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Food-Derived Modulators of the TGR5–GLP-1 Axis: Mechanisms, Evidence, and Translational Limitations

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Abstract. Glucagon-like peptide-1 (GLP-1) is a gut hormone central to glucose-dependent insulin secretion, appetite regulation, and body weight control. The clinical success of GLP-1 receptor agonists has driven interest in food-derived compounds that may raise endogenous secretion, several of which act on the bile acid receptor TGR5. This review evaluates such compounds on a four-level framework, with receptor activation, GLP-1 secretion, TGR5 dependence, and in vivo effects under relevant models and routes presenting successive levels of evidence. Among these compounds, hesperetin and naringenin provide the most complete preclinical evidence; oleanolic acid exhibits strong mechanistic evidence in enteroendocrine cells but lacks in vivo evidence linking its effects to GLP-1; ursolic acid and nomilin satisfy only part of the pathway. No compound has been shown to raise GLP-1 through TGR5 in humans, and experimental doses correspond to supplement-scale rather than dietary exposure. These gaps, with the limited tissue selectivity of TGR5, determine whether the pathway can become a practical nutrition strategy.

Keywords: TGR5, GLP-1, food-derived compounds, type 2 diabetes, obesity

1. Introduction

Type 2 diabetes and obesity share disturbances in glucose regulation, insulin action, appetite, and energy balance, and GLP-1 is relevant to all four. Released mainly from intestinal L cells after eating, it enhances glucose-dependent insulin secretion and contributes to satiety. However, GLP-1 receptor agonists treat both conditions, but interest remains in ways to increase the body's own GLP-1 response. TGR5, also called G protein-coupled bile acid receptor 1, is expressed in intestinal L cells and links bile acid sensing to GLP-1 release [1, 2]; because several food-derived compounds activate this receptor, the TGR5–GLP-1 axis has been proposed as a dietary route to endogenous secretion. Whether that proposal holds depends on the strength of the evidence, as in vitro receptor activation does not establish a receptor-dependent GLP-1 response in vivo, much less an effect achievable through ordinary food. This review therefore evaluates how strong the evidence is for the compounds most often linked to TGR5, and what would be required before the pathway could be treated as a realistic nutritional strategy. Accordingly, compounds were selected because published work connects them to TGR5, to GLP-1 secretion, or to both, in studies reporting enough detail for that connection to be assessed.

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2. TGR5–GLP-1 axis and its regulatory mechanisms

2.1. TGR5 distribution and metabolic functions

TGR5 is a membrane G protein-coupled receptor activated by bile acids. It is expressed in intestinal enteroendocrine L cells, where activation promotes GLP-1 and peptide YY (PYY) secretion in response to nutrient intake [1]; both hormones contribute to postprandial glucose control and appetite regulation. Accordingly, a food-derived ligand would therefore need to reach intestinal L cells and activate the receptor before it could support an endogenous GLP-1 response. Beyond the intestine, TGR5 is expressed in other tissues, including the gallbladder, so an absorbed compound may also act beyond the intestine; exposure location influences biological effects as much as receptor potency [1].

2.2. Bile acid signaling and GLP-1 release

Bile acids act as signaling molecules as well as digestive detergents. Their ability to activate TGR5 depends on their structure, while the bile acid pool is shaped by hepatic synthesis, intestinal reabsorption, and microbial metabolism [1]. In L cells, TGR5 mainly couples to Gαs, activates adenylyl cyclase, and raises intracellular cAMP; early studies studies linked TGR5 activation to enhanced GLP-1 secretion and improved glucose regulation, while experiments in GLUTag cells and primary murine intestinal cultures showed that bile acid stimulation increases cAMP and promotes calcium-dependent secretion [2, 3]. Thus, receptor activation amplifies L cell secretion directly rather than raising circulating GLP-1 indirectly, and studies with oleanolic acid added an Epac/PLC-ε/Ca2+ pathway, knockdown reducing cAMP, GLP-1, and peptide YY responses [4]. GLP-1 elevation alone does not, however, establish causality; stronger evidence requires that the response be attenuated by TGR5 inhibition or loss of function.

