REVIEW
Food and Health 2024;6(2):9. https://doi.org/10.53388/FH2024009

Dietary Modulation of Glucagon-like Peptide 1 Secretion: insights and innovations

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Competing interests
The authors declare no conflicts of interest.
Acknowledgments
This work was supported in part by grants from National Key Research & Development Program of China (No. 2022YFC3602102), Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (No. 2021-1-I2M-050), National Natural Science Foundation of China (No.82170856), and China Postdoctoral Science Foundation (No. 2022M710456).
Peer review information
Food and Health thanks Wenlong Wang and other anonymous reviewers for their contribution to the peer review of this paper.
Abbreviations
GLP-1: Glucagon-like peptide-1.
Citation
Wang QY, Cai JP. Dietary Modulation of Glucagon-like Peptide 1 Secretion: insights and innovations. *Food Health*. 2024;6(2):9. doi: 10.53388/FH2024009.

Executive editor: Nuo-Xi Pi.
Received: 27 December 2023; **Accepted:** 25 March 2024;
Available online: 31 March 2024.

Abstract
Glucagon-like peptide-1 (GLP-1), a signal peptide hormone produced by enteroendocrine L cells from the distal small intestine and colon, is a crucial regulator of glycemic control, gastric emptying, satiety, and body weight. Recent advancements in understanding the dietary modulation of GLP-1 through enteroendocrine L-cells have highlighted the potential of various nutrients in enhancing its endogenous secretion. This review summarizes the current knowledge on food-derived molecules, including macronutrients, polyphenols, other chemicals, and bacterial products, that can modulate GLP-1 production. It explores the efficacy and impact of various treatments and the involved signaling pathways, aiming to contribute to developing innovative strategies for enhancing endogenous GLP-1 release.

Keywords: GLP-1, intestine, enteroendocrine L-cells, nutrient, bacteria-derived product

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Introduction

Glucagon-like peptide 1 (GLP-1), originating from the intestines and secreted by L-cells, plays a crucial role in regulating blood glucose homeostasis. Numerous GLP-1 receptor agonists (GLP-1RA) have been well studied and are currently used in clinical glucose control and body weight management [1]. Besides the blood glucose control, there's also been significant interest in the protective effects of GLP-1 or GLP-1RA on inflammation [2–5], neurodegenerative diseases [6–10], and cardiovascular diseases [11–14], given that the widespread expression of GLP-1R in the heart, blood vessels, immune system, and various brain regions [15]. Ongoing research aims to uncover new mechanisms and administration methods to make GLP-1-based treatments accessible to a broader range of patient groups with diverse needs. Despite the widespread clinical application of GLP-1-based therapies [16], their cost and potential side effects restrict their universal adoption [17]. As a result, the quest for novel GLP-1 secretagogues continues, especially with a significant focus on how dietary components might elevate the endogenous L-cell GLP-1 secretion.

Our review encompassed literature from 2022 onwards, sourced from online databases such as Web of Science, Pubmed, and Google Scholar. The searching strategy was as follows: ((GLP-1) OR (glucagon like peptide 1)) AND ((Enteroendocrine) OR (L cell) OR (Gut Endocrine cell) OR (Gut secretin cell)). Publication dates from 2022-01-01 to 2023-12-31, including research and review articles (Figure 1). Apart from reviews which constituted 22.5 %, 29.9 % of the studies focused on exploring treatments (24.8 %) or surgical interventions (5.1%) that could elevate endogenous GLP-1 secretion levels. Additionally, 6.8 % focused on clinical trials or meta-analyses concerning existing GLP-1 receptor agonists (GLP-1RA); 7.7 % focused on the protective roles of GLP-1 against inflammation, cardiovascular diseases, and neurodegenerative conditions. The remaining articles investigated the GLP-1 receptor within the pancreatic islets or the effects of GLP-1 on species other than humans, monkeys, and rodents, such as Drosophila, cats, dogs, chickens, and sheep, or other topics less relevant to GLP-1. This review will describe what is known about the food-derived molecules that could regulate GLP-1 production and the signaling pathways involved. The overall goal is to inform the development of novel insights to enhance the endogenous release of GLP-1.

Food derived molecules

Enteroendocrine L-cells, express a range of transporters and receptors, finely sense and respond to various nutrients from digestion or bacteria fermentation, including carbohydrates, fats, proteins, and other chemicals, interacting with the L-cell through different mechanisms (Figure 2).

