Mediterranean Journal of Basic and Applied Sciences (MJBAS)
Volume 7, Issue 4, Pages 127-133, October-December 2023

Linoleic Acid and Oleic Acid as Inhibitors of Aldose Reductase: An *In-Silico* Approach for Diabetes Management

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DOI: https://doi.org/10.46382/MJBAS.2023.7409

Article Received: 21 October 2023 *Article Accepted: 23 December 2023* *Article Published: 30 December 2023*

ABSTRACT

Diabetes mellitus is caused by the deficiency of insulin. This disease is spread worldwide. Diabetes is of two types based on age of patient. In long term diabetic patient's various diseases occurs due to the excessive utilization of glucose by polyol pathway. First reaction of polyol pathway catalyzed by the aldose reductase enzyme. Aldose reductase can be inhibited to avoid the complications of diabetic patients. Linoleic acid is preferred as aldose reductase inhibitor because of its better drug score and interaction with the target protein.

Keywords: Diabetes mellitus; Polyol pathway; Aldose reductase; Linoleic acid.

1. Introduction

Diabetes mellitus is caused by the deficiency of endogenous insulin and combination of metabolic diseases. This disease has reached epidemic proportions and affects 700 million peoples worldwide (Stumvoll et al., 2005). Patients with long term diabetic disease develop microvascular complications such as neuropathy, retinopathy. Aldose reductase involved in polyol pathway reaction which holds one-third of the of total glucose turnover and plays a very important role in the pathogenesis of microvascular diseases (Gonzalez et al., 1984). Aldose reductase inhibition ranirestat, ponalrestat, rinalrestat, risarestat are under clinical trials (Schemmel et al., 2009).

Fatty acid has long aliphatic chain. These are saturated or unsaturated. These are divided into two types essential and non-essential.

2. Materials and Methods

The following procedure was adopted for docking.

2.1. Retrieval of protein structure

Many articles on diabetes were read for this research and Aldose reductase (PDB entry: 1ADS) was selected for the as a target for the inhibition of microvascular complications. The 3D structure of aldose reductase (PDB entry: 1ADS) was retrieved from Protein Data Bank (http://www.rcsb.org). The structure was downloaded in PDB format. The structure was opened in UCSF chimera. Aldose reductase structure was also downloaded from NCBI PubMed (http://www.ncbi.nlm.nih.gov). This 3D structure was viewed in Cn3D.

2.2. Ligand

Two fatty acids were selected for docking against the target protein. The selected ligands can be retrieved from ZINC database using their ID's. All the structures of ligands were downloaded in mol format to make the available for further docking studies.

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2.3. Finding binding pockets for ligands

The binding pockets of the target protein were determined by using DoGSiteScorer (http://dogsite.zbh.uni-hamburg.de).

2.4. Drug Scoring

Drug scoring was accomplished by using the software DSX online (http://pc1664.pharmazie.uni-marburg.de/drugscore). After registration, target structure is uploaded in its Pdb format or MOL2 format and ligands were uploaded in MOL2 format. After scoring on DSX, results were collected each ligand separately.

2.5. Molecular Docking

Swiss dock online software was used for molecular docking. The target protein (PDB: 1ADS) was uploaded in Pdb format which was downloaded from protein databank. The ligand zinc number was put for docking. Only one ligand was selected for docking at one time. The result of docking appeared after 1hr. the structure of docked compound was analyzed using Chimera software.

3. Results

3.1. Retrieval of Protein structure

The 3D structure of aldose reductase enzyme was downloaded from Protein databank.

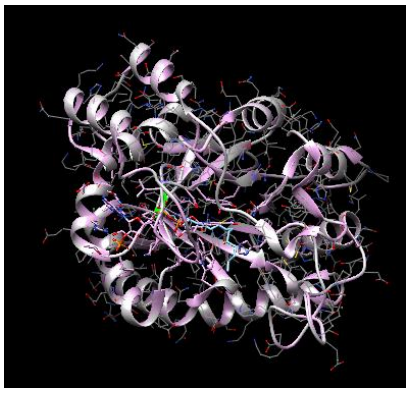

Figure 1. 3D structure of Aldose Reductase enzyme

3.2. Ligands

The selected linoleic acid and oleic acid which are to be docked are downloaded from ZINC database.

