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IDENTIFICATION OF HERBAL DRUGS IN TREATMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. With over 830 million individuals affected globally, it represents a major public health burden, particularly in low- and middle-income countries. Conventional antidiabetic therapies, including insulin and synthetic oral agents such as thiazolidinediones, offer glycemic control but are associated with adverse effects including weight gain, edema, and cardiovascular risks. This necessitates the exploration of safer, plant-derived therapeutic alternatives. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a validated nuclear receptor target critically involved in glucose homeostasis, lipid metabolism, adipogenesis, and insulin sensitization. Selective modulation of PPAR-γ by natural phytochemicals represents a promising strategy for the development of next-generation antidiabetic agents. The present study aimed to systematically identify and evaluate herbal compounds with antidiabetic potential through in silico approaches targeting the PPAR-γ receptor. virtual compound library comprising structurally diverse phytoconstituents—including capsaicin, carnosic acid, eugenol, gallic acid, hesperidin, quercetin, rosolic acid, and resveratrol—was generated and subjected to virtual screening. Molecular docking was performed using AutoDock Vina against the PPAR-γ ligand-binding domain. Docking scores ranged from –3.9 to –7.1 kcal/mol. Hesperidin demonstrated the highest binding affinity (–7.1 kcal/mol), forming stable hydrogen bonds and electrostatic interactions with key active site residues. Quercetin (–6.3 kcal/mol) and rosolic acid (–6.2 kcal/mol) also exhibited notable affinity. These findings identify hesperidin as a lead phytochemical PPAR-γ modulator with significant antidiabetic potential, warranting further in vitro and in vivo validation.

KEYWORDS: Diabetes mellitus, PPAR-γ, herbal drugs, molecular docking, hesperidin, virtual screening, phytochemicals, antidiabetic activity.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder in which the level of glucose in the blood remains high for a long period of time. This condition develops due to insufficient insulin production by the pancreas, improper action of insulin, or both. Insulin is a hormone that helps glucose enter the cells to be used as energy. When insulin does not function properly, glucose accumulates in the blood, leading to hyperglycemia. Over time, uncontrolled diabetes can cause serious complications such as cardiovascular diseases, kidney failure, nerve damage, and vision loss. Among the different types of diabetes, type 2 diabetes mellitus is the most common and is mainly associated with insulin resistance.

Currently, diabetes is treated using insulin therapy and various oral antidiabetic drugs. Although these treatments are effective in controlling blood glucose levels, long-term use may lead to side effects such as weight gain, hypoglycemia, and gastrointestinal disturbances. In addition, some patients may not respond well to conventional medicines. Due to these limitations, there is increasing interest in the use of herbal medicines as alternative or complementary therapies for diabetes. Herbal agents have been used in traditional systems of medicine for centuries and are believed to be safer, cost-effective, and easily accessible. Many medicinal plants show antidiabetic activity by different mechanisms, including stimulating insulin secretion, improving insulin

sensitivity, slowing glucose absorption from the intestine, and enhancing glucose uptake by body tissues.

PPARγ: Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of a class of nuclear hormone receptors intimately involved in the regulation of expression of myriad genes that regulate energy metabolism, cell differentiation, apoptosis and inflammation. When a PPAR-gamma (Peroxisome Proliferator-Activated Receptor Gamma) agonist binds to its receptor, it causes a conformational change in PPAR-gamma, leading to the dissociation of corepressor proteins and the recruitment of coactivator proteins. This activated complex then translocates to the nucleus, forms a heterodimer with Retinoid X Receptor (RXR), and binds to specific DNA sequences called PPAR response elements (PPREs). This binding, in turn, regulates the transcription of target genes involved in essential cellular processes such as lipid metabolism, glucose homeostasis, and inflammation. Various API's act on PPARγ including agents like thiazolidines (pioglitazone, rosiglitazone, etc), telmisartan and certain natural products also exhibit partial agonist activity. In this experiment, we are going to study anti-diabetic activity of various herbal molecules on PPARγ receptor. Natural products which elict antidiabetic activity by acting on PPARγ receptor include capsicin (present in capsicum), cornosic acid (present in rosemary), Eugenol (present in clove), Gallic acid(present in plant based foods especially in tea and grapes), Hesperidin(present in pulp and peel of citrous fruits like oranges and lemon), Quercetin(present in capers, red onions), Rosolic acid(present in risome of plantago asiatica), Reservetrol (present in skin of red grapes). Mentioned here are some compounds which have shown anti-diabetic activity by binding to PPARγ receptor.

