



Protein and Sport: Alternative Sources and Strategies for Bioactive and Sustainable Sports Nutrition

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Nutrition and sport play an important role in achieving a healthy lifestyle. In addition to the intake of nutrients derived from the normal diet, some sport disciplines require the consumption of supplements that contribute positively to improved athletic performance. Protein intake is important for many aspects related to health, and current evidence suggests that some athletes require increased amounts of this nutrient. On the other hand, society's demand for more environmentally friendly products, focus on the search for alternative food sources more sustainable. This review aims to summarize the latest research on novel strategies and sources for greener and functional supplementation in sport nutrition. Alternative protein sources such as insects, plants or mycoproteins have proven to be an interesting substrate due to their high added value in terms of bioactivity and sustainability. Protein hydrolysis has proven to be a very useful technology to revalue by-products, such as collagen, by producing bioactive peptides beneficial on athletes performance and sport-related complications. In addition, it has been observed that certain amino acids from plant sources, as citrulline or theanine, can have an ergogenic effect for this target population. Finally, the future perspectives of protein supplementation in sports nutrition are discussed. In summary, protein supplementation in sports nutrition is a very promising field of research, whose future perspective lies with the search for alternatives with greater bioactive potential and more sustainable than conventional sources.

Keywords: sports nutrition, protein hydrolysates, alternative protein sources, bioactive peptides, amino acids

INTRODUCTION

Nutrition and sports play an important role in maintaining a healthy lifestyle (1, 2). Sports nutrition is a multidisciplinary science which includes fields such as anatomy, biomechanics, biochemistry, physiology and nutrition (3). The number of studies that found a relationship between sports and diet has increased over the last 20 years, and nowadays, there is no doubt about the essential role that nutrition plays in sport. In addition, nutrition should be adapted according to the characteristics of the sport, and the importance of the personalized nutrition in sport performance is being widely studied (4). Moreover, sports nutrition is one of the fastest growing segments of the functional foods and dietary supplement markets.

In addition to the intake of nutrients derived from the normal diet, some sport disciplines require the consumption of supplements that contribute positively to improve sports performance.

These supplements, known as ergogenic aids, are defined as substances used to improve endurance, total fitness level and sports performance (5). Some of them, as creatine, caffeine, bicarbonate, protein and amino acids, have been used for different purposes: to increase energy intake, to maintain strength, to recover muscular mass or to prevent nutritional deficiencies, among others (6–9). Two of the most marketed supplements in sports nutrition are proteins and amino acids. In fact, 80% of sports nutrition sales come from protein-based products, mainly in bars and powder formats (10), although the development of functional protein beverages is playing an important role in recent years (11). On the other hand, the current demand for more environmentally friendly products has increased research into more sustainable alternative sources of protein (10).

The purpose of this review was to summarize the latest research regarding novel strategies for protein supplementation in sports nutrition, focus on alternative protein sources (insects, plant-based and mycoproteins), highlighting its added value provided in terms of bioactivity and sustainability. The benefits of protein hydrolysates and bioactive peptides on athlete's performance, sports-related complications and healthy aging and the ergogenic effects exerted by novel amino acids obtained from natural sources were also discussed. Furthermore, future perspectives for protein supplementation in sports nutrition are addressed.

PROTEINS

Proteins are a key macronutrient to maintain a good nutrition and health status, and necessary for the proper functioning of the organism. Among these functions, proteins ensure growth in childhood, support muscle and bone metabolism, contribute to the maintenance of the nervous system and help to maintain muscle mass and physical performance in later life (12). Net protein balance (NPB) is defined as the difference between skeletal muscle protein synthesis (MPS) and muscle protein breakdown (MPB). Therefore, a significant increase in skeletal MPS (anabolism) and/or decrease in MPB (catabolism) can lead to an increase in skeletal muscle mass (13). An adequate intake of proteins in the diet is important for maintaining a good health condition, and current evidence has suggested that athletes of some sport disciplines need to consume greater amounts of protein. Generally, athletes require higher amounts of high-quality protein in their diet (1.2–2.0 g/kg/day) compare to non-athletic adults (0.8–1.0 g/kg/day) and, in particular, rich in branched-chain amino acids (BCAAs), to stimulate MPS and promote a positive protein balance (8, 14). Leucine, Valine, and Isoleucine constitute the group of branched-chain amino acids (BCAAs). Around 33% of the skeletal muscle is composed of a combination of these three essential amino acids (15). Unlike other essential amino acids, BCAAs are metabolized directly in the muscle tissue and they are the first energy source used during exercise (16). In addition, these amino acids, specially leucine, promote insulin secretion, reduce central fatigue, decrease muscle soreness and mainly increase MPS by

the activation of the mammalian target of rapamycin (mTOR) pathway (17).

In nutrition, the term “protein quality” focuses on the relative composition of amino acids present in a protein source compared to a protein pattern that is considered to represent the highest quality protein (18). The Food and Agricultural Organization of the United Nations/World Health Organization (FAO/WHO) and FDA first proposed a protein quality evaluation method in 1991, the Protein Digestibility-Corrected Amino Acid Score (PDCAAS), which became the official standard in 1993. Although they included the relevance of the digestibility in the score, it also depends on numerous factors, including the amino acid absorption kinetics and the capacity of the particular dietary protein to stimulate protein synthesis in the organism (19). Consequently, in 2013, FAO proposed a new evaluation method, the Digestible Indispensable Amino Acid Score (DIAAS). This score is a more accurate rating of protein quality. Furthermore, DIAAS samples come from the ileum, while PDCAAS samples come from feces. If there are no amino acids in the feces samples, the PDCAAS method assumes digestion. But the DIAAS samples from the ileum are a more accurate representation of amino acid digestion and absorption (20).

