



Luteolin: A Potential Multiple Targeted Drug Effectively Inhibits Diabetes Mellitus Protein Targets

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Diabetes is a significant health problem that has reached worrisome proportions: almost half of the world's population now has diabetes. Diabetes mellitus, or diabetes, is a severe, long-term disease in which a person's blood glucose levels are elevated due to their body's inability to make any or enough insulin, or to properly utilise the insulin that it does produce. The chemicals extracted from medicinal plants were shown to be both safer and more bioactive than manufactured medicines.

Objective: The goal of this research was to use molecular docking to find possible binding affinities of luteolin, a phytochemical from *Rumex vesicarius* L, to five target proteins, in order to find the lead molecule against diabetes.

Methodology: One chemical was isolated from *Rumex vesicarius* L. leaves in this research. The binding affinity of the complexes was calculated using molecular docking studies. The docking procedure was carried out using AutoDock Tools 1.5.6, which brought the ligand together with the target proteins.

Results: The binding energies of Luteolin with major Glutamine-fructose-6-phosphate amido transferase (GFAT1), Pancreatic α -Amylase, Forkhead box protein O1(FOXO1), α -glucosidase, and Dipeptidyl peptidase-4 (DPP-4) were determined to be -6.89, -6.80, -6.36, -9.35, and -7.72 kcal.

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Conclusion: Our findings suggest that luteolin can target not only α -glucosidase but also DPP4 and other targets, suggesting that they may be used as type 2 diabetes mellitus inhibitors. We believe that this phytochemical, luteolin, may be utilised in preclinical studies as an anti-diabetic drug to combat diabetes mellitus.

Keywords: Luteolin, *Rumex vesicarius*, Diabetes mellitus, In silico, α -glucosidase.

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterised by abnormal protein, fat, and sugar metabolism, as well as consequences such as retinopathy, nephropathy, and neuropathy, as well as macrovascular problems [1] as a result of inadequate insulin secretion or action, or both [2] impacting individuals of all ages all across the globe [3]. The current 9th edition of the world diabetes atlas confirms that diabetes is one of the fastest increasing global health crises of the twenty-first century, according to the International Diabetes Federation. Diabetes affects 463 million people worldwide in 2019, with that figure expected to rise to 578 million by 2030 and 700 million by 2045. Because the pancreas is malfunctioning, the process of producing energy from carbohydrates does not work correctly, resulting in high glucose levels, or hyperglycaemia, which causes polyuria, polydipsia, and polyphagia. Diabetes mellitus affects more than 347 million people globally, according to the WHO, and will be the sixth largest cause of death by 2030 [4]. In India, about 77 million individuals with prediabetes are affected [5]. Diabetes may be managed in a variety of methods, including insulin injections and hypoglycemic medications, although long-term problems still exist [6].

Sulfonylureas, meglitinides, biguanides, thiazolidinediones, and alpha glycosidase inhibitors are among the five types of oral hypoglycemics now available, with others in clinical trials, such as protein tyrosine phosphatase-1 beta inhibitors [7]. Many studies have been published in the past few years that fully explain and prove the use of natural products in anti-diabetic therapy, including papers on Chinese medicinal plant-derived therapeutic compounds, flavonoids, and desert plants [8,9]. WHO has identified over 21,000 plants having significant therapeutic potential all over the globe, including 2500 species in India, of which 150 species are economically utilised on a big basis [10]. The World Health Organization Committee on Diabetes' suggestion to encourage research on hypoglycemic drugs of

plant origin used in traditional medicine has sparked a lot of interest in this field [11]. According to a literature review, over 800 plants have been utilised for empirical diabetes treatment, with one tenth of them classified as hypoglycaemic plants containing active components such as glycans, flavonoids, Triterpenes, and alkaloids [12].

Rumex vesicarius L. (Polygonaceae) is a wild edible plant known in Telugu as Chukka kura, in Hindi as Chukra, and in English as Bladder Dock. Known as sorrel, it is harvested in the spring and consumed raw or cooked. *Rumex vesicarius* L. is used to treat a variety of ailments, including liver illness, poor digestion, and as a diuretic, laxative, tonic, painkiller, purgative, and antibacterial agent. The herb has been shown to help with biliary problems and cholesterol management [13]. The phenolic compound luteolin [14] is the most prominent chemical component in this part.

It is critical to find a good candidate medication for Diabetes. This paper describes an in silico approach to using the ligand Luteolin as an inhibitor on five protein targets associated with diabetes mellitus, including Glutamine-fructose-6-phosphate amido transferase (GFAT1), Pancreatic α -Amylase, Forkhead box protein O1(FOXO1), α -glucosidase, and Dipeptidyl peptidase-4 (DPP-4). Binding energy was used to calculate the docking of the luteolin with the target proteins (more negative the energy, more the binding).

