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An update on diet and nutritional factors in systemic lupus erythematosus management

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory and autoimmune disease characterised by multiple organ involvement and a large number of complications. SLE management remains complicated owing to the biological heterogeneity between patients and the lack of safe and specific targeted therapies. There is evidence that dietary factors can contribute to the geoepidemiology of autoimmune diseases such as SLE. Thus, diet therapy could be a promising approach in SLE owing to both its potential prophylactic effects, without the side effects of classical pharmacology, and its contribution to reducing co-morbidities and improving quality of life in patients with SLE. However, the question arises as to whether nutrients could ameliorate or exacerbate SLE and how they could modulate inflammation and immune function at a molecular level. The present review summarises preclinical and clinical experiences to provide the reader with an update of the positive and negative aspects of macro- and micronutrients and other nutritional factors, including dietary phenols, on SLE, focusing on the mechanisms of action involved.

Key words: Diet: Immunomodulation: Lupus: Nutrients: Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) can be defined as a chronic inflammatory and autoimmune disease that can affect multiple organ systems, including skin, joints, kidneys and the brain, among others[1]. The clinical heterogeneity of this remarkable and challenging disorder has required the establishment of eleven criteria with four needed for the formal diagnosis of SLE[2]. The action of pathogenic factors results in the generation of autoantibodies, immune complexes, autoreactive or inflammatory T cells and inflammatory cytokines that may initiate and amplify inflammation and damage to various organs, contributing to the clinical manifestations of SLE. Moreover, heritable, hormonal and environmental factors contribute to the expression of organ damage. SLE is characterised by a deposition of immune complexes, formed in large amounts as antinuclear antibodies bind to the abundant nuclear material in blood and tissues, along with disturbances in both innate and adaptive immunity manifest by disorders in cytokines, apoptotic cell clearance, B-cell immunity and T-cell signalling[3,4].

It is also characterised by its clinical and pathogenic complexity, difficult diagnosis and the high number of complications that can affect the patients' quality of life. The high morbidity and mortality associated with patients with SLE may be related to late diagnosis, problems in access to care, less effective treatments and poor adherence to therapeutic regimens[5].

SLE incidence has been estimated to range between 1 and 10 cases per 100 000 individuals per year, and the prevalence has been reported to range between 20 and 150 cases per 100 000 individuals worldwide with large regional and ethnic variations[6]. SLE is a disease that can affect both sexes, but more than 90% of new patients presenting with SLE are women in the childbearing years. In addition, although the disease may begin at any age, it appears most often at the end of the patients' second decade of life and at the beginning of the third decade[7]. SLE affects multiple systems and its presentation and course are highly variable, ranging from indolent to fulminant. The most common clinical manifestations include fatigue, loss of appetite and weight, cutaneous lesions (mainly malar rash), arthritis, serositis (pleuritis and/or pericarditis), renal or central nervous system involvement and haematological manifestations (cytopenias) associated with several autoantibodies, particularly antinuclear antibodies[5].

Additionally, patients with SLE show an increased risk of atherosclerosis and vascular events, which contribute to increase the morbidity and mortality of these patients. In SLE, autoantibodies and cytokines are able to modulate and decrease lipoprotein lipase activity, a key enzyme in lipid metabolism, producing the 'lupus pattern' of dyslipoproteinaemia characterised by elevated levels of VLDL and TAG and low HDL-cholesterol levels, which are directly correlated with SLE disease activity index (SLEDAI) scores[8]. The mechanisms underlying this enhanced risk are still not clear, but some

Abbreviations: 2-OH, 2-hydroxyestrone; 16α-OH, 16α-hydroxyestrone; Akt, protein kinase B; BAFF, B-cell activating factor; dsDNA, double-stranded DNA; EGCG, epigallocatechin gallate; ER, oestrogen receptor; EVOO, extra virgin olive oil; FOXP3, forkhead box P3; I3C, indole-3-carbinol; IFN, interferon; LPS, lipopolysaccharide; MRL, Murphy Roths large; Nrf-2, nuclear factor E2-related factor 2; NZB/W, New Zealand black/white; ppm, parts per million; SLE, systemic lupus erythematosus; Th, T-helper; Treg, regulatory T-cell.

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theories include excess of monocyte activation, dysregulation of the complement system, oxidative stress and production of different antibodies to endothelial cells, anti-atherogenic HDL, anti-lipoprotein lipase and oxidised LDL among others[4].

Systemic lupus erythematosus aetiology

The aetiology of SLE is not fully known. Genetics is thought to play a crucial role in the development of SLE, and multiple genes that contribute to the predisposition and susceptibility to SLE have been identified, including *IRF5*, *STAT4*, osteopontin, *IRAK1*, *TREX1* and *TLR8*, and genes related to interferon (IFN) production or implicated in the signalling mechanisms mediated by T (*PTPN22*, *TNFSF4*, *PDCD1*) or B (*BANK1*, *BLK*, *LYN*) cells[9]. In addition, recent studies have shown that several regions located in the major histocompatibility complex as well as *BsmI* and *FokI* polymorphisms contribute to increased SLE risk[10,11]. Environmental factors, including extreme stress, exposure to UV light, smoking, infections, administration of certain drugs (some antidepressants and antibiotics) and hormonal factors (oestrogen) can also contribute to the disease progression[12–14]. Nevertheless, over recent years, multiple lines of evidence have supported a major role of specific dietary factors, including vitamins, mineral elements, fatty acids and polyphenols, in the modulation of immune responses. Thus, an inadequate diet could constitute an important risk factor in SLE epidemiology[15–18].

The pathological hallmark of SLE is altered immune response with loss of B and T lymphocyte self-tolerance resulting in hyperactivity, autoantibody production (antinuclear antibodies, anti-double-stranded DNA (anti-dsDNA), anti-Ro, anti-histone, anti-Smith, anti-ribonucleoprotein and anti-ribosomal P protein, among others), aberrant immune complex formation and generation of a systemic inflammatory response in which multiple organs are involved: kidneys, heart, joints, skin, lungs, blood vessels, liver and nervous system[19]. The course of the disease is unpredictable, with periods of exacerbations and remissions[3]. Autoantibodies, immune complexes and an imbalance of T-helper-cell subsets (Th1/Th2/Th17) and regulatory T-cells (Tregs) contribute to tissue damage and could be responsible for an increased proinflammatory response, especially in the active form of the disease[20]. In particular, patients with active SLE exhibit high cytokine levels, including IFN-γ, TNF, IL-4, IL-6, IL-10, IL-12, IL-17 and IL-18 in serum and plasma; by contrast, IL-2 levels are lower in comparison with healthy controls[21]. In addition, recent research has associated SLE development with changes in the dendritic cell compartment[22]. Likewise, it has been suggested that γδ T cells may be involved in the regulation of SLE owing to their functions in cytokine secretion, antigen presentation and supporting B cells in antibody production[23]. On the other hand, many studies have demonstrated quantitative and/or qualitative defects of Tregs (phenotype $CD4^+$ CD25 high forkhead box P3 $(FOXP3)^+$) in patients with SLE as well as a reduction in the number of natural killer (NK) cells. Moreover, an enhanced Th17 cell response correlates with disease activity in patients with SLE, suggesting a role for IL-17 in the pathogenesis of the disease owing to its ability to amplify local inflammation by recruiting innate immune system cells and to stimulate the adaptive immune response in conjunction with B-cell activating factor (BAFF)[24,25]. The molecular signalling pathways involved in SLE include NF-κB, FOXP3, mitogen-activated protein kinase (MAPK), Janus kinase and signal transducer and activator of transcription (JAK/STAT) and, more recently, NLR family pyrin domain-containing 3 (NLRP3) inflammasome and nuclear factor E2-related factor 2 (Nrf-2) pathways[26–30]. The processes of adhesion, extravasation and subsequent activation of neutrophils in SLE are due to increases in the expression of intercellular adhesion molecule-1 (ICAM-1), endothelial adhesins, selectins and integrins. The secretion of proteases, reactive oxygen species and myeloperoxidase by the neutrophils then contributes to the cell damage[31]. Finally, an increased apoptotic burden that determines the recognition of apoptotic-derived autoantigens and hyperactivation of innate and adaptive immune system cells has been described in human SLE and murine models of the disease[32].

Aim of systemic lupus erythematosus treatment

Nowadays, the overall aim of SLE therapy is to control disease activity. Nevertheless, SLE management remains complicated owing to the biological heterogeneity between patients and the lack of safe and specific targeted therapies. Thus, the search for new therapeutic targets and strategies that can act more selectively on certain routes or biological processes and improve the course of disease or reverse the outbreak phase without generating collateral damage to unaffected tissues and organs is the pillar underlying current research in SLE.