Table 1. Ligands for docking with their PubChem and ZINC ID

Ligand	Name	Smile	Pubchem ID	Zinc ID
1.	Linoleic acid	CCCCC/C=C\C/C=C\CCCCCCCC (=O)[O-]	5280450	4474613
2.	Oleic acid	CCCCCCCC/C=C\CCCCCCCC (=O)[O-]	445639	6845860

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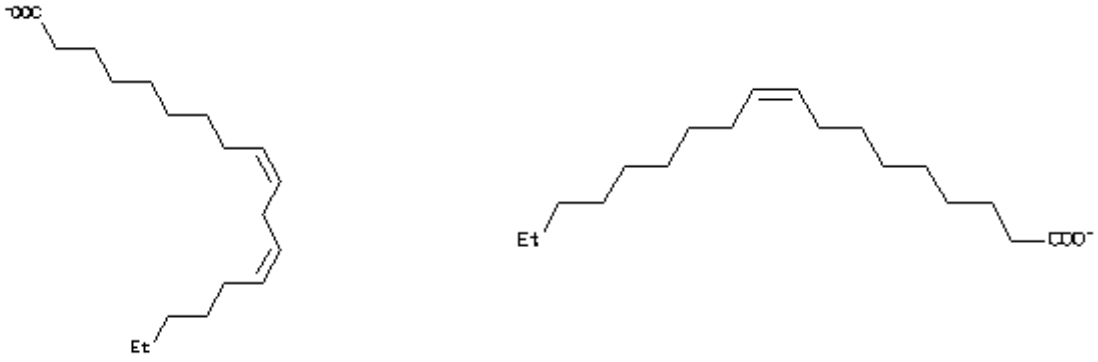

(a) (b)

Figure 2. Figure showing the structures of ligands: (a) Linoleic acid, and (b) Oleic acid

3.3. Ligand Parameters

Numerous parameters of ligands such as molecular weight, rotatable bonds, molecular formula, were also evaluated to analyze drug likeness properties of ligands.

Table 2. Table showing certain parameters of ligands

Ligand	Molecular Formula	Molecular Weight	Rotatable Bonds
Linoleic acid	C18H3202	280.454	14
Oleic acid	C18H34O2	282.470	15

3.4. Binding Pockets for Ligands

11 binding pockets were obtained by DogSiteScorer software.

Table 3. Table showing properties of pockets including their volume, surface, lipo surface, depth and drug score

Name	Volume [Å^3]	Surface [Å^2]	Lipo Surface [Å^2]	Depth [Å]	Drug Score
P0	1060.54	1103.52	755.35	20.99	0.66
P1	431.10	599.07	302.37	17.84	0.19
P2	184.77	385.52	236.91	11.70	0.00
P3	154.11	288.15	153.37	9.37	0.00
P4	139.14	256.72	147.40	12.22	0.00
P5	126.72	191.17	120.89	7.60	0.00
P6	121.41	246.27	132.32	8.11	0.00

P7	119.68	146.71	110.08	9.51	0.00
P8	109.89	242,03	181.32	7.53	0.00
P9	108.54	183.65	138.33	12.01	0.00
P10	105.02	216.93	141.41	8.25	0.00

3.5. Ligand ADMET properties

Various properties of ligands were determined. These properties gave more idea about the behavior of ligands. These properties include permeability, distribution, and topographical polar surface area.

Table 4. The ADMET properties of ligands were evaluated from MedChem Designer

Properties	**Linoleic acid**	**Oleic acid**
MlogP	4.165	4.261
S+logP	6.809	7.208
S+logD	4.515	4.928
MWt	280.454	282.470
M_NO	2.000	2.000
T_PSA	37.300	37.300
HBDH	1.000	1.000

3.6. Drug Scoring

Drug scoring of both ligands are present in the following table 5. Linoleic acid provides better results.

Table 5. The drug scoring of individual ligands are tabulated below

Ligand	**Score**
Linoleic acid	5
Oleic acid	3

3.7. Molecular Docking

Linoleic acid and oleic acid were used for docking to analyze their action as inhibitors of aldose reductase enzyme. The binding energies and hydrogen bonds formation of the ligands tells that those ligands are able to fit properly into the active pockets of the target protein. Linoleic acid provided better drug score than oleic acid so it was considered more reactive as an inhibitor of aldose reductase enzyme. Linoleic acid can be modified to use as a better anti diabetic agent in further researches.

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Table 6. The following table shows the result of docking of ligands with target protein

Ligand	Full fitness	Binding Energy	Hydrogen Bonds
Linoleic acid	-1337.86	-10.52	1
Oleic acid	-1342.90	-10.34	1