2. MATERIALS AND METHODS

2.1 Ligand Preparation

The PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) was used to find the three-dimensional SDF structure of Luteolin (CID: 5280445). Discovery studio was used to convert the 3D structure of the ligand file format from SDF to PDB. UCSF Chimera tools were used to construct the ligand from a PDB file (energy minimization, hydrogen atoms inserted, and charges added where needed).

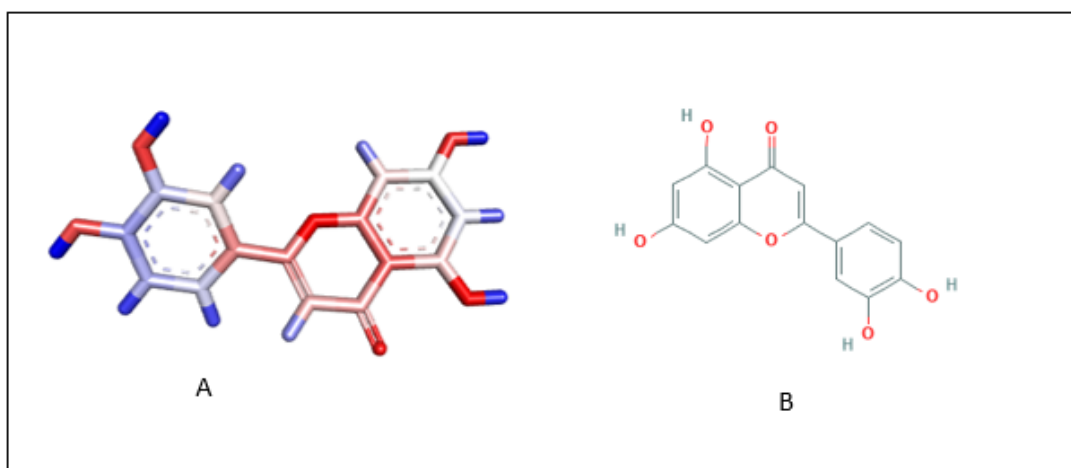


Fig. 1. A) 3D structure of Luteolin (CID: 5280445) B) 2D structure of Luteolin

2.2 Retrieval of Target Proteins

The 3D structures of discovered Diabetes mellitus proteins, such as Glutamine-fructose-6-phosphate amido transferase (GFAT1) (PDB ID = 2ZJ3), Pancreatic α -Amylase (PDB ID = 4GQR), Forkhead box protein O1 (FOXO1) (PDB ID = 3CO7), α -glucosidase (PDB ID = 3L4Y), and Dipeptidyl peptid Fig. 2 shows the three-dimensional structures of all of the target proteins.

2.3 Preparation of the Target Proteins

Molecular docking experiments could not be performed on the raw PDB protein structure. Only heavy atoms, fluids, cofactors, and metal ions make up the PDB structure, which may be multimeric. Bond ordering, topologies, and formal atomic charges are not present in these structures. Because X-ray structural analysis cannot differentiate between O and NH₂ ionisation and tautomeric states are likewise unassigned, the terminal amide groups may be misaligned. As a result, the raw PDB structure should be prepared for docking in an appropriate way.

All of the target proteins were refined and energy optimised before moving on to docking analysis. The protein was processed and prepared using the UCSF Chimera software's Protein Preparation Wizard. This Wizard guides you through the process of appropriately preparing a protein for docking. This programme can turn a PDB structure into fully built all-atom protein models. All target proteins' X-ray crystal structures were generated by eliminating all

water molecules from the structure. The implicit hydrogen atoms were added to the atoms to fulfil their proper valences, and ligands and ions of little importance present in the protein structure were removed since the original data did not include any hydrogen. The bond ordering, bond angles, and topology of the structure were then assigned, and the structure was optimised. The formal atomic charges for the amino acid residues were fixed, and energy minimization was performed.

2.4 Molecular Docking

Following the preparation of the ligands and target protein for docking, AutoDock Tools 1.5.6 was used to conduct the docking procedure by bringing the ligand and target protein together [15]. Each target protein was docked with the luteolin molecule individually. In this docking process, the different conformations for the ligand were produced, and the final energy refinement of the ligand posture happened. Each docking procedure had a total of ten runs. Furthermore, the maximum iterations were 2000, with a 100 Kcal/mol energy barrier. The lowest docked binding energy was used to choose the optimal conformations for each docking operation. The docked conformations were saved in PDB format and then visualised using Discovery studio 4.0 to assess docking site identification.

