GLP THREE™ Research Dossier

GLP THREE™ is a revolutionary product that can support healthy weight management and overall metabolic health.

The key ingredient in GLP THREE™ is our proprietary Metabolic Boost Complex-267™—aka MBC-267™—that consists of 267 naturally-occurring peptides from salmon protein hydrolysate (SPH) and mushrooms.

GLP THREE™ also includes effective amounts of saffron, ginseng, and hops that also support health of the GLP-1 enzyme, thus making GLP THREE™ a comprehensive support product for GLP-1.

THIS RESEARCH DOSSIER CONTAINS THE FOLLOWING INFORMATION:
• Data showing that GLP THREE™ helps to support a healthy weight.
• MBC-267™ and the GLP THREE™ formulation is patent-pending and exclusive to THREE International.
• GLP THREE™ is listed in the Prescriber's Digital Reference (PDR) as a resource to medical professionals.
• Peer-reviewed publications showing that peptides in mushroom and molecules in saffron, ginseng and hops can support the GLP-1 Signaling Pathway, maintain lean muscle mass, and help with sleep, mood, energy and meabolic health.

Thank you for joining us on this journey and for trusting us with your proactive wellness needs!

Be well,

Dr. Dan Gubler
Chief Scientific Officer
Three International

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Lehi, UT 84043

Study results
GLP THREE™ can support a healthy weight:

MBC-267™ and GLP THREE™ is patent pending.

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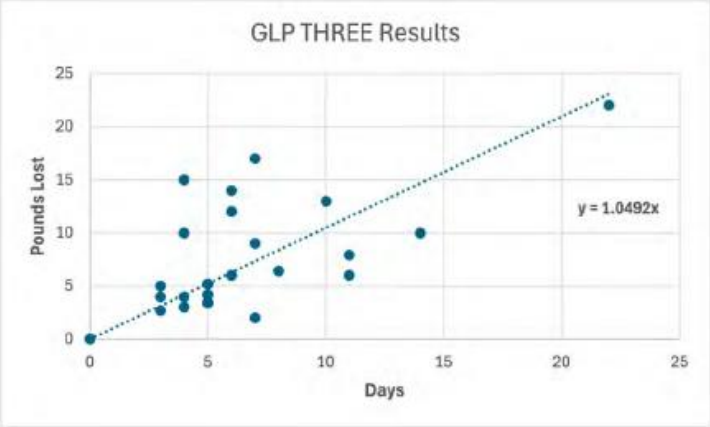
THREE

Study results

GLP THREE™ can support a healthy weight:



MBC-267™ and GLP THREE™ is patent pending.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
63/975,880	02/04/2026 05:56:38 PM Z ET	

Title of Invention

PEPTIDE-PHYTONUTRIENT COMPOSITIONS FOR SUPPORTING WEIGHT MANAGEMENT AND METABOLIC HEALTH

Application Information

APPLICATION TYPE	Utility - Provisional Application under 35 USC 111(b)	PATENT #	-
CONFIRMATION #	1196	FILED BY	
PATENT CENTER #	74336229	FILING DATE	-
CUSTOMER #		FIRST NAMED INVENTOR	Daniel A. Gubler
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Study results (Cont.)
GLP THREE™ is listed in the Prescribers' Digital Reference (PDR). See the full entry at PDR.net

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Int J Mol Sci. 2019 Apr 20;20(8):1939. doi: 10.3390/ijms20081939.

How Charge and Triple Size-Selective Membrane Separation of Peptides from Salmon Protein Hydrolysate Orientate their Biological Response on Glucose Uptake

Loïc Henaux 1 2 , Jacinthe Thibodeau 3 4 , Geneviève Pilon 5 6 , Tom Gill 7 , André Marette 8 9 , Laurent Bazinet 10 11

Affiliations

PMID: 31009989 PMCID: PMC6515250 DOI: 10.3390/ijms20081939

Abstract

The valorization of by-products from natural organic sources is an international priority to respond to environmental and economic challenges. In this context, electrodialysis with filtration membrane (EDFM), a green and ultra-selective process, was used to separate peptides from salmon frame protein hydrolysate. For the first time, the simultaneous separation of peptides by three ultrafiltration membranes of different molecular-weight exclusion limits (50, 20, and 5 kDa) stacked in an electrodialysis system, allowed for the generation of specific cationic and anionic fractions with different molecular weight profiles and bioactivity responses. Significant decreases in peptide recovery, yield, and molecular weight (MW) range were observed in the recovery compartments depending on whether peptides had to cross one, two, or three ultrafiltration membranes. Moreover, the Cationic Recovery Compartment 1 fraction demonstrated the highest increase (42%) in glucose uptake on L6 muscle cells. While, in the anionic configuration, both Anionic Recovery Compartment 2 and Anionic Recovery Compartment 3 fractions presented a glucose uptake response in basal condition similar to the insulin control. Furthermore, Cationic Recovery Compartment 3 was found to contain inhibitory peptides. Finally, LC-MS analyses of the bioassay-guided bioactive fractions allowed us to identify 11 peptides from salmon by-products that are potentially responsible for the glucose uptake improvement.

