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Research Article

Complete ADMET Profile and Molecular Docking Analysis of Phytoconstituents of *Glycyrrhiza glabra* and *Asparagus racemosus*

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ABSTRACT

The whole study was designed to find out probable anti-diabetic potential of various phytoconstituents of *Glycyrrhiza glabra* and *Asparagus racemosus.* The study was further aimed at correlating the relationship between various phytoconstituents of both plants with major receptors playing an important role in diabetes mellitus by *in silico* and *in vitro* techniques. For *in-silico* all the constituents were screened by applying ADMET filters. Selected phytoconstituents were further analyzed through molecular docking. Main four PDB's 1IR3, 1US0, 2FV6, and 20QV for Insulin receptor, Aldose Reductase, Protein tyrosine phosphatase 1 and Human Dipeptidyl Peptidase IV (DPP4), respectively considered in the study. Molegro Virtual Docker version 6.0 tool employed to carry out the whole study. In contrast to internal ligands Licoriphenone, Hyperoside, Quercetin, Licoarylcoumarin, Glyzarin, and Glabrone represent the best docking results with all the four PDB's. In *in vitro* alpha-amylase inhibitory assay, both plants' combination was examined, and results exhibited that 2:1 GAM and 1:2 GAM have higher inhibitory potential than that of individual extract in contrast standard acarbose. The whole study gives insight that both plants probably have anti-diabetic potential due to the presence of studied biomarkers.

Introduction

World Health Organization define Traditional herbal medicines as natural substances with little or no processing used in the management of the various disease for local or regional healing. Due to their natural origin and lesser side effect, these medicines have been widely used worldwide from ancient times.[1] Diabetes mellitus is characterized by hyperglycemia.[2] It occurs due to defected insulin secretion,[3] and or exhaustion of insulin response towards the cell.[4] It may cause severe conditions like Heart attack, Stroke, Neuropathy, Retinopathy, and Nephropathy.[5] Today treatment of diabetes mellitus becomes a major challenge for the modern medicine system.[6] Presently frequency of this event is expanding internationally.[7] Conventional and contemporary system neglects to treat this problem totally.[8] A list of plants has effectively been accounted for anti-diabetic potential.[9] Due to the presence of active phytoconstituents, plants are supposed to treat various illnesses.[10] Nowadays, validation and documentation of phytoconstituents have become popular.[11]

Molecular docking and ADMET studies is a remarkable methodology.[12] Different types of drug targets can be classified by using *In silico* techniques as bioinformatics parameters.[13] It is used to predict structural and functional relationship between the compounds.[14] Consolidating in-silico strategies with plants constituents operate new freedoms for the cure of diseases. Moreover, matching the digital libraries databases to the natural resources generates new pathway of drug discovery.[15] *G. glabra* have been. reported for antidepressant, antimicrobial, anticancer, antioxidant, expectorant, hepatoprotective, anti-inflammatory, anti-ulcerative, anti-diabetic, hypolipidemic and immunological activities.[16]

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On the other hand, *A. racemosus* has been reported for antiulcer, galactogogue, antisecretory, antitussive, antibacterial, Antiprotozoal, Antihepatotoxic, Antineoplastic, Hypotensive, Immunomodulatory, Antioxidant, Diuretic, and blood glucose-lowering properties.[17] *G. glabra* and *A. racemosus* contain various phytoconstituents.[18,19] among them, polyphenol, glycoside, and flavonoid show anti-diabetic potential.[20,21] Current molecular docking study was designed to determine the anti-diabetic potency of these plants based on traditional use and reliability of *in silico* technique results.

Material Methods

Software and Hardware

Various tools employed in the current study are Openbabel Version 3.0, ADMETlab 2.0 (https://admetmesh.scbdd.com/), Molegro Virtual Docker (MVD) version 6.0, Pubchem and chemspider. Window 10 64 bit with hardware including Intel i3 processor (M330 @2.13 GHz) with 3GB DDR3 RAM.

