Molecular Docking Analysis of Selected Phytochemicals Targeting GLP-1R, GIPR, and DPP4

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Article

Molecular Docking Analysis of Selected Phytochemicals Targeting GLP-1R, GIPR, and DPP4

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Abstract

Obesity and Type 2 diabetes mellitus (T2DM) are becoming major health concerns worldwide, with 890 million people being obese as of 2022 [1]. Recently developed drugs to treat T2DM have shown remarkable results in weight loss, proving themselves as efficient tools in fighting obesity. They are also called GLP-1 agonists, because they mimic the action of the natural glucagon-like peptide-1 a hormone that regulates blood sugar by stimulating insulin secretion. However, these medications are extremely expensive, so recent studies are focusing on finding natural alternatives that could be more affordable. *In silico* studies are computer simulations on how molecules interact, and may save a lot of experimental work by giving indications on which compounds could be effective for a given purpose. The present study carried out molecular docking on selected phytochemicals with reported roles in weight management and their interactions with GLP-1 receptors, as well as gastric inhibitory polypeptide receptors (GIPR) and Dipeptidyl Peptidase-4 (DPP4). The selected molecules were: berberine, chlorogenic acid, curcumin, epigallocatechin gallate (EGCG), hesperidin, quercetin and rutin. The molecular docking results show that EGCG, hesperidin and rutin may have some good affinity with the GLP-1 receptor, berberine, hesperidin and rutin to DPP4, while none of the selected molecules had significant affinity to the GIP receptor. However, these phytochemicals have much smaller molecules than the synthetic peptides that are used in the treatment of T2DM and obesity, so they may well bind to other receptors too and have little selectivity and specificity. The ADME profile indicates berberine as the most promising candidate for drug development. Further studies are needed to investigate if these molecules have practical application in the treatment of obesity and how they could be used.

Keywords: phytochemicals; herbal medicine; molecular docking; GLP-1; GIP; DPP4; obesity; type 2 diabetes mellitus; ADME profile

1. Introduction

Obesity and type 2 diabetes mellitus (T2DM) are among the most prevalent metabolic disorders worldwide, posing major health and socioeconomic challenges. According to the World Health Organization, in 2022 890 million adults were obese and 830 million were living with diabetes, figures that continue to rise sharply due to sedentary lifestyles, urbanization, and changes in dietary patterns [1]. Both conditions are closely interrelated: excess adiposity contributes to insulin resistance, chronic inflammation, and dysregulated glucose metabolism, while hyperinsulinemia and impaired satiety signaling further exacerbate weight gain. Together, obesity and T2DM significantly increase the risk of cardiovascular disease, hepatic steatosis, and premature mortality, representing a global epidemic that demands more effective and sustainable therapeutic solutions.

Incretins are peptide hormones released from the gut shortly after a meal—specifically GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). Their main action is to stimulate the release of insulin from the pancreas in a glucose-dependent manner. They act quickly (within minutes of food intake) and help regulate blood glucose levels [2].

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GLP-1 and GIP bind to their respective receptors, GLP-1R and GIPR, which are G protein-coupled receptors (GPCRs). Upon ligand binding, the receptors undergo conformational changes, which enable them to activate G proteins (in particular, G_s). This leads to cAMP production as a second messenger, and downstream signaling pathways.

Different tissues express these receptors, so the effects of incretins vary: in the pancreas, they encourage insulin secretion, in the brain, GLP-1 can promote satiety (feeling of fullness), in the gastrointestinal tract, GLP-1 slows gastric motility (delays how quickly food leaves the stomach) [3]. The active half-life of GLP-1 and GIP is short (minutes): they are degraded rapidly by the enzyme dipeptidyl peptidase-4 (DPP-4) [4].

Because incretins influence glucose regulation, they are of great interest in diabetes research and therapeutics. The structural and mechanistic understanding of how GLP-1, GIP, and related agonists bind and activate their receptors aids in drug development (designing stable, potent agonists). Synthetical peptides that mimic the action of GLP-1 are called GLP-1 agonists.

Over the past decade, major advances in metabolic pharmacotherapy have focused on modulating the **incretin system**. Synthetic **GLP-1 receptor agonists (GLP-1RAs)** such as liraglutide, semaglutide, and the dual GLP-1/GIP agonist tirzepatide have revolutionized the management of diabetes and obesity [3,5]. Clinical trials have demonstrated not only improved glycemic control but also significant body-weight reduction and cardiovascular benefits. Despite their success, these drugs have important limitations: they are typically injectable peptides requiring cold-chain storage, their cost restricts accessibility, and many patients experience gastrointestinal side effects or poor long-term adherence. Consequently, there is growing interest in identifying **non-peptidic, orally active compounds** capable of modulating the incretin axis with improved tolerability and affordability.

Plants represent a vast and chemically diverse source of bioactive molecules—**phytocompounds**—that may influence glucose and energy metabolism through mechanisms similar to synthetic incretin mimetics [6]. Natural alkaloids, flavonoids, terpenoids, and phenolic acids have been shown to stimulate GLP-1 secretion, inhibit the enzyme **dipeptidyl peptidase-4 (DPP-4)** responsible for incretin degradation, and improve insulin sensitivity. For example, berberine, quercetin, and ginsenosides display promising metabolic effects in preclinical studies [7]. However, most phytocompounds have not advanced to clinical application because of **poor bioavailability, rapid metabolism, low receptor specificity, and lack of mechanistic understanding**. Experimental screening of thousands of plant metabolites is time-consuming, costly, and often limited by compound instability and complex matrices.