Keywords: bioactive peptides; bioassay-guided validation; electrodialysis with filtration membrane (EDFM); glucose uptake; triple size-selective separation.

Figures

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J Nutr. 2015 Jul;145(7):1415-22. doi: 10.3945/jn.114.208215. Epub 2015 May 20.

Low-Molecular-Weight Peptides from Salmon Protein Prevent Obesity-Linked Glucose Intolerance, Inflammation, and Dyslipidemia in LDLR-/-/ApoB100/100 Mice

Geneviève Chevrier 1 , Patricia L Mitchell 1 , Laurie-Eve Rioux 1 , Fida Hasan 2 , Tianyi Jin 2 , Cyril Roland Roblet 3 , Alain Doyen 3 , Geneviève Pilon 1 , Philippe St-Pierre 1 , Charles Lavigne 1 , Laurent Bazinet 3 , Hélène Jacques 3 , Tom Gill 2 , Roger S McLeod 4 , André Marette 5

Affiliations

PMID: 25995281 DOI: 10.3945/jn.114.208215
Free article

Abstract

Background: We previously reported that fish proteins can alleviate metabolic syndrome (MetS) in obese animals and human subjects.

Objectives: We tested whether a salmon peptide fraction (SPF) could improve MetS in mice and explored potential mechanisms of action.

Methods: ApoB(100) only, LDL receptor knockout male mice (LDLR(-/-)/ApoB(100/100)) were fed a high-fat and -sucrose (HFS) diet (25 g/kg sucrose). Two groups were fed 10 g/kg casein hydrolysate (HFS), and 1 group was additionally fed 4.35 g/kg fish oil (FO; HFS+FO). Two other groups were fed 10 g SPF/kg (HFS+SPF), and 1 group was additionally fed 4.35 g FO/kg (HFS+SPF+FO). A fifth (reference) group was fed a standard feed pellet diet. We assessed the impact of dietary treatments on glucose tolerance, adipose tissue inflammation, lipid homeostasis, and hepatic insulin signaling. The effects of SPF on glucose uptake, hepatic glucose production, and inducible nitric oxide synthase activity were further studied in vitro with the use of L6 myocytes, FAO hepatocytes, and J774 macrophages.

Results: Mice fed HFS+SPF or HFS+SPF+FO diets had lower body weight (protein effect, $P = 0.024$), feed efficiency (protein effect, $P = 0.018$), and liver weight (protein effect, $P = 0.003$) as well as lower concentrations of adipose tissue cytokines and chemokines (protein effect, $P \leq 0.003$) compared with HFS and HFS+FO groups. They also had greater glucose tolerance (protein effect, $P < 0.001$), lower activation of the mammalian target of rapamycin complex 1/S6 kinase 1/insulin receptor substrate 1 (mTORC1/S6K1/IRS1) pathway, and increased insulin signaling in liver compared with the HFS and HFS+FO groups. The HFS+FO, HFS+SPF, and HFS+SPF+FO groups had lower plasma triglycerides (protein effect, $P = 0.003$; lipid effect, $P = 0.002$) than did the HFS group. SPF increased glucose uptake and decreased HGP and iNOS activation in vitro.

Conclusions: SPF reduces obesity-linked MetS features in LDLR(-/-)/ApoB(100/100) mice. The anti-inflammatory and glucoregulatory properties of SPF were confirmed in L6 myocytes, FAO hepatocytes, and J774 macrophages.

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Membranes (Basel). 2021 Jul 14;11(7):528. doi: 10.3390/membranes11070528.

Glucoregulatory and Anti-Inflammatory Activities of Peptide Fractions Separated by Electrodialysis with Ultrafiltration Membranes from Salmon Protein Hydrolysate and Identification of Four Novel Glucoregulatory Peptides

Loïc Henaux 1 2 , Karina Danielle Pereira 3 4 , Jacinthe Thibodeau 1 2 , Geneviève Pilon 2 5 , Tom Gill 6 , André Marette 2 5 , Laurent Bazinet 1 2

