Review Article Open Access

Functional Food Science

Nutritional supplements for athletes and personalization; a short review

Heidrun Karlic [1], Ulrike Krammer [2], Alexander Haslberger[2*]

[1]Medical University of Vienna, Vienna, Austria; [2]Department for Nutritional Sciences, University of Vienna, Vienna, Austria

[*]**Corresponding author**: Alexander Haslberger, University of Vienna, Althanstrasse 14, Vienna, Austria

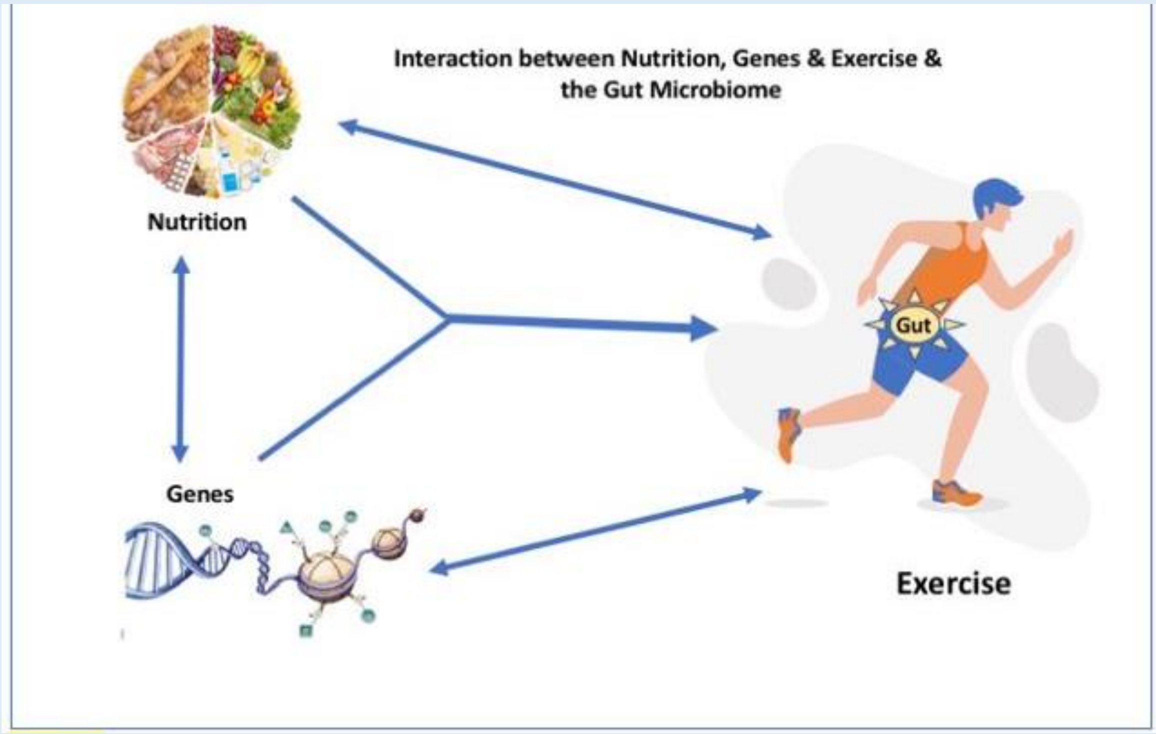
Submission Date: August 24th, 2022; **Acceptance Date:** October 16th, 2022; **Publication Date:** October 19, 2022

Please cite this article as: Karlic H., Krammer U., Haslberger A. Nutritional supplements for athletes and personalization; a short review. *Functional Food Science* 2022; 2(10): 224-241. DOI: https://www.doi.org/10.31989/ffs.v2i10.993

ABSTRACT

The main argument for the optimization of nutritional strategies in athletes, besides improved performance, is the preservation of health and the prevention of unwanted training effects. This highlights the importance of personalized nutrition strategies, as well as functional foods and phytonutrients based on individual requirements which can be precisely defined by detailed analyses, including genetics, epigenetics, gut microbiota, gender, and environmental factors. Recently, a miRNA-based “Fitness Score to Assess the Individual Response to Diet, Metabolism and Exercise” was developed by our group. Formulations of sports drinks and sports foods should be carefully considered, as they frequently contain a mixture of multiple ingredients. Macronutrient supplements, such as carbohydrates, proteins, protein components, fatty acids and probiotics are known to provide benefits for athletes with energy deficits, electrolyte imbalance, gastrointestinal issues, fatigue, and cardiovascular problems. However, micronutrient supplements, such as vitamins, minerals, trace elements and ergogenic aids (e.g., caffeine) must be administered in specific doses based on individual need. Considering the novel data on inter-organ communication (e.g., gut-muscle-brain-axis), data from systems biology highlight the importance of holistic aspects, where nutrients and probiotic supplements are gaining importance for improved performance, reduced risks of illness/ injury and enhanced recovery.

Keywords: Nutrition, additives, functional foods, exercise, microbiome, epigenetics, personalization



INTRODUCTION: Nutritional concepts and food additives are often used to improve athletic performance, but the debate about their health implications persists. The universal understanding of our unique responses to food, based upon individual characteristics of genetics, epigenetics, microbiota, and metabolomics may contribute to a better understanding of the appropriate and safe use of food additives. Recent studies demonstrate that epigenetic-based biomarkers, such as miRNAs, make a significant contribution to personalized strategies, such as the ability to reflect an increased need for specific vitamins and minerals [1].

The boundary between functional foods and medicinal products is not entirely clear and aa precise definition of functional foods is necessary. The Functional Food Center (FFC) defines functional foods as the following: "Natural or processed foods that contain biologically active compounds, which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers for the prevention, management, or treatment of chronic disease or its symptoms.". Bioactive compounds are extra nutritive components that are found in small amounts in various food sources and have useful biological functions, such as an antioxidant, cardio-, chemo preventive and even reduce the risk of certain diseases [2].

A personalized concept of nutrition also includes aspects of genetics, epigenetics, and microbiota. This concept can be observed as the opposite of the old-fashioned "one size fits all" recommendations, such as the Food Guide Pyramid.

Molecular basics: High performance athletes benefit from personalized nutrition concepts. A special focus has been given to single nucleotide polymorphisms (SNPs), which influence the expression of metabolism-associated genes [3]. This interplay is underlined by recent advances in genome research, leading to the identification of SNPs and other genetic variants with the potential to influence athletic performance directly or indirectly, similar to gene-nutrition interactions [4,6]. Furthermore, recent studies indicate that elite athletic status is a partially heritable trait, as are many of the underlying physiological, psychological and anthropometric traits. These SNPs have the potential to help identify future talented competitive athletes [8].

However, this does not only imply the genome and epigenome of the cell nucleus, but also the genome of mitochondria which can be damaged by environmental influences. In addition, aerobic exercise has been shown to impact the gastro-intestinal tract, by modifying gut microbiome diversity and functional metabolism; Thus, affecting the whole body, including the brain [5].

Genomics and epigenetics: On average, two humans differ in only 1% of their genomes. Single nucleotide polymorphisms (SNPs) make up part of this 1% and are well-studied single-base pair changes [3] For most SNPs, functional association is yet to be discovered. However, many diseases are associated with respective genetic and epigenetic variants of genes involved in, such as the caffeine-response (Cytochrome P450 1A2), non-alcoholic fatty liver disease; fat mass, obesity (e.g., alcohol dehydrogenase 1B patatin-like phospholipase domain containing 3, fatty acid desaturase), cardiovascular disorders (apolipoprotein E), etc. In the same token, most biological processes are epigenetically influenced, including dietary habits, physical exercise and lifestyle. In contrast to SNPs, they do not affect the DNA sequence, but rather histone modifications, methylation patterns of DNA around promoter regions and microRNAs (miRNAs), while they all influence gene transcription [3].

Nutritional factors and inflammation in early life stages set epigenetic markers (methyl groups) on DNA and this information is conserved throughout our life [5]. Adaptation to exercise leads to a release of miRNAs from muscle tissue and other organs into our blood circulation [7,9]. This has the potential to affect signaling pathways such as the IGF1/PI3K/AKT/mTOR axis, which are changing rapidly during exercise and recovery.

