Alkaloids and athlete immune function: Caffeine, theophylline, gingerol, ephedrine, and their congeners

David S. Senchina,[1,*] Justus E. Hallam,[2] Marian L. Kohut,[2] Norah A. Nguyen,[3] M. Ann d. N. Perera[3]

[1] Biology Department, Drake University, Des Moines, IA
[2] Department of Kinesiology, Iowa State University, Ames, IA
[3] W. M. Keck Metabolomics Laboratory, Iowa State University, Ames, IA

ABSTRACT

Plant alkaloids are found in foods, beverages, and supplements consumed by athletes for daily nutrition, performance enhancement, and immune function improvement. This paper examined possible immunomodulatory roles of alkaloids in exercise contexts, with a focus on human studies. Four representative groups were scrutinized: (a) caffeine (guaranine, mateine); (b) theophylline and its isomers, theobromine and paraxanthine; (c) ginger alkaloids including gingerols and shogaol; and (d) ephedra alkaloids such as ephedrine and pseudoephedrine. Emerging or prospective alkaloid sources (Goji berry, Noni berry, and bloodroot) were also considered. Human in vitro and in vivo studies on alkaloids and immune function were often conflicting. Caffeine may be immunomodulatory in vivo depending on subject characteristics, exercise characteristics, and immune parameters measured. Caffeine may exhibit antioxidant capacities. Ginger may exert in vivo anti-inflammatory effects in certain populations, but it is unclear whether these effects are due to alkaloids or other biochemicals. Evidence for an immunomodulatory role of alkaloids in energy drinks, cocoa, or ephedra products in vivo is weak to nonexistent. For alkaloid sources derived from plants, variability in the reviewed studies may be due to the presence of unrecognized alkaloids or non-alkaloid compounds (which may themselves be immunomodulatory), and pre-experimental factors such as agricultural or manufacturing differences. Athletes should not look to alkaloids or alkaloid-rich sources as a means of improving immune function given their inconsistent activities, safety concerns, and lack of commercial regulation.

Keywords not in title: cocoa; ephedra; ginger; guarana; Sanguinaria

* *Author for correspondence (DSS):*
2507 University Ave., Drake University, Des Moines, IA 50311
Tel. 1 515 271 2956, Fax 1 515 271 3702, dssenchina@drake.edu

FOREWORD

Many beverages, foods, and supplements consumed by athletes as ergogenic aids or health enhancers contain alkaloids (25, 38, 107). Alkaloids are simplistically characterized as nitrogen-based basic molecules, typically containing one heterocyclic ring, and originating from botanical or fungal sources. Examples include caffeine, morphine, and nicotine. Molecules such as adrenaline (epinephrine) and 5-hydroxytryptamine (serotonin) fit the structural definition of alkaloids, but are not considered members because they are produced only by animals; some amino acids and nucleic acids also technically fit the chemical description but are excluded based on historical conventions.

Several alkaloids have documented or purported immunomodulatory effects in humans (35, 57, 64, 131). For athletes experiencing immunodepression consequent to their intense training regimens (45, 49, 128), alkaloid-containing supplements may be an appealing nutritional countermeasure. Rather than encyclopedically canvass all known alkaloids consumed by athletes, this review will instead focus on the evidence supporting (or refuting) claims of immunomodulation from four representative alkaloids or alkaloid sources (Figure 1): caffeine (including pure and plant sources, such as guarana, mate, and tea); theophylline, including its isomers theobromine and paraxanthine (from cocoa); ephedrine and pseudoephedrine (from ephedra); and gingerols, shogaols, and paradols (from ginger). These four groups are diverse in their efficacy, safety, indicated uses, botanical origins, nutritional sources, current usage patterns, and current knowledge bases. After reviewing these four groups, some emerging or prospective alkaloid-rich herbs are discussed, together with the need for an interdisciplinary approach when studying alkaloids and athlete immune function.

To identify literature appropriate to the review, searches were conducted in both PubMed and Google Scholar from late July-early September 2013 as illustrated in Figure 2. All possible combinations were searched, resulting in a total of 220 unique permutations (or 440 independent searches since two databases were utilized). To further limit the scope of the review, only studies that were written in English, published in peer-reviewed journals or books, and pertaining to human data or a review of human data were considered for inclusion. Resulting hits were screened manually for relevance to the topic of alkaloids and athlete immune function; thus, papers pertaining to ergogenic benefits, cross-reactions with other substances, and doping regulations were generally omitted. Other sources may be consulted for a broad overview of performance-enhancing substances (4, 36), specific herbs used by athletes (25) and in athlete immune function (108), or molecular aspects of immunomodulatory herbs used by athletes (105).

CAFFEINE

Caffeine (Figure 1) is a methylxanthine alkaloid that can be ingested in pill or supplement form, or as a component of beverages including those that consumers readily associate with plants (Table 1), energy drinks, or soft drinks (Table 2). **Guaranine** and **mateine** are the same molecule as caffeine, named after the plant taxa from which they were originally isolated (Table 1). Caffeine is

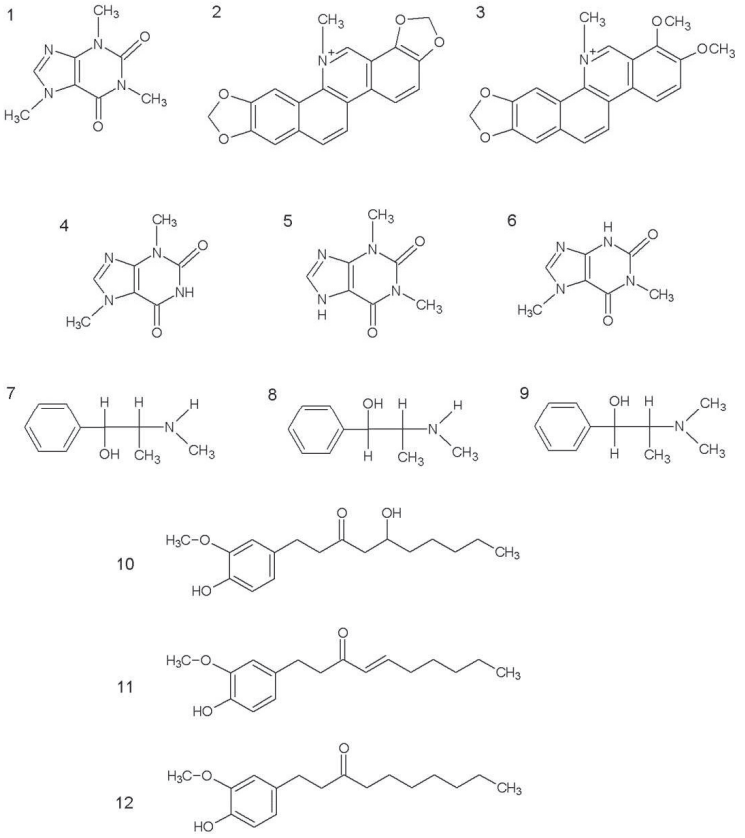

Figure 1. Representative alkaloids discussed in this review: caffeine (1); bloodroot alkaloids including sanguinarine (2) and chelerythrine (3); coca alkaloids including theobromine (4) and its congeners theophylline (5) and paraxanthine (6); ephedra alkaloids including ephedrine (7) and its congeners pseudoephedrine (8) and methylephedrine (9); and ginger alkaloids including [6]-gingerol (10) and its congeners [6]-shogaol (11) and [6]-paradol (12).

a central nervous stimulant and modulator of cardiovascular function (4). It may improve endurance performance for athletes such as adult runners at moderate doses ranging such as 2-3 mg/kg body weight (115). In human (15, 114) and mouse (60) models, the effects of caffeine are greater when abstinence from caffeine occurs at least 7 days prior to dosing, or in non-users.

A comprehensive review of the immunomodulatory effects of caffeine was published in 2006 by Horrigan et al. (57). The authors determined that studies employing *in vitro* concentrations of ≤100 μM were relevant to *in vivo* human contexts. Human *in vitro* data suggested that caffeine:

- increased or had no effect on free radical production by neutrophils at physiological doses from 10-100 μM, contingent on cell pretreatment (116, 117);

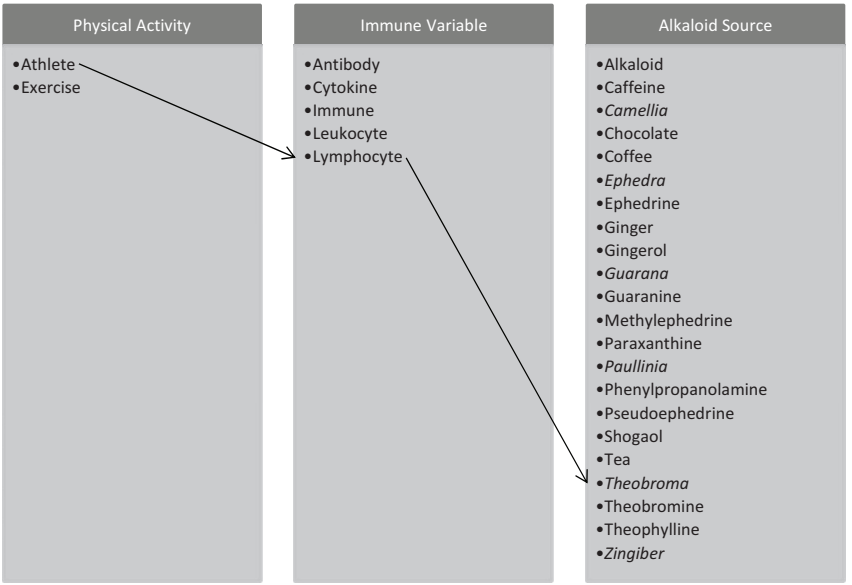

Figure 2. Search strings used in this review. A search string consisted of three terms, one representing physical activity (column 1), another representing an immune variable (column 2), and the third representing an alkaloid source or name (column 3). All possible combinations of terms from each column were used in the searches. One example search string (athlete + lymphocyte + *Theobroma*) is indicated by the arrows.

- reduced peripheral blood mononuclear cell (PBMC) proliferation at physiological concentrations of 25-100 μM (103);
- reduced whole blood production of tumour necrosis factor (TNF) and interleukin (IL)-10 at borderline physiological levels (100 μM or 200 μg/mL, with no effects at lower doses) and had no effect on IL-1β or IL-12 (43, 56, 81).

Horrigan et al. (57) concluded that caffeine exerts an anti-inflammatory pattern in humans, and that the presence or absence of effects on some immune parameters may be a function of dosing differences. With the exception of one study by Bishop et al. (16), all human data in the 2006 review were from *in vitro* studies and consequently did not address possible immunomodulatory roles of caffeine in exercise or sport contexts.

