Antidoping Concept of Play Clean to Win Clean: Implication of Herbal Supplements uses for Athletes in Competitive Sports

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors CNF, EATF, JDF and RN designed the study. Authors TW, NCK, JYN and RAЕ did data mining/case studies. All authors read and approved the final manuscript.

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ABSTRACT

The popularity of doping in competitive sports is relevant for all those involved in sports, particularly for evaluating anti-doping policy measures. However, there is a gap of information that addresses this subject so far. As a consequence, the prevalence of doping in competitive sports in resource limited countries is unknown. Even though it is challenging to uncover the exact prevalence of herbal products with prohibited activity such as doping, various methods put in place by world antidoping agency (WADA) have now been adopted to uncover parts of this particular problem, and enables the circumvention to some extend the issues of honesty, definition problems and the limits of pharmacological evidence. It is evident that current doping control test results can show a distinct underestimation of true doping prevalence in low middle income countries (LMIC). Nowadays, doping is a critical issue at international levels of sporting competitions. Athletes’ use of herbal supplements has seen a significant increase in the past two decades. At the top of the list of popular herbs used in sports are echinacea and ginseng, whereas garlic, St. John’s wort, soybean, ephedra and others are also gaining popularity or have been historically prevalent. Despite the increasing popularity of herbal supplements, recent events have illustrated possible concerns regarding efficacy and safety of herbal supplements usage. Remarkable sports performances at the end of the 20th century raised suspicions about herbal supplement use by athletes, prompting the formation of WADA. With WADA creation it was not long when the deaths of two professional athletes raised concerns that the herbal supplement ephedra, may have contributed to their deaths. These events and others have prompted clinicians and scientists to reexamine and evaluate the role of herbal supplements in competitive sports. This review attempts to give an insight into the use of herbal supplement in doping within the concept of play clean to win clean. An attempt has been made to provide guidance on the efficacy and side effect of most used herbal supplements found in sporting activities, especially in international competitive sports.

Keywords: Antidoping; herbal supplements; competitive sports; low middle income countries; WADA.

1. INTRODUCTION

Although the term doping carries a negative connotation, it does not always indicate that a substance is harmful as explained by the World Anti-Doping Agency (WADA), which publishes an annual document listing the substances banned in sports competitions worldwide. According to WADA regulation, a substance will be prohibited if it meets at least 2 of the following criteria: “1) It has the potential to enhance or enhances sport performance, 2) It represents an actual or potential health risk to the athlete, or 3) It violates the spirit of sport [1-3]. All the aspects of the antidoping rules as defined by WADA has been summarized in Fig. 1.

In sports, doping is conventionally referred to as the use of performance enhancing drugs, particularly those that are forbidden by the organizations that regulate competitions. From the biological perspective, doping can be regarded as a multifaceted issue and targets all bodily functions including cerebral, metabolic, cardiovascular, respiratory, haematological and, in the very near future, genetic variations and polymorphisms [3-5]. In general, athletes might take great athletic advantage from a variety of nutritional supplements and herbal drugs, which have been originally developed to supply nutrients that are missing or not consumed in sufficient quantity in a person’s diet or to treat pathologies, respectively [6]. However, some of these bioactive agents end up as effective means of enhancing performances, attracting unaware or naive athletes or regrettable coaches and physicians to become potential victim users [6,7]. By the World Anti-Doping Agency (WADA) definition, doping should be intended as any ‘anti-doping rule violation’, which include one or more of the following: (i) presence of a prohibited substance or its metabolites or markers in an athlete’s bodily specimen; (ii) use or attempted use of a prohibited substance or a prohibited method; (iii) refusing, or failing without compelling justification, to submit to sample collection after notification, as authorized in applicable anti-doping rules or otherwise evading sample collection; (iv) violation of applicable requirements regarding athlete availability for out-of-competition testing, including failure to provide whereabouts information and missed tests that are declared based on reasonable rules; (v) tampering, or attempting to tamper, with any part of doping control; (vi) possession of prohibited substances and methods; (vii)
trafficking in any prohibited substance or prohibited method and (viii) administration or attempted administration of a prohibited substance or prohibited method to any athlete, or assisting, encouraging, aiding, abetting, covering up or any other type of complicity involving an antidoping rule violation or any attempted violation [7,8]. WADA has set out 11 stages of the control of doping substances as developed and illustrated by authors in Fig. 2.

Fig. 1. Summary of the antidoping rules as defined by WADA (Design and conceived by author following WADA guidelines)

Fig. 2. Wada regulation criteria of banned substances (Designed conceived by author, as adopted from WADA guidelines)
Given the WADA definition of doping, the number of illicit substances or methods available to the athletes is limited to those included in the ‘Prohibited list’ [6,8]. According to reports by the American Botanical Council, herbal supplement sales recorded a net sale of $5.3 billion in the United States in 2019, a 4.5% increase from the preceding year [1]. Despite the increasing popularity of herbal supplements, recent events have raised possible concerns regarding the efficacy and safety. Remarkable sports performances at the end of the 20th century raised suspicions about herbal supplement use by athletes, prompting the formation of the World Anti-Doping Agency, or WADA [2]. Shortly thereafter, the deaths of two professional athletes raised concerns that the herbal supplement such as ephedra, may have contributed to their deaths. These events and others have prompted clinicians and scientists to develop more research and interest to reevaluate the role of herbal supplements in competitive sports [3].

