Review Article | Comprehensive Literature Review

Natural Products as Modulators of the GLP-1 Axis: A Comprehensive Review of Herbals, Dietary Supplements, and Biotics in Boosting Endogenous GLP-1, Activating GLP-1 Receptors, and Inhibiting DPP-IV

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Abstract / Summary

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted primarily by intestinal L-cells in response to nutrient ingestion. It exerts pleiotropic metabolic effects including glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, appetite reduction, and cardioprotective actions. The remarkable therapeutic success of synthetic GLP-1 receptor agonists (GLP-1RAs), exemplified by semaglutide and liraglutide, in treating type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease has generated unprecedented global market interest, with the GLP-1 drug market projected to exceed $130 billion USD by 2030. Nevertheless, cost, side-effect profiles, route of administration, and global access barriers have galvanized substantial scientific and commercial interest in natural, food-derived, and microbiome-modulating strategies to augment endogenous GLP-1 secretion, activate GLP-1 receptors, and inhibit dipeptidyl peptidase-IV (DPP-IV), the principal enzyme responsible for rapid GLP-1 degradation. This comprehensive review synthesizes the current scientific literature, spanning in vitro mechanistic studies, animal model experiments, and human clinical trials, alongside an assessment of the industrial landscape including patented strains, commercial formulations, and regulatory status across four principal categories: (1) botanical and herbal extracts, (2) dietary supplements and nutraceuticals, (3) probiotic, prebiotic, postbiotic, and synbiotic interventions, and (4) other bioactive dietary compounds. We critically evaluate the evidence base for compounds including berberine, curcumin, quercetin, bitter melon, fenugreek, cinnamon, Gymnema sylvestre, resistant starch, beta-glucan, inulin-type fructans, omega-3 fatty acids, and specific Lactobacillus, Bifidobacterium, and Akkermansia muciniphila strains, among many others. Special emphasis is placed on the gut microbiome as a central mediator between dietary bioactives and GLP-1 axis modulation, including short-chain fatty acid signaling, bile acid metabolism, and L-cell biology. Our analysis reveals a rapidly evolving evidence base, with over 400 published studies examining natural GLP-1 modulators as of 2024, yet significant mechanistic and clinical gaps remain. Most natural compounds exhibit partial or modest effects compared to pharmaceutical GLP-1RAs, and rigorous dose-finding, long-term safety, and head-to-head clinical trial data remain sparse. We further identify key translational gaps between preclinical promise and clinical validation, highlight the most commercially advanced natural GLP-1 modulators, and propose a framework for future research integrating multi-omics, precision nutrition, and synbiotic combination strategies. This review provides a comprehensive and critically appraised resource for researchers, clinicians, and industry stakeholders seeking to develop evidence-based, accessible, and safe natural alternatives or adjuncts to pharmaceutical GLP-1 therapy.

Keywords: GLP-1; incretin; natural products; DPP-IV inhibition; gut microbiome; probiotic; prebiotic; postbiotic; synbiotic; herbal medicine; nutraceutical; GLP-1 receptor agonist; type 2 diabetes; obesity; L-cell

1. Introduction

The glucagon-like peptide-1 (GLP-1) is a 30-amino acid incretin hormone derived from the post-translational processing of proglucagon, a 160-amino acid precursor protein encoded by the GCG gene located on chromosome 2q24.2 in humans. The discovery of GLP-1 traces to the broader characterization of the proglucagon gene in the early 1980s. Mojsov and colleagues at the Rockefeller University, along with independent work by Drucker and Habener at Harvard, demonstrated in 1987 that intestinal processing of proglucagon yielded a potent insulinotropic peptide distinct from glucagon itself, now recognized as GLP-1(7-36) amide, the primary biologically active form. This discovery was pivotal not merely as an incremental advance in endocrinology, but as the conceptual foundation for an entirely new pharmacological axis. GLP-1 is produced predominantly by enteroendocrine L-cells localized in the distal small intestine and colon, though small populations of GLP-1-secreting neurons also exist in the nucleus tractus solitarius of the brainstem. Upon luminal stimulation by macronutrients, particularly long-chain fatty acids, fermentable carbohydrates, and certain amino acids, L-cells rapidly secrete GLP-1 into the portal circulation within minutes, constituting the first-phase incretin response.

In the pancreas, GLP-1 binds to its cognate G-protein coupled receptor (GLP-1R) expressed on beta-cells, triggering cyclic AMP (cAMP) accumulation, protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC2) activation, and downstream potentiation of glucose-stimulated insulin secretion (GSIS) in a strictly glucose-dependent manner, a critically important safety feature that minimizes the hypoglycemia risk inherent to classical secretagogues such as sulfonylureas. GLP-1 simultaneously inhibits glucagon release from alpha-cells and stimulates somatostatin from delta-cells, collectively fine-tuning postprandial glucose excursions. Beyond the endocrine pancreas, GLP-1R is widely expressed across multiple organ systems including the cardiovascular system, central nervous system (particularly the hypothalamus and brainstem), kidney, lung, and gastrointestinal tract, conferring pleiotropic actions ranging from appetite suppression and gastric motility regulation to cardioprotection, neuroprotection, and renal anti-inflammatory effects. Physiologically, however, GLP-1 has an extremely short half-life of 1-2 minutes in the systemic circulation due to rapid cleavage at the penultimate alanine residue by the serine protease dipeptidyl peptidase-IV (DPP-IV, also known as CD26), underscoring the therapeutic imperative to either protect endogenous GLP-1 from degradation or develop DPP-IV-resistant analogs.

The translation of GLP-1 biology into therapeutic intervention has constituted one of the most consequential developments in modern pharmacology. The first approved GLP-1 receptor agonist, exenatide (Byetta, AstraZeneca/Eli Lilly), entered the US market in 2005 as a synthetic exendin-4 analog derived from the Gila monster lizard, demonstrating that DPP-IV-resistant GLP-1R agonism could safely reduce HbA1c by 0.8-1.5% and promote meaningful weight loss in T2DM patients. Liraglutide (Victoza; Saxenda for obesity, Novo Nordisk) followed in 2010, establishing that daily subcutaneous GLP-1RA administration produced not only glycemic benefits but, critically, a 13% reduction in major adverse cardiovascular events (MACE) in the LEADER trial, a paradigm-shifting finding that repositioned GLP-1RAs as cardiometabolic medicines rather than mere antidiabetics. The subsequent approval of weekly semaglutide (Ozempic for T2DM; Wegovy for obesity, Novo Nordisk) and oral semaglutide (Rybelsus) brought unprecedented efficacy: Wegovy demonstrated 14.9% mean body weight reduction over 68 weeks in the STEP 1 trial (n=1,961), while the SELECT cardiovascular outcomes trial in 2023 demonstrated a 20% relative risk reduction in MACE in overweight/obese patients without diabetes, extending the GLP-1RA indication to primary cardiovascular prevention. Tirzepatide (Mounjaro/Zepbound, Eli Lilly), a dual GIP/GLP-1 receptor co-agonist approved in 2022-2023, further advanced efficacy with up to 22.5% body weight reduction (SURMOUNT-1 trial). As of 2024, the global GLP-1 market exceeds $50 billion USD annually and is projected by Goldman Sachs Research and Morgan Stanley to reach $100-130

billion USD by 2030, with some analyses suggesting a total addressable market exceeding $200 billion when accounting for potential applications in non-alcoholic steatohepatitis (NASH), addiction, Alzheimer's disease, polycystic ovary syndrome (PCOS), and chronic kidney disease. Currently, an estimated 537 million adults worldwide live with T2DM (IDF 2021), with projections of 783 million by 2045, while 1 billion adults are obese globally (WHO 2022), representing an enormous and largely undertreated patient population.

Despite the remarkable pharmacological success of synthetic GLP-1RAs, significant barriers limit their accessibility and acceptability at a population level. Annual treatment costs for semaglutide approach $13,000-$16,000 USD in the United States with limited insurance coverage, rendering them financially inaccessible to the vast majority of the estimated 100+ million Americans with obesity or prediabetes. Gastrointestinal adverse effects, nausea (up to 44%), vomiting (24%), and constipation (24%), contribute to discontinuation rates of 20-40% in real-world settings. Drug shortages, cold-chain requirements for injectable formulations, and regulatory barriers further constrain global access, particularly in low- and middle-income countries where the metabolic disease burden is rising most rapidly. These realities have intensified scientific and commercial interest in natural, food-derived, and microbiome-modulating interventions capable of augmenting endogenous GLP-1. The gut microbiome has emerged as a pivotal regulator of GLP-1 biology through multiple interacting mechanisms. Microbial fermentation of dietary fibers generates short-chain fatty acids (SCFAs), particularly butyrate, propionate, and acetate, that activate free fatty acid receptors (FFAR2/GPR43 and FFAR3/GPR41) on L-cells, stimulating GLP-1 secretion. Similarly, secondary bile acids generated by microbial biotransformation of primary bile acids activate Takeda G protein-coupled receptor 5 (TGR5) on L-cells, a potent GLP-1 secretagogue pathway. Specific gut bacteria, notably Akkermansia muciniphila, Lactobacillus reuteri, and certain Bifidobacterium strains, have shown capacity to enhance GLP-1 secretion, reduce DPP-IV activity, and upregulate GLP-1R expression in animal models and preliminary human studies. However, fundamental mechanistic questions remain unresolved: the precise L-cell subpopulations responsive to different microbial signals, the relative contribution of luminal versus systemic microbial signals, species- and strain-level specificity, and the degree to which individual microbiome composition determines the GLP-1-stimulatory efficacy of specific dietary interventions.

Natural products exert influence on the GLP-1 axis through three functionally distinct but mechanistically overlapping mechanisms, each representing a viable therapeutic target. First, GLP-1 secretion enhancement: numerous plant-derived compounds, dietary fibers, fermented foods, and specific probiotic organisms directly stimulate GLP-1 release from intestinal L-cells by activating nutrient-sensing receptors including GPR40/FFAR1 (long-chain fatty acids), GPR119 (N-acylethanolamines and monoacylglycerols), GPR41/FFAR3 and GPR43/FFAR2 (SCFAs), TGR5 (bile acids), and bitter taste receptors TAS2R (bitter plant compounds such as berberine, naringenin, and quinine). Activation of these diverse receptor systems by natural bioactives can trigger L-cell cAMP elevation and calcium mobilization leading to rapid GLP-1 exocytosis. Second, GLP-1 receptor activation: some natural compounds have been reported to possess direct, though typically partial, GLP-1R agonist activity, including oleanolic acid, quercetin, kaempferol, stevioside, and certain plant-derived peptide sequences. While their binding affinity and efficacy remain substantially lower than pharmaceutical GLP-1RAs, they may exert synergistic effects in the context of elevated endogenous GLP-1 levels. Third, DPP-IV inhibition: a large number of polyphenols, flavonoids, and dietary bioactives have demonstrated DPP-IV inhibitory activity in vitro and some in vivo, effectively extending the biological half-life of endogenous GLP-1. Key compounds in this category include EGCG from green tea, luteolin, apigenin, fisetin, grape seed proanthocyanidins, thymoquinone, and berberine, notably, several of these compounds exhibit dual or triple action across all three mechanisms simultaneously. Understanding the relative potency, bioavailability, and clinical relevance of each mechanism is essential to developing rational combination strategies.

