RESEARCH ARTICLE

In-silico Study of an Ethnobotanical Plant; *Urtica dioica* for Assessing Anti-diabetic Potential

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Abstract

Urtica dioica L (Bicchu buti) is anethnobotanical plant.It is a wild herbaceous perennial plant found in the Himalayan region of India and commonly known as stinging nettle. It has ethnobotanical importance, and is used to treat various disorders since ancient times. The aim of this paper is *in-silico* study of the *U. dioica*'s phytochemicals on the glucose metabolism related to alpha-amylase. Therefore, in this research, we have assessed the anti-diabetic potential of *U. dioica* found in Ranikhet tehsil, by *in-silico* method. Hence, we conducted molecular docking of phytochemicals with a molecular anti-diabetic target i.e., alpha-amylase. From our study, we found4 potential phytochemicals namely; Ursolic acid, Pinoresinol , Beta-Sitosterol, and (-)-Pinoresinol which could be useful in effective drug development and helpful in the treatment of diabetes problems.

Keywords: Ethnobotany, molecular docking, phytochemicals, diabetes, alpha-amylase, *Urtica dioica*

International Journal of Plant and Environment (2023); **ISSN:** 2454-1117 (Print), 2455-202X (Online)

Introduction

Urtica genus belongs to the family Urticaceae (order Rosales) of the Angiosperms. It comprises about 54 genera Dorota *et al*.(*2018*). The most prominent member of the genus is the stinging nettle *U. dioica* . *Urtica* is a herbaceous perennial plant that can grow up to 2 m tall.The word "nettle" is derived from the Anglo-Saxon word "noedl" means "needle", while Latin name "urtica" means "to burn". This can pierce the skin and inject a substance including formic acid, histamine, acetylcholine, and serotonin inducing painful itching and burning sensation that may last up to 12 h. It is a wild plant with vigorous growth in ranikhet tehsil as well as all appropriate habitat. It is considered a weed due to its rapid growth and soil coverage. But nettle has much economic and ecological importance. According to Dreyer and Mussing, nettles can improve over-fertilized soil with nitrogen and phosphate [(Upton, 2013). It can also promote the biodiversity of local flora and fauna Dreyer and Mussig(2000), Di Virgilio *et al.* (2015). More than 40 species of insect are supported by *Urtica* Lang and Otto (2015) *U. dioica* reduces soil heavy metal content Viktorova *et al.* (2016). *Urtica* spp. can be used to prepare high-quality agricultural raw materials for the dyeing, textile, and energy sectors Di Virgilio *et al.* (2015). Nettles were used in Germany and Austria to make textiles during the First World War because of their content of tough fibers, Adhikari *et al.* (2016) . This whole plant use as a traditional healer (hepatoprotctive medicine) in ethnic communities of Uttrakhand (Fig. 1)

Type 2 diabetes is a very common type of diabetes, accounting for around 90% of the diabetic patient.Type-2 Diabetes (T2D) is a metabolic disorder characterized by chronic hyperglycemia condition together with the metabolism interference of carbohydrates, proteins, and lipids Porth (2010), Souto *et al.* (2011), Nogueira *et al.* (2013), Vieira *et al.*(2019) due to low or ineffective insulin. modern lifestyle increases the complication of diabetes Carbone (2019).International Diabetes Federation (IDF) reported approximately 537 million adults (20-79) are affected with diabetes in 2021 worldwide and predicted that it would rise to 783 million by the year 2045: (IDF,2017)

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How to cite this article: Chauhan, A., Sharma, P., Durgapal, A., Arya, D. and Chandra, S. (2023). In-silico Study of an Ethnobotanical Plant; *Urtica dioica* for Assessing Anti-diabetic Potential. International Journal of Plant and Environment. 9(1), 57-62.

