Exploring the therapeutic mechanisms of *Astonia boonei* in diabetes mellitus ligand-based virtual screening with TGR5 Receptor

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Abstract

The anti-diabetic effects of *Astonia boonei* have been demonstrated by several studies, but few have clarified the mode of action of compounds extracted from *Astonia boonei* as an agonist for the TGR5 pathways in the etiology of diabetes. TGR5 is a membrane protein receptor that has been linked to increased insulin-signaling and is an appropriate target for diabetes treatment. Nevertheless, no commercial medication that specifically targets TGR5 is currently available. This study looked into compounds that were found to be TGR5 agonists and may have therapeutic value in *A. boonei*. The compounds were selected from the literature and docked with TGR5 receptors. Following their filtration by Lipinski's rule of five (RO5), the compounds were utilized in a molecular docking investigation. Moderate indices for ADMET parameters and non-carcinogenicity were revealed by online web servers' predictions of the hit compounds' drug-likeness, pharmacokinetic, and toxicity features. The potential of compounds from *A. boonei* that might be explored as therapeutic options in the treatment of diabetes is thus illuminated by this study.

Keywords: *Astonia boonei,* Phytoconstituents, Diabetes mellitus, Molecular docking, TGR5, GLP1

1. Introduction

Large deciduous tree *Alstonia boonei* is commonly called the sour sap tree. The leaves, stem bark, and roots of the tree are commonly sold in local markets as remedies for a variety of illnesses (Bello et al., 2009; Bekoe et al., 2020). It is reported to include a number of beneficial components and chemicals (Kehinde et al., 2016). In conventional medicine, it has been investigated for the treatment of hypertension and other disorders that have some scientific backing. The stem bark's anti-rheumatic, anti-inflammatory and anti-helminthic qualities have all been reported (Kehinde et al., 2016). It has been demonstrated that the extract from *Alstonia boonei* reduces the absorption of cholesterol (Ja et al., 2017; Bekoe et al., 2020). Diabetes mellitus (DM) is a common risk factor for cardiovascular diseases and one of the world's top causes of death (Elekofehinti, 2015), according to reports (Kehinde et al., 2016). Previous research indicates that diabetes mellitus is a metabolic disorder characterized by hyperglycemia brought on by insufficient insulin production (Bekoe et al., 2020; Kehinde et al., 2016). A World Health Organization (WHO) research states that diabetes is one of the most prevalent chronic diseases affecting about 170 million people globally. Over 439 million individuals worldwide are expected to be affected by this pandemic-increasing condition by 2030, with 347 million people presently suffering from it (Elekofehinti, 2015).

The variable condition known as type 2 diabetes is marked by a reduction in the activity of the beta cells in the pancreas that generate insulin (Oyetayo et al., 2021). The main goals of T2DM treatments are to enhance insulin secretion and reduce the synthesis of glucose in the liver (Kehinde et al., 2016; Oyetayo et al., 2021). Given that glucose administration can cure type 2 diabetes by activating TGR5 and regulating glucose homeostasis, it can encourage GLP-1 to produce insulin.

The computational method known as "molecular docking" examines the conformations of tiny molecules at protein binding sites and uses scoring functions and algorithms to determine which conformation most closely resembles the binding site (Elekofehinti et al., 2021). It is the study of the interactions between two or more molecular structures, such as a medication and an enzyme or protein. The process of finding new medications is multifaceted and dependent on *in-silico* tools (Cheng, 2018; Bekoe et al., 2020). Finding the most likely ligand-protein binding mechanism is the aim of ligand-protein docking. Ligand-based simulation or docking decreases the number of animals used in research, lowers expenses, increases the success rate of studies, and aids in the comprehension of drug-protein interactions. In research on pharmaceuticals and drug development, molecular docking facilitates the rapid identification of any molecules with significant therapeutic potential. To assess the pharmacological characteristics of *Alstonia boonei* compounds against diabetes mellitus while taking into account its bioactive activities, this analytical investigation uses a computational method (Perino et al., 2014; Ja et al., 2017; John et al., 2021).

2.0 Materials and Methods

2.1. Preparation of protein and ligand

The isolated compounds from *Astonia boonei* were obtained from literature and then transformed and minimized into 3D structures using LigPrep wizard Schrodinger maestro (v11.1). With the help of Epik, a possible ionization state was generated at target pH 7.0 ± 2.0 for precise tautomer enumeration and to determine the protonation state in biological status. By keeping certain chiralities, stereoisomers were created, up to a maximum of 32 per ligand. OPLS3 was selected as the force field. The RCSB Protein Data Bank (PDB) was used to obtain the membrane protein receptor target protein, TGR5, for the docking process. The medication target, (PDB id: 7BW0), works by increasing insulin-mediated insulin receptor tyrosine kinase activity, which in turn activates post-receptor insulin signaling pathways. It might result from changes in membrane fluidity in hyperglycemic circumstances. Because TGR5 is a good target for drugs that can have an anti-diabetes effect, it is an essential agonist target. An active human TGR5 complex with the synthetic agonist 23H (PDB id: 7BW0) causes issues connected to diabetes (Hasan et al., 2021). The production wizard in Schrodinger Maestro (v11.1) was used to create the protein's 3D structure. In order to generate disulfide bonds, assign bond orders, add hydrogens, remove zero-order links to metal water molecules beyond 5◦A from het groups, and leave the het state at its default pH (7.0±2.0) using Epik, the CCD database was consulted. Lastly, heavy atoms are converged to an RMSD of 0.30 Å using the OPLS3 force field, which is used for restrained minimization.

