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In silico evaluation of verbenone and selected solubilizing compounds against diabetes-related proteins

Oluremi A. SALIU[1], Blessing EDOGBO[1], Suwaiba NASIR[1], Shehu Usman ADAMU[2], Salima Adamu SADA[1], Adamu ABDULLAHI[3], Ayodeji O. IDOWU[1], Moses Dele ADAMS[4], Habibu TIJJANI[1*]

[1]Department of Environmental Health Science, National Open University of Nigeria, Abuja, Nigeria.
[2]Department of Public Health, National Open University of Nigeria, Abuja, Nigeria.
[3]Department of Biochemistry, Sa'adu Zungur University, Bauchi, Nigeria.
[4]Clinical Biochemistry, Pharmacognosy and Biochemical Toxicology Research Laboratory (CBPBT-RL), Department of Biochemistry, Baze University, Abuja, Nigeria.

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Abstract
Verbenone is a colourless, minty liquid that is soluble in non-polar solvents with *in vitro* and *in vivo* antidiabetic activities. This study evaluates verbenone and selected solubilizing compounds *in silico* against diabetes related proteins which included glucokinase (1V4S), human pancreatic α-amylase (1B2Y), and sucrase-isomaltase (3AXH). The structures of verbenone, acarbose, and five identified solubilizing compounds were downloaded in SDF format from the PubChem database. The binding energies were computed using Autodock Vina software while physicochemical properties and ADME parameters were predicted using SwissADME server. In glucokinase and human pancreatic α-amylase, the binding affinity (Kcal/mol) of verbenone (-5.4, -5.9) was superior to lysine (-4.5, -4.7) and eudragit (-4.5, -3.6), while in sucrase-isomaltase, the binding affinity (Kcal/mol) of verbenone (-6.1) was superior to lysine (-5.2), cyclodextrin (-4.8) and eudragit (-4.0) respectively. Only cyclodextrin violated the Lipinski rule of five. More so, cyclodextrin, lysine and eudragit are very soluble, with low lipophilicity compared with verbenone. Lysine and eudragit possess high gastrointestinal absorption and are not suitable P-gp substrate, while eudragit can effectively cross blood brain barrier. The study identified cyclodextrin, lysine and eudragit as potent candidates to improve the bioactivity of verbenone, as alternate means to improve the antidiabetic activity of verbenone.

Keywords: Verbenone; Cyclodextrin; Lysine; Eudragit; Diabetes; Proteins; Solubility

INTRODUCTION

Chronic elevation of blood glucose levels is a hallmark of diabetes mellitus (DM), a metabolic disorder [1]. DM is one of the leading causes of mortality and morbidity worldwide. In 2021, people living with diabetes mellitus were estimated at 529 million worldwide with a global age-standardized total diabetes prevalence at 6·1% and highest age-standardised rates of 9·3% were observed in North Africa and the Middle East [2]. The cases are projected to rise to about 642 million

*Correspondence. *E-mail*: hatijjani@noun.edu.ng *Tel*: +234-8037327138. ISSN 0189-8442

in 2040 [1]. Heart problems, neuropathy, and retinopathy are all progressively brought on by prolonged hyperglycemia [3].

AMP-activated protein kinase, 11 β-hydroxysteroid dehydrogenases, dipeptidyl peptidase IV, C-reactive protein, alpha-glucosidase, mono-ADP ribosyltransferase-sirtuin-6, glutamine fructose-6-phosphate amidotransferase, peroxisome proliferator-activated receptor gamma, protein tyrosine phosphatases, tyrosine kinase insulin receptor, and insulin receptor are among the proteins that are essential in diabetes mellitus [4]. Modern anti-diabetic medications, such as sitagliptin, metformin, and others, have significantly advanced the treatment of diabetes mellitus by modulating or inhibiting these proteins [5]. However, these medications come with a number of drawbacks, including the potential for drug resistance, acute kidney toxicity, increased risk of heart attack, and more [6,7]. Thus, the development of a natural alternative that is safe, effective, and has fewer side effects is urgently needed. A paradigm shift in favour of natural resources has sparked a great deal of interest. In particular, plants can yield novel therapeutic moieties that present a promising alternative.

