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Original Research Article

IN SILICO STUDY OF THE ACTIVITIES OF THE CONSTITUENTS OF *Gongronema latifolium* (Benth) ON THE PEROXISOME PROLIFERATOR – ACTIVATED RECEPTOR GAMMA(PPAR-ɣ) OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a multifactorial metabolic disorder characterized by chronic hyperglycemia and impaired metabolism of proteins, fats, and carbohydrates due to inadequate insulin secretion or function. The condition causes severe physical distress and imposes financial burdens on individuals and healthcare systems. Common symptoms include polyuria, polydipsia, and polyphagia. The global prevalence of diabetes has more than doubled over the past 30 years. Although several classes of antidiabetics are available, many are associated with side effects, high cost, limited accessibility and reduced effectiveness over long-term use. This study focuses on utilizing computational methods to investigate the potential antidiabetic effects of phytochemical compounds derived from *Gongronema latifolium* on the peroxisome proliferator-activated receptor gamma (PPARγ), a receptor involved in insulin regulation. The target protein structure (6t1s) was obtained from the Protein Data Bank and prepared using Chimera 1.10.1, PyMol 2.3.0, and AutoDock Tools 1.5.6. A reference ligand (EDK) was similarly prepared. Phytochemicals from *Gongronema latifolium* were sourced from the PubChem database and DrugBank database, then screened for drug-likeness using Lipinski's Rule of Five and toxicity criteria via DataWarrior. Selected compounds were further prepared for docking. Docking protocol validation was conducted, and molecular docking was performed using AutoDock Vina 4.2.6 on Ubuntu Linux 20.04. Results were analyzed in Excel and visualized with PyMol. The reference ligand demonstrated a mean binding energy of -11.9 kcal/mol. The top ten phytochemicals, with binding energies ranging from -10.1 to -9.4 kcal/mol, showed promising binding affinities. In conclusion, the front-runners can be predicted to have antidiabetic effects; however, camptothecin exhibited the highest binding affinity of -10.1 kcal/mol, indicating its potential as an antidiabetic agent targeting the PPARγ receptor.

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INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterized by prolonged high blood sugar levels and **disruptions** in the metabolism of proteins, fats, and carbohydrates. These disruptions are primarily caused by insufficient insulin production or the body's inability to utilize insulin effectively. Over time, diabetes can result in severe complications, including organ damage and dysfunction, along with symptoms such as increased thirst, frequent urination, blurred vision, and unintentional weight loss [1].

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This arises when blood glucose levels become excessively high due to inadequate insulin secretion by the pancreas or a failure of the body's cells to respond properly to insulin. Diabetes can affect individuals of any age group.

In countries within the Eastern Mediterranean Region (EMR), diabetes mellitus has emerged as a major public health concern. Research shows that up to 10% of adults aged 20 and above have diabetes, and this prevalence could double when cases of impaired glucose tolerance are included [2]. The symptoms not only cause significant discomfort but also lead to substantial healthcare expenses. Complications may occur acutely or overtime, contributing to high rates of disability and early mortality through conditions such as neuropathy, end-stage renal disease, strokes, retinopathy, and cardiovascular disease. The widespread incidence of diabetes, particularly type 2 diabetes mellitus (DM2), presents a major health and socioeconomic challenge. In the U.S., approximately 6.6 % of adults aged 20–74 is affected, with projections suggesting this could rise to 10% in the next decade. Canada incurs an estimated $7–20 billion annually in managing DM2 and its complications. Regardless of the root cause, all forms of diabetes involve disrupted insulin secretion and/or sensitivity [3].

Gongronema latifolium Benth., a plant native to tropical Africa, is esteemed for its nutritional and therapeutic benefits. Commonly used as a spice or vegetable in soups and salads, it is traditionally applied in treating ailments like cough, diabetes, hepatitis, malaria, and digestive issues [4]. Known by various names across West African ethnic groups, such as "Utazi" (Igbo), "Utasi" (Efik/Ibibio), and "Arokeke" (Yoruba), the plant has a distinctive, sharp, bitter-sweet taste. It produces a white latex when cut and features green leaves and yellow flowers [5]. Traditional healers use *G. Latifolium* to aid pancreatic regeneration and manage several diseases, especially diabetes [4]. Various plant parts—including the fruits, seeds, leaves, roots, and stems—contain bioactive compounds. The leaves are typically chewed, brewed, or infused, while roots are usually decocted due to their tougher texture [6]. The leaves are nutritionally rich, containing lipids, proteins, vitamins, minerals, and essential amino acids. They are often used fresh or in powdered form. Phytochemical studies have identified significant levels of flavonoids, phenols, cyanides, and saponins in the dried leaves [7], with fresh leaves showing a higher alkaloid content [8]. Roots also contain higher concentrations of flavonoids, alkaloids, hydrogen cyanide, and tannins.