To address these challenges, ***in silico* methodologies**—including molecular docking, molecular dynamics simulations, and quantitative structure–activity relationship (QSAR) modeling—have emerged as powerful tools for exploring phytochemical interactions with metabolic targets at the atomic level. These computational approaches allow researchers to rapidly predict binding affinity, stability, and selectivity of natural molecules toward receptors such as GLP-1R, GIPR, and DPP-4, long before laboratory testing. Combined with pharmacokinetic modeling and machine learning-based ADMET prediction, *in silico* studies can prioritize the most promising candidates, reducing the number of experimental assays needed and guiding formulation strategies to overcome absorption and stability barriers.

By integrating traditional natural-product chemistry with modern computational pharmacology, *in silico* screening enables a rational, mechanism-driven exploration of the therapeutic potential of phytocompounds [8]. This approach not only accelerates the identification of bioactive leads but also deepens understanding of their structure–activity relationships and potential synergistic effects. Ultimately, such strategies could lead to the development of safe, affordable, and orally available **plant-derived incretin modulators**, offering a complementary path to the peptide-based therapies that currently dominate diabetes and obesity management.

To the best of the author's knowledge, this is the first *in silico* study to analyse phytocompounds' affinity to GLP-1R, GIPR, and DPP-4 (testing of dualist/ triple action), as well as pharmacokinetics, and it may provide valuable insights towards developing natural and affordable alternatives for

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obesity and M2DL treatment. The purpose of the study was not just to assess phytochemicals' potential as incretin agonists, but also to compare their affinity to receptors to those of synthetic oral drugs that are currently in advanced clinical trials.

2. Results

2.1. Literature Review

The preliminary literature review identified a large number a scientific publications focusing on phytochemicals used in the treatment of diabetes and metabolic disorders.

One of the most studied phytochemical for diabetes treatment is **berberine**, with ~47,000 search results in Google Scholar for "berberine + diabetes" and over 5,000 results for "berberine + GLP-1". It was used traditionally in treatment of gastrointestinal conditions and has clinically demonstrated effects in lowering blood glucose [9]. Coffee (**chlorogenic acid**) and green tea (**epigallocatechin gallate**) were widely proven to be associated with reduced risk of diabetes [10], while **curcumin** is also associated with anti-obesity effects [11]. **Hesperidin** has proven GLP-1R activity [12], as well as **quercetin** and **rutin**, which are incretin modulators [13,14]. They were all selected because they are present in staple foods, extracts being often included in diabetes and weight management supplements, have been subject to in vitro and in vivo clinical studies, but their profile as potential triple agonists was not yet investigated.

The molecules selected for the present *in silico* study are presented in Table 1.

Table 1. Selected phytochemicals for molecular docking study.

Compound	Main Natural Sources	Reported Mechanism	References
Berberine	*Berberis vulgaris*, *Coptis chinensis*	Enhances GLP-1 secretion, improves insulin sensitivity	[9,15–17]
Chlorogenic acid	Coffee, sunflower, potatoes	Appetite suppression, glucose metabolism	[18–21]
Curcumin	Turmeric (*Curcuma longa*)	Anti-inflammatory, reported DPP-4 interaction	[22–25]
Epigallocatechin gallate (EGCG)	Green tea (*Camellia sinensis*)	Stimulates GLP-1 secretion, DPP-4 inhibition	[26–29]
Hesperidin	Citrus fruits	Incretin secretion enhancement, DPP-4 inhibition	[12,30–32]
Quercetin	Onions, apples, berries	Incretin modulation, anti-obesity activity	[33–35]
Rutin	Buckwheat, citrus, apples	GLP-1 modulation, antioxidant	[36,37]

Berberine

Berberine is an isoquinoline alkaloid found primarily in *Berberis* species such as *Berberis vulgaris* and *Coptis chinensis*. Chemically, it consists of a quaternary ammonium salt structure conferring high polarity and limited oral bioavailability [38]. Traditionally, berberine-containing plants have been used in Chinese and Ayurvedic medicine for treating gastrointestinal (GI) infections, diabetes, and inflammatory disorders [39]. Modern pharmacological research demonstrates pleiotropic effects through activation of AMP-activated protein kinase (AMPK), modulation of lipid and glucose metabolism, and anti-inflammatory signaling. Meta-analyses of randomized clinical trials report clinically relevant reductions in fasting glucose, HbA1c, total cholesterol, and LDL cholesterol, with magnitude comparable to that of metformin in some short-term studies. Its inclusion in the present study is justified by consistent evidence of metabolic and endothelial benefits, as well as its well-characterized molecular mechanisms relevant to insulin resistance and dyslipidemia.

Chlorogenic Acid

Chlorogenic acid (CGA) is an ester of caffeic acid and quinic acid abundant in coffee beans, artichokes, apples, and many other plant foods. It is a major phenolic acid responsible for the

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antioxidant and modulating effects of coffee consumption. Traditionally, CGA-rich preparations, such as green coffee infusions, have been used as tonics to promote metabolism and vascular health [40]. Experimental and clinical research indicates that CGA can inhibit glucose absorption, enhance endothelial nitric oxide synthesis, and exert anti-hypertensive and anti-inflammatory effects. Randomized controlled trials using green coffee extract standardized for CGA (typically 300–800 mg/day) demonstrate modest reductions in blood pressure and fasting glucose. The compound's inclusion in this study is motivated by its reported effects on weight loss [18].

