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In-silico Investigation of Potential Inhibitors of 11-β-Hydroxysteroid Dehydrogenase

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus is a chronic disease plagued with insufficient insulin production or insulin resistance. New targets and disease pathways are emerging and one such is the 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) which catalyses the intracellular conversion of inert cortisone to physiologically active cortisol, functioning to enhance local cortisol action beyond what would be predicted based on simple plasma exposures. This study aimed at exploring the anti-diabetic potential of the bioactive compounds found in *Carica papaya*. In this study, 59 natural compounds were obtained from literature are used for molecular docking simulations against the 11β-HSD1 receptor target using the Python Prescription (PyRx) 0.8 software. An arbitrary docking score ≤ -8.0 kcal/mol was chosen as the cut-off value. Further screening for drug-likeness, Absorption Distribution Metabolism Excretion and Toxicity (ADMET) properties, Pan Assay Interference Compounds (PAINS), and bioactivity were performed. The compounds were compared to the 11β-HSD1 inhibitor, MK-0916 which was the reference compound and docked against the target with a binding affinity of -8.8 kcal/mol. After docking, 11 compounds emerged

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with docking of ≤-8.0 kcal/mol, the highest at -8.1 kcal/mol and lowest at -10.7 kcal/mol. The compounds were further screened using Ghose and Verber rule resulting in four compounds i.e. Ibogamine, Clausamine G, Dasycarpidan-1-methanol, acetate (ester) and Phenol-2-methyl-5-(1,2,2- trimethylcyclopentyl). Pharmacokinetic screening (ADMET and bioactivity) was carried out on the four compounds and it was discovered that they have a level of potency but Ibogamine has higher potency of exerting inhibitory function on 11β-HSD1 compared to the control.

Keywords: Diabetes mellitus; hydroxysteroid dehydrogenase type 1 (11β-HSD1); Carica papaya; ibogamine; In-silico.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic and complicated metabolic illness in which the body becomes unable to utilize glucose [1]. It is characterized by the emergence of insulin resistance, compromised insulin signalling, malfunction of the pancreatic beta cells, aberrant glucose and lipid metabolism, subclinical inflammation, and elevated oxidative stress. These metabolic problems cause long-term pathogenic diseases, such as micro- and macro-vascular pathologies, neuropathy, retinopathy, and nephropathy, which in turn lower life expectancy and raise mortality rates [2]. DM is a major threat to both the developed and developing worlds. According to the 2017 National Diabetes Statistics Report, about 30.3 million people in the U.S. are diabetic and surprisingly some 23.8% are undiagnosed [3]. Approximately 425 million people worldwide are affected by diabetes, and this is projected to increase to approximately 629 million by the year 2045 due to unhealthy diets and inactive lifestyles (Cha and Woo, 2010). There are four major types of DM. Namely, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gestational Diabetes Mellitus and Prediabetes.

The most common therapy is insulin administration but new anti-diabetic drugs targeting molecular pathways implicated in diabetes are emerging. They include blocking of cortisol, increasing cAMP signalling, and increasing incretin secretion to improve glucose tolerance amongst others [4].

Carica papaya is a plant belonging to the family Caricaceae. In Nigeria, it is commonly called pawpaw. Many scientific investigations have been conducted to evaluate the nutritional and therapeutic value of various parts of *C. papaya*, including its fruit, shoots, leaves, rinds, seeds, roots or latex. The various parts of *C. papaya* plant have been reported to possess medicinal properties in the treatment of various ailments and human diseases [5-7]. Since it is primarily grown in the tropics and subtropics, the plant has been used as ethnomedicine for decades [8]. Although it has many other therapeutic purposes, it is most frequently used as an anti-helminthic and a possible abortifacient agent. Papaya seeds and leaves have lately been linked to anticancer activity, as well as improvements in diabetes mellitus, hepatic and renal problems, fertility, hyperglycemia, and amoebic dysentery. It has been suggested that the therapeutic properties of the plant are caused by the highly concentrated phytochemicals found in papaya seeds and leaves, including flavonoids, phytosterols, carotenoids, alkaloids, phenolic compounds, and cyanogenic compounds (benzyl glucosinolate) [9- 11].

A crucial metabolic enzyme known as 11 Beta-hydroxysteroid dehydrogenase type 1 (11β - HSD1) catalyses the intracellular conversion of inert glucocorticoids (GC) into physiologically active ones in metabolically important tissues including the liver, adipose, vasculature, brain and macrophages [12]. 11β-HSD1 regulates the local GC availability in target tissues, including the skin. A study investigated whether the dysregulated expression of 11β-HSD1 and subsequent local GC levels in skin contribute to delayed wound healing in obese, diabetic db/db mice. It was concluded that insulin resistance in obesity and diabetes precludes the down-regulation of 11β-HSD1, resulting in higher endogenous GC levels in diabetic skin, which may affect individuals with DM's ability to repair wounds [13]. Studies have revealed that high levels of active glucocorticoid cortisol in the blood have been linked to a number of diseases, including diabetes mellitus, obesity, dyslipidemia, and high blood pressure [14].

2. MATERIALS AND METHODS

2.1 Materials

Protein Target: 11-Beta-Hydroxysteroid Dehydrogenase 1.

