The effects of immunostimulatory herbal supplements on autoimmune skin diseases

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The use of herbal supplements that promise to improve immune health has gained popularity among dermatology patients. However, there is little to no evidence that herbal supplements improve dermatologic conditions. Several in vitro and in vivo studies have shown that *Spirulina platensis*, *Aphanizomenon flos-aqua*, *Chlorella*, *Echinacea*, and alfalfa activate immune cells via certain cytokines and chemokines. Case reports suggest the association of ingesting immunostimulatory herbs and the clinical onset or flares of diseases characterized by an exaggerated immune response such as lupus erythematosus, dermatomyositis, and autoimmune blistering disorders. Therefore, it is imperative to investigate the prevalence of herbal supplement use in this patient population. In addition, in vitro studies should examine the underlying mechanisms by which herbs stimulate immune pathways that are already overactive in autoimmune patients. (J Am Acad Dermatol 2021;84:1051-8.)

Key words: alfalfa; *Aphanizomenon flos-aqua*; autoimmune skin diseases; *Chlorella*; complementary and alternative medicine; dermatomyositis; *Echinacea*; herbal supplement; lupus erythematosus; pemphigoid; pemphigus; *Spirulina*.

Complementary and alternative medicine (CAM) has increased in popularity in the United States.[1] A growing number of dermatology patients use CAM,[2,3] with estimates of their lifetime CAM use ranging from 35% to 69%.[2] The most common types of CAM are herbal and dietary supplements. Herbal supplement sales in the United States increased by almost 10% from 2017 to 2018, marking the greatest increase in sales growth in the past 2 decades.[4]

Products marketed to boost immune health were one of the main drivers of herbal supplement sales.[4] However, despite being touted as natural health remedies, there is little to no evidence of treatment efficacy.[3] Moreover, there is mounting evidence that certain herbal supplements have adverse dermatologic health effects, including exacerbating pre-existing autoimmune skin diseases or even precipitating the onset of such diseases[2,5-10] (Table I).[10-15]

Because an overactive immune system is one of the main drivers of autoimmune diseases, there is a concern that consuming immunostimulatory herb-based supplements may lead to clinical exacerbations and overall worsening of autoimmune skin diseases.[10,16] Various in vivo and in vitro studies have demonstrated that herbs such as *Spirulina platensis*, *Aphanizomenon flos-aqua*, *Chlorella*, *Echinacea*, and alfalfa are immunostimulatory[17-23] (Table II).[17,18,20,22-32] Indeed, there have been several reports of the association of herbal supplement use and the acute onset or flare, or both, of autoimmune cutaneous diseases, including

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dermatomyositis,[10,13,15,33] pemphigus/pemphigoid,[10,11] and lupus erythematosus (Table III).[10-14,33]

IMMUNOSTIMULATION IS A KEY STEP IN AUTOIMMUNE SKIN DISORDERS

The pathophysiology of autoimmune skin diseases involves the complex combination of environmental exposures, genetic risk factors, and cellular communication between the skin and the immune system.[34,35] Regardless of the inciting event, the common theme in these disorders is the activation of immune cells and their receptors and the secretion of cytokines and chemokines that results in an exaggerated host immune response.[16]

CAPSULE SUMMARY

- *Spirulina, Aphanizomenon flos-aqua, Chlorella, Echinacea,* and alfalfa have been shown to stimulate the immune system. The use of these herbs may be associated with the precipitation or flare of autoimmune skin diseases.
- Patients with autoimmune diseases should be screened for supplement use and should be advised to avoid these immunostimulatory herbs.

Cutaneous lupus erythematosus

Innate and adaptive immune cells play a crucial role in cutaneous lupus erythematosus.[34-36] Plasmacytoid dendritic cells in cutaneous lupus erythematosus produce elevated levels of type I interferons (IFN-α and IFN-β) compared with what is expected in a normal viral defense.[37] Type I IFNs subsequently recruit $CXCR3^+$ lymphocytes in the skin, promoting a T-helper cell type 1 inflammatory response.[38] Tumor necrosis factor (TNF)-α is a primary cytokine that recruits immune cells, promotes the release of secondary cytokines, and induces the production of nuclear antigens on the cell surface, which results in antibody production and autoreactivity.[39] The involvement of both innate and adaptive immune systems in cutaneous lupus erythematosus suggests that stimulation of either immune pathway results in acute onsets or flares, or both of disease.

