ORIGINAL ARTICLE

Identification of molecular targets of potential antidiabetic drugs using prediction of activity spectra for substances and molecular docking

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Abstract

Context: Diabetes mellitus is not a solitary sickness yet is a gathering of metabolic issue influencing countless on the planet. It is essentially described by incessant hyperglycemia because of deformities in insulin discharge or insulin activity. It is predicated that the quantity of diabetes individual on the planet could reach up to 366 million by the year 2030. Even though the instances of diabetes are expanding step by step, aside from insulin and oral hypoglycemic medications, no other method for treatment has been effectively grown up until now. **Objective:** In the present study, an initiative is tried to delineate the usefulness of prediction of activity spectra for substances (PASS) online software and molecular docking technique for providing new molecular ways of predicting new antidiabetic drug targets of potential phytoconstituents. **Materials and Methods:** In the study, important phytoconstituents having reported *in vitro* and *in vivo* antidiabetic activities have been reviewed. Among them, few phytoconstituents were selected for presenting to PASS online software. Pa and Pi value was predicted for these phytoconstituents on different antidiabetic target sites. Based on PASS prediction, five phytoconstituents were selected for molecular docking study using AutoDock Vina 4.0. Three target sites which were dipeptidyl peptidase-4 (DPP-4), glucagon-like peptide-1 (GLP-1), and α glucosidase were selected for prediction of probable affinities of these 5 selected phytoconstituents. **Result and Discussion:** Among these five constituents, diosmin showed best binding affinity with DPP-4, GLP-1, and α glucosidase that was −10.2 kcal/mol, −8.3 kcal/mol, and −9.7kcal/mol, followed by kaempferol. Results of the present study can be utilized for designing of further *in vitro* and *in vivo* antidiabetic studies for these phytoconstituents. **Conclusion:** This study suggested the usefulness of these software in predicting the probable antidiabetic targets sites of potential antidiabetic phytoconstituents.

Key words: Antidiabetic, hyperglycemia, hypoglycemia, molecular docking, phytoconstituents, prediction of activity spectra for substances

INTRODUCTION

Diabetes is the issue in which human body cannot make its own particular vitality.[1-12] Rather than getting transform into vitality, it gets changed over into sugar or supposed glucose. Pancreas is the organ which secretes the hormones called insulin which takes glucose into the phone into for vitality generation. If there should arise an occurrence of diabetes, the human system either do not secrete required insulin or is not able to utilize its own insulin extremely well. This outcome in the gathering of sugar in the blood that is the reason all called "sugar." This lack of insulin results in a condition Known as diabetes or in laymen dialect, it is known as "Sugar".[13-24] It might bring about different dangerous medical problems including heart issue, night visual deficiency, and renal dysfunctioning. This sickness is considered to be the seventh principal reason of death in The United States of America.[25]

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Type 1 also called insulin-dependent diabetes mellitus (IDDM) is the reason for 5–10% of every single announced case in most recent ten years. Risk factors are less settled for type 1 than for type 2 diabetes; however, immune system factors are engaged in the development of this type 1 diabetes.

Type 2, additionally known as non-IDDM. It is the real reason for 90–95% of every single detailed case in 10 years. Peril factors for Type 2 diabetes incorporate adult age, heftiness, and family vestige of diabetes.[19]

Another type of diabetes known as gestational diabetes advances in 2–5% of all pregnancies, however, generally vanish till the last time of gestation is gone. This happens all the more 3/4th part of the world and individuals with a domestic artifact of diabetes than in different gatherings. Pudginess is additionally connected with modern hazard.[21]

Prediction of activity spectra for substances (PASS) is applicable for distinctive pharmacological impacts, components of activity, and correct poisonous quality (mutagenicity, cancer-causing nature, teratogenicity, and embryotoxicity). The movement is generally reliant on the auxiliary idea of a compound. Naturally, dynamic substances have restorative and supplementary activities, the last noteworthy as reactions. These more up to date exercises of the compound give understanding to helpful applications.[3]