Ligands Selection and Preparation

The structure of various phytoconstituents of *G. glabra* and *A. racemosus* was retrieved by utilizing Pubchem compound database and chemspider.[22,23] Chemdraw ultra software is then used for structure cleanup.[24] Smile formats were obtained by Openbabel software.[25] Then Marvin sketch software was then used for 2D to 3D conversion and explicating hydrogen bonds.[26] The lost or missing bonds, charge along with hybridization state of the ligand, if any, can be corrected using MVD.[27]

Selection and Preparation of PDB

All 3D structures of PDB's were retrieved from Protein Data Bank (http://www.rcsb.org/). The selection of PDB was made by analyzing resolution and survey of literature for a specific target. Total four PDB were selected for respective targets, including Insulin Receptor, Aldose Reductase, Protein Tyrosine Phosphatase, and Human Dipeptidyl Peptidase IV as 1IR3, 1US0, 2F6V, and 2OQV, respectively.[28]

QSAR Analysis

Zinc15 is a free online tool that helps trace imperative parameters required for the selection and screening of ligands along with Molinspiration. Both are incorporated into the study to do QSAR studies and investigate potential activators of biological objects.[29]

ADMET Studies

ADMET studies were carried out using ADMETlab 2.0. Open babel software used for conversion of ligand's structure in 'smiles' format. Smile formats are then uploaded in ADMETlab 2.0. Various molecular aspects of ligand were then analyzed like Molecular weight, solubility, P-gpsubstrate, Lipinski rule, BBB permeation information, TPSA (Topological Polar surface area), Pfizer Rule (toxicity), GSK Rule and Golden Triangle rule (ADMET), PPB. Besides these toxicological parameters, DILI, H-HT, carcinogenicity, and toxicophore rules like Acute Toxicity Rule and SureChEMBL Rule are also analyzed in detail.[30]

Molegro Virtual Docker

MVD is a magnificent tool for the prediction of interactions between target protein and ligands. It is truly an outstanding and most recent tool for doing a proficient evaluation of docking examination. In contrast with other accessible tools, it gives the most encouraging results of binding tendencies of the ligands. The percentage of results was found 87 with MVD. On the other hand, results for FlexX2 (57.9), Surflex (75.3), Gold (78.2), and Glide (81.8) percent.[31] Selected PDB was imported after removing water and co-factor if any; protein preparation was done by repairing the warning present in the structure. Internal ligands are also present with PDB for finding surfaces for interaction. The surface was detected, followed by cavity detection. Cavities are grid points where the ligand gets fit. After importing ligand, reset view was done. Then docking has proceeded. Results of docking were analyzed, and all interactions between target and ligand were labeled. Determination of in silico results of ligand was done by calculating moldock score, several interactions, and hydrogen bonding.

In-vitro Alpha-amylase Inhibition Assay

In vitro α amylase activity was carried to trace out the anti-diabetic potential of all the extracts of *Rhus parviflora.* The method was followed according to Ali *et al.* (2006) after certain modifications. Different concentrations (8, 15, 30, 60,125 µg/mL) of plant extract were taken in a quantity of 30 µL. After that, α amylase was added in the quantity of 200 µL, followed by incubation for 20 minutes at temperature 37°C. After incubating 100 µL of starch solution in a concentration of 1% was added and again followed by 10 minutes incubation at the same temperature. 200µL mL of DNSA was added to end up the reaction. UV visible spectrophotometer was used for further analysis at 540 nm wavelength. The standard used for the protocol was acarbose. Reactions were repeated three times in order to get accurate and reproducible results.

$$\% \text{ Inhibition} = \frac{100 \times \text{absorbance of control - absorbance of sample}}{\text{Absorbance of control}}$$

Results and Discussion

Validation of Docked Complex

The co-crystallized structure of internal protein-ligand was extracted then validation was done by docking the internal ligand with specific PDB. Table 1 represents the validation data.

Lipinski's Rule of Five and ADMET Studies

Total 28 phytoconstituents of *G. glabra* were screened by ADMET filter out of which 13 followed the ADMET profile parameters, including Formonoterin, Glabrone, etc. Isoangustone A, Kumatakenin, Licoflavonol, Glyzarin, Hispaglabridin A, Kanzonol R, Licoarylcoumarin, Licochalcone A, Licoriphenone, and Semilicoisoflavone (Table 2). Similarly, 20 phytoconstituents of *A. racemosus* were screened by ADMET filter out of which only 08 followed ADMET profile parameters, including Diosgenin, Kaempferol, Hyperoside, etc Quercetin, Racemofuran, Racemosol, Sarsaspogenin, and Sitosterol (Table 3). For selecting phytoconstituents for docking, various parameters like TPSA, solubility, SA score, PAINS, human intestinal absorption, Pgp-substrate, plasma protein binding, carcinogenicity, genotoxic, carcinogenicity rule, are considered in detail.