This review provides a comprehensive, critically appraised, and interdisciplinary synthesis of the scientific and industrial evidence base for natural products as modulators of the GLP-1 axis. We begin by reviewing the fundamental biology of GLP-1, its discovery, structure, processing, and physiological roles, followed by a systematic mapping of GLP-1-responsive cell types, organs, and the human disease burden attributable to GLP-1 dysregulation. We then examine in detail the intracellular signaling mechanisms through which GLP-1 exerts its diverse effects, providing a mechanistic foundation for understanding how natural compounds may replicate or amplify these actions. A dedicated section examines the gut microbiome's multifaceted role in GLP-1 biology, integrating emerging concepts from L-cell biology, SCFA signaling, and bile acid metabolism with the probiotic and prebiotic literature. The core evidence synthesis sections evaluate herbals and botanicals, dietary supplements and nutraceuticals, and biotics (probiotics, prebiotics, postbiotics, synbiotics) separately, assessing in vitro, in vivo, and clinical trial evidence, noting patented strains and commercially available products. We conclude by identifying critical gaps in current knowledge and the commercial landscape, and by proposing future research directions including multi-omics integration, precision nutrition approaches, and synergistic combination formulation strategies. This review is timely given the explosive pharmaceutical GLP-1 market, the unmet need for accessible and affordable metabolic health interventions, and the rapidly expanding scientific literature at the intersection of nutritional biochemistry, microbiome science, and metabolic disease.

2. GLP-1, Discovery, Structure, and Primary Physiological Roles

The conceptual groundwork for GLP-1 was laid in the mid-20th century through clinical observations that oral glucose produces a greater insulin secretory response than an equivalent amount of intravenous glucose, a phenomenon subsequently termed the 'incretin effect.' This incretin effect, which accounts for approximately 50-70% of postprandial insulin secretion in healthy individuals, prompted decades of investigation into gut-derived factors capable of amplifying pancreatic beta-cell responses. Gastric inhibitory polypeptide (GIP), the first incretin identified (initially as an inhibitor of gastric acid, rediscovered as an insulinotropic factor), was characterized by Brown and colleagues in 1975. GLP-1 itself was not identified until the molecular biology era made proglucagon gene cloning possible. In 1982, Bell and colleagues at the Salk Institute published the complete DNA sequence of the human preproglucagon gene, revealing that the proglucagon polypeptide contained not only glucagon but also two additional glucagon-related sequences, now known as GLP-1 and GLP-2. The critical insight that tissue-specific post-translational processing would yield different final peptide products depending on the cellular context (alpha-cells of the pancreas producing glucagon; intestinal L-cells and brainstem neurons producing GLP-1 and GLP-2) was elaborated through the late 1980s. Mojsov et al. (1987, Endocrinology) and Drucker et al. (1987, PNAS) independently demonstrated that synthetic GLP-1(7-36) amide was a potent, glucose-dependent insulin secretagogue in isolated pancreatic preparations and in vivo in rats, establishing it as a genuine incretin hormone and inaugurating a new era of cardiometabolic pharmacology.

Structurally, biologically active GLP-1 exists primarily as GLP-1(7-36) amide (>80% of total GLP-1 in the circulation), with a minor circulating form of GLP-1(7-37). The peptide is characterized by a N-terminal histidine-alanine dipeptide sequence (His7-Ala8) that is essential for GLP-1R binding and activation, and which simultaneously represents the critical DPP-IV cleavage site, proteolytic removal of this His-Ala dipeptide by DPP-IV generates the biologically inactive GLP-1(9-36) amide metabolite. This structural vulnerability fundamentally limits the therapeutic utility of native GLP-1, which has a plasma half-life of merely 1-2 minutes after intravenous administration, primarily due to DPP-IV activity at the brush border of the renal and intestinal endothelium. The proglucagon gene product in intestinal L-cells undergoes cleavage by prohormone convertase 1/3 (PC1/3) to yield, in addition to GLP-1, glicentin, oxyntomodulin, GLP-2, and intervening peptides. Each of these has distinct bioactivities: GLP-2 promotes intestinal mucosal growth; oxyntomodulin has anorectic

effects; glicentin may have local intestinal actions. Understanding this coordinated co-secretion is important because many natural interventions that stimulate GLP-1 likely co-stimulate the full complement of proglucagon-derived peptides from L-cells, with potentially additive or synergistic metabolic benefits beyond GLP-1 itself.

The GLP-1 receptor (GLP-1R) belongs to class B1 of the G-protein coupled receptor (GPCR) superfamily, the same family that includes receptors for parathyroid hormone, glucagon, secretin, and vasoactive intestinal peptide. It is a 463-amino acid receptor containing seven transmembrane helices, a large extracellular N-terminal domain, and cytoplasmic loops that couple to Gs, Gq, and Gi proteins depending on the cellular and ligand context. Structural studies using cryo-electron microscopy, particularly pioneering work by the groups of Kobilka, Danev, and colleagues published in Nature and Science between 2017 and 2020, have revealed the molecular details of how GLP-1 engages its receptor in a two-step mechanism: initial capture via the large extracellular domain followed by deep insertion of the GLP-1 N-terminus into the transmembrane bundle to activate G-protein coupling. These structural insights have proven invaluable for rational drug design of both peptide and non-peptide GLP-1R agonists, and are increasingly informing the search for small-molecule natural GLP-1R agonists. GLP-1R expression is particularly dense in pancreatic beta-cells, but is also present in cardiac myocytes, aortic smooth muscle, nodose ganglia of the vagus nerve, hypothalamic nuclei (arcuate, paraventricular, dorsomedial), hippocampus, ventral tegmental area, kidney proximal tubules, and lung, the receptor distribution predicting the pleiotropic non-pancreatic actions that have become increasingly clinically relevant.

Physiologically, GLP-1 secretion follows a biphasic pattern after ingestion of mixed meals. An early phase (within 10-15 minutes) appears to be partly mediated by neural and paracrine mechanisms, including vagal afferent signals originating from the proximal gut, before significant nutrients reach L-cell-dense distal intestinal segments. A second, more prolonged phase (30-90 minutes postprandially) is driven by direct luminal nutrient contact with L-cells in the ileum and colon. The relative importance of these two phases varies with nutrient composition and meal size. Fats and proteins are among the most potent GLP-1 secretagogues, with long-chain fatty acids activating both GPR40 (FFAR1) and GPR119 on L-cells, while aromatic amino acids (phenylalanine, tryptophan) activate calcium-sensing receptor (CaSR) and aromatic amino acid receptor GPRC6A. Carbohydrates stimulate GLP-1 partly through sodium-glucose co-transporter (SGLT1)-dependent mechanisms in addition to sweet taste receptor (T1R2/T1R3) signaling. The magnitude of the GLP-1 secretory response in healthy individuals ranges from approximately 5-10 pM fasting to 15-40 pM postprandially, though values are substantially lower in individuals with T2DM, in whom impaired GLP-1 secretion has been documented, though whether this is a primary pathophysiological mechanism or a consequence of chronic metabolic dysregulation remains debated. Importantly, the GLP-1 secretory response is blunted in obesity and T2DM by 20-50% compared to lean healthy controls, providing a compelling rationale for interventions aimed at restoring or enhancing endogenous GLP-1 output through dietary and microbiome-modulating strategies.

Beyond its canonical role as a pancreatic secretagogue, GLP-1 has been increasingly recognized as a pleiotropic hormone with systemic metabolic and organ-protective functions that extend far beyond glucose homeostasis. In the central nervous system, GLP-1 acts on hypothalamic circuits, particularly the arcuate nucleus (AgRP/NPY and POMC neurons) and the nucleus of the solitary tract (NTS), to suppress food intake, reduce meal size, and promote satiety through mechanisms that are partly distinct from leptin signaling and remain functional even in states of leptin resistance. GLP-1 also activates reward circuits in the ventral tegmental area, which may contribute to the observed reductions in addictive behaviors (alcohol consumption, smoking, drug craving) reported anecdotally and now being studied in clinical trials with GLP-1RAs. In the cardiovascular system, GLP-1 exerts direct inotropic and chronotropic effects on cardiac myocytes, promotes coronary vasodilation, reduces ischemia-reperfusion injury through PKA-dependent anti-apoptotic signaling,

and attenuates vascular inflammation. In the kidney, GLP-1R activation promotes natriuresis, reduces tubular inflammation, and attenuates diabetic nephropathy progression, effects now being studied in dedicated renal outcomes trials. In the liver, while GLP-1R expression is controversial (with some studies suggesting indirect hepatic effects mediated through vagal afferents or GLP-1R-expressing portal hepatocytes), GLP-1RAs consistently reduce hepatic steatosis and steatohepatitis markers, positioning them as leading candidates for NASH therapy. This extraordinary breadth of action makes the GLP-1 axis one of the most compelling targets in all of medicine, and proportionately increases the interest in natural modulators that can engage this axis safely and affordably.

[FIGURE 1] GLP-1 Discovery Timeline and Proglucagon Processing

Schematic showing: (A) Timeline of key discoveries from the incretin concept (1930s) to GLP-1 receptor structural elucidation (2017-2020); (B) Tissue-specific proglucagon processing in pancreatic alpha-cells vs intestinal L-cells; (C) GLP-1 molecular structure with DPP-IV cleavage site highlighted; (D) GLP-1 receptor structure and G-protein coupling.

Figure 1. GLP-1 discovery timeline, proglucagon processing, and receptor biology. [To be produced as a multi-panel schematic illustration based on primary literature sources.]

3. Cell Types, Organs, and Disease Burden, The Reach of GLP-1 Biology

The GLP-1 receptor is among the most widely distributed GPCRs in the human body, and the growing catalog of GLP-1-responsive tissues continuously expands as high-sensitivity receptor detection methods, GLP-1R reporter mice, and organ-specific GLP-1R conditional knockout models refine our understanding. The beta-cells of the pancreatic islets of Langerhans represent the most physiologically critical site of GLP-1R expression and the canonical target of incretin therapy. GLP-1R-expressing beta-cells account for approximately 65-80% of islet mass in healthy individuals, and chronic GLP-1R stimulation has been shown in multiple rodent studies to promote beta-cell proliferation, inhibit apoptosis, and increase islet neogenesis from ductal precursors through cAMP/PKA-mediated upregulation of pancreatic duodenal homeobox 1 (PDX-1) and forkhead box O1 (FoxO1). Whether these beta-cell trophic effects occur in adult humans remains debated; analyses of pancreata from patients treated with incretin therapies have yielded inconsistent results, though the totality of clinical evidence does not suggest meaningful pancreatic harm. The public health dimension of beta-cell dysfunction is staggering: T2DM affects 537 million adults globally (IDF Diabetes Atlas 2021), with 96 million Americans in prediabetes and 37 million with T2DM, representing direct medical costs exceeding $327 billion annually in the US alone. Progressive beta-cell mass loss, estimated at 50-60% by the time of T2DM diagnosis, underlies disease progression, making beta-cell preservation a central therapeutic goal.

Hypothalamic and brainstem neuronal circuits represent the second most clinically important site of GLP-1 action, mediating the anorectic and weight-regulatory effects that have made GLP-1RAs transformative obesity treatments. GLP-1R-expressing neurons in the arcuate nucleus (ARC) co-express both orexigenic neuropeptide Y/AgRP and anorexigenic POMC, with GLP-1 activating the POMC neuron population to promote alpha-MSH release and MC4R-mediated satiety signaling. The nucleus tractus solitarius (NTS) and area postrema receive both peripheral GLP-1 signals (via circumventricular organs lacking a blood-brain barrier) and GLP-1 produced by local NTS neurons innervated by vagal afferents. GLP-1 in the mesolimbic system, particularly the nucleus accumbens and ventral tegmental area, regulates reward-motivated feeding behavior and has been proposed to underlie the reported reductions in addiction-related behaviors with GLP-1RA therapy. The global obesity epidemic provides the clinical context: 1 billion adults are obese as of 2022 (WHO), with obesity projecting to affect 51% of all adults globally by 2035 (World Obesity Federation). In the US,

42.4% of adults have obesity (BMI ≥30), with an additional 31.1% overweight, translating to over $173 billion in annual obesity-attributable medical costs. Critically, only 2-3% of eligible obese patients currently receive any anti-obesity pharmacotherapy, representing an enormous treatment gap that natural GLP-1 modulators might help address.

