Research Paper

Impact of Bougainvillea glabra on antioxidant activity by *in vitro* and *in silico* investigation of the insulin signaling pathway

Asha Monica Alex[1] | Vivekanandam Swabna[1] | Edward Arockiasamy[1] |

1. Department of Biotechnology, St Joseph's College, (Autonomous), Trichy, Tamil Nadu, India

Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, often resulting from insulin resistance and oxidative stress. With the limitations of current pharmacological treatments, there is growing interest in identifying plant-derived compounds that can modulate key components of the insulin signaling pathway. In this study, the methanolic leaf extract of *Bougainvillea glabra* was evaluated for its antioxidant, antimicrobial, and antidiabetic potential through both *in vitro* and *in silico* approaches. Phytochemical profiling using Gas Chromatography–Mass Spectrometry (GC-MS) revealed the presence of bioactive compounds, including 2-propenoic acid, 2-ethylhexyl ester and 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one. The antioxidant potential of the extract was assessed using the DPPH radical scavenging assay, which showed a concentration-dependent activity with a maximum inhibition of 77.57% at 50 μL. Antibacterial activity was demonstrated against several microbial strains, notably *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas fluorescens*, with enhanced zones of inhibition observed at higher extract concentrations. Molecular docking studies were carried out targeting insulin signaling proteins GLUT-4, IRS-1, and SREBP-1c. Among these, GLUT-4 showed the strongest binding affinity with the key phytocompounds, with docking scores of –8.7 and –7.9 kcal/mol, along with multiple hydrogen bond interactions. Pharmacokinetic and toxicity predictions using SwissADME and pkCSM indicated high gastrointestinal absorption, low mutagenicity, and favorable drug-likeness profiles for most compounds, supporting their therapeutic potential. In conclusion, *Bougainvillea glabra* demonstrated significant antioxidant, antimicrobial, and antidiabetic properties. The high binding affinity of its phytocompounds to GLUT-4 and their favorable ADMET profiles highlight their promise as candidates for plant-based drug development in the management of Type 2 Diabetes Mellitus.

1. Introduction

Diabetes is a prevalent disease affecting people worldwide, with the number of diagnosed cases steadily increasing over the years. In 1985, there were 30 million affected individuals, while by 1995, this number has increased to 135 million (Reed, Bain, and Kanamarlapudi 2021; Pradeepa and Mohan 2002). Globally, 300 million individuals are predicted to have diabetes by 2025, with Type II diabetes accounting for more than 90% of these cases (Alves-Costa *et al.* 2025; He *et al.* 2025). This increase is attributed to globalization and changes in lifestyle. Hyperglycemia results from both insulin resistance and insulin deficiency, and it can lead to pancreatic β-cell failure. It is a metabolic disorder that develops due to hyperglycemia resulting from inadequate insulin in the body (Wilcox 2005). Diabetes mellitus is still a serious worldwide health issue, even in tropical regions. The past decade has witnessed an exponential rise in its prevalence, despite significant progress in treatment strategies and prevention strategies (Unnikrishnan and Mohan 2016). Due to these limitations, new and more effective treatments are still needed in order to control diabetes better and reduce its risk factors, including hypertension, hyperlipidemia, and other related diseases. Herbal therapy is one of the various alternative drugs that have become increasingly popular. This is the reason that, over the last decade, the use of herbs has increased more than threefold. Herbal therapies for Diabetes Mellitus have shown ameliorative effects in blood glucose control Some of these therapies include Konjac-Mann, honey, *Azadirachta indica* (Vidhya Rekha *et al.* 2022; Modak *et al.* 2007; Usai, Majoni, and Rwere 2022). Originating in South America, bougainvillea, also known by its common name Glory of the Garden, is a popular plant in warm, tropical climates like the Caribbean and Southern California (Bhat *et al.* 2011). It is a woody, prickly shrub with pink, purple, red, orange, yellow, and most importantly, white blooms. Three different types of bougainvillea are *Bougainvillea glabra*, *Bougainvillea spectabilis*, and *Bougainvillea harrisi* (Ornelas Garcia *et al.* 2023; Saleem *et al.* 2021). Tropical and temperate climates both cultivate *Bougainvillea glabra* for ornamental purposes. The aqueous extract and decoction of this plant have been used by tribal people as a fertility control strategy in various cultures (Ghogar and Jiraungkoorskul 2017). Additionally, its antibacterial, anti-hyperlipidemic, anti-inflammatory, anti-cancer, antioxidant, anti-diabetic, and anti-hepatotoxic properties

