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

Priyanka Ahirwar*& Jitender K Malik
Institutes of Pharmacy, P.K. University, Shivpuri (M.P.)-India

ABSTRACT: Diabetes mellitus is a chief cause involved in the morbidity and mortality among the global population (Steppan et al., 2001). 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 proteins.

Keywords: Diabetes mellitus, ursolic acid, α-Amylase, α-glucosidase aldose reductase& Glycogen synthase kinase-3 (GSK-3).

RESEARCH PAPER

***Corresponding Author:**
Priyanka Ahirwar
Institutes of Pharmacy, P. K. University, Shivpuri (M.P.)-India

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INTRODUCTION

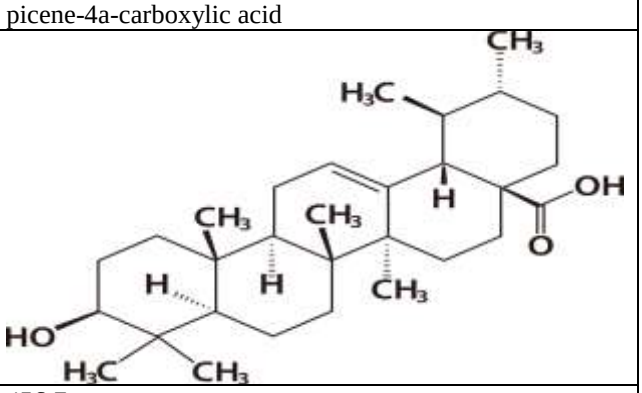
Diabetes is a condition of the glucose, lipid, and protein metabolism that is brought on by decreased insulin production or developing resistance to the hormone's activity. Diabetes-related chronic hyperglycemia results in the glycation of body proteins, which then triggers secondary problems that damage 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 hypoglycemia medication. Diabetes mellitus represents a heterogeneous group of disorders. Some diverse diabetic phenotypes can be categorized on the basis of specific etiology and or pathogenesis, but in many patients overlapping phenotypes make etiological and pathogenetic classification complicated [5].

- **Type 1 Diabetes Mellitus**
  Beta cell destruction usually leading to absolute insulin deficiency
  - Autoimmune
  - Idiopathic
- **Type 2 Diabetes Mellitus**
  - Predominantly insulin resistance
  - Predominantly insulin secretory defects
- **Other Specific Types Of Diabetes**
  - Genetic defects of beta cell dysfunction, e.g. MODY 1 to 6
  - Genetic defects in insulin action, e.g. Type A insulin resistance
  - Diseases of exocrine pancreas, e.g. Fibro calculus pancreatopathy
  - Endocrinopthies, e.g. Acromegaly, Cushings etc.,
  - Drugs or chemical - induced, e.g. glucocorticoids
  - Infections, e.g., congenital rubella
  - Uncommon forms of immune-mediated diabetes
    e.g. Stiff Man Syndrome
  - Other genetic syndromes
- **Gestational Diabetes**

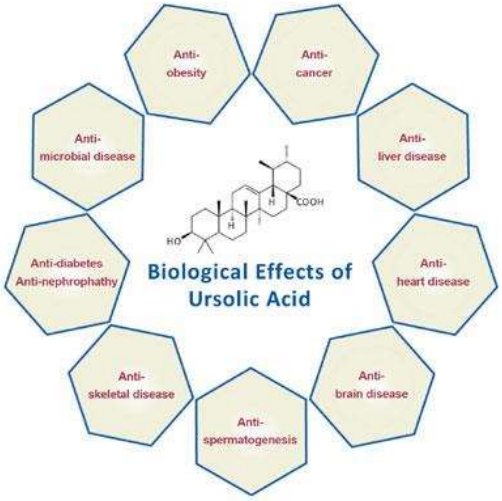
Ursolic acid (3-beta-3-hydroxy-urs-12-ene-28-oic-acid) is a phytochemical and bioactive compound commonly found in several medicinal herbs and foods. Numerous pharmacological properties of UA have been

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.	284^0C
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]