3. RESULTS AND DISCUSSION

The medication and target protein interaction screening was scored using a knowledge-based approach. According to the docking

interpretation, chosen luteolin may establish conventional hydrogen bonds with various residues to interact effectively with selected five-target proteins. It also binds to all of the protein targets thanks to the van der Waals interaction. These interactions are low-energy, implying a high confirming presence in comparison to others.

Inhibition of Diabetes mellitus target proteins occurred with binding affinities ranging from -6.36 kcal/mol to -9.35 kcal/mol, suggesting substantial binding interactions at the active site binding pocket, according to the docking results given in Table-1. Hydrogen bonds, electrostatic interactions, and hydrophobic contacts all helped to stabilise these connections. Pi-interactions, such as Pi-Pi interaction, Pi-Alkyl interaction, Pi-Sulfur interaction, Pi-Sigma, and Pi-Pi stacking, were also seen with all of the target proteins and mainly included the transfer of charges. The ligands were imbedded in the active/binding site of the target proteins thanks to these Pi interactions.

3.1 Binding Interactions of Luteolin with GFAT1 protein

The enzyme glutamine: fructose-6-phosphate amidotransferase (GFAT) catalyses the rate-limiting step in the production of hexosamine

products; this enzyme is also the main regulator in this pathway, and therefore may be implicated in the changes seen in preclinical or apparent diabetic individuals [16]. It's also known that GFAT catalyses the conversion of fructose-6-phosphate (F-6-P) to glucosamine-6-phosphate (GlcN-6-P) using glutamine as an amino-donor [17], and that GlcN-6-P is quickly transformed and activated to uridine-5'-diphosphate-N-acetylglucosamine (UDP-GlcNAc), which serves as an The vast majority of glucose will go via the glycolysis route, with just a tiny amount going through the hexosamine pathway. The hexosamine pathway products are regulated by GFAT1. As a result, this enzyme represents a potential therapeutic target for Type 2 Diabetes [18,19].

With GLU:560, luteolin had a negative binding affinity of -6.89 kcal/mol and five traditional hydrogen bonds. THR:428 According to the docking results, SER:420 CYS:373 (Tables-1 and Fig. 3). Hydrophobic interactions with GFAT1 amino acids also contribute to the binding's stability. THR:428,425,375, CYS:373, SER:376,676,422,420, GLY:374,423, LEU:556,673,419, GLU:560, VAL:471, ALA:674, LYS:675, GLN:421 THR:428,425,375, CYS:373, SER:376,676,422,420, GLY:374,423, LEU:556,673,419 (Fig. 3).

