MAKE WELLNESS FIT FEATURING PEPTISTRONG PLUS

WITH METABOLIC MATRIX TECHNOLOGY:

A NEW GENERATION OF NUTRITION TECHNOLOGY

by

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Make Wellness Fit featuring PeptiStrong Plus with Metabolic Matrix Technology

A New Generation of Nutrition Technology

Abstract: Bioactive Precision Peptides have many potential uses in nutritional science. The emergence of chronic diseases has become a global health concern, with their prevalence rising considerably in recent years. Loss of skeletal muscle mass, function, and quality significantly contributes to the loss of metabolic fitness and the onset of many chronic diseases. Utilizing a machine learning platform with artificial intelligence technology, specific bioactive precision peptides have been identified that can mitigate the adverse effects of age-related loss of skeletal muscle mass and function and preserve metabolic fitness, thereby preventing many chronic diseases and positively influencing wellness. New processing technology has also been developed to protect and preserve bioactive precision peptides' physiological activity and bioavailability in protein hydrolysates. This literature review will describe the characteristics and physiologic benefits of bioactive precision peptides derived from hydrolyzed proteins. It will detail the importance of the hydrolysis process in preserving their form and function and the protective mechanism of the protein-peptide matrix. Lastly, it will discuss the benefits of combining a specific combination of bioactive peptides with additional nutrient cofactors and coenzymes in mitigating muscle dysfunction and inflammation.

1. Introduction

Skeletal muscle is the largest metabolic organ of the human body, makes up about 40% of total human body weight, accounts for 50-75% of all bodily protein, and is responsible for more

than 80% of post-prandial glucose clearance, making the preservation of skeletal muscle mass vitally important (Nishikawa et al., 2021). Maintenance of skeletal muscle health is regulated by the multifactorial processes involved in balancing muscle protein synthesis with muscle protein breakdown (Damluji et al., 2023). As we age, skeletal muscle homeostasis can become disrupted, impacting the balance between synthesis and breakdown and resulting in loss of muscle mass (Robinson et al., 2023). Losing muscle mass begins in the third decade of life and increases to 1-2% per year over 50. If not properly managed, it can become as high as 30-40% by the eighth decade of life (Hosoi et al., 2024). Loss of muscle mass and metabolic fitness is associated with a significantly higher prevalence of chronic disease and loss of functional mobility and autonomy.

PeptiStrong Plus (PSP) is a novel functional protein hydrolysate containing PeptiStrong Bioactive Precision Peptides (BPPs) paired with a proprietary Metabolic Matrix Technology (MMT) designed to synergistically enhance the physiological benefits of the BPPs in increasing muscle protein synthesis (MPS), inhibiting muscle protein breakdown (MPB) and lessening the impact of chronic inflammation by targeting multiple underlying causes of muscle atrophy. The efficacy of BPPs is rooted in their specific mechanisms of action: The HLPSYSPSPQ peptide in PeptiStrong stimulates muscle protein synthesis through interaction with cellular signaling pathways involved in muscle growth, and TIKIPAGT reduces TNF-alpha secretion, a key pro-inflammatory cytokine. This peptide can create a more favorable environment for muscle recovery and growth by modulating inflammatory responses for many. Reduced inflammation can also contribute to overall health and potentially mitigate age-related muscle loss (Kerr et al., 2023; Weijzen et al., 2023).

The discovery of the BPPs found in PSP through AI-driven methods showcases the potential of technology to revolutionize nutritional science. This approach accelerates the

discovery process and allows more targeted and efficient identification of bioactive precision peptides with specific desired properties. Unlike traditional serendipitous approaches to nutritional intervention discovery, the AI platform allows for a targeted approach. Researchers can identify specific health needs at the beginning of the discovery process, guiding the AI to search for peptides with the most relevant properties. The AI platform rapidly selects the most promising novel candidates, significantly reducing the time and resources required for discovery. This efficiency extends to identifying the most relevant natural sources for further development and study.

