Trop J Nat Prod Res, December 2023; 7(12):5460-5469

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Mechanism of Action of Glucomannan as a Potential Therapeutic Agent for Type 2 Diabetes Mellitus Based on Network Pharmacology and Molecular Docking Simulation

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ARTICLE INFO

Article history:
Received 24 August 2023
Revised 04 December 2023
Accepted 07 December 2023
Published online 01 January 2024

ABSTRACT

Glucomannan is a polysaccharide with several health benefits such as the ability to lower blood sugar, slow gastric emptying time, accelerate satiety, and modify intestinal microbial metabolism. Therefore it has a potential as an alternative therapy for type 2 diabetes mellitus (T2DM). This study explores the mechanism of action of glucomannan as a potential therapeutic agent for T2DM through network pharmacology and molecular docking simulations. Glucomannan and T2DM target proteins were searched using GeneCard and OpenTarget Platform, respectively. The connectivity between T2DM target proteins and glucomannan were done using Cytoscape and Venny diagrams. Virtual screening was performed using Pyrx software with protein-targeted T2DM and visualization was done using Discovery Studio. There were 9 key targets related to the mechanism of action of glucomannan based on target connectivity construction. From the docking results, the lowest binding affinity of -9.6 kcal/mol was obtained between glucomannan and 3WY1 (PDB ID of GAA/alpha-glucosidase). This binding affinity was comparable to that obtained for the positive controls; acarbose and miglitol, with binding affinity of -9.7 kcal/mol for acarbose-3WY1 complex. The 3D structure visualization showed that glucomannan and acarbose occupy the same active site on the 3WY1 structure. The results of this study indicate that the most probable mechanism of action of glucomannan is inhibition of α-glucosidase, and therefore could be a potential alternative therapeutic agent for T2DM.

Keywords: Glucomannan, Type 2 Diabetes Mellitus, Network Pharmacology, Molecular Docking

Introduction

Diabetes mellitus (DM) is a chronic metabolic disoder that progressively causes microvascular and macrovascular complications and worsens the quality of life of its sufferers. DM has become the ninth leading cause of death worldwide, causing a significant health burden.[1] According to data from the International Diabetes Mellitus Federation, there are 537 million adults (20-79 years) with diabetes mellitus and this number is predicted to increase to 634 million in 2030 or 783 million in 2045, and to date there have been 6.7 million deaths due to diabetes mellitus. Treatment of diabetes with synthetic drugs is associated with side effects such as hypoglycemia, idiosyncratic hepatocellular damage, lactic acidosis, gastrointestinal disturbances, permanent neurological impairment, headache, dizziness and even death, and these drugs are normally expensive.[2,3] While, bioactive molecules derived from medicinal plants can be used with minimal side effects compared to synthetic drugs.[4]

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Citation: Karima R, Elya B, Sauriasari R. Mechanism of Action of Glucomannan as a Potential Therapeutic Agent for Type 2 Diabetes Mellitus Based on Network Pharmacology and Molecular Docking Simulation. Trop J Nat Prod Res. 2023; 7(12):5460-5469. http://www.doi.org/10.26538/tjnpr/v7i12.15

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

One of the natural compounds that have the potential as a therapy for T2DM is glucomannan. Glucomannan is a polysaccharide compound of the hemicellulose type consisting of glucose and mannose chains. Glucomannan is composed of D-glucose and D-mannose with a molar ratio of 3:2 and has a relatively high molecular weight of 200,000 to 2,000,000 daltons with a size of 0.5 to 2 mm (10 to 20 times larger from starch molecule).[5] Several studies have suggested that glucomannan can increase the absorption rate of nutrients from the small intestine, and also boosts insulin sensitivity.[6] Other studies have demonstrated that the consumption of supplements rich in glucomannan by rats can prevent plaque formation in blood vessels due to cholesterol.[7] In addition, the glycaemic content of research subjects were found to decrease gradually after a breakfast routine with glucomannan biscuits, which helped to regulate blood sugar levels.[5]

There are several mechanisms of action of glucomannan as an antidiabetic agent has been suggested, namely; inhibition of α-glucosidase activity,[6] inhibition of inflammation,[7] inhibition of oxidative stress,[1,6] enhancement of intestinal prebiotic activity, and suppression of gluconeogenesis.[8] However, there has been no report on the major mechanism of action of glucomannan as an antidiabetic agent. Knowing the major mechanism of action is very important in maximizing the resulting therapeutic effect for drug discovery and development. This research will explore the mechanism of action of glucomannan as a potential therapeutic agent for T2DM through network pharmacology and molecular docking simulation methods. This computational pharmacology and molecular docking approach can provide analytical results with high accuracy and can support the results of laboratory investigations, as well as being a tool in drug discovery.[11]

