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QUASSINOIDS ACTIVITY AS A POTENT INHIBITOR OF ALDOSE REDUCTASE ENZYME (ANTIDIABETIC ACTIVITY) – MOLECULAR DOCKING STUDIES

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ABSTRACT: The objective of the study is to analyze the inhibitory activity of selected Quassinoids from the plant *Simarouba glauca* using docking studies against Aldose Reductase complexed with known drug IDD and cofactor NADPH (PDB ID:4GCA). *In silico* is applied to screen abilities of Quassinoids as a potent inhibitor of Aldose Reductase. The 3D structure of protein was obtained from PDB database and of the ligands from PUBCHEM database. Docking analysis of the compound was performed using Ligpep 2.3, Schrodinger suite 2009. The comparison of the docking value indicated that compounds exhibited better binding affinity similar to that of the known drug IDD. Further analysis of the drug likeness by means of ADME properties were predicted using Swiss ADME online server. None of the above compounds violated Lipinski's parameters, making them potentially promising agents for biological activities. Finally, the results indicated that these compounds are potential inhibitor of Aldose Reductase and expected to be effective in diabetes.

keywords: *Simarouba glauca,* Quassinoids, ADME Properties, Aldose Reductase, Anti – Diabetic.

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1.INTRODUCTION

Simarouba glauca, generally called Laxmitaru or paradise tree belongs to the family Simaroubaceae. Common names for *S. glauca* are bitter ash, bitter damson princess tree, and Simarouba. This tree

is likewise called the “Tree of the solace of cancers” as it's broadly utilized in most cancer treatment. It produces bright green leaves of 20-50 cm in length, yellow flowers, and oval elongated crimson-colored fleshy fruits. It is ideal for temperature variance of 10-40ºC, with pH of the soil to be 5.5-8.0 [2]. The bark and leaf extracts of Simarouba is widely recognized for its distinctive varieties of pharmacological residences along with hemostatic, anthelminthic, antiparasitic, antidysentric, antipyretic, anticancerous [3], antimicrobial, antiherpetic, antiprotozoal [4], antiamoebic, antimalarial, antifungal, antioxidant and antiulcer [5] and in conjunction with hepatoprotective property. The major groups of chemical compounds in *Simarouba glauca* are quassinoids, which belong to the triterpene family. This includes: ailanthinone, canthin [6], dehydroglaucarubinone, glaucarubine, glaucarubolone, glaucarubinone, holacanthone, melianone, simaroubidin, simarolide, simarubin, simarubolide, sitosterol, tirucalla etc. [3]. After the preliminary discovery of the antileukemic action of bruceantin, a Quassinoids, those molecules won a good deal of attention [7]. Based on the chemical structure and organic residences almost a hundred and fifty Quassinoids had been secluded and classified. A huge variety of inhibitory outcomes has been proven via way of means of Quassinoids which incorporates anti-inflammatory, antiproliferative outcomes on tumor cells types [8]. Considering the destiny in producing anticancer dealers with extra energetic and much less poisonous compounds, herbal Quassinoids constitute a promising supply of small molecules. From the Quassinoids listed, 4 had been decided on (Glaucarubine, Glaucarubolone, Glaucarubinone, Melianone) primarily based totally at the PASS (Prediction of Active Spectra for Substances) on line server prediction and target hunter databases which can be used to locate the organic sports of the specific compounds. In order to apprehend the organic activity of the compounds, structural scaffold of the ligands became taken into consideration. The carefully chosen ligands had been allowed for their prediction against novel goals for which PASS prediction server is used [9] [10]. This server predicts more than three hundred pharmacological elements and biochemical mechanisms on the idea of the structural system of the compounds. The given ligands had been anticipated to have interaction with 15 targets, amongst which the anticancer target PI3K became the maximum profound target for all of the ligands. Smiles design of the ligands had been used as input for the PASS on line server. From 1980's the own circle of relatives of lipid kinases termed Phosphoinositide 3-kinases (PI3Ks) has been located to play key regulatory roles in lots of cell strategies such as mobile survival, proliferation and differentiation [11]. The anticancer potentials of Quassinoids from *S. glauca* along with docking studies and ADME analysis was reported by Ramya et al [12]. In the present study, the activity of Quassinoids against aldose reductase enzyme by docking studies is highlighted. The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study intensely associated hyperglycemia with pathogenesis and progression of micro vascular complications in type 1 and type 2 diabetes [13]. Clinical progression of diabetic nephropathy has been described in detail, though the mechanism by

which hyperglycemia causes these complications remains controversial [14]. This is due to the interrelated nature of the metabolic pathways followed in the presence of the raised glucose levels. The reduction of glucose to sorbitol in the polyol pathway catalyzed by the enzyme Aldose Reductase (AR) has been comprehensively studied for a prospective role in the development of micro vascular complications which includes early diabetic nephropathy. Aldose reductase is a monomeric reduced Nicotinamide Adenine Dinucleotide Phosphate dependent enzyme belonging to a member of Aldo-keto reductase super family. Aldose Reductase, a highly conserved and inducible enzyme, plays a physiological role in enabling cells to adjust the osmolarity of their cytoplasm in response to changes in extracellular tonicity [15]. The increase in extracellular osmolarity will tend to dehydrate the cell and aggravate shrinkage. Prompt compensation could involve adjustment of Na+ / K+ - ATPase activity through second messenger systems [16], but an abrupt osmotic gradient involving elevated electrolytes might be expected to disable this form of compensation, as steep ionic and electrical gradients are produced. The substitute form of compensation is the elevation of the intracellular concentration of an electrically neutral osmolyte such as sorbitol, which is produced from glucose by the action of Aldose Reductase **(Figure 1.1)**.

