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RESEARCH ARTICLE

TGR5 RECEPTOR ACTIVATION BY OLEANOLIC ACID: MOLECULAR DOCKING EVIDENCE OF A NATURAL COMPOUND IN METABOLIC REGULATION

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ABSTRACT

Metabolism-related studies have increasingly focused on natural products and their biotechnological potential. In this context, the present study investigates the molecular interaction between oleanolic acid and the G protein-coupled bile acid receptor 1 (TGR5), a membrane-bound receptor involved in metabolic regulation, with potential therapeutic implications for diabetes and metabolic syndrome. Oleanolic acid is a naturally occurring triterpenoid found in various plant-based foods and medicinal herbs, while TGR5 is endogenously expressed throughout the body, with higher expression levels in the liver, intestine, stomach, spleen, and brown adipose tissue. To explore this interaction in silico, three-dimensional structures of both molecules were retrieved from structural databases, and molecular docking simulations were performed using algorithm-guided software to generate stable receptor-ligand complexes. The docking results revealed that oleanolic acid exhibits specific binding affinity for a distinct site on the TGR5 receptor, forming six stable chemical interactions. These interactions suggest a favorable energetic stabilization of the receptor-ligand complex, supporting the potential role of oleanolic acid as a positive modulator of TGR5 activity. The reproducibility and strength of the interaction indicate that oleanolic acid may contribute to beneficial metabolic effects through TGR5 activation, reinforcing its potential utility in the development of therapeutic strategies targeting obesity and related metabolic disorders.

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INTRODUCTION

Natural products have historically played a pivotal role in drug discovery, particularly in the development of therapeutics for cancer and infectious diseases. Their importance, however, extends to a broader range of therapeutic areas, including cardiovascular disorders and neurodegenerative diseases such as multiple sclerosis. These biomolecules exhibit distinctive structural complexity and stereochemical diversity compared to conventional synthetic compounds, providing unique pharmacological properties. Such characteristics pose both opportunities and challenges for modern drug discovery and development pipelines (Atanasov *et al*., 2021). Beyond serving as lead structures for organic synthesis and rational drug design, natural products—especially those used in traditional medicine systems—offer valuable empirical insights regarding efficacy and safety. Phytotherapeutics and nutraceuticals, for example, are typically enriched with a diverse array of bioactive secondary metabolites, encompassing a broader chemical space than that of standard synthetic molecules, thereby expanding their therapeutic potential and applications (Atanasov *et al*., 2021). Human fascination with nature has historically been driven not only by its provision of essential resources such as food and shelter but also by its capacity to inspire intellectual inquiry and scientific innovation. The quest to understand natural phenomena and overcome environmental and pathological challenges—such as climatic extremes and disease—has been a constant driver of scientific advancement, even in the current era of high-throughput technologies and molecular engineering (Batista, 2015). The empirical use of herbs and plant-derived materials for healing purposes represents one of the earliest applications of natural products

in human history. Both Eastern and Western civilizations have long traditions of utilizing natural resources for medicinal, agricultural, and defensive purposes. Notable contributions have emerged from ancient Egyptian, Greco-Roman, and Chinese civilizations, whose pharmacopoeias laid the foundation for modern phytomedicine (Viegas Jr. *et al*., 2006). In recent years, natural products have regained prominence in the search for innovative biomedical and biotechnological solutions addressing environmental, societal, and public health challenges. Within this context, the present study aims to elucidate the structural and molecular features of oleanolic acid, a triterpenoid compound naturally found in various edible plants and medicinal herbs. Although widely recognized for its pleiotropic biological activities, oleanolic acid has shown particular promise in the prevention and management of metabolic disorders. Emerging evidence supports its beneficial effects against diabetes and metabolic syndrome, highlighting its potential as a therapeutic agent in combating obesity and related conditions (Thomas *et al*., 2009).

In vitro and in vivo investigations reported in the literature indicate that oleanolic acid enhances insulin sensitivity, preserves pancreatic β-cell functionality and viability, and mitigates complications associated with hyperglycemia and the progression of diabetes (Castellano *et al*., 2013). In this context, computational in silico approaches can provide a valuable complement to experimental data by offering molecular-level insights into the interactions between oleanolic acid and its biological targets. The present study focuses on the metabolic role of oleanolic acid, particularly its interaction with the Takeda G protein-coupled receptor 5 (TGR5), also known as G protein-coupled bile acid receptor 1 (GPBAR1). TGR5 is a plasma membrane-bound receptor broadly expressed throughout the human body, with notably high expression levels in metabolically active tissues such as the liver, intestine, stomach, spleen, and brown adipose tissue (De Melo *et al*., 2010). Besides its biotechnological relevance, oleanolic acid exhibits a broad spectrum of biological and pharmacological properties, including hepatoprotective, anti-inflammatory, analgesic, cytotoxic, and antimicrobial activities.