In the last decades, the most commonly used food protein sources in sports nutrition have been milk, egg and meat (10). All of them are considered foods with high-quality protein. Moreover, ovalbumin, a protein from egg white, has been used as standard for comparing other dietary proteins (21) due to its complete amino acid profile and its excellent digestibility, followed by whey protein (15). Worldwide, whey protein is the most consumed protein as a supplement in sports nutrition. This protein, obtained as a by-product in the production of cheese and butter, is very interesting both, economically, since it is considered a cheap by-product, and nutritionally, as a high-quality protein with a notable content in essential amino acids and BCAAs (22). There are numerous studies that prove its efficacy in sport performance, such as muscle recovery (23, 24), increment of strength or changes in body composition (25). In addition, whey proteins have shown several biological properties such as antioxidant, anticancer, antidiabetic, anti-obesity or cardioprotective activities, among others (26). These multiple benefits support whey protein as an effective sports supplement. However, the current growth of the world's population, combined with increasingly limited resources, has resulted in the need for alternative protein sources to meet global protein requirements, including sports nutrition (27).

Insect Proteins

Insects, belonging to the largest class of phylum *Arthropoda*, are small animals with segmented bodies, jointed legs, and exoskeletons. This animal group includes more than a million of species and represents more than half of all known living organisms (28). Insects are institutionally accepted as food in many regions and historically consumed (29) providing an interesting nutritional value for humans (30). Worldwide, the most consumed species of insects have been studied to determine their nutritional value and organoleptic properties. In fact, the European Regulation 2015/2283 on new foods, entered into force

in January 2018, and allowed the sale of insects at a commercial level for their use and consumption in the European Union (31).

In last decade, insects have been considered one of the most environmentally friendly sources of animal protein, as its carbon and water footprint is very low (32). The insects that are most commonly used as food are species belonging to the order *Coleoptera* (beetles), *Lepidoptera*, *Hymenoptera* and *Orthoptera* (32). In general, these insects contain large amounts of chitin, an insoluble polysaccharide composed of N-acetylglucosamine units, belonging to its exoskeleton. They also provide high levels of vitamins and minerals as well as an excellent production efficiency compared to other conventional food sources (33). Insects have a high protein content (40–60%) comparable to traditional animal protein sources as egg, milk or meat (34). In addition, they have a good amino acid profile, with an average in most of the EAAs and BCAAs higher than the recommended by the World Health Organization (WHO) (35, 36). Moreover, the average leucine content, one of the most important BCAA due to its role as a stimulator of muscle protein synthesis (37), is higher in *Coleoptera*, *Hymenoptera*, *Isoptera* and *Orthoptera*, than soy (63 mg leucine/g soy protein to 75–80 mg leucine/g insect protein) and comparable to skim milk powder (77 mg/g protein) and micellar casein (82 mg/g protein) (34, 36). Furthermore, proteins from insects have relatively high digestibility, with values among 54% for *Tenebrio molitor* (*Coleptera*) (38) to 90.5% for grasshopper (*Orthoptera*) (39). However, this parameter depends on their composition and how insects are processed. In this regard, presence of chitin can have a negative effect on digestibility (39). Therefore, the final product should reduce the chitin levels as much as possible, in order to achieve an optimal protein digestibility (34).

Although there are not many studies that relate insect protein consumption and sports, some of them have shown promising results. Vangsoe et al. (40), conducted a randomized control trial in which they compared the effect of 25 g of whey, soy or insect protein isolates on the postprandial increase of amino acids in blood of athletes. They observed that insect protein isolate intake raised blood EAAs and BCAAs concentrations similar to soy protein isolates, suggesting that they could be used as alternative source for MPS (40). These authors also reported in other study that insect protein isolate supplementation (0.8 g/kg) exerted an increase in fat free mass and muscle strength after 8 weeks of resistance training. However, these differences were not significant with the control, suggesting that the doses of insect protein isolate used should be higher (41). More recently, Hermans et al. (42), conducted a double-blind randomized controlled trial in which they compared the ergogenic effects of 30 g of lesser mealworm protein isolates with 30 g of milk protein isolates. Lesser mealworm protein consumption increased the post-prandial muscle synthesis rate both at rest and during exercise recovery, in a similar way to the results observed for milk protein. These results suggest that lesser mealworm protein can exert an ergogenic effect similar to that of a traditional high biological value protein, such as milk protein (42).

Overall, insect protein isolates could become an alternative ingredient for post-exercise recovery nutrition in sports products, since they are considered a high-quality protein source, due to

their amino acid profile and digestibility. However, it would be convenient to study the environmental impact of its isolates, since chitin is produced as a by-product, thus being a non-zero waste product.

