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Mechanistic Insight Antidiabetic Potential of Ursolic Acid: *In-Silico* Molecular Docking

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ABSTRACT: Diabetes mellitus is a chief cause involved in the morbidity and mortality among the global population (Sheoran et al., 2011). The main event of this syndrome includes elevated blood glucose level (hyperglycemia) followed by polydipsia and polyuria. The secondary complications include retinal damage, loss of kidney function and damage to nerves. Further, the diabetes mellitus will also increase the cardiovascular disease progression. Pentacyclictriterpenes are as well one of the compounds occurring in plants. In this group Ursolic acid is a well recognized compound that is accessible from various sources like seeds as well as fruits and possess many types of activities and is a bright contender for developing novel treatment approaches for treating diseases. Thus, in the current study, ursolic acid a triterpenoid was selected for evaluation of antidiabetic potential by molecular docking. A mechanistic insight for their antidiabetic potential is elucidating by interaction of ursolic acid with target protein.

Keywords: Diabetes mellitus, ursolic acid, α-amylase, α-glucosidase, molecular docking, Glycogen synthase kinase-3 (GSK-3).

RESEARCH PAPER

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INTRODUCTION

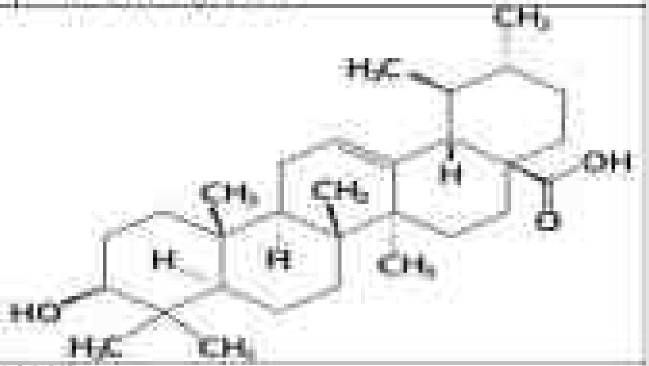
Diabetes is a condition of the glucose, lipid and protein metabolism that is brought on by decreased insulin production or developing resistance to the hormone's activity. Diabetes-related chronic hyperglycemia results in the glycation of body proteins, which then triggers secondary problems that damage the eyes, kidneys, nerves, and arteries [1]. Diabetes is associated with microvascular and macrovascular problems, which are the main causes of morbidity and mortality in diabetic subjects, in addition to hyperglycemia and abnormalities in serum lipids [2]. Exercise, nutrition, and pharmaceutical medications can help manage it, but they can be expensive, have side effects, or have other limitations [3-4]. The search for safer and more efficient hypoglycemic medication. Diabetes mellitus represents a heterogeneous group of disorders. Since diverse diabetic phenotypes can be categorized on the basis of specific etiology and its pathogenesis, but in many persons overlapping phenotypes make etiological and pathogenetic classification complicated [5].

- Type 1 Diabetes Mellitus
  - (which may sometimes rapidly progress to absolute insulin deficiency)
    - Autoimmune
    - Idiopathic
- Type 2 Diabetes Mellitus
  - (which may sometimes require insulin treatment)
    - (which sometimes require insulin for survival)
- Other specific Types Of Diabetes
  - Genetic defects of beta cell development e.g. MODY (rare)
  - Genetic defects in insulin action e.g. Type A insulin resistance
  - Diseases of exocrine pancreas e.g. fibro calculous pancreatopathy
  - Endocrinopathies e.g. acromegaly, Cushing's etc.
  - Drugs or chemical induced e.g. glucocorticoids
  - Infections e.g. congenital rubella
  - Uncommon forms of immune-mediated diabetes e.g. anti-idiotypic insulin
  - Other genetic syndromes
- Gestational Diabetes

Ursolic acid (3-beta-3-hydroxy-urs-12-ene-28-oic acid), is a phytochemical and bioactive compound commonly found in several medicinal herbs and foods. Numerous pharmacological properties of UA have been

demonstrated in studies, including anti-inflammatory, hepatoprotective, anticancer, cardioprotective, neuroprotective, antimicrobial, antihyperlipidemic, anti-diabetic, antifungal, antiviral, and trypanocidal effects [6].

Description of ursolic acid [7]

IUPAC Name	(1S,2R,4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid
Structure	
Mol. Wt.	456.7
Mol. Formula	$C_{30}H_{48}O_3$
M.P.	284°C
Solubility	One part dissolves in 88 parts methanol, 178 alcohol (35 boiling alcohol), 140 ether, 388 chloroform, 1675 carbon disulfide. Moderately soluble in acetone. Soluble in hot glacial acetic acid and in 2% alcoholic NaOH. Insoluble in petroleum ether.
Class	triterpenoid

Biological effect of Ursolic acid [8]

One of the trendiest virtual screening techniques is molecular docking, particularly when the target protein's 3D structure is available. This technique was able to predict the structure of the protein-ligand complex as well as the binding affinity between the ligand and protein, which is important knowledge for lead optimization. Indeed, for more than three decades, molecular docking has been used, and as a result, a large number of novel medications have been found and developed [9]. Although molecular docking will undoubtedly continue to play a significant role, its success rate is still far from being fully achieved. High-throughput screening is still used often in many pharmaceutical companies today for this reason as well. Virtual screening based on docking won't ever be able to replace an irreplaceable. Thus in the current investigation, ursolic acid a triterpenoid was selected for evaluation of antidiabetic potential by molecular docking. A mechanistic insight for their antidiabetic potential is elucidating by interaction of ursolic acid with different target proteins.

