In silico molecular docking studies and MM/GBSA analysis of Apigenin derivatives by using different proteins to get Antidiabetic potential against type-II Diabetes Mellitus

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Abstract

Background: The biomarkers for diabetes mellitus are numerous. For the treatment of Diabetes Mellitus, there is higher expression of PPAR-gamma, SGLT2, GLP-1, and their upregulated form; consequently, numerous medications were developed that target this protein. The FDA recently approved Vildagliptin's ability to inhibit DPP-IV enzyme (PDB ID-6B1E) in people with diabetes. By computational analysis, we have used Vildagliptin and Twenty Apigenin derivatives against this protein and seven additional proteins that are implicated for DM. For our in silico docking analysis, we used Schrödinger Maestro 2020-3 version, and primary MM-GBSA module was used to determine the relative binding energies of the ligands.

Result: Docking study revealed that among all 20 compounds, DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, DPAA16 showed the highest G score than the Vildagliptin against DPP-IV with –10.034, −7.145, − 7.386, − 7.264, 11.212, -8.896 and -9.397 kcal/mol respectively, along with individual G score of Vildagliptin (− 4.86). Prime MM-GBSA analysis gave the relative binding energies of Vildagliptin to 6B1E as –31.07 kcal/mol compared with best-docked compound DPAA12 with −34.86 kcal/mol sequentially.

Conclusion: This study sheds light on the Apigenin derivatives that, like Vildagliptin, may function as DPP-IV enzyme inhibitors. Ligand binding energies and ligand strain energies were discovered via additional primary MM-GBSA research.

Keywords: Apigenin, MM-GBSA, G score, Vildagliptin, Binding energy, 6B1E

1. Background

A metabolic endocrine illness known as diabetes mellitus, it has been called one of the biggest worldwide health emergencies of the twenty-first century. It is one of the main health issues that Africans face. Clinical failures continue to be encountered with diabetes management. Many pharmacological treatments are available to manage and control diabetes, but complete remission from the disease has proven elusive[1]. The majority of patients cannot easily afford the expensive, traditional synthetic anti-diabetic medications that are now available to manage the disease. As a result, many patients now turn to medicinal plants as an alternative form of diabetes treatment, and several of these plants have been found to have powerful anti-diabetic effects. At than 25 different medical disorders are treated with Newbouldia leaves (P. Beaux, Bignoniaceae) in traditional medicine in tropical Africa[2]. The plant's active components and leaf extract have recently been discovered to have antihyperglycemic properties. In the current investigation, we looked into the anti-diabetic properties of a substance isolated from the N. leaves leaf extract's active methanol fraction [3]. Since it was discovered that apigenin is an edible, plant-derived flavonoid with no toxicity, scientists have become quite concerned [4]. Apigenin's poor bioavailability is caused by its low water solubility, which hinders its development. In order to increase its bioavailability, new derivatives must be developed through structural change [5].

Injections of insulin and oral hypoglycemic medications are the major treatments for diabetes. Insulin injections and the oral administration of synthetic hypoglycemic medications such sulfonylureas, biguanides, glinides, glycosidase inhibitors, and thiazolidinedione derivatives are two common Western medical treatments for diabetes [6,7]. All of these drugs do, however, have particular harmful side effects, and long-term insulin administration reduces insulin

receptor sensitivity, which then results in insulin resistance and ultimately deteriorates control conditions [8]. Now, a number of new targeted medications, including SGLT-2 inhibitors, GLP-1 analogues, and DPP-4 inhibitors, have been created and are available on the market. The expensive cost of these medications, however, makes it impossible to meet the enormous demand from diabetes patients and restricts their use in clinical settings [9]. As a result, more and more research is being done to create hypoglycemic medications that are safer and more affordable [10,11]. Many studies on the hypoglycemia effects of natural goods or traditional Chinese medicine (TCM) have been conducted recently, and natural products are now a crucial source of safe and efficient hypoglycemic medications [12]. Consuming these bioactive substances in combination as natural goods is advantageous and safe since cofactors or other nearby biomolecules balance out each other's negative effects and are therefore regarded as safe. More than 5000 naturally occurring flavonoid chemicals have been identified, and flavonoids are frequently prevalent in plants. High pharmacological activity can be seen in these natural compounds[13,14,15]. Many biological actions, including anti-oxidant, anti-tumor, anti-cardiocerebrovascular disease, and anti-inflammatory properties, are present in these substances. Many studies have demonstrated that flavonoids have powerful anti-diabetic properties that include lowering blood sugar levels, blocking -glucosidase, preserving the pancreas, and reducing the risk of developing diabetes[16].