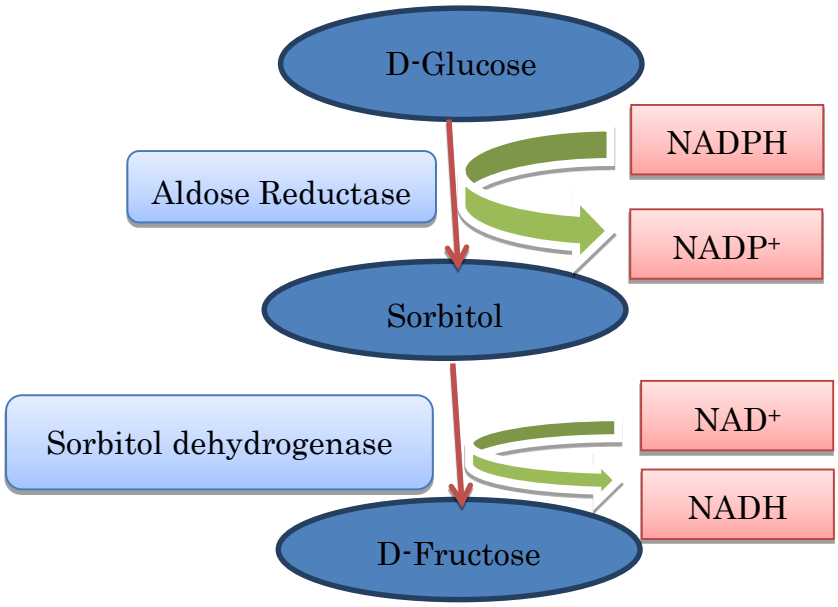


Figure 1.1: Sorbitol pathway

Aldose Reductase has low affinity for glucose and hence in normal cells less sorbitol is produced and most of the glucose is phosphorylated by hexokinase, a higher affinity enzyme. In the conditions of increased extracellular osmolarity, the synthesis of aldose reductase increases resulting in increased production of sorbitol in spite of its low affinity for the substrate. The polyol pathway [17] related to diabetes is shown in **Figure1.2**.

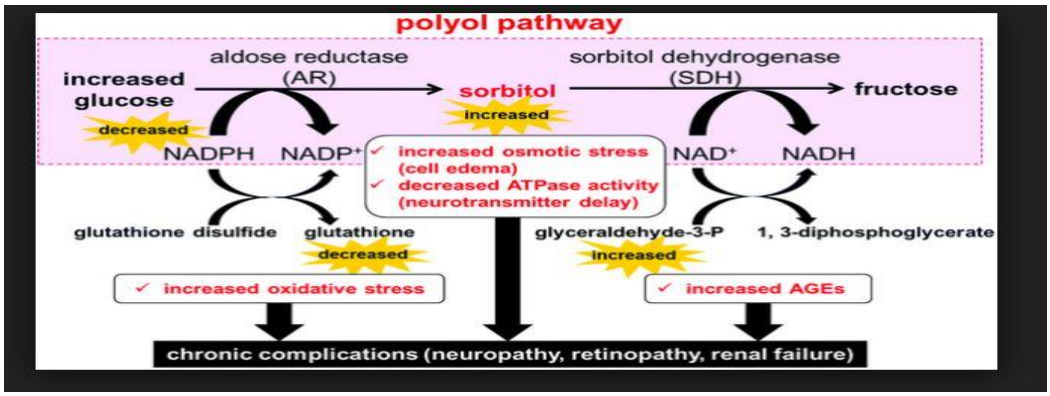
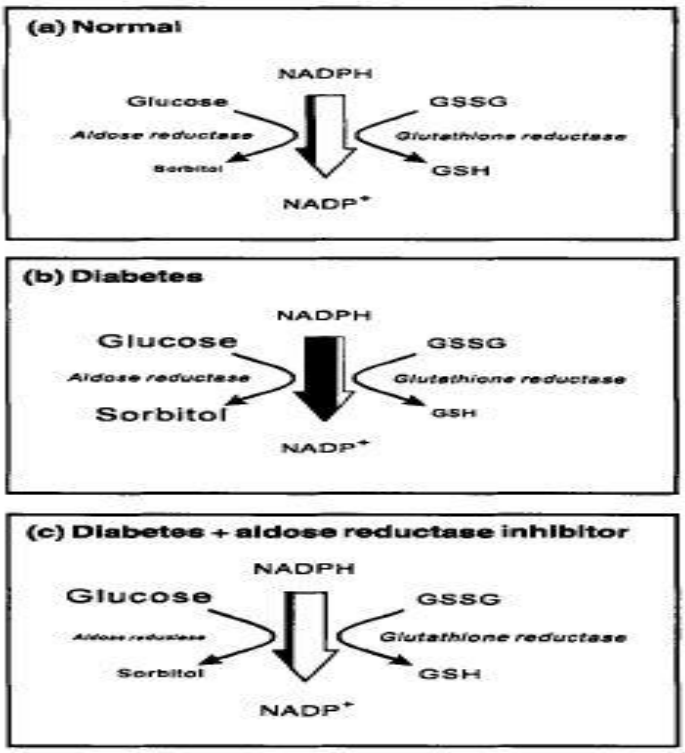


Figure 1.2: Polyol pathway related to diabetes

The inadequate sharing of NADPH by glutathione reductase and aldose reductase leading to diabetes is shown in **figure 1.3**. The illustration predicts the restriction of glutathione reduction in the presence of exaggerated sorbitol pathway flux in diabetes and correction of the shift with an inhibitor of aldose reductase.



