and guiding the adaptive immune response during inflammation. In patients with SLE, monocytes and macrophages display altered phenotypes, characterized by an overproduction of pro-inflammatory cytokines. Aparicio-Soto et al. (2016) conducted a study to

explore the potential benefits of a diet containing VOO in modulating immune-inflammatory responses in SLE (86). They randomized 60 female BALB/c mice into four experimental groups: mice injected with pristane (to induce a lupus-like disease) and fed a diet of either VOO or sunflower oil, and mice injected with a saline solution and given a diet of either VOO or sunflower oil. Notably, the release of nitrite and pro-inflammatory cytokines (IL-6, IL-17, and TNF-α) by lipopolysaccharide (LPS)-activated peritoneal macrophages from the pristane-SLE mice was significantly lower in those fed with the VOO diet compared to those on the sunflower oil diet (86). Furthermore, the same group extracted the phenolic fraction (PF) from VOO and studied its effect on LPS-treated human monocytes (87). Treatment with LPS down-regulated the expression of the anti-inflammatory PPARγ, and up-regulated the expression of the pro-inflammatory IL-6, IL-17, TNF-α, as well as toll-like receptor 4 in monocytes. However, this effect was counter-acted by PF from VOO in a dose-dependent manner. PF from VOO also blocked the genetic signature of the pro-inflammatory M1 macrophages while favouring the phenotype of anti-inflammatory M2 macrophages upon canonical polarisation of naïve monocyte-derived macrophages (87).

The adaptive immune cells also play a major role in the pathogenesis of SLE. One of the immunological characteristics of SLE patients is an altered T-cell response manifested by an imbalance of the production of cytokines like IL-6, IL-1, IL-10 and TNF-α (88). In addition, T-cell activation, characterized by increased CD69 expression, is commonly increased in SLE patients (89). To elucidate the effect of PF from EVOO on T-cell activation and cytokine release, Aparicio-Soto et al. (2017) isolated the PBMCs of SLE patients and healthy controls. Notably, their findings revealed that, while stimulation with phytohemagglutinin significantly increased the activation status of peripheral blood CD4+ T cells (as evidenced by the expression of the

CD69 surface marker), the introduction of PF from EVOO (5 and 10 μg*/mL)* reduced the frequency of CD69+ cells among CD4+ T cells in both groups after 24 hours of cell culture, in a dose-dependent manner (90). Additionally, PF from EVOO also lowered the production of phytohemagglutinin-induced pro-inflammatory cytokines such as IL-6, IL-1β, IFN- γ, and TNF-α in the PBMCs of both healthy individuals and SLE patients.

Numerous animal studies have investigated the potential effects of a diet rich in EVOO and diets that include specific phenolic compounds such as oleuropein, oleocanthal, and hydroxytyrosol on mitigating the inflammatory and oxidative damage associated with lupus nephritis. For instance, the generation of reactive oxygen species and a compromised antioxidant response have been identified as contributors to renal damage in lupus (91). In light of this, diets containing EVOO (86), oleuropein (92), oleocanthal (93), and hydroxytyrosol (94) have demonstrated their ability to upregulate the expression of antioxidant proteins, namely Nrf-2 and HO-1, while simultaneously decreasing the production of the pro-inflammatory protein, PGE2, in the kidneys of the pristane-induced SLE mouse model. Histological examinations further indicate that supplementing with EVOO and specific phenolic compounds can reverse various kidney abnormalities, such as interstitial fibrosis, thyroidization, and abundant presence of inflammatory mononuclear cells in the renal interstitium, which are seen in the pristane-induced SLE mouse model, albeit to varying extents (86,92,93).

Curcumin

Curcumin is the active ingredient in turmeric, a commonly used spice in Asian cuisines especially Indian dishes. It is a polyphenol with antioxidant, anti-inflammatory, and potential anticancer properties (95). Research spanning both human and animal models have highlighted

its therapeutic potential for autoimmune diseases including multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (96).

Of particular interest is its role in SLE. In pristane induced SLE mice model, a 16-week daily curcumin regimen at doses of 12.5, 50, and 200 mg/kg led to a simultaneous dose-dependent decrease in Th1 and Th2 (97). Concurrently, the study revealed a decline in the Th17 cell population and Th17/Treg ratios. Additionally, curcumin suppressed the production of proinflammatory cytokines, IL-6 and TNF-α, both implicated in the progression of SLE (96) and reduced arthritis score and lowered antinuclear antibodies (ANA) (97).

Lupus nephritis is one of the most severe lupus manifestations. Studies using murine models have provided valuable insights into curcumin's potential in alleviating lupus nephritis. A study on the NZBWF1 model demonstrated a decrease in spleen weight, plasma blood urea nitrogen (BUN), and glomerulosclerosis score upon a two-week administration of curcumin at 500 mg/kg (98). However, there was no significant effect on albuminuria, circulating CD45R+ B cells, IgG anti-dsDNA, and glomerular filtration rate (GFR). The study's short duration might have contributed to these outcomes. On the other hand, a longer two-month regimen with curcumin at 1000 mg/kg in the MRL.*lpr* model not only significantly reduces BUN, spleen weight and glomerulonephritis score, but also proteinuria along with IgG anti-dsDNA, IgG anti-ssDNA, IgG anti-histone, and IgM anti-histone (99). This suggests that curcumin possesses therapeutic potentials for SLE-related kidney pathologies across varying durations of treatment. The brief two-week treatment highlights curcumin's immediate therapeutic capabilities, while the extended two-month study underscores its preventative potential.

While animal studies provide insights into curcumin's effects on clinical parameters of lupus nephritis, their translation to human contexts reveals some inconsistent results. Indeed, a

systematic review of randomized controlled trials involving 631 patients with renal disorders, including lupus nephritis, highlighted that turmeric/curcumin supplementation showed positive effects on inflammatory and oxidative stress markers (100). However, apart from proteinuria, their influence on key clinical markers like BUN, creatinine, GFR, and serum albumin was limited (100). These differences highlight the importance of additional research in human clinical settings.

Other natural extracts

Beyond EVOO and curcumin, several other less-researched natural extracts also exhibit potential benefits in treating SLE. In NZBWF1 lupus mice model fed with high-cholesterol diet, lactoferrin (a glycoprotein found in colostrum and milk) demonstrated ameliorative effects on hepatic fibrosis by inhibiting TGF-b/Smad fibrotic signaling (101). Similarly, the root extract of *Gentiana macrophylla Pall.* (commonly known as qin jiao) alleviates cholesterol-aggravated cardiac apoptosis potentially by augmenting the cardiac IGF-1 survival signal through the phosphorylation of PI3K and AKT and the inhibition of both extrinsic and intrinsic apoptosis signals (102). Other natural extracts that have shown therapeutic benefits in murine lupus models include amaranth oil (103) (60), isogarcinol (104), and polysaccharide of large yellow croaker swim bladder (105).

In a retrospective cohort study, higher serum lycopene (a carotenoid hydrocarbon found in tomatoes and other red fruits and vegetables) of SLE participants was associated with lower mortality (106). On the other hand, a cross-sectional study of SLE patients identified associations between caffeine intake and lower disease activity and cytokine levels (107). However, not all natural extracts manifest positive outcomes. For example, metabolomic profiling showed

504 elevated taurine levels in SLE patients' serum (108). Moreover, taurine supplementation in mice
505 was observed to exacerbate the progression of the lupus condition (108).

506 ***General Discussion***

507 The primary focus of this review was to analyze the relationships between dietary and
508 nutritional factors and lupus pathophysiology (Figure 2). Several factors may lower lupus risk,
509 including diet quality, vitamin D, omega-3 and omega-6 fatty acids, alcohol consumption, and
510 natural products. A strong link exists between high-quality diets and lower lupus incidence and
511 severity. Poor dietary patterns, such as Western or high-salt diets, promote excess weight and
512 inflammation. Several studies show an association between higher BMI and lupus disease
513 activity (Table 1). Essential fatty acids omega-3 and omega-6 are key in maintaining immune
514 homeostasis. Omega-3 fatty acids produce anti-inflammatory mediators, while omega-6 produce
515 pro-inflammatory mediators. They regulate inflammatory balance, antigen presentation, T-cell
516 and B-cell activity, and leukocyte recruitment in lupus. Higher omega-3 and lower omega-6
517 levels support a more favorable immune state (Table 2).

518 Alcohol intake has been associated with lower lupus incidence. However, it remains
519 unclear whether this is due to alcohol itself or other compounds such as phenolics in wine. Still,
520 alcohol may be beneficial by lowering circulating stem cell factor (Table 3). In contrast, high
521 sodium intake appears to worsen lupus severity by promoting a pro-inflammatory state,
522 including increased Th1:Th2 and Th17:Treg ratios and higher anti-dsDNA IgG and C4 levels
523 (Table 4).

524 Among micronutrients, vitamin D is particularly important for reducing symptoms and
525 modulating disease progression. Adequate vitamin D levels can delay proteinuria and reduce

anti-dsDNA autoantibodies, key markers of disease activity. It also regulates IL-10, CD4+ regulatory T cells, and T-cell phenotypes, promoting a more balanced immune response. These findings suggest vitamin D may serve as both a prognostic biomarker and a therapeutic agent (Table 5). Natural compounds such as olive oil (rich in phenolics) and curcumin may also provide benefits due to their antioxidant and immunomodulatory effects (Table 6).

Strength and Limitations of Evidence

A principal strength of this scoping review is its deliberate and systematic inclusion of evidence spanning the entire translational research continuum from *in vitro* mechanistic studies through animal models to human observational studies and clinical trials. This approach, while inherently heterogeneous, offers several distinct advantages. Firstly, mechanistic exploration**.** By incorporating *in vitro* and animal studies, we discuss insights into the biological plausibility and potential mechanisms underlying observed associations in human studies. For example, while human studies demonstrate that omega-3 fatty acids are associated with reduced disease activity (35,36), animal studies elucidate the underlying immunological mechanisms, including suppression of CD4+ T-cell-related genes (Pestka et al., 2014), inhibition of B-cell and T-cell proliferation (39), and downregulation of interferon-regulated genes (40). This mechanistic grounding strengthens confidence in the causal nature of these associations.

Secondly, hypothesis generation**.** The inclusion of preclinical studies identifies promising dietary factors such as olive oil phenolics (86,87), curcumin (97,99), lactoferrin (101), and *Gentiana macrophylla* extract (102) that have limited human evidence but warrant future investigation.

Thirdly and arguably most importantly: identification of knowledge gaps**.** Mapping the full evidence landscape reveals critical discontinuities between preclinical promise and clinical validation. For instance, while curcumin shows robust effects in multiple murine lupus models, human evidence remains limited to renal outcomes with inconsistent findings. This gap identification is a core objective of scoping reviews and provides clear direction for future research. The strongest evidence for clinical application comes from human RCTs and large prospective cohort studies. Evidence from animal models should be interpreted as mechanistic and exploratory, providing biological plausibility and generating hypotheses for future human investigation rather than supporting immediate clinical recommendations.

Several factors constrain the translation of animal and in vitro findings into human clinical practice. Lupus in murine models is typically induced experimentally (e.g., pristane, crystalline silica), or genetically driven (e.g., NZB/W F1, MRL/lpr). These models are inherently biased toward specific immunopathological pathways and therefore do not fully recapitulate the clinical, genetic, and mechanistic heterogeneity of human SLE (109). In addition, species-specific differences in immune regulation, metabolism, and microbiome composition may influence responses to dietary interventions (110,111). Furthermore, translation of dosing from animal models to humans remains inherently challenging (112). As such, it is often unclear whether doses used in human studies achieve biologically equivalent exposures relative to preclinical models. Taken together, while preclinical studies provide essential mechanistic insights and support causal inference, their translational value lies primarily in hypothesis generation rather than direct clinical extrapolation.

The strongest evidence for clinical application remains derived from human randomized controlled trials and large prospective cohort studies. Future research should prioritize well-

570 designed human interventional studies to validate mechanistic findings and establish clinically
571 relevant exposure levels. Furthermore, advances in humanized mouse models, in which
572 immunodeficient mice are engrafted with components of the human immune system, may serve
573 as complementary tools to refine hypotheses prior to clinical testing (113).

574 Despite these strengths, several limitations should be considered. Dietary components are
575 unlikely to act in isolation; however, this review primarily summarizes evidence on individual
576 nutrients, as the available literature on their combined effects remains limited. Some
577 experimental studies in other inflammatory conditions (e.g., osteoarthritis) report greater
578 protective effects with combined interventions of curcumin and vitamin D compared to
579 individual components (114). Evidence from a factorial randomized trial further showed that
580 combined supplementation with vitamin D and omega-3 was associated with reduced
581 autoimmune disease risk (115). However, no significant interaction between the two
582 interventions was observed, suggesting largely independent or additive effects rather than true
583 synergy (i.e., where the effect of one intervention depends on the presence of the other) (115).
584 Overall, while combined dietary strategies may offer potential benefits, current evidence does
585 not allow definitive conclusions regarding their nature or magnitude in SLE across most dietary
586 factors. Future studies designed to evaluate multi-nutrient interventions are needed to better
587 characterize their combined impact on disease risk and progression.

588 As a scoping review, we did not perform formal quality or risk-of-bias assessments for
589 individual studies, limiting evaluation of the strength and reliability of the evidence. The lack of
590 quantitative synthesis means pooled effect estimates cannot be provided. While comprehensive,
591 the thematic approach may oversimplify complex interactions between dietary components. The

2012–2023 search window may exclude older relevant studies, but it likely captures the most current and methodologically robust evidence given rapid advances in nutrition and immunology.

