ORIGINAL ARTICLE OPEN ACCESS

Saponins from *Spondias mombin* leaves as potential PPAR gamma agonist and DPP-4 inhibitor for type 2 diabetes treatment using molecular docking studies and ADMET profiling

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ABSTRACT

Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors and peroxisome proliferator-activated receptor gamma (PPARγ) agonists are available for the clinical treatment of diabetic mellitus (DM), although the majorities have numerous negative side effects. Emerging research suggests that natural compounds, particularly those derived from medicinal plants, hold significant potential, driven by their perceived safety and bioavailability. This study seeks to determine the potential of saponins isolated from *Spondias mombin* as novel DPP-4 inhibitors and PPARγ agonist by examining their interaction with the enzyme based on the results of molecular docking studies, strength of their interaction, drug likeness and pharmacokinetic analysis.

Materials and methods: Saponins were isolated from the leaves of *Spondias mombin* and characterized using high performance liquid chromatographic procedure. Molecular docking studies was used to determine the interactions between the saponins and key anti diabetic drug targets PPAR-γ and DPP-IV The 2D diagrams and the 3D (surface) views of the protein-ligand interactions were done using Discovery studio software and Pymol software respectively, while the pharmacokinetics and drug likeness properties of the studied compounds were estimated using SwissAdme online server.

Results: Eleven saponins: Hispigenin, Solagenin, Diosgenin, Trigogenin, Neochlorogenin, Hecogenin, Sapogenin, Tribuloin, Yangonenin, Conyzorgin, Saponine were characterized from the leaves of *Spondias mombin*. Solagenin stood out as the most potent activator of PPARγ while Hecogenin was the most potent inhibitor of DPP-4. The results indicated that only Hispigenin, hecogenin, yangonenin and solagenin adhered to all four Lipinski's rules. The saponins showed no Veber violations, and readily crossed the blood brain barrier. A high gastrointestinal absorption was also shown for most of the saponins. None of the seven saponins (Hispigenin, Hecogenin, Solagenin, Diosgenin, Trigogenin, neochlorogenin, and Sapogenin) appear to be inhibitors of four key cytochrome p450 isoenzymes.

Conclusion: The study has shown that the saponins of *Spondias mombin* are drug like, highly absorbed and bioavailable and hence adding to the increasing amount of data demonstrating the effectiveness of natural products in treating type 2 diabetes.

Keywords: Diabetes; Molecular docking; *Spondias mombin;* Saponins; $PPAR_{\gamma;}$ DPP-4

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease marked by persistent hyperglycemia and is one of the most important health concerns of the twenty-first century predominantly brought on by insulin resistance (IR). T2DM has significant global economic and societal ramifications. According to the World Health Organization (WHO), diabetes caused 1.6 million deaths worldwide in 2016. By 2030, diabetes is predicted to rank as the sixth most common cause of mortality (1). Type 2diabetes is characterized by high blood sugar levels that lead to heart disease, blindness, kidney failure, and hypertension (2). In 2019, diabetes directly caused 1.5 million deaths, with 48% of all diabetes-related deaths occurring in those under the age of 70 (3). Diabetes contributed to an additional 460,000 deaths from kidney disease, and elevated blood glucose is responsible for almost 20% of fatalities from cardiovascular disease (3).

Considering the overall morbidity, mortality and loss of productive manpower inflicted by this disease, finding new chemicals and pharmacological targets that will be useful in the treatment or prevention of diabetes is of great interest. Also, in response to costly and adverse chemically derived medications, approximately 80% of people worldwide are turning to plant-based treatments containing phytoconstituents for diabetes management (4). One of such products is saponins. The use of saponin in the pharmaceutical sector is widespread due to the discovery of its medicinal qualities (5). Current efforts are focusing on harnessing saponins for more potent phytomedicines to manage type II diabetes effectively. *Spondias mombin* is the plant of interest. It is a medicinal plant grouped under the Anacardiaceae family. It is often referred to as Hog plum (6).

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It is most abundant in the Southwestern part of Nigeria and is referred to as Iyeye or Olosan in yoruba, ichikara in ibo, tsadarmasar in hausa (6).

A characteristic of saponins, which are plant glycosides, is their capacity to form a soapy lather when mixed with water. They possess both hydrophilic (sugar) and hydrophobic (aglycone, or sapogenin) moieties (7). Due to their polar nature, saponins are insoluble in nonpolar solvents yet easily soluble in water. They have different numbers of sugar side chains and are glycosides of steroid or triterpenoid aglycones. Saponins' structural complexity gives rise to a variety of beneficial properties (8,9). Several studies have reported blood glucose lowering effects of plant saponins in diabetic states (10-13). Research on saponin has also attracted a lot of interest because of their potent hypolipidemic and insulin-like properties (8,9). Other biological and pharmacological poperties of saponins includes antioxidant, hypolipidemic potential and inhibition of erythropoesis in Rattus novergicus (14). Many saponin compounds have been extracted from different plant species and have demonstrated remarkable effectiveness both in vitro and in vivo in treating type 2 diabetes and its consequences.

Saponins are promising compounds with potential to be developed into new drugs for anti-diabetes (15,16). The antidiabetic mechanism of chemicals derived from medicinal plants can be quickly and economically determined against various diabetes targets with the use of *in silico* virtual screening techniques. Dipeptidyl peptidase-4 (DPP-4) and peroxisome proliferator-activated receptors (PPARs) are two examples of such targets. PPARs are a class of nuclear receptors that bind to particular DNA response regions in heterodimers with the retinoid-X receptor (RXR) to control gene transcription (17).They are good targets for the treatment of diabetes because, upon ligand activation, they regulate the expression of genes linked to glucose and lipid homeostasis (18). This activates the PPARγ receptor, which enhances insulin sensitivity (19, 20). It has been discovered that plant extracts enhance insulin-stimulated glucose absorption via PPARγ.

The present study was designed to screen isolated saponins from *Spondias mombin* leaves as a possible PPARγ agonist and DPP-4 inhibitors for the *in silico* computational therapy of diabetes mellitus.

MATERIALS AND METHODS

Collection and Identification of Plant material

The leaves of *Spondias mombin* were obtained from fields in the University of Benin campus, Ugbowo, Benin City, Edo State. The fresh leaves were identified and authenticated by Prof. H. Akinibosun and the fresh leaves deposited in the herbarium at the University of Benin's Department of Plant Biology and Biotechnology in Benin City, Nigeria. with voucher number UBH_S 345,

Isolation of saponins

The procedure of Hostettman *et al*, (21) was used for isolating saponins**.** Ground leaves (3 kg) was weighed into sealable glass flasks and 12 litres of methanol was poured into glass flask. The contents were stirred several times a day and at the end of the third day, were filtered using filter paper and the filtrate concentrated using a rotary evaporator. Hexane and water were used to partition the crude extract (2:4 v/v). The water layer was concentrated and separated between ethyl acetate and n-butanol (2:4, v/v) after the mixture had been thoroughly shaken and let to stand overnight. The crude saponin fraction was obtained by concentrating the butanol fraction. The crude saponin fractions were then separated using on a silica gel loaded column and saponin fractions were collected.