[15]

Figure 1.3: Inadequate sharing of Glutathione reductase and aldose reductase

In hyperglycemic condition, reduction of glucose to sorbitol by aldose reductase establishes the first and rate limiting step of the polyol pathway where glucose is converted to fructose by sorbitol dehydrogenase. Both NADPH and NAD+ are utilized as cofactors for the enzyme's aldose reductase and sorbitol dehydrogenase respectively. Osmotic stress due to accumulation of sorbitol and oxidative stress due to changes in the ratio of NADPH/NADP+ and reduced NAD are the major causes of innumerable complications of secondary diabetes. The rise in the sorbitol levels in diabetic patients due to high levels of AR enzyme leads to the swelling of lens affecting clarity of

vision. The lens of the eye generally gets its nutrients from aqueous humor which provides oxygen and glucose. Due to uncontrolled glucose levels in the aqueous humor and in the lens, sorbitol level raises which causes lens to become less clear and opaquer. This in turn leads to cataract formation which makes the world appear blurry, yellowish and increased glare which is known as diabetic cataract [18]. It has been well established that the large size and extremely hydrophobic nature of the active site pocket makes the aromatic compounds suitable substrates of AR. As AR plays a key role in reducing the substrates leading to serious consequences in diabetes mellitus such as blindness, attempts have been made to explore for inhibitors of AR. Based on the fact that inhibitors of aldose reductase enzyme play a vital role in curing diabetic cataract, work on Quassinoids, a natural compound from the plant *S. glauca,* was taken up. By nature, these enzymes require NADPH cofactor for substrate binding and in view of this, induced fit docking of Quassinoids with aldose reductase in the presence of cofactor has been carried out.

Comparative analysis of the selected Quassinoids from the plant *S. glauca* with the known drug IDD was carried out using molecular docking studies.

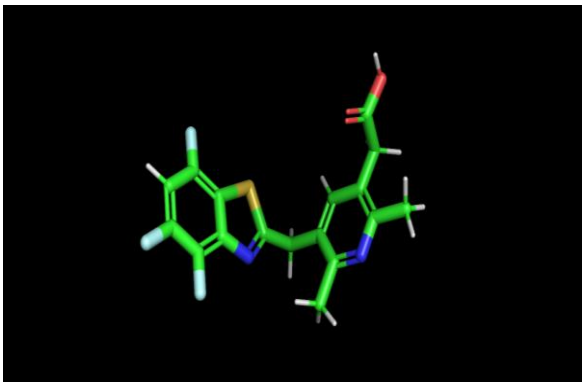
2. MATERIALS AND METHODS

2.1. Target retrieval and Binding site

The three-dimensional structure of Aldose Reductase (AR) complexed with known drug IDD and cofactor NADPH (PDB ID: 4GCA) was retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) protein Data Bank [19]. Binding sites of the protein were identified by FT site server [20]. Binding site identification has a wide range of applications which includes structure-based prediction of function, elucidation of functional relationships among proteins, protein engineering and drug design. FT Site Server describes an accurate method of binding site identification [21].

About the cocrystal IDD

The physicochemical properties of the Cocrystal IDD along with the 3D structure are shown in **Figure 2.1**.



- Molecular formula : $C_{17}H_{13}F_3N_2O_2S$
- Molecular weight: 366.36 g/mol
- Monoisotopic mass: 366.065 g/mol
- Heavy atom count: 25
- Topological polar surface area: 91.3 $Å^2$

Figure 2.1: 3D structure and physicochemical properties of the Cocrystal IDD

The Lipinski filter analysis which explains the rigidity of the cocrystal along with the ADME properties are listed in **table 2.1a** and **2.1b** respectively.

Table 2.1a: Lipinski filter analysis of the Cocrystal IDD

Ligand	Molecular weight	Hydrogen bond donor	Hydrogen bond acceptor	cLogP	Molar Refractivity
IDD (Cocrystal)	366.36 g/mol	1	8	3.31	88.22

Criteria: log *P*≤5.0, molecular weight in the range of 150–500, H-bond donor's ≤5, and H-bond acceptors ≤10.

Table 2.1b: ADMESAR Analysis of the Cocrystal IDD

Properties	**IDD (Cocrystal)**
Blood-Brain Barrier	BBB-
Human Intestinal Absorption	HIA++
Log S (scale Insoluble <-10<Poorly<-6< Moderately <-4<Soluble<-2Very<0< Highly) [Water solubility]	-5.44
Permeability – glycoprotein Substrate	Non – Substrate
Carcinogens	Non- Carcinogens
AMES mutagenicity	Non - Toxic
Acute Oral Toxicity (II – LD 50 – LD 500, LD III – LD 500 – LD 5000)	III
Synthetic accessibility [from 1 (very easy) to 10 (very difficult)]	3.09

2.2. Molecular Docking Procedures

The aim of molecular docking is to predict the binding modes of ligand and thus, define the orientation of the molecule with respect to the active or binding site. In this method, according to the affinity score in terms of kcal/mol, ranking all the binding poses of the molecule inside the catalytic site of an enzyme is being done. The selected compounds were taken for minimization using Ligpep module of Schrodinger 09 where probable tautomeric and ionization states at pH = 7 ± 1 followed by energy minimization with OPLS 2005 force field [22, 23] was carried out. The protein preparation of the target (PDB ID: 4GCA) was performed using Protein preparation wizard of Schrodinger 09 where missing hydrogen bond order were assigned followed by energy minimization.

2.3. Molecular Docking

The receptor grid was prepared keeping cocrystal (IDD) ligand on Aldose Reductase (PDB ID:

4GCA) at the center of grid with 20 Å edges bearing catalytic site. Initially docking study on the cocrystal was performed on prepared receptor grid for cross-validating the binding mode with respect to X-ray crystal structure binding mode. Further, molecular docking was performed for given ligands against PDB ID using Glide XP 5.8 Program [24,25,26]. The top analogs based on docking score as well as binding interaction with catalytic residues were allowed for induced fit docking and results were compared with the cocrystal after Glide XP. The docked conformation corresponding to the lowest free energy (or highest score) provided by Glide program was selected as the most probable binding pose of top compound.

