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Original Article

Moringa oleifera Fruit Secondary Metabolites Role in Sarcopenic Obesity via Fat Mass and Obesity-Associated Protein: An *In Silico* Analysis

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ABSTRACT

Background: Sarcopenic obesity (SO) refers to the coexistence of sarcopenia and obesity, pathogenic interaction between loss of skeletal muscle and function and fat-mass accumulation. Fat mass and obesity-associated (FTO) protein is one of the proteins that involved in pathophysiology of SO. *Moringa oleifera* is one of potential drug candidates for degenerative diseases due to its various bioactive metabolites from most parts of this plant. **Objective**: An *in silico* study, employing computational methods to simulate molecular interactions through molecular docking, aims to investigate the potential of *Moringa oleifera* fruit secondary metabolites to interact with FTO protein. **Methodology**: This study was carried out the molecular docking analysis of *Moringa oleifera* fruit secondary metabolites that was retrieved from database and have been screened for drug-likeness and toxicity for FTO protein inhibitor candidates. Molecular docking was using Pyrx v0.8, AutoDock 4.2.6 by AutoDockTools 1.5.7, and BIOVIA Discovery studio client 2025 as visualization tools. **Results**: This study showed 9 bioactive compounds from *Moringa oleifera* fruit is bioavailable and safe for oral drugs according to Lipinski Rule of 5 (RO5) and Oral Rat Acute Toxicity (LD50). Molecular docking results showed riboflavin is the most potential compound as FTO protein inhibitor as its strongest affinity and interaction in active site compared to FTO protein native ligands 3-methylthymidine (DT). **Conclusion**: Therefore, *Moringa oleifera* fruit is potential for SO therapy candidates through regulation of FTO protein activity.

Keywords: *Moringa oleifera* fruit, sarcopenic obesity (SO), FTO protein, molecular docking, and riboflavin

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INTRODUCTION

Sarcopenic obesity (SO) refers to the coexistence of sarcopenia and obesity. This degenerative disease has emerged as a significant health concern, particularly in aging populations and individuals with chronic diseases. This should be considered as separated clinical condition from sarcopenia and obesity because there is a pathogenic interaction between loss of skeletal muscle and function and fat-mass accumulation. Furthermore, this interaction increases the risk of metabolic disorders, cardiovascular diseases, functional impairment, and mortality[1,2]. Sarcopenia refers to the progressive decline in muscle mass and strength associated with aging. Obesity is defined by an excessive accumulation of adipose tissue, particularly within the visceral part[2,3]. Sarcopenic obesity arises from multiple contributing factors, including genetic susceptibility, lifestyle habits, hormonal alterations, and chronic inflammation, all of which interact in complex ways[2].

The development of sarcopenic obesity is driven by complex molecular pathways that control muscle preservation, lipid metabolism, and systemic inflammatory responses. Mechanisms such as insulin resistance, chronic inflammation, myokines dysregulation, proteolysis, and altered autophagy contribute to its distinct pathophysiology[4]. A main factor in obesity development is the fat mass and obesity-associated (FTO) protein. The FTO gene encodes an Fe(II)/2-oxoglutarate-dependent demethylase, functioning as a DNA/RNA demethylase. It is identified as the ninth member of the AlkB protein family, also referred to as ALKBH9. Encoded by the FTO gene, this enzyme plays a role in controlling adipogenesis, energy intake, energy expenditure, and lipid storage. Single nucleotide polymorphisms in the FTO gene are strongly associated with increased body mass index and obesity risk across diverse populations[5–7]. FTO is suggested to be associated with lean mass in sarcopenia[8]. Understanding the molecular mechanisms underlying sarcopenic obesity is essential for identifying potential therapeutic targets and developing effective intervention strategies.

Given the limitations of current therapeutic options for sarcopenic obesity, there is growing interest in exploring alternative and complementary approaches, including the use of natural products. *Moringa oleifera*, a plant native to South Asia, in specific Afghanistan, Bangladesh, India, and Pakistan, has garnered considerable attention for its nutritional and medicinal properties. *Moringa oleifera* has various species and is used in folk medicine due to its medicinal properties. The plant is rich a diverse array of secondary metabolites, including flavonoids, phenolic acids, phenol, polyphenol, phytosterol, fatty acid, alkaloids, glucosinolates, anthraquinones, vitamins, glycosides, and terpenes. These compounds possess antioxidant, anti-inflammatory, anti-microbial, and anti-diabetic activities[9]. Kumar et al[10] study showed that *Moringa oleifera* extract has the ability to downregulate adipogenesis gene, inhibit fat and lipase accumulation, and enhance insulin sensitivity.

