Herbal Supplements and Athlete Immune Function –What's Proven, Disproven, and Unproven?

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ABSTRACT

*The purpose of this paper is to critically evaluate current immunological and clinical literature regarding the effects of herbal preparations on athlete immune function. First, we review rates of herbal supplement use by athletes. Second, we use ginseng (*Panax ginseng*) and coneflower (*Echinacea spp.*) as models for examining how herbal supplements may influence immune function within the contexts of exercise and sport, while briefly considering several other popular herbal products. Third, we proffer several evidence-based hypotheses to explain apparent discrepancies among the cumulative data, concomitantly advancing a novel conceptual framework which may be useful to understanding herbal supplements and athlete immune function using Echinacea supplements as a model. Fourth, we apply the proposed framework to some prospective data regarding the effects of* Echinacea pallida *and* Echinacea simulata *on in vitro cytokine production and cell proliferation in peripheral blood mononuclear cells collected from male collegiate wrestlers and soccer players during training. Fifth and finally, we evaluate the current knowledge on herbal supplements and athlete immune function, identify gaps and limitations in knowledge, and advance several possible options for future research.*

Keywords: botanical supplement; dietary supplement; exercise; phytomedicine; soccer; sport; wrestler

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INTRODUCTION

The study of herbal supplements in the context of athlete immune function is both fascinating and frustrating for the same reason: its multidisciplinary nature. Simply dissecting out the major terms in the first half of the title reveals this, as in "herbal" (botany), "supplement" (nutrition), "athlete" (exercise physiology), and immunology. Intimately related to these more obvious fields are concepts from chemistry, medicine, and pharmacology. To some readers these latter fields may seem tangential or inconsequential to the primary focus of exercise immunology; however, knowledge from these other fields is integral to truly appreciate the topic and to make appropriate recommendations to athletes, coaches, and trainers. The challenge, and the humble privilege, for any author team tackling such a rich subject is to bring together these different academic disciplines into a cohesive, easily-understandable whole that increases readers' factual knowledge of the topic but also diversifies their conceptual perspectives.

We begin by surveying the extent of herbal supplement use at the level of the general public and then specifically among athletes in our first section, "Athletes' Use of Herbal Supplements." Then, we more narrowly examine those herbs with purported immune-influencing effects in "Herbal Supplement Use in the Context of Athlete Immune Function." Two individual herbs and their specific effects on athletes' immune function garner the foci of the next two sections, "Ginseng and Athlete Immune Function" and "Echinacea and Athlete Immune Function." These two plants were selected for consideration because they are widely used by athletes, are better-researched by comparison to most other options, and represent both Eastern and Western herbs. After considering the cumulative data, we switch attention to factors that have been thus far neglected in most published work but which evidence suggests will influence immune outcomes of herbal supplements in "Rationale for a Multidisciplinary Approach." Using Echinacea as a model, we develop an evidence-based conceptual framework to identify these factors (in "Reconciling Discrepancies in the Literature using Echinacea as a Model"), then demonstrate the utility of the framework via an experimental context (in "Prospective Data"). Coming full-circle, we return again to our title but this time consider its last half by surveying the cumulative evidence and critically considering which aspects of herbal supplement use by athletes have been substantiated, which have been debunked or called into question, and which remain scientifically unexplored in "Conclusions". No single scholastic work can expect to fully address all aspects of this subject, but we hope that our article might serve as a "first step".

Athletes' Use of Herbal Supplements

In this section, we will characterize the scope of herbal supplement use two ways: by society in general and by athletes specifically. Studies reviewed here span age, gender, and cultural spectra, and demonstrate that herbal supplement use is heterogeneous and influenced by several factors. Our objective is to show that herbal supplement use is prevalent in both groups (but more so in athletes), and that the volume of athlete herbal supplement use constitutes a meaningful and compelling need for continued research on the topic.

Delineating the extent of herbal supplement use among athletes is difficult for a couple reasons. Semantics are the largest impediment. Neither the scientific community nor the general public uses the term "herbal supplements" consistently. "Herbal supplements" may variously be called "botanicals," "herbs," or "phytomedicines." Often they are included under the broader category of "nutritional supplements" or "dietary supplements", which can include everything from isolated vitamins and minerals to everyday foodstuffs. From a medical standpoint, herbal supplements are frequently classified as "complementary and alternative medicine" (CAM) or, for herbs with purported performance-enhancing properties, as "ergogenic aids."

For the purposes of this review, we are defining "herbal supplements" as products derived directly from plants which contain multiple compounds; supplements containing isolated molecules such as caffeine or plant-derived steroids are excluded from consideration. Accordingly, a supplement containing ephedrine in isolation could not be considered here, but a supplement containing a root extract of Ma Huang (*Ephedra sinica*, the plant from which ephedrine is produced) could be considered. We make one exception for the isolated compound quercetin because of its presence in Echinacea (discussed later). We adopted this definition because it was most congruent with that used by the majority of researchers.

Inconsistent use of the term "herbal supplements" creates scientific problems when surveying herbal supplement use by athletes. Investigators may perceive use of the term differently than their study participants, and different researchers may interpret participants' responses to open-response surveys (which many of the investigations below are) heterogeneously. Few researchers have addressed this concern in their work, and few specifically clarify their own use of the term. As an example, in one study authors reported that elite swimmers self-defined "supplement" differently, with some focusing only on vitamins and minerals whereas others included "sports foods" and herbal products in their definition (11). In another study of division I college varsity athletes, when asked to give their own definition of "supplement", 34% of respondents variously answered that a supplement "helps increase performance, strength, muscle, and enhance recovery" (57). Curiously, the authors gave other popular definitions in addition to the variations above, yet "herb" was never mentioned. These findings suggest that athletes' responses to the same survey question may vary greatly, may not coincide with the investigators' intentions for the survey item, and may not reflect "true" supplement usage. Athletes may misreport (either over or under) their use of such supplements based on whether those products are perceived negatively or positively by their coaching staff or the society/culture in which they live.

Aware of these caveats, we can now proceed to a consideration of data. In Europe, herbal supplements constitute a $5 billion industry, but France and Germany alone account for 60% of the market, suggesting that use differs by country (43). Estimates of herbal supplement use by citizens of the United Kingdom vary from 10-25% (and are growing), and herbal supplements currently constitute a £3.8 million annual industry (70, 135). Similarly, rates of herbal supplement use in the United States have risen dramatically since the 1990s, from about 3% to about 25% of the population by one estimate or a 380% growth by another (14, 15, 49), generating to a $4.4 billion industry (26).

Herbal supplement use by the youth sector may account for some of this growth. A survey of 1280 United States adolescents found that 46% had used herbal supplements in their lifetime and that 29% were current users; leading the list of specific herbs used were herbal or green tea (4% currently; 22% in lifetime), ginseng (4% currently; 17% in lifetime), and Echinacea (6% currently; 14% in lifetime) (177). Females used herbs more often than males (though more males consumed ginseng than females), and individuals in middle adolescence (16-17 year-olds) used herbs more often than older or younger adolescents (177). A survey of Canadian adolescents found that 5.8% of females and 2.8% of males use "herbal weight control products" (which may contain caffeine and ephedrine) (12).

Economic figures and rates of use only tell part of the story. Nature-of-use also varies widely around the world. For instance, herbal medicine in China (often referred to as "traditional Chinese medicine" or TCM) has a much longer history and is regulated whereas herbal medicine use in countries like the United States is much younger and unregulated (96). China emphasizes the use of whole herbs moreso than the United States, the latter which often markets isolated compounds over multicomponent extracts (96). Today, Eastern and Western cultures are influencing each others' use of herbal supplements. To adduce, Japan has a long tradition of herbal medicine use, but Western perceptions of herbal medicine may be contributing to a decline in herbal medicine popularity in Japan (139). Taken together, these studies suggest that herbal supplement use varies by age, gender, cultural-political, and temporal factors.

Most studies of athlete supplement use focus on nutritional supplement use generally (primarily vitamins and minerals) and seldom delve into specific herbal products. Table 1 presents a brief overview of some studies which do address athlete herbal supplement use specifically (6, 11, 57, 73, 75, 90, 105, 122, 128, 152, 155, 163, 167, 189). These studies encompass individuals of differing ages, ethnicities, genders, levels of competition, and sports. However, given the relatively small number of studies in specific areas, any inferences drawn should be considered preliminary.

Athletes' use of herbal supplements is higher than that of the general public, ranging from 17-61% (11, 57, 73, 189). One study found that athletes were more willing to take herbal supplements than nonathletic controls (153), possibly because many herbal supplement marketing campaigns target athletes with promises of improving performance or decreasing side effects of training (178). Gender differences among athletes are not so clear, as some studies have found that male athletes used supplements more often than female athletes (57, 189), others have found the opposite (75, 91), and still others found no differences between genders (90, 152). However these latter studies did report that varsity men were more likely than control men to use supplements (90), and that female athletes were more likely to take ginseng and homeopathic supplements compared with males (152). No differences were found by ethnicity in a study of college varsity athletes (91).

Patterns of herbal supplement use may change throughout the year as athletes oscillate into and out of competitive seasons and/or training regimens (122). Some of the studies in Table 1 quantified use by specific herbs. Echinacea and ginseng were consistently the two most popular herbs, with usage rates ranging

Table 1. Selected reports of herbal supplement use among athletes. Ab breviations in "Key Findings": BS = botanical supplements; DS = dietary supplements; FS = food supplements; HS = herbal supplements; NS= nutritional supplements. Ma Huang is a traditional name for *Ephedra sinica*. *Spirulina* is a genus of cyanobacterium ("blue-green algae").