The term herbal supplement is itself complex. Some use it to refer to products derived directly from plants, whereas others use it to mean any product containing molecules of botanical origin, such as caffeine pills [3]. Herbal supplements are variously called botanicals, phytomedicines, dietary supplements, nutritional supplements or nutraceuticals [2,3]. In this review paper, the term herbal supplement refers to plant-derived products containing multiple bioactive molecules, with some exceptions to products of fungal or bacterial origin (which are technically not “herbal” but are often treated the same) [4].

Although the food herbal supplement industry has kept pace with athletes’ interests have simultaneously spurred them, research has lagged behind and many of the following questions have been raised by the users of herbs for sports or leisure [5]. There are issues on why the athletes consume these herbs, if they use the product directed on the label or by a doctor. There are also issues on the claims made about these supplements, and also whether the products in use are supported by any clinical research. The communities are interested to know how scientists and sports medicine personnel can best design experiments to answer the many questions raised on the side effects of herbal supplements, and to understand the obstacles in the research for information on efficacy and safety [5,6,8]. The use of herbal medicinal products and supplements has increased during the last decades. At present, some herbs are used to enhance muscle strength and body mass. Some reported evidence indicates that the health benefits from plants are attributed to their bioactive metabolites such as polyphenols, terpenoids, and alkaloids which have several physiological effects on the human body [8-10]. In some cases, manufacturers market products with banned substances with inappropriate amounts or fake supplement inducing harmful side effect. Unfortunately, so far, there is no guarantee that herbal supplements are safe for use and there is not much supporting evidence of safety to clear the confusion surrounding the herbal use especially in competitive sports [11]. Some herbal supplements have been identified according to the following categories: Ginseng, alkaloids, and other purported herbal ergogenics such as Tribulus terrestris, Cordyceps sinensis [6,12,13].

Reports also indicates that most herbal supplement effects are likely due to activation of the central nervous system via stimulation of catecholamines [14]. Ginseng was discovered to be useful as an endurance performance enhancer, while alkaloids supplementation resulted in improvements in sprint and cycling intense exercises [3,15]. Despite the prohibition of ephedral, small amount of ephedrine was usually used in combination with caffeine to enhance muscle strength in trained individuals. Some other alkaloids such as green tea extracts have been used to improve body mass and composition in athletes [16]. Other herb such as artic root (Rhodiola rosea), milk vetch (Astragalus spp) are used in relieving muscle and joint pain, but results about their effects on exercise performance are not evident [2,17].

1.1 Herbal Supplement within a Multidisciplinary Framework

Herbal supplement sales, the number of available herbs and the number of preparation types have all increased significantly in the past two decades, most especially in competitive sports among American athletes as indicated in Fig. 3. Despite this new booming industry, clinical research on herbal supplements efficacy and safety on humans still remains a big scientific challenge, and athletes are often left to trust manufacturers’ claims or teammates’ advice, when it comes to making informed choices about what herbal supplements to take and whether even to take them at all [5,18].
Early studies on herbal supplement were almost exclusively of the clinical variety. They strive to address questions of efficacy by testing supplements available for over-the-counter purchase. Studies often included detailed information on subjects’ characteristics, dosing regimens, methods for assessing efficacy and, in athletic studies, aerobic endurance exercise or anaerobic strength training regimens [7,8,19]. However, such studies most of the time did not have information on the chemical composition, botanical origin or good agricultural practices of the supplements [20]. In addition, medical pilot studies were often characterized by small sample sizes, and a paltry number of studies typically exist for a given herb [3,9]. The complexity and rudimentary nature of the study design makes results hard to replicate or interpret and makes it difficult to identify confounding variables among studies [21]. Even where the studies for herbal supplement were reviewed, one is inclined to conclude that the data were equivocal, for every study that supported efficacy, although others have refuted it [9]. The predictable outcome has been in the past years of confusion and miscommunication within the sports science community.

The combination of botany, chemistry and medical disciplines, from cell biology to physiology is absolutely critical to the advancement of research on herbal supplements in athletic contexts [10,22]. In addition to many research work on this subject, research collaborators have developed novel experimental data on previously neglected preclinical factors. The species of plant chosen, the location from which the plant was gathered, the specific organ extracted or the extraction method may in large part explain the heterogeneous clinical outcomes [6,11]. Dunne illustrated that herbal supplement needs to incorporate a process cycle that includes the planning factors, field factors, production and harvest factors, post production and storage factor and finally the consumer factors as illustrated in Fig. 4.

One of the biggest challenges such a multidisciplinary approach presents is the conception of study design for the preclinical and clinical factors that can potentially influence a trial. In a 2009 article in Exercise Immunology Review, this conceptual model was proposed for multidisciplinary approach [11, 20]. The model later revised incorporated commercial factors to better reflect the societal context of herbal supplement research [21]. The model discourages the mistaken conclusion that equivocal is synonymous with ineffectual, moving the field from simplistic questions of “Does a
given supplement ‘work’?” to “Under what conditions does a given supplement produce a given outcome?” [12].

