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DEVELOPMENT OF A NOVEL GLP-1 BOOST CONTAINING NATURAL AGONISTS OF GLP-1 AND GIP AND INHIBITORS OF DPP-4 ENZYME FOR THE MANAGEMENT OF OBESITY AND GLUCOSE METABOLISM

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1. INTRODUCTION

The prevalence of excess body weight, including obesity, and its associated risk of chronic diseases is increasing in the USA and worldwide.[1] In 2022, Centers for Disease Control and Prevention (CDC) estimated that at least 35% of adults in USA were living with obesity which increases the risk of type II diabetes. For decades, recommendations of consumption of diet low in fat and high in fiber with plenty of fruits and vegetables, reduce consumption of excess fat, carbohydrate, and caffeine, and regular physical exercise have failed to reduce weight or improve glucose metabolism because human behaviors with respect to diet and lifestyle are difficult to change. Consequently, the risk of obesity and excess weight as well as type II diabetes have increased. During 2021-2023, 40.3% Americans were obese (From CDC,2024) and in 2021, 11.61% (38.4 million had diabetes out of which 29.7% were diagnosed and 8.7 million were undiagnosed) (From National Institutes of Diabetes and Digestive and Kidney Diseases, 2024). Therefore, a novel strategy for the management of weight and improved glucose metabolism is needed. This major objective of this review is to briefly describe the discovery of two gut generated hormones GLP-1 and GIP which enhance glucose metabolism and weight loss. This review also describes history of development of synthetic and natural agonist of GLP-1 and GIP and their role in reducing obesity and improving glucose metabolism.

2. Discovery of GLP-1 and GIP and Their Role in Improving Glucose Metabolism and Reducing Body Weight

The discovery of regulation of glucose was not known until in 1922, when Frederick Banting and Charles Best discovered the hormone insulin, which controls glucose metabolism.[2] In 1932, Belgian Jean La Barre identified a hormone in the gastrointestinal tract responsible for stimulating insulin secretion. He named this hormone "incrétine" (incretin) and suggested it may be useful in the treatment of diabetes.[3] In the 1960s, investigators showed that a hormone called GIP (glucose- dependent insulinotropic polypeptide) secreted by the small intestine was partly responsible for the incretin effect on stimulating insulin secretion.[4] In the 1980s, Svetlana Mojsov identified another hormone secreted by the small intestine called GLP-1 (glucagon-like peptide 1) which also stimulates insulin secretion.[5] GIP and GLP-1 hormones could not be used in type II diabetes because they quickly are degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Therefore, agonists of GLP-1 and GIP which can increase production of these two hormones must contain inhibitors of DPP-4 to prolong the effectiveness of these two hormones.

3 Production of GLP-1 and GIP

L-cells of the intestine produce GLP-1 in response to nutrient stimulation. Small amounts of GLP-1 are also produced in the pancreas and the brain. Alpha cells of the pancreas contain a subpopulation of GLP-1–producing cells. In addition, fermentation of prebiotics by probiotics generates short-chain fatty acids, which enhance the production of GLP-1.

GIP is produced by the K-cells of the intestine. Receptors for both GLP-1 and GIP are present not only in the pancreas but also in the brain, highlighting their roles

beyond glucose metabolism. These hormones are key components of the gut–brain axis, a bidirectional communication system between the gastrointestinal tract and the central nervous system. Through neural pathways, particularly the vagus nerve, as well as endocrine signaling, GLP-1 and GIP influence appetite regulation, satiety, and energy balance. Activation of GLP-1 receptors in the hypothalamus and brainstem contributes to reduced hunger, delayed gastric emptying, and improved glucose control. Thus, enhancement of endogenous GLP-1 and GIP activity may support both metabolic regulation and appetite control through coordinated gut–brain signaling.