Study (Ref.)	Region	Sample Size	Athlete Descriptors	Key Findings
Bahr et al. 2003 (6)	Norway	81	2002 Olympics participants	• 80% used NS • 27% of NS users reported Echinacea use • NS use was not different between males and females • NS use was higher in endurance compared to technical athletes
Baylis et al. 2001 (11)	Australia	77	"Dolphin Squad" of nationally-recognized elite swimmers, both junior and adult	• 61% reported HS use • Specific supplements used (32 different brands reported): Echinacea 39% Mixed HS preparations 16% Garlic/horseradish 16% (9 different brands reported) Ginseng 8% (6 different brands reported) Evening primrose 3% "Chinese preparations" 4% Spirulina 1%
Froiland et al. 2004 (57)	United States	207	Division I university varsity athletes (56% male)	• 26.5% used herbals (10.3% female, 16.7% male) • Specific herbals used: Ginseng 13% (3.4% female, 9.9% male) Echinacea 9.7% (5.4% female, 4.4% male) Ma Huang 6.3% (1.5% female, 4.9% male) St. John's Wort 3.4% (1% female, 2.5% male) Ginkgo 3.9% (1% female, 3% male) • Reasons given for use: Prevent injury/illness 28.5% (14.7% female, 14.2% male) Help heal injury/illness 16.4% (6.8% female, 9.8% male) • Athletes were grouped into 4 categories by "sport metabolic demand." Herbals were consistently used more highly in the group defined by "relying on combination of the phosphagen system, anaerobic glycolysis, and aerobic metabolism" (track-and-field, football, wrestling, and soccer)

Table 1, continued

Herbold et al. 2004 (73)	United States	162	Collegiate female varsity athletes (mean age 19.5 y)	• 17% used HS/BS • Specific HS/BS used: Echinacea 13.7% Ginseng 6.2% Wheat germ 5.6% Ciwujia (Siberian ginseng) 3.7% Goldenseal 3.7% Spirulina 2.5% St. John's Wort 1.2% Brewer's yeast 1.2% Flax oil 0.6% Kola nut 0.6% "Ecstacy" 0.6% (this supplement was classified as an HS)
Huang et al. 2006 (75)	Canada	557	1996 (Atlanta) and 2000 (Sydney) Summer Olympics Canadian athletes	• 69% of 1996 Atlanta athletes used DS; 39% used NS • 74% of 2000 Sydney athletes used DS; 47% used NS • Supplements were used more often by females than males • Specific supplements used: Echinacea (1996=7%, 2000=6%) Ginseng (1996=4.7%, 2000=1.7%) "Blue-green algae" (1996=2.3%, 2000=0.3%) Peppermint (1996=1.9%, 2000=0.3%) Garlic (1996=1.6%, 2000=1.3%)
Kristiansen et al. 2005 (90)	Canada	211	Varsity athletes at University of British Columbia, 57% male, (mean age ~21 y)	• Echinacea was the most frequently reported "nonvitamin mineral supplement", mainly "to prevent illness"; typically used only 1 -5×/month • Ginseng, tea tree oil, Ginkgo, and guarana were "used by only1 or 2 athletes, generally 1 to 10 times a month" • Ginseng users reported taking it to "enhance performance" • Respondents were asked to indicate if they wanted to learn mor e about any supplements: Ephedra: 4 respondents: side effects and risks Echinacea: 4 respondents: general effects Ginkgo: 3 respondents: general effects Valerian: 1: influence on sleep

Table 1, continued

Massad et al. 1995 (105)	United States	509	Athletes from 6 Indiana high school s participating in at least 1 sport, 59% male, mean age 16.7 y	• 4.5% of subjects used ginseng daily-weekly • 6.7% used “steroid alternatives” (by the authors’ use, this phrase could potentially include herbal products, but no specifics are given) • Participants were given the statement “The ingredient ‘yohimbe bark’ (an ingredient in some steroid replacers) is a natural source of methyltestosterone, an illegal anabolic steroid. Since yohimbe bark is a natural ingredient, it is safe.” 66.4% of respondents believed this statement was false (correct answer), 31.5% believed it was true.
Nieper 2005 (122)	United Kingdom	32	Competitive UK junior track-and-field athletes (mean age 18 y)	• 62% used NS • 40% reported using NS for “immune system” • Specific herbs not reported
Petroczi & Naughton 2008 (128)	United Kingdom	874	“High-performing” adult athletes	• 60% used NS • Specific NS used: Echinacea (30.9%) Ginseng (<11%)
Slater et al. 2003 (152)	Singapore	160	Nationally-recognized athletes, variety of sports	• Specific supplements used: Ginseng (15%) to “improve general health” Ma Huang (4 individuals) “Caffeine/guarana” (4 individuals)
Steen et al. 2001 (155)	United States	737	Collegiate wrestlers	• Echinacea was used by 4.6% “to help the immune system” • Vitamins and minerals were also used to assist with immune function
Tsitsimpikou et al. 2009 (163)	Worldwide	1779	2004 (Athens) Summer Olympics athletes	• 48% used FS • ~1% used “homeopathic agents; ” of these, 52% of agents contained *Tribulus terrestris*
Vinci et al. 2004 (167)	United States	108	Ultramarathon runners	• 83% used NS • Specific NS used: Echinacea, ginkgo, ginseng, grape seed, saw palmetto

Table 1, continued

Ziegler et al. 2003 (189)	United States	46 m, 59 f competing in the 2001 U.S. Figure Skating National Championships, m 16.9 y, females 15.2	• 48% of females and 44% of males reported HS use • Specific HS used: Echinacea (44% female, 28% male) Ginseng (10% females, 20% males) Chamomile (2% females, 8 % males) Ginkgo (2% females, 8% males) Garlic (2% females, 5 % males) Green tea (2% females, 5 % males) St. John's Wort (2% females, 3% males) Kava kava (0% females, 5% males) Ephedra (0% females, 0% males) "Others" (0% females, 13% males) • 61% of females and 34% of males gave "prevent illness or disease" as a reason for HS use

from 6.5-39% for Echinacea and 3.2-15% for ginseng (11, 57, 73, 75, 128, 189). Athletes gave several reasons for taking supplements; from an exercise immunology perspective, those uses pertaining to health or disease bear mentioning. Most frequently, athletes reported consuming herbs to prevent or heal illnesses or injuries (57, 91, 189), to support the immune system (122, 155), or to strengthen overall health (152). Upper respiratory tract infections are one of the biggest concerns to athletes; alongside exercise training factors, nutritional supplement use has been posited as one of several lifestyle factors that may impact on infection rates (89).

Bearing in mind that many of the studies displayed in Table 1 were not designed to measure herbal supplement use specifically, future studies of herbal supplement use in athletes should focus on improving methodology, examining contributing factors to use, and being more representative. First, general surveys of "supplement use" by athletes should include indexes for herbal supplements in addition to traditional vitamin/mineral or food categories. Second, the surveys themselves should explicitly define use of the term "herbal supplement" for each respondent to ensure consistent use and clarity across participants, and survey administrators should use a consistent rubric for evaluating surveys and report their strategy in publication. Third, gender differences in herbal supplement use need to be clarified, possibly by examining confounding variables such as age, specific sports, or geographic locale. Fourth, more information needs to be collected on herbal supplement use in middle-aged or older athletes or physically-active adults.

Herbal Supplement Use in the Context of Athlete Immune Function

In this section, we will preview the research done regarding specific herbal supplements used by athletes. Our goal is to impress upon the reader that very few studies of herbal supplements in athletes include immune parameters, and to explain why ginseng and Echinacea were selected for detailed review.

Exercise scientists and other biologists have produced hundreds of scientific reports related to the use of herbal supplements in specific exercise or sport contexts. The overwhelming majority of these studies *do not* explore effects on immunity because the main use of the herb is to improve aerobic or anaerobic capacity and not immune function. Regrettably then, most such studies do not include any information that can assist with this review. For instance, two herbs with relatively-well studied effects on athletes include *Rhodiola rosea* (41, 48, 169) and *Tribulus terrestris* (5, 137), both for their purported muscle-enhancing capacities. Yet no studies pertaining to these supplements investigate immune function. Many studies of herbal "ergogenic aids" are consequently excluded from this review because no information is given related to immunity; however, excellent reviews of such preparations may be found elsewhere and encompass use across age, gender, and sport spectra (13, 18, 30, 34, 106, 138, 162). Potential herbal supplement-drug interactions are also discussed elsewhere (1, 2, 165, 178).

Few studies of herbal supplement use by athletes encompass an immune component, despite prevalent use of herbal supplements by athletes to alter immune function (discussed earlier). Table 2 presents a concordance between common names and scientific names for herbs reviewed by this article. After surveying the available literature, we selected ginseng and Echinacea for further

Table 2. Concordance between common and Latin names of herbal supplements discussed in this review, along with other taxonomic data and primary use. "Selected species" were chosen based on commercial use and relevance for this review. Abbreviations in "Genus and Selected Species": "c" = coneflower, "g" = ginseng. * Korean ginseng has some alternative, presumably phonetic, spellings historically including *P. schinseng*, *P. shinsen*, and related variations. † Syn *Acanthopanax senticosus*. ‡ The common name "St. John's Wort" has historically been applied to several species but medicinally almost always refers to *H. perforatum*.