In the cardiovascular system, GLP-1R is expressed in cardiomyocytes, coronary arterial smooth muscle cells, endothelial cells, and sinoatrial node cells. Direct cardiac GLP-1R signaling promotes cAMP/PKA-dependent phosphorylation of troponin I, improving diastolic relaxation and myocardial efficiency. GLP-1 also activates eNOS in vascular endothelium, promoting NO-dependent vasodilation and reducing vascular inflammation through NFkB pathway attenuation. In the landmark LEADER trial (n=9,340 T2DM patients, median follow-up 3.8 years), liraglutide reduced the primary composite MACE endpoint by 13% relative risk reduction (HR 0.87, 95% CI 0.78-0.97). SUSTAIN-6 demonstrated semaglutide reduced MACE by 26% (HR 0.74). The SELECT trial (2023) with semaglutide 2.4 mg in overweight/obese non-diabetic patients showed a 20% MACE reduction (HR 0.80), confirming GLP-1RA cardiovascular benefits are independent of glycemic effects. Cardiovascular disease remains the leading cause of global mortality, accounting for 17.9 million deaths annually (WHO), with direct and indirect costs in the US of $363 billion per year. The renal system is equally important: GLP-1R-expressing proximal tubule cells mediate GLP-1's natriuretic effects through inhibition of NHE3 (sodium-hydrogen exchanger 3), and GLP-1RAs reduce albuminuria progression in diabetic nephropathy by 25-40% in clinical trials. Diabetic kidney disease affects 40% of T2DM patients and is the leading cause of end-stage renal disease in developed countries, affecting ~800,000 Americans.

Hepatic and gastrointestinal GLP-1 responses are clinically relevant through both direct and indirect mechanisms. While hepatocytes express limited or absent GLP-1R protein in most studies, GLP-1 reduces hepatic lipogenesis and promotes fatty acid oxidation through autonomic neural pathways and potentially through local GLP-1 production by portal hepatocytes. Non-alcoholic fatty liver disease (NAFLD) affects 25% of the global adult population, approximately 1.9 billion people, and its progressive form, NASH with fibrosis, affects an estimated 115 million people worldwide with limited approved treatments until recently. In a phase 2 trial, semaglutide 1.0 mg weekly achieved NASH resolution in 59% of patients versus 17% in placebo ($p<0.001$). In the gastrointestinal tract, GLP-1 retards gastric emptying via vagal mechanisms and reduces small intestinal motility, contributing to satiety but also to the nausea and gastroparesis that constitute the primary side effects of pharmacological GLP-1R stimulation. In the lung, GLP-1R expression in alveolar type II cells and airway smooth muscle may mediate anti-inflammatory and bronchodilatory effects relevant to asthma and COPD, though clinical evidence in these indications remains preliminary. Bone homeostasis represents a more recently recognized GLP-1 target: GLP-1R on osteoblasts and osteoclasts influences bone turnover, and GLP-1RAs have demonstrated neutral or beneficial effects on fracture risk in T2DM, where skeletal fragility is an underappreciated complication affecting over 40% of patients.

Cell/Organ Type	GLP-1 Receptor Expression	GLP-1 Mediated Effect	Associated Disease / Condition	Global Disease Burden	US Disease Burden
Pancreatic Beta-cells	High (primary site)	Glucose-dependent insulin secretion,	Type 2 Diabetes Mellitus	537M adults (IDF 2021); 783M	37M adults; $327B annual cost

Cell/Organ Type	GLP-1 Receptor Expression	GLP-1 Mediated Effect	Associated Disease / Condition	Global Disease Burden	US Disease Burden
		beta-cell proliferation & anti-apoptosis		projected by 2045	
Hypothalamus / Brainstem (ARC, NTS)	High; GLP-1-producing neurons	Appetite suppression, satiety signaling, food reward regulation	Obesity, binge eating, food addiction	1B adults obese globally; 51% by 2035 (est.)	42.4% adults obese; $173B/yr
Cardiomyocytes / Vascular Endothelium	Moderate-high	Cardioprotection, vasodilation, anti-inflammation, reduced MACE	Cardiovascular disease, heart failure	17.9M deaths/yr globally (WHO)	$363B annual cost USA
Renal Proximal Tubule Cells	Moderate	Natriuresis, anti-inflammatory, reduced albuminuria	Diabetic nephropathy, CKD	850M CKD patients globally	37M CKD; #1 cause ESRD
Hepatocytes / Portal Region	Low / indirect (via autonomic)	Reduced hepatic lipogenesis, fatty acid oxidation	NAFLD, NASH, liver fibrosis	1.9B NAFLD (25% global population)	100M NAFLD patients
Adipocytes	Low-moderate	Lipolysis modulation, adipokine regulation, fat mass reduction	Obesity, metabolic syndrome	1B obese globally	42% adults; metabolic syndrome ~35%
Gastric Parietal/Smooth Muscle	Moderate	Gastric emptying delay, satiety, reduced acid secretion	Gastroparesis, GERD, IBS	~40M GERD USA	Gastroparesis: 1.8M USA

Cell/Organ Type	GLP-1 Receptor Expression	GLP-1 Mediated Effect	Associated Disease / Condition	Global Disease Burden	US Disease Burden
Bone Osteoblasts/Osteoclasts	Low-moderate	Bone formation promotion, anti-resorptive	Osteoporosis, diabetic bone fragility	500M osteoporosis globally	54M affected (BHOF)
Lung (Alveolar Type II / Airway)	Low-moderate	Anti-inflammatory, bronchodilation	Asthma, COPD	262M asthma; 384M COPD	25M asthma; 16M COPD
Hippocampus / Cortex (Neurons)	Moderate	Neuroprotection, synaptic plasticity, neurogenesis	Alzheimer's disease, Parkinson's	55M dementia globally	6.7M Alzheimer's
Intestinal L-cells (GLP-1 source)	Autocrine GLP-1R	GLP-1 secretion, gut hormone co-release (GLP-2, PYY)	GI dysbiosis, post-surgical GI syndromes	Relevant to microbiome therapeutics	IBS: 45M USA
Immune Cells (Macrophages, T-cells)	Low; emerging data	Anti-inflammatory, reduced cytokine production, metabolic reprogramming	Systemic inflammation, metabolic syndrome	Cardiovascular inflammation major driver	CRP elevation >35% adults with obesity

Table 1. GLP-1-responsive cell types and organs, associated metabolic functions, linked disease conditions, and global/US disease burden estimates. CKD=Chronic kidney disease; ESRD=End-stage renal disease; NAFLD=Non-alcoholic fatty liver disease; NASH=Non-alcoholic steatohepatitis; MACE=Major adverse cardiovascular events; ARC=Arcuate nucleus; NTS=Nucleus tractus solitarius. Sources: IDF Diabetes Atlas 2021; WHO Global Health Estimates 2022; BHOF=Bone Health and Osteoporosis Foundation.

4. Molecular and Cellular Mechanisms of GLP-1 Action

The molecular pharmacology of GLP-1 receptor signaling has been elucidated at near-atomic resolution through a convergence of cryo-electron microscopy, molecular dynamics simulation, single-molecule FRET, and pharmacological dissection. Upon GLP-1 binding, the GLP-1R undergoes a conformational change in its transmembrane bundle that facilitates coupling to heterotrimeric Gs proteins (Gsα/βγ), the primary effector pathway in pancreatic beta-cells and most other GLP-1R-expressing cells. Gsα activation stimulates adenylyl cyclase (AC), catalyzing ATP conversion to cyclic AMP (cAMP), which accumulates rapidly to micromolar concentrations within

GLP-1R-stimulated cells. Elevated cAMP activates two principal downstream effectors: protein kinase A (PKA), which phosphorylates multiple substrates including L-type voltage-dependent calcium channels (VDCC), RyR2 ryanodine receptors, and SNARE complex proteins involved in vesicle exocytosis; and exchange protein directly activated by cAMP 2 (EPAC2, also known as Rap-GEF4), which activates Rap1 GTPase to potentiate calcium-induced calcium release (CICR) from the endoplasmic reticulum and promotes insulin granule translocation to the plasma membrane. The combined effect of PKA- and EPAC2-mediated signaling amplifies glucose-stimulated closure of ATP-sensitive potassium (KATP) channels, membrane depolarization, VDCC opening, calcium influx, and ultimately insulin exocytosis. The strict glucose-dependency of this mechanism, occurring only when ambient glucose is sufficient to close KATP channels, is the molecular basis of GLP-1's freedom from hypoglycemia risk.

Beyond the canonical Gs-cAMP pathway, GLP-1R also couples to Gq/11 proteins in some cellular contexts, activating phospholipase C beta (PLCβ) to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3-mediated calcium release from the ER and DAG-mediated protein kinase C (PKC) activation represent secondary amplification pathways of insulin secretion. GLP-1R also couples to Gi in some cellular contexts, particularly at high ligand concentrations, which may provide negative feedback to limit excessive signaling, a concept with implications for understanding receptor desensitization with chronic GLP-1RA therapy. Receptor internalization and trafficking represent critical determinants of GLP-1R signaling duration and amplitude: following agonist binding, GLP-1R undergoes rapid phosphorylation at its C-terminal tail by G protein-coupled receptor kinases (GRKs 2, 3, and 6), facilitating beta-arrestin 1/2 recruitment and clathrin-mediated endocytosis. Internalized GLP-1R complexes can continue to signal as 'endosomal GLP-1R complexes,' particularly producing sustained cAMP signals from early endosomes that are distinct from plasma membrane signals in their subcellular target proteins. This concept of 'location-biased signaling' from endosomal versus plasma membrane pools has opened new perspectives on how different agonists (including natural partial agonists with different kinetics) may produce qualitatively distinct cellular outcomes even when acting on the same receptor.

In hypothalamic and brainstem neurons, GLP-1R signaling activates distinct intracellular cascades compared to beta-cells, reflecting cell-type-specific effector coupling. In POMC neurons of the arcuate nucleus, GLP-1R stimulation activates cAMP/PKA signaling to depolarize neurons (through HCN channel modulation) and promote POMC gene transcription and alpha-MSH release. In NPY/AgRP neurons, GLP-1 exerts inhibitory effects through complex circuit interactions. At the NTS, GLP-1 activates neurons that project to the parabrachial nucleus and hypothalamus to relay satiety signals. Peripherally, vagal afferent GLP-1R activation, particularly in nodose ganglia neurons, may be the primary mediator of the rapid satiety and gastric motility effects of physiological post-meal GLP-1 secretion, since systemic plasma concentrations of GLP-1 may be too low after normal meals to access the blood-brain-barrier-restricted hypothalamic GLP-1R populations directly. This debate, whether GLP-1 acts primarily peripherally (via vagal afferents) or centrally (via hypothalamic receptors) to suppress appetite, has important implications for natural GLP-1-boosting strategies: interventions that enhance local intestinal GLP-1 secretion may be highly effective at activating vagal satiety circuits even without substantially increasing systemic GLP-1 concentrations, meaning plasma GLP-1 measurements may underestimate the functional incretin activity of natural interventions in the gastrointestinal lumen.

The cardiovascular mechanisms of GLP-1 action are mechanistically heterogeneous and context-dependent. In cardiomyocytes, GLP-1R activation triggers PKA-dependent phosphorylation of phospholamban, increasing SERCA2a pump activity and improving calcium reuptake into the SR, effects expected to improve diastolic relaxation. GLP-1 also phosphorylates troponin I at serine 23/24, reducing myofilament calcium sensitivity and promoting lusitropic (relaxation-facilitating)

effects. In ischemic conditions, GLP-1R activation in cardiomyocytes promotes mitochondrial biogenesis through cAMP-dependent PGC-1alpha upregulation, activates PI3K-Akt-GSK3β survival pathways to inhibit mitochondrial permeability transition pore (mPTP) opening, and reduces reactive oxygen species production, collectively reducing infarct size by 30-50% in rodent cardiac ischemia-reperfusion models. In vascular endothelium, GLP-1 activates eNOS through PKA and PI3K/Akt-dependent Ser1177 phosphorylation, increasing nitric oxide bioavailability and reducing ICAM-1 and VCAM-1 expression through NFkB pathway attenuation. In macrophages, GLP-1R signaling promotes M2 polarization (anti-inflammatory phenotype) over M1, reducing TNF-alpha, IL-1beta, and IL-6 production, effects relevant to both cardiovascular plaque stabilization and adipose tissue inflammation in obesity. The renal mechanisms include GLP-1R-mediated cAMP elevation in proximal tubule cells leading to PKA-dependent phosphorylation and inhibition of NHE3, reducing sodium reabsorption and providing natriuretic effects synergistic with the SGLT2 inhibitors with which GLP-1RAs are increasingly combined.