Docking Results

All selected phytoconstituents from both plants were docked with four selected PDB by MVD. Assessment of binding affinity was done by calculating Moldock score, total number of Interactions between ligand and protein, and hydrogen. Besides that length of the hydrogen bond is also considered. All the results reflect the interaction between ligand and protein found in the range of 3 to 20. A maximum number of interactions is shown by almost all molecules that exhibit good signs of binding tendency. A comparative data between internal ligand and phytoconstituents was shown in Table 4.

Table 1: Internal Ligand and Extracted Ligand (Moldock Score)

PDB	*ligand (Internal)*	*Moldock score (Internal ligand)*	*Moldock score (Extracted Internal ligand)*
1IR3	ANP	-141.83	-139.83
1US0	LDT_320	-147.84	-147.84
2F6V	SK2_608	-91.46	-91.77
2OQV	MA9_901	-114.86	-116.23

Insulin Receptor (IR)

Moldock score value for internal ligand (ANP) was found to be -141.83. Ligand shows 7 hydrogen bonds with insulin receptors. In contrast Hyperoside, Sitosterol, Isoangustone A, Licochalcone A, Hispaglabridin A. and Glibenclamide have moldock score -117.713, 121.287, -111.544, -103.549,-103.239,-125.221 respectively. Quercetin shows remarkable 11 Hydrogen bonds with the receptor. The minimum length of the bond was found to be 1.62Å for glabrone (Fig. 1). Amino acid residues, namely Glu 1047, Asp 1150, Asn 1137, Met 1079, Leu 1002, Lys 1030 were mainly involved in the interactions.

Aldose Reductase (AR)

Internal ligand (LDT_320) gives the value of Moldock score -147.84 with Aldose Reductase. The shortest bond length was estimated as 2.4Å. In contrast to internal ligand value for moldock score were found to be Glabrone -149.823, Isoangustone A -182.006, Semilicoisoflavone B -148.14, Diosgenein -142.611, Quercetin -143.961 and Racemofuran -148.139. The shortest bond length was found to be 1.87Å

Table 2: ADMET profile of Phytoconstituents of *G. glabra*

Sr. No..	*Name*	*TPSA(0-140)*	*logS(-4-0.5)*	*logP(0-3)*	*Lipinski Rule*	*Pfizer Rule*	*GSK Rule*	*Golden Triangle*	*Pgp-substrate*	*DILI*	*Acute Toxicity alerts*	*SureChEMBL alerts*
1.	*Formononetin*	59.67	-3.566	3.233	yes	No	yes	yes	0.97	0.69	0	0
2.	*Glabrone*	79.9	-3.354	4.563	yes	yes	No	yes	0.001	0.79	0	0
3.	*Glisoflavone*	100.13	-3.457	4.101	yes	yes	No	yes	0.824	0.387	0	0
4.	*Glyzarin*	67.51	-4.071	3.477	yes	No	yes	yes	0.001	0.978	0	0
5.	*HispaglabridinA*	58.92	-3.43	6.867	yes	No	No	No	0.001	0.029	0	0
6.	*Isoangustone A*	111.13	-2.868	6.025	yes	yes	No	yes	0.937	0.518	0	0
7.	*Kanzonol R*	68.15	-4.558	5.265	yes	No	No	yes	0.109	0.045	0	0
8.	*Kumatakenin*	89.13	-3.708	3.334	yes	yes	yes	yes	0.003	0.969	0	0
9.	*Licoarylcoumarin*	100.13	-4.134	3.974	yes	yes	yes	yes	0.011	0.948	0	1
10.	*Licochalcone A*	66.76	-4.19	4.205	yes	No	No	yes	0.002	0.28	0	1
11.	*Licoflavonol*	111.13	-3.27	4.58	yes	yes	No	yes	0.043	0.976	0	0
12.	*Licoriphenone*	96.22	-3.499	4.498	yes	yes	No	yes	0.616	0.677	0	1
13.	*Semilicoisoflavone B*	100.13	-3.636	4.054	yes	yes	No	yes	0.041	0.242	0	0

