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Sphenocentrum jollyanum furanoditerpenes activates Glucagon-like peptide 1 receptor (GLP-1R): a computational evaluation

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Abstract

Sphenocentrum jollyanum is a major bio-resource used in the folkloric treatment of diabetes, unfortunately without knowledge of how or the mechanism of action. The present study focuses on using molecular docking to identify the component responsible for the anti-diabetic claim of the fruit as well as check the ADMET properties of the phytochemicals. A library of 23 phytochemicals that have been previously characterized from Sphenocentrum jollyanum fruit was generated and docked, using Autodock Vina, into 3D structures of dual-specificity tyrosine phosphorylation regulated kinase 1a (DYRK1A), peroxisome proliferator-activated receptor alpha (PPAR-α), peroxisome proliferator-activated receptor gamma (PPAR-γ), pancreatic alpha-amylase, dipeptidyl peptidase 4 (DPP4), glucagon-like peptide 1 receptor (GLP-1R), renal sodium-dependent glucose transporter (SGLUT 2). From the docking result, GLP-1R was identified as a major target for two key S. jollyanum furanoditerpenes (columbin and isocolumbin) with docking scores of -10.7 and -10.9 Kcal/mol respectively while the reference ligand (danuglipron) characterized with the GLP-1R had a score of -11.0 Kcal/mol. The protein-ligand interaction between columbin and GLP-1R showed several interactions such as hydrogen bond (H-bond), hydrophobic interactions and salt bridges, all within the extracellular domain (ECD), transmembrane domain (TM) of the receptor which is similar to that of danuglipron. Also, the ADMET profiling result was favourable as both ligands (columbin and isocolumbin) passed the Lipinski rule of 5. The results suggest that columbin identified from the docking result is most likely responsible for the antidiabetic claim of Sphenocentrum jollyanum, further investigation is needed to ascertain this claim.

Keywords: *Columbin, danuglipron, diabetes, isocolumbin, molecular docking*

INTRODUCTION

Type 2 diabetes is the most common of the types of diabetes mellitus (DM). According to the international diabetes federation (IDF), about 537 million adults will be living with diabetes worldwide in 2021 with a projection of about 643 million by 2030 (IDF, 2021). About 24 million people have diabetes in the African region and almost 4 million cases of diabetes in Nigeria (IDF, 2021). Nigeria is one of the countries regarded as low-and medium-income countries that needs a cost-effective treatment else the treatment will be inaccessible to the common populace hence, a treatment strategy available to all is inevitable.

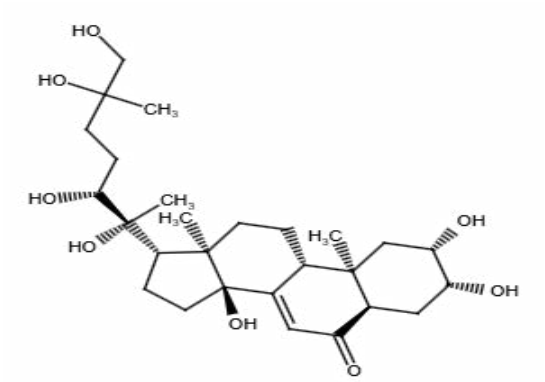
GLP-1R belongs to the class B family of G-protein coupled receptors (GPCRs). GPCRs function in the transduction of extracellular signals into intracellular stimuli. It has seven transmembrane domains (TMD 1-7) of 310-420 residues which are interconnected by the intracellular and extracellular loops (ICL and ECL) and an extracellular N-terminal domain (ECD) (Odoemelam *et al*., 2022).

GLP-1, an endogenous ligand of GLP-1R, is produced from the gastrointestinal tract (GIT) in response to food intake and is important in insulin secretion regulation, carbohydrate metabolism and control of appetite (Suhartono *et al*., 2022). However, GLP-1 is short-lived as it becomes degraded and inactive by dipeptidyl peptidase 4 (DPP-IV) within 1 to 4 minutes of secretion (Andersen *et al*., 2018). This has led to the development of different GLP-1R agonists which are longer lasting than native GLP-1 although with mild, and in some cases serious side effects. Several pharmaceutical therapies have been developed to target established pathways implicated in DM and they have been classified based on their mechanism of action or the target. Some of the classes include Sulfonylureas (SU), Biguanides,

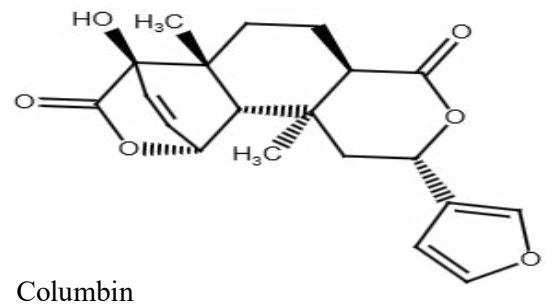
Thiazolidinediones (TZDs), and Incretin-dependent therapies (GLP1-Receptor agonists and DPP4 inhibitors) (Dahlén *et al*., 2022).