High performance liquid chromatographic characterization of isolated Saponins

Characterization of the crude saponins was done using HPLC Agilent 1200 series with a detector (Agilent 1260) at a wavelength of 230nm. The column was Novapack C18 column having a dimension of 4µm, 3.9×150mm with Hamilton microliter syringe. The mobile phase was a mixture of HPLC grade of acetonitrile and water in ratio (70:30). Samples were injected at a volume of 5 µl and eluted at a flow rate of 1.0 ml/min, the elution was isocratic.

Molecular docking

The crystal structure of the targets, human PPAR-gamma (PDB ID: 2ATH) and Human Dipeptidyl Peptidase IV (DPP-IV) (PDB ID: 1WCY), were obtained from the Protein Data Bank (PDB). The protein structures were refined using Discovery studio software. The 3D format of the bioactive compounds (ligands) and standard drugs were downloaded from Pubchem data base in structure data file (SDF) file. These SDF files were converted to PDB using Pymol software (22) prior to molecular docking studies. Prior to molecular docking, the target (protein) and the ligands were prepared using AutoDock tools. This included creating a grid box, adding charges, and polar hydrogen. The active site investigation was performed using Site finder of Molecular Operating Environment (23). A site specific molecular docking study were performed targeting Ser 342 and Tyr 547 in PPAR-γ and DPP-IV respectively using AutoDock Vina Software (24) owing to their direct involvement in ligand catalysis. The grid centers for Ser 342 of PPAR-γ included; center_x = 14.332, center_y = 10.548, center_z = 32.020 and center_x = 57.80, center_y = 63.00, center_z = 37.50 for DPP-IV respectively. The 2D diagrams and the 3D (surface) views of the protein-ligand interactions renderings were done using Discovery studio software and Pymol software (22) respectively, while

the pharmacokinetics and drug likeness properties of the studied compounds were estimated using SwissAdme online server.

RESULTS

Table 1 shows the HPLC result of saponins obtained from *Spondias mombin* leaves.

Eleven saponins were characterized from the leaves of *Spondias mombin*. Sapogenin had the highest amount (33568.0µg/100g). This was followed closely by neochlorogenin (4362.8µg/100g), saponine (14784.10µg/100g) and hispigenin (338.610µg/100g) with conyzorgin (0.0118618µg/100g) having the least amount.

Table 2 shows the binding energy of the saponins against the target drug PPAR-y and DPP-IV.

The lower the binding energy, the better the affinity of the compound with the target drug PPAR-y and DPP-IV. Hence, Solagenin with a binding energy of −9.8 kcal/mol and hecogenin with a binding energy of −9.9 kcal/mol were the best PPAR-y agonist and DPP-IV inhibitors from the result of table 2. Other good PPAR-y agonist includes Diosgenin and Sapogenin (-9.0 kcal/mol), Trigogenin, Neochlorogenin (-8.0 kcal/mol) and Tribulosin (-8.0 kcal/mol) and finally Yangonenin, with a binding energy of -7.4 kcal/mol

Table 3a shows the pharmacokinetic and drug likeness properties (ADMET) of six

saponins (Hispigenin, Hecogenin, solagenin, Diosgenin, trigogenin and sapogenin)

Only Hispigenin, Hecogenin, and Solagenin adhered to all four Lipinski's rules. All six saponin exhibited no Veber violations, further suggesting good oral bioavailability. All six saponins had high gastrointestinal absorption and high blood brain permeation. All six saponins are not inhibitors of any of the Cytochrome P450 enzymes Cytochrome P450 1A2, Cytochrome P450 2C19, Cytochrome P450 2A9 inhibitor, Cytochrome P450 2A6 inhibitor, and Cytochrome P450 3A4 inhibitor

Table 3b shows the pharmacokinetic and drug likeness properties (ADMET) of three saponins (Neochlorogenin, Tribuloin, Yangonenin)

No information on the saponin tribuloin was available. The result shows that Neochlorogenin and Yangonenin are relatively soluble in water, both had a high gastrointestinal absorption and blood brain barrier permeation. Neochlorogenin is not an inhibitor of any Cytochrome P450 whereas Yangonenin is an inhibitor of some Cytochrome P450 enzymes