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These findings suggest their potential to modulate the pathophysiology of sarcopenic obesity.

An *in silico* study, employing computational methods to simulate molecular interactions, offer a promising avenue for investigating the potential of *Moringa oleifera* fruit secondary metabolites to interact with FTO protein. This study was carried out the molecular docking analysis of *Moringa oleifera* fruit secondary metabolites that was retrieved from database and have been screened for drug-likeness and toxicity for FTO protein inhibitor candidates. Molecular docking was using Pyrx v0.8, AutoDock 4.2.6 by AutoDockTools 1.5.7, and BIOVIA Discovery studio client 2025 as visualization tools. This *in silico* study aims to provide a scientific basis for further *in vitro* and *in vivo* investigations, ultimately contributing to the development of *Moringa oleifera* fruit as a novel therapeutic for sarcopenic obesity.

METHODS

Ligand and protein preparation

Secondary metabolite ligands of *Moringa oleifera* was obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/plant-moringa-oleifera, accessed on 29 June 2025). The secondary metabolites were chosen based on the part of plant that categorized in the fruit of *Moringa oleifera*. The 3D structure of the ligands was retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/, accessed on 30 June 2025). The 3D ligand was converted to PDB format using an Open Babel module via Pyrx v0.8.[11] The compounds were subjected to ADME prediction using SwissADME to analyse drug-likeness according to Lipinski's rule of 5 (RO5). The prediction of toxicity was done via pKcSM pharmacokinetic https://biosig.lab.uq.edu.au/pkcsm/ to get LD_{50} value of oral rat acute toxicity.

The 3D structure of was retrieved from RCSB PDB with 3LFM as corresponding PDB ID[12]. Ligand molecules, non-interacting ions and water molecules in the protein structure were removed using BIOVIA Discovery studio client 2025.

Protein validation

To determine the optimal conditions of molecular docking, the docking parameters were examined by redocking the cocrystallized ligand into its respective active site in protein. The procedure was performed using the software Windows 11 Home Single Language 64-bit operating system Intel(R) Core(TM) Ultra 5 125H (1.20 GHz). 3-methylthymidine (DT) was chosen as the native ligand of FTO protein as its inhibitor. In this validation step, we assess the docking accuracy using AutoDockTools 1.5.7 by applying the default Grid box and center (x, y, z) and spacing settings. The comparison is evaluated using the RMSD, value, where the docking method is considered valid if the RMSD is ≤ 2 Å. If the RMSD exceeds 2 Å, the docking procedure is deemed invalid.

Virtual screening

PyRx v0.8[11] is a virtual screening software based on structural analysis, incorporating Open Babel for ligand preparation and AutoDock Vina 1.12 for docking simulations. The procedure was performed using the software Windows 11 Home Single Language 64-bit operating system Intel(R) Core(TM) Ultra 5 125H (1.20 GHz). In this process, the 3D structures of both ligands and protein were imported into PyRx. The protein was prepared as a macromolecule. The energy minimization of ligand was performed using the conjugate gradient algorithm with the Universal Force Field (UFF) via OpenBabel. After minimization, the structures were converted into PDBQT files. Docking was carried out with an exhaustiveness parameter of eight, generating eight docking poses that were evaluated based on their binding affinity and RMSD value. The docking parameters was followed the parameters of protein validation. The ligands with lowest binding affinity value with 0.0 RMSD was chosen for the next molecular docking.

Molecular docking

In silico analysis for 3LFM was performed using AutoDock 4.2.6 by AutoDockTools 1.5.7[13]. The procedure was performed using the software Windows 11 Home Single Language 64-bit operating system Intel(R) Core(TM) Ultra 5 125H (1.20 GHz) and for each ligands was done *triplo* (three times replications). Target protein 3LFM that has cleaned was added with polar hydrogen. Kollaman charges was computed for protein target then saved into PDBQT format. Native ligand (DT) and best compounds ligand conformations from virtual screening was processed by adding hydrogen and computing Gasteiger charges. Rotatable bond torsion counts were set up for the ligands and stored in PDBQT format. By using the Grid value from the validation result, the Gridbox parameters for the docking were configured in the Grid Options dialogue box: size x, y, z, center x, y, z, and spacing. The settings of the Lamarckian Genetic algorithm were used with a population size of 150, mutation rate of 0.02, energy evaluations of 2.5×10^6, crossover rate of 0.8, and 100 GA runs. The binding affinity in kcal/mol was predicted for every docked configuration of the protein-ligand combination. The visualization of the docked protein-ligand was done with BIOVIA Discovery studio client 2025.