Peroxisome proliferator-activated receptors (PPARs) are part of a especially involved in energy storage in vascular tissues [9]. PPAR-γ, highly expressed in adipose tissue, is crucial larger nuclear receptor family that includes receptors for hormones and vitamins. Three subtypes, PPAR-α, PPAR-β, and PPAR-γ, play essential roles in energy metabolism, with PPAR-γ for fat cell development and regulates genes involved in glucose and lipid metabolism. It is also the target of thiazolidinediones, a class of oral anti-diabetic drugs that enhance insulin sensitivity [10]. PPAR-γ can be activated by several structurally different compounds, such as thiazolidinediones, polyunsaturated fatty acids, prostaglandins, and lipoxygenase products like 15-HETE and 13-HODE [11]. Interestingly, PPAR-γ levels are higher in visceral fat among obese individuals but are more concentrated in subcutaneous fat in lean individuals. Tumour necrosis factor (TNF)-α can downregulate PPAR-γ expression, while insulin has been shown to upregulate it [12].

In silico drug design, also known as computational drug design, is increasingly applied in biology, chemistry, and pharmaceutical sciences. It enables the efficient analysis and development of new drugs using methods such as molecular visualization, homology modelling, and molecular dynamics [13,14]. As this paradigm continues to evolve, it holds promise for accelerating target discovery and the development of biologically active compounds [15,16].

MATERIALS AND METHODS

Software and web services

Commonly used tools for this study include PyMol (version 2.3.0), Chimera (version 1.10.1), AutoDock Tools (version 1.5.6), DataWarrior, Open Babel (version 2.3.2), and MGL Tools (version 1.5.6). For bioinformatic and chemoinformatics mining, we have the Protein Data Bank (PDB), PUBCHEM and Drug Bank.

Molecular docking and dynamics simulation documents include:

Conf.Text: This Ubuntu text document inputs binding site scores based on grid box size and position for accurate binding site representation in molecular docking simulations.

Bash Binbash.sh: This ODT document contains codes for molecular docking procedures. Finally, a window 10 pro laptop.

Bioinformatics Mining – Target Site Identification

A search was carried out in the Protein Data Bank (PDB) to identify potential target proteins associated with diabetes mellitus. The selection criteria included: a resolution value below 4 Å, preference for proteins with the lowest Ångström values (indicating higher structural clarity), and the presence of an organic ligand relevant to the pathogenesis of diabetes mellitus.

Chemoinformatics Mining

A total of 115 phytochemicals derived from the leaves of *Gongronema latifolium* were obtained from DrugBank and PubChem databases in Structure Data File (SDF) and PDB file formats. These files were subsequently

converted to MOL2 format using the Open Babel software.

Selection and Preparation of Target Protein

Following an extensive search in the Protein Data Bank, a protein with the ID 6T1S was selected for this study. It has a resolution of 1.65 Å and contains ligand such as (2~{S})-3-[4-[2-[methyl(pyridin-2-yl)amino]ethoxy]phenyl]-2-[[2-(phenylcarbonyl)phenyl]amino]propanoic acid (EDK) with the chemical formula C30H29N3O4, as well as a sulfate ion (SO4).

The protein (6T1S) was downloaded in PDB format from the Protein Data Bank. Initial filtration of the protein structure was performed using Chimera, and further preparation was carried out using AutoDock Tools.

The protein consists of a single chain (chain A), which was used for the analysis. The following steps were taken during preparation:

All ligands except EDK were removed, and the file was saved as "deleted 6T1S+Ligand". The EDK ligand was subsequently removed, leaving only the protein structure, which was saved as "filtered 6T1S". The resulting protein file (filtered 6T1S) was loaded into AutoDock Tools for further processing. This included adding only polar hydrogens and Kollman charges. Finally, saved in PDBQT format for docking analysis.