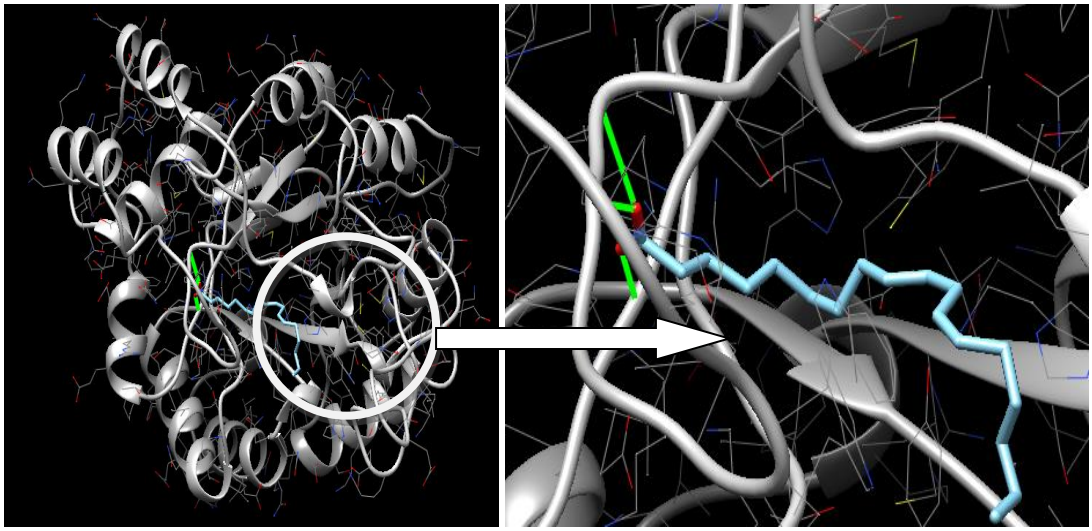

Figure 3. Figure showing the interaction of target protein with linoleic acid

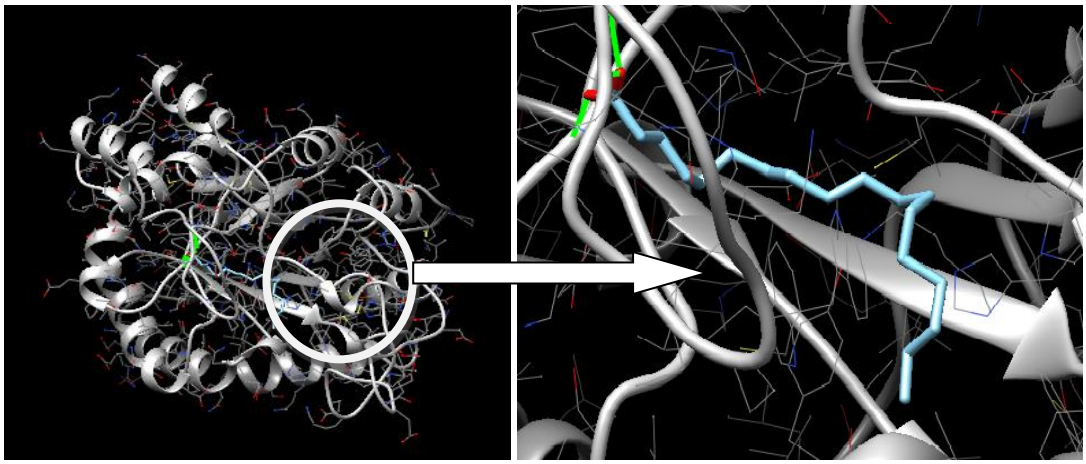

Figure 4. Figure showing the interaction of oleic acid with target protein

4. Discussions

Aldose reductase enzyme is an NADPH dependent oxidoreductase that catalyzes the reduction of many compounds to monosaccharides. It is also involved in the polyol pathway. In first step, glucose is converted to sorbitol by the utilization of NADPH (Petrash JM).

Glucose + NADPH + H^+ ⟶ Sorbitol + $NADP^+$

This conversion of glucose is increased in patient with long term diabetic disease which causes microvascular complication such as neuropathy, heart failure etc. The inhibition of aldose reductase enzyme will stop the

conversion of glucose to sorbitol. Therefore, fatty acids were used to inhibit enzyme. Molecular docking provides us the medium for analyzing molecules for their potential of drug production. It is a frequently used tool which makes us evaluate how target macromolecules and ligands which are small molecules fit together (Norgan et al., 2011) (Seeliger and de Groot Ligand, 2010).

In this article, fatty acids are used as aldose reductase inhibitors. The PubChem ID, ZINC ID and smiles of ligands are provided. The molecular formula, molecular weight and number of rotatable bonds were also evaluated for better understanding of ligand properties. Pockets of target protein were found by DogSiteScorer. Drug score of fatty acids gives information about the ability of ligand to bind to the target protein. Docking results of ligands and target protein gives information about the binding energy and number of hydrogen bonds.

The article followed for docking studies used flavonoids as aldose reductase inhibitors. The binding energy provided by the 6 flavonoids with target protein is less than the binding energy of fatty acids with the same target protein described in this article.

5. Conclusion

Docking studies provided evidence about the inhibition of target protein by the selected fatty acids. Linoleic acid is preferred as compared to oleic acid because of its better drug score. Linoleic acid stops the aldose reductase in polyol pathway and stops the conversion of glucose to sorbitol. This inhibition of enzyme will stop the overloaded catabolism of glucose and prevent the patient from getting severe diseases.

Declarations

Source of Funding

This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Consent for publication

The authors declare that they consented to the publication of this research work.

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