2.2 Identification of the active site of the receptor

A drug's propensity to bind to a specific region or target on the surface of a receptor and cause conformational changes that result in a pharmacological response is known as an active site (Hasan et al., 2021). Molecular docking assisted in determining the ligand-receptor binding active site, and the PockDrug server was utilized to ascertain the druggability influence of the target protein's active site (Hasan et al., 2021).

2.3. Generation of receptor grid

The bounding box was selected to cover the whole target site for docking simulation, and the default values for the partial charge cutoff and van der Waals radius scaling factor are 0.25 and 1, respectively.

2.4. Molecular Docking Simulation

Following completion of the prerequisite procedures, the docking simulation was run in Schrodinger maestro's SP glide (v11.1) (Cheng, 2018; Hasan et al., 2021), taking into account the penalties applied to non-cis/trans amide bonds. In this case, the partial charge cutoff was set to 0.15 and the van der Waals scaling factor was set to 0.80. Energy-minimized posture was used to calculate the final result, which is known as the glide score. Every activity's score for the chemical was noted.

2.5. ADMET evaluation

The ADME features, which were established by Lipinski's rule of five (Cheng, 2018; Hasan et al., 2021), show compound accessibility throughout the body. This rule's standard parameter is provided below:

1) Molecular weight (acceptable range: ≤ 500)

2) Hydrogen bond donor (acceptable range: ≤ 5)

3) Hydrogen bond acceptor (acceptable range: ≤ 13)

4) High lipophilicity (expressed as LogP, acceptable range: ≤ 5)

5) Molar refractivity (acceptable range: 40–130)

The QikProp module of Schrodinger maestro (v11.1) was used to ascertain the ADME (Absorption Distribution Metabolism Excretion) features of the chosen *Alstonia boonei* compounds, and an online server-based database called admetSAR was employed to ascertain the toxicity profile (Hasan et al., 2021). Figure 2 displays the proposed work's graphical representation.

3. Results

Figure 1 shows the two-dimensional structures of the *Alstonia boonei* compounds: Nα formylechitamidine, echitamidine Kaempferol, Porphyrin, Loganin, Chlorohydroquinone, Isoquercitrin, Chlorogenic acid, Alstonidine, Quercetin, Cyfluthrin, Beta Cyfluthrin, etc. The selected *Alstonia boonei* compounds' used in docking simulation for TGR5 are displayed in Figure 1. Table 1 displays the relevant docking simulation scores. The selected compounds produced promising results. Figure 3 displays the (2D and 3D) structural representations of the interaction between the compound and the target. Figure 4, Figure 5, Figure 6 and Figure 7 also show the 2D interaction of *Alstonia boonei* phytocompounds with amino acid residues in TGR5

Table 1 shows the molecular docking scores between specific *Astonia boonei* compounds and the TGR5 receptor. Table 2 reveals the results of the ADME analysis between specific *Astonia boonei* compounds and the TGR5 receptor as well as the binding interaction (hydrogen and hydrophobic) between specific *Alstonia boonei* compounds (Cyfluthrin, Nα formylechitamidine, echitamidine, Kaempferol, Porphyrin, Loganin, and Chlorohydroquinone) and the receptors. Table 3 shows the molecular docking binding free Energy MMGBSA scores between specific *Astonia boonei* compounds and TGR5 receptor, Table 4 reveals the Induced fit docking scores between specific *Astonia boonei* compounds and TGR5 receptor, and Table 5 shows the MMGBSA results between specific *Astonia boonei* compounds and TGR5 Receptor,

3.1. ADME/T evaluation

The ADME property assesses a chemical agent's capacity to function as a drug. Table 3 shows the pharmacokinetic profile of a few compounds from *Alstonia boonei* (Isoquercitrin, Chlorogenic acid, Alstonidine, Quercetin, Cyfluthrin, Beta cyfluthrin, Nα formylechitamidine, echitamidine, Kaempferol, Porphyrin, Loganin, Chlorohydroquinone), showing that none of the

criteria for the Lipinski rule have been broken and that the compounds have no mutagenic or carcinogenic properties.