Affiliations

PMID: 34357178 PMCID: PMC8305187 DOI: 10.3390/membranes11070528

Abstract

Natural bioactive peptides are suitable candidates for preventing the development of Type 2 diabetes (T2D), by reducing the various risk factors. The aim of this study was to concentrate glucoregulatory and anti-inflammatory peptides, from salmon by-products, by electrodialysis with ultrafiltration membrane (EDUF), and to identify peptides responsible for these bioactivities. Two EDUF configurations (1 and 2) were used to concentrate anionic and cationic peptides, respectively. After EDUF separation, two fractions demonstrated interesting properties: the initial fraction of the EDUF configuration 1 and the final fraction of the EDUF configuration 2 both showed biological activities to (1) increase glucose uptake in L6 muscle cells in insulin condition at 1 ng/mL (by 12% and 21%, respectively), (2) decrease hepatic glucose production in hepatic cells at 1 ng/mL in basal (17% and 16%, respectively), and insulin (25% and 34%, respectively) conditions, and (3) decrease LPS-induced inflammation in macrophages at 1 g/mL (45% and 30%, respectively). More impressive, the initial fraction of the EDUF configuration 1 (45% reduction) showed the same effect as the phenformin at 10 µM (40%), a drug used to treat T2D. Thirteen peptides were identified, chemically synthesized, and tested in-vitro for these three bioactivities. Thus, four new bioactive peptides were identified: IPVE increased glucose uptake by muscle cells, IVDI and IEGTL decreased hepatic glucose production (HGP) of insulin, whereas VAPEEHPTL decreased HGP under both basal condition and in the presence of insulin. To the best of our knowledge, this is the first time that (1) bioactive peptide fractions generated after separation by EDUF were demonstrated to be bioactive on three different criteria; all involved in the T2D, and (2) potential sequences involved in the improvement of glucose uptake and/or in the regulation of HGP were identified from a salmon protein hydrolysate.

Keywords: anti-inflammatory activity; bioactive peptides; electrodialysis with filtration membrane; glucose uptake; hepatic glucose production; salmon protein hydrolysate.

PubMed Disclaimer

Nutrients. 2020 Aug 13;12(8):2434. doi: 10.3390/nu12082434

The Potential Role of Fish-Derived Protein Hydrolysates on Metabolic Health, Skeletal Muscle Mass and Function in Ageing

Matthew J Lees 1, Brian P Carson 1,2,*

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PMCID: PMC7468851 PMID: 32823615

Abstract

Fish protein represents one of the most widely consumed dietary protein sources by humans. The processing of material from the fishing industry generates substantial unexploited waste products, many of which possess high biological value. Protein hydrolysates, such as fish protein hydrolysates (FPH), containing predominantly di- and tripeptides, are more readily absorbed than free amino acids and intact protein. Furthermore, in animal models, FPH have been shown to possess numerous beneficial properties for cardiovascular, neurological, intestinal, renal, and immune health. Ageing is

Review Nutrients. 2020 Aug 13;12(8):2434. doi: 10.3390/nu12082434.

The Potential Role of Fish-Derived Protein Hydrolysates on Metabolic Health, Skeletal Muscle Mass and Function in Ageing

Matthew J Lees 1 , Brian P Carson 1 2

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PMID: 32823615 PMCID: PMC7468851 DOI: 10.3390/nu12082434

Abstract

Fish protein represents one of the most widely consumed dietary protein sources by humans. The processing of material from the fishing industry generates substantial unexploited waste products, many of which possess high biological value. Protein hydrolysates, such as fish protein hydrolysates (FPH), containing predominantly di- and tripeptides, are more readily absorbed than free amino acids and intact protein. Furthermore, in animal models, FPH have been shown to possess numerous beneficial properties for cardiovascular, neurological, intestinal, renal, and immune health. Ageing is associated with the loss of skeletal muscle mass and function, as well as increased oxidative stress, compromised vascularisation, neurological derangements, and immunosenescence. Thus, there appears to be a potential application for FPH in older persons as a high-quality protein source that may also confer additional health benefits. Despite this, there remains a dearth of information concerning the impact of FPH on health outcomes in humans. The limited evidence from human interventional trials suggests that FPH may hold promise for supporting optimal body composition and maintaining gut integrity. FPH also provide a high-quality source of dietary protein without negatively impacting on subjective appetite perceptions or regulatory hormones. Further studies are needed to assess the impact and utility of FPH on skeletal muscle health in older persons, ideally comparing FPH to 'established' protein sources or a non-bioactive, nitrogen-matched control. In particular, the effects of acute and chronic FPH consumption on post-exercise aminoacidaemia, skeletal muscle protein synthesis, and intramyocellular anabolic signalling in older adults are worthy of investigation. FPH may represent beneficial and sustainable alternative sources of high-quality protein to support skeletal muscle health and anabolism in ageing, without compromising appetite and subsequent energy intake.

Keywords: amino acids; appetite; leucine; protein synthesis; sarcopenia.

Meta-Analysis Sleep. 2025 Apr 11;48(4):zsae280. doi: 10.1093/sleep/zsae280.