Dermatomyositis

Cellular and humoral immunity both play a role in the pathogenesis of muscle and skin disease in dermatomyositis.[40-43] Inflammatory CD4 T cells and dendritic cells infiltrate the perimysial blood vessels, perifascicular myofibers, and superficial perivascular dermal tissue, leading to atrophy and lichenoid/interface reactions in the muscle and skin, respectively.[41-43] Type I IFNs activate antigen-presenting cells and upregulate autoantigens that drive antibody production as well as cause direct tissue injury.[41] Inflammatory cytokines such as TNF-α and interleukin (IL) 6 perpetuate inflammation and cause cell death in the muscle and skin tissue.[43]

Pemphigus

Although desmoglein antibodies are sufficient to cause acantholysis in pemphigus,[44] B cells and T cells, and the cytokines that they secrete can induce and maintain pathogenic autoantibody production.[45] TNF-α, IL-6, and IL-8 have been found in the sera and blister fluid of patients with pemphigus.[45,46] These cytokines do not induce blister formation, but are involved in the inflammatory cascade accompanying acantholysis.[46]

HERBS STIMULATE THE IMMUNE SYSTEM ALONG PATHWAYS THAT ARE SIMILARLY ACTIVATED IN AUTOIMMUNE SKIN CONDITIONS

Microalgae

Food-grade microalgae that are manufactured as herbal supplements include *Spirulina*, *Aphanizomenon flos-aquae*, and *Chlorella*. These herbs have been commercialized for human use because of their nutritional value, including reported high protein, vitamin, mineral, and fiber content, and purported health benefits.[47-49] Numerous animal and human studies have shown that these algae are immune stimulating (Table II). Several case reports have illustrated the connection between microalgae-containing supplement intake and autoimmune skin diseases (Table III).

Spirulina

Spirulina platensis (also known as *Arthrospira platensis*) is a type of blue-green algae that has been called a "super food" in the health food industry due to its high protein content and supposed health benefits, such as its possible hypolipidemic, antioxidant, and anti-inflammatory properties.[50,51] It is widely used in tablet form or as a powder added to health foods such as energy bars, smoothies, and green juices.[51] Numerous studies have shown that *Spirulina* suppresses tumorigenesis and viral infections, presumably due to its ability to stimulate the immune system.[20,52,53,57,59,61]

Both in vitro and in vivo studies suggest that specific components of *Spirulina* have immune-enhancing effects that are primarily mediated via the

Abbreviations used:

CAM:	complementary and alternative medicine
IFN-α:	interferon-α
IFN-β:	interferon-β
NF-κB:	nuclear factor-κ—light-chain enhancer of activated B cells
IL:	interleukin
TNF-α:	tumor necrosis factor-α
NK:	natural killer
LPS:	lipopolysaccharide
Th1:	T-helper cell type 1
Th2:	T-helper cell type 2
mRNA:	messenger RNA

innate immune system.[24,52] Immulina (ChromaDex Los Angeles, CA), a purified functional polysaccharide isolated from *Spirulina*, was shown to activate nuclear factor-κ—light-chain enhancer of activated B cells (NF-κB) in vitro and to dramatically increase IL-1β and TNF-α messenger (m)RNA in THP-1 human monocytes, with more potent in vitro activation compared with that of lipopolysaccharides (LPS).[22]

Similarly, another study found that adding Immulina to THP-1 human monocytes dose-dependently increased the expression of genes encoding cytokines IL-8, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, macrophage inflammatory protein 1β, IFN-γ—induced protein 10, TNF-α, IL-1β, and the enzyme cyclo-oxygenase 2.[26] In another study, the addition of *Spirulina* powder to unstimulated peripheral blood mononuclear cells also led to significant increases in cytokine levels, including IL-1β, IL-4, and IFN-γ.[21] Similarly, chicks fed *Spirulina* had a dose-dependent increase in macrophage concentration and phagocytic activity.[54] They also expressed increased nitric oxide synthase activity, even in the absence of LPS, suggesting that *Spirulina* may have similar biologic functions as LPS.