Common Name	Genus and Selected Species	Family	Total # of Species in Genus	Endemic Geography	Primary Uses	References
Coneflower	Genus: *Echinacea* Selected Species: *E. angustifolia* (narrow-leaved c.) *E. pallida* (pale c.) *E. purpurea* (purple c.)	Asteraceae	9	North America	Prevention and treatment of upper respiratory infections	(9, 112)
Ginseng	Genus: *Panax* Selected Species: *P. ginseng* (Asian, Chinese, Korean g.)* *P. notoginseng* (sanchi) *P. quinquefolium* (American g.) *P. vietnamensis* (Vietnamese g.)	Araliaceae	18	East Asia (some North America)	Improve athletic performance, strengthen central nervous system	(25, 84, 95)
Ginseng, Siberian	*Eleutherococcus senticosus* †	Araliaceae	31	Asia	Improve athletic performance, anti-stress	(45, 171)
Ma Huang (Ephedra)	*Ephedra sinica*	Ephedraceae	60	Globally (dry regions)	Improve athletic performance, reduce weight	(77, 82)
Soybean	*Glycine max*	Fabaceae	9+	Asia, Australia, Pacific Islands	Food, cardiovascular health, phytoestrogen	(54, 76)
St. John's Wort	*Hypericum perforatum*‡	Hypericaceae (Clusiaceae)	~450	Globally (temperate regions)	Antidepressant	(32, 126)

study for several reasons. First, athlete surveys (Table 1) indicate these are the most widely used herbal supplements. Second, they are the only supplements for which we could find sufficient data for meaningful review. Third, ginseng represents a traditional Eastern herbal supplement and coneflower represents an archetypical Western herbal supplement. History and extent of use are consequently different between the two and provide an interesting contrast. Fourth, ginseng and Echinacea have different indications. Ginseng is indicated for a multitude of contexts including improving neurological function or strength (7, 84) whereas Echinacea is indicated almost exclusively for the prevention and treatment of upper respiratory infections (9).

Exercise immunology studies of other herbal supplements commonly used by athletes (such as ginkgo, St. John's wort, and soybean; Table 1) are next to absent. To explain, the only other studies we could locate concerning single herbal supplements and immune function in the context of exercise were swimming studies in rats for both soybean and St. John's Wort. Regarding soybean, one animal study suggested that exercise can offset immunodysregulation which accompanied soybean-based diets (reported by several labs) by restoring murine splenocyte CD4/CD8 T cell ratios and IFN-γ (but not IL-4) secretion rates (94). St. John's wort extracts fed to mice reduced immobility time in the forced swimming test, but this was only true in wild-type mice and not IL-6-knockout mice, suggesting that IL-6 may be involved in the mechanism of action for this herb (33). We also found one study where 16 long-distance runners were given an "herbal yeast" supplement also containing malt, honey, and vitamin C or placebo (61). No effects beyond those ascribed to intense training itself were noted; however, it should be mentioned here that polyherbal preparations present a challenge to data interpretation because it is often impossible to parse out which effects are due to which components.

Ephedra also deserves comment. Ephedra was an herbal supplement popularly used in the latter part of the 20th century to promote weight loss; however, its side effects quickly earned it a reputation of being unsafe, and some countries such as the United States now ban its sale (46, 82, 129). Since few studies of herbal supplement use by athletes exist from this time period, we will likely never know the true prevalence of Ephedra use, but some data from Table 1 indicates it may have been popular. We could not identify any studies that examined immunomodulatory effects of Ephedra.

The paucity of data on immune effects from herbal supplements is clearly an issue to be addressed in future exercise immunology research given their widespread use. In the next 2 sections, we will critically evaluate what is known about the 2 herbal supplements identified earlier, ginseng and Echinacea, in both athletic and immunological contexts.

Ginseng and Athlete Immune Function

The common name "ginseng" may be applied to multiple plant genera (Table 2). Most often it refers to species of the genus *Panax*; commercially important species are given in Table 2, with *P. ginseng* constituting the majority of immunological and physiological studies. Note that "red ginseng" is a moniker ascribed to *P. ginseng* material than has been heat-treated in some way and is not a taxonomic reference. Most *Panax* spp. are found in eastern Asia with the exception of 2 species endemic to North America (*P. quinquefolium* and *P. trifolium*; alternatively given as *P. quinquefolius* and *P. trifolius*). Genetic analyses using chloroplast and ribosomal sequences have confirmed the validity of all names listed in Table 2 but not some infrequently-used species; consequently, the total number of names and species recognized has been in flux even in the last 10 years (38, 95, 188). Confusingly, the name "ginseng" is also applied to so-called Siberian ginseng, originally placed in genus *Acanthopanax* but now removed to genus *Eleutherococcus* as *E. senticosus* (74). Both genera Eleutherococcus and Panax are in the same family (Araliaceae) but they are botanically distinct. We will return to *E. senticosus* following our discussion of genus Panax.

Panax spp. are best known for their over 150 ginsenosides, triterpenoid saponins (a subclass of glycosides) which have documented immunomodulatory and anti-disease (both infectious and noninfectious) properties (39, 160). Other bioactive compounds include methylxanthines such as caffeine, theophylline, and theobromine (166); peptides; polysaccharides; and various alcohols (184). Compounds within the plant may act synergistically to exert their effects (175).

Clinically, *Panax ginsen*g is the best-studied member of this group, and there are many reviews which focus on ginseng's medical role. Of the varied possible clinical applications (84), the use of ginsenosides for modulating central nervous system activity and possible applications to neurodegenerative disorders have been the most recent focus (25, 114, 132), with some other studies researching improvement of mood or cognitive function (83) and possibly quality-of-life (40). Other contexts for ginseng include treatment of cancer (29, 71, 186), cardiovascular disease (31, 187), and diabetes (168, 185). Still other uses may be found elsewhere (39). One research team has noticed a marked disjunct between the traditional Chinese medicinal use for ginseng and those currently being tested by Western methods (184). Several sources observe that clinical studies for ginseng have not been tightly-controlled and that better designs are needed to verify the use of ginseng (31, 168, 187). Clinical and pharmacological studies have also preliminarily validated potential phytomedicinal activities for *Panax notoginseng* (117) and *P. vietnamensis* (8).

The effects of ginseng on physical and mental performance and its capacity as an ergogenic aid have been reviewed elsewhere (7, 30, 123). Generally, studies have found no ergogenic/performance benefit for ginseng despite using a variety of exercise constructs (4, 51, 53, 92). Disagreement exists regarding the effects of ginseng on cardiovascular parameters. One team of researchers reported *P. ginseng* supplementation (equivalent to approximately 4 g root/d for 60 d) had no effect on heart rate, stroke volume, or cardiac output either at rest, during, or after exercise in 30 college-aged males as compared to sugar placebo (52). A different study concluded that 27 35-55 year-old adults who consumed 1.35 g of *P. notoginseng*/d for 30 d demonstrated reduced systolic blood pressure and mean arterial pressure following exercise as compared to 19 control subjects on starch placebo (98). Other studies of ginseng's effects on exercise have been published and most are congruent with the above studies in showing no effect, but the interpretation of ginseng's role in these latter studies is confounded by the presence of other herbal products in the supplements (28, 79). Performance benefits of ginseng supplementation may include altered metabolism during prolonged activity, an increase in cortisol and muscle repair/maintenance capacity (discussed further below), and preservation of immune function despite intense training (142); however, further studies are needed to corroborate these ideas.

Table 3 displays all studies of ginseng in the context of athlete immune function (22, 50, 58, 124). Given that only 4 studies addressed *Panax* spp. in exercise immunology contexts, it is likely premature to generate overarching conclusions about its efficacy in the context of athlete immune function; however, we can use these studies to evaluate preliminary hypotheses and to identify possible directions for future research. Sample sizes ranged threefold and supplementation regimens differed widely, but authors often described their regimens with fair enough thoroughness for repeatability.

In these ginseng supplementation studies, components of adaptive immunity were examined more robustly than their innate counterparts. Numbers of CD8+ T-cells increased in one study (22) but not another (58). No other cell population was influenced in any of these investigations. These athlete-associated results are consistent with data published from a general male population which received 300 mg/d of *P. ginseng* for 8 wk and demonstrated no changes in leukocyte or lymphocyte subsets during or after medication (154). Collectively, these findings may indicate that the effects of ginseng supplementation on cell subsets are not influenced by exercise.

Regarding molecular components of adaptive immunity, secretory IgA levels were not influenced following ginseng supplementation in one study (50). Regretfully, only mouse studies are available for comparison, but these have demonstrated that both intranasal and oral administration of *P. ginseng* stimulates IgA production from multiple tissues under various protocols (100, 101, 131). Two interleukins (-2 and -6) have also been examined. In one study, it was reported that *in vitro* IL-2 production was higher in ginseng-stimulated cells versus controls following acute exercise (22). Turning again to mouse studies, increased *in vitro* IL-2 production has also been observed in studies of murine splenocytes stimulated with *P. ginseng* (100, 101) and *P. quinquefolium* (170). The findings that Korean red ginseng reduced plasma IL-6, CPK, and cortisol levels (124), possibly reducing muscle damage from intense exercise, are consistent with other reports from the same lab team where they used a downhill running model of eccentric muscle damage and saw reduced plasma creatine kinase and lactate levels in the supplement treated-group from 24-72 h post-exercise (93) and with mouse models of stress where *P. ginseng* or *P. quinquefolium* supplementation reduced IL-6 production (85, 133). Finally, one team conducted a study of forced swimming in ICR ddY mice and examined TNF-α and IL-12 production from thioglycollate-elicited peritoneal macrophages stimulated with *P. ginseng*; however, the results of the cytokine assays were not analyzed with respect to the exercise bout, so the specific effect of exercise cannot be ascertained (150).