Materials and Methods

Ligands and protein sources
The protein targets of the glucomannan compounds were obtained from GeneCard Version 5.13 (www.genecards.org). Protein targets of type 2 diabetes mellitus were obtained from Open Target Platform (www.opentargets.org).
Compound and Target Connectivity Construction
The relationship between the protein targets of glucomannan and the T2DM key target were seen from the protein target slice using Venny online tools version 2.1 (www.bioinfogp.cnb.csic.es/tools/venny) was used.

Network Pharmacology
The protein-protein interaction between the key targets were obtained using Cytoscape software version 3.9.1.

Molecular Docking
The 3D structures of glucomannan and the positive control drug were obtained from the PubChem database (www.pubchem.ncbi.nlm.nih.gov/) and then converted to pdb format using Chimera 1.16 software.[9]
The crystal structure was obtained from the Brookhaven website (www.rcsb.org), and www.uniprot.org. The key target structure was prepared by removing water molecules, heteroatoms and other complexes using the Discovery Studio Client 20217 software.
The docking was performed using PyRX tool software with Open babel and Autodock Vina to simulate docking using blind docking method.[10] The grid box size: X = -12.064 Y = 1.3531 Z = 0.6672 Å and the grid size : X = 309, Y = 167 Z = 265 Å visualized the docking results observed in the 3D and 2D interactions of the protein-ligand complex using the Biovia Discovery Studio 2021.

Results and Discussion

Network Pharmacology
The key targets search for glucomannan using the GeneCard database gave 23 key targets (Table 1). These primary targets suggest a broad biological activity of glucomannan which is thought to be mainly involved in biological processes like cellular responses to various stimuli, transcriptional regulation, inflammatory response, regulation of apoptosis, etc.[11] Based on searches from the Open Target database, 5018 key targets were obtained for T2DM. We used Venny 2.1 software to search for slices of the T2DM key target and the key target of glucomannan to assess the effectiveness of glucomannan against T2DM. Figure 1 shows that there are 9 targets (0.2%) out of the 5018 T2DM key target related to glucomannan action.
A network of Glucomannan targets against T2DM by topology analysis constructed by cytoscape are shown in Figure 2. The figure explains the relationship between glucomannan targets and TD2M targets. The 9 target proteins which are slices of the key targets of glucomannan and T2DM are as follows:

INS
INS is the code for insulin. Insulin lowers blood sugar by increasing cellular permeability to monosaccharides, amino acids, and fatty acids. INS promotes glycolysis, pentose phosphate cycle and glycogen synthesis in the liver.[12]

GAA
This gene encodes a lysosomal α-glucosidase required for the breakdown of glycogen to glucose in lysosomes. The encoded preproprotein undergoes proteolysis to produce several intermediate and mature forms of the enzyme. Defects in this gene cause glycogen storage disease II, an autosomal recessive disorder with wide clinical presentation, also known as Pompe disease.[13]

NOS2
Nitric oxide is a reactive free radical that serves as a biological mediator in many processes, including neurotransmitter activity, antibacterial, and antitumor activities. This gene codes for nitric oxide synthase, which is expressed in the liver and is induced by a combination of lipopolysaccharides and several cytokines.[14] Impaired NO production leads to endothelial dysfunction, ultimately leading to the development of many diseases such as insulin resistance and T2DM.[15]

FTO
This gene is the building block protein of the non-heme iron-2-oxoglutarate-dependent oxidase superfamily, but the exact physiological function of this gene is unknown. Other non-heme iron enzymes that repair damage to alkylated DNA and RNA through oxidative demethylation.[16]

ADRB3
The protein encoded by this gene belongs to the family of beta-adrenergic receptors that mediate catecholamine-induced adenylate cyclase activation by G protein activity. This receptor is mainly present in adipose tissue and is involved in regulation of lipolysis and thermogenesis. In addition to diabetes, obesity and weight-related disorders are also correlated with specific polymorphisms of three beta-adrenergic receptor subtypes, including the ADRB3 gene.[17]

Table 1: Key Target of Glucomannan [35]