Atomic docking is an entrenched computational system which predicts the cooperation vitality between two particles. This strategy principally joins calculations such as sub-atomic progression, Monte Carlo reproduction, and piece based hunt strategies which are said in points of interest in later part. Atomic docking ponders are utilized to decide the collaboration of two particles and to locate the best introduction of ligand which would frame a complex with general least vitality. The little atom, known as a ligand, for the most part, fits inside protein's cavity which is anticipated by the inquiry calculation. These protein depressions wind up noticeably dynamic when they interact with any outer mixes and are accordingly called as dynamic locales. Docking is much of the time used to anticipate the coupling introduction of little particle medicate contender to their protein focuses on a specific end goal to foresee the fondness and movement of the little atom. Thus, docking assumes a critical part of the 158 normal medication outlines. Given the organic and pharmaceutical centrality of atomic docking, extensive endeavors have been coordinated toward enhancing the strategies used to anticipate docking. The outcomes are investigated by a measurable scoring capacity which changes over collaborating vitality into numerical esteems called the docking score; and furthermore, the communicating vitality is ascertained. The 3D stance of the bound ligand can be envisioned utilizing distinctive picturing apparatuses such as Pymol, Rasmol, and so on which could help in the surmising of the best attack of ligand. Foreseeing the method of protein-ligand association can accept the dynamic site of the protein atom and further help in protein explanation.[11]

MATERIALS AND METHODS

Analysis of phytoconstituents by PASS online software

PASS is a product item outlined as a device for assessing the general natural capability of a natural medication like a particle [Table 1 and 2]. PASS gives synchronous forecasts of many types of natural movement in view of the construction of natural mixes. Along these lines, PASS can be utilized to evaluate the natural movement profiles for virtual particles, before their concoction amalgamation and organic testing.

Procedure

A detailed hunt of existing literature based on the reported activities of phytoconstituents, Pa and Pi values were predicted for these constituents on different targets of diabetes. PASS online software was accessed from www.pharmaexpert.ru/passonline/predict.php/.

- Only the exercises for which Pa > Pi, i.e., higher Pa, have been considered for each phytoconstituent.
- If Pa > 0.7, the likelihood to get a comparable movement tentatively is apparently high; consequently, it is its shot being a simple of a current medication.
- If 0.5 < Pa < 0.7, the likelihood to acquire a comparative movement tentatively is generally less and the substance is probably going to be divergent from the current pharmaceutical specialists.
- If Pa < 0.5, the likelihood to discover the activity tentatively is lesser, however, the likelihood of finding another, basically comparative compound [Figure 1].[13]

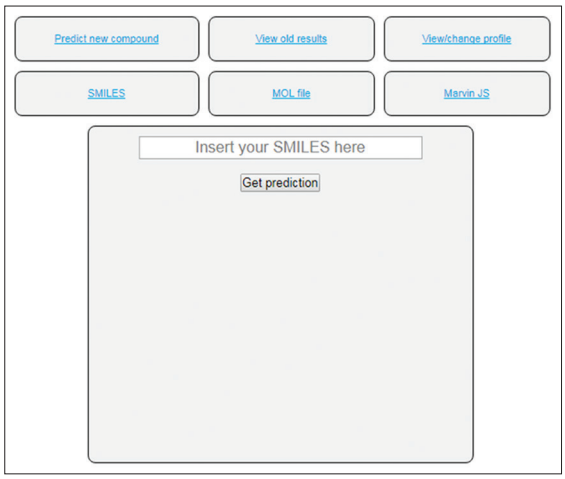

Figure 1: Tab on www.pharmaexpert.ru/ passonline/predict.php/.for prediction of activity spectra for substances prediction

Docking of classified phytoconstituents as per previous studies on common targets of diabetes

Overall steps involves

- Get the complex (CPLX) facilitates (i.e., from the PDB).
- Erase all the water and the dissolvable atoms and all noninteracting particles.
- Add the missing hydrogen's/side chain iotas and limited the mind-boggling (AMBER Program). 4. Clean the limited complex (erase all the water and the dissolvable atoms and all non-associating particles).
- Separate the limited CPLX in macromolecule (LOCK) and ligand (KEY).
- Prepare the docking reasonable records for LOCK and KEY (pdbqt. documents).
- Prepare all the requiring documents for docking (lattice parameter record, outline, and docking parameter records).
- Run the docking and break down the docking comes about.[9]

Diagrammatic representation of certain steps involved in docking of the molecules [Figures 2-6]

The Autodock Vina (ADT) 1.5.6 software was used to find out the binding affinity (Kcal/mol) of various ligands. This involved ligand preparation, protein preparation, validation and molecular docking at the binding site. In brief the 3D structures were drawn by ChemBioDraw software and optimized through energy minimization using MM2 method prior to ligand preparation. A DPP4 protein was selected and downloaded from Protein Data Bank. The protein was validated by internal ligands and docking was performed. Finally the results were analyzed for various interactions between ligand and target receptor by ADT.