Ligand: Literature guided and ligand download from Pubchem

Stand-alone offline software: Pyrex, Pymol

Database: PubChem, Protein database, Pubmed, Swiss ADME, pkCSM and Molinspiration.

2.2 Methods

2.2.1 Preparation, analysis and validation of the protein target

The target, 11-beta hydrosteroid dehydrogenase type 1(11β-HSD1) was downloaded from the Protein data bank with the code (PDB: 3BZU). Using the Pymol software, the native ligands and water molecules attached to the protein molecule were removed to free the protein thereby optimising the molecular docking process. Using the pdb fixer in the Bioinformatics Galaxy Europe web server, the protein was further optimised for molecular docking.

2.2.2 Ligand preparation

59 bioactive compounds of *Carica papaya* were obtained from the literature [15,16]. The 3D structures of these natural compounds, as well as that of the standard MK-0916, were downloaded from the PubChem online database in their Spatial Data File (SDF) formats along with the properties of these compounds such as molecular weight, canonical SMILES, hydrogen bond donors, hydrogen bond acceptors, log P, and topological polar surface area.

2.2.3 Molecular docking and virtual screening

Before docking, the natural compounds obtained from the literature were screened for bioavailability using the Lipinski and Veber rules. As stated by Lipinski, the drug-like properties include an MW ≤ 500, Hydrogen Bond Donor ≤ 5, Hydrogen Bond Acceptor ≤ 10, and a Log P value ≤ 5. Further screening was done for cellular permeability using Veber's rule. Only compounds of Topological Polar Surface Area (TPSA) values of ≤ 140 Å and number of rotatable bonds ≤ 10 were successful. Ligands were uploaded unto PyRx 0.8 through the Open Babel plug-in tool.

In preparation for molecular docking, all the ligands were uploaded on the virtual screening software, PyRx (Python prescription) 0.8 version using the Open Babel plug-in tool [17] and converted from sdf to Protein Data Bank, Partial Charge, & Atom Type (pdbqt) format [18]. For stable conformation, the Universal Force Field (UFF) was used as the energy minimization parameter and conjugate gradient descent as the optimization algorithm. Using the AutoDock Vina plug-in tool in PyRx, all ligands and the standard were docked against the target protein, 11-beta hydroxysteroid dehydrogenase type 1 using the following grid parameters. Centre X = -7.7577, Y = 19.8325, Z = 8.5671 and Dimensions (Angstrom): X = 62.7826, Y = 99.2739, Z = 85.3746. Using the Microsoft Excel software, the docked results were exported in comma-separated values (CSV) format and screened using the docking score of -8.0kcal/ mol as the cut-off. The SWISSADME, pkCSM, and Molinspiration webservers were used to predict the molar refractivity, pharmacokinetic, ADMET, and Bioavailability of all the ligands respectively [19-21].

2.2.4 Screening for potency

The first stage of the screening was for drug potency. Molecular docking was used as the first step in the virtual screening process, and the docking scores were used as empirical predictors of the strength of the intermolecular interactions between the receptors, and the ligands. A uniform docking scoring cut-off of -8.0 kcal/mol was used to serve as a general borderline for the binding energies obtained between the receptors, and the ligands.

2.2.5 Further screening for drug-likeness, promiscuity and admet properties

The application of high-throughput computer-assisted approaches to predict the relationship between the chemical properties, structure and biological activity of a compound is indeed a valuable tool in the field of drug design and discovery [22].

These drug-like properties of compounds would impart largely on their bioavailability and increase cellular uptake of biomolecules within the body. The molecular descriptors of such compounds are well described by the Lipinski (RO5), Veber, and Ghose rules. Put together, these rules state that hydrogen bond acceptors should be ≤ 10, hydrogen bond donors should be ≤5; Log P should be ≤5, molecular weight should be ≤500g/mol; the polar surface area should be ≤

140A²; molar refractivity should be between 40-130 cm³ and the number of rotatable bonds should be < 10 [23,24].

Affinity does not necessarily predict activity. Binding ligands could be either agonists or competitive inhibitors. Based on a particular drug target, a compound is considered active when its bioactivity score is more than 0.0; moderately active when the score is between −5.0 and 0.0; and inactive when the score is less than −5.0 [25].

3. RESULTS AND DISCUSSION

3.1 Results

The result of molecular docking of 11-Beta-Hydroxysteroid Dehydrogenase and its derivatives of fifty-nine (59) compounds are presented in Table 1. This result shows the bioactive components of Carica Papaya at higher binding affinity and root mean square deviation (RMSD) docked against 11-Beta-Hydroxysteroid Dehydrogenase as compared to the control.

