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Host-Microbial Interactions | Minireview

Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases

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ABSTRACT Gut microbiota exert influence on gastrointestinal mucosal permeability, bile acid metabolism, short-chain fatty acid synthesis, dietary fiber fermentation, and farnesoid X receptor/Takeda G protein-coupled receptor 5 (TGR5) signal transduction. The incretin glucagon-like peptide 1 (GLP-1) is mainly produced by L cells in the gut and regulates postprandial blood glucose. Changes in gut microbiota composition and function have been observed in obesity and type 2 diabetes (T2D). Meanwhile, the function and rhythm of GLP-1 have also been affected in subjects with obesity or T2D. Therefore, it is necessary to discuss the link between the gut microbiome and GLP-1. In this review, we describe the interaction between GLP-1 and the gut microbiota in metabolic diseases. On the one hand, gut microbiota metabolites stimulate GLP-1 secretion, and gut microbiota affect GLP-1 function and rhythm. On the other hand, the mechanism of action of GLP-1 on gut microbiota involves the inflammatory response. Additionally, we discuss the effects and mechanism of various interventions, such as prebiotics, probiotics, antidiabetic drugs, and bariatric surgery, on the crosstalk between gut microbiota and GLP-1. Finally, we stress that gut microbiota can be used as a target for metabolic diseases, and the clinical application of GLP-1 receptor agonists should be individualized.

KEYWORDS glucagon-like peptide 1, gut microbiota, type 2 diabetes, prebiotics, probiotics

Annual health spending on diabetes imposes a huge burden on society, projected to grow to 845 billion dollars in the United States by 2045, and there are huge differences between countries (1). Therefore, treating type 2 diabetes (T2D) is important. Glucose and weight control are the fundamental steps (2, 3). Recently, changes in gut microbiota composition resulting from diet, drugs, and obesity have been considered one of the pathogeneses of T2D [reviewed in references (4, 5)]. In healthy subjects, oral glucose triggers a stronger insulin secretion response than intravenous glucose because of the secretion of incretin from the gastrointestinal tract, known as the "incretin effect." Clinically, incretin-based drugs include glucagon-like peptide 1 receptor agonists (GLP-1 RA) (such as liraglutide) and dipeptidyl peptidase 4 inhibitors (DPP-4i) (such as vildagliptin). These drugs are effective in the individualized treatment of T2D with or without obesity and have been used clinically for more than a decade (6–8). In addition, bariatric surgery increased intestinal hormones such as GLP-1 and peptide YY (PYY) (9) and changed the composition of gut microbiota (10) and bile acids (BAs) (11), which all enhanced GLP-1 responses in obese individuals with T2D.

Microbiota refers to a community of microorganisms that colonize a particular site such as the skin and mucosa, and the difference is that the microbiome also includes the environment they inhabit or the collective genomes (12). The Common Fund Human Microbiome Project highlighted the interactions between microbiomes and human health issues such as T2D (13). Humans and microbes have a symbiotic relationship and

Editor Marcio Rodrigues, Oswaldo Cruz Foundation, Curitiba, Brazil

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The authors declare no conflict of interest.

See the funding table on p. 17.

Published 6 December 2023

a long history of shared ancestry (14). In the human body, the ratio of bacteria to human cells is close to 1:1 (15). Almost 65% of the human genome comes from microorganisms (16).

The human gut, or gastrointestinal tract, is the body's largest digestive and immune organ. Each part of the gut has distinct characteristics. For example, the distal colon has the densest and the most diverse bacteria (17, 18). Gut microbiota has approximately 1,000 microbial species. The human gut microbiome comprises almost 10 million genes, which are more than 150 times the size of the human genome, and includes many metabolic genes (19). Human gut microbiota are mostly dominated by phylum of the phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia (18). Gut microbiota is highly involved in fighting against disease-causing microbes (e.g., promote IgA secretion) and energy metabolism (e.g., produce monosaccharides). The composition and proportion of gut microbiota are affected by genes [FXR (20)], lifestyle [diet (21)], drugs [antibiotics (22)], aging (23), etc. In addition, the gut microbiome is affected by the host feeding pattern (24), regulating circadian rhythms and metabolism in the host [reviewed in references (25, 26)]. In summary, gut microbiota plays an important role in human health and disease, such as T2D [reviewed in references (27, 28)].

The gut microbiota is increasingly involved in the pathogenesis of diabetes. Meanwhile, both the composition and proportion of the gut microbiota are affected in patients with diabetes (Fig. 1). Patients with T2D had gut microbial dysbiosis and an increase in various opportunistic pathogens (29). Specifically, the abundance of some butyrate-producing bacteria (such as the phylum Firmicutes and genus *Bifidobacterium*) was reduced, while Gram-negative bacteria were relatively enriched such as the phyla Bacteroidetes and Proteobacteria (30, 31). However, alterations in certain gut microbiota by drugs or dietary fibers [such as decreased abundance of Firmicutes and Bacteroidetes (32)] contributed to the elevation of GLP-1 levels and the improvement

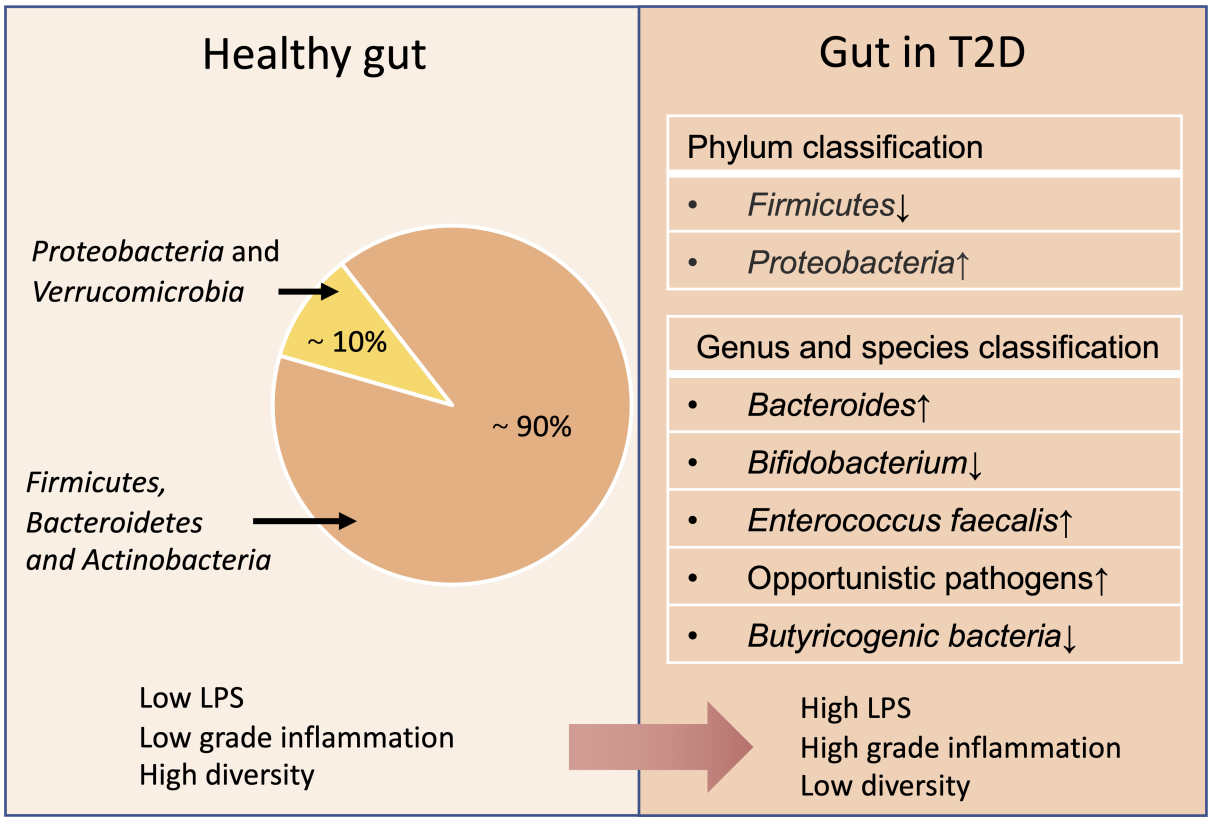

FIG 1 Comparison of intestinal flora between healthy and T2D subjects.

of obesity-induced insulin resistance. Importantly, when discussing the influence of gut microbiota on the host, the individualization of host baseline microbiota and host variables should not be ignored (33, 34). In addition, comparative studies using germ-free mouse models demonstrated the importance of the gut microbiota in regulating diet-induced dysregulation of energy homeostasis and obesity (35, 36).

In this review, we summarized the interventions that might affect gut microbiota and then the secretion of GLP-1. Additionally, we reviewed the potential mechanisms in this process. Then, we highlighted the effect of gut microbiota on GLP-1 function and rhythm. Finally, the importance of gut peptides on gut microbiota was discussed. The interaction between gut flora and gut peptides provides a personalized approach to treat obesity and T2D.

MECHANISMS BY WHICH GUT MICROBIOTA METABOLITES STIMULATE GLP-1 SECRETION

Gut microbiota affects host GLP-1 production through metabolites (37). Several metabolites have been suggested to be involved in the influence of intestinal flora on GLP-1 secretion, as discussed below (Fig. 2).

Gut microbiota produces a variety of metabolites [including 5-HT (38), short-chain fatty acids (SCFAs) (39), secondary BAs (40). and lipopolysaccharide (LPS) (41)] that regulate enteroendocrine cells (EECs) and then the expression and secretion of

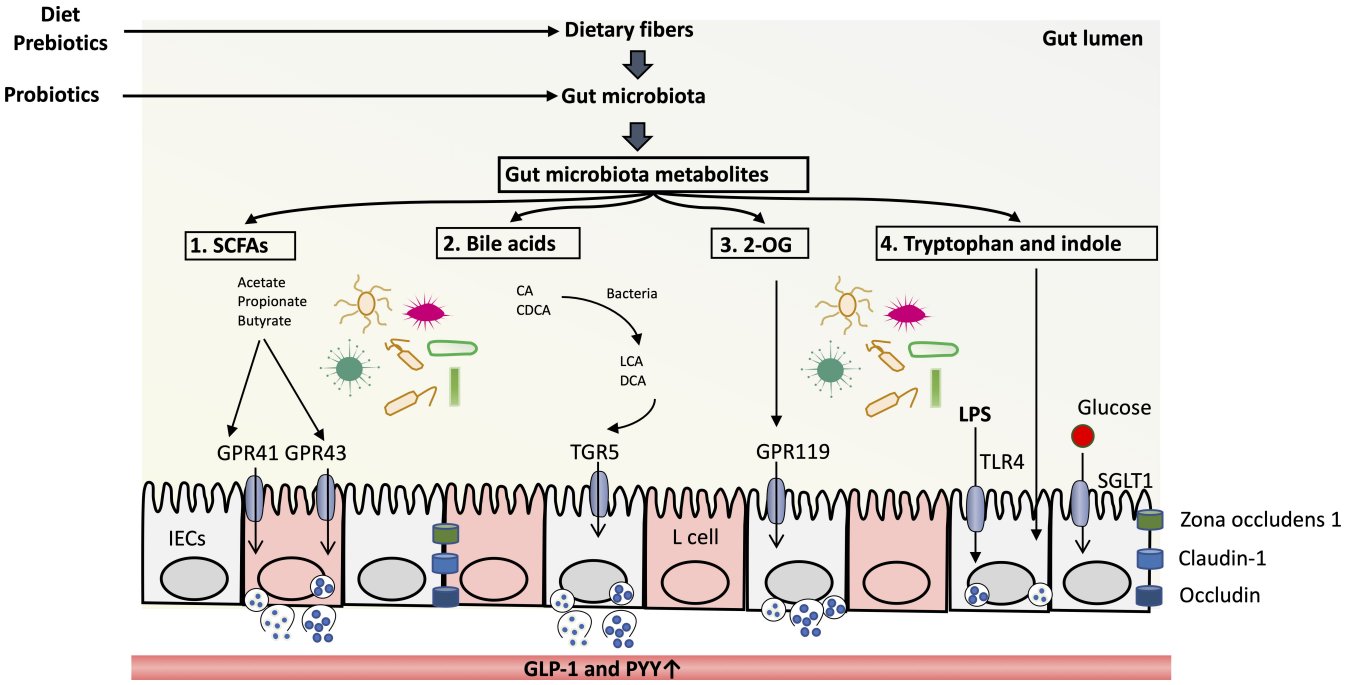

FIG 2 Gut microbiota metabolites promote GLP-1 production. The intake of prebiotics and certain diets produces dietary fibers, and the intake of probiotics may affect the function and composition of gut microbiota. (1) Dietary fibers are fermented to SCFAs by gut microbiota, which bind to GPR43 receptors on the surface of L cells and then promote the production of GLP-1. SCFAs also bind to GPR41 of L cells and promoted the PYY production. (2) Primary bile acids (CA and CDCA) are transported from the liver to the intestinal lumen, through a series of metabolism such as hydrolysis and dehydroxylation of gut microbiota, and finally are transformed into secondary bile acids (LCA and DCA). Secondary bile acids bind to TGR5 and promote the production of GLP-1. (3) Dietary fats are digested into 2-OG and fatty acids under the action of intestinal bacteria. 2-OG bind to GPR119 receptor of L cells to promote the production of GLP-1. (4) Tryptophan is the digestive product of dietary protein and then further broken down into indole. They promote the production of GLP-1. In addition, LPS on the surface of Gram-negative bacteria can bind to TLR4 receptor of L cells and then promote GLP-1 production. At the same time, intestinal epithelial cells can sense the concentration of glucose in the gut lumen and initiate the secretion of GLP-1 when the concentration reaches a certain level. 2-OG, 2-oleoyl glycerol; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GPR119, G-protein receptor 119; GPR41, G-protein receptor 41; GPR43, G-protein receptor 43; IECs, intestinal epithelial cells; LCA, lithocholic acid; LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; SGLT1, sodium-glucose cotransporters 1; TGR5, Takeda G protein-coupled receptor 5; TLR4, Toll-like receptor 4.

hormones. Microbial metabolites can be divided into three categories. The first type, such as short-chain fatty acids and 2-oleoyl glycerol (2-OG, derived from dietary fats), is produced by intestinal microorganisms directly digesting or fermenting food components. The second category is metabolites produced by the host and modified by intestinal microorganisms, such as secondary BAs. Secondary BAs are dissociated and transformed from primary BAs by intestinal 7-α/β dehydroxylation bacteria and contribute to the establishment of intestinal homeostasis in hosts. The third type is the metabolites synthesized by intestinal microorganisms, such as LPS. Gut microbiota metabolites such as SCFAs (42–56) and secondary BAs (11, 57) can stimulate GLP-1 secretion. In addition, microbial metabolites such as 2-OG (58) and indole (59) directly activate GLP-1 secretion from L cells. Therefore, prebiotics and probiotics may ameliorate obesity and T2D through the gut microbiota-SCFA-inflammation/GLP-1 mechanism. Bariatric surgery may improve body weight, glucose metabolism, and inflammation by the gut microbiota-secondary BA-GLP-1 mechanism (11).