Statistical Analysis

The result of molecular docking was analysed with GarphPad Prism 10.1.0. The normality was assessed with Shapiro-Wilk test. The normal distribution of data will be further analysed with unpaired T-test meanwhile the abnormal distribution of data will be further analysed with unpaired Mann-Whitney test. Data is significantly different if the p value is lower than 0.05.

RESULT AND DISCUSSION

Ligand and protein preparations

Nine bioactive compounds in *Moringa oleifera* fruit were obtained and predicted. Those compounds are ascorbic acid (CID: 54670067), choline (CID: 305), indole-acetic-acid (CID: 160172252), indole acetonitrile (CID: 351795), niacin (CID: 938), oxalic acid (CID: 971), riboflavin (CID: 493570), thiamine (CID: 1130), and vitamin B6 (CID: 104817). Based on Table 1, all 9 compounds were predicted to have good oral bioavailability according to Lipinski Rule of 5 (RO5). *Moringa oleifera* fruit exhibited drug-likeness indicating possible permeability and absorption of molecules through biological membranes.

There is zero violation of RO5 parameters from each compound (Table 1). It shows that all RO5 parameters were accomplished. In the drug discovery setting, the RO5 predicts that poor absorption or permeation is more likely when: Molecular Weight (MW) more than 500 g/mol; Lipophilicity (CLogP) more than 5; Hydrogen bond donor more than 5; and Hydrogen bond acceptor more than 10[14].

The bioavailability score from all compounds showed 0.55 or higher (Table 1). A bioavailability score of 0.55 or higher is a positive indicator, suggesting the compound has a good chance of being orally bioavailable, warranting further pharmacokinetic and formulation studies. While the bioavailability score complements Lipinski's Rule of Five and Veber's rules for predicting oral bioavailability, it does not replace in vitro ADME validation, which remains essential in confirming the pharmacokinetic properties of candidate compounds[15–17].

Acute toxicity parameter is commonly predicted by identifying LD_{50} values. According to Indonesian Food and Drug Authority (BPOM, 2014), oral rat acute toxicity is classified into 6 class, namely Class 1: highly toxic ≤ 1 mg/kg body weight (BW) ; Class 2: toxic 1-50 mg/kg BW; Class 3: moderately toxic 50-500 mg/kg BW; Class 4: mildly

Table 1. **Physicochemical properties**

Compound	MW (g/mol)	LogP	H-donors	H-acceptor	Violation	Bioavailability score
Choline	104.17	-1.86	1	1	0	0.55
Indole acetic acid	185.26	1.30	2	3	0	0.55
Indole acetonitrile	156.18	1.83	1	1	0	0.55
Niacin	123.11	0.32	1	3	0	0.85
Oxalic acid	90.03	-0.79	2	4	0	0.85
Riboflavin	376.36	-0.19	5	8	0	0.55
Thiamine	265.35	0.53	2	3	0	0.55
Vit B6	231.14	0.17	1	6	0	0.56
Ascorbic acid	176.12	4.22	4	6	0	0.56

Table 2. **Toxicity Prediction (LD_{50})**

Compound	Oral Rat Acute Toxicity (LD50) (mol/kg)	MW (g/mol)	Oral Rat Acute Toxicity (LD_{50}) (g/kg)	Class	Classification
Choline	1.939	104.17	201.99	6	Relatively Harmless
Indole acetic acid	2.104	185.26	389.79	6	Relatively Harmless
Indole acetonitrile	2.339	156.18	365.31	6	Relatively Harmless
Niacin	2.24	123.11	275.77	6	Relatively Harmless
Oxalic acid	1.68	90.03	151.25	6	Relatively Harmless
Riboflavin	2.17	376.36	816.70	6	Relatively Harmless
Thiamine	2.672	265.35	709.02	6	Relatively Harmless
Vit B6	2.227	231.14	514.75	6	Relatively Harmless
Ascorbic acid	1.063	176.12	187.22	6	Relatively Harmless