As shown in respective knockout mouse models [10], miRNAs such as miR-378 can be influenced as an answer to metabolic stress, as well as to the development of muscular dystrophy. However, it was found that expression of miR-378 was significantly elevated after TNF-α, IL-6, and leptin stimulation, suggesting that miR-378 is probably a novel mediator in the molecular mechanisms associated with insulin resistance and obesity. Also, miR-378 plays an important role in adipogenesis. In addition, miR-378a-3p expression is up-regulated during the differentiation of 3T3-L1 preadipocytes, as well as in adipose tissues of high-fat diet-induced obese mice [11].

Fat, metabolism, and the ketogenic diet, respectively, influence epigenetic histone modifications. When carbohydrate availability is reduced, ketone bodies such as acetoacetate, acetone, and β-hydroxybutyrate are produced during fat catabolism. They serve as an alternate source of energy for many organs. In muscle cells, they can inhibit histone deacetylases; Thus, promoting muscular adaptation processes. Acetylation and phosphorylation of histones are closely linked to transcriptional regulation. For example, acetylation of class IIa HDACs (histone deacetylases) HDAC4, -5, -7, and -9 in skeletal muscle promotes the transcription of genes involved in muscular metabolism, such as GLUT4; Nevertheless, there are other compounds that mimic or support such processes [12].

In conclusion, molecular biological nutritional diagnosis must include both genomic analyses (such as SNPs) and epigenetics, with analyses of the methylation status, miRNAs, and the investigation of histone modifications.

Mitochondria: Mitochondria are known as the essential "powerhouse" for cellular energy supply and is important for muscle fitness. They are unique organelles derived from prokaryotic cells that fused with a host cell. Mitochondria descend from symbiotic ancestors and maintain their own individual 16.5-kb genome (mtDNA), which works in conjunction with nuclear DNA for the expression of mitochondrial proteins. They are imperative for providing energy-rich ATP (adenosine triphosphate) and regulating cellular longevity across multiple organ systems. The role of mitochondrial fitness in longevity is well studied and muscle cells are a convenient model system [13,16].

Our group analyzed epigenetic biomarkers, including miR-23a, miR-30e expression, and mtDNA content, that directly target the key regulator of mitochondrial biogenesis, *PGC-1α*. It was found that *PGC-1α* methylation decreased after the intervention, while *PGC-1α* methylation increased with the consumption of red and processed meat, and mtDNA content increased with the ingestion of cruciferous vegetables. These results indicate that concurrent training could improve mitochondrial biogenesis and its functions by altering the epigenetic regulation [7]. Exercise changes the mitochondrial content and quality, which is beneficial for metabolic health. For example, when the cell is under stress during development or physical exertion, protein import is accelerated and the mitochondrial unfolded protein response (UPR^{mt}) is activated through the upregulation of HSP60 heat shock protein, and CPN10. These proteins belong to the group of chaperones that help newly synthesized proteins to get their secondary structures and that the accumulated unfolded proteins achieve their mature configuration [14].

While activation of the organelle biogenesis pathway leads to an increase in mitochondrial content due to exercise, it is also important to eliminate any mitochondrial segments that have outlived their usefulness via mitophagy to maintain the quality of the mitochondrial pool. Mitophagy occurs when double-membraned vesicles, autophagosomes, engulf damaged organelles that are marked for degradation by specialized proteins when they exhibit a reduced membrane potential and/or excessive increases in ROS (reactive oxygen species) production. Mitophagy is up-regulated by numerous cellular stresses, including the energetic imbalance caused by acute exercise. A few studies have documented an increase in autophagy and mitophagy markers in muscle as feedback to repeated bouts of exercise in the form of endurance training [15].

In ageing people, damage to mitochondria plays a role in the progression of sarcopenia, as they are important regulators of a variety of factors that contribute to the etiology of the disease, such as ATP provision, oxidative stress, proteostasis, apoptosis, inflammation and Ca^{2+} handling. The natural process of ageing, along with prolonged sedentarism, promotes impairments in mitochondrial integrity and further contributes to the progressive nature of sarcopenia. Aged muscle is associated with both fragmented mitochondria and/or atypically enlarged organelles. Therefore, exercise coupled with proper nutrition remains a reliable and non-pharmacological strategy for maintaining signaling processes involving sirtuin (SIRT) and the NAD^+ precursor nicotinamide riboside (NR). These signaling processes also play a role in metabolism and mitochondrial biogenesis in muscle, suggesting a possible benefit of NR supplementation [17,21].

The review from Custodero et al. (2020) [12] recommends NR supplementation in aging persons, particularly because the endogenous NAD+ pool is reduced in several chronic and degenerative diseases (e.g., cardiovascular diseases, Alzheimer's and Parkinson's diseases, muscular dystrophies) and during the ageing process. Recently, the NAD+ precursor nicotinamide riboside (NR), a vitamin B3 derivate, showed the ability to improve NAD+ metabolome homeostasis. This could restore energy metabolism and cellular function in various organs in animals. In addition to regular exercise, calorie restriction (CR) without malnutrition is also a promising non-genetic and non-pharmacologic nutritional intervention that prolongs lifespan in a variety of organisms, possibly by reducing overproduction of reactive oxygen species (ROS) and oxidative damage. This can help in the prevention of age-related metabolic disorders [18] and provide some bases for personalized dietary interventions.

Microbiome: The microbiome in the gut represents a critical metabolic turntable for a multitude of individuals, especially athletes. The gut is a diverse environment and contains most of our bacterial microbes. The intestinal epithelium consists of over 1100 genera of different phyla and contains nearly 39 trillion microbes. This implies a high level of symbiosis and affects all organs of the body. A special role has been assigned to the Firmicutes group and Actinobacteria contained in the microbiota, which includes the Lactobacillus and Bifidobacterium genera, which promote the crosstalk between the gut and brain during exercise [5].

It has been shown that athletes have a greater diversity of gut microorganisms in comparison to non-athletes. The research concluded that those who trained had greater diversity in Firmicutes phylum, particularly *Faecalibacterium prausnitzii,* and species from the genus Oscillospira, Lachnospira, and Coprococcus. In addition, the SCFA-producing genera from the Firmicutes phylum also appear to increase in response to exercise [19,20]. However, in elite athletes and ambitious amateurs, the equilibrium of microbiota can be disturbed. Thus, requiring individual diagnostics and personalized decisions for dietary interventions with probiotics, phytochemicals and functional foods.

Nutritional supplements: Extensive studies in the 1980s [22] showed the adverse health effects of dehydration, especially for athletes. Subsequently, various types of sports drinks appeared on the market. While feeding stations at marathons were only recommended at 15 and 30 km in the International Association of Athletics Federations (IAAF) handbook of 1953, more recent guidelines demand water supplies every 2-3 km and larger refreshment stations every 5 km. However, there is also the risk of “overdrinking” because ingesting too much water can cause hyponatremia.

Van Loon et al. [23,24] suggested that research on sports drinks should focus on different carbohydrate compositions, pre-exercise carbohydrate loads and carbohydrate supplementation during non-endurance exercise. There are a variety of carbohydrate compounds that can be absorbed or oxidized faster, which increases oxidation rates during exercise. In terms of pre-exercise carbohydrate loads, low-insulinotropic and low- glycemic loads may inhibit fat oxidation to a lesser extent than high-glycemic loads during subsequent exercise. Finally, carbohydrate supplementation during non-endurance exercise is significant as well.

The term “Sport Foods” generally refers to specifically formulated food products that are commercially developed for use by athletes. Although they often contain nutrients in similar amounts to whole foods and convenience foods sports foods can offer the practical advantage of combining all the nutrients needed for a specific goal into a single source. In addition, the use of novel food and packaging technology can facilitate the transport, hygienic storage, preparation, and consumption of sports foods, particularly in situations before, during, or after/between competition events and training sessions [25].

The publication by Gnoni et al. [25] cites recent systematic reviews and meta-analyses of approximately 160 unique studies in athlete populations and investigations regarding the prevalence of dietary supplement use (defined using the Federal Drug Administration's Dietary Supplement Health and Education Act of 1994; e.g., sports foods, iron, vitamins, etc.) by sport, sex, and athlete status (i.e., elite vs. non-elite), reporting high variability in supplement use among various sporting groups, with a combined group summary prevalence estimate (SPE) ranging from 4 to 62% across various supplement types. The study was differentiated by athlete status, the results showed that cohorts of elite athletes (SPE male: ~ 69% and SPE female: ~ 71%) had a higher rate of supplement use than their non-elite counterparts (SPE male: ~ 48% and SPE female: ~ 42%). Furthermore, there was greater use of supplemental iron reported by female athletes, while males used products such as protein, creatine and vitamin E more frequently. Although the specific use of dietary supplements in groups of athletes is difficult to quantify, such outcomes suggest that service providers (i.e., dietitians, physiologists, sports physicians) should be aware of differences in the incidence and type of use of supplements, which are often also components of sports foods [26].

