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Research Article

In-silico molecular docking and drug-likeness, medicinal chemistry, toxicity properties of antidiabetic compounds present in *Citrullus lanatus*

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ARTICLE INFO

ABSTRACT

The current study uses gas chromatography-mass spectrometry assessment, *in-silico* molecular docking, drug-likeness, medicinal chemistry, and toxicity screening to identify anti-diabetic compounds in *Citrullus lanatus* leaves. The extracts were subjected to gas chromatography-mass spectrometry and molecular docking. The gas chromatography-mass spectrometry analysis discovered the existence of seven compounds *Citrullus lanatus* leaf extracts. Also, from *in - silico* analysis, 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound from *Citrullus lanatus* leaves from Anand city found best antidiabetic potential. Furthermore, all seven compounds drug-likeness, medicinal chemistry and toxicity properties were studied. As a result *Citrullus lanatus* leaves can be a valuable pharmaceutical agent in the treatment and management of diabetes complications.

Keywords: *Citrullus lanatus*, Leaves, Molecular docking ,Drug-likeness, Medicinal chemistry, Toxicity screening

Introduction

Diabetes mellitus serves as a significant unspoken slayer that has a direct effect on the well-being of the whole human civilization. Diabetes has been associated with a higher likelihood of serious difficulties, including issues in the cardiac system, pupils, kidneys, liver, nerve cells, cartilage and bones, as well as other organs throughout the human system. 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 (Koria et al., 2013). Herbs as well as diabetes have become expanded connections in a earlier. Consequently, medicinal plants are a possible supplier of pharmaceuticals of antidiabetic (Al-Snafi et al., 2019). *Citrullus lanatus* is often used as a sympathomimetic, anti-dysenteric, and hyperlipidemia diabetes treatment (Deshmukh et al., 2015). 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.

Review of this study

A *Citrullus lanatus* science-based name comes from individually Greek as well as Latin origins. *Citrullus* is derived from the Greek word "citrus," which also refers toward the fruit. A *lanatus* portion seems to be Latin and means "woolly," going to refer to a plant's smaller just on leaf and stem. *Citrullus lanatus* was discovered in Southern Africa since it grows wild all through the region and has the largest selection of kinds. It has already grown for over four thousand years throughout Africa (Grumet et al., 2021).

Alpha-amylase is considered one of the cardinal gastrointestinal enzymes in people and serves as an eagerness to focus on the function of the breakdown of carbohydrates. Alpha-glucosidase is another significant system that catalyses the essential periods of the conversion of glucose. Pancreatic lipase is inclined to carry out accountability for breaking triacylglycerols to free acylglycerols along with fatty acids in the epithelial cells of the intestines, which facilitates the digestive process of foods with a high fat content(Tushuizen et al., 2007). A receptor of

interleukin-6 is cytokine that works to regulate the differentiation of cells, migration of cells, multiplication of cells, as well as death of cells in an effort to support the development of insulin-resistant cells and the physiological causes of type 2 diabetes (Rehman et al., 2017). An excessive weight along with diabetes, especially type 2 diabetes, are two diseases of metabolism that are influenced by tumor necrosis factor-alpha (Shi et al., 2019).

Substances that change a person's genetic blueprint, as well as the DNA molecule, are recognised as mutagenic substances and their descriptive name "mutagenicity" refers to the adverse reactions that occur. Immunotoxins are chemical compounds that have a deleterious effect on the immune system's immunity along with altering its functioning while exposed to it. The inhibition of B cell metabolism has served as the foundation for the current immunotoxicity prototype. Poisoning dosages tend to be determined by mg/kg mass of the body using the LD50 systems of measurement. The amount of drug that results in 50% of the group that was tested dying shortly after getting subjected to a particular substance is known as the median lethal dose(LD50). The worldwide and nation-wide coordinated framework for substance labelling categorization identifies harmful consequence pairs (Banerjee et al., 2018). Diabetes is related to all adverse health consequences, including toxicity of immune, toxicity of cyto, as well as toxicity of mutagen. Missense substitutions within the receptor that recognises insulin may ultimately trigger the production of manually erratic insulins with reduced biological functions along with binding capabilities, ultimately resulting in diabetic complications (Nishi & Nanjo, 2011) . The condition of diabetes brought upon through both genetic changes and changes within one gene, in particular, is referred to as characterised by monogenic diabetes. The condition of diabetes of type 2 is caused by a factor that is genetic. Immunotoxicity as well as diabetes are linked, diabetes of type one is indeed an autoimmune disorder (Berbudi et al., 2020). When cells from the pancreas are inadvertently targeted by the body's own defences, they are unwilling to generate the hormone insulin, that helps the body regulate the amount of sugar in the blood. Spontaneous low blood sugar in diabetic complications is believed to contribute to natural immunity dysfunctional functioning with regard to the toxicity of cyto, which additionally does not work to regulate the spread of foreign microorganisms among those with diabetes (Bediaga et al., 2022).

Methods

Citrullus lanatus leaves were collected from Anand, Gujarat, India. and were fresh and healthy. Methanol was used to extract the fine powder of *Citrullus lanatus* plant leaves. Before being shade-dried and made through a mixer grinder that grinds ingredients to finely grind powder, leaves are washed away from dust. The solvent gradually transfers the powder into a sanitised flask. Occasionally excited about the subject matter. At the last stage of the procedure of extraction, a micelle has been separated from its marc by the process of filtration (Abubakar & Haque, 2020) Evaluation of gas chromatography-mass spectrometry was performed in *Citrullus lanatus* leaves (Padma et al., 2019).

