Molecular Docking Study of Isolated Phytoconstituents From *Barleria Buxifolia* And *Barleria Cuspidata*

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ABSTRACT

Evaluation of molecular docking analysis of isolated phytoconstituents from *Barleria buxifolia* and *Barleria cuspidata*. Phytoconstituents such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside and luteolin 7-O-glucoside were docked with antidiabetic drug target proteins such as pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase – 3 using Autodock 4.2 software. Steroidal ligand such as β-sitosterol-β-D-glucoside shows affinity with diabetic proteins pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase – 3 with binding energy of -8.43 Kcal/mol, -11.41 Kcal/mol, -8.2 Kcal/mol and -8.88 Kcal/mol respectively. Quercetin-3-O-β-D-glucoside shows affinity with diabetic proteins pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase – 3 with binding energy of -5.96 Kcal/mol, -7.26 Kcal/mol, -6.34 Kcal/mol and -7.44 Kcal/mol respectively. 7-methoxy diderroside shows affinity with diabetic proteins pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase – 3 with binding energy of -5.31 Kcal/mol, -4.62 Kcal/mol, -2.65 Kcal/mol and -5.37 Kcal/mol

respectively. Luteolin 7-O-glucoside shows affinity with diabetic proteins pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase – 3 with binding energy of -6.96 Kcal/mol, -6.77 Kcal/mol, -6.18 Kcal/mol and -8.22 Kcal/mol respectively. The results reveal that isolated phytoconstituents are effectively interacted with antidiabetic target proteins on contrasted with standard, acarbose. By these results, steroidal ligand such as β-sitosterol-β-D-glucoside has superior affinity with well known diabetic targets. Remaining phytoconstituents such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside and luteolin 7-O-glucoside showed moderate to less binding affinity with target proteins.

Key Words: *Barleria buxifolia, Barleria cuspidata,* Molecular docking, Phytoconstituents.

1. INTRODUCTION

Molecular docking plays an efficient and important role in the field of computer aided drug design (CADD), which helps in identifying small molecules by docking at the active binding site of the protein. Novel ligands for receptors of known receptor structure are designed and their interaction energies are calculated using the scoring function [1]. The molecular docking studies of the compounds with different enzyme targets were employed. Docking studies were performed on commercial software's like GOLD from CCDC, GLIDE from Schrodinger and free-wares like Auto Dock Vina from Scripps Research Institute. Structures of different protein crystal structures were retrieved from the protein data bank (PDB). Molecular docking is a well-established computational technique which predicts the interaction energy between two molecules. Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand, which would form a complex with overall minimum energy [2]. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence, docking plays an important role in the rational drug design. The results are analyzed by a statistical scoring function

which converts interacting energy into numerical values called as the docking score; and also, the interacting energy is calculated.

Docking is most commonly used in the field of drug design and docking is applied to:

- Hit identification – docking combined with a scoring function is used to quickly screen large databases of potential drugs *in silico* to identify molecules that are likely to bind to protein target of interest.
- Lead optimization – docking is used to predict the relative orientation of a ligand that binds to a protein (also referred to as the binding mode or pose). This information is in turn used to design more potent and selective analogs.
- Bioremediation – Protein ligand docking is used to predict pollutants that are degraded by enzymes [3].

The chief objective of the existing study was to find out most suitable positions and orientations of ligands in the ligand binding center of the enzyme or receptor and to evaluate the effect of isolated phytoconstituents from *Barleria buxifolia* and *Barleria cuspidata* on antidiabetic activity.

2. MATERIAL AND METHODS

2.1. Docking software's

Among the different types of software's available for docking it used the Autodock 4.2 software for the molecular docking investigation of proteins involved in antidiabetic activity.

2.2. Phytoconstituents / Ligands

Phytoconstituents or ligands like quercetin-3-O-β-D-glucoside {*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxychromen-4-one*}; 7-methoxy diderroside {*methyl (2S,3S,4S)-3-[(1S)-1-acetyloxyethyl]-4-(2-methoxy-2-oxoethyl)-2-[(2S,3R,4S,5S,6R) -3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxy-3,4-dihydro-2H-pyran-5-carboxylate*}; β-sitosterol-β-D-glucoside {*(2R,3R,4S,5S,6R)-2-*

[[(8S,9S,10R,13R,14S,17R)-17-[(2R,5R) -5-ethyl-6-methylheptan-2-yl] -10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-yl] oxy]-6-(hydroxymethyl)oxane-3,4,5-triol}; and luteolin 7-O-glucoside {*2-(3,4-dihydroxyphenyl)-7-(β-D-glucopyranosyloxy)-5-hydroxy-4H-1-benzopyran-4-one*} were used for molecular docking studies.

2.3. Potential targets and binding sites

The 3D structures of antidiabetic drug targets such as pyruvate dehydrogenase kinase [4], human 11-beta-hydroxysteroid dehydrogenase (HSD1) [5], glucagon-like peptide-1 [6] and glycogen synthase kinase – 3 [7] were obtained from protein database bank. Based on these ligands in crystallized structures, the active sites in receptors were determined.

2.4. Protein preparation

The co-crystal structures of various proteins using in study were obtained from the protein data bank. Preparation of proteins (addition of polar hydrogens, addition of AD4 type atoms, removal of water molecules and heteroatoms) were done with Autodock 4.2 software as per default settings to obtain a biologically active protein.

2.5. Ligand preparation

The 2D structures of the phytochemical compound's quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside and luteolin 7-O-glucoside were converted to 3D structure in maestro 9.5. The 3D structures obtained were converted into structure data format (SDF) files and the activity was performed.

2.6. Docking

Docking was executed to acquire probable conformations and positions for the ligand-receptor complexes at the binding site. Binding site was determined using the previous knowledge of the original ligand's interaction site. For the stimulation runs, each ligand was kept flexible, but the aminoacid residues of active site were kept rigid and default parameters values were

taken. Diabetic targets for various proteins were selected based on the literature survey. The structures of all the receptors were obtained from PDB format.