Curcumin

Curcumin is the principal curcuminoid of *Curcuma longa* (turmeric), chemically characterized as a diarylheptanoid polyphenol with conjugated double bonds responsible for its intense yellow color and radical-scavenging activity. Traditionally employed in Ayurvedic and Southeast Asian medicine as an anti-inflammatory and digestive remedy, curcumin has since been extensively studied for its ability to modulate transcription factors such as NF-κB and Nrf2. Numerous clinical trials and meta-analyses have demonstrated that curcumin supplementation (often 500–2000 mg/day in bioenhanced forms) reduces inflammatory markers (CRP, IL-6, TNF-α), improves lipid profiles, and may alleviate symptoms in arthritis, metabolic syndrome, and gastrointestinal inflammation [41]. Its limited oral bioavailability has spurred the development of phytosomal and nanoparticle formulations. Curcumin was selected for the present study for its potential as anti-obesity treatment.

Epigallocatechin Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea (*Camellia sinensis*), chemically belonging to the flavan-3-ols with a gallate ester conferring strong antioxidant potential. Traditionally, green tea has been consumed in East Asian cultures for detoxification, alertness, and longevity. EGCG exhibits multiple bioactivities, including modulation of cellular redox status, inhibition of pro-inflammatory enzymes, and regulation of lipid metabolism and insulin signaling [42]. Clinical studies indicate that EGCG or standardized green tea extracts may modestly reduce fasting glucose, body weight, and systolic blood pressure, while contributing to improved endothelial function [43]. Additionally, EGCG has been investigated as an adjunct in cancer chemoprevention and neuroprotection. It was included in this study because of its well-established safety at dietary doses and its potential applications in diabetes treatment.

Hesperidin

Hesperidin is a citrus flavanone glycoside predominantly found in orange and lemon peels. Upon ingestion, it is hydrolyzed to hesperetin, its active aglycone. Traditionally, citrus flavonoids have been used to strengthen capillaries and treat venous insufficiency [44]. Chemically, hesperidin's structure supports free-radical scavenging and modulation of endothelial nitric oxide synthase. Clinical studies report that hesperidin supplementation (typically 500–1000 mg/day) can improve flow-mediated dilation, reduce blood pressure, and attenuate markers of oxidative stress and inflammation, although effects on glycemic indices are inconsistent. Recent studies have indicated it's potential in the treatment of diabetes, which is why it was included in the study.

Quercetin

Quercetin is a flavonol widely distributed in onions, apples, berries, and leafy vegetables. Its planar polyphenolic structure enables chelation of metal ions and potent antioxidant activity. Historically, quercetin-rich foods have been valued in traditional European and Asian diets for their anti-inflammatory and tonic effects [45]. Modern mechanistic studies reveal that quercetin modulates cytokine production, inhibits cyclooxygenase and lipoxygenase enzymes, and supports mitochondrial antioxidant defenses. Randomized trials and meta-analyses show modest but significant reductions in blood pressure and C-reactive protein at doses of 500–1000 mg/day, as well

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as possible antiviral and immunomodulatory effects. The compound was selected for its potential role in incretins modulation.

Rutin

Rutin (quercetin-3-rutinoside) is a glycoside of quercetin found in buckwheat, citrus fruits, and some medicinal herbs. The attached disaccharide (rutinose) enhances water solubility but reduces direct bioavailability until enzymatic hydrolysis in the gut. Traditionally, rutin-rich preparations have been used as vascular tonics and anti-hemorrhoidal remedies. Pharmacologically, rutin exhibits antioxidant, anti-inflammatory, and capillary-stabilizing effects, improving microcirculatory integrity [46]. Preclinical and limited clinical studies indicate benefits for lipid metabolism, venous insufficiency, and wound healing. The inclusion of rutin in this study provides a glycosylated flavonol counterpart to quercetin, allowing comparison of structure–activity relationships and exploration of how sugar conjugation affects molecular affinities, absorption and biological efficacy.

Synthetic Drug Orforglipron

Orforglipron is a novel oral medication being developed primarily for weight loss and type 2 diabetes management. It belongs to the class of GLP-1 receptor agonists, which help regulate blood sugar, appetite, and body weight by mimicking the natural hormone GLP-1 (glucagon-like peptide-1) [47,48]. Unlike most GLP-1 drugs, orforglipron is not a peptide but a small molecule, allowing effective oral absorption rather than requiring injection. It was included in the study for the purpose of comparison with natural phytocompounds in terms of molecular affinity to receptors and pharmacokinetics.

2.2. Molecular Docking

Molecular docking simulations revealed distinct binding affinity profiles for the investigated natural compounds toward **GLP-1 receptor (GLP-1R)**, **GIP receptor (GIPR)**, and **dipeptidyl peptidase-4 (DPP4)** (Table 1). The synthetic GLP-1R agonist **orforglipron**, included as a reference ligand, exhibited the highest binding affinities across all three targets (–11.4 kcal/mol for GLP-1R, –7.6 kcal/mol for GIPR, –9.8 kcal/mol for DPP4), consistent with its optimized molecular design for receptor engagement and enzymatic stability (Table 2). Detailed results, including image captures of ligands bound to receptor can be found in the **Supplementary Materials**.