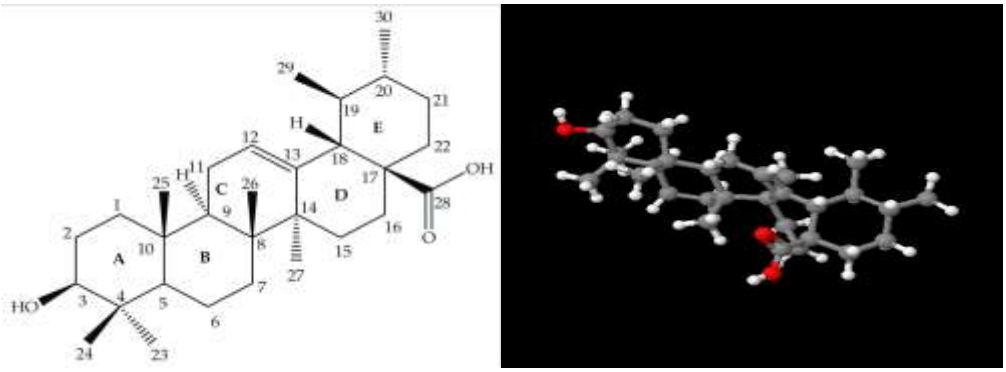
One of the trendiest virtual screening techniques is molecular docking, particularly when the target protein's 3D structure is available. This technique was able to predict the structure of the protein-ligand complex as well as the binding affinity between the ligand and protein, which is important knowledge 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.

EXPERIMENTAL WORK

Molecular docking studies

Ligand Preparation

2D Structure of ligand ursolic acid was drawn by using ChemDraw [10].The two-dimensional a structure of ligand was converted into 3-D structureswith 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	9.474	18.39
7oy5	40	40	40	0.392	23.936	-17.104	9.189

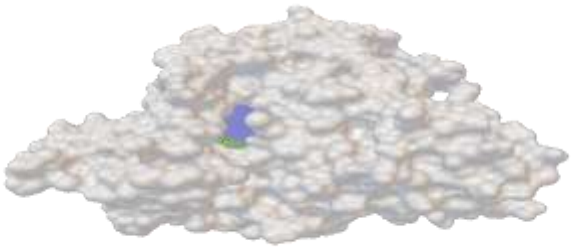


Figure 1: Grid box covering all active sites in α-glucosidase enzyme (3wy4).

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

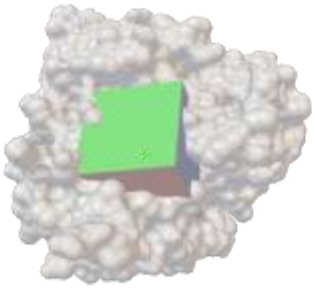


Figure 3: Grid box covering all active sites in aldose reductaseenzyme (3s3g).

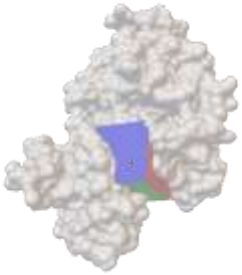


Figure 4: Grid box covering all active sites in glycogen synthase kinaseenzyme (7oy5).

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [13].

Macromolecular structure

α-glucosidase

The crystal structure of the α-glucosidase enzyme consisting of macromolecular receptor associated with bound endogenous ligand maltose is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (3wy4.pdb) registered in the Protein data bank was used. The bound ligand maltose was found within the receptor [14].

Figure 5: Crystal structure of α-glucosidase enzyme with bound ligand maltose (PDB ID-3wy4)

α-amylase

The crystal structure of the α-amylase enzyme consisting of macromolecular receptor associated with bound mechanistic inhibitor glucosylepi-cyclophellitol ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (5emy.pdb) registered in the Protein data bank was used. The bound ligand glucosylepi-cyclophellitol was found within the receptor [15].

Figure 6: Crystal structure of α-amylase enzyme with bound mechanistic inhibitor glucosylepi-cyclophellitol ligand (PDB ID-5emy)

Aldose Reductase

The crystal structure of the aldose reductase enzyme consisting of macromolecular receptor associated with bound tolmetin 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 tolmetin was found within the receptor [16].