have been established (Tran, Pham, and Le 2020). A number of phyto constituents have been implicated in being responsible for the medicinal strength of the plant. *Bougainvillea glabra* has information available for treatment of ulcers, diarrhoea, and its antimicrobial activity. As per some traditional healers, specific beetles that feed on any form of bougainvillea stem are dried, powdered, and thereafter applied as the active ingredient in common herbal medications that are claimed to cure diabetes mellitus (Abarca-Vargas and Petricevich 2018). It is considered by some that the powdered form offered by the Bougainvillea stem beetle is a crucial part of these herbal ingredients. This study aimed to identify the phytocompounds that have anti-diabetic effects in the insulin signaling pathway and assess the antioxidant and anti-microbial efficacy of *Bougainvillea glabra* (Singh *et al.* 2016). We hypothesize that the phytocompounds extracted from *Bougainvillea glabra* modulate insulin signaling proteins (GLUT-4, IRS-1, and SREBP-1c) and exhibit antioxidant and antimicrobial properties, which can be validated through *in vitro* assays and *in silico* molecular docking.

2. Materials and Methods
2.1. Collection of Plant Sample

A plant sample was collected from Srirangam (Tamil Nadu) in January 2023. It was identified by DR. S. Soosairaj, a taxonomist at the Rapinat herbarium (Muthukrishnan *et al.* 2025). The substance was crushed as a fine powder for extraction after being carefully cleaned and dried. Methanol is used to macerate the leaf powder overnight for a day, and methanolic extract derived was stored for further work (SG *et al.* 2022).

2.2. Determination of Anti-oxidants using DPPH Assay

With a traditional method, the leaf methanolic extract of *Bougainvillea glabra* was screened for free radical scavenging activity, specifically DDPH. The concentration of 0.1 mM DPPH was mixed with different concentrations of leaf extracts to provide a reaction mixture. The ratio of EA's free radical scavenging capacity was determined and quantified by using standard ascorbic acid (El-Nashar *et al.* 2025).

2.3. Determination of Anti-bacterial Activity

The plant extracts of *Bougainvillea glabra* were checked against gram-positive and gram-negative bacteria. Agar well diffusion method is employed for determining the antimicrobial activity of microbial or plant extracts. The procedure is dispersing 1ml of each of the bacterial inoculate onto the agar surface, followed by adding 2-6µl of *Bougainvillea glabra* extract solution. Positive control, such as ampicillin disc, is kept on the petri plate. The test organism is inoculated onto the agar plate and incubated at 370c for 24 hours. The plant extract suppresses the growth of the tested microorganisms from the inhibition zone in the well (Kiani *et al.* 2023).

2.4. Phytocompounds Identification through GC-MS

The phytochemical compounds of methanolic *Bougainvillea glabra* leaf extract were investigated by Gas Chromatography–Mass Spectrometry (Naz *et al.* 2020; Ogunwande *et al.* 2019). The study employed a 30 m SH-Rxi-5Sil-MS non-polar film-coated column, interfaced with a Shimadzu QP2020 mass spectrometer. Injector temperature was maintained at 250°C, and the oven initial temperature was maintained at 50°C (Saleh *et al.* 2024). A 1-milliliter solution of hexane extract from the leaves was injected in split mode with a 1:10 ratio using helium as the carrier gas. Mass spectra were acquired in electron ionization mode at 70 eV, scanning between 50–500 amu, and the ion source temperature was maintained at 200°C. Identification of the compounds was established through comparison of the obtained mass spectra with the NIST 2005 MS library and literature evidence(Koo, Kim, and Zhang 2013).