Natural foods, which are allegedly viable options for the management of diabetes, can lessen the risk of developing diabetes. A secondary class of flavonoids called apigenin, which is non-mutagenic, is distinguished by a slight degree of toxicity [17]. Anti-inflammatory, antioxidant, and anti-cancer properties of apigenin are well recognized. It also contains anti-oxidative stress and anti-DNA damage properties [18]. In addition, by reducing the production of reactive oxygen species, it can inhibit the oxidative stress that hydrogen peroxide causes to cause melanin to apoptose. By in silico analyses and comparisons of both sets of ligands with conventional Vildagliptin and Sitagliptin, our study analysis helped to shed light on the possible antidiabetic properties of these molecules. As a result, the information for the current study was gleaned from Table 1 Various proteins increased in DM and their respective PDB diverse Apigenin derivatives [19,20]. 20 compounds underwent docking research against 8 DM activated proteins. Also, a docking investigation of all 20 ligands is conducted after choosing the DPP-IV (PDB ID-6B1E) protein out of a total of 8 proteins [21]. To compare the docking results with our compounds, this protein was also docked with coumarin and its recognized inhibitor [22]. Because in silico molecular docking studies take less time, can be completed with numerous ligands, and make it simple to compare ligand scores, they promote creativity in the synthesis of novel medications [23].

With the interpretation of the behavior of the compounds in various solutions, the in-silico investigations also contribute to the knowledge of the solvation effect, molecular dynamic simulation, and molecular electrostatic potential studies [24]. The identification of medications with success stories depends heavily on in silico computational screening. The work's goals are to investigate how Apigenin derivatives affect diabetes using computational molecular docking and to use the prime MM-GBSA method to predict the relative binding free energies and energy characteristics of each ligand, receptor, and complex structure that contributes to total binding energies.

2 Methods

2.1 Selection of proteins for docking

The following proteins are closely associated with DM, according to literature review: GLP-1[25], DPP-IV[26], GPR119[27], GPR40[28], SGLT2[29], PPAR-GAMMA[30], GLUT-4[31], and PTP-1B[32]. Table 1 lists the 3D structural proteins together with their corresponding protein data bank (PDB) IDs. The protein pre-process module of Schrödinger Maestro 2020-3 version was applied to all the proteins specified after they were all downloaded from PDB [33].

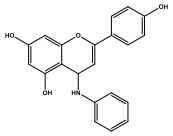
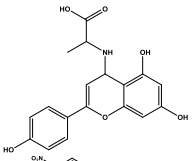
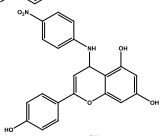
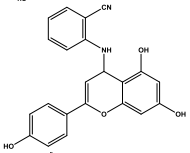
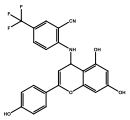
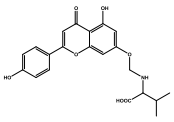
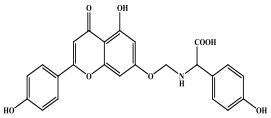
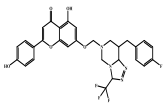
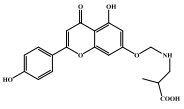
Table 1:Different Proteins upregulated in Diabetes Mellitus and their respective PDB IDs:

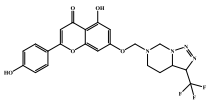
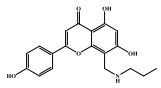
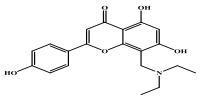
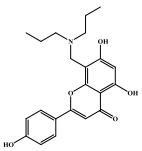
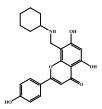
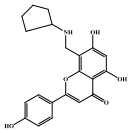
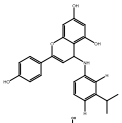
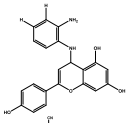
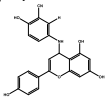
S. No	Proteins	PDB ID
1	GLP-1	3IOL
2	DPP-IV	6B1E
3	GPR119	7XZ5
4	GPR40	5TZR
5	SGLT2	7VS1
6	PPAR-Gamma	4Y29
7	GLUT-4	4XLV
8	PTP-1B	2QBP

Table 2: Schrödinger Maestro Docking score (kcal/mol) of compounds against selected up regulated proteins in DM

