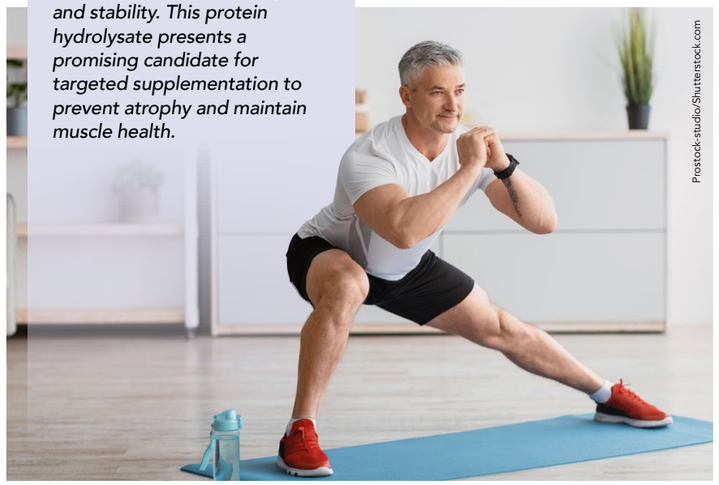
Muscle health improved using an artificial intelligence-discovered plant-based ingredient

Dr Nora Khaldi and her team at Nuritas have demonstrated the muscle-building and anti-inflammatory properties of an artificial intelligence (AI)-discovered functional hydrolysate NPN_1, or PeptiStrong™. It was shown to improve multiple aspects of muscle regeneration and maintenance, with the functional peptides responsible for these activities hidden within the hydrolysate's complex proteome. Using AI, the researchers successfully characterised two constituent bioactive peptides which increase protein synthesis, reduce inflammation, and exhibit good bioavailability and stability. This protein hydrolysate presents a promising candidate for targeted supplementation to prevent atrophy and maintain muscle health.

Nutritional interventions offer the opportunity to prevent disease and maintain health as we age. However, until recently, there has been a serendipitous approach to nutritional intervention and functional ingredient discovery. Moreover, these ingredients tend to be poorly characterised, with unknown mechanisms of action. Artificial intelligence (AI) offers the opportunity to remedy these issues, with the ability to decipher complex food and plant sources and identify key bioactive components which can subsequently be validated in a time- and cost-efficient manner.

Nuritas has developed an AI platform that combines curated unstructured and structured sets of publications, databases and patents, as well as information on disease biology, proteomic and peptidomic research of natural sources, and the phenotypic screening of bioactives in relevant physiological assays from integrated molecular biology laboratories. Using this knowledge base, the platform can predict novel key bioactives and their properties much more efficiently than individual laboratory tests, rapidly selecting the most promising novel candidates. These are then used to identify which natural sources would be most relevant for development and further study. An advantage of this approach is that it allows for the identification of a health need at the beginning of the discovery process, creating a very specific bioactive ingredient.



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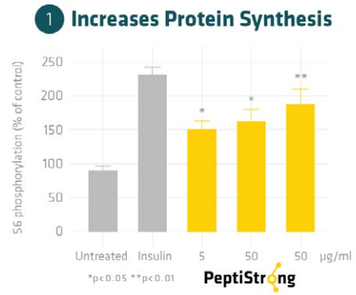
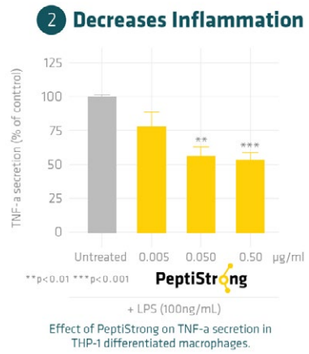
MUSCLE HEALTH

One major issue we face with advancing age is the inability to maintain skeletal muscle mass. Without proper nutrition and maintenance, muscle tissue is degraded through a dysregulation of mechanisms involved in normal muscle tissue regeneration. Healthy tissues support a balance between muscle gain and loss by counteracting the mechanisms involved in muscle turnover and rebuilding with those necessary to maintain the developed tissue. If this balance is tipped, it usually leads to increased turnover, resulting in muscle loss. This is a common side effect of ageing: muscle mass begins to atrophy as early as our mid-twenties. Reduced muscle strength and weight gain are common symptoms of this ageing process, as skeletal muscle tissue affects many aspects of our health and physical mobility, which is central to maintaining health.

Muscle maintenance involves an intricate crosstalk between muscle, other tissues, and immune cells. Systemic inflammation is one of the primary causes of muscle loss, demonstrating how skeletal muscle health is integral to overall wellbeing. This system also impacts insulin sensitivity, metabolism, and weight management. This is because muscle tissue is critical for both metabolism and disease prevention – it is our biggest metabolic organ and comprises a significant portion of our body weight and protein turnover. Targeting muscle health would improve the process of healthy ageing, help maintain general fitness, and enhance metabolism later in life. Humans are more sedentary than ever before, which further reduces physical mobility and fitness. Identifying points of intervention to preserve muscle mass would vastly improve our health throughout life.