Future exercise immunology studies of ginseng supplements can improve our knowledge base multiple ways and are needed based on prevalence of use among athletes. First, authors should continue to report the source, nature, and dosing regimens for their extracts. None of the studies in Table 3 reported chemical composition of their extracts, thus precluding any inferences about mechanisms of activity. This information should be included in future reports whenever possible. Second, more data is needed regarding both cellular and molecular components of innate immunity, and of cytokines in general, particularly in human

Table 3. Selected studies on the effects of ginseng in the context of athlete immune function. PBMC = peripheral blood mononuclear cell; PHA = phytohemagluttinin; PML = polymorphonuclear leukocyte.

Study (Ref.)	Population	Herbal Treatment	Exercise	Immune Variables Measured	Key Findings
Biondo et al. 2008 (22)	10 sedentary males (mean age 25.1 y)	Crossover design with ginseng (1125 mg/d of proprietary capsule form of "North American" ginseng root powder) or placebo (cornstarch) for 35 d with 3 mo washout between	36 min of cycling at various % VT	1) circulating leukocyte populations; 2) [3H]-thymidine uptake; 3) *in vitro* IL-2 production; 4) neutrophil oxidative burst; 5) plasma concentrations of cortsol, growth hormone, insulin, lactate	• CD8+ T cells were the only cell population influenced by ginseng: post-exercise, ginseng-treated subjects had a lower concentration of CD8+ T cells compared to placebo • Ginseng had no effect on other cells' absolute concentrations or relative percentages • Ginseng had no effect on [^{3}H]-thymidine uptake • *In vitro* ginseng stimulation of PBMC resulted in higher IL-2 levels post-exercise and during recovery as compared to placebo • Ginseng had no effect on neutrophil oxidative burst • Ginseng had no effect on plasma hormones or lactate
Engels et al. 2003 (50)	27 physically-active college-aged individuals	Participants received either ginseng (proprietary aqueous extract of *P. ginseng* in capsule form at 400 mg/d) or placebo (gelatin + lactose) for 60 d	3 consecutive 30-s Wingate tests with 3 min recovery between	Salivary IgA	• Ginseng supplementation had no effect on salivary IgA levels compared to placebo

Table 3, continued

Gaffney et al. 2001 (58)	18 competitive and training-matched 18-40 y old males	8 mL/d of one of the following for 6 wk: 1) 35% ethanol extract of *E. senticosus* dried root, proprietary formula; 2) 60% ethanol extract of *P. ginseng* dried root, proprietary formula diluted with ethanol/water to match volume of E. senticosus extract); 3) placebo (see paper, various components)	Participants continued their normal training (subject pool included cyclists, triathletes, and endurance kayakers)	1) Blood lymphocyte subsets; 2) steroidal hormones	• Neither ginseng nor Siberian ginseng had any effect on CD3+ T cells, CD4+ T cells, CD8+ T cells, NK cells, or B cells compared to placebo • Ginseng and placebo had no effect on steroid indices, but Siberian ginseng decreased the testosterone:cortisol ratio
Park et al. 2008 (124)	8 males	Treatment group received 7 g/3× d Korean red ginseng in 200 mL water; placebo was 200 mL was with "Agastachis Herba"	2 45-min bouts of uphill treadmill exercise with 5-min rest between	Plasma IL-6, CPK, cortisol, insulin, and lactate	• Korean red ginseng reduced 2-h post-exercise plasma IL-6 levels as compared to placebo • Korean red ginseng reduced 72-h post-exercise plasma CPK activity and cortisol levels as compared to placebo
Szolomicki et al. 2000 (159)	35 volunteers, 21-73 y of age	30 d of 75 drops/d of a proprietary 35% ethanol extraction of *E. senticosus* root	No exercise was prescribed but physiological parameters were measured pre- and post-supplement	1) PML phagocytosis indexes; 2) neutrophil nitro blue tetrazolium (NBT) reduction; 3) lymphocyte blastic transformation	• Siberian ginseng supplementation increased per-cell phagocytotic activity (as assessed by Wright's index) • Siberian ginseng supplementation did not alter percent phagocytotic cells (as assessed by Hamburger's index) • Siberian ginseng supplementation did not alter NBT reduction activities • Siberian ginseng supplementation increased blastic transformation of lymphocyte under both PHA-stimulated and unstimulated conditions

models of both rest and exercise. Third, studies should strive to include pediatric and geriatric populations, as data is basically lacking for these groups. Given the small number of studies available, both genders and individuals of differing physical activity levels are represented, and should continue to be considered in future work.

Returning to Siberian ginseng *(Eleutherococcus senticosus)*, fewer studies have been reported so observations of effects on athlete immune function are more limited. Ciwujianosides from leaf, eleutherosides from root, and lignans of *E. senticosus* are purported bioactive compounds and are chemically distinct from each other and from ginsenosides of *Panax* spp. (45, 161). As with *Panax* spp., most investigations have discounted herbal preparations from *E. senticosus* as performance-enhancers, usually in studies of distance runners and cyclists (36, 47, 55, 64). Although one exercise immunology study using *E. senticosus* suggested improved maximal oxygen consumption (VO_2max) post-supplementation (159), other authors have questioned its validity (64). Goulet and Dionne recommend that, if exercise immunology research is to continue on this plant, exercise duration should be no less than 2 h (64).

Two studies in Table 3 examined *E. senticosus* supplementation in exercise immunology contexts (58, 159). The one study that involved a direct exercise component found little effect on immune markers (58). At this time, little can be said about *E. senticosus* and athlete immune function. The recommendations given above for future *Panax* spp. exercise immunology research apply even more strongly for Siberian ginseng.

Echinacea and Athlete Immune Function

Echinacea is a genus of coneflowers belonging to the plant family Asteraceae (Compositae) and endemic to North America (Table 2), though Germans exported it to Europe in the early 20th century for agricultural reasons. The word "Echinacea" is used as both a common and a scientific name. When written as *"Echinacea"* it is usually being used in a taxonomic (genus) sense; when written as "Echinacea" or "echinacea" it is often being used in a more vernacular (common name) sense. Traditionally, the genus was recognized as consisting of 9 primary species (112). Though recent work by one team has suggested that the genus should be reconsidered as 4 species (20), the majority of botanists have subsequently determined that the traditional taxonomic scheme is more congruent with the accumulated data and should be maintained (27, 143, 183). Genetic analyses of the genus have been confounded due its recent intragenus evolutionary divergence (56).

Several bioactive compounds have been reported from *Echinacea*. Known bioactive compounds from the genus include alkamides and ketones, caffeic acid derivatives (phenolics, phenylpropanoids), polysaccharides, and volatile oils such as alkenes (polyenes) and alkynes (polyacetylenes) (9, 10, 68). Numerous reports have documented immunomodulatory effects of alkamides (179), which have been shown to work as cannabinoid mimics by binding to CB2 receptors (59). CB2 receptors are G-protein coupled receptors expressed primarily by leukocytes (such as monocytes/macrophages, B cells, and T cells) that bind to endogenous cannabinoids such as anandamide or virodhamine. Human pharmacodynamic studies indicate that alkamides are rapidly absorbed by the body, possibly through oral mucosa, and remain in the bloodstream indefinitely contingent on dose (66, 108, 180, 181), and that liquid and tablet preparations exhibit similar absorption kinetics (107). Immunomodulatory and antioxidant properties have also been attributed to the caffeic acid derivatives (23, 125) and polysaccharides (136, 156), though their bioavailability in human models has yet to be ascertained and they may not move from the gut to the bloodstream without modification (134). Polysaccharides may work through both TLR4-dependent and –independent pathways, ultimately activating NK-κB in macrophages (158). Flavonoids (such as quercetin, discussed more thoroughly below), anthocyanins, other free phenolic acids, and more trace compounds are also present (9). Though specific activities are attributed to individual compounds or compound classes, bioactive molecules likely act synergistically as immunomodulators in herbal supplements (37, 42), exhibit heterogeneous effects (149), and may even exhibit opposite effects depending on context (109).

The primary use of *Echinacea* preparations today is in the prevention and treatment of upper respiratory infections (9) such as "colds" (Picornaviridae: *Rhinovirus*) and "flus" (Orthomyxoviridae: *Influenzavirus*). Somewhat disarmingly, scientific studies both validate (9, 62, 141, 147) and discredit (35, 99, 151, 164) the clinical use for Echinacea in upper respiratory infections. Three species are employed commercially: *E. angustifolia* (narrow-leaved coneflower), *E. pallida* (pale coneflower), and *E. purpurea* (purple coneflower) (9).

More is known about the effects of Echinacea supplements on physical performance than on immune function within the context of this review. To examine effects of Echinacea supplements on parameters related to running, 24 young adult males were given 8 g/d of Echinacea or placebo for 28 d. VO_2max and running economy (decrease in submaximal VO_2 at the first 2 stages of the graded exercise test) were improved in the Echinacea group compared to control (172). Effects of blood-related parameters were heterogeneous: erythropoietin increased in the Echinacea-treated group (172, 173), but there were no effects on hematocrit, red blood cell count, or hemoglobin concentrations (174). At rest, no significant differences were observed in total white blood cells nor subpopulations such as eosinophils, monocytes, or neutrophils; however, within the Echinacea-treated group, there were increases in neutrophil counts and decreases in eosinophil and monocyte counts during the course of treatment (140).

