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In silico Molecular Docking Studies of Some Phytochemicals against Dipeptidyl peptidase 4

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Abstract—
Background of study: *Dipeptidyl peptidase-4 (DPP-4) is an enzyme involved in degradation of both Gastric inhibitory polypeptide (GLP-1) and Glucagon-like peptide (GIP). The inhibition of this enzyme DPP-4 increases the level of insulin released and thereby decreases the blood glucose level by insulin mediated cell glucose transport mechanism. Therefore, it is a potential target for development of novel drug for treatment of type 2 diabetes.*
Objective: *To determine the potential of some phytochemicals to inhibit DPP4 enzyme*
Method: *Phytochemicals namely plumbagin, Quercetin, Isovitexin, mangiferin, Syringin, Lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione, Diosmetin and β sitosterol and sitagliptin a standard drug were docked against DPP4 using AutoDock vina, results were analyzed using binding energy.*
Results: *Among the phytochemicals (ligands) docked in this study, 5 namely; Tiliroside, Diosmetin, Purine-2, 6-dione, isovitexin, and mangiferin showed lower binding energy than the standard dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin*
Conclusion: *According to the findings of this study, Tiliroside, Diosmetin, Purine2, 6-dione, isovitexin, and mangiferin can serve as potential source of future antidiabetic drugs.*

Keywords— *Dipeptidyl peptidase-4, Phytochemicals, AutoDock vina*.

I. INTRODUCTION

Diabetes mellitus is a major health problem in the 21st century world-wide. According to the World Health Organization (WHO) about 200 million people all over the world are suffering from diabetes and about 80% of the deaths occur every year due to diabetes in middle-income countries. 90% of cases are of type 2 diabetes mellitus (T2DM) [1]. There is a growing line of antidiabetic drugs and therapies [2, 3]. Some of the receptors targeted for the treatment of type 2 diabetes include; glycogen phosphorylase, protein tyrosine phosphatase 1-beta (PTP-1β), dipeptidyl peptidase-IV (DPPIV), glucokinase, peroxisome proliferator activated receptor (PPAR-γ), aldose reductase (AR), insulin receptor (IR) [4]. Dipeptidyl peptidase-4 (DPP-4) is an enzyme mainly involved in rapid degradation of both GLP-1 and GIP. Hence it was a proven fact the inhibition of this enzyme DPP-4 prolongs the action of both GLP-1 and GIP hence it directly increases the level of insulin released and thereby decreases the blood glucose level by insulin mediated cell glucose transport mechanism [5]. Therefore, it is a potential target for development of novel drug for treatment of type 2 diabetes. The currently used DPP4 inhibitors include; sitagliptin and saxagliptin. However, there is still a need for more effective, safer and selective DPP4 inhibitor, which does not have the inspecificity and side effects possessed by the presently available inhibitors[6].Several isolated compounds from plants have been reported to have antidiabetic activity but the mechanism of action of their antidiabetic activity has not been investigated. Compounds including Mangiferin, Quercetin, Diosmetin, plumbagin, isovitexin and syringin have all been reported to have hypoglycemic activity [7]. Molecular docking is a key apparatus in computer-assisted drug design and development. Docking has been used to perform virtual screening on extensive libraries of compounds and propose basic theories of how the ligands bind with the target with lead optimization [8]. Protein–ligand or protein–protein docking plays an important role in predicting the orientation of the ligand when it is bound to a protein receptor or enzyme using shape and electrostatic interactions to quantify it [9]. The study was conducted in order to determine the potential of some phytochemicals to inhibit DPP4 enzyme.

II. METHOD

Protein Preparation

3D crystal structure of DPP-4 with RCSB PDB code: 1J2E was downloaded from Protein Data Bank (⟨http://www.rcsb.com) [10]. The protein for docking was prepared using the protein preparation wizard of Auto dock. The missing side chains, back chains, and residues were updated. Water molecules present in the crystal structure were removed in the protein preparation process.

Ligand Preparation

The ligands were imported from www.zinc15.org. The ligands imported include, plumbagin, Quercetin, Isovitexin, Syringin, Lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione,

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mangiferin, Diosmetin and β-sitosterol, Trigonelline and Tiliroside. Energy minimization was done using MMFF94 force field. Energy minimization is done to help the docking program for identifying the bioactive conformer from the local minima.

Molecular Modeling

AutoDock Vina was used for molecular docking Studies. Auto vina docking uses gradient based conformational search by grid box defined by the box center and its dimensions X, Y, Z [11]. The grid center was set at 76.48, 57.28 and 35.73 for X, Y, Z respectively. The spacing between the grid points was 1.0 Å. The grid points were set at 129.38, 73.36 and 90.44 for X, Y, Z respectively. Phytochemicals namely plumbagin, Quercetin, Isovitexin, mangiferin, Syringin, Lupe-20-ene-3-one, 7-(2-hydroxyethyl)-3-methyl-8-(1-phenylethylideneaminoamino) purine 2, 6-dione, Diosmetin and β sitosterol and sitagliptin a standard drug were docked against DPP4 using AutoDock vina, results were analyzed using binding energy. For each ligand, a docking experiment consisting of 100 stimulations was performed and the analysis was based on binding free energies and root mean square deviation (RMSD) values, and the ligand molecules were then ranked in the order of increasing docking energies. The binding energy of each cluster is the mean binding energy of all the conformations. The clusters were ranked by the lowest-energy representative of each binding mode.