A lot of plants have been used in the folkloric treatment of diabetes unfortunately without knowledge of how or the mechanism of action. The present study identifies the component(s) responsible for the antidiabetic claim of *Sphenocentrum jollyanum* fruit, a major bioresource used in folkloric diabetes treatment. *S. jollyanum* has been reported to have anti-inflammatory properties and the furanoditerpenes (columbin, isocolumbin, fibleucin) are thought to be responsible for this property (Alvariño *et al*., 2022; Moody *et al*., 2006).

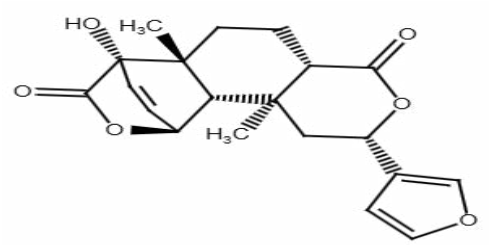
Figure 1: *Sphenocentrum jollyanum* ripe fruits on the plant (Wopara *et al*., 2018)



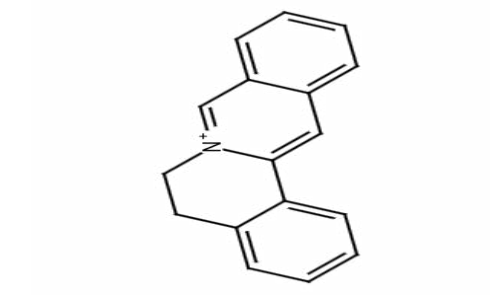
20, 26-dihydroxyecdysone



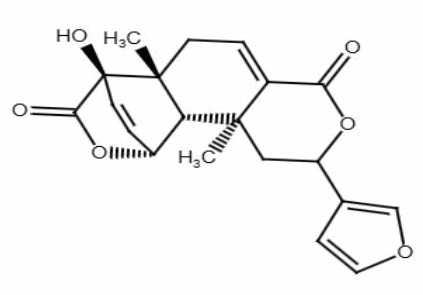
Columbin



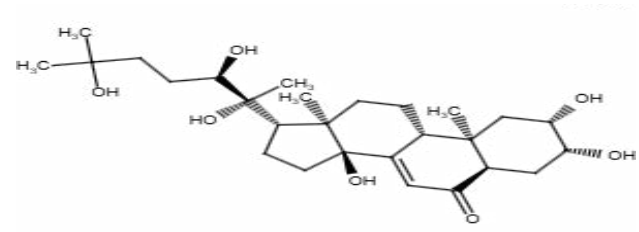
Isocolumbin



Protoberberine



Fibleucin



Ecdysterone

Figure 2: Structures of some of the compounds previously characterized from *Sphenocentrum jollyanum* fruit

MATERIALS AND METHOD

Ligand library generation and target retrieval

The two-dimensional (2D) structures of 23 compounds of *Sphenocentrum jollyanum* fruit previously identified and characterized (Moody *et al*., 2006) were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Seven therapeutic targets in the management of T2DM which include Dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) (PDB ID: 3ANR),

Peroxisome Proliferator-Activated Receptor Alpha (PPAR-alpha) (PDB ID: 4CI4), Peroxisome Proliferator-Activated Receptor Gamma (PPAR-gamma) (PDB ID: 4CI5), Pancreatic alpha-amylase (PDB ID: 4GQR), Dipeptidyl peptidase 4 (DPP-IV) (PDB ID: 5T4E), Sodium/glucose cotransporter 2 (PDB ID: 7VSI) and glucagon-like peptide-1 (GLP-1) receptor (PDB ID: 7S15) were identified and downloaded based on their resolution (≥1.20Å) from RCSB Protein Data Bank (https://www.rcsb.org/search).