Table 3. **Validation result**

Protein Target	Natural Ligand	PDB ID	Rank	Run	Lowest binding affinity (kcal/mol)	RMSD Cluster (Å)	RMSD Reference (Å)
fat mass and obesity associated (FTO) protein	3-methylthymidine	3LFM	1	6	-5.55	0.00	1.48
			1	3	-5.48	1.46	1.56
			1	4	-5.48	1.47	1.57
			1	8	-5.48	1.50	1.61
			1	7	-5.48	1.51	1.62
			1	2	-5.48	1.46	1.58
			1	1	-5.47	1.46	1.57
			1	10	-5.47	1.46	1.57
			1	5	-5.47	1.48	1.60
			2	9	-5.53	0.00	3.21

Table 4. **Gridbox parameters from validation**

Macromolecule ID	Natural Ligand ID	Gridbox Parameter					
		Center			Dimension		
		x	y	z	x	y	z
3LFM	DT	29.506	-6.644	-29.758	40	40	40

toxic 500-5000 mg/kg BW; Class 5: practically non-toxic 5-15 g/kg BW; and Class 6: relatively harmless ≥15 g/kg BW. Table 2 showed the LD50 prediction from all compounds are classified to class 6, which are relatively harmless and non-toxic for oral drug therapy.

FTO protein was chosen based on Mazurkiewicz et al[19] study that mentioned the gene that has possible role in both sarcopenic and obesity. The 3D structure was retrieved from RCSB PDB with PDB ID: 3LFM [12]. 3LFM consists of chain A that corresponds to the FTO protein (495 amino acids), origin from *Homo sapiens*. The resolution of entire structure is 2.50 Å. Figure 1 showed a clean protein structure from any ligand molecules, non-interacting ions and water molecules.

Protein validation

Validation results with default setting of AutoDockTools 1.5.7 showed that the RMSDs are lower than 2 Å (Table 3). Based on the RMSD values obtained for the formed complexes, all values were found to be below 2.0 Å, indicating that the complexes exhibit adequate stability as supported by the analysis[20]. This indicates that the docking protocol can accurately reproduce the native binding mode because the redocked native ligand pose aligns with protein target crystallographic pose of the ligand in receptor binding site[21]. Gridbox parameters from validation results (Table 4) are used for further docking in AutoDockTools 1.5.7 of the best compounds compared to the native ligand that have been screened with Pyrx.

Virtual screening

The virtual screening of 9 compounds was performed using AutoDock Vina in PyRx. According to Table 5, virtual screening molecular docking showed riboflavin has the strongest binding affinity to FTO protein in comparison with DT. This compound then proceeded into next molecular docking compared to DT.