Glucagon-like peptide-1 receptor agonists for the treatment of obstructive sleep apnea: a meta-analysis

Mingxia Li 1 , Hong Lin 1 , Qianru Yang 1 , Xiaolong Zhang 1 , Qiong Zhou 1 , Jiankuan Shi 1 , Fangfang Ge 1

Affiliations

PMID: 39626095 DOI: 10.1093/sleep/zsae280

Abstract

Study objectives: Obstructive sleep apnea (OSA) is characterized by disordered breathing during sleep and is associated with major cardiovascular complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) as an important treatment for obesity and diabetes mellitus show promising therapeutic prospects in OSA. We conducted a meta-analysis to evaluate the effect of GLP-1RA intervention in OSA individuals.

Methods: We searched the PubMed and Web of Science databases (published until July 1, 2024). The included studies evaluated the GLP-1RA in OSA individuals and the efficacy outcomes measured by the apnea-hypopnea index (AHI).

Results: Six studies with a total of 1067 participants enrolled. GLP-1RA significantly decreased AHI with an estimated treatment difference of -9.48 events per hour (95% confidence interval [CI] = -12.56 to - 6.40, I2 = 92%). The change in weight was -10.99 kg and body mass index (BMI) was -1.60 kg/m2. The mean difference in systolic blood pressure was -4.81 mmHg and in diastolic blood pressure was -0.32 mmHg. Tirzepatide significantly reduced AHI more than liraglutide with an estimated treatment difference of -21.86 events per hour (95% CI = -25.93 to -17.79) vs -5.10 events per hour (95% CI = -6.95 to -3.26). Obese individuals experienced a more significant decrease in AHI with an estimated treatment difference of -12.93 events per hour vs -4.31 events per hour. The application of continuous positive airway pressure and the duration of follow-up did not affect the therapeutic effect.

Conclusions: GLP-1RA could significantly reduce the severity of OSA, and also lead to weight loss and lower blood pressure. Further high-quality randomized controlled trials (RCTs) are needed to explore different GLP-1RA treatments and durations in OSA and identify participant subgroups that may benefit the most.

Clinical trial: NA.

Keywords: glucagon-like peptide-1 receptor agonists; meta-analysis; obesity; obstructive sleep apnea.

Review Life (Basel). 2025 Sep 10;15(9):1422. doi: 10.3390/life15091422.

GLP-1 Receptor Agonists in Mood Disorders: A Psychiatric Perspective

Pietro Carmellini 1 , Alessandro Cuomo 1 , Maria Beatrice Rescalli 1 , Andrea Fagiolini 1

Affiliations

PMID: 41010364 PMCID: PMC12471315 DOI: 10.3390/life15091422

Abstract

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the leading causes of disability worldwide and are frequently associated with treatment resistance, functional impairment, and high comorbidity with metabolic dysfunction. Increasing evidence implicates insulin resistance (IR) as a key pathophysiological factor linking metabolic and psychiatric illness. IR is associated with chronic low-grade inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, impaired neuroplasticity, mitochondrial dysfunction, and altered reward processing mechanisms that may contribute to core depressive features such as anhedonia, cognitive slowing, and emotional dysregulation. These processes are further exacerbated by the metabolic side effects of many psychotropic medications, creating a self-perpetuating cycle that worsens both psychiatric and physical health outcomes. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for type 2 diabetes and obesity, have emerged as promising candidates to address this metabolic-psychiatric interface. Beyond improving glycemic control and promoting weight loss, GLP-1 RAs exert central actions relevant to mood disorders, including modulation of dopaminergic reward pathways, enhancement of hippocampal neurogenesis, attenuation of neuroinflammation, and regulation of appetite and energy balance. Preclinical studies demonstrate that GLP-1 RAs reduce microglial activation, promote hippocampal neurogenesis, and normalize stress-induced behavioral changes. Early clinical trials in patients with metabolic disorders suggest improvements in depressive symptoms, quality of life, and cognitive function, with some effects independent of weight loss or glycemic outcomes. Observational evidence also indicates reduced antidepressant use and psychological distress in diabetic and obese populations receiving GLP-1 RAs. While these findings are promising, large randomized controlled trials in primary psychiatric populations are lacking. Key challenges include clarifying dose-response relationships, disentangling central from peripheral effects, and addressing safety and adherence concerns in individuals with comorbid psychiatric conditions. Future research should focus on biomarker-informed stratification, comparative trials with standard treatments, and integration of GLP-1 RAs into multimodal care frameworks. Overall, GLP-1 RAs represent a biologically plausible and clinically relevant approach to bridging metabolic and psychiatric care, with the potential to improve outcomes in patients with mood disorders who carry a high metabolic burden.

Keywords: GLP-1 receptor agonists; insulin resistance; mood disorders; personalized psychiatry.

