

# Activation of Autoimmunity Following Use of Immunostimulatory Herbal Supplements

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**Background:** Evidence for the scientific basis of purported therapeutic effects and adverse effects of herbal supplements continues to grow. Many herbal supplements are touted for their immunostimulatory properties, and both in vitro and in vivo experiments have supported this claim. Although this explains their beneficial effects in preventing or curtailing disease, to our knowledge, no immunostimulatory herbal supplements have been reported to exacerbate disorders of immune system overactivity.

**Observations:** We describe 3 patients whose autoimmune disease onset and/or flares correlated with ingestion of herbal supplements with proven immunostimulatory effects. *Echinacea* and the alga *Spirulina platensis* are implicated in 2 patients' flares of pemphigus vulgaris, and a supplement containing the algae *Spirulina*

*platensis* and *Aphanizomenon flos-aquae* was ingested by a third patient days before both onset and a severe flare of dermatomyositis. The third patient showed heterozygosity for a tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) promoter polymorphism (-308A), leading to increased production of TNF- $\alpha$ , which may have predisposed her to developing dermatomyositis.

**Conclusions:** Immunostimulatory herbal supplements may exacerbate preexisting autoimmune disease or precipitate autoimmune disease in persons genetically predisposed to such disorders. Increased production of TNF- $\alpha$  may play a role, although more research is needed to clarify the mechanisms of such phenomena.

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**H**ERBAL SUPPLEMENTS CONTINUE to be widely used as natural promoters of good health, many ingested for their purported immunomodulatory effects. A review<sup>1</sup> of survey data on dermatologic patients showed a lifetime prevalence of complementary medicine use of 35% to 69%. Over time, adverse effects of these supplements have become apparent.<sup>2-5</sup> The transplant community has known of the clinically significant effects of an immunosuppressive herbal extract that suppresses CD28 costimulation of human T cells to a degree comparable to cyclosporine.<sup>6</sup> The general medical literature reflects concern that immune-stimulating herbs might oppose the immunosuppressive effects of corticosteroids and cyclosporine.<sup>7</sup> It follows that immunomodulatory supplements might affect disease severity in patients with autoimmune disorders. There are a few reports on the use of herbal supplements in treating autoimmune disorders,<sup>8</sup> but no reports on immune-enhancing herbal supplements ex-

acerbating autoimmune disease. A search of the dermatologic literature reveals no reports on interactions of herbal supplements with autoimmune dermatologic disease.<sup>5,9-11</sup>

We describe 3 patients whose flares and/or onset of their dermatologic autoimmune conditions occurred within days of initial ingestion of herbal supplements shown to have immune-stimulating properties. The herbal supplements implicated are *Echinacea* and the algae *Aphanizomenon flos-aquae* and *Spirulina platensis*.

## REPORT OF CASES

### CASE 1

Patient 1 was a 55-year-old, white man who was diagnosed as having pemphigus vulgaris in 1995. His medical history was notable for chronic uveitis, which required long-term treatment with systemic steroids, and osteoporosis secondary to long-term systemic steroid use. At diagnosis, the patient had not taken sys-

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**Figure 1.** Patient 3 exhibits erythema over the knuckles of both hands, consistent with Gottron sign of dermatomyositis.

temic corticosteroids for 4 months. His disease was gradually controlled with prednisone, dapsone, and azathioprine. The patient achieved complete clearance of lesions in October 1997 and continued to be clear of lesions after prednisone and azathioprine therapy was discontinued in May 1998, after which he received low doses of dapsone.

In October 1998, he developed an upper respiratory tract infection (URI) and began taking an *Echinacea* supplement daily. He had never before taken an herbal supplement. He developed blisters on his trunk, head, and oral mucosa within 1 week of starting the supplement. He had not had oral mucosal lesions since onset of the disease. After discontinuing the use of the *Echinacea* supplement, partial disease control, but never complete remission, was achieved with prednisone, azathioprine (later changed to mycophenolate mofetil), and dapsone.