Table 1. Molecular docking of 11-Beta hydroxysteroid hydrogenase type 1 against 59 bioactive compounds of C. papaya and their binding affinities and RMSDs

S/N	Compound	Binding affinity	Rmsd/ub	Rmsd/lb
1	Clionasterol	-10.7	0	0
2	Stigmasterol	-10.6	0	0
3	Cholest-5—en-3-ol propylidene-,(3.beta)	-10.4	0	0
4	Campesterol	-10.1	0	0
5	Ibogaine	-9.9	0	0
6	Quercetin	-9.6	0	0
7	Kaemferol	-8.9	0	0
8	Crotonyl bromide	-8.5	0	0
9	Clausamine G	-8.5	0	0
10	Phenol, 2-methyl-5- (1,2,2 trimethylcyclopentyl)-, (S)	-8.3	0	0
11	Dasycarpidan-1-methanol, acetate (ester)	-8.3	0	0
12	Squalene	-7.9	0	0
13	Phytol	-7.6	0	0
14	Benzenepropanoic acid, .alpha.-	-7.4	0	0
15	(hydroxyimino)-	-7.0	0	0
16	2,4-Difluorobenzene, 1-benzyloxy-	-7.0	0	0
17	Cyclopentadecanone, 2-hydroxy-	-7.0	0	0
18	1-(2'-Methoxy-5- nitrophenyl) ethanone	-6.9	0	0
19	Caffeic acid	-6.8	0	0
20	2,4-Di-tert-butylphenol	-6.7	0	0
21	Octinoxate	-6.6	0	0
22	Phytol, acetate	-6.6	0	0
23	Ferulic Acid	-6.6	0	0
24	5,7-Dimethoxycoumarin	-6.6	0	0
25	Oleic Acid	-6.6	0	0
26	Phytol	-6.5	0	0
27	Benzenepropanoic acid,.alpha-(hydroxyamino)-	-6.5	0	0
28	Protocatechuic Acid	-6.4	0	0
29	Thiamine	-6.3	0	0
30	4-(Methylthio)butyldesulfoglucosinate p-Coumaric Acid	-6.2	0	0
31	Neophytadiene	-6.2	0	0
32	D-Limonene	-6.2	0	0
33	Oleamide	-6.1	0	0
34	2-Azido-2,4,4,6,6-pentahylheptane	-6.1	0	0
35	1-Dodecanol,3,7,11-trimethyl-	-6.0	0	0
36	Ascorbic Acid	-6.0	0	0
37	Margaric Acid	-6.0	0	0

S/N	Compound	Binding affinity	Rmsd/ub	Rmsd/lb
38	(3-Bromo-1-methlpropoxymethyl)benzene	-6.0	0	0
39	Cyclohexanone,2-(-2butylny)	-6.0	0	0
40	Vanilic Acid	-5.9	0	0
41	Citronellyl butyrate	-5.9	0	0
42	1-(3,3,3-Trifluoro-2-hydroxypropyl)piperidine	-5.8	0	0
43	Benzylnitrile	-5.8	0	0
44	6-Hydroperoxy-3,7-dimethyloct-7-en-1-ol	-5.8	0	0
45	p-Hydroxybenzoic Acid	-5.8	0	0
46	Lauric Acid	-5.7	0	0
47	3,4-Altrosan	-5.7	0	0
48	17-Octadecynoic Acid	-5.6	0	0
49	2-Methoxy-4-vinylphenol	-5.6	0	0
50	N-Methylaspartic Acid	-5.6	0	0
51	Palmitic Acid	-5.5	0	0
52	Myristic Acid	-5.5	0	0
53	L-Arabinitol	-5.4	0	0
54	Benzyl isothicyanate	-5.2	0	0
55	9-Decenoic Acid	-5.1	0	0
56	D-Arabinitol	-4.7	0	0
57	4-Mercaptophenol	-4.2	0	0
58	N-Aminomorpholine	-4.1	0	0
59	Chloroacetic Acid	-4.1	0	0

The result of Eleven (11) Screened compounds from the initial Fifty-nine (59) compounds are presented in Table 2. This result shows the screened compounds at a binding affinity of $\leq$ 8.0 kcal/mol and RMSD of 0. Any compound with a binding affinity less than -8.0 and RMSD aside 0 is screened out.

The result of seven (7) compounds that were further screened based on their physio-chemical properties using Lipinski's rule of 5, Veber Rule and Ghose rule are presented in Table 3. Four (4) compounds that did not meet the demand of the rules were screened out leaving seven (7) compounds.

The result of four (4) compounds and the control which do not violate Veber and Ghose Rules with regards to Rotatable bond (RB), TPSA, Saturation, Molar Refractivity (MR) and PAIN alert are seen in Table 4. The compounds that were not in line with these rules were cut-off.

The result of the four lead compounds and the control after undergoing pharmacokinetic studies (ADMET) is shown in Table 5. The pharmacokinetic study is based on Absorption, Distribution, Metabolism, Excretion and Toxicity.

Table 2. Cut-off from the molecular docking with a binding affinity of ≤ 8.0 kcal/mol and RMSD of 0

S/N	Compound	Binding affinity
1	Clionasterol	-10.7
2	Stigmasterol	-10.6
3	Cholest-5-en-3-ol, 24-propylidene-, (3.beta.)-	-10.4
4	Campesterol	-10.1
5	Ibogamine	-9.9
6	Quercetin	-9.6
7	Kaempferol	-8.9
8	Crotonoyl bromide	-8.5
9	Clusamine G	-8.4
10	Phenol, 2-methyl-5- (1,2,2- trimethylcyclopentyl)-,(S)	-8.3
11	Dasycarpidan-1-methanol, acetate (ester)	-8.3
12	**MK-0916(STANDARD)**	**-8.8**

Table 3. Physio-chemical properties using Lipinski's Rule of 5, Veber and Ghose Rules of lead compounds and standard