Structurally, oleanolic acid (3β-hydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid with an oleanane carbon skeleton, commonly found alongside its isomer, ursolic acid. However, oleanane-type triterpenes generally exhibit lower biological activity compared to their ursane and lupane counterparts (Vechia, 2009). Oleanolic acid has been isolated from more than 1,620 plant species, including both food crops and medicinal plants such as olive leaves, yerba mate, Panax ginseng, and clove (Caryophyllus aromaticus L.). Although some derivatives of oleanolic acid display greater biological activity, the native compound still demonstrates superior bioactivity compared to other triterpenes like lupeol (Sporn, 2000; Vechia, 2009). Has a melting point of 310 °C, molecular formula $C_{30}H_{48}O_3$, and a molecular weight of 456.68 g/mol, the compound's three-dimensional structure is available in the PubChem database under CID 10494 (Hichri, 2003) (Figure 1). Oleanolic acid, as a natural constituent of numerous medicinal herbs and edible plants, possesses a wide array of pharmacological activities and physicochemical properties. Despite its broad therapeutic potential, many of its

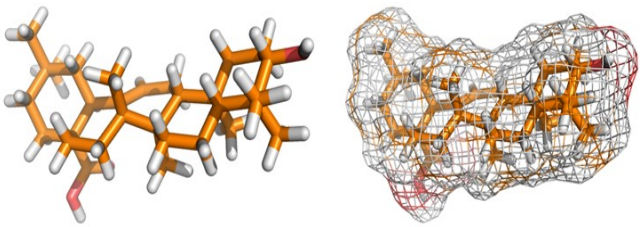

Figure 1. Three-dimensional representation of oleanolic acid (left), after energy minimization, obtained through PubChem (CID: 10494); graphical representation of the omission of electron density of oleanolic acid in its three-dimensional conformation (right)

mechanisms remain underexplored. Current evidence suggests that its multifactorial mode of action confers protective effects against diabetes and metabolic syndrome, including improved insulin responsiveness, preservation of β-cell mass, and attenuation of diabetic complications (Martin *et al*., 2010; Wang *et al*., 2013). From a pharmacological perspective, receptors are specialized proteins responsible for recognizing and responding to endogenous or exogenous chemical signals, thereby coordinating intercellular communication. The receptor theory, which arose from observations regarding the high potency, chemical specificity, and biological selectivity of drug actions, posits that drug-receptor interactions underlie most therapeutic effects. These interactions typically involve reversible or, less commonly, irreversible chemical binding. Functionally, receptors may adopt active or inactive conformational states, with agonists favoring the active state, while antagonists block receptor activation by competing with endogenous ligands (Oliveira, 2011). This study adopts an *in silico* experimental design to investigate the molecular docking of oleanolic acid with the TGR5 receptor, a target of growing interest in metabolic disease research. TGR5 not only serves as a bile acid sensor but also binds a variety of selective agonists that modulate downstream signaling pathways, including NF-κB, AKT, and extracellular signal-regulated kinases (ERK) (Guo *et al*., 2016).

Functionally, TGR5 is implicated in the regulation of bile acid homeostasis, energy expenditure, and glucose metabolism. Notably, previous studies have demonstrated that 48-hour exposure of differentiated myoblasts to oleanolic acid led to a significant increase (+47%) in the expression of mitochondrial-specific genes, indicative of enhanced mitochondrial biogenesis. This conclusion was supported by quantitative analysis of mitochondrial and nuclear DNA content in treated versus control cells (Teodoro *et al*., 2018).

Molecular docking, a cornerstone methodology in structure-based drug design, involves simulating the interaction of a small molecule (ligand) with a target macromolecule (receptor), exploring all possible binding sites to identify the most energetically favorable conformations. This approach yields crucial information on binding affinity and specificity, thus supporting both drug discovery and drug repurposing efforts (Pinzi *et al*., 2019). Based on this purpose, the present study aims to characterize the molecular interactions between oleanolic acid and TGR5 through docking simulations, thereby providing structural evidence for the bioactivities attributed to this natural compound and advancing its potential application in biotechnological and therapeutic contexts.