2.5. Pharmacokinetics

Two computer methods were employed to forecast the pharmacokinetic profiles for phenolic compounds. Initially, the SwissADME tool was employed to estimate parameters such as molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), rotatable bonds (RB), and topological polar surface area (TPSA), which were then analyzed based on Lipinski's Rule of Five (Daina, Michielin, and Zoete 2017). Then, the pkCSM platform was utilized for the analysis of ADME/T properties of the docked phytochemicals (Alici *et al.* 2025).

2.6. Ligand Preparation

The bioactive compounds isolated from the GC-MS of *Bougainvillea glabra* methanolic extract were drawn using ACD/ChemSketch 12.01 (Advanced Chemistry Development, Inc (Joshi *et al.* 2023). The geometries of the ligands were optimized with HyperChem 8.0.3 to obtain energy-minimized conformations. The optimized structures were stored in PDB format and then converted to PDBQT format using AutoDock Tools (Salamat *et al.* 2024).

2.7. Ligand Preparation

The 3D structures of the insulin signaling pathway proteins, such as GLUT-4 (PDB ID: 7WSM), IRS-1 (PDB ID: 1QQG), and SREBP-1c (PDB ID: 1AM9), were downloaded from the RCSB Protein Data Bank (Berman *et al.* 2000). Protein structures were purified by stripping away water molecules and heteroatoms using BIOVIA Discovery Studio Client 4.5. Hydrogen atoms were added and Kollman charges were assigned using AutoDock Tools (version 1.5.7) (Tang *et al.* 2022). The active binding site

was found in Discovery Studio by specifying the ligand-binding area and creating a grid box enclosing the active site residues (Mun *et al.* 2022).

2.8. Docking Procedure

AutoDock 1.5.7 molecular docking was conducted with the Lamarckian Genetic Algorithm (LGA) used for the conformational search(Ni *et al.* 2024; Guan, Zhang, and Ning 2016). Grid box size was set to encompass the designated active site area, and docking settings were left at default with 2.5 million energy evaluations. Binding energies and inhibition constants (Ki) were taken for the leading poses for analysis (Wang *et al.* 2024; Zhang *et al.* 2024).

2.9. Visualization and Interaction Analysis

Optimal docking conformations were compared and visualized by employing BIOVIA Discovery Studio Visualizer 4.5 to investigate hydrogen bonding interactions, hydrophobic contacts, and other non-covalent interactions among the target proteins and ligands.

3. Results and Discussion
3.1. Plant Identification and Extraction Process

The plant species was identified as *Bougainvillea glabra* (Voucher No. 3381) by Dr. Soosairaj, Taxonomist, PG and Research Department of Botany, St. Joseph's College, Tiruchirappalli and the herbarium sheet was attached. Soxhlet extraction is a thermally stable extraction technique used for analyzing analytes. The process involves placing a sample in a disposable thimble in a Soxhlet apparatus, refluxing the solvent, and then transferring the extract to a boiling flask. This process takes 12-24 hours. For example, to extract the leaves of *Bougainvillea glabra*, 50g of leaves were dried and packed in a Soxhlet apparatus. The sample was then decolorized, and methanol was extracted. The extraction process involved adding solvent to a distilled flask, soaking the samples overnight, and heating the mixture at 80° C for 11 cycles. After the decolorization, the methanol extraction was performed, and the plant extraction was separated into the boiling flask and stored in an amber bottle for GC-MS results.
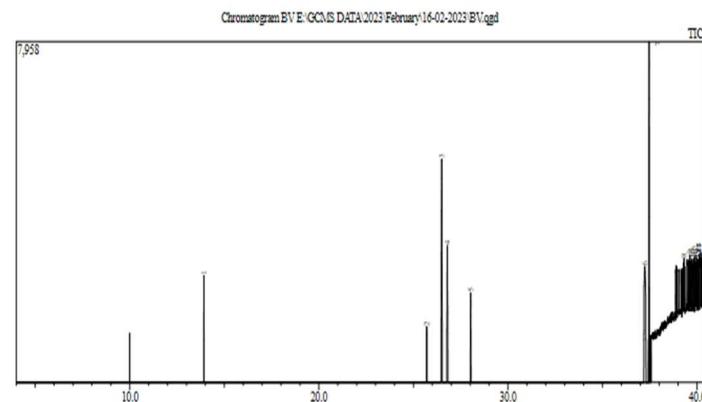