S/N	Compound	MW	xLogp	HBD	HBA
1	Ibogamine	280.4	3.9	1	1
2	Quercetin	302.23	1.5	5	7
3	Kaempferol	286.24	1.9	4	6
4	Crotonoyl bromide	148.99	1.7	0	1
5	Clausamine G	355.4	3.6	2	5
6	Phenol, 2-methyl-5- (1,2,2- trimethylcyclopentyl)-, (S)	218.33	5.1	1	1
7	Dasycarpidan-1-methanol, acetate (ester)	326.4	3.2	1	3
8	**MK-0916 (STANDARD)**	**331.8**	**3.7**	**0**	**3**

Table 4. Screened compounds and control which do not violate Veber and Ghose Rules

S/N	Compound	RB	TPSA	MR	Fraction CSP3	Pains
1	Clausamine G	6	80.8	100.78	0.25	0
2	Dasycarpidan-1-methanol, acetate (ester)	4	45.3	100.17	0.55	0
3	Ibogamine	1	19	91.96	0.58	0
4	Phenol, 2-methyl-5- (1,2,2- trimethylcyclopentyl)-, (S)	1	20.2	69.55	0.6	0
5	**MK-0916 (STANDARD)**	4	30.7	87.95	0.56	0

Table 5. Pharmacokinetic studies (ADMET) of the 4 lead compounds and the control

	ADMET PARAMETERS	MK-0916 (STANDARD)	Clausamine G	Dasycarpidan-1-m ethanol, acetate (ester)	Ibogamine	Phenol, 2-methyl-5- (1,2,2-trimethylcyclopentyl)-, (S)
ABSORPTION	Water Solubility (log mol/L)	-4.223	-4.733	-3.831	-3.591	-4.496
	CaCO2 Permeability (log Papp in 10^{-6} cm/s)	2.037	0.66	1.39	1.424	1.607
	Intestinal Absorption (Human)(% absorbed)	93.98	91.9	91.325	92.007	90.21
	Skin Permeability (log Kp)	-2.745	-2.795	-2.98	-2.818	-1.874
	P-glycoprotein Substrate (Yes/No)	No	Yes	Yes	Yes	No
	P-glycoprotein Inhibitor I (Yes/No)	Yes	Yes	Yes	No	No
	P-glycoprotein Inhibitor II (Yes/No)	No	Yes	No	No	No
DISTRIBION	VDss (Human) (log L/kg)	0.508	0.077	1.43	1.845	0.945
	Fraction Unbound (Human) (Fu)	0.046	0.056	0.169	0.284	0.052
	BB Permeability (log BB)	0.152	-0.592	0.235	0.339	0.409
	CNS Permeability (log PS)	-1.83	-2.155	-1.822	-1.632	-1.751
METABOLISM	CYP2D6 Substrate (Yes/No)	No	No	No	Yes	No
	CYP3A4 Substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes
	CYP1A2 Substrate (Yes/No)	Yes	Yes	Yes	Yes	Yes
	CYP2C19 Inhibitor (Yes/No)	Yes	Yes	No	No	No
	CYP2C9 Inhibitor (Yes/No)	Yes	Yes	No	No	No
	CYP2D6 Inhibitor (Yes/No)	No	No	Yes	Yes	No
	CYP3A4 Inhibitor (Yes/No)	No	Yes	No	No	No
EXCRETION	Total Clearance (log ml/min/kg)	-0.071	0.642	0.736	1.153	0.922
	Renal OCT2 Substrate (Yes/No)	No	No	Yes	Yes	No
TOXICITY	Max. Tolerated Dose (Human) (log mg/kg/day)	0.381	0.444	-0.515	-0.512	0.577
	hERG I Inhibitor (Yes/No)	No	No	No	No	No
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.85	2.584	1.632	3.189	0.577
	Oral Rat Chronic (LOAEL) (log mg/kg_bw/day)	1.671	1.836	2.925	2.006	2.18
	Hepatotoxicity (Yes/No)	No	Yes	Yes	Yes	No
	Skin Sensitisation (Yes/No)	No	No	No	No	Yes
	T. pyriformis Toxicity (log ug/L)	0.473	0.383	1.166	0.45	1.933
	Minnow Toxicity (log mM)	0.083	-0.593	0.628	-0.743	0.238

Table 6. The Bioactivity assessment of the control and the 3 lead compounds

Bioactivity Assay	MK-0916 (STANDARD)	Dasycarpidan-1-methanol, acetate (ester)	Ibogamine	Phenol, 2-methyl-5- (1,2,2-trimethylcyclopentyl)-, (S)
GPCR Ligand	0.13	0.4	0.6	-0.22
Ion Channel Modulator	-0.04	0.28	0.48	-0.21
Kinase Inhibitor	-0.12	-0.07	0	-0.66
Nucleic Receptor Ligand	0.11	0.01	0.03	0.08
Protease Inhibitor	-0.09	0.03	0.17	-0.48
Enzyme Inhibitor	0.48	0.09	0.22	-0.06

The result of the Bioactivity assessment of the three lead compounds (excluding Clausamine G) is shown in Table 6. The bioactivity assessment describes its interaction with other molecules or compounds.