Since that review, many *in vivo* studies have deepened our understanding of the immunomodulatory effects of caffeine in humans, and several have been conducted in athletic contexts. Those that examined possible effects of caffeine administered in "pure" form (either as capsules or dissolved in beverages) in exercise studies are summarized in Table 3. [Table 3 shows only post-exercise differences between caffeine-treated versus placebo groups, and does not indicate what effects exercise had independently of treatment. This convention will be followed for all subsequent tables]. Subjects given caffeine prior to exercise general-

Table 1. Common plant sources of caffeine in human nutrition. *Formerly Sterculiaceae.

Common Name	Scientific Name	Botanical Family	Caffeine Name
Chocolate	*Theobroma cacao* L.	Malvaceae*	Caffeine
Coffee	*Coffea* spp. L.	Rubiaceae	Caffeine
Guarana	*Paullinia cupana* Kunth	Sapindaceae	Guaranine
Kola	*Cola* spp. Schott & Endl.	Malvaceae	Caffeine
Mate, Yerba	*Ilex paraguariensis* A. St. Hil.	Aquifoliaceae	Mateine
Tea	*Camellia sinensis* (L.) Kuntze	Theaceae	Caffeine

Table 2. Caffeine content from a representative sample of energy drinks from central Iowa on September 12, 2013. Representative soft drinks and sports drinks are shown for comparison. Note differences in serving sizes across beverages; more than one serving may be included in a container. Though not included in the Table, chocolate milk or other cocoa-flavoured beverages contain trace amounts of caffeine from the cocoa, typically <10 mg/serving (112), plus other alkaloids such as theobromine. Some beverages contained additional alkaloid sources: ED1, ED3, ED6, ED9, and ED10 contained ginseng and guarana; ED4 contained guarana; and ED2 contained acacia.

Beverage	Serving Size (mL)	Calories (kcal)	Caffeine (mg/serving)
ENERGY DRINKS			
ED1	240	110	71
ED2	473	220	160
ED3	240	110	80
ED4	473	200	260
ED5	240	110	77
ED6	240	140	160
ED7	240	120	142
ED8	250	130	80
ED9	473	50	160
ED10	237	0	104
SOFT DRINKS			
SO1	355	140	34
SO2	355	170	54
SO3	355	150	38
SPORTS DRINKS			
SP1	355	80	0
SP2	360	0	0

ly exhibited unchanged or increased circulating leukocytes and lymphocytes (or specific subpopulations) post-exercise, compared to exercised but placebo-treated controls, with the exception of T-cells. Post-exercise natural killer (NK) cell activation, neutrophil activity, and plasma IL-6 and IL-10 were normally increased in caffeine-treated compared to placebo-treated subjects. Few of the outcomes from Table 3 are directly comparable to the *in vitro* data reviewed by Horrigan et al. (57), but the findings of increased neutrophil activity in response to caffeine stimulation is congruent, whilst the findings on IL-10 production are opposing.

Several of the studies in Table 3 that were conducted by Bishop and colleagues also included plasma catecholamine measurements and reported that caffeine augmented adrenaline (epinephrine) levels (16, 17, 42, 125–127), but not noradrenaline (norepinephrine) levels (42). Separately, Laurent and colleagues (65) reported that highly-trained males given 6 mg/kg caffeine 90 minutes prior to 120 minutes of cycling at 65% VO_2max demonstrated increased post-exercise plasma adrenaline, cortisol, and β-endorphin levels compared to placebo-treated controls. These findings together indicate that caffeine increases sympathetic nervous system activity via the hypothalamo-pituitary-adrenocortical (HPA) axis (92). The consequences of the interactions between caffeine, the HPA axis and its products, and the immune system are beyond the scope of this review but have been discussed elsewhere (42).

Studies that examined the immunomodulatory effects of beverages or supplements containing caffeine (alongside other possibly immunomodulatory ingredients) in exercise contexts are presented in Table 4. Several factors make it difficult to compare the results of Table 3 to Table 4 effectively. These include: differences in outcomes reported; relatively low number of studies in Table 4 versus Table 3; use of both trained and untrained subjects in Table 4 versus solely trained subjects in Table 3; chronic dosing in all Table 4 studies versus acute dosing in all Table 3 studies; lower caffeine dose to body weight ratio in Table 4 studies (where reported) compared to Table 3 studies (expounded below); and the fact that the studies from Table 4 utilized preparations with other potentially immunomodulatory compounds besides caffeine.

As represented in Table 4, many of the beverages, foods, or supplements consumed by athletes for their caffeine content frequently contain other non-caffeine and/or non-alkaloid immunomodulatory compounds. Understanding how these compounds modulate athlete immune function relative to caffeine or other alkaloids (independently, additively, synergistically, and so forth) is problematic yet important. These immunomodulatory compounds often come from plant sources.

Tea *(Camellia sinensis)* serves as a good model for examining this dilemma because it contains caffeine plus other non-alkaloid bioactive phytochemicals, including its relatively well-studied flavonoid subclasses. One flavonoid subclass present in tea is the flavanols, represented by catechins and epicatechins (often referred to simply as polyphenols, or procyanidins or tannins if they are oligomerized; epigallocatechin-3-gallate [EGCG] is the most abundant). Plasma or *in vitro* concentrations of ≤10 μM flavanols are considered physiologically relevant (84, 134), and leukocytes treated with flavanols at these concentrations exhibit anti-inflammatory, antioxidant, or T-cell-modulating effects (12, 30, 134). The cardiovascular benefits of tea consumption have been linked to these phenomena (133). If green tea leaves are processed into black or oolong tea, the green tea catechins oxidize and dimerize into theaflavins; theaflavins maintain similar antioxidant properties as catechins (67). A second flavonoid subclass present in tea is the flavonols (with an "o" instead of an "a"). The flavonol quercetin has anti-inflammatory and antioxidant effects *in vivo* that can sometimes offset the deleterious effects of exercise depending on context (74, 87, 88). Plasma or *in vitro* concentrations ranging from 0.5-1.5 μM are considered physiologically relevant and may be seen in as little as one dietary dose of quercetin, though even higher levels

Table 3. Immunomodulatory effects of pure caffeine in exercise contexts. *Cells were additionally stimulated *in vitro* with antigen (Pediacel vaccine).

Study	Subjects	Caffeine Dose	Exercise	Immunological Outcomes in Caffeine-Treated Subjects compared to Placebo-Treated Controls
Bassini-Cameron et al. **(13)**	22 ♂ soccer athletes	5 mg/kg acute dose pre-exercise	45-min of variable distance running + intermittent recovery test	↑ circulating lymphocytes and monocytes; ↑ circulating segmented neutrophils (only when combined with exercise)
Bishop et al. **(16)**	8 endurance-trained ♂	6 mg/kg acute dose pre-exercise	90-min cycling at 70% VO_2max	↓ total numbers of circulating CD4 and CD8 T-cells, but ↑ in CD4 and CD8 T-cell activation (based on ↑ CD69 expression)
Bishop et al. **(17)**	11 endurance-trained ♂	6 mg/kg acute dose pre-exercise	90-min cycling at 70% VO_2max	↑ sIgA concentrations and secretion rates
Fletcher & Bishop **(40)***	12 endurance-trained ♂ cyclists	2 or 6 mg/kg acute dose pre-exercise	90-min cycling at 70% VO_2max	↑ NK cell activation; ↑ circulating NK cells (high dose only)
Fletcher & Bishop **(41)***	15 healthy ♂	6 mg/kg acute dose pre-exercise (in 1× or 3× boluses)	6 15-min bouts of intermittent shuttle running	↑ NK cell activation (1× bolus only); ↑ circulating NK cells
Fletcher & Bishop **(42)***	9 endurance-trained ♂ cyclists	6 mg/kg acute dose pre-exercise	90-min cycling at 70% VO_2max	↓ CD4 and CD8 T-cell activation; ↑ NK cell activation
Machado et al. **(71)**	20 soccer athletes	4.5 mg/kg acute dose pre-exercise	6 sets of 10 sprints (with active recovery)	No differences in circulating leukocytes, lymphocytes, basophils, eosinophils, monocytes, neutrophils
Machado et al. **(72)**	15 ♂ soccer athletes	4.5 mg/kg acute dose pre-exercise	3 sets of 10 repetitions at 10-RM of bench press, pullover, biceps curl, triceps extension, leg extension, prone leg curl	No differences in circulating leukocytes, lymphocytes, eosinophils, monocytes, neutrophils
Mahdavi et al. **(73)**	26 ♀ basketball athletes	5 mg/kg acute dose pre-exercise	Single 30-second Wingate test	No differences in circulating leukocytes, lymphocytes, granulocytes
Pereira et al. **(94)**	15 soccer athletes	5.5 mg/kg acute dose pre-exercise	12 10-sprint sets	No differences in circulating leukocytes, lymphocytes, neutrophils
Tauler et al. **(118)**	33 running-trained ♂	6 mg/kg acute dose pre-exercise	15-km competitive run	↑ circulating leukocytes and neutrophils; ↑ plasma IL-6 and IL-10; ↑ plasma antioxidants
Vimercatti et al. **(123)**	15 trained ♂	4.5 or 5.5 mg/kg acute dose pre-exercise	60-min treadmill running at 65% VO_2max	No differences in circulating leukocytes
Walker et al. **(125)**	19 trained ♂ cyclists	6 mg/kg acute dose pre-exercise	90-min cycling at 70% VO_2max	↑ circulating lymphocytes; ↑ post-exercise fMLP-stimulated response in neutrophils; no effect on PMA-stimulated neutrophil oxidative burst
Walker et al. **(126)**	9 trained ♂ cyclists	6 mg/kg acute dose pre-exercise	90 min cycling at 70% VO_2max + time trial equivalent to 30-min cycling at 70% VO_2max	↓ circulating lymphocytes; no differences in circulating leukocytes or neutrophils; no differences in post-exercise fMLP-stimulated response in neutrophils
Walker et al. **(127)**	12 trained ♂ cyclists	6 mg/kg acute dose pre-exercise +/- carbohydrate drink	120-min cycling at 65% VO_2max	↑ post-exercise fMLP-stimulated response in neutrophils; ↑ IL-6 immediately post-exercise; variable effects on circulating leukocytes, lymphocytes, and neutrophils contingent on whether carbohydrate drink was co-ingested

Table 4. Immunomodulatory effects of caffeine-containing commercial beverages or supplements in exercise contexts. No sources examining the effects of coffee in the context of athlete immune function were retrieved by the search stratagem, though coffee is an obvious source of nutritional caffeine. Plasma protein carbonyls are indicators of oxidative burden. * EC = epicatechin; EGC = epigallocatechin, EGCG = epigallocatechin gallate.