Nat Rev Endocrinol. Author manuscript; available in PMC: 2014 Nov 14.
Published in final edited form as: Nat Rev Endocrinol. 2011 Jun 7;7(9):507–516. doi: 10.1038/nrendo.2011.77

GLP-1 and energy balance: an integrated model of short-term and long-term control

Jason G Barrera 1, Darleen A Sandoval 1, David A D'Alessio 1, Randy J Seeley 1

Author information Article notes Copyright and License information
PMCID: PMC4231434 NIHMSID: NIHMS639983 PMID: 21647189

The publisher's version of this article is available at Nat Rev Endocrinol

Abstract

Glucagon-like peptide 1 (GLP-1), a peptide secreted from the intestine in response to nutrient ingestion, is perhaps best known for its effect on glucose-stimulated insulin secretion. GLP-1 is also

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BMJ Open. 2024 Nov 24;14(11):e086424. doi: 10.1136/bmjopen-2024-086424.

Effectiveness of glucagon-like peptide-1 receptor agonists for reduction of body mass index and blood glucose control in patients with type 2 diabetes mellitus and obesity: A retrospective cohort study and difference-in-difference analysis

Sukanya Siriyotha 1 , Thunyarat Anothaisintawee 2 , Panu Looareesuwan 1 , Hataikarn Nimitphong 3 , Gareth J McKay 4 , John Attia 5 , Ammarin Thakkinstian 1

Affiliations

PMID: 39581734 PMCID: PMC11590856 DOI: 10.1136/bmjopen-2024-086424

Abstract

Objective: This study aimed to evaluate the effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1RA) in reducing body mass index (BMI) and blood glucose levels in individuals with type 2 diabetes mellitus (T2DM) using the difference-in-differences (DID) technique.

Research design and methods: This retrospective cohort study included patients with T2DM, receiving GLP1-RA or other second-line antidiabetic treatments between 2010 and 2023. A linear mixed-effect regression with heterogeneous augmented inverse probability weighting DID analysis was used to compare the effectiveness of GLP-1RA and other second-line treatments in reducing BMI, fasting plasma glucose (FPG) and haemoglobin A1C (HbA1c) in patients with T2DM. An average treatment effect on the treated (ATET) for each outcome was estimated.

Results: 1000 patients with T2DM (GLP-1RA=220, non-GLP-1RA=880) were included. Compared with other second-line drugs, GLP-1RA significantly reduced BMI by approximately 1.02 kg/m2 (95% CI -1.46 to -0.58) over 24 months of treatment. Additionally, GLP-1RA significantly decreased FPG and HbA1c levels, compared with other second-line treatments with overall ATETs (95% CI) of -21.34 mg/dL (-29.53 to -13.15) and -0.58% (-0.77% to -0.38%), respectively.

Conclusions: Our results indicate that patients with T2DM treated with GLP-1RA had a significantly greater reduction in BMI, FPG and HbA1C levels compared with those receiving other second-line antidiabetic therapies. As such, GLP-1RA might be considered the preferred treatment for obese patients with T2DM who fail to sufficiently respond to metformin monotherapy.

Keywords: Body Mass Index; Diabetes Mellitus, Type 2; Obesity.

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Review Peptides. 2018 Feb:100:75-84. doi: 10.1016/j.peptides.2017.12.013.

Control of insulin secretion by GLP-1

Ben Jones 1 , Stephen R Bloom 1 , Teresa Buenaventura 2 , Alejandra Tomas 3 , Guy A Rutter 4

Affiliations

PMID: 29412835 DOI: 10.1016/j.peptides.2017.12.013
Free article

Abstract
Stimulation of insulin secretion by glucagon-like peptide-1 (GLP-1) and other gut-derived peptides is central to the incretin response to ingesting nutriments. Analogues of GLP-1, and inhibitors of its breakdown, have found widespread clinical use for the treatment of type 2 diabetes (T2D) and obesity. The release of these peptides underlies the improvements in glycaemic control and disease remission after bariatric surgery. Given therapeutically, GLP-1 analogues can lead to side effects including nausea, which limit dosage. Greater understanding of the interactions between the GLP-1 receptor (GLP-1R) and both the endogenous and artificial ligands therefore holds promise to provide more efficacious compounds. Here, we discuss recent findings concerning the signalling and trafficking of the GLP-1R in pancreatic beta cells. Leveraging "bias" at the receptor towards cAMP generation versus the recruitment of β-arrestins and extracellular signal-regulated kinases (ERK1/2) activation may allow the development of new analogues with significantly improved clinical efficacy. We describe how, unexpectedly, relatively low-affinity agonists, which prompt less receptor internalisation than the parent compound, provoke greater insulin secretion and consequent improvements in glycaemia.

Keywords: Beta cells; Endocytic trafficking; GLP-1; GLP-1 receptor; Insulin secretion; Receptor signalling.