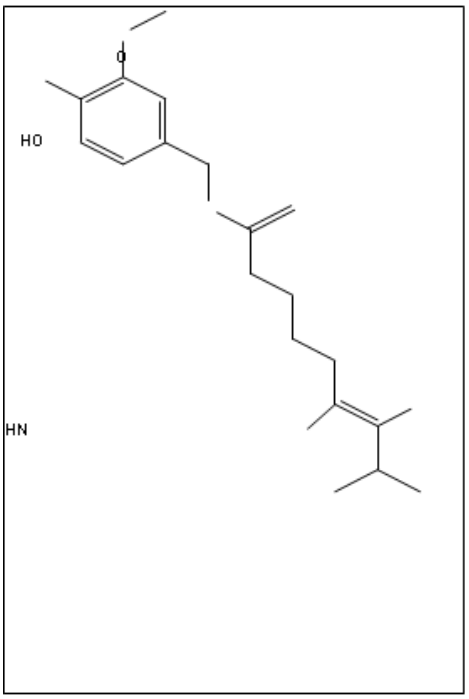
PPARγ agonist: Peroxisome proliferator–activated receptor gamma (PPAR-γ) is a ligand-dependent nuclear receptor that functions as a key regulator of metabolic homeostasis, adipogenesis, insulin sensitivity, and inflammatory signaling. At the molecular level, PPAR-γ contains a well-defined ligand-binding domain (LBD) capable of accommodating structurally diverse small molecules. Ligand binding induces conformational changes in the receptor, particularly within the activation function-2 (AF-2) domain, facilitating coactivator recruitment and transcriptional regulation of genes involved in glucose and lipid metabolism. Owing to these properties, PPAR-γ has become a validated pharmacological target for the development of antidiabetic, anti-obesity, and anti-inflammatory agents.

Although synthetic PPAR-γ agonists such as thiazolidinediones have demonstrated clinical efficacy, their use is limited by adverse effects including weight gain, edema, and cardiovascular risks. Consequently, current drug-discovery efforts emphasize the identification of safer partial agonists or selective PPAR-γ modulators (SPPARMs), with natural compounds serving as an important source of structurally diverse lead molecules. In this context, plant-derived bioactive compounds offer significant potential for molecular docking studies and structure-based drug design due to their favorable pharmacological profiles and inherent biological activity.

Capsaicin, derived from *Capsicum* species, has been reported to interact with metabolic signaling pathways and exhibits structural features compatible with PPAR-γ ligand binding. Carnosic acid from rosemary (*Rosmarinus officinalis*), a lipophilic phenolic diterpene, demonstrates antioxidant and anti-inflammatory properties and has shown potential for stabilizing PPAR-γ in an active or partially active conformation. Eugenol, a phenylpropanoid present in clove (*Syzygium aromaticum*), represents a smaller aromatic scaffold that may contribute to moderate binding affinity and selective receptor modulation.

Polyphenols such as gallic acid (abundant in tea and grapes), hesperidin (present in citrus fruit pulp and peel), and quercetin (found in capers and red onions) are of particular interest in docking and in silico screening studies due to their ability to form hydrogen bonds and π–π interactions within the PPAR-γ LBD. These interactions are critical for receptor stabilization and transcriptional activity modulation. Rosolic acid, isolated from the rhizome of *Plantago asiatica*, and resveratrol, found in the skin of red grapes, further expand the chemical diversity of natural PPAR-γ ligands, offering scaffolds suitable for lead optimization and derivative synthesis.