Study	Subjects	Caffeine Source	Exercise	Immunological Outcomes in Caffeine-Treated Subjects compared to Placebo-Treated Controls
Arent et al. **(6)**	18 weight-trained ♂	Black tea extract containing 40% theaflavins and 30% catechins (total polyphenols exceeding 95%) for 9 days; caffeine content not specified	2 × 30-second Wingate test + 8 10-second cycling intervals	No differences in plasma IL-6
Hismiogullari et al. **(54)**	10 moderately active ♂	1 energy drink prior in between the first and secondn exercise bouts 150 mg caffeine, 80 mg taurine, 11 g carbohydrate, other ingredients	3 sets of 50 maximal knee contractions on an isokinetic dynamometer	↑ circulating basophils; no differences in circulating leukocytes, lymphocytes, eosinophils, monocytes, and neutrophils
Lockwood et al. **(69)**	36 sedentary ♂	1 energy drink/day containing 200 mg caffeine /serving and including ginger, green tea, and guarana for 10 weeks	10 weeks of cross-training	↓ circulating monocytes (only in non-exercising supplement-treatment group; values within normal reference ranges)
Narotzki et al. **(85)**	22 obese elderly (13♂, 9♀)	3 servings of brewed green tea (1.5 g tea/sachet) + 1 vitamin E capsule/day for 12 weeks; caffeine content not specified	12 weeks of 30-min walking 6× per week	↓ plasma protein carbonyls; no differences in CRP
Nieman et al. **(86)**	31 trained individuals (18♂, 13♀)	40 g/day of a green tea-blueberry polyphenol soy protein complex (PSPC) containing 344 mg caffeine and 1001 mg flavanols (79% being EC, EGC, and EGCG)* for 17 days	3 consecutive days of 150-min running at 70% VO_2max; exercise started at Day 14 of supplementation	No differences in leukocyte counts, plasma protein carbonyls, or plasma CRP, IL-6, IL-8, and MCP-1

may be common in some sites including the gut (31, 55, 135). Beyond the flavonoids, other compounds in tea also exert immunomodulatory effects. Theanine is an amino acid found in green tea which is a precursor for glutamate. Glutamate is one of the three amino acid components of glutathione (GSH; the other two being cysteine and glycine), important for maintaining antioxidant status. Cystine-theanine supplementation (700 mg cystine +280 mg theanine) has been shown to reduce exercise-induced changes in plasma C-reactive protein (CRP), circulating leukocytes and neutrophils, and NK cell activity, but not plasma IL-6 or IL-8 levels (62, 82, 83).

Several other plant sources are included in energy or sports drinks for their caffeine content. Guarana *(Paullinia cupana)* seeds contain higher caffeine levels than coffee leaves, in addition to the alkaloid theobromine (discussed below) and non-alkaloid flavanols (discussed above) (18, 98). Yerba mate *(Ilex paraguariensis)* is also valued for its caffeine content and includes different flavonoids, chlorogenic acid and associated derivatives, and triterpene saponins, some of which may possess antioxidant capacities (5, 20). Ginseng *(Panax ginseng* C. A. Meyer and sister species; Araliaceae) is another common ingredient in energy drinks: it contains the alkaloids **ginsenine** and various manifestations of **carbaline,** but is better known for its bioactive non-alkaloid ginsenosides. A thorough discussion of ginseng and athlete immune function may be found elsewhere (105). Thus, for caffeine-containing beverages that derive their caffeine partially

Table 5. Immunomodulatory effects of cocoa supplements in exercise contexts. F_2-isoprsotanes are a marker of oxidative stress. *Twenty males were included in the total study, but only ten exercised.

Study	Subjects	Chocolate Treatment	Exercise	Immunological Outcomes in Cocoa-Treated Subjects compared to Placebo-Treated Controls
Allgrove et al. **(3)**	20 healthy ♂	40 g dark chocolate bar (41.6 mg caffeine, 267 mg theobromine, 15.6 mg catechin, 38.7 mg epicatechin, and 44.4 mg other polyphenols) twice daily for 2 weeks + an acute dose 2 hours pre-exercise	90-min cycling at 60% VO_2max plus 30-seconds of cycling at 90% VO_2max every 10 min	↓ plasma F_2-isoprostanes; no differences in plasma IL-1Ra, IL-6, and IL-10
Davison et al. **(33)**	14 healthy ♂	100 g dark chocolate bar (668 mg theobromine, 104 mg caffeine, 97 mg epicatechin, 39 mg catechin) pre-exercise	150-min cycling at 60% VO_2max	↑ antioxidant status; no differences in plasma IL-6, leukocytosis, neutrophilia, or neutrophil degranulation
Macdonald et al. **(70)**	21 rowers (10 ♂, 11♀)	1 chocolate-flavoured "meal replacement beverage" or 1 chocolate-flavoured milk beverage compared to 2 other beverages post-exercise; alkaloid content not stated	90-min rowing at 60-70% VO_2max with ≤ 5 5-min increased pace bouts	↓ plasma IL-6 in the cocoa beverage trials post-exercise and ↓↓ plasma IL-6 in the chocolate milk trials 6-hours post-exercise
McBrier et al. **(78)**	7 recreationally active ♂ (anaerobically trained)	330 mL of a "cocoa-based protein drink" post-exercise; alkaloid content not stated	30-min run at 75% HRmax (10% downhill grade)	No differences in plasma IL-6, IL-8, or CRP
Singh et al. **(113)**	16 healthy ♂ (8 trained, 8 untrained)	7 days of "enriched cocoa polyphenol supplements" (no other details provided) pre-exercise	60-min cycling at 70% VO_2max	No differences in circulating platelets or platelet activation
Wiswedel et al. **(132)**	10 sedentary ♂*	100 mL of either "high" (187 mg) or "low" (14 mg) flavanols and procyanidins cocoa drink pre-exercise; alkaloid content not stated	10-min cycling at 100% HRmax after warm-up	↓ plasma F_2-isoprostanes

or fully from plant sources, it is impossible to ascertain which immunomodulatory effects are due to caffeine, other alkaloids, or non-alkaloid components. Regarding cognitive or ergogenic benefits ascribed to energy drinks, McLellan and Lieberman concluded that caffeine and possibly guarana (essentially another source of caffeine), but not other alkaloid ingredients within the beverages, were responsible for observed effects (79).

The average dose of caffeine in the studies from Table 3 was 5.3 mg/kg body mass. Assuming a 75-kg athlete, the average dose of caffeine in the studies from Table 4 (where disclosed) was 3.1 mg/kg body mass. The average dose of caffeine in the Table 2 commercial energy drinks was 1.7 mg/kg body mass if athletes consumed only the serving size; however, six of the energy drinks in Table 2 contain two servings per can, so if the athlete consumes the entire can then the average dose of caffeine from Table 2 becomes 2.6 mg/kg body mass. Stated another way, an athlete consuming one energy drink from Table 2 is only ingesting half the caffeine that subjects in the studies from Table 3 consumed; however, this calculation does not necessarily account for total alkaloid content nor does it consider possibly physiologically relevant synergistic effects between caffeine and other ingredients (46, 53).

Altogether, the data from Table 3 suggest caffeine is often immunoneutral but may be immunomodulatory (most frequently immunostimulatory) when consumed as a stand-alone supplement by trained individuals. The data from Table 4

suggest caffeine-containing supplements may be immunoneutral but may improve antioxidant capacity in exercise contexts; however, the precise role of caffeine versus other alkaloids versus non-alkaloid compounds in such preparations on *in vivo* immunomodulation is essentially uncharted territory.

THEOPHYLLINE AND ITS ISOMERS

Theophylline and its isomers **theobromine** and **paraxanthine** (Figure 1) are all alkaloids originally characterized from cocoa *(Theobroma cacao)* but subsequently found in many other plants like kola and tea. Moreover, they are the natural metabolites of caffeine in the human body (7). Chocolate and cocoa (referred together as "cocoa" hereafter) are the main sources of these alkaloids for athletes, yet cocoa beverages and foods contain other naturally-occurring phytochemicals (61) including caffeine and non-alkaloid compounds such as flavanols (catechin, epicatechin and proanthocyanidins—discussed previously), flavonols (quercetin—discussed previously), plus other nonflavonoids like chlorogenic acid and its derivatives. Reviews of the immunomodulatory and cardioprotective effects of cocoa in non-exercise contexts have been published elsewhere (8, 24, 37, 48).

Studies investigating the immunomodulatory effects of cocoa in exercise contexts are presented in Table 5. No conclusions can be drawn about the effects of cocoa alkaloids on athlete immune function because alkaloid composition was only reported in two studies from Table 5 and was never correlated to immune variables. Though athletes in both studies ingested therapeutically efficacious concentrations of theobromine, those in the Davison et al. study (33) ingested only a single pre-exercise bolus while those in the Allgrove et al. study (3) were treated for two weeks. Davison et al. (33) also looked at neuroendocrine correlates but found no association between cocoa treatment and HPA stress hormones including cortisol and adrenocorticotropic hormone (ACTH). Apart from Table 5, no additional studies were found testing isolated theophylline or its congeners on athlete immune function.

Since Table 5 has few studies to draw conclusions from, the literature on *in vitro* effects or *in vivo* non-exercise studies of theophylline and its congeners on human leukocytes may shed some light on these compounds' possible immunomodulatory roles. Plasma theophylline levels of 10-20 μg/mL or 55-110 μM are considered therapeutically relevant, though recent recommendations have suggested a narrower range of 10-15 μg/mL to avoid side effects (35, 90, 136). In human monocytes or cultured macrophages, *in vitro* theophylline treatment:

- at 1.8μg/mL inhibited monocyte → dendritic cell maturation (137);
- at 2.5-20 μg/mL reduced IL-13 mRNA expression in a dose-dependent manner (136);
- at 5-20 μg/mL reduced free radical production in monocytes by inhibiting phosphodiesterases (27);
- and at 30-50 μM reduced production of IL-6 and TNF even in the presence of sambutol (an IL-6 inducer) (35).

In human eosinophils, 18 μg/mL *in vitro* theophylline treatment increased peroxisome proliferator-activated receptor-γ (PPARγ) mRNA and protein levels (120).