Table 3: ADMET profile of phytoconstituents of *A. racemosus*

Sr. No..	*Name*	*TPSA(0-140)*	*logS(-4-0.5)*	*logP(0-3)*	*Lipinski Rule*	*Pfizer Rule*	*GSK Rule*	*Golden Triangle*	*Pgp-substrate(all pass)*	*DILI*	*Respiratory Toxicity*	*Acute Toxicity alerts*	*SureChEMBL alerts*
1.	Diosgenin	38.69	-5.869	5.556	yes	No	No	yes	0.001	0.057	0.517	0	0
2.	Hyperoside	210.51	-3.871	-0.17	No	yes	No	yes	0.572	0.981	0.025	0	0
3.	Kaempferol	111.13	-3.624	2.656	yes	yes	yes	yes	0.001	0.979	0.09	0	0
4.	Quercetin	131.36	-3.671	2.155	yes	yes	yes	yes	0.005	0.98	0.072	0	0
5.	Racemofuran	62.83	-3.895	4.05	yes	No	No	yes	0.992	0.75	0.479	0	0
6.	Racemosol	58.92	-4.148	5.054	yes	No	No	yes	0.006	0.021	0.542	0	0
7.	Sarsaspogenin	38.69	5.764	6.3	yes	No	No	No	0.567	0.8	0.962	0	0
8.	Sitosterol	20.23	-7.052	7.663	yes	No	No	No	0.001	0.203	0.536	0	0

Table 4: Docking results of phytoconstituents of *A. racemosus* and *G. glabra*

Asparagus Racemosus					
S. no	*Ligand/internal ligand*	*PDB*	*MolDock Score*	*Interaction*	*HBond*
	ANP	1ir3	-141.83		
1.	Diosgenin	1ir3	-101.363	-103.932	-6.89347
2.	Kaempferol	1ir3	-93.9809	-112.557	-9.37111
3.	Hyperoside	1ir3	-117.713	-141.843	-15.3858
4.	Quercetin	1ir3	-97.9842	-118.888	-11.9745
5.	Racemofuran	1ir3	-93.4637	-99.2746	-8.66717
6.	Sarsasapogenin	1ir3	-104.28	-105.806	-4.51536
7.	Sitosterol	1ir3	-121.287	-117.546	0.35445
8.	Glibenclamide	1ir3	-125.221	-134.111	-5.71798
	LDT_320	1us0	-147.84		
1.	Diosgenin	1us0	-142.611	-145.18	-1.07002
2.	Kaempferol	1us0	-119.979	-138.063	-15.1525
3.	Hyperoside	1us0	-128.696	-160.754	-7.68709
4.	Quercetin	1us0	-143.961	-163.175	-10.204
5.	Racemofuran	1us0	-148.139	-154.223	-10.126
6.	Sitosterol	1us0	-166.158	-167.996	-2.5
7.	Glibenclamide	1us 0	-204.55	-223.683	-7.5464
	SK2_608	2f6v	-91.46		
1.	Diosgenin	2f6v	203.741	201.171	-8.95042
2.	Kaempferol	2f6v	-89.7286	-107.684	-9.52401
3.	Hyperoside	2f6v	-134.821	102.72	2.43428
4.	Quercetin	2f6v	-107.622	-126.909	-10.379
5.	Racemosol	2f6v	-113.815	-128.998	-6.17114
6.	Sarsasapogenin	2f6v	-115.413	-116.939	-3.35634
7.	Sitosterol	2f6v	-128.831	-129.66	-6.25496
8.	Glibenclamide	2f6v	150.417	128.863	-5.92574

S. no	*Ligand/internal ligand*	*PDB*	*MolDock Score*	*Interaction*	*HBond*
	MA9_901	2oqv	-114.86		
1.	Diosgenin	2oqv	-97.261	-99.8302	-10.0824
2.	Kaempferol	2oqv	-102.401	-126.756	-8.51354
3.	Hyperoside	2oqv	-113.72	-134.637	-14.9857
4.	Quercetin	2oqv	-108.016	-134.792	-11.4824
5.	Racemofuran	2oqv	-118.474	-127.736	-6.17451
6.	Sitosterol	2oqv	-122.891	-132.219	-1.61956
7.	Glibenclamide	2oqv	-133.91	-121.778	-2.6043