Table 2. Receptor affinity of selected molecules to GLP-1 R, GIP R and DPP4.

	Receptor affinity ((kcal/mol)[1]		
Ligand	**GLP-1 R**	**GIP R**	**DPP4**
Berberine	-7.6	-5,5	**-8,0**
Chlorogenic acid	-7.8	-4,3	-6,8
Curcumin	-7,5	-5,5	-7,0
Epigallocatechin gallate	**-9,1**	-5,2	-7,9
Hesperidin	**-9,2**	-5,8	**-8,3**
Orforglipron	**-11,4**	-7.6	**-9.8**
Quercetin	-7,9	-4,7	-7,5
Rutin	**-9,2**	-5,5	**-8,0**

[1] Best results are presented for each case.

Among the **natural compounds**, **hesperidin** and **rutin** displayed the strongest binding to GLP-1R (both –9.2 kcal/mol), comparable in magnitude to the synthetic agonist's affinity and notably stronger than other polyphenols. Both are glycosylated flavonoids whose bulky sugar moieties may facilitate hydrogen bonding with polar residues in the receptor's extracellular domain. **Epigallocatechin gallate (EGCG)** also showed a strong interaction (–9.1 kcal/mol), reflecting its polyhydroxylated catechin structure capable of multiple hydrogen bonds and π–π stacking

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interactions. These results suggest that complex flavonoids and catechins may stabilize the GLP-1R binding pocket despite lacking classical peptide-like motifs.

Berberine, **chlorogenic acid**, **curcumin**, and **quercetin** exhibited moderate GLP-1R binding (–7.5 to –7.9 kcal/mol). Their planar or semi-planar structures allow interaction within the hydrophobic cavity but with fewer anchoring polar contacts than seen in glycosides. The relatively strong affinity of berberine (–7.6 kcal/mol) may arise from its cationic isoquinoline ring, which can engage in electrostatic interactions with acidic residues of the receptor.

Affinity for **GIPR** was generally weaker across all natural ligands, ranging from –4.3 to –5.8 kcal/mol. This suggests lower complementarity between polyphenolic scaffolds and the GIPR binding site, which is structurally narrower and more peptide-selective. Only hesperidin (–5.8 kcal/mol) showed slightly higher affinity, possibly due to its extended conformation and hydrogen bonding potential.

Docking against **DPP4**, the enzyme responsible for incretin degradation, revealed affinities from –6.8 to –8.3 kcal/mol among natural compounds. **Hesperidin** again ranked highest (–8.3 kcal/mol), followed by **berberine** and **rutin** (–8.0 kcal/mol), and **EGCG** (–7.9 kcal/mol). These results align with prior evidence that flavonoids and alkaloids may inhibit DPP4 activity through interactions with catalytic site residues (e.g., Glu205, Glu206, Tyr547). **Curcumin**, **quercetin**, and **chlorogenic acid** displayed moderate inhibition potential (–6.8 to –7.5 kcal/mol), which could still contribute to overall incretin preservation in vivo.

Taken together, the docking data indicate that **hesperidin, rutin, and EGCG** are the most promising natural candidates for GLP-1R activation or modulation, while **berberine** and **hesperidin** appear strongest as potential **DPP4 inhibitors**. Although none matched the synthetic agonist's binding energy, several compounds displayed affinities within a pharmacologically relevant range (–7 to –9 kcal/mol), supporting their inclusion as bioactive leads in studies targeting the incretin axis. These findings corroborate existing experimental literature suggesting that polyphenols and isoquinoline alkaloids may enhance incretin signaling and glucose homeostasis via multitarget interactions.

2.2. ADME Profiles

A synthesis of the ADME analysis is presented in Table 3.

Table 3. ADME Results for analysed molecules.

Molecule	GI Absorption	BBB*	Solubility	Log P**	BS***	Notable Features
Berberine	High	Yes	Moderate	2.53	0.55	Balanced profile; multi-CYP inhibitor; good scaffold
Chlorogenic acid	Low	No	Very high	−0.39	0.11	Highly polar; poor permeability
Curcumin	High	No	Moderate	3.03	0.55	Good oral potential; metabolic liabilities
Epigallocatechin gallate	Low	No	Moderate	0.95	0.17	Too polar; low bioavailability
Hesperidin	Low	No	Soluble	−1.06	0.17	High MW; glycoside; poor permeability
Orforglipron	Low	No	Insoluble	6.51	0.17	Synthetic oral GLP-1 agonist; optimized despite poor properties
Quercetin	High	No	Soluble	1.23	0.55	Excellent scaffold; multiple CYP interactions
Rutin	Low	No	Soluble	−1.51	0.17	Large, polar glycoside; likely inactive orally

*** Blood-Brain Barrier. ** Lipophilicity (Consensus Log P). *** Bioavailability Score.**

The BOILED-Egg diagram (Figure 1) visually predicts intestinal absorption and blood–brain barrier (BBB) permeability of the selected molecules using two parameters: WLOGP (lipophilicity, y-axis) and TPSA (topological polar surface area, x-axis). Molecules located in the white region are predicted to have high human intestinal absorption (HIA), while those within the yellow region (the "yolk") are likely to penetrate the BBB. The blue and red circles indicate the interaction with P-glycoprotein (P-gp), a transporter that actively expels compounds from cells: PGP+ (blue) denotes

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predicted substrates that may be pumped out, reducing absorption or brain exposure, whereas PGP− (red) indicates non-substrates with potentially higher permeability. In this figure, berberine (PGP+) appears inside the BBB-permeant zone, suggesting possible brain penetration, while most phytochemicals—curcumin, quercetin, chlorogenic acid, and EGCG—fall in or near the white area, indicating good intestinal absorption but limited BBB access. Hesperidin and rutin, positioned outside the main zones, show poor absorption due to their large size and high polarity, consistent with their glycosidic structures.