4. DISCUSSION

Table 1 shows the result of 59 bioactive compounds of *Carica papaya* obtained from the literature that were docked against the protein target 11β-HSD1 and their various binding affinities with their best conformation at 0 RSMD. In Table 2, For screening, a uniform docking score of -8.0 kcal/mol was chosen as a cut-off value as this depicts strong protein-ligand binding. The choice of a lower docking score would increase the amount of data to be handled and also affect potency [26]. The binding affinity values reveal the strength of ligand-protein interaction. Of the total number of 59 ligands docked against the target, 11 compounds had binding affinities less than the -8.0 kcal/mol cut-off.

In Table 3, compounds were screened based on their physio-chemical properties using Lipinski rule, Ghose rule and Verber Rule. According to Lipinski et al*.,* [22], oral drugs should not have a molecular of more than 500g/mol. The significance of this is, molecules larger than 500g/mol. The octanol/water partition coefficient determines the Hydrophobicity (Water hating) or Hydroliphicity (Water loving) of a substance [25]. It is a direct measure of the transport abilities of a compound across biological membranes. Drug molecules should have enough solubility to transverse the membrane, but not be too soluble to get trapped in it [27]. Hydrogen Bond donors are determined by the number of OH and NH bonds in each molecule, while the Hydrogen Bond Acceptors are determined by summing up the nitrogen and oxygen atoms in each molecule [22]. They are a critical aspect of the drug-likeness of a molecule [28]. The 11 compounds were screened using the following rules; hydrogen bond acceptors should be ≤ 10, hydrogen bond donors should be ≤5; Log P should be ≤5, and molecular weight should be ≤500g/mol. None of the compounds violated the Molecular weight, hydrogen bond donor and hydrogen bond acceptors, but 4 compounds exceeded the Log P value of ≤ 5 and were eliminated leaving 7 compounds.

Table 4 shows four (4) compounds screened using Verber and Ghose Rules. Verber and Ghose rule state that molecular complexity which is measured by the carbon bond saturation (fraction of sp^3 carbons - fsp^3) plays a vital role in drug discovery. Saturation directly correlates with solubility and saturated hydrocarbons have the stability of the chemical bonds which makes them unreactive. All compounds with values less than 0.25 are unsaturated and therefore eliminated [29,30]. Also, molar refractivity is the measure of the total polarizability of a mole of a ligand and is dependent on the temperature, the index of refraction and pressure. The ideal molar refractivity should range from 40 to 130 [24].

Rotatable bonds are the measure of the molecular flexibility of a compound [23]. TPSA- This is the sum of the contributions to the molecular (usually Van der Waals) surface area of polar atoms such as oxygen, nitrogen and their attached hydrogens [31]. In terms of Veber's rule, compounds with a TPSA of ≤140Å and a Rotatable Bond count of ≤10 have a high probability of positive oral bioavailability for drug-like candidates [32].

The Pan Assay Interference compounds (PAINS) also known as promiscuous compounds are bioactive substances that are difficult to detect in data due to interactions with unintended biological targets (Dos Santos, 2015; Baell & Holloway, 2010). From the screening, 1 compound violated the Molar refractivity range of 40 to 130, 1 compound violated the PAINS alert of >0 and 2 compounds violated the Fraction Csp3 value of ≥0.25. A total of 3 compounds were eliminated, leaving 4 compounds.

Table 5 shows the result of the pharmacokinetic study of the four lead compounds using ADMET parameters. While screening using the physiochemical properties above speeds up the drug development process, studies have shown that these rules have limitations and on their own are insufficient to establish the exact drug-likeness of a substance [30,33].

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) is a crucial component of the drug discovery process. It is used to 'fine-tune' results obtained from drug-likeness screening. A high-quality drug candidate should not only possess sufficient efficacy against the therapeutic target but also show appropriate ADMET properties at therapeutic doses [34]. The ADMET screening was carried out using the manual by Pires et al*.,* [20]. The goal is for a molecule to have as few violations as possible, but complete non-violation is rare.

A key physiochemical factor in drug research and development is water solubility, which affects pharmacokinetic properties and formulations [35]. Ibogaine appears to be the most soluble of the chemicals based on the findings. Clausamine G is the least soluble in the group with a water solubility value of less than -4.0 log mol/L. The standard, MK-0916 was also poorly soluble [20].

Since oral administration is still the most common form of administration, in vitro permeability studies can be used to predict bioavailability as a drug is being developed. The caco-2 cell monolayers are used as a model of human intestinal absorption because they closely resemble the human intestinal epithelium in many aspects and establish tight connections between cells [36]. As observed in Table 6, Phenol, 2-methyl-5- (1,2,2- trimethylcyclopentyl)-, (S) (P2MT) showed the highest caco-2 permeability, while Clausamine G showed the lowest of all the lead compounds. The standard also showed a high Caco-2 value being higher than 0.9 [20]. The measurement of human intestinal absorption (HIA), similar to caco-2 permeability, is a crucial step in the development of new pharmaceutical substances [37]. Ibogamine gets the highest value even though all the lead compounds have high HIA. The standard also showed a high HIA value [20]. Drug penetration through the skin must be evaluated to create a transdermal medication delivery system for use on people [38]. P2MT, which is more than -2.5, exhibited the best skin permeability (LogKp) values of all the lead compounds. The standard and other lead compounds have values less than-2.5 suggesting low skin permeability [20].