Compounds	DPP-IV (6B1E)	GLP-1 (3IOL)	GPR-119 (7XZ5)	GPR-40 (5TZR)	SGLT2 (7VS1)	PPAR-Gamma (4Y29)	GLUT-4 (4XLV)	PTP-1B (2QBP)
DPAA1	-5.742	-3.130	-8.489	-8.068	-7.251	-9.752	-4.986	-3.514
DPAA2	-6.013	-2.106	-5.515	-4.652	-9.422	-11.055	-7.999	-6.303
DPAA3	**10.034**	-2.809	-3.319	-8.441	-2.811	-9.964	-8.157	-4.191-
DPAA4	-5.031	-3.193	-4.591	-6.569	-7.122	-10.135	-7.532	-5.046
DPAA5	**-7.145**	-4.032	-5.775	-6.946	-8.246	-10.923	-7.794	-4.628
DPAA6	**-7.386**	-4.089	-8.295	-9.010	-9.771	-10.279	-7.524	-7.429
DPAA7	**-7.264**	-3.719	-4.236	-10.535	-9.422	-11.840	-5.412	-5.576
DPAA8	-6.362	-3.750	-7.709	-9.678	-7.568	-9.912	-7.985	-4.630
DPAA9	-6.044	-4.182	-7.674	-7.428	-6.259	-9.372	-9.385	-6.564
DPAA10	-4.454	-2.516	-8.538	-7.717	-8.881	-4.728	-8.016	-4.217
DPAA11	-4.225	-3.437	-6.374	-9.339	-7.908	-8.394	-7.967	-4.690
DPAA12	**-11.212**	-2.990	-5.515	-4.332	-6.192	-8.286	-6.741	-4.568
DPAA13	**-8.896**	-2.540	-3.684	-4.178	-6.192	-9.159	-6.988	-4.586
DPAA14	-6.224	-2.044	-4.455	-4.798	-9.689	-10.380	-7.278	-3.847
DPAA15	-6.505	-2.972	-3.914	-5.608	-8.855	-9.326	-7.985	-4.372
DPAA16	**-9.397**	-2.988	-1.582	-7.743	-6.526	-10.597	-5.422	-5.160
DPAA17	-6.172	-3.869	-5.632	-6.876	-8.136	-9.942	-7.921	-6.387
DPAA18	-6.111	-3.615	-3.859	-4.530	-8.179	-10.017	-8.410	-4.995
DPAA19	-6.013	-2.137	-4.941	-7.989	-8.578	-11.134	-6.850	-2.674
DPAA20	-4.384	-3.155	-4.530	-7.930	-7.522	-8.658	-6.580	-4.055
Sitagliptin	-5.63	-2.747	-9.873	-9.332	-7.513	-8.658	-5.329	-4.293
Vildagliptin	-4.86	-1.441	-8.998	-4.135	-7.037	-8.107	-4.892	-3.841

Table3: Apigenin derivatives with their chemical name and structure respectively:

Compounds	Structure	Chemical name
DPAA1		2-(4-hydroxyphenyl)-4-(phenylamino)-4H-chromene-5,7-diol
DPAA2		(5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-yl)alanine
DPAA3		2-(4-hydroxyphenyl)-4-((4-nitrophenyl)amino)-4H-chromene-5,7-diol
DPAA4		2-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-yl)amino)benzonitrile
DPAA5		2-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-yl)amino)-5-(trifluoromethyl)benzonitrile
DPAA6		(((5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)methyl)valine
DPAA7		2-((((5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)methyl)amino)-2-(4-hydroxyphenyl)acetic acid
DPAA8		7-((8-(4-fluorobenzyl)-3-(trifluoromethyl)-3,7,8,8a-tetrahydro-[1,2,4]triazolo[4,3-c]pyrimidin-6(5H)-yl)methoxy)-5-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
DPAA9		3-((((5-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-7-yl)oxy)methyl)amino)-2-methylpropanoic acid

DPAA10		5-hydroxy-2-(4-hydroxyphenyl)-7-((3-(trifluoromethyl)-3,3a,4,5-tetrahydro-[1,2,3]triazolo[1,5-c]pyrimidin-6(7H)-yl)methoxy)-4H-chromen-4-one
DPAA11		5,7-dihydroxy-2-(4-hydroxyphenyl)-8-((propylamino)methyl)-4H-chromen-4-one
DPAA12		8-((diethylamino)methyl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
DPAA13		8-((dipropylamino)methyl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
DPAA14		8-((cyclohexylamino)methyl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
DPAA15		8-((cyclopentylamino)methyl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
DPAA16		2-(4-hydroxyphenyl)-4-((3-isopropylphenyl)amino)-4H-chromene-5,7-diol
DPAA17		2-(4-hydroxyphenyl)-4-((2-hydroxyphenyl)amino)-4H-chromene-5,7-diol
DPAA18		4-((2-aminophenyl)amino)-2-(4-hydroxyphenyl)-4H-chromene-5,7-diol
DPAA19		5-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-yl)amino)-2-hydroxybenzonitrile
DPAA20		4-((4-amino-3-nitrophenyl)amino)-2-(4-hydroxyphenyl)-4H-chromene-5,7-diol