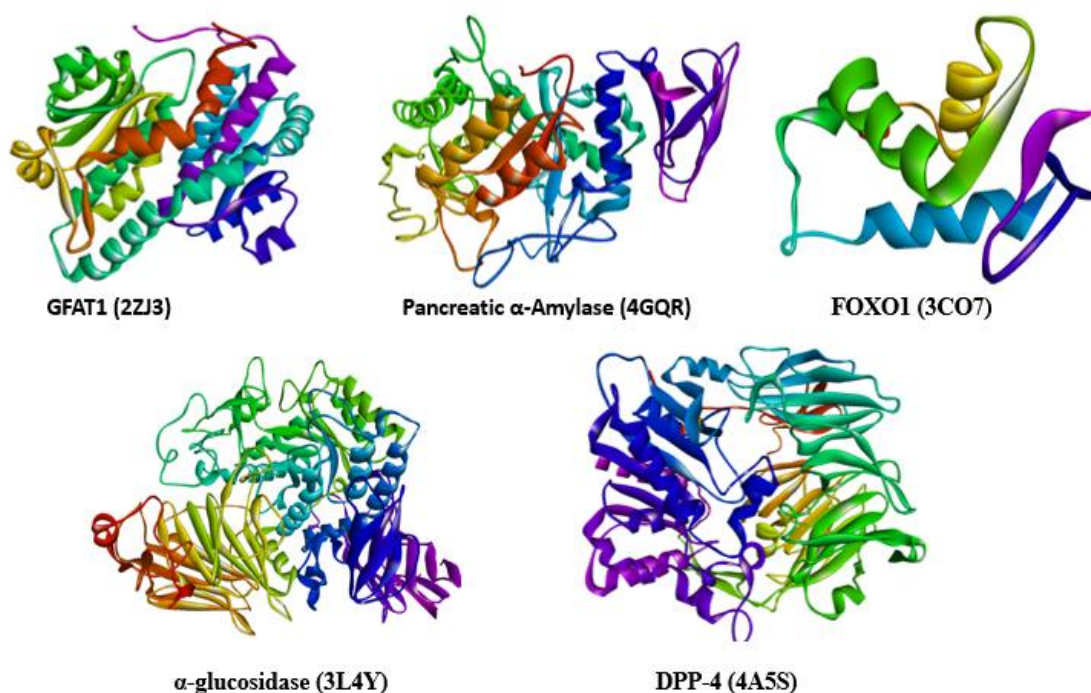


Fig. 2. 3D structures of Diabetes therapeutic target proteins

Table 1. Molecular docking score and interaction amino acid residues of luteolin docked against multiple targets of Diabetes mellitus

S. No	Target Name	PDB ID	Binding/ Docking affinity (kcal/mol)	Residue involving interaction	No. of H bonds	Interaction of residues forming H ₂ bonds
1	GFAT1	2ZJ3	-6.89	THR:428,425,375, CYS:373, SER:376,676,422,420, GLY:374,423, LEU:556,673,419, GLU:560, VAL:471, ALA:674, LYS:675, GLN:421,	5	GLU:560 THR:428 SER:420 CYS:373
2	Pancreatic α -Amylase	4GQR	-6.80	ASP:197,300, GLN:63, TRP:59,58, HIS:305,299, ALA:198, ARG:195, TYR:62, GLU:233, LEU:163	3	ASP:197 GLN:63
3	FOXO1	3CO7	-6.36	SER:205,206,212, ASN:158, ALA:159,207, GLY:208, LYS:200, TRP:160, ARG:157, TYR:165,196, TRP:209	3	SER:205,212 ASN:158
4	α -glucosidase	3L4Y	-9.35	ARG:520, GLY:533,564, SER:288,521, PHE:522,641,535, ALA:291, 537,536,285,512, PRO:566,284,287, MET:567, LYS:534,776, ILE:523,565	3	ARG:520 LYS:776 GLY:533
5	DPP-4	4A5S	-7.72	TRP:154,157,216,215,305, THR:156,199, SER:212, PHE:208, ALA:210, 213, PRO:159, LEU:214	5	TRP:154,216 THR:156 PHE:208 SER:212