Aldose Reductase

The crystal structure of the aldose reductase enzyme consisting of macromolecular receptor associated with bound tolrestat ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (3s3g.pdb) registered in the Protein data bank was used. The bound ligand tolrestat was found within the receptor [16].

Figure 7: Crystal structure of aldose reductase enzyme with bound ligand tolrestat (PDB ID-3s3g)

Glycogen Synthase Kinase

The crystal structure of the glycogen synthase kinase enzyme consisting of macromolecular receptor associated with bound ligand ARN25058 is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (7oy5.pdb) registered in the Protein data bank was used. The bound ligand ARN25058 was found within the receptor [17].

Figure 8: Crystal structure of glycogen synthase kinase enzyme with bound ligand ARN25068 (PDB ID-7oy5)

Molecular Docking Simulation Studies

Docking of ligand ursolic acid was performed against α- glucosidase, α- amylase, aldose reductase, and glycogen synthase kinase-3 enzyme was performed by Autodock to establish its probable mechanism of action. All the bonds of ligand ursolic acid were kept flexible, while no residues in receptor were made flexible [18].

Toxicity & ADME-T Studies

The pharmacokinetics of ligand molecule was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [19].

RESULT AND DISCUSSION

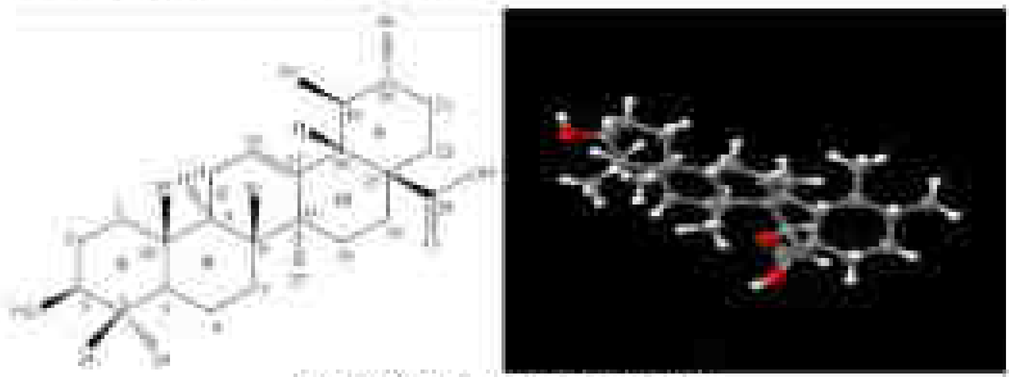
Diabetes mellitus (DM) is a chronic condition of carbohydrate metabolism that results in high blood glucose levels from an impaired glucose homeostasis. On a global scale, diabetes mellitus (DM) is acknowledged as one of the most serious diseases of the twenty-first century. Clinically, a variety of oral hypoglycemic medications have been used to manage this condition. These medications are grouped into different classes and include biguanides, sulfonylureas, thiazolidinediones (TZD), meglitinides, dipeptidyl peptidase (IV) inhibitors, sodium-glucose cotransporter (SGLT2), and -glucosidase inhibitors. Each class has a different method of action and is directed at a certain kind of organ. In reality, to boost the treatment's

EXPERIMENTAL WORK

Molecular docking studies

Ligand Preparation

2D Structure of ligand ursolic acid was drawn by using ChemDraw [10]. The two-dimensional structure of ligand was converted into 3-D structure with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [11].



2D and 3D structure of ursolic acid

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grids points can be adjusted with another thumbwheel, the value in the study taken is given in table 1 [12].

Table 1: The grid-coordinates of the grid-box used in the current study

Proteins	x-D	y-D	z-D	Spacing (Å)	x center	y center	z center
3wy4	50	50	50	0.397	31.957	24.799	22.743
5emy	40	40	40	0.442	-13.934	-16.743	24.123
3s3g	40	40	40	0.392	-8.951	9.114	18.39
7oj5	40	40	40	0.392	23.936	17.106	9.189

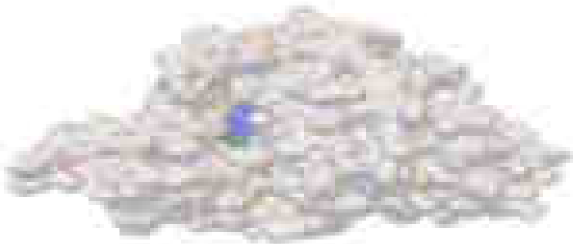


Figure 1: Grid box covering all active sites in α-glucosidase enzyme (3wy4).

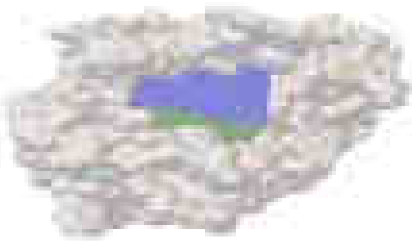


Figure 2: Grid box covering all active sites in α-amylase enzyme (5emy).