While some sports foods are similar to "everyday food", they may be low in nutrients compared to the multitude of nutrients and phytochemicals found in the former. For this reason, sports foods should not be used as a casual replacement dietary strategy for athletes, but as a supplement when a specific combination of key nutrients is required. The ergogenic properties of sports drinks and foods can be attributed to four main physiological goals: Hydration, (fluid intake to maintain or restore hydration status), osmolality (electrolyte ingestion to compensate for sweat loss), refueling (carbohydrate intake before, during, and after/between exercise) anabolism (protein ingestion to promote amino acid delivery for optimal training adaptation) and recovery [27,28].

However, manufacturers want to claim additional benefits of their specific products and proprietary blends, but these claims can be scientifically false or even beyond the benefits of each compound. Manufacturers can add performance supplements or other ingredients to sports foods and drinks. For instance, protein shakes can contain creatine, sports drinks or bars can contain caffeine and vitamins can be found in the most unexpected places such as sports/fitness "waters", offering a pleasant tasting drink, rather than addressing the individual needs of athletes. This blurs the distinction between sports foods and supplements, making it difficult for sports nutritionists to keep track of the total daily doses of supplements and micronutrients to which athletes are exposed [29].

In order to track full intake of such ingredients and reduce concerns about product contamination from raw ingredients, athletes are guided to choose brands of sports foods with the simplest formulations to achieve the specific goals for which they are designed. In general, they should focus their use of performance supplements on separate protocols and use separate products, preferably batch-tested by a third party or manufactured by large (reputable) food companies. An exception might be caffeine, which already has a crossover to the food industry as it is found in the athlete's diet via their intake of "everyday-consumer" products such as coffee, tea, iced coffee, and "energy" drinks [28].

In summary, sports foods may provide valuable contributions to an athlete's nutrition plan by providing nutrients that support training adaptation (e.g., protein) and promote performance (e.g., carbohydrates and fluid/electrolytes). However, ingredients should be carefully considered, as many of these goals can to a large extent also be obtained through "everyday" foods via their vitamin, phytochemical or mineral content.

Disadvantages of specified Sports Foods and Dietary Supplements: The decision to take a supplement tends to involve an attempt to gain a functional benefit, which is usually for health maintenance, physique management, enhanced recovery or a direct performance enhancement. In contrast with these potential benefits is the idea that the supplement inherently possesses certain risks against its use.

Although all supplements are legally bound to be sold in packages containing a list of ingredients, it must be considered that some national legislations may be stricter than others in the setting/ enforcing the list of permitted ingredients in supplements. Thus, consumers and certain athletes who are considering taking supplements to support their athletic performance should seek products with ingredients that the average consumer can identify through simple research. A "proprietary blend" that lists exotic names and claims commercial intellectual property cannot be considered a transparent listing of ingredients. Figure 1 summarizes the basics of decision-making, with a focus on nutritional supplements, which require a lot of information based on individual fitness levels, types of food and drink and the awareness of risk factors (i.e., Personal health status, medications, exercise temperature and avoidance of harmful agents). In addition, when discussing dietary supplements, the close interaction of nutrition with epigenetics, exercise and the gut microbiome should be considered [28].

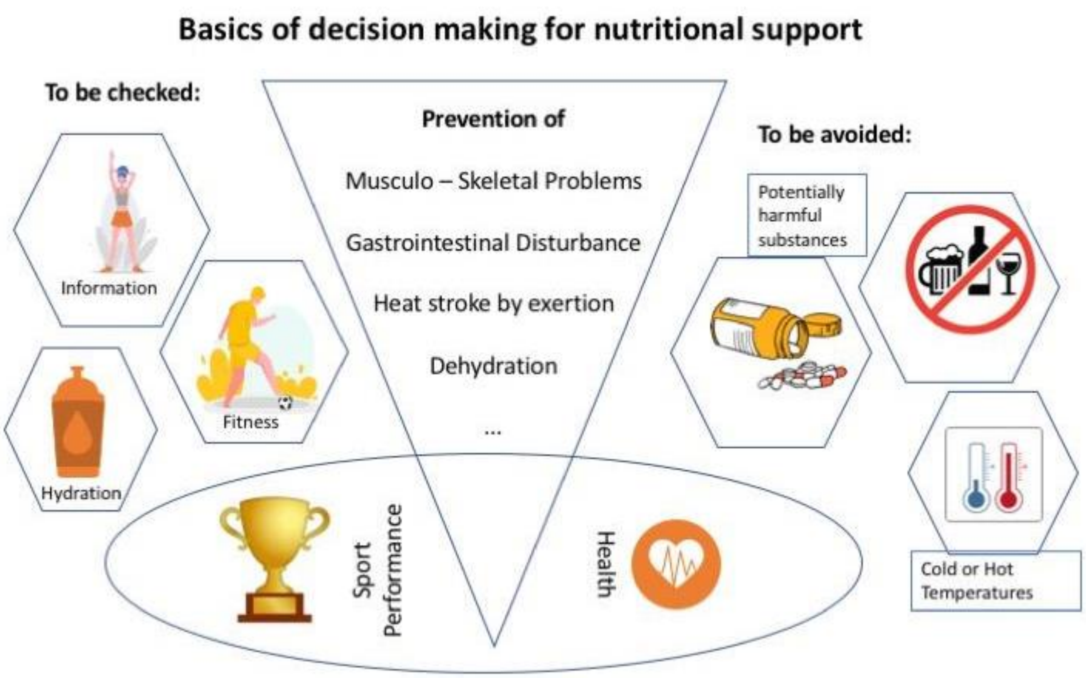


Figure 1: The decision-making process

Types of Dietary Supplements: Peeling et al (2019) [28] defined a supplement as a nutrition or nutritional component that has the potential to improve health and physical performance, as shown in Figure 2.

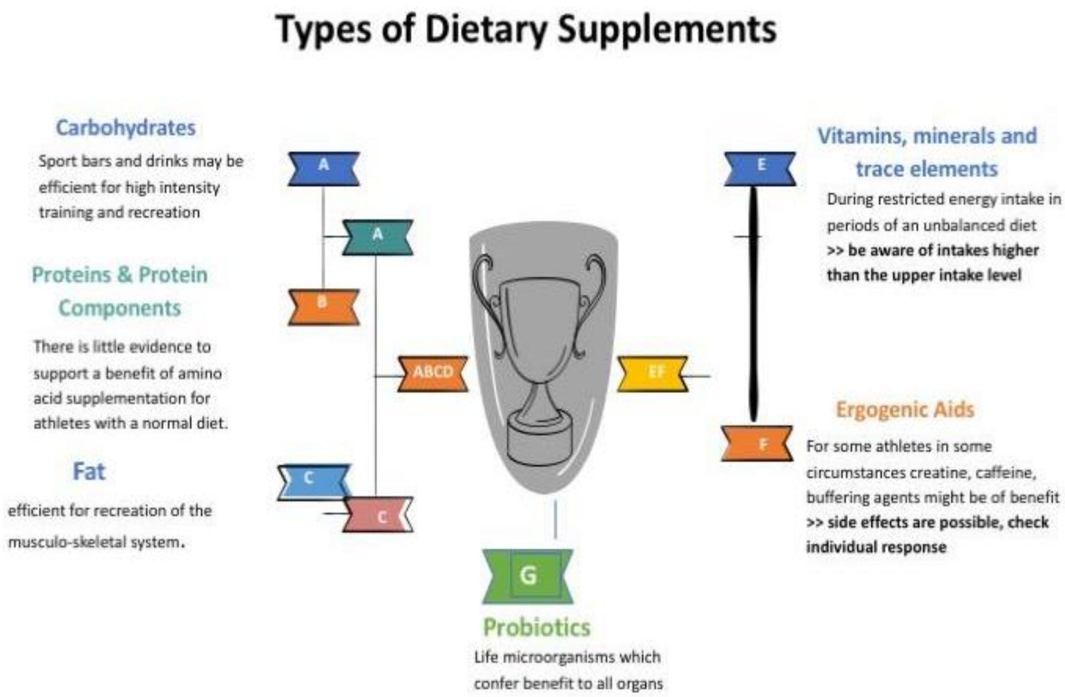


Figure 2: Presents an overview of the most important macronutrients and micronutrients that can be supplemented to improve performance and prevent illnesses and injuries.