Protein	Description	Category
NLRP3	NLR Family Pyrin Domain Containing 3	Protein Coding
MAN2C1	Mannosidase Alpha Class 2C Member 1	Protein Coding
CERNA3	Competing Endogenous LncRNA 3 For MiR-645	RNA Gene
GGH	Gamma-Glutamyl Hydrolase	Protein Coding
MANBA	Mannosidase Beta	Protein Coding
SNORD15A	Small Nucleolar RNA, C/D Box 15A	RNA Gene
FTO	FTO Alpha-Ketoglutarate Dependent Dioxygenase	Protein Coding
ADRB3	Adrenoceptor Beta 3	Protein Coding
PLIN4	Perilipin 4	Protein Coding
TRP-AGG2-5	TRNA-Pro (Anticodon AGG) 2-5	RNA Gene
TRP-AGG2-6	TRNA-Pro (Anticodon AGG) 2-6	RNA Gene
TRP-AGG2-1	TRNA-Pro (Anticodon AGG) 2-1	RNA Gene
TRP-AGG2-4	TRNA-Pro (Anticodon AGG) 2-4	RNA Gene
TRP-AGG2-3	TRNA-Pro (Anticodon AGG) 2-3	RNA Gene
TRP-AGG2-2	TRNA-Pro (Anticodon AGG) 2-2	RNA Gene
TRP-AGG2-7	TRNA-Pro (Anticodon AGG) 2-7	RNA Gene
TRP-AGG2-8	TRNA-Pro (Anticodon AGG) 2-8	RNA Gene
NOS2	Nitric Oxide Synthase 2	Protein Coding
INS	Insulin	Protein Coding
SNORD118	Small Nucleolar RNA, C/D Box 118	RNA Gene
LINC01672	Long Intergenic Non-Protein Coding RNA 1672	RNA Gene
GAA	Alpha Glucosidase	Protein Coding
AMY1A	Amylase Alpha 1A	Protein Coding

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

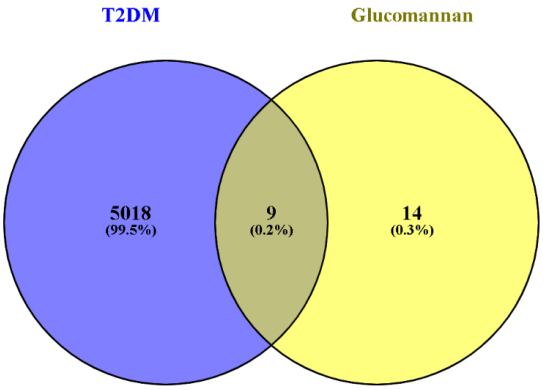

Figure 1: Target Slices of T2DM with Glucomannan

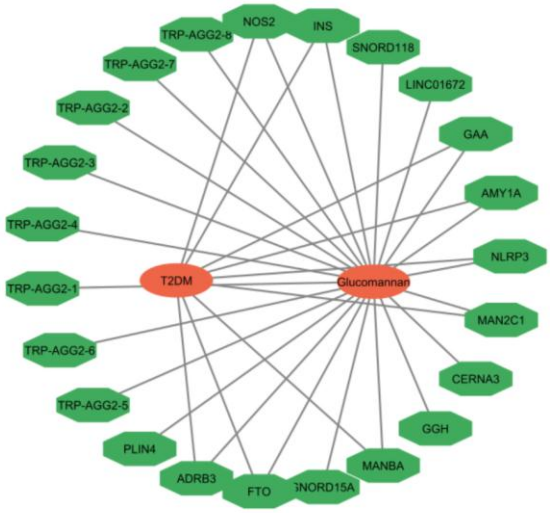

Figure 2: Network of Target Proteins of T2DM and Glucomannan

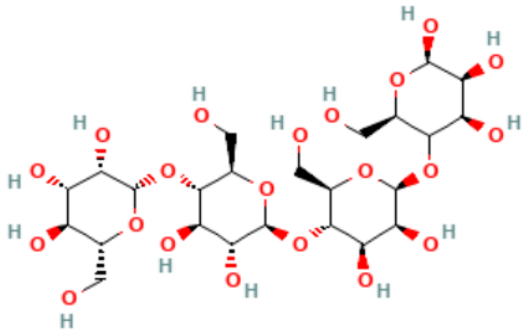

Figure 3: 2D Structure of Glucomannan [36]

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MANBA
This gene encodes a member of the glycosylhydrolase 2 family. The encoded protein localizes to lysosomes and is the terminal exoglycosidase in the N-linked glycoprotein-oligosaccharide catabolic pathway. Mutations in this gene are associated with betamannosidosis, a lysosomal storage disease with generalized neurological involvement.[18]