1.2 Important Herbal Supplements in Competitive Sports

The extent to which athletes’ use herbal supplement is still unclear, due to the problem that few studies have address this topic. Surveys of athletes’ herbal supplement use exist, but herbal supplements are often relegated to a category called “other drugs.” [25]. Even when supplements are identified as a separate category, the specific supplements used are not very often reported. In the United States alone, 17 to 61% of athletes reported using herbal supplements, although the categorization of herbal supplement varied across surveys, and this likely explains the huge discrepancy in reporting [26]. Although these numbers should be interpreted with caution, it is easier to assume and make conclusion that athletes’ use of herbal supplements is higher than in the general public.

Generally, performance-enhancing herbs include those that benefit both endurance and strength of athletes, such as ginseng (Panax species or Eleutherococcus senticosus), ephedra (Ephedra sinica) and arctic root (Rhodiola rosea) [3,17]. They also include herbs such as caltrop (Tribulus terrestris) that may primarily benefit strength athletes. Ephedra (Ephedra sinica) and ginseng are also considered central nervous system stimulants along with guarana (Paullinia cupana). Herbs taken primarily to boost immune function include echinacea (Echinacea species), elderberry (Sambucus nigra) and milk vetch (Astragalus species). Other herbs, such as caltrop (Tribulus terrestris), soy (Glycine max) and sarsaparilla (Smilax species), are believed to contain plant-produced compounds capable of modulating anabolic steroidal pathways [25]. And some supplements are promoted as having more specialized functions, such as the supposed metabolism-enhancing fungus, Cordyceps sinensis. Still others are treated as multipurpose food ingredients, for example, the cyanobacterium Spirulina (Spirulina species) [17]. Other popular supplements are Garlics, John’s wort, ginger (Zingiber officinale) cranberry and gingko (Gingko biloba), highly used but known to cause adverse drug interactions [5,7,27]. An illustrated photograph of some herbal plant supplement for sports are shown in Fig. 5.

Fig. 4. Illustration of the herbal supplement process cycle: from planning, field factors, production and harvest factors, post production and storage factor and finally the consumer factors [10,23,24]
Ginseng (*Panax ginseng*)

Ephedra (*Ephedra sinica*)

Echinacea (*Echinacea spp*)

Guarana (*Paulina cupana*)

Elderberry (*Sambucus nigra*)

Milk vetch (*Astragalus spp*)

Caltrop

St John’s wort

Sarsaparilla (*Smilax spp*)

Soy plant (*Glycine max*)

**Fig. 5. Illustrated photos of important herbal plant supplements use in competitive sports (Fokunang photographs)**
The organisms mentioned above demonstrate that these supplements are taxonomically diverse and include flowering, seedless vascular and nonvascular plants, fungi and algae with distinct evolutionary histories [5,17,28]. The bioactive molecules attributed to each taxon are equally diverse, although most are classified as secondary metabolites, phytochemicals or chemical compounds produced by living organisms but not required for their primary functions [29]. Many herbs used in sports supplements or energy drinks contain alkaloids which are small nitrogen-based compounds that contains many biologically active naturally derived molecules, from morphine to cocaine that act as stimulants [18,30]. Examples of such alkaloids include caffeine from the kola plant (Cola species), ephedrine and pseudoephedrine from ephedra, guaran in from guarana, and theobromine and theophylline from the cocoa plant (Theobroma cacao) [4,11,28].

2. ADVERSE HERBAL-DRUG INTERACTION OF SUPPLEMENTS

Current research on many botanical dietary supplements used by athletes all suffer from the multiple drug interaction problems. Two of the most well-known of these supplements, echinacea and ginseng, will serve as representative examples to elaborate on adverse drug interaction of herbal supplements.

2.1 Echinacea

Echinacea is purported to boost defense against upper respiratory infections, so athletes use it primarily to offset the deleterious effects of intense training on immunity [29,26]. Although the general public uses the genus name as the common name, genus Echinacea is comprised of nine species (some divided into subspecies). The three species most used commercially are Echinacea angustifolia, E. pallida and E. purpurea [27-30]. Bioactive molecules produced by these species include alkamides, organic molecules made of fatty acids often found in plants, and phenols, another class of organic molecules also dubbed carboxylic acids that are known for their acidity [31]. Phenols encompass caffeic acid derivatives, echinaciosoide and ketones; distributions and quantities of these molecules vary by species. It is important to differentiate these molecules because the body processes them differently and they have different effects [19,32]. Alkamides move from gut to bloodstream apparently unmodified within an hour. Complex carbohydrates have largely been discounted by multiple studies due to their inability to move from gut to bloodstream without modification. Roots contain the highest levels of these compounds, but most often manufacturers will instead harvest above ground parts, such as leaves and stems, to allow the plants to regrow and thus provide multiple harvests per planting. In North America, echinacea is most widely consumed as capsules or tablets [9,33].