2. **Structure and Function**

BPPs are specific small amino acid fragments, generally 2-20 amino acids long, obtained from natural plant and animal sources and capable of eliciting a physiochemical change beyond their nutritional value in normal body processes (Abeer et al., 2021; Purohit et al., 2024). Protein-based foods contain numerous BPPs that act as functional agents, offering numerous potential health benefits analogous to endogenous signaling molecules that influence physiological processes. Recent research has demonstrated the significance of BPPs as physiologically active and therapeutically beneficial compounds. BPPs have high oral bioavailability and are vital to human physiology, primarily acting as signaling agents that modulate physiological processes such as growth, including muscle and bone development, immunomodulation, inflammation, antioxidant potential, and gene regulation (Purohit et al., 2024; Xavier et al., 2024). The high tissue affinity of BPPs influences the mechanisms by which they interact with receptors, enzymes, and specific biomolecules within the body to precisely influence physiological processes. Their high specificity, potency, and inherent beneficial properties have led to the discovery and development of many safe, tolerable, and efficacious

peptide therapies and nutritional supplements. More than 60 bioactive peptide-based medications have been developed, with another 500 plus currently in some stage of development, further highlighting their therapeutic potential to enhance human well-being. Naturally derived, bioactive precision peptides are at the cusp of revolutionizing health and nutritional science (Zhou et al., 2024).

3. **Method of Production**

Protein hydrolysates are recognized as a viable source of releasable mixtures of BPPs with potential health benefits. Protein hydrolysates are also known as predigested hydrolyzed proteins and are mixtures of peptides and amino acids produced by the hydrolysis of proteins. BPPs are cleaved from hydrolysates during digestion by stomach pepsin and proteases to produce bio-accessible low-molecular-weight peptides. The critical determinants of BPPs physiological activity include their amino acid (AA) constituents, the nature of the AAs contained in the peptide chain, the AA residues at the N and C termini of the peptides, the molecular weight, structure, and physiochemical properties (Xavier et al., 2024). The AA sequence and composition of the peptides determine their activity once they are released from the protein-peptide matrix within which they are encrypted (Sanchez & Vázquez, 2017). Proteins of plant and animal origins are potential sources of a wide range of BPPs encrypted in their structure. To successfully produce BPPs, apart from selecting the appropriate protein source and proteases, the conditions of the hydrolysis process are of great significance. The degree of hydrolysis achieved in the isolation and concentration of BPPs significantly influences the bioavailability of the specific peptides (Xavier et al., 2024). The detection quality parameters for the industrial hydrolysis process include controlling the ratio of amino nitrogen to total nitrogen to determine the degree of hydrolysis, the content of free amino acids and total amino acids in

the hydrolysate, and the molecular weight distribution of peptides (Dullius et al., 2020). Protein source, type of protease, the molecular weight of the peptides, and conditions of the hydrolysis process, including peptidases, the substrate-to-peptidase ratio, temperature, pH, and reaction time are also critical to preserving the function and bioavailability of the BPPs (Xavier et al., 2024). Protease-catalyzed enzyme hydrolysis utilizes different proteases that cleave proteins at specific amino-acid sites and maintain the integrity of other peptide bonds (Purohit et al., 2024). Using the correct enzyme with high specificity and maintaining adequate controls over the hydrolysis process parameters is crucial to producing BPPs with the required physiological and functional properties.

4. **Absorption and Transport**

Because BPPs are smaller than proteins, they are more bioavailable and less allergenic. Unlike synthetic therapeutic peptides, which are highly unstable, broken down during digestion, and typically must be injected, food-derived BPPs are gentler, safer, and more easily absorbed (Xavier et al., 2024). To facilitate absorption, BPPs are transported across the intestinal brush-border membrane into the bloodstream via both active and passive routes. There are four main pathways by which bioactive peptides enter the blood across the intestinal epithelial cell monolayer, including peptide transporter-mediated transport, the paracellular route across tight junctions, transcytosis, and passive transcellular diffusion (X. Zhu et al., 2023). There are two known peptide transporters: H+-coupled PepT1 and Na+-coupled SOPT1 and SOPT2. PepT1 is specific to di and tripeptides, preferentially recognizing short hydrophobic, nonpolar peptides with neutral charges. SOPT1 and SOPT2 transport oligopeptides containing at least five amino acids. The paracellular pathway in the human gastrointestinal tract is regulated by paracellular diffusion pores called tight junctions that are mainly composed of occludin, zonula occludens-1,