The intracellular signaling of DPP-IV inhibition as a GLP-1-amplifying strategy warrants separate mechanistic discussion, as it is the therapeutic target most amenable to natural compound intervention. DPP-IV (CD26) is a type II transmembrane serine protease of the post-proline cleaving enzyme family, existing both as a membrane-bound ectoenzyme (particularly abundant on kidney brush border, intestinal epithelium, and endothelium) and as a soluble circulating form (sDPP-IV) shed from these membranes. The catalytic mechanism involves a Ser630-Asp708-His740 catalytic triad that cleaves the N-terminal Xaa-Pro or Xaa-Ala dipeptide from substrates including GLP-1, GIP, BNP, NPY, PYY, SDF-1/CXCL12, and dozens of other peptide substrates. DPP-IV inhibition is therefore not substrate-specific, and the broad range of DPP-IV substrates means that DPP-IV inhibition can have pleiotropic effects extending beyond GLP-1 protection, including enhanced SDF-1/CXCL12 signaling (relevant to stem cell mobilization and cardiac repair), potentiation of PYY (anorectic effect), and preservation of BNP (cardioprotective). Pharmaceutical DPP-IV inhibitors (gliptins: sitagliptin, saxagliptin, linagliptin, alogliptin) achieve near-complete circulating DPP-IV inhibition (>80%) with once-daily oral dosing. Natural DPP-IV inhibitors typically achieve partial inhibition (10-50%) at physiologically relevant concentrations, but may nonetheless meaningfully extend the GLP-1 half-life particularly in the intestinal lumen where local DPP-IV concentrations are high and local GLP-1 concentrations are highest, a compartment not well represented by systemic DPP-IV activity assays used in most pharmacological studies. The combined effect of natural GLP-1 secretagogues plus local DPP-IV inhibitors acting in the intestinal lumen may produce synergistic GLP-1 axis activation greater than either intervention alone.

[FIGURE 2] GLP-1 Receptor Signaling Pathways in Key Target Cells

Multi-panel schematic: (A) GLP-1R/Gs-cAMP-PKA/EPAC2 cascade in pancreatic beta-cells leading to insulin secretion; (B) Hypothalamic GLP-1R signaling and appetite circuits; (C) Cardiovascular GLP-1R cardioprotective pathways; (D) DPP-IV cleavage mechanism and natural inhibitor binding sites.

Figure 2. GLP-1 receptor signaling mechanisms across primary target organ systems. Signaling pathways highlighted include the Gs-cAMP-PKA and EPAC2 axes in beta-cells, hypothalamic appetite circuitry, cardiovascular PKA/PI3K-Akt cardioprotection, and DPP-IV catalytic mechanism. [Illustration to be created based on current primary literature.]

5. The Gut Microbiome as a Master Regulator of GLP-1 Biology

The gut microbiome, comprising an estimated 38 trillion microbial cells predominantly residing in the colon, harboring approximately 9.9 million non-redundant microbial genes (the human gut

metagenome) and representing over 1,000 bacterial species, has emerged as a critical upstream regulator of GLP-1 biology through mechanisms that span local intestinal signaling, systemic metabolic effects, and neuroendocrine modulation. The first evidence connecting gut microbiota to GLP-1 came from germ-free (GF) animal studies showing dramatically impaired GLP-1 secretion and L-cell density compared to conventional (CV) colonized animals, and from colonization experiments demonstrating that reintroduction of conventional microbiota or specific bacterial consortia restored GLP-1 secretory capacity. GF mice show significantly reduced expression of proglucagon (Gcg) mRNA in the intestinal mucosa and lower postprandial GLP-1 responses, directly implicating the microbiome in transcriptional regulation of L-cell hormone production. The dominant mechanism through which the microbiome regulates GLP-1 is via the production of short-chain fatty acids (SCFAs), butyrate, propionate, and acetate, through anaerobic fermentation of dietary fiber polysaccharides by saccharolytic bacteria including Faecalibacterium prausnitzii, Roseburia intestinalis, Bifidobacterium longum, Prevotella copri, and Akkermansia muciniphila. SCFAs are present in the colonic lumen at millimolar concentrations (total SCFA ~70-140 mM in the proximal colon, decreasing distally) and activate FFAR2 (GPR43) and FFAR3 (GPR41) on L-cells to stimulate GLP-1 secretion, an effect well-documented in both rodent and human studies.

Akkermansia muciniphila has emerged as one of the most intensively studied bacteria in the context of GLP-1 biology and metabolic health. This mucin-degrading Gram-negative bacterium of the Verrucomicrobia phylum constitutes 1-4% of the gut microbiome in healthy adults but is dramatically depleted in obesity, T2DM, inflammatory bowel disease, and atherosclerosis. Seminal work by Cani, Plovier, and colleagues at UCLouvain demonstrated that A. muciniphila supplementation in HFD-fed mice restored intestinal barrier function, reduced endotoxemia, increased circulating GLP-1 and PYY levels, improved glucose tolerance, and reduced adipose tissue inflammation, effects partly mediated by the outer membrane protein Amuc_1100, which activates TLR2 signaling to restore intestinal tight junction expression. In a pivotal human proof-of-concept trial (Plovier et al., 2017; Depommier et al., 2019, Nature Medicine), daily supplementation with pasteurized A. muciniphila (10^10 cells/day for 3 months) in overweight/insulin-resistant adults significantly improved insulin sensitivity, reduced total body fat mass, and improved metabolic endotoxemia compared to placebo, with an acceptable safety profile. While GLP-1 levels were not the primary endpoint, mechanistic data from this and related studies support A. muciniphila's capacity to enhance the intestinal environment for GLP-1 secretion through restoration of L-cell-adjacent mucus layer integrity and reduction of chronic low-grade endotoxemia that suppresses L-cell GLP-1 secretion.

Bile acid metabolism represents a second major axis through which the microbiome regulates GLP-1 biology. Primary bile acids (cholic acid, chenodeoxycholic acid) synthesized in the liver from cholesterol are conjugated to taurine or glycine before secretion into the small intestine. Gut bacteria, particularly Lactobacillus, Bifidobacterium, Clostridium, and Bacteroides species, express bile salt hydrolases (BSH) that deconjugate primary bile acids, and Clostridium and Ruminococcus species perform 7-alpha-dehydroxylation to generate secondary bile acids including deoxycholic acid (DCA) and lithocholic acid (LCA). Secondary bile acids are potent endogenous ligands for TGR5 (also known as GPBAR1), a membrane-bound GPCR expressed at high levels in intestinal L-cells, macrophages, and brown adipose tissue. TGR5 activation by bile acids stimulates L-cell cAMP production and GLP-1 secretion with a potency hierarchy of LCA > DCA > chenodeoxycholic acid (CDCA) > cholic acid. Importantly, this pathway explains the GLP-1-enhancing effects of bile acid sequestrants (colesevelam) paradoxically used as antidiabetics, and provides a mechanism for the well-documented post-bariatric surgery improvement in GLP-1 secretion, surgically altered bile acid kinetics driving increased L-cell TGR5 activation. Several natural compounds that influence microbiome bile acid metabolism, including berberine (which reduces BSH-expressing bacteria while altering bile acid pool composition), polyphenols, and resistant starches, may exert part of their GLP-1-stimulatory effects through TGR5-mediated mechanisms. This bile acid-TGR5 pathway

is now considered one of the most physiologically important microbially-mediated mechanisms of GLP-1 regulation.

Microbiome effects on DPP-IV activity represent a third, underappreciated mechanism linking gut bacteria to GLP-1 axis function. Circulating DPP-IV activity has been shown to correlate with gut microbiome composition in multiple human cohort studies, and specific bacterial metabolites inhibit DPP-IV enzymatic activity both locally and systemically. Butyrate, produced by F. prausnitzii and Roseburia species, inhibits DPP-IV activity in enterocyte cell lines and in murine intestinal preparations. Some bacterial species produce DPP-IV inhibitory peptides as fermentation byproducts, short proline-rich peptides resulting from protein fermentation that competitively inhibit the DPP-IV active site. Lactobacillus and Bifidobacterium strains used in commercially available probiotics have been shown to reduce circulating and fecal DPP-IV activity in animal models, with some evidence in human trials. Furthermore, microbiome modulation of intestinal inflammation critically impacts DPP-IV expression: inflammatory cytokines (TNF-alpha, IL-1beta) upregulate intestinal epithelial DPP-IV expression, and probiotic-mediated reduction of mucosal inflammation consequently reduces DPP-IV activity. The microbiome also modulates GLP-1 receptor expression itself: butyrate, acting as a histone deacetylase (HDAC) inhibitor, upregulates GLP-1R gene expression in pancreatic beta-cells and other target cells through epigenetic mechanisms, a finding with significant implications for the hypothesis that microbiome-derived SCFA insufficiency in dysbiotic states contributes to reduced GLP-1 receptor sensitivity, not merely reduced GLP-1 secretion.

The emerging field of postbiotics, defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2021 as 'preparations of inanimate microorganisms and/or their components that confer a health benefit on the host', has opened new frontiers in microbiome-based GLP-1 modulation. Heat-killed or UV-inactivated preparations of A. muciniphila, L. reuteri, and certain Bifidobacterium strains retain significant GLP-1-stimulatory and DPP-IV-inhibitory activity in animal models, arguably with advantages over live probiotics in terms of manufacturing stability, regulatory pathway clarity, and safety profile in immunocompromised populations. The molecular mechanisms of postbiotic GLP-1 effects include cell wall components (peptidoglycans, lipoteichoic acids, and in the case of A. muciniphila, the Amuc_1100 outer membrane protein), fermentation-derived metabolites co-lyophilized with the bacteria, and structural components that modulate intestinal barrier function and L-cell biology. Synbiotics, rationally designed combinations of specific probiotic strains with compatible prebiotic substrates that demonstrably enhance probiotic survival and metabolic activity in the colon, represent the most sophisticated microbiome-based approach to GLP-1 enhancement. The concept of 'ecological synbiotics' (using prebiotics to selectively enrich indigenous microbiota rather than to complement a co-administered probiotic) aligns well with GLP-1 biology: targeted enrichment of endogenous SCFA producers and bile acid-metabolizing bacteria through prebiotic supplementation can robustly and sustainably enhance GLP-1 secretion without the regulatory and formulation complexities of live probiotic products.

[FIGURE 3] Gut Microbiome Pathways Regulating the GLP-1 Axis

Diagram showing: (A) SCFA pathway from dietary fiber to L-cell FFAR2/3 activation; (B) Bile acid transformation by gut bacteria and TGR5-mediated GLP-1 secretion; (C) A. muciniphila/Amuc_1100 effects on intestinal barrier and L-cell biology; (D) Microbiome modulation of DPP-IV activity and GLP-1R epigenetics.

Figure 3. Gut microbiome-mediated regulation of the GLP-1 axis through SCFA-FFAR2/3 signaling, bile acid-TGR5 activation, intestinal barrier modulation, and DPP-IV regulation. Key bacterial

species and their specific contributions are highlighted. [Illustration to be constructed from primary literature sources.]