3. RESULTS

3.1. Molecular docking

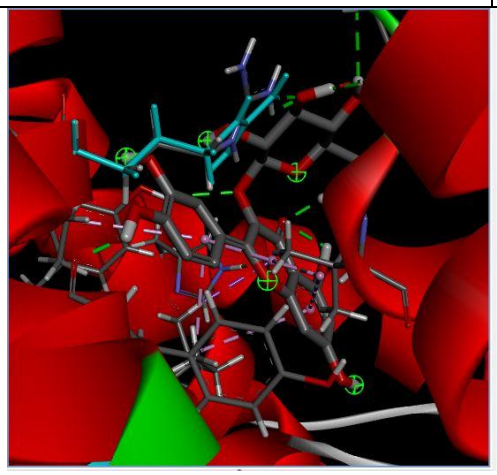
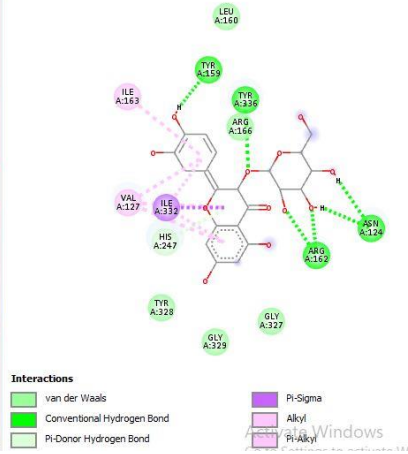
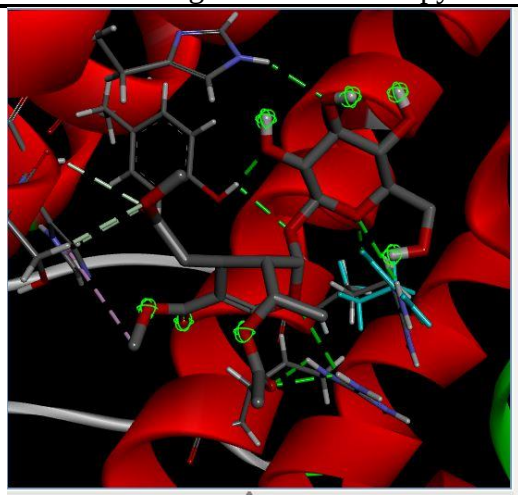
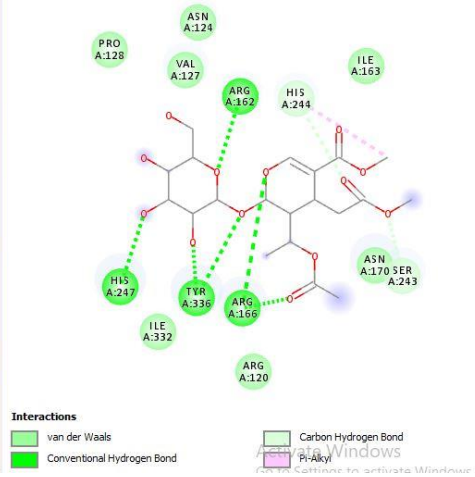
In present study, glide SP docking was performed and confirmed the conformation which shows binding affinity towards the diabetic protein's pyruvate dehydrogenase kinase (PDB: 5J71), human 11-beta-hydroxysteroid dehydrogenase (HSD1) (PDB: 2IRW), glucagon-like peptide-1 (PDB: 3IOL) and glycogen synthase kinase – 3 (PDB: 1UV5) by docking score and ligand interaction patterns. Molecules with more negative scores were selected as they imply greater and stronger interaction with the concerned protein. The phytoconstituents/ligands were docked against four different target protein receptors such as pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase (HSD1), glucagon-like peptide-1 and glycogen synthase kinase - 3. SP (standard precision) and XP (extra precision) docking workflow against diabetic proteins using selected ligands were employed and successfully identified few drug molecules as a potential hit.

3.2. Pyruvate dehydrogenase kinase

Docking studies were performed against pyruvate dehydrogenase kinase using Autodock 4.2 software with isolated phytoconstituents and standard acarbose as ligands. The results obtained in the form of binding energy and amino acids interactions by hydrogen bonding were in Table 10.1 and in Figure 10.1. Among the isolated phytoconstituents sush as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside, luteolin 7-O-glucoside shows the docked binding energy with pyruvate dehydrogenase kinase as -5.96 Kcal/mol, -5.31 Kcal/mol, -8.43 Kcal/mol and -6.96 Kcal/mol respectively. Standard acarbose shows the docked binding energy with pyruvate dehydrogenase kinase of -2.28 Kcal/mol.

Table - 1: Ligands docking study with pyruvate dehydrogenase kinase

S. No.	Ligand	Docked binding energy (Kcal/mol)	No. of. hydrogen (H) bonds formed	Amino acid interaction
1	Quercetin-3-O-β-D-glucoside	-5.96	6	Tyr159 Tyr336 Arg162 Arg162 Asn124 Asn124
2	7-methoxy diderroside	-5.31	6	Arg162 His247 Tyr336 Tyr336 Arg166 Arg166
3	β-sitosterol-β-D-glucoside	-8.43	4	Tyr336 Ile163 Arg166 Asn170
4	Luteolin 7-O-glucoside	-6.96	0	---
5	Acarbose	-2.28	8	Asn124 Asn124 Arg162 Arg162 Arg162 Arg166 Asn170 Ser243

S. No.	3D Structure	2D Structure
1		 A view of docked poses between the active compound quercetin – 3 – O – β – D – glucoside and the pyruvate dehydrogenase kinase
2		 A view of docked poses between the active compound 7-methoxy diderroside and the pyruvate dehydrogenase kinase

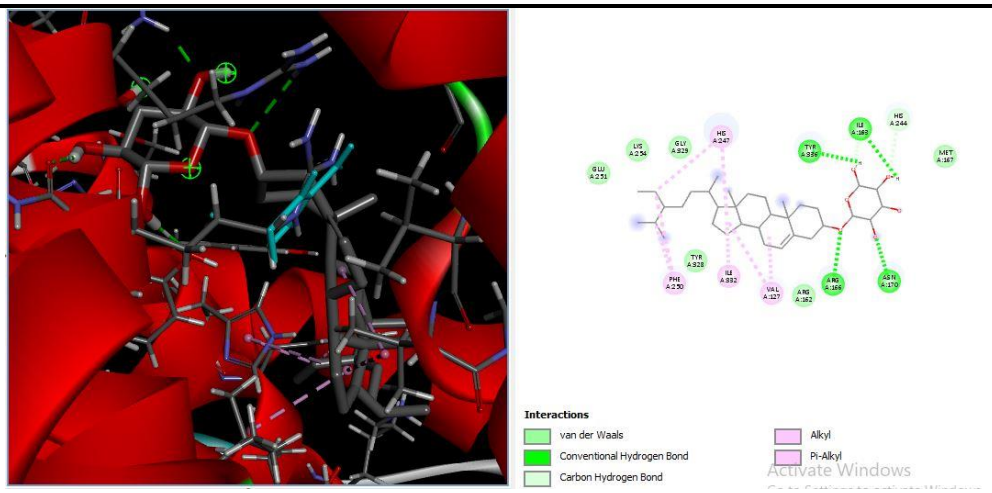
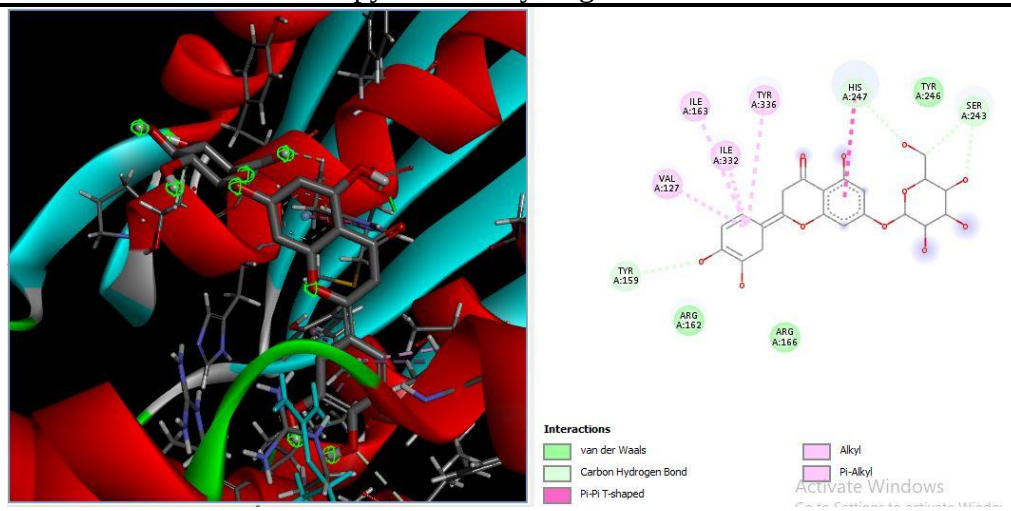
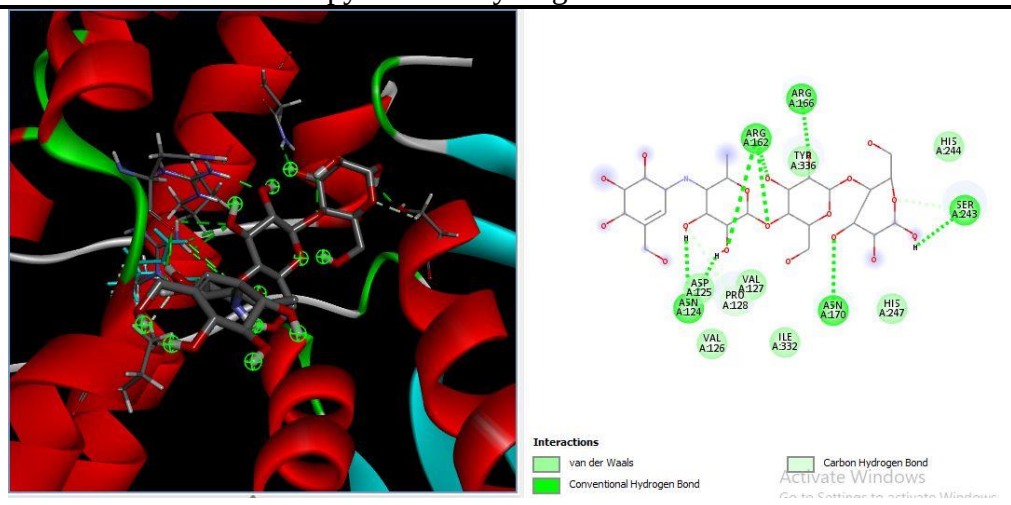
3	 A view of docked poses between the active compound β-sitosterol-β-D-glucoside and the pyruvate dehydrogenase kinase
4	 A view of docked poses between the active compound luteolin 7-O-glucoside and the pyruvate dehydrogenase kinase
5	 A view of docked poses between the active compound acarbose and the pyruvate dehydrogenase kinase