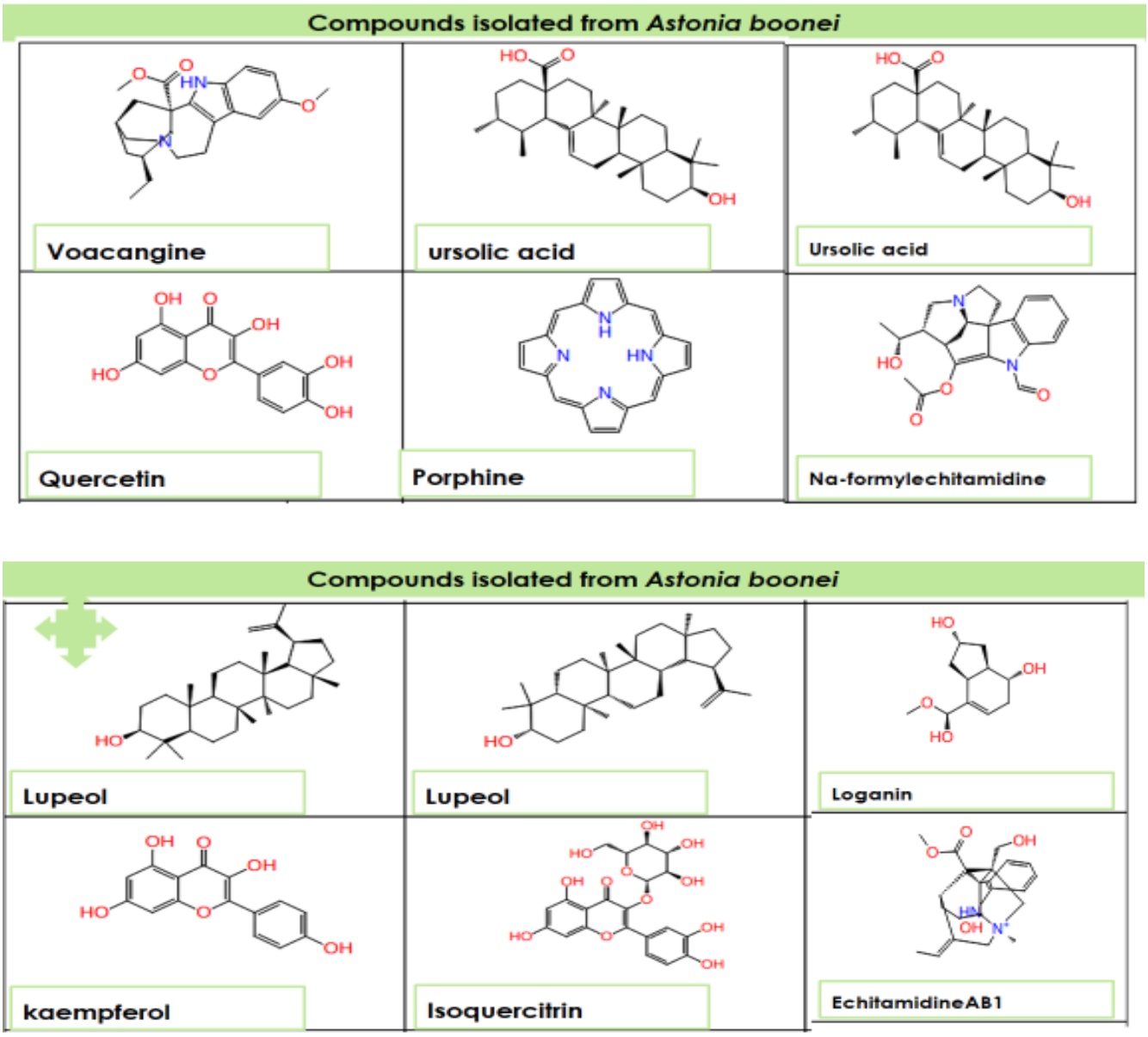

Figure 1: The two-dimensional structure of *Alstonia boonei* compounds

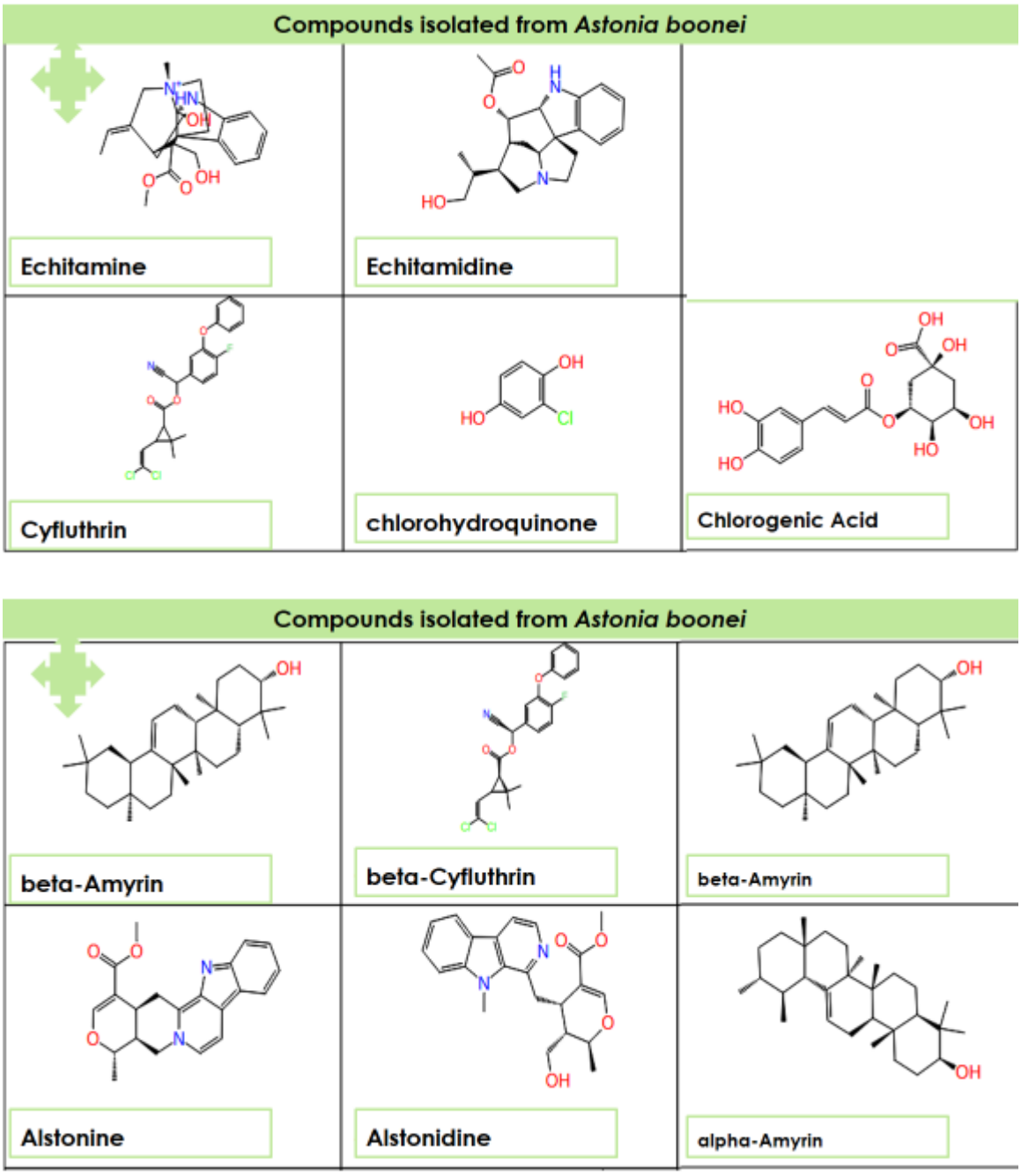

Figure 1: The two-dimensional structure of *Alstonia boonei* compounds- (continued)

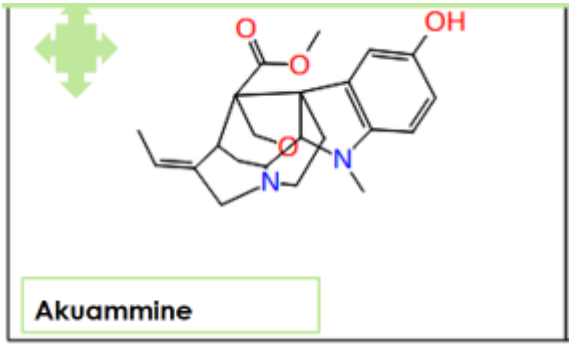

Figure 1: The two-dimensional structure of *Alstonia boonei* compounds- (continued)

Table 1: Molecular docking scores between selected *Astonia boonei* compounds and TGR5

Compounds	**docking score**
Isoquercitrin	-11.466
Chlorogenic acid	-10.661
Alstonidine	-9.982
Quercetin	-9.661
Cyfluthrin	-9.647
Beta_cyfluthrin	-9.647
Nα formylechitamidineAB3	-8.773
Echitamidine	-8.739
Kaempferol	-8.643
Porphyrin	-8.509
Loganin	-6.544
Chlorohydroquinone	-4.767

Table 2: ADME between selected *Astonia boonei* compounds and TGR5

Compounds	**donorHB**	**accptHB**	**QPlogPo/w**	**RuleOfFive**
Isoquercetrin	7	13.75	-1.308	2
Chlorogenic Acid	6	9.65	-0.457	1
Alstonidine	1	6.4	3.771	0
Quercetin	4	5.25	0.355	0
Cyfluthrin	0	4	5.69	1
beta-Cyfluthrin	0	4	5.69	1
Nα formylechitamidineAB3	1	9.2	1.397	0
echitamidineAB1	2	6.7	1.822	0
Kaempferol	3	4.5	1.047	0
Porphine	2	3	4.261	0
Loganin	3	6.8	0.165	0
Chlorohydroquinone	2	1.5	0.883	0

Table 3: Molecular Docking binding free Energy MMGBSA between selected *Astonia boonei* compounds and TGR5

Compounds	**MMGBSA dG Bind Hbond**
Isoquercetrin	-1.32
Chlorogenic Acid	-1.24
Alstonidine	-0.43
Quercetin	-1.08