SCFAs stimulate GLP-1 secretion

SCFAs are involved in maintaining health and the development of disease and have attracted considerable attention. In fact, decreased SCFA production or production potential is associated with metabolic diseases, such as T2D (60, 61). The human genome encodes fewer than 20 enzymes to digest complex carbohydrates (62), so some carbohydrate polymers (dietary fibers) that are neither digested nor absorbed in the small intestine will be fermented to SCFAs by gut microbiota through carbohydrate-active enzymes in the gastrointestinal tract [reviewed in reference (63)]. Interestingly, the colon produces high levels of SCFAs and contains many L cells (64). More than 90% of SCFAs are absorbed by the gut or used by the microbiota (65). SCFA receptors are the G-protein-coupled free fatty acid receptors GPR43 (FFAR2) and GPR41 (FFAR3) (66). GPR43 and GPR41 are relatively conserved and highly expressed in enteroendocrine L cells in rats and humans and differ in their intracellular signals [reviewed in reference (67)]. In the human and rat colon and terminal ileum, the increase in SCFAs after adding fermenting dietary fiber may activate GPR43 and lead to increased GLP-1 secretion (51). Additionally, intravenous or rectal SCFA infusion was shown to increase GLP-1 secretion in humans (44). However, when SCFAs are given to GPR43 knockout mice, GLP-1 secretion cannot be stimulated (39). The mechanism involves GPR43 and GPR41 activation leading to increased intracellular calcium in L cells (39, 56, 68). Thus, these results suggest that gut microbiota can influence the production of SCFAs and the secretion of anorexic intestinal hormones, such as GLP-1, from rodent (39, 56) and human (44) enteroendocrine L cells via the receptor GPR43, but further studies are needed to elucidate the underlying mechanisms. However, GPR43 activation by increased SCFAs increased the number of the PYY-producing cells and PYY expression, which might be an effective therapeutic target for obesity but not T2D (69). Therefore, the increase in GLP-1 might occur through the receptor GPR41 (Fig. 3).

Secondary bile acids stimulate GLP-1 secretion

Secondary BAs occur under the action of the gut microbiota, which means that alterations in the gut microbiota may change the composition of the BA pool. BAs as metabolites regulate signaling and glucose homeostasis. For example, secondary BAs have dual regulatory effects on GLP-1 secretion. On the one hand, secondary BAs activate Takeda G protein-coupled receptor 5 (TGR5) on intestinal L cells to stimulate GLP-1 secretion (70, 71). On the other hand, secondary BAs activate the farnesoid X receptor (FXR) to inhibit GLP-1 secretion (40, 72).

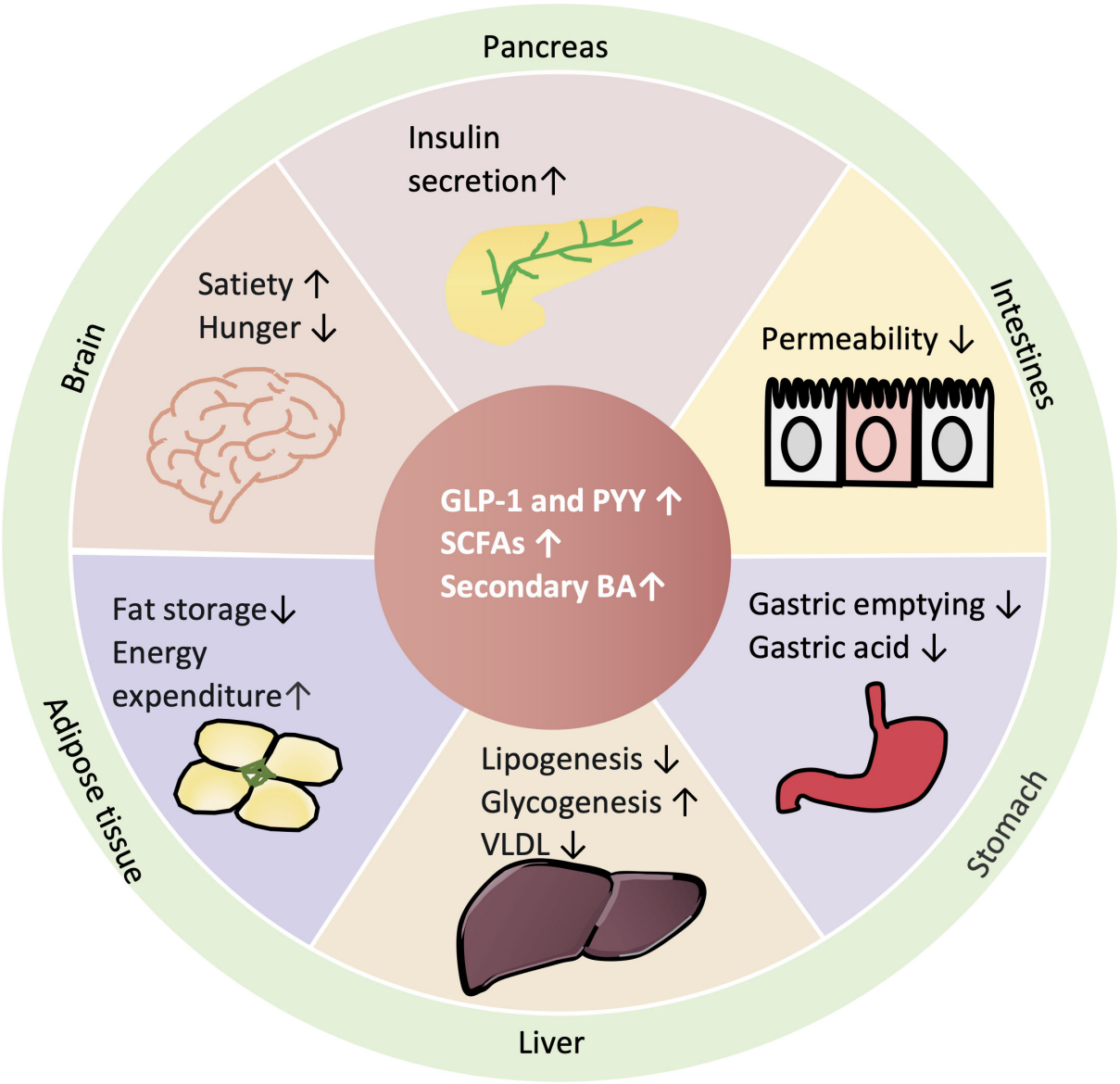

FIG 3 Physiological benefits of gut peptides and gut microbiota metabolites. GLP-1 has multiple physiological functions. It promotes insulin synthesis and secretion in pancreatic β cells and then improves glucose homeostasis, delays gastric emptying and reduces gastric acid secretion, reduces intestinal permeability and bacterial translocation, promotes lipolysis and energy expenditure, increases liver glycogen storage and decreases liver sugar output, and suppresses appetite in the hypothalamus of brain. SCFAs and secondary bile acids also help increasing insulin secretion in pancreas, energy expenditure in adipose tissue, and decreasing liver lipogenesis and VLDL (very low density lipoprotein) output.

INTERVENTIONS THAT AFFECT GUT MICROBIOTA TO PROMOTE GUT PEPTIDE SECRETION, SUCH AS GLP-1

Probiotics and prebiotics are beneficial for improving host health. They can modulate immune function, interact with the hosts' gut microbiota, improve the gut barrier and permeability, and promote GLP-1 secretion.

Prebiotics promoted GLP-1 secretion

Prebiotics can be selectively utilized by the host microbiota to improve host health (73). Recent findings suggested that prebiotic interventions lead to gut microbiota shifts to promote health (74). Prebiotics under the fermentation of gut microbiota could increase gut peptide production, such as GLP-1 and PYY (75).

In overweight/obese humans, supplementation with prebiotics such as oligofructose (76–79), fructan (75), resistant starch (42, 80), and arabinoxylan-oligosaccharide (81) has produced inconsistent results on GLP-1 and promoted SCFAs production (42, 78, 80–82) (Table 1). Of note, some oligofructose studies only found an increase in PYY, not GLP-1 (77, 78). Arabinoxylan-oligosaccharide caused a decrease in early postprandial GLP-1 accompanied by a decrease in alpha diversity and an increase in fecal *Bifidobacterium*, *Akkermansia*, and *Lactobacillus* (81). In patients with hyperinsulinemia, dietary fiber increased the production of acetate and butyrate to stimulate an increase in plasma GLP-1 and fasting and postprandial insulin levels, but the body weight stayed the same (43). An almond-based low carbohydrate diet consumption significantly increased the relative abundance of SCFA-producing bacteria *Roseburis* and *Ruminococcus* in human gastrointestinal microbiota (83, 84), as well as the GLP-1 concentration (84). Overall, human interventions with prebiotics have shown mixed results, so further work is needed.

The effects of prebiotics on GLP-1 secretion are also inconsistent. In mice, ingestion of prebiotics increased butyrate-producing bacteria (48), enhanced GLP-1 release (91), and improved diabetes symptoms (92). For example, dendrobium polysaccharides upregulated the abundance of *Akkermansia* and *Parabacteroides*, thereby increasing gut microbiota metabolites such as SCFAs, tryptophan, and indole to stimulate GLP-1 secretion [reviewed in reference (93)]. In diabetic mice, ingestion of resveratrol enhanced GLP-1 release and modified cecal bacterial composition (94). In db/db mice, tetrahydrocurcumin supplementation decreased the ratio of Firmicutes to Bacteroidetes and increased the volume of GLP-1 in the pancreas (95). Oligofructose (49), fructo-oligosaccharide (51), fructans (96), and inulin (97) caused an increase in GLP-1, PYY, and SCFAs, but the change in gut microbiota was not applicable. In T2D mice, the supplementation of modified dietary fibers increased the relative abundance of *Akkermansia muciniphila*, Verrucomicrobia, and Bacteroidetes, decreased the relative abundance of Firmicutes, Proteobacteria, and Actinobacteria, and increased the production of SCFAs. It also increased the levels of GLP-1 and PYY and then improved the metabolism of blood glucose and lipids (46). Additionally, flavonoids from *Lycium barbarum* regulate the gut microbiota and reduce pro-inflammatory cytokines to ameliorate the symptoms of T2D mice, accompanied by the elevation of GLP-1 (98). Polysaccharides from adlay seeds (PAS) increased Simpson's diversity index and GLP-1 concentrations, indicating that PAS altered the diversity and composition of the microbiota and had hypoglycemic effects in T2D mice (99) (Table 2). In conclusion, one of the mechanisms by which prebiotics regulates host health is to promote GLP-1 secretion by regulating changes in gut microbiota.

Probiotics promoted GLP-1 secretion

Probiotics are live microorganisms that bring many benefits to the host (110). Probiotic interventions have strain-specific anti-inflammatory effects on healthy adults (111). While the effects of probiotics on the host are not necessarily related to their interactions with the protoflora, their use is often associated with claims about beneficial regulation of probiotics and the normalization of disturbed flora, either as a favorable outcome of the probiotics themselves or as a mechanism by which the probiotics protect the host against disease (73). However, the effect of probiotic intake on intestinal mucosa is not necessarily fixed and is related to the host and its microbiome characteristics (112). The beneficial effects of probiotics on diabetes have been studied, and the mechanism may be related to enhancing immunity, increasing the production of anti-inflammatory cytokines, reducing intestinal permeability, and reducing oxidative stress.

In subjects with metabolic syndrome, a single duodenal *Anaerobutyricum soehngenii* bacteria infusion increased the levels of plasma secondary BAs and postprandial GLP-1 and thereby improved glucose metabolism (57). Moreover, no adverse events were observed when live *Anaerobutyricum soehng*eni was orally administered (113). Intake of *Lactobacillus reuteri* improved GLP-1 and insulin secretion in people with glucose

TABLE 1 Clinical studies on the interaction between gut microbiota therapy and gut peptides[a]

Study design and references	Subject state or condition	BMI (kg/m^2)	Intervention	Gut microbiota	Gut microbiota metabolites	Gut peptide	Outcomes
Crossover (76)	GERD (n = 9)	N/A	Oligofructose (20 g/d) for a week	N/A	N/A	GLP-1↑; PYY (-)	Breath H2↑; the rate of TLESRs↑
Double blind, R, parallel, PC (75)	Healthy (n = 10)	21.6 ± 0.99	Fructan (16 g/d) for 2 weeks	N/A	N/A	GLP-1↑; PYY↑	PBG↓; breath H2↑; hunger↓
Single blind, R, crossover (80)	T2D (n = 17)	31.0 ± 1.3	RS (40 g/d) for 12 weeks	N/A	Fasting serum propionate and butyrate↓	Fasting GLP-1↓; GLP-1↑	PBG↓; TAG↓; TNF-α↓; fasting NEFA↓; leptin or adiponectin (-)
R, crossover (42)	Healthy (n = 20)	23.6 ± 2.3	RS (17.0 g/d) and NSP (20.6 g/d) for 3 days	N/A	Fasting s-SCFA↑, (especially acetate↑)	Fasting GLP-1↑; PYY and GLP-2↑; OXM and ghrelin (-)	Breath H2↑; insulin sensitivity↑; blood glucose ↓; hunger, NEFA, and adiponectin (-)
Double blind, R, PC, P, trial (81)	Slow GI transit (n = 48)	24.7 ± 3.1	Axos (15 g/d) for 12 weeks	Alpha diversity↓; fecal *Bifidobacterium*↑, *Akkermansia*↑, *Lactobacillus*↑	Fecal and serum SCFA (-)	Early postprandial GLP-1↓; PYY (-)	Stool consistency↓; gut permeability/inflammation (-); glucose, insulin, FFA, TAG, glycerol; and appetite, hunger, satiety, and fullness ratings (-)
Double blind, R, placebo-controlled trial (77)	Overweight/obese (n = 39)	30.4 ± 3.4	FOS (21 g/d) for 12 weeks	N/A	N/A	GLP-1 (-), PYY↑; ghrelin↓;	Postprandial insulin↓; fat mass↓; energy intake↓; postprandial glucose (-); lipids (-);
Single blind, R, P, C study (78)	Healthy (n = 22)	29.7 ± 1.0	FOS (30 g/d) for 6 weeks	N/A	s-SCFA↑; acetate↑	GLP-1 (-); plasma PYY↑	Breath H2↑; appetite↓; hunger↓; fullness ↑; PBG, insulin (-); lipids, body fat (-); AST, ALT (-);
Double blind, R, crossover (79)	Healthy (n = 31)	24.8 ± 0.3	FOS (16 g/d) for 13 days	N/A	N/A	GLP-1↑; PYY↑	Energy intake↓
RCT (43)	FPI ≥40 pmol/L (n = 40)	25·7 ± 1.1	24 g fiber /d for a year	N/A	Acetate and butyrate↑	Plasma GLP-1↑	Body weight (-); fasting and postprandial insulin (-); NEFA (-)
Double blind, RCT (85)	NAFLD children (n = 44)	27.3 (24.7–28.6)	VSL#3 for 4 months	N/A	N/A	GLP-1 and activated GLP-1↑	BMI↓
Double blind, R trial (86)	Glucose tolerant (n = 21)	23.6 ± 1.7	*L. reuteri* (2 × 10^{10} cells b.i.d.) for 4 weeks	a-Diversity, overall composition, and total lactobacilli (-);	N/A	GLP-1↑; GLP-2↑	Insulin↑; C-peptide↑; PBG (-); IL-8, and MIP-1b (-); TNF-α↑; oxidative stress (-)
Double blind, R, PC crossover study (57)	MetS (n = 12)	35.9 (32.3–37.9)	Duodenal infusion *A. soehngenii* L2-7 treatment	Microbiota richness and diversity (-); fecal SCFA (-)	Plasma secondary BA (TDCA, TLCA, GDCA); butyrate↑	GLP-1↑	GPR43, TGR5, FXR5, and REG1B↑
Single blind, R, crossover (44)	Hyperinsulinemic female (n = 6)	31·0 (SEM 1.0)	Rectal or intravenous acetate infusions	N/A	Plasma acetate↑; Cecal SCFA (-)	GLP-1↑; PYY↑ ghrelin (-)	Plasma glucose or insulin (-); TNF-α and NEFA (-)
Clinical trial (87)	T2D (n = 14)	30.0 ± 3.3	Stopping metformin	Firmicutes↑; Bacteroidetes↓	Cholic acid and conjugates↑	GLP-1↓	Plasma glucose levels↑
RCT (88)	T2D (n = 19)	33.3 ± 4.1	Metformin 1,000 mg twice daily	N/A	N/A	GLP-1R; PYY↑	PBG↓; fasting glusocse levels↓