4. Role of Gila Monster Venom in the Development of GLP-1 and GIP-Based Therapies

4.1. Development of Semaglutide: In 1982, John Pisano, a biochemist, and a gastroenterologist Jean-Pierre Raufman were working with poisonous lizard venom from the Gila monster, a slow-moving reptile native to the south of the United States and north of Mexico.[6] In 1993, Drs Goke and John Eng identified a hormone -like molecule called exendin-4 from poisonous venom which acted as an agonist for GLP-1 receptor and produced increased level of GLP-1 that stimulated insulin secretion.[7] Exendin-4 was quickly metabolized by the body, therefore, could not be useful in the treatment of diabetes. Pharmaceutical companies did not want people to use a hormone derived from a poisonous venom of the lizard. Even the Medical Center where Dr Eng was working wouldn't help him in filling a patent. Eventually John Eng and Raufman convinced a small start-up company called Amylin Pharmaceuticals which quickly prepared a synthetic form of exendin-4 called Exenatide containing 39 amino acids which rapidly normalized blood glucose in type 2 diabetic mice.[8] In 2005, Exenatide received the US Food and Drug Administration (FDA) approval under the name Byetta. It soon became evident that many taking Byetta were experiencing sustained weight-loss with the benefit of reversing their diabetic symptoms. In December 2017, the FDA approved a new injectable drug to treat type 2 diabetes called semaglutide, which is known by its brand name Ozempic. It has a polypeptide of 31 amino acids.[9]

4.2. Development of Tirzepatide: Despite numerous antidiabetic medications available for the treatment of type 2 diabetes, a substantial percentage of patients fail to achieve optimal glycemic control. The fact that the incidence of obesity and type II diabetes I continues to increase additional GLP-1 product is needed. Tirzepatide, a novel dual GIP and GLP-1 receptor agonist offers a promising therapeutic option. It has 39 amino acids and produces both GLP-1 and GIP which has longer half-life than semaglutide was developed.[10] Tirzepatide is a FDA approved product under the brand name Mounjaro and Zebound. Mounjaro is approved for treatment of type II diabetes and zebound is approved for the treatment of weight loss and obstructive sleep apnea. GIP (glucose-dependent insulinotropic polypeptide) receptor agonist helps protect against the gastrointestinal toxicity of GLP-1 supplements by acting as an antiemetic. Combining GIP with GLP-1 (as in tirzepatide) reduces side effects like nausea and vomiting, while enhancing metabolic benefits such as improved glycemic control.[11]

Despite the presence of GIP in Tirzepatide GLP-1-induced gastrointestinal problems continue to occur.[12] All FDA approved products contain synthetic polypeptides varying from 31-39 amino acids which act as an agonist for GLP-1 and GIP receptors are derived from Exendin-4 which was isolated from the poisonous saliva of Gila monster, a form of Lizard. The question arises whether whole or part of the toxicity of currently used GLP-1 or GLP-1 and GIP is related to the polypeptides which acts as an agonist of receptors for GLP-1 and GIP. No studies have been performed to evaluate the toxicity of polypeptide alone.

5. Potential Toxicities of Currently Used GLP-1 Products for Weight Loss and Glucose Control

Approximately 50% of users of GLP-1 receptor agonists such as semaglutide cause gastrointestinal toxicity, including severe nausea, vomiting, diarrhea, and constipation. Other risks include dehydration, pancreatitis, and gallbladder issues. In addition, the risk of developing nutritional deficiency and hypoglycemia in patients with diabetes who are on diabetic medication exists.[13] Despite the presence of GIP in Tirzepatide GLP-1 induced gastrointestinal problems continue to occur.[12] In addition, headache, anxiety, depression, dizziness and fatigue are also observed. Late adverse effects may include renal damage, gall bladder damage, pancreatis, Thyroid cancer, and diabetic retinopathy (from Mayo clinic). It is unknown whether some of these toxicities could be related to synthetic polypeptide which acts as an agonist of GLP-1and GIP.

6. Development of Novel GLP-1 Boost Without Synthetic Polypeptide

Novel GLP-1 Boost was developed using herbs which produce GLP-1 alone as well as both GLP-1 and GIP for weight loss and maintaining normal glucose metabolism. This product has no synthetic polypeptide. Unlike semaglutide and Tirzepatide which contain synthetic polypeptide and produce serious toxicities, novel GLP-1 boost may not produce such effects. The most important feature of novel GLP-boost product is that it contains herbs which inhibit DPP-4 enzymes which degrades GLP-1. Therefore, effectiveness of novel GLP-boost may prolong for longer period of time. None of the GLP-1 products sold in the market has inhibitor of GLP-1. In addition, novel GLP-1 boost contains herbs which do not produce GLP-1 or GIP but reduce fat from the body by removing fat already present in the body and preventing the formation of new fats.