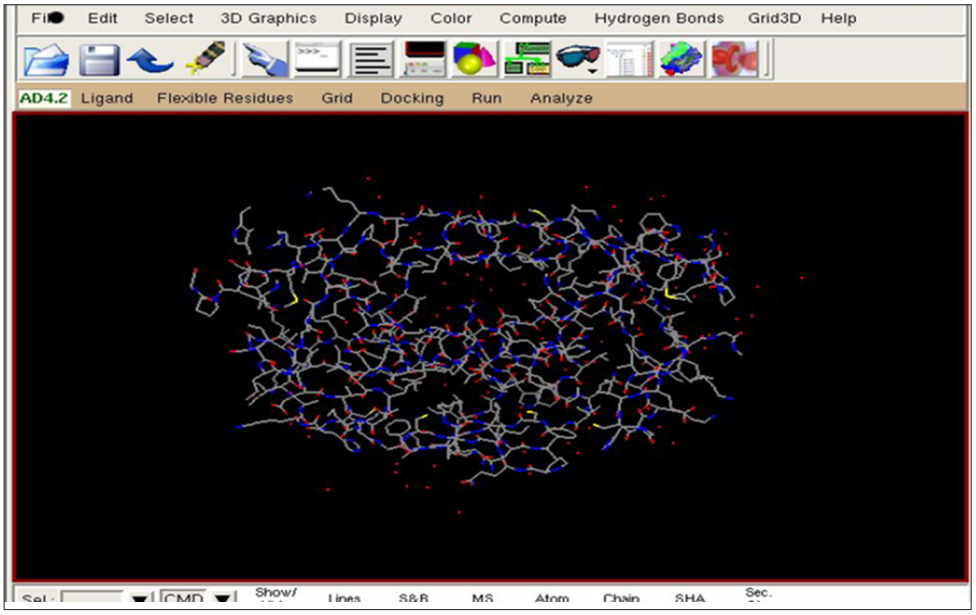

Figure 2: Representation of PDB file of the protein involved in docking studies

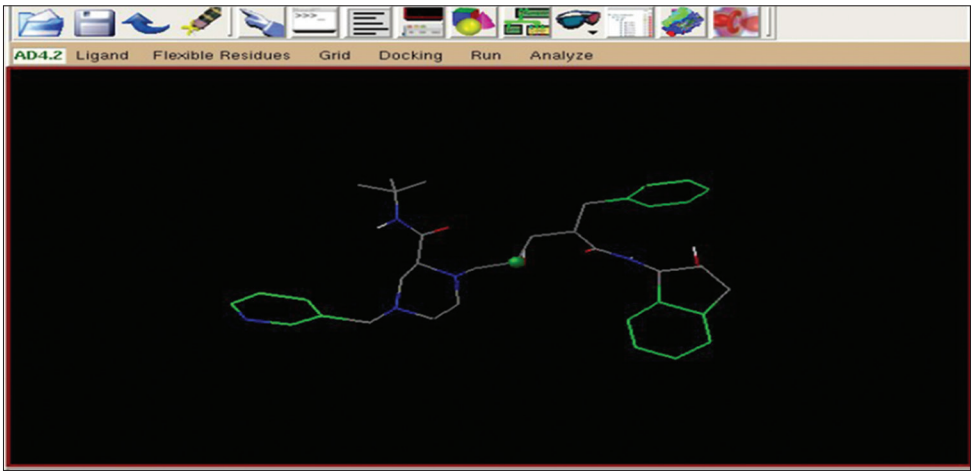

Figure 3: Representation of PDB of ligand involved in docking studies

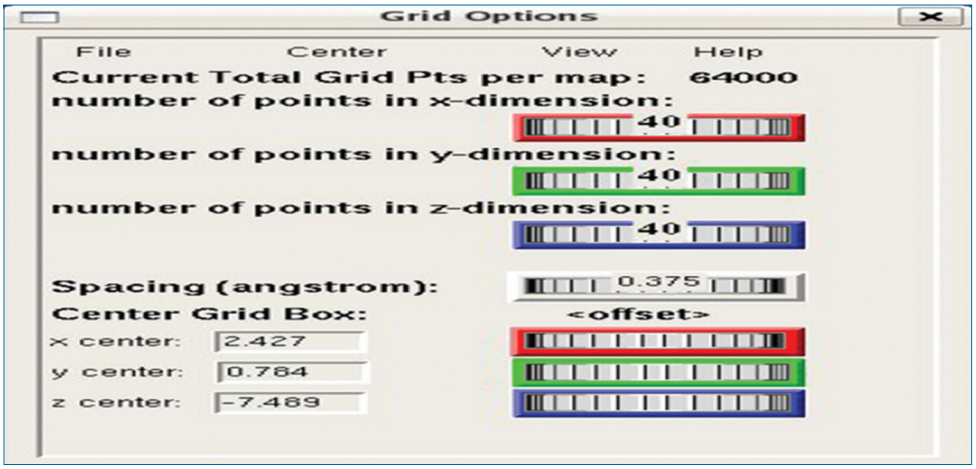

Figure 4: Representation of grid box in which center and spacing are obtained