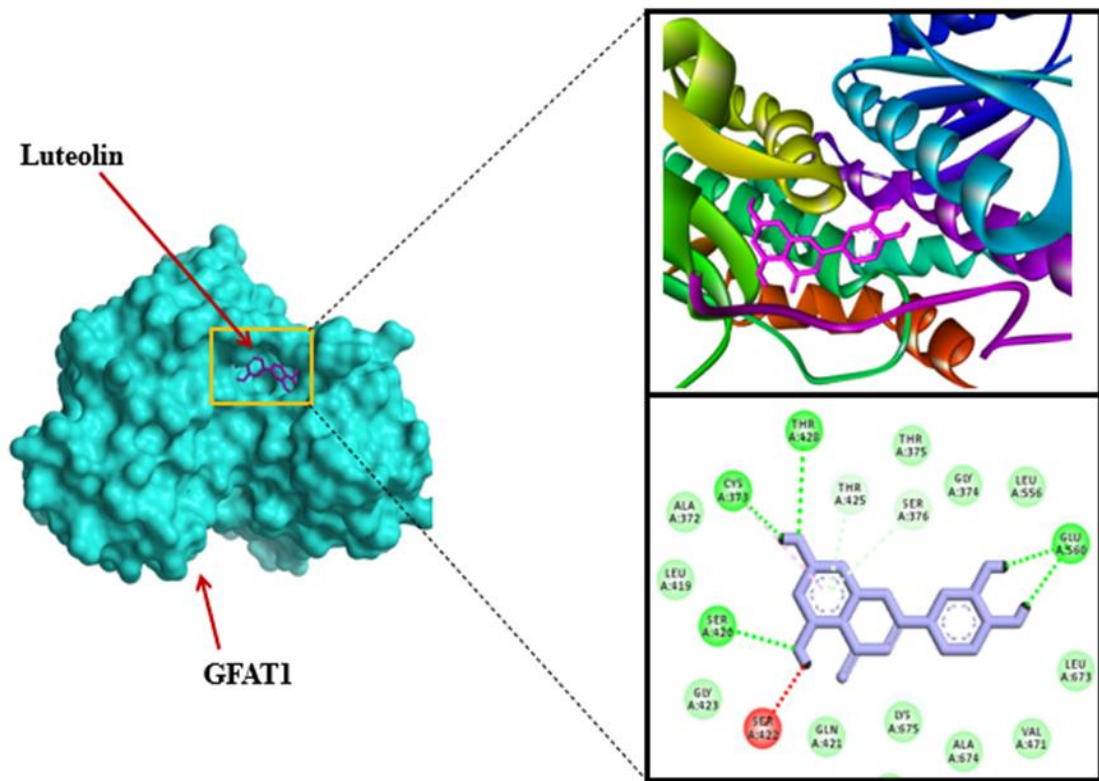


Fig. 3. Molecular interactions among GFAT1 protein (PDB ID: 2ZJ3) with luteolin

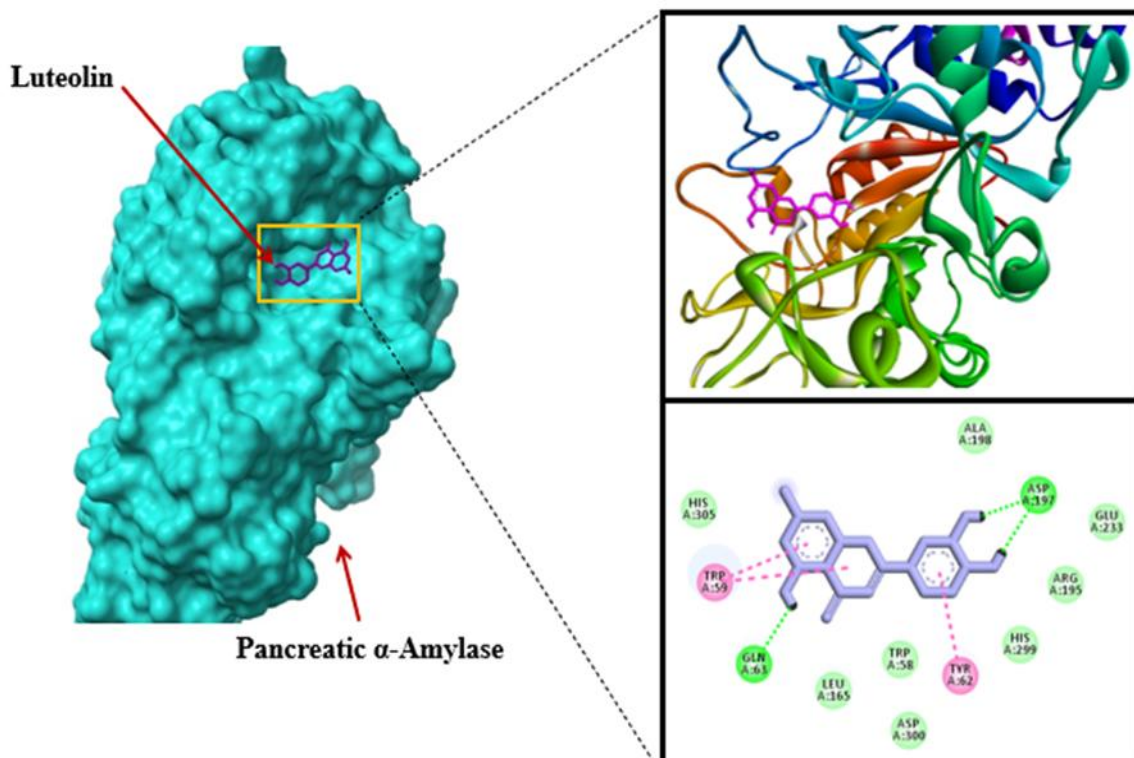


Fig. 4. Molecular interactions among Pancreatic α -Amylase (PDB ID: 4GQR) with luteolin

3.2 Binding Interactions of Luteolin with Pancreatic α -Amylase

α -Amylase is a crucial enzyme in energy acquisition because it catalyses the first stage of starch breakdown for glucose synthesis. As a result, α -amylase is a target molecule for the therapy of type 2 diabetes, and its inhibitors and connection to the illness have been studied extensively [20,21]. α -amylase digests starch in the duodenum to produce maltose or maltooligosaccharides, which are further hydrolyzed by brush-border membrane enzymes such sucrase-isomaltase [22]. Alpha amylase is a target molecule for the treatment of type 2 diabetes mellitus; its inhibitors and links to the illness have been studied extensively [23,24].

Luteolin showed stable binding with a binding affinity of -6.80 kcal/mol, according to molecular docking experiments against the α -Amylase protein (Table-1). This is due to its three conventional hydrogen bonds with ASP:197 and GLN:63, as well as hydrophobic interactions with ASP:197,300, GLN:63, TRP:59,58, HIS:305,299, ALA:198, ARG:195, TYR:62, GLU:233, LEU:163 and hydrophobic interactions with ASP:197,300, GLN:63, TRP:59,58, HIS:305 (Fig. 4). Based on these findings, Luteolin may be a possible diabetes mellitus inhibitor in the fight against diabetes.