Only five studies have been published concerning in vivo dosing of athletes with echinacea supplements. Studies by some researchers have reported incidence or duration of upper respiratory infection events after intense exercise (such as competitive sprint triathlons or laboratory sprint cycling) in athletes dosed with E. purpurea supplements for four weeks either before or after a scheduled bout of exercise [33-35]. The reduced incidence of infections was corroborated by molecular immunological data from blood, saliva and urine samples, demonstrating increases in circulating concentrations of certain antibodies and changes in circulating concentrations of several signaling molecules important in regulating inflammation [35]. White blood cells were the cells associated with the immune system, but no changes in white blood cell subsets or counts were identified [35]. Taken together, the findings suggest that echinacea may reduce incidence and severity of upper respiratory infections by changing the quantities of immune molecules produced by white blood cells, rather than changing other aspects of white blood cells, such as their rate of multiplication or specific functions. In further support of the link between echinacea, exercise and upper respiratory infections, it has been reported a reduced incidence and duration of self-reported upper-respiratory-infection symptoms in athletes dosed in a similar manner to those in the previous two studies, when compared to a control group generalized from control data in previous studies [36].

Looking at physiological parameters important in athletic performance, on a recreational group of athletes, dosed with E. purpurea for four weeks and compared to placebo-treated controls. They found that common measures of aerobic performance—maximal oxygen consumption (VO2max), running economy (oxygen use efficiency) and erythropoietin (a hormone that controls red blood cell genesis)—were higher among the echinacea-treated group than among controls [36]. However, the authors reported no
differences in total red blood cell count, hemoglobin (the molecule within red blood cells that carries oxygen) or hematocrit (packed red blood cell volume) between the two groups. The fact that there were no changes in red blood cell–associated parameters but there were changes in performance parameters it is difficult to interpret but may suggest that echinacea supplementation influences performance by modulating oxygen dynamics or metabolism at body sites distinct from the red blood cells themselves [6,37]. Other scientific teams reported relatively good tolerability and low side effects from echinacea supplements, although interactions with certain prescription medications have been documented [38].

Collectively, data from studies of echinacea in athletes suggest that different species of echinacea have different effects on the human body, and that exercise changes these effects and that effects are cell- and body site–specific [38]. The work on echinacea also suggests that preclinical factors have not been adequately accounted for across studies; further, preclinical factors are expected to vary greatly between manufacturers and even between batches from the same manufacturer. Given that awareness, and the understanding that so few studies have been conducted and often with small sample sizes, one cannot conclusively argue for or against the use of echinacea by athletes [14,39].

2.2 Ginseng

Like echinacea, ginseng is taken to augment immunity, but its primary indication is to improve performance. The name ginseng refers to any of a dozen species within the genus Panax, three of which are used most often commercially (P. ginseng is most frequently used, but also P. pseudoginseng and P. quinquefolius). Ginsenosides, from the plant steroids saponin subgroup (plant-derived chemicals that in solution produce soap-like foaming when shaken) [12,40], are the classically recognized bioactive molecules in ginseng. Roots are used most often, typically in dried or powdered form. So-called Siberian ginseng, Eleutherococcus senticosus, is sometimes confused with ginseng and is also frequently used by athletes, although it has different bioactive molecules and may be less effective in the context of performance enhancement.

Unlike echinacea, studies of ginseng or Siberian ginseng in athletic contexts have yielded conflicting results owing to differences in experimental design or outcomes measured [41]. Systematic reviews of human kinetics have concluded that human studies have not convincingly demonstrated any ergogenic benefits of ginseng supplementation in athletes, although supplementation may transiently alter cardiological or pulmonary function [3,41].

Side effects and prescription drug interactions appear to be more severe and extensive than those associated with echinacea and may include insomnia, gastrointestinal upset and heart palpitations [17,32,42]. Thus, although ginseng is a much more popular herbal supplement than echinacea among athletes in the United States and globally, experimental data supporting its use in contexts of athletics are currently weak [43]. Contrasting echinacea studies with ginseng studies reveals that immunological findings from the echinacea studies were more consistent, whereas those from the ginseng studies were more variable [35].