### CASE 2

Patient 2 was a 57-year-old, white man who was diagnosed as having pemphigus vulgaris in June 2001. His medical history was remarkable for mild asthma and allergies to animal dander and dust. Medications at initial examination were albuterol inhaler as needed and loratadine as needed. Disease control was achieved with prednisone, azathioprine, and occasional intralesional injections of triamcinolone acetonide, 5 mg/mL. Throughout 18 months, the patient's disease improved and was relatively stable with 3 small flares at least 2 months apart. Each resolved in 2 weeks with a small increase in dose of prednisone.

In January 2003, the patient was stable while taking azathioprine, 75 mg orally once a day, and prednisone, 5 mg orally every other day. He began taking a mixture of Siberian ginseng and *Ginkgo biloba* orally twice daily and Nutralite Double X Multivitamin-Multimineral (Amway Corporation, Ada, Mich) orally 3 times daily. In addition to vitamins and minerals, this supplement contains the alga *S platensis* and quercetin, a component of *G biloba*. Within 7 to 10 days, he experienced a flare of pemphigus vulgaris. By the patient's assessment, this flare was "twice as bad" as his usual flares. He immediately discontinued tak-

ing the herbal supplements (which he had never taken before this episode) and increased his prednisone dose. The flare resolved in 2 weeks. One week after clearance of this flare, a second flare occurred, still worse than his usual flares. The patient had never experienced 2 flares in such quick succession.

### CASE 3

Patient 3 was a 45-year-old, white woman with a history of hypertension, chronic migraines, and fibromyalgia (spontaneously resolved 1 year ago). In January 2002, she began taking UltraVite multivitamin (Douglas Laboratories, Pittsburgh, Pa), vitamin C, calcium, flax oil, The Essential Woman Supplement (Barlean's Organic Oils, Ferndale, Wash) ( $\omega$ 3 fatty acids, lignans, isoflavones, saponins [component of ginseng], rosemary, and vitamin C), and BioChoice immune<sup>26</sup> supplement (Legacy for Life, Melbourne, Fla) (which she stopped taking by the end of January 2002 because of diarrhea). In February 2002, she started taking a new supplement called You're My Everything (Vision Inc, Sarver, Pa), which is composed of organic cayenne pepper, methylsulfonylmethane (also known as organic sulfur), and the algae *A flos-aquae* and *S platensis*. Within 1 to 2 days, she developed redness on her face and over the knuckles of her hands. She discontinued taking You're My Everything. Evaluation by a dermatologist led to a diagnosis of rosacea. During treatment with metronidazole cream and subsequent minocycline, 50 mg orally every day, the rash extended to her neck and chest.

The skin manifestations were unchanged during the next few weeks despite 10 days of taking prednisone, 40 mg orally every day. In mid March 2002, the patient restarted taking You're My Everything and started taking E3 Enzymes Supreme (Vision Inc) (digestive enzymes, amla berry, papain, bromelain, sprout, and grass extract). Four days after rechallenge with You're My Everything, she awoke with worsening of the rash, including significant swelling of her face, eyes, and ears. Her dermatologist prescribed prednisone and desloratadine, referred her to an allergist, and discontinued her use of all vitamins and supplements. Subsequent workup by various physicians during the next 4 weeks resulted in the following laboratory findings: normal complete blood cell count; normal chemical analysis results; normal liver function test results; aldolase, 4.7 U/L (reference range, 1.2-7.6 U/L); erythrocyte sedimentation rate, 2 mm/h; total creatine kinase, 33 U/L (reference range, 24-173 U/L); and C-reactive protein, 0.8 mg/L (reference range, 0.0-4.9 mg/L). An antinuclear antibody titer was 1:160, and a biopsy specimen showed interface dermatitis with basal vacuolization.

When the patient was examined at this point, physical examination findings revealed erythema on the extensor arms, elbows, knuckles of the hands, face, upper back, and neck (**Figure 1**). She had a heliotrope rash (**Figure 2**). Based on her presentation and prior biopsy specimen, a diagnosis of dermatomyositis was made. She began taking prednisone, hydroxychloroquine sulfate, tacrolimus ointment, cetirizine hydrochloride, appropriate calcium supplementation, and a bisphosphonate.