Human pancreatic α-amylase, sucrase-isomaltase and glucokinase are important proteins in carbohydrate metabolism. Human pancreatic α-amylase catalyzes the release of maltose and dextrin through the hydrolysis of starch for further degradation by α-glucosidases to glucose [8]. Sucrase-isomaltase is an important membrane α-glucosidase that catalyze the final conversion of disaccharides and oligosaccharides to absorbable monosaccharides [9]. Glucokinase catalyze the conversion of glucose to glucose 6-phosphate, a rate-limiting step of glycolysis in the liver and pancreas [10]. Glucokinase is not sensitive to feedback suppression by physiological amounts of its product glucose 6-phosphate compared with other hexokinases [11]. Furthermore, it controls insulin secretion rate to maintain glucose homeostasis and glycogen synthesis in the pancreas and liver respectively [12]. Thus, these enzymes present strategic means for the control of DM, through their inhibition.

Glucokinase (GK) has low affinity for its substrate (glucose) with sigmoidal saturation curve [13]. The enzyme catalyses similar reaction with hexokinase I (HKI). The closed forms of GK are almost identical compared with HKI, however, a substantial difference exist in the region between Ser64 and Gly72 of GK [13]. Report has suggested that allosteric site of glucokinase could provide small synthetic activators to act as new drugs in the treatment of type 2 diabetes [13]. Human pancreatic α-amylase (HPA) is a single polypeptide chain protein, with three domains consisting of 496 amino acids (56 kDa) [14]. There are eight-stranded, β-sheet structure at the C-terminal domain, the (β}α)) barrel (domain A) contains a V-shaped depression which corresponds to the active site [15]. HPA are important in the cleavage of starch, in the early step of carbohydrate digestions. Thus, high affinity and selectivity inhibitors of α-amylase are described to be of potential applications for the treatment of diabetes [15]. Sucrase-isomaltase (SIM) plays important role in the digestion of sucrose and starch in small intestine. SIM is a single gene product with two active sites [16]. While the sucrase site splits sucrose, the isomaltase site split maltose for absorption at the brush border transporters [16]. Deficiency in sucrase-isomaltase could lead to symptoms of irritable bowel syndrome (IBS) due to the accumulation of undigested carbohydrates.

Trimethyl-bicyclo-heptenone, also known as verbenone, is a naturally occurring bicyclic ketone mono-terpene that possesses a number of pharmacological characteristics, such as anti-aggregation pheromone [17], repellent [18], anti-inflammatory, bronchodilator, and haemolytic [19]. Verbenone oxime ester is one type of

verbenone derivative that has been found to exhibit antiviral [20], antioxidant [21], antifungal [22], and anticancer [23] properties. Verbenone has significantly demonstrated antidiabetic properties [24]. However, its poor solubility has hindered its usage [25]. L-arginine has been reported to improve the solubility of verbenone *in vitro*, which could help improve the antidiabetic activities of the compound [24,25]. Thus, this study evaluates verbenone and selected solubilizing compounds *in silico* against diabetes related proteins, an attempt to identify soluble targets to improve the solubility and bioavailability of verbenone.

EXPERIMENTAL METHODS

Ligand preparation. The structures of verbenone, acarbose and five identified compounds (lysine, cyclodextrin, eudragit, ethylene glycol and poloxamer) with potentials to increase solubility over 10 folds were downloaded in SDF format from PubChem database [26]. The compounds were converted to mol2 chemical format using Open babel [27], and to dockable pdbqt format, after setting appropriate torsion centre for each ligand.