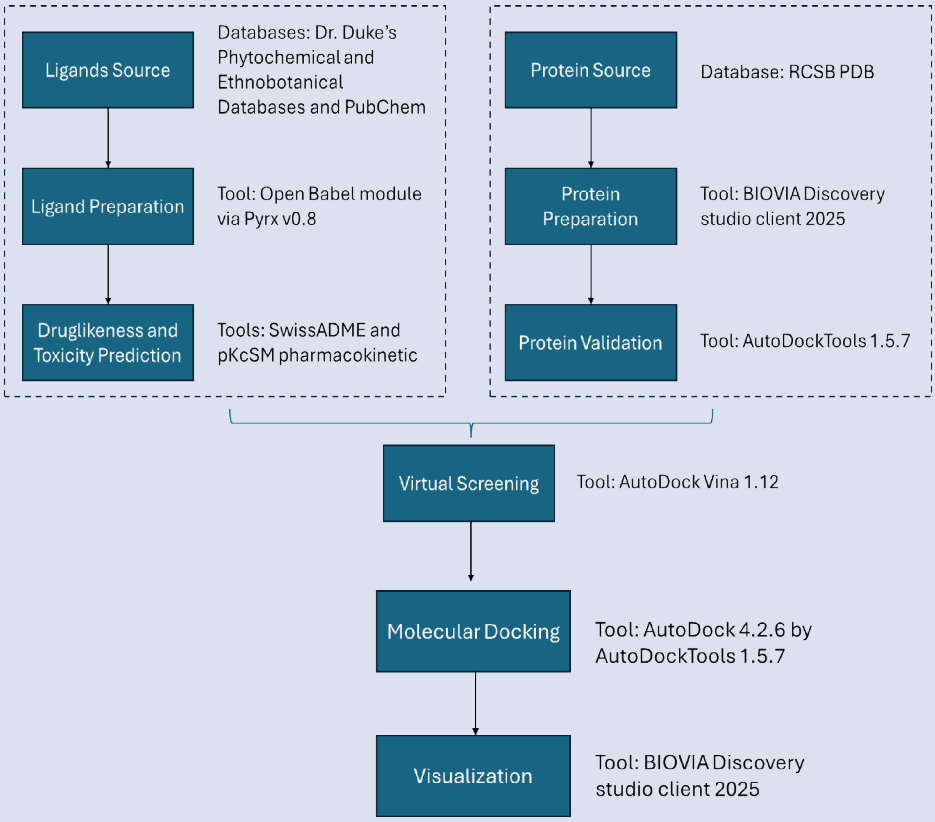


Figure 1. Workflow Chart

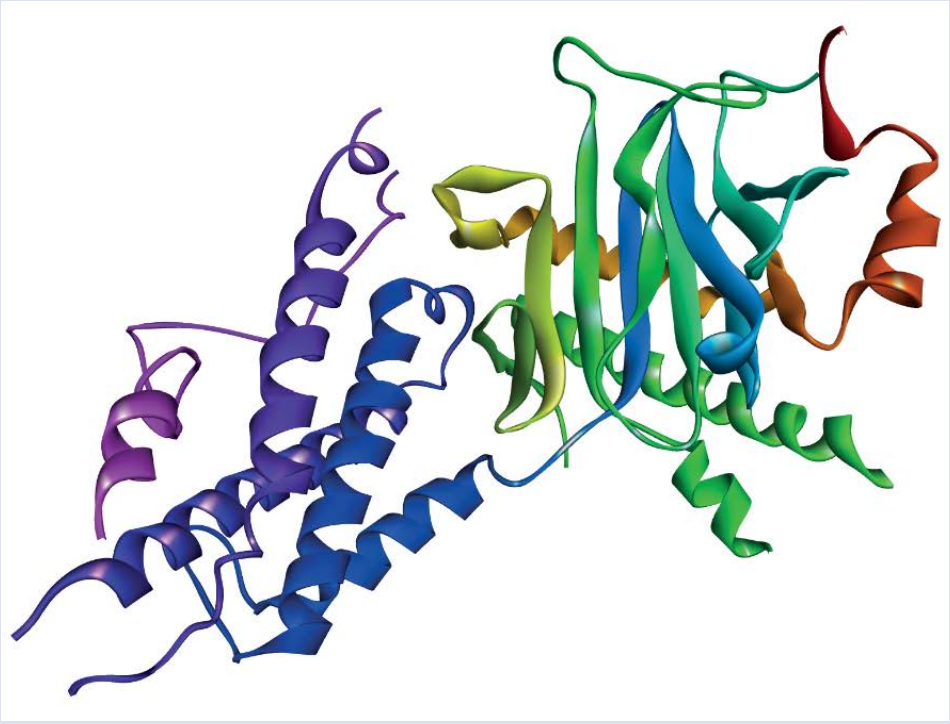


Figure 2. FTO protein conformation (PDB ID: 3LFM)