Conflict of interest: None

Submitted: 01/02/2023 **Accepted:** 15/03/2023 **Published:** 30/03/2023

Fig. 1: *U. dioica*

Table 1: Phytochemicals of *U. dioica*(source: IMPPAT and Pubchem)

S.No	Phytochemical	SMILES Structure	CID No.
1	Isorhamnetin-3-O-neohesperidoside	OCC1OC(Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)O)OC)C(C(C1O)O)OC1OC(C)C(C(C1O)O)O	CID:24204448
2	Kaempferol	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	CID:5280863
3	Quercetin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	CID:5280343
4	Isorhamnetin	COc1cc(ccc1O)c1oc2cc(O)cc(c2c(=O)c1O)O	CID:5281654
5	Scopoletin	COc1cc2ccc(=O)oc2cc1O	CID:5280460
6	Isorhamnetin-3-O-glucoside	OC[C@H]1O[C@@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)OC)O)[C@@H]([C@H]([C@@H]1O)O)O	CID:5318645
7	Nicotiflorin	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O[C@@H]1O[C@H](CO[C@@H]2O[C@@H](C)[C@@H]([C@H]([C@H]2O)O)O)O)[C@H]([C@@H]([C@H]1O)O)O)O	CID:5318767
8	Isoquercitrin	OC[C@H]1O[C@@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)O)O)[C@@H]([C@H]([C@@H]1O)O)O	CID:5280804
9	Narcissin	COc1cc(ccc1O)c1oc2cc(O)cc(c2c(=O)c1O[C@@H]1O[C@H](CO[C@@H]2O[C@@H](C)[C@@H]([C@H]([C@H]2O)O)O)O)[C@H]([C@@H]([C@H]1O)O)O)O	CID:5481663
10	Quercetin-3-glucoside	OC[C@H]1O[C@@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(c(c2)O)[O-])[C@@H]([C@H]([C@@H]1O)O)O	CID:25203368
11	Astragalin	OC[C@H]1O[C@@H](Oc2c(oc3c(c2=O)c(O)cc(c3)O)c2ccc(cc2)O)[C@@H]([C@H]([C@@H]1O)O)O	CID:5282102
12	Rutin	Oc1cc(O)c2c(c1)oc(c(c2=O)O[C@@H]1O[C@H](CO[C@@H]2O[C@@H](C)[C@@H]([C@H]([C@H]2O)O)O)O)[C@H]([C@@H]([C@H]1O)O)O)c1ccc(c(c1)O)O	CID:5280805
13	Stigmast-5-en-3beta-yl beta-D-glucopyranoside	CC[C@@H](C(C)C)CC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O[C@@H]1OC(CO)[C@H](C(C1O)O)O)C	CID:70699351
14	Luteoxanthin	C/C(=CC=CC=C(C=CC=C(C1C=C2[C@@](O1)(C)C[C@H](CC2(C)C)O)/C)/C)/C=C/C=C(/C=C/[C@]12O[C@]2(C)C[C@H](CC1(C)C)O)C	CID:12112747
15	1'-OH-gamma-carotene glucoside/(Carotenoids B-G)	OC[C@H]1O[C@@H](OC(CCC/C(=C/C=C/C(=C/C=C/C(=C/C=C/C=C(/C=C/C=C(/C=C/C2=C(C)CCCC2(C)C)C)/C)/C)/C)(C)C)C(C([C@@H]1O)O)O	CID:16061280
16	Betaine	[O-]C(=O)C[N+](C)(C)C	CID:247
17	Choline	OCC[N+](C)(C)C	CID:305
18	Lutein 5,6-epoxide	C/C(=CC=CC=C(C=CC=C(C=C[C@]12O[C@]2(C)C[C@H](CC1(C)C)O)/C)/C)/C=C/C=C(/C=C/[C@H]1C(=C[C@@H](CC1(C)C)O)C)C	CID:5281244
19	Serotonin	NCCc1c[nH]c2c1cc(O)cc2	CID:5202
20	beta-Carotene	C/C(=CC=CC=C(C=CC=C(C=CC1=C(C)CCCC1(C)C)/C)/C)/C=C/C=C(/C=C/C1=C(C)CCCC1(C)C)C	CID:5280489
21	Acetylcholine	CC(=O)OCC[N+](C)(C)C	CID:187
22	Violaxanthin	C/C(=CC=CC=C(C=CC=C(C=C[C@]12O[C@]2(C)C[C@H](CC1(C)C)O)/C)/C)/C=C/C=C(/C=C/[C@]12O[C@]2(C)C[C@H](CC1(C)C)O)C	CID:448438
23	Isolariciresinol	OC[C@@H]1Cc2cc(OC)c(cc2[C@@H]([C@H]1CO)c1ccc(c(c1)OC)O)O	CID:160521
24	Vanillin	COc1cc(C=O)ccc1O	CID:1183
25	Secoisolariciresinol	OC[C@@H]([C@@H](Cc1ccc(c(c1)OC)O)CO)Cc1ccc(c(c1)OC)O	CID:65373
26	Vanillic acid	COc1cc(ccc1O)C(=O)O	CID:8468
27	Homovanillyl alcohol	OCCc1ccc(c(c1)OC)O	CID:16928
28	beta-Sitosterol	CC[C@@H](C(C)C)CC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C	CID:222284
29	Histamine	NCCc1cnc[nH]1	CID:774
30	(-)-Pinoresinol	COc1cc(ccc1O)[C@@H]1OC[C@@H]2[C@H]1CO[C@H]2c1ccc(c(c1)OC)O	CID:12309636
31	Pinoresinol	COc1cc(ccc1O)[C@H]1OC[C@H]2[C@@H]1CO[C@@H]2c1ccc(c(c1)OC)O	CID:73399
32	Coriolic acid	CCCCCC(/C=C/C=CCCCCCCCC(=O)O)O	CID:5282947
33	Dehydrodiconiferyl alcohol	OC/C=C/c1cc2c(c(c1)OC)OC(C2CO)c1ccc(c(c1)OC)O	CID:5372367
34	(+)-Neoolivil	OC[C@H]1[C@@H](O[C@H]([C@@H]1CO)c1ccc(c(c1)OC)O)c1ccc(c(c1)OC)O	CID:9976812
35	Ferulic acid	COc1cc(/C=C/C(=O)O)ccc1O	CID:445858
36	Chlorogenic acid	O=C(O[C@@H]1C[C@@](O)(C[C@H]([C@H]1O)O)C(=O)O)/C=C/c1ccc(c(c1)O)O	CID:1794427
37	Ursolic acid	C[C@@H]1CC[C@]2([C@@H]([C@H]1C)C1=CC[C@H]3[C@@]([C@@]1(CC2)C)(C)CC[C@@H]1[C@]3(C)CC[C@@H](C1(C)C)O)C(=O)O	CID:64945
38	Erucic acid	CCCCCCCC/C=CCCCCCCCCCCCC(=O)O	CID:5281116
39	4-Hydroxycinnamic acid	OC(=O)/C=C/c1ccc(cc1)O	CID:637542

