ORYGN

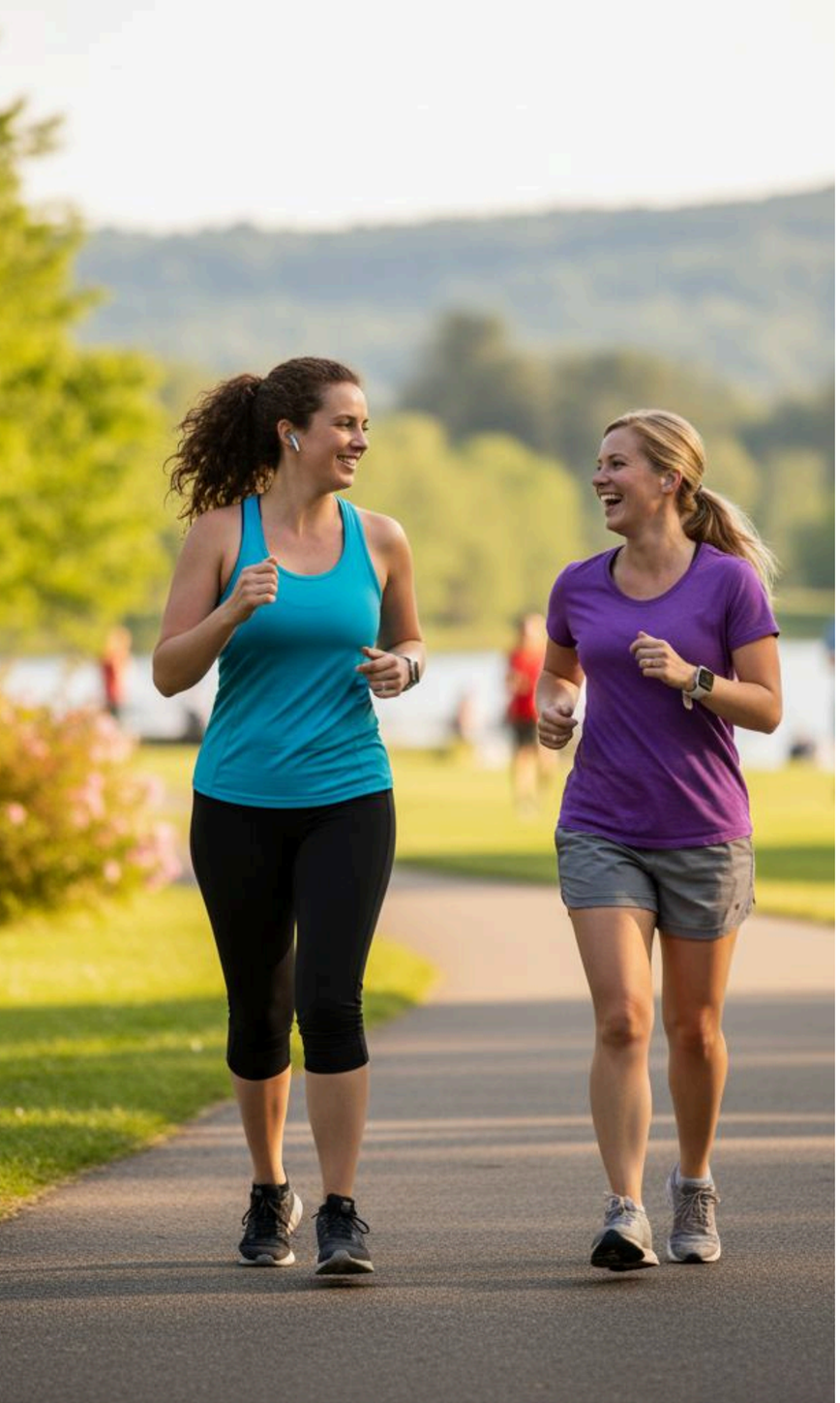
PHARMA RESULTS, NATURAL DELIVERY

ORYGN

triGLP

Three pathways in one drop

Unique patent-protected bioactive peptides
made from fresh sashimi grade Atlantic Salmon



What is Performance Aging & Metabolic Health?

- **triGLP** is a proprietary, patent protected bioactive peptide mix derived from fresh Atlantic salmon from Norway
- **triGLP** provides “Performance Aging” via improved metabolic efficiency, discovered by advanced science with clinically-proven benefits in an active and targeted way.
- It targets specific pathways that helps to **drive fat loss**, **protect overall muscle mass and boost energy levels**
- An optimal mix stimulating **GLP-1**, **GIP** (metabolism), **GLP-2** (gut health), potent anti-inflammatory and antioxidant effects supports good energy, good health, and a better quality of life.
- New qualified health claims for ferritin and hemoglobin provide a novel way to boost energy levels.

ORYGN

A Powerful Partnership

From fish to finished products using patented, gentle enzymatic hydrolysis processing

Our partners turn **only fresh sashimi-grade Norwegian salmon** into ingredients for human health

100%

33%

Salmon off-cuts for upcycling

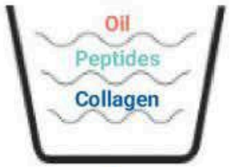
67%

Our partners produce high quality salmon fillets and portions

4°C

Arrives at facility within a few hours at <4°C

Water + Enzymes + Salmon



- 100% human grade
- No additives
- No antibiotics
- Non-GMO
- Zero Waste
- Circular Economy

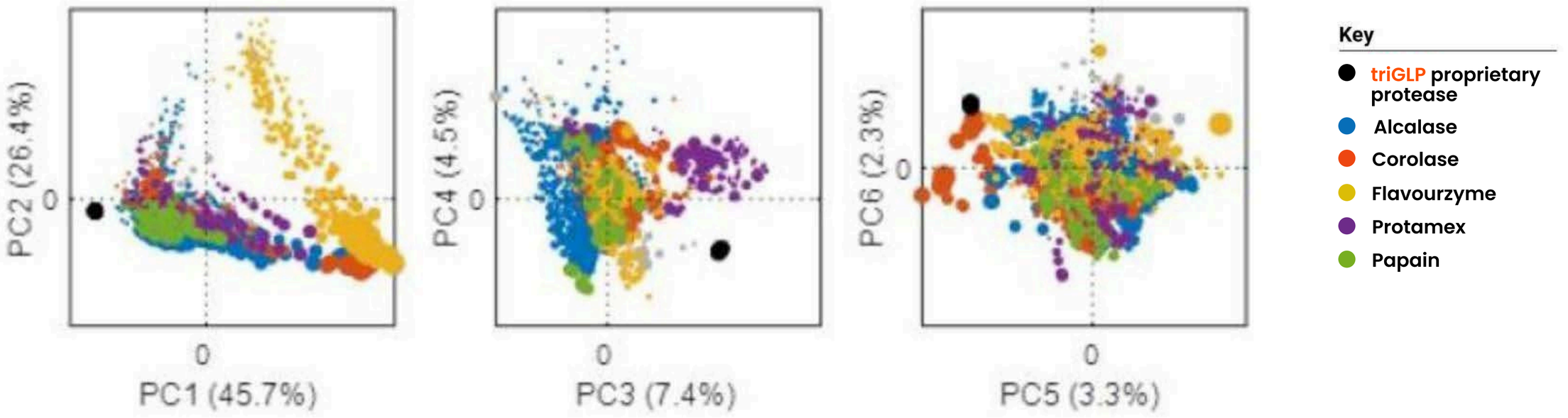
✓ > 99% protein
✓ > 35% type I & III collagen
✓ (> 90% type I and > 5% type III)

ORYGN

Unique Bioactive Peptides

Fourier-transform infrared fingerprint mapping shows that triGLP has a diffferent peptide composition from 1,324 commercially available an d research0based hydrolysates produced by other protease enzymes.