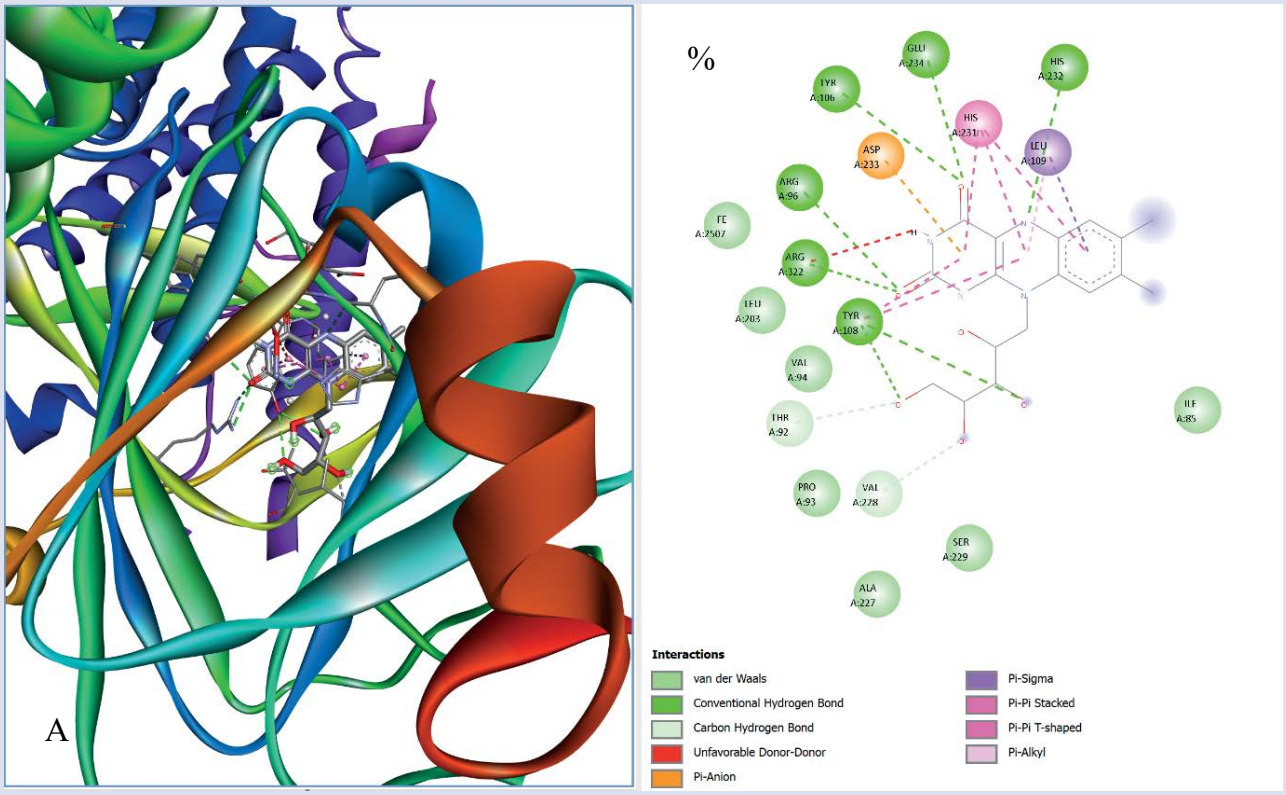


Figure 3. Docking interactions of riboflavin ligand in the active site of FTO protein (3LFM), A) 3D structure, B) 2D Structure