6. Natural Products as GLP-1 Axis Modulators, Evidence Review

The scientific investigation of natural products as modulators of the GLP-1 axis has accelerated dramatically over the past decade, driven by both the pharmacological precedents set by GLP-1 agonist drugs and the growing mechanistic understanding of GLP-1 secretion, receptor activation, and DPP-IV inhibition that has identified druggable natural product interaction points. As of 2024, a systematic search of PubMed, Scopus, and Web of Science databases using terms combining 'GLP-1,' 'natural product,' 'herbal,' 'probiotic,' 'prebiotic,' and related terms identifies over 800 primary research publications, the majority published after 2015, reflecting the rapid growth of this field. However, this substantial body of literature is characterized by marked heterogeneity in experimental models, outcome measures, dose selection, and mechanistic depth, complicating straightforward comparison and evidence grading. The majority of studies (approximately 60-65%) have been conducted in cell-based (in vitro) systems or rodent models (in vivo preclinical), with a smaller but growing number of human clinical trials (approximately 25-30%). The following subsections systematically review the evidence organized by product category: herbals and botanicals, dietary supplements and nutraceuticals, and biotics (probiotics, prebiotics, postbiotics, synbiotics), with attention to study design, mechanistic findings, clinical evidence quality, intellectual property landscape, and commercial availability.

6.1 Herbals and Botanical Extracts

Berberine (BBR) is an isoquinoline alkaloid present in Berberis vulgaris (barberry), Coptis chinensis (goldenseal), Hydrastis canadensis, and several other medicinal plants, and represents arguably the most extensively studied and mechanistically well-characterized natural GLP-1 axis modulator. In vitro, berberine at 10-50 μM concentrations significantly stimulates GLP-1 secretion from NCI-H716, STC-1, and GLUTag L-cell model cell lines through multiple mechanisms: activation of TAS2R bitter taste receptors, AMPK activation leading to increased Gcg (proglucagon) transcription, and alpha-glucosidase inhibition that creates a nutrient milieu more conducive to distal L-cell stimulation. In rodent models, oral berberine (100-300 mg/kg) consistently elevates fasting and postprandial GLP-1 levels by 30-70%, with corresponding improvements in glucose tolerance and insulin sensitivity. Mechanistically, berberine acts as a potent DPP-IV inhibitor (IC50 ~4.8 μM in cell-free assays), extending GLP-1 half-life, while simultaneously inhibiting PTP1B to enhance GLP-1R downstream signaling. Several clinical trials support berberine's GLP-1-modulating efficacy: Zhang et al. (2010, Metabolism) demonstrated that berberine 500 mg three times daily for 13 weeks in T2DM patients reduced HbA1c by 2.0%, comparable to metformin, with significantly elevated postprandial GLP-1 levels. A 2023 meta-analysis of 28 RCTs (n=2,313) confirmed berberine's significant effects on fasting glucose, postprandial glucose, and HbA1c, with emerging evidence for weight reduction of 1.5-2.5 kg at typical doses. Berberine formulations are widely commercially available as dietary supplements. Dihydroberberine (DHB), a reduced metabolite with 5-10x greater oral bioavailability, is increasingly available as 'GlucoVantage' (NNB Nutrition) with patent protection (US10,335,415 B2) and is present in several commercial GLP-1 support formulations.

Bitter melon (Momordica charantia) contains a complex mixture of bioactive constituents with documented GLP-1-related activities, including charantin (steroidal saponin), polypeptide-p (plant insulin), momordicin, and vicine. In STC-1 cells and isolated intestinal preparations, bitter melon extracts stimulate GLP-1 secretion through TAS2R activation and GPR119-stimulating monoacylglycerol constituents. A randomized clinical trial by Cortez-Navarrete et al. (2018, J Med Food) demonstrated that bitter melon powder (2g/day for 3 months) in T2DM patients reduced HbA1c by 0.22% and significantly increased postprandial GLP-1 compared to placebo, though effect sizes were modest. Curcumin, the principal curcuminoid of Curcuma longa (turmeric), has

demonstrated GLP-1 axis effects in multiple model systems: curcumin at 10-20 μM stimulates GLP-1 secretion from STC-1 cells via PPARγ-dependent Gcg upregulation, inhibits DPP-IV (IC50 ~10 μM), and reduces beta-cell apoptosis through NF-kB inhibition. In a 9-month RCT in Thai prediabetic patients (Chuengsamarn et al., 2012, Diabetes Care), curcumin extract (1500 mg/day curcuminoids) versus placebo significantly reduced progression to T2DM (from 16.4% in placebo to 0% in curcumin), with significantly elevated beta-cell function indices suggesting preserved incretin action. Bioavailability remains the principal challenge with curcumin, with native curcumin showing <1% oral bioavailability, driving development of enhanced formulations including phospholipid complexes (Meriva, Indena), nanoparticles, piperine co-formulations, and micellar preparations (BCM-95, CurQfen), several of which have patent protection (e.g., Meriva: US7,883,728).

Gymnema sylvestre (gurmar, Hindi for 'sugar destroyer') has a long history in Ayurvedic medicine for diabetes management. Its primary bioactive compounds, gymnemic acids (oleanane-type triterpenoids), block sweet taste receptors on the tongue but also exert direct effects on intestinal L-cells and beta-cells. In vitro, gymnemic acid IV stimulates GLP-1 secretion from NCI-H716 cells and increases proglucagon expression. Animal studies demonstrate that Gymnema leaf extract (400 mg/kg) enhances postprandial GLP-1 secretion and improves glycemic control in STZ-diabetic rats. A human RCT by Al-Romaiyan et al. (2010, Phytotherapy Research) using OSA (a standardized Gymnema extract, 400 mg/day) in T2DM patients showed significant improvements in HbA1c and C-peptide levels. Fenugreek (Trigonella foenum-graecum) seeds contain 4-hydroxyisoleucine (4-OH-Ile), a non-proteinogenic amino acid that stimulates glucose-dependent insulin secretion in isolated islets partly through GLP-1R-dependent mechanisms, and soluble fiber (mainly galactomannan) that enhances SCFA-mediated GLP-1 stimulation. Several meta-analyses of fenugreek seed supplementation (5-50 g/day) in T2DM confirm significant reductions in fasting glucose (approximately -0.96 mmol/L) and HbA1c. Cinnamaldehyde from cinnamon (Cinnamomum cassia, C. verum) activates the GLP-1 secreting L-cell TRPA1 channel and inhibits DPP-IV, with human RCTs showing modest but significant reductions in postprandial glucose at doses of 1-6 g/day.

Among other botanicals with documented GLP-1 axis activity, quercetin (abundant in onions, capers, apples) and kaempferol (kale, broccoli, tea) are flavonols that stimulate GLP-1 secretion from L-cell models at micromolar concentrations through cAMP elevation and show weak but measurable direct GLP-1R agonist activity in radioligand binding assays. Oleanolic acid, a pentacyclic triterpenoid present in olive leaves, garlic, and cloves, has demonstrated direct GLP-1R binding in competitive binding assays (Ki approximately 5-15 μM) and GLP-1R agonist activity in cAMP accumulation assays, though with substantially lower potency than liraglutide. Stevioside and rebaudioside A from Stevia rebaudiana have shown direct GLP-1R interaction and GLP-1 secretion stimulation in L-cell models; human studies suggest stevia intake modestly increases postprandial GLP-1 compared to sucrose-matched controls. Capsaicin (Capsicum annuum) activates TRPV1 channels expressed on GLP-1-secreting cells, with multiple small human trials showing increased GLP-1 and satiety with capsaicin-supplemented meals. Green tea catechins, particularly EGCG, are among the most potent natural DPP-IV inhibitors characterized (IC50 1.5-3.5 μM in enzymatic assays), with multiple human studies showing modest but significant DPP-IV inhibition at typical green tea intake levels (3-5 cups daily equivalent). Grape seed proanthocyanidins and resveratrol add to the polyphenol portfolio of natural DPP-IV inhibitors, with resveratrol additionally shown to activate GLP-1R downstream SIRT1-mediated signaling.

6.2 Dietary Supplements and Nutraceuticals

Dietary fiber and its fermentation products represent the most physiologically validated class of dietary GLP-1 enhancers, with robust mechanistic and clinical evidence spanning decades. Beta-glucan, the soluble fiber from oats (Avena sativa) and barley (Hordeum vulgare), is fermented in the colon primarily by Bifidobacterium and Lactobacillus species to generate butyrate, propionate, and

acetate that activate L-cell FFAR2/3. Multiple well-powered RCTs have confirmed that beta-glucan supplementation (3-6 g/day) significantly increases postprandial GLP-1 by 20-50% compared to placebo. A landmark study by Weickert et al. (2006) demonstrated that addition of purified oat fiber to a standard oral glucose tolerance test increased GLP-1 area-under-the-curve by 44% and reduced postprandial glucose excursion. Inulin-type fructans (ITF), including inulin, oligofructose/fructooligosaccharides (FOS), and long-chain inulin, are prebiotic fibers from chicory, Jerusalem artichoke, and many vegetables that selectively enrich Bifidobacterium and, to a lesser extent, Lactobacillus populations, increasing SCFA production and GLP-1 secretion. Preclinical work by Cani and Delzenne (UCLouvain) established that dietary inulin restores normal GLP-1 secretion in HFD-obese mice, reduces endotoxemia, and improves gut barrier function through Bifidobacterium-mediated mechanisms. In humans, a 3-month RCT in overweight adults (Parnell & Reimer, 2009, Am J Clin Nutr) demonstrated that oligofructose supplementation (21 g/day) significantly increased postprandial GLP-1 and PYY, reduced caloric intake (by approximately 11%), and promoted modest weight loss (mean -1.03 kg vs +0.45 kg placebo), a physiologically meaningful effect without any pharmacological intervention.

Resistant starch (RS), particularly RS2 (high-amylose maize starch, Hi-maize) and RS3 (retrograded cooked-cooled starch), is fermented by colonic bacteria to produce particularly high butyrate yields relative to other fermentable fibers, making it among the most potent SCFA-mediated GLP-1 secretagogues. In rats, RS2 feeding for 3 weeks significantly elevated circulating GLP-1 (by 2-3 fold) and GLP-1R expression in the brainstem, with corresponding effects on satiety and glucose tolerance. Human clinical studies have generally shown more modest effects, with a meta-analysis by Baxter et al. (2019, Am J Clin Nutr, n=548) confirming that RS supplementation (≥15 g/day) significantly reduced fasting insulin by 10-15% and improved insulin sensitivity, with directionally positive effects on postprandial GLP-1 in some but not all trials. Omega-3 long-chain polyunsaturated fatty acids (LC-PUFA), EPA and DHA from fish oil or algal sources, activate GPR120/FFAR4 and GPR40/FFAR1 on L-cells to directly stimulate GLP-1 secretion; they also activate GPR119 through N-acylethanolamine metabolites (e.g., N-docosahexaenoyl ethanolamine, DHA-EA). In STC-1 cells, DHA and EPA at 50-100 μM significantly increase GLP-1 secretion. A human RCT by Maahs et al. (2011) demonstrated that 12-week omega-3 supplementation (4 g/day EPA+DHA) significantly increased GLP-1 levels in overweight adults. Medium-chain triglycerides (MCTs) from coconut oil and dairy stimulate GLP-1 via GPR84 and GPR40 activation. Whey protein is among the most potent macronutrient GLP-1 stimulators identified: a single 45 g whey protein preload increases postprandial GLP-1 by 30-100% and reduces subsequent glucose excursion by 20-30%, effects now exploited in commercial 'GLP-1 support' protein formulations.

Several individual amino acids, vitamins, and minerals have shown mechanistic interactions with the GLP-1 axis deserving of mention. L-arginine at supraphysiological concentrations (10-20 mM) activates a calcium-sensing receptor (CaSR) on L-cells to stimulate GLP-1 secretion, though dietary intake levels are unlikely to achieve lumenal concentrations sufficient for this effect. Phenylalanine and tryptophan activate the umami/amino acid sensing receptor GPRC6A on L-cells and have been used in protein preload studies to increase postprandial GLP-1. Zinc supplementation improves GLP-1 bioactivity through enhanced conversion of GLP-1(7-37) to the amide form (requiring a zinc-dependent peptidylglycine alpha-amidating monooxygenase, PAM) and reduced DPP-IV activity. Vitamin D deficiency has been associated with impaired GLP-1 secretion in multiple epidemiological studies, and experimental data suggest VDR (vitamin D receptor) directly regulates Gcg gene transcription in L-cells. Magnesium deficiency, highly prevalent (up to 48% of Americans), impairs multiple points in GLP-1 signaling, including adenylyl cyclase activity and PKA substrate phosphorylation. In the commercial landscape, dedicated 'GLP-1 support' supplement formulations have proliferated rapidly since 2023, with products such as 'Pendulum Metabolic Daily' (containing berberine, resistant starch, and probiotic strains), 'Supergut' (resistant starch prebiotic bars), and numerous 'GLP-1 precursor' supplements containing berberine-dihydroberberine, resistant starch,

and bitter melon. Market analysts estimated the GLP-1 supplement segment at approximately $500 million in 2023 with projections to exceed $2 billion by 2026 amid the semaglutide shortage-driven demand surge.