MAN2C1
This gene is expected to allow α-mannosidase activity. It is believed to be involved in the catabolic process of oligosaccharides. It is located in the nucleoplasm.[19]

NLRP3
Control of T2DM by NLRP3 through regulation of glucose tolerance, insulin resistance and inflammation, stress-mediated apoptosis of the endoplasmic reticulum in adipose tissue. NLRP3 is also involved in intestinal homeostasis and inflammatory diseases.[20]

AMY1A
Salivary amylase is an enzyme that breaks the 1,4-α-glucosidic bonds of oligo- and polysaccharides and initiates the digestion of dietary starch and glycogen. AMY1 gene is involved in the regulation of starch digestion and carbohydrate metabolism. Studies have shown that people with higher salivary amylase break down starches faster and have a faster and higher glycaemic response after digesting starch.[21]

Molecular Docking Study
Structure of Glucomannan
The structure of glucomannan was obtained from the Pubchem database as shown in Figure 3. It consists of a linear chain of mixed residues assembled from 1,4-linked D-mannose and D-glucose monomers in blocks. Mannan residue may have interfered with one or two glucose residues.[25] The ratio of mannose and glucose in the glucomannan structure varies depending on the source of the glucomannan. For example, glucomannan extracted from konjac tubers has a molar ratio of 1.6:1 or 1.4:1,[26] while those extracted from Scottish orchid and pine tuber have a molar ratio of 3.6:1 and 2.1:1, respectively.[25]

Selection of Macromolecular Structures
Molecular docking is one of the most commonly used methods due to its robustness and became one of the best methods in structure-based drug design.[11] Molecular docking can predict conformation of internal small-molecule ligands suitable target binding sites with high fidelity.[27] Scoring functions are used to evaluate molecular docking systems binding energetics of predicted ligand-receptor complexes.[27] Nine key proteins were selected for docking glucomannan molecule. The selected macromolecular structures were macromolecules with resolution values of <2.5 Å and have Ramancandra outliers in the blue zone.[28] Based on these criteria, the macromolecular structures that were selected and docked with glucomannan are shown in Table 2. The 3D crystal structure were downloaded from www.rcsb.org. If the RCSB is not found then the target structure is taken from www.uniprot.org.

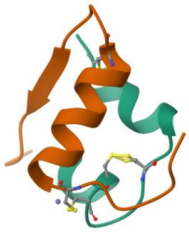
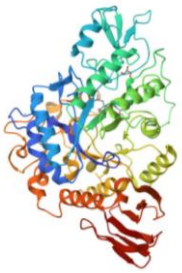
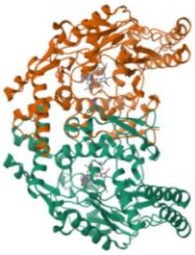
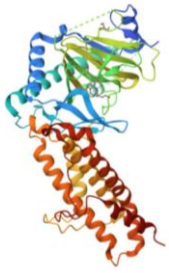
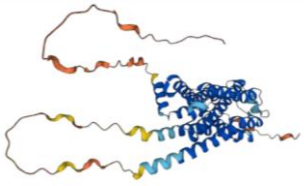
Binding Mode and Molecular Interactions of Glucomannan and the Key Target
On the basis of the docking results between the ligand and the receptor, the energy conformation of the ligand and the receptor were obtained (Table 3). The lowest binding affinity value of -9.6 kcal/mol

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

was obtained for the docking of glucomannan with GAA, and the highest binding affinity of -6.0 kcal/mol was obtained for the docking of glucomannan with INS. Binding affinity is a measure of a drug's ability to bind to a receptor, the lower the binding affinity value, the higher the affinity between the receptor and the ligand.[11] Conversely, the higher the binding affinity value, the lower the affinity between the receptor and the ligand. Similarly, the lower the binding energy obtained, the better the docking effect.[29] Binding energy of less than -5 kcal/mol, indicates that the target has some binding affinity for the compound.[30] The binding affinity score from the docking of all key targets and glucomannan were lower than -5 kcal/mol.