Compared with ginseng, fewer studies have examined Echinacea in the context of immune function (Table 4) (17, 69, 159). Since each study looked at a different array of immune parameters, it is difficult to directly compare them, but some general observations might be hazarded. It appears that both innate and adaptive immunity are impacted by Echinacea herbal supplements *in vivo*, and that supplementation was sometimes inhibitory and sometimes stimulatory in regards to immune parameters. IL-6 production is related to IgA production because IL-6 stimulates B-cell growth and maturation into antibody-producing plasma cells (78); consequently, it is interesting to note Berg et al. (17) reported that *Echinacea* supplementation increased IL-6 levels post-competition while Hall et al. reported that *Echinacea* supplementation prohibited the post-acute exercise-induced suppression of salivary IgA (69), suggesting a link between the two studies.

Future work on Echinacea studies and athlete immune function are warranted due to prevalence of use. In contrast to ginseng, only one of the exercise

Table 4. Comparison of studies on the effects of Echinacea in the context of athlete immune function. Abbreviations: IgA=immunoglobulin A; URI=upper respiratory infection.

Study (Ref.)	Population	Herbal Treatment	Exercise	Immune Variables Measured	Key Findings
Berg et al. 1998 (17)	42 male triathletes (mean age 27.5 years)	Echinacin (EC31—"pressed juice" of *Echinacea purpurea*), 8 mL at 3× a day for 28 days	Regular training (days 1-28) and triathlon competition (day 29)	At Days 1 and 28, and 1 and 20 h after competition: 1) Peripheral blood leukocyte populations; 2) IL-6 (serum, urine); 3) soluble IL-2 receptor (serum, urine); 4) URI incidence	• Treatment may have resulted in stabilizing lymphocyte subpopulations (specifically CD8 T cells) post-exercise and –competition • Treatment reduced soluble IL-2R levels in urine and (throughout) serum (post-competition), but not in CD25+ (IL-2+) cell counts, suggesting changes in sIL-2R dynamics may be related to monocytes • Treatment increased post-competition IL-6
Hall et al. 2007 (69)	32 non-smoking active adults aged 19-36 (mean ~26 years)	*Echinacea purpurea* or placebo for 28 days (dosage, preparation type not given)	3 consecutive Wingate tests pre- and post-treatment period	1) Salivary IgA quantities and flow rates; 2) URI incidence	• Reductions in salivary IgA and salivary flow rates due to exercise were less in Echinacea-treated group after 28-day period compared to control • Control group had longer duration of URI symptoms than Echinacea-treated group, though number of URI incidents was not different
Szolomicki et al. 2000 (159)	15 volunteers, 21-73 y of age	30 d of 120 drops/d of a proprietary 22% ethanol extraction of *E. purpurea* "herb" (presumably leaf)	No exercise was prescribed but physiological parameters were measured pre- and post-supplement	1) PML phagocytosis indexes; 2) neutrophil nitro blue tetrazolium (NBT) reduction; 3) lymphocyte blastic transformation	• No differences were found between subjects compared pre- and post-supplementation

immunology studies of Echinacea reported specific species used, which creates large problems both in terms of data interpretation/comparison and experimental repeatability. No studies have linked bioactivity with extract phytochemical composition, despite the fact that we know much more about Echinacea compound bioactivity than ginseng or other herbs. Additional reports examining the same immune parameters under different athlete/exercise contexts will allow for a better understanding of immune components affected by Echinacea supplements.

Quercetin

Quercetin is a flavonoid found in *Echinacea* spp. as well as many other plant taxa. Though no research has linked quercetin content in *Echinacea* supplements specifically to athlete immune function, several studies of the isolated compound in the context of exercise and sport have been published and bear brief mentioning here. In one study, 40 male cyclists were assigned to either 1g/d quercetin supplement or placebo (20 each). Supplementation started for one week, after which time all athletes cycled intensely for 3 h on 3 consecutive d (continuing to supplement), followed by 2 additional wk of supplementation. Lymphocytes obtained from blood sampled before and after each exercise session demonstrated no differences in proliferation or activity assays (121). Several cytokines and their mRNA transcripts were assayed for from blood and muscle samples after the first and third exercise sessions. Pro-inflammatory plasma cytokines TNF and IL-8 demonstrated a statistical trend for being lower in the treated versus the placebo group, and plasma IL-8 and IL-10 mRNA levels were significantly lower in the treatment group compared to placebo (120). Muscle biopsy cytokine and mRNA levels did not differ between the two groups (120). No differences in salivary IgA concentrations were seen after any exercise session (121). However, the quercetin-treated group did have lower incidence of upper respiratory infections during the study period (121). This same laboratory group has also looked at competitive runners on quercetin supplementation and has reported that 160-km endurance runners receiving 1g/d quercetin supplements for 3 wk prior to their competition exhibited no difference in muscle or leukocyte cytokine parameters (119) nor salivary IgA, leukocyte subsets, granulocyte respiratory burst, or incidence of respiratory infections (72). Taken together, this panel of studies suggests that any effects of *Echinacea* supplements on athlete immune function are not likely to be related to quercetin levels.

Rationale for a Multidisciplinary Approach

In this section we will articulate the relevance of adopting a multidisciplinary approach to not only interpreting but also conducting research on herbal supplements in the context of athlete immune function. Our goals are to demonstrate how such an approach benefits exercise immunologists or other human scientists by potentially improving quality of research and also ability to make recommendations to athletes, coaches, trainers, and the public.

The primary objectives of most exercise immunology studies on herbal supplements are to determine if those supplements have an effect on immunity and, if so, why or how the supplements work (mechanisms of activity). Both treatment and control (placebo) groups are necessary in order to determine what the effects of the supplement are versus the treatment procedure itself; implicit in this line of thinking is that the supplement must contain some substances which the placebo does not that exert an effect. The overwhelming majority of exercise immunology investigations of herbal supplements include a placebo but *do not* consider supplement chemical composition, precluding the possibility of elucidating any mechanism of activity; to adduce, none of the studies in Tables 3 or 4 included such information. Chemistry considerations are imperative to understanding the biology of any observed effects, and, by corollary, to making recommendations of supplement use or how to improve supplement quality by enriching one or more constituents.

It can be difficult to ascertain chemical information regarding supplements. For instance, some brand name supplements include chemical composition information in the label, but studies using both Ephedra (67) and Echinacea (60) supplements have repeatedly demonstrated that supplement composition and dosage do not always reflect manufacturer claims. Acknowledging this, some laboratories have gone to chemically profiling all supplements themselves, but this is not without problems itself. As this author team can personally attest for Echinacea, and as another team encountered when trying to chemically profile Siberian ginseng supplements (36), chemical standards are not always available. Manufacturers may also be reluctant to disclose proprietary formulae for competitive reasons. The lack of herbal supplement characterization in medical research has not escaped notice (182).

Extending this train of thought reveals why botanical considerations are equally important. A plant's biochemical composition (both in terms of diversity and quantity of molecules produced) is influenced by both genetic and environmental factors. Different plant genera have different biochemical profiles; within genera, different species have different biochemical profiles; and within species, different subspecies, accessions, or ecotypes often have different biochemical profiles. If chemical differences are important in understanding the exercise immunology of herbal supplements, then botanical aspects of the supplement need to be known. The use of common names muddies such clarity, as common names for plants are often applied to more than one species or genus and may vary geographically. Many exercise immunology investigations of herbal supplements do not report which specific species were used and often use common or proprietary names; thus, the same problems identified in our discussion of chemical data are amplified when botanical data are absent. All the studies in Table 3 gave nomenclatural information but only one of the studies in Table 4 did.

Clearly, there is a scientifically-validated precedent for giving consideration to a multidisciplinary approach to herbal supplement investigations in athletes. It is important to recognize that paying attention to these factors does not require compromising the primary objectives of exercise immunology research, nor does it require that exercise immunologists become experts in fields of science ancillary to their own. To the contrary, these factors enhance our understanding of exercise immunology by revealing mechanisms of supplement activity, explaining differences between studies, improving experiment repeatability, and improving potential recommendations made to athletes, coaches, trainers, and the public.

Reconciling Discrepancies in the Literature using Echinacea as a Model

In this section we will use Echinacea as a model for demonstrating how a multidisciplinary perspective may be applied to the study of herbal supplements in athletes. Our goal is to use an evidence-based approach to highlight pre-clinical and pre-laboratory factors which may impact on exercise immunology results and underscore their importance as experimental considerations. We chose Echinacea as a model for this section because more published information is available on these factors in Echinacea as compared to other herbs used in supplements.

Several sources of variation which may influence exercise immunology studies of herbal supplements have been identified in preceding sections. For instance, we noted that the name "Echinacea" encompasses up to 9 different species, but that species information was rarely given in the exercise immunology literature (Table 4). We also identified several classes of bioactive compounds produced by Echinacea which are known to have heterogeneous effects, but lamented that phytochemical profiling is typically not performed or reported in supplement studies.