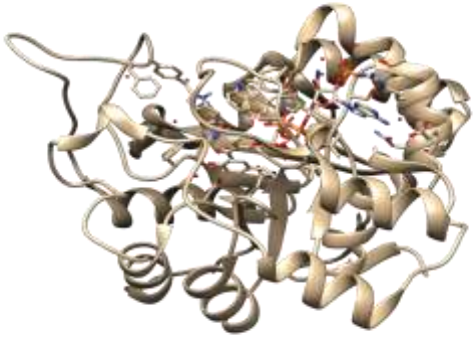


Figure 7: Crystal structure of aldose reductase enzyme with bound ligand tolmetin (PDB ID-3s3g)

Glycogen Synthase Kinase

The crystal structure of the glycogen synthase kinase enzyme consisting of macromolecular receptor associated with bound ligand ARN25068is 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 ARN25068was 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 illnesses 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

effectiveness, various anti-diabetic medication combinations are frequently employed. However, despite its benefits, these drugs also have their own long-term effects that can give out adverse effects caused by chronic administration, including cardiovascular disease, lactate acidosis, hypoglycaemia, gastrointestinal complaints and others. To date, molecular docking studies have been used recently in predicting the potential inhibitor that has been compared with marketed anti-diabetic drugs as which by seeking these natural compounds as new anti-diabetic agents with little or no adverse effects for the long term effect. Molecular docking is an important computational method for predicting possible drug-protein interactions with the selected ligand that represent bioactive compound containing in the medicinal plants.

In diabetes mellitus, control of postprandial plasma glucose level is critical in the early treatment [20]. One of the treatment methods for lowering postprandial hyperglycemia is the inhibition of enzymes involved in the metabolism of carbohydrates. Amylase and -glucosidase are important enzymes that cleave the carbohydrates necessary for the absorption of glucose into the bloodstream, making natural products a safer alternative to synthetic medications for inhibition. Because of this, acarbose, miglitol, and voglibose are a few examples of synthetic drugs that block -amylase and -glucosidase. These medications do have their limitations, though, due to their general nature, severe side effects like GI tract inflammation, and increased diabetic problems.

With reference to aldose reductase a recent proteomic study has shown that AR is abundantly expressed in human platelets, and its inhibitor, epalrestat, reduces platelet aggregation, supporting a crucial role of AR in platelet aggregation. Consistent with these findings, inhibition of AR has also been demonstrated to attenuate the hyperglycemia-induced platelet hyper aggregation in human platelet by reducing oxidative stress [21]. All these findings suggest that AR plays a central role in platelet aggregation, particularly during hyperglycemic conditions. Oxidative stress generated by the AR-dependent polyol pathway likely plays a major role in diabetic platelet hyper aggregation. Aldose reductase, an aldoketoreductase, is ubiquitous in mammalian tissues. By reducing glucose to sorbitol (the latter being oxidized to fructose) aldose reductase is responsible for the first steps in the polyol cycle. Aldose reductase has a broad substrate specificity including glucose and galactose. Generally, the affinity of aldose reductase for glucose is low, the enzyme operating at low catalytic rates. Its activity increases when hexokinase is saturated and high glucose levels are present. Sorbitol, which is produced under these conditions, accumulates in the cell, thus creating an osmotic effect and thereby tissue hydration. This may underlie, at least in part, certain complications of diabetes. Aldose reductase catalyzes the reduction of glucose to sorbitol in the polyol pathway and has been associated with development of DN.

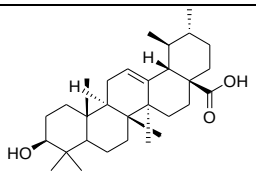
Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase at the epicenter of the control of numerous cellular processes including glycogen metabolism, gene transcription, mRNA translation, cytoskeletal regulation, cell cycle progression and apoptosis. a role for GSK-3 in the development of insulin resistance has been established. GSK-3 inhibition has been shown to enhance insulin sensitivity and promote glycogen synthesis, suggesting GSK-3 as a viable therapeutic target for the treatment of T2DM. Recent data shows that GSK-3α and GSK-3β have distinct physiological functions in insulin-sensitive tissues, particularly in glycogen metabolism [22].

In the present study ursolic was taken for evaluation of antidiabetic potential by molecular docking technique. Docking study of ursolic acid with α -glucosidase (3wy4), α -amylase (5emy), Aldose reductase (3s3g) and GSK3 (7oy5) was carried out by Auto dock to establish its probable mechanism of action. The grid box cover all active enzyme was tabulated in table1 & fig.1-4, whereas crystal structure of all enzyme shown in fig.5-8.

The outcome of docking of ursolic acid against α -glucosidase, α- amylase, aldose reductase, and glycogen synthase kinase-3 enzyme showed the binding energy + 5.24,8.14,-9.29 &-9.97 respectively(table 2). Molecular interaction of ursolic acid with selected receptors showed in fig 9-20. Molecular simulation revealed that the ursolic acid bind strongly with GSK3 receptor having covalent bond withLys-B85,Asp-B136 & Pro-B136 along with vanderwaal's interaction with other amino acid present in receptor.