Based on the results of the 2D visualization, it was found that the key target that produced the most hydrogen bonds with glucomannan was MANBA, which were 10 hydrogen bonds in the ARG125, ARG206, LYS317, LYS320, LYS441, LEU215, ARG442, SER445, GLU208, and HIS214 amino acid residues. The amino acids involved in the formation of this enzyme further suggest that these amino acids are involved in the binding interaction of the molecule at the binding site.[31] If a drug molecule has hydrogen bonding interactions both intermolecular and intramolecular, then the compound will be effective at low concentrations, and modification in the chemical structure will result in changes in its biological activity, state of equilibrium, and water solubility.[32]

Table 2: The Macromolecular Structure of the Key Target Proteins of Glucomannan

No	Target Name	PDB ID	Structure
1	INS	1BEN	
2	GAA	3WY1	
3	NOS2	3E7G	
4	FTO	4IE5	
5	ADRB3	P13945	

ISSN 2616-0684 (Print)
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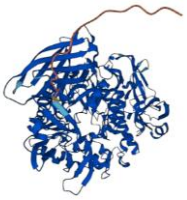
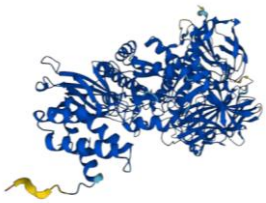
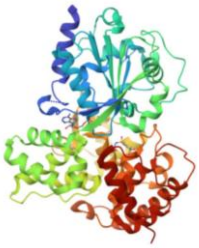
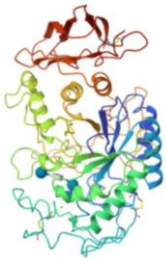
6	MANBA	O00462	
7	MAN2C1	Q9NTJ4	
8	NLRP3	7ALV	
9	AMY1A	1B2Y	

Comparison of glucomannan with synthetic drugs

The key target with the lowest binding affinity after docking with glucomannan is GAA (PDB ID: 3WY1), suggesting that the most likely mechanism of action of glucomannan is through inhibition of α-glucosidase. Glucomannan attaches to the binding sites of α-glucosidase due to its structural similarity to disaccharides or oligosaccharides.[33] We compared the mode of binding and binding affinity values of glucomannan with synthetic α-glucosidase inhibitors, namely; acarbose and miglitol. Modeling and docking studies allow detailed analysis and inference of the binding interactions between these derivatives and the catalytic site of the target protein, thus, providing a plausible explanation and a better understanding of the potent binding inhibition.[32]

Table 4 shows the binding affinity value of glucomannan (-9.6 kcal/mol) which is almost the same as that of acarbose (-9.7 kcal/mol), while miglitol has a much different value (-5.4 kcal/mol). In addition, acarbose has more hydrogen bonding modes than glucomannan and miglitol, namely; at the amino acids GLN531, ASN443, TYR530, ASP441, ASN447, HIS348, LYS352, GLU432, ARG437, ASP441, and HIS348. This shows that the inhibitory activity of glucomannan is almost the same as that of acarbose. However, further *in-vitro* analysis is needed to prove this. The best explanation for this high activity of glucomannan could be attributed to many factors such as hydrogen bonding (H-bonding), pi-pi interactions, and van der Waals interactions.[32]

Acarbose and glucomannan bind to the same binding site while miglitol binds to a different site (Figure 4). This shows that glucomannan has the same α-glucosidase enzyme inhibitory mechanism as acarbose. The primary mode of action of α-glucosidase inhibitors may involve several mechanisms; including the competitive and noncompetitive (alosteric) inhibition of glucose uptake from carbohydrates, and noncompetitive inhibition of α-glucosidase.[34]