2.4. Structural features of the complex

Once docking was performed, best poses for hydrogen bonding, Hydrophobic and π interactions were analyzed using PyMol version 1.3 (The PyMol Molecular Graphics System).

3. RESULTS AND DISCUSSION

Owing to the important functions of Aldose Reductase and challenges in designing specific inhibitors because of highly conserved active site architecture, there is a big demand for structure analysis to identify new inhibitors targeting various diseases. Together, with the above-mentioned fact and considering the importance of the *S. glauca* plant indicated against many illnesses, important compounds were selected to screen their affinity towards Aldose Reductase. This selection was guided by PASS prediction server.

3.1. Structure of Macromolecule (Aldose Reductase)

The target Aldose Reductase (AR) complexed with known drug IDD and cofactor NADPH (PDB ID: 4GCA) was used for docking studies **(Figure 3.1)**.

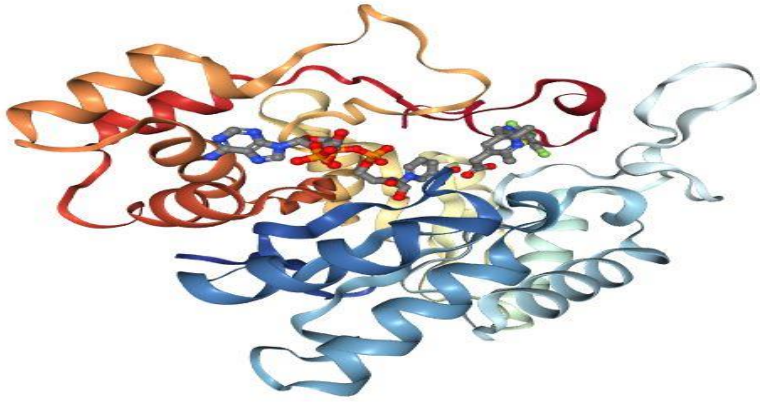


Figure 3.1: Cartoon representation of AR (PDB Code: 4GCA). IDD and Cofactor NADPH are shown as solid ball and stick.

3.2. Active sites of the Protein molecule

In this study, FT Site Server predicted the active sites of the targeted protein PI3K. Three active sites are projected in this protein (**Figure 3.2**). The active sites comprising of amino acid residues are Active site 1: GLY 18, THR 19, TRP 20, LYS 21, ASP 43, VAL 47, TYR 48, GLN 49, LYS 77, TRP 79, CYS 80, HIS 110, TRP 111, THR 113, PHE 115, PHE 122, SER 159, ASN 160,

GLN 183, TYR 209, SER 210, PRO 211, LEU 212, SER 214, ASP 216, TRP 219, ILE 260, PRO 261, LYS 262, CYS 298, ALA 299, LEU 300, CYS 303, TYR 309,PRO 310, PHE 311 Active site 2: THR 19, TRP 20, LYS 21, SER 22, PRO 23, PRO 24, VAL 47, TYR 48, GLN 49, ASN 50 Active site 3: ARG 217, TRP 219, LYS 221, ASP 224, TRP 295, ARG 296, VAL 297, CYS 298, ALA 299, LEU 300, LEU 301.

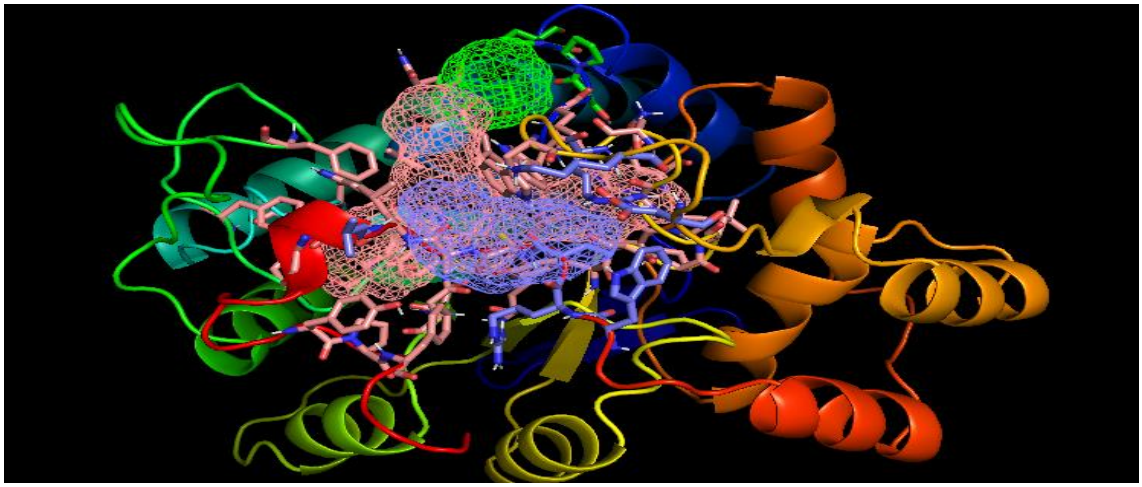


Figure 3.2: Active Sites of AR (as predicted by FT Site Server) represented as wire model

3.3. Docking Results

Results obtained from induced fit docking of compounds of the active site of AR (4GCA) are reported in **Table 3.1.** The molecular docking study of the compounds with AR receptor shows that, all the compounds have better docking score than that of the known drug IDD which predicts that the compounds chosen have better binding affinity to the receptor than the cocrystal. The hydrogen binding interactions of the compounds with AR is shown in **figure 3.3 (both 2D and 3D interactions)**. This prediction leads us to believe that the compounds will possibly be suitable to treat diabetes. The docking results mentioned in the table clearly indicates that all the compounds selected for docking study displayed excellent binding affinity when compared to the known drug IDD. Glaucarubine showed best glide energy (-54.498) followed by Glaucarubolone (-54.474) which is much better than IDD (-45.02) the co-crystal. The hydrogen bond interactions along with D…. A distance (Å) is shown in the PyMol interactions (Figure 3.3a - e). The stabilizing hydrophobic interactions are mentioned in table 3.1. So far, no reports are available on docking studies for Quassinoids against Aldose reductase enzyme.