Plant-Based Proteins

The evidence on the benefits of some animal proteins in sport performance has already been proven. Nevertheless, the demand for clean-label, non-allergenic and plant-based products is increasing. Sustainability, animal welfare and ethics-related concerns are driving the demand for new alternatives to animal proteins (43, 44). A well-designed vegan diet could provide enough energy and an adequate range of carbohydrate, fat and protein intake to support performance (45). In fact, it seems that some plant-based proteins could be as effective as animal-based proteins for muscle maintenance, providing all the essential amino acids (46).

In recent years, several human trials have been conducted using plant proteins as sport supplements with promising results. These studies are compiled in **Table 1**. In general, vegetable protein supplementation provides similar ergogenic effects to those generated with animal protein, as an increase in strength (50), an improvement in MPS (48, 52) or a reduction in body fat mass (51). However, the anabolic response in most of them, with the exception of soybean (53), was lower than the reported with whey protein. This fact is mainly due to the amino acid composition of vegetable proteins. Plant-based proteins are characterized by a lower bioavailability and a lower content of EAA and BCAA than traditional animal proteins, as whey or egg proteins (27). Moreover, it has been proven that some vegetable proteins mainly from legumes, as pea or soy protein, do contain the WHO recommended percentage of EAA (35). The physical and chemical composition of the food matrix and the structure of its proteins make vegetables a source of protein more resistant to proteolysis, which leads to a reduction in digestibility. Therefore, the isolation of these proteins to include in other food matrix or the use of different processing methods or culinary preparations could help to increase its digestibility (54). In fact, food products based on these proteins, such as tofu or soy milk, are currently one of the most marketed products as substitutes for animal-based foods and it has recently been observed that its digestibility is higher than that starting raw material (55). It is important to note that in addition to their deficiency in certain amino acids, vegetable proteins can be reduced in quality due to the presence of anti-nutrients. Anti-nutrients are substances with no nutritional value that have several effects on the body. Among them, those that most affect protein digestibility and bioavailability are the protease inhibitors, as the Kunitz or Bowman Birk. Both compounds, present in legumes such as soybeans, reduce the effect of trypsin in the organism, causing a decrease in the digestion consumed proteins (56). However, there are certain simple strategies, such as soaking or heat treatment that significantly reduce these anti-nutrients. Moreover, it has recently even been observed that techniques well suitable to the production of sports supplements, such as wet extrusion, are also very effective in eliminating these anti-nutritional factors (57).

TABLE 1 | Summary of plant-based proteins clinical studies in sports nutrition.

Type of trial	N° participants	Source	Samples	Protein dose and timing	Trial period	Remarkable effects	References
1 Double-blind, randomized, placebo-controlled trial	40 trained males	Soybean	Target: Soybean protein Placebo: Aspartame	50 g/day After training in two times	4 weeks	↓ Muscle damage compared to placebo (CP) ↓ Oxidative stress increment CP ↑ Muscle recovery CP	(47)
2 Double blind, randomized, single dose, parallel-group trial	60 healthy old men	Wheat	Target: Wheat protein Control 1: Casein Control 2: Whey protein	35 g/day (controls) 60 g/day (Target) After the trial	1 day	↑ Myofibrillar protein synthesis No significant differences with the positive control (NSD)	(48)
3 Double-blind, randomized, placebo-controlled trial	16 healthy untrained men	Oat	Target: Oat protein Placebo: Maltodextrin	25 g/day Before training Consecutive 4 days after training	19 days	↓ Muscle soreness CP ↓ Inflammation markers CP ↑ markers Recovery CP	(49)
4 Double-blind, randomized, comparative trial	15 athletes	Pea	Target: Pea protein Control: Whey protein	24 g/day Before and after training	8 weeks	↑ Muscle strength NSD	(50)
5 Double-blind, randomized, prospective, two-group parallel-arm trial	48 untrained people	Soybean	Target: Soybean protein Control: Whey protein	26 g/day (Target) 19 g/day (Control) After training	12 weeks	↑ Muscle strength ↓ Fat body mass NSD	(51)
6 Double blind, randomized, single dose, parallel-group trial	36 healthy untrained men	Wheat	Target: Wheat protein Control: Milk protein	30 g/day After the trial	1 day	↑ Myofibrillar protein synthesis NSD	(52)

Although protein quality is generally lower in plants than in animals, there are other reasons to choose them as sports supplements. In this sense, several studies affirm that diets rich in vegetables contribute to reduce oxidative stress and inflammation (54, 58). Oxidative stress is the consequence of an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense. This adverse condition can cause serious tissue and cellular damages and it is related to many disorders such as inflammation, cardiovascular diseases, and cancer (59). The relationship between exercise and oxidative stress is extremely complex. Since regular moderate training seems to be beneficial for health, it has been described that acute exercise increases oxidative stress and ROS production *via* lipid peroxidation, superoxide anion generation and incrementation in oxidized/reduced glutathione (GSSG/GSH) ratio (59–61). The increment of ROS can generate an overproduction of proinflammatory cytokines, which can lead to muscle fragility by reducing myofibrillar protein synthesis and increasing protein catabolism, leading into a negative impact on sport performance. In addition, this effect can be cyclical, generating a chronic problem (62). In this context, oral antioxidant supplementation could be a suitable non-invasive tool to prevent or reduce oxidative stress during training (63), and plant protein sources could be used for this purpose (47, 49, 60, 64, 65). In this regard, polyphenols, such as avenanthramides (66), carob phenols (67) or soy isoflavones (65) including in vegetable foods, could promote the reduction of inflammation and oxidative stress. They could be beneficial for athletes to maintain their health status after sports performance.