The pharmacokinetic profiling of the ursolic acid ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like mutagenic, reproductive effects, irritant effect, and tumorogenic properties. The pharmacokinetic and toxicity profiling results of ursolic acid was shown in figure 21.

Table 2: Result of docking study of ursolic acid against α -glucosidase, α- amylase, aldose reductase, and glycogen synthase kinase-3 enzyme

S. No	CompoundName	Structure	Binding Energy			
			α -glucosidase (3wy4)	α -amylase (5emy)	Aldose reductase (3s3g)	GSK3 (7oy5)
1	Ursolic acid		+5.24	-8.14	-9.29	-9.97
	Interacting Residues		Phe206, Phe297, Tyr65, His105, Arg400, Asp62, His332, Phe147, Phe166, Ile146, Ala229, Tyr235	Ile51, Trp59, His305, Trp58, Asp300, Gly306, Tyr62, Leu162, Leu165, Gln63, Gly104	Gln49, Val47, Phe121, Tyr48, Trp20, Pro218, Trp219, Phe122, Leu301, Leu300	Val210, Leu132, Lys199, Leu188, Ile62, Val7, Tyr134, Pro136, Arg141, Asp200, Lys85

Interactions

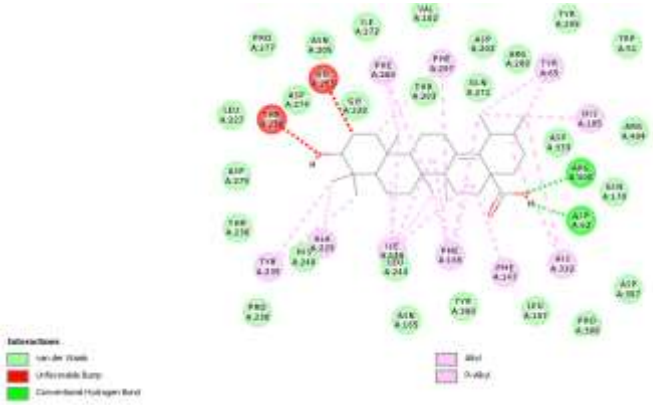


Figure 9: Two-dimensional binding interaction of ursolic acid with α -glucosidase enzyme.

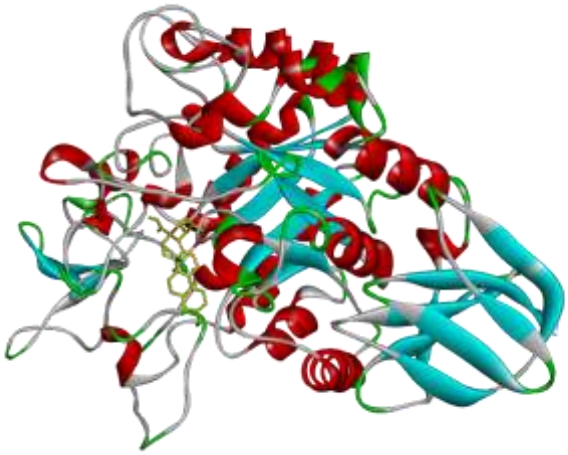


Figure 10: Three-dimensional binding interaction of ursolic acid with α -glucosidase enzyme

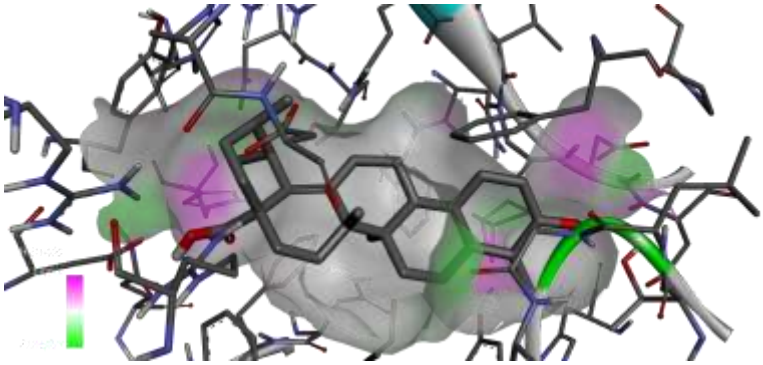


Figure 11: Binding conformation of ligand ursolic acid with α -glucosidase enzyme