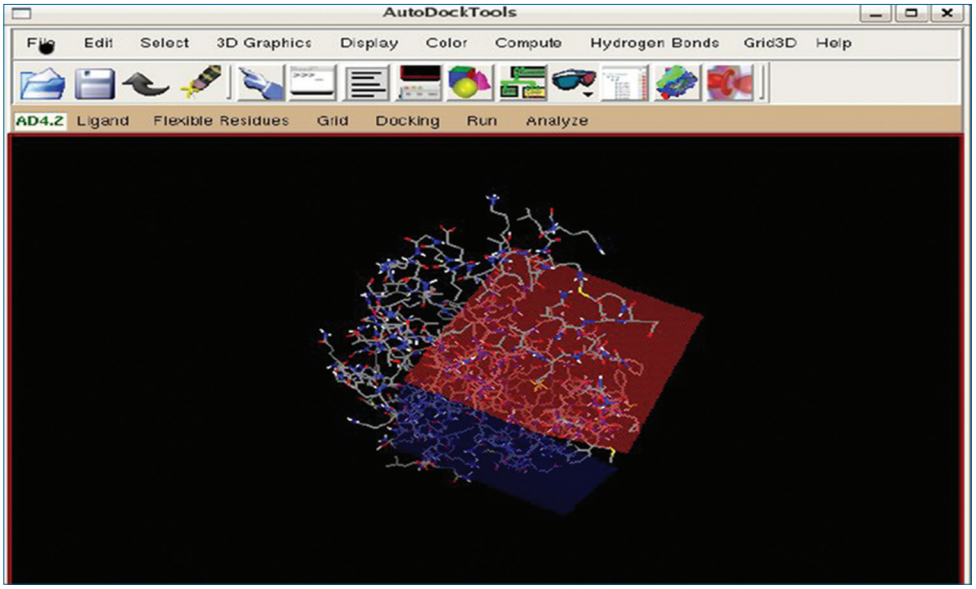

Figure 5: Representation of final ligand and protein interaction in pdbqt. format in docking studies

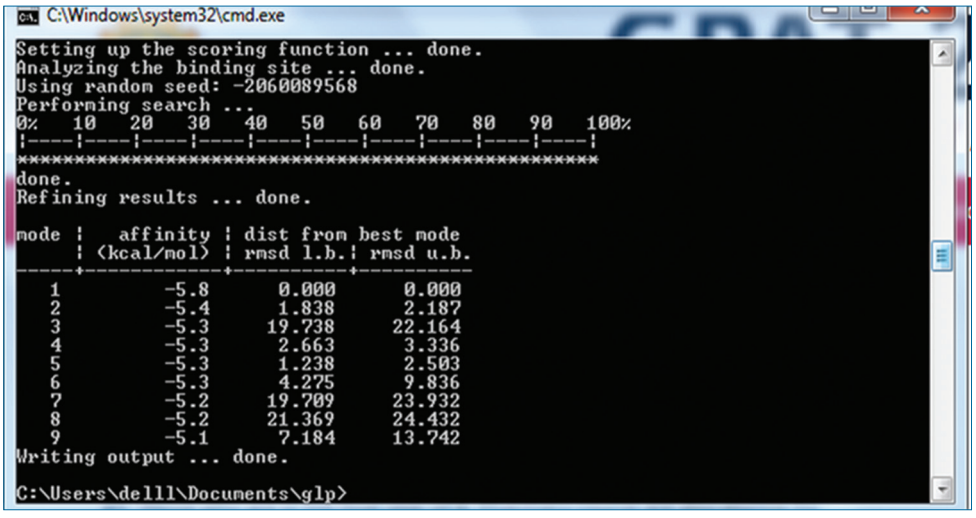

Figure 6: Representation of final result obtained, i.e, –5.8 in binding affinity of the drug with the receptor[23]