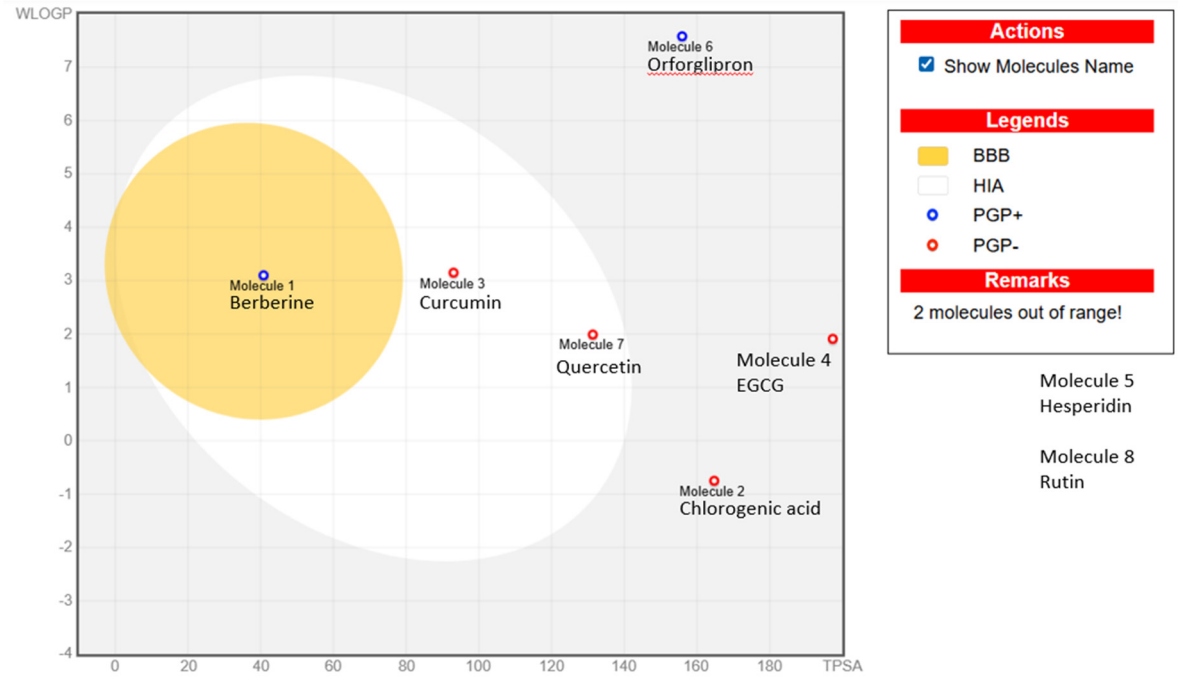

Figure 1. "Boiled Egg" representation of ADME results. Image generated by SwissADME [49].

3. Discussion

The physicochemical and pharmacokinetic properties of eight selected compounds—berberine, chlorogenic acid, curcumin, epigallocatechin gallate (EGCG), hesperidin, orforglipron, quercetin, and rutin—were evaluated using the SwissADME web platform to assess their potential as orally active agents targeting metabolic pathways related to diabetes and obesity. The results revealed considerable variation in molecular weight, lipophilicity, polarity, and bioavailability among the compounds.

Berberine, curcumin, and quercetin have molecular weights below 400 g/mol and moderate lipophilicity (consensus Log P between 2 and 3), values consistent with classical drug-likeness criteria. These parameters suggest adequate balance between solubility and membrane permeability, supporting their potential for oral administration. In contrast, chlorogenic acid, EGCG, hesperidin, and rutin displayed high polarity and large polar surface areas (TPSA values >160 Å²), together with negative or near-zero lipophilicity, indicating a low likelihood of passive diffusion through lipid membranes. Orforglipron, although a proven orally active GLP-1 receptor agonist, strongly violated Lipinski's and Veber's rules due to its large size (883 g/mol) and high lipophilicity (Log P 6.5), emphasizing that the effectiveness of such molecules arises from targeted molecular design and formulation optimization rather than intrinsic physicochemical suitability.

Predicted gastrointestinal absorption followed a similar trend. High intestinal absorption was observed for berberine, curcumin, and quercetin, while chlorogenic acid, EGCG, hesperidin, and rutin were classified as poorly absorbed. The BOILED-Egg model [50] indicated that berberine was capable of both intestinal and blood–brain barrier permeation, whereas the highly polar flavonoid glycosides are not likely to be assimilated through the GI tract. Bioavailability scores further

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supported these findings, with berberine, curcumin, and quercetin achieving a score of 0.55 (moderate oral bioavailability), in contrast to the lower scores (0.11–0.17) for the hydrophilic and glycosylated flavonoids. These differences reflect the significant influence of sugar moieties on absorption: removal of glycosidic groups (e.g., conversion of rutin to quercetin, or hesperidin to hesperetin) is expected to markedly improve permeability. However, the molecular docking results showed that quercetin has lower affinity to receptors compared to rutin.