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TABLE 1 Clinical studies on the interaction between gut microbiota therapy and gut peptides[a] (*Continued*)

Study design and references	Subject state or condition	BMI (kg/m^2)	Intervention	Gut microbiota	Gut microbiota metabolites	Gut peptide	Outcomes
R, open-labeled, two-arm trial (89)	Treatment-naive T2D (*n* = 92)	26.83 ± 1.81	Acarbose or vildagliptin for 6 months	Bacteroidetes species↓	N/A	Fasting GLP-1↑	HbA1c↓; visceral fat areas
Clinical trial (45)	Diagnosed-naive diabetes (*n* = 50)	25.82 ± 2.88	Metformin 1,500 mg/d for 12 weeks	*Phascolarctobacterium*, *Intestinimonas,* and *Clostridium* III↑	Acetic acid and propanoic acid in feces↑	Total GLP-1↑	Food intake↓; glucose control↑
Observational study (90)	Morbidly obese (*n* = 3)	40.6 ± 5.4	RYGB surgery	Firmicutes↓; Gammaproteobacteria↑; Archaea↓	N/A	N/A	N/A

[a] ALT, alaninetransaminase; AST, aspartate transaminase; *A. soehngenii* L2-7, *Anaerobutyricum soehngenii* L2-7; Axos, arabinoxylan-oligosaccharide; BMI, body mass index; C, controlled; FOS, oligo-fructose; FPI, fasting plasma insulin; GDCA, glycodeoxycholic acid; GERD, gastro-oesophageal reflux disease; *L. reuteri*, *Lactobacillus reuteri*; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NEFA, non-esterified fatty acids; NSP, non-starch polysaccharides; OXM, oxyntomodulin; P, parallel; PBG, postprandial blood glucose; PC, placebo controlled; R, randomized; REG1B, regenerating islet-protein 1B; RS, resistant starch; RYGB, Roux-en-Y gastric bypass; SEM, standard error of mean; s-SCFA, serum SCFA; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TLESRs, transient lower esophageal sphincter relaxations. Values expressed as mean ± SD or medians and IQRs. ↑, increase; ↓, decrease; (-), no change; NA, not available.

TABLE 2 Animal studies on the interaction between gut microbiota modification therapy and gut peptides[a]

Animal model and references	Invention	Gut microbiota	Gut microbiota metabolites	Gut peptide	Metabolism	Putative outcomes
Male C57Bl/6J diabetic mice (94)	Resveratrol diet (60 mg RSV/Kg/day) for 5 weeks	Modified cecal bacterial composition	N/A	Active GLP-1 in the colon↑; portal vein GLP-1↑	Insulin; proglucagon mRNA↑	N/A
db/db Mice (95)	THC for 8 weeks	Proteobacteria, Actinobacteria, and F/B ratio↓	N/A	GLP-1 in the pancreas↑;	FBG↓; insulin↑	Islet injury↓
T2D male Kunming mice (47)	Kombucha for 4 weeks	SCFAs-producing bacteria↑; Gram-negative bacteria and pathogenic bacteria↓; Firmicutes↑; Proteobacteria↓	SCFAs↑, especially butyric acid and acetic acid	GLP-1↑; PYY↑; GPR41 and GPR43↑;	FBG↓; food intake↓; BW↑; HOMA-IR↓; glycogen synthesis↑; AST, ALT, and the liver coefficient↓	LPS↓; islet cells↑; the pancreatic index↓; IL-1β, IL-6, and TFN-α↓; colonic injury recovered; tight junction proteins and mucin↑
T2D male C57BL/6 J mice (46)	Modified DFs for 4 weeks	*Akkermansia muciniphila*↑; Verrucomicrobia and Bacteroidetes↑; Firmicutes, Proteobacteria, and Actinobacteria↓; F/B ratio↓	SCFAs↑, especially acetic acid, propionic acid, and butyric acid	GLP-1↑; PYY↑	FBG↓; insulin and leptin↑; liver to body ratio↓; TC, TG, and LDL-C↓; HDL-C↑; pancreatic islets↑; liver injury↓	Glut2 and insulin receptor in the liver↓; G6Pase↑
Diabetic mice (98)	LBFs	N/A	N/A	GLP-1↑; TLR-4↓	FBG↓; HOMA-IR, HOMA-IS, and HbA1c↓; OGTT↓; TC and TG↓	LPS, TLR-4, TNF-4, IL-6, IL-10↓
T2D ICR male mice (99)	PAS	Altered the diversity and composition of the microbiota	N/A	GLP-1↑	BG↓; HbA1c↓; TC and TG↓; AC1-42↓; STZ-lesioned pancreatic cells↓	N/A
Goto-Kakizaki rat (48)	An RS diet for 10 weeks	Butyrate-producing bacteria in cecal contents↑	SCFAs↑ in cecal contents	Total GLP-1↑	FBG↓; fasting insulin↓; pancreatic β cell mass↑; insulin sensitivity↑; pancreatic insulin content↑; fat weight↓	N/A
Male Wistar rats (49)	Oligofructose (10 g/100 g diet) for 4 weeks	N/A	Butyrate↑ in the cecum and proximal colon	Portal serum GLP-1↑	Food intake, energy intake, and body weight gain↓	Enteroendocrine L-cells↑; neurogenin 3 and NeuroD↑; total cecum weight↑
C57J/B6 male mice and Lep receptor-deficiency ob/ob mice (50)	VSL#3 for 8 weeks	Butyrate-producing bacteria↑	Butyrate in the fecal and serum samples↑	GLP-1↑; FFAR3↑	FBG↓; glucose tolerance and insulin tolerance↑	Genes involved in GLP-1 synthesis (Gcg and Pcsk1) and secretion (Slc5a1) ↑
HFD-fed male C57BL/6 J mice (91)	FOS for 4 weeks	N/A	N/A	GLP-1↑	Glucose tolerance↑, FBG↓; Insulin↑, and body weight gain↓	Hepatic phosphorylation of IKK-beta and NF-B↓
Male Wistar rats (51)	Fructo-oligosaccharide (16 g/day) for 28 days	N/A	SCFA in colon and terminal ileum↑,	GLP-1↑	Densities of FFA2- and GLP-1-IR cells↑;	The weights of the cecal tissues and contents↑

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TABLE 2 Animal studies on the interaction between gut microbiota modification therapy and gut peptides[a] (*Continued*)

Animal model and references	Invention	Gut microbiota	Gut microbiota metabolites	Gut peptide	Metabolism	Putative outcomes
			especially acetate and butyrate			
Male Wistar rats (96)	Fructans (100 g) for 3 weeks	N/A	N/A	Portal vein serum GLP-1↑; ghrelin↓	Epididymal fat mass↓	N/A
WT (97)	Inulin (for 2 or 14 weeks)	N/A	SCFAs↑	PYY↑	BW gain↓; IR↓; food intake↓; glucose tolerance↑	N/A
DIO rats (100)	*L. paracasei* intervention for 3 or 12 weeks	Composition of the cecum microbiome (-)	N/A	GLP-1↑	Serum LDL-C↓; TG↓; insulin secretion↑; IR index (-); weight gain (-); TRL-C↓; BG↓; fasting cholesterol↓; MAT↓; EAT↓;	GLP-1 intervention; serum molecular signature changed; microbiome mediated
Male db/db diabetic mice (52)	10 *Lactobacillus* strains and 4 *Saccharomycetes* strains composite probiotics (6 wks)	Bacteroidetes/*Bifidobacterium*/ *Lactobacillus*/ *Clostridium leptum*/*Roseburia*, and *Prevotella*↑; Firmicutes/ Actinobacteria/*Enterococcus faecium*/ Gram-negative bacteria/*Escherichia coli* and *Bacteroides thetaiotaomicron*↓	Propionate and butyrate↑; acetate↓	GLP-1↑; PYY↑ GPR43↑; GPR41↑	PBG↓; C-peptide↑; TG, TC, and LDL-C↓; insulin↑	Improved pancreas function, immune state, and the intestinal barrier function
Male C57BL/6J diabetic mice (53)	*L. casei* CCFM419	Bacteroidetes/*Bifidobacterium*/ *Lactobacillus*/ SCFA-producing bacteria↑; Firmicutes↓	Acetic acid, butyric acid, and total SCFAs in the feces↑	GLP-1↑	PBG↓; HbA1C↓; leptin↓; LDL-C↓; HDL-C↑;	TNF-α↓; IL-6↓
Leptin receptor-deficiency db/db mice (54)	Oral gavage CB0313.1 daily (5 weeks)	N/A	N/A	N/A	Insulin sensitivity↑; improved glucose tolerance	Inflammatory tone in adipose tissue↓
C57BL/6J diabetic mice (54)	Oral gavage CB0313.1 daily (13 weeks)	Butyrate-producing bacteria↑	SCFA↑; SCFA receptor↑	GLP-1↑	Insulin sensitivity↑; glucose tolerance↑; HOMA-β↑	Inflammatory tone in adipose tissue↓; TNF-α↓; MCP-1↓
Female Wistar diabetic rats (101)	Oral *L. fermentum* MCC2759/ 2760 (4 weeks)	Pathogenic bacteria such as *Escherichia coli*, *Staphylococcus aureus*, and *Campylobacter* spp. ↓	N/A	GLP-1↑; TLR4 receptor↓	Glucose tolerance↑; plasma insulin↓; BG↓; adiponectin↑; GLUT4↑	Tight junction protein ZO-1↑; endocannabinoid receptor CB2↑;
Male albino Wistar T2D rats (55)	*L. rhamnosus* NCDC 17 (9.5 to 10 log cfu/mL) (6 weeks)	Bacteria abundance and numbers↑; *Eubacterium rectale-Clostridium coccoides*, *Bacteroides*, *Lactobacilli,* and *Bifidobacteria*↑ (cecal contents)	Acetate↑	GLP-1↑	Glucose tolerance↑; FBG↓; HDL-C↑; TG↓; VLDL-C↑; adiponectin↑	Activity of catalase and GPx↑; activity of SOD↑ ; TNF-v↓ and IL-6↓;
Male albino Wistar T2D rats (55)	*L. rhamnosus* LGG (8 to 8.5 log cfu/mL) (6 weeks)	Bacteria abundance and numbers↑; *Bacteroides*↓ (cecal contents)	Propionate↑	GLP-1↑	Glucose tolerance↓; FBG↓; HDL-C↑;	Activity of catalase and GPx↑ ; activity of SOD↑
ICR mice (102)	Oral EPSs (800 mg/kg)	N/A	N/A	GLP-1↑	BG↓; glucose consumption of the FL83B cells↑	Activation of Akt↑

(*Continued on next page*)

TABLE 2 Animal studies on the interaction between gut microbiota modification therapy and gut peptides[a] (*Continued*)

Animal model and references	Invention	Gut microbiota	Gut microbiota metabolites	Gut peptide	Metabolism	Putative outcomes
HCD-fed C57BL6 mice (103)	Oral *L. fermentum* MCC2760 (10.95 log CFU/mL) (8 weeks)	*Lactobacillus* spp. count↑; pathogen count (like *Staphylococcus* and *Campylobacter*)↓	N/A	GLP-1↑	BG↓; body weight↓; serum CHOL, TG, LDL-C, AST, and ALT↓	Bacterial translocation count↓; LPS, TNF-α, IL-6, IL-12↓. and IL-10; GSH-Px, GSH-Tr, CAT, and SOD↑; CB1↓, CB2↑; ZO-1↑
Piglets (104)	*Lactobacillus plantarum* (50 mg) (3.5×10^{10} CFU/g) daily (2 weeks)	Alpha diversity (-); Tenericutes phylum/ *Bacteroides*/*Parabacteroide*/ *Clostridium_sensu_stricto_1*/ *Ruminococcus_1*/*Desulfovibrio*↓; *Lactobacillus*/*Megasphaera*/ *Collinsella*↑	G-LCA↓; T-LCA↓; CA↑; TBA (-) (in ileum tissue)	Postprandial plasma GLP-1↓	PBG↑; genes associated with BA metabolism (-)	Genes related to inflammation and glucose transport (-); GLUT2 and SGLT1 (-)
Pig (105)	Cecal propionate infusions (0, 5, 20, and 100 mmol/L)	N/A	Exogenous propionate↑	GLP-1↑; PYY↑; FFAR2/ FFAR3 expression↑	Acute feed intake↓;	AgRP expression↓
FFAR2 (–/–) mice (56)	Colonic propionate infusions (180 mmol/L)	N/A	Exogenous propionate↑	Portal vein plasma GLP-1 and PYY (-)	N/A	N/A
Wistar rats and C57BL6 mice (56)	Colonic propionate infusions (180 mmol/L)	N/A	Exogenous propionate↑	Portal vein plasma GLP-1 and PYY↑	N/A	N/A
$FFAR2^{-/-}$ and $FFAR3^{-/-}$ mice (39)	Receptor knockout (3 to 4 months)	N/A	SCFAs↑	GLP-1↓	N/A	N/A
Male HFD-fed C57BL/6 J mice (106)	FMT	*Akkermansia*, *Bacteroides*, and *Butyricimonas* (-)	N/A	GLP-1↑; TLR1 and TLR4↑	BG↑; body weight (-); TC (-);	IL-18↓; TLR2, TLR5, and TLR6 (-);
Male HFD-fed C57BL/6 J mice (107)	Metformin (250 mg/kg) for 16 weeks	Genera *Akkermansia*, *Bacteroides*, *Butyricimonas*, and *Parabacteroides*↑	N/A	N/A	BG↓; BW↓; TC and LDL↓	IL-1β and IL-6 in epididymal fat↓
DIO male C57Bl/6 J mice (11)	SG	*Clostridiales* (-)	LCA in portal veins↑	GLP-1↑	Expression levels of mSult2A1 and Vdr in liver↑; CA7S↑	LCA-VDR-SULT2A1-CA7S pathway
Male C57BL/6 J mice, SD rats, and Zucker diabetic fatty rats (108)	Canagliflozin (0.3–30 mg/kg) and sitagliptin (10 mg/kg)	N/A	N/A	Plasma active GLP-1↑	Insulin↑; BG↓	Transient intestinal SGLT1↓
Male C57BL/6 renal failure mice (109)	Canagliflozin (10 mg/kg for 2 weeks)	*Bifidobacterium*↓	Colonic SCFAs↑	N/A	p-Cresyl sulfate and indoxyl sulfate↓; BG (-)	Intestinal SGLT1↓

