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Research Article

In Silico Molecular Docking Study of Gymnemic Acid Analogues

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ABSTRACT

Diabetes mellitus is characterized by high blood sugar levels, which cause various other disorders like cardiovascular problems, eye irritation, kidney failure, and nervous system problems. There are numerous treatments available in the market, but synthetic medicine has various side effects. Traditionally, Herbal plants are mostly used for diabetes mellitus. Gymnema sylvestre is one of the most effective plants that comes from the Apocynaceae family. It is also called gurmar in Hindi. The present study includes an in-silico study of Gymnemic acid analogues to identify the protein receptor affinity to bind, and also their ADMET and Toxicological properties by using software like Biodiscovery Studio, Avogadro, PyRx, Swiss ADME, ADMET 2.0, and Protox 3.0. In this study, the gymnemic acid analogues I-XVIII were dock with receptor SGLT-2(7vsi) and Glut(4pyp), so the result best binding affinity of SGLT-2 (PDB ID:- 7vsi) with gymnemic acid VIII (-9.3 kcal/mol) and Glut (PDB ID:- 4pyp) with gymnemic acid XVIII (-9.3 kcal/mol). The analogues show violate Lipinski's rule, only gymnemic acid VII show good GI absorption, and all gymnemic acids, showed mostly no risk of carcinogenicity, respiratory toxicity, H-HT, skin sensitivity, irritation, except gymnemic acid XV, , which has high risk of toxicity; its LD50 is 4 mg/kg. This study shows that gymnemic acid analogues of Gymnema sylvestre are highly effective as antidiabetics.

INTRODUCTION

Diabetes mellitus is characterised by persistently high blood sugar levels (hyperglycaemia), which can lead to major consequences. It can significantly affect many bodily systems this including, among other things, the kidneys, eyes, and nervous system. Numerous consequences, such as heart disease, stroke, and neuropathy, are significant for the cardiovascular system. The market provides a range of medications to successfully manage diabetes mellitus, but each one has unique side effects. This integrative approach seeks to offer comprehensive care that addresses both the disease's symptoms and underlying causes. Potential strategies for

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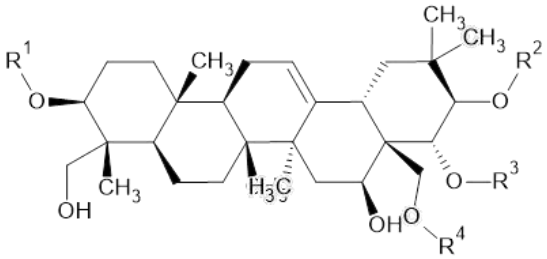
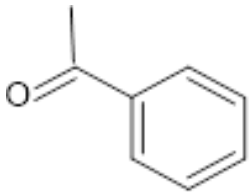
controlling and lessening the side effects of diabetes mellitus medication are provided by the combination of contemporary scientific research. The traditional knowledge of naturopathic therapies new and creative treatments can be created by utilizing the pharmacological qualities of different plant, use abundant flora to improve the quality of life for people with diabetes. There is manifold plant which are useful for diabetic disorder without side effect such as *Gymnema sylvestre is* mostly recently used and effective as antisweat agent [1-4]. *Gymnema sylvestre* R. Br. belongs to the family Apocynaceae as it previously called Asclepiadaceae. The herb is native to India, Australia, and Tropical Africa, commonly known as miracle plant in English, and Gurmar (sugar destroyer) in Hindi, chewing the leaves causes a loss of sweet taste for a short time[5,6]. Ethnomedicinally, it is a popular plant mostly used in Homeopathic, Ayurvedic, Unani, and Siddha systems of traditional medicine, advised to diabetic and toothache patients [7]. For centuries, people have turned to this remarkable plant for its powerful healing properties-protecting the liver, balancing cholesterol, fighting infections, and soothing inflammation. Even something as simple as preventing dental caries has been part of its long list of benefits, making it a treasured component of herbal medicine [8-10]. At the heart of *G. sylvestre*'s medicinal magic lies a potent mix of bioactive compounds. Gymnemic acids, saponins, and flavonoids work in harmony, offering profound therapeutic effects. Among them, gymnemic acids stand out, playing a key role in regulating blood sugar by blocking glucose absorption and enhancing insulin secretion. Meanwhile, the plant's antimicrobial, anti-inflammatory, and antioxidant properties add to its legacy of healing [11-13]. The leaves of *Gymnema sylvestre* are a powerhouse of natural compounds, each playing a unique role in the plant's medicinal potency. Among these, triterpene saponins stand out, belonging to two key classes oleanane and dammarene. The oleanane group includes gymnemic acids and gymnemasaponins, while dammarene saponins are known as gymnemasides [14-16]. Beyond these main saponins, the leaves contain a rich array of bioactive elements, including resins, albumin, and chlorophyll. They are also a natural source of carbohydrates, tartaric acid, formic acid, and butyric acid, alongside potent anthraquinone derivatives and inositol alkaloids. Furthermore, the presence of organic acids (5.5%), parabin, calcium oxalate (7.3%), lignin (4.8%), and cellulose (22%) add to the plant's structural and functional diversity. With such a diverse chemical profile, *G. sylvestre* stands as a remarkable gift from nature, offering profound therapeutic potential [17]. Gymnemic acids are primary triterpene saponins present in the leaves of *Gymnema sylvestre*. These compounds consist of various acylated derivatives of deacylgymnemic acid (DAGA), a 3-O-β-glucuronide of gymnemagenin, characterized by multiple hydroxyl groups on its oleanane skeleton. The hypoglycaemic effects of *G. sylvestre* leaf extract, particularly gymnemic acid, are attributed to several key mechanisms: 1) It causes inhibition of glucose absorption from the intestine, 2) It inhibit the absorption of glucose into cell and muscle [18,19]. The present work includes an in-silico study to compare gymnemic acid analogues to identify most antidiabetic active compound against SGLT-2 and Glut by molecular docking and in silico ADME/Tox studies. The docking method was employed for predicting the binding affinity on SGLT-2 and Glut with gymnemic acid analogues and their mechanism of action pertaining to inhibiting absorption of insulin from the intestine, muscle, and cell. Also, it helps to know their clinical efficacy and toxicity. Such a study would further establish the development of a pharmacophore for drug designing and development against di