and claudin proteins, which form a tight barrier with selective penetration (Xu et al., 2019). The presence of tight junctions explains the higher bioavailability of small peptides when compared to larger peptides or proteins. Due to the limited size and electrostatic properties of tight junctions, hydrophilic and negatively charged low molecular weight peptides are preferentially transported via paracellular pathways. Transcytosis involves apical endocytic uptake via internalization, transcytotic vesicle transport, and basolateral secretion and is an energy-dependent transcellular pathway. Highly hydrophobic and long-chain peptides with more than ten amino acids are usually absorbed through this pathway because hydrophobic BPPs must interact with the apical lipid surface via hydrophobic interactions prior to internalization. Passive transcellular diffusion involves passive uptake into cells, intracellular transport, and basolateral effusion and is the transport mechanism for positively charged and hydrophobic macromolecular peptides. Transport of BPPs via this route is influenced by many factors, including their size, charge, and hydrophobicity.

The BPPs in Fit by Make Wellness consist of the two primary peptides characterized above encrypted in a protein-peptide matrix of more than 4,000 additional peptides that protect and facilitate the transport of the PSP BPPs. These BPPs are transported by two critical transport systems: the peptide transporter-mediated transport mechanism and the paracellular transport mechanism across tight junctions in a receptor-mediated manner, as determined by their overall charge, molecular mass, hydrophobicity, and aggregation tendency (Guha et al., 2021; Yu et al., 2024).

5. **Significance of Encryption**

BPPs are encrypted and protected within larger protein-peptide matrixes and do not become active until they are released by hydrolysis (Shea et al., 2024). The encryption of the

BPPs impacts stability and bioavailability by protecting the structural and functional integrity of the BPPs. The peptide bonds of BPPs are shielded from enzymatic degradation by the protective barrier provided by the protein peptide matrix, thus increasing their stability through the GI tract (Zaky et al., 2022). The protein-peptide matrix also allows for a controlled release of the BPPs from the protein-peptide matrix, which increases and prolongs the bioavailability of the BPPs (Purohit et al., 2024). Because the BPPs are part of a more significant protein or peptide fragment, BPPs can be absorbed more efficiently than individual, unprotected peptides. The protein carrier can also facilitate transport across the intestinal barrier while buffering BPPs against pH changes in the digestive system, which further preserves structure and function (Zaky et al., 2022). Notably, the protein-peptide matrix preserves biological activity by shielding the BPPs from oxidation and allowing for a more targeted delivery of the BPPs to specific sites within the body before they are released.

6. **Difference between BPPs and Therapeutic Peptides**

Therapeutic peptides and BPPs differ primarily in how they are produced, where they originate from, and in their usage and application (Alzaydi et al., 2023; Wang et al., 2022). Therapeutic peptides are specifically designed and synthesized as pharmaceutical agents to mimic natural hormones, neurotransmitters, or growth factors. They are used in targeted therapies due to their high specificity and low immunogenicity. With molecular weights between 500 and 5,000 Da, therapeutic peptides exist as pharmaceuticals residing between small molecule drugs and large biologic agents. They target cellular receptors or pathways, binding to cell surface receptors and triggering intracellular effects with high affinity and specificity while showing less immunogenicity (Wang et al., 2022). Therapeutic peptides are designed to target specific molecular sites and achieve a particular therapeutic outcome, typically mimicking the

body's natural signaling molecules. However, therapeutic peptides typically have weak membrane permeability and poor in vivo stability, requiring administration primarily through parenteral routes due to challenges with oral bioavailability (Yang et al., 2023).

BPPs are derived from natural plant and animal protein sources and are released through enzymatic hydrolysis during digestion or from hydrolyzing protein sources with specific proteolytic enzymes (Purohit et al., 2024). BPPs are inactive in their native states but exhibit powerful physiologic effects when unlocked from their protective protein-peptide matrix. BPPs generally have a broader physiologic effect on overall health and wellness and chronic disease prevention compared to therapeutic peptides due to the likelihood of influencing multiple mechanisms of action (Shahnaz et al., 2024). In addition, BPPs do not have side effects and represent a safe and beneficial alternative to many of the drugs currently used to treat chronic diseases. BPPs have demonstrated the ability to influence multiple physiological functions, including enhancing muscle protein synthesis, preventing fatigue, and promoting brain health. BPPs also possess anti-inflammatory, antioxidant, antidiabetic, antigout, antihypertensive, immunomodulatory, antimicrobial, and cholesterol-lowering capabilities (Li et al., 2023; F. Zhu et al., 2023). As dietary interventions, these food-derived functional factors possess incomparable advantages over drugs, including early prevention, safety, effectiveness, and a lack of ideological and economic burden (Li et al., 2023). The stability and half-life of BPPs also impact their physiological benefits, with the presence of prolines embedded within the peptide sequences enhancing stability through digestion and absorption and peptides containing threonine at the N-terminus exhibiting a prolonged half-life in biological matrices(Corrochano et al., 2021). However, the protein processing technique is vital to preserving the physiological function of BPPs. The active site of the protease determines where hydrolysis will occur, and the