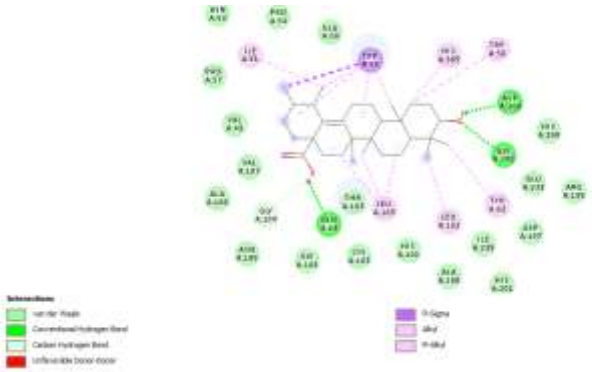


Figure 12: Two-dimensional binding interaction of ursolic acid with α –amylase enzyme

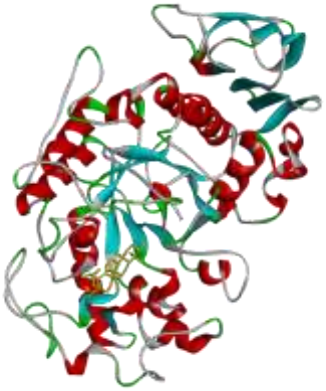


Figure 13: Three-dimensional binding interaction of ursolic acid with α –amylase enzyme

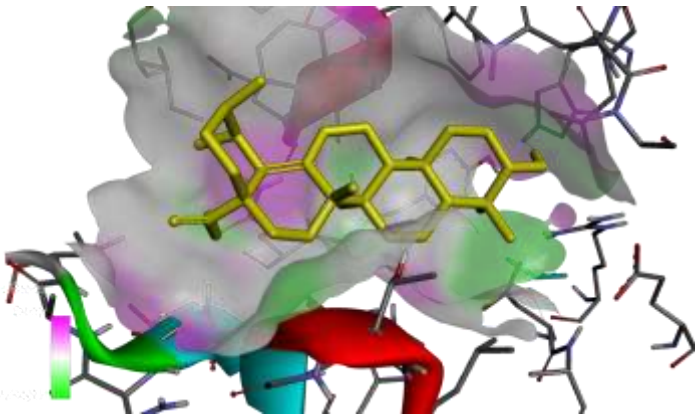


Figure 14: Binding conformation of ligand ursolic acid with α –amylase enzyme

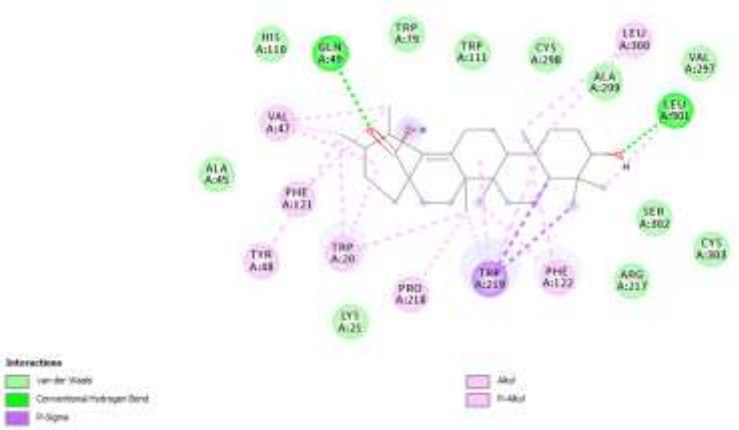


Figure 15: Two-dimensional binding interaction of ursolic acid with aldose reductase enzyme.

