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In silico discovery of a perilipin 1 inhibitor to be used as a new treatment for obesity

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Abstract. – BACKGROUND: Obesity is a chronic non-communicable disease that affects a lot of people worldwide. Current management strategies for obesity include dietary management, physical exercises and pharmacological agents but sustenance of weight loss is still a problem. Perilipin 1 is a lipid droplet protein that is involved in lipolysis in adipose tissue. Perilipin 1 degradation or knock-out is associated with leanness.

AIM: The aim of this study is to use computational servers and software to predict the 3D structure of perilipin 1 and predict potential inhibitors to be used as treatment of obesity.

MATERIALS AND METHODS: The 3D structure of perilipin 1 was predicted by I-TASSER server. ZINC database was used to obtain potential inhibitors for perilipin 1. Docking of potential inhibitors was done using Molegro Virtual Docker.

RESULTS: The predicted 3D structure of perilipin 1 had a high confidence score reflecting the reliability of the obtained structure. 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside showed a high reliable docking score suggesting its potential action as perilipin 1 inhibitor.

CONCLUSIONS: This study shows that 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside can be used as an inhibitor for perilipin 1 and a potential treatment for obesity.

Key Words:
Perilipin, I-TASSER, ZINC database, Anti-obesity, Docking, Mannopyranoside.

Introduction

Obesity is a pandemic that affects developing countries and developed countries[1]. The International Association for the Study of Obesity (IASO) declared that 18.2% of the Egyptian men and 28.3% of the Egyptian women suffer from obesity. Obesity is associated with a lot of life threatening complications[2]. There are a few drugs available in the market for the treatment of obesity like orlistat[3] and the recently approved phenteramine/topiramate combination and lorcaserin[4]. Research in the field of obesity treatment is extensively needed[5]. Adipose tissue stores lipids in the form of lipid droplets surrounded by specific proteins. Perilipin 1 is a lipid droplet protein that coats the lipid droplet guarding it from the attack of lipases[6]. Perilipin 1 is found attached to the lipid droplet and if it becomes detached from it, it will be rapidly degraded[7,8]. Although perilipin 1 doesn't interact directly with adipocyte triglyceride lipase (ATGL) like perilipin 5, it was found that it still has a major effect on lipolysis rate and perilipin 5 is selectively expressed in oxidative tissues[9]. The 3D structure of perilipin 1 hasn't been elucidated yet. The solution structure of perilipin 3 was elucidated in 2012[10]. Perilipin 3 belongs to the same family as perilipin 1 and its solved structure can be used in the computational prediction of the structure of perilipin 1. Mice models with perilipin 1 knock-out mutations exhibit leanness compared with wild mice[11]. In humans, it was proved that the lipolytic side effect exhibited by the anti-retroviral drug, nelfinavir, is due to perilipin 1 degradation[12]. Those studies suggest that degradation or knock-out of perilipin 1 will enhance lipolysis rate and may treat obesity. The objective of this study is to use computational tools to discover new compounds that can work as inhibitors for perilipin 1. This will be achieved by predicting the 3D structure of perilipin 1 using I-TASSER (Iterative Threading ASSEmbly Refinement) server[13] and utilizing this 3D structure in the docking of compounds[14] obtained from ZINC database[15] using Molegro Virtual Docker (MVD).

Materials and Methods

Obtaining Perilipin 1 Amino Acid Sequence From Swissprot

The amino acid sequence for perilipin 1 was obtained from swissprot database in FASTA format to be utilized by the I-TASSER server for the prediction of perilipin 1 3D structure.

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The I-TASSER Server

The I-TASSER server is a server that applies homology modeling and *ab initio* tools for the prediction of the 3D structure of a protein[16]. The obtained 3D structures are given a confidence score between –5 to 2 with higher scores indicating a more reliable structure.

ZINC Database

ZINC database is a database of commercially-available compounds that are available in their 3D structure and ready for utilization by further docking software for analysis[15]. Compounds with structural similarity with triglycerides, which are the natural ligand for perilipin 1, were obtained from ZINC database.

Molegro Virtual Docker

Molegro Virtual Docker (MVD) is a docking software that has been used widely in drug discovery due to its high reliability[17]. The predicted 3D structure of perilipin 1 and the 26 compounds obtained from ZINC database were imported into MVD and prepared as previously explained[14]. Cavities for ligand binding were detected for the docking of potential ligands as the exact binding site for perilipin 1 hasn't been discovered yet.

Results

Perilipin 1 3D Structure

The I-TASSER server predicted the 3D structure of perilipin 1 and returned five top structures with C-scores ranging from 0.04 to –1.75. The first structure has C-score of 0.04 which is above the cut off score of –1.5[13].

Ligands Set

A search for ZINC database was performed for compounds with structure similarity with simple triglycerides. This search returned 26 compounds. Those compounds were downloaded in mol2 format to be used for docking.

Docking Results

The 3D structure of perilipin 1 and the 26 selected compounds were imported in MVD and prepared for docking then a docking process was run. Docking results for the top 5 compounds are shown in Table I. The docking scores of 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside were promising and predicted a preferential binding to perilipin 1. Hydrogen bond interactions between perilipin 1 and 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside are shown in Figure 1.