Typical SLE management includes the use of antimalarial drugs (mainly hydroxychloroquine and chloroquine), immunosuppressive agents, biological agents and some adjunctive therapies following international recommendations[33]. Mild activity can be managed with non-steroidal anti-inflammatory drugs or low-dose glucocorticoids, but more severe manifestations require more advanced treatment[33–35]. Glucocorticoids act as anti-inflammatory and immunosuppressive agents, but they are associated with several severe side effects including osteoporosis, cataracts, hyperglycaemia and cognitive impairment, among others[36,37]. In particular, glucocorticoid therapy may increase the predisposition to obesity, leading to increased levels of proinflammatory cytokines that exacerbate the SLE symptoms and increase the risk of developing diabetes mellitus, hypertension and CHD symptoms. Moreover, the chronic use of corticosteroids in SLE is associated to an increase of total plasma cholesterol and its fractions (LDL and HDL) levels, and also TAG[8]. On the other hand, antimalarial drugs have shown beneficial effect on lipids and diabetes control in patients with SLE[38–40]. If glucocorticoid administration cannot be reduced or discontinued, the administration of immunosuppressive disease-modifying anti-rheumatic drugs, commonly mycophenolate mofetil, cyclophosphamide, azathioprine, calcineurin inhibitors (particularly tacrolimus and cyclosporine A) and methotrexate, is recommended, with a tailored treatment regimen for every patient[41,42]. However, the continuous use of immunosuppressive drugs may increase susceptibility to infections and gastrointestinal symptoms.

The increased knowledge about the aetiopathogenesis of SLE has enabled the use of biological agents specifically targeting the different pathways implicated in the disease[43]. Since B cell deregulation is one of the SLE hallmarks, B-cell-targeted therapies have become an important focus of SLE research. At present, belimumab, a monoclonal antibody that blocks BAFF, is the only approved biological drug for SLE, but other B-cell-targeted agents, such as rituximab, epratuzumab, blisibimod and tabalumab, are currently undergoing clinical evaluation, which has produced interesting results supporting their potential role in SLE treatment[44–49]. Abatacept, which acts by blocking interactions between T and B cells, has shown efficacy in lupus mouse models, but controversial results have been described in human controlled trials[50,51]. Moreover, high serum levels of IFN in patients with SLE have been correlated with SLE disease activity. Recently, anti-IFN therapies, specifically sifalimumab, rontalizumab, anifrolumab and AMG 811, have been investigated with promising results, but several hurdles in their development must still be overcome and further studies are requested to fully determine their effects in SLE[52].

Thus, although pharmacological treatment for SLE has improved during the last decade, and many potential new agents are in development, SLE and its treatments contribute to increased mortality rates and the outcome remains unoptimistic in a considerable percentage of patients[53].

Diet therapy and nutrients in systemic lupus erythematosus

Nutritional therapy, including diet modification and the use of nutritional supplements, could be a promising way to approach SLE owing to both its potential prophylactic effects, without the side effects of the classic pharmacological therapy, and its possible contribution to reducing co-morbidities and improving the quality of life of patients with SLE[54].

Diet quality in patients with SLE is important since these patients, in addition to being at higher risk of CVD, are also at higher risk of low bone mineral density, high blood homocysteine levels and anaemia, which are directly influenced by diet[55]. It is important to highlight that more than half of the patients with SLE present three or more risk factors for CVD (mostly obesity, hypertension and dyslipidaemias), been certainly more susceptible to suffer with the metabolic syndrome[56,57]. Moreover, obesity leads to increased levels of proinflammatory cytokines, which may exacerbate the inflammatory processes of SLE and increase the risk of diabetes mellitus, atherosclerosis and CHD[58]. Additionally, a hyperlipidic diet, rich in cholesterol and saturated fat, is one of the major risk factors for maintaining dyslipidaemia in patients with SLE, perpetuating and aggravating lipid profile changes[59]. Thus, we can suggest that the nutritional status and food intake of patients with SLE may interfere in the disease course and that an adequate diet may improve SLE prognosis and prevent several related diseases. Currently, a diet rich in vitamin- and mineral-rich foods and MUFA/PUFA with moderate energy consumption is recommended to control the inflammatory findings of the disease and the complications and co-morbidities resulting from SLE therapy[60,61].

The restriction of energy in the diet has, in particular, shown beneficial effects in murine lupus models. An initial study revealed that a 40 % food-restricted maize oil-based diet delayed the onset of autoimmunity in New Zealand black/white (NZB/W) F_1 lupus-prone mice[62]. Later studies demonstrated that energy restriction prevented the decline in $CD8^+$ T lymphocytes, eliminated the abnormal increase in IL-12, IFN-γ, IgA and IgG2 production, delayed the development of kidney disease and age-related immune dysfunction and prolonged the lifespan in aged NZB/W F_1 mice, probably owing to the down-regulation of mRNA expression or NF-κB[63,64].

In this regard, there is evidence that dietary factors can contribute to the geoepidemiology of autoimmune diseases[15]. Recent studies have suggested that the traditional Mediterranean diet might confer protection from certain chronic diseases related to oxidative stress, inflammation and the immune system. This diet emphasises the intake of vegetables, fruits, nuts, grains and fish, along with small amounts of wine and olive oil as the main monounsaturated fat source, and limits meat consumption. The beneficial effects of the Mediterranean diet have been proven in cancer, CVD, obesity and arthritis[65–67]. Likewise, epidemiological data have shown a lower prevalence of rheumatic diseases in Mediterranean countries when compared with Northern Europe, and some clinical trials have demonstrated that the Mediterranean diet improves rheumatic symptoms and decreases the use of anti-inflammatory drugs and classic pharmacotherapy-related side effects[68,69].

The broad range of evidence demonstrating the antioxidant, anti-inflammatory and immunomodulatory effects of some nutrients in immunoinflammatory diseases has suggested a possible supportive role for these nutrients in the primary and secondary prevention of SLE.

However, the question arises as to whether different nutrients could ameliorate or exacerbate SLE symptoms and how they could modulate inflammation and immune function at a molecular level. To this end, the present review summarises preclinical and clinical experiences to provide the reader with an update on the effects of different macro- and micronutrients and dietary phenols in SLE, focusing on the mechanisms of action involved (Tables 1, 2 and 3).

Methods: literature search strategy

A literature survey was conducted to obtain published literature to create this review. The original search was conducted in April 2016 and a second, updated search was completed in October 2016. We searched MEDLINE and SCOPUS (January 1976, to present) databases with the terms 'systemic lupus erythematosus' and 'lupus' in combination with the terms 'aetiology', 'apigenin', 'classification', 'carbinol', 'curcumin', 'diet', 'epidemiology', 'fibre', 'isoflavone', 'flavanols', 'flavones', 'flavonoids', 'flavonol', 'lignans', 'lipids', 'management', 'melatonin', 'mineral elements', 'natural products', 'nutrition', 'olive oil', 'pathogenesis', 'polyphenol', 'protein', 'resveratrol', 'stilbene', 'treatment', 'vitamins', with no language restrictions. We also searched the references of articles identified by this strategy and selected those that were relevant.

Table 1. Beneficial effects of macronutrients in systemic lupus erythematosus (SLE)

Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
Lipids				
n-3 PUFA				
Fish oil	Patients with SLE	Decreased SLEDAI, leptin and TAG	3 g/d	(77)
		Reduced erythrocyte sedimentation rate and serum IL-12 levels	Six capsules/d (2·25 g EPA and 2·25 g DHA)	(76)
		Increased serum IL-13 levels		
		Improved endothelial function	3 g/d	(78)
		Decreased platelet 8-isoprostanes		
		Increased EPA, DHA and HDL-cholesterol	6 g/d, washout period, 18 g/d	(195)
		Reduced platelet arachidonic acid, neutrophil leukotriene B_4, TAG and VLDL-cholesterol		
		Increased blood EPA concentration	20 g/d	(196)
	NZB/W F_1 mice	Decreased creatinine levels	5 % enriched diet	(197)
		Maintained GSH:GSSG ratio		
		Increased SOD, catalase, GPx, glutathione reductase and GST activities		
		Reduced total ROS and COX-derived ROS levels		
		Decreased co-stimulatory (CD80 and CD86) and adhesion (ICAM-1, PGP-1, LFA-1 and Mac-1) molecules in PBMC	5 % enriched diet	(198)
		Increased hepatic antioxidant enzymes: liver catalase, SOD and GPx	5 % enriched diet	(199)
		Decreased serum cholesterol, TAG and phospholipid and anticardiolipin antibody	180 g/kg enriched diet	(200)
		Decreased fibronectin-1, ICAM-1 and TGF-β1 mRNA levels and TGF-β1 protein in kidney	10 % enriched diet	(201)
		Decreased IL-1β, IL-6 and TNF-α in kidney	10 % enriched diet	(202)
		Increased antioxidant enzymes (catalase, GPx and SOD) in kidney		
		Decreased serum levels of four COX products	25 % enriched diet	(203)
	MRL/lpr mice	Increased IL-10 and IL-2 by spleen cells	9 % enriched diet	(204)
		Decreased IL-12, IL-4, PGE_2, leukotriene B_4 and thromboxane B_2 production by spleen cells		
		Decreased *c-myc* oncogene in spleen		
		Normalised TGF-β1 levels in spleen cells		
		Reduced production of tetraene leukotrienes	20 % enriched diet	(205)
		Enhanced production of pentaene leukotrienes in supernatant fractions from peritoneal macrophages and kidney		
	BXSB/MpJ and MRL/lpr mice	Decreased proteinuria and renal disease	25 % enriched diet	(206)
DHA-enriched fish oil	NZB/W F_1 mice	Decreased plasma autoantibodies, proteinuria and glomerulonephritis	60 g/kg enriched diet	(80)
		Down-regulated $CD4^+$ T-cell-related genes in kidney and/or spleen		
		Reduced expression of CD80, CTLA-4, IL-10, IL-18, CCL-5, CXCR3, IL-6, TNF-α and osteopontin mRNA in kidney and/or spleen		
		Decreased serum anti-dsDNA antibodies, kidney IgG deposition and LPS-induced IL-18 in serum and caspase 1 in kidney	9 % enriched diet	(81)
		Suppressed LPS-mediated PI3K, Akt and NF-κB activation in kidney		
Concen-trated fish oil (Lovaza®)	NZB/W F_1 mice	Decreased anti-dsDNA antibodies, IL-1β, IL-6 and TNF-α in splenocytes and kidney, serum TAG and liver adiposity	4 % enriched diet	(207)
		Increased renal antioxidant enzymes GPx and catalase activity		
		Down-regulated NF-κB activation		
n-6 PUFA				
Evening primrose oil	MRL/lpr mice	Decreased serum anti-dsDNA antibodies, proteinuria and clinical features	5 % enriched diet	(208)
Maize oil, soyabean oil, ruminant meat	MRL/lpr mice	Reduced oxidative stress	30 mg/d by oral administration	(88)
		Enhanced detoxifying enzyme activity (GST, NQO1 and γGCS).		
		Enhanced nuclear translocation of Nrf-2 in liver		
		25 μM: enhanced GCLC expression and intracellular GSH concentration in splenocytes	25 and 100 μM	(87)
		100 μM: down-regulated IFN-γ synthesis and cell proliferation and decreased apoptosis induction and intracellular thiols (GSH, GSSG) in splenocytes		
		Decreased anti-dsDNA and anti-tTG IgG, IL-4, IL-10 and IFN-γ mRNA and down-regulated NF-κB activity and apoptosis induction in spleen cells	30 mg/d by oral administration	
	NZB/W F_1 mice	Decreased SLE symptoms	0·5 % enriched diet	(89)
		Increased survival		
MUFA				
Extra virgin olive oil	Pristane BALB/c mice	Decreased serum MMP-3 and PGE_2 in kidney and proinflammatory cytokine production in spleen cells	100 g/kg diet	(103)
		Ameliorated Nrf-2, HO-1, JAK/STAT, MAPK and NF-κB pathways in kidney		