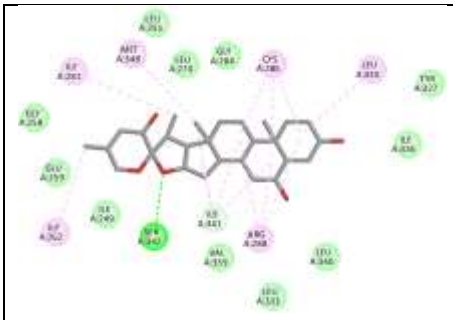
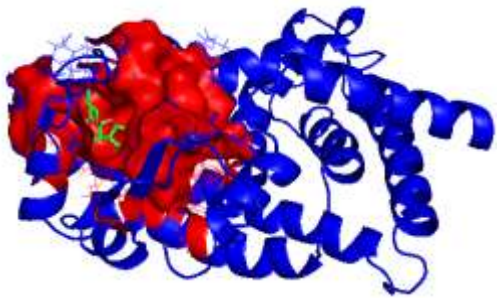
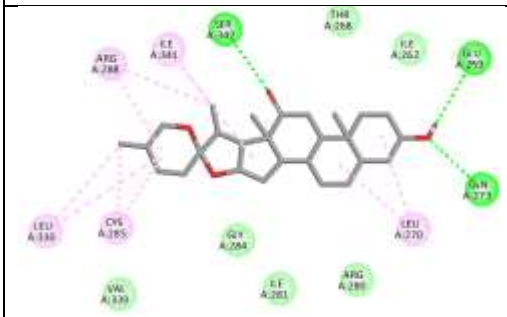
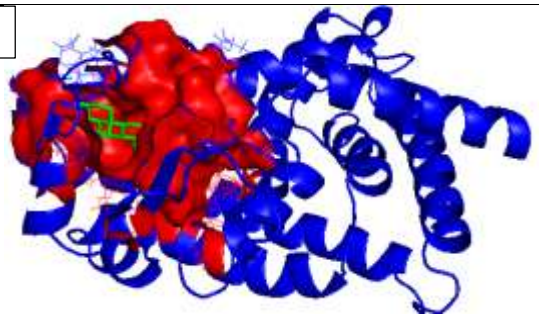
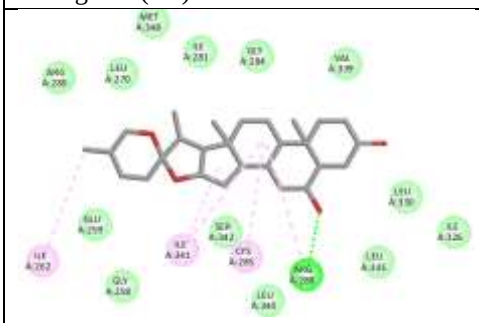
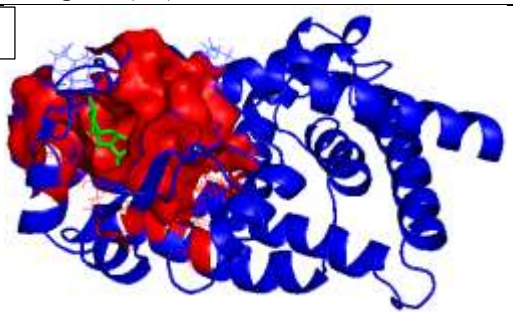
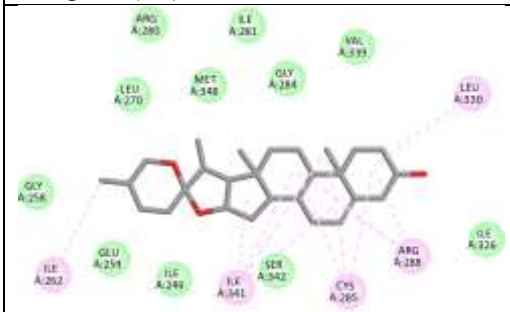
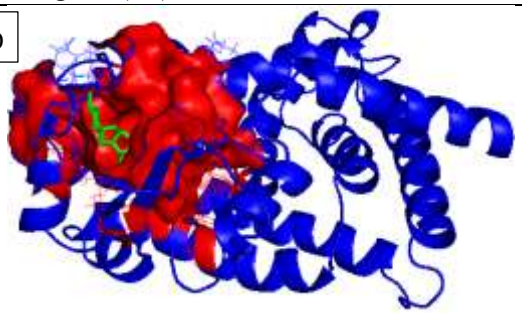
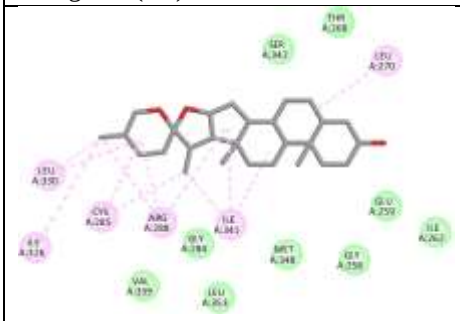
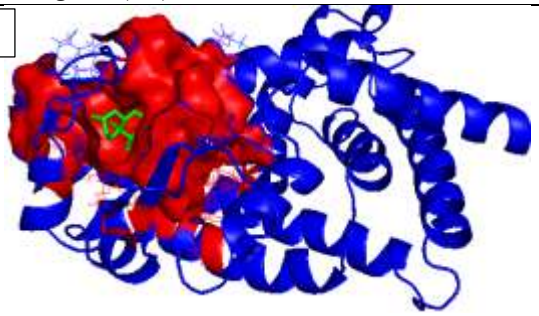
Table 1:HPLC Result of Saponins Fraction

Group name	Amount (µg/100g)
Hispigenin	338.61
Solagenin	1.97432
Diosgenin	0.487501
Trigogenin	2.66496
Neochlorogenin	4362.81
Hecogenin	0.66978
Sapogenin	33568.0
Tribuloin	0.318889
Yangonenin	0.0214037
Conyzorgin	0.011861
Saponine	14784.1

Values represent the high performance liquid chromatographic result of saponins fraction and were obtained from a single determination.

Table 2: Binding energy of the saponins against the target drug PPAR-y and DPP-IV

	Bioactive compounds	Binding energy of PPAR-y (PDB ID: 2ATH) (kcal/mol)	Binding energy of DPP-IV (1WCY) (kcal/mol)
1	Hispigenin	-8.4	-9.6
2	Hecogenin	-8.4	-9.9
3	Solagenin	-9.8	-9.2
4	Diosgenin	-9.0	-9.5
5	Trigogenin	-8.7	-9.5
6	Neochlorogenin	-8.0	-9.4
7	Sapogenin	-9.0	-9.5
8	Tribulosin	-8.0	-7.7
9	Yangonenin	-7.4	-7.1

 Hispigenin (2D)	A  Hispigenin (3D)
 Hecogenin (2D)	B  Hecogenin (3D)
 Solagenin (2D)	C  Solagenin (3D)
 Diosgenin (2D)	D  Diosgenin (3D)
 Trigogenin (2D)	E  Trigogenin (3D)