Analysis of cytochrome P450 (CYP) inhibition patterns revealed that berberine, curcumin, and quercetin act as inhibitors of multiple CYP isoenzymes, particularly CYP3A4, CYP2D6, and CYP1A2, suggesting potential for pharmacokinetic interactions with co-administered drugs. However, this property may also confer extended metabolic lifetime. The remaining polyphenols showed little or no predicted CYP inhibition, which implies a safer metabolic profile but possibly shorter systemic exposure. Solubility predictions placed most compounds in the "moderately soluble" to "soluble" range, except for orforglipron, which was classified as poorly soluble despite its therapeutic efficacy.

From a drug-likeness perspective, berberine, curcumin, and quercetin meet major criteria, including Lipinski, Ghose, Egan, and Muegge, and demonstrated low synthetic complexity (synthetic accessibility <3.5). Hesperidin, rutin, and EGCG failed multiple rules owing to their size, polarity, and hydrogen-bonding capacity, resulting in high synthetic accessibility scores (>6). Although orforglipron also violated several drug-likeness rules, its established oral activity highlights the potential of modern medicinal chemistry to overcome such constraints through structural and formulation engineering.

Overall, the in silico ADME analysis identified **berberine, curcumin, and quercetin** as the most promising phytochemical scaffolds for further development. These compounds combine favorable oral absorption, manageable polarity, and chemical simplicity with known biological activity on metabolic pathways. Conversely, the glycosylated flavonoids (hesperidin, rutin) and polyphenolic acids (chlorogenic acid, EGCG) exhibited poor pharmacokinetic characteristics that may limit their direct use but could be improved through deglycosylation, nanoencapsulation, or prodrug design. Together, these results emphasize the importance of computational pharmacokinetic screening as an initial filter for prioritizing natural compounds in drug discovery pipelines focused on incretin-based mechanisms and metabolic regulation.

Further studies are needed to evaluate the receptor specificity and selectivity of target molecules, their metabolic pathways, as well as ways of increasing their half-life and bioavailability, eventually through alternative delivery methods.

4. Materials and Methods

Literature Review

A scientific literature search was carried out in order to identify compounds of plant origin that have been tested for their activity in treatment of obesity and T2DM, including interactions with GLP-1R, GIPR and/ or DPP4. Searches were done in Google Scholar, ScienceDirect and Scopus databases, as well as using AI tools like Perplexity. Search included phrases like "phytochemicals GLP-1", "phytochemicals diabetes", phytochemicals DPP4" as well as individual names of identified compounds. The inclusion criterion was the existence of in vitro or in vivo trials indicating potential in treatment of obesity and/or diabetes. Further criteria were the number of studies, demonstrated effects of treating diabetes or weight management in humans and identification of active compound.

Molecular Structures

Molecular structures for the selected compounds were retrieved from the RCSB Protein Data Bank (RCSB PDB), isolated from existing complexes and saved as individual .pdb files. In case no .pdb structure was available (e.g. for hesperidin), the 3D structure was downloaded from the PubChem database [51] in .sdf format and converted to .pdb in Chimera [52]. An overview of compounds and the IDs of the complexes they were separated from, respectively CID from PubChem, are presented in Table 4.

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Table 4. Molecular structures used in the study processed from the RCSB Protein Database.

Short name	Name	Role	ID*	Reference
GLP-1R	Glucagon-Like Peptide-1 (GLP-1) Receptor	receptor	7KI0	[53]
GIPR	Gastric inhibitory polypeptide receptor	receptor	7FIY	[54]
DPP4	Dipeptidyl peptidase-4	receptor	5T4B	[55]
Berberine	Berberine	ligand	7X32	[56]
CGA	Chlorogenic acid	ligand	5GMU	[57]
Curcumin	Curcumin	ligand	6HDR	[58]
EGCG	Epigallocatechin gallate	ligand	4AWM	[59]
Hesperidin	Hesperidin	ligand	10621***	[51]
OFG**	Orforglipron	ligand	6XOX	[60]
Quercetin	Quercetin	ligand	8SFW	[61]
Rutin	Rutin	ligand	8C3Q	[62]

* From the RCSB Protein Database. ** Synthetic molecule/ not a phytochemical. *** PubChem CID.

Molecular Docking

The docking sites for each receptor were defined according to existing complexes, namely semaglutide bound to GLP-1R (Figure 2), tirzepatide bound to GIPR (Figure 3), and DPP4 bound to a ligand 34a (Figure 4). The docking sites are represented with green wire boxes in the figures.

Molecules preparation for docking included removal of water, adding hydrogens and adding charges. All molecular processing was carried out in UCSF Chimera software version 1.19 [52], while the actual molecular docking calculations used Autodock Vina 4.2 [63], called from Chimera module.