Figure 1. GC-MS Chromatogram of methanolic *Bougainvillea glabra* extract

3.2. GC-MS Analysis of *Bougainvillea glabra*

GC-MS determination of methanolic extract of *Bougainvillea glabra* exhibited the existence of a few bioactive molecules that can be responsible for its pharmacological action. 2-propenoic acid, 2-ethylhexyl ester and 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one are major compounds identified among them (**figure 1**). The compounds have functional groups like hydroxyl, methoxy, and ester groups, which are generally found in antioxidant, anti-inflammatory, and antidiabetic activity. The occurrence of these bioactive molecules underlines the medicinal value of this plant in its control of metabolic disease such as diabetes.

Table 1. GC-MS Chromatogram of methanolic *Bougainvillea glabra* extract

SPECIES	PC	2µL	4µL	6µL
Staphylococcus aureus	1.8	1.4	1.9	2.1
Pseudomonas fluorescens	1.4	1.1	1.9	2.4
Escherichia coli	1.4	1.5	1.7	1.8
Streptococcus pyogenes	0.4	0.3	0.4	0.5
Enterococcus faecalis	0.3	0.4	0.5	0.5
Proteus mirabilis	0.3	0.2	0.4	0.5
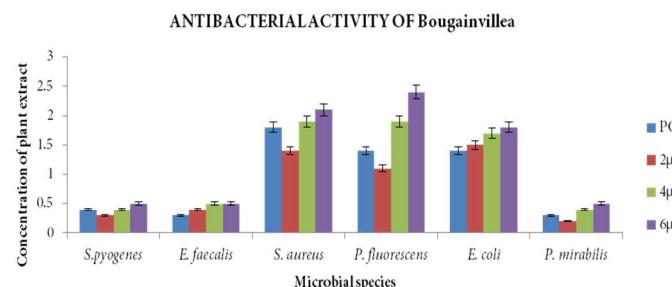
Figure 2. The graph shows the comparative analysis of antibacterial activity for the *Bougainvillea glabra*
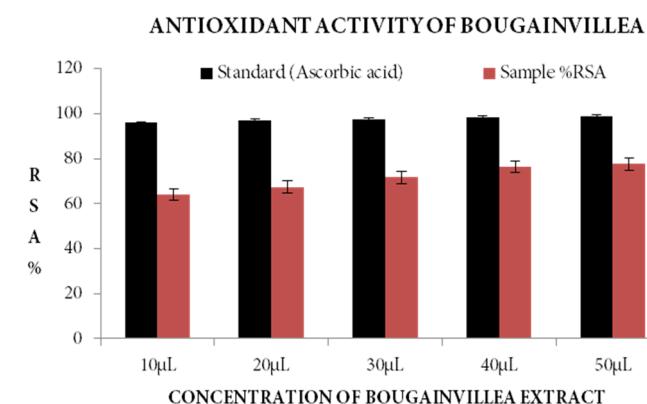
Figure 3. shows the sample % RSA of the plant *Bougainvillea glabra*

3.3. Anti - Bacterial Activity

The antibacterial activity of Bougainvillea by disc diffusion and agar well diffusion methods were compared and shown in the **(table 1; figure 2)**. Among the various concentrations used, the 6µL concentration exhibited significant results in all the tested organisms viz., S. aureus antimicrobial activity of some medical plant methanol extracts (100µg mIG1) and antibiotic (10µg MIG1) against bacterial species tested by disc diffusion assay zone of inhibition (mm). The zone of clearance was observed more in the 6µL concentration in all the species. It shows the plant extract have more antibacterial activity in this concentration. These plant extract shows more antibacterial activity with the staphylococcus species. A negative control consisting of methanol alone (the solvent used for extraction) was used in parallel with the test samples to confirm that the observed zones of inhibition were due to the plant extract and not the solvent.

