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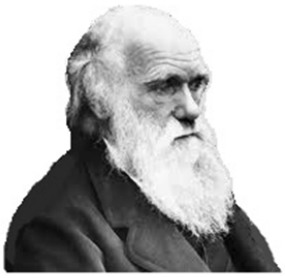

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Virtual screening and molecular docking of red *Acalypha wilkesiana* leaf extract-derived compounds as SGLT2 inhibitors for Type 2 diabetes therapy

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ABSTRACT

Diabetes mellitus is a hullmark of metabolic disorder, a life – threatening condition that affect millions of individuals globally. Ethno-medicinal and scientific reports abound on the use of *Acalypha wilkesiana leaf* extract in managing diabetic patients. This study employed gas chromatography-mass spectrometry (GC-MS) and computational approach to investigate the phytochemical profile and potential bioactive properties of *A. wilkesiana* leaf. GC-MS analysis revealed distinct variations in phytochemical composition ranging from monoterpenes, sesquiterpenes, alkaloids etc,hence identify and validate hit compounds from the crude leaf extract with the potential to inhibit SGLT-2 receptor. Molecular docking results showed that the binding affinity of the hit molecule indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- (-10.7 kcal/mol) was very close to the control drug Sotagliflozin (–11.4 kcal /mol) at this target. ADMET analysis predicted that the properties of these compounds were within acceptable limits with the hit molecule showing better druglikeness than the conventional drug used as control. These results indicate that *A. wilkesiana* holds promise as a therapeutic agent for the management of diabetes, warranting further investigation into its therapeutic potential.

Keywords: Diabetes, *Acalypha wilkesiana*, Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-, Sodium-glucose cotransporter 2 (SGLT2) Receptor, Sotagliflozin

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1. INTRODUCTION

Diabetes mellitus is the most common chronic and metabolic disease characterized by elevated levels of blood glucose (or blood sugar) [1], which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves due to absolute or relative insulin deficiency [2]. This disease is also associated with symptoms such as polyuria, fatigue, weight loss, delayed wound healing, blurred vision, increases in urine glucose levels, etc. [3]. Diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycaemia, also called raised blood glucose or sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels [4].

Diabetes cases may be classified into three main types, namely type 1, type 2, and gestational diabetes. Type 1 diabetes (T1D) is an immune-mediated illness that is primarily as a result of pancreatic beta cell destruction occurring in genetically predisposed persons [5]. Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin by itself. Type 2 diabetes (T2D) occurs due to impaired insulin secretion and increased insulin resistance and accounts for about 90% of all cases of diabetes [6].

The prevalence of T2D is higher in males than in females, and older adults have a higher prevalence than young people. T2D has been diagnosed in 20% of individuals aged≥65 years [7]. In the past 3 decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Gestational diabetes is caused by insulin-blocking hormones that are produced during pregnancy. This type of diabetes only happens during pregnancy. It is often seen in people with preexisting prediabetes and family history of diabetes [8].

Diabetes mellitus is a hullmark of metabolic disorder, a life –threatening condition that affect millions of individuals globally, harming them financially, physically and psychologically in the course of the therapy, People with diabetes have a higher risk of health problems including heart attack, stroke and kidney failure [9]. Several scientific studies have indicated that diabetes affects the human quality of life by causing major risk factors for adverse complications such as stroke, amputation, kidney failure, and blindness, leading to significant morbidity and premature mortality [10].

Diabetes poses a significant public health burden in Nigeria, with an estimated 40,000 fatalities in 2015 attributed to the disease. This substantial loss of life is largely due to inadequate healthcare delivery and diagnostic services. Alarmingly, a substantial proportion of Nigerians living with diabetes remain undiagnosed and untreated.

According to the International Diabetes Federation (IDF), approximately two-thirds of individuals with diabetes in Africa, including Nigeria, are unaware of their condition, highlighting the urgent need for improved diabetes detection, treatment, and management strategies. The WHO predicts diabetes to become the seventh leading cause of death in the world by the year 2030 [11]. WHO projects that diabetes will be the seventh leading cause of death in 2030 [12], therefore discovery of the new natural antidiabetic drugs could be of great promising solution due to minimal efficacy and side effect of current drugs for the hundreds of millions of individuals who are seeking better management of diabetes recently [13].

Diabetes is gradually reaching epidemic proportions in both industrialized and developing countries and poses a significant public health threat in the twenty-first century, causing 1.5 million deaths globally, mainly in low- and middle-income countries [14].