There are fewer studies of echinacea’s effects on athletes than ginseng’s effects on athletes, so variation in the effects of ginseng may be better documented than the variation in echinacea’s effects. Echinacea studies mostly focus on aerobic performance, whereas ginseng studies mostly focus on anaerobic, strength athletes’ performance [44]. Although the names echinacea and ginseng encompass multiple species each, studies of them in the context of athletic performance focus on one species each (E. purpurea and P. ginseng, respectively). Why a clearer pattern from the literature on echinacea’s effects on athletes is not known, but the difference in variability may be because the echinacea studies used herbal preparations that were more consistent in species, plant part used and other preclinical factors [8,45]. Both the echinacea and the ginseng studies drew their participants from diverse populations in terms of age, gender and physical activity levels. Future studies of ginseng and Siberian ginseng preparations may elicit stronger and more consistent findings if both preclinical and clinical factors are well designed and better controlled. From the above indications of adverse herbal-drug interactions of herbal supplements reported in some athletes, many more examples have been illustrated as shown in table 1, for other herbal supplements.
<table>
<thead>
<tr>
<th>Drug name</th>
<th>Common use</th>
<th>Herbal Nomenclature</th>
<th>Common Medicinal Uses</th>
<th>Adverse known drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brochodilator Theophylline</td>
<td>Bronchodilator</td>
<td>St John’s wort</td>
<td>Alleviate depression &amp; anxiety</td>
<td>Decreased theophylline concentration</td>
</tr>
<tr>
<td>Trazodone, sertraline, and nefazodone</td>
<td>Antidepressant; obsessive/compulsive disorders</td>
<td>St John’s wort</td>
<td>Alleviate depression &amp; anxiety</td>
<td>Mild serotonin syndrome, decreased bioavailability of digoxin, theophylline, cyclosporin, phenprocoumon</td>
</tr>
<tr>
<td>Serotonin-reuptake inhibitors</td>
<td>Antidepressant</td>
<td>St John’s wort</td>
<td>Alleviate depression &amp; anxiety</td>
<td>Mild serotonin syndrome, decreased bioavailability of digoxin, theophylline, cyclosporin, phenprocoumon</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Monoamine oxidase inhibitor, antidepressant</td>
<td>Ginseng</td>
<td>Stimulant</td>
<td>Headache, tremor, mania</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Antidepressant</td>
<td>St John’s wort</td>
<td>Alleviate depression and anxiety</td>
<td>Lethargy, incoherence</td>
</tr>
<tr>
<td>Anti-inflammatories, Aspirin</td>
<td>Anti-inflammatory</td>
<td>Gingko biloba</td>
<td>Increase circulation, increase short term memory</td>
<td>Spontaneous hyphemia</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Anti-inflammatory</td>
<td>Licorice</td>
<td>Expectorant, antiulcer</td>
<td>Glycyrrhetinic acid (an acid in topical anti-inflammatories) potentiates cutaneous vasoconstrictor response</td>
</tr>
<tr>
<td>Oral and topical corticosteroids</td>
<td>Anti-inflammatory</td>
<td>Licorice</td>
<td>Expectorant, antiulcer</td>
<td>Potentiates corticosteroids</td>
</tr>
<tr>
<td>Oral contraceptives Combined</td>
<td>Birth control</td>
<td>St John’s wort</td>
<td>Alleviate depression and anxiety</td>
<td>Breakthrough bleeding</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Birth control</td>
<td>Licorice</td>
<td>Expectorant, antiulcer</td>
<td>Hypertension, edema, hypokalemia</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Antidepressant</td>
<td>Panax ginseng</td>
<td>Stimulant</td>
<td>Induces mania in depressed patients</td>
</tr>
<tr>
<td>Lithium</td>
<td>Manic depression</td>
<td>Psyllium</td>
<td>Reduced cholesterol</td>
<td>Decreases lithium concentrations</td>
</tr>
</tbody>
</table>
2.3 Motivation of the use of Herbal Supplements by Athletes

Exercise is a physical stress. If the athlete’s body can manage the stress, it adapts by increasing muscle mass, optimizing metabolism or improving motor performance [13]. If the athlete’s body cannot manage the stress, then muscle soreness, malnutrition or declines in performance may manifest indicating that exercise can serve as either a positive or negative stressor [5,14].

Herbal supplements appeal to the sports community because of their potential for improving performance capacity either through conferring ergogenic benefits or through offsetting the deleterious effects of rigorous training regimens [13]. Most herbal supplements, such as ginseng and echinacea, are available over the counter, making them both legal and readily available; others, such as ephedra are now illegal. Whether a given supplement is illegal varies by country and sports regulatory agency; within the context of sports, illegality is often declared if a supplement engenders an unfair ergogenic benefit (“doping”) or constitutes a health threat. Ephedra, for example, is banned because it has no confirmed ergogenic benefits yet contains toxic alkaloids [14,45].

Curiously but not surprisingly, athletes’ rationales for choosing and using any given supplement are often discordant with contemporary indications, as evidenced by some researchers. Studies have shown that professional athletes may use supplements for reasons other than their purported purpose; ignore advice from medical professionals despite the fact that athletes consult those professionals for advice more frequently than coaches or trainers; misunderstand side effects or assume a supplement is safe because it is “natural”; and sacrifice health benefits for perceived performance benefits [2,8,15,46]. The circumstances just highlighted may be different for nonprofessional, noncollegiate athletes. It is assumed by many people that the Food and Drug Administration regulates herbal supplements, but in the United States the Dietary Supplement Health and Education Act of 1994 allows most herbal supplements to be sold without FDA approval [16,47]. Herbal supplements are placed in pharmacy stores on shelves alongside regulated items such as vitamins, which may perpetuate this perception.

3. CHALLENGES IN HERBAL SUPPLEMENTS

Promising strides have been made in the understanding of herbal supplements within the context of sports and physical exercises. However, several challenges and perhaps insoluble problems still remain. This problem cannot be resolved or expected to be resolved by a small investigative team or limited studies to address each individual factor, in which some factors may not be possible to accurately measure or may be beyond manufacturers’ control [3,48]. Preparations containing several herbs and other ingredients, such as those used in traditional Chinese medicine Materia medica, may compound the difficulty of identifying preclinical factors [11,48]. Analytical chemists have shown repeatedly that the contents of retail herbal supplements are often inconsistent with their own product labels in terms of ingredients or quantities, even when manufacturers make claims of standardization [49,50]. Given these realities, even the most diligent clinical or bench scientists cannot accurately report their findings and may unwittingly report false data.