6.1. Herbs Produce only GLP-1 Include

Pomegranate: The extract of pomegranate seed is very rich in polyphenols which stimulate the secretion of GLP-1 which increases the secretion of insulin from the pancreas into the blood. It also acts as a strong antioxidant and reduces inflammation. Pomegranate seed extract also improves heart health.[14,15] Pomegranate juice reduces hunger, and therefore, would contribute to weight loss.[16]

Extract of Gardenia jasminoides. Fruit of Gardenia has been used for thousands of years in China to treat diabetes. The fruit extract ingredients stimulate GLP-1 pathway, possess potent antioxidant and anti-inflammatory properties, promote insulin secretion from the pancreas into the blood, and improve insulin sensitivity, protect islet β cells from oxidative and inflammatory damage, and improve the function macro- and microvascular systems (17. It also causes weight loss {Park, 2021 #404).

Gentiana scabra root extract: The extract of this herb improves GLP-1 secretion causing increased release of insulin from the pancreas to the blood which decreases hyperglycemia in a type 2 diabetic mouse model.[18] Gentiopicroside, a major active component of the Gentiana scabra root extract, reduced body weight and visceral fat mass in humans by decreasing the expression of adipogenesis/lipogenesis-related genes.[19]

Berberine from Berberis Asiatica root: Berberine is an alkaloid extracted from Rhizoma coptidis which has been traditionally used in Chinese medicine to treat gastrointestinal infections.[20] It stimulates secretion of GLP-1.[21, 22] Berberine can also suppress hunger and thereby contribute to weight loss.[23] It improves beta-cell of pancreas function and thereby improves production and flow of insulin from the pancreas into the blood causing decreased levels of glucose in the blood.[24]

6.2. Herbs Producing Both GLP-1 and GIP Include

Glutamine (300mg): Glutamine is the most abundant amino acid which is made in the body as well as consumed from the diet. It increases the secretion of both GLP-1 and GIP and stimulates the secretion of insulin from the pancreas into the blood to regulate glucose level[25,26] Glutamine is also useful in weight loss.[27] GIP would help reduce potential side effects of GLP-1.

Ginsenosides (100 mg): Ginsenosides, the main active component of Panax ginseng, can stimulate the secretion of glucagon-like peptide-1 (GLP-1) and may also affect the secretion of glucose-dependent insulinotropic polypeptide (GIP).[28] This compound reduces insulin resistance and hyperglycemia and improves cognitive function in mice by increasing the level of acetylcholine by inhibiting acetylcholinesterase activity in cholinergic neurons. Acetylcholine is responsible for storing memory. In addition, Ginsenosides protect cholinergic neurons from oxidative and inflammatory damage. It also improves insulin sensitivity and decreases glucose formation in the liver[29] and reduces obesity.[30]

Curcumin: Curcumin treatment improves glucose control by increasing the secretion of GLP-1and GIP.[31-33] Curcumin also reduces oxidative stress, inflammation and adipogenesis, and enhance energy that may, in combination with other ingredients, contribute to weight loss.

7. Herbs Reduce fat without GLP-1 Include

Fenugreek seeds: Fenugreek seeds, also known as Methi, are commonly used in Ayurvedic medicine to aid digestion, regulate blood sugar levels, and promote weight loss. They are rich in soluble fiber, which helps increase satiety, reduce appetite, and promote the metabolism of fat, inhibit fat accumulation, and lower bad cholesterol (LDL).[34]

Kalonji (Nigella sativa) seed extract: Kalonji, also called black seed or black cumin, causes weight loss by reducing appetite. It also inhibits glucose absorption from the gut.[35]

8. Herbs which inhibit DPP-4 enzymes

Terminalia anogeissiana also called ghattti gum inhibits DPP-4 enzyme which degrades GLP-1 causing prolong the effectiveness of GLP-1(36). **Quercetin Dihydrate** also inhibits DPP-4 enzyme (37). **Celery extract** also inhibits DPP-4 enzyme (38). Addition of three inhibitors of DPP-4 enzyme would markedly increase the effectiveness of novel GLP-1 boost for a long period of time.

CONCLUSION

The proposed novel GLP-1 boost has potential to be much better and safer than those GLP-1 products available in the market for reducing weight and improving glucose metabolism. It is known that DPP-4 enzyme quickly degrades GLP-1. None of the commercially sold GLP-1 products has inhibitor of DPP-4 enzyme. Therefore, the effectiveness of GLP-1product is very short-lived, and requires daily or weekly injection. The proposed novel GLP-1 boost has no synthetic polypeptide but has inhibitors of DPP-4 enzyme which would prolong the effectiveness of novel GLP-1 boost. This formula should be taken in consultation with and under the supervision of your doctor.