Phytochemicals or secondary plant products: Phytochemicals are small organic compounds normally produced by plants as defense mechanisms against biological stress. These compounds are classified as secondary metabolites because they are not directly involved in plant growth, development, or reproduction. The main classes of these phytochemicals include alkaloids, polyphenols and terpenoids. Phytochemicals activate the same cellular processes as calorie restriction, fasting and exercise. These cellular processes include defense responses such as autophagy, DNA repair and the induction of antioxidant enzymes. These processes protect cells and organs from damage, mutations, reactive oxygen species (ROS) and improves health and longevity [30]. Furthermore, interactions between the mechanisms of bioactive plant compounds and viral mechanisms are discussed and provide hope that herbal therapies facilitate pre-interventions or combinations with pharmaceutically derived drugs [31].

MACRONUTRIENTS

Carbohydrates: Carbohydrates are the most important macronutrient. They are known to be the predominant fuel source in moderate to high-intensity exercise and Supplements are often offered in the form of gels and sports bars. General recommendations for daily carbohydrate intake are based on grams of carbohydrate per kilogram of body weight rather than a percentage of total dietary energy [28].

Carbohydrate intake guidelines for athletes are established based on daily exercise patterns and expressed relative to an athlete’s body weight. However, interpreting such guidelines requires an inherent knowledge of a sport and its energy requirements. The requirements can also be met through the “normal” meals and snacks of the day with a range of different foods [32].

An increase in insulin in the blood is associated with carbohydrate intake - the insulinemic response [33]. Insulin inhibits the release of fat from fat cells into the blood. A current goal is to develop carbohydrate products with a low glycemic response and a low insulinemic response. When the rise in blood glucose and insulin are moderate, fat mobilization will not be inhibited as frequently. This allows fat to be an available energy source for muscle, which spares muscle glycogen storage, positively affecting energy availability and performance. Trehalose is a carbohydrate with these characteristics. Moreover, another goal is to find specific combinations of carbohydrates, fats, and proteins that can have beneficial effects on muscle recovery and training adaptations [34]. In the same token, the development of products with specific phytochemicals that positively affect the immune response is also of interest.

Proteins and protein components: Regardless of the type of exercise, the general recommendation for the intake of proteins, commonly considered building blocks, is in the range of 1.2-1.7 g/kg body weight. The majority of athletes meet their protein requirements through normal nutrition and attempts to reduce body fat or to promote recovery by consuming more protein cannot be recommended.[35].

Fat: Different types of fats are present in most foods. Fats are necessary for the absorption of essential fat-soluble vitamins and essential fatty acids. Nutrition with healthy fats include avocados, oily fish,nuts, as well as olive oil, polyunsaturated oils and canola oil. The importance of omega-3 fatty acids is extensively reviewed by Thielecke et al. 2020 [37]. An increased amount of attention is given to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in sports nutrition. However, conclusive recommendations on the use of EPA/ DHA supplements are currently hampered by inconsistent translation into clinical endpoints.

Ramos-Campo et al. 2020 reported [36] that EPA/DHA supplementation resulted in lower concentrations of inflammation and muscle damage markers and reduced muscle However, this did not improve the strength deficit in endurance athletes.

Probiotics: Macronutrient intake is regulated via microbiota and probiotics. The essential role of these food components is reviewed by Sivamaruthi et al. 2019 [38]. The list of live probiotic microorganisms includes Lactic acid bacteria, Bifidobacteria, Pediococcus, Leuconostoc, Streptococcus, Saccharomyces, Bacillus, and Enterococcus, which are the commonly used probiotic strains. In recent decades, probiotics have been recommended as a health supplement to improve health status and manage/treat many diseases and disorders.

Micronutrients: The role of micronutrients in sports nutrition is extensively reviewed by Jeukendrup et al. 2010 [35] and play an important role in maintaining the health of physically active individuals [47]. They are defined as chemical elements or substances required in trace amounts for the normal growth and development of living organisms.

Vitamins: Vitamins have been defined as essential nutrients since the 1940s and 1950s. However, it must be considered that vitamin intake in excess and above the daily recommended amounts can even have detrimental health effects and increase the risk of cancer. [39]. B vitamins, including vitamin B12, are essential for DNA methylation, synthesis, stability, and repair and an ergogenic effect of vitamin B12 (resulting from enhanced erythropoiesis) has been considered. Athletes with a vitamin B12 concentration below 400 pg/ mL may need supplementation, but overdoses should be strictly avoided due to the risk of cancer [40].

While considering the risk of colorectal cancer, causal associations between elevated serum concentrations of vitamin B12 and circulating iron were recently confirmed in a large Mendelian randomization (=MR) study with 58,221 individuals and 67,694 controls [35]. However, the authors noted that a series of at least nine genetic loci are associated with serum vitamin B12 concentrations. The loci can be directly linked to current understanding of vitamin B12 metabolism such as absorption, transport, or enzymatic processes. Therefore, the necessity of vitamin B12 supplementation should be checked very carefully, possibly also with a focus on genetic markers such as respective SNPs and epigenetic markers such as DNA methylation status [40–42].

Furthermore, it must be mentioned that a higher serum vitamin B12 was associated with tumor-specific hypomethylation in colorectal cancer patients [4]. Vitamin B12 can be produced by the gut microbiome. Thus, additional supplementation could induce a systemic disturbance that promotes the development of colorectal cancer [43,45,57].

Minerals and Trace Elements: Hundreds of biological processes depend on minerals and trace elements (MTEs). The role of these micronutrients is extensively reviewed by Heffernan et al. 2019 [39]. While considering the negative impact of MTE deficiency, about 50% of athletes use some form of micronutrient supplements, but the data confirming their efficacy for improving performance are still limited.

Iron (Fe) plays an important role in the body and influences athletic performance probably through its functions, such as oxygen transport. In female endurance athletes, iron has been shown to support physical performance. Modest calcium (Ca) loss can lead to hormonal changes that might impair muscle function, which could be mitigated by an appropriate supplementation, although there are no clear data on the effect of functional performance. Magnesium (Mg) supplementation can normalize physiological function, but there is no clear ergogenic effect [39,54].

Many parameters, including sprint time, cycling power output, VO_{2Peak}, resting heart rate (HR), and improvement parameters of cardiac function (echocardiographic) in elite athletes are phosphate, commonly supplemented as sodium phosphate. Exercise-associated reduction in immunity can be counteracted with supplementation of zinc (Zn) and selenium (Se). Exercise-induced changes in sodium balance, particularly during heat, can be counteracted by sodium (Na) supplementation. A small effect on reducing body mass has been shown after supplementation with chromium (Cr), a trace element known to be beneficial in several diseases. Improvements in some aspects of endurance performance through multimineral supplementation are consistently discussed, especially regarding their immune-boosting role in protection against bacterial and viral infections [39].

Ergogenic aids- Performance Supplements: Ergogenic supplements including caffeine, creatine, nitrate, sodium bicarbonate, and beta-alanine are commonly used by athletes. However, only a few of them warrant consideration for trial use by athletes, as also reviewed by Peeling et al. 2019 [28].

Caffeine: Caffeine shows well-established benefits for enhancing athletic performance in both endurance-based events and short-term, supramaximal tasks, whereas its effect on maximum strength is less clear [52]. Caffeine dosages of 3–6 mg/kg of body weight) consumed approximately 60 min. prior to exercise in the form of anhydrous caffeine (i.e., pill or powder form) commonly result in performance gains [44]. However, lower caffeine doses (<3 mg/kg body weight, ~200 mg) may improve performance when consumed before events lasting 5 to 150 min. The literature on caffeine supplementation shows strong evidence during exercise and an ergogenic benefit, but it is not riskless [46].

Caffeine Risks: There are plenty of risks associated with caffeine intake. First, there are high levels of individual variability, which includes some potential for a negative response, minimal response, positive response, and super response and thorough practice is needed. Secondly, Caffeine may have repeated use for events within the same day (e.g., heptathlon and decathlon) and requires careful planning of the timing and number of doses, including whether a top-up dose is even needed. Then, its use on successive days (e.g., heats and finals of many events in major competitions) requires consideration of the effect on sleep and overall recovery, especially if the first event has a late-night schedule. Finally, its interactions with the efficacy or side effects of other supplements used at the same time must be in careful consideration and experimentation [28].