abetes, a disease affecting millions of lives worldwide [20,21].

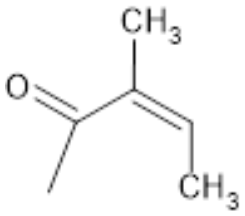


Basic structure of Gymnemic acid

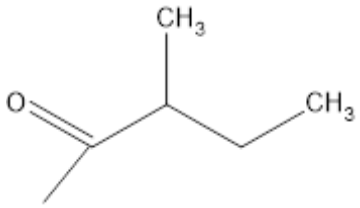
Compound	R_1	R_2	R_3	R_4
1	Gluconic acid	Tigloyl	H	Acetyl
2	Gluconic acid	2-methyl butyloyl	H	Acetyl
3	Gluconic acid	2-methyl butyloyl	H	H
4	Gluconic acid	Tigloyl	H	H
5	Gluconic acid	Tigloyl	Tiglo yl	H
6	Gluoniacid-3-glucose	Tigloyl	H	H
7	H	H	H	H
8	Gluonicacid-3-(2-oxo-glucose)	2-methyl butyloyl	H	H
9	Gluonicacid-3-(2-oxo-glucose)	Tigloyl	H	H
10	Gluconic acid	H	H	H
11	Gluconic acid	Tigloyl	H	Tigloyl
12	Gluonicacid-3-glucose	Tigloyl	H	H
13	Gluconic acid	H	H	2-methyl butyloyl
14	Gluconic acid	H	H	Tigloyl
15	H	2-methyl	Tiglo yl	H
		butyloyl		
16	Tigloyl	H	H	H
17	H	Benzyl	H	H
18	H	H	H	Benzyl



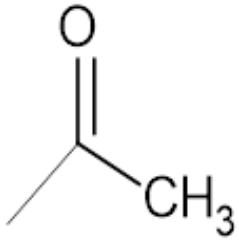
Benzyl group



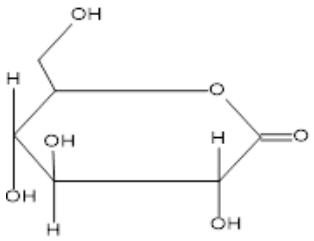
Tigloyl



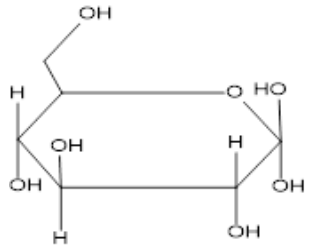
2-methyl butyloyl



Acetyl group



Gluconic acid



2-oxo glucose

Figure 1:- Structure of functional group of Gymnemic acid I-XVIII

MATERIAL AND METHOD

Material

Software was used for docking are ChemSkech (2014.1.2), Avogadro (1.2.0), Biodiscovery studio visualiser (v21.1.0.20298, BIOVIA Software) and PyRx (phyton prescription 0.8) and website used for virtual screening are PubChem, Research Collaboratory for Structural Bioinformatics (RCSB) Protein Database Bank (PDB), Swiss ADME, Protox 3.0, and ADMET 2.0.

Methods

Preparation of Ligands

Bioactive compounds present in the *G. sylvestre* plant are represented as ligand molecules, which are downloaded from PubChem. These ligands were converted to the 3D structure by using Avogadro version (1.2.0).

Preparation of Protein

The X-ray crystal structures of sodium glucose transporter-2 (SGLT-2) (PDB ID:7vsi) and Glucose transporter Glut (PDB ID: 4pyp) with resolutions of 2.95Å and 3.17Å respectively were downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Database Bank (PDB).Then remove all strain of molecular structure was done using the Merck Molecular Force Field (MMFF) and the semi-empirical Austin Model (AMI) methods, both of which are implemented in biodiscovery studio visualiser (v21.1.0.20298, BIOVIA Software).