Besides polyphenols, proteins from plants also contain several bioactive compounds that could contribute positively to improve the performance in sportspeople. In this sense, β -conglycinin, a storage protein from soybean, improved glucose uptake in skeletal muscle (68). In addition, β -glucans from oats, a soluble dietary fiber, could contribute to the maintenance of plasma glucose levels (69).

Taken together, research into the use of plant protein sources as sports supplements could be very interesting, as they could become an ergogenic, sustainable and value-added products for athletes, especially for those who exercise intensively, due to its contribution to reducing oxidative stress.

Mycoproteins

Other protein sources could also offer several benefits as sports supplements are mycoproteins. Mycoproteins are a sustainable food source derived from different species of fungi, mainly *Fusarium venenatum* (70). In relation to their nutritional value, mycoproteins are rich in dietary fiber (β -glucans and chitin), present high-quality proteins (~45% of total mass) and a biological value similar to traditional meats (84 vs. 80%). Moreover, mycoproteins are rich in essential amino acids (41% of total protein) and possess a high digestibility (0.99), similar to animal protein sources as milk (71, 72).

In the last decade, mycoproteins have emerged as an environmentally friendly and cheap source, since it can be synthesized with agronomical by-products and its carbon footprint is, at least, 10 times lower than traditional meats

(73). Furthermore, mycoproteins appeared not to be potentially allergenic (74) and they could exert benefits related to sports nutrition and cardiometabolic health, such as insulinemia and glycemia attenuation and muscle adaptation (72).

In recent years, several authors analyzed the possible ergogenic effect of mycoproteins in sports nutrition. In this sense, Dunlop et al. (75), compared the effect between 20 g of whole food mycoproteins and 20 g of milk protein concentrate intake on acute postprandial hyper aminoacidemia and hyperinsulinemia, to analyse their anabolic effect, which is directly related to these two parameters. These authors concluded that mycoprotein ingestion resulted in a slower but more sustained hyperinsulinemia and hyper aminoacidemia compared to milk protein ingestion. Moreover, it means that mycoproteins could be a useful dietary protein source with an noticeable anabolic effect in muscles (75). More recently, Monteyne et al. (76), performed a randomized controlled trial, in which they compared the ergogenic effect that a simple 70 g bolus of whole food mycoproteins or leucine-enriched milk protein could have on athlete's MPS. The results showed that mycoproteins exerted a higher postprandial induction on protein synthesis (0.040 ± 0.006 %/h) than leucine enriched milk proteins (0.018 ± 0.005 %/h), regardless of their consumption before or after training. This research indicates that this source of proteins could have a superior anabolic effect than traditional proteins used in sport supplements (76). These authors also investigated whether a simple bolus with a lower whole food mycoprotein content (35 g) enriched with BCAAs could exert the same effect as a simple 70 g bolus of whole food mycoprotein. They found that a higher dose of mycoproteins (70 g) stimulated muscle synthesis more than a lower dose (35 g) supplemented with BCAAs (77). Finally, these authors conducted a study in which they aimed to determine whether a vegan diet supplemented with mycoproteins could maintain MPS in a similar way to an omnivorous diet. Their results showed that a vegan diet high in mycoproteins contributed to maintaining daily rates of muscle protein synthesis rates both at rest and after exercise, equivalent to a high-protein omnivorous diet in healthy older adults (78).

In summary, mycoproteins have proven to be a very interesting protein source for sports nutrition, due to their remarkable anabolic effect on MPS, equivalent to that of traditional sources such as milk. In addition, they are very sustainable, since in most studies they have demonstrated their effect without being isolated, which makes them an environmentally friendly protein source that does not generate waste, since the whole food is consumed.

HYDROLYSATES AND PEPTIDES

Protein hydrolysates are a complex mixture of peptides, mainly di- and tripeptides, whose production is based on the cleavage of the structure of protein sources by thermal, acid, or enzymatic treatment. Their composition depends on several factors and can be defined by the degree of hydrolysis, which is the fraction of peptide bonds that have been cleaved in the native

protein (79). It is generally accepted that protein hydrolysates containing mostly di- and tripeptides are absorbed faster than intact proteins (80).

In sports nutrition, hydrolysates could be advantageous over native proteins because they are pre-digested. Therefore, their peptides and amino acids could be available to the muscle more rapidly after ingestion. The increase of amino acids in plasma after ingestion of protein hydrolysates can result in a stronger stimulation of MPS compared to the whole protein (80).