G. glabra

Sr no	*Ligand/internal ligand*	*PDB*	*MolDock Score*	*Interaction*	*HBond*
	ANP	1ir3	-141.83		
1.	Isoangustone A	1ir3	-111.544	-130.596	-9.05684
2.	Kumatakenin	1ir3	-95.9944	-116.005	-6.29186
3.	Glisoflavone	1ir3	-102.154	-121.497	-9.72396
4.	Kanzonol R	1ir3	-97.5428	-106.925	-6.04842
5.	Licochalcone A	1ir3	-103.549	-119.04	-7.64608
6.	Licoriphenone	1ir3	-102.559	-108.442	-14.3694
7.	Glibenclamide	1ir3	-125.221	-134.111	-5.71798
	LDT_320	1us0	-147.84		
1.	Glabrone	1us0	-149.823	-174.043	-6.57092
2.	Isoangustone A	1us0	-182.006	-210.564	-7.02217
3.	Licoflavonol	1us0	-154.528	-187.963	-6.3031
4.	Glisoflavone	1us0	-157.381	-174.236	-14.2492
5.	Hispaglabridin A	1us0	-168.73	-191.419	-5.15515
6.	Licoarylcoumarin	1us0	-147.63	-169.83	-2.64864
7.	Licochalcone A	1us0	-156.042	-169.736	-7.36327
8.	Licoriphenone	1us0	-165.916	-190.847	-11.5962
9.	Semilicoisoflavone B	1us0	-148.14	-168.013	-7.83259
10.	Glibenclamide	1us0	-204.55	-223.683	-7.5464
	SK2_608	2f6v	-91.46		
1.	Formononetin	2f6v	-105.054	-121.847	-7.45828
2.	Isoangustone A	2f6v	-134.943	-155.229	-3.62948
3.	Kumatakenin	2f6v	-106.415	-127.645	-4.96644
4.	Licoflavonol	2f6v	104.381	70.0481	-9.62547
5.	Hispaglabridin A	2f6v	152.878	124.667	-5.6906
6.	Licoarylcoumarin	2f6v	-114.753	-135.035	-6.00488
7.	Licochalcone A	2f6v	32.7586	13.3456	-5.64223
8.	Licoriphenone	2f6v	-105.928	-137.985	-8.59968
9.	Glibenclamide	2f6v	150.417	128.863	-5.92574
	MA9_901	20qv	-114.86		
1.	Glabrone	2oqv	-111.898	-139.358	-6.8764
2.	Isoangustone A	2oqv	-108.163	-138.495	-8.1896
3.	Glisoflavone	2oqv	-114.644	-138.672	-5.30978

Sr no	*Ligand/internal ligand*	*PDB*	*MolDock Score*	*Interaction*	*HBond*
4.	Glyzarin	2oqv	-101.26	-114.392	-4.30754
5.	Hispaglabridin A	2oqv	-143.253	-167.342	-8.93329
6.	Kanzonol R	2oqv	-99.3194	-111.642	-9.01675
7.	Licoarylcoumarin	2oqv	-116.265	-131.497	-7.25833
8.	Licochalcone A	2oqv	-120.769	-139.628	-4.79527
9.	Licoriphenone	2oqv	-106.985	-109.486	-8.10073
10.	Semilicoisoflavone	2oqv	-106.198	-125.137	-7.11969
11.	Glibenclamide	2oqv	-133.91	-121.778	-2.6043