The included studies show substantial heterogeneity across multiple dimensions, complicating synthesis and limiting precision. Restricting to English-language publications may introduce language bias, and publication bias is possible, as negative findings may be underreported.

Findings are sometimes contradictory, with studies reporting both positive and negative effects of individual nutrients. This may reflect the difficulty of isolating dietary effects from other lifestyle factors, or suggest that individual nutrients may be more influential than overall dietary patterns. It may also result from residual confounding in observational studies. Null findings from several high-quality studies indicate that associations between whole diets and SLE risk require further investigation. Therefore, more large-scale, diverse population studies and randomized controlled trials are needed to confirm these associations and inform dietary recommendations.

Conclusion

In conclusion, the present review illustrates a link between dietary and nutritional factors and lupus incidence and severity. The integration of nutritional and dietary guidance into the management of lupus represents a promising adjunct to conventional pharmacological treatments. The evidence collected in this review underscores the potential of specific dietary interventions to modulate immune function, reduce inflammation, and possibly decrease the frequency and severity of lupus flares. Future research should aim to establish more precise dietary recommendations and explore the mechanisms by which diet influences lupus activity.

Large-scale, randomized controlled trials are needed to confirm the therapeutic potential of dietary and nutritional interventions and to integrate them effectively into the standard of care for lupus management.

Data Availability

Data described in the manuscript will be made available upon reasonable request.

Authors' contribution

Justin N. Jaya: writing original draft, and review and editing; Michael Pudjihartono: writing original draft, and review and editing; Nicholas Pudjihartono: writing original draft, and review and editing; Ivan Damara: writing original draft; Fahrul Nurkholis: Visualization; Felix Zulhendri: conceptualization, methodology, writing original draft, review and editing, supervision, visualization, and funding acquisition

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Figure Captions

Figure 1. The flow chart of the study identification and selection process.

Figure 2. The summary of the effects of different dietary and nutritional factors in influencing the risks of lupus incidence and severity.

Table List

Table 1. The effect of macronutrients, ultra-processed foods, and general dietary factors on lupus incidence and severity.

Study Design	Organism	Interventions/Nutrient	Outcome measured	Study result	Reference
Case control	Human	-	• Risks for SLE and MCTD	• Smoking and walking a longer time showed an increased age-adjusted risk for MCTD as well as SLE. • Frequent intake of bread increased the risk of MCTD and high intake of green tea decreased the risk of MCTD. • Westernization of dietary habits (i.e. frequent intake of bread and low intake of green tea) may increase the risk of MCTD, while walking may increase the risk of SLE among Japanese females.	(116)
Case control	Human	-	• Prevalence Of Systemic	• The estimated prevalence of SLE in	(117)

			Lupus Erythematosus (SLE) • Gender Difference in the Prevalence of SLE • Age Specific Prevalence of SLE • Environmental Factors Associated With SLE	rural areas of Anhui Province was 37.56 per 100,000 persons. • There was a significant gender difference in the prevalence of SLE, with a higher prevalence among females. • Several factors were associated with an increased risk of SLE, including preterm/post-term births, consumption of sweet food, animal oil, preference for light taste, sunlight exposure, insufficient sleep, lack of physical activities, drinking water from a pond or well, experiencing a negative life event, receiving hepatitis B vaccination, and age at birth of first child.	

				• Fruit consumption, residing in a flat area, and age at menarche were associated with a reduced risk of SLE.	
Randomized, double blind, placebo controlled, crossover trial	Human	Creatine	• Muscle function (assessed by a battery of tests including 1 maximum repetition (1-rm) tests, the timed up and go test, the timed stands test, and the handgrip test) • Body composition • Biochemical markers of bone remodeling • Aerobic conditioning • Quality of life • Physical capacity • Muscle phosphoryl creatine	• Intramuscular phosphoryl creatine content was not significantly different between creatine and placebo before or after the intervention. • No significant changes between placebo and creatine for any muscle function and aerobic conditioning parameters, lean mass, fat mass, bone mass, and quality of life scores. • No side effects were noticed with creatine supplementation.	(118)

			content		
Case report	Human	-	• Severe dental erosion and carries	• The consumption of carbonated soft drinks and the presence of bulimia are widely recognized factors contributing to teeth degradation in wealthy nations. The adoption of a Western diet in the Pacific region has resulted in a rise in the prevalence of tooth caries and erosions. The individual's pronounced dental erosion can be attributed to the concurrent presence of xerostomia and the habitual consumption of limes for alleviation.	(119)
Case control	Human	-	• SLE disease activity (SLEDAI) • Ceruplasmin, Alb, and trace	• Serum concentrations of albumin (Alb), zinc (Zn), copper (Cu) and selenium (Se) were lower in patients	(120)

			elements including Zn, Cu and Se. • Anti-double stranded DNA (anti-dsDNA), complement serum values including C3, C4, creatinine, full blood count, urinary sedimentation (red blood cell count (RBC) or white blood cell count (WBC) cast) and 24 h urine protein excretion	with SLE than in healthy controls. • Serum Alb and Cu concentrations were negatively correlated with lupus disease activity. • The Zn to Cu ratio (Zn/Cu R) was also lower in SLE patients than in healthy controls.	
Case control	Human	Fasting	• SLE Disease Activity Index (SLEDAI) • Lipid Profile • Quality of Life with Short Form 36 (SF-36) Health Survey	• Ramadan fasting had no effect on SLE patients' disease activity and their quality of life in the quiescent phase of disease. • Anti-ds DNA and C3 increased in	(121)

				cases after 24.1 ± 5.4 days of fasting but returned to baseline after 3 months. • Total cholesterol decreased in cases after Ramadan fasting, but not in controls.	
Case report	Human	Gluten-free diet	• Presence and intensity of auditory and visual hallucinations • Depressed mood • Social withdrawal • Academic performance • Presence of antinuclear antibodies (ANA) • Gluten sensitivity • Psychotic symptoms • Dosage of risperidone	• Improvement in psychotic symptoms after a gluten-free diet in a boy with complex autoimmune illness	(122)

			• Anxiety • Hearing loss • Autoimmune inner ear disease		
Retrospective analysis	Human	-	• Fasting Blood Glucose (FBG) • Levels of Diseases: # of tests, Mean, Median, -Log10 p value	• 57/64 diseases including type 2 diabetes, pancreatitis, diabetic nephropathy, and pancreatic cancer had significantly increased FBG levels compared to healthy controls. • 6/64 diseases including preeclampsia, Wilms' tumor, and lupus erythematous had significantly decreased FBG levels compared to healthy controls. • Increased FBG levels might be a consequence but not the cause for either prediabetes or type 2 diabetes.	(123)
Observational and	Human and	Animal study: Choline	• Multivariate statistical	• Patients with RA and SLE showed a	(124)

In vivo trial	Rat	rich diet, Lipopolysaccharide (LPS) and cultured in interferon (IFN-γ) or Interleukin 4 (IL-4) and Interleukin 13 (IL-13)	analysis of 1H NMR spectrum of human urine • Integral area of corresponding metabolites comparing healthy, SLE, and RA patients: TMAO (trimethylamine-N-oxide), Dimethylamine, Citrate, Succinate, p-Cresol sulfate • Patient Characteristics: Age, Gender, Hypertension, Diabetes Mellitus, Symptom duration, RF positive, ACPA positive, ESR, CRP, Prednisolone, NSAIDs, Methotrexate, Hydroxychloroquine, Anti-TNF-α	distinct urinary metabolomics pattern, with markers of altered gut microbiota (TMAO) and oxidative stress (dimethylamine) upregulated, and markers of mitochondrial dysfunction (citrate and succinate) and metabolic waste products (p-CS) downregulated. • TMAO and dimethylamine were negatively associated with serum inflammatory markers in RA patients. • A choline-rich diet reduces experimentally induced arthritis, suggesting that the interaction between diet and the intestinal microbiota contributes to the RA phenotype.	

			• Cluster correlation analysis: ESR, DAS28, CRP, IL-6. CCL2, IL-8, WBC, p-CD, Citrate, Succinate, DMA, TMAO, Hb, Albumin • Comparison of urinary metabolite levels: Succinate, TMAO, Citrate, p-Cresol sulfate, Dimethylamine with ESR, CRP, DAS28, Hb • Radiographic Progression: TMAO, Dimethylamine, p-Cresol sulfate, Citrate, Succinate • Multivariate logistic regression analysis Odds Ratio:		

			HCQ, p-CS, Disease Duration, IL-6 • Arthritis score • Relative expression: iNOS, Arg1, IL-6		
Case control	Human	-	• Subject Characteristics: Survival status, Sex, Age at onset of disease, Age, Days since diagnosis, SLEDAI score, Thrombocytopenia status, ANA test, Anti-dsDNA test, Nutritional status • Univariate and multivariate analysis of risk factors and predictors of mortality: Hypertension, Seizures,	• 84 children with SLE were included in the study, of which 72 were female. Most subjects were well-nourished (n = 62), while somewhere moderately malnourished (n = 14), and few were severely malnourished (n = 8). • Hypertension and infection were significantly associated with mortality on bivariate analysis. • On logistic regression analysis, infection was the only significant	(125)

			Proteinuria, SLEDAI score, Infection	predictor of mortality.	
Observational	Human	-	• Descriptive characteristics of patients: Sex, gender, Height, Weight, BMI, Antimalarial, Immunosuppressor, Corticoid use, Total cholesterol, Albumin, Lymphocyte count, Anti-dsDNA, Complement C3, C4, WBC count, Platelet count, hsCRP, SLEDAI score, SDI score, PNI (prognostic nutritional index), CONUT (controlling nutritional status), NRI (nutritional risk index) • Linear regression and logistic	• PNI and NRI were significantly lower in active SLE patients than in inactive SLE patients. • PNI was inversely correlated with the SLEDAI score and NRI positively correlated with SLEDAI and SDI scores. • PNI and NRI were independent predictors of active SLE.	(22)

			regression analysis between clinical disease activity variables and immuno-nutritional indexes and SLEDAI and SDI scores: hsCRP, anti-dsDNA, C3, C4, WBC count, Platelet count, PNI, CONUT, NRI		
Multi-center	Human	-	• Prevalence of CD in diseases: SLE, primary Sjögren's syndrome (pSS), systemic sclerosis (SSc) • Epidemiological features comparing CD and healthy control population: Total subjects, Age, Gender,	• Celiac disease (CD) prevalence is significantly increased in primary Sjögren's syndrome (pSS) and diffuse cutaneous form of systemic sclerosis (SSc) when compared to the general population. While SLE associations with CD remain uncertain as they trend towards significance (p = 0.058).	(126)

			Previously diagnosed CD and prevalence, Subclinical CD, Overall CD prevalence, Age at Autoimmune Diagnosis (AD) • Epidemiological features of CD related to SSc (Diffuse or Limited subset): Total subjects, Age, Previously diagnosis CD and prevalence • Age of Symptom onset	• Subclinical CD was found in two SLE patients and one pSS patient. • CD diagnosis usually preceded that of AD, and autoimmune thyroiditis was associated with pSS and CD.	
Cross-sectional	Human	-	• Demographics and clinical characteristics: Age, Education level, Occupation status, Residence (urban/rural), Disease duration, Age at onset of diagnosis	• More than three quarters of SLE patients were overweight and obese. • Disease activity (SLEDAI) correlated with increased BMI, body weight, and disease duration. • Inadequate nutrient intake and	(23)

			• Anthropometric, medical, and laboratory characteristics: Weight, height, BMI, Hemoglobin, Anemic, TLC (total lymphocyte count), Albumin, Steroid duration, SLEDAI score • Daily Caloric and Macronutrient Intake: Energy (kcal), Proteins, Total fats, Dietary fibers • Daily Iron and Calcium Intake • Associations between demographics, medical, and laboratory variables with BMI: Education, Occupation,	excessive consumption of lipids and low intake of fibers were revealed.	