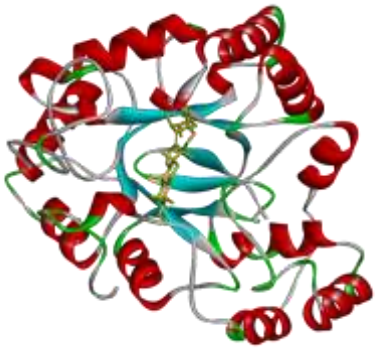


Figure 16: Three-dimensional binding interaction of ursolic acid with aldose reductase enzyme

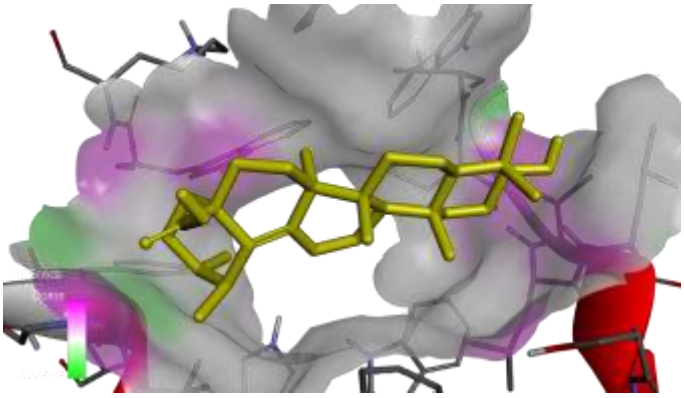


Figure 17: Binding conformation of ligand ursolic acid with aldose reductase enzyme