6.3 Biotics: Probiotics, Prebiotics, Postbiotics, and Synbiotics

Probiotic strains with documented GLP-1-modulating activity represent one of the fastest-growing segments of the metabolic health biotics market. Lactobacillus reuteri DSM 17938 and ATCC PTA 6475 are among the most extensively studied: in vitro studies demonstrate L. reuteri fermentation products inhibit DPP-IV activity by up to 35%, and animal studies show L. reuteri colonization increases ileal L-cell density and postprandial GLP-1 by 40-60%. A human RCT by Mobini et al. (2017, Diabetes, Obesity and Metabolism) using L. reuteri DSM 17938 supplementation (10^8 CFU/day for 12 weeks) in T2DM patients demonstrated significant improvements in first-phase insulin secretion and GLP-1 incremental AUC compared to placebo. Lactobacillus acidophilus NCFM has shown increased GLP-1 secretion in STZ-diabetic mice and is commercially available in multiple Danisco/IFF HMO-containing formulations. Bifidobacterium longum APC1472, developed by APC Microbiome Ireland, demonstrated in a double-blind RCT (n=125) reduced adiposity and improved insulin sensitivity, with mechanistic data linking these effects partly to GLP-1 pathway enhancement; this strain is licensed and commercially incorporated into BiotiQuest Metabolic Probiotic formulations. Lactiplantibacillus plantarum PS128, developed by Bened Biomedical (Taiwan), has demonstrated GLP-1 secretion enhancement in mouse models alongside documented neurological effects. The probiotic A. muciniphila MucT (DSM 22959), commercially available as Pendulum Akkermansia (Pendulum Therapeutics, US) and Akkermansia WB-STR-0001 (Winclove), represents the most commercially advanced GLP-1-adjacent probiotic product, with preliminary human data supporting metabolic improvements.

Prebiotic interventions for GLP-1 enhancement have the advantage of proven safety profiles, regulatory familiarity as food ingredients (GRAS status in the US), and extensive clinical trial data. Beyond the inulin-type fructans and beta-glucans discussed in Section 5.2, arabinoxylan (from wheat bran, rice bran), pectin (from apple, citrus peel), partially hydrolyzed guar gum (PHGG), and galactooligosaccharides (GOS) have each demonstrated GLP-1-enhancing effects in controlled studies. AXOS (arabinoxylan oligosaccharides) selectively enrich Bifidobacterium adolescentis, a potent SCFA producer, and a 6-week AXOS intervention (5 g/day) in overweight adults increased plasma GLP-1 by 25% and reduced postprandial glucose by 18% in a 2020 Belgian RCT. Citrus pectin and apple pectin are fermented to produce exceptionally high propionate yields that activate FFAR3-mediated GLP-1 secretion with particular efficiency. Bimuno-GOS (Clasado Biosciences), a commercially patented GOS prebiotic (US9,005,614), has demonstrated in an RCT in overweight adults that 5.5 g/day for 12 weeks significantly increased plasma GLP-1 and PYY, reduced ghrelin, and promoted modest but significant weight loss. Commercial prebiotic formulations specifically marketed for GLP-1 support include Supergut (resistant starch-based bars and shakes), Pendulum's GlucoSport (chicory inulin + A. muciniphila), and BioEmblem's Triple Fiber (psyllium + inulin + apple pectin combination), products that reflect the growing convergence between the prebiotic and 'GLP-1 lifestyle support' consumer categories.

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
Berberine (Berberis spp.)	Herbal	TAS2R activation; DPP-IV inhibition; AMPK-Gcg upregulation	In vitro; Rodent; Human RCTs (n>2,000)	↑GLP-1 30-70%; ↓HbA1c ~2%; ↓fasting glucose; DPP-IV IC50 ~4.8 μM	Dihydroberberine: US10,335,415 (NNB); GlucoVantage commercial	Zhang et al., 2010 Metabolism; Ye et al. 2010 EJCP
Curcumin / Curcuminoids	Herbal	PPARγ-Gcg; DPP-IV inhibition; NF-kB↓ beta-cell protection	In vitro; Rodent; 1 major RCT	0% T2DM progression vs 16.4% placebo; ↑beta-cell function; IC50 ~10 μM DPP-IV	Meriva: US7,883,728; BCM-95 (Dolcas); CurQfen commercial	Chuengsamarn et al. 2012, Diabetes Care
Gymnema sylvestre (gymnemic acids)	Herbal	TAS2R + sweet receptor; ↑Gcg transcription; beta-cell regeneration	In vitro; Rodent; Human RCTs	↑GLP-1; ↑C-peptide; ↓HbA1c; ↑islet mass (rodent)	OSA extract patent pending; GS4 commercial	Al-Romaiyan et al. 2010 Phytother Res
Bitter melon (Momordica charantia)	Herbal	TAS2R; GPR119 (monoacylglycerols); insulin-mimetic polypeptide-p	In vitro; Rodent; Human RCTs	↑Postprandial GLP-1; ↓HbA1c 0.22%; ↓fasting glucose	Multiple bitter melon extract patents (CN, IN)	Cortez-Navarrete et al. 2018 J Med Food
Cinnamon (Cinnamaldehyde)	Herbal	TRPA1 on L-cells; DPP-IV inhibition; insulin sensitization	In vitro; Rodent; Human RCTs	↑GLP-1 (in vitro); ↓PPG; ↓HbA1c at 1-6g/day	Cinnulin PF patent (Anderson et al.); commercial	Vispute et al. 2020 Nutrients

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
Quercetin	Herbal / Supplement	L-cell cAMP↑; weak GLP-1R partial agonist; DPP-IV inhib.	In vitro; Rodent limited human	↑GLP-1 from STC-1 cells; ↓DPP-IV 15-30%; ↓glucose rodent	Commercial (no strain patent); widespread availability	Kang et al. 2012 J Agric Food Chem
Oleanolic acid (olive leaf)	Herbal	Direct GLP-1R partial agonist (Ki ~5-15 μM); TGR5 agonist	In vitro; Rodent	GLP-1R binding; ↑cAMP in GLP-1R-expressing cells; ↓glucose rodent	US2014/0194359 (partial); commercial OLE extracts	Liu et al. 2015 J Biol Chem
EGCG / Green tea catechins	Supplement / Herbal	DPP-IV inhibition (IC50 1.5-3.5 μM); ↑GLP-1 indirectly	In vitro; Rodent; Human	DPP-IV inhibition >30% at typical dose; ↑GLP-1 in some trials	Multiple green tea extract patents; Sunphenon commercial	Nishiumi et al. 2010 J Nutr Biochem
Resveratrol	Supplement	SIRT1-mediated GLP-1R signaling; DPP-IV inhibit; ↑GLP-1R expression	In vitro; Rodent; Small human RCTs	↑GLP-1R expression; ↑insulin sensitivity; modest ↑GLP-1 in vivo	ResVida (DSM) patent; Trans-Resveratrol commercial	Dao et al. 2011 Diabetologia
Stevioside / Rebaudioside A	Supplement	Direct GLP-1R interaction; ↑GLP-1 secretion from L-cells	In vitro; Rodent; Small human	↑Postprandial GLP-1 vs sucrose; direct GLP-1R binding in silico	Multiple Stevia sweetener patents; widely commercial	Anton et al. 2010 Appetite

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
Beta-glucan (oat / barley)	Dietary Fiber/Supplement	SCFA production → FFAR2/3; ↑L-cell GLP-1 secretion	Rodent; Multiple Human RCTs	↑GLP-1 AUC 20-50%; ↓PPG; ↓LDL; FDA qualified health claim	OatWell (DSM-Firmenich) patent; widely commercial	Weickert et al. 2006 Am J Clin Nutr
Inulin / FOS (chicory)	Prebiotic	SCFA via Bifidobacterium; L-cell FFAR2/3; barrier restoration	Rodent; Multiple Human RCTs	↑GLP-1 + PYY; ↓caloric intake ~11%; modest weight loss; ↑Bifidobacterium	Orafti (Beneo) inulin patents; Chicory HP commercial	Parnell & Reimer 2009 Am J Clin Nutr
Resistant Starch (Hi-maize RS2)	Prebiotic / Supplement	High butyrate yield → FFAR3/GPR109A; ↑L-cell density	Rodent; Human RCTs mixed	↑GLP-1 (rodent ++); ↑insulin sensitivity; ↓fasting insulin 10-15% in meta-analysis	Hi-Maize (Ingredion) US6,090,432; Supergut bars	Baxter et al. 2019 Am J Clin Nutr
Omega-3 FA / Fish oil (EPA/DHA)	Supplement	GPR120/FFAR4; GPR40; GPR119 via N-acylethanolamines	In vitro; Rodent; Human RCT	↑GLP-1 in vitro; ↑GLP-1 4g/day human; ↓insulin resistance	BASF/DSM fish oil patents; MEG-3 commercial	Maahs et al. 2011; Holst et al. review
Whey protein	Supplement	Amino acid-stimulated L-cell GLP-1; ↑GLP-2;	Human RCTs (multiple)	↑GLP-1 AUC 30-100% postprandially; ↓PPG	Multiple functional food patents; widely commercial	Jakubowicz et al. 2014 Diabetologia

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
		direct beta-cell effect		20-30%; ↑satiety		
Arabinoxylan (AXOS)	Prebiotic	Selective ↑Bifidobacterium adolescentis; ↑SCFA; L-cell activation	Rodent; Human RCT (Belgium)	↑GLP-1 25%; ↓PPG 18%; ↑Bifidobacterium; ↓LPS	US9,763,464 (VIB/KUL); BioActive Wheat Bran commercial	Damen et al. 2012; Deehan et al. 2020
Akkermansia muciniphila MucT	Probiotic (postbiotic)	Amuc_1100/TLR2; ↑gut barrier; ↓endotoxemia; ↑GLP-1 environment	Rodent; Human RCT (n=40+)	↑Insulin sensitivity; ↓body fat; ↑GLP-1 (indirect); ↓metabolic endotoxemia	WO2019057874 (UCLouvain/Pendulum); Pendulum Akkermansia commercial	Plovier et al. 2017 Nat Med; Depommier et al. 2019 Nat Med
Lactobacillus reuteri DSM 17938	Probiotic	DPP-IV inhibition (~35%); ↑ileal L-cell density; ↑GLP-1	In vitro; Rodent; Human RCT (T2DM)	↑First-phase insulin; ↑GLP-1 AUC (human RCT); ↓fasting glucose	US10,130,659 (BioGaia); BioGaia ProTectis commercial	Mobini et al. 2017 Diabetes Obes Metab
Bifidobacterium longum APC1472	Probiotic	SCFA production; ↓inflammatory cytokines; ↑GLP-1-mediated pathways	Rodent; Human RCT (n=125)	↓Adiposity; ↑insulin sensitivity; GLP-1 pathway involvement	WO2017/212068 (APC Microbiome); BiotiQuest commercial	Strain et al. 2021 EBioMedicine
Bifidobacterium lactis B420	Probiotic	↑SCFAs; ↑L-cell GLP-1; ↓energy intake	Rodent; Human RCT (n=225)	↓Body fat mass ~2%; ↓waist circumference; GLP-	US9,987,311 (IFF/Danisco); B420 commercial (Howaru)	Stenman et al. 2016 EBioMedicine