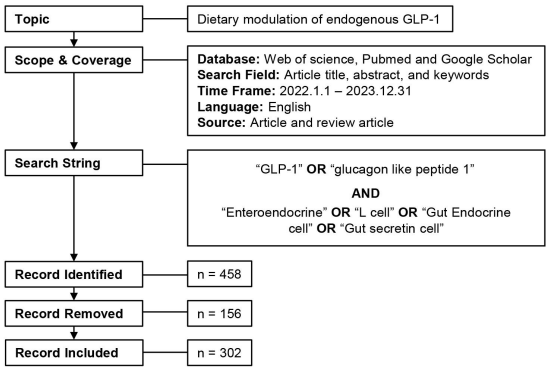

Figure 1 Flow diagram of the search strategy

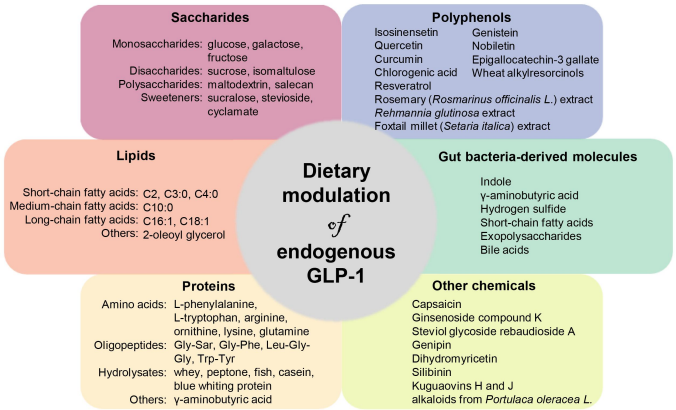

Figure 2 Dietary molecules that modulate endogenous GLP-1 secretion, including saccharides, lipids, proteins, polyphenols, gut bacteria-derived molecules, and other chemicals.

Saccharides

L-cells utilize sodium/glucose cotransporter 1 (SLC5A1) to intake monosaccharides such as glucose and galactose, with glucose recognized as a significantly effective GLP-1 secretagogue among others [1]. Fructose enhances GLP-1 release through glucose transporter 5 (GLUT5) and mitochondrial ATP production in L-cells [18]. Disaccharides such as sucrose and isomaltulose are known to stimulate GLP-1 secretion *in vivo*, though detailed molecular mechanisms remain elusive [19, 20]. In addition, short-clustered maltodextrin, generated by rearranging α-1,4 and α-1,6-glycosidic bonds in starch molecules, triggers the GLP-1 secretion by gradually releasing glucose into the distal ileum. However, this effect is not seen with a mix of normal maltodextrin and resistant dextrin [21]. The natural β-glucan, salecan, has been shown to attenuate insulin resistance and improve GLP-1 release in type 2 diabetic mice [22]. The sweet taste receptor (STR), a heterodimer composed of T1R2/T1R3, also plays a role in nutrient sensing within L-cells. Sucralose has been identified to stimulate GLP-1 secretion through STR activation in various enteroendocrine cell lines, though this has not been consistently replicated in primary cultures [23]. Other sweeteners, such as stevioside and cyclamate, have been recognized as significant inducers of GLP-1 secretion in primary human epithelial cells [24]. Of note, the response of L-cells to glucose differs by species and location in the gut. *In vitro* experiments show that murine proximal and colonic L-cells are stimulated by glucose with concentrations over 1 mM and 0.1 mM, respectively [25], whereas human ileal L-cells require concentrations over 200 mM [26].

Lipids

Various ingested lipids were found to be a potent stimulus of the GLP-1 secretion from L-cells. Different types of fatty acids engage specific receptors on the L-cell surface. GPR41 and GPR43 mediate the signals from short-chain fatty acids (SCFAs), GPR40 and GPR120 interact with medium-chain fatty acids (MCFAs) and long-chain fatty acids (LCFAs), while GPR119 is involved in GLP-1 secretion stimulated by LCFA derivatives and 2-monoacylglycerol [27, 28]. The MCFA intake, specifically C10:0, enhances GLP-1 secretion through the MCFA receptor GPR84 [29]. Primary rat intestinal cells and murine GLUTag cell lines have shown that carbon length, unsaturation, and esterification are critical factors in stimulating GLP-1 production [30, 31]. Research also suggests that long-chain monounsaturated lipids may be more effective than medium-chain or saturated lipids in enhancing GLP-1 production [32, 33].