In recent years, some studies confirm the hypothesis that hydrolysates seem to generate a faster muscle recovery effect than intact proteins (81, 82). It seems to be related to an increase in the bioavailability of amino acids, especially BCAA and EAA, as they have a positive effect on MPS (83). This increase in the bioavailability of amino acids is due to the fact that since they are pre-digested, the release of amino acids in the intestine is greater. In addition, it seems that peptides, especially di- and tripeptides, can be absorbed through specific transporters, leading to an even greater increase in blood aminoacidemia (84). Apparently, this hyper aminoacidemia also seems to be related to a possible thermogenic effect, which could have beneficial effects in athletes to reduce their fat body mass. Although further research is needed to confirm all these effects (85, 86). Other beneficial effects of protein hydrolysates on sport performance could be related to the generation of bioactive peptides. Bioactive peptides are defined as amino acid sequences that are not active in the precursor protein structure but that can exert physiological functions in the organism after their release through *in vivo* (gastrointestinal digestion) or *in vitro* hydrolysis (chemical or enzymatic). Since bioactive peptides were discovered in 1979, different biological activities have been described as antioxidant, antimicrobial, opioid, immunomodulatory, anti-inflammatory, antihypertensive, antidiabetic or hypocholesterolemic, among others (87, 88). In this sense, some studies reported that certain bioactive peptides may exert a positive effect on muscle glucose uptake and glycogen restore by activating insulin-independent AMP-activated protein kinase signaling in skeletal muscle cells (89, 90). Moreover, endogenous insulin appears to exert a positive effect on MPS due to their vasodilator effect by stimulating endothelial nitric oxide production, and increasing skeletal muscle glucose uptake (91). On the other hand, insulin has a similar structure to insulin-like growth factor-1 (IGF-1). IGF-1 is a hormone capable of exerting an anabolic effect on skeletal muscle. Therefore, insulin may simulate this effect (92). Some bioactive peptides could also increase plasma concentrations of glucose-dependent insulinotropic polypeptide, which implies an enhancement of insulin release from pancreatic beta cells (93). In fact, the greater insulinotropic effect observed after consumption of protein hydrolysates compared to intact proteins could explain their increase in MPS rate (94).

Other biological activities related to protein hydrolysates or their bioactive peptides such as antioxidant, immunomodulatory or anti-inflammatory properties could be especially useful to control sport performance and some complications derived from sport practice. Some of them are explained in detail below.

Protein Hydrolysates in Joint Soreness

Strenuous exercise, especially in high-impact sports, can lead to a continued joint pain in athletes, and can affect negatively in their performance (95). Collagen is the most abundant animal protein and it is present in the connective tissue of animals, being generally a by-product of the meat industry (96). This protein is often used in comparative studies to observe the impact of protein quality on muscle recovery, being used as a negative control due to its low biological value (96, 97). However, the hydrolysis of this by-product has become a sustainable way to revalue it. In this sense, researchers have investigated the effect of specific collagen peptides (SCP) by their biological properties (98, 99), some of them related to joint soreness. Clark et al. (100), pioneered the analysis of the effect of SCP supplementation in sportsmen's joint soreness. A 24-week prospective, randomized, placebo-controlled, double blind study was conducted with 147 athletes. They consumed 10 g of a collagen hydrolysate or placebo. The results showed that a daily treatment of 10 g of a collagen hydrolysate was able to reduce joint discomfort, both at rest and during movement (100).

More recent studies have also noted the possible positive effects of these collagen derived peptides. Exercise combined with 15–20 g of collagen hydrolysates, preferably after training, for over a week, leads to an improvement in lean body mass, and reduces joint and muscle pain in athletes and physically active people (101–106). The mechanisms by which the collagen peptides exerted their effect have not yet been elucidated. However, it has been suggested that faster remodeling of affected tissues could be related to an increase in collagen synthesis in the connective tissues surrounding the muscle and/or to a modulation of the inflammatory response (107). The main limitation of human studies is that, it is often difficult to establish the mechanism of action because it is complicated to take muscle biopsy samples, analyse biomarkers or explore the signaling pathways in the tissues. Nevertheless, some authors have studied the effect of exercise and collagen peptide supplementation, using proteomic techniques on muscle biopsies. They found that some proteins, such as Collagen 5 α 1, associated to myofibrillar recovery, are upregulated, so this could explain the positive effects mentioned above (108, 109).

In summary, the consumption of collagen hydrolysates could represent an environmentally friendly strategy to reduce joint pain in high-performance athletes.

Anti-fatigue Hydrolysates and Peptides

Fatigue is defined as a reduction in the maintenance of physical conditions such as power and strength, which impairs physical performance. The main causes of fatigue include: increased acidity in the muscle cells, depletion of energy sources such as phosphocreatine and glycogen, accumulation of ammonia and urea in the blood and tissues, oxidative stress and muscle inflammation (107, 110). Fatigue is a factor that should not be underestimated in sports nutrition. This condition, prolonged over time, can lead to the development of chronic fatigue syndrome, which not only affects athlete's performance, but his or her health may also be affected (111).

In recent years, it was observed in the literature that certain by-products from natural sources could be substrates to produce anti-fatigue peptides. These studies are summarized in **Table 2**. In general, most of these studies were conducted with murine models, in which the anti-fatigue effect of the peptides was assessed by a weight-loaded swimming test. The reduction in fatigue was reflected externally by the improvement in the time that mice can swim without becoming exhausted (115). In general, the studies referenced in **Table 2** showed that the consumption of a certain amount of protein hydrolysates (200–600 mg/day) before training, and for a 4-weeks period, could lead to a very noticeable improvement in the time to exhaustion, being in several cases higher than 100%, and even better than traditional protein sources such as whey from milk (114).