Sodium-glucose cotransporter 2 (SGLT2) plays an important role in glucose reabsorption in the kidney and is involved in the reabsorption of most glucose in primary urine [15]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors exert their therapeutic effect by selectively blocking renal glucose reabsorption. This pharmacological intervention enhances urinary glucose excretion by inhibiting the reabsorption of glucose in the kidneys [16]. The SGLT2 receptor is primarily expressed in the kidneys, specifically in the proximal convoluted tubules of the nephrons. Its primary function is to reabsorb glucose from the filtrate back into the bloodstream, thereby regulating blood glucose levels. In patients with type 2 diabetes, inhibiting SGLT2 reduces glucose reabsorption, increases urinary glucose excretion, and ultimately lowers blood glucose levels. SGLT2 inhibitors, a novel oral hypoglycemic agent, have attracted increasing attention for NAFLD patient treatment [17]. In preclinical studies on rodent models, SGLT2 inhibitors significantly reduce body weight while improving hepatic steatosis and fibrosis. Nevertheless, multiple clinical studies have revealed that SGLT-2 inhibitors decrease TG levels, increase HDL-cholesterol levels, and increase LDL-cholesterol levels, which may lead to ambiguous cardiovascular risk [18]. The activities of this hormone can be expressed and stimulated by high glucose level, high sodium level and insulin.

Recently, many new therapies have been discovered, including blocking enzymes involved in the degradation of dietary polysaccharides in the gut, which might also result in lower blood glucose levels after a meal by reducing monosaccharide absorption via the small intestine's entrecote [19]. Insulins, liraglutide, and pramlintide are presently available therapies for T2D Mellitus. Other medications include metformin, meglitinides, sulfonylureas, sitagliptin, saxagliptin, dapagliflozin etc. Conventional treatments for these conditions are effective but often limited by adverse reactions, such as dizziness, depression, anxiety, weight gain, and high costs. Herbal remedies have shown promise in managing diabetes with numerous studies validating the pharmacological properties of plant-derived phytochemicals [20].

Phytomedicine has acquired global popularity recently due to its efficacy in treating T2D mellitus. In tropical Africa, numerous studies have given credence to the pharmacological properties of plant-derived phytochemicals in the management of several diseases including diabetes, plants like *Andrographis paniculata, Aloe vera, Azadirachta indica, Caesalpinioideae, Pachira aquatic, Gongronema latifolium, Vernonia amygdalina Nigella sativa, Ocimum tenuiflorum, Acalypha wilkesiana* etc. have been recorded to posses antidiabetic potentials [3].

A. wilkesiana, a native to Fiji and neighboring South Pacific Islands commonly called Irish petticoat, Jacobs coat or copper leaf is a fast-growing tropical shrub in the spurge family (*Euphorbiaceae*) [21]. The genus name *Acalypha* comes from the Greek name for nettles because of the nettle-like appearance of the leaves. It is an evergreen shrub growing to 3 metres (9.8 ft) high and 2 metres (6 ft 7 in) across [22]. It has a closely arranged crown, with an erect stem and many branches. Both the branches and the leaves are covered in fine hairs. The leaves, which may be flat or crinkled, are large and broad with teeth around the edge. They can be 10–20 centimetres (3.9–7.9 in) long and 15 centimetres (5.9 in) wide.It has 4 to 8-inch heart-shaped leaves that come in a variety of mottled color combinations of green, purple, yellow, orange, copper, crimson, pink, or white. Separate male and female flowers appear on the same plant, male spikes long and hanging with female spikes short.

In Southern Nigeria, the leaves of *Acalypha wilkesiana* are eaten as vegetables in the management of hypertension. The expressed juice or boiled decoction is used for the treatment of gastrointestinal disorders, fungal skin infections, hypertension, diabetes mellitus and other

cardiovascular diseases [23]. Plants from *Acalypha* genus are traditionally used in the treatment and/or management of diverse ailments such as diabetes, jaundice, hypertension, fever, liver inflammation, schistosomiasis, dysentery, respiratory problems including bronchitis, asthma and pheumonia as well as skin conditions such as scabies, eczema and mycoses [24]. The basis of the use of *Acalypha wilkesiana* leaves in the management of diabetes mellitus, as well as the biochemical impact of their administration on the diabetic is yet to be clearly understood. Earlier, researchers had reported the hypoglycemic effect of the leaf supplementation on salt-loaded rats [24].

Yet there is limited scientific evidence on the specific compounds responsible for its effects, their suitability as drug candidates and safety profile. Therefore, this study assessed the hypoglycemic activity of the small molecule agonists in the crude leaf extract of *Acalypha* using insilico methods. Molecular docking simulations were employed to identify potential hit compounds from the leaf extract that target the SGLT2 receptor. Subsequent druglikeness assessments was conducted to evaluate the efficacy of the compounds as prospective therapeutic candidates for the treatment of diabetes.