Cyfluthrin	-0.32
beta-Cyfluthrin	-0.32
Nα formylechitamidine	-0.3
Echitamidine	-0.03
Kaempferol	-0.64
Porphine	0
Loganin	-0.49
Chlorohydroquinone	-0.3

Table 4: Induced fit docking between selected *Astonia boonei* compounds with TGR5 Receptor

Compounds	docking score	glide redock method	IFDScore
Chlorogenic acid	-8.805	confgen	-533.89
Isoquercitrin.	-8.746	confgen	-531.15
Alstonidine	-5.61	confgen	-528.94
Quercetin	-7.559	confgen	-528.66
Loganin	-5.721	confgen	-527.87
Porphyrin	-5.888	confgen	-527.18
NÎ±-formylechitamidine	-6.295	confgen	-524.79

Table 5: MMGBSA between selected *Astonia boonei* compounds and TGR5 Receptor

Compounds	MMGBSA dG Bind	MMGBSA dG Bind Coulomb	MMGBSA dG Bind Covalent	MMGBSA dG Bind Hbond	MMGBSA dG Bind Lipo	MMGBSA dG Bind Solv GB	MMGBSA dG Bind vdW
Isoquercitrin	-71.52	-37.34	8.22	-1.32	-37.01	31.9	-35.37
Chlorogenic acid	-71.28	-21.33	2	-1.24	-33.54	23.9	-41.06
Alstonidine	-88.62	-7.69	5.01	-0.43	-51.63	16.21	-49.71
Quercetin	-55.21	-15.43	0.96	-1.08	-23.22	19.26	-34.73
Cyfluthrin	-90.97	-8.41	-0.63	-0.32	-47.02	15.6	-50.1
beta-cyfluthrin	-90.97	-8.41	-0.63	-0.32	-47.02	15.6	-50.1
NÎ±-formylechitamidin	-78.47	-8.25	0.67	-0.3	-41.89	18.63	-47.04
Echitamidine	-74.72	-1.22	2.4	-0.03	-48.1	18.95	-46.43
Porphyrin	-61.13	0.25	1.33	0	-34.74	14.63	-41.89
Loganin	-49.2	-14.7	1.3	-0.49	-29.36	15.21	-21.16
Chlorohydroquinone	-33.78	-7.66	0.75	-0.3	-16.69	9.16	-18.35