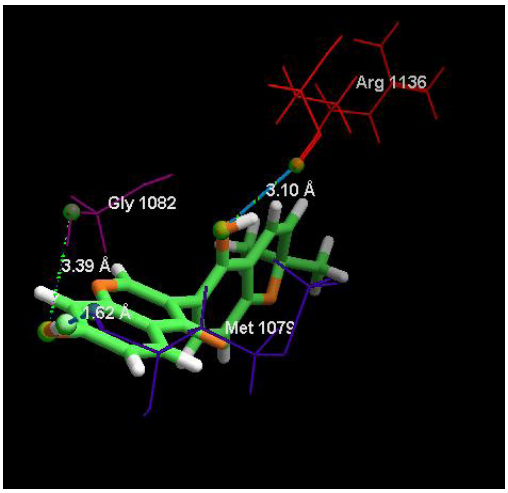

Fig. 1: PDB-1IR3, Ligand Glabrone

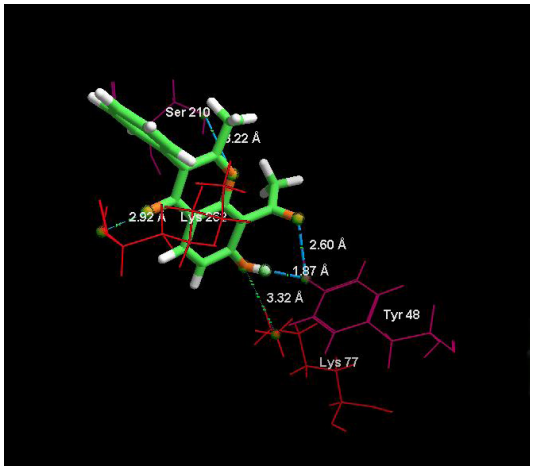

Fig. 2: PDB-1US0, Ligand Glyzarin

for Glyzarin. (Fig. 2). Maximum 20 interactions was shown by hyperoside amino acid residues involved are Trp 111, His 110, Tyr 48, Trp20, Thr 19, Asp 43, Lys 262, Asp 216, Ser 214, and Ser 210 (Fig. 3) .

Protein Tyrosine Phosphatase 1

Internal ligand (SK2-608) gives the moldock score -91.46 with 2F6V. All phytoconstituents show comparatively larger values for Moldock score as Hyperoside -134.821, Quercetin. -107.622, Formonotenin -105.054, Isoangustone A -134.943, Licoarylcoumarin -114.753 and licoriphenone -105.928. Maximum compounds formed more of a number

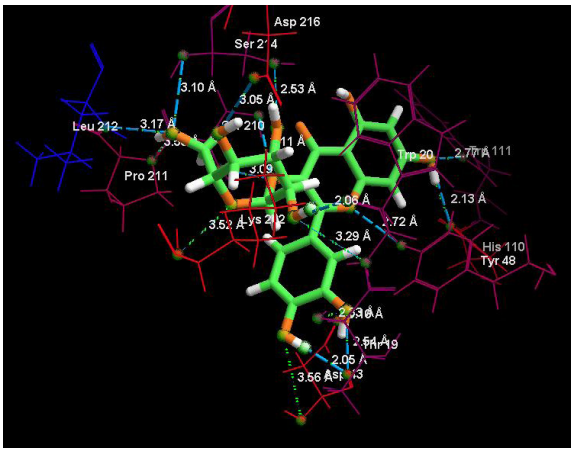

Fig. 3: PDB-1US0, Ligand Hyperoside

of hydrogen bonds than the internal ligand. Trp 179, Gly 183, Gln 266, Gln 262, Arg 221, Asp 181, Asn 111, Lys 120, Tyr 146 were mainly involved amino acid residues. Maximum interactions 16 was found for Hyperoside (Fig. 4).

Human Dipeptidyl Peptidase IV (DPP4)

Value for moldock score of internal ligand was found to be -114.86. The value for the shortest bond length was estimated 2.69 Å. The internal ligand shows a maximum number of 6 Hydrogen bonds. Whereas hand value for moldock sore was found for Glabrone -111.898, Hispaglabridin A -143.253, Licoarylcoumarin -116.265, Licochalcone A -120.769, Hyperoside -113.72, Racemofuran -118.474 and Sitosterol -122.891. Formononetin shows the smallest bond length 1.47Å, with receptor (Fig. 5).