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Table 1. *Continued*

Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
Proteins Royal jelly	NZB/W F_1	Reduced IL-10, anti-ssDNA and anti-erythrocyte surface antigen level Decreased number of splenic autoreactive B cells Increased survival	2 mg by oral administration	(106)
Amino acids: taurine Eggs, meat, seafood	NZB/W F_1	Reduced cardiac abnormalities Increased fibrotic signalling molecules and IGF1R survival signalling components Reduced caspase-3 activity, TUNEL-positive cells and Fas- and mitochondrial-dependent apoptosis Increased Akt, ERK1/2 and p65 NF-κB phosphorylation Decreased p38 phosphorylation	1 % enriched diet 1 % enriched diet	(107) (108)
Fibre Beans, cereals, whole grains, vegetables	Patients with SLE	Decreased risk of active disease by decreasing levels of some cytokines and homocysteine	>4·7 g soluble fibre or >14 g insoluble fibre/d	(111)

Akt, protein kinase B; CCL-5, chemokine (C-C motif) ligand 5; COX, cyclo-oxygenase; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; CXCR3, C-X-C motif chemokine receptor-3; dsDNA, double-stranded DNA; ERK, extracellular signal-regulated protein kinase; GCLC, γ-glutamylcysteine ligase catalytic subunit; γGCS, γ glutamyl cysteine synthetase; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidised glutathione; GST, glutathione-*S*-transferase; HO-1, haem oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IGF1R, insulin-like growth factor receptor-1; IFN, interferon; JAK, Janus kinase; LFA-1, lymphocyte function-associated antigen-1; LPS, lipopolysaccharide; Mac-1, macrophage-1 antigen; MAPK, mitogen-activated protein kinase; MMP-3, metalloproteinase-3; MRL, Murphy Roths large; NQO1, NAD(P)H: quinone oxidoreductase-1; Nrf2, nuclear factor E2-related factor-2; NZB/W, New Zealand black/white; PBMC, peripheral blood mononuclear cell; PGP-1, permeability glycoprotein-1; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SLEDAI, SLE disease activity index; SOD, superoxide dismutase; ssDNA, single-stranded DNA; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; tTG, tissue transglutaminase; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling.

Macronutrients in systemic lupus erythematosus

Lipids

Among traditional atherosclerotic risk factors in SLE, dyslipidaemia is believed to decisively affect the long-term prognosis of patients with SLE, not only with regard to cardiovascular events but also by influencing other manifestations, such as lupus nephritis and brain damage among others[70]. Therefore, dyslipidaemia in SLE should be prompt and adequately treated in order to reduce overall morbidity and mortality and improve patients' quality of life. Moreover, dyslipaemia is considered as a modifiable risk factor that can be managed with an accurate treatment, which includes the promotion of a healthy and varied diet[70–72].

Specifically, there is both preclinical and clinical evidence that patients with SLE may benefit from the consumption of certain lipids. In particular, the *n*-3 PUFA possess the most potent immunomodulatory activity; among them, EPA and DHA are the most biologically active. These *n*-3 PUFA suppress proinflammatory cytokine production, lymphocyte proliferation, cytotoxic T-cell activity, macrophage-mediated cytotoxicity and neutrophil/monocyte chemotaxis[73]. Some of the effects of *n*-3 PUFA are produced by the modulation of the amount and types of eicosanoids, but other effects have eicosanoid-independent mechanisms, including modulation of intracellular signalling pathways, transcription factor activity and gene expression[74]. As humans and other mammals require PUFA but cannot synthesise them, the consumption of PUFA through the daily diet is essential. The available data show that an increased daily intake of dietary *n*-3 PUFA decreased the severity of autoimmune disorders. A low intake of *n*-3 PUFA and high intake of carbohydrate in SLE appear to be associated with worse disease activity, adverse serum lipids and plaque presence[75]. Similarly, consumption of fish oil, which is rich in *n*-3 PUFA, has been shown to be useful in preventing and/or ameliorating SLE symptomatology. In fact, different clinical studies have assessed the association between dietary supplements and fish oil in patients with SLE, revealing a number of positive effects, including reducing cardiovascular, inflammatory and neuromotor symptoms and improving depressive symptoms and fatigue[76–79]. In addition, *n*-3 PUFA from fish oil have demonstrated anti-inflammatory effects when used as supplements in murine SLE models, decreasing autoantibody production and inflammatory gene expression in the kidney and spleen, suppressing glomerulonephritis and extending lifespan[80,81]. However, a major question in the use of PUFA is whether the doses required to suppress autoimmunity and inflammation could have a negative impact on innate and adaptive immune responses against pathogens or neoplastic events[82].

Conjugated linoleic acid (CLA) is the term used to describe positional and geometric isomers of the *n*-6 PUFA linoleic acid (18 : 2*n*-6). The main sources of CLA in the human diet are ruminant meat and dairy products, which are extensively used in Western diets, but it can be also found in small amounts in oils derived from plants[83,84]. CLA has shown potential anti-inflammatory and cancer-preventive properties, most probably through its ability to modify eicosanoid signalling by altering cell membrane composition and modulate genes through PPAR[85,86]. CLA has shown beneficial effects in SLE mouse

Table 2. Beneficial effects of micronutrients in systemic lupus erythematosus (SLE)

Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
Vitamins				
Vitamin A				
Carrot, sweet potato, fish, spinach, liver, tropical fruits	Patients with SLE	Decreased Th17 cells	0·3 μg/ml retinoic acid	(118)
		Increased Treg percentages in $CD4^+$ T cells cultures from hypovitaminosis A patients		
		Decreased proteinuria	10 mg/d ATRA	(116)
	NZB/W F_1 mice	Reduced IL-2, IFN-γ and IL-12 and IL-4 in serum	0·1 mg ATRA i.p.	(117)
		Improved survival and proteinuria		
		Suppressed iNOS and MCP-1 in kidney		
		Reduced IgG2-specific anti-DNA antibody		
		Improved survival, splenomegaly, proteinuria and renal pathological findings and serum anti-DNA levels	0·5 mg ATRA i.p.	(116)
		Reduced IFN-γ, IL-2 and IL-10 in splenic $CD4^+$ T cells		
	MRL/lpr mice	Reduced dermal thickness	5–10 mg/kg etretinate by oral administration	(120)
		Suppressed appearance of skin lesions by inducing apoptosis and regulation of cytokine expression		
		Reduced lymphoproliferation and glomerulonephritis	10 mg/kg per d	(119)
Vitamin B_6				
Fish, beef, liver, potatoes, fruits, cereals	Patients with SLE	Suppressed active inflammation and prevented the occurrence of SLE flares	>1·7 mg/d	(111)
Vitamin C				
Fruits, broccoli, tomatoes	Patients with SLE	Decreased lipid peroxidation	500 mg/d	(143)
		Decreased risk of active disease	109·99 mg/d	(60)
Vitamin D				
Animal-based foods, fish oil, mushrooms	Patients with SLE	Decreased IL-17A-producing T cells increasing FOXP3 expression	2000, 4000 or 50000 IU/week for 6 months	(131)
		Reduced IL-6 secretion	400000 and 20000 IU/week	(135)
		Augmented angiogenic capacity and paracrine regulation of endothelial NOS		
		Decreased disease activity	50000 IU/week	(136)
		Improved fatigue in juvenile-onset SLE		
		Regulatory effects on apoptosis and cell cycle progression in PBMC	50 nM	(134)
		Up-regulated expression of *Bcl-2*		
		Down-regulated expression of *Bax* and FasL		
		Decreased endothelial cell early apoptosis through inhibition of externalised neutrophil elastase in neutrophils	10 nM	(209)
		Inhibited DC maturation, decreased CD40, CD86 and HLA-DR expressions and cytokine secretion of IL-12p70	10 nM	(128)
		Decreased percentage of Th17 cells and IL-17A levels in $CD4^+$ T cells		
		Restored immune homeostasis through inhibitory effects on DC maturation and activation.	10 nM	(210)
	BALB/c mice with activated chromatin	Reduced IL-6 and IL-10 mRNA expression	50 ng/d by oral administration	(133)
		Increased TGF-β and FOXP3 mRNA expression		
		Enhanced Treg percentage in spleen		
	MRL/lpr mice	Reduction of proteinuria and serum anti-ssDNA	0·1 μg–0·15 μg/d i.p	(132)
Vitamin E				
Sunflower seeds, almonds, groundnuts, cereals, spinach, asparagus, avocado	Patients with SLE	Suppressed anti-dsDNA autoantibody production via antioxidant activity independent mechanism	150–300 mg/d	(141)
		Decreased lipid peroxidation	800 IU/d	(143)
	NZB/W F_1 mice	Increased survival	250 mg/kg enriched diet	(140)
		Increased IL-2 in splenocytes		

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Table 2. *Continued*

Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
		Decreased oxidative stress and anti-dsDNA antibodies	275 mg/kg enriched diet	(139)
		Regulated cytokines and lymphocyte subsets		
	MRL/lpr mice	Improved survival and proteinuria	0·4 mg/d five times per week	(211)
		Normalised mitogenic responses of B and T cells		
		Decreased anti-dsDNA antibodies and amyloid P component in serum		
Mineral elements				
Se				
Plants, grains	NZB/W F_1 mice	Improved survival	4 ppm in water	(144)
		Increased natural killer cell activity		

ATRA, all-*trans*-retinoic acid; Bax, BCL2 associated X protein; Bcl-2, B-cell lymphoma 2; DC, dendritic cell; dsDNA, double-stranded DNA; FasL, Fas ligand; FOXP3, forkhead box P3; HLA-DR, human leucocyte antigen – antigen D related; IFN, interferon; iNOS, inducible NO synthase; i.p., intraperitoneally; MCP-1, monocyte chemoattractant protein-1; MRL, Murphy Roths large; NOS, NO synthase; NZB/W, New Zealand black/white; PBMC, peripheral blood mononuclear cell; ppm, parts per million; ssDNA, single-stranded DNA; TGF, transforming growth factor; Th, T-helper; Treg, regulatory T cell.

models, reducing splenomegaly, autoantibody and cytokine production, NF-κB activity (independent of PPAR-γ activation) and oxidative stress, thus improving SLE symptoms and survival rates[87–89]. Moreover, some animal studies have shown that CLA consumption has anti-sclerotic and anti-oxidative effects and improves the blood lipid profile, which could be also beneficial for SLE[90,91]. On the other hand, a previous study suggested that dietary CLA may accelerate the appearance of autoimmune symptoms in NZB/W F_1 mice, despite protecting against disease-related body-weight loss and prolonged survival[92]. By the way, only a few studies examined the effects of CLA in human subjects *in vivo* and their results do not show the favourable results observed in animal studies[93–95]. In this sense, the majority of the clinical studies did not provide conclusive evidence for the effectiveness of CLA on human health, except for anti-obesity properties[96,97]. Although the interest in CLA still remains, there are multiple questions related to the safety and efficacy on its consumption that must be scientifically solved[98].

Controversially, an essential fatty acid-deficient diet has shown beneficial effects in NZB/W F_1 mice by reducing levels of arachidonic acid (20 : 4*n*-6), a precursor of proinflammatory eicosanoids, PG and leukotriene metabolites, decreasing autoantibody production and improving nephritis[99]. Furthermore, an increased intake of *n*-6 PUFA may increase the production of proinflammatory cytokines and the incidence of autoimmune diseases by increasing free radicals and decreasing antioxidant enzyme mRNA levels[100].

Recent experimental and clinical studies have confirmed that regular extra virgin olive oil (EVOO) consumption can exert positive effects in rheumatic diseases[101,102]. The beneficial properties of EVOO are linked to its high MUFA content and also to its multiple minor components, particularly polyphenol compounds such as flavonoids, lignans and secoiridoids and their hydrolysis products (hydroxytyrosol and tyrosol, among others). Recently, we evaluated the effects of an EVOO diet in a pristane-induced SLE model in mice, and we demonstrated that the EVOO diet significantly reduced renal damage and decreased metalloproteinase (MMP)-3 serum and PGE_2 kidney levels as well as proinflammatory cytokine production in splenocytes. In addition, our data indicated that Nrf-2 and haem oxygenase protein expression was up-regulated by the EVOO diet and that the activation of the Janus kinase and signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinases (MAPK) and NF-κB pathways was markedly ameliorated, supporting the interest in EVOO as a beneficial functional food exerting a preventive/palliative role in the management of SLE[103].

Proteins

The restriction of dietary protein has been shown to have beneficial effects in controlling renal disease progression in animal models and human studies. Specifically, a protein-restricted diet (0·6 g/kg per d) improved nutritional status and glomerular filtration rate in patients with SLE with chronic kidney disease[104]. In addition, excessive protein intake has been shown to produce bone mineral loss in patients with juvenile SLE[105]. By contrast,

Table 3. Beneficial effects of phenolic compounds in systemic lupus erythematosus (SLE)

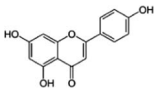
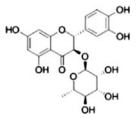
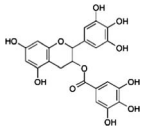
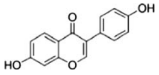
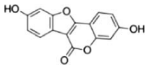
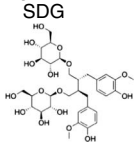
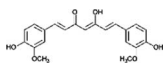
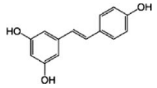
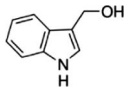
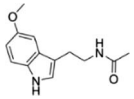
Phenol	Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
Polyphenols					
Flavonoids					
Flavones					
Apigenin 	Parsley, thyme, peppermint, chamomile olives	SNF1 mice	Suppressed IFN-γ response and anti-dsDNA, anti-ssDNA, anti-nucleosome and anti-histone autoantibody production in splenocytes Decreased IL-6 production by DC Suppressed IFN-γ and IL-17 production in antigen-presenting cells Induced apoptosis of T cells, B cells, DC and macrophages Reduced IFN-γ and IL-17 in splenocytes Decreased anti-dsDNA, anti-ssDNA, anti-nucleosome and anti-histone autoantibodies in serum and spleen cells Improved lupus nephritis Reduced COX-2 expression in antigen-presenting cells, $CD4^+$ T cells, B cells, DC and macrophages	0·3–100 μM 20 mg/kg per d i.p.	(150)
Flavonols					
Astilbin 	Grapes, *Smilax glabra*	MRL/lpr mice	Reduced serum antinuclear antibodies and cytokines (IFN-γ, IL-17A, IL-1β, TNF-α and IL-6) Decreased functional activated T and B cells from splenocytes Improved renal damage	10, 20 or 40 mg/kg enriched diet	(153)
Flavanols					
EGCG 	Green tea	NZB/W F_1 mice	Decreased ROS levels in serum, urine and kidney Prevented proteinuria and maintained renal function Increased Nrf-2 and NF-κB pathways and GPx in kidney Inhibited renal NLRP3 inflammasome expression Decreased mature caspase-1, IL-1β and IL-18 in kidney and IL-1β and IL-18 levels in serum Enhanced splenic regulatory Treg activity	120 mg/kg enriched diet	(159)
		MRL/lpr mice	Activated AMPK Blocked induced expression of iNOS and production of NO and IL-6 Attenuated inflammation via PI3K/Akt/mTOR pathway by decreasing Akt phosphorylation in mesangial cells	50 μM	(160)
			Decreased lymph node hyperplasia, fatty accumulation, proteinuria and blood urea N Increased survival Decreased serum levels of anti-DNA antibodies and kidney immune complexes Improved glomerulonephritis and nephric vasculitis	2 % green tea-enriched diet	(158)
		Human primary epidermal keratinocytes	Down-regulated the expression of antinuclear autoantibodies SS-B/la and SS-A/Ro, coilin, DNA topoisomerase I and α-fodrin	100 μM	(161)
Isoflavones					
Daidzein 	Soya beans	MRL/lpr mice	Improved body weight and survival Decreased anti-dsDNA IgG and anticardiolipin IgG serum levels Decreased *in vitro* IFN-γ production on mitogen-stimulated T cells from spleen	20 mg soya isoflavones/kg BW/d by oral administration	(163)
Coumestrol 	Lucerne, soya beans, Brussels sprouts, spinach, legumes	MRL/lpr mice	Delayed the onset of proteinuria Improved renal function and survival Suppressed TNF-α and IL-1β from LPS-stimulated peritoneal exudate cells and IFN-γ and IL-4 from concanavalin A-stimulated splenocytes	25 mg lucerne sprout ethyl acetate extract/kg BW by oral administration	(170)
		BALB/c mice	Reduced serum levels of TNF-α, IL-6, and IL-1β and improved survival after 9 h of LPS challenge Inhibited IL-6 and TNF-α production in LPS-primary macrophages	25 mg lucerne sprout ethyl acetate extract/kg BW by oral administration 50 μg/ml	(169)
		NZB/W F_1 mice	Decreased splenomegaly and proteinuria	0·01 % enriched diet	(168)