Ligand and target preparation

Autodock Vina plugged in PyMol was used for preparation and docking. To dock using Autodock and Vina, receptor and ligand need to be represented in "pdbqt" format. The pdbqt format contains atomic charges, atomic type definitions and rotatable bonds in the case of ligands. For the ligand preparation, the directory containing the library was specified and using scripts (babel *.sdf *.pdbqt –gen3D -r -h), the ligands were converted from sdf format to pdbqt.

Binding site definition

Binding site definition in both Autodock and Vina uses rectangular boxes which are defined either by providing clear-cut coordinates or by selecting reference ligands on the more user-friendly PyMol interface (Seeliger and de Groot, 2010). In this study, the reference ligand characterized with the receptor was selected to define the binding site and the docking box was displayed in the PyMol window.

Molecular docking

After ligand and target preparation and binding site generation, docking using Autodock/Vina can be launched straight from PyMol or command lines can be written for the docking runs. The flexibility of predefined sidechains during docking is allowed in both Autodock and Vina (Seeliger and de Groot, 2010). The reference ligand was extracted and re-docked on PyMol and the other ligands were docked using script.

Drug-likeness and pharmacokinetic properties of the phytochemicals

The ADMET properties of the phytochemicals were performed using Qikprop calculation which uses 2D and 2D QSAR molecular descriptors. Different parameters which are related to drug-likeness and dynamics were checked. For example, hydrogen bond donor, hydrogen bond acceptor, molecular weight, Lipinski's rule of five, human oral absorption, water-octanol partition coefficient, etc were determined.

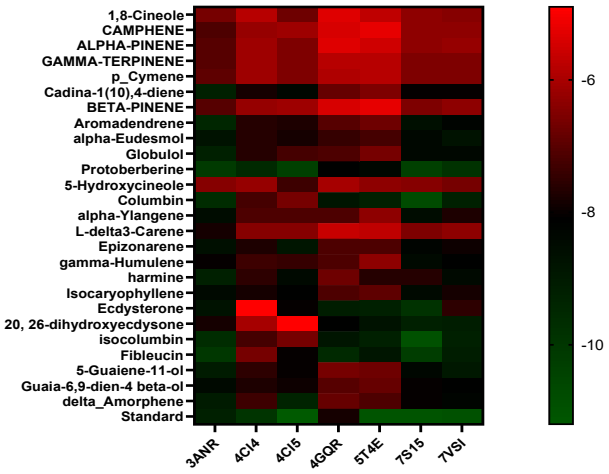
RESULTS

Shown in Table 1 below is the docking score of the phytochemicals recovered from literature against dual-specificity tyrosine phosphorylation regulated kinase 1α (DYRK1A) (3ANR), Peroxisome Proliferator-Activated Receptor Alpha (PPARα) (4CI4), Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) (4CI5), Alpha-Amylase (4GQR), Dipeptidyl peptidase 4 (DPP-IV) (5T4E), glucagon-like peptide-1 receptor (GLP-1R) (7S15), Sodium/glucose cotransporter 2 SGLT2 (7VSI).