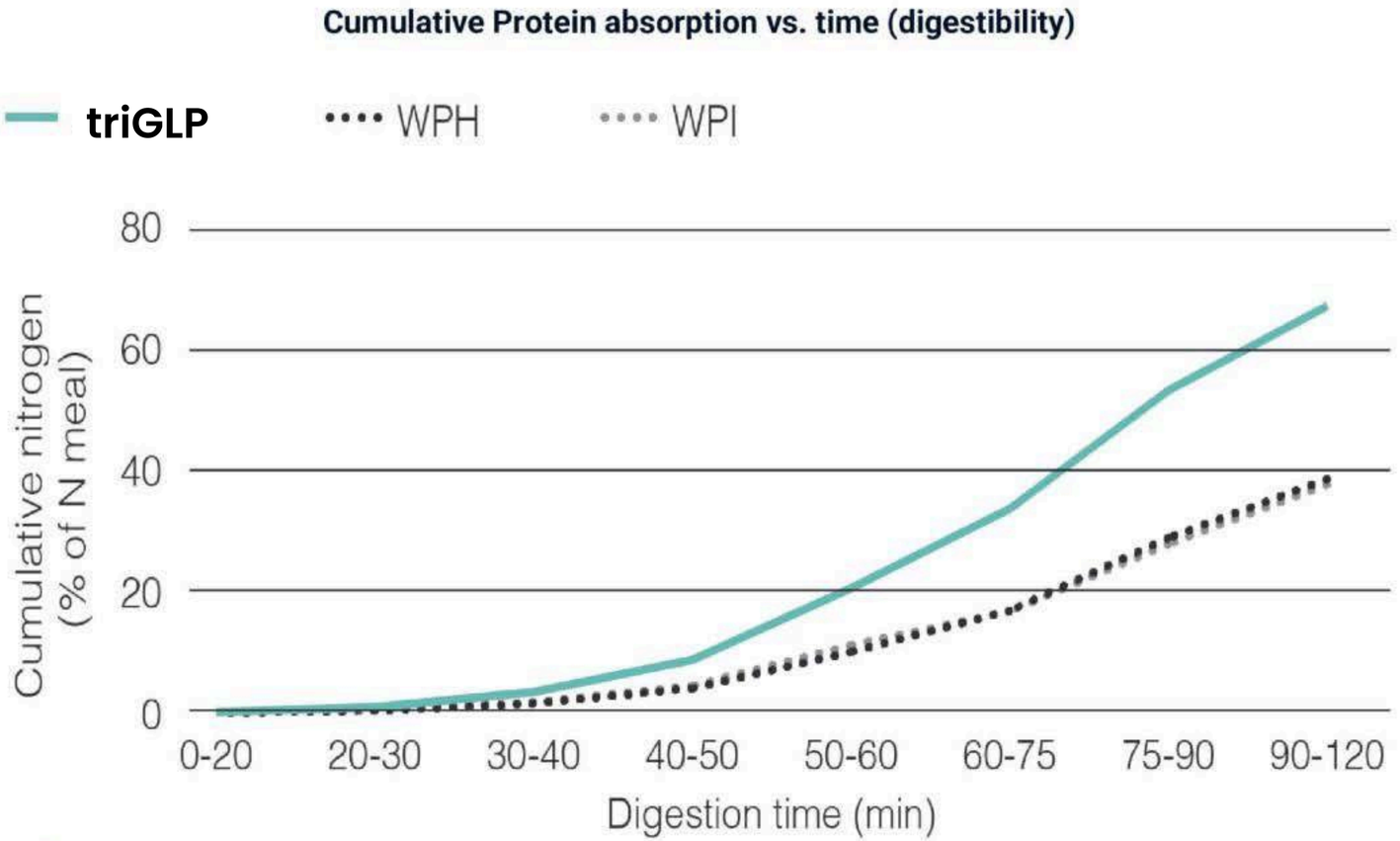
triGLP, (the black dot in all 3 scatter chanrts) stands out as unique and hence why its properties are markedly different from the other hydrolysates.



ORYGN

Faster Absorption for Recovery

- Up to pure 100% protein with type I & III collagen
- Patent-protected and trade secrets
- **+67.5% more absorption than highly hydrolysed whey protein (which is not even commercially available) over just 2 hours**
- **Higher bioavailability**
- **Better digestibility**
- **Light stomach feel**



Tested vs :
highly hydrolysed protein hydrolysate (WPH) and regular whey protein isolate (WPI)

ORYGN

Why is triGLP different?
Unique Health Benefits & Mode of Action

- GLP-1, GIP & GLP-2 – supporting weight control and better gut health
- Protecting Muscle Mass
- Boosting energy levels
- New and unique health claims

→ **Advanced Science:** Powerful Gene Expression Modulation

>3x FTH1 upregulation

Effects:

- Improves iron absorption from the daily diet
- Enhances energy levels
- None of the adverse effects of iron supplementation

>3x HMOX1 upregulation

Effects:

- Supports GI health via important targeted protective pathways
- Provides antioxidant benefits

>3x ALOX-12 downregulation

Effects:

- Increases fat burn
- Increases insulin sensitivity
- Better body profile and weight control

ORYGN

triGLP Health Claims & Regulatory Status

triGLP has been classified as a New Dietary Ingredient (NDI) by the US FDA with self GRAS

	Iron metabolism	Metabolic efficiency	Skin
Health Canada Approved Qualified Health Claims	• **Helps maintain healthy levels of ferritin and hemoglobin** • **Helps maintain healthy levels of blood components required for oxygen transport**	• **Provides antioxidants for the maintenance of good health**	• **Helps promote healthy skin**
US FDA Structure Function claims	• Supports healthy ferritin and hemoglobin levels • Supports red blood cell production • Helps maintain iron-rich blood • **Assists in iron absorption from your daily diet**	• **Acts as an antioxidant** • Supports Gastrointestinal and Immune System Health • Supports a healthy response to gut inflammation. • Promotes energy utilization and reduces occasional fatigue and general feelings of occasional tiredness	• Helps with dry skin and promote healthy skin • Supports skin health and appearance • **Reduces wrinkles and promotes skin smoothness** • Prevents an increase in trans-epidermal water loss • Reduces oxidative stress caused by free radicals

ORYGN

GLP-1 & Better Metabolic Health

The 21st century has seen a progressive increase in the body fat in the population

Over 70% of US adults are either overweight or obese

Avoiding substantial weight gain with ageing can be challenging

On average an adult's BMI will increase by 1.5 per decade: an overweight 40-year-old is at significant risk of obesity by their 60s. So for instance, a 40yr old with a BMI of 27 will have on average a BMI of 31.25 by the age of 65.

Obesity impacts health, quality of life and life expectancy

A preventative approach to obesity to support healthy ageing is urgently needed…

ORYGN

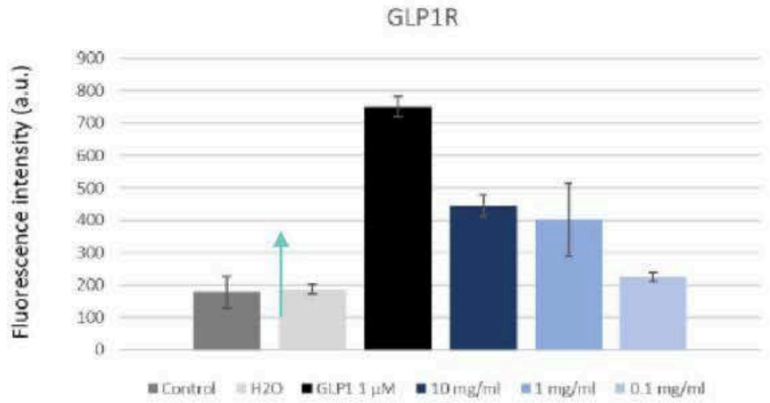
GLP-1 Based Healthy Fat Loss with triGLP