			Residence, Age, Age at disease onset, Disease duration, Hemoglobin, TLC, Albumin, Steroid duration, SLEDAI score • SLEDAI score association with anthropometric and laboratory investigation: Age, disease duration, age at onset of diagnosis, weight, height, BMI, Hb, TLC, Albumin, Steroid duration		
Survey based	Human	-	• Demographics: Sex, Age • Responses by date: Cumulative number of responses, Weeks • Survey responses regarding	• Patients with systemic lupus erythematosus reported a lack of clinical counselling regarding diet but would be willing to change their diet if they knew it would help their symptoms.	(127)

			patient opinion on diet in and out of clinic • Age group response comparison • Survey responses regarding patient experiences with diet including reasons, types and outcomes •cText analysis of Dietary modifications and reasonings behind changes, alongside observed benefits • Text analysis of responses thought to should be investigated	• Patients expressed an interest in using diet to treat fatigue and manage disease flares. • An anonymous social media platform was used to successfully gather patient information regarding diet and systemic lupus erythematosus over a short timeframe.	
Observational	Human	-	• Demographic Data: Age, Sex,	• The CONUT score and PNI had the	(128)

			Follow-up duration • SLE activity-related measures: SLEDAI-2K, WBC count, Platelet count, C3, C4, Anti-dsDNA, Urinary P/Cr ratio • Clinical features: Skin rash, Photosensitivity, Oral ulcer, Arthritis, Serositis, Neurologic disorder, Hematologic disorder, Immunologic disorder • Laboratory data: Lymphocyte count, ESR, CRP, Cr, GFR, Total Cholesterol, Serum albumin, AST, ALT • Renal biopsy data Lupus	highest correlation between the SLE disease activity index-2000. • PNI was independently associated with ESRF along with creatinine and chronicity index. • The renal survival rate was significantly lower in patients with PNI ≤35.41 than in those with PNI >35.41.	

			nephritis class: Class I,II, Pure class III, IV, V, Mixed class V, Class V + II, V + III, V + IV, VI • Activity and Chronicity index • Nutritional indices: CONUT (controlling nutritional status) score, PNI (prognostic nutirtional index), NRI (nutritional risk index), NLR (neutrophil to lymphocyte ratio), BMI (body mass index) • Correlation analysis between variables and nutritional indices at lupus nephritis diagnosis: SLE activity-related measures, laboratory data, renal biopsy		

			data with nutritional indices • Correlation analysis between nutritional indices and lupus nephritis subclasses at diagnosis • Receiver operator characteristic curve of nutritional indices at lupus nephritis diagnosis in predicting end-stage renal failure: Sensitivity against 100-Specificity • Kaplan-Meier curve analysis of renal survival rate based on PNI • Cox-proportional hazard		

			analysis of variables associated with end-stage renal failure during follow-up (univariate and multivariate analysis): SLE activity-related measures, Laboratory data, Nutritional indices		
Case report	Human	Gluten free dietary regimen	• Congenital and acquired thrombophilia • Lupus anticoagulant • antiphospholipid syndrome (APS) diagnosis • Coeliac disease screening • APGAR score • Screening for adverse pregnancy outcomes	• Successful pregnancy and lupus anticoagulant remission after gluten-free diet in a woman affected by coeliac disease and antiphospholipid syndrome. • Coeliac disease is associated with other comorbidities, including autoimmune conditions and extra-intestinal manifestations. • Strict adherence to a gluten-free diet is	(129)

			• Patient immunological status	the only treatment for coeliac disease.	
Cross-sectional	Human	-	• Demographics: BMI, Gender, Socioeconomic, CVD Risk, Physical Activity, Waist/Height Ratio, Body fat % • Dietary Intake: Total Fat, Saturated Fat, Trans Fat, Cholesterol, Carbohydrate • Biomarkers of Lipid Metabolism: Lipid Profile, Apolipoproteins AI/B, Triglycerides, HDL, LDL, C-reactive proteins, Fasting Blood glucose	• Overweight and dyslipidemia were observed in a high proportion of both parents and children with chronic rheumatic diseases (80% similarity), indicating an environment conducive to chronic non-communicable disease development. • There was a moderate association between total fat intake and a weak association between saturated fat intake and cholesterol intake between parents and their children. • There was a weak association between parents and children for triglycerides, but no association between parents and	(130)

				children concerning physical activity.	
Retrospective cohort	Human	-	12 Organ Specific Morbidities Comorbidities: • Neoplasms (Malignant & Benign) • Blood disorders • Endocrine, nutritional and metabolic disorders • Mental and behavioral disorders • Nervous system disorders • Circulatory system disorders • Other Chronic pulmonary diseases • Noninfective Enteritis and colitis	• 91.2% of SLE patients had at least one comorbidity, compared to 66.7% of comparators. • Musculoskeletal, cardiovascular and genitourinary conditions were the most common comorbidities. • "Men with SLE had a significantly higher risk for diseases of the genitourinary system and endocrine, nutritional and metabolic diseases compared to women with SLE."	(131)

			• Musculoskeletal diseases • Genitourinary diseases • Rate Ratios of Comorbid Diseases & Cardiovascular Disease • Gender • Education Level		
Cross-sectional observational	Human	-	• Demographics: Gender, Age, Disease duration, Weight, Height, BMI • Levels of Dietary C3 And C4 • 24-H Proteinuria	• Majority of patients had a normal body mass index and worked out regularly. • Decreased values of C3 were found in patients who often consumed meat, and decreased values of C4 in patients who often consumed fast food. • Dietary habits can influence the disease course of SLE.	(132)
Retrospective	Human	-	• Demographics, Clinical, and	• Dyslipidemia is common in children	(133)

cross-sectional			Laboratory Features: Gender, Age, Disease progression, BMI, Z-score Height for Age, Z-score BMI, Nutritional Status, SLEDAI, SLICC, CRP, ESR, Corticosteroid dose, Biologics, Non-Biologics • Lipid Profile: Triglycerides (TG), Total Cholesterol (TC), Low Density Lipoprotein (LDL-C), High Density Lipoprotein (HDL-C), Very Low Density Lipoprotein (VLDL-C), Non HDL Cholesterol (NHDL-C), Dyslipidemia	and adolescents with ARDs, especially JIA, jSLE, and JDM. • The most common alteration in the lipid profile of these patients was decreased HDL-C. • Systemic JIA and cumulative corticosteroid dose in jSLE were associated with an increase in LDL-C and a decrease in HDL-C, respectively.	

Cross-sectional	Human	-	• Demographics: Gender, Age, Urban area, Census region, Race, Smoking, BMI, Health conditions, Metabolic Syndrome • Biochemistry profile: Serum alanine aminotransferase, aspartate aminotransferases, albumin, bicarbonate, alkaline phosphatase, lactate dehydrogenase, total protein, globulin, creatinine, cholesterol, glucose, total bilirubin, calcium, CRP, FSH, LH, transferrin saturation, urinary albumin, cadmium,	• Prevalence of lupus in the US was 241 per 100,000. • Risk factors for lupus included smoking, elevated serum levels of chloride, globulin, lactate dehydrogenase, uric acid, cholesterol, and lutein or zeaxanthin. • Protective factors against lupus included non-white race, obesity, elevated serum levels of bicarbonate, creatinine, total calcium, and vitamin B12, as well as elevated urinary albumin and iodine.	(134)

			creatinine, iodine • Nutrition biomarkers: plasma fibrinogen, serum beta carotene, beta cryptoxanthin, cholesterol, lutein/zeaxanthin, selenium, vit. A, vit. B12, vit. C, vit. E • Antibody tests: serum rubella antibody, tetanus antibody, toxoplasmosis antibody, latex antibody, hepatitis A, hepatitis B		
Cross- sectional	Human	-	• Demographics: Gender, Age, BMI • Clinical data: # of complications, SLEDAI-2K,	• A cross-sectional study of 193 SLE patients revealed a significant association between free sugars intake and disease activity, number of	(17)

			SDI Damage Index, hsCRP (C reactive protein), Hcy (homocysteine), Anti-dsDNA, Complement C3, Complement C4 • Medication used: Antimalarials, Immunosuppressors, Corticoids • Cardiovascular Risk Factors: Hypertension, Diabetes, Obesity, Dyslipidemia, TC (total cholesterol), TG (triglycerides), HDL-C, LDL-C, SBP (systolic blood pressure), DBP (diastolic blood pressure), ABI (ankle brachial	complications, and SLEDAI. • Patients with active SLE had significantly lower dietary sugar intake than those with inactive SLE. • Free sugars intake was associated with increased CVD risk markers.	

			index) • Nutrients: Energy, Total Carbohydrates, Proteins, Fats, Starch, Total sugars, Intrinsic sugars, Free sugars		
Prospective cohort	Human	-	• Demographics: Age, Race, BMI, Smoking, Physical Activity, Household income, Oral contraceptive, Menopausal status, Energy Intake, Symptom Diagnosis, Organ system Involvement • Anti-dsDNA/SLE Risk	• A higher prudent dietary pattern score was not associated with SLE risk. • A higher Western dietary pattern score was not associated with SLE risk. • Incident anti-dsDNA positive SLE and anti-dsDNA negative SLE were not associated with either dietary pattern.	(24)
(89)	Human	-	• Demographics: Gender, Age, Weight, Height, BMI, Nutritional Status	• Malnutrition is still high in jSLE, affecting 45.16% of all subjects. • Malar rash and bicytopenia were	(135)

			• Mexican MEX-SLEDAI • Laboratory test: C3, ANA test, Anti-dsDNA, Hb, WBCs, PLTs • Organ manifestation and Disease Activity: Skin, Hematology, Renal, Neurological, Hepar, Musculoskeletal	significantly higher in active jSLE than inactive. • Renal manifestation was correlated with active jSLE and had the highest risk in active jSLE.	
Cross-sectional association	Human	-	• Patient Characteristics: Gender, Age, Disease Duration SLEDAI, C3, C4, Anti-dsDNA, Medications, Vit. B6, B9, B12 • CpG17, CpG22, ad CD40L Methylation Status In T Cells • Micronutrient Intake: Methionine, Folate, Choline,	• Dietary methyl donors and products were associated with CD40L methylation status in SLE patients. • Hypomethylation of CpG17 and CpG22, and not CD40L, was associated with increased disease activity in SLE patients (SLEDAI). • Dietary products with the highest	(136)

			Cysteine, Vit. B6, and B12 • Dietary product intake: Pizza, Dairy products, Chips/French fries, cooked potatoes, White bread, Beer, Fruit/Herbal tea, Meat, Ice cream	impact on methylation included meat, ice cream, white bread, and cooked potatoes.	
Observational multicenter	Human	-	• Type/Frequency of Rheumatic Disease: rheumatoid arthritis, SLE, Behçet's disease, systemic sclerosis, ankylosing spondylitis, psoriatic arthritis, Dermatomyositis, Relapsing polychondritis, familial Mediterranean fever, Adult onset Still's disease, ulcerative colitis	• Nutritional deficiency is common among RD patients, especially elderly. • Type and duration of RD did not significantly affect symptoms or signs of nutritional deficiency. • Age, azathioprine, methotrexate, and hydroxychloroquine were associated with nutritional deficiency manifestations.	(137)

			• Nutritional deficiency indicators: Wasting, Skin rash, Hair/Nail Changes, Nail Spooning, Night Blindness, Glossitis, Peripheral edema, Tetany, Active LOM (limitation of movement), Passive LOM, GI, Thyromegaly, Weight loss, Anorexia • Demographics: Gender, Age, Disease Duration, Medication usage		
Observational	Human	-	• Patient Characteristics: Gender, SLICC, SLEDAI, BMI, Body Fat %, Waist Circumference	• A total of 77 patients (68.8%) patients presented a score of 0 in the SLICC, similar to scores for disease activity, with 73 patients (62.5 %) presenting a	(138)

			Daily Intake of Micronutrients • Association of Metabolic Risk and Insufficient Micronutrient Intake (Choline, Sulfur, Vitamin B9) • Prevalence Of Metabolic Syndrome (LDL, HDL, Cholesterol, Triglycerides)	score of 0 in the SLEDAI. • MR was present in 58 patients (51.8%) who showed an association between MR and low dietary intake of vitamin B9, choline, and sulfur • 37.5% of patients were classified with degree II obesity by BMI and 76.8% by abdominal obesity.	
Case series	Human	-	• Patient Characteristics: Gender, Family History, Age of suspected cSLE, Identified Genetic Variations • SLIICC • Laboratory Data: WBC, Lymphocytes, Hemoglobin, Platelets, anti-dsDNA Ab, C3,	• Genetic etiologies and lupus mimickers were found among a substantial proportion of patients suspected with early-onset SLE. • Detail clinical evaluation and genetic testing are important for tailored care and personalized treatment. • Hypoproteinemic diets were given to a	(139)

			C4, ANA, Proteinuria, Hematuria • Symptoms and comorbidities: Growth and development, CNS, Cardiovascular, Gastrointestinal, Renal, Metabolic, Mucocutaneous, Musculoskeletal, Serology, Invasive infections • Treatment: Prednisolone, Cyclophosphamide, Azathioprine, Cyclosporin, MMF/MPA, Hydroxychloroquine, Other treatments • Anthropomorphic	cSLE patient as an alternative for immunosuppressants, sometimes accompanied by vitamin supplementation such as citrulline and/or carnitine.	

