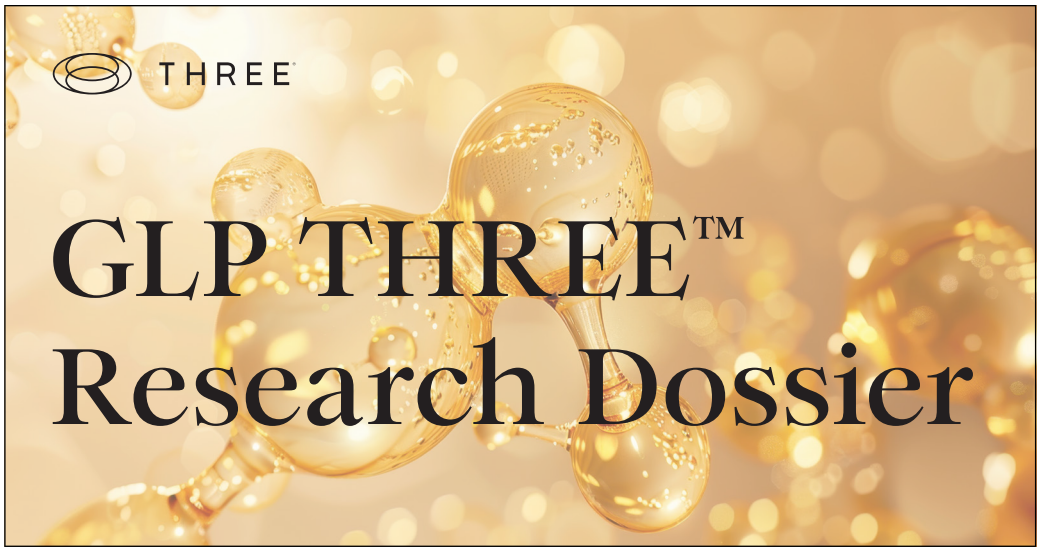


GLP THREE™ is a revolutionary product that can support healthy weight management and overall metabolic health.

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 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:

- MBC-267™ binds to the GLP-1 receptor in a mechanism of action like synthetic GLP-1 agonists.
- Data showing that GLP THREE™ helps to support a healthy weight.
- Research showing that GLP THREE™ promotes lean muscle mass growth.
- 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 healthy GLP-1 levels in the body.