Table 3. *Continued*

Phenol	Source	Experimental system	Mechanism(s) of action	Effective dose	Reference
Lignans					
SDG 	Flax, pumpkin, sunflower, sesame seeds	Patients with SLE	Decreased serum creatinine and microalbumin	30 g ground flaxseed/d	(177)
			Improved renal function, decreasing serum creatinine, plasma lipids, blood viscosity and increasing complement C3 l	30 g ground flaxseed/d	(176)
		MRL/lpr	Decreased proteinuria and improved renal function	600, 1200 and 4800 μg by oral administration	(175)
			Improved survival Delayed and decreased proteinuria and splenic lymphocyte proliferation Attenuated glomerular filtration and lymphoproliferation	15 % flaxseed-enriched diet	(174)
Diarylheptanoids and arylalkanones					
Curcumin 	*Curcuma longa* L.	Patients with SLE	Modulated Th17/Treg balance of $CD4^+$ T cells by reducing Th17 response and IL-17A production and increasing Treg differentiation and TGF-β1 production	0·1 and 1 μg/ml	(178)
			Decreased proteinuria levels and systolic blood pressure	22·1 mg three times/d	(181)
		MRL/lpr	Delayed onset of anti-RNP, anti-Sm, ANA and anti-dsDNA autoantibodies and proteinuria Decreased salivary gland infiltration and lymphadenopathy	5 mg/ml in water	(179)
		NZB/W F_1 mice	Decreased proteinuria, serum levels of IgG1, IgG2a and anti-dsDNA and IgG glomeruli immune complex deposition Reduced TNF-α and MCP-1 in kidney and FOXP3 in spleen	1 % enriched diet	(180)
Stilbenes					
Resveratrol 	Grapes	Pristane BALB/c mice	Decreased proteinuria, IgG and IgM Ig deposition in kidney and glomerulonephritis and serum IgG1 and IgG2a	50–75 mg/kg enriched diet	(184)
			Suppressed CD69 and CD71 expression on $CD4^+$ T cells, $CD4^+$ T cell proliferation, induced $CD4^+$ T cell apoptosis, decreased CD4 IFN-γ+ Th1 cells and Th1:Th2 ratio in splenic mononuclear cells Inhibited IgG1, IgG2a, IgG2b, IgG3, IgM and IgA antibody production and proliferation of stimulated B lymphocytes from splenic mononuclear cells	0, 10, 20, 40 or 80 μM	
Indole-3-carbinol 	Cruciferous vegetables	NZB/W F_1	Increased lifespan	0·2 g/kg enriched diet	(185)
			Decreased proteinuria, glomerulonephritis and interstitial nephritis Decreased proteinuria and renal abnormalities and prolonged survival Decreased anti-dsDNA, anti-chromatin and anti-RNA helicase A antibody levels Increased 2-OH:16α-OH ratio metabolites Blocked B- and T-cell maturation	2000 ppm enriched diet	(186)
		Patients with SLE	Changed urinary ratio of 16α-OH:2-OH by an increase of 2-hydroxylation	375 mg/d	(187)
Melatonin 	Fruits, vegetables, olive oil and nuts	Patients with SLE	Increased number of Tregs expressing FOXP3 and BAFF mRNA expression	1×10^{-4} M	(194)
		Pristane BALB/c mice	Antagonised increasing levels of IgM, anti-ssDNA and histone autoantibodies Decreased renal lesions Decreased induced IL-6 and IL-13 production Increased IL-2 levels in stimulated splenocytes	0·01, 0·1, 1·0 mg/kg intragastric	(193)
		MRL/lpr mice	Decreased serum IgG, IgM, anti-dsDNA and anti-CII autoantibodies, cytokines (IL-2, IL-6, IFN-γ, TNF-α, and IL-1β) and nitrite/nitrate production in females Increased IL-10 in females	30 mg melatonin/kg BW in water	(191)

2-OH, 2-hydroxyestrone; 16α-OH, 16α-hydroxyestrone; Akt, protein kinase B; AMPK; adenosine 5'-monophosphate-activated protein kinase; ANA, antinuclear antibodies; BAFF, B-cell activating factor; BW, body weight; COX, cyclo-oxygenase; DC, dendritic cell; dsDNA, double-stranded DNA; EGCG, epigallocatechin gallate; FOXP3, forkhead box P3; GPx, glutathione peroxidase; IFN, interferon; iNOS, inducible NO synthase; i.p., intraperitoneally; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MRL, Murphy Roths large; mTOR, mammalian target of rapamycin; NLRP3, NLR family pyrin domain containing 3; Nrf-2, nuclear factor E2-related factor-2; NZB/W, New Zealand black/white; PI3K, phosphoinositide 3-kinase; ppm, parts per million; RNP, ribonucleoprotein; ROS, reactive oxygen species; SDG, secoisolariciresinol diglucoside; SNF, sucrose non-fermenting; ssDNA, single-stranded DNA; TGF, transforming growth factor; Th, T-helper; Treg, regulatory T cell.

oral supplementation with royal jelly, a honeybee secretion rich in proteins, free amino acids, SCFA and vitamins, has also been considered beneficial because its reduces cholesterol and has immunomodulating and anti-inflammatory activities. In fact, the intake of 2 mg of protein from royal jelly induced a reduction of IL-10, anti-single-stranded DNA and anti-erythrocyte surface antigen autoantibody serum levels, decreased the number of splenic autoreactive B cells and increased survival in NZB/W F_1 mice, suggesting a beneficial effect in preventing the early onset of SLE and in controlling the active progression of SLE manifestations[106].

Taurine, the major intracellular free β-amino acid in most mammalian tissues, is obtained largely from the diet through eggs, meat and seafood, and it plays crucial roles in protecting biological systems owing to its antioxidant, anti-inflammatory and anti-apoptotic properties. The potential benefits of taurine intake in SLE have been demonstrated in an *in vivo* model of NZB/W F_1 mice fed with a cholesterol-rich diet supplemented with taurine (1 %); taurine supplementation ameliorated cardiac abnormalities with reductions in aggravated histopathological changes, Fas- and mitochondrial-dependent apoptosis and fibrotic signalling molecules and an increase in insulin-like growth factor receptor 1 survival signalling components[107]. In another study with NZB/W F_1 mice that were fed a cholesterol-rich diet supplemented with taurine (1 %), taurine significantly reduced caspase-3 activity, terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL)-positive cells and Fas- and mitochondrial-dependent apoptosis, increased phosphorylation of protein kinase B (Akt), extracellular signal-regulated protein kinases 1 and 2 and p65 NF-κB proteins and decreased phosphorylation of p38 protein in the liver. These results strongly suggest the therapeutic potential of taurine intake in SLE management[108]. By contrast, an increased intake of the amino acid L-arginine increased the severity of renal fibrosis and the likelihood of death in Murphy Roths large (MRL)/lpr mice by enhancing cytotoxic NO generation via inducible NO synthase (iNOS)[109]. Moreover, a diet with restricted phenylalanine and tyrosine had beneficial effects on NZB/W F_1 mice by decreasing autoantibody production[110].

Fibre

An adequate intake of dietary fibre is recommended in SLE because of the beneficial effects of fibre in decreasing cardiovascular risk, promoting gut mobility and reducing serum levels of inflammation markers such as C-reactive protein, cytokines and homocysteine. A study with 279 women with SLE showed an inverse association between dietary fibre intake and SLE; increased dietary fibre decreased the risk of active disease in patients with SLE by decreasing the levels of some cytokines and homocysteine[111]. However, excessive fibre intake may reduce the absorption of vitamins, minerals and proteins[59].

Micronutrients

Vitamins

Several epidemiological studies have explored the potential role of antioxidant nutrient intake and supplementation in patients with SLE. In SLE, oxidative stress acts as an autoimmunity trigger that contributes to immune system dysregulation, abnormal apoptotic events and autoantibody production. Levels of oxidative stress have been shown to be correlated with SLE disease activity and organ damage in patients and in SLE-prone mouse models[112,113]. In addition to spreading inflammation through the bloodstream, mediators of oxidative stress contribute to organ damage, including the cardiovascular system, kidneys and skin. Thus, suppressing pathways of oxidative stress may reduce the toxicity of immunosuppressive therapies, decrease disease activity and improve the quality of life of patients with SLE[114].