Selection and Preparation of Ligands

Preparation of both the standard ligand and the phytochemicals was carried out using Open Babel and AutoDock Tools on a Windows 10 Pro system, following these steps [16]:

Ligands originally in SDF or PDB formats were converted to MOL2 format using Open Babel, ensuring all structures retained their 3D coordinates before conversion. The converted MOL2 files were then transferred to the Windows environment for further processing in AutoDock Tools. In AutoDock Tools, Gasteiger charges were assigned, and all torsional bonds were set to non-rotatable.

Finally, the ligands were saved in PDBQT format, making them ready for molecular docking.

Validation of Docking Protocol

With the protein prepared and the binding site identified, molecular docking was initiated using AutoDock Tools on a Windows 10 Pro system. The reference ligand was first extracted from the protein structure using Chimera, and both the ligand and the processed protein were then loaded into AutoDock Tools. A grid box was defined to encompass the binding site of the ligand, with its center coordinates and dimensions carefully documented for accurate docking simulation.

Molecular Docking

Molecular docking simulations were carried out using AutoDock Vina on the Ubuntu operating system. The PDBQT files of the target protein (6T1S), various phytochemical ligands, and the reference ligand (EDK) were organized into a designated directory. The terminal was then used to navigate to this folder, from where the docking simulations were executed using appropriate command-line instructions.

Post-Docking Analysis

Following the completion of docking at four separate time points, the results were consolidated in Excel for analysis. The mean binding affinities and standard deviations for each phytochemical ligand were calculated. These averages were then compared to those of the reference ligand to identify the most effective candidates. The ligand conformations within the binding pocket were visualized using PyMOL, with each ligand displayed in a distinct colour for easy identification. The interactions between the ligands and surrounding amino acid residues were also examined. To support visual interpretation, snapshots of the binding interactions were taken and saved in PNG format.

RESULTS

A total of 115 phytochemicals were sourced from PubChem and DrugBank databases and initially screened using DataWarrior to evaluate their drug-likeness based on Lipinski's rule of five and their toxicity profiles. This preliminary assessment helped identify promising candidates for further investigation. Following this, molecular docking was conducted to analyze the binding affinities of these compounds with the target protein. The findings are divided into two parts: the first focuses on screening outcomes based on drug-likeness and toxicity, while the second highlights post-docking results, comparing the phytochemicals to the standard ligand. The table showcases the top 10 compounds that demonstrated stronger binding affinities than the reference ligand (EDK) when docked with protein 6T1S.

Table 1 represents the Centre and Dimension of the Grid Box. This enables the ligand to locate the exact position of the binding pocket.

Table 2 represents the binding affinities of the leading compounds. These front-runners exhibit very high binding affinity to the 6T1S receptor, surpassing that of the reference ligand (EDK). Figure 1 illustrates a visual representation of how these top compounds fit within the binding pocket of the 6T1S receptor. Each of them aligns precisely within the pocket, like the reference ligand.

Table 3 evaluates whether the leading phytochemicals adhere to Lipinski's Rule of Five. The top ten compounds were analyzed using DataWarrior software to verify compliance with the rule, which specifies that a ligand should:

- Have no more than five hydrogen bond donors
- Have no more than ten hydrogen bond acceptors

- Possess a molecular weight of 500 g/mol or less
- Have a partition coefficient (log P) not exceeding five

Table 4: While phytochemicals offer various health benefits, they can also present toxicity concerns affecting reproduction, mutagenicity, tumourigenicity, and irritant responses. For example:

Reproductive toxicity: Elevated doses of quercetin and kaempferol have been reported to impair fertility in male rats [17].

Mutagenicity: Certain phytochemicals, such as safrole and estragole, have demonstrated mutagenic properties in bacterial tests [18].

Tumourigenicity: High concentrations of compounds like resveratrol and curcumin have been linked to tumour-promoting effects in animal models [19]

Irritant effects: Phytochemicals, including capsaicin and piperine, can induce irritation of the skin and eyes [20].