For *in-silico* molecular docking studies anti-diabetic binding proteins have been picked for docking investigation. Target receptors have been identified using the protein data bank format, which serves as the only global preserve containing biological molecular structure information regarding structure. and used for docking research via www.rcsb.org. 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 (Ferreira et al., 2015).

The substances of interest that demonstrated anti- diabetic effects were identified through analysis of Gc-ms of *Citrullus lanatus* leaves extracts from 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.

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(Bakchi et al., 2022). 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 (Banerjee et al.,2018).

Receptor-ligand development were observed along with reconfiguring using Pymol computer software. First, the CB-dock2 and patch dock programme was utilised to evaluate the pharmaceutical effects approaches affinity for attachment among the molecules of the ligand as

well as the protein that serves as the receptor. SwissADME, an online tool that is free, was used to assess medicinal chemistry and determine in computational form drug-likeness. The accessible via the web programme ProTox-II was utilised to forecast the toxicity of chemical variables.

Results

GCMS analysis of *Citrullus lanatus*, plant leaves confirms the presence of various volatile compounds using main spectrum**(Figure: 1**). The research conducted using the technique of gas chromatography-mass spectrometry revealed that the leaf extract contained seven different compounds of *Citrullus lanatus* of Anand city respectively. Names of all seven compounds from *Citrullus lanatus* of Anand city was represented in **(Table: 1)**In accordance with the wide selection of sites of binding characteristics, six targeted proteins were selected for *in-silico* docking with molecules. For the purpose of choosing among the most effective anti-diabetic molecules, each ligands must be docked with all six of the receptors selected.

Also from docked results, it was observed that among the seven compounds from *Citrullus lanatus* leaves from Anand city,2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound 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(-9.3, -8.7, -6.3, -8.7, -8.0 and -9.1 kcal/mol)respectively. Among all compounds from this plant in Anand city 3-ethyl-3-hydroxy-5alpha-androstan-17-one showed highest binding efficiency with receptor of beta-glucosidase were (-12.1 kcal/mol)**(Table 2).**

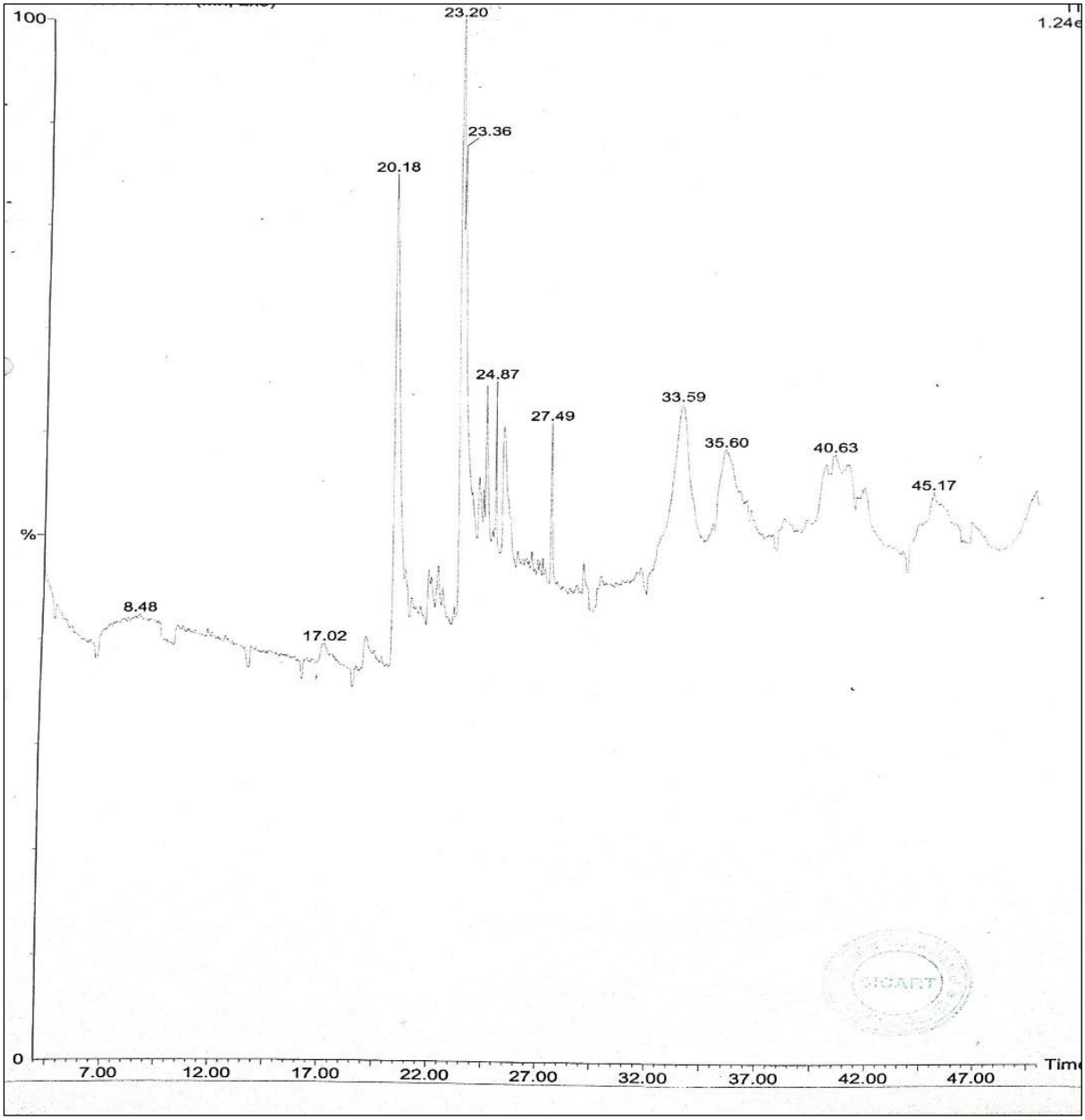

Figure 1 : GCMS chromatogram of *Citrullus lanatus* plants from Anand.