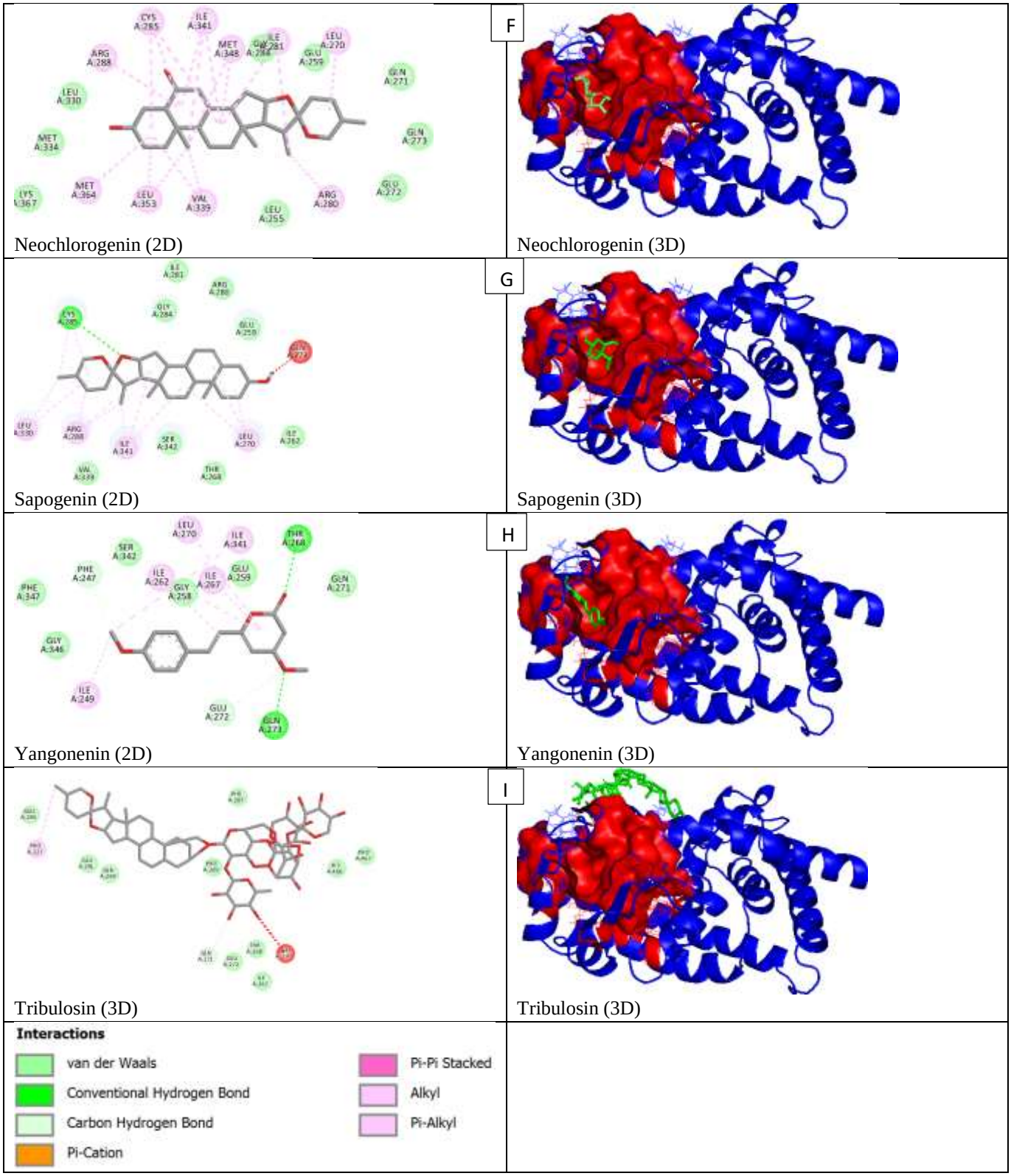
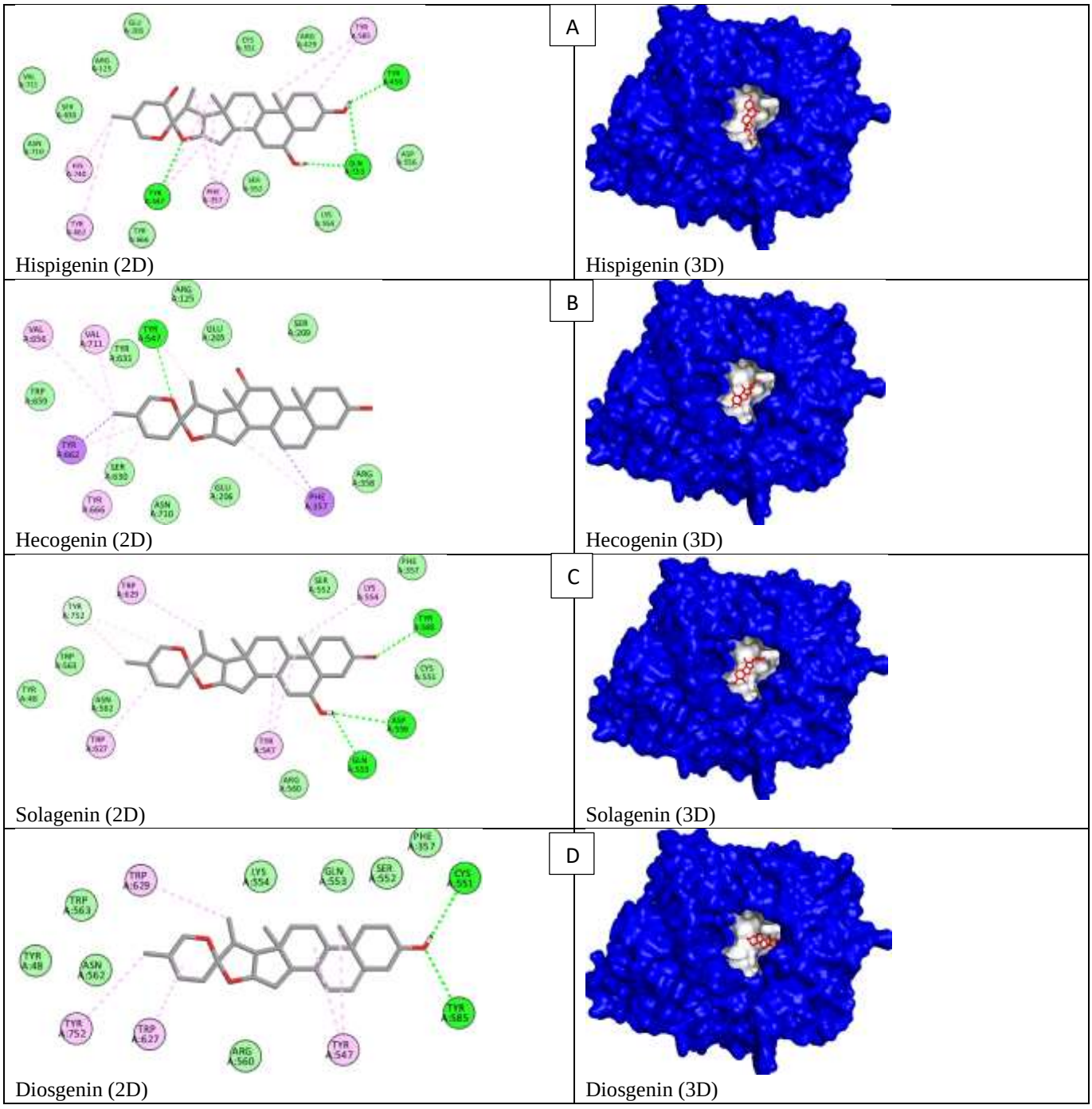
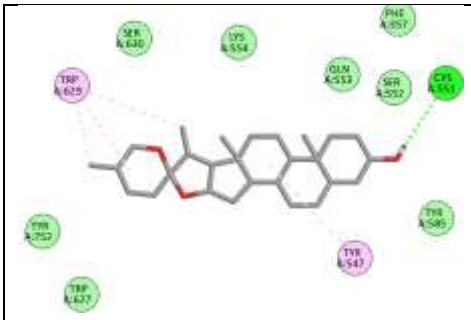


Figure 1: 2Dimensional and 3Dimensional interaction of the saponins in the active site of PPAR-y

A shows 2D and 3D structure of molecular docking interactions between the compound hispigenin and PPAR-y
B shows 2D and 3D structures of molecular docking interactions between the compound hecogenin and PPAR-y
C shows 2D and 3D structures of molecular docking interactions between the compound solagenin and PPAR-y
D shows 2D and 3D structures of molecular docking interactions between the compound diosgenin and PPAR-y
E shows 2D and 3D structures of molecular docking interactions between the compound Trigogenin and PPAR-y
F shows 2D and 3D structures of molecular docking interactions between the compound Neochlorogenin and PPAR-y