Overview of study being done on the common targets considered for docking of five phytoconstituents

Following are the targets being studied in this study which is mentioned below:

Dipeptidyl peptidase-4 (DPP-4)

Is a generally communicated biochemical transducing activities through a moored transmembrane particle and a solvent coursing protein. Both layers related and dissolvable DPP-4 apply reactant movement, dividing proteins containing a position 2 alanine or proline. DPP-4-intervened enzymatic cleavage, on the other hand, inactivates peptides or creates new bioactive moieties that may apply contending or novel exercises. The across the board utilization of particular DPP-4 inhibitors for the treatment of type 2 diabetes has increased enthusiasm for the sub-atomic instruments through which DPP-4 inhibitors apply their pleiotropic activities.[16]

Glucagon-like peptide-1 (GLP-1)

Is a hormone discharged in the gastrointestinal tract after dinners which animate insulin emission, hinders glucagon discharge, defers gastric exhausting, decreases sustenance allow, and standardizes fasting, and postprandial insulin emission. The GLP-1 agonists imitate these impacts. The GLP-1 receptor agonists are regulated subcutaneously and are shown in the treatment of type 2 diabetes mellitus.[22]

Alpha-glucosidase

Alpha-glucosidase is a compound which is the fundamental purpose behind this, and consequently, by utilizing its inhibitors, we can restrain the abundance of glucose creation. Alpha-glucosidase inhibitors assume a key part in stifling hoisted glucose fixation in blood. Great inhibitors are acarbose, voglibose, and miglitol which are as of now accessible in the market and use as medications.[5]

Table 1: Reported activities of antidiabetic phytoconstituent

Class	Compounds	Sources	Mode of actions
Flavone	Apigenin	Parsley Celery Oregano Thyme Basil	Beginning of ERK1/2
		Thyme Basil Coriander Chamomile Cloves	Weakens the manufacture of pro-inflammatory cytokines such as TNF-α[18]
	Diosmin	Lemon Orange Buddha fingers	Disabling of NF-κB Concealment of monocyte chemoattractant tumor rot factor[8]
Flavonol	Quercetin	Capers Onions Cranberries Blueberries Chokeberries	Reticence of NF-κB[15]
	Kaempferol	Tomatoes Pota Broccoli Brussels Sprouts Squash	AMPK beginning Modified insulin resistance[1]
	Eriodictyol	Lemons Mountain balm	Inhibits the NF-κB system[28]

(Contd...)

Table 1: *Continued*

Class	Compounds	Sources	Mode of actions
Flavanone	Naringenin	Grapefruit Oranges Tomatoes	Inhibits TNF-κB pathways[24]
	Hesperetin	lemon orange Peppermint Tangerine	Starting with NF-κB system[12]
	Baicalein	Parsley Cellery Capsicum Pepper	Overpowers fatty acid synthesis, β-oxidation[27]
	Chrysin	Skullcap Honey	Destruction of TNF-α manufacture and instigation of NF-κB start[2]
Flavonol	Catechin	Green tea Chocolate Beans Cherry	stimulation of NF-κB system through the inhibition cytokines constructions[17]
	Morin	Indian guava Green tea extract Almond	Lessen the promotion of inflammatory TNF-α[10]
Isoflavonoid	Genistein	Soy flour Soy milk Soybeans	Constrains the beginning of ERK and P38 phosphorylation[7]
Phenolic acid	Curcumin	Turmeric Curry powder Mango ginger	Conquest of ICAM-1 terminologies and ROS[26]
	Colchicine	Saffron Colchicum	Conquest of MCP-1 and ICAM-1 face[14]
Stilbene	Resveratrol	Grapes Wine Grape Peanuts Cocoa Berries	Regulates the COX-2[6]
	Emodin	Japanese knotweed	Conquer the instigation of NF-κB scheme[29]

Further studies were carried out on the commonly reported targets of reported phytoconstituents mentioned in table using PASS online software. TNF-α: Tumor necrosis factor alpha, NF-κB: Nuclear factor kappa B, AMPK: AMP-activated protein kinase, ROS: Reactive oxygen species, ICAM-1: Intercellular adhesion molecule-1, MCP-1: Monocyte chemoattractant protein-1, COX-2: Cyclooxygenase-2, PASS: Prediction of activity spectra for substances

RESULTS

Overall study of interaction of drug-protein interaction obtained by docking

Naringenin with DPP-4 [Figure 7]

- In Figure 7, there is 7 amino acid which is taking part in intermolecular bonding which is lysine, valine, tryptophan, tyrosine, glutamate, etc.
- In Figure 7, there is no hydrogen bond, hence, no hydrogen donor and acceptor, respectively

Red and blue color spheres will show hydrophilic and lipophilic interaction among each other by the representation of the red and blue sphere.