Figure - 1: Receptors and ligand interaction of pyruvate dehydrogenase kinase (5J71) protein data with 5 compounds

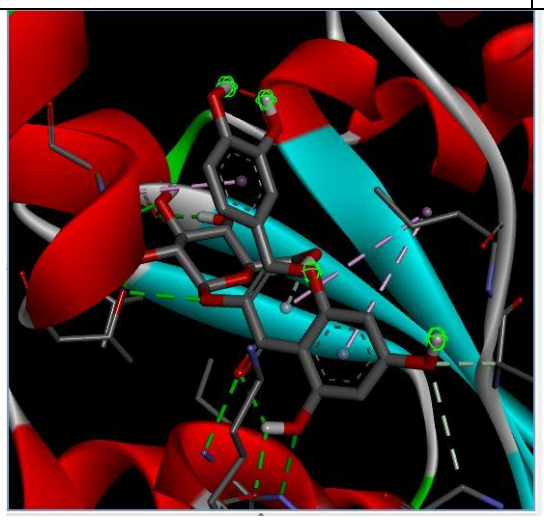
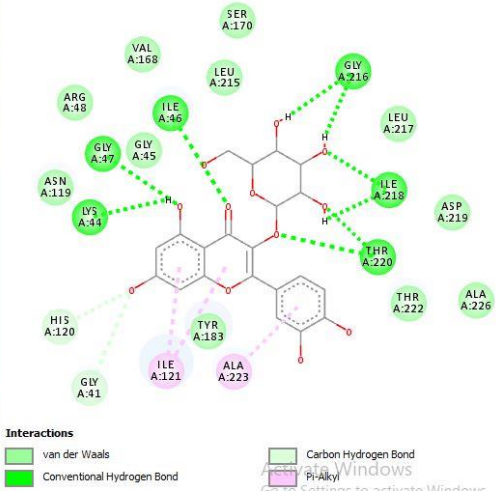
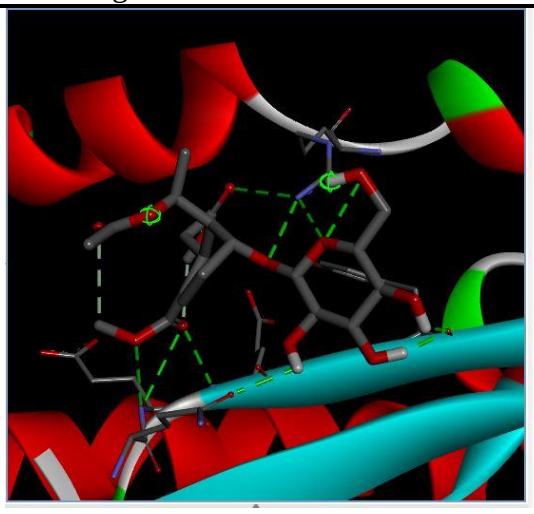
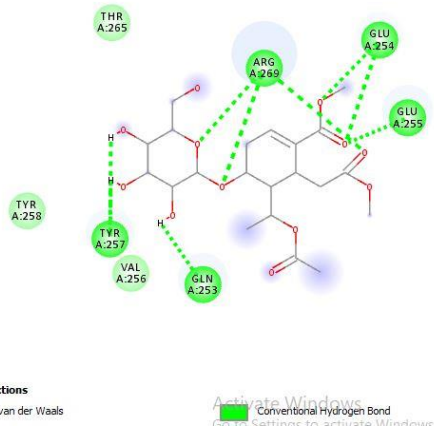
3.3. Human 11-beta-hydroxysteroid dehydrogenase

Docking studies were performed against human 11-beta-hydroxysteroid dehydrogenase using Autodock 4.2 software with isolated phytoconstituents and standard acarbose as ligands. The results obtained in the form of binding energy and amino acids interactions by hydrogen bonding were tablulated in Table 10.2 and in Figure 10.2. Among the isolated phytoconstituents sush as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside, luteolin 7-O-glucoside shows the docked binding energy with human 11-beta-hydroxysteroid dehydrogenase as -7.26 Kcal/mol, -4.62 Kcal/mol, -11.41 Kcal/mol and -6.77 Kcal/mol respectively. Standard acarbose shows the docked binding energy with human 11-beta-hydroxysteroid dehydrogenase of -5.39 Kcal/mol.

