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Molecular docking, drug-likeness, medicinal chemistry, and toxicity characteristics of antidiabetic compounds found in the Citrullus lanatus plant leaves from Vadodara city

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ABSTRACT:

This study's primary goal is to perform molecular docking analysis and screen for drug-likeness, medicinal properties, and toxicity properties of identified active compounds obtained from Citrullus lanatus leaves using gas chromatography-mass spectrometry. Molecular docking and gas chromatography-mass spectrometry were applied to the extracts. The leaf extracts of Citrullus lanatus were found to contain five compounds according to the gas chromatography-mass spectrometry analysis. While 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound from Vadodara city showed the best effectiveness in antidiabetic action, the results of the in silico molecular docking studies demonstrated that all five compounds have antidiabetic potential. All five compounds exhibit promising drug-likeness properties, medicinal chemistry, and toxicity. Citrullus lanatus leaves may therefore be a useful pharmaceutical agent in the management and treatment of complications associated with many therapeutic applications including diabetes.

Keywords: Leaves, Gas Chromatography-Mass Spectrometry, Molecular Docking, *Citrullus Lanatus*, Drug-Likeness, Medicinal Chemistry, Toxicity

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1. Introduction

Diabetics have been documented since the Hindu scriptures. It was named a madhu meha because madhu implies honey, as well as meha, which implies passing it out via excrement[(1).] Gujarat has the highest rate of instances of diabetes within the country, as per to an agencies of the central bureau of health intelligence's as well as national health credentials from 2015. The medical summary indicates that 1,61,578 people in Gujarat have diabetes, making up 20.5% of the 7,87,435 individuals in the community who were checked. The international federation of diabetes states that 5 crore citizens of India suffer from diabetes. 8 to 10% of sceptical cases of diabetes are in Gujarat. Approximately 10% of cases encompass either type 1 or just juvenile diabetes; the remaining 90% include diabetes of the type 2 variety.[(2)].
Herbs as well as diabetes have become expanded connections in earlier. Consequently, medicinal plants are a possible supplier of pharmaceuticals of antidiabetic. These contained within enhancing regeneration or else improvement of pancreatic beta cells which are damaged, also protects against additional injury, insulin synthesis of enhancing and secretion from the beta-cells, decreasing glucose absorption from the gastrointestinal, cumulative insulin compassion of the tissues, keeping insulin imitating properties, and ever-changing the action of some enzymes concerned in glucose metabolism[(3)].
Citrullus lanatus is commonly found in Gujarat. Plant's leaf parts are commonly used for many purposes. Citrullus lanatus is often used as a sympathomimetic, anti-dysenteric, and hyperlipidemia diabetes treatment [(4).] Docking, drug-likeness criteria, medicinal chemistry, as well as toxicity are all extensively utilised extensively within the context of medicinal product development along with discovery.

2. Materials and methods

2.1 Extraction and Evaluation of gas chromatography-mass spectrometry

Citrullus lanatus leaves were collected from Vadodara, Gujarat, India. and were fresh and healthy. Methanol was used to extract the fine powder of Citrullus lanatus plant leaves. Extraction was done by maceration process [(5)]. Evaluation of gas chromatography-mass spectrometry was performed in Citrullus lanatus leaves of Vadodara city [(6).]

2.2 In-silico molecular docking studies

2.2.1 Target protein and ligand selection

Collaboration in research for protein databank structural bioinformatics provided the three-dimensional computational models of the subject of study protein structures including receptor of pancreatic lipase, receptor of alpha-amylase, receptor of beta-glucosidase, receptor of interleukin 6, receptor of tumor necrosis factor-alpha alongside receptor of alpha-glucosidase[(7)]. The substances of interest that demonstrated anti- diabetic effects were identified through analysis of gcms of leaves extracts from Citrullus lanatus plants, and those compounds were selected for docking research. Every ligand has been achieved to the highlight where it is commonly utilised for the structure data file (SDF) library offering of the substance framework information collected by PubChem. These structures of ligands were processed to.pdb form using the Openbabel programme.