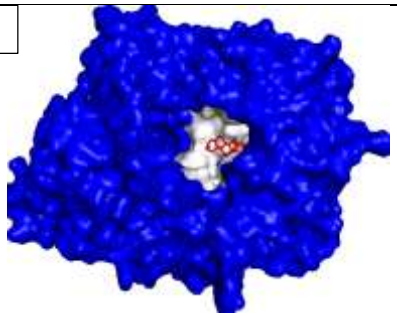
G shows 2D and 3D structures of molecular docking interactions between the compound Sapogenin and PPAR-y
H shows 2D and 3D structures of molecular docking interactions between the compound Yangonenin and PPAR-y
I shows 2D and 3D structures of molecular docking interactions between the compound Tribulosin and PPAR-y



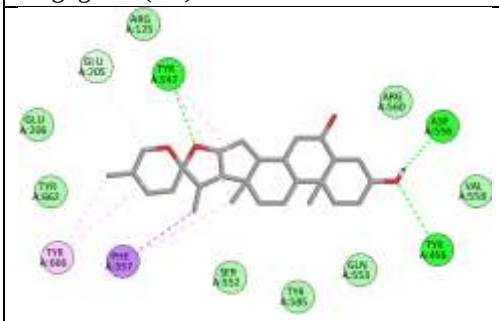


Trigogenin (2D)

E

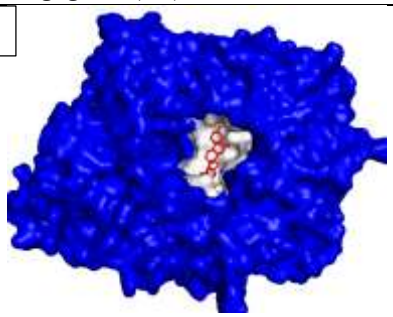


Trigogenin (3D)

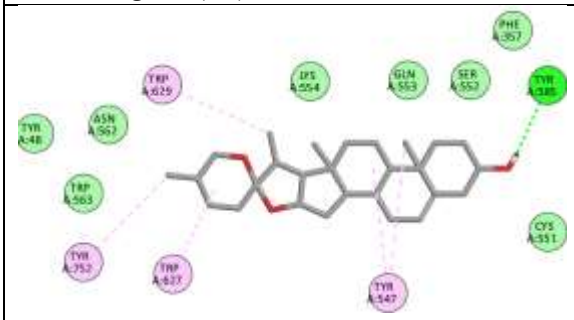


Neochlorogenin (2D)

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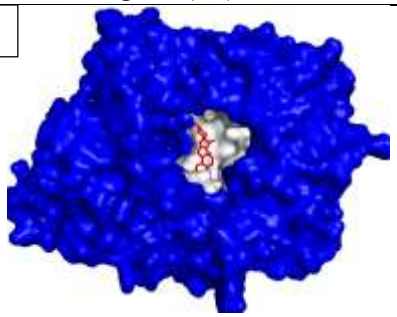


Neochlorogenin (3D)

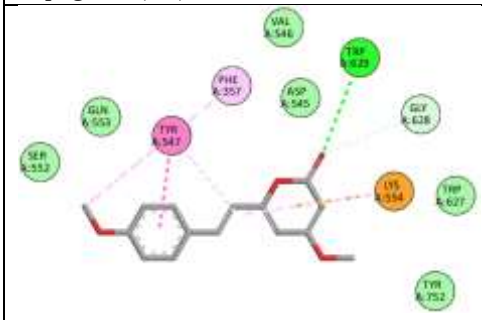


Sapogenin (2D)

G

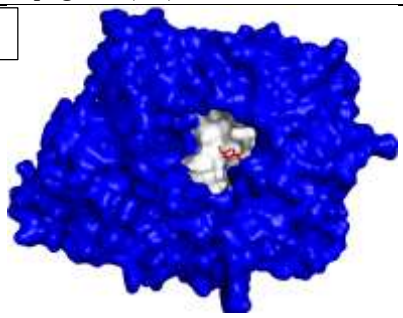


Sapogenin (3D)

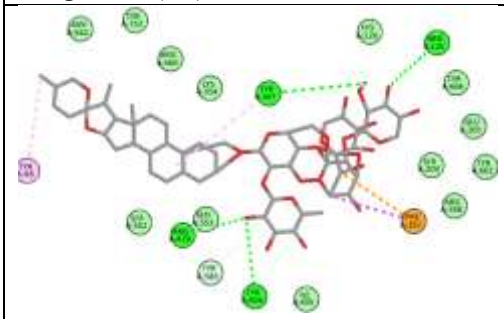


Yangonenin (2D)

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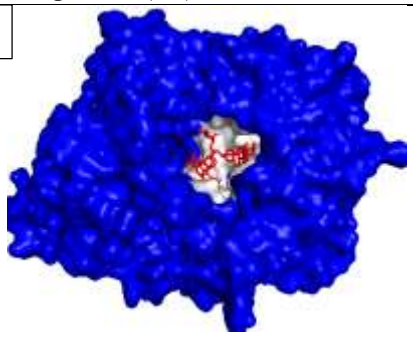


Yangonenin (3D)



Tribulosin (2D)

I



Tribulosin (3D)

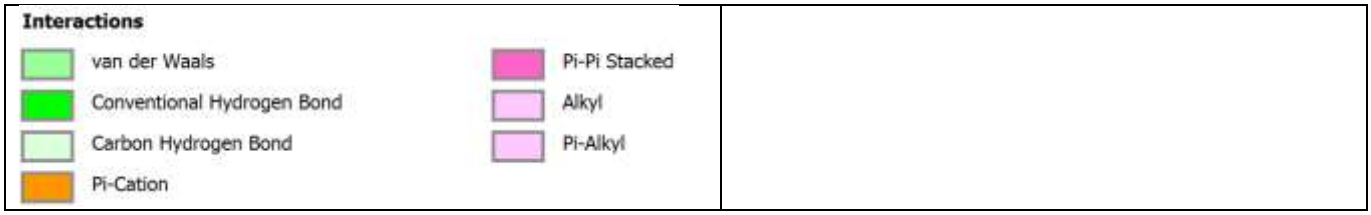


Figure 2: 2Dimensional and 3Dimensional interaction of saponin compounds in the active site of DPP-IV

A shows 2D and 3D structures of molecular docking interactions between the compound hispigenin and DPP−IV
B shows 2D and 3D structures of molecular docking interactions between the compound hecogenin and DPP−IV
C shows 2D and 3D structures of molecular docking interactions between the compound solagenin and DPP−IV
D shows 2D and 3D structures of molecular docking interactions between the compound diosgenin and DPP−IV
E shows 2D and 3D structures of molecular docking interactions between the compound Trigogenin and DPP−IV
F shows 2D and 3D structures of molecular docking interactions between the compound Neochlorogenin and DPP−IV
G shows 2D and 3D structures of molecular docking interactions between the compound Sapogenin and DPP−IV
H shows 2D and 3D structures of molecular docking interactions between the compound Yangonenin and DPP−IV
I shows 2D and 3D structures of molecular docking interactions between the compound Tribulosin and DPP−I**Table 3a:** Pharmacokinetic and Drug likeness properties (ADMET) of identified compounds

