A comparative molecular docking study of *Syzygium cumini* to understand the binding pattern with four different proteins used for anti - diabetic activity

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ABSTRACT

Background: Diabetes mellitus is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time which is seen worldwide. In past years *Syzygium cumini* has been used for the treatment of diabetes. Method: The current work, *In-silico* study was carried out by molecular docking using Argus lab on four 2ath, 5y7h, 5qij, receptors. Results: In the present work, we have completed molecular docking and as a conclusion we have further findings such as, when the docking of gallic acid, ferullic acid, egallic acid and myricetin acid was performed the result found ferullic acid is -10.27 and in reference ligand pioglitazone was found -12.53. Afterwards there was comparison study of test ligand and reference ligand was done and shows that there is protein binding with amino acid. In 2D structure hydrogen bonding is visible along with conventional hydrogen bond and vander-wal interactions. Conclusion: The result of this investigation shows that *Syzygium cumini* was found the potential to inhibit the diabetes mellitus.

KEYWORDS Diabetes mellitus, *Syzygium cumini*, Receptors, Molecular docking, In-silico study

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of the endocrine system. The disease

occurs worldwide and its incidence is increasing rapidly in most parts of the global. People suffering from diabetes are not able to produce or properly use insulin in the body, so they have a high level of blood glucose[1]. DM is a leading cause of end stage kidney disease, cardiomyopathy and heart attacks, strokes, retinal degeneration leading to blindness and non-traumatic amputations[2]. Dyslipidemia, quite common in diabetic patients, is the main risk factor for cardiovascular and cerebrovascular diseases. Diabetes is a serious illness with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in various countries. As diabetes aggravates and b-cell function deteriorates, the insulin level begins to fall below the body's requirements and causes prolonged and more severe hyperglycemia. This is basically four types Type I, II, III, IV[3]. *S. cumini* (syn.Eugeniajambolana), a member of family Myrtaceae is commonly known as Jamun in Hindi and Black Plum or Indian Blackberry in English. *S. cumini* is an evergreen tree distributed in the Indian sub- continent, south-east Asian countries and eastern Africa[(4)]. *S. cumini*, is widely used in different countries including India for the treatment of many disorders including diabetes. Various parts of this plant have been recognized to possess several medicinal properties in the traditional system of medicine[(5)]. The bark of the plant is carminative, digestive, anti-hyperglycemic,anti-helminthic and antibacterial. The fruits and seeds are used to treat diabetes, pharyngitis, spleenopathy, urethrorrhea and ringworm infection[(6)]. The leaves possess antibacterial property and are used to strengthen teeth and gums. The leaves have also been extensively used to treat diabetes, constipation,leucorrhoea, fever, gastropathy,dermopathy and to inhibit blood discharges in the feces. [(7)] **Different targets used for docking**

2ath is a ppar gamma agonist and drugs are act on the peroxisome proliferator activated receptor; they are used in treatment of metabolic disorder, generally used in low the blood sugar[(8)]. Thoazolidines acts by activating PPAR gamma activated PPAR it increases the transcription of number of specific genes and transcription of other the main effects is an increase in the storage of fatty acid in adipose site thereby decreasing the amount of fatty acid present in circulation[(9)]. **5y7h** in complex with inhibitor (dipeptidyl peptidase) agonist: Inhibition of DPP4. **DDP4** is an enzyme which

involved in rapid metabolism of glucagon like peptide, therefore inhibition of DPP4 increase the action of incretins the incretins increase glucose depended insulin secretion.[10] Thus, inhibition of the DPP4 is a therapeutic of approach in the therapeutic of approach in the treatment of TYPE-2 diabetics.[11] **3w37** receptor α-Glucosidase inhibitors produce a significant reduction of postprandialhyperglycemia and postprandial insulin with a significant decrease of HbA_{1c} (~0.7%), by delaying