Table 3.1: Induced fit docking results describing energetics and geometry of binding

Ligand	**Docking Score**	**Glide Energy (Kcal/mol)**	**Hydrogen Bond**	**D…. A Distance(Å)**	**Hydrophobic Interactions**
Glaucarubine	-12.355	-54.498	(O-H---O) Tyr 48 Ala 299 (O-H---O) Trp 20 (H---NH)	2.2 1.7 2.2	PHE 122, PRO 218, ALA 299, LEU 300, LEU 301, TRP 219, VAL 297, TRP 20, VAL 47, TRP 79, TYR 48
Glaucarubinone	-8.792	-46.779	His 110 (N-H---O) Gln 49 (N-H---O) (O-H---O) Val 47	2.3 2.1 2.0	ALA 299, CYS 298, PHE 311, TYR 209, PRO 218, LEU 124, TRP 20, VAL 47, TYR 48, TRP 111
Glaucarubolone	-13.045	-54.474	Ala 299 (N-H---O) Trp 111 (N-H---O) Trp 20 (N-H---O)	2.0 2.5 2.0	ALA 299, VAL 297, TRP 219, PRO 218, LEU 300, PHE 122, TRP 20, TYR 48, VAL 47, TRP 79, TRP 111
Melianone	-8.83	-54.181	His 110 (N-H---O) (O-H---O) Val 47 Ser 302 (N-H---O)	2.1 1.8 2.1	TYR 48, VAL 47, TRP 20, TRP 111, TRP 79, PHE 122, LEU 124, LEU 301
IDD (Cocrystal)	-7.6	-45.02	His 110 (N-H---O) Trp 111 (N-H---O) (O-H---O) Tyr 48	2.7 2.9 2.7	PHE 122, TRP 111, TRP 79, CYS 80, TYR 309, ALA 299, CYS 298, TRP 219