3. Food-derived compounds associated with TGR5–GLP-1 regulation

Compounds are graded on four levels according to how far their published data close the chain between receptor and hormone. At the Level 1, TGR5 activation is shown in a reporter or transfected-cell assay, with no hormone measured. At the Level 2, measured GLP-1 secretion is added in an enteroendocrine model. At the Level 3, evidence is added that the secretion depends on TGR5, most securely through knockdown or knockout and less securely through pharmacological blockade. At the Level 4, an in vivo effect is required under an administration route and disease model relevant to dietary use. Each level presupposes the one before it, so a compound is placed at the highest level it satisfies without a gap. The level records how far the chain has been closed, not whether the exposure resembled a dietary one. Thus, compounds at the same level may differ in value due to different limitations.

3.1. Compounds with the strongest available evidence

Both compounds here carry loss-of-function evidence from TGR5 knockdown, placing them at Level 3 or above. However, they are not equivalent: hesperetin and naringenin also reach Level 4, with an oral in vivo effect in a diet-induced model, while the in vivo work on oleanolic acid predates the mechanistic studies and does not identify GLP-1 as the mediator.

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3.1.1. Oleanolic acid

Oleanolic acid, a pentacyclic triterpenoid widely distributed in edible and medicinal plants, was among the first food-related compounds reported to activate TGR5. Sato et al. isolated it from olive leaves and showed TGR5 activity in a reporter system without activating FXR [5]. After ten weeks of high-fat feeding, mice with metabolic abnormalities received oleanolic acid at 100 mg/kg/day, which lowered fasting glucose and insulin and partially improved glucose tolerance. However, marked increases in liver enzymes and bilirubin occurred in two of eight treated animals, leading the authors to consider this dose the upper limit of the pharmacological range [5]. However, the experiment supports metabolic activity without establishing intestinal GLP-1 signaling as the primary mediator.

More directly, a later enteroendocrine study provided more direct mechanistic evidence. In STC-1 cells, oleanolic acid activated Gαs, increased cAMP, stimulated phosphoinositide and Ca^{2+} signaling, and promoted GLP-1 and PYY release [4]. TGR5 knockdown reduced GLP-1 release by about 78%, PYY by about 88%, and the cAMP response by about 81%, while inhibition of PLC-ε or of intracellular Ca^{2+} strongly reduced secretion [4]. For oleanolic acid, the receptor–secretion link therefore rests on cellular evidence rather than on the original mouse data.

3.1.2. Hesperetin and naringenin

Hesperetin and naringenin are the most comprehensive preclinical example in this set. Notably, Zhang et al. screened a 1,561-compound traditional Chinese medicine library in a proglucagon reporter GLUTag model, then tested the selected flavanones in GLUTag cells and primary mouse ileal epithelial cells [6]; both increased GLP-1 secretion, cAMP, and intracellular calcium.

In 293T reporter cells, both activated human TGR5, with EC50 values of 0.17 μM and 0.45 μM, while reporter activity at other L cell-relevant receptors was much weaker or absent [6]. CETSA provided cellular target-engagement evidence for a direct flavanone–TGR5 interaction, and TGR5 siRNA in GLUTag cells sharply reduced the cAMP and GLP-1 responses to both compounds [6]. These findings link TGR5 activation to downstream signaling and GLP-1 secretion.

In vivo, a single oral dose of 100 mg/kg increased glucose-stimulated serum GLP-1 and improved glucose tolerance in high fat diet-induced diabetic mice, and pretreatment with the GLP-1 receptor antagonist Exendin-(9-39) attenuated the glucose-lowering effect [6]. In a separate four-week experiment, daily oral treatment reduced body weight gain and improved glucose and insulin tolerance, but food intake was also lower in the treated groups [6]. Without pair-fed or intake-matched controls, reduced body weight gain cannot be separated from reduced energy intake; the acute GLP-1 and glucose tolerance findings are unaffected, but the chronic weight outcome is consistent with, rather than demonstrative of, a GLP-1-mediated effect. The long-term dose was 100 mg/kg/day and normal citrus intake was not tested, so whether realistic food intake achieves the required intestinal exposure remains unclear.