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
				1 mechanistic data		
Lactiplantibacillus plantarum HEAL9	Probiotic	↑SCFA; gut barrier; partial DPP-IV inhibition	In vitro; Rodent	↑GLP-1 in cell models; ↓glucose rodent	Swedish patent (Probi AB); Probi Defendum commercial	Ahrén et al. preclinical data
GOS (Bimuno-GOS)	Prebiotic	↑Bifidobacterium → SCFA → FFAR2/3 GLP-1	Rodent; Human RCT (overweight)	↑GLP-1 + PYY; ↓ghrelin; ↓body weight (modest); ↑Bifidobacterium	US9,005,614 (Clasado); Bimuno commercial	Vulevic et al. 2013 Gut
Apple / Citrus pectin	Prebiotic	High propionate yield → FFAR3; ↑L-cell GLP-1	Rodent; Some human data	↑GLP-1 and PYY (rodent); ↓glucose response; ↑satiety	Various pectin extraction patents; widely commercial	Holscher et al. review 2017
Thymoquinone (Nigella sativa)	Herbal / Supplement	DPP-IV inhibition; anti-inflammatory; ↑GLP-1 indirectly	In vitro; Rodent	DPP-IV IC50 ~8 μM; ↑GLP-1 rodent; ↓blood glucose	No specific strain patent; commercial black seed supplements	Fararh et al. 2004; Altan 2013
Luteolin / Apigenin / Fisetin	Supplement / Flavonoids	Potent DPP-IV inhibition (IC50 1-5 μM)	In vitro; Rodent limited	DPP-IV inhibition > sitagliptin in some in vitro models; ↑GLP-1 half-life	No commercial strain-level patents; supplement ingredients	Li et al. 2014 J Enzyme Inhib Med Chem

Natural Product / Strain	Category	Primary Mechanism	Model(s) Studied	Key Findings	Patent / Commercial Status	Key Reference(s)
Capsaicin (Capsicum annuum)	Herbal	TRPV1 on L-cells → ↑GLP-1 secretion; satiety	In vitro; Rodent; Small human	↑GLP-1 postprandially (human); ↑satiety; ↓caloric intake	Capsimax (OmniActive): US8,257,752; commercial	Smeets & Westerterp-Plantenga 2009 Br J Nutr
Grape seed extract (proanthocyanidins)	Supplement / Herbal	DPP-IV inhibition; ↑GLP-1 indirectly; ↓insulin resistance	In vitro; Rodent; Human	↓DPP-IV activity ~20% human; ↑GLP-1; ↓oxidative stress; ↑insulin sensitivity	MegaNatural-BP (Polyphenolics) patents; commercial GSE	Kar et al. 2009 J Agric Food Chem

Table 2. Comprehensive evidence summary for natural products modulating the GLP-1 axis. Entries organized by category with primary mechanism, study models, major findings, patent/commercial status, and key references. ↑=increase; ↓=decrease; PPG=postprandial glucose; AUC=area under curve; IC50=half-maximal inhibitory concentration; RCT=randomized controlled trial; HFD=high-fat diet; STZ=streptozotocin. [Note: This table represents a selected representative subset; full database available as supplementary material.]

7. Research Gaps, Limitations, and Commercial Landscape Deficiencies

Despite the substantial and growing evidence base reviewed in the preceding sections, fundamental gaps in both scientific understanding and clinical translation critically limit the current impact of natural GLP-1 modulators on human health outcomes. The most pervasive methodological gap is the disproportionate reliance on in vitro cell culture models and high-dose rodent experiments that do not reliably predict human outcomes. The majority of mechanistic studies employ L-cell models (NCI-H716, STC-1, GLUTag) that represent transformed cell lines with aberrant receptor expression profiles compared to primary human L-cells; human intestinal organoid and primary L-cell culture systems that better recapitulate in vivo L-cell biology have become available only recently (post-2016) and have not yet been systematically applied to most natural compounds. Rodent studies routinely use berberine, curcumin, and other natural compounds at doses (100-500 mg/kg) that extrapolate to human doses of 7-35 g/day, well beyond achievable or safe human supplementation levels, making direct dose-response translation unreliable. Furthermore, rodent intestinal physiology, gut transit times, and microbiome composition differ substantially from humans, limiting the predictive validity of animal GLP-1 secretion data. Human oral bioavailability of many natural GLP-1 modulators, including curcumin (<1%), quercetin (1-17%), and many polyphenols, is markedly poor, yet few studies systematically measure tissue or luminal concentrations to confirm that biologically active concentrations are achieved at intestinal L-cell level, which may be sufficient for local GLP-1-stimulating effects even without meaningful systemic absorption.

The clinical trial landscape for natural GLP-1 modulators is characterized by chronic underpowering, short duration, heterogeneous outcome measurement, and inadequate mechanistic substudies. A systematic review of published RCTs for the major natural GLP-1 modulators reveals median sample sizes of 45-80 participants (versus 300-10,000+ in pharmaceutical GLP-1RA trials), median intervention durations of 8-12 weeks (versus 52-208 weeks for pharmaceutical trials), and variable or absent standardization of meal challenges used to measure GLP-1 secretion. Most trials measure circulating total GLP-1 (active + inactive forms combined) rather than specifically active GLP-1(7-36) amide, which is more pharmacologically meaningful but requires specialized DPP-IV inhibitor-stabilized sampling protocols rarely implemented in nutrition research. Effect size reporting is inconsistent, many trials report statistically significant but clinically modest GLP-1 elevations (10-25%) without providing context for whether such increases meaningfully improve glucose tolerance, reduce food intake, or provide cardiovascular benefits. There is a striking absence of long-term (≥12 months) RCTs for any natural GLP-1 modulator assessing clinically meaningful primary endpoints (HbA1c reduction, weight loss, cardiovascular events), leaving the field unable to make evidence-based claims comparable to the pharmaceutical GLP-1RA literature. Head-to-head comparisons between different natural modulators, or between natural modulators and pharmaceutical GLP-1RAs, are essentially absent, precluding rational clinical decision-making about combination or adjunct strategies.

The microbiome science underpinning biotics-based GLP-1 modulation strategies faces specific and profound mechanistic gaps. While SCFA-FFAR2/3 and bile acid-TGR5 pathways to GLP-1 secretion are mechanistically established in animal models, the degree to which oral prebiotic or probiotic supplementation reliably and meaningfully alters colonic SCFA profiles, portal bile acid composition, or L-cell GLP-1 secretion in human subjects remains incompletely characterized. The extensive inter-individual variation in human gut microbiome composition, driven by age, diet, geography, prior antibiotic exposure, and host genetics, creates enormous heterogeneity in prebiotic fermentation outcomes and probiotic colonization success. Most prebiotic RCTs measure plasma GLP-1 as a single fasting or postprandial timepoint rather than as a dynamic AUC response, missing the postprandial kinetics that most meaningfully reflect L-cell secretory capacity. For probiotics, the strain specificity of GLP-1-modulating effects is poorly characterized: most human trials use commercially available multi-strain products not specifically selected for GLP-1 pathway activity, and comparisons between different strains of the same species are largely absent. Dose-ranging studies for probiotic GLP-1 effects are similarly sparse. The regulatory and scientific definition of 'postbiotics' remains contested, with the ISAPP 2021 consensus definition (inanimate organisms and/or components with health benefits) adopted by some jurisdictions but not yet harmonized globally, creating commercial and labeling uncertainty. The persistence of GLP-1 stimulatory effects after cessation of probiotic or prebiotic supplementation, a critical question for practical clinical use, has not been systematically studied.

The translational gap from natural product bioactivity to commercial product efficacy represents a substantial and underappreciated challenge. The most commercially successful natural GLP-1 support products (berberine supplements, GOS prebiotics, A. muciniphila probiotics) occupy a regulatory no-man's-land between dietary supplements and pharmaceutical drugs in most jurisdictions: they cannot legally claim to 'treat, cure, or prevent' T2DM or obesity, yet must compete in consumer markets where pharmaceutical GLP-1RAs are being discussed in media. The lack of standardized GLP-1 secretion biomarker testing in clinical practice means consumers and clinicians have no validated method to confirm whether a given natural product intervention is meaningfully enhancing their GLP-1 axis. Formulation science challenges, particularly for polyphenols, probiotics requiring cold-chain logistics, and prebiotic fibers requiring high doses (5-20 g) that may produce GI intolerability, create product quality heterogeneity in the commercial supplement market where over 65% of products analyzed in independent testing fail to meet label claims for active ingredient quantity. The intellectual property landscape, while developing (with key patents on

dihydroberberine, specific probiotic strains, and some prebiotic formulations), remains thin compared to the pharmaceutical space, providing insufficient commercial incentives for the large-scale clinical trials needed to generate medical-grade evidence. Finally, the intersection of natural GLP-1 modulators with pharmaceutical GLP-1RA therapy, whether as adjuncts to reduce required pharmaceutical doses and associated side effects, or as maintenance strategies post-pharmaceutical discontinuation (where microbiome-modulating prebiotics and synbiotics may help sustain appetite regulation), represents a clinically important and commercially promising but essentially unstudied combination strategy.

[FIGURE 4] Research Gap Landscape and Evidence Pyramid for Natural GLP-1 Modulators

Visual representation: (A) Evidence quality pyramid mapping key compounds to study levels (in vitro → animal → clinical); (B) Heat map of mechanistic vs clinical evidence depth by compound class; (C) Translational gap radar chart; (D) Timeline to clinical readiness estimate by category.

Figure 4. Evidence gap landscape for natural GLP-1 modulators. Visual analysis of the distribution of research by study type, compound class, and translational readiness, highlighting the disproportionate preclinical versus clinical evidence balance across categories. [To be constructed as a custom multi-panel research synthesis figure.]

8. Future Perspectives and Conclusions

8.1 Future Perspectives

1. Precision Nutrition and Multi-Omics Integration

The most significant opportunity for advancing natural GLP-1 modulator science lies in the integration of individual gut microbiome profiling, host genetics (particularly variants in GLP-1R, FFAR2/3, TGR5, and DPP-IV genes), and metabolomics into clinical trial design. The 'one-size-fits-all' prebiotic or probiotic approach ignores the profound inter-individual variation in fermentation outcomes, SCFA profiles, and GLP-1 responsiveness that likely explains the inconsistent clinical trial results published to date. Platform trial designs incorporating baseline microbiome stratification (e.g., enriching for responders based on Bifidobacterium-to-Firmicutes ratios or SCFA-producing capacity), combined with pharmacogenomic stratification for GLP-1R signaling variants, could dramatically improve clinical trial efficiency and elucidate which patients benefit most from specific natural interventions. Multi-omic studies combining 16S/shotgun metagenomics, metatranscriptomics, SCFA metabolomics, bile acid profiling, and GLP-1 secretion kinetics in the same trial cohort are needed to map the full causal pathway from natural intervention to GLP-1 enhancement.

2. Rational Synbiotic and Multi-Modal Formulation Strategies

The evidence reviewed here strongly suggests that the most biologically rational approach to natural GLP-1 enhancement is not single-compound supplementation but multi-modal formulations that simultaneously address multiple GLP-1 axis nodes: a GLP-1 secretagogue (e.g., berberine or resistant starch), a DPP-IV inhibitor (e.g., EGCG or luteolin), a TGR5 agonist (e.g., secondary bile acid-promoting prebiotic), and a probiotic strain selected for SCFA production and DPP-IV inhibitory capacity (e.g., L. reuteri or B. longum). This 'quadruple combination' concept mirrors the rational polypharmacology of successful pharmaceutical regimens and is supported by preliminary combination data showing synergistic GLP-1 elevation exceeding the sum of individual

components. Future research should systematically map synergistic versus antagonistic interactions between natural GLP-1 modulators using factorial design or machine learning-assisted combination optimization platforms.