			Observations • Brain changes (CT scan) • Genomic Sequencing • Proteinuria (urine protein/creatinine ratio)		
Observational	Human	-	• Musculoskeletal Health • Osteoporosis • Sarcopenia • Levels of Serum Inflammatory Markers • Bone Loss • Incidence of Fractures • Inflammatory Status • Hyperlipidemia • Low Density Lipoprotein Cholesterol (LDL-C)	• The dietary inflammatory index (DII) score was related to musculoskeletal health, such as osteoporosis and sarcopenia, among older adults older than 65 years. • A less inflammatory dietary pattern approach may decrease levels of serum inflammatory markers and, further, may prevent bone loss, sarcopenia, and the incidence of fractures. • Hyperlipidemia, levels of LDL-C, and	(140)

			• Rheumatoid Arthritis • Autoimmune Inflammatory Diseases	the use of statins should be adjusted in this study, as well as other autoimmune inflammatory diseases, such as systemic lupus erythematosus (SLE).	
Observational	Human	-	• Prevalence Of Self-Reported Diagnosis/Treatment of SLE • Dietary patterns • Smoking history	• Vegetarians had lower odds of doctor-diagnosed SLE with an increasing trend in prevalence from stricter vegetarians to pesco-vegetarians to non-vegetarians. • Ever smokers were more likely to report prevalent SLE than those who had never smoked (OR 1.71, 95% CI 1.27, 2.31).	(141)
Observational and cross-sectional	Human	-	• Plasma Selenium Levels • Erythrocyte Glutathione	• Approximately 50% of jSLE adolescents had below reference	(142)

			Peroxidase Activity (GPx) • Plasma Malondialdehyde (Mda) • Ultrasensitive C Reactive Protein (UsCRP) • Insulin Levels • Glycemia (Homeostasis Model Assessment For Insulin Resistance—Homa Ir) • SLE Disease Activity (Measured By SLEDAI-2K) • Lipid	selenium levels. • GPx activity was more frequently below reference levels in the jSLE group compared to controls. • There was an independent inverse association between selenium and c-LDL levels in both groups.	
Cross-sectional	Human	-	• Self-Reported Disease Symptoms • General Aspects of Health • Symptom Severity Ratings	• Over 80% of SLE patients who changed their eating patterns to include more plant-based foods and limit processed foods and animal products	(143)

			• Weight Loss • Fatigue • Joint/Muscle Pain • Mood	reported improvements in their disease symptoms. • The greatest decreases in symptom severity were provided by low/no dairy, low/no processed foods and vegan eating patterns. • Weight loss, fatigue, joint/muscle pain and mood were the most cited symptoms that improved with dietary change.	
Cross-sectional	Human	-	• Dietary Patterns • Lifestyle Habits • Clinical Features • Autoantibody Spectrum	• Patients with SLE complicated with gastrointestinal involvement (SLE-GI) had higher proportions of vegetarians and lower proportions of omnivores than healthy controls. • SLE-GI patients had higher rates of	(144)

				taking traditional Chinese medicine and having a surgical history than healthy controls. • SLE-GI patients had lower frequencies of taking fried/pickled food and dietary supplements than healthy controls.	
Cross-sectional	Human	-	• Hyperuricemia • Clinical Activity • Renal Activity • Triglycerides • Hs-CRP • Kannel Score • BMI • HDL-C	• Adequate protein and carbohydrate intake, healthy HDL-C serum levels, and hydroxychloroquine treatment were associated with a lower risk of hyperuricemia in SLE patients. • SLE patients with hyperuricemia presented a higher risk of clinical and renal activity, as well as worse cardiometabolic status. • Prednisone treatment was associated	(145)

				with a high risk of hyperuricemia.	
Cross-sectional	Human	-	• Mediterranean Diet Adherence Score (MEDAS) • Physical activity energy expenditure (PAEE) • Smoking status • SLE Disease Activity (Measured By SLEDAI-2K) • Depression Scale (CES-D) • Fatigue Severity (FSS) • Functional status (FFbH) • Physical and mental quality of life (PCS, MCS).	• The SLE patients that followed a healthy lifestyle showed a higher physical quality of life, lower depression, lower fatigue, and lower dsDNA-antibodies compared to their SLE counterparts that did not follow a healthy lifestyle regiment. • Physical activity had the highest impact on the various health domains when compared to smoking or diet adherence	(146)
In vivo trial	Mice	3 different commercial diets: Teklad 7013, Harlan 2018, or Research	• Proteinuria • Glomerular Immune Complex Deposition	• Diet alone can have an impact on immune complex glomerulonephritis, renal cellular infiltrates, microbiota and	(147)

		Diets Inc	• C3 • Total IgG • IgG1 • IgG3 • CD11B+ Cellular infiltration into the Glomeruli • Cytokine Production • Fecal Microbiota • MicroRNAs (MiRNAs) • DNA Methylation	molecular behavior of cells after LPS activation	
In vivo trial	Mice	dietary resistant starch (RS)	• Percent survival • Weight (Spleen and Liver) • Relative Expression: IFNA1, IFNB (spleen and ileum) • Systemic Type 1 IFN • CD11c and PDCA-1 pDCs	• Western lifestyle is linked to autoimmune and metabolic diseases, driven by changes in diet and gut microbiota composition. • Lactobacillus reuteri can drive autoimmunity but is ameliorated by	(26)

			(CD45+ cells) • Glomerulonephritis (histopathologic scores) • Proteinuria • Fecal bacterial DNA sequenced with linear discriminant analysis effect size (LDA) score • Bacterial Translocation • Translocation distribution • Relative abundance of bacteria • Frequencies of pDCs in spleen, MLN, SI-LP • Blood Urea Nitrogen	dietary resistant starch (RS). • RS suppresses the abundance and translocation of L. reuteri, inhibiting its growth and decreasing pDCs, interferon pathways, organ involvement, and mortality in lupus-prone hosts.	
In vivo trial	14		• Global GF index	• A total of fourteen species investigated	(148)

	Organisms: Cow, sheep, goat, pig, chicken, turkey, duck, tilapia, salmon, rice, quinoa, soybean, rye, wheat)		• Shared epitopes and Unique epitopes • Diseases with single species epitope matches (number of hits): Alopecia aerata, Antiphospholipid syndrome, Autoimmune atherosclerosis, Bullous pemphigoid, Cutaneous lupus erythematosus, Demyelinating polyneuropathy, Dermatomyositis, Goodpasture's syndrome, Gullain-Barre syndrome, non-insulin dependent diabetes mellitus, Reactive arthritis, Rheumatic myocarditis, Vitiligo	could be divided into three broad categories regarding their content in human autoimmune epitopes, which we represented using a new metric, the Gershteyn-Ferreira index (GF index). • Strikingly, pig contains a disproportionately high number of unique autoimmune epitopes compared to all other species analyzed. • This work uncovers a potential new link between pork consumption and autoimmunity in humans and lays the foundation for future studies on the impact of diet on the pathogenesis and progression of autoimmune disorders.	

			• Autoimmune unique GF index		
In vivo trial	Mice	HFD (high fat diet)	• Body weight gain, Spleen weight • Flow cytometry: B220GLT7+CD38- GC B cell in splenocytes, effector memory CD4+ and CD8+ T cells, expression of CD3, CD4, CD8, CD44, and CD62L, Treg cells (CD4+Foxp3+) and their activation status (CD44+CD69+) • Serum anti-DNA and anti-RNA, and IgM autoantibodies • Kidney pathology • Liver inflammation	• TLR7 signaling is implicated in high fat diet (HFD)-induced metabolic syndrome and exacerbation of lupus autoimmunity in TLR8-deficient (TLR8ko) mice. • HFD led to an increase of TLR7 expression in WT mice, that was coupled with increased TNF production by DCs, and this phenotype was more profound in TLR8ko mice. • TLR7 might be a novel approach as a tailored therapy in SLE and metabolic diseases.	(27)

			• Expression level of TNF, IL-6, IL-1β mRNA, Foxp3, IL-10, TLR7 • Glucose tolerance test levels		
In vivo trial	Mice	3 different diets (control, Western diet, caloric restriction)	• Phenotyping Complex traits in AIL mice: CRP, ANA, NASH, NAFLD, Ballooning, Steatosis, biGal, Sial/gal, termGal, G2S2, G2S1, G1S1, G2, G1, G0, G/M, A/M, A/G, AG, IgM, IgG, IgA, MPV, PLT, RDW, MCHC, MCH, MCV, HCT, HB, RBC, BA%, EO%, MO%, LY%, NE%, BA, EO, MO, LY, NE, WBC, Spleen, LDL, HDL, Cholesterol, WT(6M),	• Diet substantially contributes to the variability of complex traits and unmasks additional genetic susceptibility quantitative trait loci (QTL). • Whole-genome sequencing of the AIL founder strains resolves these QTLs to few or single candidate genes. • Diet modulates genetic susceptibility to lupus and shifts intestinal bacterial and fungal community composition. • With most negative outcomes for lupus	(149)

			WT(4M), WT(2M), AG/M, AGM, Sial, Gal, MonoGal • Manhattan plot showing QTL (quantitative trait locus) in the AIL population associations with various complex traits • Schematic representation of fine-mapped genes for weight in chromosome 5 • Impact of diet and sex on body weight, Proteinuria, Crescent formation score, Frequence of PAS+ depositions (kidney injury), and presence of ANA (antinuclear antibodies) • Alpha diversity (Chao1 index	being demonstrated with Western diet over caloric restriction of control diet.	

			and Shannon index species richness) of mice, alongside Principal coordination analysis (PCoA) of beta diversity of microbiota • Abundance of mycobiota and microbiota taxa • Fungal microbial (FMC) and fungal community (FFC) trait correlations between Sex, Diet, Stage, and Disease, and correlations between FMC s with FFCs • Differentially expressed genes: FFC4, FMC1, Diet, Disease, Tg, Irf7, Oas2, Zbp1,		

			Sct, Ms4a6c, Gcnt2, Nr4a1, Dhx58, TIr7, Pik3r6, Mapkapk2, SIc39a1, Rtp4, Ifi44, Oas1g, Oas1a, CbIn1, Cys1, Tnxb, Gabrq, PId5, Stmn2, SIco2b1, PIekha6, Iqgap2, Cnn3, Mturn, Ighv1-31, Ighv1-18,22,25,26, OlfmI2a, SIc16a5, 9030619P08Rik, Mir7649, Gm15987 • Prescence of ANA • Genes present in the ANA QTL on chromosome 17 • Differential Expression of genes for the ANA phenotype and present within the ANA		

			QTL: H2-Eb2, Myo1f, Tap1, Cfb, C2, H2-K1, Psmb9, Psmb8, Tnxb, Rps28, Col11a2		
In vivo trial	Mice	high cholesterol diet	• Clinical features: Body weight • Biochemical: Total Cholesterol, LDL, HDL, Triglyceride, FFA, Glycaemia • Hematology: Hb, RBC, WBC, Lymphocytes, PLT • Inflammation: MPO, TIMP-1, CXCL1 • Atherosclerotic Lesion Size, Atherosclerotic • Macrophage And Neutrophil Infiltration • Collagen	• Apoe−/−Nba2.Yaa mice and Apoe−/− mice subject to a high cholesterol diet had similar atherosclerosis lesion size in aortic roots and abdominal aorta. • Apoe−/−Nba2.Yaa mice showed higher levels of macrophage and neutrophil infiltration, collagen, MMP-8 and MMP-9 and pro-MMP-9 expression, indicating features of atherosclerotic plaque vulnerability. • Apoe−/−Nba2.Yaa mice had higher anti-apoA-1 and anti-dsDNA IgG levels, which correlated with mRNA levels of	(150)

			• MMP-8 and MMP-9 • Pro MMP-9 Expression • Anti-apoA-1 IgG Levels • Anti-dsDNA IgG Levels • Kidney Size • Splenomegaly • Lymph Nodes Hypertrophy • mRNA Levels Of GATA3	GATA3, IL-4, Bcl-6 and CD20 in the spleen and aortic arch.	
(105)	Mice	High-fat diet (model for atherosclerosis)	• Lesion area • Serum Cholesterol and LDL • CD4+, CD45+, CD25+, Monocytes, MHCII Macrophages • Anti-dsDNA, Anti-oxLDL IgG, Anti-heart, Anti-ApoH, anti-cardiolipin IgG, IgG2a	• Pbx1d-transgenic T cells exacerbated some phenotypes of atherosclerosis in Ldlr-/- mice, which was associated with higher autoantibody production, increased Tfh cell frequency, and impaired Treg cell regulation. • Dyslipidemia and Pbx1d-transgenic expression independently impaired the	(151)

			• Spleen Weight and cell count • Phenotypes of Atherosclerosis • Differentiation and Function of Treg Cells • Proliferation index, CD25, Foxp3+, B6, Pbx1d, IL-21	differentiation and function of Treg cells in vitro. • The combination of Pbx1d expression in T cells and dyslipidemia exacerbates both atherosclerosis and autoimmunity, at least in part through a dysregulation of Treg cell homeostasis.	
In vivo trial	Mice	low fiber intake	• Mortality: Survival %, Albustix Score, Proteinuria • Autoantibody production: Anti-dsDNA-IgG, anti-dsDNA-IgG1, anti-dsDNA-IgG2a, • Immune dysregulation: O.D., Lymphoproliferation, Spleen Weight, Kidney Leukocyte Infiltration, CD45+ Cells/Live	• Low dietary fiber intake is linked to the development of obesity and lupus pathogenesis. • Short-chain fatty acids and gut microbiota are implicated in the mode of action of beneficial fiber effects. • Low fiber-fed mice showed an increase in white adipose tissue mass, fat-inflammation and a disrupted	(152)

			cells, CD4+ and CD8+ T cells, activated CD4+ and CD8+ T cells, IL-10+/CD4+ T cells, T reg, effector Treg cells, Tfh cells, IL-6, IL-1β, TNFα • Disrupted Intestinal Homeostasis: Body weight, Gonadal WAT (White Adipose Tissue), Feces quantity, Food intake, Energy intake, Colon length, Small Intestinal Length, Intestinal Permeability • Gene expression: Muc2, Reg3, ZO1, IL-18, IL-6, IL-1β, TNFα • Serum concentration: Leptin,	intestinal homeostasis, leading to systemic, low-grade inflammation driving autoimmunity.	