Table - 2: Ligands docking study with human 11-beta-hydroxysteroid dehydrogenase

S. No.	Ligand	Docked binding energy (Kcal/mol)	No. of. hydrogen (H) bonds formed	Amino acid interaction
1	Quercetin-3-O-β-D-glucoside	-7.26	9	Lys44 Gly47 Ile46 Gly216 Gly216 Ile218 Ile218 Thr220 Thr220
2	7-methoxy diderroside	-4.62	9	Tyr257 Tyr257 Gln253 Arg269 Arg269 Arg269 Glu254 Glu254 Glu255
3	β-sitosterol-β-D-glucoside	-11.41	2	Pro178 Pro178
4	Luteolin 7-O-glucoside	-6.77	2	Pro178 Ile230
5	Acarbose	-5.39	10	Gly47 Asn119 Ile46 Ile121 Ser170 Gly216 Gly216 Ile218 Thr220

				Thr220

S. No.	3D Structure	2D Structure
1		
	A view of docked poses between the active compound quercetin – 3 – O – β – D – glucoside and the human 11-beta-hydroxysteroid dehydrogenase	
2		
	A view of docked poses between the active compound 7-methoxy diderroside and the human 11-beta-hydroxysteroid dehydrogenase	

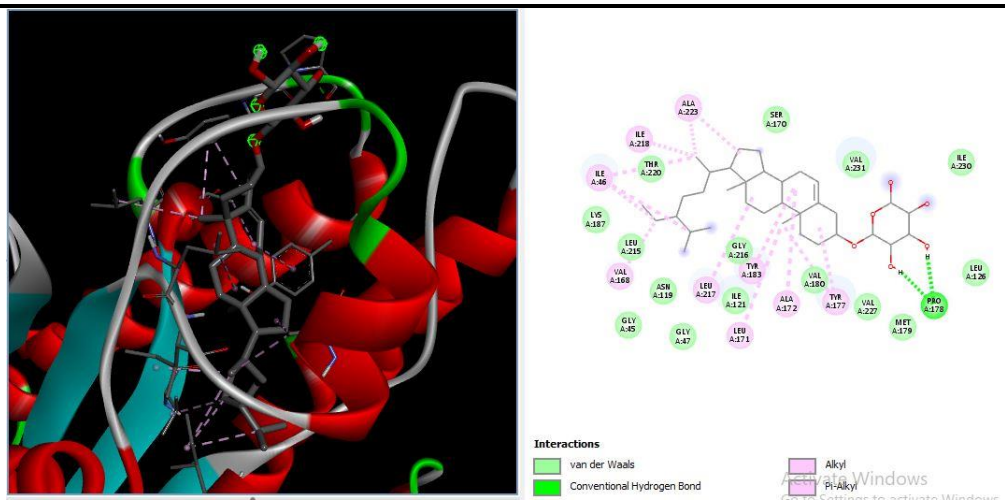
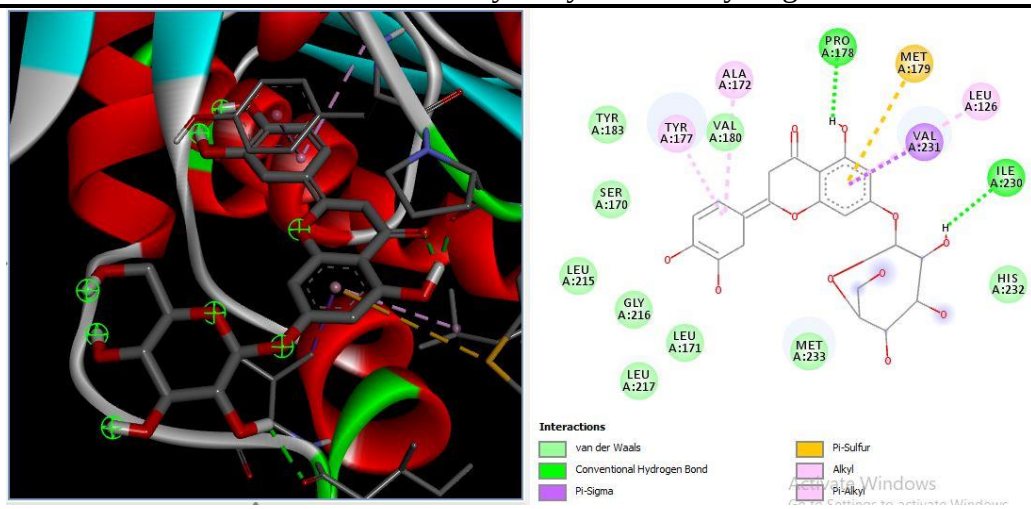
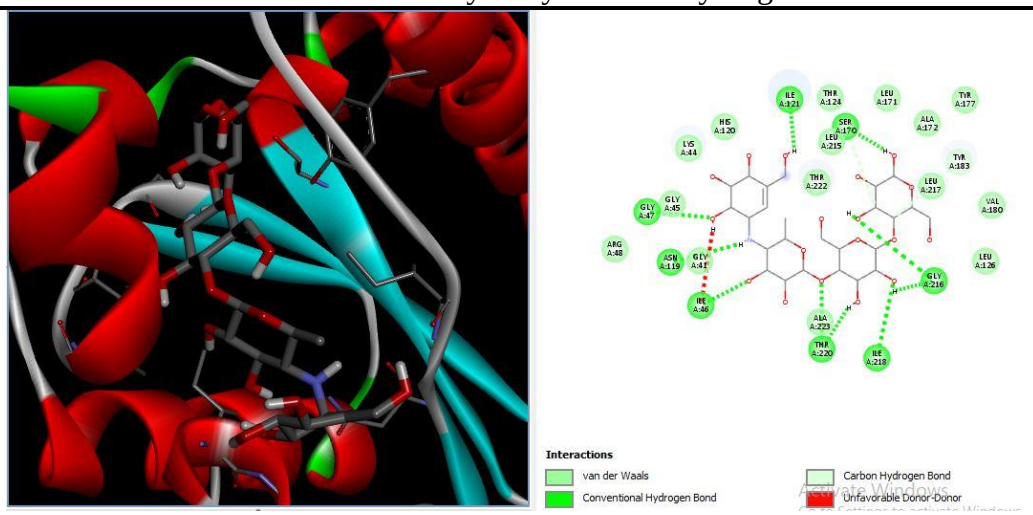
3	 A view of docked poses between the active compound β-sitosterol-β-D-glucoside and the human 11-beta-hydroxysteroid dehydrogenase
4	 A view of docked poses between the active compound luteolin 7-O-glucoside and the human 11-beta-hydroxysteroid dehydrogenase
5	 A view of docked poses between the active compound acarbose and the human 11-beta-hydroxysteroid dehydrogenase