Vitamin A is essential for multiple functions, including the maintenance of immune system integrity, and its physiological form, all-*trans*-retinoic acid (ATRA), regulates gene transcription by binding to nuclear retinoic acid receptors. ATRA has demonstrated paradoxical effects on the development of autoimmune lupus in the MRL/lpr mouse, decreasing inflammation in some organs while generating more severe disease in others[115]. However, ATRA has also shown beneficial effects, alone or in combination with low-dose immunosuppressive drugs, in lupus nephritis and cytokine modulation in both mouse models and patients with SLE, suggesting that ATRA treatment significantly alleviates hyper-reactive autoimmune and renal disorder, most likely via cytokine regulation[116–119]. Furthermore, oral treatment with etretinate, a synthetic vitamin A derivative, every 2 d for 2 months in lupus mice reduced dermal thickness through the inhibitory effects on collagen synthesis and inhibited skin lesions by inducing apoptosis in dermal infiltrating cells and, perhaps, regulating cytokine production[120].

Higher serum levels of homocysteine are associated with atherosclerotic vascular events in patients with SLE. In this sense, an increase of one log unit of homocysteine concentrations led to a 2·4-fold increase in the risk of stroke, and a 3·5-fold increase in the risk of arterial thrombosis in SLE[121]. In this regard, dietary intake of vitamin B_6, which has been shown to decrease homocysteine levels and acts as a coenzyme in the metabolism of antibodies and cytokines, decreased the risk of active SLE in female patients, suggesting that its daily intake may lead to the suppression of active inflammation and prevent the occurrence of SLE flares. However, in the present study there was no significant association between B_6 intake and a decreased risk of atherosclerotic vascular events[111].

Vitamin C may mediate the oxidative stress response in SLE and, consequently, exert beneficial effects on the repair of abnormal immune components and inflammation. Vitamin C intake (500 mg/d for 6 weeks) may positively modulate oxidative DNA damage in healthy subjects, but these positive effects were not observed in patients with SLE. These significant differences in the response to vitamin C supplementation between patients with SLE and healthy subjects might be associated with DNA repair abnormalities observed in SLE[122]. Another study reported that vitamin C intake (109·99 mg/d) is inversely associated with the risk of active SLE, decreasing oxidative stress and suppressing autoantibody production, suggesting that its intake may prevent the occurrence of SLE flares[60].

Vitamin D is found in small quantities in eggs, fatty fish, and supplemented dairy products; however, the main source of vitamin D is sunlight exposure[123].Vitamin D has a critical role in Ca homeostasis, mineralisation of bone tissue, muscle

function and coordination. Indeed, low levels of vitamin D result in a decrease of the Ca reserves in bone in an attempt to correct for the reduced Ca that will be absorbed from the gut[124]. Nowadays it is clear that vitamin D deficiency contributes to the morbidity and mortality of multiple chronic diseases, including SLE[125]. Particularly, vitamin D deficiency is even more prevalent in patients with SLE than in the general population, in part because patients with SLE are recommended to avoid the sun, in order to prevent disease flares[126]. In this sense, some studies have shown that vitamin D deficiency increases predisposition to suffer SLE partly owing to the photosensitive nature of the disease, exacerbates symptoms, decreased bone health and it is correlated with the disease activity[127–129]. Moreover, in a study with adolescent women with SLE supplemented with Ca and vitamin D (400–800 IU daily), a lack of vitamin D was associated with a decrease of bone mineral density, highlighting the importance of well-defined vitamin D supplementation protocols in SLE[130]. Vitamin D supplementation (2000, 4000 or 50000 IU weekly for 6 months) in patients with SLE showed positive immunological effects by decreasing IL-17A-producing T cells and increasing FOXP3 expression, confirming the relationship between vitamin D status and immunological balance[131]. Furthermore, vitamin D consumption attenuated the disease progression and increased the number of regulatory T cells in mouse models[132,133]. In patients with SLE, *in vitro* treatment with vitamin D (50 nM) has regulatory effects on apoptosis and cell cycle progression and modifies the expression levels of apoptotic genes[134]; in addition, vitamin D intake (400 000 IU followed by 20 000 IU weekly for 12 weeks) can positively modulate endothelial function in patients with stable SLE, reducing cardiovascular risk[135]. Moreover, vitamin D supplementation (50 000 IU per week for 24 weeks) has been shown to be effective in decreasing disease activity and improving fatigue in juvenile-onset SLE[136]. Therefore, vitamin D supplementation is currently recommended as a treatment for some patients with SLE, although determining the effectiveness and safety of vitamin D use as a treatment in SLE, as well as establishing the exact doses, still requires additional extensive interventional studies[137]. Nevertheless, general international recommendations have established that vitamin D supplementation with 800 to 1000 IU/d or 50000 IU monthly is safe for most individuals and can ensure levels of vitamin D within the optimal range. This intake is within the currently recommended safe upper tolerable limit for vitamin D of 2000 IU/d for those aged 1 year and older[138].

Vitamin E is a potent free radical and peroxyl radical scavenger and an essential nutrient for maintaining the normal function of the immune system. A diet supplemented with vitamin E decreased oxidative stress and anti-dsDNA antibody production, regulated cytokines and lymphocyte subsets and alleviated the severity of SLE under oxidative stress in NZB/W F_1 mice[139]. However, while low vitamin E supplementation increased the survival of MRL/lpr mice, high supplementation had the opposite effect and inhibited the Th1 pathway, which may not be beneficial for Th2-prone autoimmune diseases, such as SLE. This duality might be due to selective modulation through PGE_2 production or through PPARγ, inhibitor of NF-κB (IκB-α) and apoptotic pathways under different doses of vitamin E[139,140]. In patients with SLE, the oral administration of vitamin E (150–300 mg/d) together with prednisolone decreased autoantibody production but not the urinary levels of 8-hydroxydeoxyguanosine, an indicator of oxidative DNA damage, suggesting that vitamin E can suppress autoantibody production via a mechanism independent of antioxidant activity[141].

Despite the aforementioned evidence, a survey study showed that the dietary intake of antioxidant nutrients, including vitamins A, C and E, α-carotene, β-carotene, cryptoxanthin, lycopene and lutein, from foods and supplements does not change the risk of developing SLE in women, suggesting that antioxidants do not offer protection against SLE[142]. In addition, a study investigating the effects of vitamin E and C supplementation (500 mg vitamin C and 800 IU vitamin E daily) on endothelial function and markers of oxidative stress and antioxidant defence in patients with SLE showed that their combined administration decreased lipid peroxidation but did not affect endothelial function after 3 months of therapy[143]. Insufficient dosing and/or the inability of these vitamins to regulate intracellular signalling pathways within the immune system may explain this lack of therapeutic efficacy.

Mineral elements

Se, a trace mineral widely distributed in plants and grains, is a required nutrient for animals and humans that has been shown to have immunological and anti-inflammatory properties. Se supplementation (sodium selenite 4 parts per million (ppm) in the drinking water) demonstrated beneficial effects in female NZB/W F_1 mice, improving survival and increasing natural killer (NK) cell activity. However, Se supplementation had no effect on autoantibody production[144].

Nowadays, it is recommended that patients with SLE follow a Na-restricted diet because evidence suggests that excess sodium chloride content in the diet might be a potential risk factor for autoimmune diseases. A study in MRL/lpr mice demonstrated that excessive dietary sodium chloride intake aggravated lupus nephritis through the effect of the inducible serine/threonine protein kinase 1 pathway on the Th1/Th2 and Th17/Treg balance *in vivo*[145].

Dietary restriction of Zn also has shown beneficial effects in SLE. Moderate (5·0 ppm daily) to severe (2·5 ppm daily) dietary restriction of Zn and decreased energy intake in NZB/W F_1 mice decreased the onset of haemolytic anaemia, autoantibody production and renal disease[110]. In MRL/lpr mice, a Zn-restricted diet has been shown to reduce lymphoproliferation and anti-dsDNA titres and improve glomerulonephritis[146].

Dietary phenols in systemic lupus erythematosus

Polyphenols

Polyphenols are common constituents of plant-based foods and the main dietary source of antioxidants through vegetables, fruits, cereals, legumes and drinks such as tea, coffee and wine. The term polyphenol comprises a wide variety of molecules with phenolic structural features that are classified into several groups according to their number of phenol rings and the structural elements that bind these rings together. The main

categories of polyphenols are phenolic acids, flavonoids, diarylheptanoids and arylalkanones lignans and stilbenes. There is marked variation in bioavailability among polyphenols, mainly owing to differences in chemical structure. Furthermore, the most abundant polyphenols in our diet are not necessarily those that present the best bioavailability profile[147].

In recent years, the interest in dietary polyphenols has increased considerably among nutritionists and food scientists owing to their beneficial roles in human health; polyphenols act as anti-inflammatory, anti-cancerous and immunomodulatory agents in several diseases. The potential beneficial effects of polyphenols in SLE are derived from their abilities to protect against oxidative damage, modulate different inflammation-related enzymes and interact with signal-transduction pathways, cell cycle regulators and cell receptors implicated in the immuno-inflammatory process[65,148]. Evidence from both *in vitro* and *in vivo* studies demonstrates the beneficial effect of phenolic compounds in the management of SLE (Table 3).