Proteins

Studies have demonstrated the effectiveness of proteins or amino acids on L-cell stimulation both *in vivo* and *in vitro*. Whey, peptone, and fish protein hydrolysates have been reported to elevate GLP-1 release in both *in vitro* and *in vivo* studies [34–36]. Casein hydrolysate and the blue whiting protein hydrolysates demonstrated a potent GLP-1 response *in vivo* [37, 38]. L-phenylalanine, L-tryptophan, and peptones increase GLP-1 secretion by activating calcium-sensing receptors and voltage-dependent calcium channels [39, 40]. Other amino acids such as arginine, ornithine, and lysine increased GLP-1 secretion via the GPR-C6A receptor [41]; glutamine induces GLP-1 production through increasing both cAMP and Ca^{2+} levels; aromatic amino acids stimulate L-cells via the G protein-coupled receptor GPR142 [42]. In addition, oligopeptides can elevate GLP-1 secretion via electrogenic uptake through peptide transporter-1 (SLC15A1) or PEPT1 [35], with Trp-Tyr identified as a particularly potent dipeptide in stimulating secretion in murine GLUTag cells [43]. In addition, γ-aminobutyric acid (GABA), the active fraction of the aqueous extract from corn zein protein, was reported to promote GLP-1 release alone and synergistically with L-phenylalanine [44].

Polyphenols

Various polyphenols, well known for their antioxidant properties, have been reported to stimulate GLP-1 secretion. Epigallocatechin-3 gallate from tea and chlorogenic acid from coffee are among the substances that have demonstrated this effect, with the latter promoting secretion by enhancing cAMP levels [45, 46]. Isosinensetin has been shown to increase GLP-1 secretion through the G (beta-gamma)-mediated pathway in NCI-H716 cells [47]. Quercetin was found to act as a GLP-1 secretagogue under conditions where glucose and high extracellular calcium coexist in GLUTag cells [48]. Curcumin, the principal active component of turmeric, has been reported to increase the L-cell number in ob/ob mice [49] and activate GLP-1 secretion through G protein-coupled receptor 55 (GPR55) [50]. The rosemary (*Rosmarinus officinalis L.*) extract, which contains a high concentration of polyphenols, elevated the fasting GLP-1 levels in rats [51]. In addition, wheat alkylresorcinols, possessing a lipophilic polyphenol structure, have been shown to elevate GLP-1 secretion *in vivo* and *in vitro* [52]. *Rehmannia glutinosa* is a Chinese herbal that can be used in medicine and food. Polyphenols extracted from it can act as GLP-1 stimuli in STC-1 cells [53]. Polyphenols extract from Foxtail millet (*Setaria italica*), including the active phenolic compounds such as ferulic acid, p-coumaric acid, 2-hydroxycinnamic acid, and coniferaldehyde, were reported to promote the endogenous GLP-1 secretion in diet-induced-obese mice [54]. Other polyphenols that have been shown to stimulate the L-cells, including resveratrol, genistein, and nobiletin are lack of the underlying molecular evidence [55–57], and further validation in animal models is necessary before considering their potential clinical applications.

Gut microorganisms and bacteria-produced molecules

Gut microorganisms and their metabolites play a significant role in stimulating L-cell secretion of GLP-1. Specific microbes such as *Akkermansia muciniphila*, *Staphylococcus epidermidis*, and *Anaerobutyricum soehngenii*, contribute through their metabolites, including indole, GABA, hydrogen sulfide, and SCFAs [1, 58]. Exopolysaccharides derived from *Lactobacillus plantarum* JY039, which is known for its intestinal adhesion properties, promoted the GLP-1 secretion levels in mouse models [59].

Dietary fibers, which are fermented by gut flora, particularly soluble viscous fibers like β-glucan, alginate, guar gum, and psyllium, in stimulating GLP-1 secretion is significant [60]. SCFAs, primarily acetate, propionate, and butyrate, are a major product of this microbial metabolism and influence GLP-1 secretion via GPR41/GPR43. These SCFAs typically need to be absorbed and then reach the basolateral side of L-cells to exert their effect [1, 61]. Bile acids, including primary and microbe-generated secondary bile acids, have been reported to stimulate L-cell secretion through TGR5 (PKA-activating receptor) [62]. Deoxycholic acid, one of the bile acids the produced by gut microbiota, is known to induce GLP-1 secretion by elevating intracellular Ca^{2+} and cAMP levels in mGLUTag cells [63]. Conversely, pathogenic bacteria like Salmonella can adversely affect GLP-1 secretion, as seen in infected piglets with increased blood glucose and decreased GLP-1 content due to induced L-cell pyroptosis [64].