protease used will define the degree of hydrolysis and the profile of released peptides (Rivero-Pino, 2023). The use of the wrong protease or deviations in the manufacturing processes will lead to the destruction of the BPPs and loss of physiological benefit. Therefore, the consistent production of specific stable and physiologically active BPPs depends on the precision and skill of the manufacturer producing the protein hydrolysate. To be clear, BPPs are built by nature yet preserved and protected by science and technology.

7. **Fit Mechanisms of Action**

The BPPs in PSP work by activating the PI3K/Akt/mTOR pathway, inhibiting the ubiquitin-proteasome system pathway, augmenting S6 phosphorylation, downregulating genes related to muscle atrophy, and reducing the secretion of the pro-inflammatory cytokine TNF-α, thus promoting the efficient synthesis of muscle proteins, inhibiting their degradation, and reducing overall systemic inflammation (Cal et al., 2020). Phosphorylation of S6 induces the translation of mRNA transcripts for ribosomal proteins and elongation factors, ultimately leading to muscle protein synthesis. The cytokine TNF-α produces chronic inflammation, which is implicated in skeletal muscle dysfunction. TNF-α has also been shown to inhibit the regeneration of satellite cells, precursors to skeletal muscle cells, in dystrophic muscle. Pre-clinical, in vitro testing in murine skeletal muscle cells and human macrophages was carried out to determine the effects of PSP against phosphorylated S6, atrophy gene expression, and TNF-α activity. Additionally, the efficacy of the BPPs in PSP on attenuating muscle wasting in vivo demonstrated that after 18 days of supplementation, treated mice exhibited significantly reduced muscle loss in the suspended soleus muscle, increased mitochondrial biogenesis and myogenesis markers, as well as enhanced integrated density of type I and II muscle fibers (Cal et al., 2020; Kerr et al., 2023). Two primary peptides identified within a Vicia faba-derived hydrolysate were

shown to significantly increase protein synthesis through S6 phosphorylation (histidine–leucine–proline– serine–tyrosine–serine–proline–serine–proline–glutamine; HLPSYSPSPQ) and reduce proinflammatory cytokine release via anti- TNF-α activity (threonine–isoleucine–lysine–isoleucine–proline–alanine– glycine–threonine; TIKIPAGT) in vitro (Cal et al., 2020; Corrochano et al., 2021).

Corrochano et al. (2021) characterized the efficacy and bioavailability of the BPPs found in the proteome of PSP using a machine learning and artificial intelligence platform based on selective targets of the phospho-S6 pathway in skeletal muscle cells and TNF-α secretion in macrophages. The predicted peptides consistently survived simulated gastrointestinal digestion, crossed the Caco-2:HT29 intestinal barrier, and exhibited a favorable in vitro bioavailability and stability profile. Additionally, the stability of both peptides in human plasma was examined. Structurally and physiochemically, HLPSYSPSPQ contains 10 AA residues with a molecular weight of 1112.19 Da with a neutral net charge. TIKIPAGT consists of 8 AA with a molecular weight of 799.95 Da and a net charge of 1. TIKIPAGT was identified within parent protein, B0BCL7. In contrast, HLPSYSPSPQ was distributed across three parent proteins: Q43674, Q43673 and P05190.

