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Research Article

In silico Molecular Docking Studies of compounds from *Rumex vesicarius* against Pancreatic α-Amylase

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ABSTRACT

In spite of the global occurrence of type-2 diabetes mellitus (T2DM) infection and lack of auspicious treatment for Diabetes patients, there are only a few drugs accepted for the managing of infected patients. There is an urgent need to discover newer anti-diabetic drugs with novel mechanism of action and with efforts to reduce attrition rate in early drug discovery stages. The objective of this study is the evaluation of *Rumex vesicarius* compounds for anti-T2DM activity. In silico anti-T2DM lead prioritization was performed on a set of known compounds from R. vesicarius medicinal plant. The energy minimized structures of these molecules were docked into Pancreatic α-Amylase. Docking experiments were done using Autodock software for seven compounds docking with α-Amylase. Rhein was found to be a lead with better docking scores. The results showed that there is scope for the improvement of activity of Isovitexin analogs to discover a potent anti-T2DM compound.

1. Introduction

Diabetes mellitus is most common metabolic disease all over the world and number of diabetic patients is still on rise. Diabetes, characterized by hyperglycemia and metabolic disturbance on lipids, carbohydrates, and proteins, affect the life quality of patients by bringing huge pressure to society and public health [1]. Nearly 2.2% of total death in the world is caused by diabetes [2]. Type II diabetes, considered as the common form of diabetes, will affect the health of 8 billion people in the world till 2025 [3]. Persistent hyperglycemia in diabetes mellitus leads to the development of secondary complications including neuropathy, nephropathy, and retinopathy [2]. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [4].

Rumex vesicarius Linn. (Polygonaceae) is commonly called as Chukka kura in Telugu, Chukra in Hindi, Bladder Dock in English [5]. *Rumex vesicarius* L. is a wild edible plant used as a sorrel and collected in spring season and eaten fresh or cooked. *Rumex vesicarius* L. has many important medicinal uses such as treatment of hepatic diseases, bad digestion, diuretic, laxative, tonic, analgesic, purgative and antibacterial agents. The plant can be used to reduce biliary disorders and control cholesterol levels [6-7]. Diabetes mellitus is the sixth leading cause of death globally. Many of the drugs have been used in the management of this disease. These drugs have many side effects and a search for new class of compounds is essential to overcome diabetic problems. Traditionally, a number of plants have been used in various herbal preparations in the management of diabetes and only few of them have been proven scientifically. Anti-bacterial and Antioxidant activities of *Rumex vesicarius* were performed. So far there is no *in silico* anti-diabetic study report so this paper is aimed to report the *in silico* docking of phytochemicals present in this plant against target enzyme, α-Amylase.

Alpha amylase is an important enzyme which is secreted primarily by the salivary glands and the pancreas contributing its fundamental role in the metabolism of starch and glycogen, which are commonly present in plants, microorganisms and also in higher organisms [8]. Alpha amylase is a target molecule for the treatment of type 2 diabetes mellitus; its inhibitors and its relationship with the disease have been extensively investigated [9-11].

2. Material and Methods

2.1 Data Set:

Phytoconstituents from the *R. vesicarius* and standard drug compounds (3D PDB) were downloaded from the IMPPAT database (https://cb.imsc.res.in/imppat/home). The molecular properties and structure of the selected compounds (apigenin, Chrysophanol, emodin ,Isovitexin, Physcion, thiamine and Vitexin) were shown in table-1.

2.2 Bioactive Score Prediction:

Drug score values indicate overall potential of a compound to be a drug candidate. Mol inspiration is a web-based tool used to predict the bioactivity score of the synthesized compounds against regular human receptors such as GPCRs, ion channels, kinases, nuclear receptors, proteases and enzymes

2.3 Evaluation of Drug Likeliness:

Lipinski's rule of five is helpful in describing molecular properties of drug compounds required for estimation of important pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and toxicity (ADMET). The rule is helpful in drug design and development. The drug-likeness and molecular property prediction were done by molsoft server (http://molsoft.com/mprop/).

2.4 Docking Methodology

2.4.1 Preparation of Ligand and Protein

The three dimensional structure of the target Pancreatic α-Amylase (4GQR) was obtained from Protein data bank database (https://www.rcsb.org/) and downloaded in PDB format. The ligands and water molecules were removed from the protein and the chemistry of the protein was corrected for the missing hydrogen followed by the energy minimization of the protein. Drug molecule and phytoconstituents optimization, addition of charges and hydrogen bonds was carried out using Autodock tools.

2.4.2 Molecular Docking

The docking of 4GQR with selected 40 phytochemical molecules were performed by using Autodock 4 [12]. The docking calculations were verified using docking server. Gasitier partial charges were added to ligand. Nonpolar hydrogen atoms were merged and rotatable hydrogen bonds were defined. Docking calculations were carried out on receptor. Essential hydrogen atoms, kollaman charges and salvation parameters were added affinity (grid) maps 25 Å grid points and 0.500Å were generated using the autogrid program. Autodock parameters set and distance dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using Lamarckian algorithm (LGA) and Solis and Wet local search methods. Initial position torsion and orientation of the drug molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after 250000 energy calculations [13]. The population size was set to 150. During search the translational step 0.2 Å and quaternion and torsion step 5 were applied.