2. MATERIALS AND METHODS

2. 1. Identifcation and Preparation of *A. Wilkesiana* Crude Extract

Whole plants of *Acalypha wilkesiana* were collected from a garden in Eastern Nigeria and identified at Plant Science and Biotechnology, Imo State University, Owerri, Nigeria. Fresh leaves of *Acalyha wilkesiana* were plucked, washed with deionized water, and spread on a clean cotton cloth for a few minutes to remove water. They were mashed in a porcelain mortar and pestle, and 5g of the paste was dispersed in 100 mL of 70% ethanol [25,26] in an airtight container, left to stand for 24h then filter, after which rotary evaporation was used to recover the crude extract from the solvent. The extract was stored in a refrigerator at 4 °C before use.

Plate 1. Picture of *Acalypha wilkesiana* leaf.

2. 2. GC-MS Analysis of Crude Extract

The leaf extract of *A. wilkesiana* was analyzed using a Gas Chromatography-Mass Spectrometer (GC-MS) instrument (Model: 7890 GC and 5977B MSD, Agilent Technologies, (USA), following the method as described by [27,28]. The extract was fully scanned at 40–500 m/z, and the results were compared using the NIST mass spectral library search program.

2. 3. Molecular Docking Protocol

Three-dimensional (3D) structures of compounds in the crude extract identified by GC-MS analysis were retrieved from the PubChem web server in structure data format (SDF). The compounds were optimized using Open Babel in Python Prescription (version 0.8), which converted them to their most stable structures using Merck Molecular Force Field 94 (MMFF94). The 3D structure of the human SGLT2-MAP17 complexed with Sotagliflozin [29] was retrieved from the protein data bank (PDB) with identity 8HG7. The protein was then prepared for docking by first removing the native ligand from its receptor, and the receptor protein was minimized using the relevant tools. The General Amber Force Field (GAFF) was used for the protein minimization, with a gradient cutoff of 0.200 kcal/mol/A and iterations were set to 2000 iterations. The molecular docking was performed through a fexible docking protocol [30]. Python Prescription 0.8, a suite that bears the Auto Dock Vina module, was used for the molecular docking study of the compounds at the protein receptor. The specific target site on the receptor was set using a grid box with dimensions 16.006 ×21.104 ×25.235 Å. At the end of the molecular docking, the binding poses of the protein-ligand complex were generated, and their scoring results were also created.

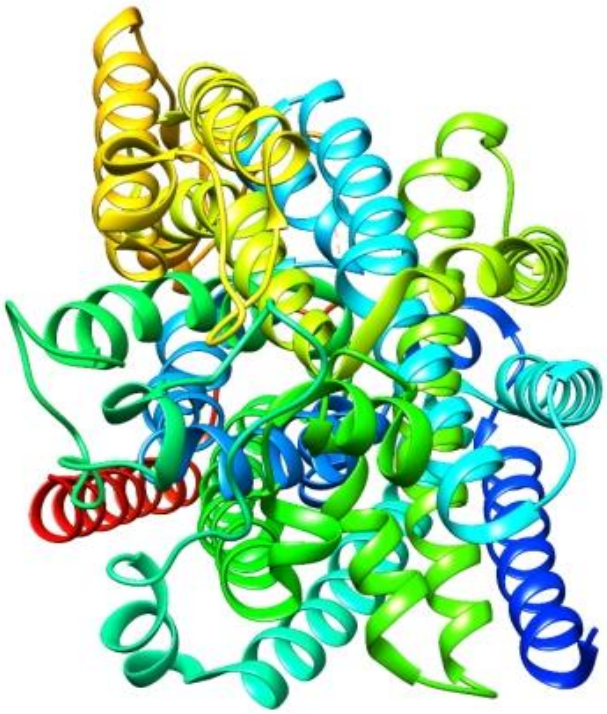


Fig. 1. Human SGLT2-MAP17 (PDB ID: 8HG7)

2. 4. Absorption, Distribution, Metabolism, Elimination, and Toxicity (ADMET) Studies

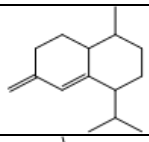
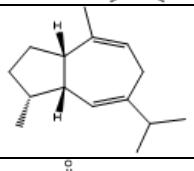
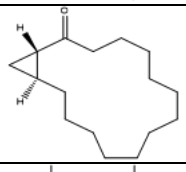
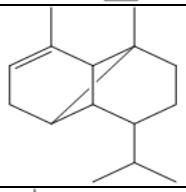
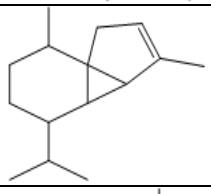
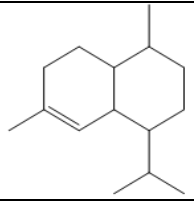
Compounds with the lowest binding energy on the protein target was selected and submitted to toxicity study to determine the druglikeness properties.