[a] AgRP, agouti-related protein; ALT, alanine transaminase; AST, aspartate aminotransferase; BW, body weight; CA, cholic acid; CAT, catalase; CB0313.1, *Clostridium butyricum* CGMCC0313.1; CFU, colony-forming units; CHOL, cholesterol; DFs, dietary fibers; DIO, diet-induced obese; DOP, dendrobium polysaccharide; EAT, epididymal adipose tissue; EPSs, exopolysaccharides; FBG, fasting blood glucose levels; F/B ratio, the ratio of Firmicutes to Bacteroidetes; FMT, fecal microbiota transplantation; G6pase, glucose-6-phosphatase catalytic subunit 1; GB-IL, bile diversion to the ileum; G-LCA, glycolithocholic acid; GSH-Px, glutathione peroxidase; GSH-Tr, glutathione transferase; HCD, high-cholesterol diet; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-IS, homeostasis model assessment of insulin sensitivity; IL, interleukin; IR, insulin resistance; *L. fermentum*, *Lactobacillus fermentum*; *L. Paracasei*, *Lactobacillus paracasei*; LBFs, flavonoids from *Lycium barbarum*; LDL-C, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; MAT, mesenteric adipose tissue; MCP-1, monocyte chemotactic protein 1; NSS, not statistically significant; PAS, polysaccharides from adlay seeds; PBG, postprandial blood glucose; RSV, resveratrol; SG, sleeve gastrectomy; SOD, superoxide dismutase; T1D, type 1 diabetes; TBA, total bile acids; TC, total cholesterol; TG, triglycerides; THC, tetrahydrocurcumin; T-LCA, total lithocholic acid; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRL-C, triglyceride-rich lipoprotein cholesterol; VSL#3, a commercial product containing a total of eight probiotic strains including *Streptococcus thermophilus*, *bifidobacterium* (*B. breve*, *B. infantis*, *B. longum*), *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. delbrueckii* subsp. *bulgaricus*; ZO, zonula occludens-1.↑, increase; ↓, decrease; (-), no change; NA, not available.

tolerance (86). Supplementation with VSL#3 (a commercial product containing a total of eight probiotic strains including *Streptococcus thermophilus*, *bifidobacterium* [*B. breve*, *B. infantis*, *B. longum*], *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. delbrueckii* subsp. *bulgaricus*) for 4 months increased GLP-1 and decreased BMI in nonalcoholic fatty liver disease children (85).

In T2D mice, Kombucha (polyphenols and organic acid active substances) administration improved the inflammation state and intestinal tight conjunction, such as decreasing the levels of LPS and pancreatic index and increasing the protein zona occludens 1, claudin-1, occludin, and mucin (47). At the same time, the abundance of SCFA-producing bacteria was increased, thereby increasing SCFAs and elevating the concentrations of GLP-1 and PYY (47). Exopolysaccharides from *Bacillus amyloliquefaciens* could increase GLP-1 levels by interacting with intestinal tissues (102). Supplementation with VSL#3 for 8 weeks increased the abundance of butyrate-producing bacteria, butyrate, and GLP-1 and improved fasting blood glucose, glucose, and insulin tolerance in both C57J/B6 male mice and $Lep^{ob/ob}$ mice (50). A recombinant microbe *Lactobacillus paracasei* NFBC 338 was successfully transformed to express a long-acting analog of GLP-1. The short-term or long-term administration of *L. paracasei* NFBC 338 did not change the composition of the cecum microbiome but improved glucose or lipid metabolism in diet-induced obese (DIO) rats (100). Supplementation with composite probiotics stimulated the secretion of GLP-1 and PYY by changing the composition of the gut microbiota and the production of SCFAs. At the same time, the metabolism of blood glucose and lipids, immune state, and pancreas function were improved in db/db diabetic mice (52). In T2D mice, oral administration of *Lactobacillus casei* increased the abundance of Bacteroidetes, *Bifidobacterium*, and *Lactob*acillus, and butyrate production increased, which stimulated GLP-1 secretion (53). Daily administration of *Clostridium butyricum* CGMCC0313.1 for 13 weeks decreased Firmicutes/Bacteroidetes ratios and increased SCFA-producing bacteria and SCFA receptors FFAR2 and FFAR3 in T2D mice. Moreover, serum and ileal GLP-1 levels increased, but this improvement has not been observed in leptin receptor-deficient db/db mice (54). This may be related to the time of administration and the different mouse models. Supplementation with *L. fermentum* MCC2759/*L. fermentum* MCC2760 orally or intragastrically decreased the count of pathogenic bacteria and increased the production of GLP-1 and *Lactobacillus* spp. count (101, 103). Two different concentrations of L. rhamnosus LGG increased the bacterial abundance, number, and GLP-1 levels. However, the increased types of SCFAs were acetate or propionate (55). In piglets, the supplementation with L. *plantarum* reduced the abundance of *Bacteroides* and *Parabacteroides*, and also decreased the levels of lithocholic acid (LCA), eventually increasing BG (104). In conclusion, probiotics regulate host health by regulating changes in gut microbiota.

EFFECT OF GUT MICROBIOTA ON GLP-1 FUNCTION

Incretin-based drugs are effective in treating individuals with diabetes. Many studies have demonstrated that the incretin effect is impaired in obesity, IGT (impaired glucose tolerance), and T2D patients. However, sometimes it is necessary for patients to stop their treatment with GLP-1 RA due to a lack of efficacy. This phenomenon is a state of GLP-1 resistance (114). This state could be caused by gut microbiota dysbiosis (115).

In a human study, different gut microbiota compositions have different responses to GLP-1 RA (116). T2D patients on a treatment with GLP-1 RA (liraglutide or dulaglutide) for 12 weeks were divided into GLP-1 RA responders (n = 34) and non-responders (n = 18). The former had both decreased levels of HbA1c and BMI, and the latter had no change in these two variables. The beta diversity of gut microbiota was significantly differed between these two groups, as well as some bacteria, such as *Bacteroides dorei* and *Roseburia inulinivorans*. So, the signature of gut microbiota may predict the GLP-1 RA efficacy. In 2017, how gut microbiota dysbiosis induces GLP-1 resistance was well exhibited in mice (117). In this study, two T2D mouse models were created: a diabetic obese model and a diabetic lean model. At 15 min after OGTT (oral glucose tolerance

test) experiments, glycemia was almost similar between these two diabetic groups and normal control mice. However, in the diabetic lean model, the plasma GLP-1 concentration was higher, but the plasma insulin concentration was lower than that in the diabetic obese model and normal model. This suggested that GLP-1 resistance existed in the diabetic lean model. Then, the ileum microbiota was transplanted from the two diabetic groups and the normal control group to germ-free mice. The results demonstrated that the incretin effect was impaired, while GLP-1R expression was slightly higher in germ-free mice after fecal transplantation from diabetic lean mice compared to other groups. This result suggested that the function of GLP-1 was dependent on the normal gut microbiota. Gut microbiota dysbiosis impaired GLP-1 responsiveness (117). Therefore, the gut microbiota is closely responsible for GLP-1 function (89).

EFFECT OF GUT MICROBIOTA ON GLP-1 RHYTHM

Circadian rhythms refer to physiological changes in an organism's activities that occur almost every 24 hours, also known as the biological clock (118). This biological clock exists not only in the brain but also in peripheral organs, such as the pancreas and gastrointestinal tract. It has been proven that pancreatic islets have circadian genes such as CLOCK and BMAL1 in *Homo sapiens* and rodents (119, 120), and disruption of circadian genes leads to diabetes (121). Moreover, the secretion of insulin abides by a circadian clock pattern (122). In humans, it was revealed that GLP-1 secretion has temporal differences because early GLP-1 release was more prominent in the morning than in the afternoon (123). A significant circadian rhythm in GLP-1 secretion by intestinal L cells (124) or GLP-1 responsiveness (125) was found in animal experiments. In mice, the peak time of GLP-1 release was 8 p.m. (ZT14). The bottom time of GLP-1 secretion was 8 a.m. (ZT2). Taken together, there is clear evidence that GLP-1 secretion has a circadian rhythm. The composition and function of the gut microbiota also exhibit some oscillations that follow the host dietary pattern. In return, gut microbiota regulate host circadian rhythms and metabolism [reviewed in reference (26)].

The regulation of GLP-1 secretion rhythm by gut microbiota is essential. First, gut microbiota disorders can affect the rhythmic secretion of GLP-1. In germ-free mice without gut microbiota, there was no circadian rhythm of insulin secretion. However, after fecal transplantation from normal diet-fed mice, the insulin rhythm reappeared (126). Therefore, the homeostasis of the gut microbiota environment was significant for the rhythmic secretion of GLP-1 (126). Second, the same team demonstrated that the biological rhythms of L cells regulated GLP-1 release. The core biological clock gene Bmal1 in intestinal L cells regulates the rhythm of GLP-1 secretion (127), as do Per1/2/3, Dbp, and Tef (126). Knockdown of Bmal1 in L cells impaired GLP-1 circadian secretion (128). In summary, the circadian rhythm of GLP-1 release is mediated by L cells and regulated by the gut microbiota (Fig. 4).

EFFECT OF GLP-1 ON GUT MICROBIOTA

GLP-1 analogs and DPP-4 inhibitor changed the composition and abundance of gut microbiota

The GLP-1 RA liraglutide, but not saxagliptin (129), changed the overall structure of the gut microbiota, especially some bacteria related to glucolipid metabolism and intestinal inflammation (130, 131). For example, liraglutide treatment of diabetic male rats changed the gut microbiota, such as increasing SCFA-producing bacteria (*Bacteroides* and *Lachnospiraceae*) and probiotics (*Bifidobacterium*) (132). In addition, liraglutide treatment in wild-type mice and db/db mice significantly increased the abundance of intestinal *Akkermansia muciniphila* (130, 133, 134). In humans, liraglutide significantly increased the diversity and richness of the gut microbiota, especially Bacteroidetes, Proteobacteria, and *Bacilli* (135). However, a recent randomized controlled trial suggested that liraglutide and sitagliptin did not change the alpha or beta diversity of the gut microbiota, when they were used as add-on therapies with metformin or sulfonylureas (136). Additionally, a

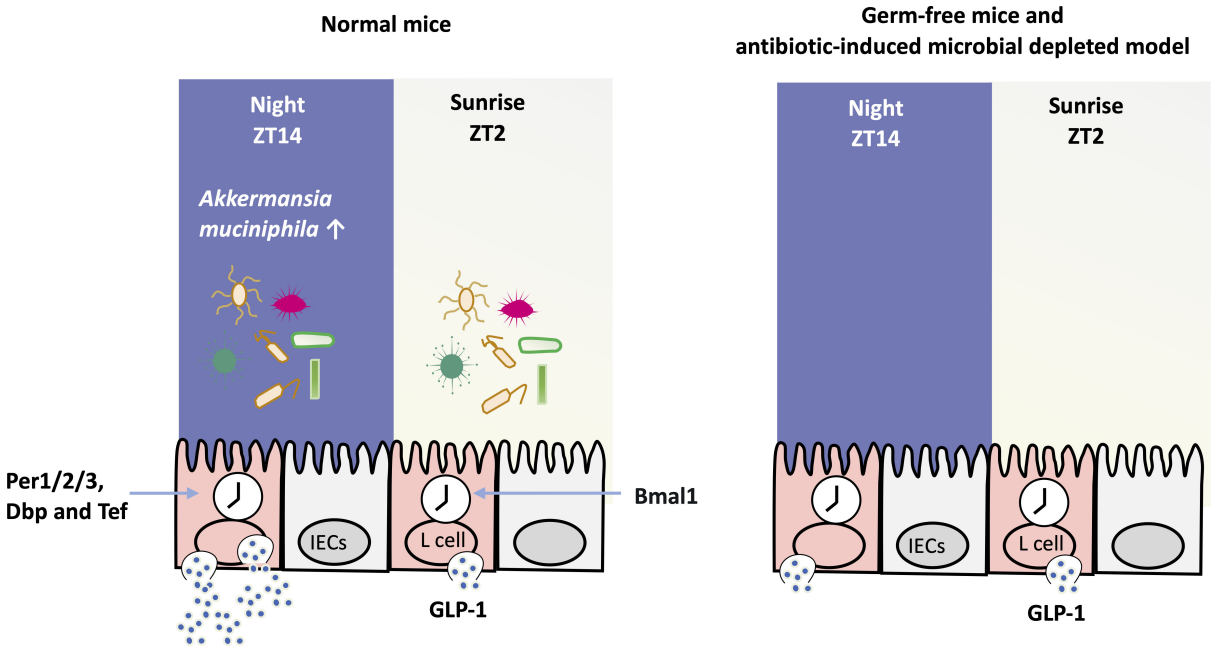

FIG 4 The circadian rhythm of GLP-1 release mediated by L cells and regulated by gut microbiota. GLP-1 secretion in normal mice showed a circadian rhythm, with the peak of 8 p.m. (ZT14) and the bottom line of 8 a.m. (ZT2). The abundance of *Akkermansia muciniphila* which was closely related to the secretion of GLP-1 was higher at ZT14 than at ZT2. While in germ-free mice and antibiotic-induced microbial depleted model, the GLP-1 rhythm was not exhibited. And the biological rhythms of L cells regulated GLP-1 release. The clock gene Bmal1 was significantly increased at ZT2. While Per1/2/3, Dbp, and Tef increased at ZT14.

fixed combination of liraglutide and degludec for 6 months did not change the microbiome biodiversity or community among a group of very old T2D subjects (mean age 82 years) (137). The possible reason was that the combination of drugs masked the effect. In addition, liraglutide can activate the sympathetic nervous system of the gut (138). In conclusion, the GLP-1 analog liraglutide modulated the gut microbiota structure.