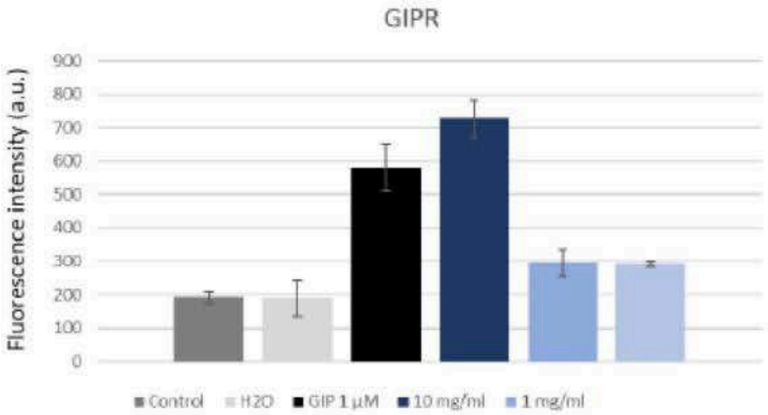
New mode of action

- **triGLP has consistently shown a 6-7% reduction in BMI via a reduction in body fat only**
- **triGLP was assayed for GLP=1 & GIP activity to try and determine the mode of action of weight loss**
- **At 1mg/ml triGLP doubled the activity of the GLP1 receptor equivalent to a 2.3-fold increase for the 10mg/ml dose**
- **GIP receptor activity increased 1.5-fold with SPH at 0.1mg/ml & 1mg/ml, and 3.8-fold increase with 10mg/ml**
- **GIP has an important role in regulating nutrient metabolism, adding to the actions of GLP-1**
- **Biologically relevant increases in GLP-1 and GIP activity explain the mechanism behind the weight loss with triGLP**

Innoprot research: The charts show the results from a proprietary fluorescent biosensor assay. This measured cellular response (via fluorescence intensity) in a GLP1 & GIP receptor cell line following activation of the receptors by SPH at 0.1mg/ml, 1mg/ml and10mg/ml.

triGLP GLP-1 & GIP activity demonstrated in vitro

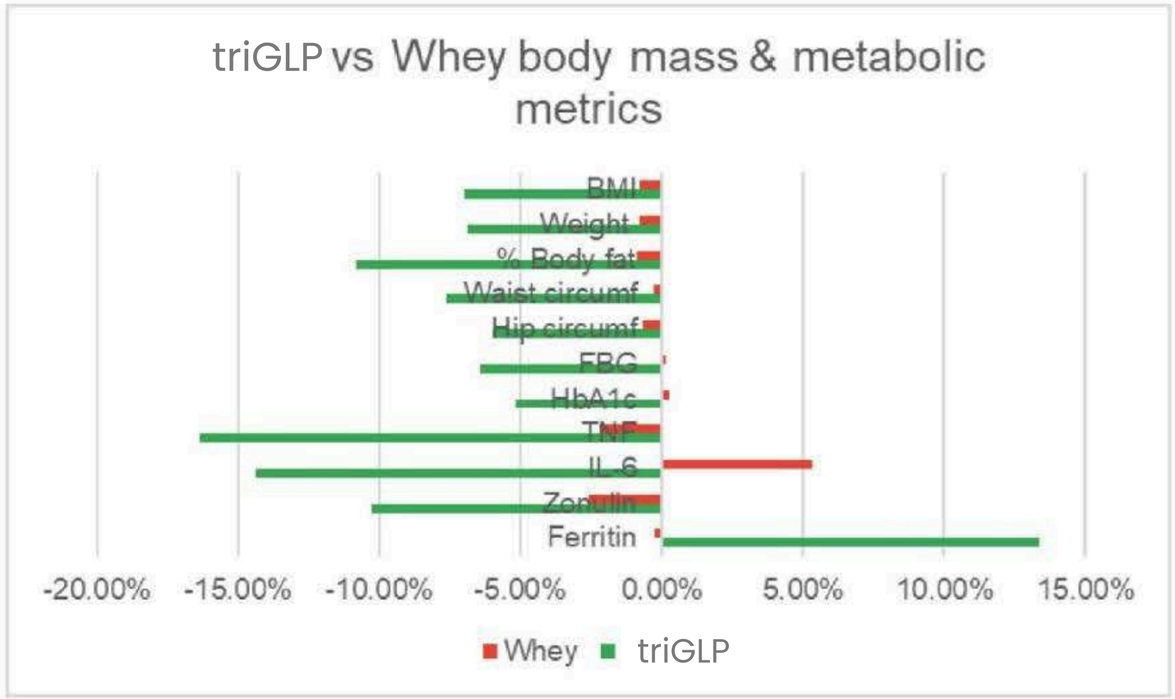




ORYGN

triGLP Clinical Study: Metabolic Health

Bioactive Peptides Clinical Trial		
14 healthy subjects	12g/day	8 weeks



	Weight	BMI	Hip circumf	Waist circumf	% Body fat	% Body water	IL-6	TNF	HbA1c	FBG
Pep Ty	-6.90%	-6.97%	-6.00%	-7.67%	-10.81%	0%	-14.40%	-16.40%	-5.18%	-6.43%
Whey	-0.80%	-0.78%	-0.68%	-0.31%	-0.91%	0%	5.30%	-2.20%	0.26%	0.15%

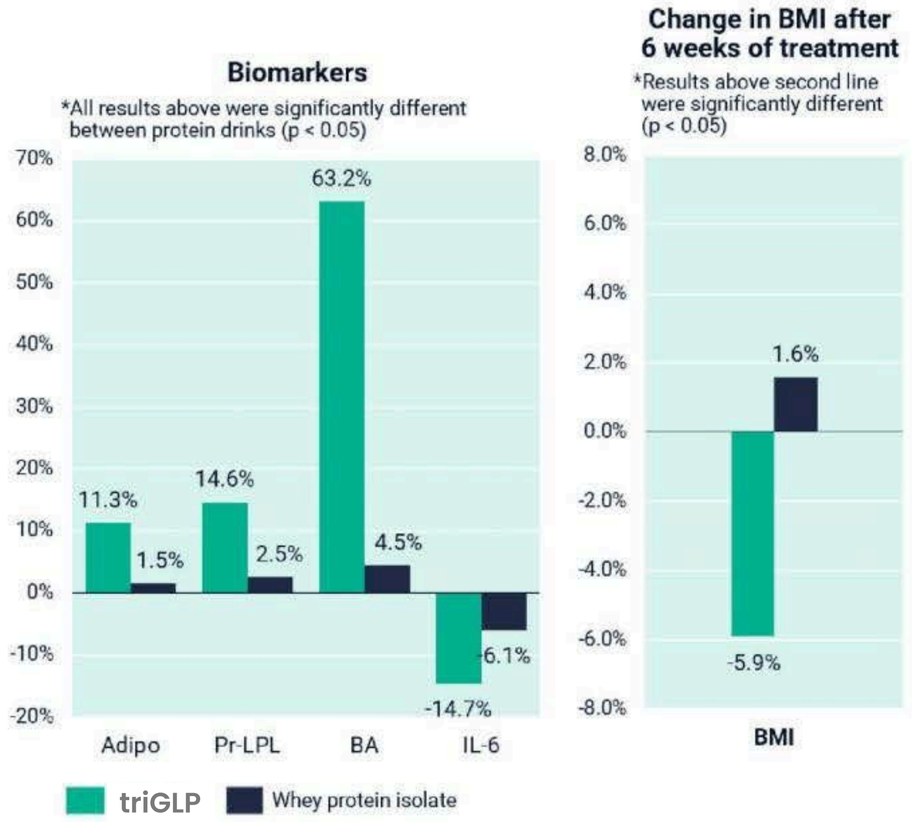
- **BMI reduced by 7%** (28.6kg/m² to 26.6kg/m²) after just 8 weeks of triGLP
- **Body fat declined by 10% with no change in body water** - demonstrating the BMI reduction was fat loss
- **Blood sugar declines** indicate improved insulin effectiveness & better glucose uptake
- **Reduction in zonulin** a marker of leaky bowel
- **Significant declines in inflammatory markers, TNF and IL-6** which are strongly associated with ill health
- **Marked increase in ferritin,** reflecing improved iron stores and a **better ability to use oxygen**