III. RESULTS

TABLE 1. The properties of Ligands.

S/N	Ligands	Ligand code	Molecular formula	Molecular weight	Number of atoms
1	Trigonelline	ZINC00001082	$C_7H_7NO_2$	137.14	17
2	Tiliroside	ZINC17654711	$C_{30}H_{26}O_{13}$	594.52	69
3	Mangiferin	ZINC4098535	$C_{19}H_{18}O_{11}$	422.34	48
4	Quercetin	ZINC3869685	$C_{15}H_{10}O_7$	302.24	32
5	Syringin	ZINC3779261	$C_{17}H_{24}O_9$	372.37	50
6	Diosmetin	ZINC5733652	$C_{16}H_{12}O_6$	300.26	34
7	B-sitosterol	ZINC8681784	$C_{29}H_{50}O$	414.71	80
8	Purine2,6 dione	ZINC5218933	$C_{16}H_{18}N_6O_3$	342.35	43
9	Plumbagin	ZINC58187	$C_{11}H_8O_3$	188.18	22
10	Isovitexin	ZINC4095704	$C_{21}H_{20}O_{10}$	432.38	51
11	Sitagliptin	ZINC1489478	$C_{16}H_{16}F_6N_5O$	408.32	44

TABLE 2. Molecular Docking Studies Analysis of Phytochemicals against DPP-4.

S/N	Ligands	Energy of contact	Binding affinity Kcal/mole
1	Trigonelline	586.57	-5.2
2	Tiliroside	90.95	-10.2
3	Mangiferin	393.64	-8.6
4	Quercetin	275.03	-7.8
5	Syringin	375.80	-6.6
6	Diosmetin	238.34	-9.2
7	B-sitosterol	870.03	-8.4
8	Purine2,6 dione	493.01	-8.6
9	Plumbagin	127.17	-7.0
10	Isovitexin	420.45	-8.9
11	Sitagliptin	503.64	-8.4

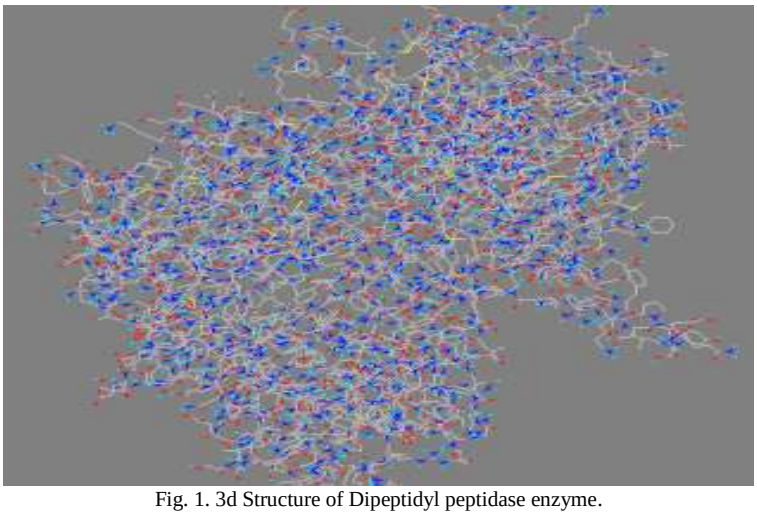

Fig. 1. 3d Structure of Dipeptidyl peptidase enzyme.