Parameters	**Hispigenin**	**Hecogenin**	**Solagenin**	**Diosgenin**	**Trigogenin**	**Sapogenin**
Phytochemical Properties						
Molecular formular	$C_{27}H_{44}O_5$	$C_{27}H_{42}O_4$	$C_{27}H_{42}O_4$	$C_{27}H_{42}O_3$	$C_{27}H_{44}O_3$	$C_{27}H_{42}O_3$
Molecular weight(g/mol)	448.64	430.62	430.62	414.62	416.64	414.62
Number of H-Bond acceptor	5	4	4	3	3	3
Num. H-Bond donor	3	1	1	1	1	1
Molar refractivity	124.39	122.27	122.27	121.59	122.07	121.59
Drug Likenness						
Lipophilicity $CLogP_{o/w}$ value	3.54	4.40	4.34	5.02	5.24	5.02
Water solubility	Moderately soluble	Moderately soluble	Moderately soluble	Moderately soluble	Poorly soluble	Soluble
Obeys Lipinski rule?	Yes	Yes	Yes	No; 1 violation: MLOGP>4.15	No; 1 violation: MLOGP>4.15	No; 1 violation: MLOGP>4.15
No Verber violations	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55
Pharmacokinetics						
Gastrointestinal absorption	High	High	High	High	High	High
Blood brain barrier permeant	No	Yes	Yes	Yes	Yes	Yes
P-glycoprotein substrate	Yes	Yes	Yes	No	No	No
Cytochrome P450 1A2 inhibitor	No	No	No	No	No	No
Cytochrome P450 2C19 inhibitor	No	No	No	No	No	No

Cytochrome P450 2A9 inhibitor	No	No	No	No	No	No
Cytochrome P450 2A6 inhibitor	No	No	No	No	No	No
Cytochrome P450 3A4 inhibitor	No	No	No	No	No	No
Log K_p (cm/s)(skin permeation)	-6.08	-5.50	-5.57	-4.80	-4.23	-4.80

Table 3b: Pharmacokinetic and Drug likeness properties (ADMET) of identified compounds

Parameters	**Neochlorogenin**	**Tribuloin**	**Yangonenin**
Molecular formular	$C_{27}H_{44}O_4$	$C_{55}H_{90}O_{25}$	$C_{15}H_{14}O_4$
Phytochemical Properties			
Molecular weight(g/mol)	432.64	1151.3	258.27
Num. H-Bond acceptor	4	-	4
Num. H-Bond donor	2	-	0
Molar refractivity	123.23	-	73.33
Drug Likenness			
Lipophilicity *CLogP*$_{o/w}$ value	4.36	-	2.72
Water solubility	Moderately soluble	-	Soluble
Obeys Lipinski rule?	No; 1 violation: MLOGP>4.15	-	Yes
No Verber violations	Yes	-	Yes
Bioavailability score	0.55	-	0.55
Pharmacokinetics			
GI absorption	High	-	High
BBB permeant	Yes	-	Yes
P-glycoprotein substrate	Yes	-	No
CYP1A2 inhibitor	No	-	Yes
CYP2C19 inhibitor	No	-	Yes
CYP2A9 inhibitor	No	-	Yes
CYP2A6 inhibitor	No	-	No
CYP3A4 inhibitor	No	-	No
Log K_p (cm/s)(skin permeation)	-5.28	-	-5.94

DISCUSSION

The chronic metabolic disease known as type 2 diabetes mellitus (T2DM) is typified by insulin resistance and beta-cell dysfunction in the pancreas affecting millions worldwide. A critical target in T2DM management is the peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor that plays a pivotal role in regulating glucose and lipid metabolism, and improving insulin sensitivity (25−27) by causing the expression of genes that regulates glucose and lipid homoestasis. Another key target in managing T2DM is Dipeptidyl peptidase-4 (DPP-4), an enzyme that inactivates incretin hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Inhibiting DPP-4 prolongs the action of these incretins, leading to enhanced insulin release and reduced glucagon secretion, ultimately improving glycemic control (28).

This study determined the potential of saponins isolated from *Spondias mombin* as novel DPP-4 inhibitors and PPARγ agonist, examining their interaction with the enzyme based on the results of molecular docking studies and the strength of their interaction, quantified by binding energy. Lower (more negative) binding energy values generally indicate a stronger and more favorable interaction. The substantial binding energies observed for several *Spondias mombin* saponins, particularly Solagenin, Diosgenin, and Sapogenin, provide strong computational evidence for their potentials as PPARγ agonists (Table 2). Activation of PPARγ by these compounds could lead to improved insulin sensitivity by promoting the differentiation of adipocytes and enhancing glucose uptake in

peripheral tissues, regulation of lipid metabolism by influencing fatty acid storage and metabolism (29−31).

The results of *Spondias mombin* saponins to act as DPP-4 inhibitors shown in table 2 indicates that Hecogenin exhibited the strongest binding affinity, this was followed closely by Hispigenin, Diosgenin, Trigogenin, Sapogenin, Neochlorogenin. Solagenin. While Tribulosin and Yangonenin, were the weaker inhibitors of DPP-4.

Assessing the potential of chemicals found in medicinal plants as therapeutic candidates requires an understanding of their pharmacokinetic and drug-likeness (ADMET) characteristics. A drug's overall safety and effectiveness are determined by its ADMET qualities, which comprise absorption, distribution, metabolism, excretion, and toxicity (32). Evaluating these properties is essential for identifying promising leads and optimizing drug development strategies. Studies by Nazar *et al*. (33), Rajasekaran *et al*.; (34), Ramya *et al.* (35) and Ramya *et al.* (36) show that identification, isolation, purification, and ADMET characterization, followed by clinical trials prior to market launch, are essential for the effective commercialization of plant-based natural products.

To determine the drug likeness of the identified compounds, the lipophilicity, water solubility, Lipinski rule, and bioavailability score is determined. The affinity of a molecule for a lipophilic environment, is a crucial physicochemical property that influences a compound's absorption, distribution, metabolism, and excretion (ADME) within the body. The lipophilicity of these sapogenins, as measured by their log P values, varies: Hispigenin: 3.54. Hecogenin: 4.40 Solagenin: 4.34, Diosgenin: 5.02, Trigogenin: 5.24, Sapogenin: 5.02. While a certain degree of lipophilicity is necessary for a compound to cross biological membranes, excessive lipophilicity can lead to poor solubility, increased plasma protein binding, and rapid clearance, ultimately hindering its bioavailability.