Protein preparation. The structures for carbohydrate metabolizing proteins including glucokinase (1V4S, 2.30 Å, GK), human pancreatic α-amylase (1B2Y, 3.20 Å, HPA), and sucrase-isomaltase (3AXH, 1.8 Å, SIM) were downloaded from the protein databank [28] with their respective PDB code. These selected proteins were prepared by removing existing ligands and water molecules, while missing polar hydrogen atoms were added using Autodock v4.2 program, Scripps Research Institute. Thereafter, non-polar hydrogen was merged while polar hydrogen added to each enzyme. The coordinates were set at 1V4S (size_x, y, z 50, 50, 50, center_x, y, z 29.169, 1.487, 62.874), 1B2Y (size_x, y, z 50, 50, 50 center_x, y, z 19.718, 10.876, 54.252) and 3AXH (size_x, y, z 40,40,40 center_x, y, z -25.472, -4.795, -18.981) before saving in dockable pdbqt format for molecular docking studies.

Molecular docking. The molecular docking studies of verbenone, acarbose, the five identified compounds and carbohydrate metabolizing protein targets were carried out using AutodockVina [29]. The binding energies of each compound were recorded. The top compounds with high binding affinities for carbohydrate metabolism were analysed and viewed using Discovery Studio Visualizer, BIOVIA, 2021.

ADMET and physicochemical properties. The compounds with top binding affinities were screened for their absorption, distribution, metabolism, elimination, and toxicity (ADMET) and physicochemical properties using SwissADME [30] and ADMETlab. The Lipinski's rule of five was used to screen for ligands with drug-likeness [31].

RESULTS AND DISCUSSION

Managing diabetes mellitus has remained challenging. The increasing prevalence of diabetes mellitus poses a significant challenge since the anti-diabetic medications currently on the market either have severe adverse effects or low efficacy [32]. As a result, identifying biological targets is now necessary for the creation of novel classes of antidiabetic drugs with bioactive ingredients and unique mechanisms. Moreover, one primary goal is to continue developing molecules that trigger therapeutic intervention. Verbenone is an antidiabetic active compound with poor solubility which could hinder its full usage as antidiabetic compound. Improving its solubility will enhance its solubility and bioavailability. More so, time and resources can be saved by using *in-silico* techniques as a persuasive tool to improve its solubility, other druggability data and comprehend mechanism of action [4].

In the current study, the binding affinity (Kcal/mol) of verbenone (-5.4, -5.9) in glucokinase and human pancreatic α-amylase, was superior to lysine (-4.5, -4.7) and eudragit (-4.5, -3.6), while in sucrase-isomaltase, the binding affinity (Kcal/mol) of verbenone (-6.1) was superior to lysine (-5.2), cyclodextrin (-4.8) and eudragit (-4.0) respectively (Table 1).

Table 1: Binding energies of verbenone and selected solubilizing compound against diabetes-related proteins

Compounds	PubChem CIDs	Binding energy (Kcal/mol)		
		1V4S	1B2Y	3AXH
Acarbose	9811704	-8.7	-7.5	-9.0
Verbenone	29025	-5.4	-5.9	-6.1
Lysine	5962	-4.5	-4.7	-5.2
Cyclodextrin	320760	-7.2	-6.9	-4.8
Eudragit	6658	-3.9	-3.6	-4.0
Ethylene glycol	174	-3.3	-3.4	-3.3
Poloxamer	24751	-2.7	-2.4	-2.6

Glucokinase (1V4S), human pancreatic α-amylase (1B2Y), sucrase-isomaltase (3AXH)

Table 2: Interacting amino acid residues of verbenone and selected solubilizing compounds against diabetes related proteins