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Protein (RefSeq)
PubChem Compound (MeSH Keyword)

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Randomized Controlled Trial Eur J Nutr. 2022 Mar;61(2):687-701.
doi: 10.1007/s00394-021-02674-1. Epub 2021 Sep 10.

Fortifying a meal with oyster mushroom powder beneficially affects postprandial glucagon-like peptide-1, non-esterified free fatty acids and hunger sensation in adults with impaired glucose tolerance: a double-blind randomized controlled crossover trial

Lisa Dicks 1 2 , Linda Jakobs 1 3 , Miriam Sari 1 , Reinhard Hambitzer 1 , Norbert Ludwig 1 , Marie-Christine Simon 3 , Peter Stehle 4 , Birgit Stoffel-Wagner 5 , Hans-Peter Helfrich 6 , Jenny Ahlborn 7 , Martin Rühl 7 , Bolette Hartmann 8 , Jens J Holst 8 , Sabine Ellinger 9 10

Affiliations

PMID: 34505919 PMCID: PMC8854321 DOI: 10.1007/s00394-021-02674-1

Abstract

Purpose: Impaired glucose tolerance (IGT) is a pathophysiological condition characterized by insulin resistance with known metabolic consequences such as postprandial hyperglycemia and hypertriglyceridemia. We hypothesized that fortifying a meal with mushrooms rich in β-glucans may diminish glucose and triglyceride responses by improving postprandial gastrointestinal hormone release.

Methods: In a randomized controlled crossover study, 22 subjects with IGT ingested a meal either enriched with 20 g powder (8.1 g β-glucans) of oven-dried Pleurotus ostreatus (enriched meal, EN) or without enrichment (control meal, CON). Blood was collected before and repeatedly within 4 h after the meal to determine AUC of glucose (primary outcome), insulin, triglycerides, non-esterified free fatty acids (NEFAs), glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP) and ghrelin. Appetite sensations (hunger, satiety, fullness, and desire to eat) were assessed before and after meal consumption by visual analog scales.

Results: Postprandial glucose, insulin, triglycerides, GIP and ghrelin concentrations as well as the corresponding AUCs did not differ between EN and CON. NEFAs-AUC was 14% lower (P = 0.026) and GLP-1-AUC 17% higher (P = 0.001) after EN compared to CON. Appetite ratings did not differ between treatments, except for hunger (AUC 22% lower after EN vs. CON; P = 0.031).

Conclusion: The observed immediate postprandial metabolic changes indicate that an easily manageable fortification of a single meal with powder from dried oyster mushrooms as β-glucan source may improve postprandial metabolism. If the effect is preserved long term, this measure can diminish the risk for further development of overweight/obesity and type 2 diabetes in subjects with IGT.

Clinical trial registration: German Clinical Trial Register on 09/08/2018; trial-ID: DRKS00015244.

nutrients
Article

Identification of Crocetin as a Dual Agonist of GPR40 and GPR120 Responsible for the Antidiabetic Effect of Saffron

Xiaodi Zhao 1 , Dohee Ahn 2 , Gibeom Nam 1 , Jihee Kwon 1 , Songyi Song 1 , Min Ji Kang 1 , Hyejin Ahn 1 and Sang J. Chung 1,2, *

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Abstract: Crocin, a glycoside of crocetin, has been known as the principal component responsible for saffron's antidiabetic, anticancer, and anti-inflammatory effects. Crocetin, originating from the hydrolytic cleavage of crocin in biological systems, was subjected to ligand-based virtual screening in this investigation. Subsequent biochemical analysis unveiled crocetin, not crocin, as a novel dual GPR40 and GPR120 agonist, demonstrating a marked preference for GPR40 and GPR120 over peroxisome proliferator-activated receptors (PPAR)γ. This compound notably enhanced insulin and GLP-1 secretion from pancreatic β-cells and intestinal neuroendocrine cells, respectively, presenting a dual mechanism of action in glucose-lowering effects. Docking simulations showed that crocetin emulates the binding characteristics of natural ligands through hydrogen bonds and hydrophobic interactions, whereas crocin's hindered fit within the binding pocket is attributed to steric constraints. Collectively, for the first time, this study unveils crocetin as the true active component of saffron, functioning as a GPR40/120 agonist with potential implications in antidiabetic interventions.