3. Results and Discussion

Computational docking is an extremely useful tool to gain an understanding about synthesized compounds and their interactions with biological drug targets, which is very important in drug discovery research. The Molecular Docking software predicted the amino acids in active site region of the studied target proteins.

3.1 Evaluation of Drug Likeliness:

Lipinski's rule of five (RO5) is used to evaluate drug likeliness of a chemical compound possessing properties that would make it a likely or potential drug in humans. The oral activity of a drug compound is predicted by calculating certain molecular parameters like log P (partition coefficient), polar surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight. The rule states that most metal complexes with good membrane permeability have log P ≤5, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤5. In general, an orally active drug has no more than one violation of the given criteria. In the present study, the synthesized ligand and its complexes were found to be in good agreement with the given criteria and can be said to possess good oral bioavailability.

Evaluation of drug likeliness based on Lipinski's rule of five of ligands was showed in Table-1. Based on the drug likeliness evaluation, most of ligands are maintained the Lipinski's rule of five.

3.2 Bioactivity Score Prediction:

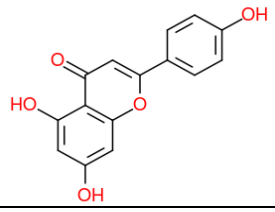
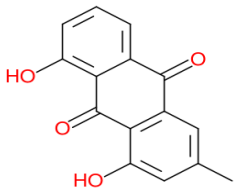
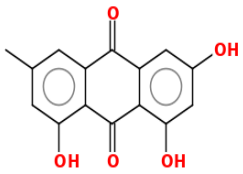
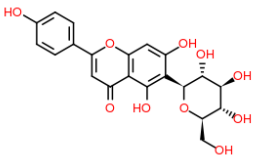
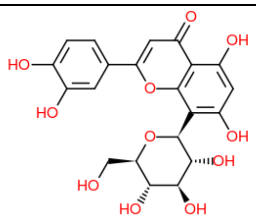
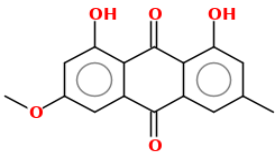
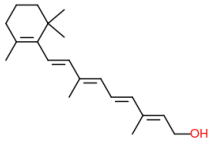
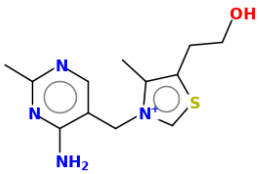
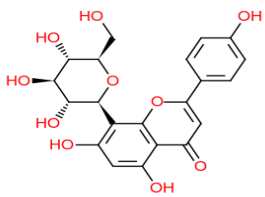
The pharmacological activity describes the beneficial effects of drugs in living beings. The drug is supposed to bind with a biological target. Biological targets are the most common proteins such as enzymes, ion channels, and receptors. The biological target is also referred to as drug target. The bioactivity scores of the synthesized complexes were calculated for different parameters such as binding to G protein-coupled receptor (GPCR) ligand and nuclear receptor ligand, ion channel modulation, kinase inhibition, amaidotransferase inhibition, and enzyme activity inhibition. All the parameters were calculated with the help of online software Molinspiration (www.molinspiration.com), which predicted moderate biological activity for the synthesized complexes. The bioactivity score is given in Table-2. It is known that for metal complexes, if the bioactivity score is more than 0.0, then the complex is active; if it is between −5.0 and 0.0, then the complex is moderately active, and if the bioactivity score is less than −5.0, then it is inactive.

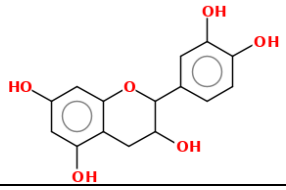
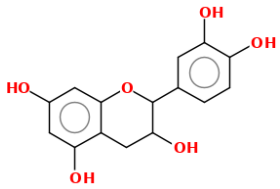
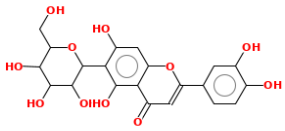
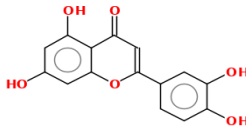
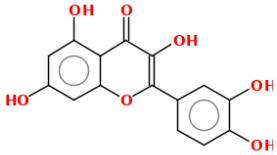
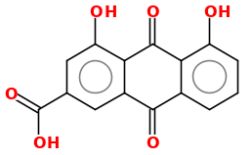
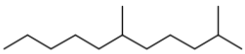
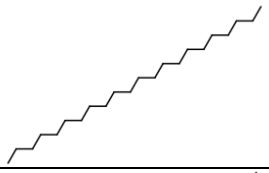
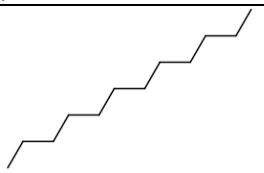
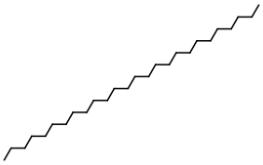
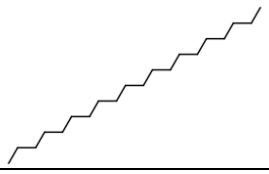
As seen in Table-2, the bioactivity scores of the ligand as well as all the complexes were above −5.0 and 0.0, which clearly indicate that they possess such properties as are enquired for the complexes to act as potential drugs with some modifications in chemical structure.