			IL-1β, IFNγ, IL-23, IL-6, TNFα, GM-CSF, MCP-1, IL-17A, IL-10, IL-27, IFNβ • SLEDAI with CRP, BMI, Leptin, and LPS		
In vivo trial	Mice	chow diet vs. high fat diet, and methylprednisolone treatment	• Percent Survival • Percent Proteinuria • Urine protein/Creatinine • Anti-dsDNA antibodies • BUN • Intraperitoneal Glucose Tolerance Test (IPGTT) • Body Composition: Body Weight, Fat Mass, Lean Mass • Flow Cytometry: T cell, T helper cell subset, and	• Treatment with methylprednisolone significantly increased the survival in the control diet group, but not in the HFD group. An HFD significantly increased the incidence of severe proteinuria and glucose intolerance. • Treatment with methylprednisolone significantly lowered the serum levels of IL-6, MCP-1, and TNF-α in the control diet group, but not in the HFD group. • These data improve our understanding	(153)

			macrophage proportions in the spleen, Inflammatory cells in stromal vascular cells from epididymal white adipose tissue • Kidneys Analysis: Mesangial proliferation, Inflammatory cell infiltration, Tubular dilation, Fibrosis, IgG Deposition, C3 Deposition • Serum cytokines: IFN-γ, IL-1β, IL-2, IL-4, IL-10, IL-12p70, IL-15, IL-17A, IP-10, IL-6, MCP-1, TNF-α, MIP1b • Serum Insulin, Leptin, PAI1, Resistin, Adiponectin, FFA, Glycerol, TC, TG	of the effect of HFD on the therapeutic efficacy of corticosteroids in SLE treatment, which could have clinical implications.	

In vivo trial	Mice	High-dose methyl diet	• Anti-dsDNA IgG antibodies levels • Proteinuria levels • Skin lesion score • % of Survival • IFN-γ and IL4 secretion score • Glomerular score • DNA methylation levels	• Methyl-rich diet was found to decrease levels of proteinuria, anti dsDNA antibodies, and modulate cytokine profiles in MRL/lpr mice. • Methyl-rich diet limited kidney failure and prevented the development of skin lesions in MRL/lpr mice.	(154)
In vivo trial	Mice	TLR7 agonist imiquimod (IMQ) and a high fat, high sucrose "Western diet" (HFD) intervention	• Spleen Weights • Anti-Nuclear Antibody (ANA) Positivity • Body Weight • Gonadal Fat Pad Mass • Plasma Leptin Levels • Fasting Blood Glucose Levels • Fasting Insulin Concentrations	• TLR7 agonist treatment combined with a high fat, high sucrose diet (HFD) affects the early-stage development of SLE or MetS features. • TLR7 agonist treatment and HFD exposure increased body weight, gonadal fat pad mass, and plasma leptin levels.	(155)

				• TLR7 agonist treatment affected fasting insulin concentrations in a diet-dependent manner, resulting in hyperinsulinemia in IMQ-HFD treated mice.	
In vivo trial	Mice	iron supplementation	• Tfh Cell Expansion • Proinflammatory Cytokine Secretion • Autoantibody Production • Antigen Specific Gc Response	• Iron overload promotes Tfh cell expansion, proinflammatory cytokine secretion, and autoantibody production in lupus-prone mice. • Iron supplementation contributes to Tfh cell differentiation, while iron chelation inhibits Tfh cell differentiation. • The miR-21/BDH2 axis drives iron accumulation during Tfh cell differentiation and further promotes	(156)

				Fe2+-dependent TET enzyme activity and BCL6 gene demethylation.	
In vivo trial	Mice	high fat diet (HFD)	• Anti DsDNA • Proteinuria • Increased Creatinine • Fluorescein Isothiocyanate Dextran • Serum Lipopolysaccharide (LPS) • Serum Interleukin (IL-6) • Alanine Transaminase (ALT) • Liver and Kidney Pathology • Activated Caspase 3 • Aorta thickness	• Obesity (induced by HFD) exacerbates lupus activity in FcgRIIb-/- lupus mice, partly through saturated fatty acid-induced gut barrier defect and systemic inflammation. • High-fat diet administration in FcgRIIb-/- mice resulted in increased lupus nephritis, gut barrier defect, serum lipopolysaccharide, serum interleukin-6, liver injury, organ fibrosis, spleen apoptosis, and aorta thickness. • Combined palmitic acid and lipopolysaccharide induced higher tumor necrotic factor-α, interleukin-6,	(157)

				and interleukin-10 in FcgRIIb-/- macrophages compared to wild-type macrophages.	
In vivo trial	Mice	high fat diet (HFD)	• Bregs and their Regulatory Effects • Th17/Treg Cell Balance • Release of Downstream Inflammatory Factors	• CD19+CD5+CD1d+ Bregs are present in mice with systemic lupus erythematosus complicated with atherosclerosis. • Bregs regulate the Th17/Treg balance and the release of downstream inflammatory factors. • Bregs may play a role in maintaining the Th17/Treg balance in mice with systemic lupus erythematosus complicated with atherosclerosis.	(158)
In vitro trial	Human	low or high dose folate co-culturing	• Secretion of Interleukin (IL-10) from Regulatory Cells	• Folic acid co-culturing with PBMCs from lupus patients and healthy	(159)

			• Methylation level of B lymphocytes	volunteers resulted in increased IL-10 secretion from regulatory B lymphocytes. • Low dose folic acid co-culturing had a greater effect on IL-10 secretion than high dose folic acid co-culturing. • Folic acid co-culturing had no effect on IL-10 secretion from non-regulatory B lymphocytes.	
Systematic review	Human	-	• Pain • Disability • Outcomes of People with RMDs • Diet • Exercise • Weight loss	• Five overarching principles and 18 specific recommendations were developed based on available evidence. 1. OP 1: Lifestyle improvements complement medical treatment and do not replace it 2. OP 2: Lifestyle improvements are an	(160)

			• Smoking • Working	essential part of RMD management and add to overall health benefits 3. OP 3: World Health Organization recommendations for a healthy lifestyle are also applicable to people with RMDs 4. OP 4: Lifestyle recommendations for individuals with RMD depend on factors such as age, sex, health condition, pregnancy and comorbidities 5. OP 5: There should be regular discussions between people with RMDs and health professionals regarding lifestyle factors • Recommendations emphasize the importance of a healthy lifestyle, how	

				lifestyle modifications should be implemented, and their role in relation to medical treatments.	

Table 2. The relationships between essential fatty acids and lupus incidence and severity.

Detailed Study Design	**Organism**	**Interventions/Nutrient**	**Outcome measured**	**Study result**	**Reference**
Observational	Human	-	• Demographic: Age, Gender, Race/Ethnicity, BMI, Fat	• Dietary intake of omega-3 and omega-6 fatty acids was associated with	(35)

			Energy intake, Dietary n-3 and n-6 intake, Flaxseed/Fish oil supplementation • Patient Reported Outcomes In Systemic Lupus Erythematosus (SLE): Systemic Lupus Activity Questionnaire (SLAQ), Survey Criteria for Fibromyalgia (FM Scale), Patient-Reported Outcomes Measurement Information System (PROMIS), RAND Medical Outcomes Study Short Form 36 (SF-36), LupusQoL domains	patient-reported outcomes in SLE. • Higher intake of omega-3 fatty acids was associated with lower levels of fatigue, pain, and depression. • Higher intake of omega-6 fatty acids was associated with higher levels of fatigue, pain, and depression.	

Cross-sectional	Human	-	• Patient characteristics: Gender, Disease duration, BMI, Systemic Lupus Activity Questionaire (SLAQ), Brief Index of Lupus Damage (BILD), CRP, C3c, Medications • Distribution of PUFAs: Arachidonic acid (AA), Linoleic acid (LA), Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), Alpha-Linoleic acid (ALA), Omega-6%, Omega-3%, Delta-5 desaturase index, Delta-6 desaturase index	• Omega-6 PUFAs were associated with higher levels of systemic inflammation (measured by CRP). • Omega-3 PUFAs were associated with lower levels of systemic inflammation. • Increased dietary PUFA consumption from fish was linked to higher omega-3 status and lower self-reported damage.	(36)

			• Associations of PUFA and Clinical Parameters in SLE patients: omega-6% and omega 3% in HUFA with CRP levels, omega-3 salute and BILD Score with PUFA fish intake		
Randomized controlled trial	Human	Fish oil (EPA & DHA)	• Physician Global Assessment (PGA) • Rand Short Form-36 (Rand SF-36) • Fatigue Severity Scale (FSS) • SLE Disease Activity Index (SLEDAI) • Serum IL-12	• Fish oil supplementation improved Physician Global Assessment (PGA) compared to placebo (p=0.015). • Trends of improvement were seen in RAND SF-36 Energy/fatigue and Emotional well-being scores (p=0.092 and 0.070). • Erythrocyte sedimentation rate and serum IL-12 were reduced (p=0.008 and	(37)

			• Serum IL-13 • Erythrocyte Sedimentation Rate (ESR)	0.058); while serum IL-13 was increased by fish oil supplementation (p=0.033).	
Clinical trial	Human	Supplementation with omega-3	• Circulating Levels of Inflammatory Mediators • Biochemical Markers • CRP Levels • Serum Concentrations Of IL-6 • Serum Concentrations Of IL-10 • Leptin Levels • Adiponectin Levels • Total Cholesterol Levels (TC) • LDL Cholesterol Levels	• Omega-3 supplementation in women with low-activity SLE didn't affect IL-6, IL-10, leptin, and adiponectin levels but significantly reduced C-reactive protein levels and potentially affected total and LDL-cholesterol.	(38)

			(LDL)		
In vivo trial	Mice	1) n-3 PUFA-rich diet containing docosahexaenoic acid-enriched fish oil, 2) n-6 PUFA-rich Western-type diet containing corn oil or 3) n-9 monounsaturated fatty acid (MUFA)-rich Mediterranean-type diet containing high oleic safflower oil	• Plasma Autoantibodies • Proteinuria • Glomerulonephritis • Expression of 84 Genes Associated with CD4+ T Cell Function in the Spleen And Kidney • CD80 mRNA Expression In Kidney and/or Spleens • CTLA-4 mRNA Expression in Kidney and/or Spleens • IL-10 mRNA Expression in Kidney and/or Spleens • IL-18 mRNA Expression in Kidney and/or Spleens	• Mice fed a n-3 PUFA-rich diet containing docosahexaenoic acid-enriched fish oil (DFO) had significantly reduced plasma autoantibodies, proteinuria and glomerulonephritis compared to mice fed n-6 PUFA or n-9 MUFA diets. • Consumption of the n-3 PUFA diet was associated with a generalized downregulation of CD4+ T cell-related genes in kidney and/or spleen at wk 34. • Quantitative RT-PCR of representative affected genes confirmed that n-3 PUFA consumption was associated with reduced expression of CD80, CTLA-4,	(43)

				IL-10, IL-18, CCL-5, CXCR3, IL-6, TNF-α and osteopontin mRNAs in kidney and/or spleens as compared to mice fed n-6 PUFA or n-9 MUFA diets. • These genes are associated with the inflammatory response, antigen presentation, T cell activation, B cell activation/differentiation and leukocyte recruitment in kidney and/or spleens.	
In vivo trial	Mice	Docosahexaenoic acid (DHA)	• Inflammatory and autoimmunity markers in lung, blood, and kidney	• DHA suppressed lung inflammation. • DHA reduced serum levels of pro-inflammatory cytokines, antibodies, and B-cell proliferation. • DHA reduced glomerulonephritis in kidney.	(161)
In vivo trial	Mice	Docosahexaenoic acid	• Pulmonary Ectopic	• Dietary DHA prevents silica induced	(39)

		(DHA)	Germinal Center Formation. • Glomerulonephritis. • Inflammation in Lungs • B Cell and T Cell Accumulation in Lungs • IgG+ Plasma Cell Appearance in Lungs	development of pulmonary ectopic germinal centers, glomerulonephritis, as well as increased B-cell, T-cell, follicular dendritic cell (FDC), and IgG+ plasma cell appearance in the lungs of lupus prone NZBWF1 mouse	
In vivo trial	Mice	Docosahexaenoic acid (DHA)	• Acute transcriptional response of immune-associated genes in DHA-supplemented mice • PCA plot of differentially expressed genes (PC1 and PC2) • Global and directed significance scores for	• Dietary supplementation with docosahexaenoic acid (DHA) suppresses autoimmune pathogenesis and nephritis in lupus-prone female NZBWF1 mice. • DHA consumption interferes with upregulation of critical genes associated with cSiO2-triggered murine lupus. • DHA dose-dependently suppresses	(40)

			immune pathways: Adaptive, Adhesion, Antigen Processing, Apoptosis, B-cell functions, CD molecules, Cancer progression, Cell Cycle, Chemokines & Receptors, Complement Pathway, Cytokines & Receptors, Dendritic cell functions, Humoral, Inflammation, Innate, Interferon, Interleukins, Leukocyte functions, MHC, Macrophage functions, Microglial functions, NK Cell functions, Pathogen response,	interferon (IFN)- and chemokine-related gene pathways in response to cSiO2 treatment.	