Molecular Docking

The protein was added in the Pyrex and convert it into micromolecular then add ligand from open bable. Energy minimization and preparation of the ligand into. pdbqt was done by using open bable tool. To identify the binding site of the protein structure, a sphere binding site with a radius of 9 Å was defined around the attached ligand. The ligand SD files were then imported into the Pyrex virtual screening tool, where they were utilized to dock the receptors that have been prepared. The ligand selects a conformation in the internal coordinate space at random and then moves to a new random position that is independent of the previous one but follows a specified continuous probability distribution. The result of the best scored binding energy, and inhibition constant of all the ligands were reported. Save this data in cvs. file form The 2D structure of protein-ligand interaction was prepared by using Biodiscovery Studio Visualiser (v21.1.0.20298, BIOVIA Software).

Virtual Screening

Swiss ADMET is a web-based platform designed to predict the absorption, distribution, metabolism, and elimination (ADME) properties, and Protox 3.0 was utilized to evaluate the toxicity of the chemical compounds. This tool helps generate a drug-like library, streamlining the assessment of potential therapeutic agents. For this analysis,

Copy the smiley of compound from Chemsketch or from PubChem and paste it into the website and upon processing, the results indicated favourable physiochemical properties, ADME characteristics, and Toxicity. The bioactive compound which demonstrated less or non-toxic properties and exhibited drug-likeness, reinforcing their potential as viable candidates for further pharmaceutical exploration.

RESULT AND DISCUSSION

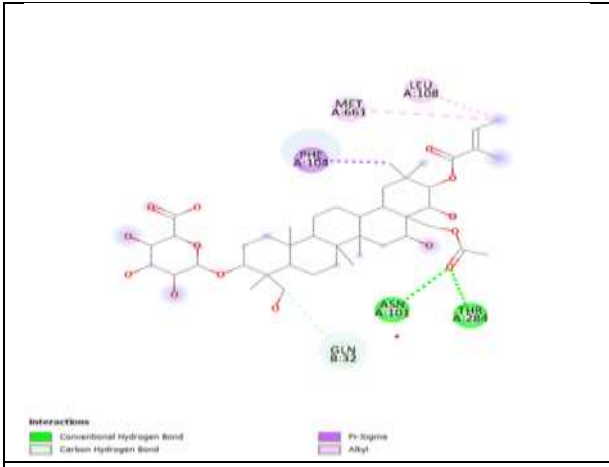
In the present work, the main purpose of the docking study is to know whether the given compounds are able to inhibit the anti-diabetic target Sodium glucose transporter-2 (SGLT-2) (PDB ID: - 7vsi) and Glucose transporter (GluT) (PDB ID: - 4pyp) to study their possible mechanism of action. The binding affinity potential of the studied compounds was measured in terms of docking energy (kcal mol-1). The binding affinity obtained in the docking study was used to compare the activity of gymnnic acid analogues with each other to know which one is more effective. In which, It gives best inhibitory activity against SGLT-2 with gymnemic acid VIII (-9.3 kcal/mol), gymnemic acid VI and XIII (-9.1kcal/mol), gymnemic acid XVI (-8.9), gymnemic acid I, VII, XIV (-8.8 kcal/mol), gymnemic acid II (-8.7 kcal/mol), rest of compound like gymnemic acid III, gymnemic acid IV, gymnemic acid V, gymnemic acid VIII, gymnemic acid IX, gymnemic acid X, gymnemic acid XII, gymnemic acid XVII show good binding affinity with except gymnemic acid XI, gymnemic acid XV, gymnemic acid XVII show very low binding affinity. Also, Best binding affinity of GluT show with gymnemic acid XVIII (-9.3 kcal/mol), gymnemic acid IX (-9 kcal/mol), gymnemic acid III, V, XVII (-8.7 kcal/mol), gymnemic acid XV (-8.6 kcal/mol) and gymnemic acid I (-8.5 kcal/mol) rest of compound like gymnemic acid II, gymnemic acid IV, gymnemic acid VII, gymnemic acid VIII, gymnemic acid X, gymnemic acid XI, gymnemic acid XIII, gymnemic acid XVI, gymnemic acid XVI show good binding affinity and gymnemic acid VI show very low binding affinity.

Table 1: - Molecular Docking Results of receptor Sodium Glucose Transporter (SGLT-2) and Glucose Transporter (Glut) with ligand molecule like Gymnemic acid analogues.