The mechanism of action of anti-fatigue peptides can be investigated by analyzing several biomarkers. Depletion of glycogen stores in muscle and liver results in a reduction of available blood glucose, leading to hypoglycaemia and fatigue (118). Therefore, maintenance of glycogen content may result in decreased fatigue generation. According to **Table 2**, anti-fatigue peptides could induce glycogen turnover through activation of glycogen synthase in skeletal muscle and improve blood insulin levels (116). Moreover, it has been postulated that some of these peptides upregulated the AMPK signaling pathway (117, 119), which could induce an increase of the fat catabolism (120). Glycerol is produced by lipolysis and could act positively as a direct substrate for gluconeogenesis, enhancing the regeneration of glycogen in liver and muscle (121). In certain situations, proteins can be used as energy source and urea is the main metabolite from protein catabolism and one of the main blood biomarkers of fatigue (122). This compound is produced in the liver, transported to the kidney and then excreted in the urine. The results of different assays showed that the peptides did not promote urea excretion, suggesting that preservation of glycogen storage could be the reason for the decrease in blood urea levels. Therefore, it suggests that the maintenance of glucose prevents the consumption of muscle protein as an energy substrate (116). The main metabolite of anaerobic catabolism of glucose is lactic acid. This compound in excess can lead to a reduction in muscular endurance through acidosis, that is one of the main causes of fatigue in the human body (123). According to some authors, referred to in **Table 2**, these peptides could also increase the lactate dehydrogenase activity, which catalyzes the formation of pyruvate from lactic acid, leading to a reduction in lactic acid, and thus a possible reduction in fatigue (112).

Other important factor related to fatigue is oxidative stress. In this situation, it seemed that anti-fatigue peptides could act as antioxidant agents. They can act by reducing blood oxidative stress biomarkers, such as malonaldehyde (MDA) and by improving the activity of antioxidant enzymes (113, 121), such as superoxide dismutase (SOD), which removes oxygen radicals in the organism, and glutathione peroxidase (GSH-Px), that contributes to the elimination of peroxides *in vivo* (124). The increase in SOD and GSH-Px activities could also reduce oxidative stress, cell membrane and muscle fibers damage by the reduction in ROS, allowing an increase of training time without exhaustion (113, 125). There is also a correlation between fatigue

TABLE 2 | Summary of anti-fatigue peptides studies in rodent's model.

Source	N° subjects	Samples	Dose and timing	Increase of time of exhaustion ^b	Effects	References	
1	Croceine Croaker	48 mice	Control:physiological saline Sample: Croceine croaker bladderhydrolysate.	Control: 0.1 mL/10 g Body Weight (BW)/day Sample: 50 mg–200mg/kg BW/day 30 min before exercise 28 days	57.9% - (16 min → 25.4 min) 107.5% - (16 → 33.4 min)	↑Antioxidant enzymes ↓BUN, BLA, BOSB ^a ↑ Muscle glucose ↑Glycogen restore	(112)
2	Manchurian walnut	100 mice	Control: Deionized water Sample: Manchurian Walnut hydrolysate	Control: <i>Ad libitum</i> Sample 800 mg/kg BW/day 30 min before exercise 28 days	78.43%-(51 → 91 min)	↑Antioxidant enzymes ↓BUN, BLA, BOSB ↑ Muscle glucose ↑Glycogen restore Immunomodulatory	(113)
3	American Ginseng	240 mice	Control 1: Distilled water Control 2: Whey protein Sample: Gingseng peptides	Control 1:0.1mL/g BW/day Control 2: 450 mg/kg BW/day Sample:225–900 mg/kg BW/day 30 days	Control 2 (15min) 35.24%- (14 → 19.93 min) 82.62%- (14 → 25.5min)	↑Antioxidant enzymes ↓BUN, BLA, BOSB ↑ Muscle glucose ↑Glycogen restore ↑ Mitochondrial function	(114)
4	Egg	30 mice	Control 1: Casein Control 2: Egg White protein Sample: Egg white hydrolysate	Controls and sample: 20% of its diet 14 days	90.9%-(2.2 → 4.2 min)	↑Antioxidant capacity	(115)
5	Pea	150 mice	Control 1: Distilled water Control 2: Pea protein isolate Sample: Pea peptides	Control 1: mL/g BW/day Control 2: 200 mg/kg BW/day Sample: 100–400 mg/kg BW/day 30 days	Control 1: 22.3%- (10.41 → 12.73 min) 66.5%- (10.41 → 17.3 3 min) Control 2: 12.9%- (11.28 → 12.73 min) 53.6%- (11.28 → 17.33 min)	↑Antioxidant enzymes ↓BUN, BLA ↑ Muscle glucose ↑Glycogen restore Immunomodulatory Anti-inflammatory	(116)
6	Spirulina	80 mice	Control: Distilled water Sample: Spirulina peptides	Control: mL/g BW/day Samples:125–2,000 mg/kg BW/day 28 days	177.7%- (20 → 55.54 min) 264.9%- (20 → 72.98 min)	↑Antioxidant enzymes ↓ BLA ↑ Fat catabolism	(117)

^aBody weight (BW), Blood Urea Nitrogen (BUN) Blood Lactic Acid (BLA), Blood Oxidative stress biomarkers (BOSB).