Creatine Monohydrate: Creatine monohydrate (CM) supplementation increases muscle creatine and phosphocreatine stores and sustains exercise otherwise limited by the inability of phosphocreatine resynthesis to keep up with exercise fuel demands during single and repetitive high-intensity exercise bouts, with the most noticeable effects occurring on tasks < 30 sec [28].

Indeed, creatine supplementation received widespread attention in 1992 when the first report on successful loading protocols was published [33] at the same time as anecdotes emerged from the Barcelona Olympic Games of its use by British gold medal-winning track and field sprinters. In addition, chronic training adaptations such as lean mass gains and improvements in muscular strength and power have also been noted, with both direct and indirect mechanisms proposed. On the other hand, some performance benefits for endurance athletes have also been suggested [28]. In regard to resistance training, taking a low dose of creatine for six weeks showed an increase in plasma creatine concentration and improved fatigue resistance during repeated bouts of high-intensity contractions [59].

Creatine Risks: The are a few risks of creatine use, the most popular being weight gain. Weight gain of 1–2 kg associated with creatine supplementation can be counterproductive in weight-sensitive events, like jumps and distance races. However, a low-dose approach that avoids the creatine monohydrate “loading phase” may avoid such issues. Interactions with the efficacy or the side effects of other supplements used at the same time must be carefully examined and experimented. There has been long and ambiguous speculation that the independently achieved performance benefits of creatine supplementation might be mitigated by caffeine supplementation [28].

L-Carnitine: On a theoretical basis, the benefits of carnitine supplementation for skeletal muscle during exercise in athletes have been documented in many athletes participating in placebo-controlled trials. However, there are inter-individual differences in response to supplementation as an ergogenic aid and for weight management. Therefore, no general recommendation for this supplement can be provided so far and potential intolerance risks should be considered when carnitine is applied [41].

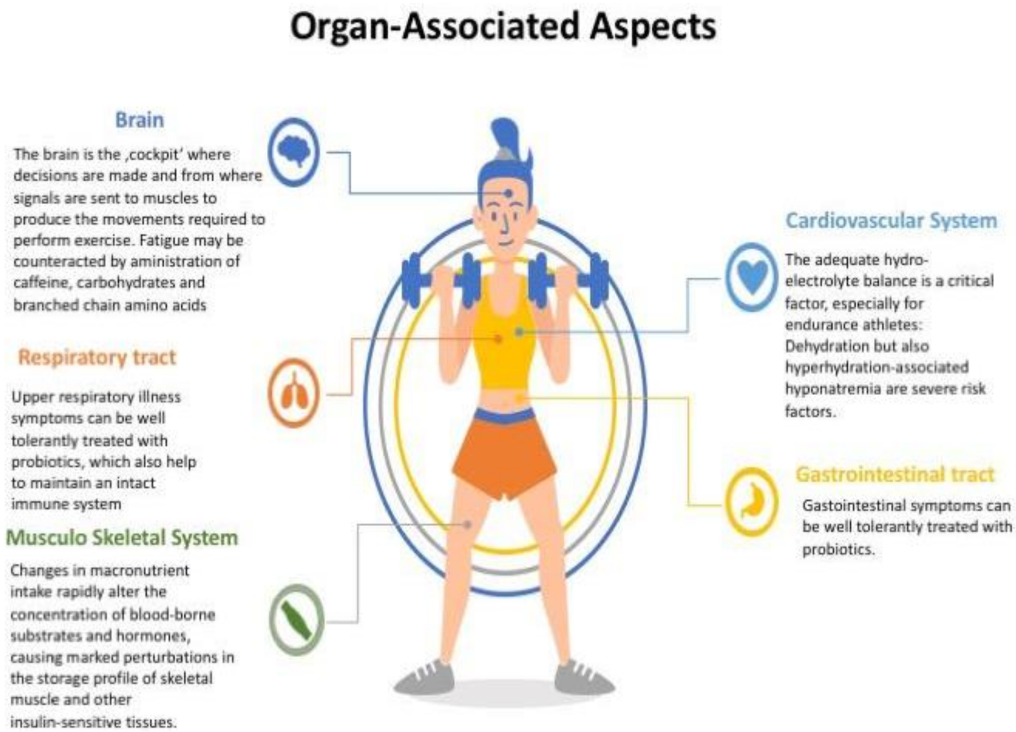


Figure 3: Organ-associated benefits of supplements

Organ-associated benefits of supplements. The potential benefits of nutrient supplementation for various organs are shown in Figure 3. A mechanism demonstrating how exercise stimulates the release of molecules into the circulation was detected by Whitham et al. 2018 [48]. Using quantitative proteomic techniques, led to the concept that inter-tissue signaling proteins are important mediators of adaptations to exercise. Extracellular vehicles (EVs) transport packaged protein and nucleic acids throughout the body. Recent data can provide some explanation for previous observations of our group [1], which suggested similar expression patterns of metabolic enzymes in muscle biopsies and white blood cells [63].

Brain: The brain and the rest of the body interact at rest, but also during prolonged exercise. Fatigue is considered a result of such disturbed communication and supplementing with branched-chain amino acids (BCAA) might counteract this process [49]. In addition, caffeine ingestion in combination with water and carbohydrate is known to reduce central fatigue [17].

Upper Respiratory tract: Antioxidants regulate immune function and may play a role in upper respiratory tract infections. Fondell et al. 2011[50] investigated the potential effects of dietary intake from food and supplements use of vitamins C and E. Supplements containing vitamin E and vitamin C may reduce the risk of upper respiratory tract infections, especially in male athletes, who tend to have lower intakes of vitamin C from food than women. However, there is evidence that many more nutrients with antioxidant potential help to support the immune system against various bacterial and viral infections in both athletes and sedentary people.

***Musculo-skeletal system*:** To improve muscle mass, food components should stimulate protein synthesis. The evidence for creatine and dehydroepiandrosterone (DHEA), is hypothetical. There is positive evidence for branched-chain amino acids (BCAAs), in combination with carbohydrates [51,53].,

While considering bone and joint conditions, many food components on the market promise to improve bone mass, cartilage disease, or synovial fluid conditions. These include amino acids such as proline or lysine, combinations of certain minerals, phytoestrogens, glucosamine, vitamin K and cartilage preparations, but the claimed beneficial effects of these components are all hypothetical [51].

Cardiovascular system: Strenuous exercise leads to cardiovascular modifications. Slight diastolic modifications and minor cardiac changes have been observed in half-marathon runners, while strenuous exercise induces cardiovascular sympathetic modulation in triathletes [55].
Therefore, electrolyte equilibrium must be carefully monitored, as both dehydration and hyperhydration (causing hyponatremia) can cause serious problems. In addition, the antioxidants and probiotics mentioned above can prevent damage to the cardiovascular system [56].

Systemic action of probiotics: The possible mechanisms behind the beneficial effects of probiotic supplementation on athletes' health have been summarized in Figure 4. Sivamaruthi et al. 2019 [38] described the mechanism of probiotic action as follows: In general, probiotics improved the health status of the consumer by enhancing the intestinal permeability, regulating the immune system, improving microbiota composition and eliminating pathogens through intestinal pH value reduction, increasing the short-chain fatty acids and mucus production and bacteriocin production. Intense exercise can lead to oxidative stress, muscle damage, inflammation and immune alteration, especially in elite athletes, but also in ambitious amateurs.