2.3 In silico drug-likeness, medicinal chemistry and toxicity prediction

Veber along with Lipinski carried out drug-likeness applications through rule assessment. The rule of PAINS, the rule of Brenk, and the portability of synthetic substances were assessed within the field of medicinal chemistry[(8)]. Predictions of toxicity have been offered regarding

the toxicity of cyto, toxicity of mutagen, toxicity of immuno, along toxicity of hepato of various chemical compounds [(9)]. Also, receptor-ligand development were observed along with reconfiguring using Pymol computer software. Additionally, the independent application suite patchdock alongside CB-Dock2 is primarily utilised for simulation testing as well as receptor-ligand multifaceted the docking process. SwissADME and ProTox-II were utilised to forecast the drug-likeness, medicinal chemistry and toxicity of chemical variables.

3. Results and Discussion

Through gcms, we can find active volatile components in leaves of Citrullus lanatus of Vadodara city. The research conducted using the technique of gas chromatography-mass spectrometry revealed that the leaf extract contained five different compounds of Citrullus lanatus of Vadodara city. Names of all five compounds from Citrullus lanatus of Vadodara city was represented in (Tables 1). Discovered the best molecules according to their binding effectiveness, number of receptor sites docked.

From docked results, it was observed that among the five compounds from in-habitat Citrullus lanatus leaves from Vadodara city 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide showed binding efficiency with all six target proteins. The binding energy of this compound observed against receptor of alpha-amylase(4GQR), receptor of alpha-glucosidase(5NN5), receptor of interleukin 6(1ALU), receptor of tumor necrosis factor-α(1TNF-α), receptor of beta-glucosidase(2ZOX) and receptor of pancreatic lipase(2OXE) were(-6.8, -6.6, -6.1, -8.0, -8.8 and -6.7 kcal/mol)correspondingly. Among every compounds as of this plant in Vadodara city 3beta-hydroxy-27-norcholest-5-en-25-one showed highest binding efficiency with receptor of beta-glucosidase were (-10.6 kcal/mol) (Table 2).

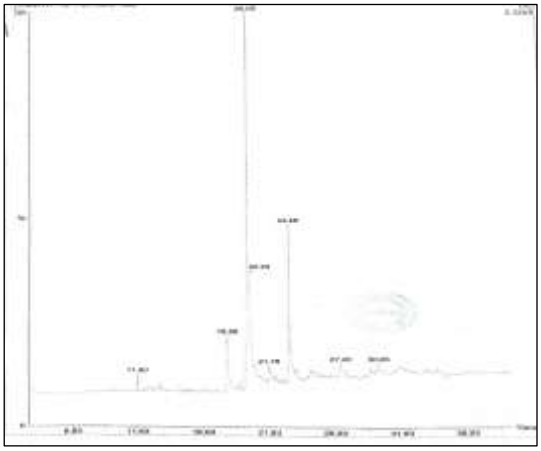


Figure 1: GCMS chromatogram of Citrullus lanatus plants from Vadodara city

All active volatile compounds were evaluated through drug-likeness,medicinal chemistry as well as toxicity predictions. Wher**e** drug-likeness candidature was implemented by two rule based filters lipinski as well as veber rules. In plant Citrullus lanatus from Vadodara city all five compounds,2,2, 7,7- tetra methyl tri cyclo [6.2.1.0 (1,6)] undec-4-en-3- one compound; citronellol compound; n~1 ~[3- cyano-6- (tert- pentyl)-4,5,6,7-tetra hydro-1-benzo thio phen-2-yl]-2-ethyl butan amide compound; 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound; as well as 3beta-hydroxy-27-norcholest-5-en-25-one compound followed lipinski as well as veber rule base filters (Table 3).

The rules of PAINS, rule of brenk, and rule of synthetic accessibility were assessed in medicinal chemistry. In plant, Citrullus lanatus from Vadodara city, citronellol compound and 3beta-Hydroxy-27-norcholest-5-en-25-one compound did not show PAINS alert but showed a

brenk alert. Other three compounds, 2,2, 7,7- tetra methyl tri cyclo [6.2.1.0 (1,6)] undec-4-en-3- one compound; n~1 ~[3- cyano-6-(tert- pentyl)-4,5,6,7-tetra hydro-1-benzo thiophen-2-yl]-2-ethyl butan amide compound; as well as 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound didn't show any alert in both rules (Table 4).