Table 6: Some *Astonia boonei* compound's molecular weight

Compounds	**Docking score (Da)**
Isoquercitrin	464.382
Chlorogenic acid	354.313
Quercetin	302.24
Loganin	214.261
Chlorohydroquinone	144.557
Kaempferol	286.24
Voacangine	368.475
Cyfluthrin.	434.293
Akuammine	382.458
a-Amyrin palmitate	454.778
Kaempferol	286.24
echitamidineAB1	356.464
NÎ±-formylechitamidineAB3	368.432
Porphyrin	310.357
Echitamidin	340.421
Beta_cyfluthrin	380.443
Chlorohydroquinone	144.557
Lupeol	426.724
Beta_cyfluthrin	380.443
alpha-Amyrin	426.724
lupeolAB5	440.751
b-Amyrin	426.724

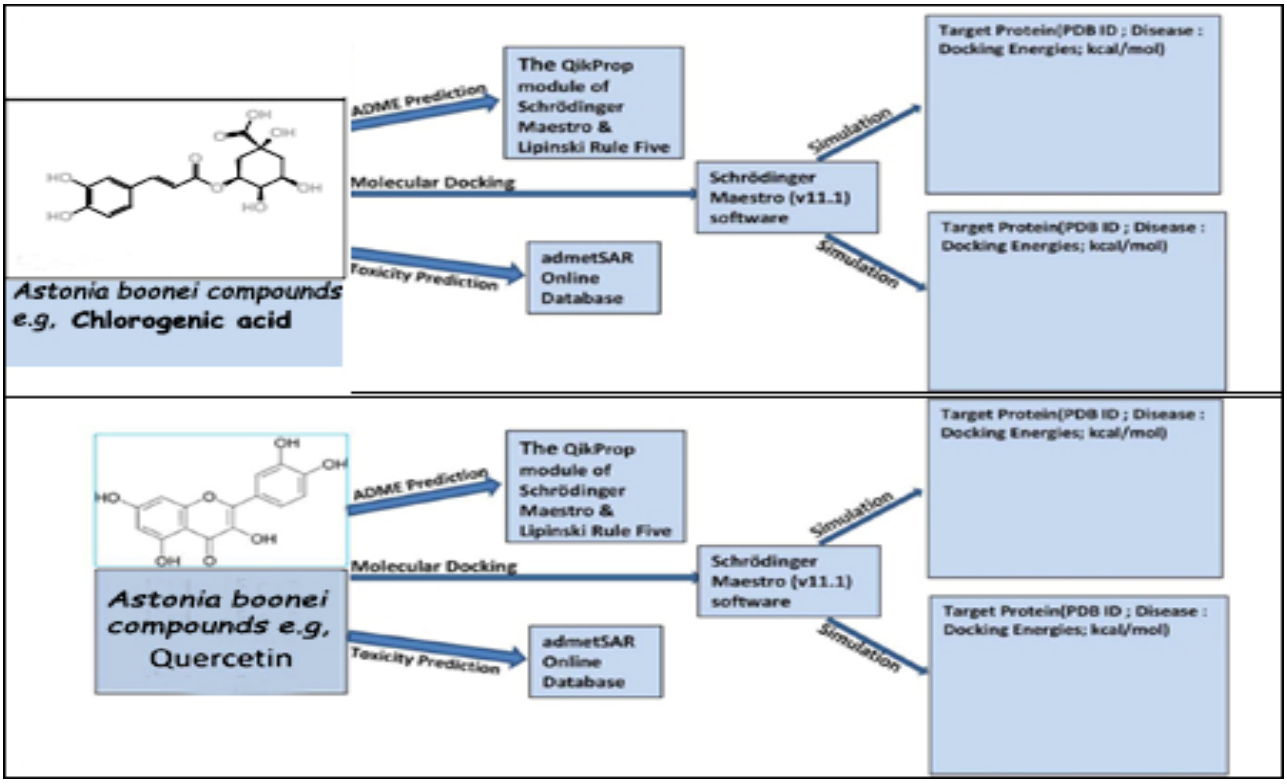

Figure 2: Broad-spectrum therapeutic potential against diabetes as assessed by in silico molecular docking and ADME/T analysis of certain *Alstonia boonei* compounds, utilizing quercetin and chlorogenic acid as examples.