Keywords: crocetin; GPR40/120 dual agonist; glucose-stimulated insulin secretion (GSIS); glucagon-like peptide (GLP)-1

Citation: Zhao, X.; Ahn, D.; Nam, G.; Kwon, J.; Song, S.; Kang, M.J.; Ahn, H.; Chung, S.J. Identification of Crocetin as a Dual Agonist of GPR40 and GPR120 Responsible for the Antidiabetic Effect of Saffron. Nutrients 2023, 15, 4774. https://doi.org/10.3390/nu15224774
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1. Introduction

Diabetes mellitus is one of the leading causes of morbidity and mortality globally, and the burden of this disease has not been adequately addressed by the development of therapeutics. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia. It is caused by insulin resistance, which is impaired insulin action in target tissues, and insufficient secretion of insulin from pancreatic β-cells [1]. The pro-longed synergy of hyperglycemia with other metabolic abnormalities in patients with diabetes can lead to organ damage and, ultimately, disabling and life-threatening consequences [2]. In the practical approach to managing patients, biguanides, sulfonylureas, and thiazolidinediones (TZDs) are usually utilized with the risks of heart failure, hypo-glycemia, renal impairment, and weight gain [3]. Consequently, research institutions and pharmaceutical companies throughout the world have worked on developing new, and safer anti-T2DM targets to produce better-tolerated antidiabetic medications.

Apart from being vital sources of energy, free fatty acids (FAs) also function as signaling molecules that control insulin secretion and sensitivity, inflammation, body weight, and various other metabolic processes [1]. Especially, the beneficial effects of omega-3 fatty acids (ω-3 FAs) have been thoroughly documented due to their physiological function in stimulating insulin and gut hormone secretion, improving insulin sensitivity, anti-inflammatory effects, increasing glucose uptake, preventing metabolic disorder, and enabling homeostasis of healthy fat tissue [2]. The medium- to long-chain free fatty acids, including linoleic acid (LA), eicosatrienoic acid, and docosahexaenoic acid (DHA), are known as endogenous

Nutrients 2023, 15, 4774. https://doi.org/10.3390/nu15224774
https://www.mdpi.com/journal/nutrients

J Asian Nat Prod Res. 2025 Feb;27(2):176-188. doi: 10.1080/10286020.2024.2378821.
Epub 2024 Jul 22.

Screening of GLP-1r agonists from natural products using affinity ultrafiltration screening coupled with UPLC-ESI-Orbitrap-MS technology: a case study of Panax ginseng

Hong-Ping Wang 1 , Zhao-Zhou Lin 2 , Qiong Yin 1 , Jing Du 3

Affiliations

PMID: 39037429 DOI: 10.1080/10286020.2024.2378821

Abstract
In our study, a method based on affinity ultrafiltration screening coupled with UPLC-ESI-Orbitrap-MS technology was established to select Glucagon-like peptide-1 receptor (GLP-1R) agonists from natural products, and as an example, the GLP-1R agonists from Panax ginseng was selected using our established method. As a result, total five GLP-1R agonists were selected from Panax ginseng for the first time. Our results indicated that activating GLP-1R to promote insulin secretion probably was another important hypoglycemia mechanism for ginsenosides in Panax ginseng, which had great influence on the study of the anti-diabetes effect of ginsenosides.

Keywords: GLP-1R agonists; Panax ginseng; UPLC-ESI-Orbitrap-MS technology; affinity ultrafiltration screening; ginsenosides.

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Meta-Analysis Nutrients. 2022 Jun 9;14(12):2401. doi: 10.3390/nu14122401.

The Efficacy of Ginseng (Panax) on Human Prediabetes and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Results from different clinical trials on the effects of ginseng on prediabetes and type 2 diabetes (T2DM) are still inconsistent. To fill this knowledge gap, we investigated the overall effects of ginseng supplementation on improving cardiometabolic biomarkers among these patients. A systematic literature search was conducted on PubMed/MEDLINE, Scopus, Web of Science, and Cochrane library. A random-effect model was applied to estimate the weighted mean difference and 95% CI for each outcome. Overall, 20 eligible RCTs were included. Meta-analyses revealed that ginseng supplementation significantly reduced serum concentration of FPG, TC, IL-6, and HOMA-IR values. It also increased HR and TNF-α levels. Ginseng supplementation changed HOMA-IR and HDL-C significantly based on dose and changed HOMA-IR and LDL-C significantly based on study duration in a non-linear fashion. Furthermore, meta-regression analyses indicated a linear relationship between ginseng dose and absolute changes in HDL-C. Moreover, subgroup analyses showed that ginseng supplementation changed TC and LDL-C when the supplementation dose was ≥2 g/day. Our findings suggest that ginseng supplementation may be an effective strategy for improving cardiometabolic profiles in individuals with prediabetes and T2DM.

Keywords: Panax; blood lipid; cardiometabolic indicators; diabetes mellitus; ginseng; inflammation; prediabetes.

Figures

J Endocrinol. 2013 Apr 15;217(2):185-96. doi: 10.1530/JOE-12-0502. Print 2013 May.