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

Name of the Compound	Molecular Formula	Molecular structure	Spectrum
cis-10-Nonadecenoic acid	C19H36O2		
1-Heneicosanol	C21H44O		
Cyclohexanone, 2,3,3-trimethyl-2-(3-methyl-1,3-butadienyl)-, (E)-	C14H22O		
3-Ethyl-3-hydroxy-5alpha-androstan-17-one	C21H34O2		
1-(3,5-Dinitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triene	C21H28N2O5		
2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	C17H30O3		
2-[(5-Isobutyl-2-methyl-furan-3-carbonyl)-amino]-benzoic acid	C17H19NO4		

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

Name of ligand	Name of protein receptor	Docked binding energy (Kcal/mol)
cis-10-Nonadecenoic acid	Alpha-amylase	NA
	Alpha-glucosidase	-5.2
	Interleukin 6	-4.5
	Tumor necrosis factor-α	-5.7
	Beta-glucosidase	-6.4
	Pancreatic lipase	-5.0
1-Heneicosanol	Alpha-amylase	-5.2
	Alpha-glucosidase	NA
	Interleukin 6	NA
	Tumor necrosis factor-α	NA
	Beta-glucosidase	NA
	Pancreatic lipase	-4.4
Cyclohexanone, 2,3,3-trimethyl-2-(3-methyl-1,3-butadienyl)-, (E)-	Alpha-amylase	-5.5
	Alpha-glucosidase	-5.6
	Interleukin 6	-5.0
	Tumor necrosis factor-α	NA
	Beta-glucosidase	-7.3
	Pancreatic lipase	-5.7
3-Ethyl-3-hydroxy-5alpha-androstan-17-one	Alpha-amylase	NA
	Alpha-glucosidase	NA
	Interleukin 6	NA
	Tumor necrosis factor-α	NA
	Beta-glucosidase	-12.1
	Pancreatic lipase	NA
1-(3,5-Dinitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triene	Alpha-amylase	NA
	Alpha-glucosidase	-7.0
	Interleukin 6	NA
	Tumor necrosis factor-α	NA
	Beta-glucosidase	-8.9
	Pancreatic lipase	-7.2
2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	Alpha-amylase	-9.3
	Alpha-glucosidase	-8.7
	Interleukin 6	-6.3
	Tumor necrosis factor-α	-8.7
	Beta-glucosidase	-8.0
	Pancreatic lipase	-9.1
2-[(5-Isobutyl-2-methyl-furan-3-carbonyl)-amino]-benzoic acid	Alpha-amylase	-7.4
	Alpha-glucosidase	NA
	Interleukin 6	NA
	Tumor necrosis factor-α	-8.3
	Beta-glucosidase	-8.8
	Pancreatic lipase	-6.9