Other chemicals

Capsaicin, found in chili peppers, acts as a GLP-1 secretagogue by activating the transient receptor potential channels vanilloid 1 (TRPV1) in STC-1 cells [65]. Ginsenoside compound K (20-O-b-D-glucopyranosyl20(S)-protopanaxadiol) increases L-cell abundance and GLP-1 production via TGR5/YAP signaling activation in db/db mice [66]. Steviol glycoside rebaudioside A, from *Stevia rebaudiana*, stimulates GLP-1 release via bitter taste receptors Tas2r108, Tas2r123, and Tas2r134 and is modulated by the presence of GABA and 6-methoxyflavanone [67]. Genipin is derived from the fruits of *Gardenia jasminoides* Elli and *genipa americana*, and it can also be generated from an iridoid glycoside geniposide by the intestinal enzyme β-glucosidase. Study has shown that genipin stimulates GLP-1 release via PLC/Ca^{2+} pathways with an increase in intracellular Ca^{2+} levels [68]. Dihydromyricetin, a vine tea component, stimulates GLP-1 release by affecting AMPK signaling and reducing ERK1/2 and IRS-1 phosphorylation in STC-1 cells [69]. Silibinin, the major component of the silymarin extract, activates the Nrf2-antioxidant pathway, reduces

the reactive oxygen species generation, and improves GLP-1 release both in GLUT cells and in rat models [70]. Based on a double-blind crossover study, hop extract has been shown to have GLP-1 secretagogue effects [71]. Kuguaovins H and J, the compounds extracted from wild *Momordica charantia* vines, have shown the stimulatory effect of GLP-1 secretion in STC-1 cells [72]. The novel alkaloids from *Portulaca oleracea L.* showed an influx of intracellular Ca^{2+} and a GLP-1 secretion-promoting effect in STC-1 cells [73].

Challenges and future directions

Challenges

Exploring food-derived molecules as functional ingredients to enhance GLP-1 secretion is promising, yet our grasp on the subject is still evolving and at times inconsistent, posing challenges for clinical application. A recent study has pointed out significant differences in L-cell distribution and characteristics between humans and rodents, especially in regions of the colorectum enriched in L-cells, underscoring biological discrepancies that may impact the translatability of findings [74]. The duration of treatment is also critical, as prolonged exposure to saturated lipids has been shown to suppress GLP-1 secretion by reducing nicotinamide adenine dinucleotide and ATP synthesis [75]. Similarly, chronic type 2 diabetes mellitus (T2DM) conditions might lead to diminished GLP-1 production, associated with continuously disturbed blood glucose levels and lipid profiles [74]. Thus, although there is a recent surge in studies due to the successful implementation of GLP-1R agonists for type 2 diabetes and obesity patients is promising, translating these findings and potential novel targets into therapeutic approaches that enhance endogenous GLP-1 secretion remains a significant challenge.

Future directions

With the increasing prevalence of obesity and related metabolic diseases, as well as the rising economic burden on healthcare systems, there is an urgent need for a more comprehensive understanding of the regulatory mechanisms of GLP-1 exocytosis and L-cell lineage commitment under various conditions. Breakthroughs in these areas could lead to innovative strategies for managing metabolic disorders beyond just glucose management and weight control. Moreover, ensuring a comprehensive translation of research findings from cell lines to animal models and human applications is critical for developing effective and reliable therapeutic options. This would involve enhancing our basic scientific knowledge and focusing on how these insights can be practically applied to improve patient outcomes and public health.

Conclusion

GLP-1 has been widely studied for its critical role in maintaining glycemic homeostasis, delaying stomach emptying, inducing satiety, and reducing weight gain. In this review, we summarized and discussed the effects of various dietary components, including macronutrients, polyphenols, and other food-derived chemicals, which could potently stimulate endogenous GLP-1 release. Utilizing nutrients from daily consumption and targeting the enteroendocrine L-cells might offer a potential way to induce the endogenous GLP-1 release to prevent excess energy intake and quickly respond to blood glucose fluctuation.

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