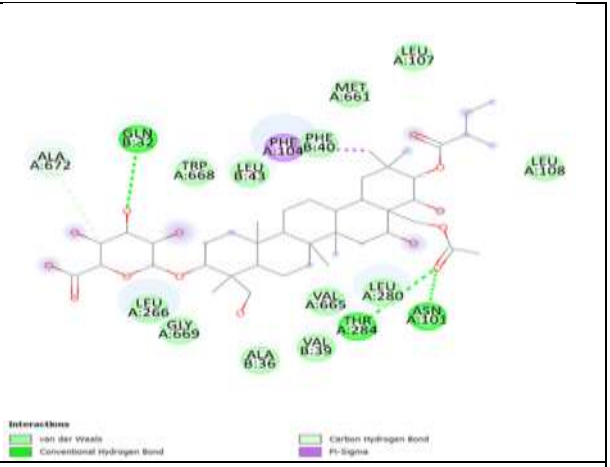
Sr.no	Constituents	Binding Affinity with SGLT-2	Binding Affinity with Glut
1	Gymnemic acid I	-8.8	-8.5
2	Gymnemic acid II	-8.7	-8.3
3	Gymnemic acid III	-8.5	-8.7
4	Gymnemic acid IV	-8.4	-8
5	Gymnemic acid V	-8.6	-8.7
6	Gymnemic acid VI	-9.1	-7.8
7	Gymnemic acid VII	-8.8	-8.3
8	Gymnemic acid VIII	-9.3	-8.2
9	Gymnemic acid IX	-8.2	-9
10	Gymnemic acid X	-8.6	-8.3
11	Gymnemic acid XI	-7.6	-8.4
12	Gymnemic acid XII	-8.1	-8.4
13	Gymnemic acid XIII	-9.1	-8.1
14	Gymnemic acid XIV	-8.8	-8.2
15	Gymnemic acid XV	-7.7	-8.6
16	Gymnemic acid XVI	-8.9	-8.3
17	Gymnemic acid XVII	-8.6	-8.7

18	Gymnemic acid XVIII	-7.5	-9.3

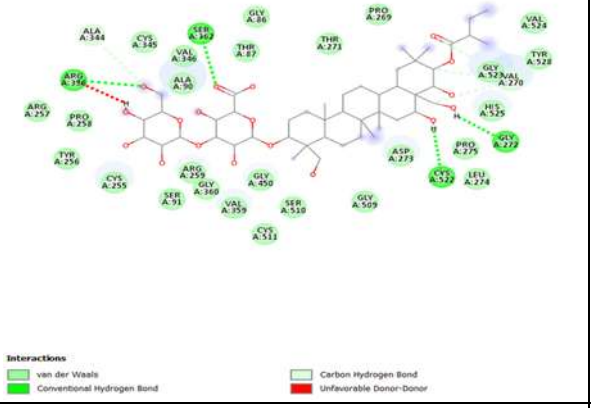
Molecular docking shows the binding affinities of all the ligands with the sodium glucose transporter-2 (SGLT-2) and glucose transporter (Glut). Other interactions, such as hydrogen bonds, van der Waals interactions, hydrophobicity, as well as pi-bonds, cannot be discarded in the inhibitory activities of gymnemic acid against SGLT-2 and Glut. The 2D structure of protein-ligand interaction shows amino residues in interaction. For the SGLT-2 protein conserved binding site amino acid residues of gymnemic acid I are ASN-101, THR-284, and GLN-32, which participate in hydrogen bonding. Additionally, PHE-104, MET-661, and LEU-108 are involved in pi-sigma and alkyl bonding. In Gymnemic acid II, GLN-32, ALA-672, PHE-104, LEU-280, ASN-101 take part in bonding. In gymnemic acid VI, ARG-356, ALA-344, SER 362, GLY-523, VAL-270, GLY-272, CYS-522 take part in bonding. In gymnemic acid VII, CYS-522, GLY-509, ARG-336, PHE-254, ARG-259, CYS-255, ARG-257, ASP-454, SER-508 are the amino group does bond. In gymnemic acid VIII, HIS-525, ARG-336, CYS-255, ASP-454, CYS-522 take part in bonding. In gymnemic acid XIII, GLU-503, TYR-462, ALA-90, SER-362, ASP-454, CYS-255, HIS-525, TYR-526, ARG-499, VAL-524 take part in bonding. For the Glut protein conserved binding site, amino residues of gymnemic acid XI are ARG-212, ARG-400, GLU-247, ARG-153, and THR-137 take part in bonding, and in gymnemic acid XVIII, THR-137, ARG-153, ARG-212, GLY-145, GLY-147, and PRO-141, residue take part in bonding. These docking results suggest that high binding affinity and strong hydrophobic interactions of gymnemic acid analogues are the reason for conformational stability and therefore resulted in significant activity.



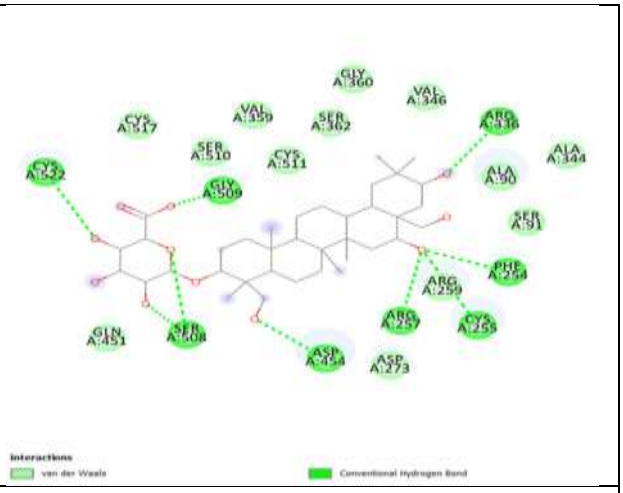
Interaction of Gymnemic acid I with SGLT-2