			Senescence, T-cell functions, TLR, TNF superfamily, Transporter functions • Pathway Z scores and network interaction visualization: Adaptive, Antigen Processing, CD molecules, Chemokines & Receptors, Inflammation, Innate, Interferon, Interleukins, MHC, Macrophage functions, T-cell functions • Unsupervised clustering by gene depict log2 expression ratio: Innate, Adaptive		

			Inflammation, Chemokines & Receptors, Interferon • Log2 ratio values: Ccl7, Ccl12, Cxcl10, Fcer2a, Fcgr1, Ifi44, Ifit1, Ifit3, Ifrf7, Isg15, Klrg1, Mx2, Oas2, Ppbp, Zbp1, Nlrc5, Irgm2, Clec4a2, Cfd, Mx1, Mx2, Marco, Cxcl9, Ccl8, Cxcl13, Ccr6, Stat1, C3ar1, Tlr1, Cd180, Ly86, Il1b, Fos, Cxcl5, Ccl17, Ccl20, Ccr5, Fos, Clec4a2, Lcn2, S100a8, Ccl8, Cd5, Il1b, Il1m, Elane, Tlr8, Tlr4, Ly86, Cx3cr1, Cxcl14, Ccl24, Fcer1g, Ccl24, H2-		

			Dmb2, H2-Eb1, Icam1, Sh2d1b1, Nlrc5, gene • Percent ω-3 HUFA in erythrocytes (ω-3 HUFA score)		
In vivo trial	Mice	dietary ω-3 polyunsaturated fatty acid docosahexaenoic acid (DHA)	• IgG AAb responses in BALF and Plasma • IgM AAb responses in BALF and Plasma • IgA AAb in BALF And Plasma • ELS development • Glomerulonephritis	• Crystalline silica (cSiO2) exposure induces a wide spectrum of autoantibodies (AAbs) in the pulmonary and systemic compartments of lupus-prone NZBWF1 mice. • cSiO2 triggers robust IgG and IgM AAb responses against lupus-associated antigens, including DNA, histones, ribonucleoprotein, Smith antigen, Ro/SSA, La/SSB, and complement. • Dietary docosahexaenoic acid (DHA)	(162)

				intervention prevents cSiO2-induced inflammation and onset of autoimmunity (suppressed increases in IgG and IgM AAbs in BALF and plasma).	
In vivo trial	Mice	ω-3 highly unsaturated fatty acids (HUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)	• Indicators of Autoimmune Pathogenesis in the cSiO2-Triggered Lupus Flaring Model • Expression of Interferon Regulated Genes • Proinflammatory Cytokine Production • Leukocyte Infiltration • Ectopic Lymphoid Structure Development in the Lung	• Increases in both the ω-3 HUFA score (>40%) and the O3I (>10%) were strongly associated with suppression of cSiO2-triggered autoimmune pathogenesis in the lung, autoantibody production, and glomerulonephritis. • The ω-3 HUFA scores in RBCs were comparatively more robust than the O3I at predicting HUFA balances in the kidney, liver, spleen, and lung. • These findings identify achievable ω-3	(42)

			• Pulmonary and Systemic Autoantibody Production • Glomerulonephritis • ω-3 highly unsaturated fatty acids (HUFA) score & mega-3 Index (O3I)	HUFA scores and O3I thresholds that could be targeted in future human intervention studies querying how ω-3 HUFA consumption influences lupus and other autoimmune diseases.	
In vivo trial	Mice	western fed diet, and group supplemented with dietary ω-3 polyunsaturated fatty acid (PUFA) docosahexaenoic acid (DHA)	• Weight gain • % Total Fatty Acids: RBC, Lung, Kidney, Liver, Spleen • IFN Score comprised of: Ccl7, Zbp1, Ifi44, Ifit1, Irf7, Isg15, Mx1, Oas1, Oas2, Oasl1, Psmb8, Rsad2, Siglec1, Ccl8, Cxcl10 • Cytokine levels: MCP-1, MCP-3, TNF-alpha, IL-	• Consumption of a modified Total Western Diet (mTWD) containing docosahexaenoic acid (DHA) at the caloric equivalent to a human dose of 5 g/day dramatically suppressed induction of all lupus-associated endpoints in NZBWF1 mice exposed to crystalline silica (cSiO2). • Decreasing saturated fatty acid (SFA) and omega-6 (ω-6) in mTWD modestly	(163)

			1alpha, IL-6, IL-18, IL-17A, IL-22, BAFF • Immune cell accumulation in BALF: Total cells, Monocytes, Lymphocytes, Neutrophils, Lymphocytes • CD45R+ and CD3+ cells in the Lungs • Autoantibodies in BALF and plasma: Anti-dsDNA, ANA • Ectopic Lymphoid Structure (ELS) Neogenesis • Histology Score (Glomerulonephritis)	inhibited some disease markers, but DHA addition to this diet was required for maximal protection against lupus development. • DHA supplementation at a translationally relevant dose was highly effective in preventing cSiO2-triggered lupus flaring in NZBWF1 mice.	
In vivo trial	Mice	dietary supplementation	• Autoantibody Production:	• Dietary supplementation with	(164)

		with eicosapentaenoic acid (EPA)	ANA (anti-nuclear antibodies), Anti-dsDNA, Anti-Histone, IgG, C3, IgM, BAFF • IFN-α/β, White Pulp (WP) area • Serum fatty acid, TG, cholesterol • Spleen Plasma Cell Count: Total CD4+, Naïve, Teff (T effector cells), Treg (T regulatory cells), Tfh (T folicular helper cells), Total B, FOB, MXM, GCB, Plasma, Population, Cell count, DNT (double negative	eicosapentaenoic acid (EPA) inhibits plasma cell differentiation and attenuates lupus autoimmunity. • EPA remodels the lipid composition and fluidity of B cell membranes, preventing B cell differentiation into autoantibody-producing plasma cells. • EPA supplementation may be beneficial for therapy of lupus.	

			T cells), Total B, FOB (Folicular B cells), MZB (marginal zone B cells), GCB (germinal center B cells) • Inflammatory Cytokines: IL-12p40, IL-6, TNF-α, IFN-β. IL-12p70, IFN-α/β, • Gene Expression: Baff, Veh, LPS, R848, Cd79b, Prdm1, Xbp1, Irf4m • Blimp1 (Mean Fluorescene Intensity) • Total and Free fatty acids, Free cholesterol, Amount of PC phosphatidylcholine (PC) and PE		

			(phosphatidylethanolamine) species		
In vivo trial	Mice	docosahexaenoic acid (DHA)	• Body Weight • % Total Fatty Acids: DHA-EPA and ARA concentration in Kidney, Lung, and Plasma • Inflammatory Cell Recruitment: Total Leukocytes, Macrophages, Neutrophils, Lymphocytes • ELS (Ectopic Lympoid Structure) Score • CD45R+ T cell infiltration, CD21/35+ follicular dendritic cell infiltration • IgG antibodies	• Dietary supplementation with docosahexaenoic acid (DHA) beginning 2 weeks prior to cSiO2 challenge prevented inflammation and autoimmune flaring in NZBWF1 mice. • Dietary intervention with high but not low DHA after cSiO2 treatment suppressed or delayed recruitment of T cells and B cells to the lung, development of pulmonary ELS, and elevation of a wide spectrum of plasma autoantibodies associated with lupus. • DHA consumption dose-dependently increased ω-3 PUFA content in the	(165)

			• Selected Autoantigens: C3, C1q, SP100, PR-3, LC1, Nup62, MI-2, Vimentin • Nephritis Score (Glomerulonephritis) • Kidney CD3+ T cell infiltration • Percent proteinuria • Percent survivors	plasma, lung, and kidney at the expense of the ω-6 PUFA arachidonic acid.	
In vivo trial	Mice	dietary supplementation with the ω-3 polyunsaturated fatty acid docosahexaenoic acid (DHA)	• Inflammatory Proteins In Bronchoalveolar Alveolar Lavage Fluid (BALF) • Inflammatory Proteins in Plasma	• Intranasal instillation of lupus-prone mice with crystalline silica (cSiO2) induces inflammatory gene expression and ectopic lymphoid neogenesis in the lung. • Dietary supplementation with the ω-3 polyunsaturated fatty acid	(166)

				docosahexaenoic acid (DHA) suppresses cSiO2-induced inflammatory proteins in bronchoalveolar alveolar lavage fluid (BALF) and plasma of lupus-prone mice. • High density multiplex array profiling of 200 inflammatory proteins revealed that DHA supplementation blocked or delayed the induction of chemokines, enzymes, adhesion molecules, co-stimulatory molecules, TNF superfamily proteins, growth factors, and signal transduction proteins.	
In vivo trial	Mice	ω-3 polyunsaturated fatty acid (PUFA) supplementation and	• Blood Urea Nitrogen (BUN) • Proteinuria • Hematuria	• Sub chronic intraperitoneal injection of rough LPS (R-LPS) induced robust glomerulonephritis in NZBWF1 mice,	(167)

		soluble epoxide hydrolase (sEH) inhibition	• Kidney Histopathology • Spleen Enlargement • Lymphoid Hyperplasia • Inflammatory Cell Recruitment in the Liver • Blood Fatty Acid Profiles • Epoxy Fatty Acid Concentrations • Glomerular IgG Deposition • Plasma Antibody Responses	while smooth LPS (S-LPS) and saline vehicle (VEH) did not. • Dietary supplementation with omega-3 docosahexaenoic acid (DHA) and/or the soluble epoxide hydrolase (sEH) inhibitor TPPU suppressed R-LPS-induced glomerulonephritis. • Lipidome modulation by dietary omega-3 PUFA supplementation or sEH inhibition suppressed R-LPS-accelerated glomerulonephritis in lupus-prone mice.	

19 Table 3 summarizes the effect of alcohol consumption on lupus incidence and severity.

Detailed Study Design	**Organism**	**Interventions/Nutrient**	**Outcome measured**	**Study result**	**Reference**
Observational cohort	Human	Daily mean intake of 49 nutrients (e.g., vitamins, alcohol, fatty acids, etc).	• Glucocorticoid use over two-year period as a proxy for SLE disease activity.	• Linoleic acid (n-6 PUFA), beta-carotene, and vitamin B6 was inversely associated with unchanged/increased glucocorticoid dose. • Total energy intake was associated with higher glucocorticoid dose. • Alcohol was inversely associated with glucocorticoid treatment.	(168)
Observational cohort	Human	-	• Alcohol consumption • Risk of systemic lupus erythematosus	• An inverse association between moderate alcohol consumption (≥5 grams or 0.5 drink/day) and SLE risk in women.	(44)
Cohort	Human	-	• Participant	• Moderate alcohol consumption was	(45)

			characteristics: Age, smoking, alcohol intake, income, BMI, Race, Residence Region, Contraceptive use, Menopause, Steroid use • Cytokine/Chemokine Concentration: Stem Cell Factor (SCF), Interferon Inducible Protein-10 (IP-10), Interferon Alpha (IFN-α), B	associated with lower stem cell factor levels in female nurses without systemic lupus erythematosus. • Other cytokines were not significantly associated with alcohol intake. • "moderate alcohol consumption was associated with lower stem cell factor levels, suggesting a plausible mechanism through which alcohol may lower systemic lupus erythematosus risk might be by decreasing circulating stem cell factor."	

			Lymphocyte Stimulator (BLyS), Interleukin-10 (IL-10) • Antinuclear autoantibodies (ANA) • Double Stranded DNA (dsDNA) • Extractable Nuclear Antigens (ENA)		

Table 4. The effect of excessive salt intake on lupus incidence and severity

Detailed	**Organism**	**Interventions/Nutrient**	**Outcome measured**	**Study result**	**Reference**

Study Design					
Clinical trial	Human	Sodium intake	• 24-Hour Urinary Sodium Excretion • Frequency of T Helper 17 (Th17) Cells in Peripheral Blood • Function of Th17 Cells in Peripheral Blood • Frequency of Regulatory T Cells (Treg) in Peripheral Blood • Function of Regulatory T Cells (Treg) in Peripheral Blood • Serum Levels of Cytokines	• A decrease in Th17 cells and an increase in Treg cells was observed. This trend reversed upon return to a normal-sodium diet. • The study also found reduced IL-9 levels in SLE patients.	(58)

			(TGF-β and IL-9)		
Cross-sectional	Human	-	• Anti dsDNA Level • Complement C4 Level • Complement C3 Level • hsCRP Level	• Higher dietary sodium and lower dietary potassium intakes were associated with an increased risk of higher hsCRP in SLE patients. • Dietary sodium intake was significantly associated with anti-dsDNA and complement C4 level. • Dietary potassium intake was associated with complement C3 level.	(60)
Observational	Human	-	• Food intake • Intestinal Permeability using plasma zonulin • Gut microbiota • SLE Disease Activity	• Increased *Megamonas funiformis* abundance, elevated plasma zonulin, and higher sodium intake may contribute to reduced C3 complement levels in women with	(61)

			(SLEDAI-2K) • C3 Complement Levels • C4 Complement Levels • C Reactive Protein Levels (CRP)	inactive SLE	
In vivo trial	Mice	Sodium intake	• Survival Rate • Disease Severity • Frequencies of Th1 and Th17 Cells • Ratios of Th1/Th2 and Th17/Treg • Serum TGF-β	• High salt diet (HSD) worsens lupus nephritis (LN) in MRL/lpr mice, increasing disease severity and decreasing survival rate. • HSD increases the frequencies of Th1 and Th17 cells, and the ratios of Th1/Th2 and Th17/Treg. • High salt treatment of CD4(+) T cells from SLE patients and healthy donors increases Th17 cells, and	(55)

				this effect is reversed by SGK1 inhibitor.	
In vivo trial	Mice	Sodium intake	• Plasma Anti-dsDNA Autoantibodies IhG • Urinary Albumin • Mean Arterial Pressure • Albuminuria, Urinary albumin excretion rate, Urinary Endothelin-1 (ET-1) Excretion • Endothelin receptor protein expression (anti-ET-A, anti-ET-B) • Renal mRNA Expression of NOS1, NOX2, MCP-1, TNF-α, SGK1, and IL-2	• Female NZBWF1 mice fed a high salt diet had increased circulating autoantibodies, but high salt diet did not significantly affect albuminuria or arterial pressure. • Urinary ET-1 excretion was increased, whereas renal endothelin A receptor and IL-2 expression were decreased in response to a high salt diet. • Chronic high salt diet may not accelerate cardiovascular and renal consequences commonly associated with SLE.	(57)

In vivo trial	Mice	Sodium intake	• Lupus Progression • DC Activation and cell ratios: MHC II, CD 80, CD 86 • DC Activation and maturation: CD11c, MHC II, CD 80, CD 86, CD 69, CD 40 • Division and Proliferation Indexes of T cells (Antigen Presenting Ability Of DC(s)) • Production of Autoantibodies: IgG, C3, anti-dsDNA levels, IgG1, IgG2a, IgG2b • Proinflammatory Cytokines: IL-10, IL-17a, IFN-γ, IL-6,	• A high-salt diet (HSD) accelerates the progression of murine lupus. • HSD increases the activation, maturation, and antigen-presenting ability of dendritic cells (DCs). • The p38 MAPK–STAT1 pathway plays an important role in NaCl-induced DC immune activities.	(56)

			IL-4, TNF, IL-2 • Splenomegaly • Lymphadenopathy • Pathological Renal Lesions, Interstitial fibrosis, and Glomerular damage • Proteinuria levels • p38 MAPK–STAT1 pathway		

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24 Table 5 summarizes the beneficial effects of vitamin D on lupus incidence and severity.