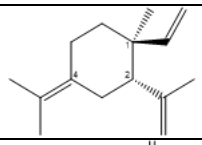
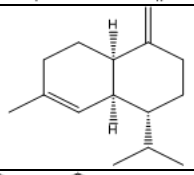
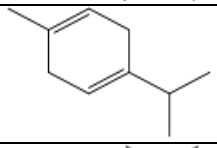
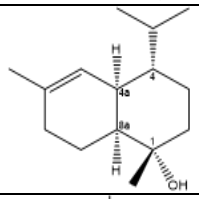
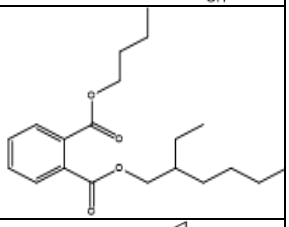
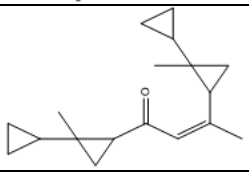
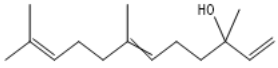
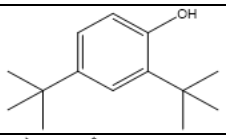
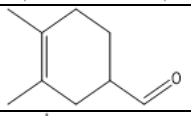
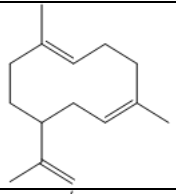
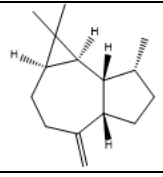
3. RESULTS AND DISCUSSION

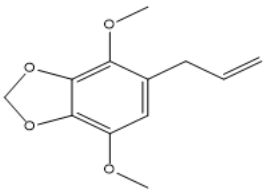
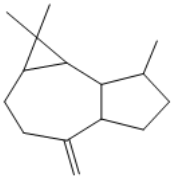
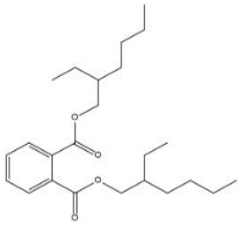
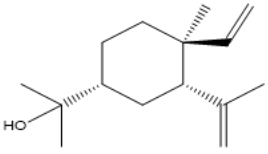
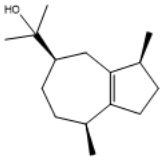
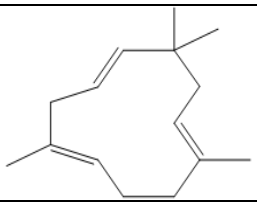
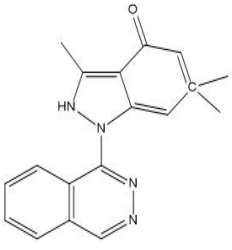
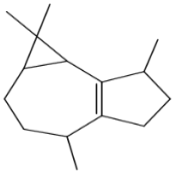
3. 1. Phytochemical Analysis and Docking Results

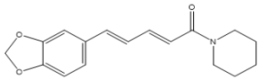
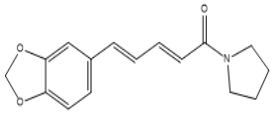
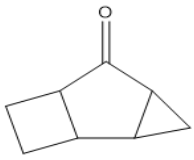
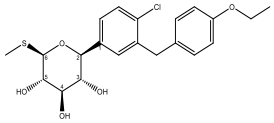
The GC–MS analysis of *Acalypha wilkesiana* leaf extract gave 27 peaks for the bioactive compounds, their percentage composition, retention time, structures and formulas were recorded in the Table 1.

Table 1. Identified phytochemicals from *A. wilkisiana.*

Phytochemicals	% Area	Formula	Molecular weight (g/mol)	Structure
(+)-epi-bicyclosesquiphellandrene	3.74	$C_{15}H_{24}$	204.35	
(1R,3aS,8aS)-7-Isopropyl-1,4-dimethyl-1,2,3,3a,6,8a-hexahydroazulene	0.28	$C_{15}H_{24}$	204.35	
(1S,15S)-bicyclo[13.1.0]hexadecan-2-one	0.30	$C_{16}H_{28}O$	236.39	
.alpha.-Copaene	1.34	$C_{15}H_{24}$	204.35	
.alpha.-Cubebene	0.15	$C_{15}H_{24}$	204.35g	
.alpha.-Muurolene	0.37	$C_{15}H_{24}$	204.35g	