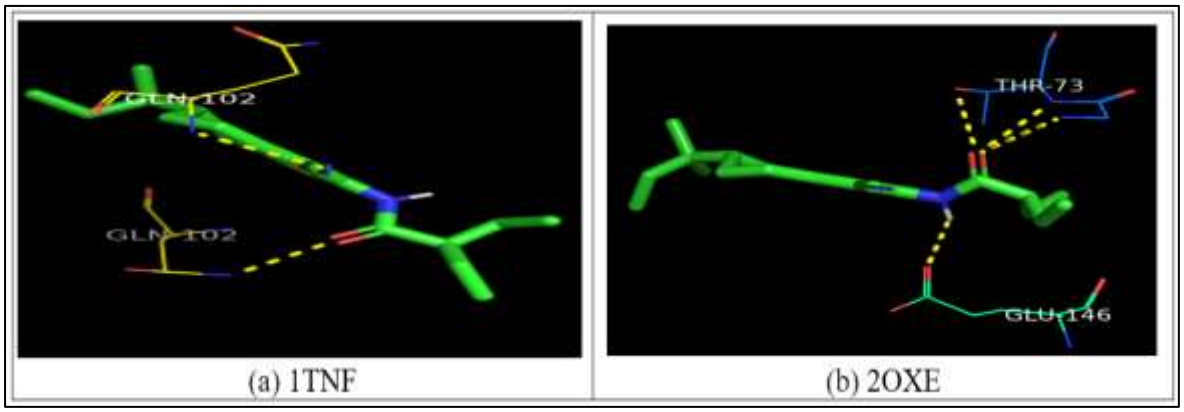
Toxicity of cyto, Toxicity of mutagen, toxicity of immune, and toxicity of hepato were predicted depending on the compound's toxicity. All the toxicity properties were related to diabetes mellitus. In plant, Citrullus lanatus from Vadodara city 3beta-Hydroxy-27-norcholest-5-en-25-one compound gave active output in immunotoxicity. Other four compounds, 2,2, 7,7-tetra methyl tri cyclo [6.2.1.0 (1,6)] undec-4-en-3- one compound; citronellol; n~1 ~[3- cyano-6-(tert- pentyl)-4,5,6,7-tetra hydro-1-benzo thiophen-2-yl]-2-ethyl butan amide compound as well as 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound gave inactive outputs in all toxicity (Table 5).

Table 1: Molecular information with spectrum of active compounds found in leaves of the Citrullus lanatus of Vadodara city

Name of the Compound	Molecular Formula	Molecular structure	Spectrum
2,2,7,7-Tetramethyltricyclo [6.2.1.0(1,6)]undec -4-en-3-one	C15H2O		
Citronellol	C10H20O		
N~1~-[3-Cyano-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2 ethyl butanamide	C20H30N2OS		
5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide	C20H21NO2		
3beta-Hydroxy-27-norcholest-5-en-25-one	C26H42O2		

Table 2: Ligand docking study of Citrullus lanatus leaves in Vadodara city

Name of ligand	Name of protein receptor	Docked binding energy (Kcal/mol)
2,2,7,7-Tetramethyltricyclo [6.2.1.0(1,6)]undec -4-en-3-one	Alpha-amylase	NA
	Alpha-glucosidase	-6.5
	Interleukin 6	-6.1
	Tumor necrosis factor-α	NA
	Beta-glucosidase	NA
	Pancreatic lipase	NA
Citronellol	Alpha-amylase	-4.8
	Alpha-glucosidase	-5.6
	Interleukin 6	-4.5
	Tumor necrosis factor-α	-5.0
	Beta-glucosidase	NA
	Pancreatic lipase	-5.3
N-1-[3-Cyano-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2 ethyl butanamide	Alpha-amylase	NA
	Alpha-glucosidase	NA
	Interleukin 6	NA
	Tumor necrosis factor-α	-8.1
	Beta-glucosidase	NA
	Pancreatic lipase	-6.8
5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide	Alpha-amylase	- 6.8
	Alpha-glucosidase	-6.6
	Interleukin 6	-6.1
	Tumor necrosis factor-α	-8.0
	Beta-glucosidase	-8.8
	Pancreatic lipase	-6.7
3beta-Hydroxy-27-norcholest-5-en-25-one	Alpha-amylase	NA
	Alpha-glucosidase	NA
	Interleukin 6	-6.5
	Tumor necrosis factor-α	-9.3
	Beta-glucosidase	-10.6
	Pancreatic lipase	-7.2