A set of rules for estimating a drug candidate's oral bioavailability is provided by Lipinski's Rule of Five. Compounds with poor absorption or penetration frequently break more than one of these principles. The rules state that, in general, an orally active drug should have: Not more than 5 hydrogen bond donors (expressed as the sum of OHs and NHs), No more than 10 hydrogen bond acceptors (expressed as the sum of Os and Ns), molecular weight less than 500 Daltons and a calculated LogP (MLOGP) value of less than 5. From the results of table 3a and table 3b, Hispigenin, Hecogenin, Yangonenin and Solagenin adhered to all four Lipinski's rules, suggesting a higher probability of good oral bioavailability based on these parameters. They also exhibit no Veber violations, further suggesting good oral bioavailability. However, Diosgenin, Trigogenin and Sapogenin each violated one of Lipinski's rules, specifically the MLOGP < 5 rule. Their MLOGP values exceed 4.15, indicating higher lipophilicity. This violation suggests potentially lower oral bioavailability compared to Hispigenin, Hecogenin, and Solagenin. However, they also exhibit no Veber violations, further suggesting good oral bioavailability.

The pharmacokinetics of the saponins were determined using the GI absorption, metabolism and blood brain penetration ability. High GI absorption was shown for all eight sapogenins. This is a positive indicator, suggesting that these compounds are readily taken up from the intestines into the bloodstream. The high GI absorption also indicates that oral administration could be a viable route for delivering these sapogenins. On distribution through blood brain barriers, Hispigenin appears to be BBB-impermeable, while Hecogenin, Solagenin, Diosgenin, Trigogenin, neochlorogenin, Yangonenin and Sapogenin all demonstrate BBB permeation. This difference in BBB permeability has significant implications for their potential therapeutic applications. The ability to cross the BBB suggests potential for treating neurological disorders. Kandeepan *et al*. (37) on their studies on bioactive compounds of *Moringa oleifera* also showed that all the compounds exhibited good gastrointestinal absorption with enhanced pharmacokinetic properties and low blood-brain barrier permeability.

P-glycoprotein (P-gp) is an efflux transporter protein that actively pumps certain molecules out of cells, including the brain. This can significantly affect drug distribution and bioavailability. According to the result, Hispigenin, Hecogenin, and Solagenin are substrates for P-gp meaning they are likely to be transported out of cells by this protein. This could limit their accumulation in certain tissues, including the brain, even for those that can initially cross the BBB. In contrast, Diosgenin, Trigogenin, yangonenin, and Sapogenin are not P-gp substrates potentially allowing for higher concentrations in targeted tissues. Understanding the interaction with P-gp is essential in designing effective delivery strategies, perhaps by co-administering P-gp inhibitors.

Saponins, like other xenobiotics, can be metabolized by enzymes in the body, primarily cytochrome P450 (CYP) enzymes. Inhibition of these enzymes can lead to drug-drug interactions. The result obtained indicates that none of the seven sapogenins (Hispigenin, Hecogenin, Solagenin, Diosgenin, Trigogenin, neochlorogenin, and Sapogenin) appear to be inhibitors of four key CYP enzymes: CYP1A2, CYP2C19, CYP2A9, CYP2A6, and CYP3A4 only Yangonenin inhibited CYP1A2, CYP2C19, and CYP2A9. This suggests a lower risk of drug interactions associated with these specific CYP enzymes. However, further research is necessary to investigate potential interactions with other CYP enzymes and other metabolic pathways.

The promising binding affinities observed for several saponins from *Spondias mombin* warrant further investigation. These computational results serve as a strong foundation for

subsequent experimental studies, including enzyme inhibition assays and confirmation of their therapeutic efficacy in preclinical models of T2DM.

If these *Spondias mombin* saponins demonstrate potent inhibitory activity against DPP-4 *in vitro* and *in vivo*, they could pave the way for the development of novel, plant-derived therapeutic agents for T2DM management. This could offer a natural alternative to existing synthetic drugs, potentially with improved safety profiles and synergistic effects when used in combination with other antidiabetic treatments.

Conclusion

In conclusion, the molecular docking studies presented here highlight the substantial potential of saponins isolated from *Spondias mombin*, particularly Hecogenin and Hispigenin, as effective DPP-4 inhibitors while Solagenin, Diosgenin, and Sapogenin as effective PPARγ agonist This research contributes to the growing body of evidence supporting the use of natural products as a source for developing new therapeutic in drug discovery and offers a promising avenue for innovative approaches to tackling the global challenge of type 2 diabetes. The high GI absorption and BBB permeability of neochlorogenin and yangonenin suggest promising bioavailability and potential CNS activity. However, their differential interaction with P-gp and CYP enzymes highlights the importance of considering potential drug interactions, particularly with yangonenin. Further research is necessary to validate these findings and to fully elucidate the pharmacokinetic profiles of these compounds, paving the way for their safe and effective use.

Conflict of interest

The authors declare no conflict of interest

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REFERENCES

1. Sun H., Saeedi P., Karuranga S., Pinkepank M., Ogurtsova K., Duncan B. B., Stein C., Basit A., Chan J. C. N, Mbanya J. C., Pavkov M. E., Ramachandaran A., Wild S. H., James S., Herman W. H., Zhang P., Bommer C., Kuo S., Boyko E. J., Magliano D. J. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes *Research and Clinical Practice*. 2022; 18, 109119.
2. Deshpande A. D., Harris-Hayes, M., & Schootman, M. Epidemiology of diabetes and diabetes-related complications. *Physical Therapy*. 2008; 88, 1254-1264.
3. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019. Results. Institute for Health Metrics and Evaluation. (2020). (https://vizhub.healthdata.org/gbd-results/).
4. Srinivasan K., Viswanad B., Asrat L., Kaul C. L., & Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. *Pharmacology Research*. 2005; 52(4), 313-320.
5. Vinarov D. R., Katev V., Slavka T., & Denkov, N. Solubilisation of Hydrophobic Drugs by Saponins. Indian *Journal of Pharmaceutical Sciences*. 2018; 80(4), 709-718.
6. Fred-Jaiyesimi A. A., Wilkins, M. R., & Abo, K. A. Hypoglycaemic and amylase inhibitory activities of leaves of Spondias mombin Linn. *African Journal of Medicine and Medical Sciences*. 2008; 38(4), 343-349.
7. Hostettmann K, Marston A. 2005. Saponins. Cambridge (US): Cambridge University Press, https://doi.org/10.1016/B0-12-369397-7/00548-3
8. Francis G., Kerem Z., Makkar H. P., & Becker K. The biological action of saponins in animal systems: a review. *British Journal of Nutrition*. 2002; 88(6), 587-605.
9. Das T. K., Banerjee D., Chakraborty D .M. C., Pakhira B., Shrivastava, R. C. Kuhad Saponin: role in animal system. *Vet. World*. 2012; 5(4), 248-254.
10. Bhavsar S. K., Singh S., Giri S., Jain M. R., & Santani D. D. Effect of saponins from Helicteres isora on lipid and glucose metabolism regulating genes expression. *Journal of Ethnopharmacology*. 2009; 124, 426-433.
11. McAnuff M. A., Harding W. W., Omoruyi F. O., Jacobs H., Morrison E. Y., Asemota H. N. Hypoglycemic effects of steroidal sapogenins isolated from Jamaican bitter yam, Dioscorea polygonoides. *Food Chem Toxicol*. 2005; 43(11), 1667-1672.
12. Zheng, T., G. Shu, Z. Yang, S. Mo, Y. Zhao and Z. Mei, 2012. Antidiabetic effect of total saponins from Entada phaseoloides (L.) merr. In type 2 diabetic rats. *Journal of Ethnopharmacology*, 139: 814-821.
13. Elekofehinti O. O. Saponins: Anti-diabetic principles from medicinal plants - A review. *Pathophysiology*. 2015; 22, 95-103.
14. Keller A. C., Ma J., Kavalier A.K., Anne-Marie B. B., & Edward J. K. Saponins from the traditional medicinal plant Momordica charantia stimulate insulin secretion in vitro. *Phytomedicine*. 2011; 19(1), 32-37.
15. Elekofehinti O.O., Adanlawo I. G., Saliu J.A., & Sodehinde S.A. Saponins from Solanum anguivi fruits

exhibit hypolipidemic potential in Rattus novergicus. *Pharmacy Letters*. 2012; 4, 811-814.