Detailed Study Design	**Organism**	**Interventions/Nutrient**	**Outcome measured**	**Study result**	**Reference**
Cross-sectional and observational	Human	oral vitamin D supplementation of cholecalciferol vitamin	• Serum 25-Hydroxyvitamin D [25(OH)D] Levels • Cutaneous Lupus	• Vitamin D deficiency is more prevalent in CLE patients than in healthy controls.	(75)

		D3 and calcium carbonate	Erythematosus Disease Area and Severity Index (CLEDASI) • Number Of Exacerbations • Duration Of Active Lesions • Patient Assessment	• Increasing age and disease duration are associated with higher odds of having vitamin D deficiency. • Treating vitamin D insufficiency is associated with improved disease severity according to physician and patient assessments.	
In vitro	Human	oral vitamin D3 supplementation	• Externalization of Neutrophil Elastase (NE) during NETosis • Myeloperoxidase (MPO) Absorbance During NETosis • Early Apoptosis of Endothelial Cell • Late Apoptosis of Endothelial Cell	• Vitamin D 1,25(OH)2D3 can reduce endothelial damage by decreasing NETosis activity in SLE patients with hypovitamin D. • Significant decrease in early apoptosis was found with 10 nM of 1,25(OH)2D3 compared to control group. • Moderate positive correlation	(169)

				between NE externalizations with early apoptosis was found	
Observational	Human	vitamin D supplementation	• Body Composition • Bone Mineral Density (BMD)	• The decrease in bone mineral density (BMD) observed in adolescents with juvenile systemic lupus erythematosus (JSLE) has been found to be correlated with the absence of vitamin D supplementation.	(170)
Randomized controlled trial	Human	oral vitamin D3 supplementation	• Flow Mediated Dilation (FMD) •25(OH) Vitamin D (25(OH)D) Levels	• Half of SLE patients with 25(OH)D levels <20 ng/mL who achieved 25(OH)D levels of ≥32 ng/mL experienced increases in FMD. • Those with increases in FMD had significantly higher final 25(OH)D	(171)

				levels. • Future studies designed to test the effect of repleting 25(OH)D on FMD in vitamin D–deficient SLE patients will require 35 patients in each group.	
Randomized controlled trial	Human	oral vitamin D3 supplementation	• Interferon (IFN) Signature	• Vitamin D supplementation significantly reduced the IFN signature in patients with SLE. • Vitamin D supplementation was well tolerated and had no adverse effects. • Vitamin D supplementation may be a potential therapeutic option for SLE.	(172)
Randomized	Human	oral vitamin D3	• 25-OH Vitamin D Levels	• Intensive regimen (IR) of vitamin	(173)

controlled trial		supplementation	• Disease Activity (SLEDAI) • SLE Serology • Bone Metabolism Markers	D supplementation was found to be safe and effective in raising vitamin D serum levels in SLE patients. • No significant differences in disease activity and SLE serology were found between the standard and intensive regimens. • No changes in mineral metabolism were observed.	
Randomized controlled trial	Human	oral vitamin D3 supplementation	• Visual Analogue Scale (Vas) Scores of Pain Perception • Serum Levels of Leukotriene B4 (LTB4) • Serum Levels of Interleukin 6 (IL-6) • Serum Levels of Tumor	• Adding 4000 IU of vitamin D to analgesic regimens in patients with musculoskeletal pain led to a faster decline in VAS scores and a decrease in levels of inflammatory and pain-related cytokines. • The need for analgesic ‘rescue	(174)

			Necrosis Factor Alpha (TNF-α) • Serum Levels Of Prostaglandin E2 (PGE2)	therapy' was significantly lower among the vitamin D-treated group. • TNFα and PGE2 levels decreased by 54.3% and 39.2%, respectively, in the group treated with vitamin D.	
Prospective	Human	oral vitamin D3 supplementation	• Phenotypic analysis of peripheral T lymphocyte • Quantification of cytokine production from peripheral blood mononuclear cells (PBMCs) • Number of t reg cells • Total amount of CD4+CD45RA+CCR7− T cells • Reduction of cd8+cd28− T	• Vitamin D supplementation in SLE patients resulted in an increase in the number of T-reg cells and the total amount of CD4+CD45RA+CCR7− T-cells, and a reduction of CD8+CD28− T-cells. • Analysis of PBMCs from 8 patients following the intensive regimen showed a reduction of the IFN-γ/IL-4 ratio among CD8+ T-cells after 12 months.	(80)

			cells • Reduction of the IFN-γ/IL-4 ratio among CD8+ T cells	• Vitamin D supplementation may enhance T-reg cells and the production of Th2 cytokines in SLE patients.	
Case Report	Human	medical nutrition therapy and oral vitamin D3 supplementation	• Malnutrition (ASPEN criteria) • BMI, Fat Free Mass Index (FFMI), Skeletal Mass Index (SMI), Waist circumference • Patient's functional capacity (Karnofsky Score) • LupusQoL • Nutritional Intake: Macronutrients, Fat composition intake, saturated fatty acids, monounsaturated	• Medical nutrition therapy (MNT) is an important part of comprehensive management of SLE. Nutritional supplementation includes "vitamin B complex 1 tablet t.i.d, folic acid 0.5 mcg q.d, calcium carbonate 500 mg t.i.d, and omega 3 fatty acid 1000 mg t.i.d. Cholecalciferol 6000 IU/day". • Long-term corticosteroid use in SLE patients can lead to malnutrition, sarcopenia,	(175)

			fatty acids	hypovitaminosis D, hypertension, and obesity. • Vitamin D supplementation combined with MNT improved nutritional status and quality of life in SLE patients.	
Cross-sectional analysis	Human	oral vitamin D supplementation	• Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) • Total SDI • SLE Disease Activity Index (SLEDAI)	• Patients with vitamin D supplementation were younger, received higher doses of prednisolone, and had higher estimated glomerular filtration rates than those without supplementation. • Disease-related SDI, total SDI, and SLE Disease Activity Index (SLEDAI) did not significantly	(77)

				differ between patients receiving and not receiving vitamin D supplementation.	
In vivo trial	Mice	oral vitamin D supplementation	• Overall Survival • Onset of Proteinuria • Concentrations of Anti-Double Stranded DNA (anti-dsDNA) Autoantibodies • IL-10-Expressing CD4+ T Cells • Regulatory CD4+ T Cells • IL-10-Expressing B Cells	• Low dietary vitamin D intake accelerates lupus progression, reflected in reduced overall survival and an earlier onset of proteinuria, as well higher concentrations of anti-double-stranded DNA autoantibodies. • Low VD intake consistently hampered the adoption of a regulatory phenotype in lymphocytes, significantly reducing both IL-10-expressing and regulatory CD4+ T cells.	(78)

				• Low VD intake did not have consistent effects on the phenotype and function of innate immune cells.	

Table 6. The effects of natural products on lupus incidence and severity.

Detailed Study Design	**Organism**	**Interventions/Nutrient**	**Outcome measured**	**Study result**	**Reference**
Case control	Human	polyphenols from oranges and apples	• Association between flavone Intake and Blautia in SLE Group • Association between flavanones Intake and Lactobacillus in SLE group • Association between dihydrochalcones intake and Bifidobacterium In SLE group • Association between dihydroflavanols intake and	• Positive associations between flavone intake and Blautia, flavanones and Lactobacillus, and dihydrochalcones and Bifidobacterium were found in the SLE group. • Dihydroflavonols were directly associated with Faecalibacterium, whereas flavanol intake was inversely associated with Bifidobacterium in the control group.	(14)

			Faecalibacterium in control group • Association between flavanol intake And Bifidobacterium in control group • Association between orange intake	• Orange intake was directly associated with Lactobacillus and apple with Bifidobacterium in SLE, whilst red wine was the best contributor to Faecalibacterium variation.	
Retrospective cohort	Human	Lycopene	• Mortality	• Higher serum lycopene has protective effect on mortality in SLE patients	(106)
Clinical trial	Human	Phenolic fraction (PE) of extra virgin olive oil (EVOO)	• Frequency of CD69+ Cells • Secretion of IFN • Secretion of TNF A • Secretion of IL-6 • Secretion of IL-1B	• PE modulates cytokine production and attenuates induced T-cell activation, probably through NF-κB signaling pathway.	(90)

			• Secretion of IL-10 • Expression of I Kappa B-A • Extracellular Signal Regulated Kinase Phosphorylation		
Cross-sectional	Human	-	• Caffeine intake • SLE Related Disease Phenotype • SLE Disease Activity Index 2000 (SLEDAI-2K) • Cytokine Serum Levels (IL-6, IL-10, IL-17, IL-27, IFN-γ, IFN-α)	• Caffeine intake was negatively correlated with SLE disease activity, as measured by SLEDAI-2K. • Patients with a low intake of caffeine had a higher prevalence of lupus nephritis, neuropsychiatric involvement, hematological manifestations, hypocomplementemia and anti-dsDNA positivity.	(107)

				• Patients with a high intake of caffeine had lower serum levels of IFN-γ, IFN-α, IL-17, and IL-6.	
Systematic review of randomized controlled trials	Human	curcumin/turmeric supplementation	• Inflammation • Oxidative Stress • Blood Urea Nitrogen (BUN) • Creatinine • Glomerular Filtration Rate (GFR) • Serum Albumin • Proteinuria • Lipid Profile (TG, VLDL, Cholesterol) • Fasting blood sugar, HbA1c • Alanine and aspartate aminotransferase (ALT, ALP)	• Curcumin/turmeric supplementation had favorable effects on renal diseases, particularly in terms of inflammation and oxidative stress. • Curcumin/turmeric supplementation had no considerable positive impact on clinical outcomes of kidney diseases, apart from proteinuria. • No serious adverse effects were reported following curcumin/turmeric	(100)

			(Liver function)	supplementation.	
In vivo trial	Mice	polysaccharide of large yellow croaker swim bladder (PLYCSB)	• Levels of serum inflammatory cytokine levels of IL-6 • Levels of serum inflammatory cytokine levels of IL-12 • Levels of serum inflammatory cytokine levels of TNF-α • Levels of serum inflammatory cytokine levels of IFN-γ • Serum creatinine (sCR) levels • BUN serum levels	• High concentration (50 mg/kg dose) of PLYCSB reduced the levels of serum inflammatory cytokines compared to a low concentration (25 mg/kg dose) and control mice. • PLYCSB significantly induced inflammation in kidney tissues of mice by downregulating NF-κB-p65, TGF-β1, Fas, FasL and upregulating IκB-α. • PLYCSB showed a potential curative effect on lupus nephritis as a drug or functional food.	(105)

			• TC serum levels • TG serum levels • TP serum levels		
In vivo trial	Mice	Extract of Gentiana macrophylla Pall. (GM)	• GM root extract significantly reduced cholesterol-aggravated apoptosis of the left ventricle in NZB/W F1 mice. • GM suppressed both intrinsic and extrinsic apoptotic pathways. • GM increased cardiac insulin-like growth factors (IGF)-1 survival signaling and anti-apoptotic proteins in LV tissues.	• GM root extract significantly reduced cholesterol-aggravated apoptosis of the left ventricle in NZB/W F1 mice. • GM suppressed both intrinsic and extrinsic apoptotic pathways. • GM increased cardiac insulin-like growth factors (IGF)-1 survival signaling and anti-apoptotic proteins in LV tissues.	(102)

In vivo trial	Mice	isogarcinol	• Proteinuria • Serum biochemical indicators • Amount of serum antibodies • Renal histopathology score • Activation of CD4 T cells •expression of inflammatory genes and cytokines in the kidneys and peritoneal macrophages	• Oral administration of isogarcinol (60 mg/kg) significantly reduced proteinuria, corrected abnormal serum biochemical indicators, and decreased the amount of serum antibodies and renal histopathology score. • Isogarcinol alleviated the abnormal activation of CD4 T cells and decreased the expression of inflammatory genes and cytokines in the kidneys and peritoneal macrophages. • The mechanism of action of isogarcinol is associated with downregulation of CD4 T cells and	(104)

				inflammatory effects.	
In vivo trial	Mice	Extra virgin olive oil (EEVO) diet	• Kidney damage • Kidney expression of pro- and anti-inflammatory biomarkers, serum level • MMP-3 and splenocyte production of pro-inflammatory cytokines	• EEVO diet reduce kidney damage, kidney expression of pro-inflammatory biomarkers (PGE2), kidney activation of pro-inflammatory pathways (JAK/STAT, MAPK and NF-κB), serum MMP-3 level, splenocyte expression of pro-inflammatory cytokines. • EEVO intake increase kidney expression of anti-inflammatory biomarkers (Nrf-2, HO-1)	(86)
In vivo trial	Mice	Lactoferrin	• Levels of antioxidant • Levels of inflammatory biomarkers	• Lactoferrin increases antioxidant level in liver and serum, decreases pro-inflammatory indices and	(101)