Factors such as species used in a supplement or chemical composition of that supplement may be considered "pre-clinical" or "pre-laboratory" sources of

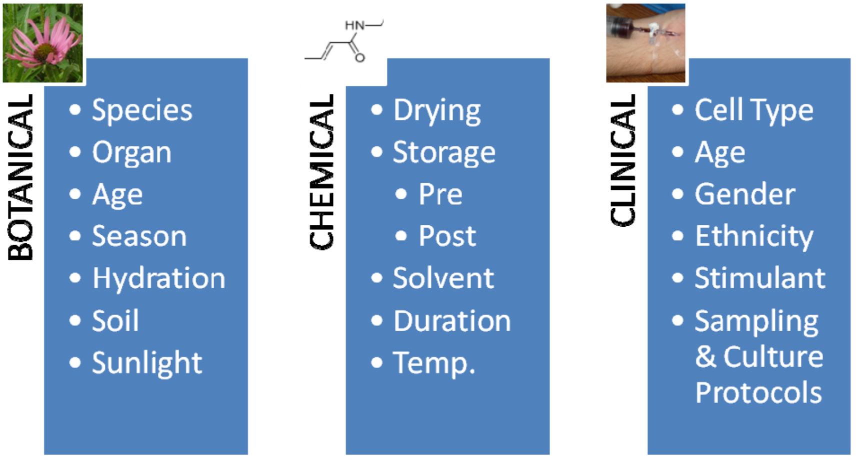

Figure 1. Multidisciplinary approach model as applied to Echinacea supplements specifically. This model emphasizes variables that impact on immune outcomes in studies of herbal supplements. "Botanical" factors are those associated with the herb itself, including its biology and ecology. "Chemical" factors include those aspects associated with harvest, processing, and storage. "Clinical" factors encompass such variables as subject characteristics and specific experimental techniques. Specific studies examining the roles of each of these factors are discussed and referenced in the text. All illustrations are the authors'.

variation from an exercise immunology perspective. Previously-cited studies suggest these variables likely influence immune outcomes, arguing for a need to report these data in exercise immunology studies of athlete herbal supplement use. However, these examples are just 2 of several such possible pre-clinical sources of variation. Figure 1 provides several others that are known for Echinacea, and will serve as an organizational framework for the remainder of this section.

Under the heading of "botanical" we have included plant-associated factors which impact on extract performance. Our laboratory team has devoted much energy to demonstrating that different species have different *in vitro* immunomodulatory effects (111, 143, 144) which also vary by plant organ (flower, leaf, root, or stem) (144, 145). Phytochemical composition varies in a species-specific manner (146, 183), likely explaining immunomodulatory differences. Other researchers have found congruent results which suggest that even within members of the same species (*E. angustifolia*), phytochemistry can vary substantially by geography or organ (19, 21), section of organ (130), or by age (65). Field factors such as drought stress (related to hydration) (65) and soil composition (130) are known to influence plant phytochemistry, but to the best of our knowledge the role of quantity of sunlight exposure has yet to be explored. Such factors have been proposed to explain differences between clinical studies (44). Together, these data argue that "botanical" (species, organ, plant age) and "ecological" factors (time-of-harvest, plant hydration status, soil, sunlight) likely play strong roles in determining the immunological activities of Echinacea extracts.

Under the heading of "chemical" we have identified chemistry-associated factors related to extract preparation which impact on extract performance. Drying at different temperatures or lengths of time is known to alter individual Echinacea phytochemicals heterogeneously (80, 81, 86, 87, 97, 127, 157). The solvent used to extract plant material (i.e., hydrophobic vs. hydrophilic solvents) impact on which phytochemicals are extracted and to what efficiency, and resultant *in vitro* immunomodulatory effects (127, 144, 145). Extract storage time, temperature, and exposure to sunlight also influence the composition of extracts (111, 127, 144, 145, 176). One team even considered that the physical damage harvested plants undergo during transport from field to factory may influence extract composition, but found no differences by treatment (176). Together, these studies argue that "chemical" factors (drying regimens, storage conditions, solvent selection) also likely play strong roles in determining the biological properties of Echinacea extracts.

Under the heading of "clinical" we have listed clinical- or laboratory-associated factors which impact on immune variables. Whereas the factors in the "botanical" and "chemical" columns relate to plants and extracts, factors in the "clinical" column relate to the human subjects participating in the study or experimental techniques. Reporting of many of these factors is routine in both clinical and exercise immunology literature because their importance is understood and will not be addressed here. Albers et al. stress that researchers conducting nutritional intervention studies (such as herbal supplement studies) need to carefully select the immune variables they study in terms of which variables are most likely to be influenced by the supplement or which are most strongly associated with clinical outcomes such as infection rates, and to include multiple, diverse markers (3). Related to this, how well the supplement is absorbed may be impacted by the state of the athlete's gut; the health of the gut also impacts on their immunity, physical performance, and overall health (16). Interested readers may find more information on links between some specific immune factors and age (63, 88), gender (110, 148), and ethnicity (102, 113) elsewhere.

From an exercise immunology vantage, the list of variables included in this section is likely overwhelming. And from a logistical standpoint, it is unrealistic to expect any team of investigators to be able to consider all these factors (either from an experimental or a statistical standpoint). However, being aware of these variables helps explain some of the variation in the literature. The more of these factors that are reported per study, the better we will be able to make direct comparisons between studies and consequently better elucidate the role of each factor in exercise immunology contexts. Exercise scientists should make strides to better articulate as many factors as is pragmatic in their reports. In the following section, we will demonstrate how consideration of some of these factors can aid in interpretation of the effects herbal supplements in an exercise context.

Prospective Data

In this section we will provide pilot data from *in vitro* studies of peripheral blood mononuclear cells collected from college wrestlers and soccer players after exercise and stimulated with Echinacea extracts which highlight the importance of several of the factors from Figure 1. Our goal is to experimentally demonstrate the role that these factors may play within the context of exercise immunology research (i.e., why a multidisciplinary approach is valuable). We have opted for an *in vitro* approach (a) to better focus attention on the role of these factors, and (b) because it allows for us to control for more experimental variables than an *in vivo* approach would.

Our work is different from previous studies in 3 main ways. First, we worked with the plants from field to bench, allowing for accountability and control of several of the factors from Figure 1 in a manner never before synthesized. Second, we incorporated phytochemical profiling (in the form of high-performance liquid chromatography, or HPLC) and endotoxin analysis into our study. To the best of our knowledge, the reports here are the first to reconcile observed effects of herbal extracts on athlete immune function with actual extract composition. Third, we specifically identified and selected two Echinacea species (*E. pallida* and *E. simulata*) with contrasting immunomodulatory effects (143), which have not been investigated in the scope of exercise immunology literature reviewed here.

The same Echinacea extracts were used for both studies. Extract characteristics are given in Table 5; we have attempted to address all of the major factors from Figure 1 based on the literature. Importantly, although all environmental factors could not be accounted for due to lack of information, all plants grew under the same environmental conditions, thus eliminating this as a possible confounding factor. Extract from *E. pallida* contained a greater diversity and quantity of bioactive compounds including some amides absent from the *E. simulata* extract (146). Background endotoxin levels present in the extracts are not likely sufficient to elicit an immune response in our model based on previous experimental evidence (146).

Two different groups of athletes were recruited to the research, male college wrestlers and soccer players. Human subjects research committees (institutional review boards or IRBs) at both Drake University and Iowa State University approved all procedures (Drake IRB 2006-07001/2006-07011 and ISU IRB 06-390). Subject characteristics for both teams are given in Table 5. Blood was collected at rest and after 2 h of exercise from both teams. Peripheral blood mononuclear cells (PBMCs) were separated and stimulated with extracts or vehicle con-

Table 5. Botanical, chemical, and clinical factors (sensu Figure 1) in our experiment. Information in the botanical and chemical columns pertain to the extracts; more details for these factors may be found in (146). EU = endotoxin units. Information in the clinical columns pertain to the subjects in the 2 studies, respectively. PBMC = peripheral blood mononuclear cell.

Botanical	Chemical	Clinical: Wrestling Study	Clinical: Soccer Study
Species: *E. pallida* (PI631275), *E. simulata* (PI631604A)	**Drying:** 16 months at 25.5-26.5°C, 38% relative humidity	**Cells:** PBMCs	**Cells:** PBMCs
Organ: Roots	**Storage:** Pre-Extraction: Same as drying; Post-Extraction: -20°C for 18 mos. (wrestling study) or 24 mos. (soccer study)	**Age:** 20.7 ± 1.8 y, n=8	**Age:** 20.4 ± 1.1 y, n=7
Age: Three growing seasons old	**Extraction:** 50% ethanol/50% water at a ratio of 1:9 parts plant:solvent; extracted for 20 min at room temperature	**Gender:** Male	**Gender:** Male
Season: Fall harvest (day after first frost)	Endotoxin (expressed as EU/mL): *E. pallida*=8.553, *E. simulata*=8.255	**Ethnicity:** Caucasian	**Ethnicity:** African-American, Caucasian, and Hispanic
Hydration, Soil, Sunlight: Unknown, but all plants were grown in the same common garden (so they experienced all the same ecological forces)	**Phytochemistry** (expressed as mg/mL): *E. pallida*: amide 2=0.0008, amide3=0.0087, ketone 22=0.054, ketone 24=0.1668, caftaric acid=0.0535, chlorogenic acid=0.0079, cichoric acid=0.0141, echinacoside=0.0885; *E. simulata*: ketone 22=0.0148, ketone 24=0.0093, caftaric acid=0.0359, chlorogenic acid=0.0069, echinacoside=0.0476	**Stimulant, Sampling, and Cultural Protocols:** See Text	**Stimulant, Sampling, and Cultural Protocols:** See Text

trols *in vitro* and assayed for cytokine production or cell proliferation as detailed below.