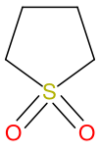
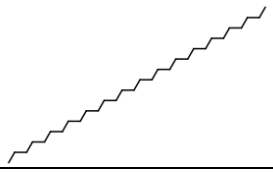
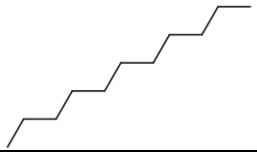
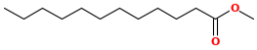
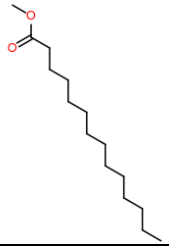
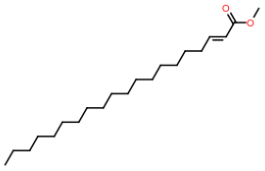
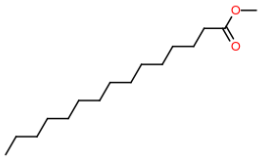
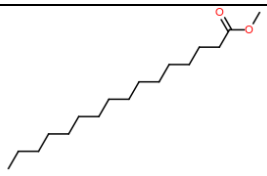
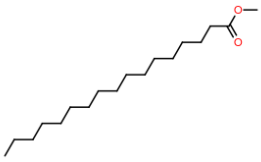
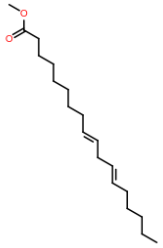
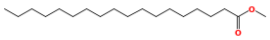
3.3 Docking Interactions:

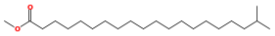
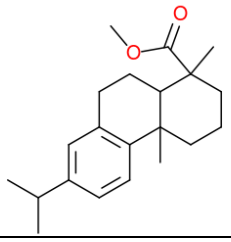
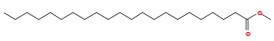
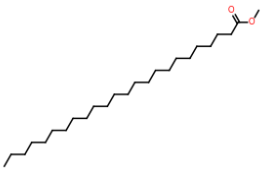
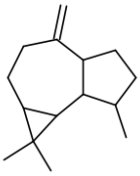
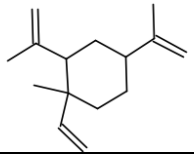
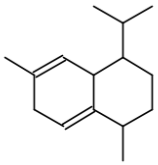
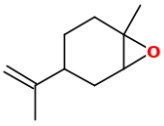
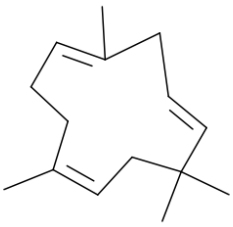
Physicochemical properties of the 40 compounds of R.vesicarius were examined and the results of docking were tabulated. On docking against α- amylase, the compound Rhein showed greater binding affinity towards enzyme and got a best ligand pose energy of -7.74 and the residues involving in the interaction are: SER:3, PHE:229, PRO:228, ILE:230, ASN:5,250, :GLY:249, LYS:208, 227, TYR:2. In the present study,40 compounds (apigenin, Chrysophanol, emodin, Isovitexin, Physcion and Thiamine, Vitexin etc..) of Rumex vesicarius were docked into Pancreatic α-Amylase enzyme and out of 40, five compounds, Chrysophanol (-7.09 kcal/mol), Isovitexin (-7.31 kcal/mol), Catechin (-7.21 kcal/mol), Rhein (-7.77 kcal/mol), Alloaromadendrene (-7.56 kcal/mol), Methyl dehydroabietate (-7.17 kcal/mol) indicated high binding score (-7.31 kcal/mol).

Table-1. Evaluation of drug likeliness based on Lipinski's rule of five of ligands.

S.N	Compound Name	Structure	Molecular formula	Molecular weight	Number of HBA	Number of HBD	Log P
1	Apigenin		C15 H10 O5	270.24	5	3	2.46
2	Chrysophanol		C15 H10 O4	254.24	4	2	3.54
3	emodin		C15 H10 O5	270.24	5	3	3.01
4	Isovitexin		C21 H20 O10	432.38	10	7	0.52
5	Orientin		C21 H20 O11	448.38	11	8	0.03
6	Physcion		C16 H12 O5	284.27	5	2	2.98
7	retinol		C20 H30 O	286.46	1	1	5.92
8	thiamine		C12 H17 N4 O S	265.36	4	3	0.51
9	Vitexin		C21 H20 O10	432.38	10	7	0.52