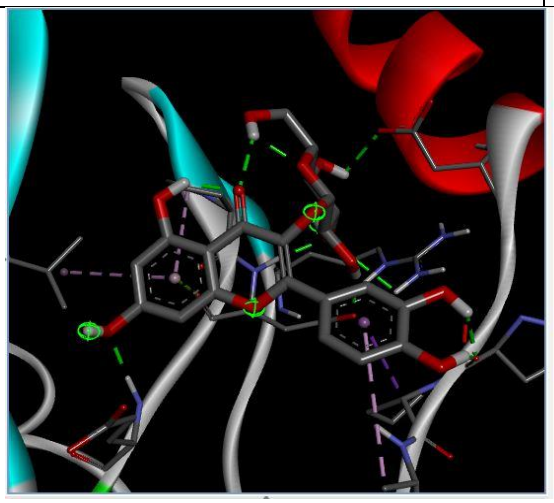
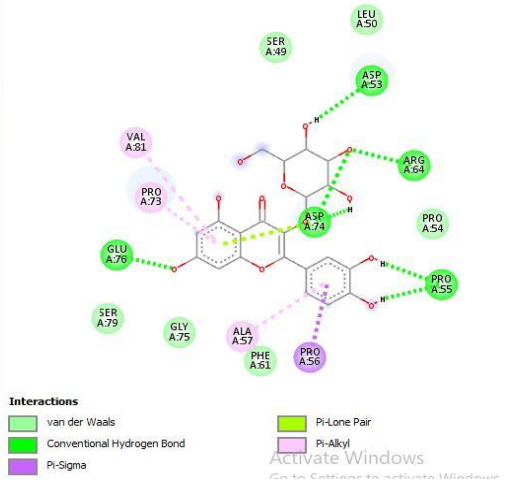
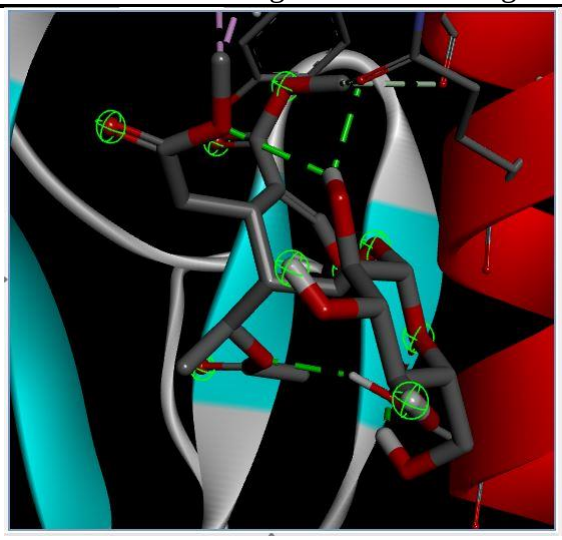
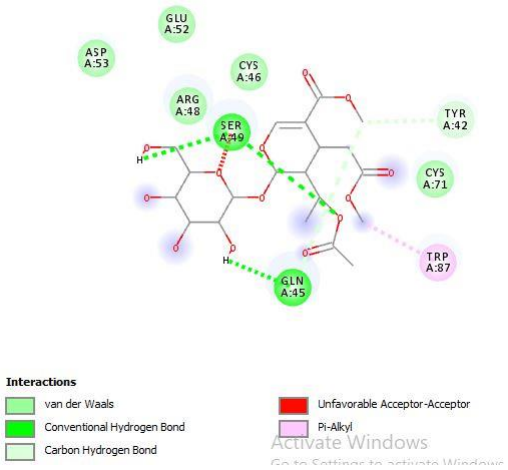
Figure - 2: Receptors and Ligand Interaction of human 11-beta-hydroxysteroid dehydrogenase (2IRW) Protein data with 5 compounds

3.4. Glucagon-like peptide-1

Docking studies were performed against glucagon-like peptide-1 using Autodock 4.2 software with isolated phytoconstituents and standard acarbose as ligands. The results obtained in the form of binding energy and amino acids interactions by hydrogen bonding were tablulated in Table 10.3 and in Figure 10.3. Among the isolated phytoconstituents sush as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside, luteolin 7-O-glucoside shows the docked binding energy with glucagon-like peptide-1 as -6.34 Kcal/mol, -2.65 Kcal/mol, -8.2 Kcal/mol and -6.18 Kcal/mol respectively. Standard acarbose shows the docked binding energy with glucagon-like peptide-1 of -2.98 Kcal/mol.

Table - 3: Ligands docking study with glucagon-like peptide-1

S. No.	Ligand	Docked binding energy (Kcal/mol)	No. of. hydrogen (H) bonds formed	Amino acid interaction
1	Quercetin-3-O-β-D-glucoside	-6.34	7	Glu76 Asp53 Arg64 Asp74 Asp74 Pro55 Pro55
2	7-methoxy diderroside	-2.65	3	Ser49 Ser49 Gln45
3	β-sitosterol-β-D-glucoside	-8.2	4	Asp74 Ser79 Phe80 Phe80
4	Luteolin 7-O-glucoside	-6.18	9	Asn82 Asn82 Asn82 Ser84 Asp53 Gln45 Tyr42 Tyr42 Trp87
5	Acarbose	-2.98	3	Arg64 Arg64 Phe66

S. No.	3D Structure	2D Structure
1		
	A view of docked poses between the active compound quercetin – 3 – O – β – D – glucoside and the glucagon-like peptide-1	
2		
	A view of docked poses between the active compound 7-methoxy diderroside and the glucagon-like peptide-1	