3.3 Binding Interactions of Luteolin with the FOXO1

Proliferation, differentiation, cell survival, glucose metabolism, longevity, and oxidative stress resistance are all essential activities of the FoxO1 transcription factor [25]. The downstream substrates of the PI3K-Akt pathway include human FOXO1 and other members of the FOXO family [26]. The current emphasis of DM research is on improving pancreatic cell regeneration and suppressing apoptosis in pancreatic cells. The FOXO1 (forkhead box protein O1) transcription factors are believed to play an essential role in the control of pancreatic cell regeneration. The inhibition of FOXO1 transcription factors migration to the nucleus or FOXO1 deactivation in the nucleus is one of the strategies for preventing apoptosis and increasing pancreatic cell proliferation [27,28]. As a result, the particular advantages of suppressing FOXO1 in diabetes repair must be investigated experimentally [29].

The Luteolin forms three hydrogen bonds with SER:205,212 ASN:158 and thirteen hydrophobic

bonds with ASN:158, ALA:159,207, GLY:208, LYS:200, TRP:160, ARG:157, TYR:165,196, SER:205,206,212, TRP:209, yielding a binding energy of -6.36 kcal/mol (Table-1 and Fig. 5). These findings suggest that luteolin may be used as a therapeutic candidate to treat diabetes mellitus by inhibiting FOXO1.

3.4 Binding Interactions of Luteolin with the α -glucosidase

α -Glucosidase is a carbohydrate digesting enzyme found in the small intestine's brush border. It differs from α -glucosidase in that it acts on 1,4-bonds. α -Glucosidase is a catalytic enzyme that converts starch and disaccharides into glucose [30]. The process of carbohydrate digestion is slowed when α -glucosidase is inhibited, which helps to avoid postprandial hyperglycemia, which is a primary cause of chronic diabetes and its consequences [31].

The luteolin docking score is shown in Table-1. The docking results show that luteolin has the greatest binding affinity against α -Glucosidase, with 9.35 kcal/mol, and interacts with three hydrogen bonds with ARG:520 LYS:776 GLY:533. Luteolin interacts hydrophobically with the amino acids ARG:520, GLY:533,564, SER:288,521, PHE:522,641,535, ALA:291, 537,536,285,512, PRO:566,284,287, MET:567, LYS:534,776, ILE:523,565 (Fig. 6). Luteolin inhibits the activity of α -Glucosidase, according to the docking findings of this research.

3.5 Binding Interactions of Luteolin with the Dipeptidyl peptidase-4 (DPP-4)

Dipeptidyl-peptidase4 (DPP4), also known as CD26, is a 110-kDa glycoprotein that was discovered by Hopsu-Havu and Glenner [32]. These so-called gliptins raise incretin levels, thus prolonging insulin activity after a meal. Since soluble DPP4 is classified as an adipokine, it also corresponds with metabolic syndrome markers [33]. DPP4 inhibition, on the other hand, plays an important role in increasing GLP-1 and GIP circulation in humans, which leads to a decrease in blood glucose levels and many other benefits associated with antidiabetic therapies, such as a lower risk of hypoglycemia, the potential for weight loss, and the potential for pancreatic β -cell regeneration and differentiation [34,35]. Table-1 shows that the docking scores of luteolin chosen for the investigation of inhibition of Dipeptidyl peptidase-4 (DPP-4) are -7.72 kcal/mol.