Table 6. Immunomodulatory effects of ginger supplements in exercise contexts. *Thirty-two males were included in the study, but only 16 exercised and only 8 of those 16 received ginger supplement plus exercise. †The raw ginger contained 8.2 mg 6-gingerol, 1.3 mg 8-gingerol, 1.9 mg 10-gingerol, 2.2 mg 6-shogaol. ‡The heated ginger contained 2.8 mg 6-gingerol, 1.0 mg 8-gingerol, 1.6 mg 10-gingerol, 2.6 mg 6-shogaol. §Sixty women enrolled in the study, but 20 were given a cinnamon supplement and are not considered here; 49 completed the study, but it is unclear what the final numbers per group were.

Study	Subjects	Ginger Treatment	Exercise	Immunological Outcomes in Ginger-Treated Subjects compared to Placebo-Treated Controls
Atashak et al. **(9)**	16 obese, sedentary ♂*	4 250-mg ginger root capsules/day for 10 weeks; alkaloid content not stated	Progressive resistance training program including chest press, leg press, lateral pulldown, triceps pushdown, knee extension, seated row, bicep curl, and abdominal curl	↓ plasma CRP
Ayaz et al. **(11)**	20 obese ♀ with breast cancer	4 750-mg ginger root capsules/day for 6 weeks; alkaloid content not stated	40-80 min water aerobics (individualized per subject) 4 days/week for 6 weeks	↓ plasma CRP and IL-6
Black et al. **(19)**	74 individuals (73% ♀)	2 g raw ginger† or 2 g heated ginger‡ for 11 days	18 eccentric contractions of the elbow flexors	No differences in plasma prostaglandin E_2
Mashhadi et al. **(75)**	40 athletic ♀§	3 g ginger powder/day for 8 weeks; alkaloid content not stated	Acute bout of resistance training exercises (specific to the sport of each subject)	No differences in plasma IL-6

Finally, in human leukocytes *in vitro* treatment with 5 μM theophylline reduced production of the leukotrienes B_4 and C_4 (111). Regarding *in vivo* effects, chronic obstructive pulmonary disease (COPD) patients treated with 400 mg/d theophylline (which should correspond to plasma theophylline levels of ~10-15 μg/mL) demonstrated reduced sputum levels of IL-8, TNF, and neutrophils (58). In COPD patients treated with standard steroid therapy or standard steroid therapy plus low-dose theophylline (200 mg/d), patients in the latter group had greater declines in plasma TNF and IL-8 than the former (32). Thus, non-exercise *in vitro* and *in vivo* studies both show efficacy of theophylline as an immunomodulator at therapeutic or even subtherapeutic concentrations.

GINGEROLS AND CONGENERS

The major category of alkaloids from ginger *(Zingiber officinale* Roscoe; Zingiberaceae) are the **gingerols**, a series of chemical homologues (Figure 1) important in both flavouring and bioactivity, and structurally analogous to capsaicin (110). When ginger is dried, these compounds are dehydrated to **shogaols. Paradols** are also present, though in more minor quantities. Ginger supplements are indicated for various conditions including cardiovascular diseases, diabetes, and gut disorders (23, 76) because of anti-inflammatory, antioxidant, antimicrobial properties ascribed to their alkaloids. Ginger has also been suggested for pain management, though this application remains unproven (119). Volatiles, including mono- and sesquiterpenes, are also important co-occurring chemicals (23).

Anti-inflammatory effects have been shown in human *in vitro* studies, as reviewed elsewhere (28).

Although no plasma thresholds have been declared as therapeutic standards, some studies have looked as plasma responses to ginger supplementation in humans. After human subjects were given a single oral bolus of 2 g ginger supplement containing ~135 mg gingerols and related congeners, peak plasma concentrations of free gingerol (9.5 ng/mL) and free shogaol (13.6 ng/mL) were observed 1 hour post-consumption, with peak concentrations of numerous metabolites also observed at that time (138). Separately, Zick et al. (139) dosed human subjects with anywhere from 100 mg-2g standardized ginger supplement (containing ~98.4 mg gingerol and related congeners per 2 g ginger). They found no free plasma gingerols or shogoals; however, peak metabolites of these compounds were observed between 45-120 minutes, with peak concentrations of gingerol metabolites at 0.5-1.7 ng/mL and shogaol metabolites at 0.2 ng/mL. From these limited findings, it appears that plasma concentrations of gingerols or related congeners peak 1-2 hours post-supplementation and can vary markedly.

Studies that examined the immunomodulatory effects of ginger supplementation in exercise contexts are shown in Table 6. Atashak et al. and Avaz et al. showed reduced plasma CRP and/or IL-6 (9, 11), whereas Black et al. and Mashhadi et al. showed no effect of ginger supplementation on IL-6 or PGE_2 (19, 75). Across Table 6, subjects were diverse in terms of sex and fitness levels. Subjects in the first two studies were clinically obese whereas subjects in the latter two studies were not, possibly suggesting that any anti-inflammatory effects of ginger may only be manifested in overweight individuals. Whether these effects are due to gingerols, paradols, shogaols, their congeners, or other compounds remains to be ascertained. Given the lack of data from humans, it is interesting to note that both *in vitro* and *in vivo* rodent models also show anti-inflammatory effects from ginger supplementation, as reviewed elsewhere (66). For example, at concentrations of 5-50 μM, gingerols block NF-κB and MAPK activation, c-Jun N-terminal kinase (JNK) phosphorylation, and TNF-α expression in *in vitro* or mouse skin models (59, 63).

EPHEDRINE AND CONGENERS

Ephedrine and **pseudoephedrine** (Figure 1) are stereoisomers first isolated from Ma Huang or the ephedra plant (*Ephedra sinica* Stapf.; Ephedraceae [formerly Gnetaceae]) of traditional Chinese medicine (TCM) (80), but are found in all members of the genus including the North American species Mormon tea (*Ephedra viridis* Coville). **Methylephedrine** and other congeners are structurally similar and also naturally-occurring in this genus, whereas **phenylpropanolamine** is a synthetic analogue of ephedrine. These compounds are described as sympathomimetic alkaloids because their *in vivo* actions are similar to amphetamine and include tachycardia, hypertension, and smooth muscle relaxation (hence their application in cough syrups, decongestants, and weight loss products) (89). Normal human plasma concentrations after one or a couple doses of ephedra extract range from 80-400 ng/mL, with lower concentrations being more common (52, 101, 130). Other alkaloids present in ephedra include caffeine, theobromine, and

theophylline (discussed earlier). Ephedrine and ephedrine-like alkaloids act synergistically when combined with drugs such as aspirin (129) or other alkaloids such as caffeine (51), as is often the case in energy drinks. Additional ephedra phytochemicals may exert immunomodulatory activities—for example, carbohydrates from the plant may dose-dependently inhibit complement components C2 and C9 in human sera (68).

There are no *in vivo* studies of the effects of these compounds on athlete immune function. Human *in vitro* studies are ample and may provide some insight on possible effects. In a study by Wilasrusmee et al. (131), PBMC stimulated *in vitro* with an aqueous extract of *Ephedra sinica* dried powder (ephedrine quantity not provided) showed no differences in cellular proliferation, IL-2 production, or IL-10 production compared to controls. In a separate study by Attard and Vella (10), human PBMC were stimulated *in vitro* with pure ephedrine across ten-fold dilutions ranging from 0.69-69 μg/mL ephedrine or aqueous-benzene extracts from different *Ephedra fragilis* aerial parts standardized to 69 μg/mL ephedrine content. PBMC proliferation increased, but not significantly. A comparison of these results to rodent models has been given elsewhere (107). Regarding isolated compounds, Fiebich et al. (39) demonstrated that when Jurkat T-cells were treated with pseudoephedrine *in vitro* at doses ranging from 1-5 mM, the following were diminished: transcriptional activity of NFAT, NF-κB, and AP-1; c-Jun activation; and TNF and IL-2 gene transcription. In a study by Watson et al. (129), ephedrine and phenylpropanolamine (both at 50 μmol/L, administered independently) inhibited platelet aggregation when administered *in vitro* to human platelet-rich plasma. Given the absence of data, little can be concluded about the effects of ephedra alkaloids on athlete immune function. Limited research suggests they may have anti-inflammatory effects, but this needs to be demonstrated convincingly *in vivo*.

EMERGING ALKALOID SOURCES

This review has so far considered only those alkaloids or alkaloid-rich plants that are appreciably consumed by athletes. Several other plants, either obscure or only recently surging in popularity, also contain alkaloids that may be therapeutic immunomodulators relevant to athletes.

Noni berry (*Morinda citrifolia* L.; Rubiaceae) is escalating in popularity among Western athletes, though it has long been used by Polynesians. One of its primary bioactive compounds is the alkaloid **xeronine.** Reviews have concluded that noni berry has immunomodulatory (e.g., cytokine- and cannabinoid receptor-modulating) activities in mice (91) and marginal anticancer properties (21), though the molecules responsible for the latter (possibly alkaloids) are yet to be determined. Noni berry presents a diverse array of phytochemicals including alkaloids, other flavonoids, phenylpropanoids, and triterpenoids (93). Much work remains to determine the bioactive role of noni berry alkaloids (50), or whether noni might be efficacious for bolstering athlete immune function.

Goji berry or wolfberry (*Lycium barbarum* L. and *Lycium chinense* Mill.; Solanaceae) supplements and juices are also growing in popularity among Western athletes (97). Along with carotenoids, sterols, and the organic acid taurine,

Table 7. Effects of 50% ethanol bloodroot extracts of proximal, middle, or distal rhizomes on in vitro cytokine production by human PBMC (previously unpublished work). PBMC were isolated from the blood of eight healthy adult donors, plated at 1.0×10^6 cells per well, and cultured with LPS or extract as detailed elsewhere (95, 107). Cytokine production was determined by ELISA. *Significant ($p<0.005$) differences compared to solvent vehicle (media) control. †Significant ($p<0.005$) differences compared to both solvent vehicle and LPS controls.