There is evidence that *Spirulina* also stimulates natural killer (NK) cells in vivo. In humans who consumed a hot water extract of *Spirulina*, NK cell activity was upregulated, as measured by increased IFN-γ levels and increased cytolysis.[20] In a pilot study of 10 healthy patients who consumed Immulina, 400 mg/d for 7 days, there was a 40% average increase in NK cell activity ($P < .01$), as measured by killing of K562 tumor cells.[24] In a double-blind, placebo-controlled, crossover study, 11 healthy Danish individuals received placebo or Immulina at 200 mg or 400 mg daily for 7 days. After ingesting 200 mg or 400 mg Immulina, mRNA expression of NK group 2D, an NK cell marker, increased by 37 % ($P = .02$) and by 55 % ($P = .0003$), respectively. Administration of 400 mg Immulina also led to a 75% increase in mRNA expression of the NK and T-cell marker perforin ($P = .008$).[24] Prior studies suggest that Immulina's proinflammatory effect is primarily mediated via a Toll-like receptor 2—dependent process, further highlighting that components of *Spirulina* activate the innate immune system.[55]

Table I. Herbs that are reported to induce or trigger autoimmune skin diseases

Microalgae
Spirulina platensis (also known as *Arthrospira platensis*)[10,11]
Aphanizomenon flos-aquae[10]
Purple cornflower (*Echinacea purpurea*)[10,12,15]
Alfalfa/lucerne (*Medicago sativa*)[13,14]

Although *Spirulina*'s immunostimulatory effects appear to be mediated primarily via the innate immune system,[20-22,24,26,27] several studies also suggest that *Spirulina* stimulates the adaptive immune response.[56,57] For instance, numerous parallel studies in which patients positive for HIV received *Spirulina* supplementation for periods ranging from 2 to 12 months showed an increase in CD4 count and a decrease in viral load.[25,58-61] Moreover, in a study in which patients ingested Immulina, subsequent stimulation of CD4 T cells and B cells with *Candida albicans* antigen in vitro increased T and B cell proliferation for up to 14 days after intake.[56]

Relatively less attention has been focused on the potential adverse dermatologic and health effects of *Spirulina*, but several case reports suggest that *Spirulina*'s immunostimulatory properties can exacerbate or even precipitate autoimmune skin disease (Table III).

Aphanizomenon flos-aquae

Several in vitro studies suggest that *Aphanizomenon flos-aquae* activates human monocytes and macrophages.[23,62] A water-soluble preparation of *Aphanizomenon flos-aquae* significantly activated NF-κB—directed *Luciferase* expression in THP-1 human monocytic cells and also increased mRNA levels of IL-1β and TNF-α.[23] A follow-up study further found that a specific high-molecular-weight polysaccharide preparation of *Aphanizomenon flos-aquae* significantly increased expression of TNF-α and IL-1β to levels comparable to those induced by LPS-activated pathways.[22] Similarly, an in vitro study showed that

Table II. Immune mechanisms of herb-induced immunostimulation

Herb	Mechanism of immune stimulation
Spirulina	• Increases NK cell activity.[20,22,24,25] • Activates Toll-like receptors and increases NK-mediated IFN secretion via elevated IL-12 and IL-18.[20] • Increases gene expression of cytokines IL-8, MCP-1, MIP-1α, MIP-1β, IP-10, TNF-α, IL-1β, and the enzyme COX-2.[26] • Acts on Th1 cells and increases production of Th1 cytokines, such as IL-2 and IFN-γ.[21,27,28,56]
Aphanizomenon flos-aquae	• Activates NK cells.[62] • Activates NF-κB[23] and increases TNF-α and IL-1β expression.[22,23]
Chlorella	• Increases TNF-α and IL-1β expression.[22] • Augments Th1 cells response.[30] • Increases NK cell activity and production of IFN-γ and IL-12.[66]
Echinacea	• Increases extracellular cytotoxic effects of macrophages to similar levels compared with IFN-γ.[18] • Increases production of various ILs, including IL-1, IL-10, and TNF-α.[17] • Stimulates NK cell activity and increases antibody-dependent cell cytotoxicity.[31]
Alfalfa	• Novel epitopes created by L-canavanine–laden aberrant proteins trigger autoantibody production or cytotoxicity.[32]