10	Catechin		C15 H14 O6	290.08	6	5	1.88
11	Epicatechin		C15 H14 O6	290.08	6	5	1.88
12	Iso orientin		C15 H15 N O3	257.11	3	1	1.93
13	Luteolin		C15 H10 O6	286.05	6	4	2.68
14	Quercetin		C15 H10 O7	302.04	7	5	2.11
15	Rhein		C15 H8 O6	284.03	6	3	2.19
16	2_6-Dimethylundecane		C13 H28	184.22	0	0	6.38
17	Docosane		C22 H46	310.36	0	0	10.95
18	Dodecane		C12 H26	170.20	0	0	6.13
19	Hexacosane		C26 H54	366.42	0	0	12.88
20	Eicosane		C20 H42	282.33	0	0	9.98

21	Tetra methylene_ sulfone		C4 H8 O2 S	120.02	2	0	0.44
22	Triacontane		C30 H62	422.49	0	0	14.80
23	Undecane		C11 H24	156.19	0	0	5.65
24	Methyl_ laurate		C13 H26 O2	214.19	2	0	5.08
25	Methyl_ myristate		C15 H30 O2	242.22	2	0	6.04
26	methyl_ eicosenate		C21 H40 O2	324.30	2	0	9.08
27	methyl_pentadecanoate		C16 H32 O2	256.24	2	0	6.52
28	Methyl_palmitate		C17 H34 O2	270.26	2	0	7.00
29	methyl_margarate		C18 H36 O2	284.27	2	0	7.49
30	methyl_ linoleate		C19 H34 O2	294.26	2	0	7.08
31	Methyl_ stearate		C19 H38 O2	298.29	2	0	7.97

32	Methyl_eicosanoate		C22 H44 O2	340.33	2	0	9.25
33	Methyl_dehydroabietate		C21 H30 O2	314.22	2	0	5.66
34	Methyl_docosanoate		C23 H46 O2	354.35	2	0	9.90
35	Methyl_lignocerate		C25 H50 O2	382.38	2	0	10.86
36	Alloaromadendrene		C15 H24	204.19	0	0	4.85
37	Beta-Elemene		C15 H24	204.19	0	0	5.39
38	Cadina-1_4-diene		C15 H24	204.19	0	0	6.02
39	Cis-Limonene		C10 H16 O	152.12	1	0	2.95
40	Humulene		C15 H24	204.19	0	0	5.47

The former compound is thus an effective inhibitor among the other compounds that can stop the function of α-amylase. However, further *in vitro* and *in vivo* studies of individual phytoconstituents is needed to validate their biological potential. Ball and socket model of respective drug molecule and phytoconstituents interacting with active site are shown in Table-3.

4. Conclusion

Understanding the interactions between proteins and ligands is crucial for the pharmaceutical and functional food industries. The emergence of bioinformatics has offered a platform to explore diseases at molecular level using computational tools. The Protein-Ligand interaction plays a significant role in structure based drug designing. Finally from this analysis it was found that, among the all compounds six compounds are effectively inhibit T2DM- α-amylase and the phytochemicals of this plant can act as T2DM- α-amylase inhibitors.

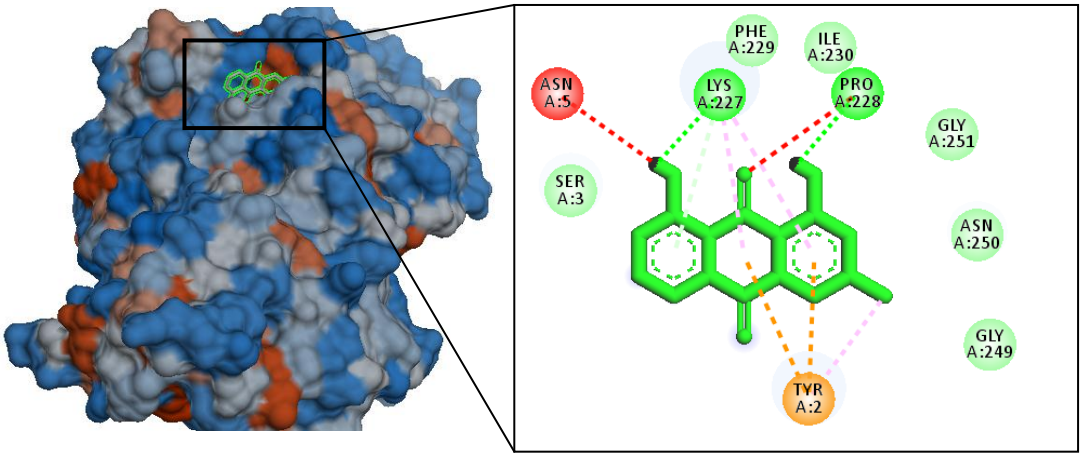
Table-2. Bioactivity score of the ligands