MATERIALS AND METHODS

The interaction between oleanolic acid and the TGR5 receptor was investigated through an *in silico* molecular docking approach, employing computational algorithms designed to predict the most stable ligand–receptor complexes based on binding energetics and spatial complementarity. Docking simulations were performed using the software AutoDock Vina, using 3-way multithreading and Lamarkian Genetic Algorithm (Trott, 2019). Centralized throughout the receptor, the grid box was defined with parameters of 180 Å x 180 Å x 180 Å. The most stable complexes (receptor-ligand) found were ordered in an increasing way in relation to the values of interaction energies calculated. The program automatically evaluates multiple potential docking poses by calculating shape-based interactions and estimating binding energies. The docking protocol was configured with the following parameters: Correlation type: shape only; FFT mode: 3D; Receptor range: 180°; Ligand range: 180°; Torsion range: 360°; Distance range: 40 Å. These settings were chosen to ensure exhaustive sampling of potential ligand orientations and receptor binding pockets, maximizing the accuracy of the docking predictions. The resulting ligand–receptor complexes were visualized and analyzed using PyMOL version 1.4.7 (DeLano, 2010). Structural evaluations included assessments of binding affinity, hydrogen bonding, hydrophobic interactions, and identification of the specific amino acid residues involved in the interaction interface. Additionally, conformational changes in the receptor and ligand upon binding were examined to elucidate potential mechanistic implications of the molecular recognition process.

RESULTS AND DISCUSSION

Among the 50,000 possible conformations generated by the docking algorithm, the ten most energetically favorable clusters for oleanolic acid were selected for detailed analysis. Remarkably, eight of these clusters converged upon the same primary binding site, whereas the remaining two were located in adjacent regions, suggesting high binding specificity and spatial preference. These findings also indicate the possibility of secondary binding site interactions, a feature often observed in ligands with polypharmacological profiles and flexible bioactivity (Figure 2).

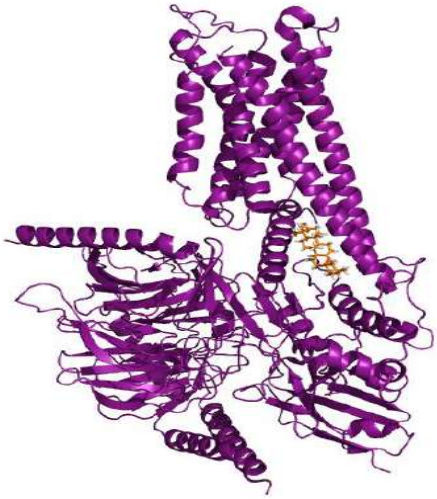

Figure 2. Oleanolic acid demonstrating high specificity for a structural pocket of the TGR5 receptor; 8 of the 10 most energetic clusters overlap at the same site

The most energetically stable cluster revealed six key molecular interactions within a distance of ≤1.5 Å, involving six amino acid residues of the TGR5 receptor: Gln195, Asp198, Leu202, Pro361, Asp381, and Gln384. These residues are strategically positioned within a conserved helical domain, contributing to ligand recognition and stabilization. Notably, the spatial compatibility between the ligand and the binding cavity was reinforced by a significant reduction in conformational flexibility of the receptor, indicative of a tightly formed complex (Figure 3).

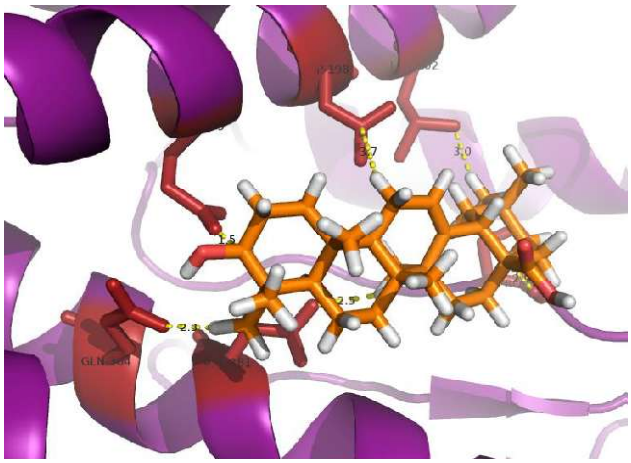

Figure 3. Binding site of oleanolic acid (orange) with the TGR5 receptor (purple), establishing 6 chemical bonds (1.5 to 3.7 angstroms) with 6 amino acid residues of the receptor (red)

The observed binding interactions and molecular specificity are supported by the docking affinity energies presented in Table 1. These values were comparable to, and in some cases surpassed, those obtained in redocking simulations of TGR5 with its reference agonist 23H (Chen *et al*., 2020). Such energetic profiles reinforce the hypothesis that oleanolic acid possesses a favorable binding landscape for TGR5, underscoring its potential as a bioactive modulator Table 1. Binding energies between oleanolic acid and the TGR5 channel, compared to the ligand in the crystallographic structure (Etotal - Kcal/mol).