The patient's course improved slowly, but her condition did not completely resolve. Six months later, new muscle weakness developed with elevated levels of aldolase (22.6 U/L), total creatine kinase (2018 U/L), aspartate aminotransferase (142 U/L), and alanine aminotransferase (66 U/L). She was also heterozygous for the -308A tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) promoter polymorphism, whose phenotype is increased TNF- $\alpha$  production.

## COMMENT

### CASE 1

*Echinacea*, or the purple cornflower, has been used for centuries for its medicinal effects. Of the most commonly used species (*Echinacea angustifolia*, *Echinacea purpurea*, and *Echinacea pallida*), *E purpurea* has become one of the most popular herbal supplements in Europe and the United States.<sup>12</sup> Today, *Echinacea* is popularly known as an immune-enhancing agent for shortening the duration of common URIs. Relative composition of active components varies by species, growth conditions, and stage of development at time of harvest. Commercial preparations contain various amounts of any or all 3 species and may contain plant (or herb) portions only, root portions only, or both.<sup>12,13</sup>

Both murine and human studies support the immune-enhancing effect of *Echinacea*. Purified polysaccharide portions of *E purpurea* were shown in vitro to significantly increase murine macrophage production of interleukin (IL) 1, IL-6, and TNF- $\alpha$  compared with controls, but to a lesser extent than that induced by lipopolysaccharides (LPSs), and to have no effect on T-cell activation or B-cell proliferation.<sup>14,15</sup> The first of these studies<sup>14</sup> showed that macrophage cytotoxic effects increased to a degree comparable to that induced by interferon gamma. These results were achieved in both peritoneal macrophages (collected after stimulation by intraperitoneal injection of either starch or thioglycolate) and bone marrow-derived macrophages, whose activity would not be influenced by prior activation or co-existing T lymphocytes. The second study<sup>15</sup> demonstrated that macrophage activity increased 10-fold in vivo after intravenous (IV) injection of the purified polysaccharide. An in vitro study<sup>4</sup> on human lymphocytes confirmed that *E purpurea* had no lymphoproliferative effect and showed no effect on lymphocyte production of IL-2 or IL-10. Burger et al<sup>16</sup> first reported use of an unpurified extract of *E purpurea* in human macrophages, which increased production of IL-1, IL-10, and TNF- $\alpha$  to levels comparable to that achieved with LPSs. Production of IL-6 was stimulated to levels less than that accomplished by LPSs. To address the questionable reliability of applying in vitro and IV in vivo studies to the situation of ingested *Echinacea*, Rininger et al<sup>17</sup> subjected extracts of both the *E purpurea* and *E angustifolia* species to a simulated digestion protocol, before applying the extracts to murine macrophages, and found increased production of IL-1, IL-6, IL-10, TNF- $\alpha$ , and nitric oxide (as a measure of macrophage activity).

*Echinacea* has shown stimulating effects on natural killer (NK) cells. An herbal extract of *E purpurea* applied in vitro to human cells increased NK function and



Figure 2. Heliotrope rash in patient 3.

antibody-dependent cell cytotoxicity. Immune cell activity in treated cells of patients with chronic fatigue syndrome or acquired immunodeficiency syndrome approached levels found in untreated cells from healthy subjects.<sup>18</sup> The *E purpurea* root extracts ingested by mice increased NK cell function in aged mice to levels found in young adult mice<sup>19</sup> and increased numbers of splenic NK cells in a mouse erythroleukemia model, resulting in a significantly increased life span.<sup>20,21</sup>