Leaner, healthier body with more energy

ORYGN

triGLP Clinical Study: Overweight Subjects

Bioactive Peptides Clinical Trial		
48 overweight subjects	16g/day	6 weeks



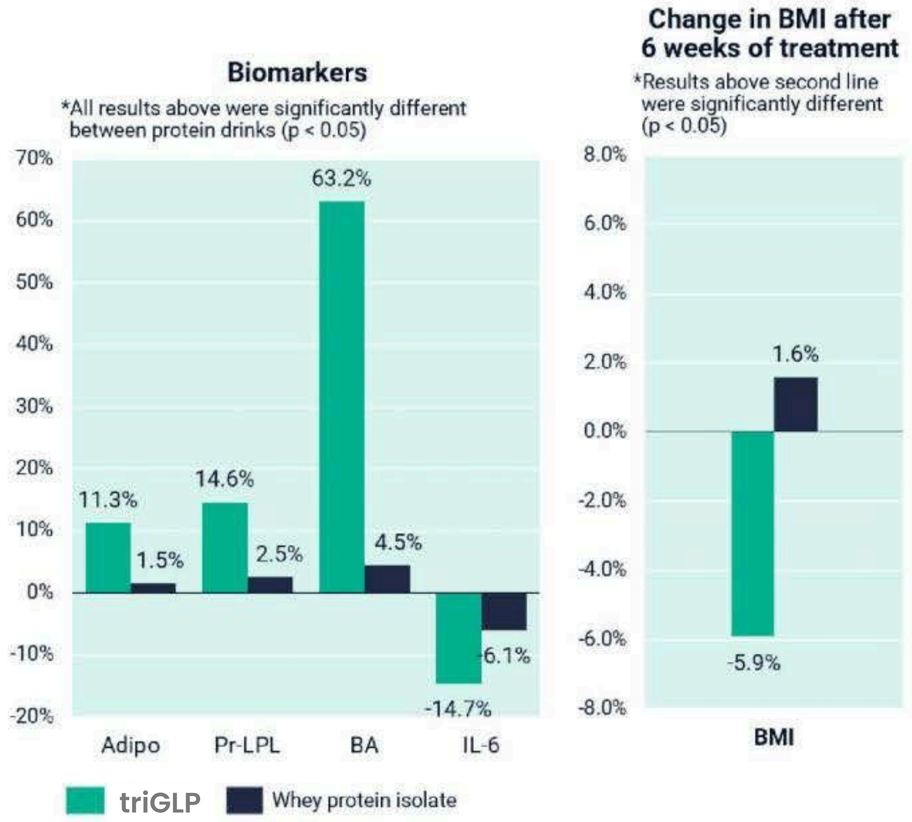
- **Confirmatory -6% BMI reduction** in just 6 weeks
- **Further pro-metabolic efficiency gains** seen through key markers of improved insulin sensitisation (adiponectin) and reduced blood cholesterol (lipoprotein lipase)
- **Significant bile acid (BA) boost** (remaining within healthy limits) boosting fat burn
- **Significant reductions in inflammation:** IL-6, an important driver of ill health, reduced by 15%

Published:
Framroze et. al. **A placebo-controlled, randomized study on the impact of dietary salmon protein hydrolysate supplementation on body mass index in overweight human subjects**. J. of Obesity & Weight Loss Therapy 2016

ORYGN

triGLP Clinical Study: Overweight Subjects

Bioactive Peptides Clinical Trial		
48 overweight subjects	16g/day	6 weeks

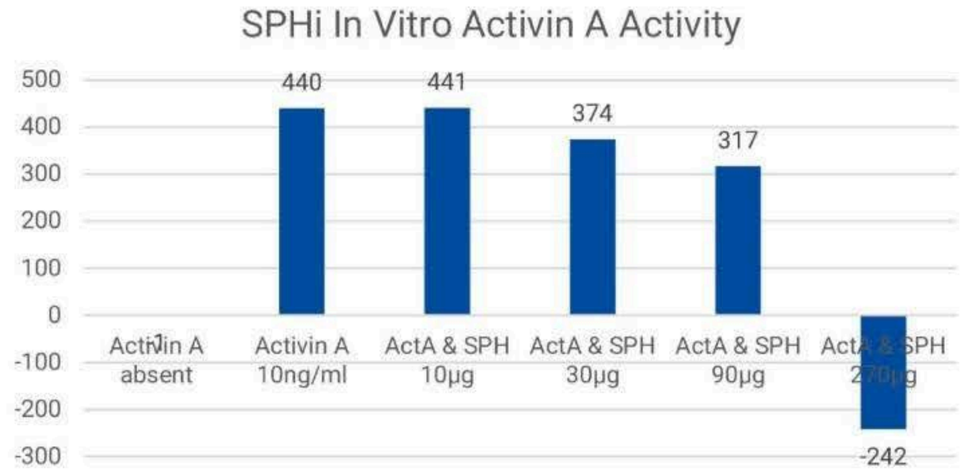


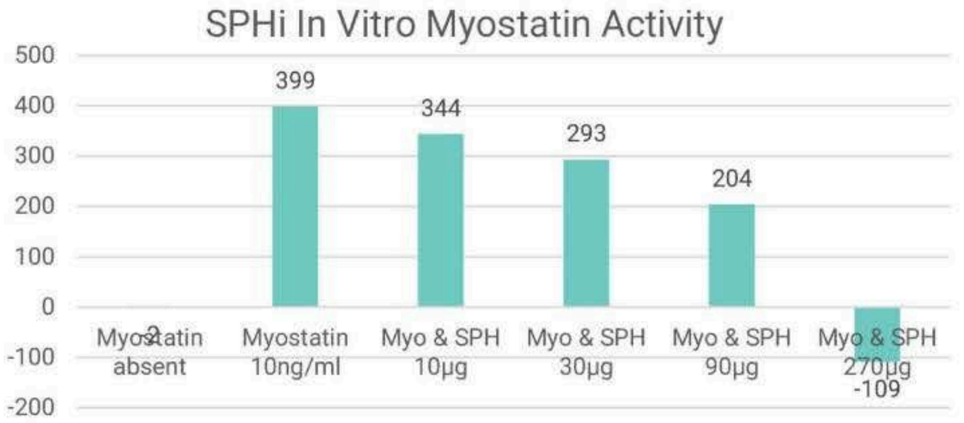
- **Confirmatory -6% BMI reduction** in just 6 weeks
- **Further pro-metabolic efficiency gains** seen through key markers of improved insulin sensitisation (adiponectin) and reduced blood cholesterol (lipoprotein lipase)
- **Significant bile acid (BA) boost** (remaining within healthy limits) boosting fat burn
- **Significant reductions in inflammation:** IL-6, an important driver of ill health, reduced by 15%

Published:
Framroze et. al. **A placebo-controlled, randomized study on the impact of dietary salmon protein hydrolysate supplementation on body mass index in overweight human subjects**. J. of Obesity & Weight Loss Therapy 2016

ORYGN

triGLP Protects Against Muscle Mass Loss





- **Activin A and myostatin are negative regulators of skeletal muscle mass**
- Increased activity of activin A and myostatin is associated with ageing & in other inflammatory conditions
- **Our studies show very strong inhibition of these agents** resulting in increased muscle mass with improved survival in cachexia animal models
- A recent obesity animal model showed that combining an activin inhibitor with a GLP-1 therapy **increased fat loss** & **increased muscle mass**[1]
- In vitro assays shows a dose-dependent inhibition of activin and myostatin by peptides contained in SPHi (presented at MASCC* 2023 meeting)
- **This suggests SPH can protect muscle mass combined with the weight loss effects of its GLP-1 effects**

[1]E Nunn et al Mol Metab 2024; *MASCC = Multinational Association of Supportive Care in Cancer