Conclusion

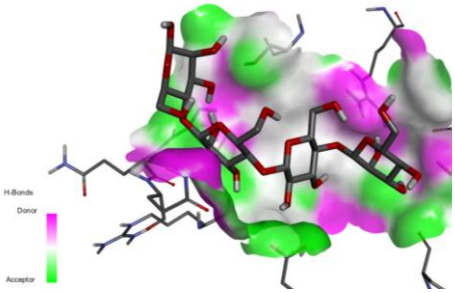
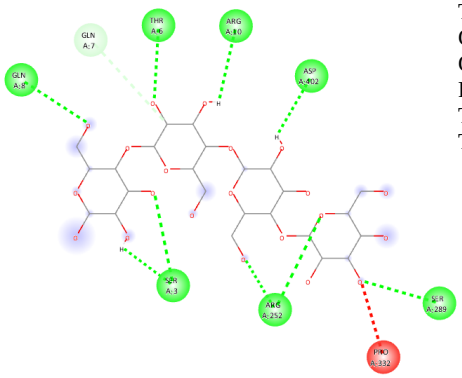
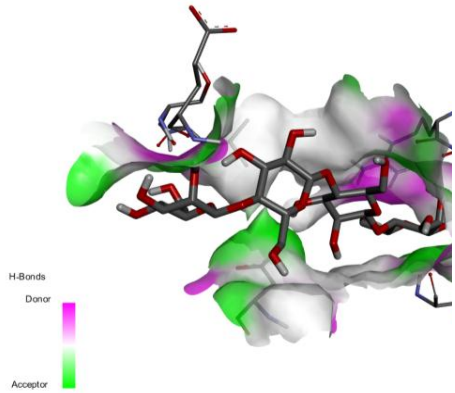
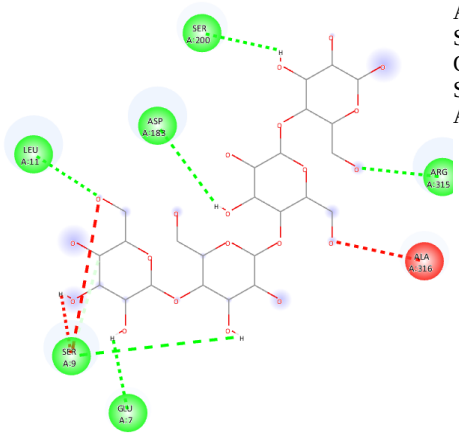
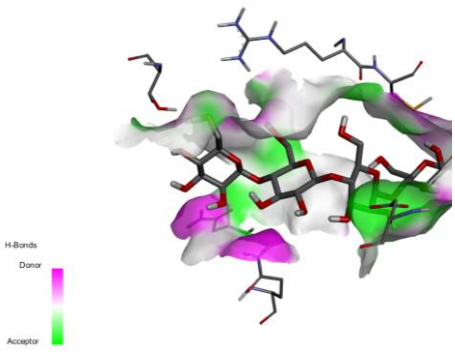
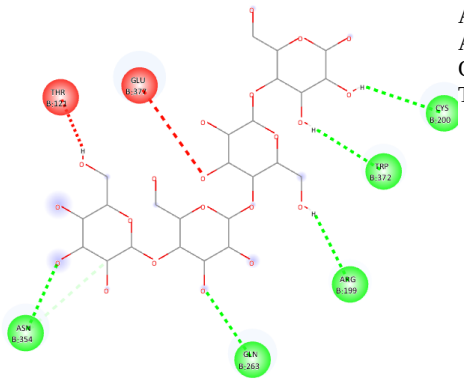
The mechanism of action of glucomannan as a potential therapeutic agent against T2DM has been explored in this study using network pharmacology and molecular docking. Based on network pharmacology analysis constructed by cytoscape, there are nine (9) key targets related to the pathogenesis of T2DM. The molecular docking between the nine key targets and glucomannan resulted in the prediction of the docking interaction between glucomannan and GAA with the lowest binding affinity (α-glucosidase PDB ID: 3WY1). The subsequent docking with acarbose and miglitol, both synthetic drugs with the same mechanism, yielded almost the same binding affinity scores for 3WY1 with acarbose having binding affinity of -9.7 kcal/mol and glucomannan having binding affinity of -9.6 kcal/mol. Glucomannan and acarbose attach to the same binding sites in 3WY1. Based on the results of molecular docking, the most probable mechanism of action of glucomannan is inhibition of α-glucosidase. Therefore, glucomannan can be used as an alternative to acarbose in the treatment of T2DM.