carbohydrate absorption. For diabetic patients, α-glucosidase inhibitors are safe agents that can be used either as monotherapy or in combination with other oral hypoglycemic agents or insulin.[12] The reduction of HbA_{1c} should substantially decrease microvascular complications and could diminish macrovascular events. α- Glucosidase inhibitors should be considered as a treatment of choice for newly diagnosed diabetic patients.[13] For those not well- controlled with any other type of treatment, it can result in metabolic improvement without any additional risk. To minimize gastrointestinal side effects, treatment should be initiated at a low dose and titrated slowly. In patients with impaired glucose tolerance, acarbose has proven to be efficient in preventing or delaying the occurrence of type 2 diabetes as well as decreasing macrovascular events. [14] **5qij**-A series of studies with (nonselective) 11β- HSD inhibitors has suggested that reduced 11β-HSD1 activity increases insulin sensitivity and/or reduces plasma glucose and perhaps lipid levels in a variety of animal models and humans *in vivo.* [15] This appears to be due to attenuated responses of glucocorticoid-sensitive gluconeogenic enzymes in the liver, indicating a reduction in glucocorticoid levels within the hepatocyte. This contention is supported by lower levels of other glucocorticoid- sensitive enzymes in the liver, including those catalyzing the metabolism of lipidsThis associates with reduced plasma triglycerides and increased HDL cholesterol levels, producing an apparently “cardioprotective” lipid profile. As predicted, 11β-HSD1 knockout mice are insulin sensitized both overall in plasma and in specific cells and tissues, notably liver and adipose tissue. [16

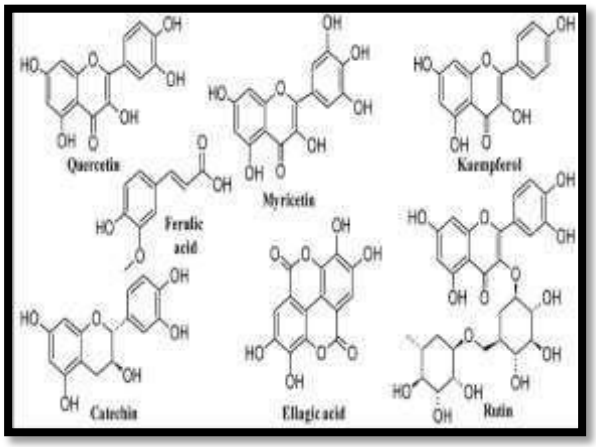


Fig 1.1: Different Stages of *Syzium cumini*- (a) Flowering stage of *Syzium cumini*, (b) Fruiting stage of *Syzium cumini*, (c) Matured *Syzium cumini*, (d) Seeds of *Syzium cumini*

Fig 1.2: Phenolic compounds from *Syzium cumini* with potential antidiabetic activity

Molecular Docking

Molecular docking is an attractive scaffold to understand drug bimolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity. [16] The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes. At present, docking technique is utilized to predict the tentative binding parameters of ligand-receptor complex beforehand. [17]

The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy. [18] The net predicted binding free energy (ΔG_{bind}) is revealed in terms of various parameters, hydrogen bond (ΔG_{hbond}), electrostatic (ΔG_{elec}), torsional free energy (ΔG_{tor}), dispersion and repulsion (ΔG_{vdw}), desolvation (ΔG_{desolv}), total internal energy (ΔG_{total}) and unbound system's energy (ΔG_{unb}). Therefore, good understanding of the general ethics that govern predicted binding free energy (ΔG_{bind}) provides additional clues about the nature of various kinds of interactions leading to the molecular docking. [19] Practical application of molecular docking requires data bank for the search of target with proper PDB format and a methodology to prepare ligand as a PDB file. To do this,

there are various software's (Discovery studio, etc., available from where the ligand can be made in PDB format.[20] These tools provide the organization to ligands based upon their ability to interact with given target proteins/DNA. Molecular docking of small molecules to a target includes a pre- defined sampling of possible conformation of ligand in the particular groove of target in an order to establish the optimized conformation of the complex[21]. This can be made possible using scoring function of software. Since the infrared spectroscopy, X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy are the techniques for the investigation and establishment of three dimensional structures of any organic molecule/ biomolecular targets. Hence homology modeling makes it possible to determine the tentative structure of proteins of unknown structure with high sequence homology to known structure. This provides a substitute approach for target structure establishment, which forms starting point for *in silico* drug discovery. [22] There are various databases available, which offer information on small ligand molecules such as CSD (Cambridge Structural Database), ACD (Available Chemical Directory), MDDR (MDL Drug Data Report) and NCI (National Cancer Institute Database). While performing docking, different interacted conformers are generated and compared with each other. [23] In the condition of rejection, new conformers are obtained and again search procedure continues to its endpoint after acceptance of one conformation. The docked conformers according to their experimental binding affinities and binding free energies seem to be more difficult than their binding orientation. To overcome this problem, different scoring functions are employed such as consensus scoring; appliance of number of score functions to the same docked pose in order to eliminate false positives. A huge number of attempts has been made for the development of efficient docking protocols. [24] No doubt, significant progress has been made in the computational prediction of docking modes