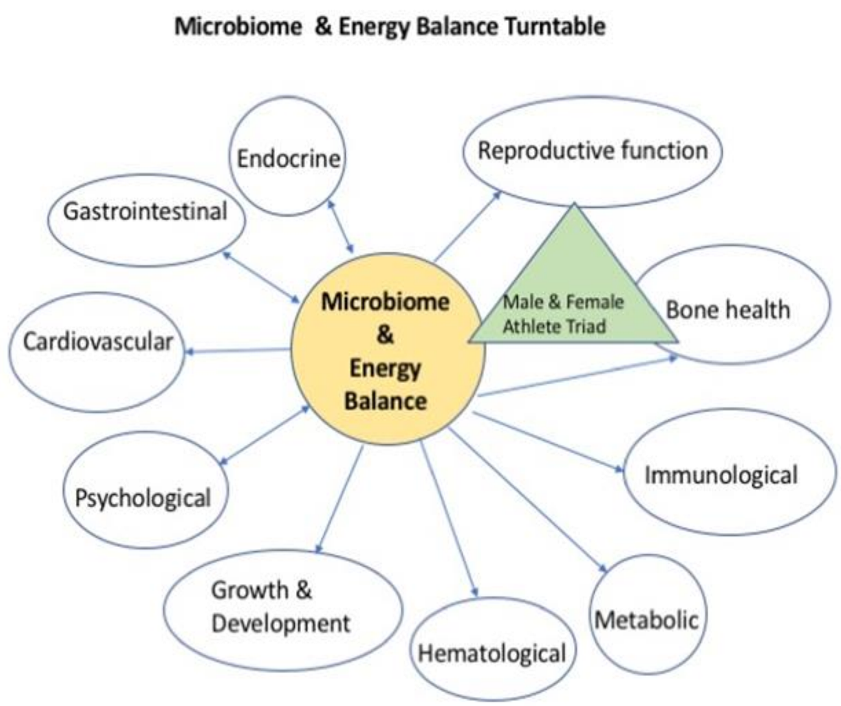


Figure 4: Turntable illustrating the key role of the microbiome in energy-balance

Probiotic supplementation could improve the overall immune status of athletes and provide several health benefits. Probiotic (Lactobacillus species; single-strain and multispecies probiotic supplement) activates T- and B-lymphocytes, increase the secretion of cytokines (interferon-γ, immuneolobulin A, Interleukin-10), and suppressed the expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-8). Upper respiratory tract infection (URTI) is a common health issue among athletes. It has been suggested that immune cells can migrate from one site to another to provide protection, especially prevent URTI [38].

Toll-like receptor (TLR)-2 activation by probiotics can activate NF- κB pathway and innate immune signaling via MyD88, resulting in better immune regulation and enhanced inflammatory cascades in elite athletes. In addition, a multigenic supplementation of probiotics mediated TLR-2 activation and enhanced production of zonulin (tight junction protein), which may improve intestinal integrity [38].

The beneficial effects of probiotics also include improving antioxidant levels to reduce oxidative stress by decreasing the formation of ROS (reactive oxygen species) or by neutralizing the ROS. Habitual intake of probiotics has been suggested to have the potential to restore or maintain intestinal microbiota balance, reduce oxidative stress, and exhibit beneficial cardiovascular effects. The improvement of radical scavenging potential was observed in athletes after supplementation with a multispecies probiotic (*L. rhamnosus* IMC 501® and *L. paracasei* IMC 502®) [38].

The effect of probiotic supplementation on oxidative stress in athletes was analysed by Martarelli et al. 2011 [58]. The antioxidant potential of *L. rhamnosus* IMC 501® and L. paracasei IMC 502® has been confirmed in vitro. Healthy athletes supplemented with a probiotic mixture (*L. rhamnosus* IMC 501® and *L. paracasei* IMC 502®; approximately 10^9 cells per day) during an extensive training period for four weeks. The microbiological examination showed that the fecal Lactobacillus load was significantly increased in the probiotic group compared to baseline and placebo controls. Notably, *L. rhamnosus* IMC501® and *L. paracasei* IMC 502® strains were found in the fecal microbiota of the probiotic supplemented group, which was not detected at baseline assessments. Reactive oxygen metabolite levels were elevated after the exercise period in both groups compared to baseline, but the probiotic supplementation was found to neutralize reactive oxygen species (ROS). Likewise, the athlete's antioxidant potential increased during probiotic supplementation. The results indicate that supplementation with a mixture of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® improved the antioxidant status during strenuous exercise training [38].

According to Strasser et al. 2016 [60] , probiotic (*B. bifidum* W23, *B. lactis* W51, *E. faecium* W54, *L. acidophilus* W22, *L. brevis* W63, and *L. lactis* W58) supplementation reduces exercise-induced tryptophan deficiency and aids to increase the availability of serotonin, which improves the mental status in athletes and may establish gut-brain communication.

Factors Influencing the Effect of Probiotic Supplementation: Exercise is known to influence gut microbiota. In addition, the literature provides evidence that probiotics may support athletic performance by enhancing training adaptions, moderating physiological responses during port-exercise recovery, and improving mood and mental responses after intense exercise [62]. Several factors affect the outcomes: dose and duration of the intervention, formulation of probiotics, and the ability of the strains are the most influential factors of probiotic intervention. Supplementing an adequate amount of probiotics over a long period confers health benefits. Still, the amount of probiotics for an athlete is the question with several unclear answers. In fact, the required amount of probiotics is unique to each individual and is based on the host's physical, metabolic, and mental status [38].

A minimal intervention time is required to induce a positive immune response in athletes. The multi-strain probiotic formulation has the potential to increase the likelihood of adhesion and colonization of probiotic strain in the host's GI tract. When the strains are compatible with each other, they confer synergetic effects. Using multi-strain probiotic formulations could shorten the duration of supplementation [38].

The health status of elite distance runners improved with personalized probiotic supplementation attributed to the ability of L. fermentum VRI-003 to colonize the intestinal tract. Short-term supplementation with probiotics did not improve the athlete's health. However, administration of the high dose of probiotics for short period (7 days) did not significantly improve the systemic cytokine profile and intestinal permeability when compared to the placebo group [38].

Therefore, probiotic supplementation is recommended for athletes to maintain or improve health and overcome disease. The health-promoting property of the probiotic is species-, strain-, and host-specific. Some of the strains or combinations showed protective effects against gastrointestinal symptoms and respiratory tract infections. Age, weight, body fat percentage, and food intake have no influence on the species composition of proteobacteria and verrucomicrobia [38,61].

CONCLUSION: The sports foods and drinks market are very attractive to the food industry. There is a wide variety of supplements and sports foods and drinks on the market that labelled with various claims of benefit. However, the clinical evidence is still limited, especially regarding physical performance.

After careful medical examination, using a variety of laboratory parameters, athletes can benefit from precise personalized supplementation strategies to manage and prevent problems in the psyche, respiratory tract, musculoskeletal and cardiovascular system as well as the gastrointestinal tract and above all the immune system.

Abbreviations: BCAA: branched-chain amino acids; CM: Creatine monohydrate; CR: calorie restriction; DHA: docosahexaenoic acid; DHEA: dehydro-epiandrosterone; EPA: eicosapentaenoic acid; EVs: Extracellular vesicles; FFC: Functional Food Center; HDACs: histone deacetylases; HR: heart rate; IAAF: International Association of Athletics Federations; MR: Mendelian randomization; MTEs: minerals and trace elements; NR: NAD+ precursor nicotinamide riboside; ROS: reactive oxygen species; SIRT: sirtuin; SNPs: single nucleotide polymorphisms; SPE: summary prevalence estimate; TLR: Toll-like receptor; UPRmt: mitochondrial unfolded protein response; URTI: Upper respiratory tract infection

Competing Interests: Authors declare no conflict of interest.

Acknowledgment/Funding: This work received no special funding

REFERENCES

1. Krammer UDB, S Tschida, J Berner, S Lilja, OJ Switzeny, B Hippe, P Rust, and AG Halsberger. MiRNA-based "Fitness Score" to Assess the Individual Response to Diet, Metabolism and Exercise. *J. Int. Soc. Sports Nutr.* 2022; 19: 455–473. DOI: https://doi.org/10.1080/15502783.2022.2106148
2. Gur J, M Mawuntu, and D Martirosyan. FFC' s Advancement of Functional Food Definition. *Funct. Foods Heal. Dis.* 2018; 8: 385–397.
3. Bhatti JS, GK Bhatti, and PH Reddy. Mitochondrial dysfunction and oxidative stress in metabolic disorders — A

step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta - Mol. Basis Dis.* 2017; 1863: 1066–1077. DOI: https://doi.org/10.1016/j.bbadis.2016.11.010