P-glycoprotein (Pgp), a member of the ATP-binding cassette (ABC) superfamily of transporter proteins, is expressed in the cells of several organs and affects the ADMET properties of drugs. The PgP is a unidirectional efflux pump that extrudes its substrate from inside to outside of cells, including toxins, drugs, and other xenobiotics [39]. From the results, only P2MT and the standard are not P-gP substrates. This implies that while the bioavailabilities of the P-gp substrates would be reduced by P-glycoprotein, that of p2MT and the standard will not.

The volume of distribution steady state (VDSS) is the theoretical volume required to maintain the whole dose of a drug delivered at the same blood plasma concentration. Important pharmacokinetic characteristics control a drug's half-life and frequency of dose [40]. Of all the compounds, Ibogamine has the highest VDSS value (1.845l/kg) while Clausamine G is the lowest requiring only 0.077 l/kg to maintain uniform distribution to give the same concentration in plasma [20].

A drug's effectiveness is influenced by how strongly it binds to plasma proteins. With less binding, the drug can enter cellular membranes more effectively [20]. The percentage unbound (human) readings for the standard and Clausamine G indicate that they are the least available for biological activity because they are below the 0.1 cutoff. The most widely accessible is Ibogamine [20].

Most drugs cannot cross the blood-brain barrier (BBB), which is anatomically and physiologically unique. But some medications with particular chemical characteristics can pass through the BBB via lipid-mediated free diffusion [41]. According to the findings, all lead compounds have log BBB values of more than -1.0, indicating that they are all mildly to moderately distributed in the brain. The best-predicted brain distribution is for the P2MT, while the worst is for Clausamine G. [20].

The majority of drugs used in clinical settings are biotransformed by cytochrome P450 (CYP), which is also the main driver of drug pharmacokinetic variability. The liver's major CYPs are 3A4, 2C9, and 1A2, while 2D6 and 2C19 are less common [42]. Remarkably, Clausamine G is predicted to be an inhibitor of CYP2C19, CYP2C9 and CYP3A4 molecules. A drug's total clearance from the blood is the sum of its clearance through the kidneys, the liver, and all other tissues [43]. The total clearance ranges from 0 to 1.0 depending on the functionality of the implicated organs and several other variables. The findings indicate that Ibogamine has a total clearance value above 1.0, indicating that it is eliminated from the plasma at a very rapid rate [20].

The proximal epithelial cells' basolateral membrane contains the renal organic cation transporter 2 (ROCT2) protein, which is involved in the uptake and secretion of cationic drugs. Only Dasycarpidan-1-methanol, acetate (ester) and Ibogamine are ROCT2 substrates that will be carried from the plasma into the cells of the proximal convoluted by the ROCT2 [20]. The human ether-a-go-go-related gene (hERG) expresses a potassium channel protein that is

crucial for cardiac repolarization and arrhythmias induced by long QT waves [44]. The research also revealed that the standard and the lead compounds were predicted not to be hERG I protein inhibitors, demonstrating no possible cardiotoxic effect [20]. The maximum tolerated dosage (MTD) of a drug is the largest dose that does not cause overt toxicity or unfavourable side effects within a specific amount of time, as determined through early human clinical trials [45]. In the present study, only P2MT have high MTD being higher than 0.477 (log mg/kg/day) [20]. The Oral acute toxicity or LD50 is a measurement of how much of a drug is necessary to kill 50% of rats in a test, whereas the oral rat chronic toxicity is the lowest dose of a substance that results in an observed unfavourable effect over time [20]. In terms of acute toxicity and chronic toxicity, Ibogamine is the safest of all the compounds. Similarly, for toxicity to *Tetrahymena pyriformis*, p2MT is the safest while for Minnows, Dasycarpidan-1-methanol, acetate (ester) is the safest. Even though the liver is the most common target organ for drug candidates in animal toxicity tests, hepatotoxicity seldom causes drug development to be halted during the preclinical stage. When a drug has great therapeutic promise, hepatotoxicity in humans may be tolerable because it is frequently reversible and dose-dependent [46]. At this stage of virtual screening based on ADMET properties, Clausamine G was eliminated because it was predicted to be inhibitor of P-gp I, P-gp II, and CYPs 2C19, 2C9, and 3A4.

Table 6 shows the result of the bioactivity assay of the control and the 3 lead compounds. The lead compounds should have a pharmacological effect in addition to ligand binding to the proper target. GCPR ligands, ion channel modulators, kinase inhibitors, protease inhibitors, nuclear receptor ligands, and enzyme inhibitors are some of the drug candidates that are categorized depending on their bioactivity [21].

Enzyme inhibitors are molecules that interact with enzymes (Temporarily or permanently) is some way and reduce the rate of an enzyme-catalysed reaction or prevent an enzyme from working in a certain way [47,48]. Since the target protein of this study is an enzyme, the results show that the P2MT has a poor enzyme inhibitor with a bioactivity score lower than zero. The standard and the two other lead compounds have bioactivity scores greater than zero [20]. Ibogaine is a significantly better enzyme inhibitor than Dasycarpidan-1-methanol, acetate (ester).

5. CONCLUSION

The need for assessable and inexpensive drugs for the management of DM is of utmost importance. Inactive and unhealthy lifestyles have given rise to the prevalence of DM in both developed and developing countries. While sensitization will go a long way in disease prevention, sustainable treatment options for the millions of sufferers are much needed. Insulin therapy which has been the most widely used for disease management is expensive and saddled with side effects like dizziness, fatigue, seizures, and loss of consciousness.