The eventual aim behind diabetes treatment is to lower and maintain the glycosylated hemoglobin level below 7% to prevent various vascular complications associated with the disease Stein et al., (2013). For the treatment of T2D, insulin sensitizers, insulin secretagogues, and external insulin delivery (insulin analogs) are mostly used. Combinations of different drugs are used to control diabetes. However, the adverse side effects associated with many synthetic anti-diabetic drugs have rejuvenated interest in traditional ayurvedic systems Sharma *et al.*(2021).

In the modern age, computational approaches are a constitutive part of drug discovery. These computational techniques reduce the time and cost of drug development Yang (2010), Mukesh (2011). The target-based drug discovery has been a widely used approach due to its accurate and specific nature. There are many molecular targets have been reported to develop new drugs against T2D like- glucagon-like peptide-1 (GLP-1) agonists, sodium-dependent glucose transporter 2(SGLT2) inhibitors, Aldose Reductase (AR), Peroxisome proliferator-activated receptor gamma (PPAR-c), free fatty acid receptor 1(GPR40) and dipeptidyl peptidase-4 (DPP4),etc. are being clinically approved. Although *Urtica dioica* is a potential anti-diabetic plant but the specific phytochemicals of *U. dioica* and their molecular targets are not been explicitly discovered. Hence, to find out the specific targets and phytochemicals involved in exerting the anti-diabetic effect of *U. dioica*, *in-silico* screening was carried out by molecular docking using the receptors; alpha-amylase against 39 phytochemicals (Table 1). Virtual Screening (VS) results revealed that 3BAJ might be the most prominent target on which phytochemicals of *U. dioica* exert their action to reduce blood glucose levels. Human pancreatic alpha-amylase (BAJ) is a single polypeptide chain having 496 amino acids that bind to calcium, chloride, and nitrate ions. This enzyme is responsible for the hydrolysis of small oligosaccharides in the small intestine, into glucose. Inhibition of HPA gives an effective target for the treatment of type 2 diabetes.