(a) 1TNF (b) 2OXE

Figure 2: 3D structure of receptors 1TNF, 2OXE and ligan n~1 ~[3- cyano-6-(tert- pentyl)-4,5,6,7-tetra hydro-1-benzo thiophen-2-yl]-2-ethyl butan amide interaction with amino acids

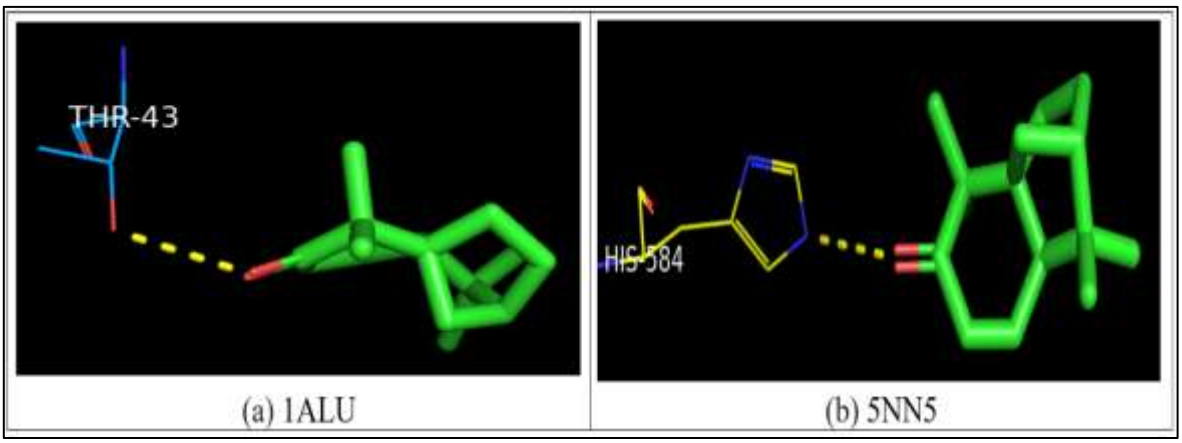


Figure 3: 3D structure of receptors 1ALU, 5NN5 and ligand 2,2 7,7- tetra methyl tri cyclo [6.2.1.0 (1,6)] undec-4-en-3- one interaction with amino acids