.gamma.-Elemene	2.76	$C_{15}H_{24}$	204.35	
.gamma.-Muurolene	0.46	$C_{15}H_{24}$	204.35	
.gamma.-Terpinene	1.09	$C_{10}H_{16}$	136.23	
T-Muurolol	0.21	$C_{15}H_{26}O$	222.37	
1,2-Benzenedicarboxylic acid butyl 2-ethylhexyl ester	0.36	$C_{20}H_{30}O_4$	334.4	
1,3-Bis-(2-cyclopropyl,2-methylcyclopropyl)-but-2-en-1-one	0.79	$C_{18}H_{26}O$	258.399	
1,6,10-Dodecatrien-3-ol,3,7,11-trimethyl-	2.59	$C_{15}H_{26}O$	222.37	
2,4-Di-tert-butylphenol	1.45	$C_{14}H_{22}O$	206.32	
3-Cyclohexen-1-carboxaldehyde,3,4-dimethyl-	0.11	$C_9H_{14}O$	138.21	
8-Isopropenyl-1,5-dimethyl-cyclodeca-1,5-diene	0.37	$C_{15}H_{24}$	: 204.35	
Alloaromadendrene	1.89	$C_{15}H_{24}$	204.35	

Apiol	0.16	$C_{12}H_{14}O_4$	222.24	
Aromandendrene	6.56	$C_{15}H_{24}$	204.35	
Bis(2-ethylhexyl)phthalate	0.49	$C_{24}H_{38}O_4$	390.6	
Cyclohexanemethanol, 4-ethenyl-.alpha.,alpha., 4-trimethyl-3-(1-methylethenyl)-,[1R-(1.alpha.,3.alpha.,4.beta]-	0.37	$C_{15}H_{26}O$	222.37	
Guaiol	0.58	$C_{15}H_{26}O$	222.37	
Humulene	1.90	$C_{15}H_{24}$	204.35	
Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-	0.68	$C_{18}H_{18}N_4O$	306.4	
Isoledene	0.46	$C_{15}H_{24}$	204.35	

Piperine	0.68	$C_{17}H_{19}NO_3$	285.34	
Pyrrolidine,1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(E,E)-	0.15	$C_{16}H_{17}NO_3$	271.31	
Tricyclo[4.2.0.0(2,4)]octan-5-one, (1.alpha.,2.beta.,4.beta.,6a)-	1.79	$C_8H_{10}O$	122.16	
Sotagliflozin (control)		$C_{21}H_{25}ClO_5S$	424.9g	

Gas chromatography-mass spectrometry (GC-MS) was employed to provide a comprehensive analysis of the chemical constituents present in the *A. wilkesiana* leaf extract. The resulting GC-MS chromatograms afford a visual representation of the separation and detection of *Acalypha* crude extract's chemical composition, facilitating the identification of diverse compounds based on their characteristic retention times and mass-to-charge ratios. This enables the elucidation of the phytochemical profile of the extract, which is essential for understanding their potential bioactive properties. *Acalypha wilkesiana* leaf extract is characterized by the presence of monoterpenes, sesquiterpenes, alkaloids and other natural products with notable pharmacological properties. These include aromadendrene (6.56%) a sesquiterpenes with anti-inflamatory, anticancer and antibacterial properties [31]. (+)-epi-bicyclosesquiphellandrene (3.74%) had antitumor activity against colon cancer cells. Generally terpenoid enhance insulin sensitivity and reduce blood glucose levels. Additionally, sesquiterpenes like beta-caryophyllene exhibit anti-inflammatory effects [9]. Piperine is an alkaloid that is mainly present in black pepper, it can improve insulin resistance and glucose intolerance, it can also provide additional benefits to diabetes by its antioxidant and anti-obesity properties [32]. Various alkaloids have been identified as promising hypoglycemic agents and have been recorded to decrease the level of insulin resistance in diabetic mice induced by a high-fat diet [33]. These phytocompounds could contributed to the efficacy of this plant especially in diabetes management.

Table 2. Result of Binding affinities of phytochemicals and the control drug with the disease protein.