Table 1: The docking scores of the phytochemicals with the receptor

Phytochemicals	PubChem ID	3ANR	4CI4	4CI5	4GQR	5T4E	7S15	7VSI
Reference		-9.2	-9.9	-11.2	-7.8	-11	-11	-10.9
1,8-Cineole	2758	-6.6	-5.8	-6.7	-5.3	-5.7	-6.3	-6.4
Camphene	6616	-7.1	-6.2	-6.1	-5.4	-5.2	-6.3	-6.3
alpha-Pinene	6654	-7	-6.1	-6.5	-5.3	-5.5	-6.3	-6.2
Gamma-terpinene	7461	-7	-6.1	-6.5	-5.8	-5.8	-6.5	-6.5
p_Cymene	7463	-6.9	-6.1	-6.5	-5.9	-5.8	-6.5	-6.5
Cadina-1(10),4-diene	10223	-9.2	-7.8	-8.3	-6.8	-6.5	-8	-8
beta-Pinene	14896	-7	-6.2	-6.1	-5.4	-5.2	-6.5	-6.3
Aromadendrene	91354	-9.4	-7.6	-7.7	-7	-6.7	-8.6	-8.2
alpha-Eudesmol	92762	-8.7	-7.6	-7.8	-7.4	-7.2	-8.3	-8.7
Globulol	101716	-9.2	-7.6	-7.2	-7.1	-6.6	-8.3	-8.3
Protoberberine	114943	-10.1	-9.5	-10.3	-8.1	-8.3	-10.3	-9.8
5-Hydroxycineole	439906	-6.4	-6.2	-7.3	-6	-6.3	-6.4	-6.6
Columbin	**442015**	**-9.6**	**-7.2**	**6.6**	**-8.8**	**-9.2**	**-10.7**	**-9.2**
alpha-Ylangene	442409	-8.5	-7.1	-7.1	-7.1	-6.3	-8.5	-7.7
L-delta3-Carene	442461	-7.8	-6.4	-6.4	-5.6	-5.7	-6.5	-6.3
Epizonarene	595385	-8.6	-7.7	-8.8	-7.1	-7.1	-8.2	-7.9
gamma-Humulene	3015263	-8	7.3	-7.4	-7.1	-6.3	-8.4	-8.1
Harmine	5280953	-9.2	-7.5	-8.4	-6.7	-7.6	-7.6	-8.4
Isocaryophyllene	5281522	-8.4	-7.8	-8.1	-7.1	-6.9	-8.4	-7.8
Ecdysterone	5459840	-8.7	-4.9	-8	-9.1	-9.2	-9.8	-7.5
20, 26-dihydroxyecdysone	21123946	-7.8	-6	-4.9	-8.1	-8.7	-9.2	-9.1
Isocolumbin	**24721165**	**-9.6**	**-7.2**	**-6.6**	**-8.8**	**-9.2**	**-10.9**	**-9.2**
Fibleucin	56678199	-10	-6.6	-8	-9.5	-8.8	-10.2	-9.1
5-Guaiene-11-ol	91747222	-9	-7.5	-8	-6.6	-6.7	-8.3	-8.9
Guaia-6,9-dien-4 beta-ol	91750034	-8.4	-7.7	-7.9	-7	-6.8	-8	-8.1
Danuglipron	134611040	-10.4	-9.8	-11.5	-9.1	-9.8	-11.1	-12
delta_Amorphene	348286014	-9	-7.3	-9.3	-6.8	-7.1	-8	-8.2

As shown in Figure 3 below, the docking scores in Table 1 were used to plot a heat map for better visual representation.



3ANR = DYRK1A, 4CI4 = PPARα, 4CI5 = PPARγ, 4GQR = Alpha-Amylase, 5T4E = DPP-IV, 7S15 = GLP1R, 7VSI = SGLT2
Figure 3: Heat map showing the docking scores of the phytochemicals from S. jollyanum against the receptors

From this result, columbin and isocolumbin had good binding scores against GLP-1R especially when compared with the score of the synthetic inhibitor downloaded with the receptor. A closer look at the heat map revealed that across the board, these two compounds were the only ones with good docking scores relative to the standard. While the synthetic inhibitor, danuglipron, had a docking score of -11.1 Kcal/mol, columbin and isocolumbin both had a docking score of -10.7 kcal/mol and -10.9 kcal/mol respectively. These two compounds were therefore regarded as our hit compounds and their 2D and 3D interaction with the amino acids at the active site were analyzed further.

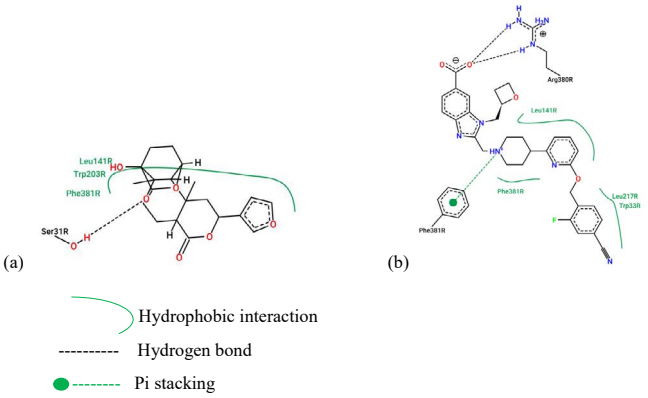
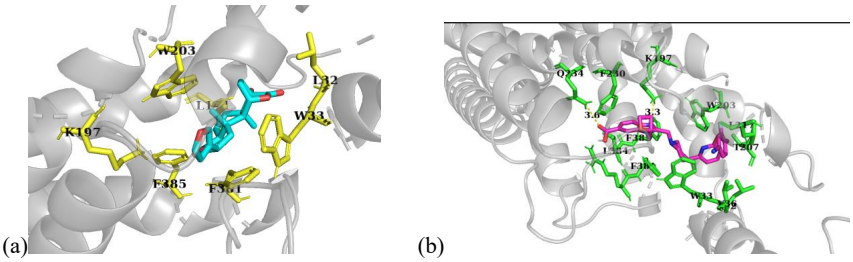