2.2 Preparation of proteins for docking:

Protein preparation wizard was used to create all 8 of the proteins that were used for docking. Hydrogen bond assignments, bond ordering, hydrogen additions, protein optimization, protein minimization, and the removal of waters from the het group that were more than number 5 were

all part of the preparation. Using Sitemap tool analysis, highly prospective binding sites for ligands on proteins were identified. Grids for protein receptors were produced by the Glide application (assignment of ligand binding site for docking). Also, the ligand docking module of glide was used to dock each ligand. Glide score visualisation utilised extra-precision (XP-visualizer module) (G score). In Table 2, [34], the docking results of the DPAA series (1 to 20) with all 8 proteins are succinctly shown.

2.3 Preparation of ligands:

Schrödinger Maestro software is used to prepare the 20 ligands' 3D structures. Using the OPLS-2005 force field module, all ligands were minimized. Table 3 lists each ligand structure along with its corresponding chemical name. Using ESP atomic charges from the OPLS2005 force field, the electrostatic potential values plotted on the surface of ligands are shown in Fig. 1 [35].

2.4 Prime MM-GBSA

The relative binding-free energy (G bind) of each ligand molecule was determined using the prime MMGBSA method. The results are shown in Table 4.

The expanded formula is provided below: Where: G(bind) = G(solv) + E(MM) + G(SA)

- Gsolv is the difference between the PIK3CA-inhibitor complex's GBSA solvation energy and the total of the solvation energies of the complex's unliganded PIK3CA and inhibitor.
- EMM is the difference between the energies of the unliganded PIK3CA and inhibitor and the energies of the PIK3CA-inhibitor complex.
- The GSA is the difference between the surface area energy of the complex and the total of the surface area energies of the PIK3CA and inhibitor when they are not liganded.

The energy of optimal free receptors, free ligand, and a complex of the ligand and a receptor are all calculated by prime MM-GBSA. By putting the ligand in a solution that was automatically created by the VSGB 2.0 suit, it also estimates the ligand strain energy. The visualization of energy was offered by the primary energy visualizer [36].

Table4: The relative binding free energies (Kcal/mol) obtained by Prime MM-GBSA, where MMGBSA dg Bind = Complex – Receptor- Ligand and MMGBSA dg Bind(NS) = Complex – Receptor(from optimized complex)- Ligand (from optimized complex)=MMGBSA dg Bind – Receptor strain- Ligand Strain. NS in the table is no strain: it is the binding energy without considering for the receptor and ligand conformational changes needed for the formation of complex:

Compound	MMGBSA dg-Binding energy	MMGBSA dg-Bind in Coulomb	MMGBSA-dg-bind (NS)	MMGBSA dg-Bind (NS)in Coulomb
DPAA1	-36.62	-16.98	8.01	-13.80
DPAA2	-35.56	-26.39	8.25	-24.89
DPAA3	**-34.13**	-29.16	6.72	-16.38
DPAA4	-35.33	-26.41	8.29	-17.83
DPAA5	**-46.04**	-27.11	2.2	-15.78
DPAA6	**-40.95**	-33.61	7.16	-20.68
DPAA7	**-34.25**	-23.51	2.1	-2.75
DPAA8	-39.75	-24.87	7.5	-10.22
DPAA9	-26.96	-13.13	5.96	-21.59
DPAA10	-29.16	-27.16	3.07	-18.81
DPAA11	-27.42	-35.27	3.8	-20.64
DPAA12	**-34.86**	-24.61	5.84	-23.24

DPAA13	**-37.76**	-31.93	2.66	-5.85
DPAA14	-34.23	-25.76	6.72	-24.22
DPAA15	-39.61	-11.82	7.21	-14.82
DPAA16	**-41.08**	-21.03	2.81	-19.45
DPAA17	-3.021	-30.81	7.81	-17.67
DPAA18	-37.08	-26.1	2.61	-24.97
DPAA19	-35.16	-17.03	7.36	-36.45
DPAA20	-30.16	-37.23	10.08	-13.47
Sitagliptin	-33.79	-20.31	3.05	-18.2
Vildagliptin	-31.07	-32.05	0.02	-10.85