There is urgent need for future research and funding-oriented research by stakeholders in herbal supplements for sports use. Hundreds of herbal supplements are currently used by athletes and nonathletes alike, and most of those substances have not been clinically tested [51-53]. Those herbs need more research and development to validate their safety for use. For instance, elderberry is an herbal supplement with increasing popularity in sports contexts, and it appears to have immune-modulating attributes similar to those of echinacea and may provide similar benefits [17,54]. The elderberry contains lectins and anthocyanins biological active compounds associated with antioxidant activities, but these compounds may also interfere with influenza binding to human cells [29,55]. Research have indicated that elderberry extracts may lower exercise-induced lactate levels [56].

Many herbal supplements have the potential to improve both human health and athletic performance, but as the examples show, the potential benefits are greatly influenced by preclinical studies, necessitating an interdisciplinary approach and clinical investigation studies of herbal supplements [56]. Scientists and sports medicine professionals are taking steps towards clinical research, with the hope of improving the scientific understanding of
the mechanism of actions of the active metabolites biological, pharmacological and safety of herbal supplements [41,57,58]. This approach will provide information on how supplements work, or don’t work, to aid human performance.

3.1 Herbal Supplement in Performance Enhancement

Athletes looking to improve athletic performance, enhance immunity, or manage a health concern may be interested in trying herbs in their nutrition program. Herbs have a long history of use and it is conceivable that some herbs may be of benefit for athletes and also for non-active people alike [9, 35]. However, quality research on herbs—both for health effects and performance-enhancement on the athletic field—is very limited; there is insufficient scientific support for the use of any herb to improve performance [58-60]. In addition, many minor studies on a variety of herbs have noted potential benefits, including immune enhancement, decreases in inflammation, and the potential ability to recover faster from common colds and other ailments [3,17,61].

3.2 Regulation of Herbal Supplement

In the United States, herbs are regulated by the U.S. Food and Drug Administration (FDA) as dietary supplements as part of the 1994 Dietary Supplement Health and Education Act (DSHEA) [19]. Herbs are not required to be standardized, and there are different interpretations of what standards should be followed so there is little consistency among different batches of products from different manufacturers [5,62]. In other words, it is often impossible to know what is contained in a given package containing herbs. Athletes should be concerned on ingesting herbs with unproven ingredients that have unproven effects on health and performance and may cause harmful side effects. Unfortunately, athletes believe in what they read on the label or just accepting word of mouth confirmation of effectiveness from peers before start of use [63]. Side effects in most cases are not contained in the label as there general believe is that plants are safe due to long generation of usage [15,29,64].

3.3 Specific Herbs, Potential Benefits, and Examples of Safety Concerns

Some information has been made available of many herbs’ athletes may be interested in using with the goal of enhancing sports performance, managing a health concern, or maintaining optimal immune status and overall health. As herbs may contain potent natural chemicals, there is the potential for interaction with other herbs, foods, and medications. If athletes incorporate herbs into their overall nutrition and performance plan, working with a health care team to monitor potential side effects and interactions between herbs and other herbs or herbs and medications is strongly recommended [1,15,65]. A key element for use of herbal supplements is to ensure that an herb is safe, confirming that it contains the recommended amounts of active ingredients, and determining the appropriate dosage for use [66].

Nowadays doping is critical issue at International level in sport Physiology. This is not only concerned with health matter but also with the moral as well as ethical values of humanity affecting honest team spirit in competitive sports [67], and this has directly affected sports, competitions around the world. Initially, the term ‘doping’ was restricted only with blood doping, but today the area of doping has increased in such a way that the available tests become helpless for doping detection [29,68]. However, avoidance of doping is a necessity, and therefore the duty of experts to update their knowledge in the field of research and development of doping substances, and sensitize users of misused consequences [3,11,69]. Any form of practices leading to use of specific drugs with an objective to improve performance or stamina in sport can be referred to as Doping. This is considered as unethical by respective organizations where such incidences are repetitively occurring, either at National as well as International level. International Olympic committee declares this issue as unlawful and unethical. These committees often charge regular serious actions against such events [3,8]. This organization is constantly sensitizing and enforcing regulations in place to roll back doping in sports. Doping is widely used by sports persons in an attempt to improve their performance without any fear or unawareness related to their consequences or side effects. These practices not only hamper the quality of sports but it may be considered as corruption in sports, thus affecting sport spirit [2,27]. Blood doping is the misuse of specific substances to increase one’s red blood cell mass, which allows the body to transport more oxygen to muscles and therefore increase performance and stamina of athletes [70]. This can be achieved either by direct use of either
erythropoietin (EPO), synthetic oxygen carriers or direct blood transfusions. The first documented organized doping controls were carried out in the 1970s [12,19]. In 1993, the Czech Antidoping Charter was signed and the Antidoping Committee was established. The medical commission of International Olympic Committee decides and declares regularly, which substances and methods should be prohibited [3].

4. CASE STUDY OF HERBAL FOOD SUPPLEMENTS

4.1 Natural Herbal Products Higenamine

Despite being marketed as “natural”, Higenamine is one of the leading causes of positive doping tests in Australia [13]. Higenamine and other banned substances have been found in a number of supplements and not all of those products have those banned substances listed on the ingredients label. If detected in an athlete’s sample, the athlete can face an up to four-year ban from sport. Higenamine is found in many popular supplements and can also be called: Norcoclaurine, Demethylcoclaurine, Aconite, Annona squamosal, Nandina domestica, Tinospora crispa [6]. Higenamine is also present in various plants and exists in Plumula nelumbinis, a part of lotus seeds, which is commonly used as an ingredient in cuisines, herbal medicines and nutritional supplements in China and other countries in East Asia [41,71]. Higenamine, a S3 class Beta-2 Agonist, allows lungs to take in more oxygen and is prohibited in- and out-of-competition. However, as a cardiotonic, higenamine can increase heart rate, putting an athlete at an increased risk of heart problems such as palpitations and irregular heartbeat [72,73].