COX-2, Cyclo-oxygenase 2; *IFN*, interferon; *IL*, interleukin; *IP-10*, interferon-γ–induced protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MIP*, macrophage inflammatory protein *NF-κB*, nuclear factor-κ–light-chain enhancer of activated B cells; *NK cell*, natural killer cell; *Th1*, T-helper cell type 1; *TNF-α*, tumor necrosis factor-α.

an extract of *Aphanizomenon flos-aquae* activates NK cells, as seen by increased CD69 expression, and that this effect depended on the activation of other cells such as monocytes and macrophages.[62] Furthermore, cutaneous dermatomyositis developed in a 45-year-old white woman 1 day after ingesting a supplement containing this microalgae, and this association was confirmed via rechallenge.[10] This patient had a TNF-α polymorphism that may have predisposed her to dermatomyositis.[10]

Chlorella

Several *Chlorella* species exist, with *C vulgaris* and *C pyrenoidosa* being the most used species in the supplement industry.[10,47,63] Some of the cited benefits are lowering of cholesterol levels, prevention of atherosclerotic plaques, and antitumor and antimicrobial actions.[47]

There are no reports of *Chlorella* inducing autoimmune disorders to date; however, several in vitro and in vivo experiments demonstrate that it can stimulate the immune system.[22,64-66] Immurella, a polysaccharide derived from *C pyrenoidosa*, substantially increased the mRNA levels of IL-1β and TNF-α in human monocytes.[22] Oral administration of *Chlorella* extract augmented the T-helper cell type 1 response in both normal and immunocompromised hosts and enhanced resistance to infection with the intracellular *Listeria monocytogenes*.[30] A study of healthy Korean volunteers who took 5 g of *Chlorella* for 8 weeks showed an increase in the NK cell activity as well as the production of T-helper cell type 1–induced cytokines IFN-γ, IL-12, and IL-1β.[66] In a placebo-controlled study of healthy controls, intake of 30 tablets for 4 weeks of a *C pyrenoidosa*-derived supplement resulted in significantly elevated salivary IgA production.[65]

Echinacea

Clinical trials have shown that various preparations of *Echinacea*, or purple cornflower, shorten the duration and severity of upper respiratory infections.[67] *E angustifolia*, *E purpurea*, and *E pallida* have been the most commonly studied for their immune-enhancing effects.

One murine study found that stimulation with polysaccharides from *E purpurea* activated macrophages to similar levels as stimulation with IFN-γ, independent of prior activation or influence from lymphocytes.[18] In human macrophages, *E purpurea* increased production of IL-1, IL-10, and TNF-α to levels comparable to those induced by LPS.[17] In addition, *E purpurea* has been found to stimulate NK cell activity and increase antibody-dependent cell cytotoxicity in vitro in human cells.[31]

However, in a double-blinded, placebo-controlled crossover study in healthy humans, an oral preparation of *E purpurea* did not affect macrophage production of TNF-α and IL-1β.[68] In addition, in a review of 5 studies of healthy adults consuming *E purpurea*, only 2 studies found a significant increase in the phagocytic activity of neutrophils.[69] However, the negative results are difficult to interpret due to differences in methods, baseline variation in phagocytic activity throughout the study, and a limited sample size.[69]

We found one case report suggesting that *Echinacea* induced a pemphigus vulgaris flare in a

Table III. Reports of activation of autoimmune skin disease after ingestion of herbal supplements

Herbal supplement	Autoimmune skin disease
Food supplement containing *Spirulina platensis*, *Ginkgo biloba*, and ginseng	Pemphigus vulgaris[10]
You're My Everything,* a supplement containing *Spirulina platensis*, *Aphanizomenon flos-aquae*, organic cayenne pepper, and methylsulfonylmethane	Dermatomyositis[10]
Spirulina	Mixed immunoblistering disorder with features of bullous pemphigoid and pemphigus foliaceus confirmed via histopathology and direct/indirect immunofluorescence[11]
Spirulina	Dermatomyositis[33]
Echinacea	Erythema nodosum[12]
Echinacea	Pemphigus vulgaris[10]
Echinacea[15]	Dermatomyositis
Alfalfa	Systemic lupus erythematosus[14]
IsaLean† weight loss shake (contains alfalfa and a proprietary enzyme blend of *Aspergillus oryzae*, *Rhizopus oryzae*, *Trichoderma longibrachiatum*, *Saccharomyces cerevisiae*, *Bacillus subtilis*, *Ananas comosus*, *Aspergillus niger*)	Dermatomyositis[13]