3.2. Compounds with partial pathway evidence

Each compound in this group has a different evidence gap. Ursolic acid reaches Level 3, but its receptor dependence rests on pharmacological blockade rather than knockdown, and its in vivo evidence comes from a model and route without dietary relevance. Nomilin remains at Level 1, because GLP-1 was never measured, so its metabolic effects are not connected to the pathway under

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review. It is the nature of the missing step, not the size of the effect, that keeps both below the strongest tier.

3.2.1. Ursolic acid

Ursolic acid is present in foods such as apple peel, grape skin, cranberries, herbs, and spices. Lo et al. examined it in CHO-K1 cells transfected with human TGR5, measuring 2-NBDG glucose uptake and cAMP by ELISA [7]. Both increased concentration-dependently, with EC50 values near 4.19 and 4.18 μM, and neither response appeared in cells lacking transfected TGR5 [7]. The cAMP measurement is the informative readout here; CHO-K1 cells do not secrete GLP-1, so glucose uptake speaks to receptor engagement rather than to the enteroendocrine pathway.

In enteroendocrine models, ursolic acid increased active GLP-1 secretion, and in human NCI-H716 cells the TGR5 blocker triamterene reduced both cellular responses and GLP-1 release [7]. In vivo, it increased plasma GLP-1 and reduced glucose in streptozotocin (STZ)-induced diabetic rats, with both effects reduced by TGR5 blockade [7].

Although these findings support TGR5-dependent GLP-1 regulation, two limitations keep ursolic acid below the strongest evidence category. The in vivo work used STZ-induced, type 1-like diabetic rats, a model of insulin deficiency rather than the obesity-associated, insulin-resistant state in which a GLP-1-based dietary strategy would be applied. In addition, ursolic acid was given intraperitoneally rather than orally, bypassing the gut conditions needed for a food-derived compound to reach L cell TGR5. Besides, TGR5 dependence in vivo rested on pharmacological blockade rather than genetic loss of function. Current evidence therefore supports a TGR5-related mechanism but does not establish whether dietary ursolic acid produces similar effects.

3.2.2. Nomilin

Nomilin is a citrus limonoid with a distinct evidence profile. In HEK293 reporter cells it activated TGR5 dose-dependently without activating FXR [8]; the related limonoid obacunone was also active whereas limonin was not, indicating that activity varies among structurally related limonoids.

In high fat diet-fed mice, nomilin at 0.2% of the diet for 77 days was associated with lower body weight, serum glucose and insulin, reduced epididymal adipose tissue, and improved oral glucose tolerance [8]. Because an earlier experiment showed reduced food intake, pair-fed controls were included, and metabolic differences persisted at matched intake [8], so the effects were not explained by reduced energy intake alone. The evidence does not, however, establish a TGR5–GLP-1 mechanism: GLP-1 was not measured and TGR5 knockout models were not used [8]. Nomilin is therefore a food-derived TGR5 activator whose GLP-1 contribution remains unverified.

3.3. Compounds with receptor-level evidence

Corosolic acid and maslinic acid, pentacyclic triterpene acids identified from allspice and clove extracts, are representative TGR5 activators at this stage. Ladurner et al. showed reporter activation with EC50 values of approximately 0.5 and 3.7 μM, respectively, and reconstructed mixtures reproduced the activity of the source extracts [9]. However, GLP-1 secretion, TGR5-dependent signaling, and in vivo metabolic effects have not been evaluated, leaving the evidence at receptor level [9]. These profiles are summarized in Table 1.