Apigenin with DPP-4

- In Figure 8, there is 8 amino acid which is taking part in intermolecular bonding which is lysine, valine, tryptophan, tyrosine, glutamate, arginine, aspartame, etc.
- In Figure 8, there is no hydrogen bond, hence, no hydrogen donor and acceptor, respectively
- Red and blue color spheres will show hydrophilic and lipophilic interaction among each
- Other by the representation of the red and blue sphere

Diosmin with DPP-4

- In Figure 9, there is 11 amino acid which is taking part in intermolecular bonding which is lysine, valine, tryptophan, tyrosine, glutamate histidine arginine, serine, glycine, etc.
- In Figure 9, there is two hydrogen bond represented in green color.
- Red and blue color spheres will show hydrophilic and lipophilic interaction among each other by the representation of the red and blue sphere.

Kaempferol with DPP-4

In Figure 10, there is 8 amino acid which is taking part in intermolecular bonding which is lysine, valine, tryptophan, tyrosine, glutamate, etc.

Table 2: Canonicals SMILES of selected phytoconstiuents for PASS prediction

Phytoconstituent	Smiles
Naringenin	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
Apigenin	C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
Diosmin	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=CC(=C4C(=C3)OC(=CC4=O)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Kaempferol	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Eriodictyol	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC(=C(C=C3)O)O
Hesperetin	COC1=C(C=C(C=C1)C2CC(=O)C3=C(C=C(C=C3O2)O)O)O
Baicalein	C1=CC=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)O)O)O
Chrysin	C1=CC=C(C=C1)C2=CC(=O)C3=C(C=C(C=C3O2)O)O
Catechin	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
Morin	C1=CC(=C(C=C1O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O

PASS: Prediction of activity spectra for substances

- In Figure 10, there is one hydrogen bond which is represented in green color
- Red and blue color spheres will show hydrophilic and lipophilic interaction among each other by the representation of the red and blue sphere.

Diosmin with GLP-1

- In Figure 11, there is 12 amino acid which is taking part in intermolecular bonding, which is lysine, valine, tryptophan, tyrosine, glutamate, etc.
- In Figure 11, there are 4 hydrogen bonds which are represented in green color
- Red and the blue color sphere will show hydrophilic and lipophilic interaction among each other by the representation of the red and blue sphere.

Based on PASS prediction five phytoconstituents were selected for molecular docking study using AutoDock Vina 4.0 [Table 3]. Three target sites which were DPP-4, GLP-1, and α glucosidase, perhaps were selected for prediction of probable affinities of these 5 selected phytoconstituents among these five constituents, diosmin showed best binding