3.4. Antioxidant Properties of *Bougainvillea glabra*

As per Yamagishi and Matsui (2010), an antioxidant is any compound that prevents or retards oxidative damage to target molecules. Antioxidant capacity of the extracts was assayed by the DPPH free radical scavenging assay. Findings showed concentration-dependent increase in radical scavenging activity of methanolic extract of *Bougainvillea glabra* with maximum inhibition (~78%) at 50 µL (**figure 3**). This confirms the existence of bioactive compounds with good hydrogen-donating activity, which could neutralize free radicals. The activity was as good as that of ascorbic acid, a reference antioxidant, indicating the extract has flavonoids and phenolic compounds, already known for their ability to reduce oxidative stress, a key player in the etiology of diabetes mellitus. The findings were presented as ascorbic acid equivalents (AAE, mg/g) and IC$_{50}$ values of *Bougainvillea glabra* extracts

3.5. Pharmacokinetics

A subfield of pharmacology called pharmacokinetics studies how drugs interact with living things. Any chemical xenobiotic, including prescription medications, insecticides, food additives, cosmetics, etc., is one of the compounds of interest. From the time a chemical is injected until it is fully removed from the body, it makes an analysis of the chemical. A medicine must pass through cell membranes in order to be absorbed, distributed, metabolized, and excreted. The drug's dosage and mode of administration have an impact on its pharmacokinetic characteristics. The pkCSM analysis provided valuable insights into the drug-likeness and toxicity profiles of the identified phytocompounds from *Bougainvillea glabra*.

Notably, most compounds exhibited no AMES toxicity, indicating they are non-mutagenic and potentially safe for therapeutic applications. The absence of hERG I inhibition in all but one compound suggests a low risk of cardiotoxicity, which is a common cause of drug attrition during development. Additionally, the compounds displayed high gastrointestinal absorption, favorable bioavailability scores (0.55), and compliance with multiple drug-likeness filters (Lipinski, Veber, Egan). However, one compound showed positive hepatotoxicity, indicating the need for further in vivo validation and possible structural modifications. Overall, the pkCSM predictions support the drug-likeness of these compounds, especially 2-propenoic acid, 2-ethylhexyl ester and 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one, which demonstrated optimal pharmacokinetic and safety profiles, making them promising candidates for further development as antidiabetic agents.

3.6. Molecular Docking

Docking experiments were done for three proteins that play a crucial role in the insulin signaling pathway, namely GLUT-4, IRS-1, and SREBP-1c. Out of these, GLUT-4 showed maximum binding interaction with the potential phytocompounds identified, 2-propenoic acid, 2-ethylhexyl ester and 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one, with binding energies of −8.7 kcal/mol and −7.9 kcal/mol, respectively (Table 2). IRS-1 and SREBP-1c, on the other hand, were weaker in terms of binding affinity (less than −6.0 kcal/mol) and restriction in hydrogen bond development, reflecting relatively lower interaction stability. Hence, these are only detailed docking scores shown for GLUT-4, reflecting the strongest and biochemically meaningful interactions.