Increased glucagon-like peptide-1 secretion may be involved in antidiabetic effects of ginsenosides

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Abstract

Panax ginseng is one of the most popular herbal remedies. Ginsenosides, major bioactive constituents in P. ginseng, have shown good antidiabetic action, but the precise mechanism was not fully understood. Glucagon-like peptide-1 (GLP1) is considered to be an important incretin that can regulate glucose homeostasis in the gastrointestinal tract after meals. The aim of this study was to investigate whether ginseng total saponins (GTS) exerts its antidiabetic effects via modulating GLP1 release. Ginsenoside Rb1 (Rb1), the most abundant constituent in GTS, was selected to further explore the underlying mechanisms in cultured NCI-H716 cells. Diabetic rats were developed by a combination of high-fat diet and low-dose streptozotocin injection. The diabetic rats orally received GTS (150 or 300 mg/kg) daily for 4 weeks. It was found that GTS treatment significantly ameliorated hyperglycemia and dyslipidemia, accompanied by a significant increase in glucose-induced GLP1 secretion and upregulation of proglucagon gene expression. Data from NCI-H716 cells showed that both GTS and Rb1 promoted GLP1 secretion. It was observed that Rb1 increased the ratio of intracellular ATP to ADP concentration and intracellular Ca2+ concentration. The metabolic inhibitor azide (3 mM), the KATP channel opener diazoxide (340 μM), and the Ca2+ channel blocker nifedipine (20 μM) significantly reversed Rb1-mediated GLP1 secretion. All these results drew a conclusion that ginsenosides stimulated GLP1 secretion both in vivo and in vitro. The antidiabetic effects of ginsenosides may be a result of enhanced GLP1 secretion.

Medical

Review Crit Rev Food Sci Nutr. 2019;59(3):528-535. doi: 10.1080/10408398.2017.1378168.
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Could hop-derived bitter compounds improve glucose homeostasis by stimulating the secretion of GLP-1?

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Abstract
Hops (Humulus lupulus L.) is by far the greatest contributors to the bitter property of beer. Over the past years, a large body of evidence demonstrated the presence of taste receptors in different locations of the oral cavity. In addition to the taste buds of the tongue, cells expressing these receptors have been identified in olfactory bulbs, respiratory and gastrointestinal tract. In the gut, the attention was mainly directed to sweet Taste Receptor (T1R) and bitter Taste Receptor (T2R) receptors. In particular, T2R has shown to modulate secretion of different gut hormones, mainly Glucagon-like Peptide 1 (GLP-1), which are involved in the regulation of glucose homeostasis and the control of gut motility, thereby increasing the sense of satiety. Scientific interest in the activity of bitter taste receptors emerges because of their wide distribution in the human species and the large range of natural substances that interact with them. Beer, whose alcohol content is lower than in other common alcoholic beverages, contains a considerable amount of bitter compounds and current scientific evidence shows a direct effect of beer compounds on glucose homeostasis. The purpose of this paper is to review the available literature data in order to substantiate the novel hypothesis of a possible direct effect of hop-derived bitter compounds on secretion of GLP-1, through the activation of T2R, with consequent improvement of glucose homeostasis.

Keywords: GLP-1; Glucose Homeostasis; Hop-derived Bitter Compounds.

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Mol Nutr Food Res. 2024 Nov;68(21):e2400559. doi: 10.1002/mnfr.202400559.
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Humulus lupulus L.: Evaluation of Phytochemical Profile and Activation of Bitter Taste Receptors to Regulate Appetite and Satiety in Intestinal Secretin Tumor Cell Line (STC-1 Cells)

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Abstract

Scope: Inflorescences of the female hop plant (Humulus lupulus L.) contain biologically active compounds, most of which have a bitter taste. Given the rising global obesity rates, there is much increasing interest in bitter taste receptors (TAS2Rs). Intestinal TAS2Rs can have beneficial effects on obesity when activated by bitter agonists. This study aims to investigate the mechanism of action of a hydroalcoholic hop extract in promoting hormone secretion that reduces the sense of hunger at the intestinal level through the interaction with TAS2Rs.

Methods and results: The results demonstrate that the hop extract is a rich source of bitter compounds (mainly α-, β-acids) that stimulate the secretion of anorexigenic peptides (glucagon-like peptide 1 [GLP-1], cholecystokinin [CCK]) in a calcium-dependent manner while reducing levels of hunger-related hormones like ghrelin. This effect is mediated through interaction with TAS2Rs, particularly Tas2r138 and Tas2r120, and through the activation of downstream signaling cascades. Knockdown of these receptors using siRNA transfection and inhibition of Trpm5, Plcβ-2, and other calcium channels significantly reduces the hop-induced calcium response as well as GLP-1 and CCK secretion.

Conclusions: This study provides a potential application of H. lupulus extract for the formulation of food supplements with satiating activity capable of preventing or combating obesity.

Keywords: Tas2rs; bitter acids; calcium; gut hormones; hops.

Related information

MedGen

PubChem Compound (MeSH Keyword)