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Conflicts: The authors are Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

REFERENCES

1. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022; 133: 155217.
2. Lewis GF, Brubaker PL. The discovery of insulin revisited: lessons for the modern era. J. Clin. Invest., 2021; 131(1).
3. Marks V. Rebirth of the Incretin Concept: Its conception and early development. Peptides. 2018; 100: 3-8.
4. Marks V. The early history of GIP 1969-2000: From enterogastrone to major metabolic hormone. Peptides. 2019; 122: 170155.
5. Friedman JM. The discovery and development of GLP-1 based drugs that have revolutionized the treatment of obesity. Proc. Natl. Acad. Sci., U. S. A. 2024; 121(39): e2415550121.
6. Raufman JP, Jensen RT, Sutliff VE, Pisano JJ, Gardner JD. Actions of Gila monster venom on dispersed acini from guinea pig pancreas. Am. J. Physiol., 1982; 242(5): G470-4.
7. Goke R, Fehmann HC, Linn T, Schmidt H, Krause M, Eng J, et al. Exendin-4 is a high potency agonist and truncated exendin-(9-39)-amide an antagonist at the glucagon-like peptide 1-(7-36)-amide receptor of insulin-secreting beta-cells. J. Biol. Chem., 1993; 268(26): 19650-5.
8. Davidson MB, Bate G, Kirkpatrick P. Exenatide. Nat Rev Drug Discov., 2005; 4(9): 713-4.
9. Knudsen LB, Lau J. The Discovery and Development of Liraglutide and Semaglutide. Front Endocrinol (Lausanne). 2019; 10: 155.
10. Avgerinos I, Kakotrichi P, Karagiannis T, Bekiari E, Tsapas A. The preclinical discovery and clinical evaluation of tirzepatide for the treatment of type 2 diabetes. Expert Opin, Drug Discov., 2024; 19(5): 511-22.
11. Hayes MR, Borner T, De Jonghe BC. The Role of GIP in the Regulation of GLP-1 Satiety and Nausea. Diabetes. 2021; 70(9): 1956-61.
12. Mishra R, Raj R, Elshimy G, Zapata I, Kannan L, Majety P, et al. Adverse Events Related to Tirzepatide. J. Endocr. Soc., 2023; 7(4): bvad016.
13. Jalleh RJ, Talley NJ, Horowitz M, Nauck MA. The science of safety: adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications. J Clin. Invest., 2026; 136(4).
14. Wang Y, Alkhalidy H, Liu D. The Emerging Role of Polyphenols in the Management of Type 2 Diabetes. Molecules. 2021; 26(3).
15. Virgen-Carrillo CA, Martinez Moreno AG, Valdes Miramontes EH. Potential Hypoglycemic Effect of Pomegranate Juice and Its Mechanism of Action: A Systematic Review. J. Med., Food. 2020; 23(1): 1-11.
16. Stockton A, Al-Dujaili EAS. Effect of Pomegranate Extract Consumption on Satiety Parameters in Healthy Volunteers: A Preliminary Randomized Study. Foods. 2022; 11(17).
17. Zhang F, Ning J, Chen C, Li B, Wei Y. Advances in the mechanisms of Gardenia jasminoides Ellis in improving diabetes and its complications. Fitoterapia. 2024; 178: 106140.
18. Suh HW, Lee KB, Kim KS, Yang HJ, Choi EK, Shin MH, et al. A bitter herbal medicine Gentiana scabra root extract stimulates glucagon-like peptide-1 secretion and regulates blood glucose in db/db mouse. J Ethnopharmacol. 2015; 172: 219-26.
19. Choi RY, Nam SJ, Lee HI, Lee J, Leutou AS, Ri Ham J, et al. Gentiopicroside isolated from Gentiana scabra Bge. inhibits adipogenesis in 3T3-L1 cells and reduces body weight in diet-induced obese mice. Bioorg. Med. Chem. Lett., 2019; 29(14): 1699-704.
20. Xu JH, Liu XZ, Pan W, Zou DJ. Berberine protects against diet-induced obesity through regulating metabolic endotoxemia and gut hormone levels. Mol. Med. Rep., 2017; 15(5): 2765-87.
21. Lu SS, Yu YL, Zhu HJ, Liu XD, Liu L, Liu YW, et al. Berberine promotes glucagon-like peptide-1 (7-36) amide secretion in streptozotocin-induced diabetic rats. J. Endocrinol., 2009; 200(2): 159-65.
22. Yu Y, Liu L, Wang X, Liu X, Liu X, Xie L, et al. Modulation of glucagon-like peptide-1 release by berberine: in vivo and in vitro studies. Biochem. Pharmacol., 2010; 79(7): 1000-6.
23. Park HJ, Jung E, Shim I. Berberine for Appetite Suppressant and Prevention of Obesity. Biomed. Res. Int., 2020; 2020: 3891806.
24. Lv X, Zhao Y, Yang X, Han H, Ge Y, Zhang M, et al. Berberine Potentiates Insulin Secretion and Prevents beta-cell Dysfunction Through the miR-204/SIRT1 Signaling Pathway. Front Pharmacol., 2021; 12: 720866.
25. Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A, et al. Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. Am J. Clin. Nutr. 2009; 89(1): 106-13.
26. Reimann F, Williams L, da Silva Xavier G, Rutter GA, Gribble FM. Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells. Diabetologia. 2004; 47(9): 1592-601.
27. Abboud KY, Reis SK, Martelli ME, Zordao OP, Tannihao F, de Souza AZZ, et al. Oral Glutamine Supplementation Reduces Obesity, Pro-Inflammatory Markers, and Improves Insulin Sensitivity in DIO Wistar Rats and Reduces Waist Circumference in Overweight and Obese Humans. Nutrients. 2019; 11(3).
28. Liu C, Zhang M, Hu MY, Guo HF, Li J, Yu YL, et al. Increased glucagon-like peptide-1 secretion may be involved in antidiabetic effects of ginsenosides. J. Endocrinol., 2013; 217(2): 185-96.
29. Bai L, Gao J, Wei F, Zhao J, Wang D, Wei J. Therapeutic Potential of Ginsenosides as an