ORYGN

Maintaining Muscle Mass for Metabolic Rate and Health with Age

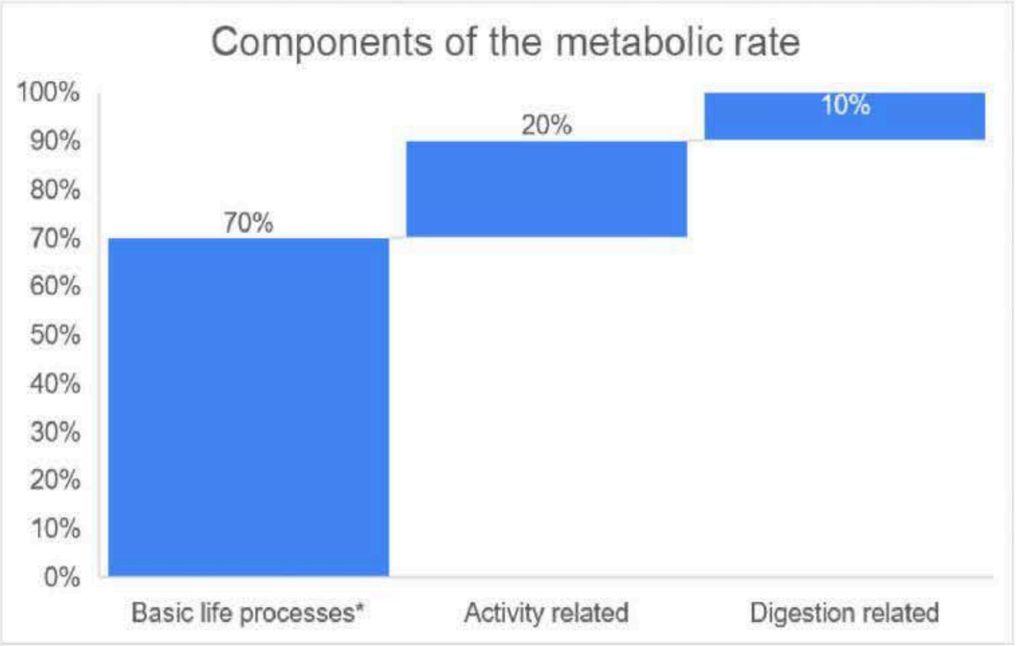
Our Metabolic Rate is comprised of:

1. A Basal Rate for functions such as heat & energy production and for basic life processes*
2. An Activity-related rate
3. Diet-related & digestion effects

Muscle is important for heat production and burning calories, however, muscle mass loss occurs from 3rd decade of life onwards and does not stop.

A reduction in muscle mass will have a significant impact on the metabolic rate and change the ratio of the calories converted into energy vs stored as fat

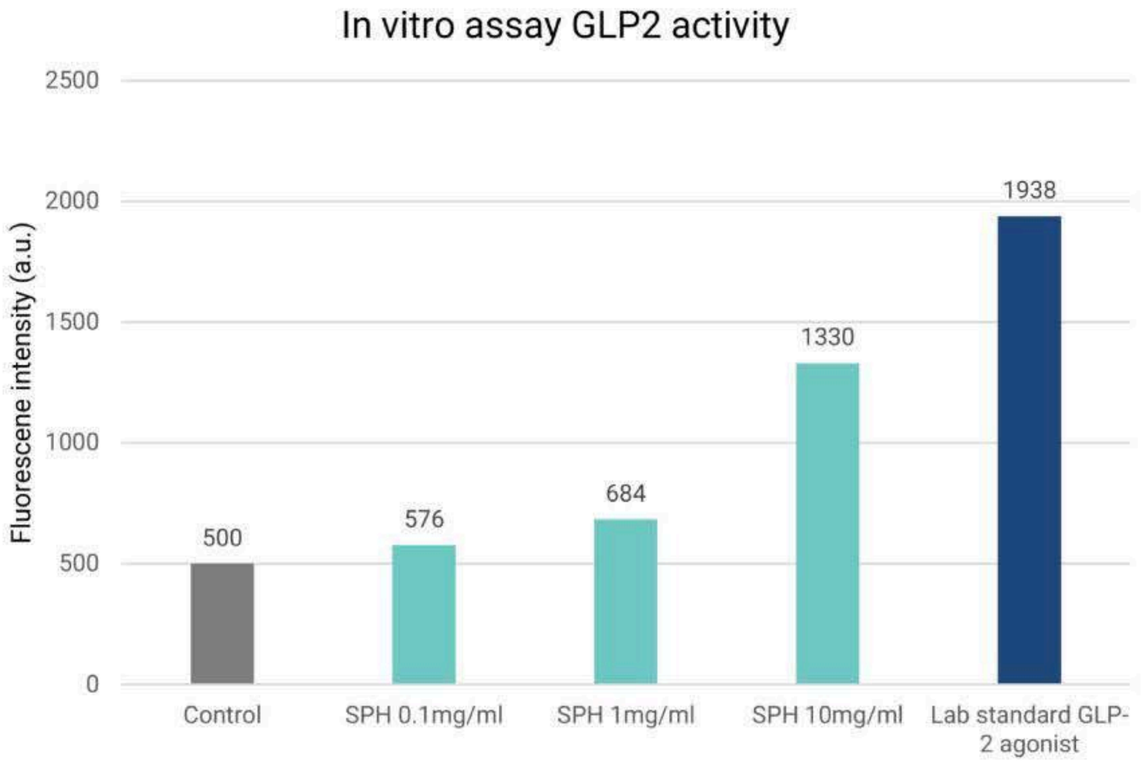
Preservation of muscle mass is central to supporting Performance Ageing



**functions such as breathing, heart beating, muscle tone, heat generation (liver and muscle), protein synthesis etc*

ORYGN

Key Benefits of GLP-2 Activation



A proprietary fluorescent biosensor assay (Innoprot) using a GLP-2 receptor cell line. GLP-2 receptor activity reflected by level of fluorescence intensity. A.U. = arbitrary units.

The gut can become leakier with age which reduces nutrient absorption and provides a less effective barrier against toxins

GLP-2 has a variety of roles important for normal GI functioning:

- Delay of gastric emptying
- Support the barrier function to keep microbes and toxins out
- Support the absorption of nutrients, especially protein, via the expansion of the GI mucosa surface area

In vitro assay of GLP-2 receptor activity of SPH at three dose levels vs negative control

SPH showed a 1.3-fold and 2.6-fold increase in GLP-2 receptor signalling at 1mg/ml and 10mg/ml & lab standard GLP-2 agonist showed a 3.8-fold increase

This suggests SPH has the potential to support GI health and help to avoid inadequate protein intake / absorption that can be seen in weight-loss programs including GLI