NA=Not Applicable

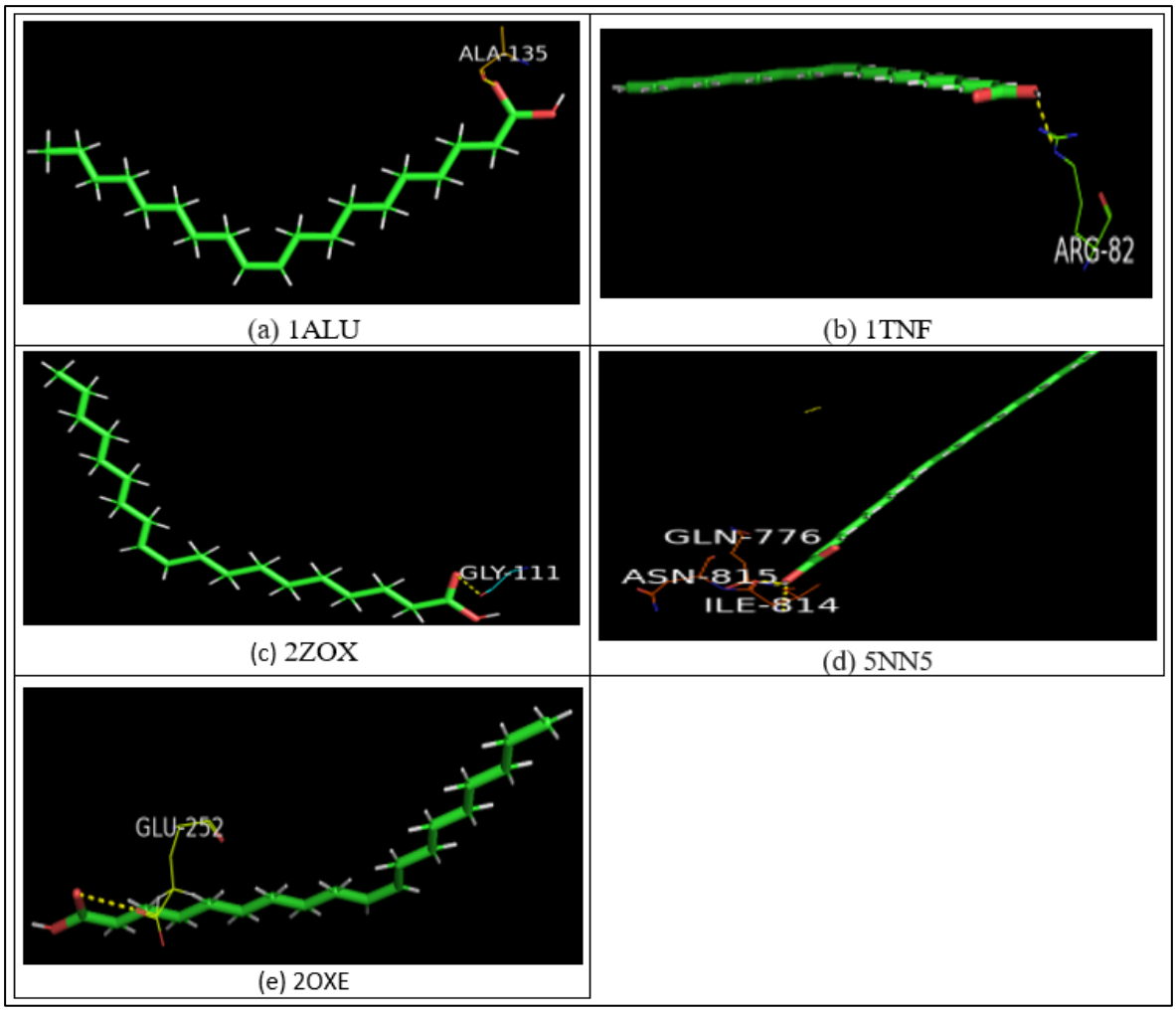

Figure 2: 3D structure of receptors 1ALU,1TNF,5NN5,2ZOX,2OXE and ligand cis-10-nonadecenoic acid interaction with amino acids

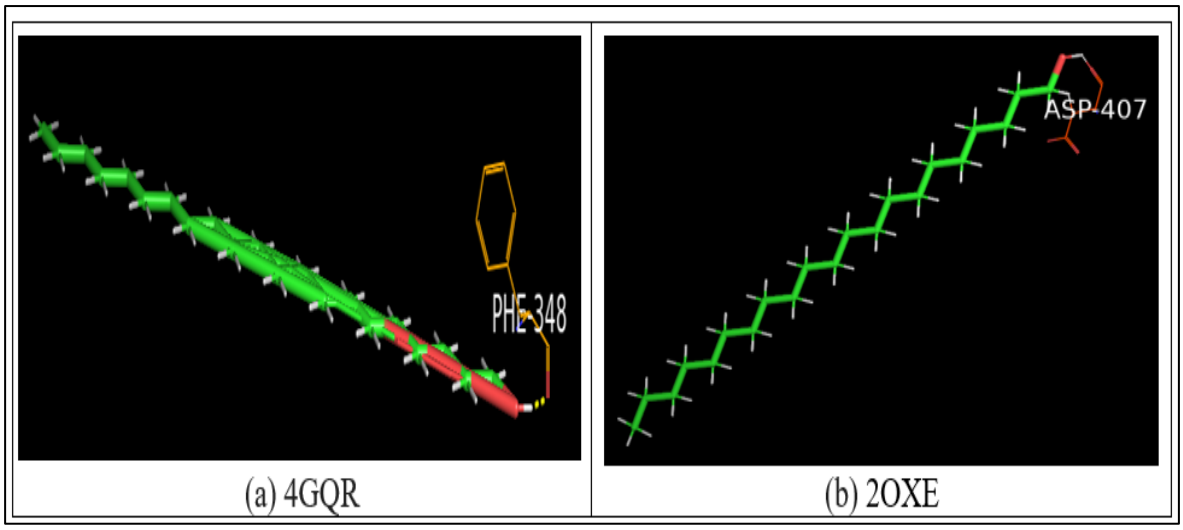

Figure 3: 3D structure of receptors 4GQR,2OXE and ligand 1-heneicosanol interaction with amino acids