Protein Target	Compounds	Binding Interactions
1V4S	Verbenone	TYR214 (3.52), ILE211 (4.83), MET210 (3.70), SER64 (3.62)
	Cyclodextrin	ARG327 (3.06), GLY328 (3.14), LYS296 (3.26), GLU300 (3.31), PHE330 (3.36), THR332 (3.02), THR116 (3.24)
	Lysine	TYR215 (2.01), ILE211 (5.04), VAL455 (4.48), ARG63 (2.13), VAL452 (452), VAL62 (3.72)
	Eudragit	PRO66 (3.78), THR65 (3.78)
	Acarbose	GLY328 (2.86), LYS296 (2.55), GLY229 (3.20), ASP78 (2.76), GLY81 (3.57), THR228 (2.80), GLY295 (2.26), THR332 (2.31), THR82 (2.16)
1B2Y	Verbenone	LEU162 (4.85), LEU165 (4.79), HIS101 (4.40)
	Cyclodextrin	ASP197 (2.91), TRP59 (3.55), GLY306 (3.15), GLU240 (3.15), HIS305 (3.21), THR163 (3.02), TYR62 (3.95)
	Lysine	ARG303 (2.57), ILE312 (2.47), GLY309 (2.66), THR314 (2.11), ARG346, GLN302 (2.58), ASP353 (2.66)
	Eudragit	TYR62 (3.59), ASP197 (3.75), GLU233 (3.73)
	Acarbose	TRP280 (1.91), PHE406, GLY403 (2.30), ASP402 (2.39), SER289 (2.58), HIS331 (2.61)
3AXH	Verbenone	PHE314 (4.61), ILE419 (4.22), ALA418 (3.77), SER236 (3.18), TRP238 (3.70)
	Cyclodextrin	LEU520 (2.08), ASP325 (2.41), GLU322 (2.28), LYS324 (2.07), ASP521(2.07)
	Lysine	ILE419 (4.90), PHE314 (3.93), GLY160 (3.69), GLY161 (3.34), SER236 (2.47), HIS423 (1.99), ASN235 (2.45), GLU422 (2.96)
	Eudragit	PHE314 (3.88), GLU422 (3.50)
	Acarbose	VAL216 (2.57), HIS280 (2.11), SER240 (2.99), ASP242 (2.26), GLU411 (2.45), ARG442 (2.49), ASP352 (2.58), TYR158 (3.19)

Acarbose = Reference compound, Numbers in brackets after each amino acid represent distance (Å)

Table 3: Physicochemical properties and Lipinski filter analysis of verbenone and selected solubilizing compounds

Properties	Verbenone	Cyclodextrin	Lysine	Eudragit
Formula	$C_{10}H_{14}O$	$C_{36}H_{60}O_{30}$	$C_6H_{14}N_2O_2$	$C_5H_8O_2$
Molecular weight (g/mol)	150.22	972.84	146.19	100.12
No. heavy atoms	11	66	10	7
No. aromatic heavy atoms	0	0	0	0
No. rotatable bonds	0	6	5	2
No. H-bond acceptors	1	30	4	2
No. H-bond donors	0	18	3	0
Molar Refractivity	45.42	194.30	38.14	26.96
Lipinski violation	No	3 violations: MW>500, NorO>10, NHorOH>5	No	No

N or O = Nitrogen or Oxygen, NH or OH = Amine or Hydroxyl

Table 4: ADME and SAR of verbenone and selected solubilizing compounds

Sub-properties	Verbenone	Cyclodextrin	Lysine	Eudragit
Water Solubility				
Log *S* (ESOL)	-2.18	2.63	1.51	-1.20
Solubility	$1.00x10^0$ mg/ml	$4.17x10^5$ mg/ml	$4.68x10^3$ mg/ml	$6.34x10^0$ mg/ml
Class	Soluble	Highly soluble	Highly soluble	Very soluble
Pharmacokinetics				
Skin permeation (Log K_p)	-5.63 cm/s	-21.37 cm/s	-9.36 cm/s	-5.93 cm/s
P-gp substrate	No	Yes	No	No
GI absorption	High	Low	High	High
CYP3A4 inhibitor	No	No	No	No
CYP2D6 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP2C19 inhibitor	No	No	No	No
CYP1A2 inhibitor	No	No	No	No
BBB permeant	Yes	No	No	Yes
Lipophilicity				
Log $P_{o/w}$ (iLOGP)	2.19	1.20	0.97	1.83
Log $P_{o/w}$ (XLOGP3)	2.23	-12.87	-3.05	1.38
Consensus Log $P_{o/w}$	2.25	-9.77	-1.19	1.05