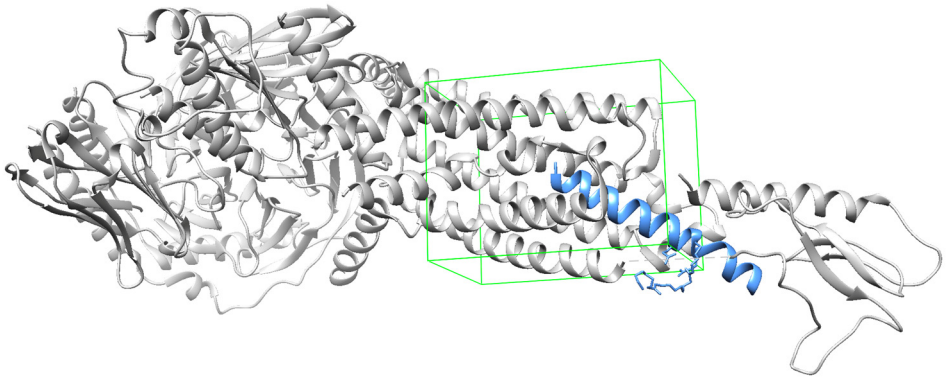

Figure 2. Semaglutide-bound Glucagon-Like Peptide-1 (GLP-1) Receptor (image generated by author with Chimera 1.19 based on 7KI0 [53]).

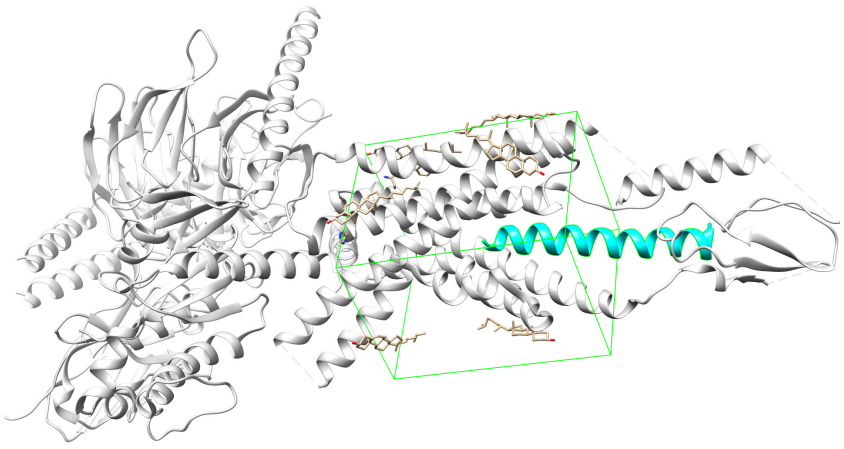

Figure 3. Tirzepatide bound to GIP receptor grid box (image generated by author with Chimera 1.19 based on 7FIY [54]).

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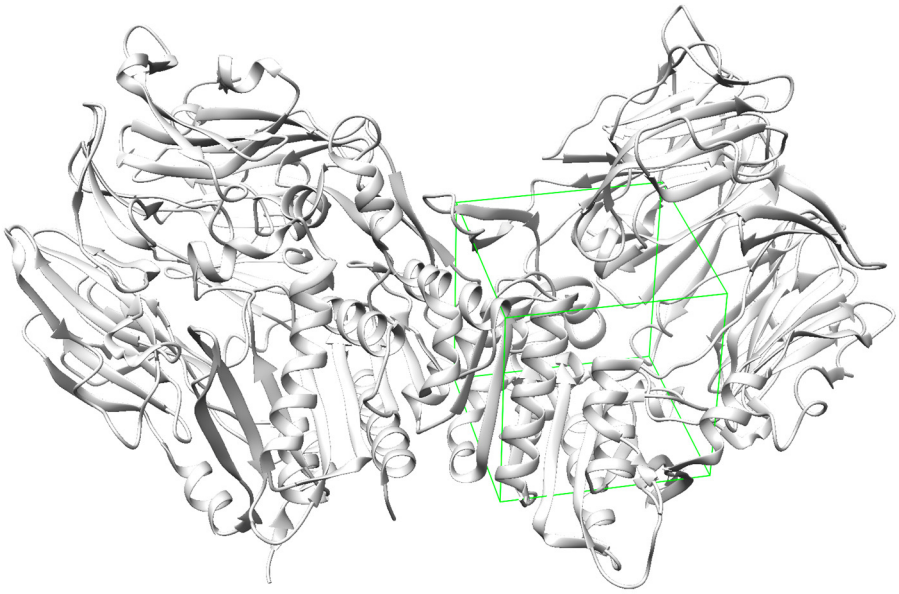

Figure 4. Ligand 34a bound to human DPP4 (image generated by author with Chimera 1.19 based on 5T4B [55]).

ADME Profile

An ADME profile describes how a compound is Absorbed, Distributed, Metabolized, and Excreted by the body, offering a snapshot of its pharmacokinetic behavior and drug-likeness. It can be rapidly estimated in the early stages of drug discovery using free *in-silico* platforms such as SwissADME [49], which predicts key properties like gastrointestinal absorption, blood–brain barrier penetration, lipophilicity (LogP), solubility, metabolic interactions (e.g., CYP450 inhibition), P-glycoprotein substrate status, and medicinal chemistry filters (Lipinski, Veber, etc.).

An overview of the ADME profile in presented in Table 5.

Table 5. Main Characteristics of the ADME profile.

Phase	Key Organs	Main Parameters	Determines
Absorption	GI tract, lungs, skin	Bioavailability (F)	How much drug enters circulation
Distribution	Blood, tissues	Volume of Distribution (Vd)	How widely the drug spreads
Metabolism	Liver (mainly)	Clearance, metabolic rate	How the drug is modified
Excretion	Kidneys, bile, lungs	Half-life (t½), Clearance (Cl)	How long the drug stays in the body

By inputting a SMILES (Simplified Molecular Input Line Entry System) string or drawing the molecule, SwissADME automatically runs computational models to generate a predictive ADME report, enabling researchers to screen candidate compounds efficiently before moving to experimental testing.