C. papaya is found in abundance in Nigeria and can be easily accessed. While studies have been carried out extensively on its ethnomedicinal and therapeutic use such as its anti-diabetic effects, the bioactive compounds responsible have not been identified and explored.

This study indicates that Ibogamine (an alkaloid), can serve as an alternative inhibitor of 11β-Hydroxysteroid Hydrogenase (11β-HSD1) which is supported by Krengel et al*.,* 2019 who researched the root bark of the African Shrub, *Tabernanthe iboga*. Therefore, Ibogamine can be a potential drug candidate for the treatment of type 2 diabetes. In vitro and in vivo studies are required to evaluate the efficacy and safety of Ibogamine.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Shrivastava SR, Shrivastava PS, Ramasamy J. Role of self-care in management of diabetes mellitus. Journal of Diabetes & Metabolic Disorders. 2013; 12:14
2. Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, Booker L, Yazdi H. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evidence Report/ Technology Assessment (Summary). 2005;128:1–11.
3. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Juliana CN, Mbanya JC, Pavkov

ME, Ramachandaran A, Wild SH, James S, William H. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Research and Clinical Practice. 2022;183:109119. Available:https://doi.org/10.1016/j.diabres.2021.109119

4. Kanwal A, Kanwar N, Bharati S, Srivastava P, Singh SP, Amar S. Exploring new drug targets for Type 2 Diabetes: Success, challenges and opportunities. Biomedicines. 2022;10:331.
5. Okeniyi J, Ogunlese T, Oyelami O, Adeyemi L. Effectiveness of dried *Carica papaya* seeds against human intestinal parasitosis. A pilot study. Journal of Medicinal Chemistry. 2007;10:194-196.
6. Owoyele BV, Adebukola OM, Funmilayo AA, Soladoye AO. Anti- inflammatory activities of thanolic extract of *Carica papaya* leaves. Inflammopharmacology. 2008;16:168-173.
7. Adigwe CC, Oremosu AA, Gbotolorun SC, Kuseiju TO, Akang EN, Noronha C, Okalanwon AO. Effects of the alcoholic root extract of the male Carica papaya on ovulation, gestation and fetal parameters in female Sprague- Dawley rats. Journal of Medicinal Plants Research. 2012;6(16): 3093-3097.
8. Singh SP, Mathan SV, Dheeraj A, Tailor D, Singh RP, Acharya A. Anticancer effects and associated molecular changes of *Carica papaya* against prostate cancer, In American Association for Cancer Research Annual Meeting, American Association for Cancer Research; 2019. DOI:10.1158/1538-7445.AM2019-3004
9. Wang X, Contreras MDM, Xu D, Xing C, Wang L, Yang D. Different distribution of free and bound phenolic compounds affects the oxidative stability of tea seed oil: A novel perspective on lipid antioxidation. LWT. 2020;129:09389, DOI:10.1016/j.lwt.2020.109389 medicalnewstoday.com/articles/323627. Accessed 15th December, 2022.
10. Olcum M, Tastan B, Ercan I, Eltutan IB, Genc S. Inhibitory effects of phytochemicals on NLRP3 inflammasome activation: A review Phytomedicine. 2020; 75(2020):153238, DOI:10.1016/j.phymed.2020.153238
11. Doan MTN, Huynh MC, Pham ANV, Chau NDQ, Le PTK. Extracting seed oil and phenolic compounds from papaya seeds by ultrasound-assisted extraction method and their properties. Chemical Engineering Transactions. 2020;78:493-498. DOI:10.3303/CET2078083
12. Chuanxin Z, Shengzheng W, Lei D, Duoli X, Jin L, Fuzeng R, Ge Z. Progress in 11β-HSD1 inhibitors for the treatment of metabolic diseases: A comprehensive guide to their chemical structure diversity in drug development. European Journal of Medicinal Chemistry. 2020;191: 112134.
13. Brazel CB, Simon JC, Tuckermann JP, Saalbach A. Inhibition of 11β- HSD1 expression by insulin in skin: Impact for diabetic wound healing. Journal of Clinical Medicine. 2020;9(12): 3878.
14. Cooper MS, Stewart PM. 11Beta-hydroxysteroid dehydrogenase type 1 and its role in the hypothalamus-pituitary-adrenal axis, metabolic syndrome, and inflammation. Journal of Clinical Endocrinology and Metabolism. 2009;94: 4645–4654.
15. Iyappan G, Daniel D, Poovannalingan. Ascertaining the phytocomponents in the crude ethanolic extracts of Carica papaya seeds by GC-MS. World Journal of Pharmacy & Pharmaceutical Sciences. 2014;3(9):942-949.
16. Khadam S, Afzal U, Gul H, Hira S, Satti M, Yaqub A, Ajab H, Gulfraz M. Phytochemical screening and bioactivity assessment of leaves and fruits of *Carica papaya*. Pakistan. Journal of Pharmaceutical Sciences. 2019;32(5): 1941-1948.
17. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods in Molecular Biology. 2015;1263:243–250.
18. Gacche RN, Meshram RJ, Dawane AA, Kamble SS, Shinde GP, Dhabadge VN, Patil KK. Modeling studies of arginase from Helicobacter pylori divulge novel inhibitor-protein interactions. Chemistry. 2016;1(3):54-61.
19. Daina A, Olivier M, Vincent Z. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Science Report. 2017;7: 42717
20. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based

signatures. Journal of Medicinal Chemistry. 2015;58(9):4066-72.
DOI: 10.1021/acs.jmedchem.5b00104