The Australia sports antidoping agency (ASADA) warns the consumer has no way of determining how much higenamine is in a supplement even if it is on the label as the levels vary widely. ASADA further warns that manufacturers’ ingredients vary from product to product, and flavour to flavour. ASADA does not approve or endorse any supplements as they pose too much of a risk to an athlete’s health and career [27]. Some herbal supplements have been tested to contain higenamine as shown in table 2.

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Substance Flavour</th>
<th>Herbal supplement</th>
</tr>
</thead>
<tbody>
<tr>
<td>The one</td>
<td>Green Apple</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Blaze</td>
<td>Pineapple Splash</td>
<td>Higenamine</td>
</tr>
<tr>
<td>End of Days</td>
<td>Lemon Lime</td>
<td>Higenamine</td>
</tr>
<tr>
<td>The Guerrilla Chemist</td>
<td>Guerrilla Juice</td>
<td>Higenamine</td>
</tr>
<tr>
<td>BZRK</td>
<td>Peach</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Loco</td>
<td>Vanilla</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Spazmatic</td>
<td>Watermelon Taffy</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Cobra 6 Extreme</td>
<td>Kiwi Strawberry</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Viper X</td>
<td>Kiwi Strawberry</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Crack3D-U4X</td>
<td>Berry Lemonade</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Albutarex v2</td>
<td>Berry Colada</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Awaken</td>
<td></td>
<td>Higenamine</td>
</tr>
<tr>
<td>Thermoshred</td>
<td>Pineapple Mango</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Ripped Thermogenic</td>
<td>Mixed Berry</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Staunch</td>
<td>Peach Mango</td>
<td>Higenamine</td>
</tr>
<tr>
<td>Dust</td>
<td>Cotton Candy</td>
<td>Nelumbo Nelumina</td>
</tr>
</tbody>
</table>
4.3 Here are four Reasons why anyone should be Skeptical if they see “All Natural” on a Label

4.3.1 “All-natural” is not always natural

Unfortunately, some companies intentionally mislead consumers about the ingredients in their supplements. For instance, some manufacturers may advertise an “all-natural” weight loss pill, but then spike it with sibutramine, which is an investigational drug that was removed from the market for safety reasons [30,77]. Other companies may advertise herbal sex-enhancement pills, but when tested, these pills frequently contain powerful and synthetic Viagra-like drugs. For more examples of these kinds of contaminated supplements, you can visit the FDA Tainted Supplements page and USADA’s Supplement High Risk List [21].

4.3.2 Natural is not always safe

There are plenty of things that are natural that are not safe, such as hemlock, arsenic, and various other poisons produced by plants and animals. Because anyone can produce supplements without prior experience or training, it is not prudent to assume that manufacturers understand ingredients or how to use them safely [2,15]. In the supplement industry, another issue is that some manufacturers try to make ingredients appear natural by using misleading names. For example, there are numerous supplements available to consumers that list “geranium oil” on the label, but the products actually contain methylhexanamine, a synthetically produced stimulant that is prohibited in-competition [78].

4.3.3 Natural doesn’t mean there are no prohibited ingredients

“Natural” herbal products may also pose an anti-doping risk to athletes because, although it is rare, some plants naturally produce substances prohibited in sport. For example, Cannabis sativa naturally produces prohibited THC; the ephedra plant produces prohibited ephedrine and pseudoephedrine; Citrus aurantium (orange peel or bitter orange) produces prohibited octopamine; and Tinospora crispain produces prohibited higenamine [39,56,79]. In addition, herbal supplements sometimes naturally contain compounds that could interact with each other or with medications. In case of consideration of using a herbal product, a specialist should be consulted to understand what compounds are produced by the plant and the potential interactions [3,19].

4.3.4 Safe is not always natural

There are many safe and healthy supplement ingredients that are not naturally derived or harvested. For example, the FDA allows some nutrients to be synthesized in a factory and sold in supplements, such as vitamin C. This means that too much stake should not be put in the fact that something is “natural,” or think that it is inherently better just because it’s natural [80].

4.3.5 Understanding the Risks of herbal supplements

While athletes and consumers need to be particularly aware of these four things when considering “all-natural” products, it’s also important to remember that the use of any dietary supplement is at your own risk. It is therefore important for sports men, those who use herbal supplements for relaxation and trainers to understand these products, potential adverse drug-herbal interaction and the regulation and potential legal consequences of abuse. As US swimmer Michael Phelps fiercely splashed his way to a record [19,81]. Olympic medals at the London 2012 summer Games, most spectators sat on their couches and watched in awe at his near-superhuman abilities. Few people doubt the physical differences among athletes and non-athletes. While many people struggle to run a mile in 10 minutes, world record-holders Hicham El Guerraj of Morocco ran the fastest mile in 3 minutes and 43 seconds. Most sports viewers would jump ship at the mere thought of doing a cartwheel, while US Olympic gold medalist Gabrielle Douglas spun, leaped, and kicked her way to becoming a modern legend known as the “Flying Squirrel” [5,82].