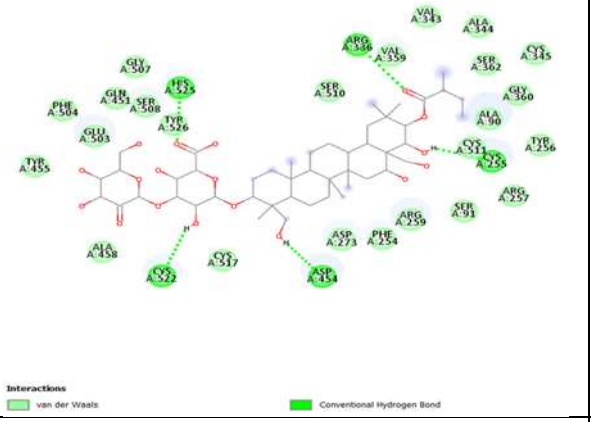
Interaction of Gymnemic acid II with SGLT-2



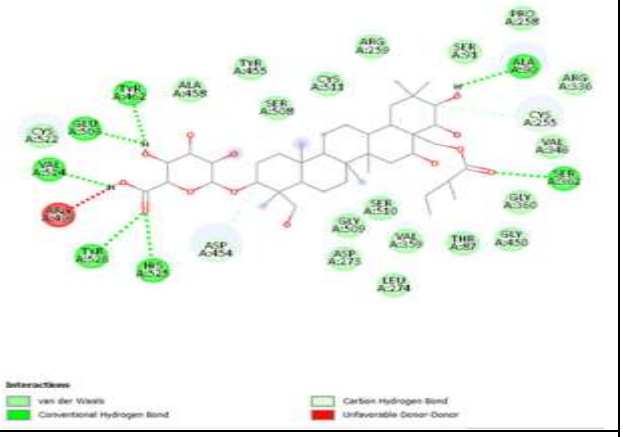
Interaction of Gymnemic acid VI with SGLT-2



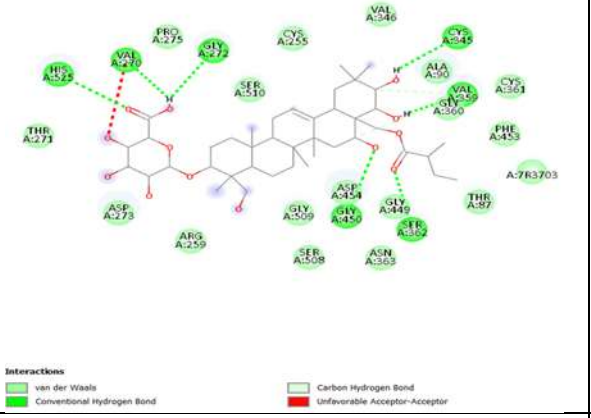
Interaction of Gymnemic acid VII with SGLT-2



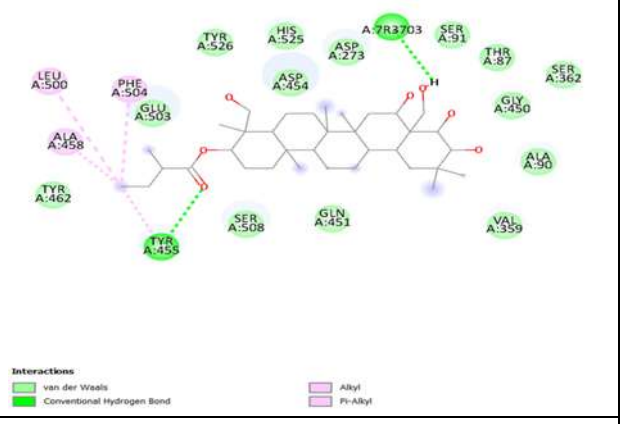
Interaction of Gymnemic acid VIII with SGLT-2



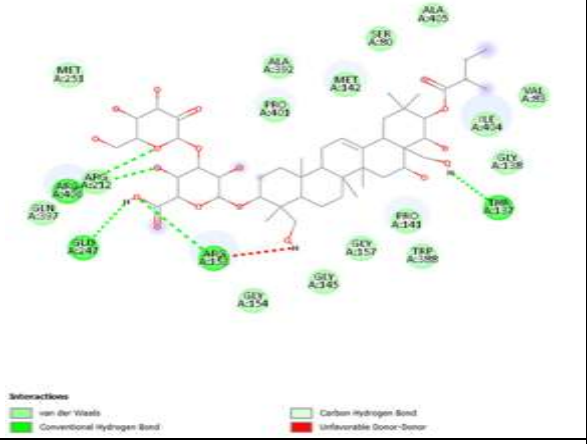
Interaction of Gymnemic acid XIII with SGLT-2