In contrast to these studies, *E purpurea* juice given orally to healthy humans in a double-blind, placebo-controlled, crossover study<sup>22</sup> had no effect on phagocytic activity of polymorphonuclear lymphocytes (PMNLs) or macrophages and no effect on macrophage production of TNF- $\alpha$  or IL-1 $\beta$ . A review<sup>23</sup> of 5 randomized studies that examined immunomodulatory effects of *Echinacea* on humans, as measured by phagocytic activity of PMNLs, reported that 2 studies showed significantly increased phagocytic activity, whereas the remaining studies showed no effect. This review illustrates the problems in comparing studies on *Echinacea*: variation in mode of extract administration (oral vs IV vs in vitro), variation in the preparation of extract used (plant portion vs root portion vs both, species variation, and mode of extraction), and variation in methods of measuring outcome. No adverse effects on cell viability were found at concentrations of *Echinacea* extracts greater than those at which immune-enhancing effects were seen.<sup>14,15,17</sup>

Most of these cytokine studies that provide substantial evidence for the stimulatory effect of *Echinacea* on the human immune system are in vitro or in vivo with IV administration of *Echinacea*, which might prompt one to question the reliability of extrapolating these effects to human oral consumption of *Echinacea*. Because there are conflicting results in the few human, oral ingestion studies<sup>23</sup> looking at the effect of *Echinacea* on PMNL activity, it would be premature to conclude with current data that ingested *Echinacea* does not stimulate proinflammatory cytokine production in humans.



In this patient whose pemphigus vulgaris had been in remission with minimal medication for several months, the temporal relationship of his disease flare with ingestion of *Echinacea*, which has known immune-stimulating properties, is strongly suggestive of a causal relationship. We cannot rule out the possibility that patient 1 experienced an exacerbation as part of the natural course of his condition, nor can we dismiss the possibility that his URI contributed to his flare. However, because he had been free of lesions for a year while taking low doses of medication and had contracted other URIs during that time without disease exacerbations, one must consider the effect *Echinacea* might have had on his disease.

## CASE 2

Like *Echinacea*, there are 3 medicinal species of ginseng: *Panax ginseng* (Chinese or Korean ginseng), *Panax japonicus* (Japanese ginseng), and *Panax quinquefolius* (American ginseng). Siberian, or Russian, ginseng belongs to the same family (Araliaceae) as *P ginseng* but to a different genus: *Eleutherococcus senticosus*.<sup>24</sup> Relative amounts of active components in extracts vary, depending on growing conditions, age of the plant at time of harvest, and season of harvest.<sup>25</sup>

Data to date on *Eleutherococcus* support mainly an immune-inhibiting effect. Murine studies showed dose-dependent decreases in anaphylaxis-induced death from orally ingested extracts, decreases in IgE-mediated cutaneous allergic reactions, in vitro inhibition of histamine and TNF- $\alpha$  production,<sup>26,27</sup> and no effect on macrophage cytokine production.<sup>28</sup> In vitro studies<sup>29</sup> on human whole blood showed nonstatistically significant, variable effects of *Eleutherococcus* on IL-12, IL-6, IL-4, and IL-5. A single study<sup>30</sup> showed immune-enhancing effects via increased lymphocytic blastic transformation and increased PMNL phagocytic activity in humans after oral ingestion of an *Eleutherococcus* root extract.

Extracts of *G biloba* have also induced mainly immune-inhibiting effects. In vivo (intraperitoneally administered extract) studies<sup>31,32</sup> showed decreased LPS-induced nitric oxide and TNF- $\alpha$  production in murine macrophages. An in vitro examination of human PMNLs showed stimulation of the respiratory burst in a concentration window of 2 to 5  $\mu$ M, outside of which the effect was inhibitory. This led the authors to conclude that *G biloba* extract acted as a partial agonist on PMNLs rather than a pure antagonist.<sup>33</sup>

Based on these studies, the evidence is lukewarm that either *Eleutherococcus* or *G biloba* produces a sufficient immune-stimulating effect that might have led to the pemphigus vulgaris flare in patient 2. A more likely candidate is *S platensis*, the alga found in Nutrilite Double X Multivitamin-Multimineral. *Spirulina* is commercially produced as an agricultural feed additive and nutritional supplement for humans due to its high concentration of protein, vitamins, and minerals. In vitro studies<sup>34</sup> on cat macrophages demonstrated that *Spirulina* induced increased phagocytic activity against *Escherichia coli* and sheep red blood cells. Cytotoxic effects were negligible. More confidently applicable to human consumption of the supplement is an in vivo study<sup>35</sup> that showed that chicks given *Spirulina*-laced feed produced increased num-

bers of macrophages with a corresponding overall increased phagocytic activity and increased nitrite production (both LPS and non-LPS induced). Finally, a human study<sup>36</sup> revealed that an orally administered hot water extract of *Spirulina* enhanced NK cell function, as measured by interferon  $\gamma$  production and cytolysis.