Materials and Method

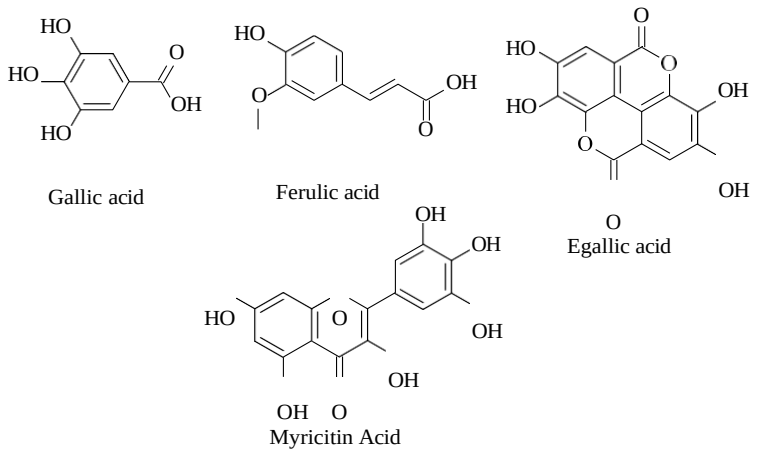
Hardware and Software

The software used was CORINA Classic from Molecular Networks GmbH and Altamira, LLC (https://www.mn-am.com/products/corina)[25], ArgusLab 4.0.1 from Mark Thompson and Planaria Software LLC (http://www.arguslab.com/arguslab.com/ArgusLa b.html)[26], and Discovery Studio Visualizer.v20.1.0.19295.from.Dassault.Syst

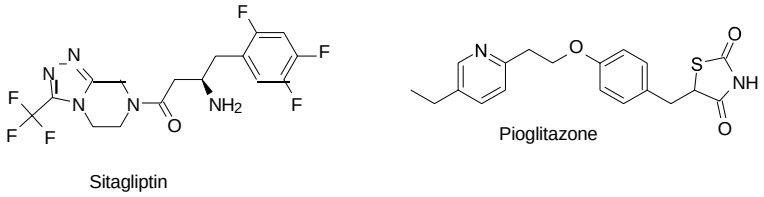
emes.BIOVIA.(https://www.3ds.com/productsservices/biovia/products/molecular-modelingsimulation/biovia-discovery-studio/visualization)[27]

Ligand

The compounds included in the study were Gallic acid (PubChem ID 370), Egallic acid (PubChem ID 13915428), Ferulic Acid (PubChem ID 445858), Myricitin acid, (PubChem ID 5281672) which downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).[28]



(a) Test Ligands



(b) References Ligand

Fig 1:3 (a) and (b) two dimensional structure of all test and references ligand

Protein/Receptor

The receptor used in anti-diabetics drug (PDB-ID) used are **2ath, 5y7h, 5qij, 3w37** each with the ligand of gallic acid, ferulic acid and ellagic acid and myrictin acid this four receptors are responsible for anti-diabetic activity with different mode of action.[29]. A detail of this three-dimensional structure of protein was found from the

website of Protein Data Bank (http:// www.rscb.org). [30]

Docking protocol

Preparation of ligands

The ligand structures were generated using the tool CORINA Classic. Three-dimensional optimizations of the ligand structures were done and saved as .mol file. Geometry optimizations of the ligands were performed according to the Hartree–Fock

(HF) calculation method using ArgusLab 4.0.124.[31]

Preparation of protein

The protein sequence was retrieved in the FASTA format, and the 3D structure was determined using the CPH model server. All water molecules were removed, and hydrogen atoms were added to the target protein molecule[32]

Protein-ligand docking

ArgusLab is an electronic structure program that was based on quantum mechanics. It predicts the potential energies, molecular structures, geometry optimization of the structure and vibration frequencies of coordinates of atoms, bond length, and bond angle.[33] The selected bioactive compounds were docked using ArgusLab Software. The interaction was carried out to find the favorable binding geometries of the ligand with the protein. Docking of the protein-ligand complex was mainly targeted only to the predicted active site.[34] Docking simulations were performed by selecting "Argus Dock" as the docking engine. The selected residues of the receptor were defined to be a part of the binding site. A spacing of 0.4 Å between the grid points was used, and an exhaustive search was performed by enabling the "High precision" option in the Docking precision menu, "Dock" was chosen as the calculation type, "flexible" for the ligand, and the "AScore" was used as the scoring function. A maximum of 150 poses was allowed to be analyzed; the binding site box size was 20 × 20 × 20 Å to encompass the entire active site.[35] The A Score function, with the parameters read from the AScore.prm file, was used to calculate the binding energies of the resulting docked structures. All the ligands in the dataset were docked into the protein's active site using the same protocol. The docking poses saved for each compound were ranked according to their docking score function[36]. The pose having the highest docking score was selected for further analysis. Discovery Studio Visualizer was used for the visualization of 2D and 3D pose views[37.38].