S. No.	Compound	Parameters of Bioactivity score					
		GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Apigenin	-0.07	-0.09	0.18	0.34	-0.25	0.26
2	Chrysophanol	-0.23	-0.17	0.06	0.02	-0.26	0.16
3	Emodin	-0.14	-0.14	0.07	0.17	-0.21	0.21
4	Isovitexin	0.12	0.02	0.15	0.23	0.04	0.47
5	Orientin	0.12	-0.14	0.20	0.20	0.01	0.45
6	Physcion	-0.17	-0.23	0.04	0.11	-0.23	0.14
7	Retinol	-0.01	0.32	-0.25	1.02	-0.16	0.66
8	Thiamine	0.26	0.01	-0.37	-1.72	-0.64	1.12
9	Vitexin	0.13	-0.14	0.19	0.23	0.03	0.46
10	catechin	0.41	0.14	0.09	0.60	0.26	0.47
11	Epicatechin	0.41	0.14	0.09	0.60	0.26	0.47
12	Isoorientin	0.11	0.01	0.16	0.20	0.01	0.46
13	Luteolin	-0.02	-0.07	0.26	0.39	-0.22	0.28
14	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
15	Rhein	-0.08	-0.10	0.01	0.29	-0.06	0.28
16	2_6-Dimethylundecane	-0.57	-0.18	-0.93	-0.67	-0.56	-0.27
17	Docosane	0.02	0.00	-0.07	0.02	-0.02	0.03
18	Dodecane	-0.71	-0.23	-0.93	-0.83	-0.85	-0.35
19	Hexacosane	0.04	0.00	-0.04	0.04	0.04	0.03
20	Icosane	-0.04	0.00	-0.14	-0.05	-0.11	0.03
21	tetramethylene_sulfone	-3.73	-3.88	-3.91	-3.92	-3.56	-3.67
22	Triacontane	0.04	0.00	-0.04	0.04	0.03	0.02
23	Undecane	-0.84	-0.31	-1.08	-0.98	-0.98	-0.44
24	alloaromadendrene	-0.67	-0.47	-0.98	-0.21	-0.67	-0.30
25	beta-elemene	-0.36	0.18	-1.02	0.43	-0.38	0.30
26	Cadina-1_4-diene	-0.33	-0.15	-0.85	-0.09	-0.77	0.19
27	cis- -Limonene_oxide	-0.65	-0.40	-2.04	0.15	-0.63	0.37
28	Humulene	-0.14	0.02	-0.93	0.34	-0.67	0.31
29	Methyl_laurate	-0.41	-0.13	-0.73	-0.43	-0.46	-0.11
30	Methyl myristate	-0.24	-0.07	-0.51	-0.24	-0.28	-0.02
31	methyl_eicosenate	0.02	-0.08	-0.23	0.12	0.07	0.07
32	methyl_pentadecanoate	-0.17	-0.06	-0.42	-0.16	-0.20	0.01
33	Methyl_palmitate	-0.11	-0.05	-0.34	-0.09	-0.13	0.04
34	methyl_margarate	-0.07	-0.05	-0.28	-0.04	-0.08	0.05
35	methyl_linoleate	0.15	0.07	-0.20	0.14	0.03	0.23
36	Methyl_stearate	-0.03	-0.04	-0.23	0.00	-0.03	0.05
37	methyl_eicosanoate	0.03	-0.02	-0.20	0.07	0.14	0.04
38	methyl_dehydroabietate	0.40	0.20	-0.26	0.85	0.02	0.36
39	methyl_docosanoate	0.02	-0.04	-0.16	0.05	0.06	0.04
40	methyl_lignocerate	0.02	-0.04	-0.15	0.05	0.06	0.04

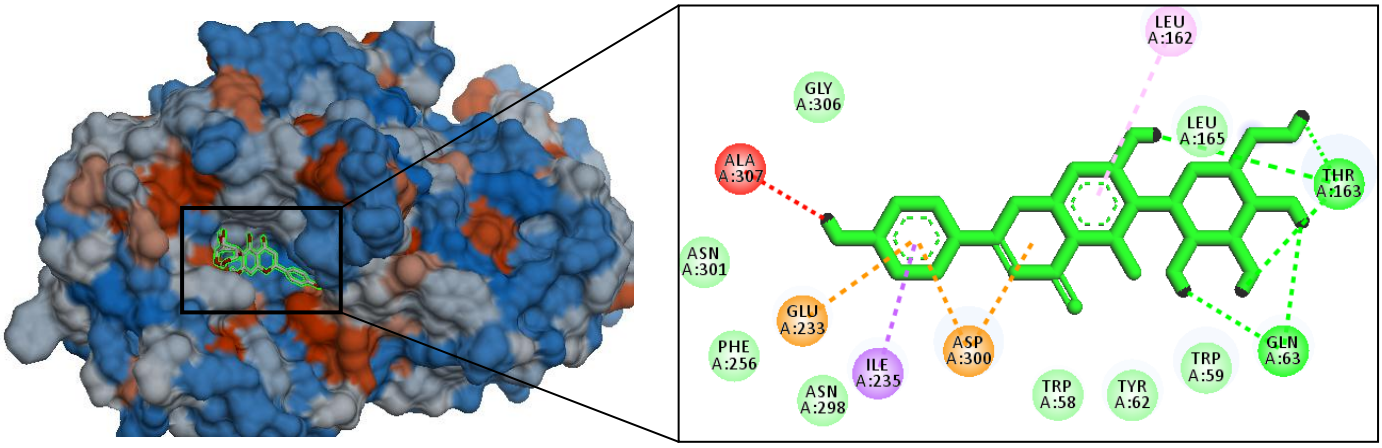
Table-3. Phytochemical compounds docked against T2DM- Pancreatic α- amylase