ESOL =Estimated SOLubility, P-gp = p-glycoprotein, GI = Gastrointestinal, CYP = Cytochrome, BBB = Blood Brain Barrier

However, the binding affinity were lower compared with acarbose (-8.7, -7.5 and -9.0 Kcal/mol) respectively. The ligands interacted with triad amino acids: glycine (GLY328), lysine (LYS296), and threonine (THR332) in glucokinase (1V4S) residues (Table 2, Figures 1-3). Human pancreatic α-amylase, sucrase-isomaltase and glucokinase are important proteins in carbohydrate metabolism. Human pancreatic α-amylase catalyses the release of maltose and dextrin through the hydrolysis of starch for further degradation by α-glucosidases to glucose [8]. Sucrase-isomaltase is an important membrane α-glucosidase that catalyses the final conversion of disaccharides and oligosaccharides to absorbable monosaccharides [9]. Glucokinase catalyses the conversion of glucose to glucose 6-phosphate, a rate-limiting step of glycolysis in the liver and pancreas [10]. Glucokinase is not sensitive to feedback suppression by physiological amounts of its product glucose 6-phosphate compared with other hexokinases [11]. Furthermore, it controls insulin secretion rate to maintain glucose homeostasis and glycogen synthesis in the pancreatic and liver cells respectively [12]. Thus, these enzymes present strategic means for the control of DM, through their inhibition. Verbenone exhibited favourable binding in these enzymes and superior to most of the evaluated solubilizing compounds, suggesting favourable combinations especially when used with cyclodextrin, lysine or eudragit.

Exploring the interaction of biomolecules is important aspect of understanding their metabolic processes, which could provide insight for innovative strategies for drug design and their therapeutic application [33]. In glucokinase and human pancreatic α-amylase, the binding affinity of verbenone was superior to lysine, cyclodextrin and eudragit respectively. On the other hand, the binding affinities were lower in comparison to acarbose. The amino acids—lysine (LYS296), threonine (THR332), and glycine (GLY328) interacted with the ligand (Figure 1-3). The study further evaluated the physicochemical properties and Lipinski filter analysis of verbenone and selected solubilizing compound and the ADME/SAR of verbenone and selected solubilizing compound (Table 3 – 4). Only cyclodextrin violated the Lipinski rule of 5 due to its high molecular weight, numbers of oxygen and hydroxyl compounds (Table 3). More so, cyclodextrin, lysine and eudragit are very soluble, with low lipophilicity compared with verbenone. Lysine and eudragit possess high gastro intestinal (GI) absorption and are

not suitable P-gp substrate, while eudragit can effectively cross blood brain barrier (Table 4). The Lipinski rule of five was only broken by cyclodextrin because of its large molecular weight, numerous oxygen atoms, and hydroxyl compounds. Furthermore, compared to verbenone, cyclodextrin, lysine, and eudragit are very soluble and have low lipophilicity. While eudragit can successfully cross the blood-brain barrier, lysine and eudragit have high GI absorption and are not suitable P-gp substrates.