One experience that does unite most modern humans is the desire to be a better version of oneself. Athletes yearn to run faster, jump higher, train longer. Non-athletes long to be thinner, healthier, or more energized. Millions of Americans turn to herbal and dietary supplements with these objectives every year [83,22]. Athletes also consider herbal products as a natural way to improve their wellbeing and performance should be easily understood and athletes, coaches, and health professionals who work closely with athletes are consistently looking for sound, effective ways to enhance
health and performance with foods, fluids, and dietary supplements [23]. Still, dietary and herbal supplements almost always have a negative reputation when discussed in the context of sports. During the recent 2012 Summer Olympic Games, mainstream media outlets and several sporting and anti-doping organizations vilified supplements, calling them ineffective and risky, and warned athletes of unsafe use [6,84,85].

5. GOVERNMENT REGULATION AND INDUSTRY RESPONSE TO HERBAL SUPPLEMENTS

The dietary supplements industry often stresses the fact that if a product labeled as a dietary supplement does contain prohibited or designer pharmaceutical ingredients, it is no longer a dietary supplement and is instead a drug being sold illegally as a supplement. It also often claims that companies participating in such activities, referred to as economically motivated adulteration, represent a small, rogue portion of the industry and that most manufacturers and retailers are reputable businesses [19,27]. FDA has no official data on the number of companies marketing tainted products as sports supplements although sports supplements represent one of the top 3 areas of concern for FDA, along with supplements marketed for weight loss and sexual enhancement [53,69]. A compound in a supplement, generally is not there by accident, and drug substances are not at levels that would indicate a cross-contamination problem. They are at large levels intended to have a profound biological effect [27,86].

Sometimes dietary supplement trade publications reinforce the image of an industry whose problems have been unfairly exaggerated. Nutral ingredients USA, for example, reported after the London Olympics that the synthetic substance DMAA, a banned stimulant also called methylhexaneamine, or MHA, was implicated in only one Olympics doping ban [16,87]. Some companies said DMAA can be found in extremely small quantities in the oil of the geranium plant (Pelargonium graveolens, Geraniaceae), and therefore, according to the companies, it is actually a natural product, although at least 3 peer-reviewed analytical studies have determined that it is synthetic [15]. This lone DMAA doping case represented 12.5% of the 8 total 2012 Summer Olympics doping cases. According to the Anti-Doping Database, 172 professional athletes have tested positive for DMAA since 2009 [17], a number that includes failed drug tests in all sports, not just the 2012 Olympics, and thus provides a more comprehensive assessment. The most suspensions occurred in 2011 when 95 athletes tested positive for DMAA [17,88].

Although many mainstream media stories (and some sports governing bodies) claim that dietary supplements are not regulated and thus athletes have no protection against adulterated sports supplements, in fact, FDA can provide some degree of enforcement through market surveillance, inspections of facilities’ Good Manufacturing Practices (GMPs), and more. FDA is committed with sports International federation to use whatever tools at their disposal to take action on manufacturers who are really marketing drugs as dietary supplements [24,89,90]. Some sanctions have been documented for example in August of 2012, the largest online retailer of bodybuilding supplements, Bodybuilding.com, was ordered to pay $8.1 million for selling steroid products labeled as dietary supplements, which FDA uncovered at a GMP inspection in 2008 [18]. The inspections revealed some of the challenges the firm had, but still, FDA has experienced a high rate of non-compliance with good manufacturing practice (GMP) inspections, as inspections do not prevent tainted products from entering the marketplace, nor do they offer total protection against the few banned substances that are legal for normal consumers not involved in professional sports [76,91,92].

6. CONCLUSION

The increasing interest of doping in competitive sports is relevant for all those involved in sports, particularly for evaluating anti-doping policy measures. Doping from natural herbal products is not only a safety issue when there is little information on the bioactive molecules, but a public health concern to the users. There is a significant gap of information that addresses this subject so far. As a consequence, the prevalence of doping in competitive sports in resource limited countries is unknown. Even though it is challenging to understand the prevalence and health incidence herbal products with prohibited activity such as doping, various methods put in place by world antidoping agency (WADA) have now been adopted to uncover parts of the problem of use in sports, and enables actors to some extent to use pharmacological evidence to manage the problem of use and prevention in sports. It is evident that current doping control
test results can show a distinct underestimation of true doping prevalence in low middle income countries (LMIC).

The relationship between professional athletes and dietary and herbal supplements is nothing less than complex. Despite the negative representation and reputation of dietary supplements in and among mainstream media outlets as well as major sporting and anti-doping organizations, little evidence proves that herbal dietary supplements pose a risk in this context. Some evidence even suggests that various botanicals can have safe, beneficial effects on athletic performance. Still, evidence fails to exonerate all cases of potentially intentional adulteration by dietary supplement manufacturers. In order to progress toward resolving these issues, responsible parts of the dietary supplements industry, analysis labs, sports and anti-doping organizations, and the media must collaborate to support athletes through education, vigilance, and openness toward the reality of the situation.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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