These tight interactions in GLUT-4 can be explained by the presence of polar residues like ASN A:431 and GLN A:299 at the binding site, which made stable hydrogen bonds with functional groups of the docked ligands. This indicates a possible mechanism of increased glucose uptake and enhanced insulin sensitivity. Hence, these are only detailed docking scores shown for GLUT-4, reflecting the strongest and biochemically meaningful interactions. These tight interactions in GLUT-4 can be explained by the presence of polar residues like ASN A:431 and GLN A:299 at the binding site, which made stable hydrogen bonds with functional groups of the docked ligands (**figure 4**). This indicates a possible mechanism of increased glucose uptake and enhanced insulin sensitivity.
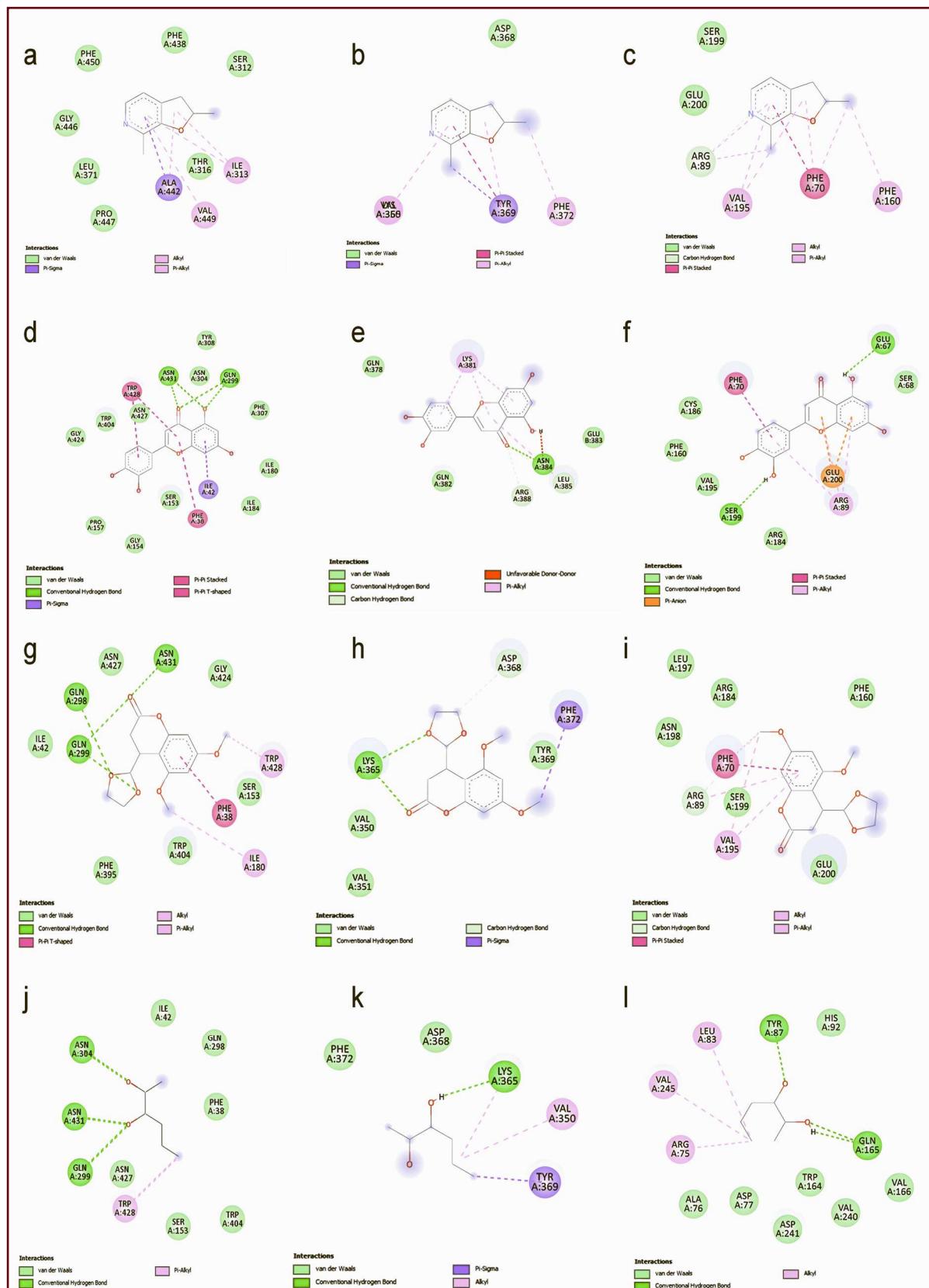
Figure 4. Docking results of target proteins GLUT, SREBP-1c, & IRS-1 with phytocompound Furo [2, 3-c] pyridine, 2,3-dihydro-2,7-dimethyl,2-Propenoic acid, 2-ethylhexyl ester, 3,4-Dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one, (SS)- or (RR)-2,3-hexanediol