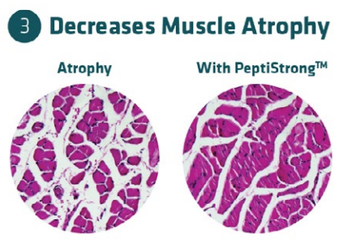
Effect of PeptiStrong treatment of C2C12 muscle cells on S6 phosphorylation.



Effect of PeptiStrong on TNF-a secretion in THP-1 differentiated macrophages.

A naturally derived network of peptides the research team found to be particularly effective was a hydrolysate derived from V. faba (NPN_1), which was branded PeptiStrong™.

To gauge whether a compound has any effect on the skeletal-muscular system, the team at Nuritas examined biomarkers specific to muscle maintenance. Several of these biomarkers are used to indicate protein synthesis and degradation. For example, the mammalian target of Rapamycin (mTOR) complex 1 (mTORC1) regulates protein translation and is integral to maintaining muscle mass and function. mTORC1 regulates the S6 ribosomal protein and eukaryotic initiation factor 4E binding protein 1 to help maintain muscle mass. In contrast, the ubiquitin proteasome pathway is responsible for muscle atrophy (wasting). Under normal conditions, this interplay would regulate healthy muscle turnover, but muscle tissue degradation will occur if wasting is not balanced with an equal rate of muscle production. The phosphorylation of S6 is a useful indicator of mTORC1 activity and downstream muscle protein synthesis. S6 phosphorylation was therefore of particular interest to researchers for identifying an increase in muscle mass. Phosphorylated S6 can be easily detected via mass spectrometry or an enzyme-linked immunosorbent assay (ELISA), and its phosphorylation is indicative of mTOR activity, which is associated with increased muscle mass.



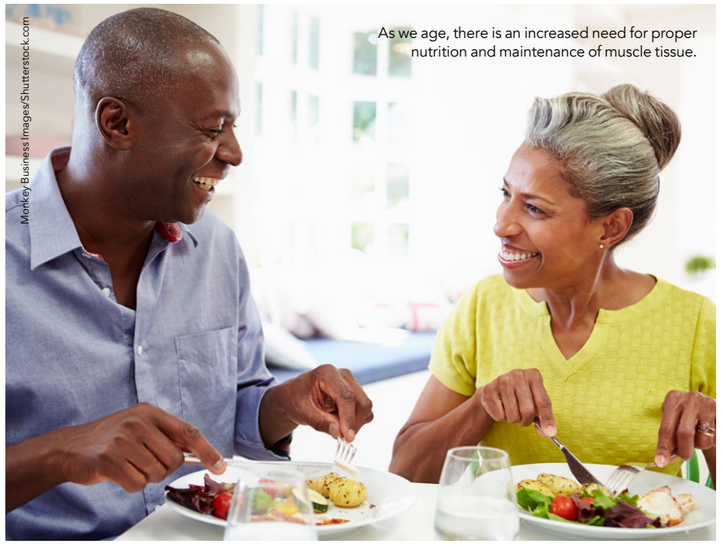
Effect of PeptiStrong on soleus muscle mass following hindlimb unloading. C57Bl/6 mice were treated with casein or PeptiStrong (650mg/kg/d) over 18 d.

Currently, interventions to prevent muscle wasting focus on activating the mTOR complex by supplementing leucine, an essential amino acid, but the effectiveness of this approach has not been confirmed experimentally. The team therefore looked toward AI-discovered, naturally derived peptides and their networks as a new approach to treat muscle atrophy. Peptides are protein fragments that engage in protein–protein interactions and execute signalling ('communication'). They can be found in food but provide more than simple nutrients when they interact in metabolic or signalling pathways. Before food-derived peptides can reach their target, they must first be made bioavailable by freeing them from the food proteome. Whole foods are nutritious, but the individual nutrients within them are not always accessible. The human digestive system can fail to either break down or absorb proteins and protein fragments necessary for a balanced diet.

BROADER BEAN APPLICATIONS

Hydrolysis is a natural process of protein digestion in which the larger protein is split, or hydrolysed, into smaller components. A hydrolysate is the total of the fragments of the split protein, where hydrolysis made the components more bioavailable. Nutritional interventions, such as foods enriched with more easily digestible legume blends, have been shown to increase muscle protein synthesis in rats. *Vicia faba* in particular is also associated with anti-fungal, anti-cancer, and anti-diabetic properties. Evidently, *V. faba* may harbour a diverse compilation of potent bioactive compounds.