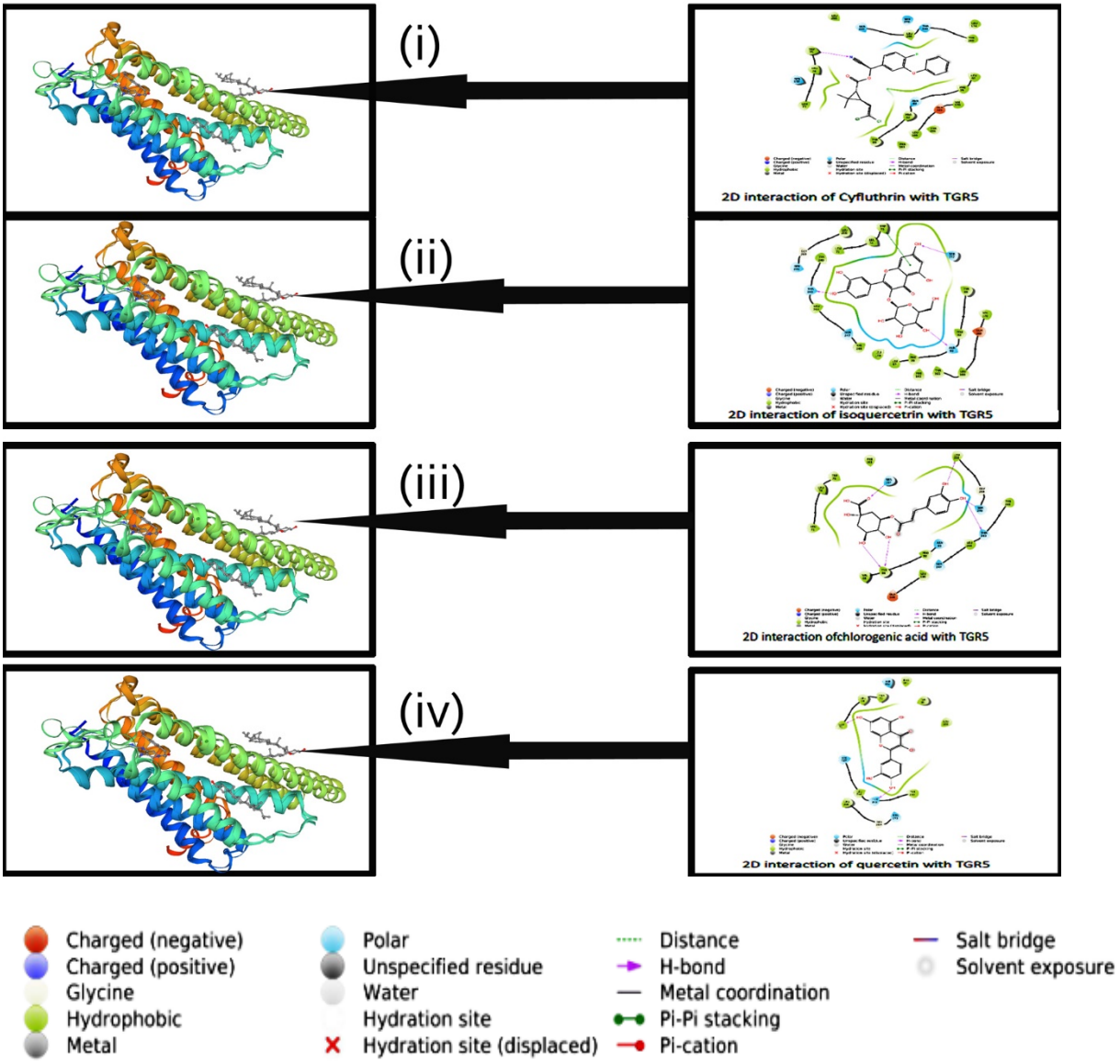

Figure 3. Analysis of molecular docking simulation, the following interactions have been observed: (i) Interaction of Cyfluthrin with TGR5 (PDB id: 7BW0), (ii) Interaction of Isoquercitrin with TGR5 (PDB id: 7BW0), (iii) Interaction of Chlorogenic acid with TGR5 (PDB id: 7BW0), (iv) Interaction of Quercetin with TGR5 (PDB id: 7BW0).