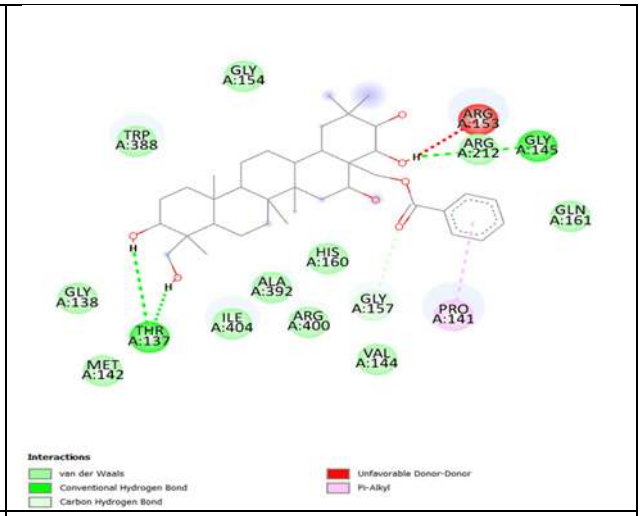
Interaction of Gymnemic acid XIV with SGLT-2



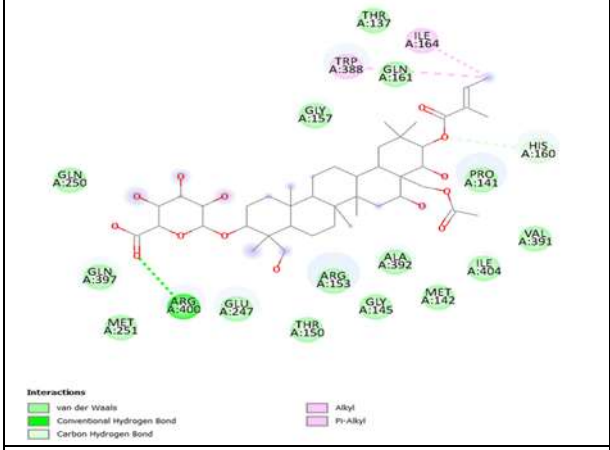
Interaction of Gymnemic acid XVI with SGLT-2



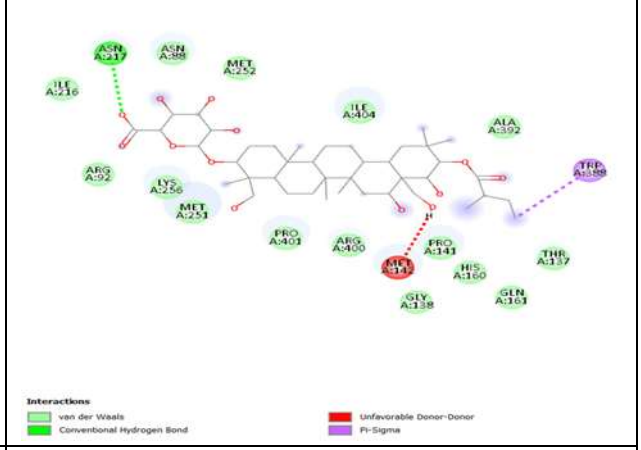
Interaction of Gymnemic acid IX with Glut



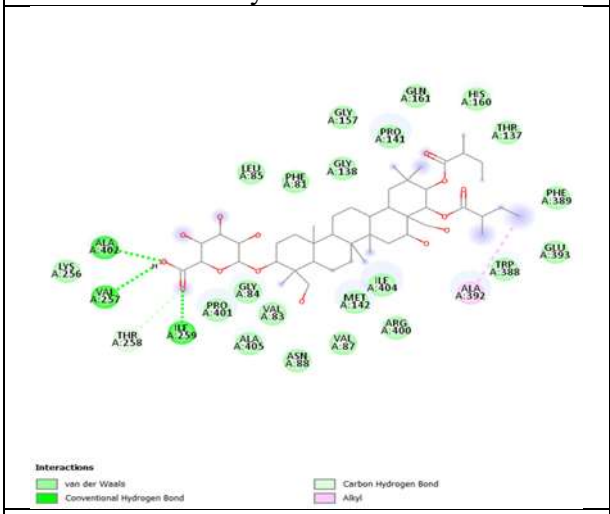
Interaction of Gymnemic acid XVIII with Glut



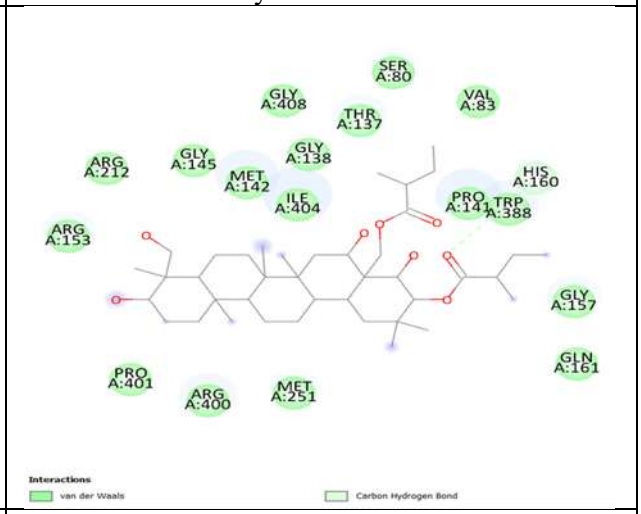
Interaction of Gymnemic acid I with Glut