ORYGN

triGLP and Improved Glucose Metabolism

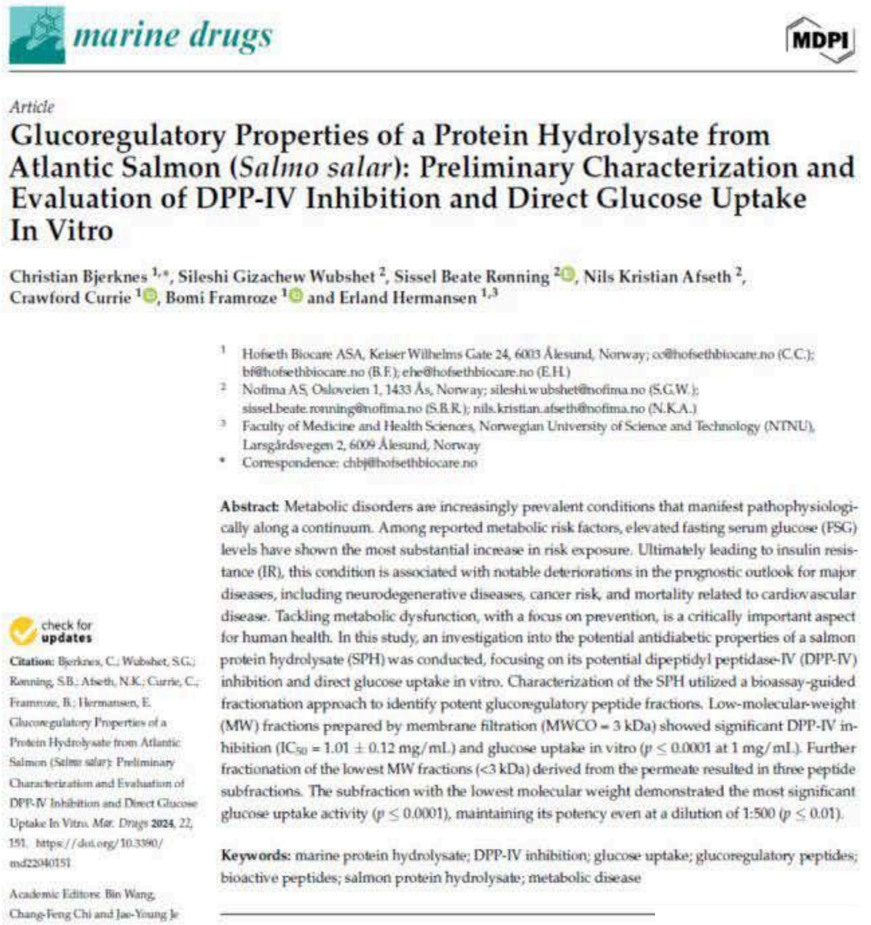
- **triGLP has consistently shown a 3-6% reduction in fasting blood glucose and improved energy levels in clinical studies**

- In vitro studies were initiated to assess both insulin-dependent and independent mechanisms of action

- This showed that the smaller peptides in **triGLP helped improve energy levels by:**

  1. **Direct uptake of glucose into muscles**

  2. **DPP-IV inhibition to improve insulin's effectiveness to move glucose from the blood into the muscles**



marine drugs MDPI

Article

Glucoregulatory Properties of a Protein Hydrolysate from Atlantic Salmon (*Salmo salar*): Preliminary Characterization and Evaluation of DPP-IV Inhibition and Direct Glucose Uptake In Vitro

Christian Bjerknes [1,*], Sileshi Gizachew Wubshet [2], Sissel Beate Rønning [2], Nils Kristian Afseth [2], Crawford Currie [1], Bomi Framroze [1] and Erland Hermansen [1,3]

[1] Hofseth Biocare ASA, Keiser Wilhelms Gate 24, 6003 Ålesund, Norway; cc@hofsethbiocare.no (C.C.); bf@hofsethbiocare.no (B.F.); ehe@hofsethbiocare.no (E.H.)
[2] Nofima AS, Osloveien 1, 1433 Ås, Norway; sileshi.wubshet@nofima.no (S.G.W.); sissel.beate.ronning@nofima.no (S.B.R.); nils.kristian.afseth@nofima.no (N.K.A.)
[3] Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Larsgårdsvegen 2, 6009 Ålesund, Norway
* Correspondence: chbj@hofsethbiocare.no

Abstract: Metabolic disorders are increasingly prevalent conditions that manifest pathophysiologically along a continuum. Among reported metabolic risk factors, elevated fasting serum glucose (FSG) levels have shown the most substantial increase in risk exposure. Ultimately leading to insulin resistance (IR), this condition is associated with notable deteriorations in the prognostic outlook for major diseases, including neurodegenerative diseases, cancer risk, and mortality related to cardiovascular disease. Tackling metabolic dysfunction, with a focus on prevention, is a critically important aspect for human health. In this study, an investigation into the potential antidiabetic properties of a salmon protein hydrolysate (SPH) was conducted, focusing on its potential dipeptidyl peptidase-IV (DPP-IV) inhibition and direct glucose uptake in vitro. Characterization of the SPH utilized a bioassay-guided fractionation approach to identify potent glucoregulatory peptide fractions. Low-molecular-weight (MW) fractions prepared by membrane filtration (MWCO = 3 kDa) showed significant DPP-IV inhibition (IC_{50} = 1.01 ± 0.12 mg/mL) and glucose uptake in vitro ($p \leq 0.0001$ at 1 mg/mL). Further fractionation of the lowest MW fractions (<3 kDa) derived from the permeate resulted in three peptide subfractions. The subfraction with the lowest molecular weight demonstrated the most significant glucose uptake activity ($p \leq 0.0001$), maintaining its potency even at a dilution of 1:500 ($p \leq 0.01$).

Keywords: marine protein hydrolysate; DPP-IV inhibition; glucose uptake; glucoregulatory peptides; bioactive peptides; salmon protein hydrolysate; metabolic disease

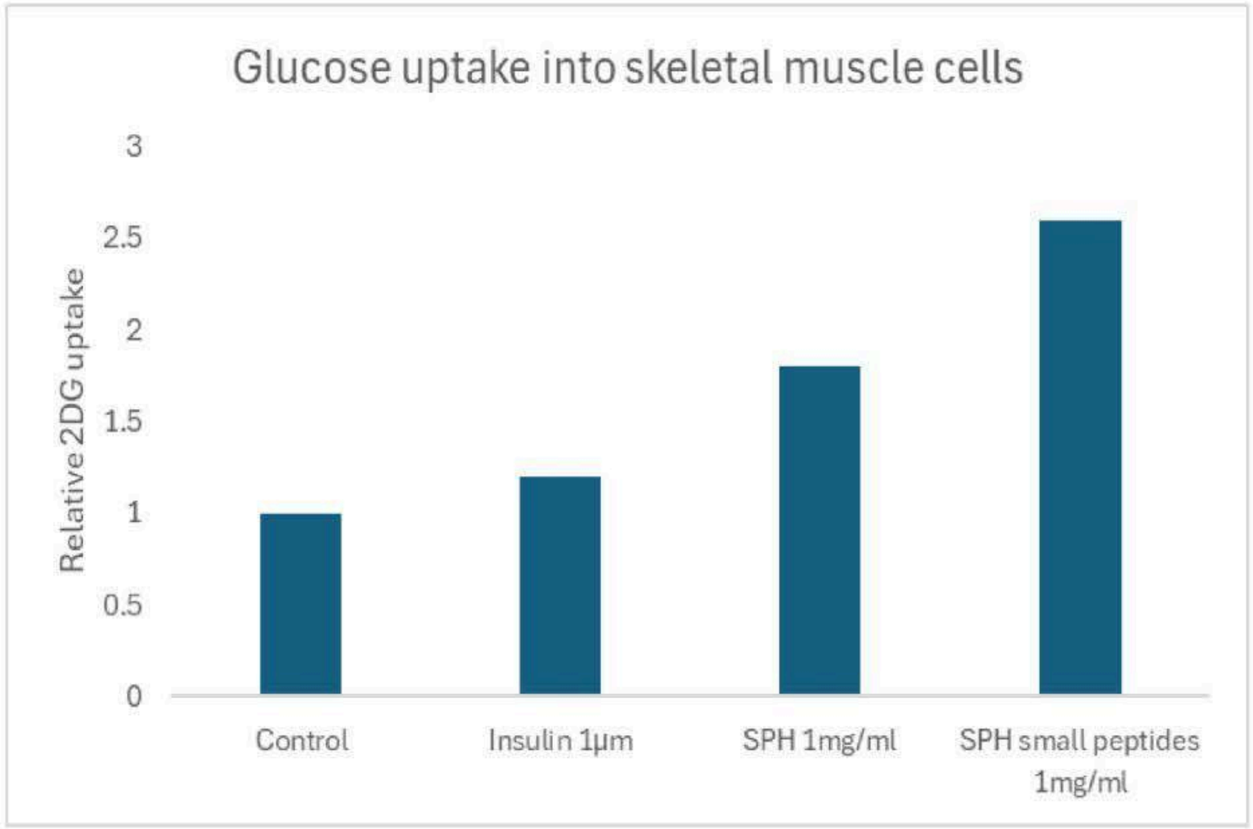
check for updates

Citation: Bjerknes, C.; Wubshet, S.G.; Rønning, S.B.; Afseth, N.K.; Currie, C.; Framroze, B.; Hermansen, E. Glucoregulatory Properties of a Protein Hydrolysate from Atlantic Salmon (*Salmo salar*): Preliminary Characterization and Evaluation of DPP-IV Inhibition and Direct Glucose Uptake In Vitro. *Mar. Drugs* **2024**, *22*, 151. https://doi.org/10.3390/md22040151