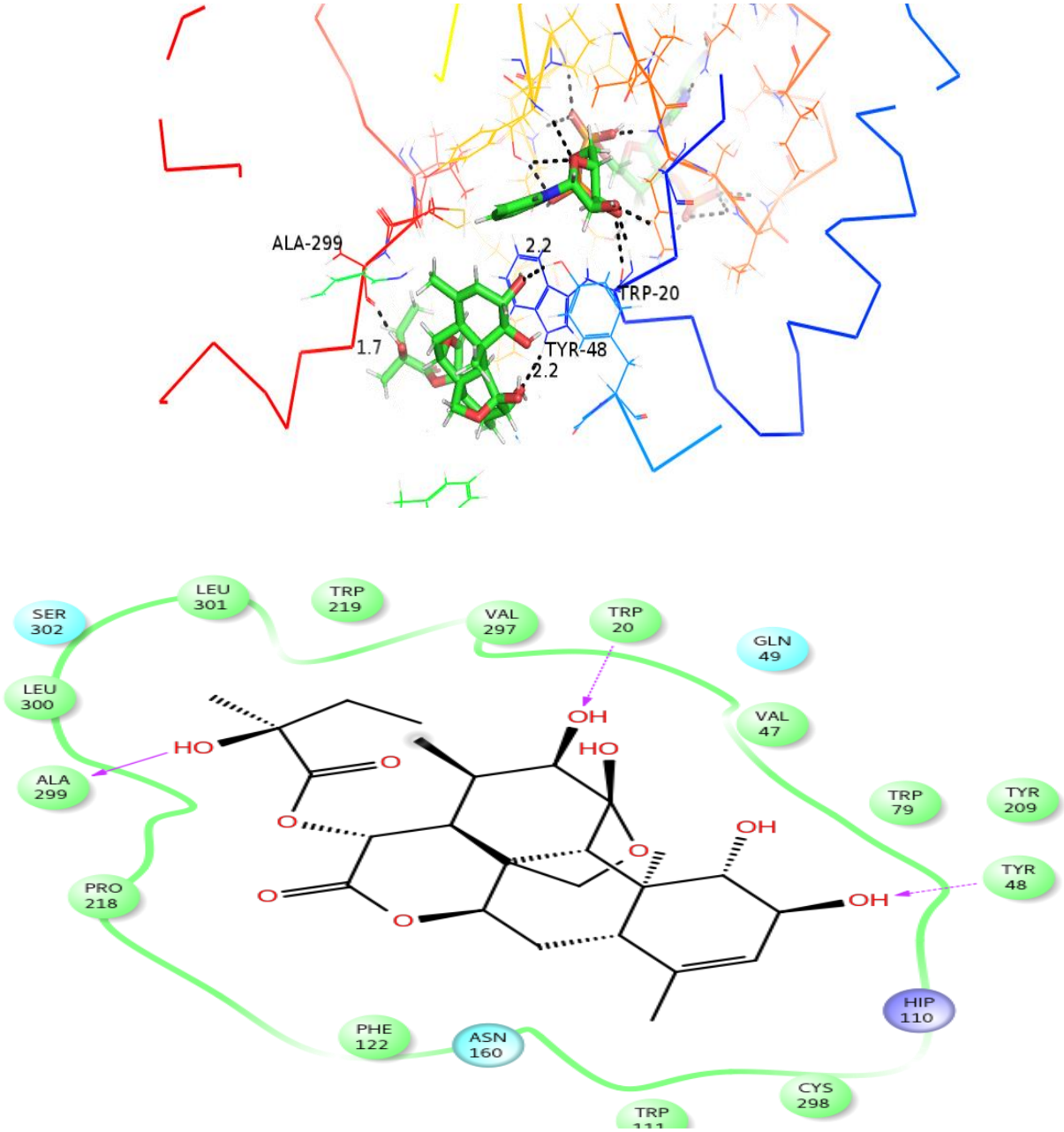


Figure 3.3a: Glaucarubine at the active site of the target protein

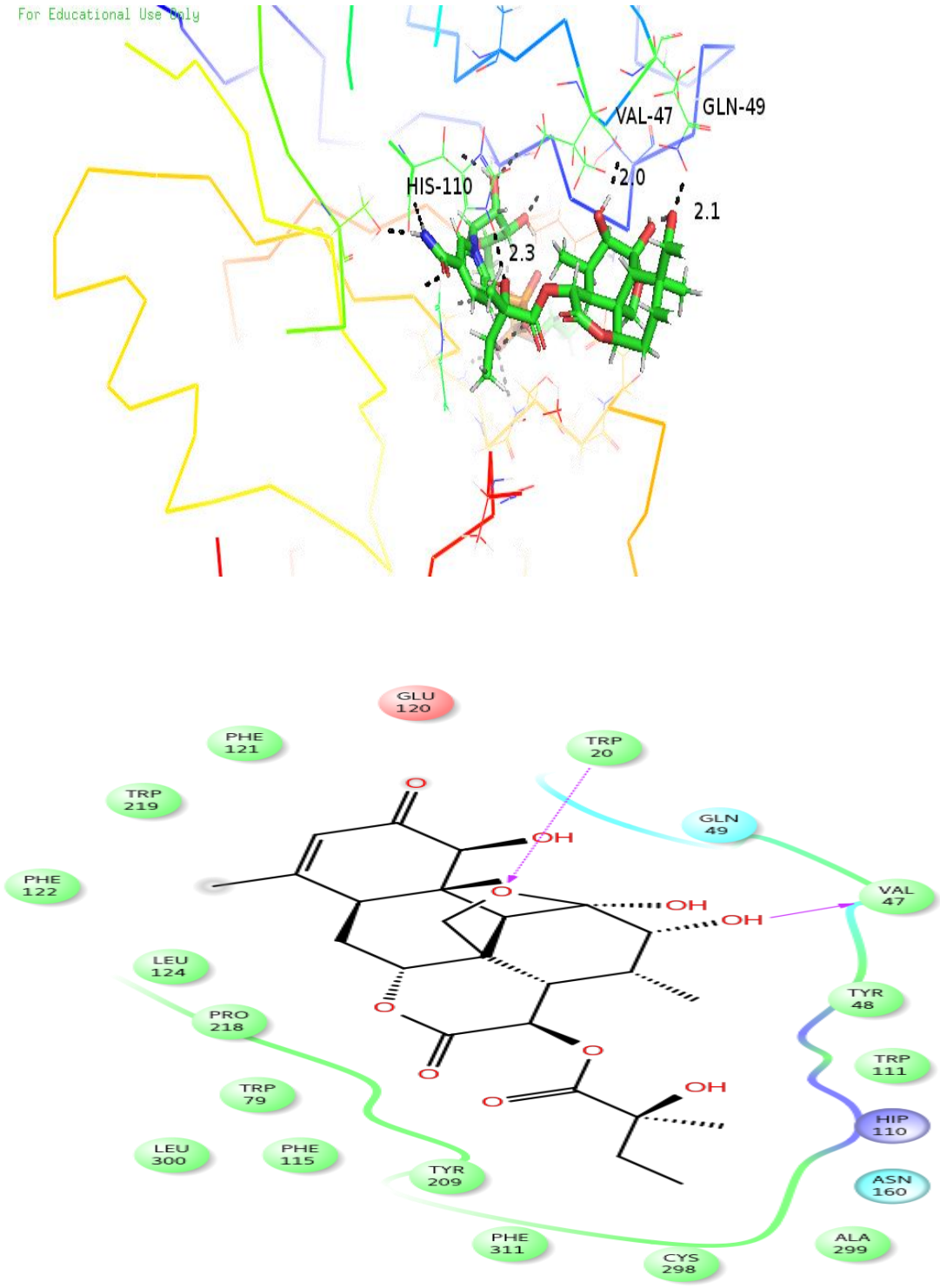


Figure 3.3 b: Glaucarubinone at the active site of the target protein

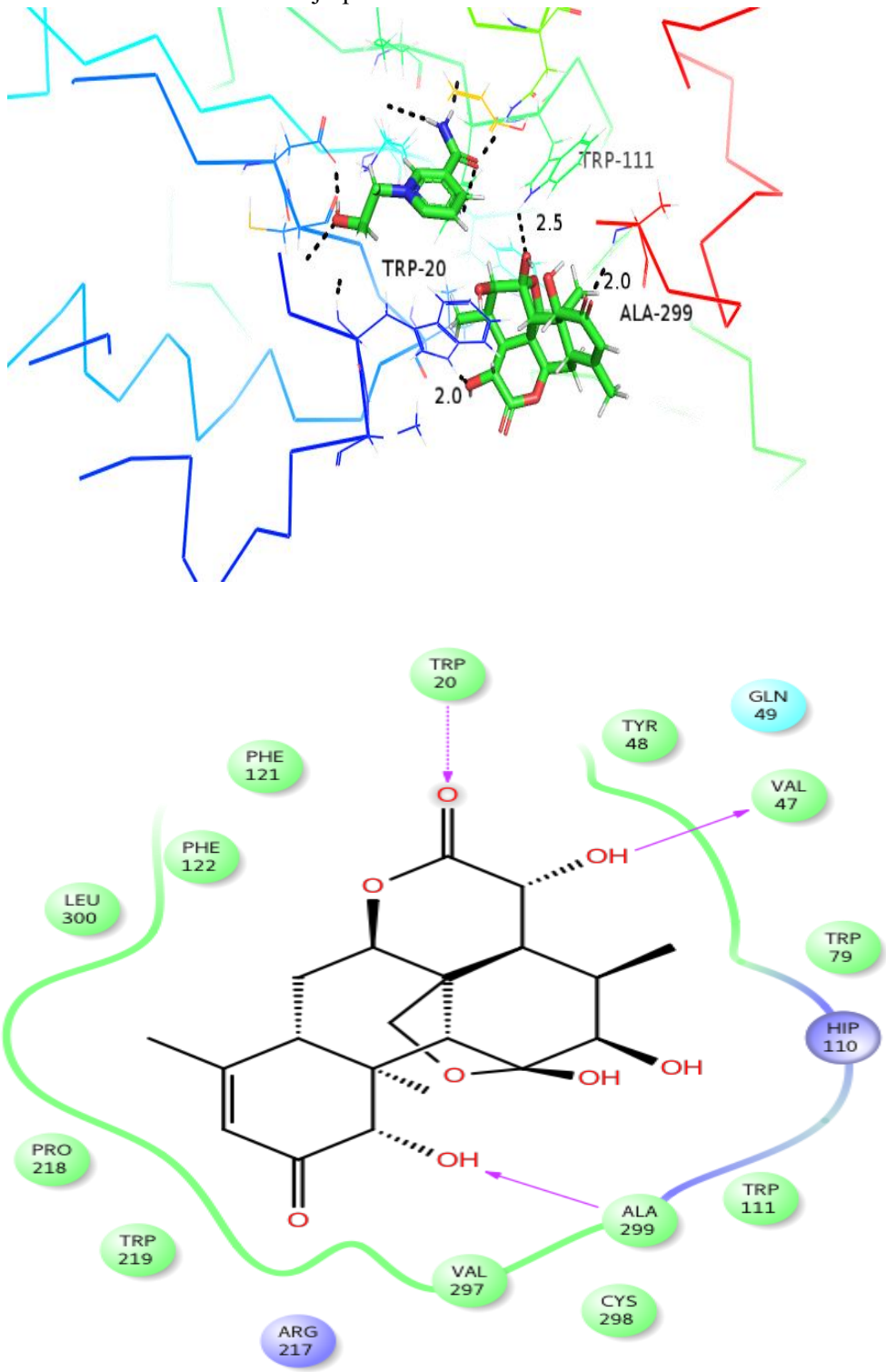


Figure 3.3c: Glaucarubolone at the active site of the target protein

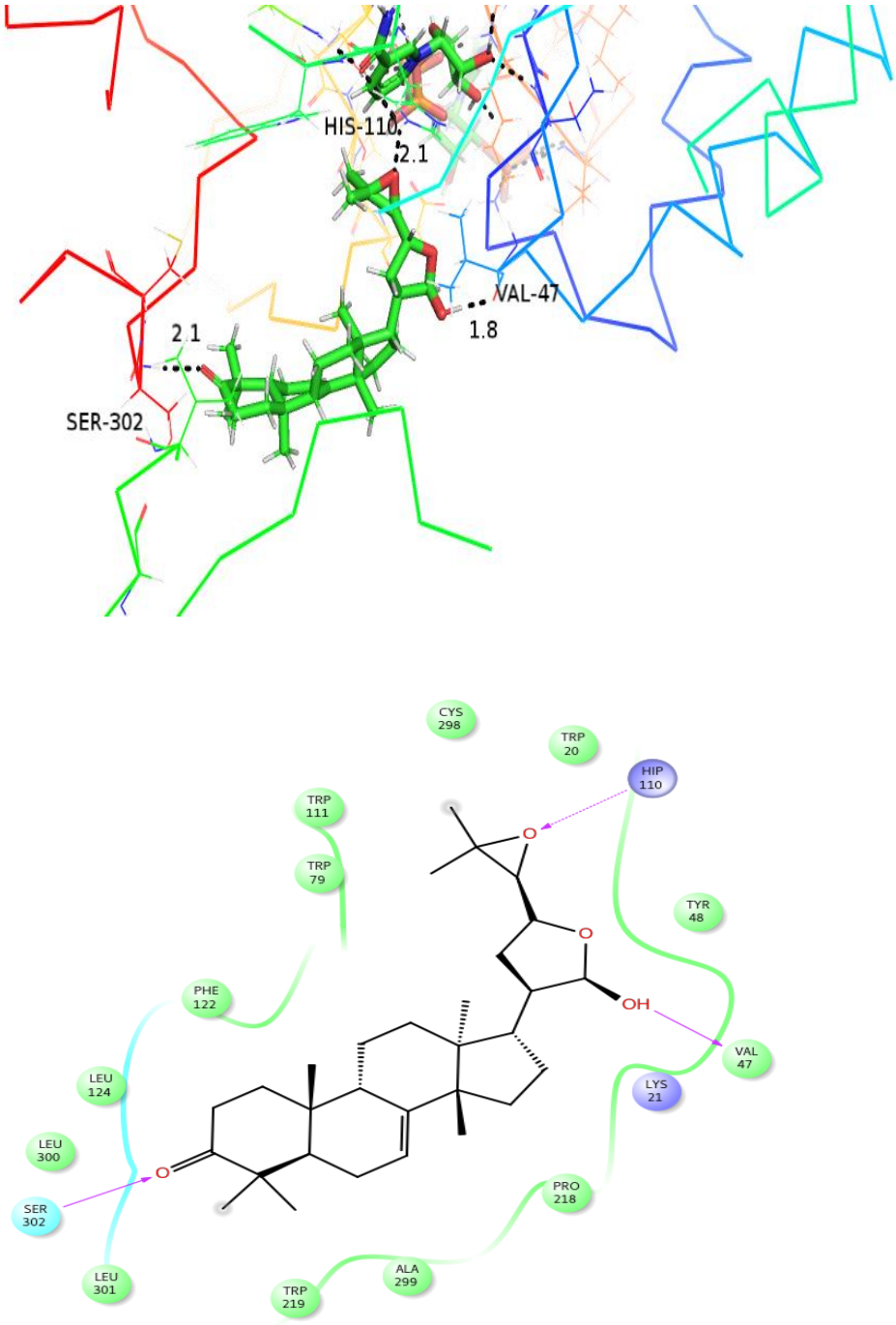


Figure 3.3d: Melianone at the active site of the target protein

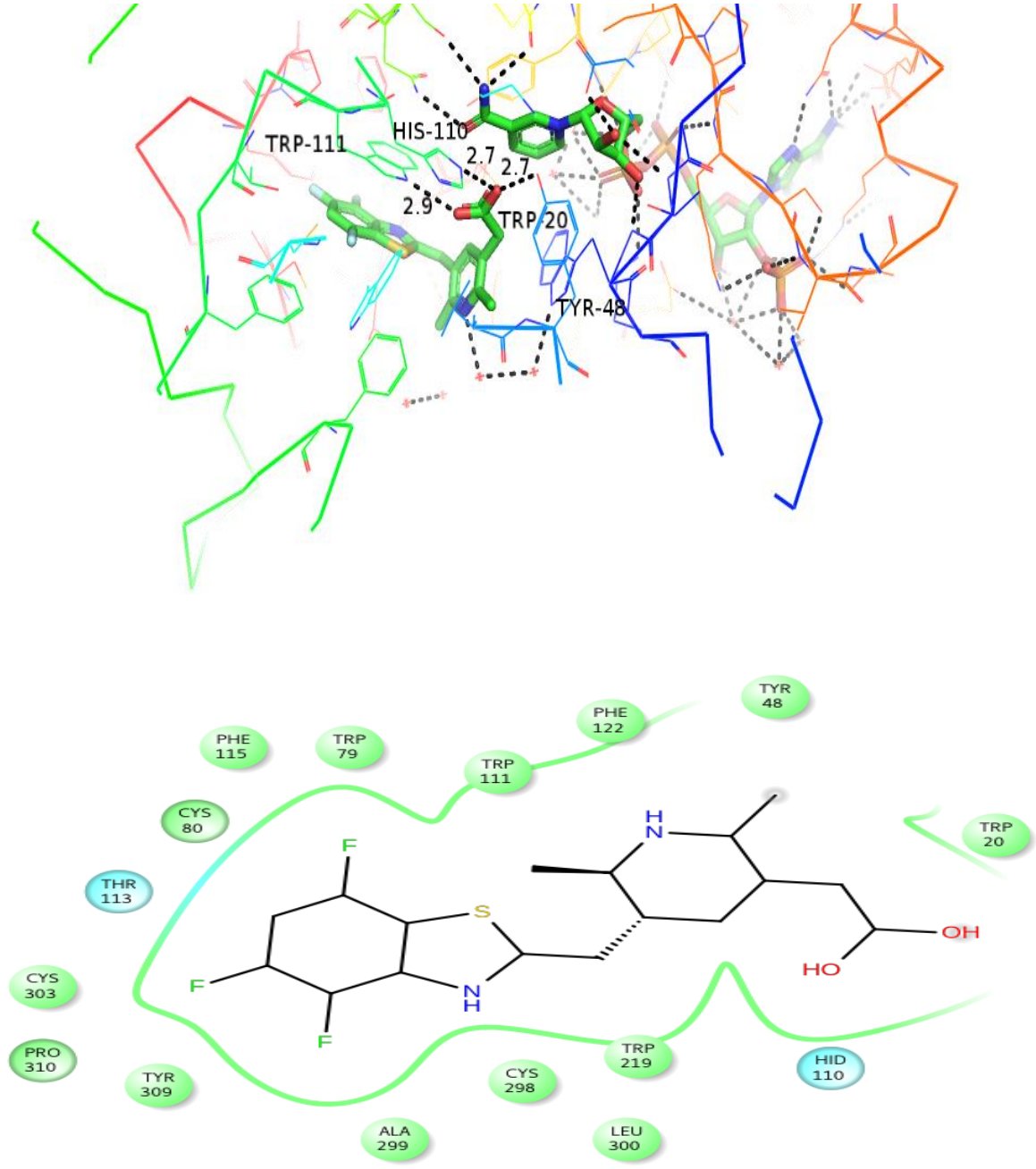


Figure 3.3e: IDD (Co-crystal) at the active site of the target protein

4. CONCLUSION

The *in-silico* studies of the selected Quassinoids from the plant *S. glauca* showed favorable results, thereby, indicating its potential as an inhibitor of Aldose Reductase enzyme. The compounds bound with more competency to the binding sites similar to the known drug IDD. The chosen compounds showed better results in *in silico* analysis with better binding efficiency in terms of glide energy compared to IDD. Based on the ADME predictions, Melianone has high absorption when compared to the known drug IDD. The exposed polar surface area (PSA) of IDD is 91.3 $Å^2$ which is less than the selected compounds except Melianone whose PSA is 59.1 $Å^2$ though the mass is 470 g/mol. The BOILED-EGG prediction revealed that all the compounds

selected are absorbed easily by human intestine which make them potent for oral administration. Hence, it has been predicted that all the compounds can possibly act as new leads for the treatment of cataract diabetes. These results may, in future, be the foundation for *in vivo* experiments to test their potential in the treatment of secondary complications of diabetes.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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