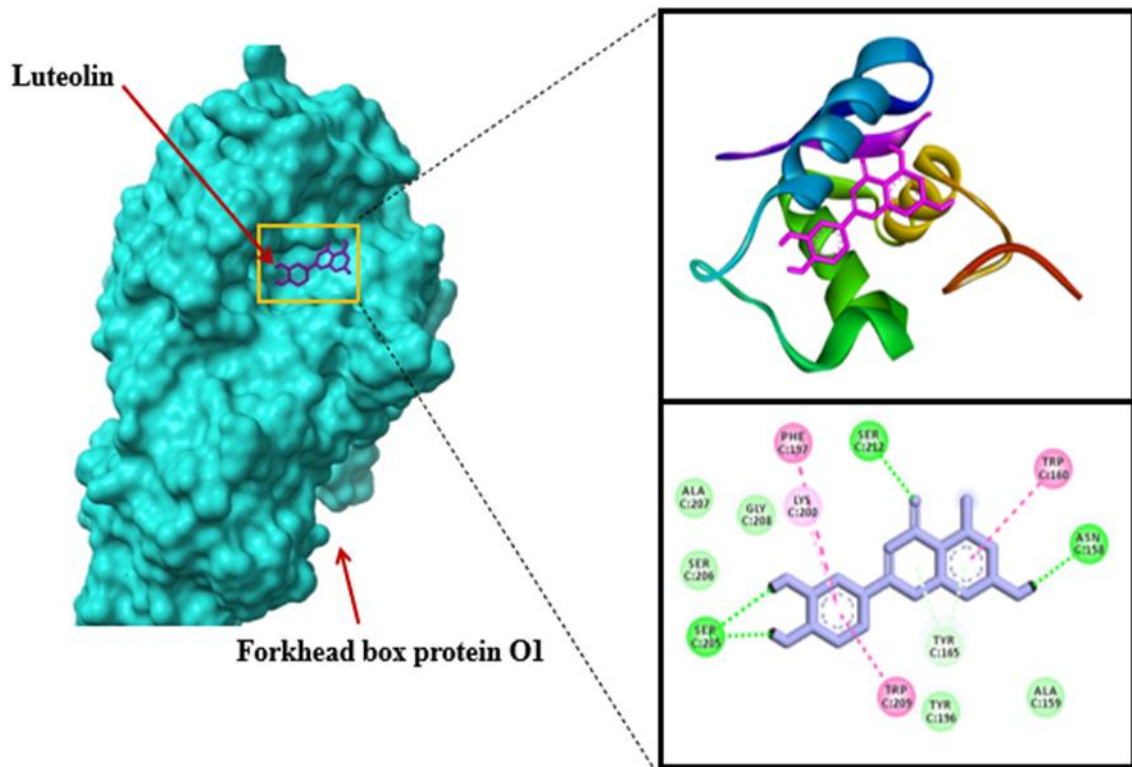


Fig. 5. Molecular interactions among FOXO1 (forkhead box protein O1) (PDB ID: 3CO7) with luteolin

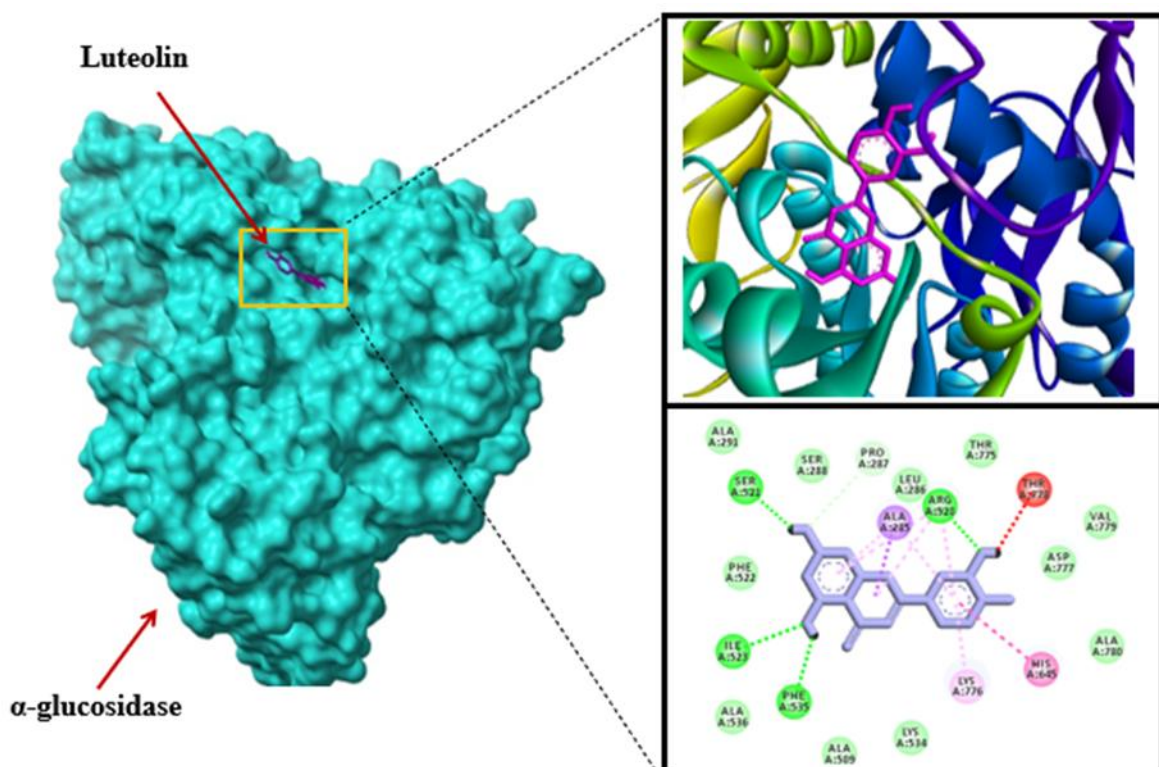


Fig. 6. Molecular interactions among α -Glucosidase (PDB ID: 3L4Y) with luteolin.