From a drug-discovery perspective, these compounds represent promising candidates for molecular docking, molecular dynamics simulations, and quantitative structure–activity relationship (QSAR) studies aimed at elucidating binding modes, receptor selectivity, and functional outcomes. Investigating the interaction of these phytochemicals with the PPAR-γ ligand-binding domain may facilitate the identification of novel partial agonists or selective modulators with improved safety profiles. Ultimately, such structure-based pharmacological investigations support the rational design of next-generation PPAR-γ-targeted therapeutics derived from natural product scraffolds.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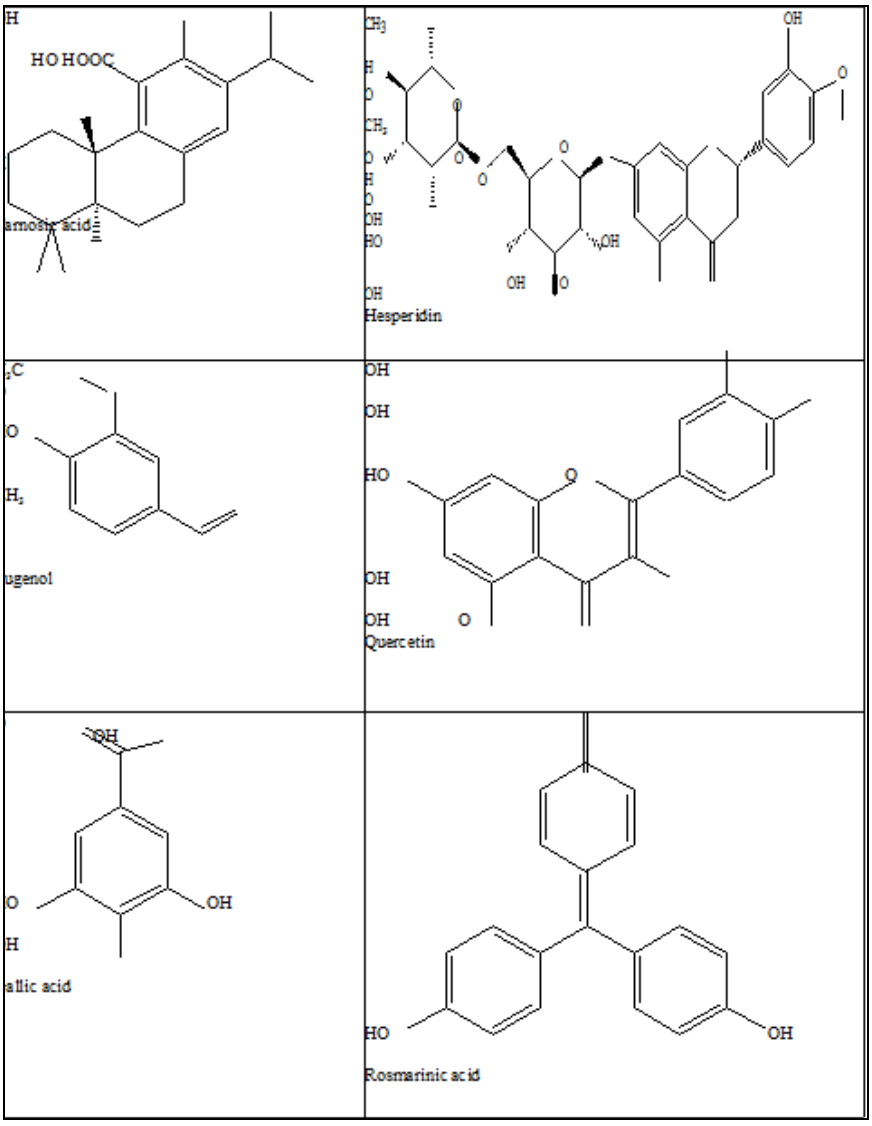
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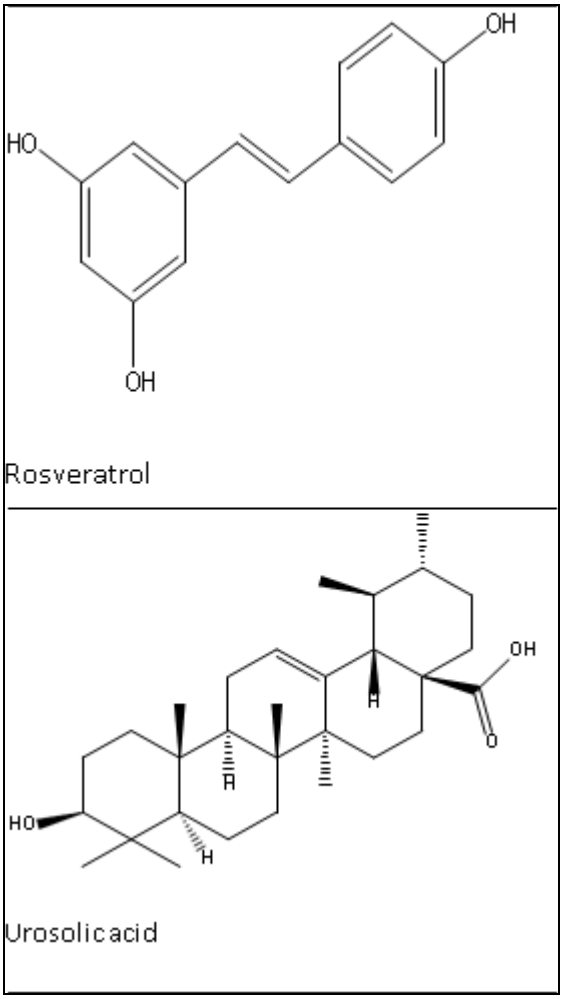