Phlebotomy, cell isolation, and *in vitro* cell experimental protocols were the same in both studies. Forty mL of venous blood was drawn from each subject pre- and post-exercise (more details on the exercise protocol given later). PBMCs were isolated using Ficoll-Paque (GE Healthcare) gradient centrifugation, counted manually on a hemacytometer, and standardized to 1.0×10^6 cells in AIM-V medium (GIBCO/Invitrogen). *E. pallida* extract, *E. simulata* extract, and solvent vehicle control preparations were further diluted 1:12.5 in AIM-V medium just prior to use. For cytokine production, 1 mL of cells were cultured with 50μL of either of the three preparations. ELISA (BD Biosciences/Pharmingen) was used to assess TNF production at 24 h, IL-1β production and IFN-γ at 48 h, and IL-10 at 72 h. [TNF was formerly called TNF-α]. For proliferation, 100μL of cells were cultured with 5μL of either of the three preparations for 72 h. Each condition was replicated in triplicate and proliferation quantified using a formazine salt assay (CellTiter; Promega). Statistically, each subject served as their own control. All statistical procedures were conducted in SPSS 15.0. Main effects of exercise (time), extract (treatment), and exercise × extract interactions were determined via ANOVA. When significant effects were discovered, follow-up posthoc tests were performed. Bivariate correlations (Pearson) were used to relate bioactive compound levels to observed immune effects. More experimental details may be found in Senchina et al. (145).

Table 6: Specific activities of the conditioning sessions on Days 1 and 15 of the wrestling study, including their duration, heart rates observed, and the estimated relative exercise intensity values based on those heart rates.

Activity Description (Repetitions)	Total Duration (min)	Heart Rate (bpm)	Estimated Intensity (as %VO_2max)
Warm-Up	10-15	130-160	50
1-mile Run (1)	6-9	155-170	80-85
Active Recovery	3		
30-second Sprints (3-5)	6-10	160-190	60-95
Active Recovery	3		
Stadium Stair Sprints (4-6)	6-10	189-194	95-100
"Buddy Carries" (2)	6-10	185-196	95-100
Active Recovery	5		
Hill Sprints (3-5)	4-8	185-196	95-100
Hill "Buddy Carries" (1-2)	3-5	180-196	95-100
Wheelbarrows (1-2)	2-4	180-196	95-100
Active Recovery	3		
1-mile Jog (1)	7-11	130-160	50-60

For the wrestling study, we drew blood at rest and following the exercise protocol described in Table 6. Results are presented in Figure 2. For TNF (Fig. 2a), there was a main effect of extract such that *E. simulata* stimulated greater TNF production than control or *E. pallida* ($p<0.001$), and a main effect of exercise such that TNF production was lower post-exercise ($p=0.001$), but no exercise × extract interaction. IL-1β production (Fig. 2b) also showed a significant effect of extract such that *E. simulata* stimulated greater IL-1β than control or *E. pallida* ($p<0.001$), but there was no main effect of exercise or exercise × extract interaction. No significant differences were seen in any comparisons for IFN-γ (Fig. 2c). For IL-10 (Fig. 2d), there was a significant effect of extract such that *E. simulata*

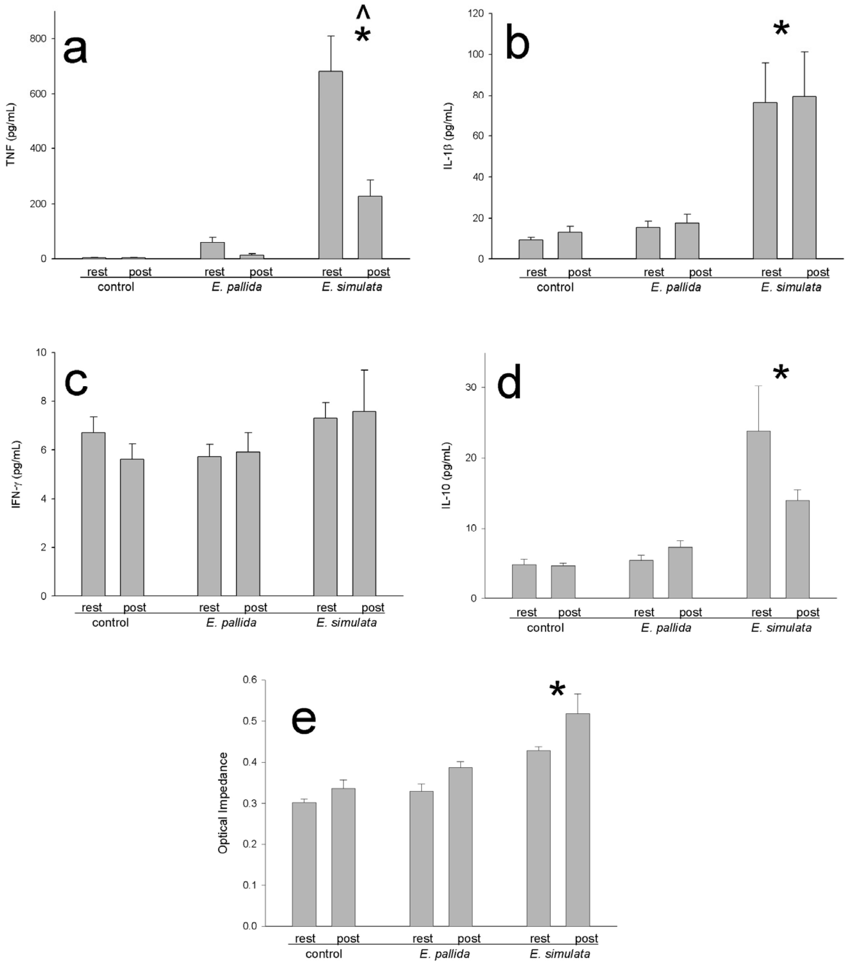

Figure 2. Immune results from the wrestling study. Asterisks (*) indicate statistically significant differences between *E. simulata*-stimulated cultures compared to both control and *E. pallida*-stimulated cultures. Carats (^) indicate a trend towards a statistical difference between pre- and post-exercise cultures within the same species.

stimulated greater IL-10 than control or *E. pallida* ($p<0.001$), but there was no main effect of exercise or exercise × extract interaction. For proliferation (Fig. 2e), there was a main effect of extract such that *E. simulata* stimulated greater proliferation than control or *E. pallida* ($p<0.001$), and a main effect of exercise

Table 7. Correlations between extract phytochemical composition and observed effects. Bivariate correlation Pearson values (p-value) are given for TNF,IL-1B, IL-10, IFN-γ, proliferation as correlated with phytochemical composition of *E. pallida* and *E. simulata* extracts used in both studies. Asterisks (*) indicate statistically significant differences (p ≤0.05) and daggers (†) indicate trends (0.05 <p< 0.1). Plus and minus symbols indicate correlation direction. Chlor. acid = chlorogenic acid.

Compound	TNF		IL-1B		IFN-γ		IL-10		Proliferation	
	Wrestling	Soccer	Wrestling	Soccer	Wrestling	Soccer	Wrestling	Soccer	Wrestling	Soccer
Amide 2	-0.315 (0.029)*	-0.376 (0.014)*	-0.298 (0.039)*	-0.361 (0.019)*	-0.182 (0.215)	-0.192 (0.224)	-0.253 (0.083)†	-0.293 (0.063)†	-0.184 (0.211)	0.291 (0.062)†
Amide 3	-0.315 (0.029)*	-0.376 (0.014)*	-0.298 (0.039*)	-0.361 (0.019)*	-0.182 (0.215)	-0.192 (0.224)	-0.253 (0.083)†	-0.293 (0.063)†	-0.184 (0.211)	0.291 (0.062)†
Ketone 22	-0.135 (0.362)	-0.185 (0.242)	-0.125 (0.398)	-0.17 (0.280)	-0.122 (0.409)	-0.088 (0.580)	-0.093 (0.531)	-0.158 (0.325)	-0.004 (0.978)	0.472 (0.002)*
Ketone 24	-0.283 (0.051)†	-0.342 (0.027)*	-0.268 (0.066)†	-0.328 (0.034)*	-0.172 (0.242)	-0.173 (0.272)	-0.224 (0.125)	-0.269 (0.089)†	-0.151 (0.305)	0.326 (0.035)*
Caftaric Acid	0.182 (0.284)	0.158 (0.318)	0.180 (0.221)	0.17 (0.283)	-0.003 (0.982)	0.096 (0.544)	0.185 (0.207)	0.093 (0.561)	0.292 (0.044)*	0.695 (0.000)*
Chlor. Acid	0.323 (0.025)*	0.312 (0.044)*	0.315 (0.029)*	0.322 (0.038)*	0.054 (0.714)	0.179 (0.257)	0.307 (0.034)*	0.210 (0.189)	0.414 (0.003)*	0.754 (0.000)*
Cichoric Acid	-0.315 (0.029)*	-0.376 (0.014)*	-0.298 (0.039)*	-0.361 (0.019)*	-0.182 (0.215)	-0.192 (0.224)	-0.253 (0.083)†	-0.293 (0.063)†	-0.184 (0.211)	0.291 (0.062)†
Echinacoside	0.077 (0.603)	0.043 (0.788)	0.079 (0.595)	0.056 (0.726)	-0.045 (0.764)	0.035 (0.827)	0.093 (0.528)	0.008 (0.960)	0.196 (0.182)	0.634 (0.000)*

such that proliferation was greater post-exercise (p=0.003), but no exercise × extract interaction. Published studies similar to ours in wrestlers are few. Regarding the pro-inflammatory cytokines, other researchers have found that serum levels of TNF, IL-1β, and IL-6 increase in adolescent males as a result of an acute, lone 1.5 h wrestling session but also over the course of a wrestling season (115, 116). Our results may at first appear to be in opposition to previous reports; however, closer inspection of Fig. 2a provides an explanation. TNF production from unstimulated cultures was no different from rest to post-exercise (4.3 ± 0.8 and 4.4 ± 1.1 pg/mL, respectively). Declines in TNF production were seen only in the *E. pallida* and *E. simulata* stimulated cultures, and were only significant in the latter. No studies could be located for comparison of IFN-γ, IL-10, or proliferation results.