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

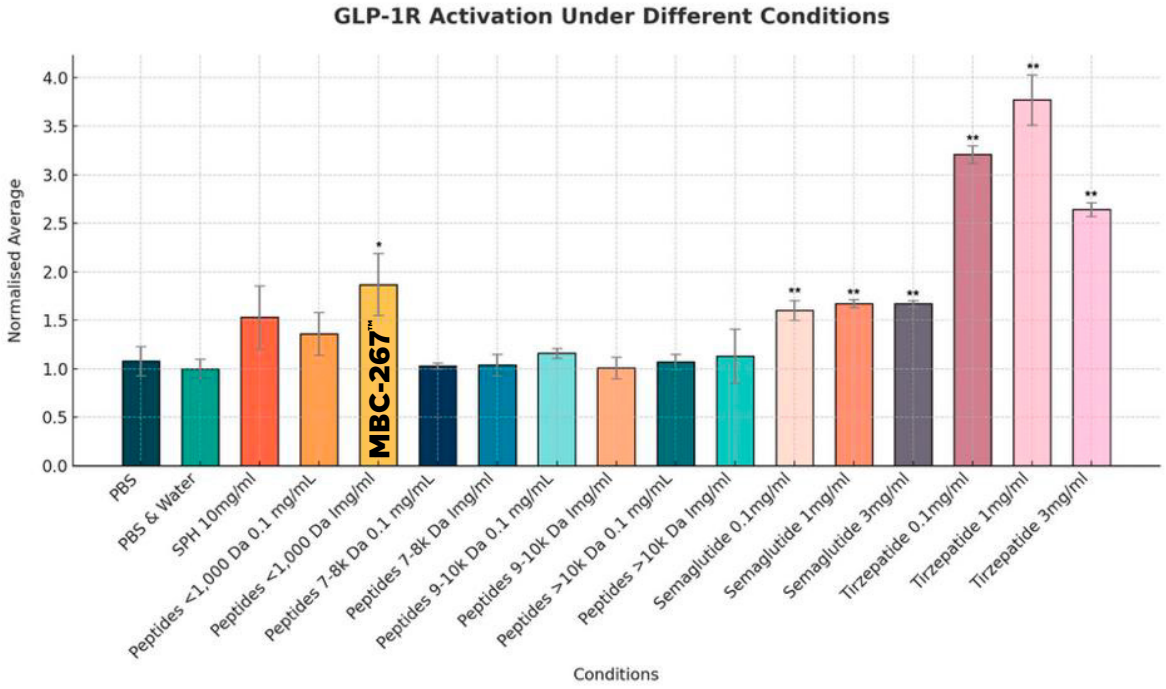
Be well,

Dr. Dan Gubler
Chief Scientific Officer
Three International

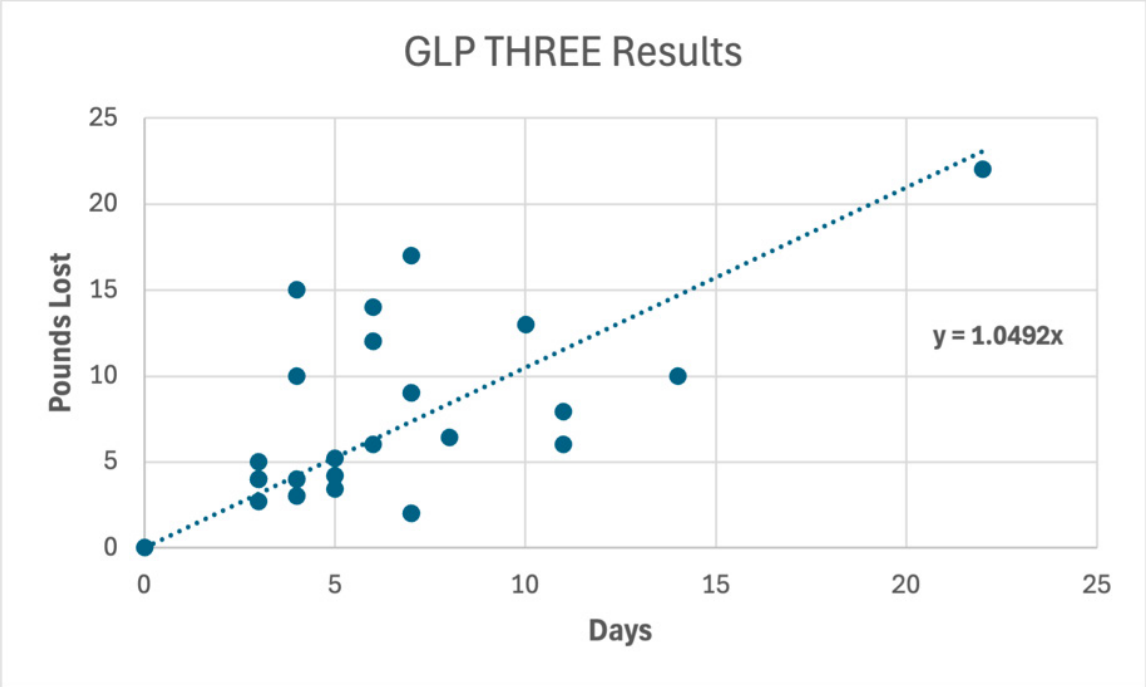
1441 W Innovation Way, Suite 100
Lehi, UT 84043

Study results

GLP THREE™ binds to the GLP-1 receptor:



GLP THREE™ can support a healthy weight:



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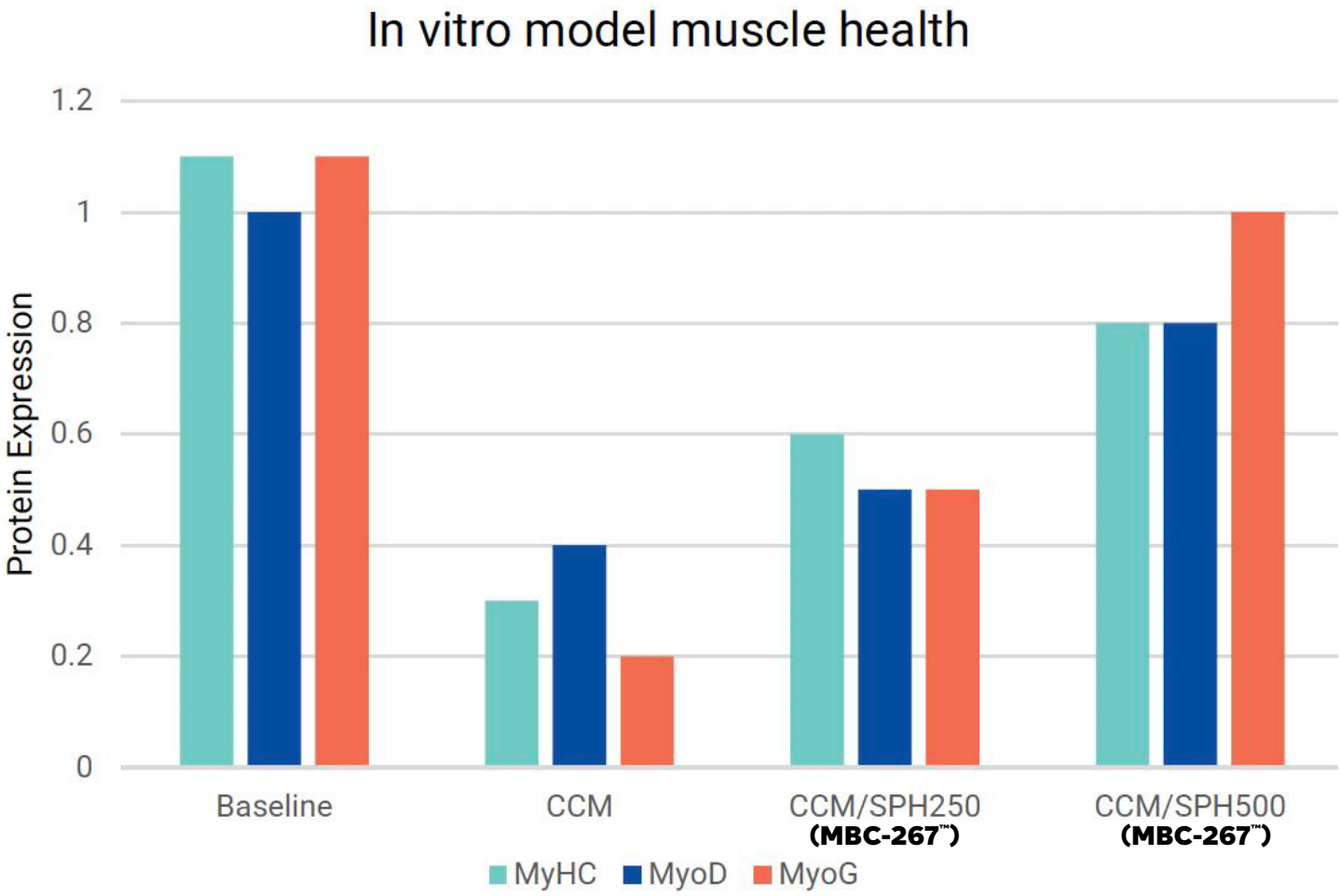
Study results (Cont.)

GLP THREE™ can promote growth of lean muscle mass.



Cultured human skeletal muscle cell expression of MyHC, MyoD & MyoG when exposed to conditioned culture media (**CCM**) derived from C26 colon cancer

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Study results (Cont.)

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

UNITED STATES PATENT AND TRADEMARK OFFICE

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

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

Title of Invention

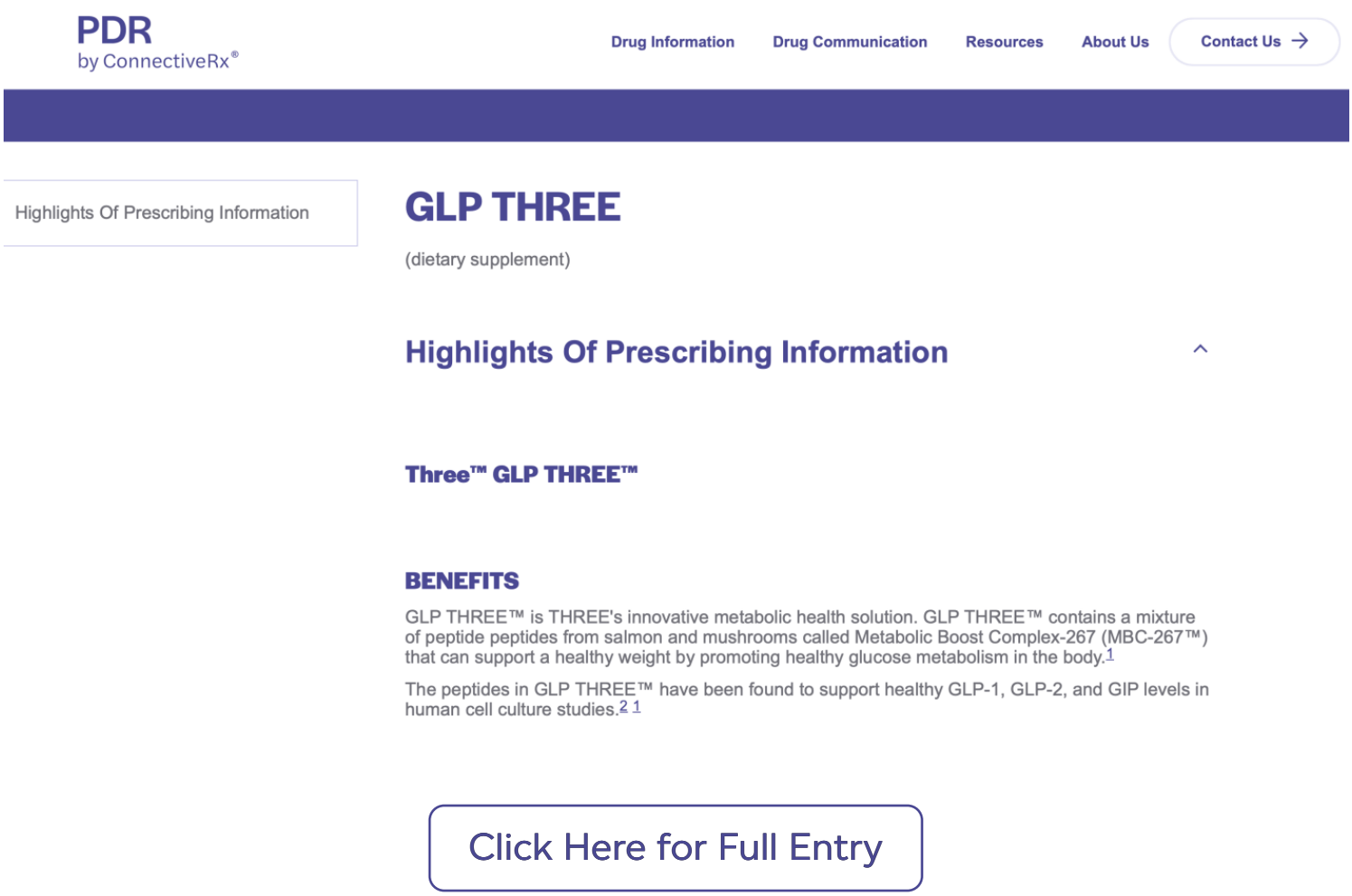
PEPTIDE-PHYTONUTRIENT COMPOSITIONS FOR SUPPORTING WEIGHT MANAGEMENT AND METABOLIC HEALTH