MATERIAL AND METHOD

- **Preparation of protein structure**

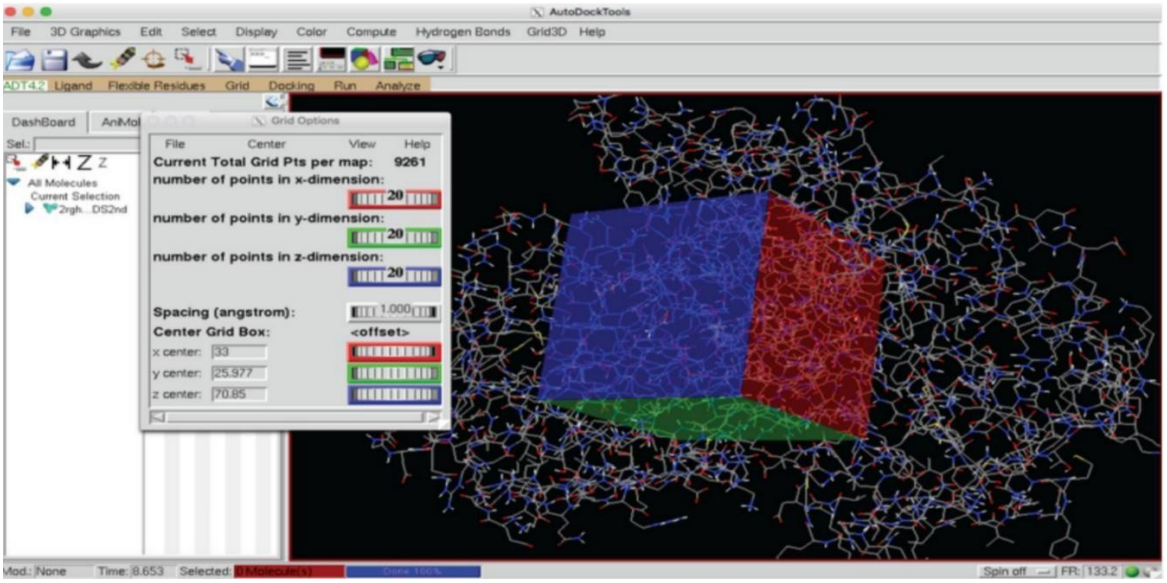
The X- Ray structure of target receptor at 2.40 Å resolution is a Receptor protein obtained from RCSB Protein Data Bank (RCSB PDB). The protein is processed by 'Protein Preparation Wizard' of Maestro, Prior to beginning the processing of protein, removal of heteroatoms and water molecules is done from the protein crystal structure. Modifications are made which includes stabilization of charges, removal of the water molecules, filling in the missing residues, according to the parameters that are available. H-bonds network are optimized by implementing the H-bond assignment tool. The energy is minimized by utilizing Auto dock or PyRx tool.