Conflict of Interest

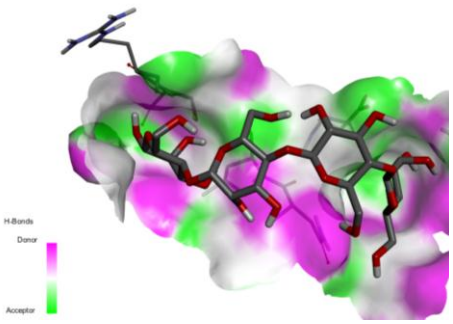
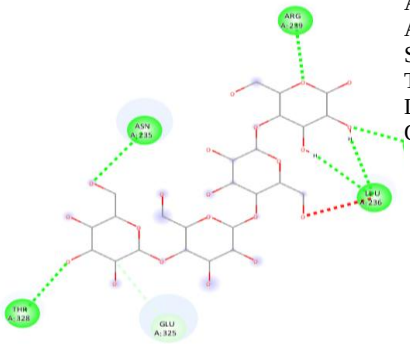
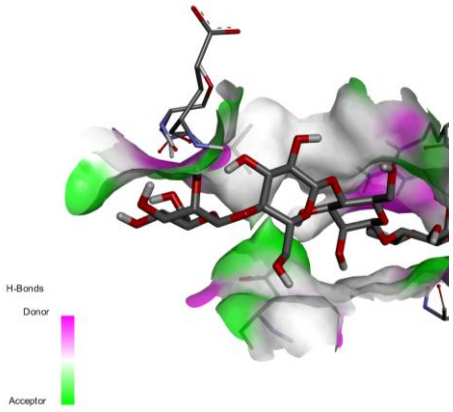
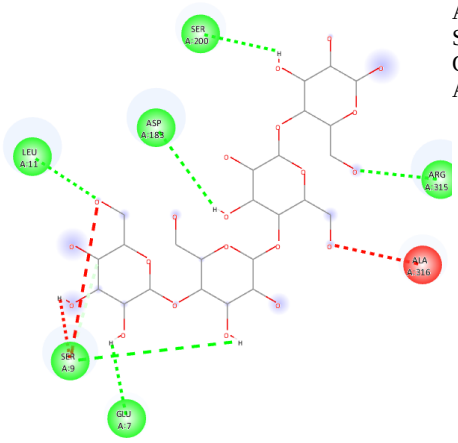
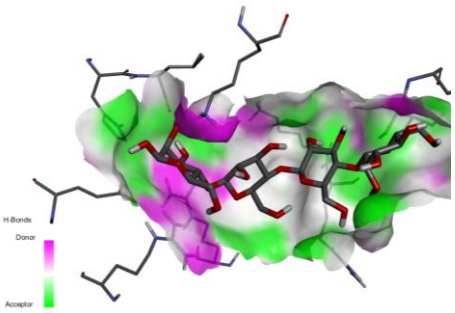
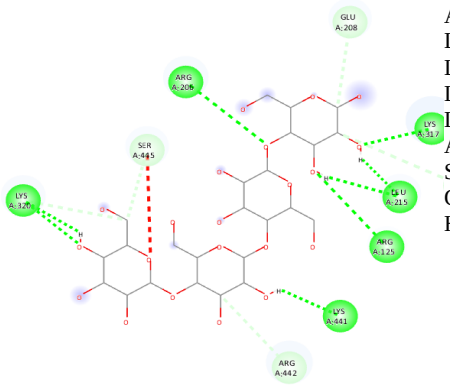
The authors declare no conflict of interest.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 3: Docking Result of Glucomannan with Key Targets of T2DM

Key Target	Binding Affinity (kcal/mol)	3D pose	2D interaction	H Bond
INS	-6.0			PHE25 THR27 CYS20 GLU4 PRO28 TYR19 THR27
				
GAA	-9.6			LEU11 ARG315 SER9 GLU7 SER200 ASP183
				
NOS2	-7.2			GLN263 ASN354 ARG199 CYS200 TRP372
				

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

FTO	-6.7			ASN235 ARG239 SER240 THR328 LEU236 GLU325
				
ADRB3	-7.0			LEU11 ARG315 SER9 GLU7 ASP183
				
MANBA	-8.9			ARG125 ARG206 LYS317 LYS320 LYS441 LEU215 ARG442 SER445 GLU208 HIS214
				

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ISSN 2616-0692 (Electronic)