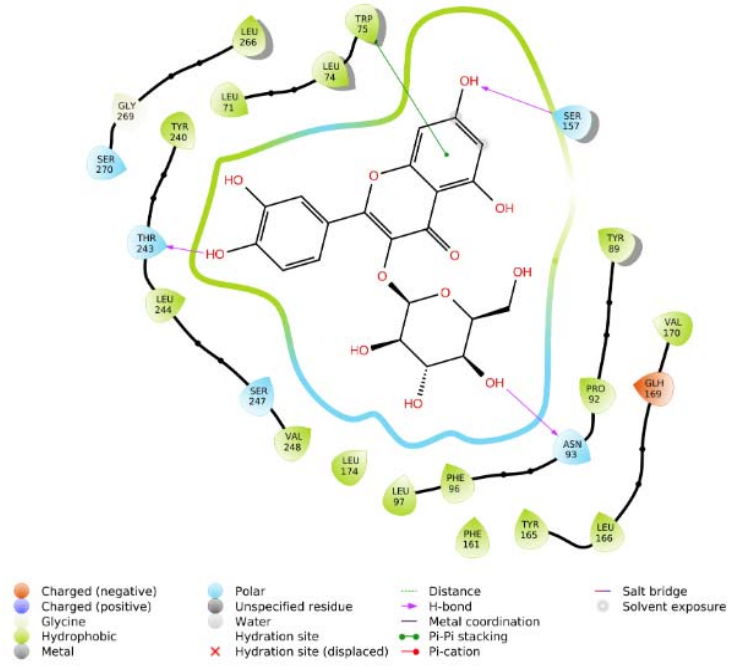

Figure 4: 2D interaction of isoquercetrin with TGR5

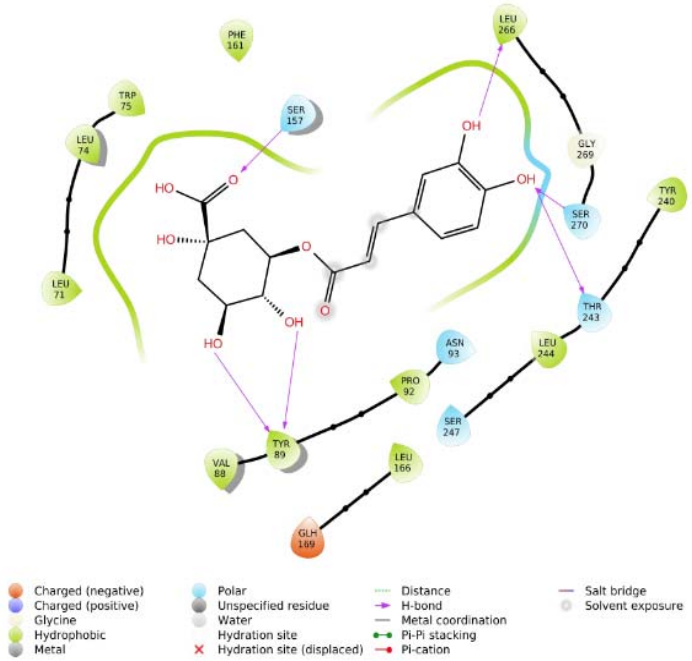

Figure 5: 2D interaction of chlorogenic acid with TGR5

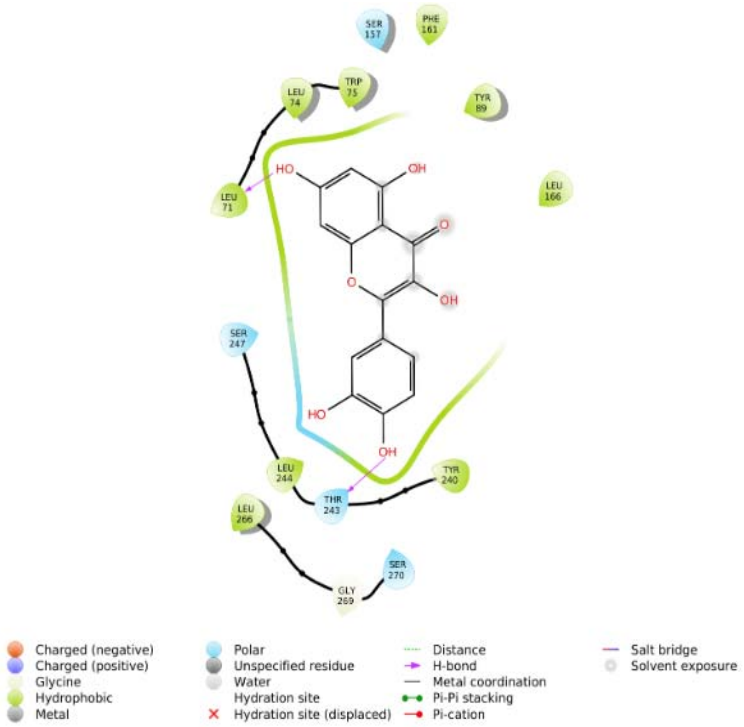

Figure 6: 2D interaction of quercetin with TGR5

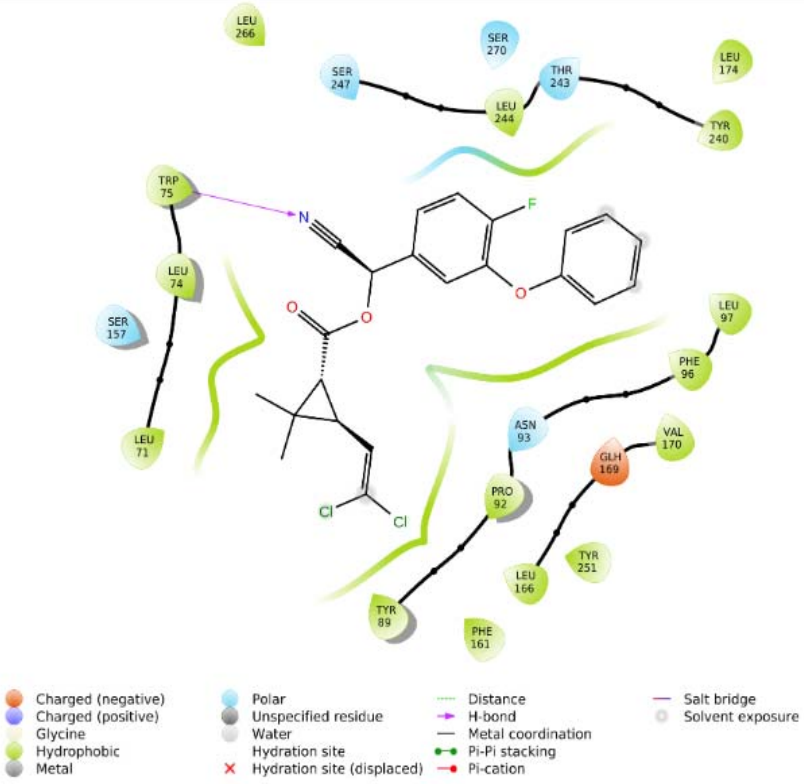

Figure 7: 2D interaction of Cyfluthrin with TGR5

4. Discussion

This study examined some specific *Alstonia boonei* compounds, including codonamycin, isoquercitrin, alstonidine, quercetin, cyfluthrin, beta cyfluthrin, Nα formylechitamidine, echitamidine, kaempferol, porphyrin, loginin, and chlorohydroquinone. A computational method called "molecular docking" is one of the tools used to examine the conformations of small molecules at protein binding sites, it uses scoring algorithms to identify the conformation that most closely resembles the binding site. The results of this investigation will aid in comprehending the inhibitory mechanism and in precisely forecasting the activities of novel inhibitors in light of docking scores (Cheng, 2018; Hasan et al., 2021). Understanding the pharmacological activity of bioactive compounds in curative conditions can be accomplished by the utilization of the findings and understanding derived from *in silico* molecular docking studies. Recent research has demonstrated the potential therapeutic benefits of compounds isolated from *Alstonia boonei*, such as the inhibition of Enoyl Acyl Carrier Protein Reductase in Plasmodium falciparum (PfENR) (Johnson et al., 2021; Olalekan et al., 2021), which acts as an antimalarial agent. We employed molecular docking and ADME/T studies to investigate the mode of action of specific compounds from *Alstonia boonei* as an agonist for the TGR5 pathways in diabetes. Our study confirms previous research showing that drugs with higher docking scores are more effective against disease. Specifically, the compounds from *Alstonia boonei*, such as isoquercitrin, chlorogenic acid, alstonidine, quercetin, beta-cyfluthrin, Nα formylechitamidine, etc. have higher docking scores (-11.466, -10.661, -9.982, -9.661, -9.647, -9.647, etc.) kcal/mol, and their molecular docking binding free energy (MMGBSA score) for isoquercitrin, chlorogenic acid, alstonidine, and quercetin (-1.32, -1.24, -0.43, -1.08), as well as an agonist to the receptor protein (7BW0). Based on the information provided, we can infer that isoquercitrin has the greatest MMGBSA and docking score compared to other compounds. Based on docking scores, it can be observed that isoquercitrin is potentially, a very effective compound against diabetes, with docking scores following suit. Other compounds that interact with proteins through the formation of covalent and non-covalent chemical bonds include echitamidine, Nα formylechitamidine, alstonidine, quercetin, cyfluthrin, beta-cyfluthrin, Kaempferol, porphyrin, and Loganin (Cheng, 2018). When evaluating a novel drug's efficacy, hydrophobic and hydrogen bond interactions are critical elements to take into consideration. The drug's binding affinity is also essential for the development of suitable pharmacologic and therapeutic qualities. Hydrogen bonds have a critical role in drug-receptor interactions as well as the structural stability of many bioactive compounds (Bekoe et al., 2020). Hydrogen bonds (H-bonds) are present between proteins and ligands and enhance a number of biological processes, as the hydrogen bond gets closer to faultless geometry, its strength increases (Johnson et al., 2021).