a) GLUT vs 2-Propenoic acid, 2-ethylhexyl ester
c) GLUT vs 3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-dimethoxy-1(2H)-Benzopyran-2-ONE
d) GLUT vs (SS)- or (RR)-2,3-hexanediol
e) SREBP-1c vs 2-Propenoic acid, 2-ethylhexyl ester
g) SREBP-1c vs 3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-dimethoxy-1(2H)-Benzopyran-2-ONE
 i) IRS-1(C) vs 2-Propenoic acid, 2-ethylhexyl ester

b) GLUT vs Furo [2, 3-c] pyridine, 2,3-dihydro-2,7-dimethyl
f) SREBP-1c vs Furo [2, 3-c] pyridine, 2,3-dihydro-2,7-dimethyl
h) SREBP-1c vs (SS)- or (RR)-2,3-hexanediol
j) IRS-1(C) vs Furo [2, 3-c] pyridine, 2,3-dihydro-2,7-dimethyl-
k) IRS-1(C) vs 3,4-Dihydro-4-(1,3-Dioxolan-2-yl)-5,7-dimethoxy-1(2H)-Benzopyran-2-ONE
l) IRS-1(C) vs (SS)- or (RR)-2,3-hexanediol

Table 2. Scoring values of phytocompounds

Phytocompound	Binding Energy	Hydrogen Bond Interactions
Furo[2,3-c] pyridine, 2,3-dihydro-2,7-dimethyl	-5.8	Not specified
2-Propenoic acid, 2-ethylhexyl ester	-8.7	AS:431, GLN299
3,4-Dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one	-7.9	ASN431, GLN298, GLN299
(SS)- or (RR)-2,3-hexanediol	-4.5	ASN304, ASN431, GLN299

Hence, these are only detailed docking scores shown for GLUT-4, reflecting the strongest and biochemically meaningful interactions. These tight interactions in GLUT-4 can be explained by the presence of polar residues like ASN A:431 and GLN A:299 at the binding site, which made stable hydrogen bonds with functional groups of the docked ligands (**figure 4**). This indicates a possible mechanism of increased glucose uptake and enhanced insulin sensitivity.

4. Discussion

Dietary modification plays a crucial role in the prevention and management of chronic metabolic disorders such as diabetes. Consistent intake of fruits and vegetables has been linked to a reduced risk of diabetes and other lifestyle-related diseases, largely due to the presence of bioactive phytochemicals (Xiao *et al.* 2024; Alyafei and Daley 2025). *Bougainvillea glabra* (Nyctaginaceae family), also referred to as Choisy, is an ornamental flower that is also used in traditional medicine for the treatment of conditions like diarrhea, hypotension, gastrointestinal upset, inflammation, and pain (Ornelas Garcia *et al.* 2023). GC-MS analysis in this work indicated several bioactive compounds in methanolic extract of *B. glabra*, described in **table 1**. Oxidative stress caused by reactive oxygen species (ROS) has been implicated in chronic diseases such as cancer, cardiovascular disorders, and diabetes (Arika *et al.* 2019). Antioxidant techniques like DPPH and FRAP are commonly utilized to quantify the ROS-scavenging activity of nature's extracts (Chaves, Santiago, and Alias 2020). Research has already reported and indicated higher antioxidant activity of encapsulated extracts than that of free extracts, whereas few researchers indicated with clearly illustration on how hydroxyl-abundant compounds such as nettle seed gum are involved in free radical scavenging (Kenari and Razavi 2022). In our study, the methanolic extract of *B. glabra* exhibited significant antioxidant activity, supporting its therapeutic potential. Natural plant extracts have also gained importance in the food and pharmaceutical industries due to their nontoxic, renewable, and eco-friendly nature (Kumar *et al.* 2023). In this context, both free and encapsulated *B. glabra* extracts demonstrated antimicrobial activity, consistent with previous reports and have observed strong antibacterial effects of Bougainvillea extracts against pathogens including *Bacillus subtilis, S. aureus, E. coli,* and *Klebsiella pneumoniae* (Wu *et al.* 2022; Saleem *et al.* 2020). Molecular docking results further supported the pharmacological value of *B. glabra*. Docking studies involving GLUT-4, IRS-1, and SREBP-1c proteins showed that GLUT-4 had the highest binding affinities with key phytocompounds such as 2-propenoic acid, 2-ethylhexyl ester (–8.7 kcal/mol) and 3,4-dihydro-4-(1,3-dioxolan-2-yl)-5,7-dimethoxy-1(2H)-benzopyran-2-one (–7.9 kcal/mol). These compounds formed strong hydrogen bond interactions, particularly with amino acid residues ASN A:431, GLN A:298, and GLN A:299. Among all the tested proteins, GLUT-4 consistently demonstrated stronger and more stable interactions, suggesting its potential as a key molecular target in managing Type 2 Diabetes Mellitus through phytocompound intervention.