Sl.No	Plant Name	Compound Name	Binding energy	Inhibition constant	Intermolecular energy
1		Apigenin	-6.68 kcal/mol	12.60 uM	-7.88 kcal/mol
2		Chrysophanol	-7.09 kcal/mol	6.34 uM	-7.69 kcal/mol
3		Emodin	-6.92 kcal/mol	8.52 uM	-7.81 kcal/mol
4		Isovitexin	-7.31 kcal/mol	4.35 uM	-10.30 kcal/mol
5		Physcion	-6.93 kcal/mol	8.38 uM	-7.82 kcal/mol
6		Retinol	-7.54 kcal/mol	2.96 uM	-9.33 kcal/mol
7		Thiamine	-6.09 kcal/mol	34.23 uM	-7.88 kcal/mol
8		Vitexin	-6.48 kcal/mol	17.68 uM	-9.47 kcal/mol
9		Catechin	-7.21 kcal/mol	5.14 uM	-9.00 kcal/mol
10		Epicatechin	-6.58 kcal/mol	15.11 uM	-8.37 kcal/mol
11		Isoorientin	-6.24 kcal/mol	26.67 uM	-9.52 kcal/mol
12		Luteolin	-6.80 kcal/mol	10.42 uM	-8.29 kcal/mol
13		Quercetin	-6.59 kcal/mol	14.87 uM	-8.38 kcal/mol
14		Rhein	-7.74 kcal/mol	2.14 uM	-8.93 kcal/mol
15		2,6-Dimethylundecane	-5.13 kcal/mol	173.59 uM	-7.52 kcal/mol
16		Docosane	-5.61 kcal/mol	76.90 uM	-11.28 kcal/mol
17		Dodecane	-4.50 kcal/mol	506.68 uM	-7.18 kcal/mol
18		Hexacosane	-4.85 kcal/mol	280.01 uM	-11.71 kcal/mol
19		Icosane	-4.76 kcal/mol	322.90 uM	-9.83 kcal/mol
20	*Rumex*	Tetramethylene_Sulfone	-4.28 kcal/mol	728.99 uM	-4.28 kcal/mol
21	*vesicarius*	Triacontane	-4.87 kcal/mol	267.49 uM	-12.93 kcal/mol
22		Undecane	-4.24 kcal/mol	777.24 uM	-6.63 kcal/mol
23		Alloaromadendrene	-7.56 kcal/mol	2.87 uM	-7.56 kcal/mol
24		Beta-Elemene	-6.97 kcal/mol	7.77 uM	-7.87 kcal/mol
25		Cadina-1_4-Diene	-7.17 kcal/mol	5.53 uM	-7.47 kcal/mol
26		Cis-___-Limonene_Oxide	-5.63 kcal/mol	74.83 uM	-5.93 kcal/mol
27		Humulene	-6.96 kcal/mol	7.89 uM	-6.96 kcal/mol
28		Methyl_Laurate	-4.68 kcal/mol	369.45 uM	-7.96 kcal/mol
29		Methyl_Myristate	-4.30 kcal/mol	700.39 uM	-8.18 kcal/mol
30		Methyl_Eicosenate	-4.62 kcal/mol	409.12 uM	-10.29 kcal/mol
31		Methyl_Pentadecanoate	-4.74 kcal/mol	333.16 uM	-8.92 kcal/mol
32		Methyl_Palmitate	-4.59 kcal/mol	432.60 uM	-9.06 kcal/mol
33		Methyl_Margarate	-4.65 kcal/mol	393.04 uM	-9.42 kcal/mol
34		Methyl_Linoleate	-5.36 kcal/mol	118.44 uM	-9.83 kcal/mol
35		Methyl_Stearate	-4.36 kcal/mol	633.76 uM	-9.43 kcal/mol
36		Methyl_Eicosanoate	-4.26 kcal/mol	755.02 uM	-9.93 kcal/mol
37		Methyl_Dehydroabietate	-7.17 kcal/mol	1.69 uM	-8.77 kcal/mol
38		Methyl_Docosanoate	-4.58 kcal/mol	436.35 uM	-10.85 kcal/mol
39		Methyl_Lignocerate	-4.96 kcal/mol	230.67 uM	-11.82 kcal/mol
40		Orientin	-5.31 kcal/mol	4.35 uM	-10.30 kcal/mol
41	REFERENCE	Acarbose	-2.24 kcal/mol	22.98 mM	-8.80 kcal/mol

Figure-1. ***In silico*** **Molecular Docking Studies of compounds (a- Chrysophanol; b- Isovitexin; c- Catechin; d- Rhein; e- Alloaromadendrene; f- methyl_dehydroabietate) from *Rumex vesicarius* against Pancreatic α-Amylase**