Table 1: Centre and Dimension of Grid Box

Grid box	Centre	Dimension
X	-4.765	16
Y	-0.568	16
Z	21.543	16

Table 2: Binding energies (P1-P4) of the phytochemicals (front runners) when docked with 6T1S receptor

Ligands	P1	P2	P3	P4	MEAN	S/D
EDK(reference ligand)	-11.8	-11.8	-12.0	-11.8	-11.9	0.1
Camptothecin	-10.1	-10.1	-10.1	-10.1	-10.1	0.0
Myricetin	-9.7	-9.7	-9.7	-9.7	-9.7	0.0
Oxoassoanine	-9.6	-9.6	-9.6	-9.6	-9.6	0.0
Diadzein	-9.5	-9.5	-9.6	-9.6	-9.6	0.1
Catechin	-9.5	-9.5	-9.5	-9.5	-9.5	0.0
Chicoricacid	-9.5	-9.6	-9.5	-9.4	-9.5	0.1
Malvidin	-9.5	-9.5	-9.5	-9.5	-9.5	0.0
Silymarin	-9.5	-9.5	-9.5	-9.5	-9.5	0.0
Acronycine	-9.4	-9.4	-9.4	-9.4	-9.4	0.0

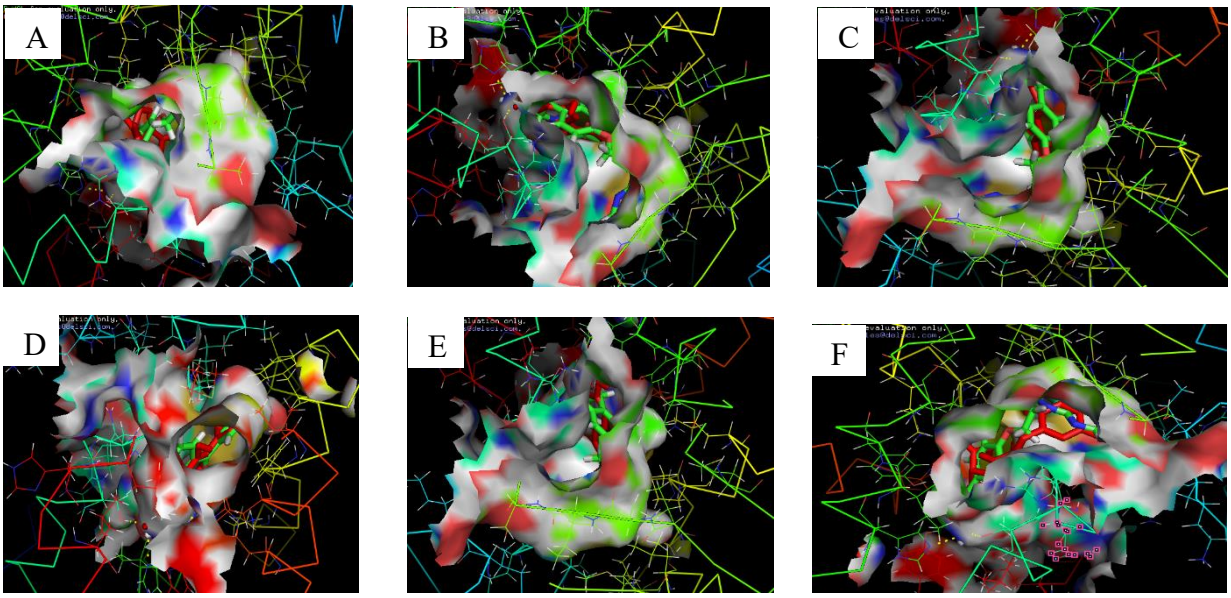

Figure 1: A-F displays the front runners 1-6 on table 2 binding to the 6T1S receptor in its binding pocket. Each front-runner ligand is displayed in red and the reference ligand in green.

Table 3: Molecular descriptors of the front-runners

S/N	NAMES OF LIGANDS	CHEMICAL FORMULA	MW	ClogP	HBA	HBD
1.	Camptothecin	$C_{20}H_8N_2O_4$	331.299	1.3896	6	0
2.	Myricetin	$C_{21}H_{18}O_{14}$	494.36	-1.0422	14	9
3.	Oxoassoanine	$C_{17}H_{15}NO_3$	281.31	2.9035	4	0
4.	Diadzein	$C_{15}H_{14}O_4$	258.272	1.4797	4	3
5.	Catechin	$C_{15}H_{12}O_6$	288.254	1.2386	6	5
6.	Chicoric acid	$C_{22}H_{18}O_{12}$	474.373	0.4222	12	6
7.	Malvidin	$C_{17}H_{15}O_7$	331.299	1.8437	7	4
8.	Silymarin	$C_{25}H_{18}O_{10}$	478.408	2.996	10	5
9.	Acronycine	$C_{20}H_{19}NO_3$	321.375	4.0777	4	0
10.	Biochanin	$C_{16}H_{12}O_5$	284.266	1.9029	5	2