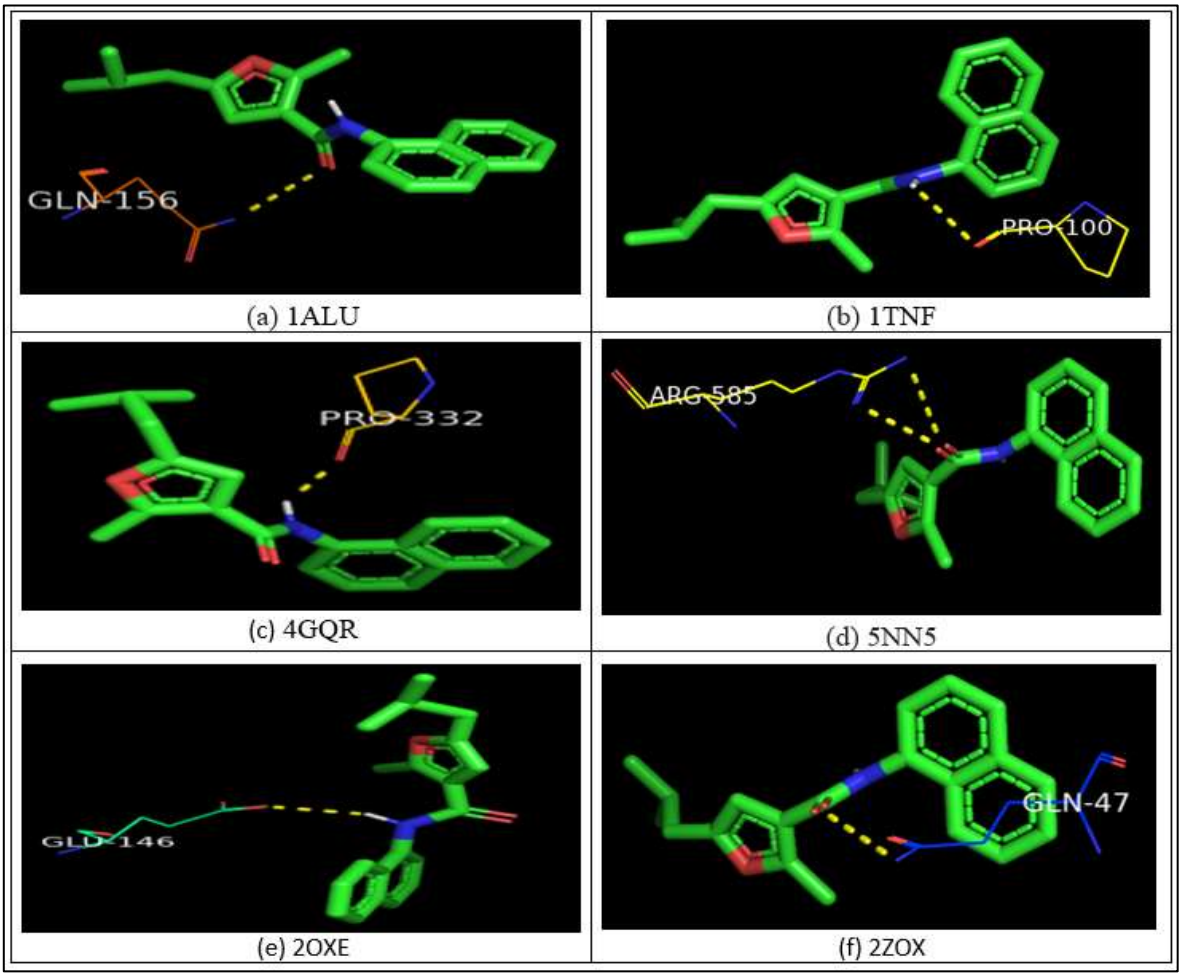


Figure 4: 3D structure of receptors 1TNF, 1ALU,4GQR,5NN5,2OXE,2ZOX and ligand 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide interaction with amino acids

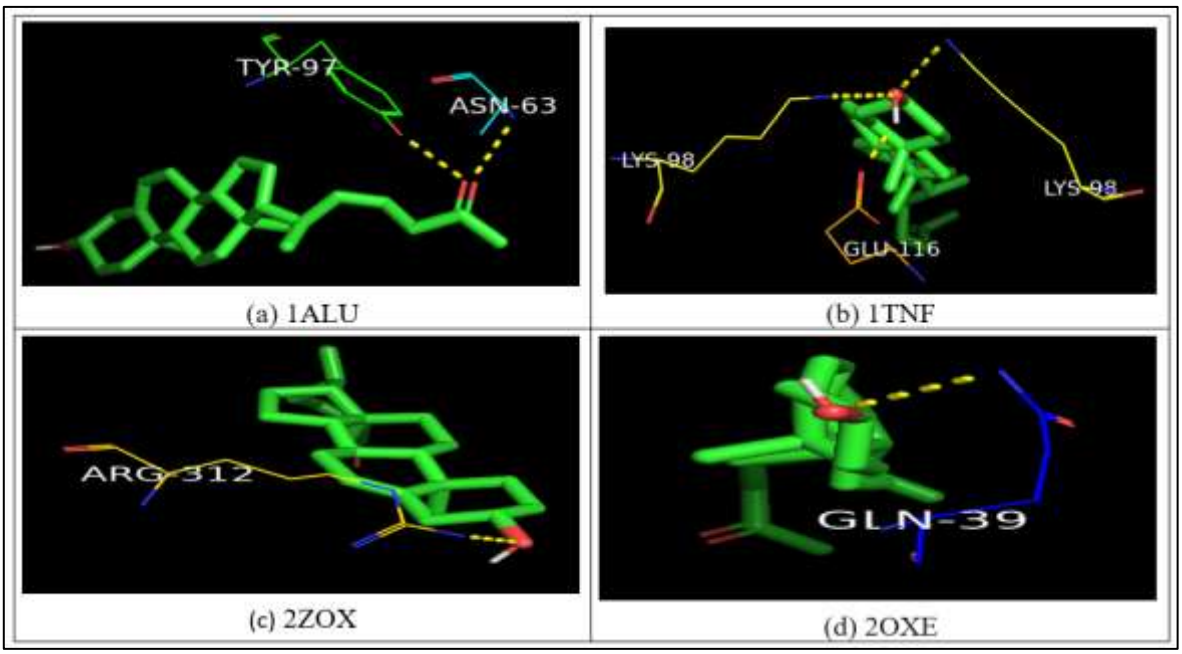


Figure 5: 3D structure of receptors 1TNF, 1ALU, 2OXE, 2ZOX and ligand 3beta-hydroxy-27-norcholest-5-en-25-one interaction with amino acids