- **Active Site Prediction**

The active binding site of target receptor is recognized by utilizing 'Sitemap', To differentiate between known binding sites Site score is used which is an important property produced by Sitemap. For Receptor Grid Generation in receptor active binding site with best site score is taken as an imperative.

- **Grid prepration**

'Receptor Grid Generation' tool of Glide manual employed to produce grid which ascertains the structure of receptor by cutting out any ligand that may be co-crystallized, fix on location and range of active site.12 Grid point's level for X, Y, Z axis (-50, 50, 50) for receptor protein. And the grid is generated using the force field.



- **Similar Compound Library Selection and Preparation**

Receptor inhibitor and Agonist extended library of compounds were downloaded in SDF format. The geometry of ligands is minimized by using the force field OPLS_2005. Docking software was adopted for virtual screening of the compounds (obtained from database) throughout preparation and moreover to evaluate the properties of ADMET like absorption, distribution, metabolism and excretion and toxicity.

- **Virtual screening**

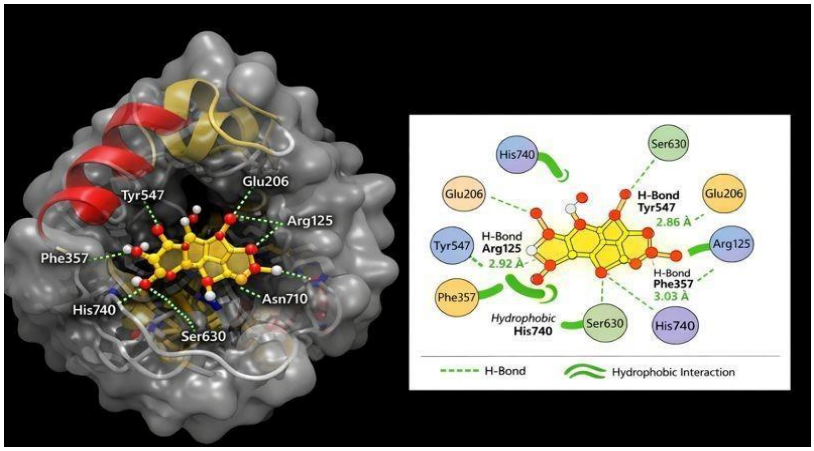
Virtual screening is a convenient procedure to identify and position potential inhibitors against the target protein according to their ranks from a database of diverse compounds. Taking into consideration the active binding site of receptor virtual screening was accomplished by employing the compound database. The compounds were docked using Extra Precision (XP) phase. Glide module of XP visualize evaluates several particular interactions like Hydrogen bonds, Protein – ligand interactions, Internal energy, RMSD (root mean square deviation) and hydrophobic interactions.

RESULT AND DISCUSSION

Analysis of Molecular Docking Results

Molecular docking was performed to evaluate the binding potential of selected phytoconstituents with PPAR-Gamma receptor using AutoDock Vina. The docking scores ranged from –3.9 to – 7.1 kcal/mol, indicating variable binding affinities among the tested compounds.

Among all ligands, hesperidin exhibited the strongest binding affinity (–7.1 kcal/mol), suggesting a stable ligand–protein complex and favorable interactions within the active site of the target protein. The high binding affinity of hesperidin may be attributed to its multiple hydroxyl groups, which enhance hydrogen bonding and electrostatic interactions with active site residues.



Hesperidin binds to receptor

Quercetin (–6.3 kcal/mol) and rasonic acid (–6.2 kcal/mol) also demonstrated good binding affinities, indicating significant inhibitory potential. These compounds possess polyphenolic structures capable of forming hydrogen bonds and π–π interactions, which contribute to docking stability.