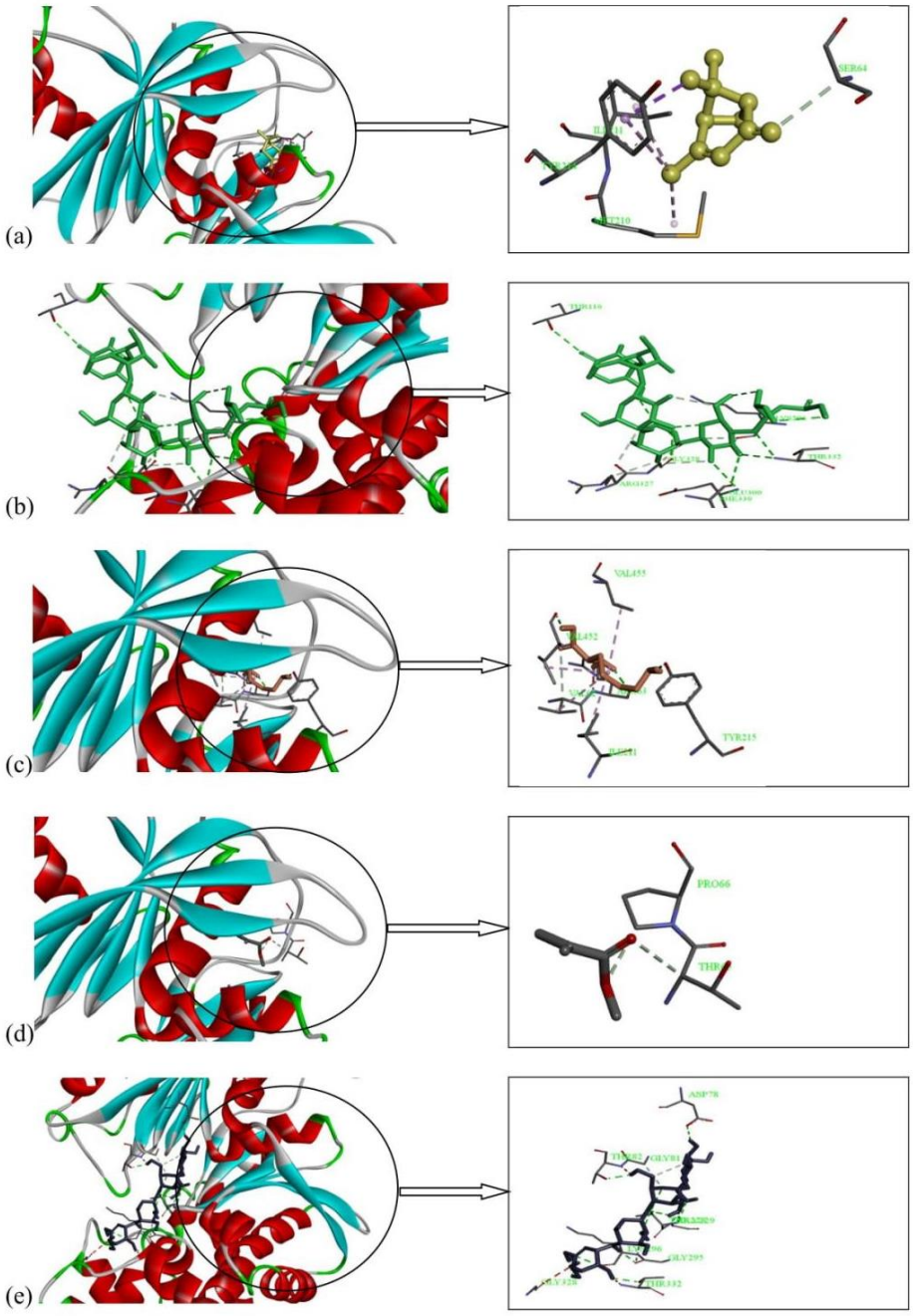

Figure 1: Binding pocket view of verbenone and selected solubilizing compound against 1V4S proteins (a) Verbenone (b) Cyclodextrin (c) Lysine (d) Eudragit (e) Acarbose