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Table 1. Evidence profiles of representative food-derived TGR5 modulators

Compound and source	Evidence level	TGR5 evidence	GLP-1 / metabolic findings	Main limitation
Oleanolic acid / Olive leaves, spices	Level 3 (knockdown)	Reporter assay; TGR5 knockdown with cAMP and hormone readouts	GLP-1 and PYY release in enteroendocrine cells; improved glucose in HFD mice [4, 5]	In vivo GLP-1 mediation not shown; hepatic signals at 100 mg/kg/day
Hesperetin and naringenin / Citrus	Level 4	Human TGR5 reporter, CETSA target engagement, TGR5 siRNA	GLP-1 secretion in L cells and mice; improved glucose tolerance and weight gain [6]	Preclinical only; purified 100 mg/kg; weight result not intake-matched
Ursolic acid / Fruit skins, herbs	Level 3 (blockade only)	TGR5-transfected cells; cAMP; pharmacological blockade	Increased GLP-1 in NCI-H716 cells and STZ rats [7]	Type 1-like model; intraperitoneal route; blockade less specific than knockout
Nomilin / Citrus	Level 1	TGR5 reporter activity; no FXR activation	Lower weight, glucose, insulin; improved glucose tolerance in pair-fed mice [8]	GLP-1 not measured; TGR5 dependence not tested genetically in vivo
Corosolic and maslinic acids / Allspice, clove	Level 1	Reporter EC50 about 0.5 and 3.7 μM [9]	No GLP-1 or in vivo outcome reported [9]	Receptor-assay level only

4. Evidence assessment and nutritional translation barriers

4.1. Strength of the evidence and human research gap

Because each level presupposes the one before it, what a study licenses is fixed by the level it reaches. Docking or predicted binding sits below Level 1, identifying candidates without demonstrating activation or a biological effect [10]. Level 1 shows receptor engagement but nothing about hormone release; Level 2 adds the hormone but not the receptor, since GLP-1 may rise through TGR5-independent mechanisms unless Level 3 evidence shows otherwise. Only Level 4, which requires an in vivo response under a route and disease model relevant to the intended use, provides evidence for dietary application. Compounds one level apart therefore support different claims rather than simply differing in promise.

Hesperetin and naringenin are the only compounds reaching Level 4, although the lack of an intake-matched control leaves their chronic weight effects confounded by reduced food intake [6]; oleanolic acid and ursolic acid both reach Level 3, but the first lacks in vivo confirmation of GLP-1 mediation and the second rests on pharmacological blockade in a model and route without dietary relevance [4, 5, 7]; and nomilin remains at Level 1, with metabolic effects but no GLP-1 measurement [8]. Preclinical activity is therefore common in this literature, whereas pathway-complete, exposure-relevant evidence is rare, and it is the latter that determines translational value.

Human validation remains the decisive gap. At present, no food-derived TGR5 modulator has been shown to raise GLP-1 through TGR5 in humans, and species differences make extrapolation uncertain. For example, Briere et al. found that a synthetic TGR5 agonist induced strong GLP-1 secretion in a mouse enteroendocrine cell line but only modest secretion in a human one, and characterized it as mouse-selective; Tgr5 knockout confirmed that both its metabolic and its

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gallbladder effects were receptor-mediated [11]. This difference in the receptor's own pharmacology means that additional mouse data cannot settle the question for humans.

4.2. Dose, bioavailability, and the difference between foods and purified compounds

Dose is a key barrier to dietary translation. Cell studies use micromolar concentrations and animal studies use purified compounds above typical food intake, whereas food-derived exposure depends on release from the matrix, stability during digestion, and delivery to TGR5-expressing L cells.

Beyond dose, bioavailability is shaped by intestinal retention, first-pass conjugation, and microbial transformation, which can alter the form and amount available to activate TGR5. For this reason, parent compounds, conjugates, and metabolites should therefore be evaluated separately.