The antidiabetic potential of *Bougainvillea glabra* aligns well with other known medicinal plants. For instance, *Azadirachta indica* (neem) and *Momordica charantia* (bitter melon) are rich in bioactives like flavonoids and terpenoids that mimic insulin action and enhance antioxidant defense. Compounds such as charantin and vicine in *M. charantia* are known to promote GLUT-4 translocation and improve insulin sensitivity. Similarly, *Trigonella foenum-graecum* (fenugreek) contains 4-hydroxyisoleucine, a compound that stimulates insulin secretion. The strong docking affinities observed between *B. glabra* phytocompounds and GLUT-4 suggest a mechanism similar to these traditional antidiabetic agents. When compared to standard antidiabetic drugs such as metformin, which acts indirectly via AMPK activation, *B. glabra* offers a potentially direct interaction with key glucose transporter proteins, possibly with fewer adverse effects. Therefore, the current findings support the therapeutic potential of *Bougainvillea glabra* as a promising natural candidate for further pharmacological development in diabetes management.

5. Conclusion

The properties of *Bougainvillea glabra* plant extract were performed, and it showed certain properties like antidiabetic, antibacterial, antioxidant and pharmacokinetic properties. The result shows that the extract has good antibacterial activity. The antioxidant activity also performed by following DPPH assay showed high antioxidant so, it has property of prevention of type 2 diabetes. The molecular docking studies recommended that *Bougainvillea glabra* was used for the identification of selected target gene in insulin signaling pathway with highest binding energies. Future research should prioritize human trials, mechanistic pathway elucidation, and formulation strategies to enhance bioavailability. Overall, *B. glabra* emerges as a safe, accessible, and multifunctional botanical with unique GLUT-4 targeting potential. Its integration into standardized Phyto therapeutics could provide an affordable, culturally acceptable complement to conventional diabetes therapies, offering new opportunities in addressing the global diabetes epidemic.

6. Disclosure Statements

6.1. Author Contribution

A.M: Writing-Original Draft Preparation; Methodology; Software; Validation; **S.V:** Conceptualization; Supervision. **E.A:** Writing-Review and Editing.

6.2. Declaration of Generative AI

The authors declare that no generative AI tools were used in the drafting, writing, or editing of the manuscript. All scientific interpretations and conclusions are the authors' own. AI-based tools were used only for language grammar refinement and formatting purposes, and the final content was verified and approved by the authors.

6.3. Ethics approval (for clinical/animal studies)

This study did not involve the participation of human subjects, the use of identifiable human data or tissue, or any experiments on live animals. Consequently, the requirement for ethical approval or informed consent did not apply.

6.4. Informed Consent Statement

Not applicable.

6.5. Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

6.6. Acknowledgment

6.7. Funding Statement

6.8. Conflicts of Interest

The authors declare that they have no known financial, personal, academic, or other relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript. All authors confirm that there are no competing interests to declare.

6.9. Corresponding Author Contact Information

The corresponding author **Dr. Asha Monica A** can be contacted via email ashamonica7[at]gmail.com

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