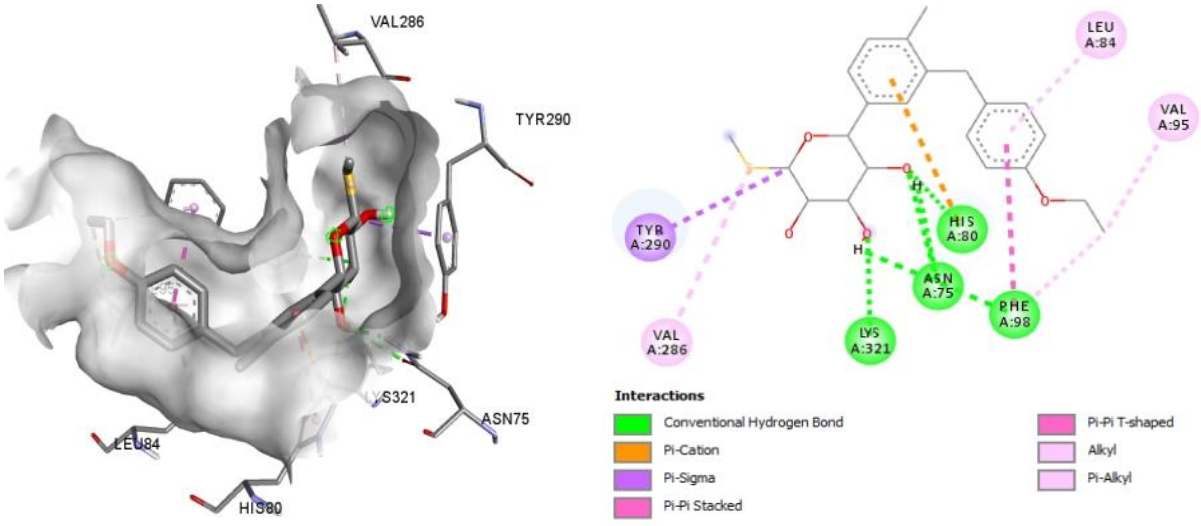
Phytochemicals	**PubChem CID**	**Binding affinity**
(+)-epi-bicyclosesquiphellandrene	521496	-7.4
(1R,3aS,8aS)-7-Isopropyl-1,4-dimethyl-1,2,3,3a,6,8a-hexahydroazulene	14190792	-7.2

(1S,15S)-bicyclo[13.1.0]hexadecan-2-one	13760785	-8.4
.alpha.-Copaene	19725	-7.8
.alpha.-Cubebene	86609	-7.7
.alpha.-Muurolene	101708	-7.1
.gamma.-Elemene	6432312	-7.0
.gamma.-Muurolene	6432308	-7.8
.gamma.-Terpinene	7311	-7.2
T-Muurolol	3084331	-7.3
1,2-Benzenedicarboxylic acid butyl 2-ethylhexyl ester	6818	-8.0
1,3-Bis-(2-cyclopropyl,2-methylcyclopropyl)-but-2-en-1-one	5362887	-7.5
1,6,10-Dodecatrien-3-ol,3,7,11-trimethyl-	8888	-7.1
2,4-Di-tert-butylphenol	7311	-7.2
3-Cyclohexen-1-carboxaldehyde,3,4-dimethyl-	537551	-6.3
8-Isopropenyl-1,5-dimethyl-cyclodeca-1,5-diene	5365775	-7.4
Alloaromadendrene	10899740	-6.7
Apiol	10659	-6.8
Aromandendrene	91354	-7.8
Bis(2-ethylhexyl)phthalate	8343	-8.6
Cyclohexanemethanol, 4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-,[1R-(1.alpha.,3.alpha.,4.beta.)]-	547972	-7.8
Guaiol	227829	-8.7
Humulene	5281520	-7.1
Indazol-4-one,3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-	5293334	-10.7
Isoledene	530426	-7.8
Pyrrolidine,1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(E,E)-	636537	-9.1
Tricyclo[4.2.0.0(2,4)]octan-5-one, (1.alpha.,2.beta.,4.beta.,6a)-	543748	-6.5

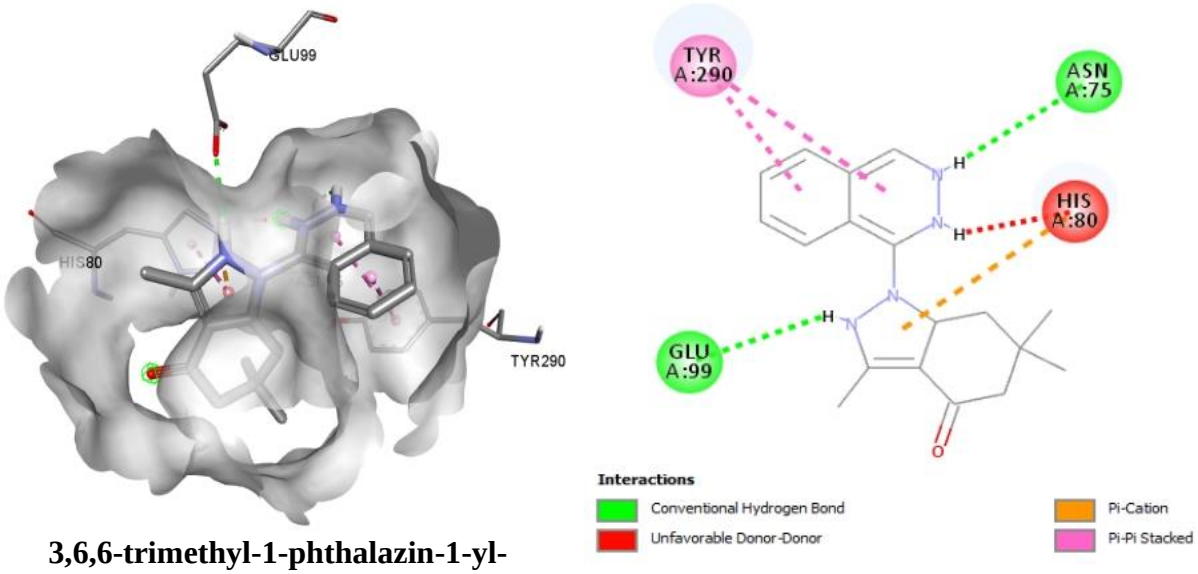
Sotagliflozin (control)	24831714	-11.4
Piperine	638024	-9.8