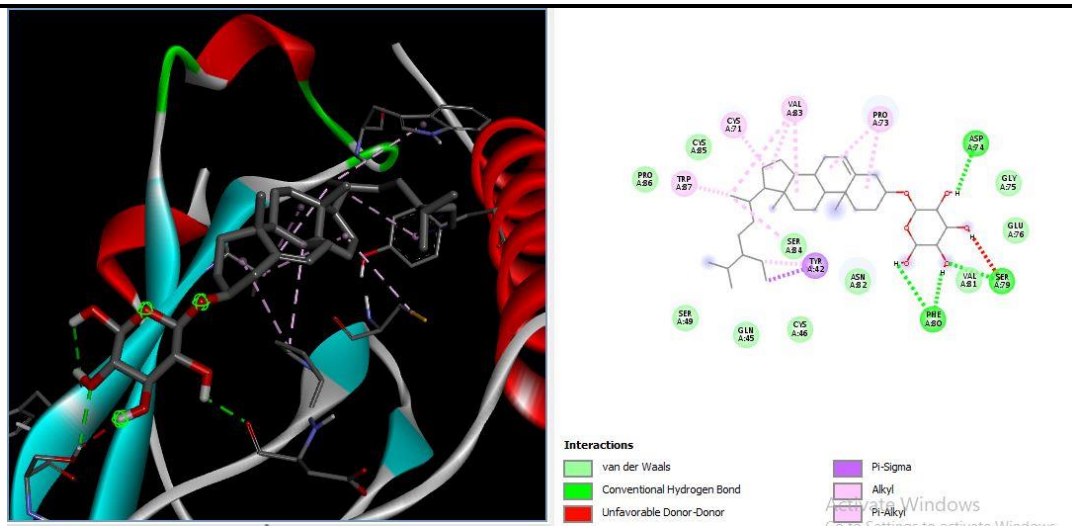
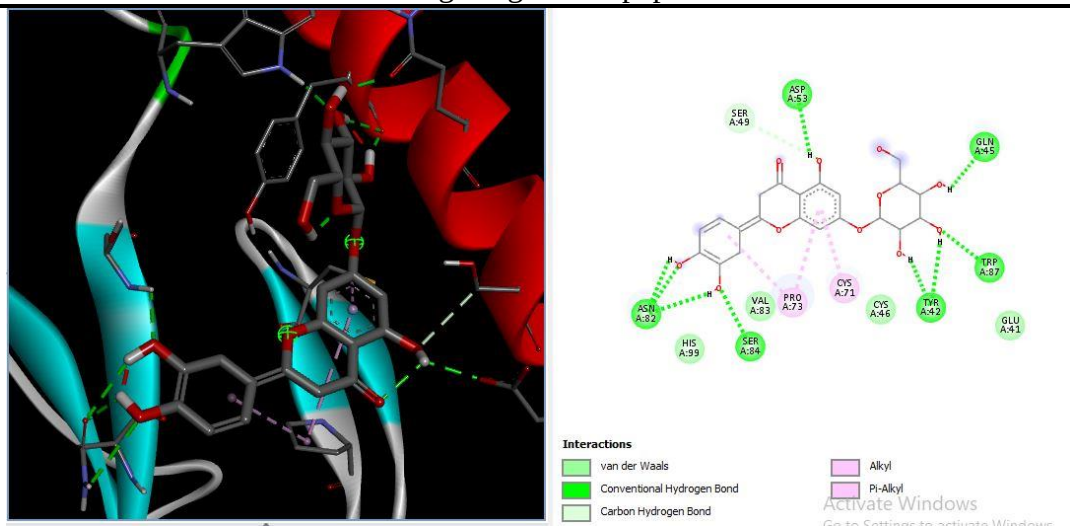
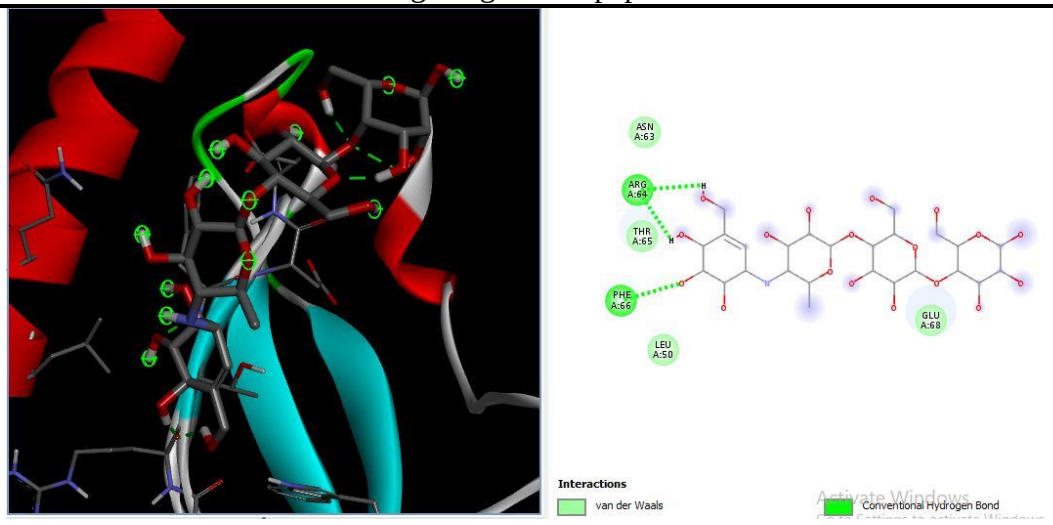
3	 A view of docked poses between the active compound β-sitosterol-β-D-glucoside and the glucagon-like peptide-1
4	 A view of docked poses between the active compound luteolin 7-O-glucoside and the glucagon-like peptide-1
5	 A view of docked poses between the active compound acarbose and the glucagon-like peptide-1

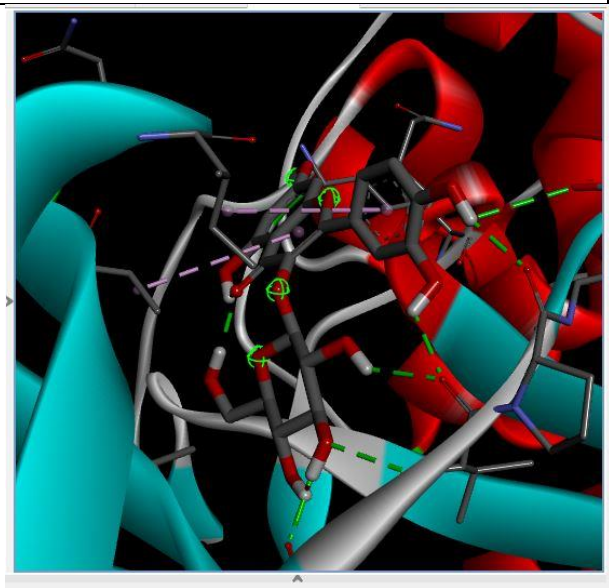
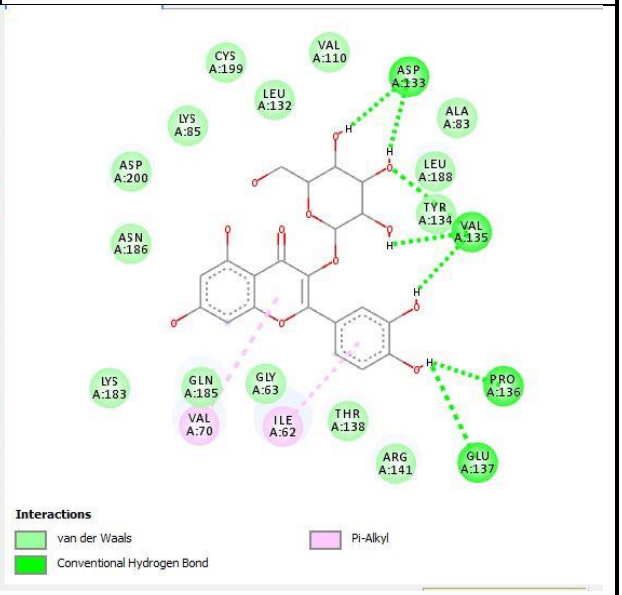
Figure - 3: Receptors and ligand interaction of glucagon-like peptide-1 (3IOL) protein data with 5 compounds