Figure 4: Two-dimensional (2D) protein-ligand interaction between GLP-1R and (a) Columbin, (b) Danuglipron



Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	33R	TRP	3.66	3836	38
2	141R	LEU	2.96	3831	1061
3	203R	TRP	3.74	3831	1670
4	203R	TRP	3.96	3827	1667
5	381R	PHE	3.58	3830	3394
6	381R	PHE	3.76	3833	3392
7	381R	PHE	4.00	3836	3397
8	385R	PHE	4.00	3832	3439

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Accep Atom
1	32R	LEU	3.27	3.60	100.92	✓	×	18 [Nam]	3848 [O2]
2	33R	TRP	2.57	3.02	106.66	✓	×	27 [Nam]	3848 [O2]

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Aton
1	197R	LYS	4.71	✓	Carboxylate	3846, 3847

Hydrophobic Interactions

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
1	32R	LEU	3.79	3845	25
2	33R	TRP	3.66	3831	34
3	33R	TRP	3.45	3844	39
4	36R	VAL	3.65	3844	68
5	203R	TRP	3.90	3836	1667
6	207R	THR	3.61	3836	1710
7	217R	LEU	3.65	3844	1819
8	217R	LEU	3.63	3843	1817
9	230R	PHE	3.64	3853	1957
10	381R	PHE	3.52	3831	3396
11	381R	PHE	3.88	3834	3392
12	384R	LEU	3.30	3852	3428

Hydrogen Bonds

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein donor?	Side chain	Donor Atom	Acceptor Atom
1	197R	LYS	2.74	3.32	116.46	✓	✓	1610 [N3+]	3828 [Nar]
2	234R	GLN	2.79	3.58	135.76	✓	✓	1995 [Nam]	3862 [O.co2]

π-Cation Interactions

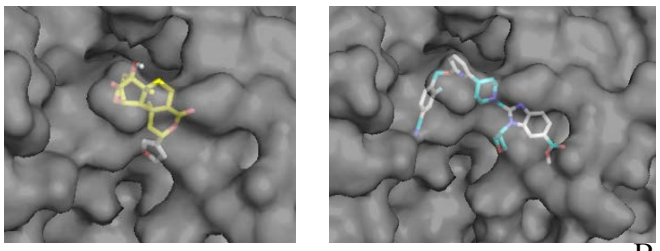
Index	Residue	AA	Distance	Offset	Protein charged?	Ligand Group	Ligand Atoms
1	381R	PHE	3.78	0.70	×	tertamine	3825

Salt Bridges

Index	Residue	AA	Distance	Protein positive?	Ligand Group	Ligand Atoms
1	380R	ARG	3.76	✓	Carboxylate	3862, 3863

Figure 5: Three-dimensional (3D) protein-ligand interaction between (a) Columbin (b) Danuglipron and GLP-1R.

Figure 4 and Figure 5 show the 2D and 3D interactions of the amino acids at the active site of GLP-1R with Columbin (representative of the hit compounds) and Danuglipron (reference ligand). There were interactions with key amino acids known for activation of GLP-1R in the extracellular domain and transmembrane domains of the receptor such as hydrogen bonds and salt bridges with Leu-32, Trp-33, Lys-197, Phe-381 and Leu-384 to mention a few.



A B

Figure 6: Three-dimensional surface interactions of (a) Columbin and (b) Danuglipron with GLP-1r

Figure 6 shows the 3D surface interaction of our hit compound and the reference ligand with the GLP-1 receptor. The hit compound and the reference ligand showed their ability to penetrate deep into the active site pockets and interact with the amino acid residues. Although the synthetic agonist traversed the pocket owing to its large size, the natural compound too penetrated well enough to have important interactions with the amino acid residues at the binding pocket.