The biological activity of the two primary peptides contained in PSP was assessed in vitro (Corrochano et al., 2021). The effect of HLPSYSPSPQ on protein synthesis was measured using S6 phosphorylation. The treatment of differentiated myoblasts with 0.05 μg/mL of predicted constituent bioactive peptide HLPSYSPSPQ significantly increased the phosphorylation of S6 by 50% compared to untreated cells ($P < 0.01$). TIKIPAGT significantly decreased TNF-α secretion by 55% in LPS-stimulated macrophages at 0.05 μg/mL compared to untreated cells ($P < 0.001$). The stability of HLPSYSPSPQ and TIKIPAGT was assessed in vitro

through the upper gut tract. The primary peptides HLPSYSPSPQ and TIKIPAGT survived the proteolytic effect of pepsin, the acidic conditions of the stomach, and, subsequently, the effects of a 2-h simulated gastric and intestinal digestion. The bioavailability of HLPSYSPSPQ and TIKIPAGT was tested by treating a Caco-2:HT29 intestinal barrier with simulated gastrointestinal digestion using an FDA-approved technique to measure human intestinal permeability. The results demonstrated that HLPSYSPSPQ and TIKIPAGT are resistant to stomach and intestinal proteases and to the metabolic activity of brush border enzymes such as aminopeptidases, endopeptidases, and carboxypeptidases. An explanation for the stability of the primary peptides within the gut transit is the presence of prolines embedded within the peptide sequences. HLPSYSPSPQ contains three prolines, rendering it less susceptible to proteolytic degradation than TIKIPAGT, which contains one. Furthermore, HLPSYSPSPQ is more hydrophobic than TIKIPAGT, suggesting easier passage through the intestinal layer. Both peptides exhibited good stability in human plasma. Notably, HLPSYSPSPQ showed a half-life of 65.79, ± 3.79 min and reached the limit of detection at 8 hours. TIKIPAGT presented a half-life of 16.85, ±0.40 min with a limit of detection reached at 2 h.

8. Results of Randomized Controlled Trials

Kerr et al. (2023) investigated the effect of the BPPs utilized in PSP on strength recovery in a double-blind, placebo-controlled clinical trial in 30 healthy male volunteers aged between 30 and 45 years with a BMI between 18 and 30 kg/m^2 (NCT05159375). In this study, BPP supplementation improved strength recovery, reduced fatigue, and suppressed myostatin expression in a healthy male population following exercise-induced muscle damage (EIMD). Over a 72-hour, post-resistance exercise period, a significant recovery in muscle strength was observed with the supplementation group compared to placebo ($p = 0.020$). Over the same 72-

hour period, fatigue was significantly decreased ($p = 0.041$), and the release of myostatin was beneficially modulated ($p = 0.006$) in the BPP-supplemented group compared to the placebo. 72 hours after EIMD, iAUC analysis showed a 54% improvement in the performance of isokinetic leg extension with BPP supplementation compared to placebo. Myokine expression was also measured in this study. The expression of irisin, which can induce glycogenesis, was increased, and IL-15, which has been linked to increased muscle mass and can promote myoblast differentiation, was significantly increased in the BPP-supplemented group compared to the placebo ($p = 0.159$). Myostatin expression was significantly suppressed in the BPP-supplemented group compared to the placebo throughout the trial, as was the release of fibroblast growth factor 21 in the BPP group at time points 0 and 2 h. These combined data indicate clinical evidence of attenuation of muscle breakdown with BPP supplementation. Interestingly, in the present study, IL-6 expression was transiently increased at 0 h post-EIMD in the BPP group, which may aid in the improved strength recovery observed. As changes return to baseline quite quickly, the likely source of IL-6 is the myocyte, as opposed to an immune cell release of IL-6. The upregulation of myokines such as fractalkine, osteocrin/musclin, and osteonectin/SPARC has been shown to play a role in regeneration, mitochondrial biogenesis, and adaptation of muscle to exercise. The significant increase in expression of fractalkine ($p = 0.030$) and osteonectin/SPARC ($p = 0.025$) in the BPP-supplemented group may contribute to the reduced fatigue experienced following EIMD (Kerr et al., 2023).