	Solvent Vehicle	LPS (no extract)	Proximal (no LPS)	Middle (no LPS)	Distal (no LPS)	Proximal + LPS	Middle + LPS	Distal + LPS
IL-6	15.12 ± 1.74	1176.07 ± 112.03*	11.49 ± 3.98	8.52 ± 2.64	9.2 ± 1.86	11.35 ± 1.19	13.07 ± 1.47	11.45 ± 1.88
IL-8	1487.22 ± 157.52	2022.69 ± 72.99*	17.97 ± 2.08†	18.07 ± 1.32†	16.68 ± 1.99†	17.42 ± 1.74†	16.7 ± 2†	15.61 ± 2.32†
IL-10	9.73 ± 1.54	675.4 ± 100.5*	15.13 ± 2.5	14.44 ± 2.02	15.32 ± 2.69	17.26 ± 2.12	16.46 ± 2.88	13.34 ± 1.88
TNF	12.76 ± 2.65	1222.73 ± 142.04*	11.77 ± 1.71	11.34 ± 2.03	9.98 ± 1.12	13.44 ± 3.53	9.24 ± 1.77	7.6 ± 1.49

Goji berries also contain alkaloids including small amounts of **atropine.** Using influenza-infected rats, Ren et al. (100) showed that wolfberry supplementation for 4 weeks (containing 530 mg/g wolfberry fruit) augmented the immune response to infection and spurred T-cell responses by upregulating IL-2 production. Du et al. (34) performed a similar study with similar results, and showed that wolfberry supplementation improved activity and maturation of antigen-presenting dendritic cells, which in turn improved antigen-specific T-cell proliferation and CD4 T-cell production of IL-4 and IFN-γ *in vitro.* While these results suggest a possible immunotherapeutic role for Goji berry in athletes, human tests still need to be conducted (including safety determinations). It is presently unclear which Goji berry components produced these effects.

Bloodroot (*Sanguinaria canadensis* L., Papaveraceae) produces a phalanx of benzophenanthridine alkaloids. While **sanguinarine** and **chelerythrine** (Figure 1) are the most frequently researched, others are present in lesser quantities. Bloodroot alkaloids are found in greatest concentrations in the rhizomes (underground stems) and increase in concentration from proximal to distal (Figure 3). When human PBMC were stimulated *in vitro* with 50% ethanol extracts produced from different rhizome regions, the extracts had no effect on IL-6, IL-10, and TNF production, but suppressed IL-8 production compared to media-treated controls (Table 7). When PBMC were co-stimulated with both bloodroot extract and lipopolysaccharide (LPS), cells produced lower levels of all cytokines compared to cells treated with LPS alone. In two separate pilot studies in athletes, the same or identically produced extracts reduced *in vitro* TNF and IL-10 production and PBMC proliferation, regardless of the effects of exercise (a graded treadmill VO_2max test or 90 minutes of cycling at 85% ventilatory threshold), and also abrogated the effects of LPS or phytohaemagluttinn (PHA) co-stimulation (107). Observed effects are unlikely to be due to toxicity, as two groups have shown sanguinarine or sanguinarine-containing extracts are toxic to human cancerous cells but promote proliferation of healthy human PBMC *in vitro* (2, 104). Together, these data may suggest an immunosuppressive effect of bloodroot rhizome extracts, which would be counterproductive to athletes trying to offset the immunodepressive effects of intense training. However, in a previous study where subjects completed both a graded cycling VO_2max test and 90 minutes of cycling at 85% ventilatory threshold, 50% ethanol flower extracts (but not 50% ethanol root extracts) stimulated post-exercise *in vitro* PBMC production of TNF,

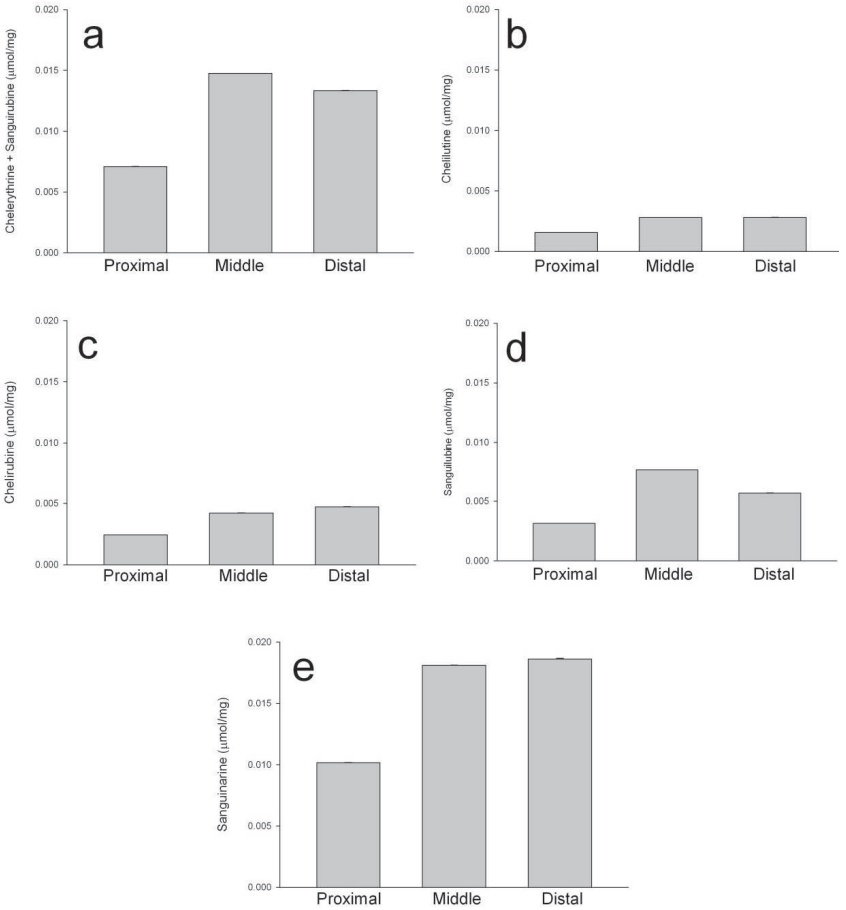

Figure 3. Alkaloid composition of 50% ethanol extracts produced from the proximal, middle, and distal portions of bloodroot rhizomes (previously unpublished work). Plants were harvested from an upland ravine in south Story County, Iowa, April 2010. Rhizome regions were demarcated by measuring the length of each individual rhizome and dividing it by thirds. Extraction and LC/MS were conducted as detailed elsewhere (107). All extracts were tested in triplicate. Assayed alkaloids include chelerythrine and sanguirubine, which co-eluted and were indistinguishable (a); chelilutine (b); chelirubine (c); sanguilutine (d); and sanguinarine (e). Standard deviation bars are present but invisible at this scale; by ANOVA, alkaloid content differed significantly for every possible comparison (all $p<0.001$).

IL-1β, and IL-10 following both exercise bouts (106). The data in Figure 3, Table 7, and previous studies collectively suggest that bloodroot ethanol extracts may be immunostimulatory or immunosuppressive depending on which plant organ is harvested. The roles of its alkaloid constituents are less clear, sometimes correlating negatively or not at all with immune effects; for example, even though alka-

loid content differed significantly across the three rhizome extracts for all alkaloids (Figure 3; $p<0.001$), there were no significant differences in immune effects across the three extracts (Table 7).

CONCLUSIONS AND INTERDISCIPLINARY VIEWPOINTS

As the previous examples of green tea and bloodroot have shown, plant-based alkaloid sources are replete with known immunomodulatory alkaloids, other known non-alkaloid immunomodulatory compounds, and a panoply of unknown (or unattended) potentially immunomodulatory compounds. Plants can vary considerably in biochemical composition from species to species, interindividually, or even intraindividually (discussed below). In a previous issue of *EIR*, we proposed a framework to help account for these factors experimentally from an exercise immunologist's viewpoint using an interdisciplinary structure including botanical, chemical, and clinical considerations (108), and that framework has subsequently been expanded into the "seed to stomach" model to address manufacturing and consumer factors (109). The "seed to stomach" model is a useful tool for considering the current state of research regarding alkaloids and athlete immune function.

Based on the search stratagem used for this review, there were a much greater number of studies examining possible *in vivo* immunomodulatory roles of caffeine in human exercise contexts than other alkaloids or alkaloid sources. Only a handful of sources were uncovered examining possible *in vivo* immunomodulatory roles of cocoa or ginger in human exercise contexts. None were found for ephedra. However, the search stratagem used in this review may not have uncovered all germane references, particularly those written in non-English languages. This review did not address the library of rodent exercise studies: these may prove to be applicable to human exercise contexts in the future.

Human *in vitro* and *in vivo* studies on alkaloids and immune function are disjointed, making it difficult to form generalizations about the roles of alkaloids in athlete immune function. There is some evidence that caffeine can serve as an immunostimulatory, immunoneutral, or immunodepressing agent, depending on subject and exercise characteristics and immune variables measured, though no clear patterns emerge from the reviewed studies. It may also exhibit antioxidant properties. Ginger may exert anti-inflammatory effects, but it is unclear whether these effects are due to alkaloids or other biochemicals. Evidence for an immunomodulatory role of marker alkaloids in multi-compound preparations such as energy drinks, cocoa, or ephedra products is weak to nonexistent. For alkaloid sources derived from plants, variability in the reviewed studies may be due to the presence of other alkaloids or non-alkaloids, which may be immunomodulatory themselves. Pre-experimental factors such as growth or manufacturing differences may also play a part.

From an athlete's or coach's perspective, the data on alkaloids and athlete immune function are inconsistent and inconclusive. Although the health benefits of several of the plants in this review appear well-founded and have been discussed above, including cocoa (8), ginger (23), and green tea (102), it is unclear what role (if any) alkaloids are playing. For many athletes, proper diet is the best

nutrition and additional supplementation is often unnecessary (77, 121). Other caveats forewarn consideration of alkaloids as nutraceuticals. Safety and/or overdosing concerns are well-documented for sources such as caffeine (1, 47) and bloodroot (29, 124) and has led to the prohibition or regulation of ephedrine and its congeners by governments and sports regulatory agencies (96, 121). The sports supplement industry is poorly regulated and supplements may not contain adequate safety warnings (99). Package labels may not accurately reflect actual ingredients, even if manufacturers' claims of standardization are provided (22, 44). The preponderance of studies on alkaloids and athlete immune function have used males exclusively, so it is unclear whether the same outcomes would accrue with female athletes, though it appears caffeine has similar pharmacokinetics in both sexes (14, 46).

From the vantage points of botany and chemistry, the range of immune effects arising from alkaloids is logical given their structural diversity. The plants used in sports supplements are also evolutionarily diverse (105). A lack of correlation between marker components and supplement immune activity is reported for other medicinal plant genera, such as *Echinacea* (122) and *Pueraria* (26), so is perhaps unsurprising for the plant sources in this review. Exacerbating the problem are botanical or chemical factors that occur prior to or during extract preparation; summarily, these factors include planning factors (species selection, genetic variables), field factors (environmental conditions during growth), production factors (harvesting and manufacturing methods), and post-production factors (storage conditions) (109). Though it is pragmatically impossible for any research team to simultaneously attend to all these factors within a single study, future exercise immunology endeavors can add to the knowledge base by either controlling or accounting for a handful of these factors. For exercise immunologists who are already juggling kinesiology, immunology, physiology, and related disciplines in their experiments, widening the interdisciplinary approach may be daunting or even unmanageable. In such a situation it may even be beneficial to recruit scientists from other disciplines to the team.