21. Molinspiration Cheminformatics. Calculation of Molecular Properties and Bioactivity Score; 2020.
Available:http://www.molinspiration.com/cgi-bin/properties Accessed 8th December 2020
22. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews. 2001;46 (1-3):3-26.
23. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry. 2002;45(12):2615-2623.
24. Ghose AK, Viswanadhan VN, Wendoloski JJ. A Knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. Journal of Combinatorial Chemistry. 1999;1:55-68.
25. Khanna V, Ranganathan S. Physiochemical property space distance among human metabolites, drugs and toxins. BMC Bioinformatics. 2009;10 (Suppl. 15):S10.
26. Hopkins AL. Pharmacological Space in the Practice of Medicinal Chemistry. (4th ed.). Pages 395-408.USA: Elsevier; 2015.
27. Hansch C, Bjorkroth JP, Leo A. Hydrophobicity and the central nervous system agents: On the principle of minimal hydrophobicity in drug design. Journal of Pharmaceutical Sciences. 1987;76(9):663-687.
28. Chen X, Li H, Tian L. Analysis of the physio-chemical properties of acaricides based on Lipinski's Rule of 5. Journal of Computational Biology. 2020;27:1397-1406.
29. Putra PP, Abdullah SS, Rahmatunisa R. Structure, activity, and drug-likeness of pure compounds of Sumatran lichen (*Stereocaulon halei*) for the targetd ACE2 protein in COVID-19 disease. Pharmacina. 2020;10:135.
30. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. Journal of Combinatorial Chemistry. 1999;1:55-68.
31. Prasanna S, Doerksen RJ. Topological polar surface Area: A Useful Descriptor in 2D-QSAR. Current Medicinal Chemistry. 2009;16(1): 21-41.
32. Medjahed S, Belaidi S, Djekheba S. Computational study of molecular electrostatic potential, drug-likeness screening and structure-activity/property relationships of thiazolidine-2,4-dione derivatives. Journal of Bionanoscience. 2016;10:118-126.
33. Oprea TI. Property distribution of drug-related chemical databases. Journal of Computer-Aided Molecular Design. 2000; 14(3):251–264.
Available:Https://Doi.Org/10.1023/A:1008130001697
34. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, Liu G, Tang Y. ADMET-Score- A comprehensive scoring function for evaluation of chemical drug-likeness. Comprehensive Medicinal Chemistry. 2019;10(1):148-157.
35. Cui Q, Lu S, Ni B, Zeng X, Tan Y, Chen YD, Zhao H. Improved prediction of aqueous solubility of novel compounds by going deeper with deep learning. Frontiers in Oncology. 2020;10:121.
36. Peng Y, Yadava P, Heikkinen AT, Parrott N, Railkar A. Applications of a 7 day Caco-2 cell model in drug discovery and development. European Journal of Pharmaceutical Sciences. 2014;56:120-130.
37. Hou T, Wang J, Li Y. ADME evaluation in drug discovery. 8. The prediction of human intestinal absorption by a support vector machine. Journal of chemical Information and Modelling. 2007;47(6):2408-2415.
38. Supe S, Takudage P. Methods for evaluating penetration of drug into the skin: A review. Skin Research and Technology. 2021;27(3):299-308.
39. Prachayasittikul V, Prachayasittikul V. P-glycoprotein transporter in drug development. EXCLI Journal. 2016;15: 113.
40. Smith Dennis A. Volume of distribution in drug design: Miniperspective." Journal of

Medicinal Chemistry 58. 2015;15:5691-5698.
41. Pardridge WM. Drug transport across the blood–brain barrier. Journal of Cerebral Blood Flow & Metabolism. 2012;32(11): 1959-1972.
42. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics. 2013;138(1):103-141.
43. Horde GW, Gupta V. Drug clearance. Government Medical College Amritsar. Study Guide from Stat Pearls Publishing, Treasure Island (FL); 2020. PMID:32491690
44. Babcock JJ, Li M. hERG channel function: beyond long QT. Acta Pharmacologica Sinica. 2013;34(3):329-335.
45. Stampfer HG, Gabb GM, Dimmitt SB. Why maximum tolerated dose?. British Journal of Clinical Pharmacology. 2019;85 (10):2213-2217.
46. Ballet F. Hepatotoxicity in drug development: detection, significance and solutions. Journal of Hepatology. 1997;26: 26-36.
47. Kuddus M. Introduction to food enzymes. Enzymes in Food Biotechnology. 2019;1-18.
48. Krengel F, Chevalier Q, Dickinson J, Herrera Santoyo J, Reyes Chilpa R. Metabolite profiling of anti-addictive alkaloids from four mexican tabernaemontana species and the entheogenic african shrub *Tabernanthe iboga* (Apocynaceae). Chemistry & Biodiversity. 2019;16(4):e1800506.

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