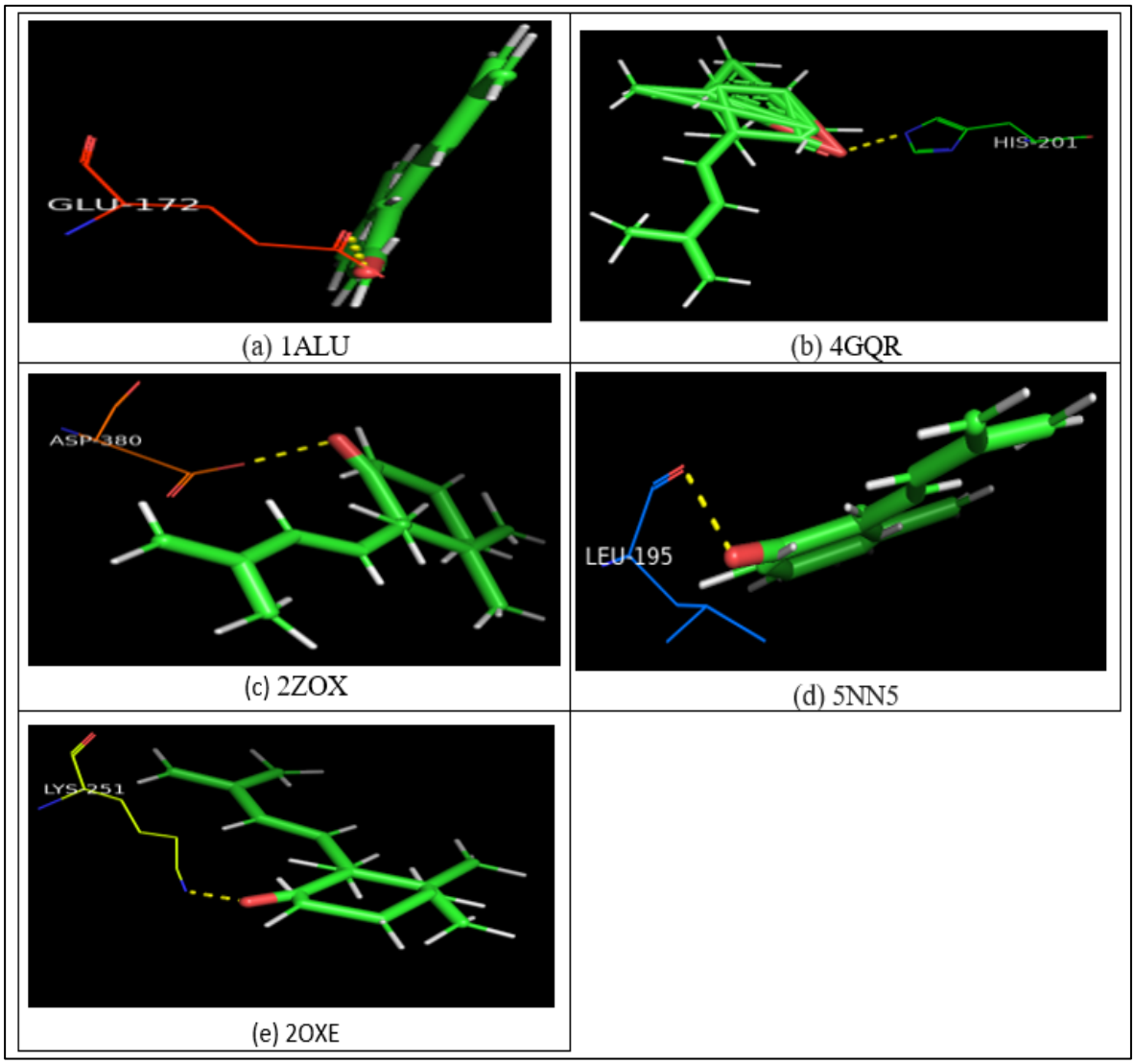

Figure 4: 3D structure of receptors 1ALU, 4GQR, 5NN5,2ZOX,2OXE and ligand cyclo hexanone, 2,3,3-tri methyl-2-(3-methyl-1,3-buta dienyl)-, (e)- **interaction with amino acids**

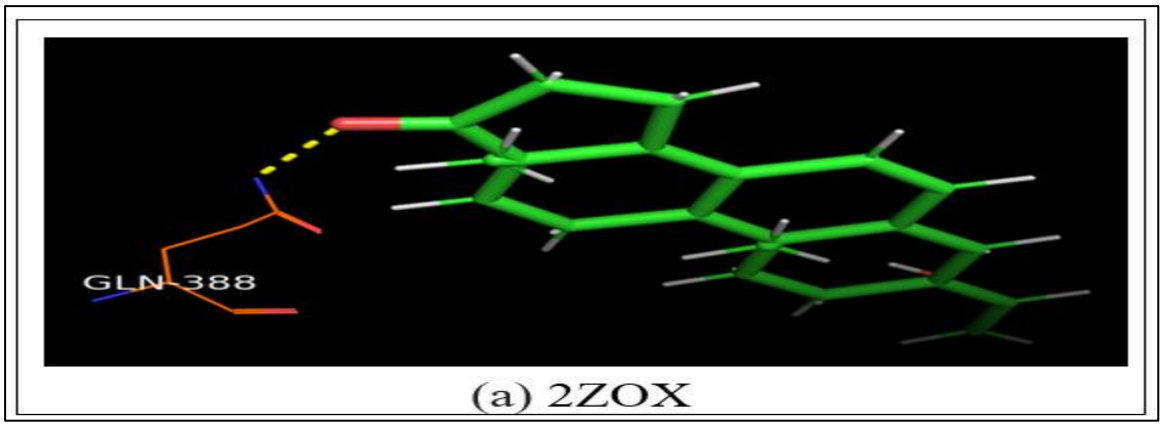

Figure 5: 3D structure of receptors 2ZOX and ligand 3-ethyl-3-hydroxy-5alpha-androstan-17-one interaction with amino acids