ACKNOWLEDGMENTS

DSS wrote the paper. The biochemistry work (Figure 3) was from NAN and MAP. The immunology work (Table 7) was from DSS, JEH, and MLK.

REFERENCES

1. Abbott PJ. Caffeine: a toxicological overview. Med. J. Aust. 145: 518–521, 1986.
2. Ahmad N, Gupta S, Husain MM, Heiskanen KM, Mukhtar H. Differential antiproliferative and apoptotic response of sanguinarine for cancer cells versus normal cells. Clin. Cancer Res. 6: 1524–1528, 2000.
3. Allgrove J, Farrell E, Gleeson M, Williamson G, Cooper K. Regular dark chocolate consumption's reduction of oxidative stress and increase of free-fatty-acid mobilization in response to prolonged cycling. Int. J. Sport Nutr. Exerc. Metab. 21: 113–123, 2011.

4. Angell PJ, Chester N, Sculthorpe N, Whyte G, George K, Somauroo J. Performance enhancing drug abuse and cardiovascular risk in athletes: implications for the clinician. Br. J. Sports Med. 46 Suppl 1: i78–84, 2012.
5. Arçari DP, Porto VB, Rodrigues ERV, Martins F, Lima RJ de, Sawaya ACHF, Ribeiro ML, Carvalho P de O. Effect of mate tea (Ilex paraguariensis) supplementation on oxidative stress biomarkers and LDL oxidisability in normo- and hyperlipidaemic humans. J. Funct. Foods 3: 190–197, 2011.
6. Arent SM, Senso M, Golem DL, McKeever KH. The effects of theaflavin-enriched black tea extract on muscle soreness, oxidative stress, inflammation, and endocrine responses to acute anaerobic interval training: a randomized, double-blind, crossover study. J. Int. Soc. Sports Nutr. 7: 11, 2010.
7. Arnaud MJ. Pharmacokinetics and metabolism of natural methylxanthines in animal and man. Handb. Exp. Pharmacol. : 33–91, 2011.
8. Arranz S, Valderas-Martinez P, Chiva-Blanch G, Casas R, Urpi-Sarda M, Lamuela-Raventos RM, Estruch R. Cardioprotective effects of cocoa: clinical evidence from randomized clinical intervention trials in humans. Mol. Nutr. Food Res. 57: 936–947, 2013.
9. Atashak S, Peeri M, Azarbayjani MA, Stannard SR, Haghighi MM. Obesity-related cardiovascular risk factors after long- erm resistance training and ginger supplementation. J. Sports Sci. Med. 10: 685–691, 2011.
10. Attard E, Vella K. Effects of ephedrine and Ephedra fragilis crude extracts on human peripheral lymphocytes. Pharmacogn. Res. 1: 38–42, 2009.
11. Ayaz A, Roshan VD. Effects of 6-weeks water-based ntermittent exercise with and without Zingiber officinale on pro-inflammatory markers and blood lipids in overweight women with breast cancer. J. Appl. Pharm. Sci. 2: 218–224, 2012.
12. Babu PVA, Liu D. Green tea catechins and cardiovascular health: an update. Curr. Med. Chem. 15: 1840–1850, 2008.
13. Bassini-Cameron A, Sweet E, Bottino A, Bittar C, Veiga C, Cameron L-C. Effect of caffeine supplementation on haematological and biochemical variables in elite soccer players under physical stress conditions. Br. J. Sports Med. 41: 523–530; discussion 530, 2007.
14. Beaudoin M-S, Allen B, Mazzetti G, Sullivan PJ, Graham TE. Caffeine ingestion impairs insulin sensitivity in a dose-dependent manner in both men and women. Appl. Physiol. Nutr. Metab. Physiol. Appliquée Nutr. Métabolisme 38: 140–147, 2013.
15. Bell DG, McLellan TM. Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. J. Appl. Physiol. 93: 1227–1234, 2002.
16. Bishop NC, Fitzgerald C, Porter PJ, Scanlon GA, Smith AC. Effect of caffeine ingestion on lymphocyte counts and subset activation in vivo following strenuous cycling. Eur. J. Appl. Physiol. 93: 606–613, 2005.
17. Bishop NC, Walker GJ, Scanlon GA, Richards S, Rogers E. Salivary IgA responses to prolonged intensive exercise following caffeine ingestion. Med. Sci. Sports Exerc. 38: 513–519, 2006.
18. Bittencourt LS, Machado DC, Machado MM, Dos Santos GFF, Algarve TD, Marinowic DR, Ribeiro EE, Soares FAA, Barbisan F, Athayde ML, Cruz IBM. The protective effects of guaraná extract (Paullinia cupana) on fibroblast NIH-3T3 cells exposed to sodium nitroprusside. Food Chem. Toxicol. 53: 119–125, 2013.

19. Black CD, Herring MP, Hurley DJ, O'Connor PJ. Ginger (Zingiber officinale) reduces muscle pain caused by eccentric exercise. J. Pain 11: 894–903, 2010.
20. Bracesco N, Sanchez AG, Contreras V, Menini T, Gugliucci A. Recent advances on Ilex paraguariensis research: minireview. J. Ethnopharmacol. 136: 378–384, 2011.
21. Brown AC. Anticancer activity of Morinda citrifolia (Noni) fruit: a review. Phytother. Res. 26: 1427–1440, 2012.
22. Buell JL, Franks R, Ransone J, Powers ME, Laquale KM, Carlson-Phillips A, National Athletic Trainers' Association. National Athletic Trainers' Association position statement: evaluation of dietary supplements for performance nutrition. J. Athl. Train. 48: 124–136, 2013.
23. Butt MS, Sultan MT. Ginger and its health claims: molecular aspects. Crit. Rev. Food Sci. Nutr. 51: 383–393, 2011.
24. Castell M, Perez-Cano FJ, Bisson J-F. Clinical Benefits of Cocoa: An Overview. In: Chocolate in Health and Nutrition, edited by Watson RR, Preedy VR, Zibadi S. Humana Press, 2013, p. 265–275.
25. Chen CK, Muhamad AS, Ooi FK. Herbs in exercise and sports. J. Physiol. Anthropol. 31: 4, 2012.
26. Cherdshewasart W, Sutjit W. Correlation of antioxidant activity and major isoflavonoid contents of the phytoestrogen-rich Pueraria mirifica and Pueraria lobata tubers. Phytomedicine 15: 38–43, 2008.
27. Chorostowska-Wynimko J, Kus J, Skopińska-Rózewska E. Theophylline inhibits free oxygen radicals production by human monocytes via phosphodiesterase inhibition. J. Physiol. Pharmacol. 58 Suppl 5: 95–103, 2007.
28. Chrubasik S, Pittler MH, Roufogalis BD. Zingiberis rhizoma: a comprehensive review on the ginger effect and efficacy profiles. Phytomedicine 12: 684–701, 2005.
29. Cienki JJ, Zaret L. An Internet misadventure: bloodroot salve toxicity. J. Altern. Complement. Med. 16: 1125–1127, 2010.
30. Coimbra S, Castro E, Rocha-Pereira P, Rebelo I, Rocha S, Santos-Silva A. The effect of green tea in oxidative stress. Clin. Nutr. 25: 790–796, 2006.
31. Conquer JA, Maiani G, Azzini E, Raguzzini A, Holub BJ. Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. J. Nutr. 128: 593–597, 1998.
32. Cosio BG, Iglesias A, Rios A, Noguera A, Sala E, Ito K, Barnes PJ, Agusti A. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. Thorax 64: 424–429, 2009.
33. Davison G, Callister R, Williamson G, Cooper KA, Gleeson M. The effect of acute pre-exercise dark chocolate consumption on plasma antioxidant status, oxidative stress and immunoendocrine responses to prolonged exercise. Eur. J. Nutr. 51: 69–79, 2012.
34. Du X, Wang J, Niu X, Smith D, Wu D, Meydani SN. Dietary Wolfberry Supplementation Enhances the Protective Effect of Flu Vaccine against Influenza Challenge in Aged Mice. J. Nutr. 144: 224-229, 2014.
35. Ezeamuzie CI, Shihab PK. Interactions between theophylline and salbutamol on cytokine release in human monocytes. J. Pharmacol. Exp. Ther. 334: 302–309, 2010.
36. Fernandez MMF, Hosey RG. Performance-enhancing drugs snare nonathletes, too. J. Fam. Pract. 58: 16–23, 2009.

37. Fernández-Murga L, Tarín JJ, García-Perez MA, Cano A. The impact of chocolate on cardiovascular health. Maturitas 69: 312–321, 2011.
38. Ferreira MP, Gendron F, McClure K, Kindscher K. North American Bioactive Plants for Human Health and Performance. Glob. J. Res. Med. Plants Indig. Med. 1: 568–582, 2012.
39. Fiebich BL, Collado JA, Stratz C, Valina C, Hochholzer W, Muñoz E, Bellido LM. Pseudoephedrine inhibits T-cell activation by targeting NF-κB, NFAT and AP-1 signaling pathways. Immunopharmacol. Immunotoxicol. 34: 98–106, 2012.
40. Fletcher DK, Bishop NC. Effect of a high and low dose of caffeine on antigen-stimulated activation of human natural killer cells after prolonged cycling. Int. J. Sport Nutr. Exerc. Metab. 21: 155–165, 2011.
41. Fletcher DK, Bishop NC. Effect of a single and repeated dose of caffeine on antigen-stimulated human natural killer cell CD69 expression after high-intensity intermittent exercise. Eur. J. Appl. Physiol. 111: 1329–1339, 2011.
42. Fletcher DK, Bishop NC. Caffeine ingestion and antigen-stimulated human lymphocyte activation after prolonged cycling. Scand. J. Med. Sci. Sports 22: 249–258, 2012.
43. Van Furth AM, Seijmonsbergen EM, Langermans JA, van der Meide PH, van Furth R. Effect of xanthine derivates and dexamethasone on Streptococcus pneumoniae-stimulated production of tumor necrosis factor alpha, interleukin-1 beta (IL-1 beta), and IL-10 by human leukocytes. Clin. Diagn. Lab. Immunol. 2: 689–692, 1995.
44. Gilroy CM, Steiner JF, Byers T, Shapiro H, Georgian W. Echinacea and truth in labeling. Arch. Intern. Med. 163: 699–704, 2003.
45. Gleeson M. Can nutrition limit exercise-induced immunodepression? Nutr. Rev. 64: 119–131, 2006.
46. Graham TE. Caffeine and exercise: metabolism, endurance and performance. Sports Med. 31: 785–807, 2001.
47. Graham TE. Caffeine, coffee and ephedrine: impact on exercise performance and metabolism. Can. J. Appl. Physiol. 26 Suppl: S103–119, 2001.
48. Gu Y, Lambert JD. Modulation of metabolic syndrome-related inflammation by cocoa. Mol. Nutr. Food Res. 57: 948–961, 2013.
49. Gunzer W, Konrad M, Pail E. Exercise-induced immunodepression in endurance athletes and nutritional intervention with carbohydrate, protein and fat-what is possible, what is not? Nutrients 4: 1187–1212, 2012.
50. Gupta RK, Patel AK. Do the health claims made for Morinda citrifolia (Noni) harmonize with current scientific knowledge and evaluation of its biological effects. Asian Pac. J. Cancer Prev. 14: 4495–4499, 2013.
51. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N. Engl. J. Med. 343: 1833–1838, 2000.
52. Haller CA, Jacob P, Benowitz NL. Short-term metabolic and hemodynamic effects of ephedra and guarana combinations. Clin. Pharmacol. Ther. 77: 560–571, 2005.
53. Haskell CF, Dodd FL, Wightman EL, Kennedy DO. Behavioural effects of compounds co-consumed in dietary forms of caffeinated plants. Nutr. Res. Rev. 26: 49–70, 2013.
54. Hismiogullari AA, Punduk Z, Hismiogullari SE, Yavuz O. The acute effect of commercial "energy drink" on hematological, biochemical and strength parameters induced by eccentric contractions. Isokinet. Exerc. Sci. 21: 247–252, 2013.