The SMILES strings of the selected compounds were retrieved from the PubChem database and submitted to the SwissADME online tool, which returned the ADME profile of each compound (Table 6).

Table 6. SMILES and PubChem CID of studied molecules submitted to SwissADME.

Molecule	PubChem CID	SMILES
Berberine	2353	COC1=C(C2=C[N+]3=C(C=C2C=C1)C4=CC5=C(C=C4CC3)OCO5)OC
Chlorogenic acid	1794427	C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O
Curcumin	969516	COC1=C(C=CC(=C1)/C=C/C(=O)CC(=O)/C=C/C2=CC(=C(C=C2)O)OC)O

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Epigallocatechin gallate	65064	C1[C@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)OC(=O)C4=CC(=C(C(=C4)O)O)O
Hesperidin	10621	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=CC(=C4C(=O)C[C@H](OC4=C3)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O
Orforglipron	137319706	C[C@H]1C[C@]1(C2=NOC(=O)N2)N3C4=C(C=C(C=C4)[C@H]5CCOC(C5)(C)C)C=C3C(=O)N6CCC7=NN(C(=C7[C@@H]6C)N8C=CN(C8=O)C9=C(C1=C(C=C9)N(N=C1)C)F)C1=CC(=C(C(=C1)C)F)C
Quercetin	5280343	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Rutin	5280805	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O

Artificial Intelligence (AI)

AI was used to search and analyse published articles and research results and to summarise findings. Main AI platforms used were perplexity.ai and chatgpt.com.

5. Conclusions

Among the tested compounds, **Berberine, Curcumin, and Quercetin** show the most favorable *in silico* pharmacokinetic profiles and drug-likeness. Their properties suggest potential for oral delivery after optimisation, however, molecular docking did not reveal any particular affinity of these compounds to the target receptors.

Docking analyses revealed that several phytochemicals can interact strongly with incretin-related targets, with **hesperidin, rutin, and epigallocatechin gallate** demonstrating high affinity for GLP-1R and **hesperidin** also binding effectively to DPP-4. These findings suggest that certain flavonoids may act as dual modulators of incretin signaling—combining receptor engagement with enzyme inhibition. However, their pharmacological translation is limited by unfavorable physicochemical properties. In contrast, **berberine** showed moderate affinity but better predicted absorption and metabolic stability, making it a more practical scaffold for optimization.

Further studies are needed to assess the **selectivity and specificity** of molecular affinities between receptors and ligands, as well as improving the bioavailability and extending the half-life of bioactive compounds.

Overall, this analysis demonstrates how *in silico* molecular docking and ADME modeling can effectively guide the selection and rational design of natural compounds targeting GLP-1, GIP, and DPP-4 pathways for obesity and diabetes management.

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Abbreviations

The following abbreviations are used in this manuscript:

ADME	Absorption, Distribution, Metabolism, and Excretion; the four key pharmacokinetic processes determining how a compound behaves in the body
AGI	Alpha-Glucosidase Inhibitor; a type of antidiabetic compound that slows carbohydrate digestion in the gut

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AI	Artificial Intelligence
AMPK	Alpha-Glucosidase Inhibitor; a type of antidiabetic compound that slows carbohydrate digestion in the gut
BBB	Blood–Brain Barrier; a selective barrier between the bloodstream and brain tissue that restricts the passage of many molecules
BOILED-Egg model	Brain Or IntestinaL EstimateD permeation method; a visual predictor of gastrointestinal absorption and blood–brain barrier permeability used in SwissADME
CNS	Central Nervous System; includes the brain and spinal cord
CYP	Cytochrome P450; a family of liver enzymes responsible for metabolizing many drugs
DPP-4	Dipeptidyl Peptidase-4; an enzyme that degrades incretin hormones such as GLP-1 and GIP
EC50	Half Maximal Effective Concentration; the concentration of a compound that produces 50% of its maximal effect
EGCG	Epigallocatechin Gallate; a bioactive polyphenol found in green tea
GI	Gastro-Intestinal
GIP	Glucose-Dependent Insulinotropic Polypeptide; an incretin hormone that stimulates insulin release in response to food intake
GIPR	Glucose-Dependent Insulinotropic Polypeptide Receptor; the receptor that binds GIP
GLP-1	Glucagon-Like Peptide-1; an incretin hormone involved in glucose metabolism and appetite regulation
GLP-1R	Glucagon-Like Peptide-1 Receptor; the receptor that mediates the effects of GLP-1
HIA	Human Intestinal Absorption
Log P	Partition Coefficient; a measure of a compound's lipophilicity or its tendency to dissolve in fats versus water
PGP+	P-glycoprotein Substrate (Yes)
PGP−	P-glycoprotein Non-Substrate (No)
PK	Pharmacokinetics; the study of how a compound is absorbed, distributed, metabolized, and excreted by the body
SwissADME	Swiss Absorption, Distribution, Metabolism, and Excretion; a web tool for predicting pharmacokinetic and drug-likeness properties of small molecules
T2DM	Type 2 Diabetes Mellitus; a metabolic disorder characterized by insulin resistance and high blood glucose
TEER	Transepithelial Electrical Resistance; a measure of the integrity of cell layer barriers, such as intestinal or epithelial monolayers
TPSA	Topological Polar Surface Area
WLOGP	Wildman–Crippen LogP

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