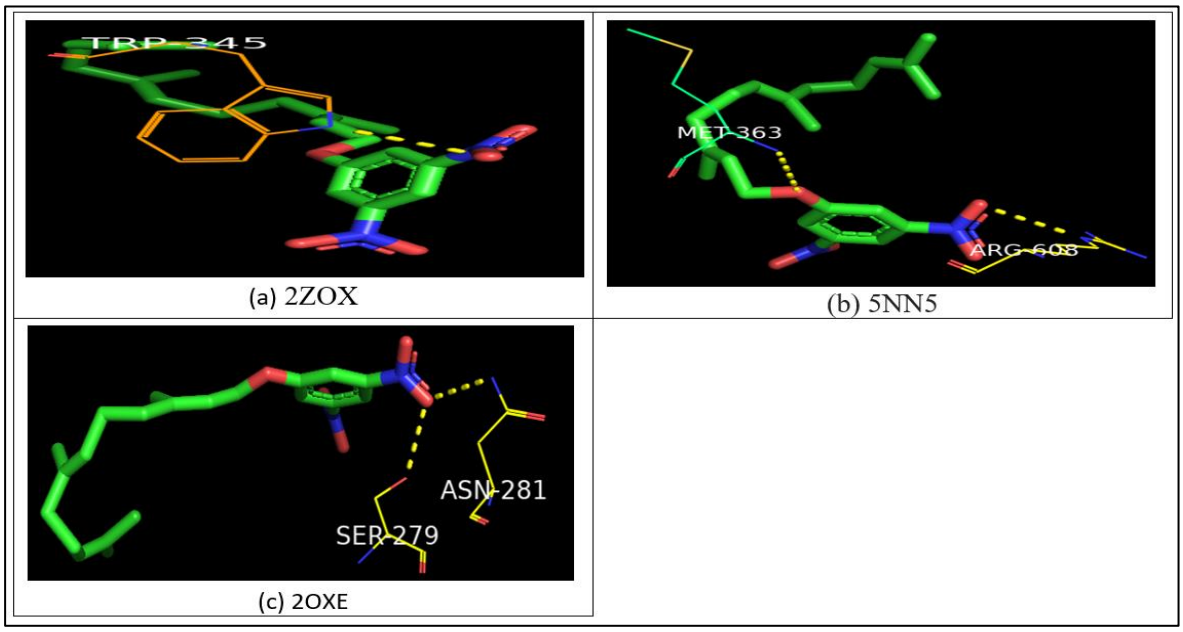

Figure 6 : 3D structure of receptors 5NN5,2ZOX,2OXE and ligand 1-(3,5-denitrophenoy)-3,7,11-trimethyl-dodaca-2,6,10-triene interaction with amino acids

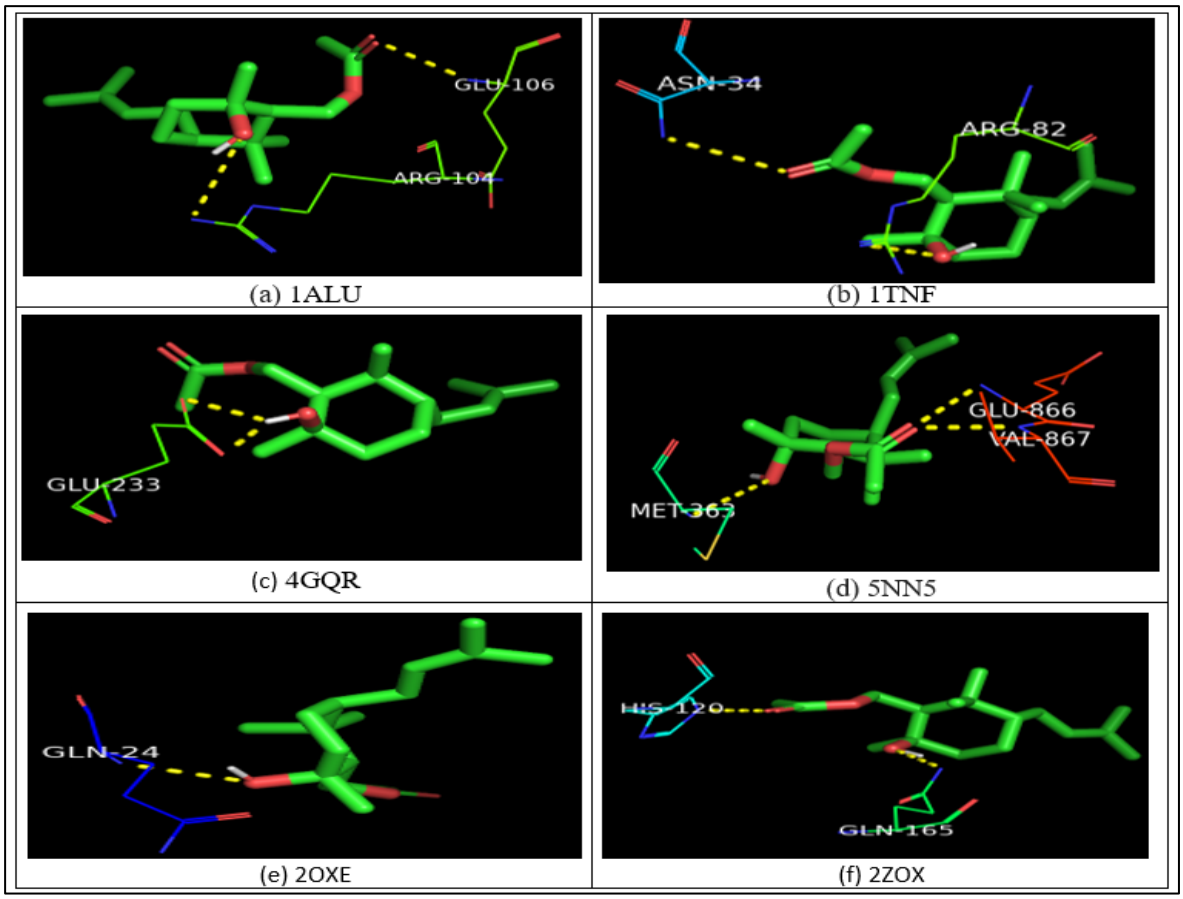

Figure 7: 3D structure of receptors 5NN5, 2ZOX, 2OXE, 1ALU, 4GQR, 1TNF and ligand 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol interaction with amino acids