^bIncrease of time of exhaustion: In comparison with control group. In the case that two values appear, the first one coincides with the group that consumed the lowest dose of hydrolysate and the second one with the highest dose of hydrolysate.

and the immune system. When the body feels depleted, the action of the immune system is often reduced, resulting in increased vulnerability to disease (126). In this context, some peptides could enhance immune response by increasing the concentration of phagocytes and IgA, which represent the first-line defense. These peptides also decreased the levels of proinflammatory cytokines IL-6 and TNF- α , which could help maintain normal immune system function, and could have a positive impact on reducing fatigue, because if there is less inflammation in muscle fibers, this body tissue could work longer without soreness (116, 127).

Although in most cases animal studies have been performed to analyse the effect on the reduction of physical fatigue, some human studies have also been carried out. Oe et al. (128), performed a randomized, double-blind, controlled trial, to evaluate the ability of peptides from an egg white hydrolysate (EWH) on mental fatigue in athletes. The results showed that the 2-week intake of 5 g/day of EWH 1 h before exercise, induced a significant reduction in mental fatigue compared to a placebo group (128). According to the authors, it seemed that the mechanism involved in this effect is associated with the promotion of nitric acid-related signaling (128, 129).

In summary, anti-fatigue peptides obtained from natural sources may be a very interesting supplement to increase the performance time of an athlete, being especially interesting in endurance sports. However, further studies in humans are needed to confirm this effect.

Protein Hydrolysates in Sports Rehabilitation

An adequate and balanced diet is very important in recovery and rehabilitation. Specialized nutrition for recovery from injury in athletes follows similar dietary patterns to those of general sports nutrition, except for differences concerning the risk prevention of reduced anabolic sensitivity, sarcopenia, malnutrition or dysphagia, among others (130). Reduced anabolic sensitivity could be defined as the reduction of the MPS produced by several factors, such as aging, decreased in physical activity (131), reduced insulin sensibility or attenuation of aminoacidemia (132). If left untreated, this complication can lead to sarcopenia. Sarcopenia is a condition characterized by extreme muscular failure due to a reduction in the quality and quantity of skeletal muscle tissue (133). This disorder may also be related to inflammation (134), malnutrition related to loss of appetite (135) and oxidative stress (136). An increase in protein intake (137), and physical exercise (138) are the main recommendations to reduce the effects of this condition. Recently, it has been observed that protein sources such as fish (139) or whey (140) could give very promising results in the production of hydrolysates for the treatment of sarcopenia. In fact, protein hydrolysates could be considered a very beneficial supplement for subjects with this condition. On the one hand, their insulinotropic effect and their increase in aminoacidemia could facilitate, with a lower dose than intact proteins, the MPS of their muscles, despite anabolic resistance. On the other hand, the bioactive peptides generated after hydrolysis could exert an anti-inflammatory and

antioxidant effect, reducing the risk generated by oxidative stress (141). Finally, another advantage of hydrolysates is that, being pre-digested, they may have a smooth texture that could be easier to swallow (142). This property could help protein intake in patients with dysphagia and mouth and throat problems, disorders closely related to aging (143).

In conclusion, hydrolysates have demonstrated several advantages over intact proteins, such as a higher speed in the MPS or the production of peptides with specific bioactivities that could act from a multifunctional point of view, in the improvement of sport performance and their related disorders.

AMINO ACIDS

In previous sections, it has been noted that the amino acids are responsible for several benefits attributed to proteins in sports nutrition. Among the amino acids, the most studied and the most consumed as supplements are BCAAs (leucine, valine and isoleucine), glutamine and β -alanine (144).

In recent decades, the study of the ergogenic effect of amino acids present in vegetable sources has increased, with citrulline and theanine being the most outstanding.

L-citrulline is a non-essential amino acid found mainly in watermelon (145). In the last decade, it has been observed that this amino acid could exert an ergogenic effect through two main pathways. L-citrulline is a potent endogenous precursor of L-arginine which acts as a precursor of nitric oxide (NO) (146). NO has numerous functions in the body, the most prominent being its vasodilator effect, which increases blood flow to the muscle, thereby increasing the bio accessibility of nutrients and the excretion of muscle waste products (147). On the other hand, citrulline is an intermediary metabolite of the urea cycle, which exerts an anti-fatigue effect by enhancing the excretion of ammonia produced by muscle catabolism during strenuous exercise (148). The reduction of ammonia levels in muscle could be reflected in a reduction of muscle glycolysis and lactate production (149). In recent studies, citrulline appears to show other ergogenic effect such as antioxidant capacity, immunomodulation, energy production and increase of MPS (150–152).

Theanine is an amino acid whose main source is green tea, and it is responsible for its characteristic flavor (153). This amino acid has demonstrated numerous beneficial properties, highlighting its high antioxidant and antihypertensive capacity (154). Regarding its ergogenic effect, it has been observed that theanine could improve movement accuracy (155) and possibly exerts an immunomodulatory and anti-inflammatory effect by contributing to the balance of th1/th2 leukocytes (156, 157). On the other hand, the demands of training and performance can be a source of stress and anxiety for elite athletes, and can negatively affect their health (158). Recently, it has been analyzed that theanine could exert a relaxing effect, reducing stress levels by blocking pro-stress glutamine signaling and increasing alpha waves in the brain (159). All this could indicate that theanine could exert a very interesting positive effect on stress reduction in athletes.

In summary, these alternative amino acids from plant sources could have a fundamental role in sports nutrition for their effect on many functions related to exercise.