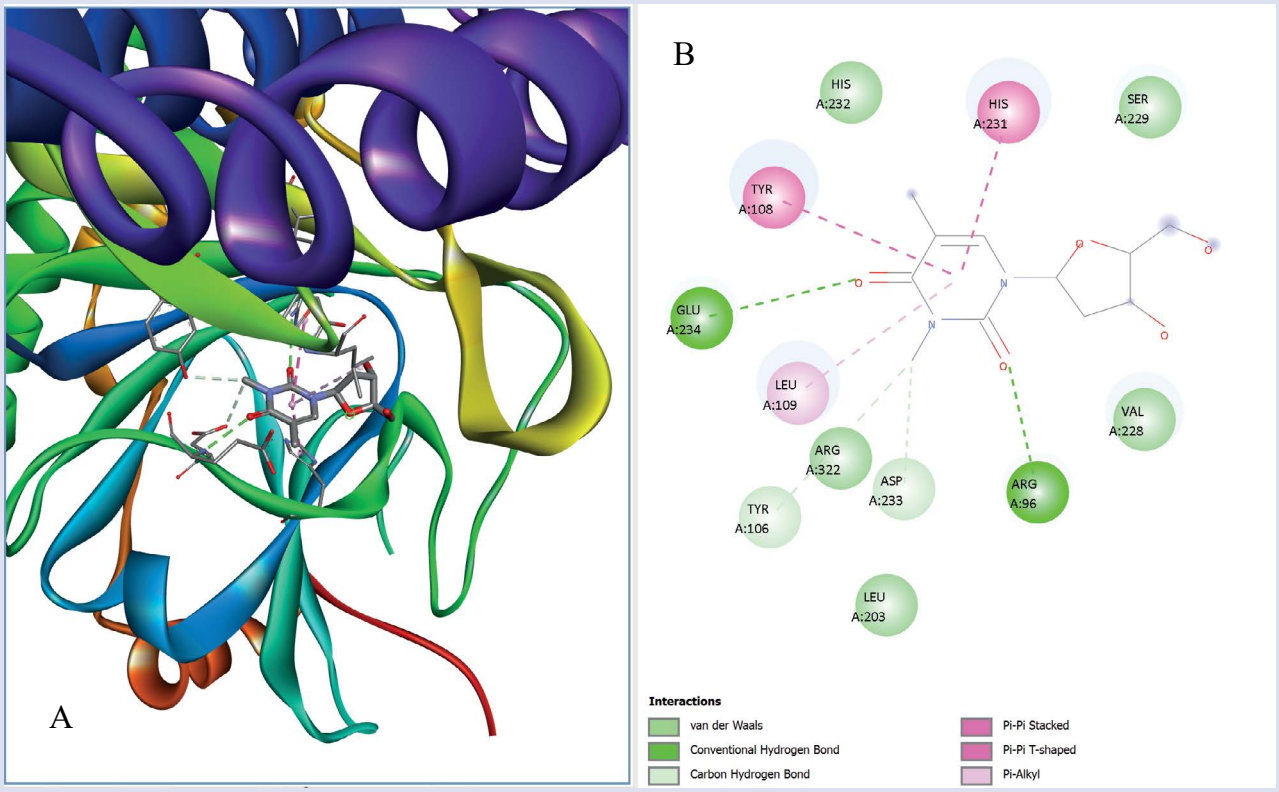


Figure 4. Docking interactions of DT ligand in the active site of FTO protein (3LFM), A) 3D structure, B) 2D Structure

Table 5. Virtual screening compounds

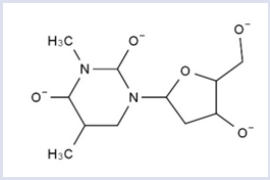
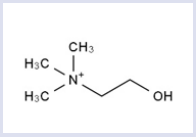
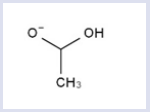
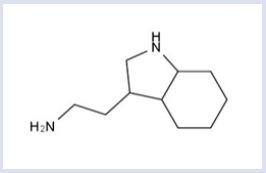
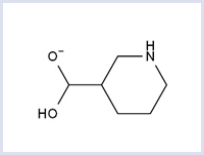
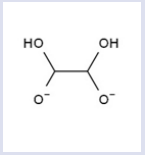
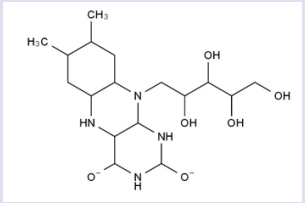
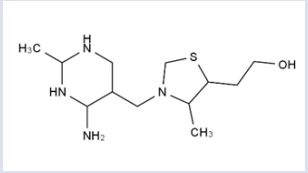
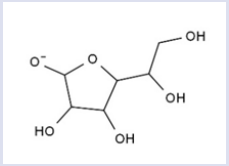
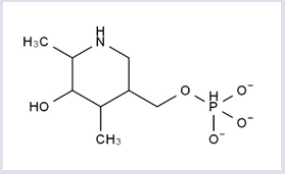
Compound ID	Compound Name	2D Structure	Binding Affinity (kcal/mol)	RMSD
DT	3-methylthymidine (FTO Inhibitor /Native Ligand)		-6.4	0
305	Choline		-3.5	0
160172252	Indole acetic acid		-3.5	0
351795	Indole acetonitrile		-5.4	0
938	Niacin		-4.8	0
971	Oxalic acid		-4.6	0
493570	**Riboflavin**		**-8.2**	**0**
1130	Thiamine		-5.3	0
54670067	Vit B6		-5.7	0
104817	Ascorbic acid		-5.7	0

Table 6. Comparison of native ligand DT and riboflavin interactions with FTO protein (3LFM)

Compound	Binding affinity (kcal/mol) from Pyrx 0.8	Binding affinity (kcal/mol) from AutoDockTools 1.5.7	Mean of Binding affinity (kcal/mol) from AutoDockTools 1.5.7	p	Interaction with amino acid residue	
					Hydrogen bond interaction	Non-hydrogen bond interaction
3-methylthymidine	-6.4	-6.02 -5.97 -5.99	-5.99±0.02	0.0005	Arg (A:96), Glu (A:234)	Tyr (A:106), Asp (A:233), Ser (A:299), His (A: 232), Arg (A:322), Leu (A:203), Val (A:228), His (A:231), Tyr (A:108), Leu (A:109)
Riboflavin	-8.0	-7.48 -7.18 -7.09	-7.25±0.17		Arg (A:96), Glu (A:234), His (A:232), Tyr (A:106), Arg (A:322), Tyr (A:108)	Thr (A:92), Val (A:228), Fe (A:2507), Leu (A:203), Val (A:94), Pro (A:93), Ala (A:227), Ser (A:229), Ile (A:85), Leu (A:109), His (A:231), Asp (A:233), Tyr (A:108)