As with patient 1, the temporal relationship of a pemphigus vulgaris flare occurring within days of ingesting these supplements is highly suggestive of a causal relationship. We cannot exclude the possibility that this patient may have experienced a flare in conjunction with a standard prednisone taper. However, the fact that this flare diverged from the usual behavior of his disease in severity and proximity to the second flare occurring after supplement ingestion suggests that the herbal substances played a role in these events. Of all the substances ingested by patient 2, the evidence for immune-stimulating properties is strongest for *S platensis*.

## CASE 3

Although patient 3 ingested many substances, the only one temporally related to both onset and severe flare of her dermatomyositis was the supplement You're My Everything, the only new supplement taken before onset of her symptoms and before the severe flare. You're My Everything contains the algae *S platensis* (*Pacifica* strain) and *A flos-aquae*; both are used as nutrient-dense food supplements in domesticated animals and humans. The evidence for immune-stimulating properties in both *Spirulina* and *A flos-aquae*, along with the clinical history, led us to believe these substances may have precipitated her autoimmune disease.

Two in vitro studies<sup>37,38</sup> on the effect of *A flos-aquae* on human monocytes and macrophages showed activation of the NF- $\kappa$ B pathway comparable to LPS-induced activation and increased expression of IL-1 $\beta$  and TNF- $\alpha$ . TNF- $\alpha$  has been implicated in the pathogenesis of systemic lupus erythematosus in that on UV light stimulation its increased production induces keratinocyte apoptosis, which in turn brings nuclear antigens to the cell surface.<sup>39</sup> Antibody production to these exposed nuclear antigens results in development of lupus. In addition, a polymorphism of the TNF- $\alpha$  promoter (-308A) has been associated with systemic lupus erythematosus,<sup>40,41</sup> subacute cutaneous lupus erythematosus,<sup>42</sup> and dermatomyositis,<sup>43</sup> all photosensitizing conditions. This polymorphism produces a phenotype of increased TNF- $\alpha$  secretion, which may predispose an individual to developing a photosensitizing autoimmune disease. Because pathogenesis of autoimmune disease is multifactorial, including genetic and environmental factors, this evidence strongly suggests that in the setting of a genetic predisposition to developing a photosensitive autoimmune disease, ingestion of an immune-stimulating herbal supplement may have been the final step in producing clinical disease.

## CONCLUSIONS

We describe 3 patients with either pemphigus vulgaris or dermatomyositis in which autoimmune disease onset and/or flares occurred within days of herbal supplement inges-

tion. We propose that the immune-enhancing effects of these herbal supplements significantly contributed to disease activity. Animal and human studies on the herb *Echinacea* and the algae *Splatisensis* and *A flos-aquae* support a role for these substances in increasing activity of macrophages, NK cells, and neutrophils and promoting production of the proinflammatory primary cytokines IL-1 and TNF- $\alpha$ , among other effects. It may be that in a background of genetic predisposition to autoimmunity, such as the -308A TNF- $\alpha$  polymorphism associated with photosensitizing autoimmune conditions such as dermatomyositis, an immune-stimulating supplement tips the scales in favor of producing clinical disease. Additional studies are necessary to explain the mechanisms of herb-induced exacerbations in pemphigus vulgaris, although TNF- $\alpha$  is implicated in the pathogenesis of the disease.<sup>44,45</sup> This is the first report, to our knowledge, that describes exacerbation of an autoimmune process precipitated by immune-stimulating herbal supplements.

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