Discussion

The predicted secondary structure of perilipin 1 consists of alpha helices only which is consistent with its hydrophobic nature, this was also shown in the X-ray crystallography of perilipin 3[10,18]. Trans-10, cis-12 conjugated linoleic acid (CLA) and the soy isoflavone genistein are believed to affect perilipin expression and hence can be used as anti-obesity drug[19-21]. In another study, CLA supplementation was proved to reduce perilipin 1 and cause aberrant lipolysis in epididymal adipose tissue of mice by affecting its translation and transcription[22]. It was previously shown that the lipolytic effect of nelfinavir is mediated through the degradation of perilipin 1[12]. The docking scores for tricaproin and triheptanoin were -109.33 and –109.43 respectively. These results are consistent with our notion that perilipin 1 originally interacts with the triglyceride backbone of the lipid droplet. The effect of 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside on other lipolysis factors and inflammatory mediators like (Tumor Necrosis Factor-α (TNFα), Peroxisome Proliferator-activated Receptor (PPAR)

Table I. Docking scores for top 5 hits and scores of top 5 poses of 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside.

Name	MolDock score
4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside	–133.633
Glycovir	–127.041
[3-decanoyloxy-2-[(2S)-2-(3-fluoro-4-phenyl-phenyl)propanoyl]oxy-propyl]	–122.469
[(2R,3R,4S,5S,6R)-3-acetoxy-2-(acetoxymethyl)-5-hexanoyloxy-6-[(2S,3R)-2,3,4-trihydroxybutoxy]tetrah	–119.788
[3-decanoyloxy-2-[(2R)-2-(3-fluoro-4-phenyl-phenyl)propanoyl]oxy-propyl]	–119.367

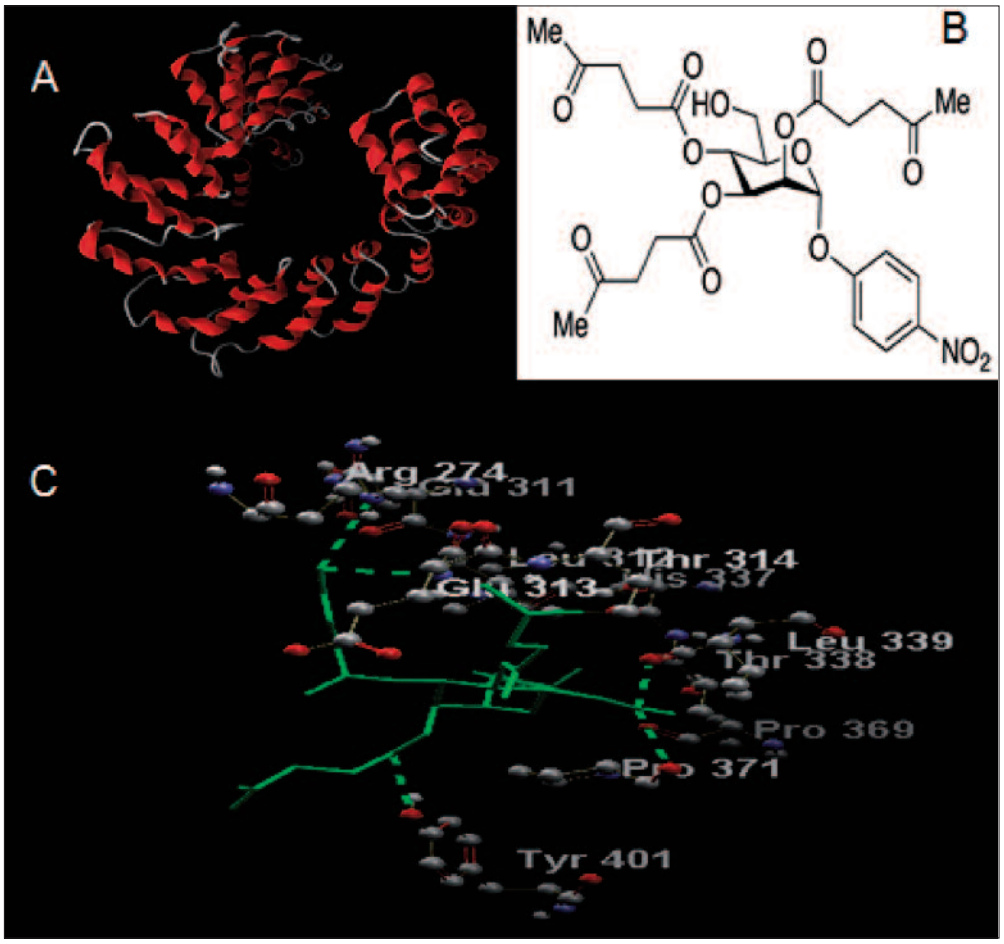

Figure 1. ***A,*** Predicted 3D structure of perilipin 1. ***B,*** Structure of 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside. ***C,*** Hydrogen bonds formed between perilipin 1 and its predicted inhibitor.

and leptin should be evaluated experimentally as it couldn't be predicted *in silico*. The results of this study shows that 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyranoside can bind preferentially to perilipin 1 and prevent it from attaching to the lipid droplet exposing it for lipases action and subsequent lipolysis. Those simulations results should be confirmed experimentally through the assessment of protein-ligand interaction *in vitro* and *in vivo*.

Conclusions

This study suggests that 4-Nitrophenyl 2,3,4-Tri-O-levulinoyl-α-D-mannopyrano-side can be used as a perilipin 1 inhibitor, so it can treat obesity by increasing lipolysis rate. Some investigations and trials are still needed before this drug can reach the market.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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