DPP-4 inhibitors could improve oral glucose intolerance and raise plasma GLP-1 concentrations. Additionally, they impacted on the composition and function of the gut microbiota. Vildagliptin monotherapy reduced the *Bacteroidetes* species in treatment-naive T2D patients, similar to acarbose (89). However, DPP-4 inhibitors [linagliptin (139) and sitagliptin (140)] increased the abundance of Bacteroidetes and succinate in mice. Moreover, vildagliptin mainly decreased *Oscillibacter* spp. and increased *Lactobacillus* spp. and propionate in Western diet-fed mice (141) and Zucker diabetic fatty rats (142). Similarly, DPP-4 inhibitor (PKF-275-055 or vildagliptin) treatment was reported to significantly decrease Firmicutes/Bacteroidetes ratios and increase butyrate-producing bacteria in diabetic and obese mice, similar to metformin (143, 144). Overall, treatment with a DPP-4 inhibitor moderately corrected the dysbiosis of the microbiota in obese and T2D mice.

Effect of GLP-1 on the gut microbiota is involved in the inflammatory response

Disturbance of the gut microbiota can promote endotoxemia and insulin resistance. Increased Gram-negative *Enterobacteriaceae* and decreased acetic acid-producing bacteria (such as *Bifidobacteria*) associated with T2D resulted in increased LPS release and decreased acetic acid, respectively. Then, LPS from the gut lumen binds Toll-like receptor 4 (TLR4) to damage the intestinal barrier (145), and serum LPS moderately increases, which is an inflammatory state of prediabetes (146, 147). However, EECs increased the incretion of GLP-1 after sensing LPS as compensation (41). Similarly, inflammatory cytokine IL-6 (148) also acts on gut endocrine L cells to promote GLP-1 secretion. GLP-1 exerts a variety of physiological functions, such as promoting insulin

synthesis and secretion, increasing satiety, and reducing food intake by binding to GLP-1R (149). GLP-1R is expressed in intestinal intraepithelial lymphocytes, and the GLP-1R agonist exendin-4 significantly inhibits inflammatory cytokines and macrophage infiltration (59). Many interventions that increase GLP-1 levels improve the intestinal inflammatory response (Tables 1 and 2). These findings suggested that the mechanism of GLP-1 action on gut microbiota involved inflammatory responses.

Gut hormones affect the composition and function of gut microbiota

The gut microbiota is symbiotic with EECs. Distinct EEC subtypes are scattered among the epithelial cells of the gut mucosa and secrete different hormones. L cells that produce GLP-1 and PYY are distributed toward the distal intestine and are finally high in the colon (64, 150). These gut peptides can influence appetite, satiety, and food types. In return, alterations in gut microbiota could also affect eating behaviors (151, 152). In addition, gut peptides could regulate intestinal motility and intestinal permeability (153). Drosophila peptides have antimicrobial effects (154) and then regulate gut microbiota composition and abundance. Food peptides are multifunctional and can prevent gut dysbiosis (155). For example, a novel peptide, D3, increased the abundance of *Akkermansia muciniphila* and also suppressed appetite to improve DIO (156). Some milk-derived short peptides can enhance intestinal barrier function (157). In conclusion, gut peptides mediate the crosstalk between the gut microbiota and the host.

INTERVENTIONS THAT MAY AFFECT GUT MICROBIOTA PROMOTE GUT PEPTIDE SECRETION, SUCH AS GLP-1

Oral antidiabetic drugs promoted the GLP-1 secretion

In addition to dietary factors, nonantibiotic drugs also affect the microbiota composition and function. In turn, the gut microbiota can influence the effects of drugs. A well-known example is that Nature published an article providing support for the microbiota variation associated with the oral antidiabetic drug metformin in 2015. Treatment with metformin in T2D patients increased *Escherichia* spp. and decreased *Intestinibacter* spp. compared to untreated patients (158). In addition, a recent meta-analysis indicated that antidiabetic drugs (metformin) have a strong association with the relative abundance of microbiota (159).

In T2D patients, oral metformin increased the abundance of *Phascolarctobacterium*, *Intestinimonas,* and *Clostridium* III and the levels of GLP-1 and PYY (45, 88). However, stopping metformin decreased the Bacteroidetes abundance and the GLP-1 concentrations (87). Treatment with acarbose or vildagliptin in treatment-naive T2D patients decreased the abundance of Bacteroidetes and increased GLP-1 levels.

In DIO mice, the abundance of *Akkermansia muciniphila*, *Bacteroides*, *Butyricimonas*, and *Parabacteroides* was significantly increased by metformin treatment (107, 160). However, fecal transplantation from metformin-treated 16-week-old mice increased the GLP-1 concentration without changing the composition of gut microbiota and body weight (106). In hyperglycemic rats, SGLT2 inhibitor, canagliflozin, can also inhibit intestinal SGLT1, which is the primary transporter for glucose and galactose, to elevate plasma active GLP-1 level and reduce post-prandial glucose (108). Moreover, canagliflozin increased cecal SCFA production and changed the intestinal microbiota in renal failure mice (109). Dual SGLT1/2 inhibitors, sotagliflozin and licogliflozin, exert more selectivity for SGLT1 than canagliflozin, which may give dual SGLT1/2 inhibitors specific anti-hyperglycemia efficacy and cardiovascular and renal safety characteristics (161). So, although SGLT2 inhibitors are considered to act mainly through the kidneys, their effects on the microbiome deserve further evaluation. Therefore, the relationship between increased GLP-1 concentrations and gut microbiota after antidiabetic drug administration needs to be further confirmed.

Bariatric surgery promoted the GLP-1 secretion

Bariatric surgery, which alters gut microbiota ecology, improved obesity and T2D well (11, 162). After Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) surgery, significant weight loss was exhibited along with the improved glycemia and changed gut microbiota. One of the main mechanisms is increased endogenous GLP-1 signaling (163). For example, RYGB surgery decreased Firmicutes and Archaea and increased Gammaproteobacteria (90). Therefore, in bariatric surgery, what is the exact relationship between gut microbiota and GLP-1 is still not clear.

Increased GLP-1 after bariatric surgery may be the result of rapid gastrointestinal nutrient input and increased plasma BAs (164). In healthy subjects, postprandial plasma BA concentrations were positively correlated with GLP-1 and PYY (165). In DIO mice, SG increased the LCA levels in portal veins without changing the abundance of *Clostridiales* to stimulate the GLP-1 production (11). Therefore, future studies of the crosstalk between gut microbiota and GLP-1 in bariatric surgery should start with BAs.

CONCLUSION AND PROSPECTS

The interaction between GLP-1 and gut microbiota influences the host metabolism and health. Hosts in different metabolic states or with specific preferences will consume in different kinds and contents of the diet. Food can be derived into metabolites of the gut microbiota under the action of the gut, such as SCFAs. Some gut microbiota metabolites promote the secretion of GLP-1. GLP-1 exerts an influence on the brain, intestine, and pancreas to improve host metabolism. In addition, some interventions, such as prebiotics, probiotics, antidiabetic drugs, and bariatric surgery, changed the composition and function of the gut microbiota and then exerted benefits on the body, suggesting that gut microbiota is a target for diseases, such as obesity and T2D.

However, the relationship between gut microbiota, GLP-1 secretion, and the host still has many black boxes to uncover. In the future, the development of multiomics technology will help to interpret the relationship between GLP-1 and gut microbiota. In the clinical application of GLP-1RA, the effects of gut microbiota should be considered, and individualized programs should be given.

ACKNOWLEDGMENTS

This research was funded by National Natural Science Foundation of China [grant numbers 81870545, 81870579, 82170854, 81570715, 81170736]; Beijing Natural Science Foundation [grant number 7202163]; Beijing Municipal Science & Technology Commission [grant number Z201100005520011]; National Key Research and Development Program of China [grant numbers 2017YFC1309603, 2021YFC2501700, 2016YFA0101002, 2018YFC2001100]; Scientific Activities Foundation for Selected Returned Overseas Professionals of Human Resources and Social Security Ministry, Beijing Dongcheng District Outstanding Talent Funding Project [grant numbers 2019DCT-M-05]; Medical Epigenetics Research Center, Chinese Academy of Medical Sciences [grant numbers 2017PT31036, 2018PT31021]; the Non-Profit Central Research Institute Fund of Chinese Academy of Medical Sciences [grant numbers 2017PT32020, 2018PT32001]; Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences [grant numbers CIFMS2017-I2M-1-008, CIFMS2021-I2M-1-002]; National High Level Hospital Clinical Research Funding [grant numbers 2022-PUMCH-C-019, 2022-PUMCH-B-121].

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FUNDING

Funder	Grant(s)	Author(s)
MOST | National Natural Science Foundation of China (NSFC)	81870545, 81870579, 82170854, 81570715, 81170736	Qian Zhang Xinhua Xiao
Natural Science Foundation of Beijing Municipality (Beijing Natural Science Foundation)	7202163	Qian Zhang Xinhua Xiao
Beijing Municipal Science and Technology Commission, Adminitrative Commission of Zhongguancun Science Park	Z201100005520011	Qian Zhang Xinhua Xiao
MOST | National Key Research and Development Program of China (NKPs)	2017YFC1309603, 2021YFC2501700, 2016YFA0101002, 2018YFC2001100	Qian Zhang Xinhua Xiao
Beijing Municipal Human Resources and Social Security Bureau (BMHRSSB)	2019DCT-M-05	Qian Zhang Xinhua Xiao
Chinese Academy of Medical Sciences (CAMS)	2017PT31036, 2018PT31021	Qian Zhang Xinhua Xiao
Chinese Academy of Medical Sciences (CAMS)	2017PT32020, 2018PT32001	Qian Zhang Xinhua Xiao
Chinese Academy of Medical Sciences (CAMS)	CIFMS2017-I2M-1-008, CIFMS2021-I2M-1-002	Qian Zhang Xinhua Xiao
National High Level Hospital Clinical Research Funding	2022-PUMCH- C-019, 2022-PUMCH-B-121	Qian Zhang Xinhua Xiao

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REFERENCES

1. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, Bommer C, Esteghamati A, Ogurtsova K, Zhang P, Colagiuri S. 2020. Global and regional estimates and projections of diabetes-related health expenditure: results from the international diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract 162:108072. https://doi.org/10.1016/j.diabres.2020.108072
2. Gram-Kampmann EM, Hansen CD, Hugger MB, Jensen JM, Brønd JC, Hermann AP, Krag A, Olsen MH, Beck-Nielsen H, Højlund K. 2022. Effects of a 6-month, low-carbohydrate diet on glycaemic control, body composition, and cardiovascular risk factors in patients with type 2 diabetes: an open-label randomized controlled trial. Diabetes Obes Metab 24:693–703. https://doi.org/10.1111/dom.14633
3. Bonnet F, Chen H, Cooper A, Gomes MB, Ji L, Leigh P, Ramirez L, Shestakova MV, Shimomura I, Siddiqui A, Tang F, Vora J, Watada H, Khunti K. 2021. What are the factors associated with long-term glycaemic control in patients with type 2 diabetes and elevated glycated haemoglobin (≥7.0%) at initiation of second-line therapy? results from the DISCOVER study. Diabetes Obes Metab 23:2336–2343. https://doi.org/10.1111/dom.14476
4. Meijnikman AS, Gerdes VE, Nieuwdorp M, Herrema H. 2018. Evaluating causality of gut microbiota in obesity and diabetes in humans. Endocr Rev 39:133–153. https://doi.org/10.1210/er.2017-00192
5. Canfora EE, Meex RCR, Venema K, Blaak EE. 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat Rev Endocrinol 15:261–273. https://doi.org/10.1038/s41574-019-0156-z
6. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB, DeFronzo RA, NN8022-1922 Study Group. 2015. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. JAMA 314:687–699. https://doi.org/10.1001/jama.2015.9676
7. Meier JJ. 2012. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 8:728–742. https://doi.org/10.1038/nrendo.2012.140
8. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, Meeran K. 2018. Association between use of sodium-glucose

cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA 319:1580–1591. https://doi.org/10.1001/jama.2018.3024
9. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, Lönroth H, Fändriks L, Ghatei MA, Bloom SR, Olbers T. 2007. Gut hormones as mediators of appetite and weight loss after roux-en-Y gastric bypass. Ann Surg 246:780–785. https://doi.org/10.1097/SLA.0b013e3180caa3e3
10. Tremaroli V, Karlsson F, Werling M, Ståhlman M, Kovatcheva-Datchary P, Olbers T, Fändriks L, le Roux CW, Nielsen J, Bäckhed F. 2015. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab 22:228–238. https://doi.org/10.1016/j.cmet.2015.07.009
11. Chaudhari SN, Luo JN, Harris DA, Aliakbarian H, Yao L, Paik D, Subramaniam R, Adhikari AA, Vernon AH, Kiliç A, Weiss ST, Huh JR, Sheu EG, Devlin AS. 2021. A microbial metabolite Remodels the gut-liver axis following Bariatric surgery. Cell Host & Microbe 29:408–424. https://doi.org/10.1016/j.chom.2020.12.004
12. Young VB. 2017. The role of the microbiome in human health and disease: an introduction for clinicians. BMJ 356:j831. https://doi.org/10.1136/bmj.j831
13. Anonymous. 2019. The integrative human microbiome project. Nature 569:641–648. https://doi.org/10.1038/s41586-019-1238-8
14. McFall-Ngai M, Hadfield MG, Bosch TCG, Carey HV, Domazet-Lošo T, Douglas AE, Dubilier N, Eberl G, Fukami T, Gilbert SF, Hentschel U, King N, Kjelleberg S, Knoll AH, Kremer N, Mazmanian SK, Metcalf JL, Nealson K, Pierce NE, Rawls JF, Reid A, Rumpho M, Sanders JG, Tautz D, Wernegreen JJ. 2013. Animals in a bacterial world, a new imperative for the life sciences. Proc Natl Acad Sci U S A 110:3229–3236. https://doi.org/10.1073/pnas.1218525110
15. Sender R, Fuchs S, Milo R. 2016. Are we really vastly outnumbered? revisiting the ratio of bacterial to host cells in humans. Cell 164:337–340. https://doi.org/10.1016/j.cell.2016.01.013
16. Domazet-Loso T, Tautz D. 2008. An ancient evolutionary origin of genes associated with human genetic diseases. Mol Biol Evol 25:2699–2707. https://doi.org/10.1093/molbev/msn214
17. Sommer F, Bäckhed F. 2013. The gut microbiota--masters of host development and physiology. Nat Rev Microbiol 11:227–238. https://doi.org/10.1038/nrmicro2974
18. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. 2005. Diversity of the human intestinal microbial flora. Science 308:1635–1638. https://doi.org/10.1126/science.1110591
19. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, Arumugam M, Kultima JR, Prifti E, Nielsen T, et al. 2014. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol 32:834–841. https://doi.org/10.1038/nbt.2942
20. Gonzalez FJ, Jiang C, Patterson AD. 2016. An intestinal microbiota-farnesoid X receptor axis modulates metabolic disease. Gastroenterology 151:845–859. https://doi.org/10.1053/j.gastro.2016.08.057
21. Wolter M, Grant ET, Boudaud M, Steimle A, Pereira GV, Martens EC, Desai MS. 2021. Leveraging diet to engineer the gut microbiome. Nat Rev Gastroenterol Hepatol 18:885–902. https://doi.org/10.1038/s41575-021-00512-7
22. Becattini S, Taur Y, Pamer EG. 2016. Antibiotic-induced changes in the intestinal microbiota and disease. Trends Mol Med 22:458–478. https://doi.org/10.1016/j.molmed.2016.04.003
23. O'Toole PW, Jeffery IB. 2015. Gut microbiota and aging. Science 350:1214–1215. https://doi.org/10.1126/science.aac8469
24. Zarrinpar A, Chaix A, Yooseph S, Panda S. 2014. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. Cell Metab 20:1006–1017. https://doi.org/10.1016/j.cmet.2014.11.008
25. Pearson JA, Wong FS, Wen L. 2020. Crosstalk between circadian rhythms and the microbiota. Immunology 161:278–290. https://doi.org/10.1111/imm.13278
26. Choi H, Rao MC, Chang EB. 2021. Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism. Nat Rev Gastroenterol Hepatol 18:679–689. https://doi.org/10.1038/s41575-021-00452-2
27. Yang G, Wei J, Liu P, Zhang Q, Tian Y, Hou G, Meng L, Xin Y, Jiang X. 2021. Role of the gut microbiota in type 2 diabetes and related diseases. Metabolism 117:154712. https://doi.org/10.1016/j.metabol.2021.154712
28. Muscogiuri G, Balercia G, Barrea L, Cignarelli A, Giorgino F, Holst JJ, Laudisio D, Orio F, Tirabassi G, Colao A. 2018. Gut: a key player in the pathogenesis of type 2 diabetes? Crit Rev Food Sci Nutr 58:1294–1309. https://doi.org/10.1080/10408398.2016.1252712
29. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, et al. 2012. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 490:55–60. https://doi.org/10.1038/-nature11450
30. Larsen N, Vogensen FK, van den Berg FWJ, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. 2010. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 5:e9085. https://doi.org/10.1371/journal.pone.0009085
31. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E. 2014. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514:181–186. https://doi.org/10.1038/nature13793
32. Hwang I, Park YJ, Kim YR, Kim YN, Ka S, Lee HY, Seong JK, Seok YJ, Kim JB. 2015. Alteration of gut microbiota by vancomycin and bacitracin improves insulin resistance via glucagon-like peptide 1 in diet-induced obesity. FASEB J 29:2397–2411. https://doi.org/10.1096/fj.14-265983
33. Rashidi A, Ebadi M, Rehman TU, Elhusseini H, Nalluri H, Kaiser T, Holtan SG, Khoruts A, Weisdorf DJ, Staley C. 2021. Gut microbiota response to antibiotics is personalized and depends on baseline microbiota. Microbiome 9:211. https://doi.org/10.1186/s40168-021-01170-2
34. Vujkovic-Cvijin I, Sklar J, Jiang L, Natarajan L, Knight R, Belkaid Y. 2020. Host variables confound gut microbiota studies of human disease. Nature 587:448–454. https://doi.org/10.1038/s41586-020-2881-9
35. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. 2008. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe 3:213–223. https://doi.org/10.1016/j.chom.2008.02.015
36. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. 2006. An obesity-associated gut Microbiome with increased capacity for energy harvest. Nature 444:1027–1031. https://doi.org/10.1038/nature05414
37. Han H, Yi B, Zhong R, Wang M, Zhang S, Ma J, Yin Y, Yin J, Chen L, Zhang H. 2021. From gut microbiota to host appetite: gut microbiota-derived metabolites as key regulators. Microbiome 9:162. https://doi.org/10.1186/s40168-021-01093-y
38. Bellono NW, Bayrer JR, Leitch DB, Castro J, Zhang C, O'Donnell TA, Brierley SM, Ingraham HA, Julius D. 2017. Enterochromaffin cells are gut Chemosensors that couple to sensory neural pathways. Cell 170:185–198. https://doi.org/10.1016/j.cell.2017.05.034
39. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F, Gribble FM. 2012. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes 61:364–371. https://doi.org/10.2337/db11-1019
40. Trabelsi MS, Daoudi M, Prawitt J, Ducastel S, Touche V, Sayin SI, Perino A, Brighton CA, Sebti Y, Kluza J, et al. 2015. Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. Nat Commun 6:7629. https://doi.org/10.1038/ncomms8629
41. Lebrun LJ, Lenaerts K, Kiers D, Pais de Barros J-P, Le Guern N, Plesnik J, Thomas C, Bourgeois T, Dejong CHC, Kox M, Hundscheid IHR, Khan NA, Mandard S, Deckert V, Pickkers P, Drucker DJ, Lagrost L, Grober J. 2017. Enteroendocrine L cells sense LPS after gut barrier injury to enhance GLP-1 secretion. Cell Rep 21:1160–1168. https://doi.org/10.1016/j.celrep.2017.10.008
42. Nilsson AC, Johansson-Boll EV, Björck IME. 2015. Increased gut hormones and insulin sensitivity index following a 3-d intervention with a barley kernel-based product: a randomised cross-over study in healthy middle-aged subjects. Br J Nutr 114:899–907. https://doi.org/10.1017/S0007114515002524
43. Freeland KR, Wilson C, Wolever TMS. 2010. Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased

wheat fibre intake for 1 year in hyperinsulinaemic human subjects. Br J Nutr 103:82–90. https://doi.org/10.1017/S0007114509991462
44. Freeland KR, Wolever TMS. 2010. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin and tumour necrosis factor-alpha. Br J Nutr 103:460–466. https://doi.org/10.1017/S0007114509991863
45. Huang Y, Lou X, Jiang C, Ji X, Tao X, Sun J, Bao Z. 2022. Gut Microbiota is correlated with gastrointestinal adverse events of metformin in patients with type 2 diabetes. Front Endocr (Lausanne) 13:1044030. https://doi.org/10.3389/fendo.2022.1044030
46. Li X-X, Zhang X-X, Zhang R, Ni Z-J, Elam E, Thakur K, Cespedes-Acuña CL, Zhang J-G, Wei Z-J. 2021. Gut modulation based anti-diabetic effects of carboxymethylated wheat bran dietary fiber in high-fat diet/streptozotocin-induced diabetic mice and their potential mechanisms. Food Chem Toxicol 152:112235. https://doi.org/10.1016/j.fct.2021.112235
47. Xu S, Wang Y, Wang J, Geng W. 2022. Kombucha reduces hyperglycemia in type 2 diabetes of mice by regulating gut microbiota and its metabolites. Foods 11:754. https://doi.org/10.3390/foods11050754
48. Shen L, Keenan MJ, Raggio A, Williams C, Martin RJ. 2011. Dietary-resistant starch improves maternal glycemic control in goto-kakizaki rat. Mol Nutr Food Res 55:1499–1508. https://doi.org/10.1002/mnfr.201000605
49. Cani PD, Hoste S, Guiot Y, Delzenne NM. 2007. Dietary non-digestible carbohydrates promote L-cell differentiation in the proximal colon of rats. Br J Nutr 98:32–37. https://doi.org/10.1017/S0007114507691648
50. Yadav H, Lee JH, Lloyd J, Walter P, Rane SG. 2013. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. J Biol Chem 288:25088–25097. https://doi.org/10.1074/jbc.M113.452516
51. Kaji I, Karaki S-I, Tanaka R, Kuwahara A. 2011. Density distribution of free fatty acid receptor 2 (FFA2)-expressing and GLP-1-producing enteroendocrine L cells in human and rat lower intestine, and increased cell numbers after ingestion of fructo-oligosaccharide. J Mol Histol 42:27–38. https://doi.org/10.1007/s10735-010-9304-4
52. Wang Y, Dilidaxi D, Wu Y, Sailike J, Sun X, Nabi X-H. 2020. Composite probiotics alleviate type 2 diabetes by regulating intestinal microbiota and inducing GLP-1 secretion in db/db mice. Biomed Pharmacother 125:109914. https://doi.org/10.1016/j.biopha.2020.109914
53. Li X, Wang E, Yin B, Fang D, Chen P, Wang G, Zhao J, Zhang H, Chen W. 2017. Effects of *Lactobacillus casei* CCFM419 on insulin resistance and gut microbiota in type 2 diabetic mice. Benef Microbes 8:421–432. https://doi.org/10.3920/BM2016.0167
54. Jia L, Li D, Feng N, Shamoon M, Sun Z, Ding L, Zhang H, Chen W, Sun J, Chen YQ. 2017. Anti-diabetic effects of *Clostridium butyricum* CGMCC0313.1 through promoting the growth of gut butyrate-producing bacteria in type 2 diabetic mice. Sci Rep 7:7046. https://doi.org/10.1038/s41598-017-07335-0
55. Singh S, Sharma RK, Malhotra S, Pothuraju R, Shandilya UK. 2017. *Lactobacillus Rhamnosus* NCDC17 ameliorates type-2 diabetes by improving gut function, oxidative stress and inflammation in high-fat-diet fed and streptozotocintreated rats. Benef Microbes 8:243–255. https://doi.org/10.3920/BM2016.0090
56. Psichas A, Sleeth ML, Murphy KG, Brooks L, Bewick GA, Hanyaloglu AC, Ghatei MA, Bloom SR, Frost G. 2015. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int J Obes 39:424–429. https://doi.org/10.1038/ijo.2014.153
57. Koopen A, Witjes J, Wortelboer K, Majait S, Prodan A, Levin E, Herrema H, Winkelmeijer M, Aalvink S, Bergman J, et al. 2022. Duodenal *Anaerobutyricum soehngenii* infusion stimulates GLP-1 production, ameliorates glycaemic control and beneficially shapes the duodenal transcriptome in metabolic syndrome subjects: a randomised double-blind placebo-controlled cross-over study. Gut 71:1577–1587. https://doi.org/10.1136/gutjnl-2020-323297
58. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, Andersen UB, Holst JJ, Hansen HS. 2011. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. J Clin Endocrinol Metab 96:E1409–17. https://doi.org/10.1210/jc.2011-0647
59. Yusta B, Baggio LL, Koehler J, Holland D, Cao X, Pinnell LJ, Johnson-Henry KC, Yeung W, Surette MG, Bang KWA, Sherman PM, Drucker DJ. 2015. GLP-1R agonists modulate enteric immune responses through the intestinal intraepithelial lymphocyte GLP-1R. Diabetes 64:2537–2549. https://doi.org/10.2337/db14-1577
60. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, et al. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464:59–65. https://doi.org/10.1038/nature08821
61. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto J-M, Kennedy S, et al. 2013. Richness of human gut microbiome correlates with metabolic markers. Nature 500:541–546. https://doi.org/10.1038/nature12506
62. Cantarel BL, Lombard V, Henrissat B. 2012. Complex carbohydrate utilization by the healthy human microbiome. PLoS One 7:e28742. https://doi.org/10.1371/journal.pone.0028742
63. Garron ML, Henrissat B. 2019. The continuing expansion of cazymes and their families. Curr Opin Chem Biol 53:82–87. https://doi.org/10.1016/j.cbpa.2019.08.004
64. Eissele R, Göke R, Willemer S, Harthus HP, Vermeer H, Arnold R, Göke B. 1992. Glucagon-like peptide-1 cells in the gastrointestinal tract and Pancreas of rat, pig and man. Eur J Clin Invest 22:283–291. https://doi.org/10.1111/j.1365-2362.1992.tb01464.x
65. Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. 1987. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 28:1221–1227. https://doi.org/10.1136/gut.28.10.1221
66. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdock PR, Holder JC, Marshall FH, Szekeres PG, Wilson S, Ignar DM, Foord SM, Wise A, Dowell SJ. 2003. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem 278:11312–11319. https://doi.org/10.1074/jbc.M211609200
67. Martin-Gallausiaux C, Marinelli L, Blottière HM, Larraufie P, Lapaque N. 2021. SCFA: mechanisms and functional importance in the gut. Proc Nutr Soc 80:37–49. https://doi.org/10.1017/S0029665120006916
68. Kimura I, Ichimura A, Ohue-Kitano R, Igarashi M. 2020. Free fatty acid receptors in health and disease. Physiol Rev 100:171–210. https://doi.org/10.1152/physrev.00041.2018
69. Forbes S, Stafford S, Coope G, Heffron H, Real K, Newman R, Davenport R, Barnes M, Grosse J, Cox H. 2015. Selective FFA2 agonism appears to act via intestinal PYY to reduce transit and food intake but does not improve glucose tolerance in mouse models. Diabetes 64:3763–3771. https://doi.org/10.2337/db15-0481
70. Harach T, Pols TWH, Nomura M, Maida A, Watanabe M, Auwerx J, Schoonjans K. 2012. TGR5 potentiates GLP-1 secretion in response to anionic exchange resins. Sci Rep 2:430. https://doi.org/10.1038/srep00430
71. Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Mataki C, Pruzanski M, Pellicciari R, Auwerx J, Schoonjans K. 2009. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab 10:167–177. https://doi.org/10.1016/j.cmet.2009.08.001
72. Ducastel S, Touche V, Trabelsi MS, Boulinguiez A, Butruille L, Nawrot M, Peschard S, Chávez-Talavera O, Dorchies E, Vallez E, Annicotte JS, Lancel S, Briand O, Bantubungi K, Caron S, Bindels LB, Delzenne NM, Tailleux A, Staels B, Lestavel S. 2020. The nuclear receptor FXR inhibits glucagon-like peptide-1 secretion in response to microbiota-derived short-chain fatty acids. Sci Rep 10:174. https://doi.org/10.1038/s41598-019-56743-x
73. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G. 2017. Expert consensus document: the international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14:491–502. https://doi.org/10.1038/nrgastro.2017.75
74. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. 2019. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol 16:642. https://doi.org/10.1038/s41575-019-0199-6
75. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, De Backer F, Neyrinck AM, Delzenne NM. 2009. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose

response after a meal. Am J Clin Nutr 90:1236–1243. https://doi.org/10.3945/ajcn.2009.28095
76. Piche T, des Varannes SB, Sacher-Huvelin S, Holst JJ, Cuber JC, Galmiche JP. 2003. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. Gastroenterology 124:894–902. https://doi.org/10.1053/gast.2003.50159
77. Parnell JA, Reimer RA. 2009. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr 89:1751–1759. https://doi.org/10.3945/ajcn.2009.27465
78. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, Costabile A, Childs CE, Pedersen C, Goldstone AP, Frost GS. 2014. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity 22:1430–1438. https://doi.org/10.1002/oby.20754
79. Verhoef SPM, Meyer D, Westerterp KR. 2011. Effects of oligofructose on appetite profile, glucagon-like peptide 1 and peptide YY3-36 concentrations and energy intake. Br J Nutr 106:1757–1762. https://doi.org/10.1017/S0007114511002194
80. Bodinham CL, Smith L, Thomas EL, Bell JD, Swann JR, Costabile A, Russell-Jones D, Umpleby AM, Robertson MD. 2014. Efficacy of increased resistant starch consumption in human type 2 diabetes. Endocr Connect 3:75–84. https://doi.org/10.1530/EC-14-0036
81. Müller M, Hermes GDA, Emanuel E C, Holst JJ, Zoetendal EG, Smidt H, Troost F, Schaap FG, Damink SO, Jocken JWE, Lenaerts K, Masclee AAM, Blaak EE. 2020. Effect of wheat bran derived prebiotic supplementation on gastrointestinal transit, gut microbiota, and metabolic health: a randomized controlled trial in healthy adults with a slow gut transit. Gut Microbes 12:1704141. https://doi.org/10.1080/19490976.2019.1704141
82. van der Beek CM, Canfora EE, Kip AM, Gorissen SHM, Olde Damink SWM, van Eijk HM, Holst JJ, Blaak EE, Dejong CHC, Lenaerts K. 2018. The Prebiotic inulin improves substrate metabolism and promotes short-chain fatty acid production in overweight to obese men. Metabolism 87:25–35. https://doi.org/10.1016/j.metabol.2018.06.009
83. Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. 2018. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. Nutrients 10:126. https://doi.org/10.3390/nu10020126
84. Ren M, Zhang H, Qi J, Hu A, Jiang Q, Hou Y, Feng Q, Ojo O, Wang X. 2020. An almond-based low carbohydrate diet improves depression and glycometabolism in patients with type 2 diabetes through modulating gut microbiota and GLP-1: a randomized controlled trial. Nutrients 12:3036. https://doi.org/10.3390/nu12103036
85. Alisi A, Bedogni G, Baviera G, Giorgio V, Porro E, Paris C, Giammaria P, Reali L, Anania F, Nobili V. 2014. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 39:1276–1285. https://doi.org/10.1111/apt.12758
86. Simon M-C, Strassburger K, Nowotny B, Kolb H, Nowotny P, Burkart V, Zivehe F, Hwang J-H, Stehle P, Pacini G, Hartmann B, Holst JJ, MacKenzie C, Bindels LB, Martinez I, Walter J, Henrich B, Schloot NC, Roden M. 2015. Intake of *Lactobacillus reuteri* improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diab Care 38:1827–1834. https://doi.org/10.2337/dc14-2690
87. Napolitano A, Miller S, Nicholls AW, Baker D, Van Horn S, Thomas E, Rajpal D, Spivak A, Brown JR, Nunez DJ, Zhu Z. 2014. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. PLoS ONE 9:e100778. https://doi.org/10.1371/journal.pone.0100778
88. DeFronzo RA, Buse JB, Kim T, Burns C, Skare S, Baron A, Fineman M. 2016. Once-daily delayed-release metformin lowers plasma glucose and enhances fasting and postprandial GLP-1 and PYY: results from two randomised trials. Diabetologia 59:1645–1654. https://doi.org/10.1007/s00125-016-3992-6
89. Zhang X, Ren H, Zhao C, Shi Z, Qiu L, Yang F, Zhou X, Han X, Wu K, Zhong H, Li Y, Li J, Ji L. 2022. Metagenomic analysis reveals Crosstalk between gut microbiota and glucose-lowering drugs targeting the gastrointestinal tract in chinese patients with type 2 diabetes: a 6 month, two-arm randomised trial. Diabetologia 65:1613–1626. https://doi.org/10.1007/s00125-022-05768-5
90. Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. 2009. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A 106:2365–2370. https://doi.org/10.1073/pnas.0812600106
91. Cani PD, Knauf C, Iglesias MA, Drucker DJ, Delzenne NM, Burcelin R. 2006. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. Diabetes 55:1484–1490. https://doi.org/10.2337/db05-1360
92. Pichette J, Fynn-Sackey N, Gagnon J. 2017. Hydrogen sulfide and sulfate prebiotic stimulates the secretion of GLP-1 and improves glycemia in male mice. Endocrinology 158:3416–3425. https://doi.org/10.1210/en.2017-00391
93. Li M, Trapika IGSC, Tang SYS, Cho J-L, Qi Y, Li CG, Li Y, Yao M, Yang D, Liu B, Li R, Yang P, Ma G, Ren P, Huang X, Xie D, Chen S, Li M, Yang L, Leng P, Huang Y, Li GQ. 2021. Mechanisms and active compounds polysaccharides and bibenzyls of medicinal dendrobiums for diabetes management. Front Nutr 8:811870. https://doi.org/10.3389/fnut.2021.811870
94. Dao T-MA, Waget A, Klopp P, Serino M, Vachoux C, Pechere L, Drucker DJ, Champion S, Barthélemy S, Barra Y, Burcelin R, Sérée E. 2011. Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. PLoS One 6:e20700. https://doi.org/10.1371/journal.pone.0020700
95. Yuan T, Yin Z, Yan Z, Hao Q, Zeng J, Li L, Zhao J. 2020. tetrahydrocurcumin ameliorates diabetes profiles of db/db mice by altering the composition of gut microbiota and up-regulating the expression of GLP-1 in the pancreas. Fitoterapia 146:104665. https://doi.org/10.1016/j.fitote.2020.104665
96. Cani PD, Dewever C, Delzenne NM. 2004. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. Br J Nutr 92:521–526. https://doi.org/10.1079/bjn20041225
97. Brooks L, Viardot A, Tsakmaki A, Stolarczyk E, Howard JK, Cani PD, Everard A, Sleeth ML, Psichas A, Anastasovskaj J, Bell JD, Bell-Anderson K, Mackay CR, Ghatei MA, Bloom SR, Frost G, Bewick GA. 2017. Fermentable carbohydrate stimulates FFAR2-dependent colonic PYY cell expansion to increase satiety. Mol Metab 6:48–60. https://doi.org/10.1016/j.molmet.2016.10.011
98. Yang T, Zhou W, Xu W, Ran L, Yan Y, Lu L, Mi J, Zeng X, Cao Y. 2022. Modulation of gut microbiota and hypoglycemic/hypolipidemic activity of flavonoids from the fruits of *Lycium barbarum* on high-fat diet/streptozotocin-induced type 2 diabetic mice. Food Funct 13:11169–11184. https://doi.org/10.1039/d2fo01268e
99. Chen LC, Fan ZY, Wang HY, Wen DC, Zhang SY. 2019. Effect of polysaccharides from adlay seed on anti-diabetic and gut microbiota. Food Funct 10:4372–4380. https://doi.org/10.1039/c9fo00406h
100. Ryan PM, Patterson E, Kent RM, Stack H, O'Connor PM, Murphy K, Peterson VL, Mandal R, Wishart DS, Dinan TG, Cryan JF, Seeley RJ, Stanton C, Ross RP. 2017. Recombinant incretin-secreting microbe improves metabolic dysfunction in high-fat diet fed rodents. Sci Rep 7:13523. https://doi.org/10.1038/s41598-017-14010-x
101. Archer AC, Muthukumar SP, Halami PM. 2021. *Lactobacillus fermentum* MCC2759 and MCC2760 alleviate inflammation and intestinal function in high-fat diet-fed and streptozotocin-induced diabetic rats. Probiotics Antimicrob Proteins 13:1068–1080. https://doi.org/10.1007/s12602-021-09744-0
102. Chen YC, Huang SD, Tu JH, Yu JS, Nurlatifah AO, Chiu WC, Su YH, Chang HL, Putri DA, Cheng HL. 2020. Exopolysaccharides of bacillus amyloliquefaciens modulate glycemic level in mice and promote glucose uptake of cells through the activation of AKT. Int J Biol Macromol 146:202–211. https://doi.org/10.1016/j.ijbiomac.2019.12.217
103. Palani Kumar MK, Halami PM, Serva Peddha M. 2021. Effect of *Lactobacillus fermentum* MCC2760-based probiotic curd on hypercholesterolemic C57Bl6 mice. ACS Omega 6:7701–7710. https://doi.org/10.1021/acsomega.1c00045
104. Lin S, Yang X, Long Y, Zhong H, Wang P, Yuan P, Zhang X, Che L, Feng B, Li J, Zhuo Y, Lin Y, Xu S, Wu D, Fang Z. 2020. Dietary supplementation with *Lactobacillus plantarum* modified gut microbiota, bile acid profile and glucose homoeostasis in weaning piglets. Br J Nutr 124:797–808. https://doi.org/10.1017/S0007114520001774
105. Zhang Y, Li X, Huang G, Wang H, Chen H, Su Y, Yu K, Zhu W. 2022. Propionate stimulates the secretion of satiety hormones and reduces