The identified compounds from the leaf extracts were docked on SGLT2 protein to determine their binding affinities and compared with that of control drug Sotagliflozin.The docking result showed that the hit compound Indazol-4-one,3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- (-10.7 kcal/mol) has binding affinity very close to control. Piperine has affinity -9.8 kcal/mol, Pyrrolidine,1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]-,(E,E)- has affinity -9.1 kcal/mol while Guaiol and Bis(2-ethylhexyl)phthalate both has -8.7 and -8.6 kcal/mol respectively. (1S,15S)-bicyclo[13.1.0]hexadecan-2-one (-8.4 kcal/mol) while 1,2-Benzenedicarboxylic acid butyl 2-ethylhexyl ester has 8.0kcal/mol. Cyclohexanemethanol, 4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-,[1R-(1.alpha.,3.alpha.,4.beta.)]-, Isoledene, Aromandendrene, gamma.-Muurolene,alpha.-Copaene (7.8) and alpha.-Copaene (7.7 kcal/mol). This affinity result has significant implications for drug discovery and development The binding affinity of Indazol-4-one,3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- suggested that it is a potential lead compound for further research. Figures 2 illustrate the molecular interactions between the native ligand of the enzyme target and the hit compounds with the amino acids at the enzyme's active sites, providing a detailed visual representation of the binding modes and interactions of these ligands with the target enzyme.

The binding analysis of SGLT2 target with the ligands revealed distinct interaction profiles. The native ligand formed conventional hydrogen bonds,pi-sigma, pi-pi T- shaped, and pi-cation, pi- alkyl, and pi-pi stacked interactions with the target. The hit compound exhibited a binding mode characterized by conventional hydrogen bonds, pi-pi stacked, and unfavourable donor donor interactions. Both the control and hit compound has conventional hydrogen bond and pi-pi stack interaction. The above result was summarized in Table 3.



Sotagliflozin (Control drug)



3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydroindazol-4-one

Figure 2. Visuals of protein-ligand interactions at the SGLT2 target

Table 3. Docking results showing the type of interaction and amino acid involved.

Compound	Type of interaction	Amino acids involved
Indazol-4-one,3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-	Conventional hydrogen bond Unfavourable donor donor Pi-Pi stacked	GLU 99, ASN 75 HIS 80 TYP 290
Sotagliflozin	Conventional hydrogen bond Alkyi & Pi Alkyl Pi Sigma	HIS 80. PHE 98 LYS 321, ASN 75 Val 95, LEU 84, VAL 286 TYR 290

3. 2. ADMET Analysis

The druglikeness of the hit compound was assessed using ADMETlab 3.0 [34], a robust online platform that integrates multiple physicochemical and pharmacokinetic descriptors to predict a compound's potential as a viable drug candidate.

Specifically, the compounds were evaluated against Lipinski's Rule of Five, which encompasses molecular weight, lipophilicity (log P), hydrogen bond acceptors, and hydrogen bond donors. Furthermore, their topological polar surface area (TPSA), rotatable bond count, and molecular flexibility were also scrutinized to determine their compliance with established drug-like properties.