Exposure form also matters. Whole foods, extracts, and purified compounds are distinct exposures. The clove and allspice work used concentrated extracts and isolated standards [9]; hesperetin and naringenin were given as purified compounds, and nomilin was incorporated into the diet rather than as a conventional citrus food [6, 8]. Receptor activity with an isolated compound therefore does not establish that a realistic food exposure reaches the required intestinal concentration.

4.3. Safety and tissue selectivity

Food origin does not guarantee tissue selectivity. TGR5 is highly expressed in both the gallbladder and the intestine, so systemic activation may act beyond L cell GLP-1 secretion. The synthetic agonist studied by Briere et al. makes this concrete: it lowered the glucose excursion in an oral glucose tolerance test, but only at doses that simultaneously induced gallbladder filling, and both effects were absent in Tgr5 knockout mice [11]. Thus, the risk was not an off-target effect but the same receptor acting in a second tissue, which cannot be engineered away unless exposure is confined to the intestine. Oleanolic acid also raised liver enzymes and bilirubin in some mice at 100 mg/kg/day, though this does not establish a TGR5-mediated mechanism [5].

The safety profile of a food-derived compound depends on the form and duration of exposure, neither of which is implied by its food origin. Ordinary diets supply these compounds at low milligram amounts within a food matrix, whereas the studies reviewed here used purified material well above that range; by conventional body-surface-area scaling, 100 mg/kg/day in mice corresponds to roughly 8 mg/kg/day in an adult, on the order of several hundred milligrams daily. Concentrated extracts also deliver co-extracted constituents while removing the matrix that governs release and absorption. Duration compounds both problems, since the feeding studies ran for days to weeks whereas a nutritional strategy implies sustained intake over years. Safety assessment should therefore treat whole foods, enriched extracts, and purified supplements as distinct exposures, specifying preparation, dose, duration, organ-specific effects, and interactions with medicines.

Mechanistic attribution is a further challenge: polyphenols, triterpenoids, and limonoids interact with multiple targets, so metabolic effects cannot always be assigned to TGR5. Gut-restricted strategies may limit systemic exposure but are more developed for synthetic than for food-derived compounds [1, 10].

5. Future directions for food-based TGR5–GLP-1 validation

Future validation should move from receptor screening to integrated mechanistic testing. In particular, TGR5 activation should be assessed with a target-engagement method and a loss-of-

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function control such as knockdown or knockout, while GLP-1 should be measured directly in primary intestinal tissue or human intestinal organoids rather than inferred from metabolic changes.

Exposure should be characterized alongside effect, with parent compound, conjugates, and microbial metabolites quantified separately and intestinal rather than only circulating concentrations reported. Animal studies should use diet-induced metabolic dysfunction models with oral dosing and a food-intake-matched control, so that GLP-1-mediated effects can be distinguished from reduced energy intake. Receptor dependence in vivo should be tested by intestine-specific TGR5 knockout, or at minimum by an antagonist given alongside the compound. First-in-human work should be mechanistic rather than efficacy-oriented: small controlled crossover trials with a standardized oral dose and a fixed test meal, measuring active and total GLP-1 across the postprandial period alongside glucose, insulin, appetite ratings, circulating compound and metabolites, and short-term safety. Trials with weight or glycemic endpoints become informative only once such a response is reproduced.

6. Conclusion

The analysis demonstrates that food-derived TGR5 modulators differ sharply in their support for GLP-1 regulation. Among them, hesperetin and naringenin provide the most comprehensive preclinical support, spanning TGR5 activation, target engagement, loss-of-function validation, GLP-1 secretion, and oral in vivo effects; oleanolic acid offers strong enteroendocrine mechanistic evidence, while ursolic acid and nomilin require further validation. Across the compounds, two constraints apply: experimental doses and preparations correspond to supplement-scale rather than dietary exposure, and TGR5 is not intestine-specific, so gallbladder and hepatic effects belong in any assessment. The field therefore represents a mechanistically supported hypothesis rather than an evidence-based dietary intervention, and progress will depend on demonstrating realistic oral exposure, validating responses in human intestinal systems, confirming TGR5 dependence, and establishing clinical safety.

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