Academic Editors: Bin Wang, Chang-Feng Chi and Jae-Young Je

ORYGN

Increase in Glucose Uptake in Muscles



- **triGLP's smaller peptides drive the improved direct uptake of glucose into muscle by 100% compared to control**

This provides:

1. **Increased energy for an active lifestyle**
2. **Better regulation of blood glucose levels**
3. **Better metabolic health with lower inflammatory levels and less stress on the body**

ORYGN

triGLP Clinical Study: Energy, Vitality & Mood

Bioactive Peptides Clinical Study Safety study for Health Canada QHCs		
20 healthy subjects	4g/day	128 days

↑ **57%** anti-inflammatory IL-10 levels

↓ **7%** red cell variability

↑ **4.2x** HMOX-1 gene expression

↓ **9%** oxidative stress

↑ **3.8x** FTH-1 gene expression

↑ **Vitality** p=0.005

↑ **Waking up energized** p=0.004

↓ **Irritability** p=0.001

A proof-of-concept study to evaluate the efficacy of SPH powder on energy increase, hair/nail/skin health and anti-inflammatory modulation in healthy males and females

- Improved metabolic efficiency at lower doses
- Anti-inflammatory effects via significant increase in IL-10
- Less red blood cell variability demonstrating less stress on the body
- Significant HMOX1 increase for protecting gut health
- Better overall wellbeing
- The same benefits from 4g to 16g doses

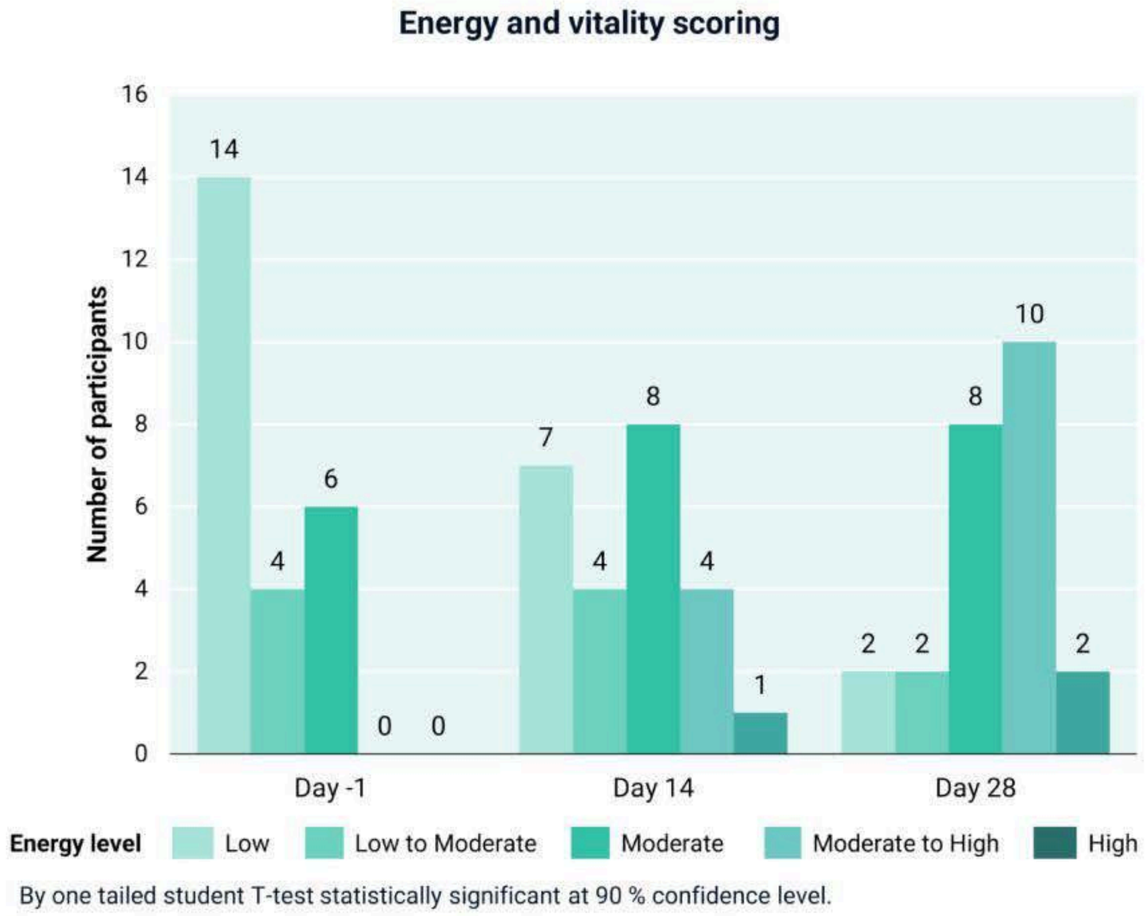
Publication pending

ORYGN

triGLP Clinical Study: Energy Improvement

Bioactive Peptides Human Survey		
24 subjects	4g/day	4 weeks

- On Day one, 100% (18/24) of subjects reported moderate to low energy levels
- By the last day of the trial, only 8% (2/24) reported low energy levels and 83% reported moderate high energy levels
- 87% (21/24) of subjects showed a statistically significant increase in energy and vitality



By one tailed student T-test statistically significant at 90 % confidence level.

Unpublished study. Data on file.

ORYGN

Stanford Research

FTH1

HMOX1

triGLP Clinical Study: Gut Health

biomolecules

MDPI

Article

Soluble Protein Hydrolysate Ameliorates Gastrointestinal Inflammation and Injury in 2,4,6-Trinitrobenzene Sulfonic Acid-Induced Colitis in Mice

Jingjing Wei [1,2], Guozhong Tao [1,*], Baohui Xu [1], Kewei Wang [1,3], Junlin Liu [1,4], Chih-Hsin Chen [1], James C. Y. Dunn [1], Crawford Currie [5], Bomi Framroze [1,5] and Karl G. Sylvester [1,*]

1 Department of Surgery, Stanford University School of Medicine, Stanford, CA 94304, USA
2 Department of Pediatrics, Shanxi Medical University, Taiyuan 030001, China
3 Department of Gastrointestinal Surgery, The First Hospital of China Medical University, Shenyang 110001, China
4 Department of General Surgery, The People's Hospital of Liuyang City, Liuyang 410300, China
5 R&D Department, Holseth BioCare AS, 6033 Aalesund, Norway
* Correspondence: gtao@stanford.edu (G.T.); sylvester@stanford.edu (K.G.S.)