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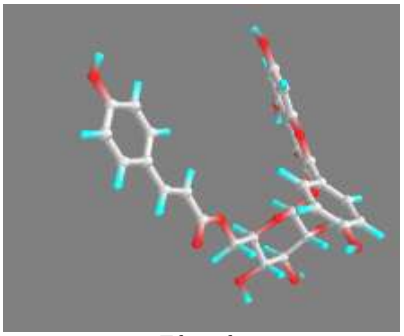
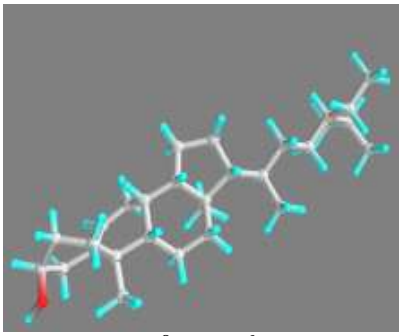
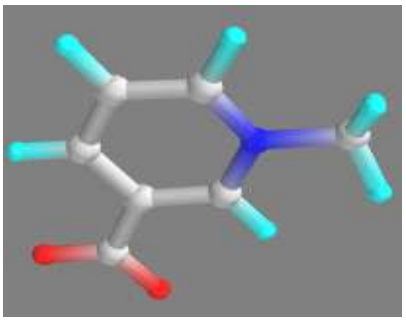
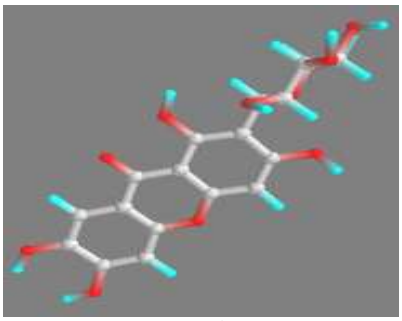
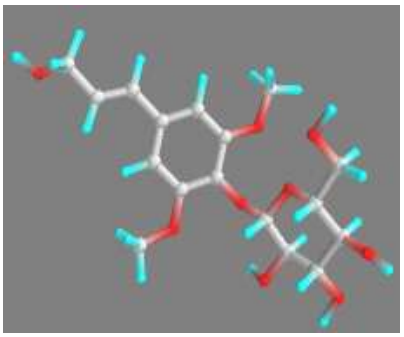
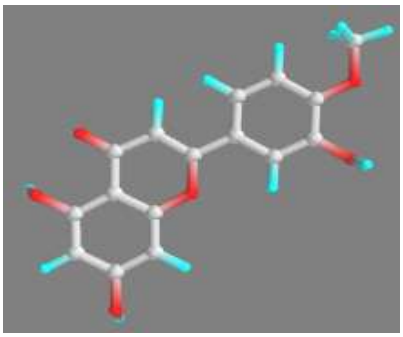

Tiliroside

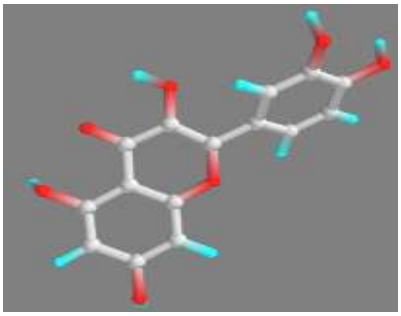

β-sitosterol

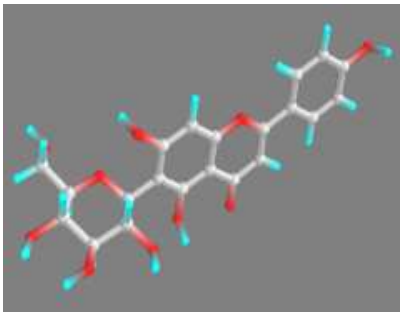

Trigonelline

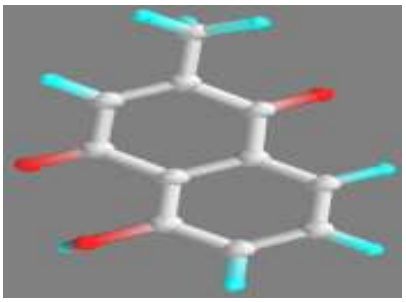

Mangiferin


Syringin


Diosmetin


Quercetin


Isovitexin


Plumbagin

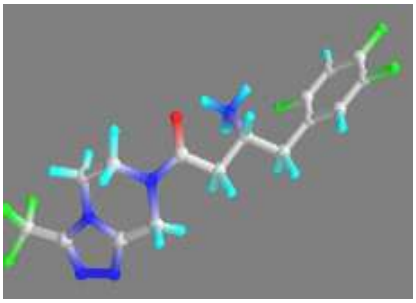

Sitagliptin

Fig. 2. 3D structures of the Ligands.

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IV. DISCUSSION

Molecular docking continues to be a promising area of computer based drug design which screens ligands by orienting and scoring them in binding site of a protein [12]. Protein–ligand docking plays an important role in predicting the orientation of the ligand when it is bound to a protein receptor or enzyme using shape and electrostatic interactions to quantify it. The van der Waals interactions also play an important role, in addition to Coulombic interactions and the formation of hydrogen bonds. The sum of all these interactions is approximated by a docking score, which represents potential of binding [9].The lower the binding energy the higher the binding capacity of the ligand [13]. Among the phytochemicals (ligands) docked in this study, 5 namely; Tiliroside, Diosmetin, Purine2, 6-dione, isovitexin, and mangiferin showed lower binding energy than the standard dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin as depicted in Table 2. These phytochemicals have potential antidiabetic activity via this mechanism.

V. CONCLUSION

According to the findings of this study, Tiliroside, Diosmetin, Purine2, 6-dione, isovitexin, and mangiferin can serve as potential source of future antidiabetic drugs.

Conflict of Interest statement
There is no conflict of interest

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