3. Results:

Various molecular changes in different types of genes cause DM. There are many identified biomarkers for DM. In our study, we used 8 upregulated proteins in DM against 20Apigenin derivatives. The accomplishment of all 8 proteins receptor grid generation using SiteMap module predicted the top three binding sites for ligands on proteins surfaces. Our present work considered the greatest G score exhibiting receptors of the respective protein. Among all proteins, 6B1E has shown the highest G score from DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, DPAA16 compounds. As a screening result, we identified greater binding energy for DPP-IV protein. Evidently, DPP-IV enzyme leads to very fast degradation of incretin hormones due to their short half-life of 1-2 min which leads to decrease in insulin concentration and thereby increase in sugar level. Hence, inhibition of DPP-IV enzyme is an attractive target for numerous therapeutic approaches. The binding of all compounds to the active site of protein is given in Fig. 1. Vildagliptin is a known inhibitor of DPP-IV which was approved as a drug for Type-II by FDA. Therefore, in this study, we used 20Apigenin derivatives for docking study along with Vildagliptin, and the G score values are given in Table 5. Vildagliptin has a binding affinity G score of –4.86 kcal/mol with four hydrogen bonds (Fig. 2), against 6B1E protein. The best docked compound is DPAA12 with –11.212 kcal/mol. Out of 20compounds some compounds like DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, DPAA16have higher score than standard Vildagliptin except DPAA10,DPAA11,DPAA20 as depicted in Fig. 3,4, compound DPAA12and DPAA7 interacts with 6B1E more tightly than other compounds with H-bond of length 2.14 Å with GLU205,GLU206, TYR666 and Pi-Pi stacking between TYR547 residue which is again important for binding in active site. Prime MM-GBSA analysis revealed the binding energy ΔG of Vildagliptin to 6B1E as –31.07 kcal/mol compared with best-docked compound DPAA12 with −34.86 kcal/mol. Prime energy calculation analysis describes the relative binding energies of each molecule.

Table5: Schrödinger Maestro Docking score (kcal/mol) of compounds against DPP-IV enzyme (PDB ID: 6B1E)

Compound Name	G Score	Dock Score	Lipophilic score	H Bond Score
DPAA1	-5.742	-5.742	-2.44	-1
DPAA2	-6.013	-6.013	-2.08	-2.38
DPAA3	10.034	10.034	-2.48	-1.78
DPAA4	-5.031	-5.031	-2.5	-1.49
DPAA5	-7.145	-7.145	-1.49	-1.14
DPAA6	-7.386	-7.386	-3.03	-2.55
DPAA7	-7.264	-7.264	-3.23	-2.92
DPAA8	-6.362	-6.362	-3.21	-1.18
DPAA9	-6.044	-6.044	-2.73	-2.62
DPAA10	-4.454	-4.454	-2.32	-1.62

DPAA11	-4.225	-4.225	-1.98	-1.81
DPAA12	-11.212	-11.212	-0.98	-2.24
DPAA13	-8.896	-8.896	-1.69	-2.24
DPAA14	-6.224	-6.224	-2.06	-1.33
DPAA15	-6.505	-6.505	-3.87	-1.56
DPAA16	-9.397	-9.397	-3.45	-1.23
DPAA17	-6.172	-6.172	-1.92	-1.68
DPAA18	-6.111	-6.111	-2.55	-1.54
DPAA19	-6.013	-6.013	-2.45	-1.32
DPAA20	-4.384	-4.384	-2.43	-1.14
Sitagliptin	-5.63	-5.63	-1.87	-0.61
Vildagliptin	-4.86	-4.86	-1.8	-1.49