(a)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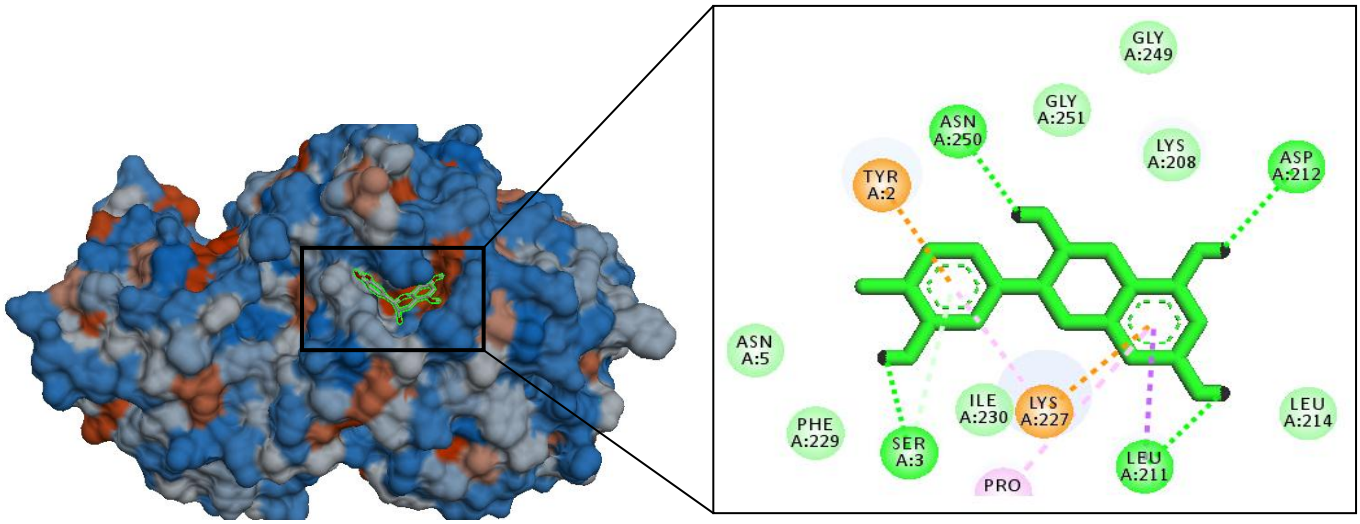
(b)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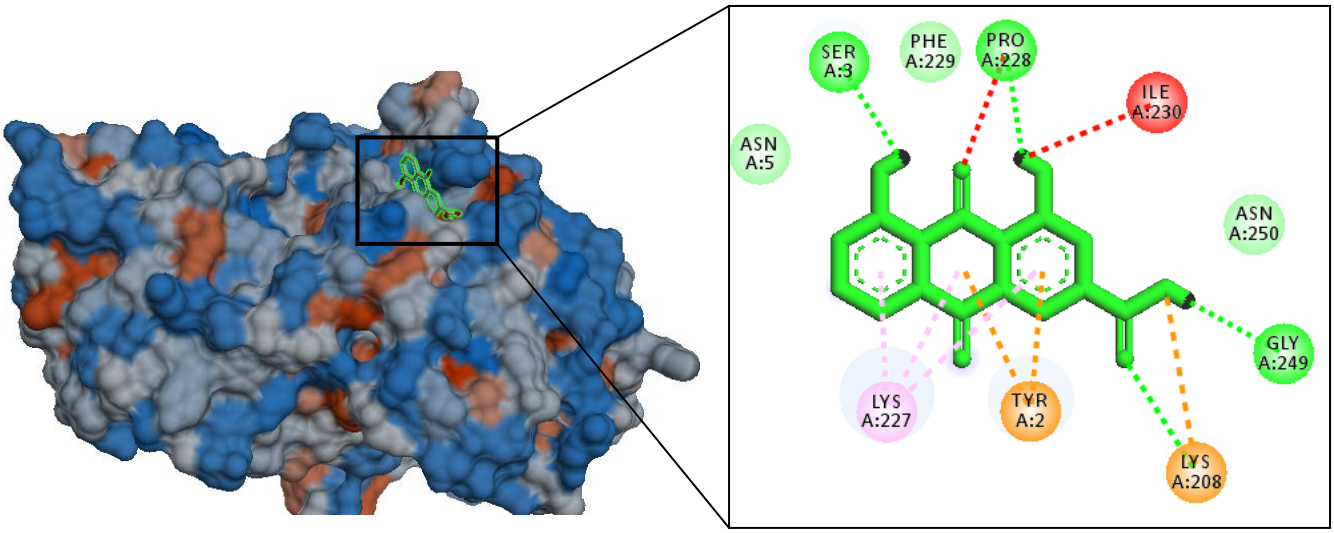
PRO