55. Hollman PC, vd Gaag M, Mengelers MJ, van Trijp JM, de Vries JH, Katan MB. Absorption and disposition kinetics of the dietary antioxidant quercetin in man. Free Radic. Biol. Med. 21: 703–707, 1996.
56. Horrigan LA, Kelly JP, Connor TJ. Caffeine suppresses TNF-alpha production via activation of the cyclic AMP/protein kinase A pathway. Int. Immunopharmacol. 4: 1409–1417, 2004.
57. Horrigan LA, Kelly JP, Connor TJ. Immunomodulatory effects of caffeine: friend or foe? Pharmacol. Ther. 111: 877–892, 2006.
58. Iiboshi H, Ashitani J-I, Katoh S, Sano A, Matsumoto N, Mukae H, Nakazato M. Long-term treatment with theophylline reduces neutrophils, interleukin-8 and tumor necrosis factor-alpha in the sputum of patients with chronic obstructive pulmonary disease. Pulm. Pharmacol. Ther. 20: 46–51, 2007.
59. Isa Y, Miyakawa Y, Yanagisawa M, Goto T, Kang M-S, Kawada T, Morimitsu Y, Kubota K, Tsuda T. 6-Shogaol and 6-gingerol, the pungent of ginger, inhibit TNF-alpha mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. Biochem. Biophys. Res. Commun. 373: 429–434, 2008.
60. Kaplan GB, Greenblatt DJ, Kent MA, Cotreau-Bibbo MM. Caffeine treatment and withdrawal in mice: relationships between dosage, concentrations, locomotor activity and A1 adenosine receptor binding. J. Pharmacol. Exp. Ther. 266: 1563–1572, 1993.
61. Katz DL, Doughty K, Ali A. Cocoa and chocolate in human health and disease. Antioxid. Redox Signal. 15: 2779–2811, 2011.
62. Kawada S, Kobayashi K, Ohtani M, Fukusaki C. Cystine and theanine supplementation restores high-intensity resistance exercise-induced attenuation of natural killer cell activity in well-trained men. J. Strength Cond. Res. 24: 846–851, 2010.
63. Kim SO, Kundu JK, Shin YK, Park J-H, Cho M-H, Kim T-Y, Surh Y-J. [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. Oncogene 24: 2558–2567, 2005.
64. Lantz RC, Chen GJ, Sarihan M, Sólyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine 14: 123–128, 2007.
65. Laurent D, Schneider KE, Prusaczyk WK, Franklin C, Vogel SM, Krssak M, Petersen KF, Goforth HW, Shulman GI. Effects of caffeine on muscle glycogen utilization and the neuroendocrine axis during exercise. J. Clin. Endocrinol. Metab. 85: 2170–2175, 2000.
66. Leiherer A, Mündlein A, Drexel H. Phytochemicals and their impact on adipose tissue inflammation and diabetes. Vascul. Pharmacol. 58: 3–20, 2013.
67. Leung LK, Su Y, Chen R, Zhang Z, Huang Y, Chen ZY. Theaflavins in black tea and catechins in green tea are equally effective antioxidants. J. Nutr. 131: 2248–2251, 2001.
68. Ling M, Piddlesden SJ, Morgan BP. A component of the medicinal herb ephedra blocks activation in the classical and alternative pathways of complement. Clin. Exp. Immunol. 102: 582–588, 1995.
69. Lockwood CM, Moon JR, Smith AE, Tobkin SE, Kendall KL, Graef JL, Cramer JT, Stout JR. Low-calorie energy drink improves physiological response to exercise in previously sedentary men: a placebo-controlled efficacy and safety study. J. Strength Cond. Res. 24: 2227–2238, 2010.

70. Macdonald SL, Perry TL, Rose MC. Glycaemic, insulinaemic, and immune responses to commercially available beverages consumed during recovery from rowing training. Eur. J. Sport Sci. 10: 337–345, 2010.
71. Machado M, Antunes WD, Tamy ALM, Azevedo PG, Barreto JG, Hackney AC. Effect of a Single Dose of Caffeine Supplementation and Intermittent-interval Exercise on Muscle Damage Markers in Soccer Players. J. Exerc. Sci. Fit. 7: 91–97, 2009.
72. Machado M, Koch AJ, Willardson JM, dos Santos FC, Curty VM, Pereira LN. Caffeine does not augment markers of muscle damage or leukocytosis following resistance exercise. Int. J. Sports Physiol. Perform. 5: 18–26, 2010.
73. Mahdavi R, Daneghian S, Homayouni A, Jafari A. Effects of caffeine supplementation on oxidative stress, exercise-induced muscle damage and leukocytosis. Pharm. Sci. 18: 117–182, 2012.
74. Malaguti M, Angeloni C, Hrelia S. Polyphenols in exercise performance and prevention of exercise-induced muscle damage. Oxid. Med. Cell. Longev. 2013: 825928, 2013.
75. Mashhadi NS, Ghiasvand R, Askari G, Feizi A, Hariri M, Darvishi L, Barani A, Taghiyar M, Shiranian A, Hajishafiee M. Influence of ginger and cinnamon intake on inflammation and muscle soreness endued by exercise in Iranian female athletes. Int. J. Prev. Med. 4: S11–15, 2013.
76. Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L, Mofid MR. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. Int. J. Prev. Med. 4: S36–42, 2013.
77. Maughan R. The athlete's diet: nutritional goals and dietary strategies. Proc. Nutr. Soc. 61: 87–96, 2002.
78. McBrier NM, Vairo GL, Bagshaw D, Lekan JM, Bordi PL, Kris-Etherton PM. Cocoa-based protein and carbohydrate drink decreases perceived soreness after exhaustive aerobic exercise: a pragmatic preliminary analysis. J. Strength Cond. Res. 24: 2203–2210, 2010.
79. McLellan TM, Lieberman HR. Do energy drinks contain active components other than caffeine? Nutr. Rev. 70: 730–744, 2012.
80. Mehendale SR, Bauer BA, Yuan C-S. Ephedra-containing dietary supplements in the US versus ephedra as a Chinese medicine. Am. J. Chin. Med. 32: 1–10, 2004.
81. Meiners I, Hauschildt S, Nieber K, Münch G. Pentoxyphylline and propentophylline are inhibitors of TNF-alpha release in monocytes activated by advanced glycation endproducts. J. Neural Transm. 111: 441–447, 2004.
82. Murakami S, Kurihara S, Koikawa N, Nakamura A, Aoki K, Yosigi H, Sawaki K, Ohtani M. Effects of oral supplementation with cystine and theanine on the immune function of athletes in endurance exercise: randomized, double-blind, placebo-controlled trial. Biosci. Biotechnol. Biochem. 73: 817–821, 2009.
83. Murakami S, Kurihara S, Titchenal CA, Ohtani M. Suppression of exercise-induced neutrophilia and lymphopenia in athletes by cystine/theanine intake: a randomized, double-blind, placebo-controlled trial. J. Int. Soc. Sports Nutr. 7: 23, 2010.
84. Nakagawa K, Okuda S, Miyazawa T. Dose-dependent incorporation of tea catechins, (-)-epigallocatechin-3-gallate and (-)-epigallocatechin, into human plasma. Biosci. Biotechnol. Biochem. 61: 1981–1985, 1997.
85. Narotzki B, Reznick AZ, Navot-Mintzer D, Dagan B, Levy Y. Green Tea and Vitamin E Enhance Exercise-Induced Benefits in Body Composition, Glucose Homeostasis, and Antioxidant Status in Elderly Men and Women. J. Am. Coll. Nutr. 32: 31–40, 2013.