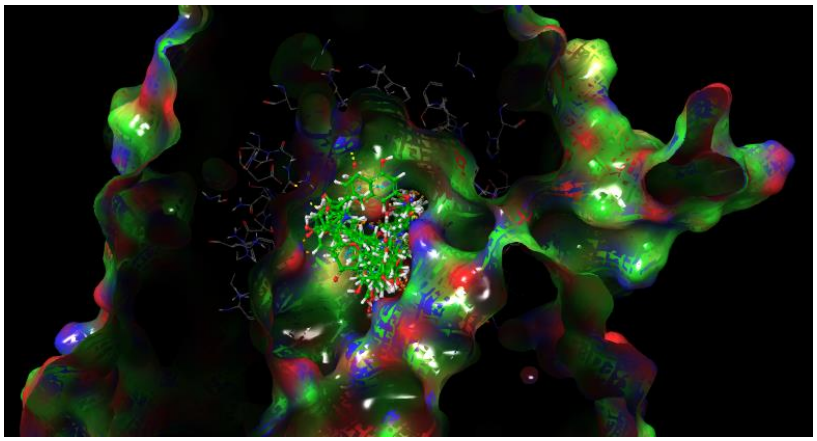


Fig.1:The figure depict interaction of all compounds with DPP-IV (PDB ID-6B1E) protein active site. Electrostatic potential value plotted surface of DPP-IV with the conformations of ligand compounds and crystal structure of proteins. The carbon atoms DPP-IV are coloured by magenta, cyan, and green, respectively (electropositive charge, blue; electronegative charge, red; and neutral, white)

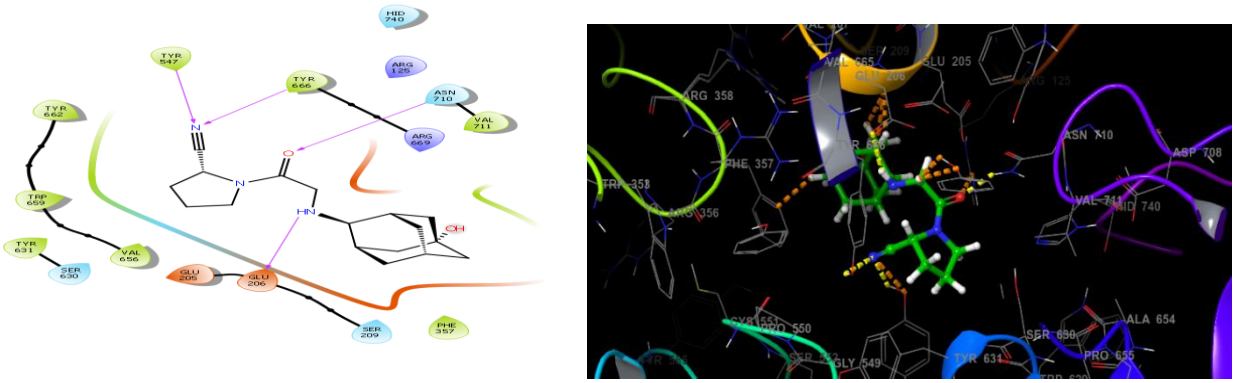
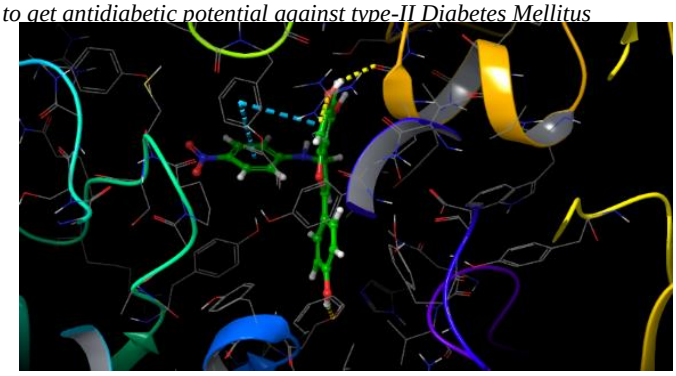
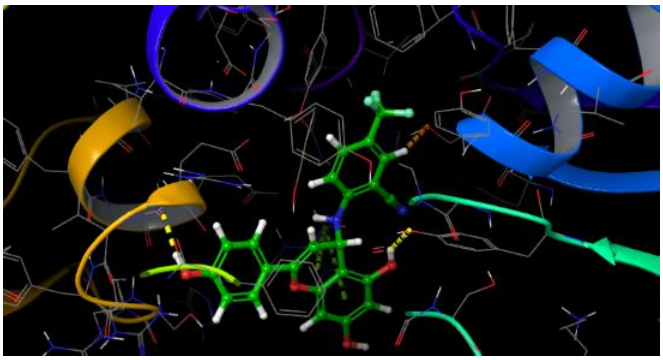


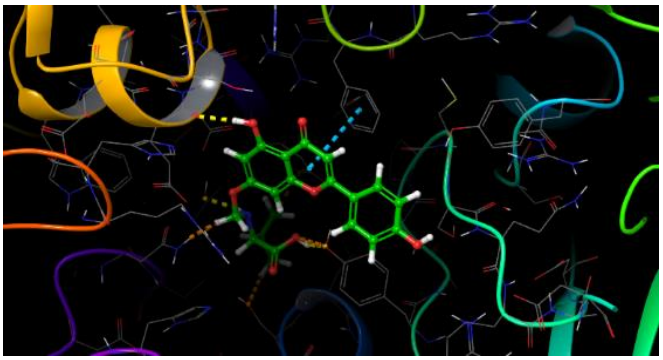
Fig. 2 Interaction of Vildagliptin with DPP-IV, both 3D and 2D diagrams, is given below with yellow dotted line represents H-bond.