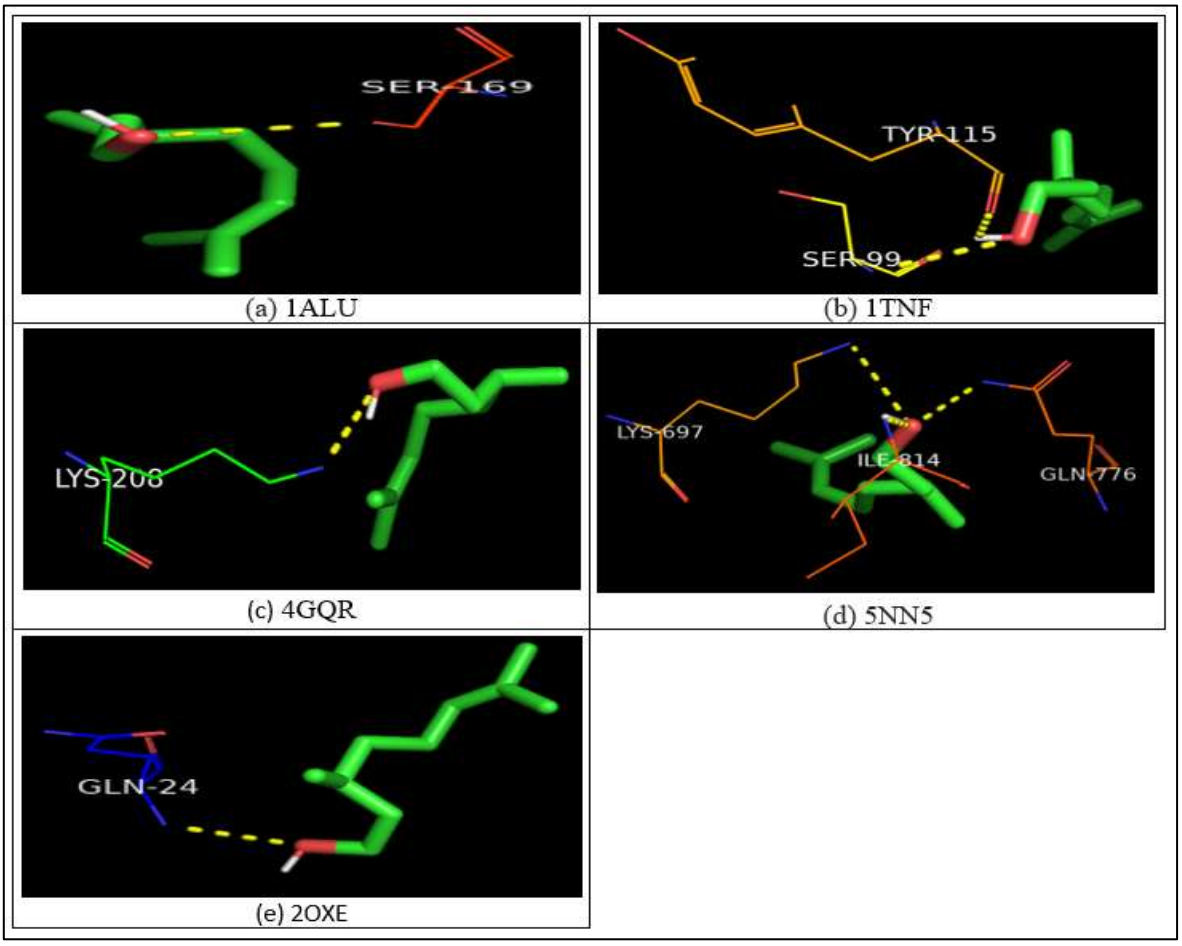


Figure 6: 3D structure of receptors 1ALU, 1TNF, 5NN5, 4GQR, 2OXE and ligand citronellol interaction with amino acids