A naturally derived network of peptides the research team found to be particularly effective was a hydrolysate derived from *V. faba* (NPN_1), which was branded PeptiStrong™. In vitro, NPN_1 was shown to reduce gene expression related to muscle atrophy in cells, chemically induced to deteriorate. NPN_1 was able to mitigate the effect of this deterioration. It worked by reducing the expression of the *Fbxo32*



As we age, there is an increased need for proper nutrition and maintenance of muscle tissue.

and *Trim63* genes, both of which are associated with muscle breakdown. NPN_1 was shown to have no adverse side effects on mouse muscle cells, even in doses up to 500µg/mL.

Using a hindlimb unloading model, mice with muscle atrophy were treated with NPN_1, which protected the muscle tissue in their immobilised back leg from losing mass more effectively than the Bowman–Birk inhibitor (BBI), a protease inhibitor often used to treat muscle wasting. NPN_1 also worked at a lower dose. These results indicate promising applications for NPN_1 in alleviating disease-induced muscle atrophy in humans. The NPN_1 hydrolysate was able to protect both Type I endurance and Type II rapid movement muscle fibres from atrophy, where supplementation with casein had little effect. NPN_1 was also shown to not alter antioxidant or fatty acid oxidation pathways, indicating it may have fewer adverse reactions in cells. Muscle wasting is a complex process involving a number of interacting metabolic pathways. Ideally, a mixture of peptides would target multiple tissue maintenance mechanisms. The hydrolysate combination in NPN_1 was shown to reduce inflammation, increase muscle synthesis, and downregulate genes linked to muscle atrophy. Its modes of action offer a multifaceted approach that addresses several aspects of muscle tissue repair.

ARTIFICIAL INTELLIGENCE CHARACTERISATION

The multi-targeted effectiveness of NPN_1 is likely due to multiple functional peptides within the hydrolysate, each with a specific mode of action. Bioactive peptides, functional protein fragments which interact with an organism's physiology, have vast potential to improve human health, but it is hard to find the right peptide for the right function and the ones that survive gut transit and reach their target once digested. Traditionally, functional peptides were found through generating peptide libraries or testing peptides generated randomly through hydrolysis. This can be time- and resource-consuming, involving expensive fractionation, isolation, and multiple testing steps. However, as Nuritas peptides are predicted with specific activities at the beginning of the discovery process, key constituent actives are already characterised and so can be synthesised and investigated for efficacy and stability.

A machine-learning model predicted two novel peptides within the NPN_1 hydrolysate, which exhibited strong bioactive properties. One peptide, HLPSYSPSPQ, increases protein synthesis, while another peptide, TIKIPAGT, reduces TNF-alpha secretion, thereby conveying an anti-inflammatory effect. Importantly, both predicted peptides exhibited good bioavailability and stability, which are essential to the efficacy of a functional ingredient. As we live longer and more sedentary lives, research into nutritional interventions effective for muscle health will help many to prolong their engagement in physical activities, increase their healthspan, reduce the need for drugs, and retain their strength well into old age. Combined, these results highlight the potential for an effective bioactive ingredient for maintaining muscle health and the opportunity for AI to aid the discovery and characterisation of nutritional ingredients.

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Nuritas' AI platform can predict novel key bioactives and their properties much more efficiently than fractionate screening.

Behind the Research


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www.youtube.com/watch?v=dIcRtEZqdFs

Research Objectives

Nuritas uses AI to develop novel food-derived bioactive peptides. The team recently validated PeptiStrong™, a functional food ingredient derived from fava bean that improves/maintains muscle health.

Detail

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Bio
Dr Nora Khaldi is the CEO and founder of Nuritas. Dr Khaldi is a pure mathematician with a PhD in Molecular Evolution and Bioinformatics. She is an extensively published author, a multi-Tedx speaker, and has won an accolade of awards, including Woman of the Decade by the Women Economic Forum. Dr Khaldi was inducted into the World Economic Forum's Young Global Leaders in 2019.

Dr Audrey Wall is the Global Communication – Scientific Lead at Nuritas and has a unique perspective gained in molecular biology, clinical research, and pharma. She has extensive experience in the field of scientific communications, medical information, and education, including several successful grant applications and peer-reviewed publications.

Alish Kerr, MSc is an accomplished research scientist and Project Lead at Nuritas. Her background is in genetics, data analytics, and molecular medicine. Kerr has a passion for healthy ageing and uses her expert knowledge in metabolism, muscle health, and inflammation to develop many of Nuritas' lead ingredients including PeptiStrong™.

References

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Personal Response

What are some potential applications for the two peptides identified by the AI model if they prove to be effective in humans?

"These two peptides, as essential components of PeptiStrong™, have many possible applications. PeptiStrong™ has opportunities as a functional ingredient within food or beverages or as a dietary supplement. The benefits seen with PeptiStrong™ have implications for supporting healthy ageing, active adults, athletes, and bodybuilders, as well as a possible application in the recovery of muscle mass post-immobilisation."

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