Materials and Methods

Data Source

The IMPPAT database (https://cb.imsc.res.in/imppat/home) and PubChem were used to download phytochemicals of *U. dioica* and standard drug compounds (3D PDB). Phytochemical's name with canonical smiles and CID no. is shown in Table 1.

Preparation of Ligands

PubChem and IMPPTdata bases were used to find the 3D-SDF structures of phytochemicals of *U. dioica*. Open Babel GUI software was used to convert the ligand file format from SDF to a 3D PDB file.

Preparation of Target Protein

RCSB PDB online site was used for obtaining Human pancreatic alpha-amylase 3BAJ that already had a co-crystallized inhibitor (ARE) (Fig. 2). Molecular docking could not be performed on the raw PDB protein because 3D protein has different unwanted molecules like metal ions, water molecules, etc. Thus, before moving on to the docking analysis, the target protein was refined and energy-optimized.

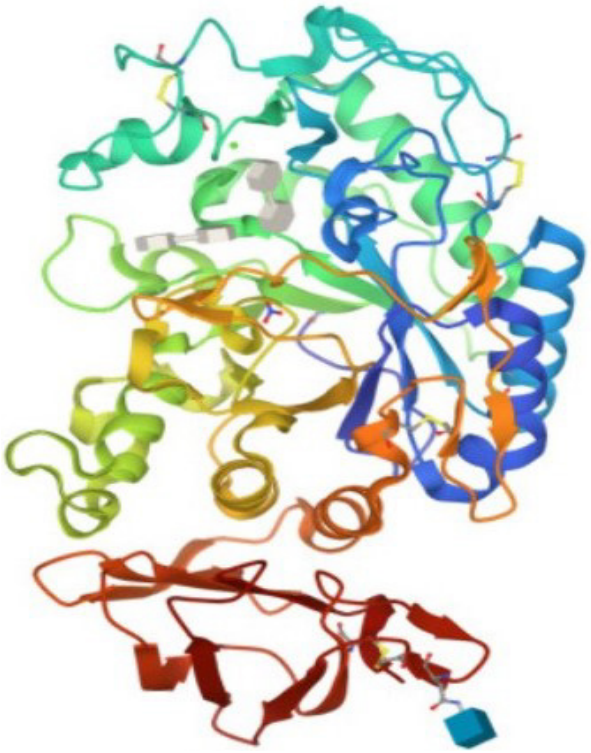


Fig. 2: 3D Model of Human pancreatic alpha-amylase (PDB Id 3BAJ)

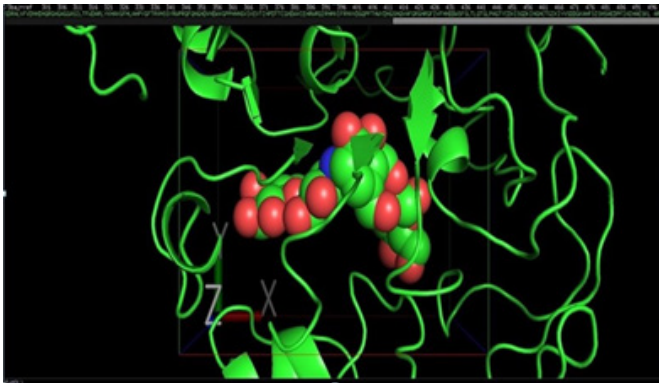


Fig. 3: Binding Pocket of Reference Molecule

Using PyMOL software, we obtained coordinates of the binding pocket of ARE inhibitor to the protein alpha-amylase (3BAJ)and then prepared 3D PDBs of protein with inhibitor. A binding pocket is a 3D configuration in which an inhibitor binds with the target protein and inhibits its function (Fig. 3). Binding pockets of reference molecule obtained by PyMOL were-

Center- X (8.7), Y(15.4), Z(40.2)
Size- X(26.6), Y(19.7), Z(21.7)

Molecular Docking

InstaDockv1.1(https://instadock.webs.com) was used for docking to dock clean 3BAJ protein with reference molecules and 39 phytochemicals of *U. dioica*.