Hydrophobic interactions arise when proteins' non-polar side chains come into direct contact with the lipophilic groups of the ligand. Research has demonstrated that hydrophobic interactions significantly boost the binding affinity of ligands with a high concentration of lipophilic groups (Hasan et al., 2021). Hydrophobicity affects a number of biological processes, such as the movement, dispersion, and metabolism of biological molecules. The bioavailability of drug molecules increases with an increase in the distance between hydrophobic interactions (Lucien et al., 2015). The selected compounds from *Alstonia boonei* exhibit lower bond distance (Å) in hydrogen bond interactions and higher distance values in hydrophobic interactions with the receptor at the active site. These values suggest that the compounds have a higher binding

affinity for TGR5 receptor molecules and are also associated with relevant bioavailability properties. To make more precise assumptions, further preliminary research on ligand binding is needed. Toxicological analysis and pharmacokinetics studies are essential components of drug discovery (Johnson et al., 2021). Table 2 indicates that all the selected compounds, except isoquercetrin, have a hydrogen-bond donor (donorHB) values not greater than seven and hydrogen-bond receptor (accptHB) values not greater than ten. This suggests that isoquercetrin has a higher binding affinity and better absorption, as demonstrated by its high lipophilicity, and a partition co-efficient of less than five (logP).

Drug-like molecules have molar refractivity between 40 and 130, molecular weight between 160 and 480 g/mol, and a logarithm of the partition coefficient (logP) between 0.4 and 5.6, which varies according to the molecule's volume and molecular weight (Bekoe et al., 2020). In particular, compounds from *Alstonia boonei*, particularly isoquercitrin, chlorogenic acid, alstonidine, quercetin, beta-cyfluthrin, Nα formylechitamidine, echitamidine, Kaempferol, Porphyrin, Loganin, and chlorohydroquinone, docked with TGR5, fulfilled the requirements of Lipinski's rules of five, including absorption analysis, distribution, metabolism, excretion, and shows good oral bioavailability (Lipinski, 2004). Additionally, a computer simulation study and the ADME analysis demonstrated that the compounds are safe because there was no evidence of mutagenicity or carcinogenicity, and the toxicity value is within the permissible range. It takes clinical research to ascertain overall toxicity. This work demonstrates that intestine glucagon-like peptide-1 (GLP-1) can be released when TGR5 signaling is activated, leading to an increase in pancreatic activity and an improvement in glucose tolerance. The results of this study demonstrate that TGR5 is activated by specific TGR5 agonists found in *Alstonia boonei* compounds, such as isoquercitrin, chlorogenic acid, alstonidine, quercetin, cyfluthrin, beta cyfluthrin, Nα formylechitamidine, echitamidine, kaempferol, porphyrin, loginin, and chlorohydroquinone, among others. These effects are associated with increased intracellular calcium mobilization and ATP/ADP ratio levels.

5. Conclusion

The study reveals that the TGR5 signaling pathway plays a significant role in controlling intestinal GLP-1 production. It also suggests that pharmacologically targeting the TGR5 receptor may provide a potential approach for the treatment of diabetes. These findings highlight the potent compounds of *Alstonia boonei* with significant activity and offer insight into its potential that could be explored as therapeutics in diabetes treatment.

Author Contribution

Sunday Ayodele Alonge: Conceptualization, Methodology, Resources, Investigation, Writing – Original Draft and Editing. Olusola Olalekan Elekofehinti: Conceptualization, Investigation, Writing – Review, Methodology, Supervision. Moses Orimoloye Akinjiyan: Investigation, Writing – Review, Methodology, Supervision. Isaac Iseoluwa Ajayi: Formal analysis, Investigation, Methodology, Supervision, Data Curation.

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Availability of data and material

All the data used in this study has been included in the manuscript

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