Flavonoids: flavones. Apigenin, a flavonoid widely distributed in dietary plants such as parsley, thyme and chamomile, among others, has vasorelaxing, antiplatelet and antioxidant properties, which may reduce the risk of coronary disease and improve endothelial function in SLE[149,150]. Apigenin has shown beneficial effects in an SLE mouse model, suppressing autoantibody production and the IFN-γ and IL-17 response of stimulated splenocytes, IL-6 production by lupus dendritic cells and inducible isoform of cyclo-oxygenase-2 (COX-2) expression in $CD4^+$ T cells, B cells, dendritic cells and macrophages. Both IFN-γ-producing Th1 cells and IL-17-producing Th17 cells are critical for help in the production of pathogenic autoantibodies and the development of lupus nephritis[151,152]. In addition, apigenin treatment *in vitro* induced significant apoptosis of T cells, B cells, dendritic cells and macrophages after 24 h of incubation[150]. Nevertheless, the presence of apigenin in the diet is insufficient to reach bioavailable therapeutic levels owing to first-pass metabolism in the gut and liver, but its bioavailability could potentially be improved by the pharmaceutical industry.

Flavonoids: flavonols. Astilbin, a natural flavonol found in some food and medicinal plants, exhibits multiple pharmacological functions, including anti-inflammatory and immunomodulatory properties through the induction of apoptosis in activated T cells and the suppression of activated T-cell adhesion and migration and modulation of dendritic cells. Oral administration of astilbin, isolated from the rhizome of *Smilax glabra* Roxb (family Liliaceae), delayed disease development in lupus-prone mice when preventive oral administration was started before the onset of disease and also when the treatment was started after disease onset. In addition, astilbin treatment reduced levels of circulating antinuclear antibodies and several serum cytokines and decreased functional activated T and B cells, suggesting that astilbin treatment decreases the capacity of B cells to stimulate T lymphocytes[153].

Flavonoids: flavanols. Several studies suggest that the regular consumption of tea, the most widely consumed beverage in the world after water, is associated with an array of health benefits. In particular, epidemiological studies indicate that the incidence of death due to heart, cerebrovascular and respiratory diseases is considerably lower in China and Japan, the two leading green tea-consuming countries[154–156]. All tea is derived from *Camellia sinensis* (L.) kuntze, an evergreen shrub of the Theaceae family, whose health benefits are mainly associated with its high concentration of flavanols known as catechins[154]. Epigallocatechin gallate (EGCG), the major bioactive polyphenol present in green tea, has been reported to have antioxidant and anti-inflammatory effects by inhibiting NF-κB and suppressing T-cell activation[157]. A number of studies have proved the beneficial effects of green tea or EGCG supplementation in SLE models. An *in vivo* study demonstrated that a diet supplemented with green tea powder increased mouse survival and improved SLE progression by decreasing serum levels of anti-DNA antibodies and renal damage[158]. Furthermore, daily treatment with EGCG by oral administration in lupus-prone mice had prophylactic effects by promoting the Nrf-2 antioxidant signalling pathway, inhibiting NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation in the kidney and enhancing Treg activity[159]. The potential therapeutic role of EGCG has also been studied in mesangial cells, which are macrophage-like cells resident in the kidney with immune and vascular functions, from lupus mice pre-treated with EGCG and stimulated with lipopolysaccharide (LPS) or IFN-γ. EGCG activated the metabolic regulator adenosine 5'-monophosphate-activated protein kinase (AMPK), which has been shown to inhibit the production of several proinflammatory mediators, and blocked the induced expression of iNOS and NO and IL-6 production via a mechanism partially independent of the AMPK activation. Furthermore, EGCG attenuated inflammation via the immune-stimulated phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K-Akt-mTOR) pathway by decreasing phosphorylation of the kinase Akt[160]. EGCG has also been reported to decrease the expression of different autoantigens at the mRNA and/or protein levels in an *in vivo* model of normal human primary epidermal keratinocytes, a cell type particularly affected in patients with SLE, reducing the expression of several antinuclear autoantibodies[161]. All these data suggest the potential therapeutic role of EGCG as an important component in novel approaches to SLE management by regulating inflammation and preventing lupus nephritis.

Flavonoids: isoflavones. Nowadays, it is clear that high oestrogen levels exacerbate SLE symptoms and kidney disease and increase numbers of autoreactive B cells and autoantibodies[162]. Phyto-oestrogens are plant-derived compounds that are found in a wide variety of foods and that are structurally and/or functionally similar to mammalian oestrogens and their active metabolites. Phyto-oestrogens can interact with oestrogen receptors (ER) with oestrogenic or anti-oestrogen activities. Genistein and daidzein are the major bioactive isoflavones, and they are mainly available in soya, the cornerstone of the traditional Asian diet. Soya has shown anti-inflammatory effects and is able to reduce proteinuria and renal pathological lesions associated with progressive renal failure, which could be beneficial for SLE. *In vivo* studies showed that

dietary supplementation with soya isoflavones extracted from natural soya germ, containing 50 % daidzin, 30 % glycitin and 20 % genistein, alleviated disease severity in lupus mice and decreased autoantibody levels and *in vitro* IFN-γ production in splenocytes. Furthermore, methanol extracts of soya isoflavones demonstrated a higher affinity for ERβ than ERα, suggesting that ER activation is selectively modulated[163]. These results are consistent with those of previous studies, which proved that SLE disease severity is aggravated by ERα agonists but ameliorated by ERβ agonists in a murine lupus model[164]. By contrast, a previous study showed that a diet supplemented with 20 % soyabean protein and 5 % soyabean oil exacerbated the SLE clinical course in autoimmune MRL/lpr mice, decreasing survival and increasing renal damage, thymus weight and T-cell proliferation in the spleen and B cells in lymph nodes. Thus, further research on the mechanism underlying the effect of soya-rich diets is necessary to evaluate the potential for isoflavone supplementation in patients with SLE[165]. However, in recent years isoflavone research in SLE has not evolved so far. Even though animal data showed that isoflavones have a wide range of molecular, cellular and behavioural effects at doses and plasma concentrations attainable in humans, the consumption of soya or soya phyto-oestrogen has produced mixed and often conflicting results and potential adverse effects on humans, which may limit their use in further studies[166,167].

Coumestrol is the major phyto-oestrogen in lucerne sprouts but can be also found in beans and other vegetables. Dietary supplementation with coumestrol in SLE mice ameliorated some aspects of the disease[168]. Furthermore, a diet supplemented with lucerne sprout ethyl acetate extract significantly improved proteinuria, prolonged lifespan and suppressed the production of proinflammatory cytokines in stimulated peritoneal cells and splenocytes from SLE mice. However, there was no change in SLE autoantibody production, suggesting that its beneficial effects might be more attributable to the down-regulation of inflammatory cytokines rather than autoantibody regulation. Nevertheless, a group of mice fed a diet supplemented with lucerne sprouts had similar proteinuria progression and lifespan as the lupus group, suggesting that the ingestion of whole lucerne sprouts had no beneficial effects on SLE. Accordingly, lucerne sprout ethyl acetate extract reduced serum levels of proinflammatory cytokines and improved survival after 9 h of LPS challenge, suggesting that lucerne sprout ethyl acetate extract alleviated acute inflammatory hazards. Moreover, pretreatment with lucerne sprout ethyl acetate extract significantly inhibited proinflammatory cytokine production in LPS-stimulated primary macrophage[169,170]. By contrast, previous reports have shown that lucerne seed or sprouts can induce SLE-like disease in monkeys and exacerbate disease severity in patients with SLE who have ingested lucerne tablets[171,172].

Lignans. Flaxseed (*Linum usitatissimum* L.), the richest source of lignan precursors, has been a part of the human diet for thousands of years. The principal dietary lignan precursor in flaxseed is the secoisolariciresinol diglucoside (SDG), which has demonstrated possible nutraceutical actions to prevent and alleviate lifestyle-related diseases[173]. A flaxseed-supplemented diet in a lupus mouse model improved renal damage and decreased splenic lymphocyte proliferation[174]. Similarly, oral administration with SDG from flaxseed showed dose-dependent protective effects in the kidney, with similar effects to those previously noted for dietary supplementation with flaxseed[175]. In a randomised cross-over trial, flaxseed supplementation over 17 weeks was well tolerated by patients with lupus nephritis and exerted significant positive effects on renal function[176]. In another randomised cross-over trial, daily supplementation with flaxseed in patients with SLE appeared to be renoprotective at the end of the 2-year study[177].