Molecular docking-based virtual screening of a library of 39 compounds with 3BAJ clean protein was performed to predict their binding affinity and detailed interactions with the protein. The docking was performed by using InstaDock

Table 2: List of phytochemicals of *U. dioica* showed the best binding affinity

s. no.	Name of the ligand	Binding energy (kcal/mol)	pKi	Ligand Efficiency (kcal/mol/non-Hatom)
1	Ursolic acid (64945)	-9	6.6	.2727
2	Pinoresinol (73399)	-8.7	6.38	.3346
3	beta-Sitosterol (222284)	-9.5	6.97	.3241
4	Lutein 5,6-epoxide (5281244)	-8.6	6.31	.2
5	Luteoxanthin (12112747)	-8.9	6.53	.2023
6	(-)-Pinoresinol (12309636)	-8.8	6.45	.3385
7	ARE(REF)	-8.9	6.53	.2030

software, a single-click molecular docking tool that automates the entire process of molecular docking-based virtual screening Mohammad *et al.,* (2020). The binding energies of molecules with 3BAJ protein were calculated using molecular docking.

For docking, we made a folder and put instadock exe file, PDB of clean protein, reference molecule, and 39 phytochemicals of *U. dioica* in it then opened instadock.exe file, clicked on the tool and clicked on prepare receptor. InstaDock change PDB file into PDBQT format. After preparing the receptor, a configuration file was generated. The coordinate of this configuration file was set according to the calculation of the center of mass as determined by PyMOLsoftware. After that , prepare ligand option was clicked on prepare ligand(s), InstaDock changed all phytochemicals PDB into PDBQT as well as started docking. After docking, the docking folder had an autogenerated result folder, a conf file, and PDBsand PDBQTs of protein, references, and ligands. The resulting folder had log and out files of reference and ligands, affinity result file, and InstaDock result summary. Six phytochemicals showed the best binding affinity with protein after the result analysis.

Affinity result file

Out file contains 9 models of dockedligand. The model which showed a maximum affinity with reference was selected for analysis. We made PDB of clean protein and selected a model of the ligand with the help of PyMOL. With the help of this PDB,ligPLOTwasmade to shows protein-ligand interaction. Afterthat drug-likeness and ADMETproperties of selected phytochemicals were checked .

Evaluation of Drug Likeliness

There are two main rules for checking drug-likeness- Lipinski's rule of five and Muegge et al rule. Lipinski's rule of five (RO5) is used to assess the drug-likeliness of a chemical or biochemical molecule. It possesses qualities that would make it a likely or potential drug in humans Davella and Mamidala, (2019)**.** Calculating molecular properties such as log P (partition coefficient), number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight might help forecast a pharmacological compound's oral action. The compound that follows the criteria in this investigation indicates that they have good oral bioavailability. Both rules are useful for characterizing the molecular features of medicinal compounds that are needed to estimate critical pharmacokinetic parameters like absorption, distribution, metabolism, excretion, and toxicity (ADMET). The rules are useful in medication development and design Stein *et al.* (2013). The IMPPAT and admetSAR server was used to estimate drug similarity and molecular properties

Table 3: The molecular structure, drug-likeness properties and Lipinski Rule of 5

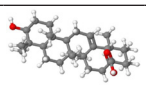
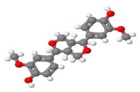
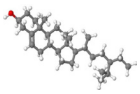
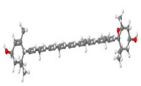
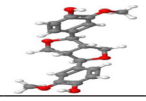
s. no	Name of phytochemical	Molecular formula And Weight	Structure	AlogP	HBA	HBD	Lipinski rule of 5
1	Ursolic acid (64945)	456.71		7.09	2	2	passed
2	Pinoresinol (73399)	358.393		3.19	6	2	Passed
3	Beta-Sitosterol (222284)	414.72		8.02	1	1	Passed
4	Lutein 5,6-epoxide (5281244)	584.89		9.61	3	2	failed
5	Luteoxanthin (12112747)	600.88		8.97	4	2	failed
6	(-)-Pinoresinol (12309636)	358.39		3.19	6	2	Passed