(c)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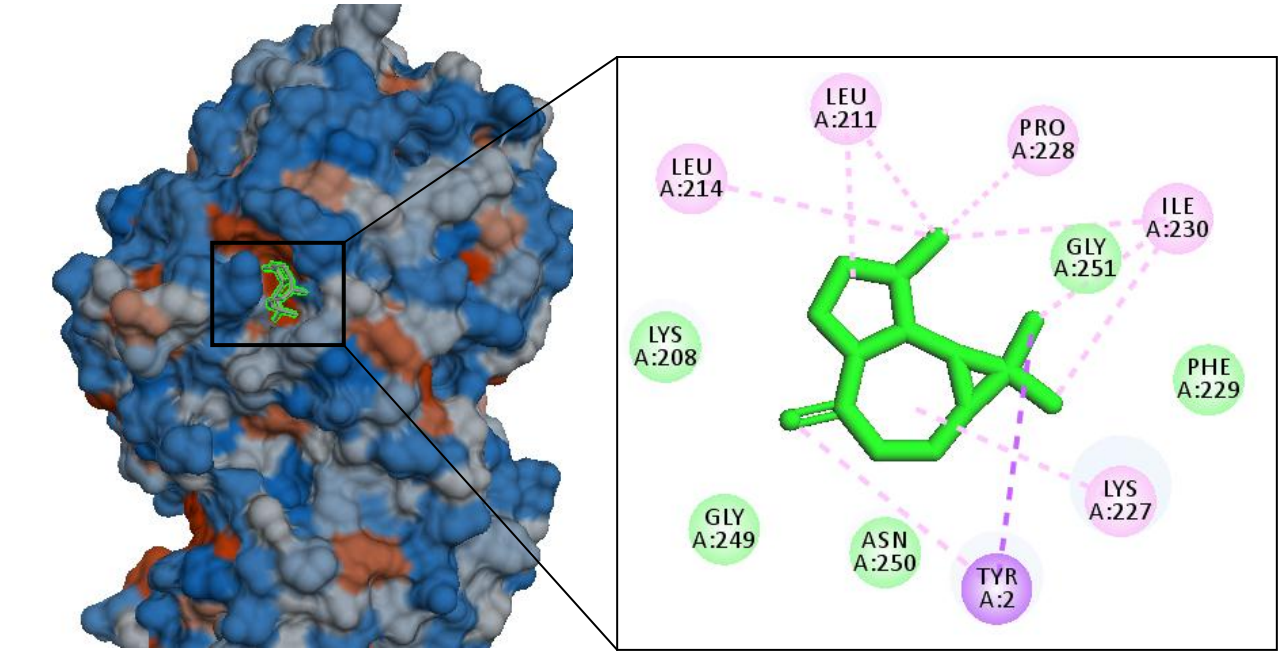
(d)



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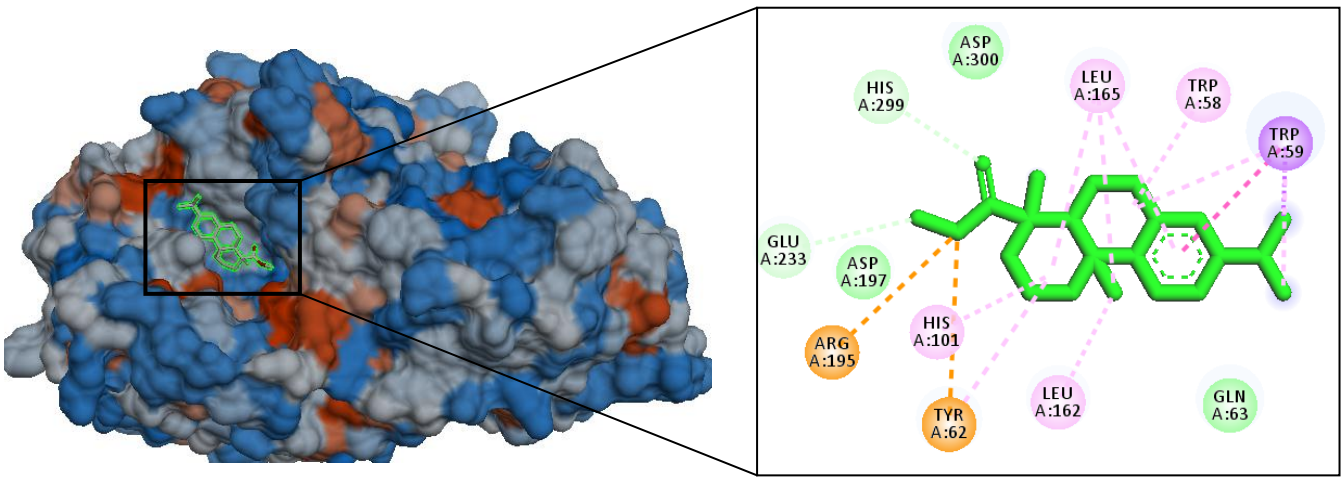

(f)

Therefore, this study emphasizes the importance of small molecules from various plant sources and their use to enhance protein-ligand interaction studies in silico. Further investigations can be done on our in silico approach to produce more effective and potential T2DM- α-amylase inhibitors through ligand based drug designing approaches..

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Conflicting Interests

The authors have declared that no conflicting interests exist.

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