Table 2: ADMETox properties of the phytochemicals (compounds) of *Sphenocentrum jollyanum*

Entry Name	A	B	C	D	E	F	G	H	I	J	K
1,8-Cineole	154.252	0	0.75	-2.596	0.605	5899.293	0.224	3	100	7.184	0
5-Guaiene-11-ol	222.37	1	0.75	-3.104	0.16	2605.588	0.722	3	100	19.445	0
5-Hydroxycineole	170.251	1	2.45	-2.463	0.209	2337.029	-0.132	3	100	27.264	0
20, 26-dihydroxyecdysone	496.64	7	11.05	-4.206	-2.959	6.549	-0.204	2	43.581	164.655	1
alpha-Eudesmol	222.37	1	0.75	-3.019	0.2	2867.958	0.659	3	100	19.15	0
alpha-Pinene	136.236	0	0	-2.758	0.871	5899.293	0.349	3	100	0	0
alpha-Ylangene	204.355	0	0	-3.382	1.084	5899.293	0.959	1	100	0	1
Aromadendrene	204.355	0	0	-3.089	1.05	5899.293	0.958	1	100	0	1
beta-Pinene	136.236	0	0	-2.525	0.857	5899.293	0.348	3	100	0	0
Cadina-l(10),4-diene	204.355	0	0	-3.205	1.094	5899.293	0.952	1	100	0	1
Camphene	136.236	0	0	-2.574	0.859	5899.293	0.325	3	100	0	0
Columbin	358.39	1	7.25	-3.674	-0.468	302.582	-0.081	3	88.125	96.83	0
Danuglipron	555.607	1	10	-6.386	-1.934	5.926	0.602	1	47.323	124.454	1
delta_Amorphene	204.355	0	0	-3.215	1.095	5899.293	0.956	1	100	0	1
Ecdysterone	480.64	6	9.35	-4.249	-2.452	17.732	0.115	2	56.313	142.125	1
Epizonarene	204.355	0	0	-3.399	1.121	5899.293	1.001	1	100	0	1
Fibleucin	356.374	1	7.25	-4.344	-0.872	123.177	-0.049	3	80.865	103.099	0
gamma-Humulene	204.355	0	0	-3.026	1.02	5899.293	0.974	1	100	0	1
gamma-Terpinene	136.236	0	0	-3.407	0.849	5899.293	0.402	3	100	0	0
Globulol	222.37	1	0.75	-2.93	0.277	3024.683	0.697	3	100	18.14	0
Guaia-6,9-dien-4 beta-ol	220.354	1	0.75	-3.353	0.173	2759.64	0.72	3	100	19.416	0
Harmine	212.251	1	1.75	-4.442	0.182	2416.97	0.204	3	100	33.447	0
Isocaryophyllene	204.355	0	0	-3.138	1.058	5899.293	1.005	1	100	0	1
Isocolumbin	358.39	1	7.25	-3.132	-0.453	271.963	-0.124	3	86.204	101.536	0
L-delta3-Carene	136.236	0	0	-2.988	0.889	5899.293	0.385	3	100	0	0
p_Cymene	134.221	0	0	-3.714	0.702	5899.293	0.343	3	100	0	0

A = mol_MW [Molecular weight of the molecule in g/mol (Range:130.0 to 725.0)]
B = donorHB [Number of hydrogen bond donors (Range: 0.0 to 6.0)]
C = accptHB [Number of hydrogen bond acceptors (Range: 2.0 to20.0)]
D = QPlogHERG [Predicted IC50 value for blockage of HERGK+ channels (Range: concern below -5)]
E = QPlogBB [Predicted brain/blood partition coefficient (Range: -3.0 to 1.2)]
F = QPPMDCK [Predicted apparent MDCK cell permeability in nm/sec (Range:<25 poor, >500 great)]
G = QPlogKhsa [Prediction of binding to human serum albumin (Range: -1.5 to 1.5)]
H = Human Oral Absorption [1= very low, 2= moderate, 3= high]
I = Percent Human Oral Absorption
J = Polar surface area [PSA: Van der Waals surface area of polar nitrogen and oxygen atoms (Range 7.0 – 200.0)]
K = Rule of Five [Number of violations of Lipinski's rule of five (Range: maximum is 4)]

DISCUSSION

Molecular docking (MD) is a structure-based *in silico* method widely accepted in drug discovery as it is inexpensive and saves time identifying hit compounds that have high chances of eventually translating to drug candidates (Torres *et al*., 2019). MD uses scoring functions to rank predicted ligands' poses in the target's "pocket" and values known as docking scores (Pinzi and Rastelli, 2019). Usually, the lower the score, the better suggesting a stronger affinity between the ligand and the receptor binding pocket. Table 1 above shows the docking scores of the ligands (*S. jollyanum* phytochemicals) and the receptors they were docked with, alongside those of the reference ligands serving as a standard to compare the scores. The scores were plotted as a heat map as shown in Figure 3, for better visualization. On the heat map, two distinct colours (red and green) were used to represent the score as shown on the legend. The red color represents the ones with high binding scores and as such lower affinity when compared with the green which represents lower values but higher affinity hence a good binding score. A closer look at the map reveals that columbin and isocolumbin against GLP-1R (7S15) have a good binding affinity compared with the standard (reference ligands).