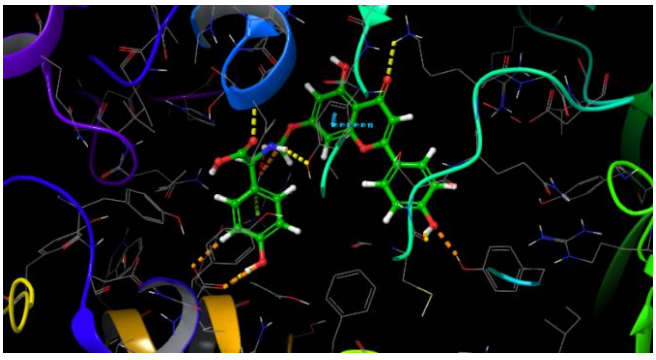
DPAA3



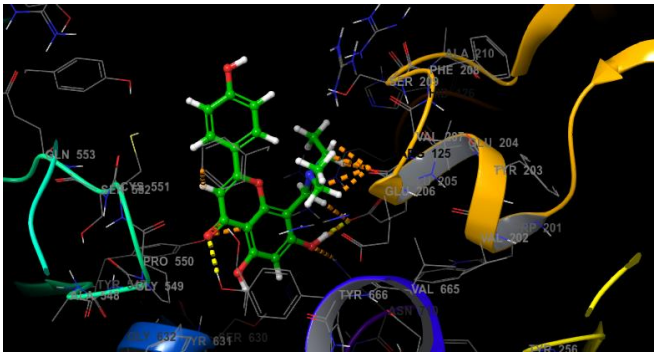
DPAA5



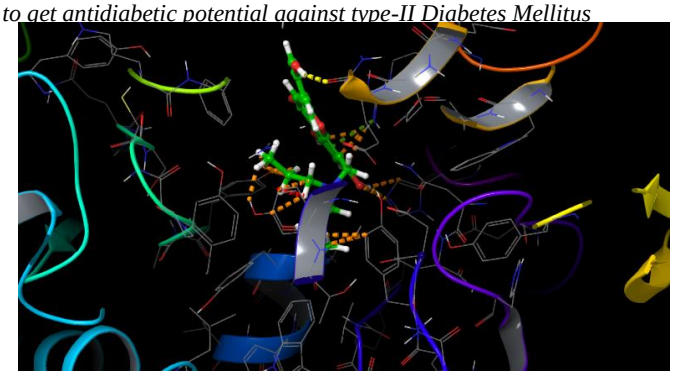
DPAA6



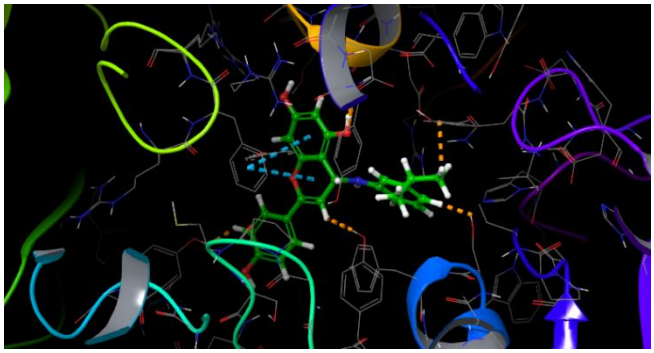
DPAA7



DPAA12

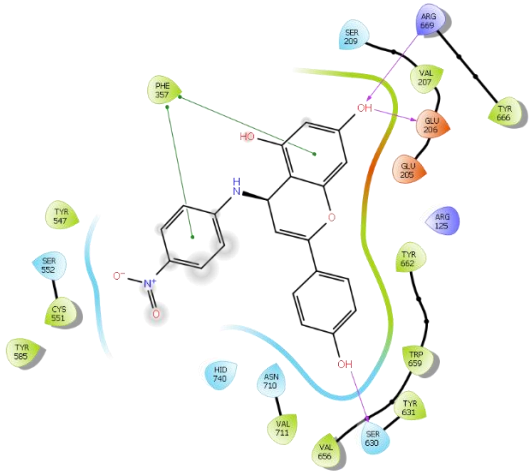


DPAA13

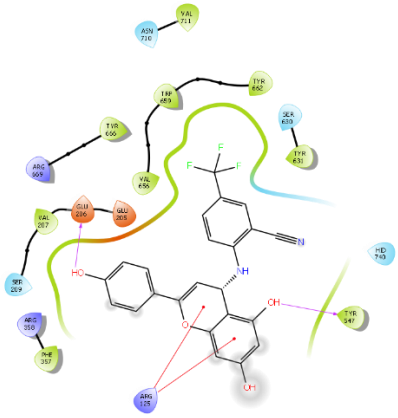


DPAA16

Fig.3 Interaction of DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, DPAA16respectively with DPP-IV, 3D diagrams is given below with yellow dotted line represents hydrogen bond sky blue dotted lines represents pi-pi stacking interaction.

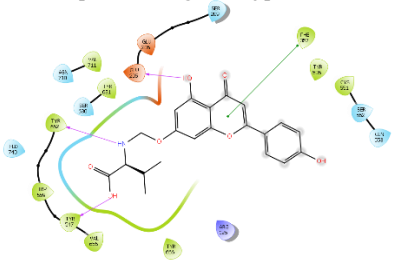


DPAA3

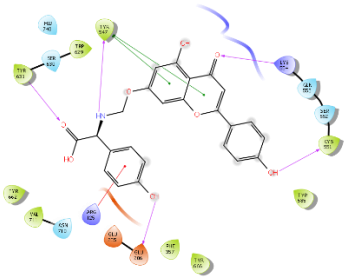


DPAA5

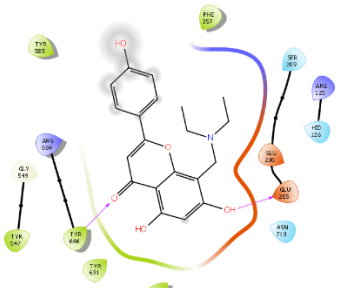
DPAA6



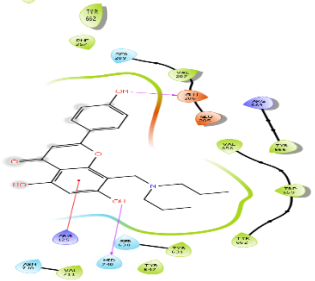
DPAA7



DPAA12



DPAA13



DPAA16

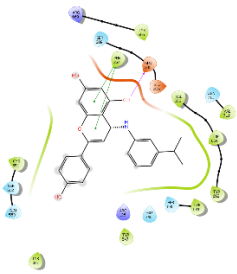


Fig.4 Interaction of DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, DPAA16 respectively with DPP-IV,2D diagrams is given.

4 Discussion:

Apigenin and its synthetic analogues have antibacterial, anti-inflammatory, and anticancer effects. A relatively common flavonoid known as apigenin has the ability to mimic insulin and increase insulin levels. In order to evaluate their potential as antidiabetic drugs through in silico analysis, our test included derivatives of apigenin. Some of these compounds scored higher on the G scale than Vildagliptin, the typical medication used to inhibit the DPP-IV protein. Seven of