acute appetite in a cecal fistula pig model. Anim Nutr 10:390–398. https://doi.org/10.1016/j.aninu.2022.06.003
106. Lee H, Kim J, An J, Lee S, Choi D, Kong H, Song Y, Park IH, Lee CK, Kim K. 2019. Downregulation of IL-18 expression in the gut by metformin-induced gut microbiota modulation. Immune Netw 19. https://doi.org/10.4110/in.2019.19.e28
107. Lee H, Lee Y, Kim J, An J, Lee S, Kong H, Song Y, Lee CK, Kim K. 2018. Modulation of the gut microbiota by metformin improves metabolic profiles in aged obese mice. Gut Microbes 9:155–165. https://doi.org/10.1080/19490976.2017.1405209
108. Oguma T, Nakayama K, Kuriyama C, Matsushita Y, Yoshida K, Hikida K, Obokata N, Tsuda-Tsukimoto M, Saito A, Arakawa K, Ueta K, Shiotani M. 2015. Intestinal sodium glucose cotransporter 1 inhibition enhances glucagon-like peptide-1 secretion in normal and diabetic rodents. J Pharmacol Exp Ther 354:279–289. https://doi.org/10.1124/jpet.115.225508
109. Mishima E, Fukuda S, Kanemitsu Y, Saigusa D, Mukawa C, Asaji K, Matsumoto Y, Tsukamoto H, Tachikawa T, Tsukimi T, Fukuda NN, Ho HJ, Kikuchi K, Suzuki C, Nanto F, Suzuki T, Ito S, Soga T, Tomioka Y, Abe T. 2018. Canagliflozin reduces plasma uremic toxins and alters the intestinal microbiota composition in a chronic kidney disease mouse model. Am J Physiol Renal Physiol 315:F824–F833. https://doi.org/10.1152/ajprenal.00314.2017
110. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. 2014. Expert consensus document. The International scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term Probiotic. Nat Rev Gastroenterol Hepatol 11:506–514. https://doi.org/10.1038/nrgastro.2014.66
111. Kekkonen RA, Lummela N, Karjalainen H, Latvala S, Tynkkynen S, Jarvenpaa S, Kautiainen H, Julkunen I, Vapaatalo H, Korpela R. 2008. Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults. World J Gastroenterol 14:2029–2036. https://doi.org/10.3748/wjg.14.2029
112. Petersiel N, Shresta S, Tamrakar R, Koju R, Madhup S, Shresta A, Bedi T, Zmora N, Paran Y, Schwartz E, Neuberger A. 2018. The epidemiology of typhoid fever in the Dhulikhel area, Nepal: A prospective cohort study. PLoS One 13:e0204479. https://doi.org/10.1371/journal.pone.0204479
113. Seegers JFML, Gül IS, Hofkens S, Brosel S, Schreib G, Brenke J, Donath C, de Vos WM. 2022. Toxicological safety evaluation of live *Anaerobutyricum soehngenii* strain CH106. J Appl Toxicol 42:244–257. https://doi.org/10.1002/jat.4207
114. Hemmer A, Maiter D, Buysschaert M, Preumont V. 2019. Long-term effects of GLP-1 receptor agonists in type 2 diabetic patients: a retrospective real-life study in 131 patients. Diabetes Metab Syndr 13:332–336. https://doi.org/10.1016/j.dsx.2018.09.007
115. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE. 2006. Metagenomic analysis of the human distal gut microbiome. Science 312:1355–1359. https://doi.org/10.1126/science.1124234
116. Tsai C-Y, Lu H-C, Chou Y-H, Liu P-Y, Chen H-Y, Huang M-C, Lin C-H, Tsai C-N. 2021. Gut microbial signatures for glycemic responses of GLP-1 receptor agonists in type 2 diabetic patients: a pilot study. Front Endocri (Lausanne) 12:814770. https://doi.org/10.3389/fendo.2021.814770
117. Grasset E, Puel A, Charpentier J, Collet X, Christensen JE, Tercé F, Burcelin R. 2017. A specific gut microbiota Dysbiosis of type 2 diabetic mice induces GLP-1 resistance through an Enteric NO-dependent and gut-brain axis mechanism. Cell Metab 26:278. https://doi.org/10.1016/j.cmet.2017.06.003
118. Panda S. 2016. Circadian physiology of metabolism. Science 354:1008–1015. https://doi.org/10.1126/science.aah4967
119. Pulimeno P, Mannic T, Sage D, Giovannoni L, Salmon P, Lemeille S, Giry-Laterriere M, Unser M, Bosco D, Bauer C, Morf J, Halban P, Philippe J, Dibner C. 2013. Autonomous and self-sustained circadian oscillators displayed in human islet cells. Diabetologia 56:497–507. https://doi.org/10.1007/s00125-012-2779-7
120. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH, Lopez JP, Philipson LH, Bradfield CA, Crosby SD, JeBailey L, Wang X, Takahashi JS, Bass J. 2010. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. Nature 466:627–631. https://doi.org/10.1038/nature09253
121. Petrenko V, Gandasi NR, Sage D, Tengholm A, Barg S, Dibner C. 2020. In pancreatic islets from type 2 diabetes patients, the dampened circadian oscillators lead to reduced insulin and glucagon exocytosis. Proc Natl Acad Sci U S A 117:2484–2495. https://doi.org/10.1073/pnas.1916539117
122. Jarrett RJ, Baker IA, Keen H, Oakley NW. 1972. Diurnal variation in oral glucose tolerance: blood sugar and plasma insulin levels morning, afternoon, and evening. Br Med J 1:199–201. https://doi.org/10.1136/bmj.1.5794.199
123. Lindgren O, Mari A, Deacon CF, Carr RD, Winzell MS, Vikman J, Ahrén B. 2009. Differential islet and incretin hormone responses in morning versus afternoon after standardized meal in healthy men. J Clin Endocrinol Metab 94:2887–2892. https://doi.org/10.1210/jc.2009-0366
124. Gil-Lozano M, Mingomataj EL, Wu WK, Ridout SA, Brubaker PL. 2014. Circadian secretion of the intestinal hormone GLP-1 by the rodent L cell. Diabetes 63:3674–3685. https://doi.org/10.2337/db13-1501
125. Grasset E, Puel A, Charpentier J, Klopp P, Christensen JE, Lelouvier B, Servant F, Blasco-Baque V, Tercé F, Burcelin R. 2022. Gut microbiota dysbiosis of type 2 diabetic mice impairs the intestinal daily rhythms of GLP-1 sensitivity. Acta Diabetol 59:243–258. https://doi.org/10.1007/s00592-021-01790-y
126. Martchenko SE, Martchenko A, Cox BJ, Naismith K, Waller A, Gurges P, Sweeney ME, Philpott DJ, Brubaker PL. 2020. Circadian GLP-1 secretion in mice is dependent on the intestinal microbiome for maintenance of diurnal metabolic homeostasis. Diabetes 69:2589–2602. https://doi.org/10.2337/db20-0262
127. Martchenko SE, Martchenko A, Biancolin AD, Waller A, Brubaker PL. 2021. L-cell arntl is required for rhythmic glucagon-like peptide-1 secretion and maintenance of intestinal homeostasis. Mol Metab 54:101340. https://doi.org/10.1016/j.molmet.2021.101340
128. Biancolin AD, Martchenko A, Mitova E, Gurges P, Michalchyshyn E, Chalmers JA, Doria A, Mychaleckyj JC, Adriaenssens AE, Reimann F, Gribble FM, Gil-Lozano M, Cox BJ, Brubaker PL. 2020. The core clock gene, Bmal1, and its downstream target, the SNARE regulatory protein secretagogin, are necessary for circadian secretion of glucagon-like peptide-1. Mol Metab 31:124–137. https://doi.org/10.1016/j.molmet.2019.11.004
129. Wang L, Li P, Tang Z, Yan X, Feng B. 2016. Structural modulation of the gut microbiota and the relationship with body weight: compared evaluation of liraglutide and saxagliptin treatment. Sci Rep 6:33251. https://doi.org/10.1038/srep33251
130. Liu Q, Cai BY, Zhu LX, Xin X, Wang X, An ZM, Li S, Hu YY, Feng Q. 2020. Liraglutide modulates gut microbiome and attenuates nonalcoholic fatty liver in db/db mice. Life Sci 261:118457. https://doi.org/10.1016/j.lfs.2020.118457
131. Madsen MSA, Holm JB, Pallejà A, Wismann P, Fabricius K, Rigbolt K, Mikkelsen M, Sommer M, Jelsing J, Nielsen HB, Vrang N, Hansen HH. 2019. Metabolic and gut microbiome changes following GLP-1 or dual GLP-1/GLP-2 receptor agonist treatment in diet-induced obese mice. Sci Rep 9:15582. https://doi.org/10.1038/s41598-019-52103-x
132. Zhang Q, Xiao X, Zheng J, Li M, Yu M, Ping F, Wang T, Wang X. 2018. Featured article: structure moderation of gut microbiota in liraglutide-treated diabetic male rats. Exp Biol Med (Maywood) 243:34–44. https://doi.org/10.1177/1535370217743765
133. Wang H, Wang L, Li Y, Luo S, Ye J, Lu Z, Li X, Lu H. 2021. The HIF-2α/PPARα pathway is essential for liraglutide-alleviated, lipid-induced hepatic steatosis. Biomed Pharmacother 140:111778. https://doi.org/10.1016/j.biopha.2021.111778
134. Moreira GV, Azevedo FF, Ribeiro LM, Santos A, Guadagnini D, Gama P, Liberti EA, Saad M, Carvalho C. 2018. Liraglutide modulates gut microbiota and reduces NAFLD in obese mice. J Nutr Biochem 62:143–154. https://doi.org/10.1016/j.jnutbio.2018.07.009
135. Ying X, Rongjiong Z, Kahaer M, Chunhui J, Wulasihan M. 2023. Therapeutic efficacy of liraglutide versus metformin in modulating the gut microbiota for treating type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Front Microbiol 14:1088187. https://doi.org/10.3389/fmicb.2023.1088187
136. Smits MM, Fluitman KS, Herrema H, Davids M, Kramer MHH, Groen AK, Belzer C, de Vos WM, Cahen DL, Nieuwdorp M, van Raalte DH. 2021. Liraglutide and sitagliptin have no effect on intestinal microbiota composition: a 12-week randomized placebo-controlled trial in adults with type 2 diabetes. Diabetes Metab 47:101223. https://doi.org/10.1016/j.diabet.2021.101223

137. Rizza S, Pietrucci D, Longo S, Menghini R, Teofani A, Piciucchi G, Montagna M, Federici M. 2023. Impact of insulin Degludec/Liraglutide fixed combination on the gut microbiomes of elderly patients with type 2 diabetes: results from A Subanalysis of A small non-randomised single arm study. Aging Dis 14:319–324. https://doi.org/10.14336/AD.2023.0118
138. Kato S, Sato T, Fujita H, Kawatani M, Yamada Y. 2021. Effects of GLP-1 receptor agonist on changes in the gut bacterium and the underlying mechanisms. Sci Rep 11:9167. https://doi.org/10.1038/s41598-021-88612-x
139. Silva-Veiga FM, Miranda CS, Vasques-Monteiro IML, Souza-Tavares H, Martins FF, Daleprane JB, Souza-Mello V. 2022. Peroxisome proliferator-activated receptor-alpha activation and dipeptidyl peptidase-4 inhibition target dysbiosis to treat fatty liver in obese mice. World J Gastroenterol 28:1814–1829. https://doi.org/10.3748/wjg.v28.i17.1814
140. Liao X, Song L, Zeng B, Liu B, Qiu Y, Qu H, Zheng Y, Long M, Zhou H, Wang Y, Du Y, Xu J, Shen R, Tong Q, Cai L, Li X, Guo S, Yang G, Zhu Z, Pu X, Wei H, Zheng H. 2019. Alteration of gut microbiota induced by DPP-4I treatment improves glucose homeostasis. EBioMedicine 44:665–674. https://doi.org/10.1016/j.ebiom.2019.03.057
141. Olivares M, Neyrinck AM, Pötgens SA, Beaumont M, Salazar N, Cani PD, Bindels LB, Delzenne NM. 2018. The DPP-4 inhibitor vildagliptin impacts the gut microbiota and prevents disruption of intestinal homeostasis induced by a Western diet in mice. Diabetologia 61:1838–1848. https://doi.org/10.1007/s00125-018-4647-6
142. Zhang M, Feng R, Yang M, Qian C, Wang Z, Liu W, Ma J. 2019. Effects of metformin, acarbose, and sitagliptin monotherapy on gut microbiota in zucker diabetic fatty rats. BMJ Open Diabetes Res Care 7:e000717. https://doi.org/10.1136/bmjdrc-2019-000717
143. Ryan PM, Patterson E, Carafa I, Mandal R, Wishart DS, Dinan TG, Cryan JF, Tuohy KM, Stanton C, Ross RP. 2020. Metformin and dipeptidyl peptidase-4 inhibitor differentially modulate the intestinal microbiota and plasma metabolome of metabolically dysfunctional mice. Can J Diabetes 44:146–155. https://doi.org/10.1016/j.jcjd.2019.05.008
144. Zhang Q, Xiao X, Li M, Yu M, Ping F, Zheng J, Wang T, Wang X, Peterson JM. 2017. Vildagliptin increases butyrate-producing bacteria in the gut of diabetic rats. PLoS ONE 12:e0184735. https://doi.org/10.1371/journal.pone.0184735
145. Guo S, Al-Sadi R, Said HM, Ma TY. 2013. Lipopolysaccharide causes an increase in intestinal tight junction permeability *in vitro* and *in vivo* by inducing enterocyte membrane expression and localization of TLR-4 and CD14. Am J Pathol 182:375–387. https://doi.org/10.1016/j.ajpath.2012.10.014
146. Zhou S-Y, Gillilland M III, Wu X, Leelasinjaroen P, Zhang G, Zhou H, Ye B, Lu Y, Owyang C. 2018. FODMAP diet modulates visceral nociception by lipopolysaccharide-mediated intestinal inflammation and barrier dysfunction. J Clin Invest 128:267–280. https://doi.org/10.1172/JCI92390
147. Chen Q, Ma X, Li C, Shen Y, Zhu W, Zhang Y, Guo X, Zhou J, Liu C. 2020. Enteric phageome alterations in patients with type 2 diabetes. Front Cell Infect Microbiol 10:575084. https://doi.org/10.3389/fcimb.2020.575084
148. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, Eppler E, Bouzakri K, Wueest S, Muller YD, Hansen AMK, Reinecke M, Konrad D, Gassmann M, Reimann F, Halban PA, Gromada J, Drucker DJ, Gribble FM, Ehses JA, Donath MY. 2011. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med 17:1481–1489. https://doi.org/10.1038/nm.2513
149. Costa A, Ai M, Nunn N, Culotta I, Hunter J, Boudjadja MB, Valencia-Torres L, Aviello G, Hodson DJ, Snider BM, Coskun T, Emmerson PJ, Luckman SM, D'Agostino G. 2022. Anorectic and aversive effects of GLP-1 receptor agonism are mediated by brainstem cholecystokinin neurons, and modulated by GIP receptor activation. Mol Metab 55:101407. https://doi.org/10.1016/j.molmet.2021.101407
150. Jorsal T, Rhee NA, Pedersen J, Wahlgren CD, Mortensen B, Jepsen SL, Jelsing J, Dalbøge LS, Vilmann P, Hassan H, Hendel JW, Poulsen SS, Holst JJ, Vilsbøll T, Knop FK. 2018. Enteroendocrine K and L cells in healthy and type 2 diabetic individuals. Diabetologia 61:284–294. https://doi.org/10.1007/s00125-017-4450-9
151. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, Zink EM, Casey CP, Taylor BC, Lane CJ, Bramer LM, Isern NG, Hoyt DW, Noecker C, Sweredoski MJ, Moradian A, Borenstein E, Jansson JK, Knight R, Metz TO, Lois C, Geschwind DH, Krajmalnik-Brown R, Mazmanian SK. 2019. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. Cell 177:1600–1618. https://doi.org/10.1016/j.cell.2019.05.004
152. Breton J, Tirelle P, Hasanat S, Pernot A, L'Huillier C, do Rego J-C, Déchelotte P, Coëffier M, Bindels LB, Ribet D. 2021. Gut microbiota alteration in a mouse model of anorexia nervosa. Clin Nutr 40:181–189. https://doi.org/10.1016/j.clnu.2020.05.002
153. Ren HX, Tang QC, Yan L, Xia H, Luo HS. 2018. Evodiamine inhibits gastrointestinal motility via CCK and CCK1 receptor in water-avoidence stress rat model. Life Sci 209:210–216. https://doi.org/10.1016/j.lfs.2018.08.003
154. Marra A, Hanson MA, Kondo S, Erkosar B, Lemaitre B, Ja WW, McFall-Ngai MJ. 2021. *Drosophila* antimicrobial peptides and lysozymes regulate gut microbiota composition and abundance. mBio 12:e0082421. https://doi.org/10.1128/mBio.00824-21
155. Tsafack PB, Li C, Tsopmo A. 2022. Food peptides, gut microbiota modulation, and antihypertensive effects. Molecules 27:27. https://doi.org/10.3390/molecules27248806
156. Li Z, Zhang B, Wang N, Zuo Z, Wei H, Zhao F. 2023. A novel peptide protects against diet-induced obesity by suppressing appetite and modulating the gut microbiota. Gut 72:686–698. https://doi.org/10.1136/gutjnl-2022-328035
157. Tanabe S. 2012. Short peptide modules for enhancing intestinal barrier function. Curr Pharm Des 18:776–781. https://doi.org/10.2174/138161212799277653
158. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, et al. 2015. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature 528:262–266. https://doi.org/10.1038/nature15766
159. Lindell AE, Zimmermann-Kogadeeva M, Patil KR. 2022. Multimodal interactions of drugs, natural compounds and pollutants with the gut microbiota. Nat Rev Microbiol 20:431–443. https://doi.org/10.1038/s41579-022-00681-5
160. Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, Bae JW. 2014. An increase in the *Akkermansia* spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut 63:727–735. https://doi.org/10.1136/gutjnl-2012-303839
161. Koufakis T, Doumas M, Zebekakis P, Kotsa K. 2022. Dual sodium-glucose cotransporter (SGLT) 1/2 versus pure SGLT2 inhibitors: two distinct drug categories or one class with multiple faces? Expert Opin Pharmacother 23:1497–1502. https://doi.org/10.1080/14656566.2022.2113385
162. Albaugh VL, Banan B, Antoun J, Xiong Y, Guo Y, Ping J, Alikhan M, Clements BA, Abumrad NN, Flynn CR. 2019. Role of bile acids and GLP-1 in mediating the metabolic improvements of bariatric surgery. Gastroenterology 156:1041–1051. https://doi.org/10.1053/j.gastro.2018.11.017
163. Svane MS, Bojsen-Møller KN, Nielsen S, Jørgensen NB, Dirksen C, Bendtsen F, Kristiansen VB, Hartmann B, Holst JJ, Madsbad S. 2016. Effects of endogenous GLP-1 and GIP on glucose tolerance after Roux-en-Y gastric bypass surgery. Am J Physiol Endocrinol Metab 310:E505–14. https://doi.org/10.1152/ajpendo.00471.2015
164. Hutch CR, Sandoval D. 2017. The role of GLP-1 in the metabolic success of bariatric surgery. Endocrinology 158:4139–4151. https://doi.org/10.1210/en.2017-00564
165. Roberts RE, Glicksman C, Alaghband-Zadeh J, Sherwood RA, Akuji N, le Roux CW. 2011. The relationship between postprandial bile acid concentration, GLP - 1, PYY and ghrelin. Clin Endocrinol (Oxf) 74:67–72. https://doi.org/10.1111/j.1365-2265.2010.03886.x