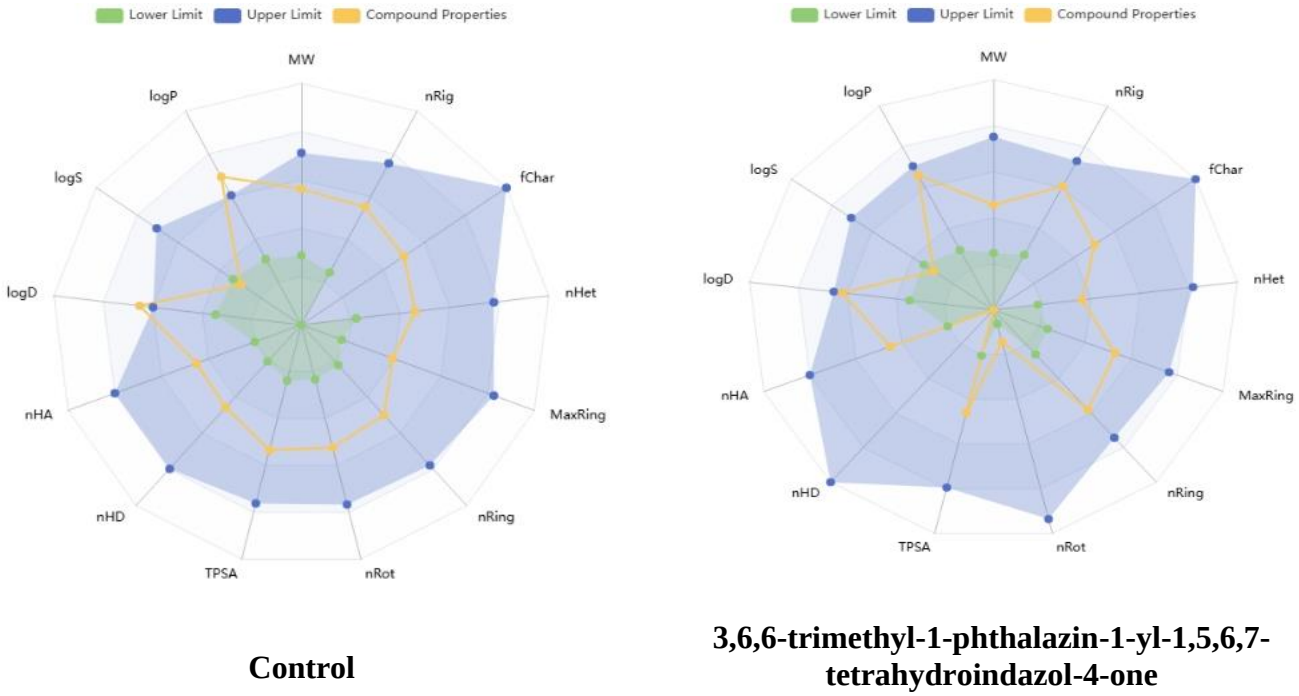
3. 3. Analysis of druglikeness of hit compound

The pharmacokinetic and pharmaceutical profiles of the hit molecules were assessed using the ADMETLab 3.0 web server to predict their likelihood of exhibiting desirable drug-like properties. A radial plot visualization of the key physicochemical descriptors is presented in Figure 3, providing a comprehensive overview of the molecule's pharmacological potential.

Table 4. Summary of druglikeness metrics from ADMET evaluation.

Compounds	MW	nA	nRing	HBD	HBA	logP	nRB	TPSA	Carcinogenicity
Indazol-4-one,3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-	306.36 g/mol	5	4	0	5	2.68	1	60	0.87
Sotagliflozin	424.11	5	3	3	5	3.87	6	79	0.22

MW = Molecular weight; nA = Number of Atoms; nRing = Number of Rings; HBD = Hydrogen Bond Donors; HBA = Hydrogen Bond Acceptors; logP = Octanol-Water Partition Coefficient; nRB = Number of Rotatable Bonds; TPSA = Topological Polar Surface Area



Control **3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydroindazol-4-one**

Fig. 3. Radial plot of the studied physicochemical properties from ADMET

From the plot, the hit compound portrays a better druglikeness than the control Sotagliflozin exhibiting desirable pharmacological and pharmaceutical properties evaluated with more compliance to Lipinski's Rule of Five.

4. CONCLUSIONS

This comprehensive study employed gas chromatography-mass spectrometry, molecular docking simulations, and ADMET studies to access hypoglycemic activities of phytocompounds from crude ethanol extract of *Acalypha wilkesiana* at SGLT2 receptor. Molecular docking studies identified indazol-4-one, 3,6,6-trimethyl-1- phthalazin-1-yl-1,5,6,7-tetrahydro- as hit compound at this target with binding affinity very close to the regular medication and the control Sotagliflozin used by diabetic patients.

The ADMET and druglikeness characteristics of these compounds revealed that the identified hit compound was a better promising candidate for managing T2D underscoring its potential for managing diabetes. Notably, Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydroexhibited a favorable pharmacokinetic profile better than the control drug emphasizing its potential for managing diabetes. The identification of this hit compound as a potent binder to SGLT2 has significant implications for the development of novel therapeutics targeting these enzyme.

This phytocompounds offer improved efficacy, reduced side effects, and enhanced pharmacological profiles, warranting further investigation into its potential as a therapeutic agent. This study underscores the importance of integrating experimental and computational approaches in drug discovery highlighting the potential of natural products in addressing complex diseases. Future studies should focus on optimizing pharmacological properties and evaluating its in vivo efficacy in this disease models.

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