Table 3 shows molecular structure, properties, and the results of a drug likeliness evaluation based on Lipinski's rule of five of 10 ligands. Lipinski's rule of five is maintained for the majority of ligands based on drug likeliness evaluation.

Lipinski rules of 5 is useful for characterizing the molecular features of medicinal compounds that are needed to estimate critical pharmacokinetic parameters like absorption, distribution, metabolism, excretion, and toxicity (ADMET) (Table 4). The rules are useful in medication development and design Stein et al. (2013). The IMPPAT and admet SAR server were used to estimate drug similarity and molecular properties.

Table 4: ADME properties of selected Phytochemicals

S. no.	Phytochemical name	Bioavailability score	Ames mutagenesis	BBB	GI absorption	Water solubility	Carcinogenicity (binary)	P- glycoprotein Inhibitor	Biodegradation
1	Ursolic acid(64945)	.85	-	-	Low	-4.388	-	-	-
2	Pinoresinol (73399)	.55	+	+	Yes (High)	-3.298	-	+	-
3	beta-Sitosterol (222284)	.55	-	+	Low	-4.703	-	-	-
4	Lutein 5,6-epoxide (5281244)	.17	+	+	Low	-3.546	-	+	-
5	Luteoxanthin (12112747)	.55	-	+	High	-4.22	-	+	-
6	(-)-Pinoresinol (12309636)	.55	+	+	High	-3.298	-	+	-

Ligplot v.2.2.7 was used to show various hydrogen and hydrophobic interaction between selected phytochemicals and different amino acids (AA) residues of the target protein (Fig. 4).

Results

A computational study is one of the preclinical approach which can be used for traditional medicinal plantsfor assessment of different pharmacological activities, and it provides valuable leads for the development of safe and effective medicine. Itis a method for analyzing the manufactured compounds and their interactions with biological targets proteins, which is crucial in drug development. The amino acids in the active site region of the target protein were predicted using the molecular docking program. From docking, we found 6 phytochemicals (Ursolic acid (64945), Pinoresinol (73399), beta-Sitosterol (222284), (-)-Pinoresinol (12309636), Lutein 5,6-epoxide (5281244), Luteoxanthin (12112747) of *U. dioica* that showed the best affinity with ARE protein(Type-2- Diabetes target). When drug-likeness and ADME properties of these phytochemicals were checked by different software and online tools, we obtained 4 eligible