Diarylheptanoids and arylalkanones. Curcumin (1,7-bis-[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione), a component of the rhizomes of the golden spice turmeric (*Curcuma longa* L.), has demonstrated antioxidant, anti-tumour and anti-inflammatory activities. Recent studies have suggested that curcumin may have therapeutic effects in SLE treatment. In *in vitro* studies, low doses of curcumin modulated the Th17/Treg balance of $CD4^+$ T cells isolated from patients with SLE without affecting $CD4^+$ T cells of healthy subjects. As SLE pathogenesis involves the enhancement of Th17 cells with a parallel reduction in the Treg population in patients with SLE, the regulation of this balance has become a subject of interest in SLE management, which is intended to improve the clinical outcome and prevent organ damage[178]. Curcumin has also shown beneficial effects in SLE mouse models, producing a delayed onset of autoantibody production and proteinuria and significantly decreasing salivary gland infiltration and lymphadenopathy compared with the control group[179]. Moreover, a curcumin-supplemented diet improved renal damage and autoantibody and proinflammatory cytokine production in female lupus mice. Interestingly, these therapeutic effects disappeared after Treg depletion by anti-CD25 antibody injection, suggesting that the protective effects of curcumin involve, at least partially, its interaction with Tregs[180]. In addition, a randomised and placebo-controlled study demonstrated that oral supplementation with curcumin (three capsules per d over 3 months, each capsule containing 500 mg of turmeric (22·1 mg of curcumin)) has beneficial effects without side effects in lupus patients with refractory nephritis, suggesting that short-term curcumin supplementation may be used safely as an adjuvant therapy in patients with SLE[181]. However, curcumin (30 mg/kg body weight administered from 12 to 20 weeks by daily intraperitoneal injection) showed negative effects in the central nervous system of MRL/lpr mice, increasing IgG and anxiety behaviour and decreasing central complement protein (C3) deposits in the brain and circulation. Curcumin also worsened brain atrophy, reduced the volume of the hippocampus and increased the mRNA and protein expression of aquaporin 4, the main water channel of the brain, aggravating brain oedema. Furthermore, increased splenocyte proliferation was suggestive of peripheral immune response activation. Therefore, until a safe dose range is established by additional studies, caution is warranted in the use of curcumin even as adjuvant therapy for central nervous system lupus[182].

Stilbenes. Resveratrol (3,5,4'-trihydroxystilbene) is a natural compound found in various plants and fruits, especially in grapes, that possess anti-inflammatory, immune-regulatory, antioxidant and blood fat-regulatory activities. In particular, resveratrol can modulate inflammatory genes and signalling transcription factors,

such as STAT3, NF-κB and COX-2, with critical roles in SLE pathogenesis[183]. A recent study showed that resveratrol had protective effects in a pristane-induced lupus BALB/c mouse model after 7 months of treatment and *in vitro* immunomodulatory effects on splenic mononuclear cells, suggesting that it may represent a novel approach for the management of SLE[184].

Indole-3-carbinol. Indole-3-carbinol (I3C), the breakdown product of glucobrassicin, is obtained from the dietary consumption of cruciferous vegetables (family Brassicaceae), such as broccoli, cabbage, Brussels sprouts and cauliflower. An *in vivo* study showed that I3C dietary supplementation (0·2 g/kg) increased the lifespan of lupus-prone NZB/W F_1 mice and decreased proteinuria, glomerulonephritis and interstitial nephritis. Furthermore, I3C supplementation was effective when initiated before or after disease onset and may be beneficial in SLE prevention as well as in the early stages of SLE. In addition, the ratio of the urine oestrogen metabolites 2-hydroxyestrone (2-OH) and 16α-hydroxyestrone (16α-OH) was greater after the I3C diet, showing anti-oestrogenic activities[185]. Similarly, another study demonstrated that a diet enriched with 2000 ppm I3C preserved renal function by decreasing proteinuria and renal pathological abnormalities and prolonged survival when fed to NZB/W F_1 mice for 40 weeks. I3C supplementation decreased anti-dsDNA, anti-chromatin and anti-RNA helicase A antibody levels; increased the ratio of 2-OH to 16α-OH metabolites by maintaining 2-OH oestrone levels; and blocked B- and T-cell maturation, inhibiting disease progression. In addition, *in vitro* concanavalin A stimulation of T cells from the spleen of I3C-diet mice produced Th1 cytokines (IL-2 and IFN-γ) in contrast to the higher production of Th2 cytokines (IL-4 and IL-10) in the SLE control animals[186]. Oestrogen metabolism in women with SLE is weighted towards 16α-OH, which might increase SLE disease activity. In an open-label 1-week metabolic study in women with SLE, the consumption of 375 mg/d of I3C changed the ratio of urinary 16α-OH to 2-OH predominantly owing to an increase in 2-hydroxylation, demonstrating that I3C could play a role in the therapy of SLE by attenuating oestrogen-dependent disease activity[187]. These studies provide a preliminary understanding of mechanisms whereby I3C leads to the amelioration of lupus-like disease and suggest that I3C may be an effective adjunctive therapy for the human disease.

Melatonin. Melatonin (*N*-acetyl-5-methoxytryptamine) is an indoleamine synthesised from the essential dietary amino acid tryptophan, which can be found in a several components of the diet, for example, fruits, vegetables, olive oil and nuts. Consuming such foods gives rise to a significant increase in serum melatonin levels[188,189]. Melatonin concentrations are decreased in lupus patients and inversely correlated with disease activity. Melatonin administration has shown immunomodulatory effects, stimulating the immune system under basal immunosuppressive conditions and inhibiting exacerbated immune responses[190]. Administration of melatonin to MRL/lpr mice at a dose of 30 mg/kg body weight in drinking water over 1 month improved the histological kidney pattern in females and worsened it in males. Moreover, female mice treated with melatonin showed a decrease in serum IgG, IgM, anti-dsDNA and anti-CII autoantibodies, proinflammatory cytokines (IL-2, IL-6, IFN-γ, TNF-α and IL-1β) and nitrite/nitrate production and an increase in anti-inflammatory cytokines (IL-10). However, in male mice the treatment with melatonin elicited the opposite effect, worsening all the immunological parameters with elevated autoantibodies titres and a prevalence of proinflammatory *v.* anti-inflammatory cytokines. Similar results were obtained when lymphocytes from the spleen and lymph nodes were cultured: the indoleamine decreased the proinflammatory cytokines and increased the anti-inflammatory cytokines produced by lymphocytes in females but had the opposite effect in males, suggesting that melatonin action in MRL/lpr mice is sex dependent, probably through the modulation and inhibition of sex hormones[191]. In MRL/lpr mice treated with the same amount of melatonin and hormone therapy, adding testosterone to female mice and oestradiol to males, melatonin alone prevented lupus development in females, but the addition of testosterone to melatonin-treated female mice produced a similar negative pattern to that observed previously in male lupus mice. These effects were similar in oestradiol-treated males, confirming that melatonin action in MRL/lpr mice could be sex dependent through the modulation of sex hormones[192]. Furthermore, melatonin treatment (0·01, 0·1, 1·0 mg/kg) in pristane-induced SLE BALB/c mice antagonised the increasing levels of IgM, anti-single-stranded DNA and histone autoantibodies and decreased renal lesions caused by pristane. In an *in vitro* experiment with concanavalin A- or LPS-stimulated splenocytes isolated from melatonin-treated mice, melatonin decreased induced IL-6 and IL-13 production and increased IL-2 levels, showing that the indoleamine could modulate the disturbance of the cytokine network in SLE mice by regulating the Th1/Th2 cytokine imbalance[193]. *In vitro* administration of melatonin (1×10^{-4} M) in peripheral mononuclear cells from treated patients with SLE increased the number of Tregs expressing FOXP3 and BAFF mRNA expression in patients with SLE, whereas it caused up-regulation of BAFF mRNA levels in healthy subjects, supporting the dual role of melatonin in the cells of patients *v.* controls and its potential use as an immunomodulatory therapy or co-therapy for SLE[194].

Conclusion

The increasing body of evidence linking the intake of different nutrients to the potential beneficial effects derived from their antioxidant, anti-inflammatory and immunomodulatory properties suggests a possible supportive role of diet therapy in the primary and secondary prevention and management of SLE. Over previous years, human and mouse models have supplied several dietary candidates and have shed light on the possible mechanisms underlying the response to different nutrients, with promising results.

Although the studies are not conclusive and further research is required, it seems to be clear that a balanced diet can be helpful in the prevention and management of SLE, contributing to the management of the disease activity as well as the reduction of co-morbidities, thus improving health and quality of life of patients with SLE. In particular, widespread evidence highlighted the importance of a diet rich in vitamins

(mainly A, B_6, C, D and E) and MUFA/PUFA (particularly *n*-3 PUFA and MUFA) with an adequate fibre intake, protein and Na restriction and moderate energy consumption in reducing co-morbidities and preventing SLE flares, thus minimising unnecessary burden in patients with SLE. It is also remarkable the promising role of dietary polyphenols included in the diet through vegetables, fruits, cereals, legumes and drinks such as tea and wine in the management of SLE. Likewise, it is important to encourage patients to stop smoking, avoid being overweight and optimise their blood pressure, lipid profile, and control of disease activity to decrease cardiovascular morbidity.

Currently, researchers continue to search and identify potential dietary candidates that could play beneficial roles in SLE. Nevertheless, despite the positive preliminary results obtained over the last years, most of the reported beneficial effects need further verification before they can be translated into clinical practice. The efficacy of these dietary candidates and other nutrients, as well as the effect of dietary interventions aimed at promoting adequate nutritional status in SLE patients, requires further evaluation through prospective and randomised trials in human subjects.

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