Correlations between extract composition and observed immune effects in the wrestling study are given in Table 7. Amide 2, amide 3, ketone 24, and cichoric acid all correlated negatively with inflammatory cytokine (TNF, IL-1β) production, whereas all of these except ketone 24 also correlated negatively with IL-10 production. Chlorogenic acid was positively correlated with TNF, IL-1β, and IL-10 production, and both chlorogenic and caftaric acid were positively correlated with proliferation. None of the phytochemicals correlated with IFN-γ.

For the soccer study, we drew blood at rest and following 1 h of aerobic drills coupled with 1 h of soccer scrimmage. Results are presented in Figure 3. For both TNF (Fig. 3a) and IL-1β (Fig. 3b), there was a main effect of extract such that *E. simulata* stimulated greater TNF production than control or *E. pallida* (p<0.001), but there was no main effect of exercise or exercise × extract interaction. For IFN-γ (Fig. 3c), there was a main effect of extract such that *E. simulata* stimulated greater IFN-γ production than control or *E. pallida* (p=0.003). There was a main

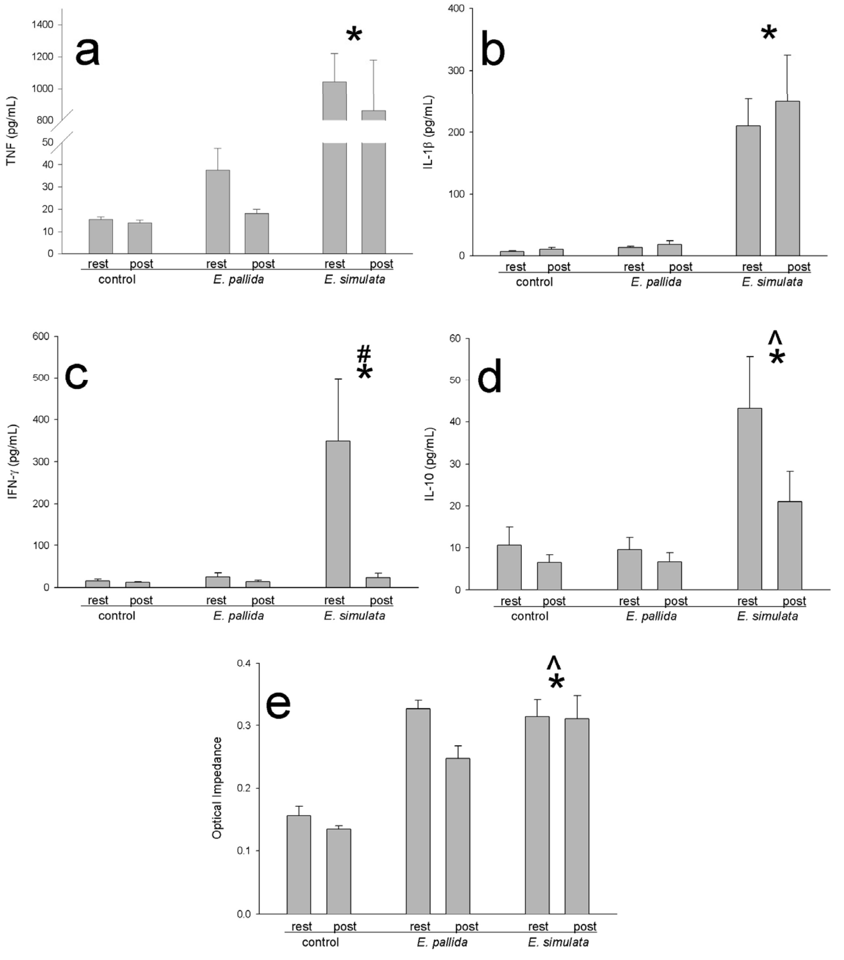

Figure 3. Immune results from the soccer study. Asterisks (*) indicate statistically significant differences between *E. simulata*-stimulated cultures compared to both control and *E. pallida*-stimulated cultures. Pound signs (#) indicate statistically significant differences between pre- and post-exercise cultures within the same species whereas carats (^) indicate a statistical trend in this direction.

effect of exercise (p=0.025) such that IFN-γ production decreased from rest to post-exercise. There was an exercise × extract interaction (p=0.014); posthoc tests revealed a statistically significant decrease in IFN-γ production with *E. simulata* from rest to post-exercise (p<0.001). For IL-10 (Fig. 3d), there was a main effect of extract such that *E. simulata* stimulated greater IL-10 production than *E. pallida* or control (p<0.001). There was a trend for a main effect of exercise (p=0.065) such that IL-10 production decreased from rest to post-exercise. For proliferation (Fig. 3e), there was a main effect of extract such that *E. simulata* stimulated greater proliferation than control or *E. pallida* (both $p \leq 0.014$), and *E. pallida* stimulated greater proliferation than control ($p < 0.001$). There was a trend for a main effect of exercise ($p = 0.068$) such that proliferation decreased from rest to post-exercise. The effects of exercise on immune alterations in soccer players have been reported (24, 103, 104), but regretfully none of the previously published studies examined the same immune parameters investigated here. A review of nutritional supplements in this group of athletes specifically has been written (118).

Correlations between extract composition and observed immune effects in the soccer study are also presented in Table 7. Among the cytokines, amide 2, amide 3, ketone 24, and cichoric acid were negatively correlated with TNF, IL-1β, and IL-10, whereas chlorogenic acid was positively correlated with TNF and IL-1β. None of the phytochemicals correlated with IFN-γ. All of the phytochemicals tested were positively correlated with proliferation.

The value of the multidisciplinary approach is seen when these 2 studies are considered individually and in comparison to each other. Most notably, we showed how important it is to report specific species used, as *E. pallida* extracts had much less effect in our assays than did *E. simulata* extracts (Figures 2 and 3). We were able to link specific plant constituents to our observed immune outcomes. Generally, amide 2, amide 3, ketone 24, and cichoric acid were negatively correlated with TNF, IL-1β, and IL-10 (but not IFN-γ) production whereas chlorogenic acid was positively correlated with these cytokines (Table 7). By contrast, proliferation was positively correlated with caftaric acid and chlorogenic acid in both studies (Table 7). These results suggest that PBMC cytokine production and cell proliferation were influenced through different biochemical mechanisms. Differences between the studies might be attributable to differences in exercise regimens used and/or subject characteristics. From the perspective of an athlete, coach, or trainer, our results suggest that species selection, extract phytochemical composition, and desired outcomes of the herbal supplement are important factors to consider when choosing an *Echinacea* product.

CONCLUSIONS

Having reviewed the current literature on herbal supplements and athlete immune function, identified areas of discrepancy and opportunities for growth, and experimentally shown how a multidisciplinary approach can enrich exercise immunology research, the question posited in our title can now be examined—what's proven, disproven, or unproven?

It has been proven that herbal supplement use in athletes is higher than in the general population, and that athletes purposefully use certain herbs (such as ginseng and Echinacea) more often than others. It has also been proven that these herbs (and others) exert effects on the human immune system which are contingent on botanical and chemical characteristics of those preparations in addition to traditional considerations such as subject characteristics or exercise protocols. However, with so few studies published, the effects of these preparations on specific immune parameters (such as individual cytokines or cell functions) remain largely unproven. Also unproven are possible mechanisms of activity for herbal supplements because many studies do not report sufficient extract characteristic information, though sometimes mechanisms have been established by other researchers in non-exercise contexts. Ergogenic effects of these herbs have been largely disproven or occasionally proven in certain situations.

The challenges for exercise immunologists researching herbal supplements in the context of athlete immune function are many. It is imperative to acknowledge that numerous factors previously neglected impact on experimental results. Adopting such a cognitive framework will move the field from somewhat simplistic questions such as "does a given herbal supplement work or not work" to more scientifically valid questions such as "under what conditions will a given herbal supplement exert or not exert a specific effect." The multidisciplinary approach modeled here might provide a launching point for such maneuvers. Investigations should integrate considerations of multiple factors, and our previous knowledge should be re-evaluated in light of these factors. It is necessary to maintain a systematic approach as knowledge is expanded. At the moment the collective knowledge is "patchwork" in the sense that it is difficult to compare studies to one another because they differ by so many variables. While data volume increases with continued research, it is critical to be aware of how new studies articulate with previous findings and to "fill in the gaps" whenever possible. Aware of these challenges, the field of exercise immunology will be optimally poised to not only expand empirical knowledge but also provide practical advice to the exercise and sports community.

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