In-vitro Results

Methanolic extract 2:1 ratio of both plants produced significant inhibition 54.25 ± 0.16percent ($p<0.05$), whereas 1:2 ratio of the same extract inhibited α-amylase by 47.62 ± 1.25 percent at 125 µg/mL concentration. The higher inhibition of methanol extracts can be correlated with the solubility of the phytochemicals in solvent as insignificant results were obtained in petroleum ether extract and chloroform extract individually. The lowest inhibition was 47.62 ± 1.25 percent in the case of 1:2 ratio of *G. glabra* and *A. recemosus* methanolic extracts. Though individually both plants are anti-diabetic, both

	Concentrations (µg/mL)				
Extract/ ratio	*8*	*15*	*30*	*60*	*125*
Acarbose	37.74 ± 0.41	39.61 ± 0.17	41.23 ± 0.17	44.32 ± 0.11	47.83 ± 0.76
2:1 GAM	35.35 ± 10.12	36.21 ± 9.16	43.71 ± 7.14	50.97 ± 0.33	54.25 ± 0.16
1:2 GAM	36.93 ± 1.57	40.12 ± 0.40	43.14 ± 1.23	46.83 ± 0.23	47.62 ± 1.25

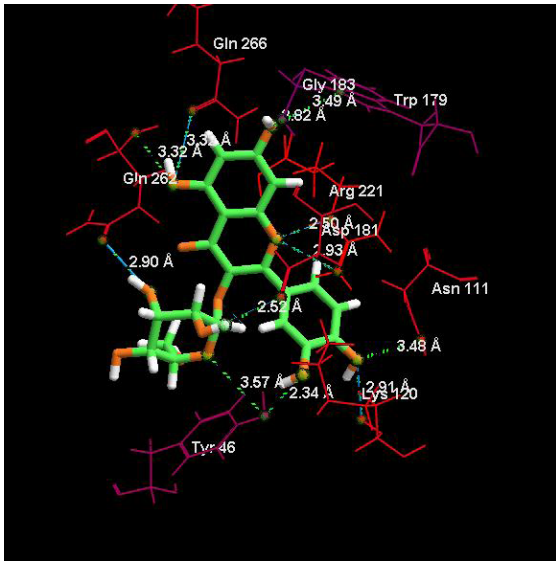

Fig. 4: PDB-2F6V, Ligand Hyperoside

plants might show synergistic action against α- amylase. This synergism may be due to pharmacokinetic or pharmacodynamic.

Conclusion

This study was designed to trace the anti-diabetic potential of different phytoconstituents of *G. glabra* and *A. Racemosus* by molecular docking analysis. Before docking analysis, ADMET profile of each phytoconstituents was studied in detail. ADMET profile gives detailed information regarding the molecule in every aspect. ADMET data obtained from ADMETlab 2.0[31] provides the basic molecular aspect and absorption, dissolution, metabolism, excretion, and toxicity parameters in detail. These parameters aid in evaluating the drug-likeness of the selected phytoconstituents. Total 13 out of 28 Constituents of *G. glabra* and 8 out of 20 constituents from *A. racemosus* show a good ADMET profile. Besides that, other parameters like SA score PAINS, Human Intestinal Absorption, Plasma Protein binding, carcinogenicity, genotoxic carcinogenicity rule (GCR) are also considered in detail. Selected phytoconstituents further proceeded for molecular docking analysis. Comparative analysis of docking shows that a maximum number of phytoconstituents of both plants has comparable value for moldock score. Besides that, the value for hydrogen bonding and several interactions were found permissible. Based on ADMET profile and docking results, it can be concluded that most

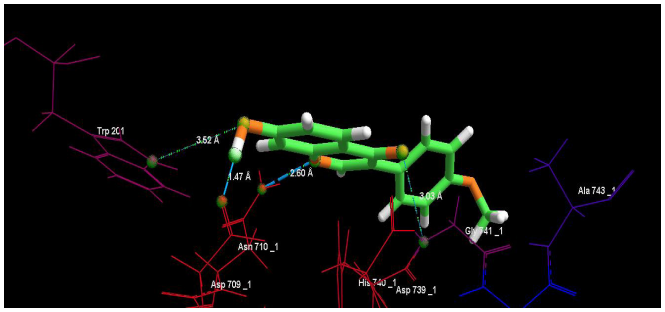

Fig. 5: PDB-2OQV, Ligand Formononetin

above-listed compounds have great binding affinity with all receptors used in the study.

Along with in silico study, the *in-vitro* alpha-amylase inhibitory assay showed promising results for the combined extracts of both plants. The anti-diabetic potential of the mentioned two plants is well established with the study of four receptors by in silico approach and a comparative study carried by in vitro anti-diabetic assay. Thus, after further analysis and research, selected phytoconstituents of *G. glabra* and *A. racemosus* are probably used to manage diabetes mellitus.

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