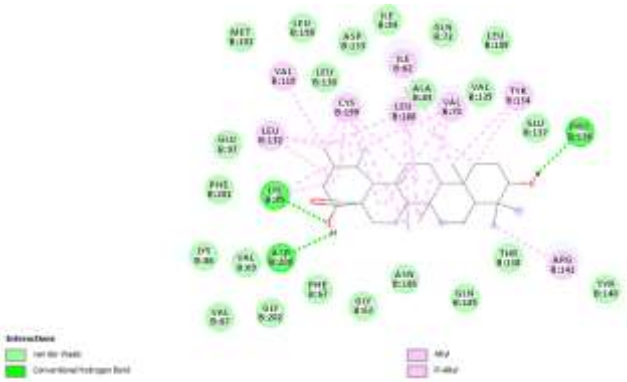


Figure 18: Two-dimensional binding interaction of ursolic acid with GSK3enzyme

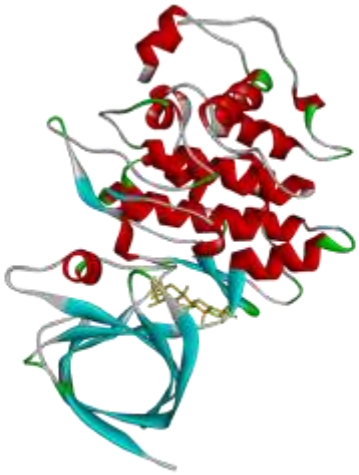


Figure 19: Three-dimensional binding interaction of ursolic acid with GSK3enzyme

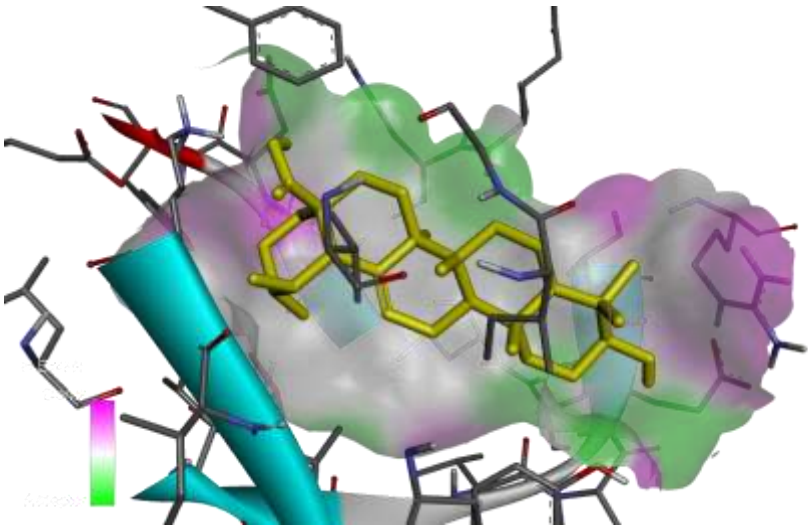


Figure 20: Binding conformation of ligand ursolic acid with GSK3 enzyme

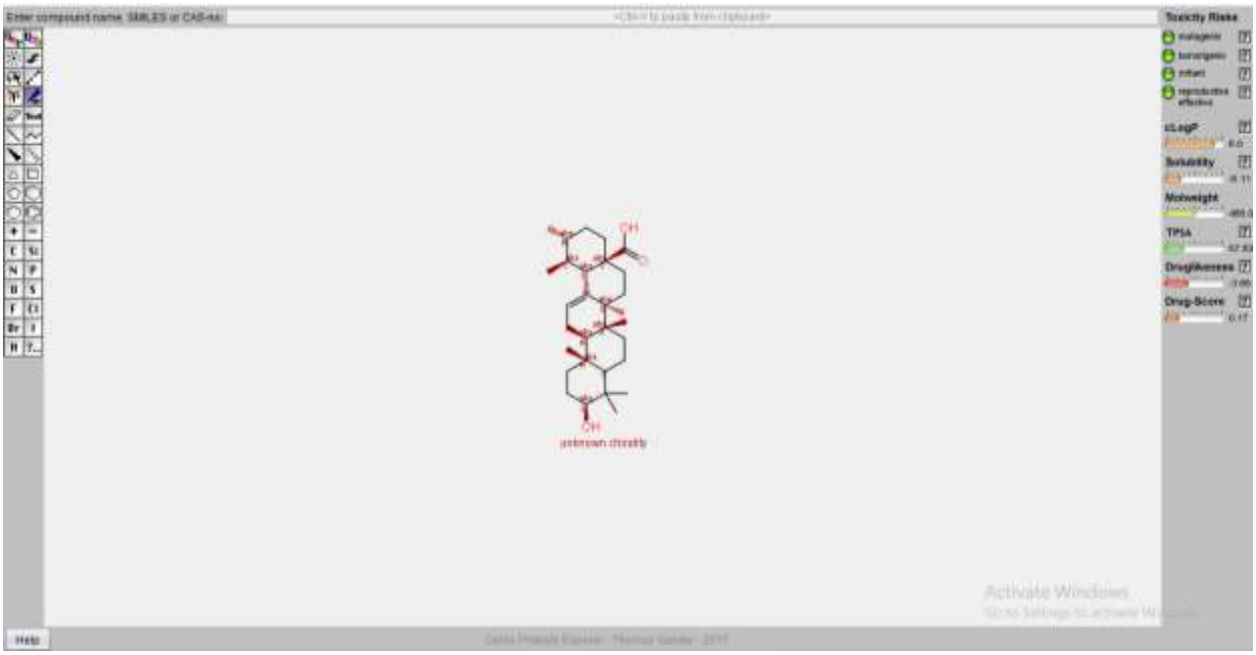


Figure 21: Pharmacokinetic and toxicity profiling of ursolic acid

CONCLUSION

Ursolic Acid (3β-hydroxyurs-12-en-28-oic acid) is a pentacyclictriterpenoid compound that has been found in large amounts in berries (such as cranberries) and mostly in the peel. The occurrence of ursolic acid and its derivatives as major metabolites in medicinal plants could be associated with their biological activities. In spite of the pharmacological effects that have already been demonstrated, they exhibit antimycotic, antitumoral, antibacterial, antiviral, and antiparasitic properties, suggesting that these compounds are important classes of prototypical natural antibiotic molecules. Thus, in the current study, ursolic acid a triterpenoid was selected for evaluation of antidiabetic potential by molecular docking. Docking study of ursolic acid with α -glucosidase (3wy4), α -amylase (5emy), Aldose reductase (3s3g) and GSK3 (7oy5) was carried out by Auto dock A mechanistic insight for their antidiabetic potential is elucidating by interaction of ursolic acid with target proteins. The outcome of investigation showed the covalent bounding interaction of ursolic acid with GSK3 protein along with vanderwaal's binding *via* Val210, Leu132, Lys199, Leu188, Ile62, Val7, Tyr134, Pro136, Arg141, Asp200, Lys85. The result revealed that ursolic acid is potent inhibitor GSK3 protein.GSK-3 inhibition has been shown to enhance insulin sensitivity and promote glycogen synthesis, suggesting GSK-3 as a viable therapeutic target for the treatment of DM. The plants containing ursolic acid are traditionally utilized for the cure of DM and related disorders from the immortal time. The exact mechanism of action for the diabetic response of ursolic acid was still not revealed. With intent to propose the most probable mechanism of action of ursolic acid the docking based computational analysis has been performed against the diabetic drug targets like α -glucosidase, α- amylase, aldose reductase, and glycogen synthase kinase-3 enzyme. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the ursolic acid is executing its anti-diabetic y response *via* inhibiting the GSK3enzyme.

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