	E_{total} (Kcal/mol)	
Cluster of TGR5	Oleanólic acid	23H (agonist)
01	- 289,89	- 238.30
02	- 288,35	- 225.92
03	- 287,44	- 211.25
04	- 286,98	-209.50
05	- 285,65	- 196.25
06	- 271,14	- 183.85
07	- 270,02	- 181.89
08	- 256,90	- 179.85
09	- 243,24	- 163.69
10	- 241,09	- 153.55

The docking pose showed that several reactive moieties of oleanolic acid engaged in hydrogen bonds and hydrophobic interactions with no detectable steric hindrance or spatial blockage from side-chain residues within the receptor pocket (Figure 4). These interactions likely contributed to the optimal accommodation of the ligand, as the structural cavity exhibited sufficient volume and physicochemical compatibility to allow proper anchoring of oleanolic acid. The molecular docking results indicate a high affinity of oleanolic acid for a site enriched in α-helical secondary structures and devoid of obstructive residues, supporting the notion that its previously

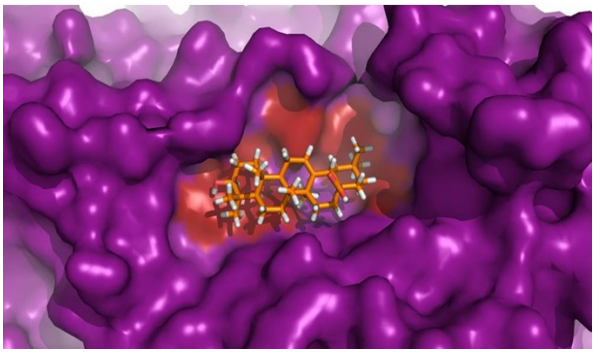

Figure 4. Fitting of oleanolic acid (orange) into a "structural pocket" of the TGR5 receptor (purple), free from steric hindrances

reported metabolic effects (Castellano *et al*., 2013) may be mediated via direct interaction with the TGR5 receptor. In particular, the most stable ligand–receptor complex exhibited highly localized binding interactions (≤1.5 Å), centralized around polar but uncharged residues—especially Gln195—whose spatial positioning within the tertiary fold likely facilitated precise molecular recognition and complexation. The aliphatic polar side chain of glutamine plays a critical role in extending the binding interface, allowing hydrogen bonding with distal reactive groups of the ligand. These findings are aligned with prior evidence suggesting that TGR5 activation contributes to anti-inflammatory signaling and metabolic regulation, particularly in obesity-related contexts (Djeziri *et al*., 2018). The ability of natural bioactive compounds such as oleanolic acid to serve as agonists of G-protein-coupled receptors (GPCRs) like TGR5 demonstrates the biochemical sophistication of phytochemicals in modulating key physiological pathways (Kim *et al*., 2014). Additionally, the biomedical potential of natural products lies in their inherent structural diversity, which allows them to target specific proteins involved in energy homeostasis, bile acid metabolism, and glucose regulation (Zhou *et al*., 2021). Thus, the interaction between oleanolic acid and TGR5 may not only justify its documented bioactivity but also position it as a promising lead compound in the development of metabolic disorder therapeutics.

CONCLUSION

The results of this study demonstrate that oleanolic acid exhibits a high affinity for a specific binding site on the TGR5 receptor. The molecular docking analysis revealed consistent and energetically favorable interactions, characterized by high specificity, spatial complementarity, and reproducibility. These findings provide strong molecular evidence supporting the biotechnological activities attributed to oleanolic acid in metabolic contexts, particularly its role in modulating key signaling pathways through G-protein-coupled receptors.

The approach adopted herein proved effective in elucidating the molecular basis underlying the interaction between oleanolic acid and TGR5, contributing valuable insights into the pharmacological potential of this natural compound. Importantly, this work reinforces the relevance of integrative and multidisciplinary methodologies—combining bioinformatics, structural biology, and pharmacology—in advancing the understanding of plant-derived bioactive molecules. Based on the evidence presented, it can be concluded that computational simulations, particularly molecular docking, serve as a powerful and cost-effective strategy in the early-phase exploration of natural products. Such tools not only facilitate the identification of promising biomolecular targets but also broaden the scope of biotechnological applications for phytochemicals. This reinforces the potential of natural compounds as viable leads in the discovery and development of therapeutics targeting metabolic diseases and related disorders.

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CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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