Molecular docking

Molecular docking with AutoDockTools 1.5.7 also showed that binding affinity of riboflavin is significantly stronger than DT native ligand in FTO protein (Table 6). According to the amount of hydrogen bonds between amino acid residues in FTO protein and the ligand, riboflavin has more hydrogen bonds than DT (Table 6, Figure 2 and 3). Riboflavin and DT have similar hydrogen bonds, which is at Arg (A:96) and Glu (A:234). Furthermore, van der Waals bond at His (A:232) and Arg (A:322) also carbon-hydrogen bond at Tyr (A:106) in the FTO-DT complex change to hydrogen bond in the FTO-riboflavin complex. FTO-riboflavin complex has 2 Pi interactions and 2 hydrogen bonds in Tyr (A:108), meanwhile FTO-DT complex only has 1 Pi interaction in Tyr (A:108). His (A:231) has additional 2 Pi interactions, Leu (A:109) has additional 1 Pi interaction, and 1 new Pi interaction in Asp (A:233) (changed from carbon hydrogen bond) in FTO-riboflavin complex (Table 6, Figure 2 and 3). These changes caused binding affinity of FTO-riboflavin complex is stronger than FTO-DT complex Figure 4.

Binding affinity and patterns of interaction between the protein and the ligand are frequently used to evaluate protein–ligand binding activity. The binding affinity measures the strength of the connection between protein and ligand, while the interaction pattern explains the contacts (hydrogen bonds, hydrophobic interactions, etc.) made with amino acid residues at the binding site. For predicting biological activity, both variables are essential. These two variables are crucial for determining whether a drug can bind and perhaps modify a target protein, according to computational and experimental research. A compound may not reproduce the biological function of a natural ligand if it exhibits optimal binding energy but does not interact with the same or similar amino acid residues. For a compound to behave as a functional mimic or inhibitor, it must interact with significant residues, particularly those involved in the activity of the natural ligand[22–24].

Hydrogen bonding is a key factor influencing the specificity of ligand binding. This importance is directly integrated into computational approaches aimed at locating energetically favorable ligand binding sites on target molecules with known structures[25]. Hydrogen bonds can improve receptor–ligand binding when both the donor and acceptor possess stronger or weaker hydrogen bonders than water's hydrogen and oxygen atoms, while mismatched strong–weak pairs can reduce affinity by interfering with water interactions. This provides mechanistic insight into why non-selective strengthening of receptor–ligand hydrogen bonds often show a poor correlation with experimental binding affinity measurements[26]. Strong hydrogen bonds are essential for most high-affinity ligands, with proteins typically prefer act as hydrogen bond donors. This preference is thought to arise because evolution has selected for geometrically constrained H-bond donors in proteins. Therefore, accurate representation of hydrogen bonding in scoring functions is necessary for reliable binding affinity predictions[27].

Carbon-hydrogen (C-H) bond is known to be the weakest hydrogen bond compared to conventional hydrogen bond (O-H, N-H)[28]. Therefore, the change of bonds at Tyr (A:106) and ASP (A:233) made the interactions stronger, and increased binding affinity of riboflavin-FTO complex compared to FTO-DT complex.

These results exhibit *Moringa oleifera fruit* has a potential as SO therapy because it contains riboflavin that predicted to be FTO protein inhibitor as its strongest binding affinity and interaction with identical amino acid residue in active site of FTO protein. Riboflavin is water soluble organic compound that essential as a cofactor of various enzymes in most organisms and easily uptake from many kinds of foods. This vitamin consists of methylated isoalloxazine core and ribityl side chain that play roles in increasing its solubility and promoting biosynthesis of active cofactors[29]. Riboflavin activates lipolysis mechanisms[30]. Deficiency of riboflavin may lead to hepatic lipid accumulation due to upregulation of PPARγ expression[31]. Furthermore, this deficiency enhanced reactive oxygen species (ROS) accumulation and promotes pro-inflammation activity of adipocytes[32]. Riboflavin plays a significant role in SO by enhancing mitochondrial biogenesis, preventing the accumulation of ROS, and suppressing the expression of muscle atrophy-related genes[33]. The risk of SO increases in elderly people who didn't meet the recommended riboflavin intake[34].

CONCLUSION

Moringa oleifera fruit is bioavailable and non-toxic according to Lipinski Rule of 5 (RO5) and LD50 of Oral Rat Acute Toxicity. Furthermore, it has potential as a SO therapy candidate due to the presence of riboflavin that predicted to be FTO protein inhibitor as its strongest binding affinity and interaction with identical amino acid residue in active site of FTO protein.

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