16. Kim S. H., Hyun S. H., & Choung, S. Y. Antidiabetic effect of cinnamon extract on blood glucose in db/db mice. *Journal of Ethnopharmacology*. 2006; 104(1-2), 119-123.

17. Begum S., Fathima S., Priya S., Sundararajan R., & Hemalatha S., "Screening Indian Medicinal Plants to Control Diabetes–An *In silico* and *In vitro* Approach. *General Medecine (Los Angeles).* 2017; 5(2), 1000289.

18. Chen T. H., Tsai M. J., Fu Y. S., & Weng C. F. The Exploration of Natural Compounds for Anti-Diabetes from Distinctive Species Garcinia linii with Comprehensive Review of the Garcinia Family. *Biomolecules*. 2019; 9(11), 641.

19. Brusotti G., Montanari R., Capelli D., Cattaneo G., Laghezza A., Tortrrella P., Loiodice F., Peiretti F., Bornardo B., Pairiadini A., Calleri E., & Pochetti G. Betulinic acid is a PPARγ antagonist that improves glucose uptake, promotes osteogenesis and inhibits adipogenesis. *Scientific Report*. 2017; 7(1), 5777.

20. Kume S., Uzu T., Isshiki K., & Koya D., "Peroxisome proliferator-activated receptors in diabetic nephropathy," *PPAR Research.* 2008; 879523.

21. Hostettmann K. (Ed.). Method in plant Biochemistry, assays for bioactivity. Academic press, London. 1999; 6, 142-148.

22. DeLano W.L. The PyMOL Molecular Graphics System. Delano Scientific, San Carlos. http://www.ccp4.ac.uk/newsletters/newsletter40/11_pymol.pdf. 2002

23. MoE. Education Sector Development Program V (ESDP V). 2015/16-2019/20 2008-2012 E.C. Addis Ababa, Ethiopia. 2015.

24. Trott, O. & Olson, A. J. AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading. *Journal of Computational Chemistry*, 2010; 31(2), 455-461.

25. Tharaheswari M., Kumar J. S. P., Reddy N. J., Subhashree S., & Rani S. S. Fenugreek Seed Extract Stabilize Plasma Lipid Levels in Type 2 Diabetes by Modulating PPARs and GLUT4 in Insulin Target Tissues. *American Journal of Phytomedicine Clinical Therapy*. 2014; 2(5), 587-602.

26. Frkic R. L, Marshall A. C., Blayo A. L, Pukala T. L, Kamenecka, T. M., Griffin P. R., & Bruning J. B. PPARγ in Complex with an Antagonist and Inverse Agonist: a Tumble and Trap Mechanism of the Activation Helix. *iScience*. 2018; 27(5), 69-79.

27. Chen T. H., Tsai M. J., Fu Y. S., & Weng C. F. The Exploration of Natural Compounds for Anti-Diabetes from Distinctive Species Garcinia linii with Comprehensive Review of the Garcinia Family. *Biomolecules*, 2019; 9(11), 641.

28. Capuano A., Sportiello L, Maiorino, M. I., Rossi F., Giugliano D. & Esposito K. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy--focus on alogliptin. *Drug Design Development and Therapy*. 2013; 7, 989-1001.

29. Berthiaume M., Henrike S., Josée L., Yves G., André T., Denis R, & Yves D. Actions of PPARgamma agonism on adipose tissue remodeling, insulin sensitivity and lipemia in absence of glucocorticoids. *American Journal of Physiology Regulatory Integrative and Comparative Physiology*. 2004; 287(5), R1116-R1123.

30. Kintscher U. & Law R. E. PPAR gamma- mediated insulin sensitization: The importance of fat versus muscle, American *Journal of Physiology Endocrinology and Metabolism*. 2005; 288, 287-291

31. Yki-Jarvinen H. (2004). Thiazolidinediones. *The New England Journal of Medicine.* 2004; 351, 1106-1118.

32. Egan W. J., Merz K. M., & Baldwin J. J. Prediction of drug absorption using multivariate statistics. *Journal of Medicinal Chemistry*. 2000; 43(21), 3867-3877.

33. Nazar S., Jeyaseelan M. & Jayakumararaj R. Local Health Traditions, Cultural Reflections and Ethno-taxonomical Information on Wild Edible Fruit Yielding Medicinal Plants in Melur Region of Madurai District, TamilNadu, India. *Journal of Drug Delivery and Therapeutics*. 2022; 12(3), 138-157.

34. Rajasekaran C., Kalaivani T., Ramya S., & Jayakumararaj R. Studies on hepatoprotective activity of ethanolic extracts of fruit pulp of Aegle marmelos (L.). *Journal of Pharmacy Research*. 2009; 2(9), 1419-1423.

35. Ramya S., Loganathan T., Chandran M., Priyanka R., Kavipriya K., Pushpalatha G. G., Aruna D., Ramanathan L., Jayakumararaj R., & Saluja V. Phytochemical Screening, GCMS, FTIR profile of Bioactive Natural Products in the methanolic extracts of Cuminum cyminum seeds and oil. *Journal of Drug Delivery and Therapeutics*. 2022; 12(2-S):110-118.

36. Ramya S., Neethirajan K., & Jayakumararaj R. Profile of bioactive compounds in Syzygium cumini-a review. *Journal of pharmaceutical Research*. 2012; 5(8), 4548-4553.

37. Kandeepan C., Suganandam K., Jeevalatha A., Kavitha N., Senthilkumar N., Sutha S., Mohamed A. S., Sanyam G., Ramya S., Grace L. P. G., Abraham G. C., King I. J., Jayakumararaj R. ADMET-Evaluation, Pharmacokinetics, Drug-likeness and Medicinal Chemistry of GCMS Identified Bioactive Compounds of Moringa oleifera Natural-Ripened Dried Methanolic Pod Extract (MOMPE) as a Potential Source of Natural Drug Frontrunner for Next Generation Drug Design,

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