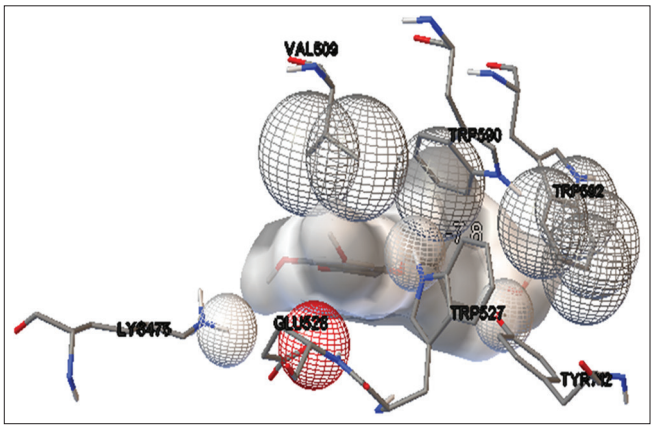

Figure 7: Binding interaction between naringenin and dipeptidyl peptidase-4

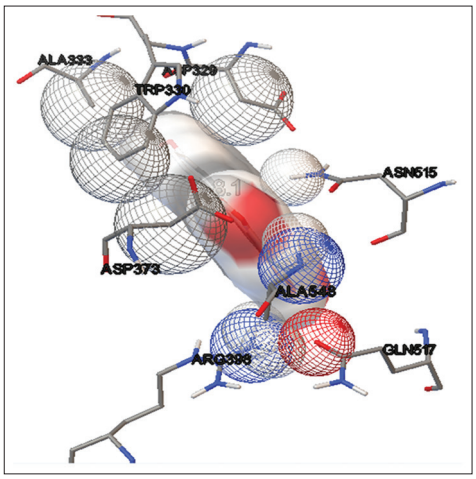

Figure 8: Binding interaction between apigenin and dipeptidyl peptidase-4

Table 3: Representation of PASS prediction of phytoconstituents

Compound	Nature	Reported activity	PASS predicted activated (Pi value Pa value)						
			Antidiabetic symptomatic	Antidiabetic	TNF expression inhibitor	VEGF expression inhibitor	Insulysin inhibitor	Interleukin agonist	Fatty acid synthase inhibitor
Naringenin	Phytoconstituent	TNF-α inhibitor	0.300/0.039	0.228/0.132	0.502/0.029	0.223/0.004	0290/0.146	0.221/0.047	0.254/0.002
Apigenin	Phytoconstituent	TNF-α inhibitor	0.320/0.029	0.181/0.025	0.608/0.002	0.324/0.002	0.730/0.005	0.252/0.031	0.312/0.002
Diosmin	Phytoconstituent	TNF-α inhibitor	0.344/0.021	0.471/0.028	0.203/0.189	#	#	0.423/0.005	0.133/0.006
Quercetin	Phytoconstituent	TNF-α inhibitor	0.363/0.018	0.195/0.019	0.501/0.029	0.267/0.003	0.46/0.001	0.645/0.017	0.322/0.029
Kaempferol	Phytoconstituent	Improved insulin resistance	0.371/0.018	0.202/0.016	0.476/0.035	0.283/0.003	#	0.615/0.022	0.452/0.001
Eriodictyol	Phytoconstituent	VEGF inhibitor	0.299/0.040	0.208/0.154	0.526/0.024	0.210/0.005	0.325/0.122	#	0.270/0.002
Hesperetin	Phytoconstituent	TNF-α inhibitor	0.288/0.046	#	0.584/0.015	0.195/0.007	0.352/0.108	#	0.225/0.003
Baicalein	Phytoconstituent	Fatty acid synthase inhibitor	0.341/0.022	0.144/0.064	0.490/0.032	0.218/0.005	0.762/0.004	#	0.356/0.002
Chrysin	Phytoconstituent	TNF-α inhibitor	0.317/0.031	0.181/0.025	0.584/0.015	0.313/0.003	0.732/0.005	#	0.308/0.002
Catechin	Phytoconstituent	TNF-α inhibitor	#	0.396/0.045	0.517/0.026	0.163/0.018	#	#	0.577/0.001
Morin	Phytoconstituent	TNF-α inhibitor	0.389/0.014	0.181/0.025	0.476/0.035	0.254/0.004	0.626/0.020	#	0.450/0.001

#Compound nature reported activities PASS predicted anti-AD activities (Pa value/Pi value). PASS: Prediction of activity spectra for substances, TNF-α: Tumor necrosis factor alpha, VEGF: Vascular endothelial growth factor

affinity followed by kaempferol, which showed equal affinity. Based on these results, it can be concluded diosmin is having best affinity for all these three targets sites.

DISCUSSION

Progressive growth of diabetes in the current scenario is the burning issue to all the medical associations; hence, new approach has been followed in this report using PASS prediction followed by docking. Phytoconstituent having reported *in vitro* and *in vivo* antidiabetic activity on different target sites was reviewed. Among them, few phytoconstituents were selected for presenting to PASS online software. Pa and Pi value was predicted for these phytoconstituents on different diabetic target sites.

Based on PASS prediction five phytoconstituents were selected for molecular docking study using AutoDock Vina 4.0. Three target sites which were DPP-4, GLP-1, and α glucosidase, perhaps were selected for prediction of probable affinities of these 5 selected phytoconstituents. Among these five constituents, diosmin showed best binding affinity followed by kaempferol, which showed equal affinity. Based on these results, it can be concluded diosmin is having a best affinity for all these three targets sites [Table 4].