*Simply Divine Botanicals, Las Vegas, Nevada.
†Isagenix, Gilbert, Arizona.

white man with a previously quiescent disease course. The patient had taken *Echinacea* supplements for the first time after an upper respiratory tract infection. He had had several previous upper respiratory tract infections that had not triggered his pemphigus vulgaris, suggesting that *Echinacea* supplements may have played a role in triggering the flare.[10] Similarly, erythema nodosum developed in a patient with the flu after ingesting *Echinacea*. After discontinuing *Echinacea*, the erythema nodosum improved despite persistence of the flu-like symptoms.[12] A 53-year old female with amyopathic dermatomyositis well-controlled by low-dose naltrexone flared after ingesting *Echinacea* supplements, which then resolved after discontinuing the herb.[15]

Alfalfa

Earlier experiments on rats, rabbits, and monkeys suggested that alfalfa, or lucerne (*Medicago sativa*), has anticholesterol and antiangiogenic properties, leading to several clinical studies to better examine these effects.[70,71] In a pilot study of healthy human volunteers, 1 individual who ingested up to 160 g of ground seeds daily developed lupus-like laboratory abnormalities (pancytopenia, hemolytic anemia, presence of antinuclear antibodies, and hypocomplementemia), but was asymptomatic except for splenomegaly.[72] Similarly, monkeys fed alfalfa sprouts developed a lupus-like syndrome, including an erythematous macular rash.[73] In another study, 4 previously healthy patients who consumed 12 to 24 alfalfa tablets daily for up to 7 months developed a symptomatic lupus-like disease, manifesting as rash, joint and muscle pains, and positive antinuclear antibodies.[14] After discontinuation of the alfalfa tablets, the symptoms and antinuclear antibodies disappeared.[14]

According to several more recent case reports, patients developed systemic lupus erythematosus or had an exacerbation of their disease, although no cutaneous findings were mentioned in these events.[32] Moreover, in a case series, 2 patients who ingested a weight loss shake, with alfalfa being one of the main ingredients, had acute onset/flares of dermatomyositis shortly after consumption.[13] This weight loss shake also contained other fungi-derived enzymes as proprietary active ingredients.[13]

The suspected culprit in alfalfa is L-canavanine, which is a nonprotein amino acid that is known to replace L-arginine during protein synthesis.[14,32] As a result, aberrant misfolded proteins are produced that are then ubiquinated and degraded, leading to peptides that can be presented by major histocompatibility complex molecules to CD4 and CD8 cells.[32] These novel epitopes created by L-canavanine-laden aberrant proteins and apoptotic cells may then trigger a cascade of events that involve autoantibody production or cytotoxicity.[32]

Given the apparent correlation between alfalfa ingestion and disease onset or flares, several experts,

including the Lupus Foundation of America, have recommended avoiding the consumption or supplementation of alfalfa among patients with systemic lupus erythematosus.[32,74]

CONCLUSION

CAM, particularly herbal supplements, is becoming increasingly popular among dermatology patients. Several studies have shown microalgae (*Spirulina*, *Aphanizomenon flos-aqua*, *Chlorella*), *Echinacea*, and alfalfa upregulate cytokines and inflammatory pathways that are already aberrantly increased in a variety of autoimmune skin diseases. At the same time, case reports suggest that there is a connection between herbal supplement use and skin disease onset or flare. Therefore, it is reasonable to screen patients with autoimmune skin diseases for herbal supplement use and to encourage compliance with evidence-based treatment instead. Future research should investigate whether there is a temporal relationship between ingestion and flare or acute onset of the disease using a larger cohort of patients. In addition, in vitro studies could be performed to investigate how herbal supplements affect cytokines and to identify pathways that are upregulated specifically in patients with autoimmune skin diseases.

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