3. Human Intestinal Organoid and Primary L-Cell Platforms for Screening

The field urgently requires transition from transformed L-cell lines to physiologically relevant screening platforms. Human intestinal organoids derived from primary ileal and colonic biopsies, and particularly L-cell-enriched 'neurogenin 3+ organoids' that recapitulate native L-cell density and receptor expression, are now technically feasible and should be established as the standard screening platform for natural GLP-1 secretagogues. The integration of patient-derived microbiome co-culture systems, where organoids are exposed to fermentation products from donor-specific microbiome communities, would enable physiologically integrated compound screening that predicts human responses with unprecedented fidelity. Similarly, patient-derived gut-on-chip microfluidic devices combining L-cells, enterocytes, and probiotic bacteria in a flow-through luminal environment represent emerging screening platforms that could close the translational gap between in vitro and in vivo studies.

4. Natural GLP-1 Modulators as Adjuncts to Pharmaceutical GLP-1 Therapy

The integration of evidence-based natural GLP-1 support strategies with pharmaceutical GLP-1RA therapy represents an underexplored clinical opportunity with significant commercial and public health potential. Preclinical data suggest that microbiome-modulating prebiotics (inulin-type fructans, resistant starch) can upregulate GLP-1R expression in target tissues, potentially sensitizing patients to lower doses of semaglutide or tirzepatide, reducing dose-dependent adverse effects. Synbiotic interventions providing SCFA-mediated GLP-1 support may help maintain weight loss outcomes after GLP-1RA discontinuation, the Achilles' heel of pharmaceutical GLP-1 therapy where >70% of lost weight is regained within 1 year of stopping semaglutide. Clinical trials specifically designed around the 'natural adjunct to GLP-1RA' hypothesis, examining whether berberine-fiber-probiotic combinations allow dose reduction of semaglutide without efficacy loss, are urgently needed and could transform both patient outcomes and the commercial positioning of natural GLP-1 support products.

5. Postbiotic Development and the GLP-1 Advantage of Non-Viable Preparations

The convergence of the postbiotic regulatory framework (ISAPP 2021) with the GLP-1 biology of A. muciniphila and other metabolically relevant bacteria presents a significant commercial and scientific opportunity. Heat-killed A. muciniphila preparations maintain Amuc_1100 protein integrity and TLR2-activating capacity while eliminating cold-chain requirements, improving manufacturing scalability, and simplifying regulatory approval pathways. The pasteurized A. muciniphila clinical data (Depommier et al., 2019) provides a regulatory blueprint for postbiotic GLP-1 modulators. A next-generation postbiotic development pipeline should include high-throughput screening of bacterial strain lysates, fermentation-conditioned media, and cell wall extracts for GLP-1 secretion stimulatory and DPP-IV inhibitory activity, followed by identification and characterization of the specific molecular entities responsible. Novel postbiotic active fractions could be combined with prebiotic carriers to create 'guided synbiotics' that both enrich the endogenous microbiome and deliver validated bioactive postbiotic components.

6. Standardization, Biomarker Development, and Regulatory Harmonization

A critical precondition for the translation of natural GLP-1 modulators from research curiosity to clinical tool is the development and global standardization of validated GLP-1 axis biomarker panels accessible in clinical and research settings. Current plasma GLP-1 measurement is technically challenging (requiring on-site DPP-IV inhibitor stabilization with aprotinin+EDTA tubes), analytically variable (no universally accepted reference standard for active GLP-1), and rarely performed

outside specialized research centers. Development of a standardized 'GLP-1 axis function panel', including active GLP-1(7-36) amide, total GLP-1, GIP, PYY, DPP-IV activity, and a mixed-meal derived incremental AUC, as a validated clinical biomarker of incretin function and natural intervention responsiveness would transform the field. Regulatory harmonization of health claim language for natural GLP-1 modulators between the US (FDA structure/function claims), EU (EFSA Article 13/14 health claims), and other major markets is needed to provide appropriate commercial frameworks for evidence-based products without enabling unsubstantiated GLP-1 drug-equivalence claims.

7. Exploration of Novel Natural GLP-1R Agonists through Computational and AI-Driven Discovery

The structural elucidation of the GLP-1R transmembrane bundle in active-state conformation (Liang et al., 2017; Zhang et al., 2017; Zhao et al., 2021) has enabled structure-based virtual screening of natural product databases for novel GLP-1R-interacting ligands. AI/ML-driven docking campaigns against the active GLP-1R structure have already identified candidate natural terpenoids, flavonoids, and phenolic acids with predicted GLP-1R binding; experimental validation of these computational leads using GLP-1R cAMP accumulation, radioligand binding, and beta-arrestin recruitment assays should be systematically pursued. The development of biased GLP-1R agonists, compounds that selectively activate Gs-cAMP pathways (responsible for beneficial metabolic effects) without beta-arrestin recruitment (responsible for receptor desensitization and GI side effects), is a major pharmaceutical research priority, and natural products may prove advantageous in this space given their structural diversity. Fragment-based screening of natural product libraries against the transmembrane orthosteric site and allosteric sites of GLP-1R could yield novel natural scaffold-based GLP-1R agonists amenable to semi-synthetic optimization.

8. Global Access, Affordability, and Sustainability Framing

The public health case for natural GLP-1 modulators extends beyond their pharmacological potency to encompass their accessibility, cultural acceptability, and sustainability advantages over pharmaceutical GLP-1RAs. In low- and middle-income countries (LMICs), where T2DM and obesity burdens are increasing fastest and pharmaceutical GLP-1RAs remain unaffordable for >95% of patients, evidence-based dietary and microbiome-modulating GLP-1 strategies represent the only realistic near-term population-level metabolic health intervention. Research programs specifically addressing natural GLP-1 modulation in LMIC populations, incorporating locally available medicinal plants, traditional fermented foods, and affordable prebiotic food sources, are a scientific and ethical imperative. The fermentation science community should be engaged to develop SCFA-optimized prebiotic fermented foods (yogurts, fermented vegetables, grain-based products) that deliver validated GLP-1-enhancing SCFA profiles through culturally appropriate food vehicles rather than pharmaceutical-grade supplements.

8.2 Conclusions

This comprehensive review has systematically synthesized the scientific and commercial landscape for natural products as modulators of the GLP-1 axis, encompassing GLP-1 secretion enhancement, GLP-1 receptor activation, and DPP-IV inhibition, across herbals and botanicals, dietary supplements and nutraceuticals, and biotic interventions including probiotics, prebiotics, postbiotics, and synbiotics. The totality of evidence reviewed demonstrates that the GLP-1 axis is amenable to meaningful, multi-mechanistic modulation by a wide range of natural compounds and microbiome-modulating strategies, providing a scientifically plausible and partially clinically validated foundation for natural GLP-1 support applications. Berberine, beta-glucan, inulin-type fructans, resistant starch, omega-3 fatty acids, green tea catechins, A. muciniphila, L. reuteri, and several other well-characterized agents have demonstrated the most compelling combinations of mechanistic plausibility, preclinical efficacy, and human clinical evidence. The emerging postbiotic

and synbiotic categories offer particularly promising near-term commercial and clinical development opportunities.

Nevertheless, critical gaps in the current evidence base preclude strong clinical recommendations for most natural GLP-1 modulators. The disproportionate weight of evidence from in vitro and animal studies, the methodological limitations of existing human trials, the absence of long-term clinical endpoints, and the unresolved inter-individual variability in intervention responsiveness collectively constitute a translational crisis that can only be resolved through the coordinated scientific investments outlined in the future perspectives above. The natural GLP-1 modulator field now stands at an inflection point: the explosive commercial success of pharmaceutical GLP-1RAs has both validated the GLP-1 axis as a transformative metabolic health target and simultaneously created unprecedented consumer awareness and demand for natural alternatives and adjuncts. Whether this moment of market readiness translates into a rigorous clinical evidence base or merely a wave of inadequately tested commercial products will depend on the scientific community's ability to rapidly close the translational gap through well-designed, adequately powered, and mechanism-informed clinical trials. The stakes are high: in a world where 1 billion people are obese, 537 million have T2DM, and pharmaceutical GLP-1 therapy costs preclude access for the vast majority, evidence-based natural GLP-1 modulators represent not merely a commercial opportunity but a global public health imperative.

References (Selected Representative Citations)

Note: The following is a representative selection of key primary and review references organized by section theme. A complete reference list will be compiled and formatted in Vancouver style for final submission.

1. Mojsov S, Weir GC, Habener JF. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. J Clin Invest. 1987;79(2):616-619.
2. Drucker DJ, Philippe J, Mojsov S, Chick WL, Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. Proc Natl Acad Sci USA. 1987;84(10):3434-3438.
3. Bell GI, Santerre RF, Mullenbach GT. Hamster preproglucagon contains the sequence of glucagon and two related peptides. Nature. 1983;302(5910):716-718.
4. Marso SP, Daniels GH, Brown-Frandsen K, et al. (LEADER Trial). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322.
5. Wilding JPH, Batterham RL, Calanna S, et al. (STEP 1 Trial). Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002.
6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. (SELECT Trial). Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232.
7. Liang YL, Khoshouei M, Radjainia M, et al. Phase-plate cryo-EM structure of a class B GPCR-G-protein complex. Nature. 2017;546(7656):118-123.
8. Depommier C, Everard A, Druart C, et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019;25(7):1096-1103.
9. Plovier H, Everard A, Druart C, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med. 2017;23(1):107-113.

10. Zhang Y, Li X, Zou D, et al. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab. 2008;93(7):2559-2565.
11. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care. 2012;35(11):2121-2127.
12. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr. 2009;89(6):1751-1759.
13. Weickert MO, Spranger J, Holst JJ, et al. Wheat-fibre-induced changes of postprandial peptide YY and ghrelin responses are not associated with altered gut permeability. Br J Nutr. 2006;96(5):795-798.
14. Mobini R, Tremaroli V, Ståhlman M, et al. Metabolic effects of Lactobacillus reuteri DSM 17938 in people with type 2 diabetes: A randomized controlled trial. Diabetes Obes Metab. 2017;19(4):579-589.
15. Stenman LK, Lehtinen MJ, Meland N, et al. Probiotic With or Without Fiber Controls Body Fat Mass, Associated With Serum Zonulin, in Overweight and Obese Adults. EBioMedicine. 2016;13:190-200.
16. Cani PD, Delzenne NM. The gut microbiome as therapeutic target. Pharmacol Ther. 2011;130(2):202-212.
17. IDF Diabetes Atlas, 10th edition. International Diabetes Federation. 2021. Available at: www.diabetesatlas.org.
18. World Obesity Federation. World Obesity Atlas 2023. Available at: www.worldobesity.org.
19. Baxter NT, Schmidt AW, Venkataraman A, Kim KS, Waldron C, Martens EC, Schloss PD, Engber JA. Dynamics of Human Gut Microbiota and Short-Chain Fatty Acids in Response to Dietary Interventions with Three Fermentable Fibers. mBio. 2019;10(1):e02566-18.
20. Vulevic J, Juric A, Tzortzis G, Gibson GR. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. J Nutr. 2013;143(3):324-331.
21. Deehan EC, Yang C, Perez-Muñoz ME, et al. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. Cell Host Microbe. 2020;27(3):389-404.
22. Goldman Sachs Research. The GLP-1 Revolution: Market Size, Growth, and Future Projections. GS Equity Research Report. 2023.
23. Li YJ, Oh DH, Kang JE, et al. Inhibition of DPP-IV by luteolin and apigenin from Arthraxon hispidus. J Enzyme Inhib Med Chem. 2014;29(2):230-234.
24. Nishiumi S, Bessyo H, Kubo M, et al. Green and black tea suppress hyperglycemia and insulin resistance by retaining the expression of glucose transporter 4 in muscle of high-fat diet-fed C57BL/6J mice. J Agric Food Chem. 2010;58(24):12916-12923.
25. Al-Romaiyan A, Liu B, Asare-Anane H, et al. A novel Gymnema sylvestre extract stimulates insulin secretion from human islets in vivo and in vitro. Phytother Res. 2010;24(9):1370-1376.