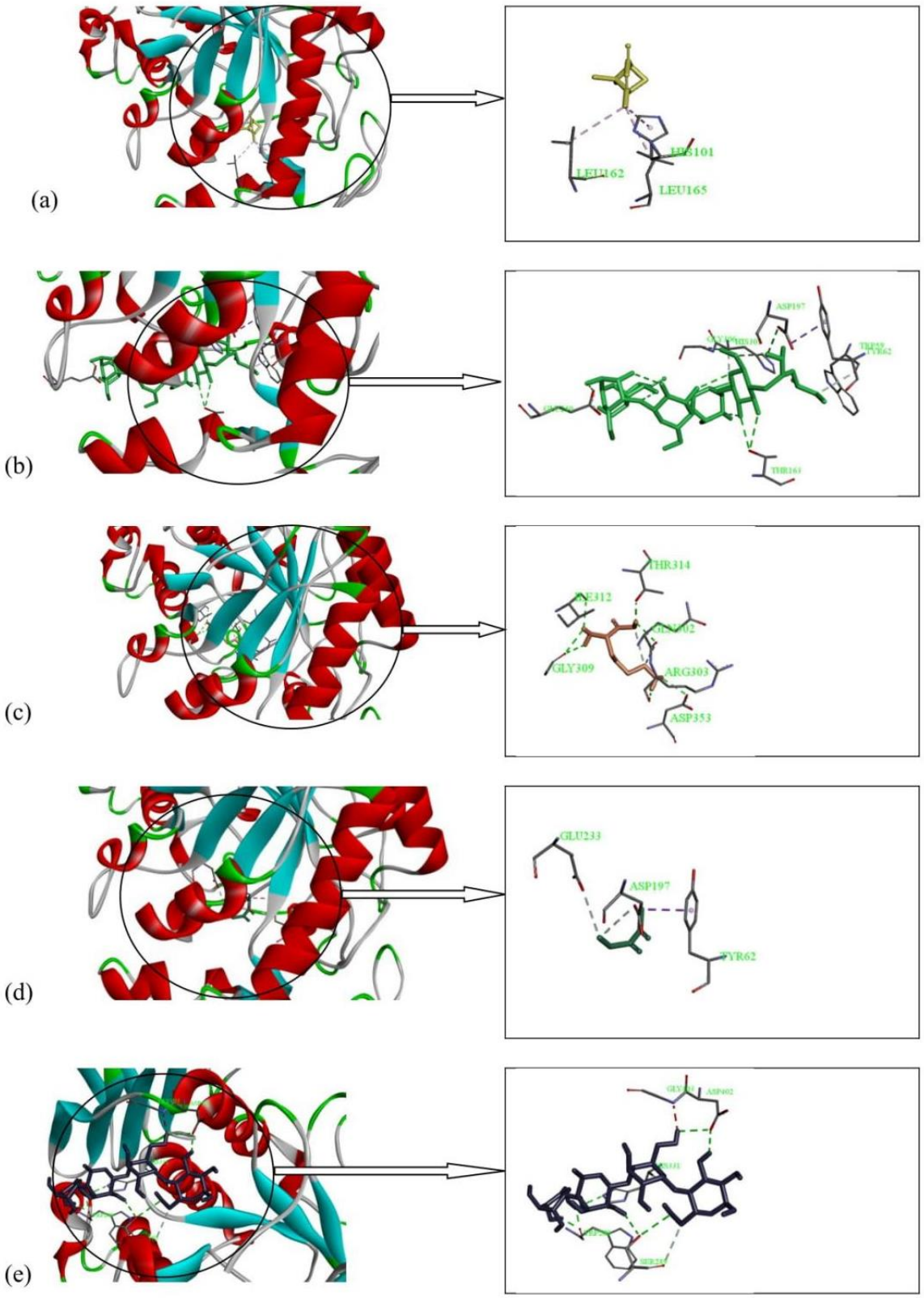

Figure 2: Binding pocket view of verbenone and selected solubilizing compound against 1B2Y proteins (a) Verbenone (b) Cyclodextrin (c) Lysine (d) Eudragit (e) Acarbose