10.3.5. Glycogen synthase kinase – 3

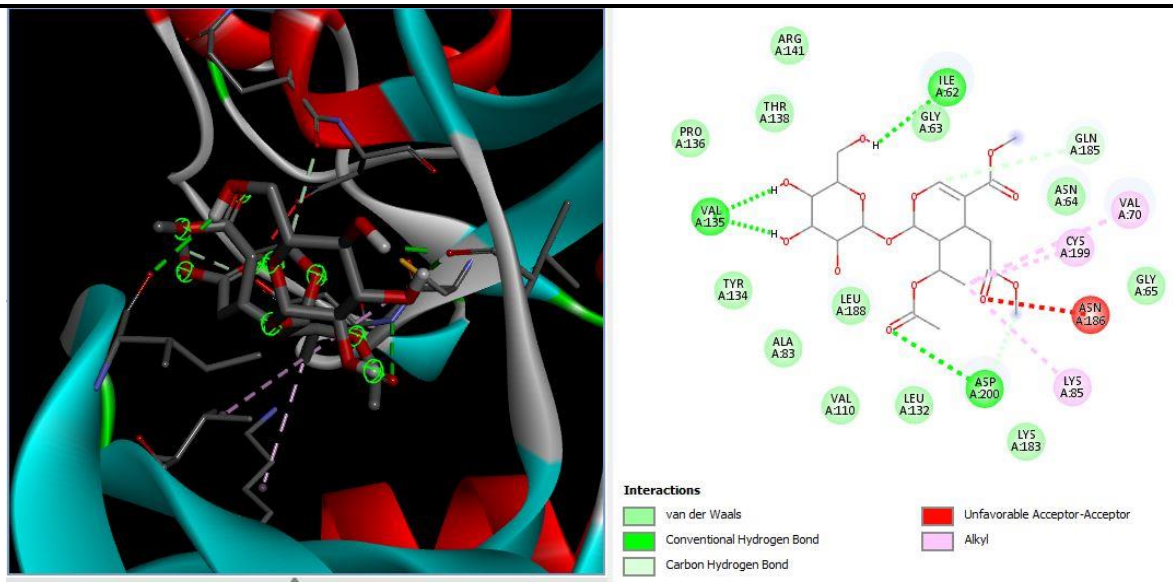
Docking studies were performed against glycogen synthase kinase – 3 using Autodock 4.2 software with isolated phytoconstituents and standard acarbose as ligands. The results obtained in the form of binding energy and amino acids interactions by hydrogen bonding were tablulated in Table 10.4 and in Figure 10.4. Among the isolated phytoconstituents sush as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside, luteolin 7-O-glucoside shows the docked binding energy with glycogen synthase kinase – 3 as -7.44 Kcal/mol, -5.37 Kcal/mol, -8.88 Kcal/mol and -8.22 Kcal/mol respectively. Standard acarbose shows the docked binding energy with glycogen synthase kinase – 3 of -2.23 Kcal/mol.

Table - 4: Ligands docking study with glycogen synthase kinase – 3

S. No.	Ligand	Docked binding energy (Kcal/mol)	No. of. hydrogen (H) bonds formed	Amino acid interaction
1	Quercetin-3-O-β-D-glucoside	-7.44	4	Asp133 Val135 Pro136 Glu137
2	7-methoxy diderroside	-5.37	4	Val135 Val135 Ile62 Asp200
3	β-sitosterol-β-D-glucoside	-8.88	3	Asp181 Lys183 Ser66
4	Luteolin 7-O-glucoside	-8.22	5	Glu97 Glu97 Val135 Val135 Gln185
5	Acarbose	-2.23	6	Glu221 Glu221 Glu99 Glu99 Glu99 Gln206

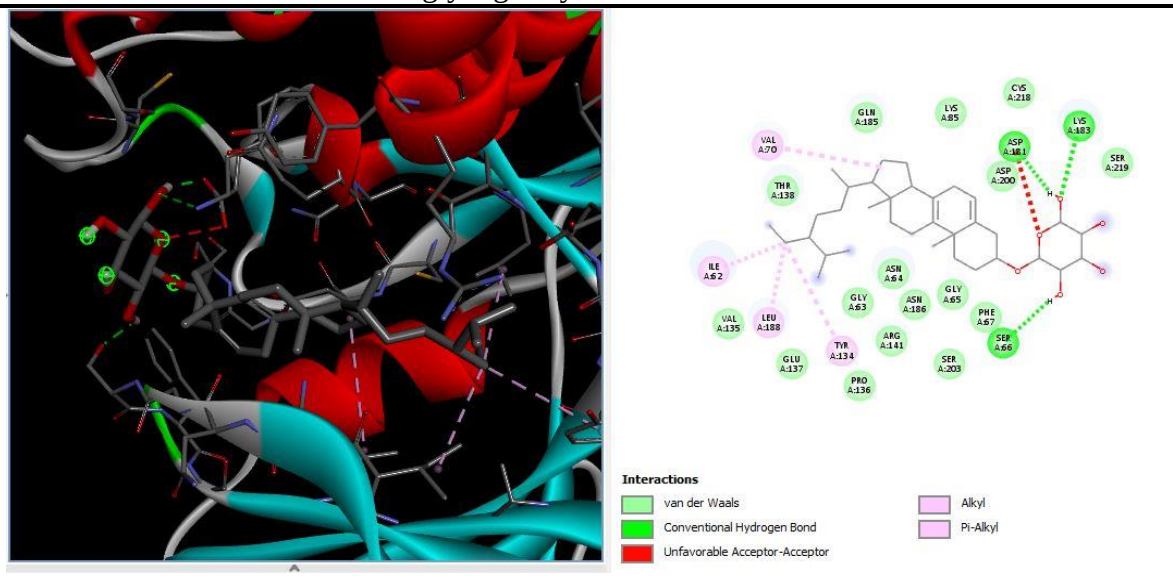
S. No.	3D Structure	2D Structure
1		
	A view of docked poses between the active compound quercetin – 3 – O – β – D – glucoside and the glycogen synthase kinase – 3	

2



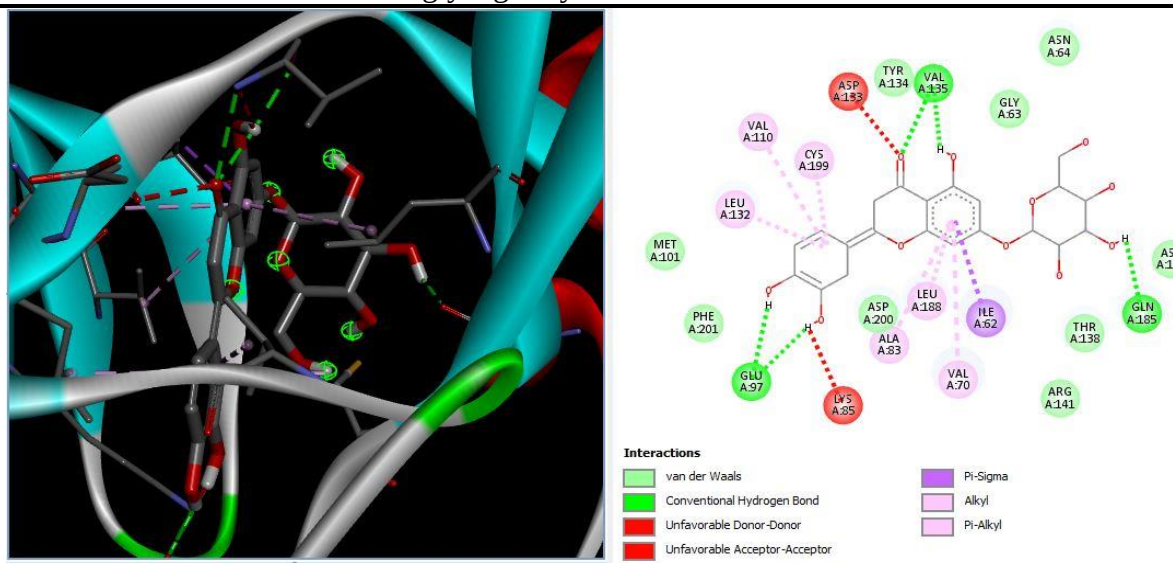
A view of docked poses between the active compound 7-methoxy diderroside and the glycogen synthase kinase – 3

3



A view of docked poses between the active compound β-sitosterol-β-D-glucoside and the glycogen synthase kinase – 3