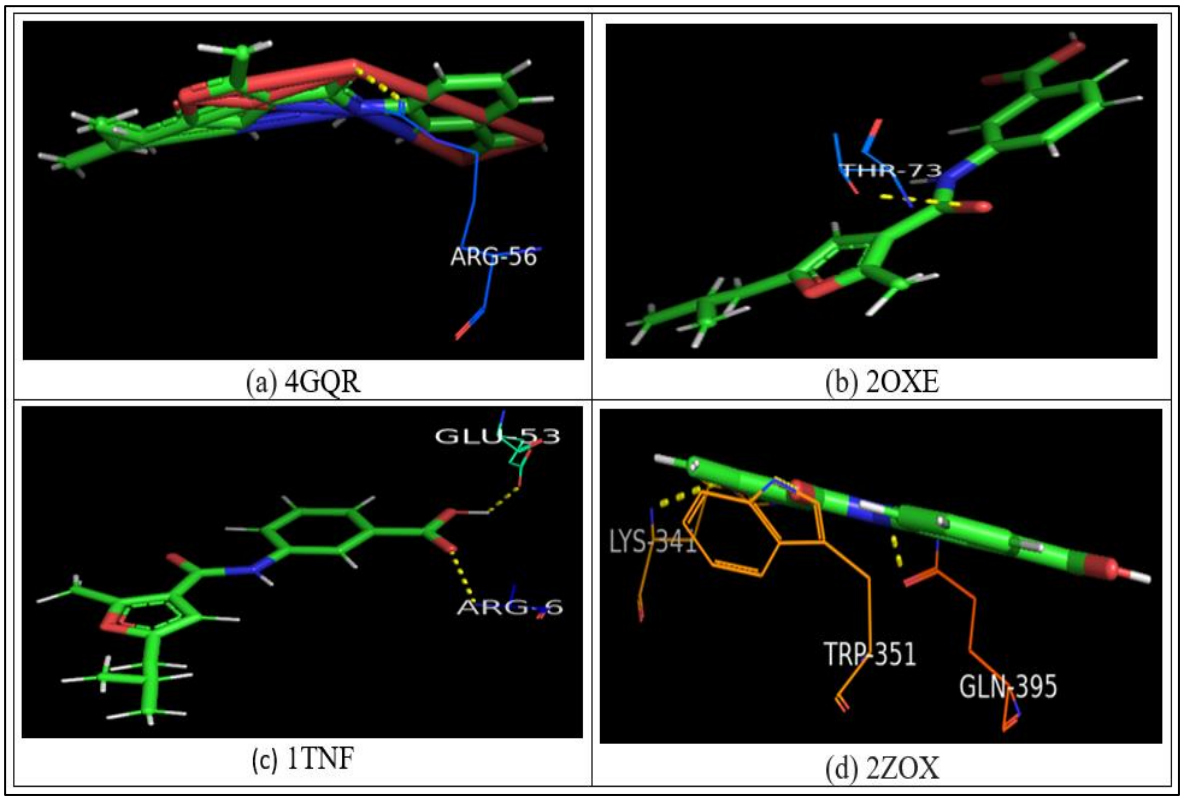

Figure 8 : 3D structure of receptors 4GQR, 2OXE, 1TNF, 2ZOX and ligand 2-[(5-iso butyl-2-methyl -furan- 3-carbonyl)-amino]- benzoic acid interaction with amino acids

All active compounds were evaluated through drug-likeness, medicinal chemistry as well as toxicity predictions. Where drug-likeness candidature was implemented by two rule based filters lipinski as well as veber rules. In plant *Citrullus lanatus* from Anand city cis-10-nonadecenoic acid; 1-heneicosanol as well as 1-(3,5-dinitrophanoxy)-3,7,11-tirmethyl-dedoca-2,6,10- triene; compounds followed a lipinski rule but not a veber rule. Other four compounds,2-[(5-iso butyl-2-methyl -furan- 3-carbonyl)-amino]- benzoic acid compound; and 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound;3-ethyl -3 -hydroxy-5 alpha– andro stan-17-one compound; as well as cyclo hexanone, 2,3,3-tri methyl-2-(3-methyl-1,3-buta dienyl)-, (e)- compound followed both lipinski as well as veber rule based filters **(Table: 3).**

The rules of PAINS, rule of brenk, and rule of synthetic accessibility were assessed in medicinal chemistry. Compounds that don't trigger an alert signal indicate that there aren't any indiscriminate moieties present and therefore metabolic activity is unstable. *Citrullus lanatus* of Anand city 1-heneicosanol compound; 3-ethyl-3-hydroxy-5alpha-androstan-17-one

compound; and 2-[(5-iso butyl-2-methyl -furan- 3-carbonyl)-amino]- benzoic acid compound didn't show any alert in both rules. Other four compounds cis-10-Nonadecenoicacid compound; cyclo hexanone, 2,3,3-tri methyl-2-(3-methyl-1,3-buta dienyl)-, (e)- compound; 1-(3.,5-dianitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triane compound; as well as 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound didn't show PAINS alert but showed a brenk alert(**Table :4**).