GLP-1R activation by native GLP-1 has been confirmed to reduce plasma glucose levels in type 2 diabetes patients by delaying gastric emptying and suppressing hypersecretion of glucagon (Nauck *et al*., 2021). This has led to a search for different molecules, either natural or synthetic, with the capacity to activate GLP-1R and not be degraded by DPP-IV. Examples of such molecules include exenatide, semaglutide, albiglutide, dulaglutide, liraglutide, danuglipron and so on. In this study, danuglipron served as a reference ligand to compare its interaction at the active site of GLP-1R with the compounds from *S. jollyanum*. Figure 4 shows the 2D structures of the interaction of columbin and danuglipron at the active site of GLP-1R and Figure 5 shows the 3D structures of interaction between columbin, danuglipron, and the residues at the active site of GLP-1R. Similar interactions such as hydrophobic interactions, hydrogen bonds, and salt bridges were present both in columbin and danuglipron while pi-cation interactions, in addition, were observed between GLP-1R and danuglipron.

To activate GLP-1R, GLP-1 interacts with all segments of the transmembrane domain (TM) except TM4, however from our study, the reference ligand, danuglipron, interacted with the residues within the TM1, TM2, TM3, TM7, ECD and ECL1 which is consistent with a previous study by Kawai *et al* (Kawai *et al*. 2020). Columbin on the other hand interacted with residues within the TM1, TM2, TM7, and ECD and not with TM3 and ECL1 as in the case of danuglipron. However, several molecules have been studied on their interactions at the active site of GLP-1R each adopting a slightly different orientation which could mean a different form of activation but in all, GLP-1R is activated either fully or partially (Kawai *et al*., 2020). This result suggests that columbin from *S. jollyanum* activates GLP-1R to perform its antidiabetic claim. It is safe to say this is in tandem with a previous study that has traced the insulinotropic activity of *Tinospora crispa* to columbin (Noor *et al*., 1989.). It is important to note that columbin and isocolumbin are diterpene furanolactone compounds also referred to as furanoditerpenes (Moody *et al*., 2006).

Another interesting fact to consider is the surface interaction in Figure 6. danuglipron, our reference ligand looks well embedded in the binding pocket as well as columbin as they interact with key amino acid residues in the different domains such as H-bond with Leu-32, Trp-33, and salt bridge with Lys-197 as shown in Figure 5. columbin, though with a lower molecular weight (358 g/mol) compared to that of danuglipron (555 g/mol), looks well embedded to make interactions important for activation.

Furthermore, the ADMETox properties calculated using Schrodinger-Qikprop depicted in Table 2 indicate the prediction of the physicochemical properties, medicinal chemistry, and toxicity behaviour of the compounds of *S. jollyanum.* The physical and chemical properties of a compound determine the type of interaction it would have with the receptor (Bunally *et al*., 2019). Properties such as hydrogen bond donor, hydrogen bond acceptor, and molecular weight had values within range for all the compounds. However, for the synthetic compound, danuglipron, the value for QPlogHERG (-6.38) slightly exceeded the normal range of -5, raising concern. Also, columbin, isocolumbin, and other compounds have values indicating high human intestinal absorption (HIA). This property is important as it predicts how effective the compound is as a drug molecule since this involves the processes involved in the absorption of the drug compound from the gastrointestinal system into the bloodstream. All the compounds had values within range of the brain barrier suggesting they cannot cross the barrier to cause harm to the brain, hence they are safe (Stéen *et al*., 2022).

CONCLUSION

Overall, the molecular docking result depicts the furanoditerpenes as the compounds acting as GLP-1R agonists and this could be the mechanism of its anti-

diabetic action claim. However, more intensive studies such as molecular dynamics simulation and *in vivo* experiments must be carried out to be certain. Also, the ADMETox profiling suggests it is safe however, toxicity studies should be done to affirm this.

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