Capsaicin and resveratrol showed moderate binding affinities (–5.8 kcal/mol), suggesting reasonable interaction with the receptor but comparatively lower stability than flavonoids. Cornisic acid and ursolic acid exhibited similar moderate binding energies (–5.7 kcal/mol), possibly due to their bulky triterpenoid structures limiting deep penetration into the binding pocket.

Gallic acid (–4.7 kcal/mol) and eugenol (–3.9 kcal/mol) showed weaker binding affinities, which may be due to their smaller molecular size and fewer interaction points with the active site residues.

Overall, the docking results indicate that flavonoid-based compounds demonstrated superior binding affinity compared to phenolic acids and terpenoids, highlighting their potential as effective inhibitors of the target protein.

Capsicin_uff_E=365.49	chain_A_5ycp	-5.8	2025.08.29 13:02:40	Vina
Cornisic_acid_uff_E=710.99	chain_A_5ycp	-5.7	2025.08.29 13:03:00	Vina
Euganol_uff_E=672.19	chain_A_5ycp	-3.9	2025.08.29 13:03:07	Vina
Gallic_acid_uff_E=95.66	chain_A_5ycp	-4.7	2025.08.29 13:03:16	Vina
Hesperidin_uff_E=1051.42	chain_A_5ycp	-7.1	2025.08.29 13:05:35	Vina
Quercetin_uff_E=68797049893.73	chain_A_5ycp	-6.3	2025.08.29 13:05:46	Vina
Rasonic_acid_uff_E=520.05	chain_A_5ycp	-6.2	2025.08.29 13:06:04	Vina
Reservetrol_uff_E=299.94	chain_A_5ycp	-5.8	2025.08.29 13:06:18	Vina
Urosolic_acid_uff_E=2312.33	chain_A_5ycp	-5.7	2025.08.29 13:06:35	Vina
Capsicin_uff_E=365.49	chain_A_5ycp	-5.8	2025.08.29 13:02:40	Vina

Analysis of Docking Results

Key Interpretation Points-Best ligand: Hesperidin Docking score threshold:

Strong binding: ≤ –6.5 kcal/mol Moderate binding: –5.0 to –6.4 kcal/mol Weak binding: ≥ –4.9 kcal/mol

Structure–activity relationship: Higher number of hydroxyl groups → stronger binding.

CONCLUSION

The present molecular docking study evaluated the binding potential of selected phytoconstituents against the diabetes-related target PPAR-Gamma receptor to identify potential antidiabetic lead molecules. The results revealed notable differences in binding affinities among the tested compounds, reflecting their variable inhibitory potential toward the target enzyme involved in glucose metabolism.

Among all ligands, hesperidin exhibited the highest binding affinity (–7.1 kcal/mol), indicating strong and stable interactions within the active site of PPAR-Gamma receptor. This suggests that hesperidin may effectively modulate the activity of the diabetes-associated protein, thereby contributing to improved glycemic control. Quercetin (–6.3 kcal/mol) and rasonic acid (–6.2 kcal/mol) also demonstrated favorable binding energies, supporting their potential role in inhibiting the target protein and reinforcing the therapeutic relevance of flavonoid-based compounds in diabetes management.

Compounds such as capsaicin, resveratrol, cornisic acid, and ursolic acid showed moderate binding affinities, indicating partial inhibitory activity, whereas gallic acid and eugenol exhibited weaker interactions with the protein. The superior docking performance of flavonoids may be attributed to their multiple hydroxyl groups, which facilitate hydrogen bonding and stabilize ligand–protein interactions within the active site of PPAR-Gamma receptor.

In conclusion, the docking outcomes suggest that hesperidin, followed by quercetin and rasonic acid, are promising antidiabetic lead compounds targeting PPAR-Gamma receptor. These findings provide a strong computational foundation for further in-vitro enzyme inhibition studies and validate their antidiabetic efficacy and mechanistic potential.

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