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
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	

Study results (Cont.)

GLP THREE™ is listed in the Prescribers' Digital Reference (PDR). See the full entry at PDR.net



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Lehi, UT 84043

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

MDPI

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,*]

[1] Department of Biopharmaceutical Convergence, Sungkyunkwan University, Suwon 16419, Republic of Korea; zhaoxiaodi1019@gmail.com (X.Z.); skarlqja12@g.skku.edu (G.N.); yg1549@naver.com (J.K.); songe1997@naver.com (S.S.); minjii_q@naver.com (M.J.K.); hyejin0930@skku.edu (H.A.)

[2] School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea; ehgml94@naver.com

* Correspondence: sjchung@skku.edu; Tel.: +82-31-290-7703

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

Academic Editor: Dan Ramdath

Received: 22 October 2023
Revised: 4 November 2023
Accepted: 10 November 2023
Published: 13 November 2023

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

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.

Related information

MedGen
PubChem Compound (MeSH Keyword)

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Full Text Sources
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Other Literature Sources
figshare - Access datasets and other research materials.

Research Materials
NCI CPTC Antibody Characterization Program

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

Kaveh Naseri [1], Saeede Saadati [2], Amir Sadeghi [3], Omid Asbaghi [4], Fatemeh Ghaemi [5], Fatemeh Zafarani [6], Hua-Bin Li [7], Ren-You Gan [1 8]

Affiliations

PMID: 35745129 PMCID: PMC9227417 DOI: 10.3390/nu14122401

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

Can Liu [1], Mian Zhang, Meng-Yue Hu, Hai-Fang Guo, Jia Li, Yun-Li Yu, Shi Jin, Xin-Ting Wang, Li Liu, Xiao-Dong Liu

Affiliations
PMID: 23444389 DOI: 10.1530/JOE-12-0502

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.

Related information

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Review Crit Rev Food Sci Nutr. 2019;59(3):528-535. doi: 10.1080/10408398.2017.1378168.
Epub 2017 Oct 17.

Could hop-derived bitter compounds improve glucose homeostasis by stimulating the secretion of GLP-1?

Luigi Barrea [1], Giuseppe Annunziata [2], Giovanna Muscogiuri [1], Angela Arnone [2], Gian Carlo Tenore [3], Annamaria Colao [2], Silvia Savastano [2]

Affiliations
PMID: 28910546 DOI: 10.1080/10408398.2017.1378168

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.

Related information

PubChem Compound (MeSH Keyword)

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Mol Nutr Food Res. 2024 Nov;68(21):e2400559. doi: 10.1002/mnfr.202400559.
Epub 2024 Oct 10.

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)

Ludovica Lela [1], Vittorio Carlucci [1], Chrissa Kioussi [2], Jaewoo Choi [3], Jan F Stevens [2 3], Luigi Milella [1], Daniela Russo [1 4]

Affiliations
PMID: 39388530 DOI: 10.1002/mnfr.202400559

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)