Adjuvant Treatment for Diabetes. Front Pharmacol. 2018; 9: 423.
30. Hong Y, Lin Y, Si Q, Yang L, Dong W, Gu X. Ginsenoside Rb2 Alleviates Obesity by Activation of Brown Fat and Induction of Browning of White Fat. Front Endocrinol (Lausanne). 2019; 10: 153.
31. Takikawa M, Kurimoto Y, Tsuda T. Curcumin stimulates glucagon-like peptide-1 secretion in GLUTag cells via Ca2+/calmodulin-dependent kinase II activation. Biochem. Biophys. Res. Commun., 2013; 435(2): 165-70.
32. Alli-Oluwafuyi AM, Luis PB, Nakashima F, Gimenez-Bastida JA, Presley SH, Duvernay MT, et al. Curcumin induces secretion of glucagon-like peptide-1 through an oxidation-dependent mechanism. Biochimie. 2019; 165: 250-7.
33. Kato M, Nishikawa S, Ikehata A, Dochi K, Tani T, Takahashi T, et al. Curcumin improves glucose tolerance via stimulation of glucagon-like peptide-1 secretion. Mol. Nutr. Food Res., 2017; 61(3).
34. Kumar P, Bhandari U, Jamadagni S. Fenugreek seed extract inhibit fat accumulation and ameliorates dyslipidemia in high fat diet-induced obese rats. Biomed. Res. Int., 2014; 2014: 606021.
35. Al Asoom L. Is Nigella sativa an Effective Bodyweight Lowering Agent and a Mitigator of Obesity Risk? A Literature Review. Vasc Health Risk Manag., 2022; 18: 495-505.
36. Ansari P, Hannon-Fletcher MP, Flatt PR, Abdel-Wahab YHA. Effects of 22 traditional anti-diabetic medicinal plants on DPP-IV enzyme activity and glucose homeostasis in high-fat fed obese diabetic rats. Biosci. Rep., 2021; 41(1).
37. Singh AK, Patel PK, Choudhary K, Joshi J, Yadav D, Jin JO. Quercetin and Coumarin Inhibit Dipeptidyl Peptidase-IV and Exhibits Antioxidant Properties: In Silico, In Vitro, Ex Vivo. Biomolecules. 2020; 10(2).
38. Mathur V, Alam O, Siddiqui N, Jha M, Manaithiya A, Bawa S, et al. Insight into Structure Activity Relationship of DPP-4 Inhibitors for Development of Antidiabetic Agents. Molecules. 2023; 28(15).