Table 3 Parameters that are predicted to be drug-likeness content of compounds identified in the leaves of Vadodara city in plant Citrullus lanatus

Compounds	**Lipinski rules**					**Veber rules**			**Bioavailability Score**
	MW < 500	HBA <10	HBD <5	MLogP <4.15	Lipinski #Violation	nRB <10	TPSA Å <140	Veber #Violation	
2,2,7,7-Tetramethyltricyclo[6.2.1.0(1,6)]undec-4-en-3-one	218.33	1	0	3.56	Yes #0	0	17.07	Yes #0	0.55
Citronellol	156.27	1	1	2.70	Yes #0	5	20.23	Yes #0	0.55
N~1~-[3-Cyano-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2 ethylbutanamide	348.53	2	1	3.39	Yes #0	7	81.13	Yes #0	0.55
5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide	312.39	3	1	2.14	Yes #0	5	66.03	Yes #0	0.55
3beta-Hydroxy-27-norcholest-5-en-25-one	386.61	2	1	5.10	Yes #1	5	37.30	Yes #0	0.55

Table 4 Predicted medicinal chemistry parameters of compounds identified in a leaves of Vadodara city in plant Citrullus lanatus

Compounds	**PAINS #alerts**	**Brenk #alerts**	**Synthetic accessibility**
2,2,7,7-Tetramethyltricyclo [6.2.1.0(1,6)]undec-4-en-3-one	0	0	4.97
Citronellol	0	1	2.61
N~1~-[3-Cyano-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2 ethyl butanamide	0	0	4.97
5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide	0	0	3.90
3beta-Hydroxy-27-norcholest-5-en-25-one	0	1	5.63

Table 5. Predicted toxicity parameters of compounds identified in a leaves of Vadodara city in plant Citrullus lanatus

Compounds	**Hepatotoxicity #Probability**	**Immunotoxicity #Probability**	**Mutagenicity #Probability**	**Cytotoxicity #Probability**	**Toxicity class**	**LD_{50} (mg/kg)**
2,2,7,7-Tetramethyltricyclo[6.2.1.0(1,6)]undec-4-en-3-one	Inactive #0.74	Inactive #0.93	Inactive #0.85	Inactive #0.68	5	2300
Citronellol	Inactive #0.84	Inactive #0.99	Inactive #0.96	Inactive #0.86	5	3450
N~1~-[3-Cyano-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]-2 ethylbutanamide	Inactive #0.77	Inactive #0.99	Inactive #0.75	Inactive #0.74	4	1200
5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide	Inactive #0.50	Inactive #0.89	Inactive #0.58	Inactive #0.78	4	1000
3beta-Hydroxy-27-norcholest-5-en-25-one	Inactive #0.54	Active #0.99	Inactive #0.96	Inactive #0.90	6	8800

4. Conclusion

Therefore, it can be concluded from the results that from Vadodara city of medicinal plant Citrullus lanatus leaves citronellol compound, n~1 ~[3- cyano-6-(tert- pentyl)-4,5,6,7-tetra hydro-1-benzo thiophen-2-yl]-2-ethyl butan amide compound, 2,2, 7,7- tetra methyl tri cyclo [6.2.1.0 (1,6)] undec-4-en-3- one compound, 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound, 3beta-Hydroxy-27-norcholest-5-en-25-one compound were identified by gas-chromatography– mass spectrometry analysis. Also, from in - silico analysis, 5-isobutyl-2-methyl-N~3~-(1-naphthyl)-3-furamide compound from Citrullus lanatus leaves from Vadodara city found best antidiabetic potential. Furthermore, all five compounds drug-likeness, medicinal chemistry and toxicity properties were studied. Based on the present research work findings, it was identified that medicinal plant Citrullus lanatus leaves have effective in antidiabetic action. All these plant leaves possessed significant antidiabetic activity may be due presence of compounds. There are very few studies on these plant leaves for anti-diabetic properties. Therefore, the current study has presented helpful information on the quality of these herbal materials to verify the authenticity, safety, and efficacy before commercial interest in both research institutes and pharmaceuticals companies for the manufacturing of newdrugs for the dealing of various diseases specifically diabetes mellitus by using an in silico pharmacoinformatic approach with a view to validate and prioritize promising compounds for further studies.

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