			• Fibrotic-related molecules in liver and serum.	fibrotic-related molecules in liver.	
In vivo trial	Mice	Diets supplemented with hydroxytyrosol (HTy) and hydroxytyrosyl acetate (HTy Ac)	• Cytokines Levels • Renal Changes of Inflammatory Markers • Signaling Pathways	• Dietary phenol supplementation significantly reduced pro inflammatory cytokines and prevented renal damage with a considerably blockage of different inflammatory related pathways suggesting that HTy and HTy Ac supplementation might provide a basis for developing a new dietary strategy for prevention and management of SLE.	(94)
In vivo trial	Mice	Curcumin	• Arthritis Score • Proteinuria Level • Body Weights	• Decreased arthritis score, proteinuria levels, Th1, Th2, and Th17 percentages, as well as serum	(97)

			• Adaptive Immune System Components (Th1, Th2, Th17, And Treg Percentages) • Proinflammatory Cytokines (Interleukin-6 (IL-6), Interferon Alpha (IFN-A)) •Autoantibody Production (Antinuclear Antibody (ANA))	IL-6, IFN-α, and antinuclear antibody (ANA) levels, while Treg percentages showed a slight increase	
In vivo trial	Mice	diets enriched with oleuropein and its new derivate, peracetylated oleuropein	• Renal Histology • MMP-3 serum levels • iNOS/β-Actin, mPGEs-1/β-Actin, PGE2 protein expression in kidneys • Upregulation and Densitometry Analysis of	• Dietary oleuropein (OL) and its new derivate, peracetylated oleuropein (Per-OL), attenuated murine lupus nephritis. • OL and Per-OL increased the expression of antioxidant proteins HO-1 and Nrf2.	(92)

			Nrf2, HO-1, β-actin, pSTAT3, NFkB-p65, IkB-α, NLRP3, ASC, IL-18, Procaspase-1, Cleaved Caspase-1, Procaspase-11, Part-cleaved Caspace-11, Cleaved Caspase-11	• OL and Per-OL suppressed the activation of JAK/STAT, MAPK, NF-κB and NLRP3 inflammasome pathways.	
In vivo trial	Mice	oral curcumin administration	• Body Weight And Composition (Body fat %) • Spleen Weight • Circulating dsDNA Autoantibodies • B Lymphocytes (CD45R+ Cells) • Renal Injury (Albumin Excretion,	• Oral administration of curcumin attenuates autoimmunity and renal injury in female NZBWF1 mice with SLE. • Curcumin treatment reduced spleen weight and glomerulosclerosis when treatment started at 26 weeks of age. • When curcumin treatment started	(98)

			Glomerulosclerosis Score, Blood Urea Nitrogen (BUN)) • Hemodynamic Function (Glomerular Filtration Rate (GFR), Mean Arterial Pressure (MAP))	at 32 weeks of age, renal injury (glomerulosclerosis, BUN) was reduced in SLE mice compared to vehicle-treated SLE mice.	
In vivo trial	Mice	curcumin	• Proteinuria • Blood Urea Nitrogen (BUN) • Serum Creatinine • Glomerulonephritis (GN Score) • Crescent Formation • Tubule Interstitial Pathology • Lymphocytic Infiltration • Renal lymphoid cell infiltration: CD3+ cells,	• Curcumin treatment reduced proteinuria, blood urea nitrogen, glomerulonephritis, crescent formation, tubule-interstitial disease, and renal infiltration by lymphocytes in both the anti-GBM and MRL.lpr mouse models. • Curcumin treatment reduced activation of the NFkB, MAPK, AKT and pBAD pathways either	(99)

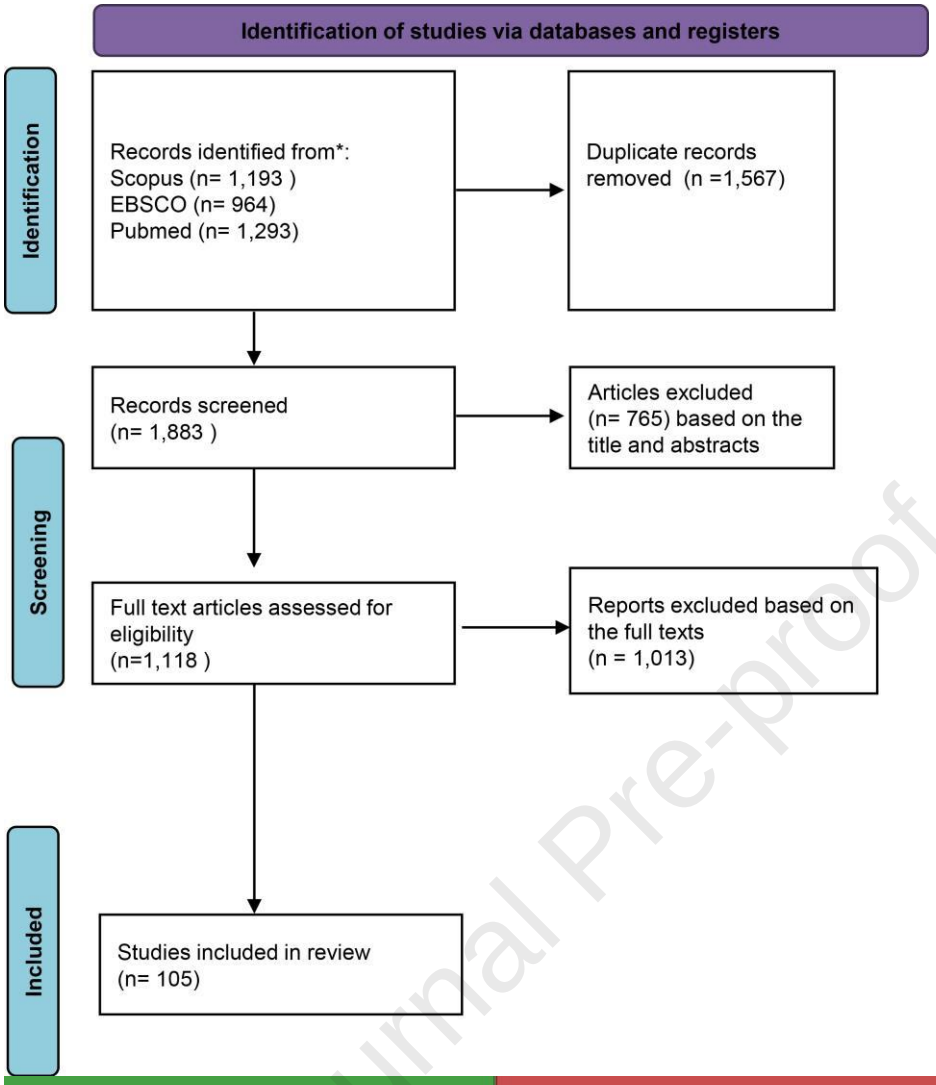
			B220+ cells, CD11b+ cells, CD11c+ cells • Phosphorylation Cell signaling: NF-κB, P38, Erk1,2 and Bad, AKT, IκB and Bcl-2 Serum Autoantibody Levels • Splenomegaly (Spleen weight, Splenocyte, Splenic B and T cells, macrophage, dendritic cells, populations, and activation status) • Autoantibody production: IgG anti-dsDNA, anti-histone, and anti-ssDNA, and IgM anti-dsDNA, anti-	systemically, or within the inflamed kidneys. • Curcumin ameliorated kidney disease in the two mouse models with either acute or chronic nephritis.	

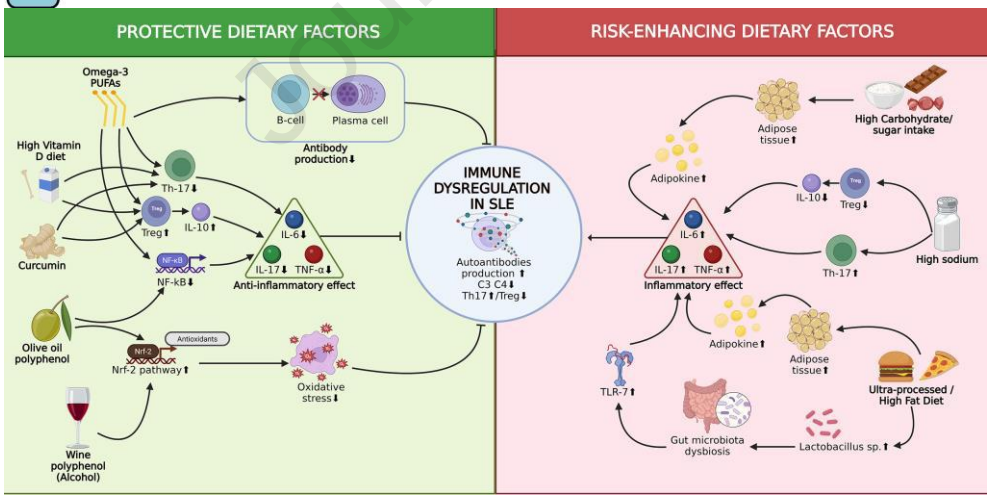
			ssDNA, and anti-histone • Complete Blood Count: WBC, RBC, HGB, HCT, MCV, MCHC, RDW, Alanine Aminotransferase Activity, Aspartate Aminotransferase Activity		
In vivo trial	Mice	orally administered amaranth oil	• IgG And IgM Histone Autoantibody Absorbance Levels • IgG dsDNA, ssDNA, and Nucleosome Autoantibody Absorbances • IgM dsDNA, ssDNA, and Nucleosome Autoantibody Absorbances	• Mice receiving amaranth oil showed decreased IgG and IgM histone autoantibody absorbance levels throughout the study. • IgG dsDNA, ssDNA, and nucleosome autoantibody absorbances were lower than that of the control group for the first 42 days.	(103)

			• Splenic Immune Cell Populations	• IgM dsDNA, ssDNA, and nucleosome autoantibody absorbances were lower only for the first 14 days. • "There were no significant differences found amongst the splenic immune cell populations tested between the control and experimental groups."	
In vivo trial	Mice	Oleocanthal (OLE) supplemented diet	• Renal damage • Aortic endothelial dysfunction • Cytokine levels (interleukin (IL)-17, tumor necrosis factor (TNF)-α, IL-1β, IL-6, and interferon (IFN)-γ)	• Dietary OLE supplementation reduced Th1/Th17 pro-inflammatory cytokines production and alleviated renal damage by decreasing immunoglobulin complexes deposition, and inflammation-mediating enzymes	(93)

			• Presence of immunoglobulin G (IgG) and IgM immune complexes • Signaling pathways and oxidative-inflammatory-related mediators	expression. • Dietary OLE improved aortic endothelial dysfunction and vascular reactivity, normalizing endothelial nitric oxide synthase (eNOS) uncoupling, and NADPH oxidase-1 (NOX-1) overexpression.	
In vitro trial	Human and Mice	dietary taurine	• Serum Amino Acids Levels of Metabolism in SLE patients: Taurine, L-Histidine, L-Phenylalanine, L-Tryptophan • Expression of: IFN-α, IFN-β, TNF-α, ifit1 mRNA, ifr7 mRNA, mx1 mRNA, oas 1 mRNA, anti-dsDNA	• Metabolic abnormalities in SLE can dysregulate multiple immune cells. • Supplement of taurine promoted IFN-I induced genes' expression, activated lymphocyte, increased autoantibodies, and proteinuria, leading to more serious nephritis. • Taurine metabolism can aggravate	(108)

			• Proteinuria levels • IgG levels • ROS levels • NADP+/NADPH levels • MHC II & CD 86 expression levels • B cell and T cell count and Activity • SLEDAI	the progression of lupus by promoting the function of plasmacytoid dendritic cells.	


Identification of studies via databases and registers
Identification
Records identified from*:
Scopus (n= 1,193)
EBSCO (n= 964)
Pubmed (n= 1,293)
Duplicate records removed (n =1,567)
Screening
Records screened (n= 1,883)
Articles excluded (n= 765) based on the title and abstracts
Full text articles assessed for eligibility (n=1,118)
Reports excluded based on the full texts (n = 1,013)
Included
Studies included in review (n= 105)


PROTECTIVE DIETARY FACTORS
RISK-ENHANCING DIETARY FACTORS
Omega-3 PUFAs
B-cell
Plasma cell
Antibody production
High Vitamin D diet
Th-17
Treg
IL-10
IL-6
IL-17
TNF-α
Anti-inflammatory effect
Curcumin
NF-κB
Olive oil polyphenol
Antioxidants
Nrf-2 pathway
Oxidative stress
Wine polyphenol (Alcohol)
IMMUNE DYSREGULATION IN SLE
Autoantibodies production
C3 C4
Th17/Treg
Adipose tissue
High Carbohydrate/ sugar intake
Adipokine
IL-6
IL-17
TNF-α
Inflammatory effect
IL-10
Treg
Th-17
High sodium
Adipokine
Adipose tissue
TLR-7
Ultra-processed / High Fat Diet
Gut microbiota dysbiosis
Lactobacillus sp.