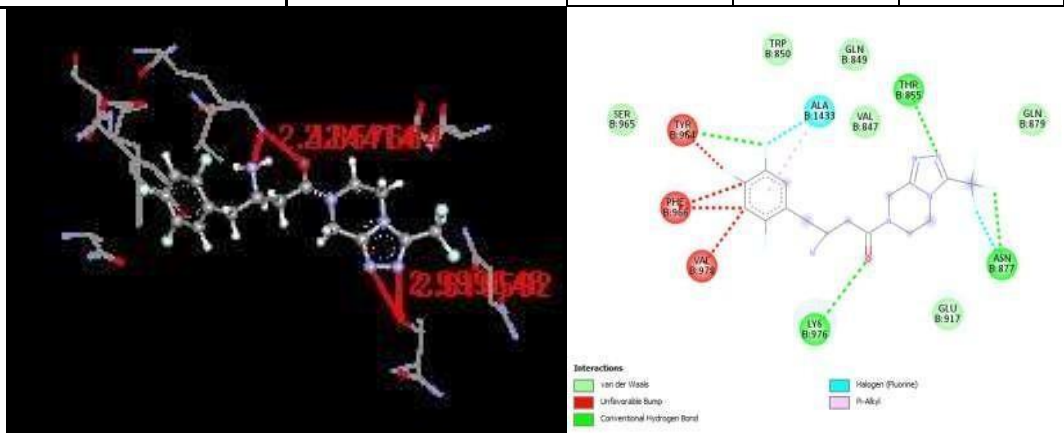
Result & Discussion

In the current work, the docking of all the test and reference ligands showed exciting results with some results consistent patterns in four receptor 2ath, 5y7h, 5qij and 3w37[39,40]. Firstly, there is a visible variance between in the ranking order of ΔG value of all the test ligand and reference in the four receptors, represent in **Table 1.1.** The ΔG value of some test ligand is low at the 2ath, 5y7h Egallic acid and Meristic acid but high in 5qij and 3w37 Ferulic acid and Gallic

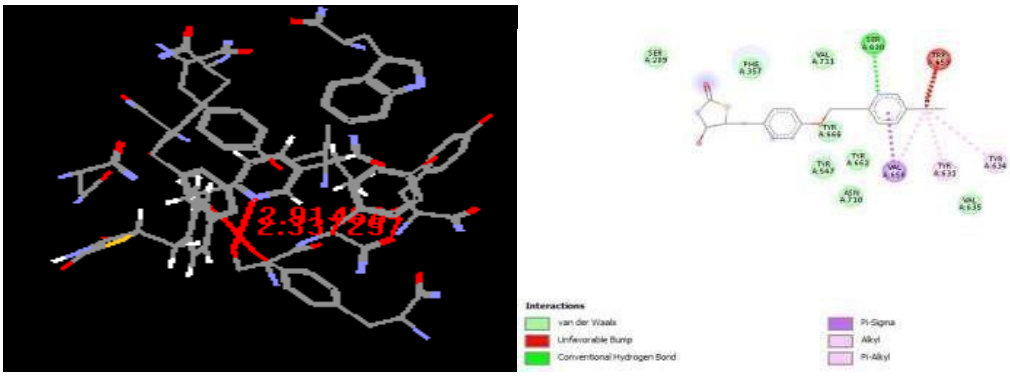
acid[41,42] . Where as the ΔG value of some references ligand is low at the 3w37 for both sitagliptin and pioglitazone acid but highin 2ath. This showed that ligand have interaction patterns that are more suited to the orientation of the 2ath, 5y7h receptor that binds to test ligands that are not too large in size[43,44]. On the other hand, some ligands consistently have a smaller ΔG value than standard ligands on four receptors[45].