4. Boughanem H, P Hernandez-Alonso, A Tinahones, N Babio, J Salas-Salvadó, FJ Tinahones, and M Macias-Gonzalez. Association between serum vitamin B12 and global dna methylation in colorectal cancer patients. *Nutrients* 2020; 12: 1–12. DOI: https://doi.org/10.3390/nu12113567
5. Brouns F. *Essential of sports nutrition*. John Wiley & Sons. 2003
6. Heck AL, CS Barroso, ME Callie, and MS Bray. Gene-nutrition interaction in human performance and exercise response. *Nutrition* 2004; 20: 598–602. DOI: https://doi.org/10.1016/j.nut.2004.04.010
7. Krammer UDB, A Sommer, S Tschida, A Mayer, S V Lilja, OJ Switzeny, B Hippe, P Rust, and AG Haslberger. PGC- 1α Methylation , miR-23a , and miR-30e Expression as Biomarkers for Exercise- and Diet-Induced Mitochondrial Biogenesis in Capillary Blood from Healthy Individuals: A Single-Arm Intervention. *Sports* 2022; 10: 73 DOI: https://doi.org/doi.org/10.3390/sports10050073
8. Pickering C, J Kiely, J Grgic, A Lucia, and J Del Coso. Can genetic testing identify talent for sport? *Genes (Basel).* 2019; 10:. DOI: https://doi.org/10.3390/genes10120972
9. Buford TW, RB Kreider, JR Stout, M Greenwood, M Spano, T Ziegenfuss, H Lopez, J Landis, and J Antonio. International Society of Sports Nutrition position stand: creatine supplementation and exercise. *J. Int. Soc. Sports Nutr.* 2007; 4: 1–8. DOI: https://doi.org/10.1186/1550-2783-4-Received
10. Li Y, J Jiang, W Liu, H Wang, L Zhao, S Liu, P Li, S Zhang, C Sun, Y Wu, S Yu, X Li, H Zhang, H Qian, D Zhang, F Guo, Q Zhai, Q Ding, L Wang, and H Ying. MicroRNA-378 promotes autophagy and inhibits apoptosis in skeletal muscle. *Proc. Natl. Acad. Sci. U. S. A.* 2018; 115: E10849–E10858. DOI: https://doi.org/10.1073/pnas.1803377115
11. Quintanilha BJ, BZ Reis, GB Silva Duarte, SMF Cozzolino, and MM Rogero. Nutrimiromics: Role of micrornas and nutrition in modulating inflammation and chronic diseases. *Nutrients* 2017; 9: 1–24. DOI: https://doi.org/10.3390/nu9111168
12. Custodero C, S Saini, M Shin, Y Jeon, M McDermott, C Leeuwenburgh, S Anton, and R Mankowski. Nicotinamid riboside-a missing piece of the puzzle in exercise therapy in older adults? *Exp. Gerontol.* 2020; 137: 110972. DOI: https://doi.org/10.1016/j.exger.2020.110972.Nicotinamide
13. Dalton A, C Mermier, and M Zuhl. Exercise influence on the microbiome–gut–brain axis. *Gut Microbes* 2019; 10: 555–568. DOI: https://doi.org/10.1080/19490976.2018.1562268
14. Inigo JR and D Chandra. The mitochondrial unfolded protein response (UPRmt): shielding against toxicity to mitochondria in cancer. *J. Hematol. Oncol.* 2022; 15: 1–18. DOI: https://doi.org/10.1186/s13045-022-01317-0
15. Hsu P and Y Shi. Regulation of autophagy by mitochondrial phospholipids in health and diseases. *Biochim. Biophys. Acta (BBA)-Molecular Cell Biol. Lipids* 2017; 176: 139–148. DOI: https://doi.org/10.1016/j.bbalip.2016.08.003.Regulation
16. Memme JM, AT Erlich, G Phukan, and DA Hood. Exercise and mitochondrial health. *J. Physiol.* 2021; 599: 803–817. DOI: https://doi.org/10.1113/JP278853
17. Del Coso J, E Estevez, and R Mora-Rodriguez. Caffeine effects on short-term performance during prolonged exercise in the heat. *Med. Sci. Sports Exerc.* 2008; 40: 744–751. DOI: https://doi.org/10.1249/MSS.0b013e3181621336
18. Domańska-Senderowska D, MJN Laguette, A Jegier, P Cięszczyk, A V. September, and E Brzeziańska-Lasota. MicroRNA profile and adaptive response to exercise training: a review. *Int. J. Sports Med.* 2019; 40: 227–235. DOI: https://doi.org/10.1055/a-0824-4813
19. Evans M, KE Cogan, and B Egan. Metabolism of ketone bodies during exercise and training: physiological basis for exogenous supplementation. *J. Physiol.* 2017; 595: 2857–2871. DOI: https://doi.org/10.1113/JP273185
20. Remely M, B Hippe, I Geretschlaeger, S Stegmayer, I Hoefinger, and A Haslberger. Increased gut microbiota diversity and abundance of Faecalibacterium prausnitzii and Akkermansia after fasting: A pilot study. *Wien. Klin. Wochenschr.* 2015; 127: 394–398. DOI: https://doi.org/10.1007/s00508-015-0755-1
21. Stocks B, SP Ashcroft, S Joanisse, LC Dansereau, YC Koay, YS Elhassan, GG Lavery, LE Quek, JF O'Sullivan, AM Philp, GA Wallis, and A Philp. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *J. Physiol.* 2021; 599: 1513–1531. DOI: https://doi.org/10.1113/JP280825
22. Williams J, V Tzortziou-Brown, P Malliaras, M Perry, and C Kipps. Hydration strategies of runners in the London marathon. *Clin. J. Sport Med.* 2012; 22: 152–156. DOI: https://doi.org/10.1097/JSM.0b013e3182364c45
23. Van Loon LJC, PL Greenhaff, D Constantin-Teodosiu, WHM Saris, and AJM Wagenmakers. The effects of increasing exercise intensity on muscle fuel utilisation in humans. *J. Physiol.* 2001; 536: 295–304.

DOI: https://doi.org/10.1111/j.1469-7793.2001.00295.x

24. Van Loon LJC, AE Jeukendrup, WHM Saris, and AJM Wagenmakers. Effect of training status on fuel selection during submaximal exercise with glucose ingestion. *J. Appl. Physiol.* 1999; 87: 1413–1420. DOI: https://doi.org/10.1152/jappl.1999.87.4.1413
25. Gnoni A, S Longo, G V. Gnoni, and AM Giudetti. Carnitine in human muscle bioenergetics: Can carnitine supplementation improve physical exercise? *Molecules* 2020; 25: 182. DOI: https://doi.org/10.3390/molecules25010182
26. Knapik JJ, RA Steelman, SS Hoedebecke, KG Austin, EK Farina, and HR Lieberman. Prevalence of Dietary Supplement Use by Athletes: Systematic Review and Meta-Analysis. *Sport. Med.* 2016; 46: 103–123. DOI: https://doi.org/10.1007/s40279-015-0387-7
27. Orrù S, E Imperlini, E Nigro, A Alfieri, A Cevenini, R Polito, A Daniele, P Buono, and A Mancini. Role of functional beverages on sport performance and recovery. *Nutrients* 2018; 10: 1–21. DOI: https://doi.org/10.3390/nu10101470
28. Peeling P, LM Castell, W Derave, O De Hon, and LM Burke. Sports foods and dietary supplements for optimal function and performance enhancement in track-and-field athletes. *Int. J. Sport Nutr. Exerc. Metab.* 2019; 29: 198–209. DOI: https://doi.org/10.1123/ijsnem.2018-0271
29. Kreider RB, CD Wilborn, L Taylor, B Campbell, AL Almada, R Collins, M Cooke, CP Earnest, M Greenwood, DS Kalman, CM Kerksick, SM Kleiner, B Leutholtz, H Lopez, LM Lowery, R Mendel, A Smith, M Spano, R Wildman, DS Willoughby, TN Ziegenfuss, and J Antonio. ISSN exercise and sport nutrition review: Research and recommendations. *J. Int. Soc. Sports Nutr.* 2010; 7: 1–43. DOI: https://doi.org/10.1186/1550-2783-7-7
30. Martel J, DM Ojcius, YF Ko, PY Ke, CY Wu, HH Peng, and JD Young. Hormetic Effects of Phytochemicals on Health and Longevity. *Trends Endocrinol. Metab.* 2019; 30: 335–346. DOI: https://doi.org/10.1016/j.tem.2019.04.001
31. Alexander Haslberger G, U Jacob, B Hippe, and H Karlic. Mechanisms of selected functional foods against viral infections with a view on COVID-19: Mini review. *Funct. Foods Heal. Dis.* 2020; 10: 195–209. DOI: https://doi.org/10.31989/ffhd.v10i5.707
32. Burke LM, GR Cox, NK Cummings, and B Desbrow. Guidelines for Daily Carbohydrate Intake. *Sport. Med.* 2001; 31: 267–299. DOI: https://doi.org/10.2165/00007256-200131040-00003
33. Harris RC, K Soderlund, and E Hultman. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin. Sci.* 1992; 83: 367–374. DOI: https://doi.org/10.1042/cs0830367
34. Hamada N, T Wadazumi, Y Hirata, H Watanabe, N Hongu, and N Arai. Effects of Trehalose Solutions at Different Concentrations on High-Intensity Intermittent Exercise Performance. *Nutrients* 2022; 14:. DOI: https://doi.org/10.3390/nu14091776
35. Jeukendrup A. *Sports Nutrition-From lab to Kitchen*. Meyer & Meyer Sport, February 1st, 2010
36. Ramos-Campo DJ, V Ávila-Gandía, FJ López-Román, J Miñarro, C Contreras, F Soto-Méndez, JCD Pedrol, and AJ Luque-Rubia. Supplementation of re-esterified docosahexaenoic and eicosapentaenoic acids reduce inflammatory and muscle damage markers after exercise in endurance athletes: A randomized, controlled crossover trial. *Nutrients* 2020; 12: 1–17 DOI: https://doi.org/10.3390/nu12030719
37. Thielecke F and A Blannin. Omega-3 fatty acids for sport performance—are they equally beneficial for athletes and amateurs? A narrative review. *Nutrients* 2020; 12: 1–28. DOI: https://doi.org/10.3390/nu12123712
38. Sivamaruthi BS, P Kesika, and C Chaiyasut. Effect of probiotics supplementations on health status of athletes. *Int. J. Environ. Res. Public Health* 2019; 16:. DOI: https://doi.org/10.3390/ijerph16224469
39. Heffernan SM, K Horner, G De Vito, and GE Conway. The role of mineral and trace element supplementation in exercise and athletic performance: a systematic review. *Nutrients* 2019; 11:. DOI: https://doi.org/10.3390/nu11030696
40. Krzywański J, T Mikulski, A Pokrywka, M Młyńczak, H Krysztofiak, B Frączek, and A Ziemba. Vitamin B12 status and optimal range for hemoglobin formation in elite athletes. *Nutrients* 2020; 12:. DOI: https://doi.org/10.3390/nu12041038
41. Karlic H and A Lohninger. Supplementation of L-carnitine in athletes: Does it make sense? *Nutrition* 2004; 20: 709–715. DOI: https://doi.org/10.1016/j.nut.2004.04.003
42. Surendran S, A Adaikalakoteswari, P Saravanan, IA Shatwaan, JA Lovegrove, and KS Vimaleswaran. An update on vitamin B12-related gene polymorphisms and B12 status. *Genes Nutr.* 2018; 13: 1–35. DOI: https://doi.org/10.1186/s12263-018-0591-9
43. Baffoni L, F Gaggìa, D Di Gioia, and B Biavati. Role of intestinal microbiota in colon cancer prevention. *Ann. Microbiol.* 2012; 62: 15–30. DOI: https://doi.org/10.1007/s13213-011-0306-6