Table 3 Parameters that are predicted to be drug-likeness content of compounds identified in the leaves of Anand city from *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	
cis-10-Nonadecenoic acid	296.49	2	1	4.80	Yes #1	16	37.30	No #1	0.85
1-Heneicosanol	312.57	1	1	5.62	Yes #1	19	20.23	No #1	0.55
Cyclohexanone, 2,3,3-trimethyl-2-(3-methyl-1,3-butadienyl)-, (E)-	206.32	1	0	3.21	Yes #0	2	17.07	Yes #0	0.55
3-Ethyl-3-hydroxy-5alpha-androstan-17-one	318.49	2	1	4.15	Yes #1	1	37.30	Yes #0	0.55
1-(3,5-Dinitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triene	374.43	5	0	2.90	Yes #0	11	100.87	No#1	0.55
2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	282.42	3	1	3.06	Yes#0	5	46.53	Yes#0	0.55
2-[(5-Isobutyl-2-methyl-furan-3-carbonyl)-amino]-benzoic acid	301.34	4	2	2.11	Yes#0	6	79.54	Yes#0	0.56

Table 4: Predicted medicinal chemistry parameters of compounds identified in a leaves of Anand city from *Citrullus lanatus*

Compounds	**PAINS #alerts**	**Brenk #alerts**	**Synthetic accessibility**
Cis-10-Nonadecenoic acid	0	1	3.18
1-Heneicosanol	0	0	2.87
Cyclohexanone, 2,3,3-trimethyl-2-(3-methyl-1,3-butadienyl)-, (E)-	0	1	3.94
3-Ethyl-3-hydroxy-5alpha-androstan-17-one	0	0	4.11
1-(3,5-Dinitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triene	0	3	3.72
2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	0	1	3.88
2-[(5-Isobutyl-2-methyl-furan-3-carbonyl)-amino]-benzoic acid	0	0	2.98

Toxicity of cyto, Toxicity of mutagen, toxicity of immune, and toxicity of hepato were predicted depending on the compound's toxicity. *Citrullus lanatus* from Anand city 1-(3,5-dianitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triane compound; and 3-ethyl-3-hydroxy-5alpha-androstan-17-one compound gave active output in mutagenicity and immunotoxicity respectively. Other four compounds, cis-10-Nonadecenoic acid compound; 1-heneicosanol compound; cyclo hexanone, 2,3,3-tri methyl-2-(3-methyl-1,3-buta dienyl)-, (e)- compound; and 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound; as well as 2-[(5-iso butyl-2-methyl -furan- 3-carbonyl)-amino]- benzoic acid compound gave inactive outputs in all toxicity **(Table: 5).**

Table 5: Predicted toxicity parameters of compounds identified in a leaves of Anand city from *Citrullus lanatus*

Compounds	Hepatotoxicity #Probability	Immunotoxicity #Probability	Mutagenicity #Probability	Cytotoxicity #Probability	Toxicity class	LD_{50} (mg/kg)
cis-10-Nonadecenoic acid	Inactive #0.55	Inactive #0.99	Inactive #1.0	Inactive #0.71	2	48
1-Heneicosanol	Inactive #0.90	Inactive #0.97	Inactive #1.0	Inactive #0.83	4	1000
Cyclohexanone, 2,3,3-trimethyl-2-(3-methyl-1,3-butadienyl)-, (E)-	Inactive #0.63	Inactive #0.97	Inactive #0.92	Inactive #0.89	5	5000
3-Ethyl-3-hydroxy-5alpha-androstan-17-one	Inactive #0.52	Active #0.79	Inactive #0.96	Inactive #0.82	5	3000
1-(3,5-Dinitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triene	Inactive #0.70	Inactive #0.85	Active #0.65	Inactive #0.71	4	750
2R-Acetoxymethyl-1,3,3-trimethyl-4t-(3-methyl-2-buten-1-yl)-1t-cyclohexanol	Inactive #0.70	Inactive #0.95	Inactive #0.70	Inactive #0.89	6	6800
2-[(5-Isobutyl-2-methyl-furan-3-carbonyl)-amino]-benzoic acid	Inactive #0.52	Inactive #0.99	Inactive #0.79	Inactive #0.75	4	1000

Conclusion

Therefore, it can be concluded from the results that from Anand city of medicinal plant *Citrullus lanatus* leaves cis-10-Nonadecenoic acid compound, 1-Heneicosanol compound, cyclo hexanone, 2,3,3-tri methyl-2-(3-methyl-1,3-buta dienyl)-, (e)- compound, 3-ethyl -3 -hydroxy-5 alpha– andro stan-17-one compound, 1-(3,5-dianitrophenoxy)-3,7,11-trimethyl-dodeca-2,6,10-triane compound, 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo hexanol compound, 2-[(5-iso butyl-2-methyl -furan- 3-carbonyl)-amino]- benzoic acid compound were identified by gas-chromatography– mass spectrometry analysis. Also, from *in - silico* analysis, 2r- acetoxy methyl- 1,3,3 -tri methyl- 4t-(3-methyl- 2- buten-1-yl)-1t-cyclo

hexanol compound from *Citrullus lanatus* leaves from Anand city found best antidiabetic potential. Furthermore, all seven compounds drug-likeness, medicinal chemistry and toxicity properties were studied. In order to verify as well as set priorities for promising compounds for some further *in-vivo* experimentation, the recent research offers useful data on the effectiveness of these herbal materials to verify their authenticity, safety, and efficacy prior to commercial interest across both research centers as well as healthcare industry for the dealing of various diseases, specifically diabetes.

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