Table 4: Toxicity profile of the front runners

S/N	Names of ligands	Mutagenicity	Tumorigenicity	Effect on reproduction	Irritant effect
1.	Camptothecin	None	None	None	None
2.	Myricetin	None	Low	None	None
3.	Oxoassoanine	None	None	None	None
4.	Diadzein	None	None	High	None
5.	Catechin	Low	None	None	None
6.	Chicoric Acid	None	None	None	None
7.	Malvidin	None	None	None	None
8.	Silymarin	None	None	None	None
9.	Acronycine	None	None	High	None
10.	Biochanin	None	None	None	None

DISCUSSION

The binding affinities of phytochemicals to receptors play a vital role in evaluating their potential therapeutic benefits [14]. In this study, we determined the binding affinities of phytocompounds of *Gongronema latifolium* on the peroxisome proliferator-activated receptor gamma (PPARγ), a receptor involved in insulin regulation, compared to the reference ligand EDK with in silico molecular docking simulation. Binding affinity is often estimated using scoring methods, which provide a rapid, basic measure linked to Gibbs free energy [21]. A more negative Gibbs binding energy suggests spontaneous and stronger interaction, meaning that the lower the value, the tighter the ligand binds to its target. Conversely, a positive or less negative value indicates weaker binding [22].

In this study, 115 phytochemicals were docked using Autodock-Vina. The reference ligand (EDK) exhibits a very high binding affinity of -11.9 kcal/mol. Most compounds exhibited high affinity, although some exceptions were noted. Compounds not on the table, like paclitaxel, emetine, tigogenin, echitamine, neochlorogenin, solagenin, hecogenin, capsaicin, taraxeron, tetrandrine, lycopene, carotene, and lutein, displayed no affinity toward the 6T1S receptor. Compounds like campothecin and myricetin exhibited very high binding affinity of -10.1 kcal/mol and -9.7 kcal/mol, respectively, to the 6T1S receptor.

The drug-likeness of molecules was studied using Lipinski's Rule of Five, a well-established guideline used to assess the drug-likeness of molecules by predicting their potential for oral absorption and bioavailability [23]. Molecules that break two or more of these criteria generally exhibit poor oral bioavailability [23]. Subsequent research has supported the rule's effectiveness in drug development [24,25], although some have proposed refinements to include factors like polar surface area (PSA) and molecular flexibility [26]. In this study, myricetin and chicoric acid did not meet the Lipinski criteria due to excessive hydrogen bond donors and acceptors, while the other compounds satisfied all the requirements.

The toxicity profiles of these front-runners were further studied as it is important to evaluate the toxicity profiles carefully when considering phytochemicals for drug development. Table 4 presents the toxic screening of the leading compounds. Camptothecin, oxoassoanine, chicoric acid, malvidin, silymarin, and biochanin showed no toxic effects based on DataWarrior analysis. Myricetin exhibited low tumourigenic potential, indicating a minimal risk of tumour formation or promotion. Catechin was found to have low mutagenic potential, suggesting a limited likelihood of causing genetic mutations. However, Daidzein and acronycin demonstrated significant reproductive toxicity, implying they may affect fertility, embryonic or fetal development, hormone balance, or cause birth defects.

CONCLUSION

In conclusion, based on the results, a comparison between the phytochemicals and the reference ligand reveals that most phytochemicals exhibit good binding affinities, with camptothecin showing the highest affinity after the reference ligand. Among the leading compounds, eight phytochemicals meet the criteria of Lipinski's Rule of Five, indicating their potential as drug candidates. Additionally, these compounds show no toxic effects that would hinder their development as future treatments for diabetes mellitus. This suggests that camptothecin, oxoassoanine, malvidin, silymarin, biochanin, daidzein, and acronycin could be promising anti-diabetic agents when isolated from the leaves of *Gongronema latifolium*.

Phytocompounds from *Gongronema latifolium* demonstrate a capacity to bind to the peroxisome proliferator-activated receptor gamma (PPAR-γ), which may contribute to therapeutic effects against diabetes mellitus, as supported by this *in silico* study. Computer-aided drug design remains a valuable and efficient approach in drug discovery, reducing the need for extensive laboratory testing and thereby saving time and resources.

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AUTHORS' CONTRIBUTION

The study was conceptualized and designed by **ECO**, the data was analysed and drafted by **CCE**, and the experiment was conducted by **IMO** and **AJM**.

CONFLICT OF INTEREST

The authors stated in this study declare no conflict of interest.

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