EMERGING STRATEGIES AND FORTHCOMING RESEARCH

Protein Blends

In the previous sections, it has been shown that each protein source contains a different set of beneficial properties. Therefore, it is possible to think that a blended protein supplement can potentially provide greater benefit by combining their ergogenic effects (160). Several studies have evaluated the effect of soy-dairy or vegetable-dairy protein blend supplementation in athletes. The hypothesis was that the ergogenic effect could be improved by combining the MPS-enhancing capacity of whey with the antioxidant and anti-inflammatory activity of soy and other plant-based proteins (161). The results showed that vegetable-dairy protein blends could exert ergogenic effects such as a reduction of fatigue (162), a slight enhancement of lean body mass (163) or an equal increase of MPS and more balanced post-prandial amino acid availability compared to whey (52, 164, 165). In general, vegetable proteins are deficient in certain essential amino acids, such as methionine in pulses, and cysteine and lysine in cereals (27). Protein blends could also be a promising solution to improve the quality of vegetable protein and favoring a greater ergogenic effect (166). In this regard, Brennan et al. (167), compared the effect of plant-based protein mixtures to whey protein. The results indicated that plant protein mixtures were not bioequivalent to whey protein, although they observed a faster increase of blood hyper aminoacidemia than individual vegetable proteins (167).

Thus, protein mixtures are an interesting line of research, as the combination of the ergogenic effects of different protein sources could be beneficial in sports supplementation.

Probiotic and Protein

As we previously described, proteins have many benefits for athletes. However, a high protein intake together with exercise could induce oxidative stress, that could have a negative impact on the gut microbiota (13, 168). The intestinal microbiota contributes to the regulation of host physiological processes and plays a key role in the maintenance of intestinal homeostasis, nutrient absorption and the synthesis of bioactive metabolites such as EAA, short-chain fatty acids and vitamins (169). It has been observed that dietary proteins can exert a regulatory effect on the production of these beneficial metabolites, so an excess in protein intake can lead to adverse effects, generating a mismatch in the gut microbiota (170).

The negative effects of high-protein diets on the microbiota might be reduced by two strategies: the addition of prebiotics or probiotics. According to International Society of Sports Nutrition (ISSN), probiotics might also contribute positively to the improvement of athlete's health by increasing the integrity of the gut-barrier function, enhancing its immune system or

reducing muscle damage (171). In this context, Jäger et al. (172), observed that the probiotic *Bacillus coagulans* GBI-30, 6,086 improved the absorption of proteins and amino acids (172). Therefore, they decided to evaluate its *in vitro* and *in vivo* synergistic effects in conjunction with plant-based proteins in athletes. In this trial, it was observed that the absorption rate of amino acids was higher than the absorption in the placebo group. It was considered that this effect could happen due to the proteolytic enzymes contained in the probiotics, which acted in the large intestine using undigested proteins and peptides as substrate, therefore generating more easily absorbable products (166). In a more recent study, the effect of this strain was tested with milk proteins, obtaining similar results (173).

Taken in total, the combination of probiotics with proteins could reduce the quality differences of protein sources naturally lower in leucine, such as some plant proteins, improving their bioactive properties, and possibly overcoming the microbiota problems related to high protein diet.

CONCLUSION

In conclusion, protein supplementation in sports nutrition is a very broad field that includes proteins, hydrolysates, peptides, and amino acids. It encompasses very different areas as sport performance (increase energy, reduce fat body mass, maintain strength muscle, promote muscle protein synthesis, recovery muscular mass, or prevent nutritional deficiencies), sport-related complications (joint soreness, fatigue, sport injuries and rehabilitation) and disciplines, such as food chemistry, immunology or physiology.

Although protein quality is generally lower in plants than in animals, there are other novel sources of protein, both animal and vegetable, whose effects on sports activity could be very interesting along with other environmental reasons to choose them as sports supplements. The future directions of these investigations highlight an interest on the development of protein products that not only improve sports nutrition, but also contain added value, such as a higher bioactive capacity or greater sustainability. In fact, the UN Nutrition aims to use resources more efficiently and reduce greenhouse gas emissions to secure the future of food and the environment. In fact, they suggested that a replacement of basic animal protein sources such as milk and eggs with more sustainable food alternatives is needed.

In this context, plant protein sources contain compounds that can help to protect the body against high levels of oxidative stress in exercise. Insect proteins are also a good-quality protein source, which can become a viable ingredient in liquid or solid food sports products, and mycoproteins could have more anabolic effect than traditional sport supplement protein with a much-reduced carbon footprint. Moreover, protein hydrolysates or their bioactive peptides could be especially beneficial from a multifunctional point of view, to improve sport performance, complications associated to the sport practice and healthy aging.

It is a fact that, in recent years, the demand for alternative proteins has been growing considerably and it is estimated

that it will continue to do so in the next 20 years. In this context, sports nutrition will be an interesting target market and those new products that combine protein quality and bioactivity, including ergogenic capacity, and are friendly to the environment will be better accepted by athletes. Although alternative proteins present a great potential as natural source of biologically active compounds, the scientific evidence related to the biological properties of new sources of protein is almost limited to *in vitro* assays and it will be necessary more studies in animal models and human trials to evaluate their efficacy, safety, and their impact in human health before its commercialization.

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