them out of the total have a higher G score for one of the eight proteins, 6B1E. (Table 2). Although DPP-IV inhibitors were used to treat Type-II, our analysis revealed that the majority of derivatives had the H bonding interaction between chemicals and GLU (205, 206) amino acid residues of the protein as a result, the present study can be used to treat Diabetes Mellitus by inhibiting the DPP-IV enzyme.

5 Conclusion:

The binding energies of the ligands against the eight proteins were determined by molecular docking studies, and the majority of the compounds had higher G scores for DPP-IV. Of the 20 Apigenin derivatives, DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, and DPAA16 showed higher G scores than Vildagliptin, a well-known inhibitor of the DPP-IV protein. The binding energy calculations are improved using prime MM-GBSA analysis rather than by molecular docking energies. Following that, MM-GBSA research revealed the ligands' greater affinity to the receptors. Vildagliptin and compound DPAA12 had stronger binding to DPP-IV than other ligands, according to our findings. Consequently, it is beyond a doubt that the molecules DPAA3, DPAA5, DPAA6, DPAA7, DPAA12, DPAA13, and DPAA16 could be used as lead compounds when developing DPP-IV inhibitors.

Ethics approval and consent to participate:
Not applicable.
Human and animal rights:
No animals/humans were used for studies that are the basis of this research.
Consent for publication:
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Availability of data and materials:
Not applicable.
Funding:
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Conflict of interest:
The authors declare no conflict of interest, financial or otherwise.

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