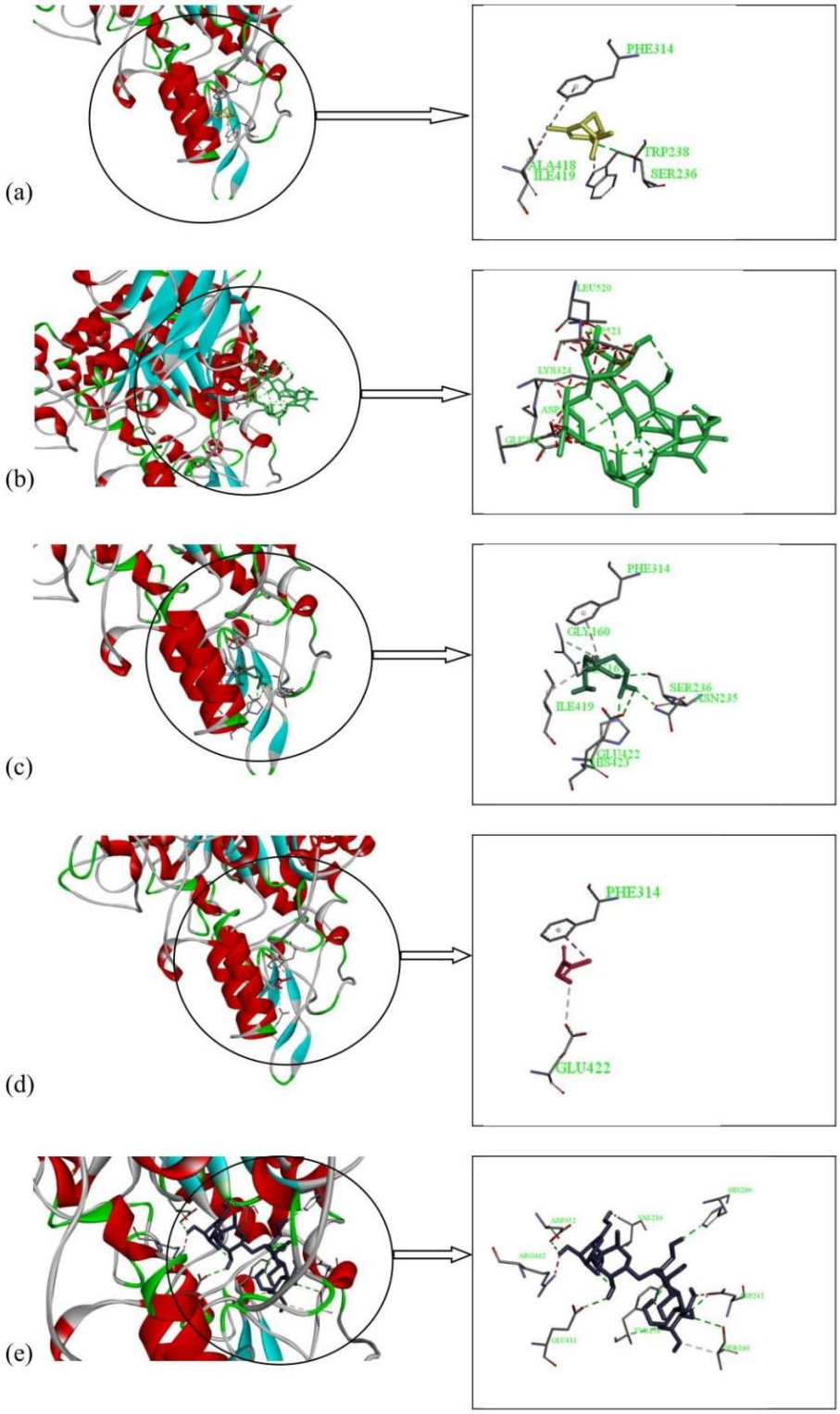

Figure 3: Binding pocket view of verbenone and selected solubilizing compound against 3AXH proteins (a) Verbenone (b) Cyclodextrin (c) Lysine (d) Eudragit (e) Acarbose

Conclusion. The study identified eudragit, cyclodextrin, and lysine as potent candidates to improve the solubility and bioactivity of verbenone when administered in combination or used as hybrid compounds. These could serve as alternate means to improve the antidiabetic activity of verbenone.

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