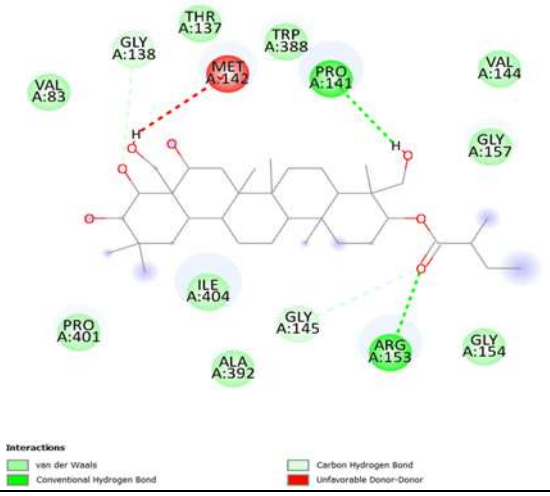
Interaction of Gymnemic acid III with Glut



Interaction of Gymnemic acid V with Glut



Interaction of Gymnemic acid XV with Glut



Interaction of Gymnemic acid XVI with Glut

Figure 2:- 2D structure of the Protein-Ligand interaction of Gymnemic acid analogues with SGLT-2 and Glut receptor

The oral bioavailability of active gymnemic acid analogues was assessed through Lipinski's rule of five. And it showed that all gymnemic acid analogues violate Lipinski's rule of five, by two or more parameters, such as molecular weight, log p, H-bond acceptor and donor, so limiting the oral bioavailability.

Table 2:- Compliance of Gymnemic acid analogues to the oral bioavailability parameters of drug likeness (Lipinski's rule of five).

Sr. no	Constituents	MW g/mol	H-bond acceptor	H-bond donor	Log p	Rotation bond	Lipinski rule	TPSA (Å^2)
1	Gymnemic acid I	806.98	14	7	3.57	10	no	229.74
2	Gymnemic acid II	808.99	14	7	5.29	11	no	229.74
3	Gymnemic acid III	766.45	13	8	3.46	9	no	223.67
4	Gymnemic acid IV	764.94	13	8	3.45	8	no	223.67
5	Gymnemic acid V	847.04	14	7	4.58	11	no	229.74
6	Gymnemic acid VI	926.49	18	11	1.922	11	no	302.82
7	Gymnemic acid VII	666.84	11	8	2.81	5	no	197.37
8	Gymnemic acid VIII	926.49	18	10	2.195	12	no	299.66
9	Gymnemic acid IX	924.47	18	10	2.057	11	no	299.66
10	Gymnemic acid X	724.4	13	8	2.004	7	no	223.67
11	Gymnemic acid XI	846.48	14	7	4.348	11	no	229.74
12	Gymnemic acid XII	968.5	19	10	2.297	13	no	308.89
13	Gymnemic acid XIII	766.45	13	8	3.45	9	no	223.67
14	Gymnemic acid XIV	764.43	13	8	3.28	8	no	223.67
15	Gymnemic acid XV	762.46	8	4	5.7	9	no	133.52
16	Gymnemic acid XVI	588.4	7	5	4.2	5	no	127.45
17	Gymnemic acid XVII	610.39	7	5	4.5	5	no	127.45
18	Gymnemic acid XVIII	610.39	7	5	4.6	5	no	127.45

In-silico study is used to predict ADMET properties, which is intended to know the Pharmacokinetics and toxic properties. It screens out the novel entity without wasting time on a lead molecule that may show low bioavailability and toxicity. In this study, the aqueous prediction (defined in water at 25℃) of predicted active lead compounds, namely, all gymnemic acid except gymnemic acid XVIII, show low aqueous solubility, low blood-brain barrier permeability. Orally administered drug absorb are either from the stomach or the intestine. In this regard, the absorption screening result showed good absorption ability for gymnemic acid VII. The clearance rate predicts excretion rate. If it is high, then the drug quickly excretes out, and if it is low, then the drug remains in the body for a long time, causing toxicity. The high clearance rate is given by gymnemic acids XV, XVII, and XVIII, and the lowest clearance rate is given by gymnemic acids VI, XII. Lastly, the half-life of the gymnemic constituent is low. Half-life shows that half of the Drug is released from the body in a time interval.

Table 3:- Predicted ADME parameters of Gymnemic acid analogues.