4



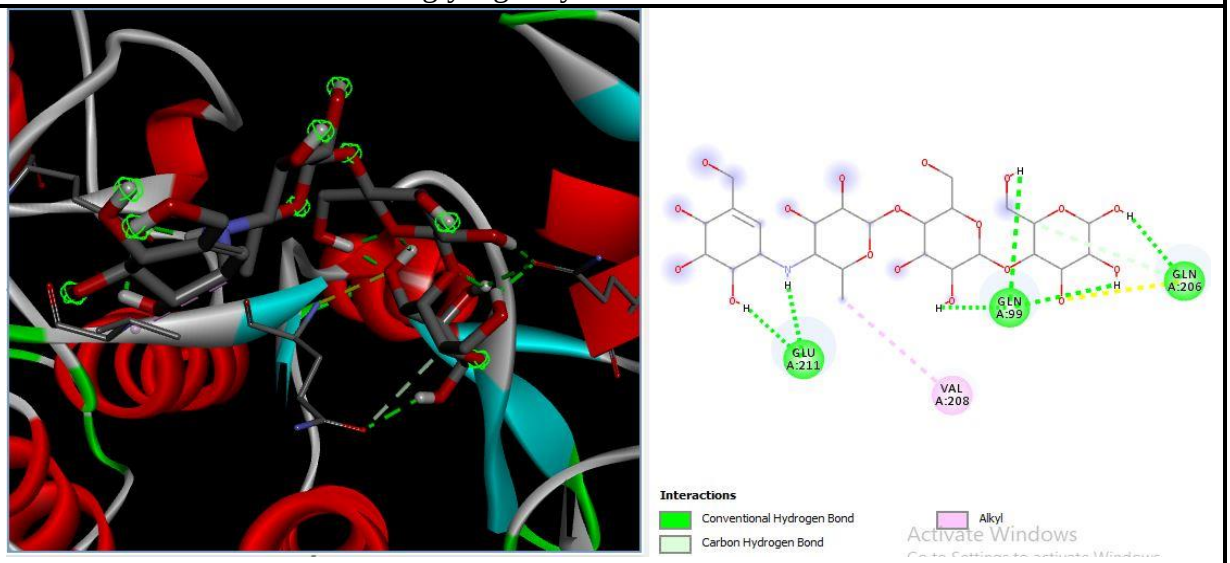
	A view of docked poses between the active compound luteolin 7-O-glucoside and the glycogen synthase kinase – 3
5	
	A view of docked poses between the active compound acarbose and the glycogen synthase kinase – 3

Figure - 4: Receptors and ligand interaction of glycogen synthase kinase – 3 (1UV5) protein data with 5 compounds

4. DISCUSSION

Molecular docking is an effective and competent tool for *in silico* screening and plays an important and ever-increasing role in rational drug design. Docking is a computational procedure of searching for an appropriate ligand that fits both energetically and geometrically the protein's binding site [8]. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes [9].

In the current research four proteins such as pyruvate dehydrogenase kinase (PDB: 5J71), human 11-beta-hydroxysteroid dehydrogenase (HSD1) (PDB: 2IRW), glucagon-like peptide-1 (PDB: 3IOL) and glycogen synthase kinase – 3 (PDB: 1UV5) were selected as drug targets for antidiabetic activity, their binding sites and 3D structures of interaction were determined using Autodock 4.2 software.

For pyruvate dehydrogenase kinase, the ligand β-sitosterol-β-D-glucoside isolated from *Barleria cuspidata* showed the highest docked binding energy of -8.43 Kcal/mol on compared to other isolated phytoconstituents and that of standard. Also forms four hydrogen bond interaction with four amino acids. Similarly the other ligands isolated from *Barleria buxifolia* and *Barleria cuspidata* such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside and luteolin 7-O-glucoside shows the good docked binding energy of -5.96, -5.31 and -6.96 Kcal/mol respectively. The standard compound acarbose exhibited -2.28 Kcal/mol.

For human 11-beta-hydroxysteroid dehydrogenase, the ligand β-sitosterol-β-D-glucoside isolated from *Barleria cuspidata* showed the highest docked binding energy of -11.41 Kcal/mol on compared to other isolated phytoconstituents and that of standard. Also forms two hydrogen bond interaction with two amino acids. Similarly the other ligands isolated from *Barleria buxifolia* and *Barleria cuspidata* such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside and luteolin 7-O-glucoside shows the good docked binding energy of -7.26, -4.62 and -6.77 Kcal/mol respectively. The standard compound acarbose exhibited -5.39 Kcal/mol.

For glucagon-like peptide-1, the ligand β-sitosterol-β-D-glucoside isolated from *Barleria cuspidata* showed the highest docked binding energy of -8.2 Kcal/mol on compared to other isolated phytoconstituents and that of standard. Also forms two hydrogen bond interaction with two amino acids. Similarly the other ligands isolated from *Barleria buxifolia* and *Barleria cuspidata* such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside and luteolin 7-O-glucoside shows the good docked binding energy of -6.34, -2.65 and -6.18 Kcal/mol respectively. The standard compound acarbose exhibited -2.98 Kcal/mol.

For glycogen synthase kinase – 3, the ligand β-sitosterol-β-D-glucoside isolated from *Barleria cuspidata* showed the highest docked binding energy of -8.88 Kcal/mol on compared to other isolated phytoconstituents and that of standard. Also forms three hydrogen bond interaction with three amino acids. Similarly the other ligands isolated from *Barleria buxifolia* and

Barleria cuspidata such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside and luteolin 7-O-glucoside shows the good docked binding energy of -7.44, -5.37 and -8.22 Kcal/mol respectively. The standard compound acarbose exhibited -2.23 Kcal/mol.

The above outcomes will reveal that the isolated four phytoconstituents from *Barleria buxifolia* and *Barleria cuspidata* such as quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside and luteolin 7-O-glucoside are effectively interacted with antidiabetic drug target proteins such as pyruvate dehydrogenase kinase, human 11-beta-hydroxysteroid dehydrogenase, glucagon-like peptide-1 and glycogen synthase kinase – 3. These results will promote the additional research to know the exact mechanism of action for its antidiabetic activity. With the conformations of docking binding score for the isolated compounds they may be use as antidiabetic drugs.

5. CONCLUSION

Among the *in silico* docking study for isolated phytoconstituents from *Barleria buxifolia* and *Barleria cuspidata*, the steroid such as β-sitosterol-β-D-glucoside has superior affinity with well known diabetic targets. All the remaining ligands also shows the best docking binding energy with the targets when contrasted with the used standard acarbose. This efferts will choose for further study and chemical sysnthesis as antidiabetic drugs for the management of diabetes mellitus. In future it may lead to the development of innovative quercetin-3-O-β-D-glucoside, 7-methoxy diderroside, β-sitosterol-β-D-glucoside and luteolin 7-O-glucoside agonists for antidiabetic activity.

6. ACKNOWLEDGEMENT

The authors are sincerely thankful to the administration of GITAM (deemed to be university), Vishakhapatnam and management of P. Rami Reddy Memorial College of Pharmacy, Kadapa, Andhra Pradesh, India, for giving vital offices to complete the research work.

7. FINANCIAL SUPPORT

The authors announce that they have no financing support for this investigation.

8. CONFLICT OF INTEREST

The authors declared that there was no conflict of interest in this research.

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