Table 1.1: Comparison Between Reference Ligand And Test Ligand

MOLECULE		**PROTEIN MOLECULE**			
	DockingScores (ΔG in Kgcal/mol)	**2ath**	**5y7h**	**5qij**	**3w37**
Pioglitazone		-12.53	-11.49	-11.64	-10.24
Sitagliptin		-9.95	-8.94	-9.15	-8.38
Gallic acid		-8.06	-8.22	-7.9	-8.23
Egallic acid		-7.9	-8.4	-8.53	-8.23
Ferulic acid		-8.37	-10.77	-8.27	-8.44
Myricetin acid		-8.82	-7.86	-7.97	-7.4



(a)



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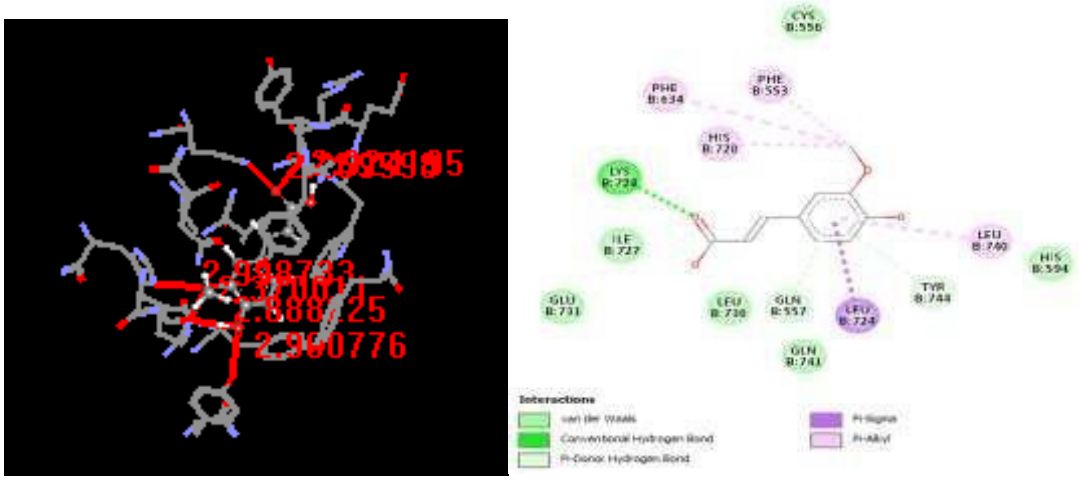

(c)

Figure 1 - Amino acid interactions, hydrogen bonds representations by 3D and 2D pose of (a) PIOGLITAZONE, (b) SITAGLIPTIN, (c) FERULIC ACID

The field of molecular docking has emerged in recent decades and is now an important aspect of drug discovery and development. Molecular docking is used to predict protein-ligand complexes and is made up of two components: a search algorithm, which generates possible protein-ligand complex geometries and thus performs the process of "pose generation," and a scoring function, which predicts the ligand's binding affinity to the protein based on the complex geometry. The chemical constituent of *Syzygium cumini* test ligand such as gallic acid, ferullic acid, egallic acid and myricetin acid are compared with standard ligand sitagliptin and pioglitazone. The four test ligand gallic acid, ferullic acid, egallic acid and myricetin acid and two standard sitagliptin and pioglitazone are docked with the help of argus lab in which four protein

molecules i.e. 2ath, 5y7h5qij and 3w37 has been taken. The four proteins were docked with the two references ligand and four test ligand and by this different docking score have been obtained. when gallic acid is docked with protein 2ath, 5y7h5qij and 3w37 and result found to be -8.06, -8.22, -7.9 and -8.23 furthermore ferullic acid was docked with same protein molecule with the help of argus lab software the result would found to be -8.37, -10.77, -8.27 and -8.44 as well as egallic acid and myricetin acid also docked with 2ath, 5y7h5qij and 3w37 and result was -7.9, -8.4, -8.53 and -8.23 and -8.82, -7.86, -7.97, and -7.4. When the docking of gallic acid, ferullic acid, egallic acid and myricetin acid was performed the result found ferullic acid is -10.27 and in reference ligand pioglitazone was found -12.53. Afterwards there was comparison study of test ligand and reference ligand was done and shows that there is protein binding with amino acid. As we seen that some common amino acids (102 arg, 109 glu 467 tyretc) of test ligand such as ferullic acid and myricetin acid are near to be standard ligand sitagliptin and pioglitzone (Figure 1) .

Conclusion

In the study, we have briefly mentioned about the comparison study of different test ligand with standard ligand with the help of argus lab software used in molecular modeling , that is actively playing role in drug discovery and development. . In 2D structure hydrogen bonding is visible along with conventional hydrogen bond and vander-wal interactions. All the compounds show good affinity towards the selected protein particularly ferullic acid shows comparable results as compare to references.The current investigation is a preliminary work which necessitates future preclinical and clinical studies for verification of the results and expected to be the first step in development.

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