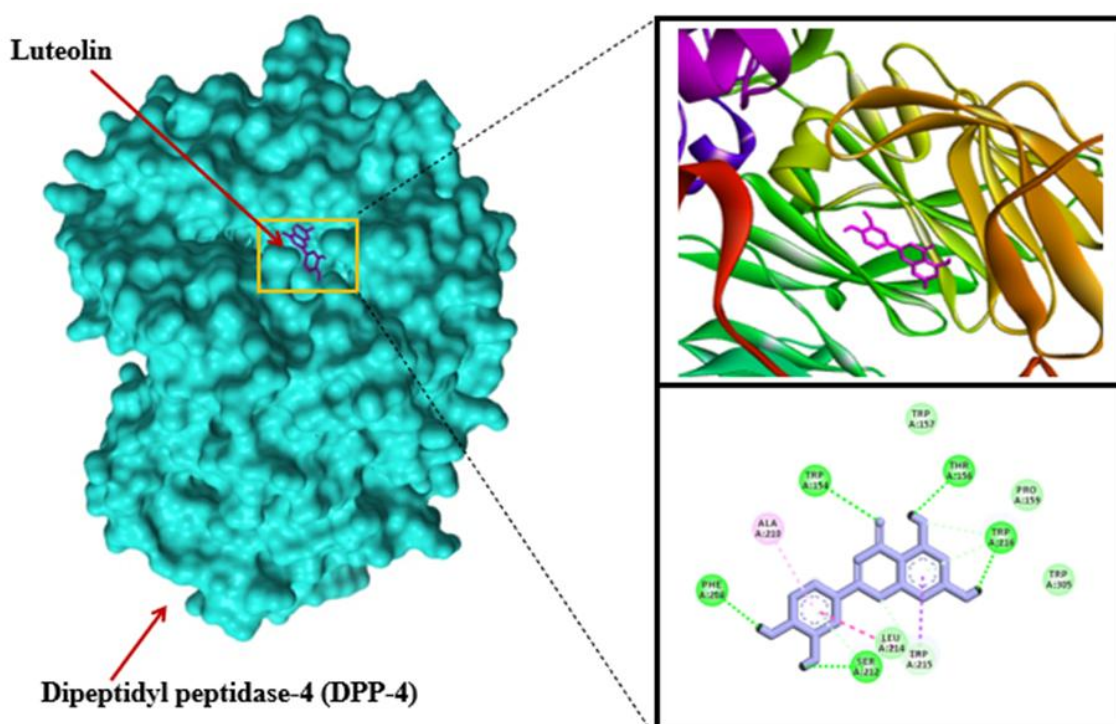


Fig. 7. Molecular interactions among Dipeptidyl peptidase-4 (4A5S) with luteolin.

Chimera studied Molecular Docking utilising AutoDock for the Luteolin. Fig. 7 shows that Luteolin has a binding energy of 7.72 kcal/mol and forms 5 H-bonds with DPP4. Hydrophobic interactions are also shown, with hotspot residues TRP:154,157,216,215,305, THR:156,199, SER:212, PHE:208, ALA:210, 213, PRO:159, LEU:214 clearly demonstrating their capacity to bind and inhibit interactions with active site residues. When these findings are analysed, it is clear that luteolin has a low binding energy with DPP4, indicating that further in vitro and in vivo research is needed before they can be considered as possible medicines for type 2 diabetes.

4. CONCLUSION

Finally, luteolin has the potential to be a medication for the treatment of diabetes mellitus. Because luteolin binds to alpha Amylase and DPP4 effectively, it may be involved in preventing glucose synthesis. It also binds to GFAT1 and FOXO1, suggesting that it may help to avoid hyperglycemia. The great efficiency with which luteolin binds to alpha glucosidase suggests that it has a function in preventing glucose synthesis. As a result of the in silico molecular docking analysis, luteolin is the best recommended medication, and it may serve as a

powerful inhibitor against type 2 Diabetes mellitus targets. We believe that this phytochemical, luteolin, may be utilised in preclinical studies as an anti-diabetic drug to combat diabetes mellitus. In vitro and in vivo studies may be used to confirm this hypothesis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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