Abstract: Inflammatory bowel diseases (IBD) are chronic, recurring gastrointestinal diseases that severely impair health and quality of life. Although therapeutic options have significantly expanded in recent years, there is no effective therapy for a complete and permanent cure for IBD. Well tolerated dietary interventions to improve gastrointestinal health in IBD would be a welcome advance especially with anticipated favorable tolerability and affordability. Soluble protein hydrolysate (SPH) is produced by the enzymatic hydrolysis of commercial food industry salmon offcuts (consisting of the head, backbone and skin) and contains a multitude of bioactive peptides including those with anti-oxidant properties. This study aimed to investigate whether SPH ameliorates gastrointestinal injury in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced mouse colitis model. Mice were randomly assigned to four groups: Control (no colitis), Colitis, Colitis/CP (with control peptide treatment), and Colitis/SPH (with SPH treatment). Colitis was induced by cutaneous sensitization with 1% TNBS on day −8 followed by 2.5% TNBS enema challenge on day 0. Control peptides and SPH were provided to the mice in the Colitis/CP or Colitis/SPH group respectively by drinking water at the final concentration of 2% *w*/*v* daily from day −10 to day 4. Then, the colon was harvested on day 4 and examined macro- and microscopically. Relevant measures included disease activity index (DAI), colon histology injury, immune cells infiltration, pro- and anti-inflammatory cytokines and anti-oxidative gene expression. It was found that SPH treatment decreased the DAI score and colon tissue injury when compared to the colitis-only and CP groups. The protective mechanisms of SPH were associated with reduced infiltration of $CD4^+$ T, $CD8^+$ T and $B220^+$ B lymphocytes but not macrophages, downregulated pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-6), and upregulated anti-inflammatory cytokines (transforming growth factor-β1 and interleukin-10) in the colon tissue. Moreover, the upregulation of anti-oxidative genes, including ferritin heavy chain 1, heme oxygenase 1, NAD(P)H quinone oxidoreductase 1, and superoxide dismutase 1, in the colons of colitis/SPH group was observed compared with the control peptide treatment group. In conclusion, the protective mechanism of SPH is associated with anti-inflammatory and anti-oxidative effects as demonstrated herein in an established mice model of colitis. Clinical studies with SPH as a potential functional food for the prevention or as an adjuvant therapy in IBD may add an effective and targeted diet-based approach to IBD management in the future.

Keywords: soluble protein hydrolysate; IBD; TNBS; anti-inflammatory; anti-oxidative

1. Introduction

Inflammatory bowel diseases (IBD) affect more than 1.5 million Americans, with over 70,000 new cases diagnosed annually (https://www.crohnscolitisfoundation.org/

check for updates

Citation: Wei, J.; Tao, G.; Xu, B.; Wang, K.; Liu, J.; Chen, C.-H.; Dunn, J.C.Y.; Currie, C.; Framroze, B.; Sylvester, K.G. Soluble Protein Hydrolysate Ameliorates Gastrointestinal Inflammation and Injury in 2,4,6-Trinitrobenzene Sulfonic Acid-Induced Colitis in Mice. *Biomolecules* **2022**, *12*, 1287. https://doi.org/10.3390/biom12091287

Academic Editor: Piotr Grzelczyk

Received: 2 August 2022
Accepted: 8 September 2022
Published: 13 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

triGLP upregulates anti-oxidative gene expression to support gut health & protect against inflammation

A standard mouse model of inflammatory bowel disease (IBD)
Three groups with chemically-induced IBD were treated with:

1. **Water**
2. **Collagen peptides (Vital Protein) or**
3. **triGLP bioactive peptides**

Fourth group acted as control & therefore had no bowel disease

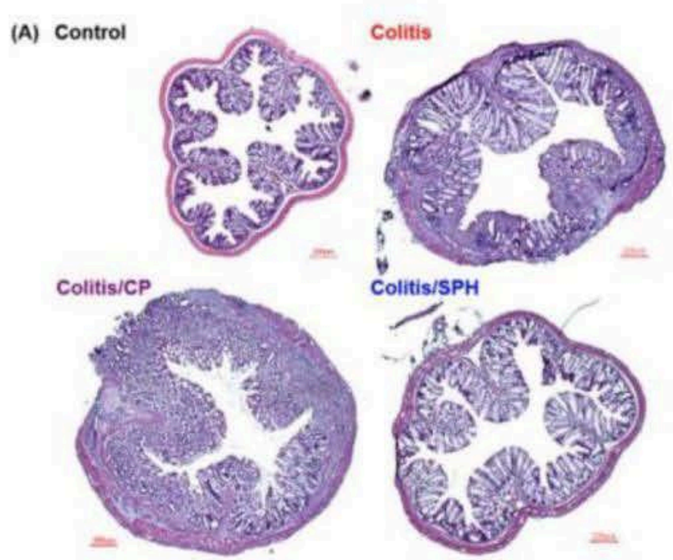
triGLP provided faster recovery for the gut and overall health via an increase in HMOX1 and FTH1

This was NOT a nutritional effect supporting healing - the control peptides (Vital Protein) had no benefit for gut health or overall health

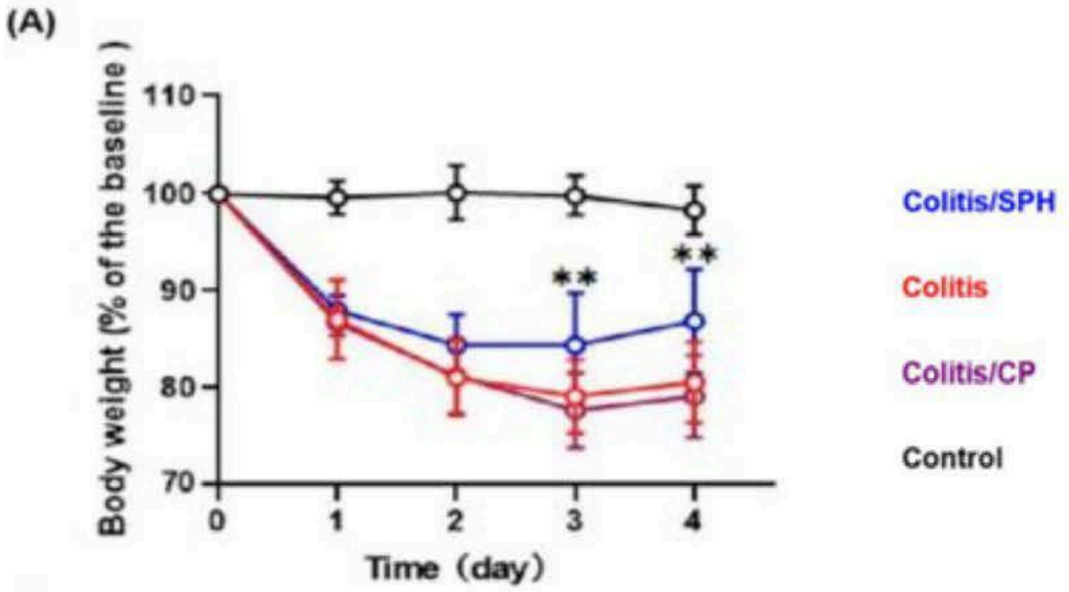
ORYGN

Improved GI & Overall Health

Normal structure of the gut protected indicating better gut function maintained



Protecting gut function led to a significantly improved recovery as indicated by the weight profile



triGLP helped to reduce swelling, maintain the gut lining and reduce stress on the body enabling faster weight recovery – weight loss is an important marker of disease severity and weight regain on the effectiveness of treatment in inflammatory bowel disease

The group fed bovine collagen peptides suffered severe damage to the gut, with gross swelling and damage indicating significant loss of bowel function reflected in the very weak recovery

J Wei, G. Tao, K Sylvester et al. Soluble protein hydrolysate ameliorates GI inflammation and injury in 2,4,6 TNBS-induced colitis in mice, Biomolecules 2022, 12,1287.

Summary & Conclusions

triGLP modulation of HMOX-1 gene-expression shows:

1. triGLP upregulates HMOX-1, an antioxidant gene system needed to sustain & enhance GI health
2. triGLP supports gut health & overall health by re-balancing the immune system and resolving inflammation & oxidative stress
3. ***Beyond simple nutrition — with a protein collagen of bovine source there was no discernible GI or overall health benefits***

The collaborative preclinical study found that the soluble protein hydrolysate triGLP powder:

- Significantly reduces clinical severity (weight loss) and improved structural integrity of the gut
- Reduces gut inflammation, by rebalancing the number of immune cells in the gut wall
- Significantly reduces inflammatory mediators & increases anti-inflammatory mediators
- Immunomodulatory action with upregulation of protective, antioxidant gene pathways including HMOX1
- Overall, helps restore a healthy balance within the gut immune system and markedly improves gut health in inflammatory bowel disease (IBD)

Study PDF available at
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9496120/pdf/biomolecules-12-01287.pdf