86. Nieman DC, Gillitt ND, Knab AM, Shanely RA, Pappan KL, Jin F, Lila MA. Influence of a Polyphenol-Enriched Protein Powder on Exercise-Induced Inflammation and Oxidative Stress in Athletes: A Randomized Trial Using a Metabolomics Approach. PLoS ONE 8: e72215, 2013.
87. Nieman DC, Laupheimer MW, Ranchordas MK, Burke LM, Stear SJ, Castell LM. A-Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance--Part 33. Br. J. Sports Med. 46: 618–620, 2012.
88. Nieman DC. Quercetin's bioactive effects in human athletes. Curr. Top. Nutraceutical Res. 8: 33–44, 2010.
89. Norton RP, Lehnhard RA, Kearns CF, McKeever KH. Ephedra increases VO2, impairs thermoregulation and cardiovascular function, but does not enhance exercise performance. Comp. Exerc. Physiol. 9: 109–117, 2013.
90. Ohta K, Fukuchi Y, Grouse L, Mizutani R, Rabe KF, Rennard SI, Zhong N-S. A prospective clinical study of theophylline safety in 3810 elderly with asthma or COPD. Respir. Med. 98: 1016–1024, 2004.
91. Palu AK, Kim AH, West BJ, Deng S, Jensen J, White L. The effects of Morinda citrifolia L. (noni) on the immune system: its molecular mechanisms of action. J. Ethnopharmacol. 115: 502–506, 2008.
92. Patz MD, Day HEW, Burow A, Campeau S. Modulation of the hypothalamo-pituitary-adrenocortical axis by caffeine. Psychoneuroendocrinology 31: 493–500, 2006.
93. Pawlus AD, Kinghorn DA. Review of the ethnobotany, chemistry, biological activity and safety of the botanical dietary supplement Morinda citrifolia (noni). J. Pharm. Pharmacol. 59: 1587–1609, 2007.
94. Pereira R, Machado M, Sampaio-Jorge F, Barreto JG, Lazo Osorio RA. Intermittent exercise and caffeine supplementation: effects on the white blood cells. Rev. Int. Med. Cienc. Act. Física El Deporte 8: 353–361, 2008.
95. Perera MADN, Robinson JR, Shearn CT, Noble TM, Hallam JE, Kohut ML, Senchina DS. Effects of bloodroot (Sanguinaria canadensis L.) rhizome ethanol extracts on cytokine production by blood mononuclear cells during flowering and fruiting. J. Herb. Med. doi: 10.1016/j.hermed.2013.11.001.
96. Rados C. Ephedra ban: no shortage of reasons. FDA Consum. 38: 6–7, 2004.
97. Ranchordas MK, Burd NA, Godfrey RJ, Senchina DS, Stear SJ, Burke LM, Castell LM. A-Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance: Part 43. Br. J. Sports Med. 47: 399–400, 2013.
98. Rath M. Energy drinks: what is all the hype? The dangers of energy drink consumption. J. Am. Acad. Nurse Pract. 24: 70–76, 2012.
99. Raynor DK, Dickinson R, Knapp P, Long AF, Nicolson DJ. Buyer beware? Does the information provided with herbal products available over the counter enable safe use? BMC Med. 9: 94, 2011.
100. Ren Z, Na L, Xu Y, Rozati M, Wang J, Xu J, Sun C, Vidal K, Wu D, Meydani SN. Dietary supplementation with lacto-wolfberry enhances the immune response and reduces pathogenesis to influenza infection in mice. J. Nutr. 142: 1596–1602, 2012.
101. Roman MC. Determination of ephedra alkaloids in urine and plasma by HPLC-UV: collaborative study. J. AOAC Int. 87: 15–24, 2004.

102. Rosen T. Green tea catechins: biologic properties, proposed mechanisms of action, and clinical implications. J. Drugs Dermatol. 11: e55–60, 2012.
103. Rosenthal LA, Taub DD, Moors MA, Blank KJ. Methylxanthine-induced inhibition of the antigen- and superantigen-specific activation of T and B lymphocytes. Immunopharmacology 24: 203–217, 1992.
104. Senchina DS, Flinn GN, McCann DA, Kohut ML, Shearn CT. Bloodroot (Sanguinaria canadensis L., Papaveraceae) enhances proliferation and cytokine production by human peripheral blood mononuclear cells in an in vitro model. J. Herbs Spices Med. Plants 15: 45–65, 2009.
105. Senchina DS, Hallam JE, Cheney DJ. Multidisciplinary perspectives on mechanisms of activity of popular immune-enhancing herbal supplements used by athletes. Front. Biol. 8: 78–100, 2013.
106. Senchina DS, Hallam JE, Dias AS, Perera MA. Human blood mononuclear cell in vitro cytokine response before and after two different strenuous exercise bouts in the presence of bloodroot and Echinacea extracts. Blood Cells. Mol. Dis. 43: 298–303, 2009.
107. Senchina DS, Hallam JE, Thompson NM, Nguyen NA, Robinson JR, Perera MA. Alkaloids and endurance athletes. Track Cross Ctry. J. 2: 2–18, 2012.
108. Senchina DS, Shah NB, Doty DM, Sanderson CR, Hallam JE. Herbal supplements and athlete immune function--what's proven, disproven, and unproven? Exerc. Immunol. Rev. 15: 66–106, 2009.
109. Senchina DS. Athletics and herbal supplements. Am. Sci. 101: 134–141, 2013.
110. Shao X, Lv L, Parks T, Wu H, Ho C-T, Sang S. Quantitative analysis of ginger components in commercial products using liquid chromatography with electrochemical array detection. J. Agric. Food Chem. 58: 12608–12614, 2010.
111. Shimizu T, Kristjánsson S, Wennergren G, Hansson GC, Strandvik B. Inhibitory effects of theophylline, terbutaline, and hydrocortisone on leukotriene B4 and C4 generation by human leukocytes in vitro. Pediatr. Pulmonol. 18: 129–134, 1994.
112. Shively CA, Tarka SM Jr. Methylxanthine composition and consumption patterns of cocoa and chocolate products. Prog. Clin. Biol. Res. 158: 149–178, 1984.
113. Singh I, Quinn H, Mok M, Southgate RJ, Turner AH, Li D, Sinclair AJ, Hawley JA. The effect of exercise and training status on platelet activation: do cocoa polyphenols play a role? Platelets 17: 361–367, 2006.
114. Van Soeren MH, Graham TE. Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. J. Appl. Physiol. 85: 1493–1501, 1998.
115. Stear SJ, Castell L, Burke L, Spriet LL. BJSM reviews: A–Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance Part 6. Br. J. Sports Med. 44: 297 –298, 2010.
116. Sullivan GW, Carper HT, Mandell GL. Pentoxifylline modulates activation of human neutrophils by amphotericin B in vitro. Antimicrob. Agents Chemother. 36: 408–416, 1992.
117. Sullivan GW, Luong LS, Carper HT, Barnes RC, Mandell GL. Methylxanthines with adenosine alter TNF alpha-primed PMN activation. Immunopharmacology 31: 19–29, 1995.
118. Tauler P, Martínez S, Moreno C, Monjo M, Martínez P, Aguiló A. Effects of caffeine on the inflammatory response induced by a 15-km run competition. Med. Sci. Sports Exerc. 45: 1269–1276, 2013.

119. Terry R, Posadzki P, Watson LK, Ernst E. The use of ginger (Zingiber officinale) for the treatment of pain: a systematic review of clinical trials. Pain Med. 12: 1808–1818, 2011.
120. Usami A, Ueki S, Ito W, Kobayashi Y, Chiba T, Mahemuti G, Oyamada H, Kamada Y, Fujita M, Kato H, Saito N, Kayaba H, Chihara J. Theophylline and dexamethasone induce peroxisome proliferator-activated receptor-gamma expression in human eosinophils. Pharmacology 77: 33–37, 2006.
121. Vernec A, Stear SJ, Burke LM, Castell LM. A–Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance: Part 48. Br. J. Sports Med. 47: 998–1000, 2013.
122. Vimalanathan S, Arnason JT, Hudson J. Anti-inflammatory activities of Echinacea extracts do not correlate with traditional marker components. Pharm. Biol. 47: 430–435, 2009.
123. Vimercatti NS, Zovico PVC, Carvalho AS, Barreto JG, Machado M. Two doses of caffeine do not increase the risk of exercise-induced muscle damage or leukocytosis. Phys. Educ. Sport 52: 96–99, 2008.
124. Vlachojannis C, Magora F, Chrubasik S. Rise and fall of oral health products with Canadian bloodroot extract. Phytother. Res. 26: 1423–1426, 2012.
125. Walker GJ, Caudwell P, Dixon N, Bishop NC. The effect of caffeine ingestion on neutrophil oxidative burst responses following prolonged cycling. Int. J. Sport Nutr. Exerc. Metab. 16: 24–35, 2006.
126. Walker GJ, Dziubak A, Houghton L, Prendergast C, Lim L, Bishop NC. The effect of caffeine ingestion on human neutrophil oxidative burst responses following time-trial cycling. J. Sports Sci. 26: 611–619, 2008.
127. Walker GJ, Finlay O, Griffiths H, Sylvester J, Williams M, Bishop NC. Immunoendocrine response to cycling following ingestion of caffeine and carbohydrate. Med. Sci. Sports Exerc. 39: 1554–1560, 2007.
128. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P. Position statement. Part one: Immune function and exercise. Exerc. Immunol. Rev. 17: 6–63, 2011.
129. Watson R, Woodman R, Lockette W. Ephedra alkaloids inhibit platelet aggregation. Blood Coagul. Fibrinolysis 21: 266–271, 2010.
130. Wei F, Zhang M, Feng Y-Q. Combining poly (methacrylic acid-co-ethylene glycol dimethacrylate) monolith microextraction and on-line pre-concentration-capillary electrophoresis for analysis of ephedrine and pseudoephedrine in human plasma and urine. J. Chromatogr. B Analyt. Technol. Biomed. Life. Sci. 850: 38–44, 2007.
131. Wilasrusmee C, Siddiqui J, Bruch D, Wilasrusmee S, Kittur S, Kittur DS. In vitro immunomodulatory effects of herbal products. Am. Surg. 68: 860–864, 2002.
132. Wiswedel I, Hirsch D, Kropf S, Gruening M, Pfister E, Schewe T, Sies H. Flavanol-rich cocoa drink lowers plasma F(2)-isoprostane concentrations in humans. Free Radic. Biol. Med. 37: 411–421, 2004.
133. Wolfram S. Effects of green tea and EGCG on cardiovascular and metabolic health. J. Am. Coll. Nutr. 26: 373S–388S, 2007.
134. Wong CP, Nguyen LP, Noh SK, Bray TM, Bruno RS, Ho E. Induction of regulatory T cells by green tea polyphenol EGCG. Immunol. Lett. 139: 7–13, 2011.

135. Van der Woude H, Gliszczyńska-Swigło A, Struijs K, Smeets A, Alink GM, Rietjens IMCM. Biphasic modulation of cell proliferation by quercetin at concentrations physiologically relevant in humans. Cancer Lett. 200: 41–47, 2003.
136. Yao P-L, Tsai M-F, Lin Y-C, Wang C-H, Liao W-Y, Chen JJW, Yang P-C. Global expression profiling of theophylline response genes in macrophages: evidence of airway anti-inflammatory regulation. Respir. Res. 6: 89, 2005.
137. Yasui K, Kondo Y, Wada T, Yashiro M, Tsuge M, Morishima T. Theophylline inhibits the differentiation of human monocyte into dendritic cell potentially via adenosine receptor antagonism. Clin. Exp. Allergy 39: 1857–1865, 2009.
138. Yu Y, Zick S, Li X, Zou P, Wright B, Sun D. Examination of the pharmacokinetics of active ingredients of ginger in humans. AAPS J. 13: 417–426, 2011.
139. Zick SM, Djuric Z, Ruffin MT, Litzinger AJ, Normolle DP, Alrawi S, Feng MR, Brenner DE. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiol. Biomark. Prev. 17: 1930–1936, 2008.