Sr. No.	Constituents	Aqueous Solubility	GI absorption	BBB permeant	P-Glycoprotein	CL (ml/min)	$T^{1/2}$ (H^{-1})
1	Gymnemic acid I	Low	Low	no	Yes	1.094	0.848
2	Gymnemic acid II	Low	Low	no	Yes	1.193	0.813
3	Gymnemic acid III	Low	Low	no	Yes	1.309	0.819
4	Gymnemic acid IV	Low	Low	no	Yes	1.148	0.828
5	Gymnemic acid V	Low	Low	no	Yes	1.287	0.715
6	Gymnemic acid VI	Low	Low	no	Yes	0.797	0.827
7	Gymnemic acid VII	Low	Good	no	Yes	1.198	0.813
8	Gymnemic acid VIII	Low	Low	no	Yes	1.242	0.754
9	Gymnemic acid IX	Low	Low	no	Yes	1.116	0.77
10	Gymnemic acid X	Low	Low	no	Yes	0.987	0.867
11	Gymnemic acid XI	Low	Low	no	Yes	1.189	0.676
12	Gymnemic acid XII	Low	Low	no	Yes	0.75	0.847
13	Gymnemic acid XIII	Low	Low	no	Yes	1.085	0.771
14	Gymnemic acid XIV	Low	Low	no	Yes	1.014	0.805
15	Gymnemic acid XV	Low	Low	no	Yes	8.31	0.236
16	Gymnemic acid XVI	Low	Low	no	Yes	4.907	0.411
17	Gymnemic acid XVII	Low	Low	no	Yes	6.189	0.503
18	Gymnemic acid XVIII	Good	Low	no	Yes	6.058	0.431

In the present study, we calculate toxicity risk parameters such as carcinogenicity, respiratory toxicity, H-HT, Skin-sensitivity, rat oral acute toxicity, eye irritation, and LD50. The toxicity risk assessment screening result of predicted active lead compound for anti-diabetic activity, namely, all gymnemic acids, showed mostly no risk of carcinogenicity, respiratory toxicity, H-HT, skin sensitivity, irritation, except gymnemic acid XV, which has high risk of toxicity; its LD50 is 4 mg/kg, LD50 is the maximum dose in which toxicity occur so low LD50 value means a small quantity of dose can produce toxicity. Therapeutic dose of the drug should be 1/10 of its LD50 value.

Table 4: - In-silico screening result of Gymnemic acid analogues for toxicity risk assessment at high doses/long-term use

Sr. No.	carcinogenicity	respiratory toxicity	H-HT	Skin-sensitivity	Rat oral acute toxicity	Eye irritation	LD_{50}
1	0.103	0.969	0.146	0.443	0.606	0.016	2000
2	0.115	0.975	0.22	0.369	0.647	0.012	1750
3	0.116	0.977	0.286	0.408	0.673	0.013	3220
4	0.108	0.973	0.166	0.485	0.624	0.016	1750
5	0.117	0.96	0.225	0.605	0.216	0.023	134
6	0.047	0.959	0.188	0.278	0.105	0.01	1750
7	0.242	0.987	0.276	0.184	0.685	0.016	4500
8	0.119	0.976	0.376	0.161	0.388	0.009	3220
9	0.121	0.974	0.203	0.175	0.449	0.01	1750
10	0.091	0.979	0.117	0.274	0.883	0.014	3220
11	0.1	0.966	0.181	0.661	0.37	0.023	2000
12	0.053	0.952	0.183	0.251	0.109	0.009	590
13	0.101	0.976	0.172	0.413	0.811	0.014	1190
14	0.086	0.974	0.156	0.477	0.798	0.018	1750
15	0.109	0.983	0.839	0.625	0.966	0.018	4
16	0.102	0.983	0.135	0.663	0.955	0.02	2000
17	0.099	0.982	0.099	0.622	0.949	0.017	5500
18	0.095	0.984	0.087	0.601	0.969	0.02	5000

CONCLUSION

The molecular docking and in silico ADMET studies-based identification of active gymnemic acid analogues against diabetes showed that gymnemic acid VIII, gymnemic acid VI and gymnemic acid XIII possess the most significant activity against diabetes and explored the mechanism of action by targeting human SGLT-2 receptor. Also, gymnemic acid XVII and gymnemic IX show significant activity against diabetes and explored the mechanism of action by targeting the human GluT receptor. The molecular docking studies showed that most active gymnemic acid possess higher binding affinity and effectiveness against SGLT-2 and GluT receptor. ADMET studies based on other predicted active gymnemc acid analogues were gymnemic acid I, gymnemic acid II, gymnemic acid III, gymnemic acid VIII, gymnemic acid X, gymnemic acid XII, gymnemic acid XIV, and gymnemic acid XVIII. The binding site revealed that tyrosine, serine, valine, glycine and alanine take part in compound binding. Oral bioavailability of these active analogues is still a limiting factor and therefore requires further lead optimization. Before conducting an in vivo study to evaluate antidiabetic activity, it is beneficial to perform in vitro studies because it gives effective in cost efficacy and save time. These preliminary studies help to eliminate fewer active compounds. Additionally, molecular docking with various receptors can offer insights into the potential mechanisms of action of the active compounds. The results of these structure-activity relationship analyses can be extremely valuable for the design and discovery of antidiabetic drugs derived from natural products.

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