44. Ganio MS, JF Klau, DJ Casa, LE Armstrong, and CM Maresh. Effect of caffeine on sport-specific endurance performance: A systematic review. *J. Strength Cond. Res.* 2009; 23: 315–324. DOI: https://doi.org/10.1519/JSC.0b013e31818b979a
45. Degnan PH, ME Taga, and AL Goodman. Vitamin B12 as a modulator of gut microbial ecology. *Cell Metab.* 2014; 20: 769–778. DOI: https://doi.org/10.1016/j.cmet.2014.10.002
46. Spriet LL. Exercise and Sport Performance with Low Doses of Caffeine. *Sport. Med.* 2014; 44: 175–184. DOI: https://doi.org/10.1007/s40279-014-0257-8
47. Woolf K and MM Manore. B-vitamins and exercise: Does exercise alter requirements? *Int. J. Sport Nutr. Exerc. Metab.* 2006; 16: 453–484. DOI: https://doi.org/10.1123/ijsnem.16.5.453
48. Whitham M, BL Parker, M Friedrichsen, JR Hingst, M Hjorth, WE Hughes, CL Egan, L Cron, KI Watt, RP Kuchel, N Jayasooriah, E Estevez, T Petzold, CM Suter, P Gregorevic, B Kiens, EA Richter, DE James, JFP Wojtaszewski, and MA Febbraio. Extracellular Vesicles Provide a Means for Tissue Crosstalk during Exercise. *Cell Metab.* 2018; 27: 237-251.e4. DOI: https://doi.org/10.1016/j.cmet.2017.12.001
49. Meeusen R and P Watson. Amino acids and the brain: do they play a role in “central fatigue”? *Int. J. Sport Nutr. Exerc. Metab.* 2007; 17 Suppl: 37–46. DOI: https://doi.org/10.1123/ijsnem.17.s1.s37
50. Fondell E, O Bälter, KJ Rothman, and K Bälter. Dietary Intake and Supplement Use of Vitamins C and E and Upper Respiratory Tract Infection. *J. Am. Coll. Nutr.* 2011; 30: 248–258. DOI: https://doi.org/10.1080/07315724.2011.10719967
51. Brouns F. Sports Nutraceuticals for Performance Enhancement: Are They Effective. *Wellbeing Perform.* 2003; 41.
52. Pickering C and J Kiely. Are the Current Guidelines on Caffeine Use in Sport Optimal for Everyone? Inter-individual Variation in Caffeine Ergogenicity, and a Move Towards Personalised Sports Nutrition. *Sport. Med.* 2018; 48: 7–16. DOI: https://doi.org/10.1007/s40279-017-0776-1
53. Cameron A and J Rosenfeld. Nutritional issues and supplements in amyotrophic lateral sclerosis and other neurodegenerative disorders. *Curr. Opin. Clin. Nutr. Metab. Care* 2002; 5: 631–643. DOI: https://doi.org/10.1097/00075197-200211000-00005
54. Sim M, LA Garvican-Lewis, GR Cox, A Govus, AKA McKay, T Stellingwerff, and P Peeling. Iron considerations for the athlete: a narrative review. *Eur. J. Appl. Physiol.* 2019; 119: 1463–1478. DOI: https://doi.org/10.1007/s00421-019-04157-y
55. Dalla Vecchia L, E Traversi, A Porta, D Lucini, and M Pagani. On site assessment of cardiac function and neural regulation in amateur half marathon runners. *Open Hear.* 2014; 1: 1–8. DOI: https://doi.org/10.1136/openhrt-2013-000005
56. Pearce EA, TM Myers, and MD Hoffman. Three Cases of Severe Hyponatremia During a River Run in Grand Canyon National Park. *Wilderness Environ. Med.* 2015; 26: 189–195. DOI: https://doi.org/10.1016/j.wem.2014.08.007
57. Yuan S, P Carter, M Vithayathil, S Kar, AM Mason, S Burgess, and SC Larsson. Genetically predicted circulating B vitamins in relation to digestive system cancers. *Br. J. Cancer* 2021; 124: 1997–2003. DOI: https://doi.org/10.1038/s41416-021-01383-0
58. Martarelli D, MC Verdenelli, S Scuri, M Cocchioni, S Silvi, C Cecchini, and P Pompei. Effect of a probiotic intake on oxidant and antioxidant parameters in plasma of athletes during intense exercise training. *Curr. Microbiol.* 2011; 62: 1689–1696. DOI: https://doi.org/10.1007/s00284-011-9915-3
59. Rawson ES, MJ Stec, SJ Frederickson, and MP Miles. Low-dose creatine supplementation enhances fatigue resistance in the absence of weight gain. *Nutrition* 2011; 27: 451–455. DOI: https://doi.org/10.1016/j.nut.2010.04.001
60. Strasser B, D Geiger, M Schauer, JM Gostner, H Gatterer, M Burtscher, and D Fuchs. Probiotic supplements beneficially affect tryptophan–kynurenine metabolism and reduce the incidence of upper respiratory tract infections in trained athletes: A randomized, double-blinded, placebo-controlled trial. *Nutrients* 2016; 8: 1–15. DOI: https://doi.org/10.3390/nu8110752
61. Leite GSF, AS Resende Master Student, NP West, and AH Lancha. Probiotics and sports: a new magic bullet? *Nutrition* 2019; 60: 152–160. DOI: https://doi.org/10.1016/j.nut.2018.09.023
62. Marttinen M, R Ala-Jaakkola, A Laitila, and MJ Lehtinen. Gut microbiota, probiotics and physical performance in athletes and physically active individuals. *Nutrients* 2020; 12: 1–39. DOI: https://doi.org/10.3390/nu12102936
63. Zeibig J, H Karlic, A Lohninger, R Dumsgaard, and G Smekal. Do blood cells mimic gene expression profile alterations known to occur in muscular adaptation to endurance training? *Eur. J. Appl. Physiol.* 2005; 95: 96–104. DOI: https://doi.org/10.1007/s00421-005-1334-3