Results of the present study can be utilized for designing of further *in vitro* and *in vivo* studies for these phytoconstituents. This study suggested the usefulness of these software in predicting the probable antidiabetic targets sites of potential antidiabetic phytoconstituents.

Furthermore, there are a variety of compounds that can be screened vigorously for the better treatment opportunity and the proper curing of the patients. This study gives a brief knowledge regarding the compounds that can be helpful for the treatment of diabetes in future, although mechanistic and pharmacological studies are required to prove that matter in details.

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Table 4: Drug and ligand interaction with the protein showing value of binding affinity

Drug name	DPP-4 (5olj)		GLP-1 (3c59)		Alpha-glucosidase (3wy1)	
	Phytoconstituent (Kcal/mol)	Control (GOL801) (Kcal/mol)	Phytoconstituent (Kcal/mol)	Control (10M) (Kcal/mol)	Phytoconstituent (Kcal/mol)	Control (PRU602) (Kcal/mol)
Naringenin	−7.8	−4.2	−6.6	−5.8	−7.9	−7.2
Apigenin	−8.1	−4.2	−6.7	−5.8	−7.9	−7.2
Diosmin	−10.2	−4.2	−8.3	−5.8	−9.7	−7.2
Quercetin	−8.2	−4.2	−6.8	−5.8	−8.1	−7.2
Kaempferol	−7.8	−4.2	−7.8	−4.2	−8.1	−7.2

**Yellow highlighted shows better binding affinity. DPP-4: Dipeptidyl peptidase-4, GLP-1: Glucagon-like peptide-1

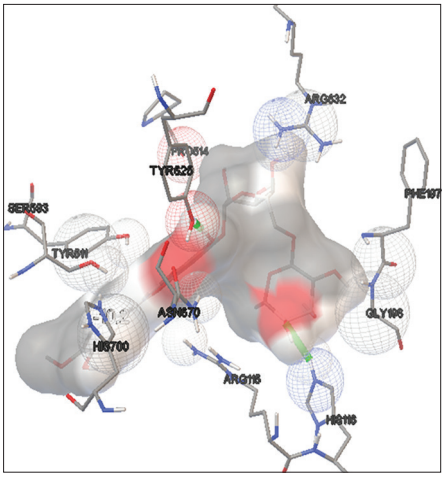

Figure 9: Binding interaction between diosmin and dipeptidyl peptidase-4

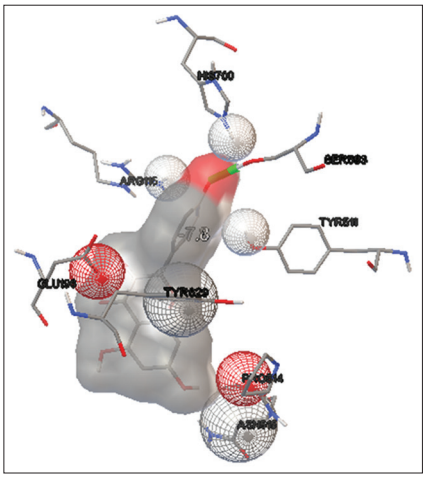

Figure 10: Binding interaction between kaempferol and dipeptidyl peptidase-4

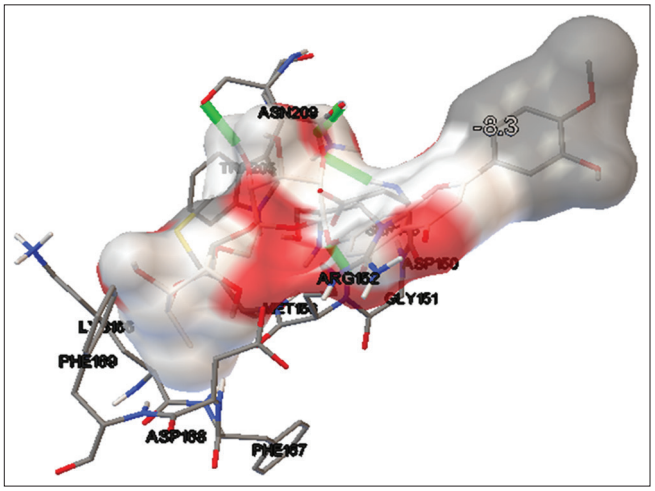

Figure 11: Binding interaction between diosmin and glucagon-like peptide-1

"antidiabetic effect of young and old ethanolic leaf extracts of *Vernonia amygdalina*: A comparative study". J Diabetes Res 2017;2017:5618548.
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