Weijzen et al. (2023) conducted a double-blind, placebo-controlled clinical trial of 30 healthy young men to compare the effects of the BPPs contained in PSP to an isonitrogenous control of milk protein on muscle mass and strength loss during limb immobilization and regain during remobilization. It was hypothesized that BPP supplementation during recovery from a

period of immobilization may also support a more rapid regain of muscle size and strength by stimulating muscle protein synthesis rates in healthy adults. The study also aimed to compare the impact of supplementing BPPs derived from a plant source with a high-quality animal-derived protein reference on muscle size and strength loss and regain during immobilization and subsequent remobilization. The thirty test subjects were subjected to seven days of single-leg immobilization that resulted in a substantial decline in daily muscle protein synthesis rates and a loss of muscle size and strength, which were only partially recovered following 14 days of remobilization. No differences were observed between the BPP or milk protein concentrate supplementation for the loss of muscle size and strength during short-term immobilization or the regain of muscle size and strength during subsequent remobilization. Despite the absence of differences during the immobilization and remobilization phases, BPP supplementation resulted in significantly higher muscle protein synthesis rates when compared to milk protein concentrate supplementation (50% vs. 13%) during the remobilization period (Weijzen et al., 2023). Higher myofibrillar protein synthesis rates during recovery from a period of immobilization indicate more significant or more rapid reconditioning of muscles.

9. **The Synergy of the Make Wellness Metabolic Matrix Technology**

The Make Wellness MMT supports numerous mechanisms of action enhanced by the BPPs contained in Fit. Combining the BPPs with the MMT nutrient cofactors and coenzymes in PSP offers a multifaceted approach to supporting muscle health and quality. The BPPs in PSP may stimulate muscle protein synthesis directly, while the supporting nutrients ensure optimal conditions for this process. By targeting various aspects of muscle metabolism, protein synthesis, and cellular function, this combination has the potential to synergistically enhance muscle protein synthesis and improve metabolic fitness. The Make MMT contains a nutrient cofactor

precursor to nicotinamide adenine dinucleotide (NAD+), a crucial coenzyme involved in cellular energy metabolism and other vital processes. This cofactor increases cellular NAD+ levels, which decline with age. Higher NAD+ levels support mitochondrial function and energy production in muscle cells. NAD+ activates sirtuins, a family of proteins involved in cellular health and longevity. Sirtuins have been implicated in regulating muscle mass and potentially influencing myostatin activity. The MMT cofactors are crucial in DNA synthesis, red blood cell formation, and neurological function. It is involved in the metabolism of proteins and amino acids. It supports the production of energy in cells, including muscle cells. The MMT is essential for maintaining healthy nerve function, which is crucial for muscle control and strength.

The Make MMT also has a significant coenzyme effect in numerous enzymatic reactions, particularly those involving amino acid metabolism. It plays a role in the production of neurotransmitters that regulate muscle function. The MMT is involved in glycogen metabolism and with better maintenance of muscle mass in older adults. It is crucial for ATP production, muscular contraction, and the function of ribosomes, the cellular structures where protein synthesis occurs. It helps maintain calcium homeostasis and improve bone health while promoting the differentiation of muscle precursor cells into mature muscle fibers. The MMT also has anti-inflammatory properties that may protect against muscle damage and support recovery. It supports methylation cycles by acting as methyl donors, influencing gene expression and DNA repair, and optimizing the synthesis of neurotransmitters and hormones. The combination of cofactors and coenzymes found in the Metabolic Matrix Complex works synergistically with PSP to enhance the muscle protein synthesis metabolic pathways and improve the efficiency and efficacy of BPPs.

10. Conclusion

The discovery of BPPs by AI-driven methods ushered in a new age of nutrition technology. This method accelerates the discovery process and enables more targeted and effective identification of bioactive peptides with specific desired properties. Recently, a clinically validated dose of PSP has been shown to improve strength recovery and reduce fatigue during strenuous activity. It also alters plasma concentrations of myokines associated with muscle health and glycogen metabolism. The mechanisms of action of PSP with MMT have exhibited cell-specific signaling for protein synthesis and anti-inflammatory effects, helping to balance muscle protein synthesis, muscle protein breakdown, and inflammation. The multi-targeted approach of combining peptides, coenzymes, and cofactors with various physiological functions offers a comprehensive strategy for supporting muscle health. Future research should continue expanding the knowledge of the muscle-preserving benefits of PSP with MMT and the potential to counteract age-related muscle loss. As our understanding of the complex interplay between nutrition and muscle metabolism grows, such targeted nutritional interventions may play an increasingly important role in maintaining muscle health throughout the lifespan.

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