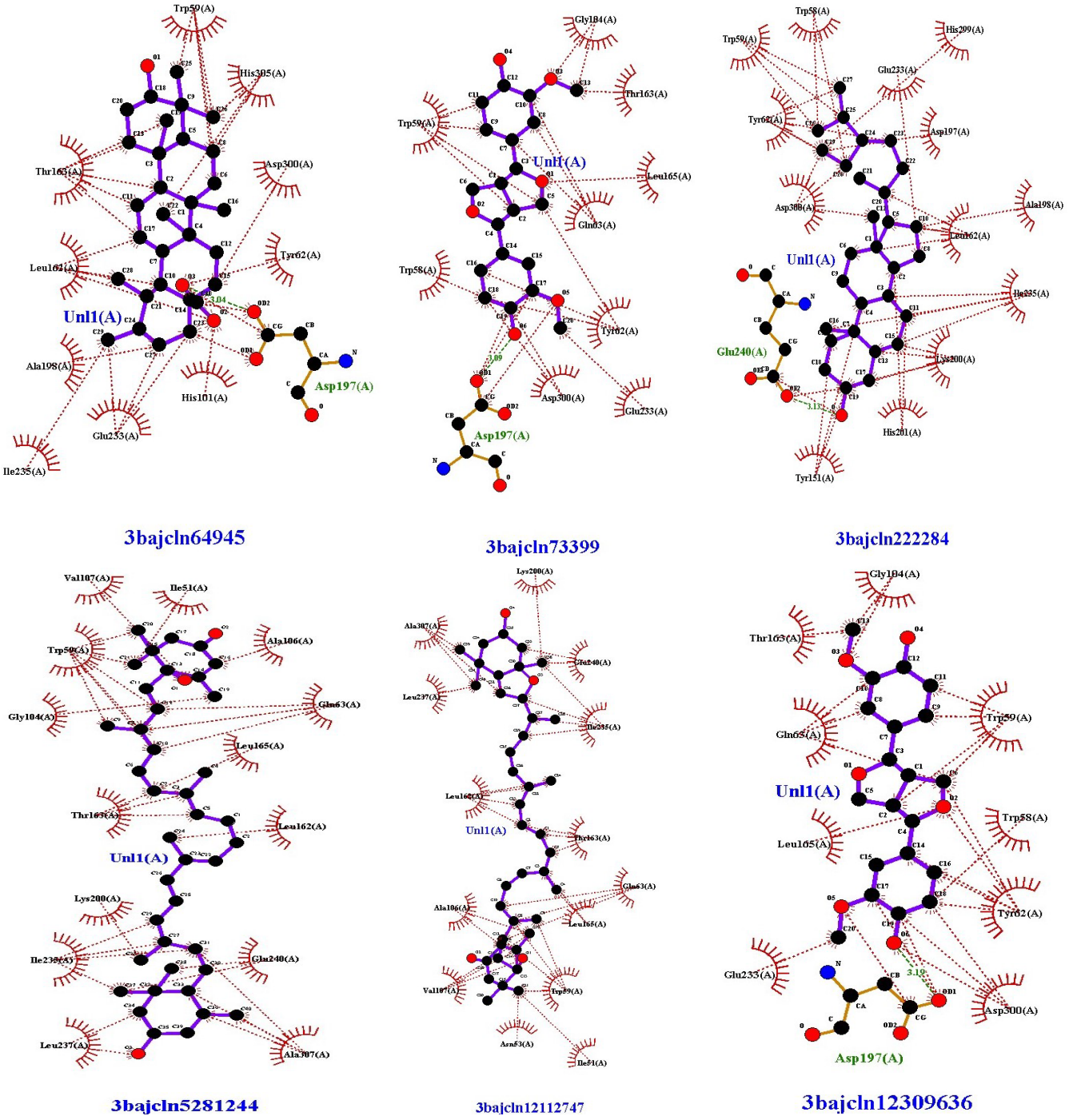


Fig. 4: LIGPLOT showing hydrogen and hydrophobic bonds between U.dioica's phytochemicals and 3BAJ

phytochemicals Ursolic acid (64945), Pinoresinol (73399), beta-Sitosterol (222284), (-)-Pinoresinol (12309636) that follow the Lipinski rule and different criteria of ADME.

Conclusion

Understanding the interaction between protein and phytochemicals (ligands) is the most important parameter for the pharmaceutical and food industries. Bioinformatics has offered a program to explore disease at the molecular level using computational tools. According to the docking results, the selected phytochemicals may form hydrogen bonds and hydrophobic bonds with various residues of selected proteins to interact effectively. The docking procedure reveals that several phytochemicals that have a great affinity with DM target protein 3BAJ. However, the mechanisms related to these effects need to be further investigated but computer-based drug designing plays a significant role in structural-based drug designing. The result of molecular docking is important for pharmacophore modeling which is used catalytic activity of the enzyme because docking had a high affinity and nearby near the active site pocket of alpha-amylase. In conlusion, we can say that docking experiments reveal many potential phytochemicals of *U. dioica* which can be further explored to develop potential anti-diabetic drugs.

Acknowledgment

Authors thankDr.Prachi Joshi, HOD of Department of Botany, Govt. P.G.College, Ranikhet for their valuable support.Head , Department of Botany, SSJ Campus, Amora, Soban Singh JeenaUniversity is acknowledged for providing facility to conduct computational experiments.

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