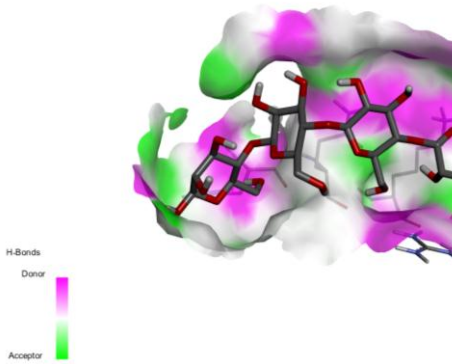
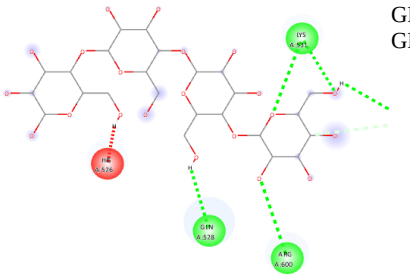
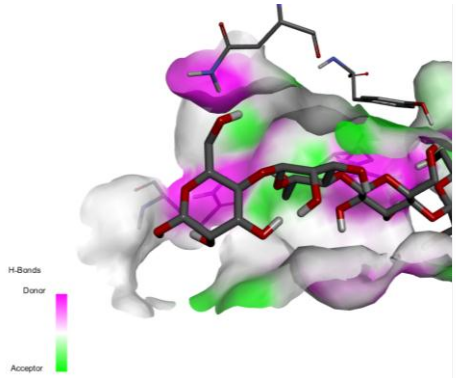
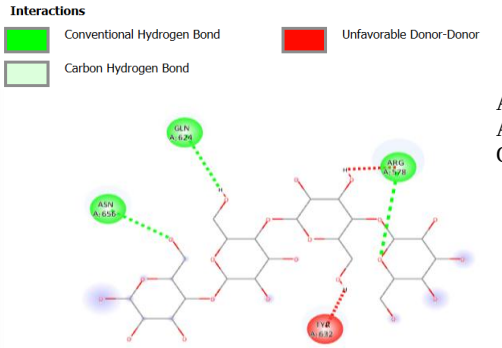
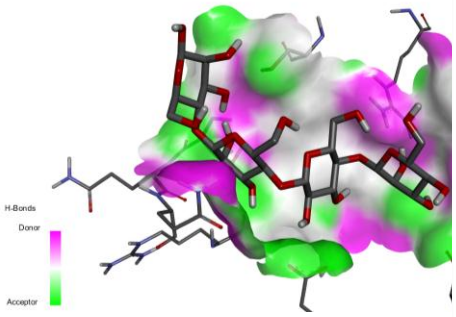
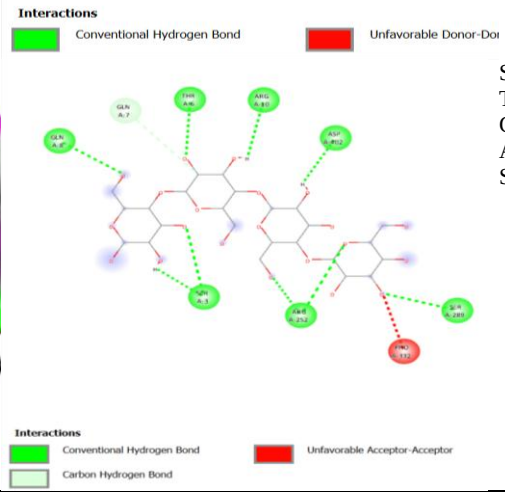
MAN2C1	-7.1			LYS531 ARG600: GLU535 GLN528
NLRP3	-7.3			ARG578 ASN656 GLN624
AMY1A	-7.3			SER3 THR6 GLN8 ARG252 SER289

Table 4: Docking Result of Glucomannan and Synthetic Drugs against the Target GAA (PDB ID: 3WY1)

Ligand	Binding Affinity (kcal/mol)	H Bond
Glucomannan	-9.6	LEU11; ARG315; SER9; GLU7; SER200; ASP183
Acarbose	-9.7	GLN531; ASN443; TYR530; ASP441; ASN447; HIS348; LYS352; GLU432; ARG437; ASP441; HIS348
Miglitol	-5.4	VAL380; ALA378:O; GLU377

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.\

Acknowledgments

The authors are grateful to Universitas Indonesia and Center for Standardization and Services for the Pharmaceutical Chemical and Packaging Industry for facilitating the research. The authors also thank Ika Widiawati and Retno Yunilawati for their support.

References

1. Hackett RA and Steptoe A. Type 2 diabetes mellitus and psychological stress-a modifiable risk factor. Nat Rev Endocrinol. 2017;13(9):547–560.
2. Hui H, Tang G, Go VLW. Hypoglycemic herbs and their action mechanisms. Chin Med. 2009; 4:11.
3. Bibi S, Kalsoom S, Rashid H. Ligand based approach for pharmacophore generation for identification of novel compounds having antidiabetic activity. Int J Pharm Pharm Sci. 2013; 5(SUPPL.4):303–314.
4. Do NHN, Truong QT, Le PK, Ha AC. Recent developments in chitosan hydrogels carrying natural bioactive compounds. Carbohydr Polym. 2022; 294:119726.
5. Wardhani DH, Cahyono H, Dwinanda MFH, Nabila PR, Aryanti N, Pangestuti DR. Effect of KOH as Deacetylation Agent on Physicochemical Properties of Glucomannan. J Phys Conf Ser. 2019; 1295:012037.
6. Luo W, Liu F, Qi X, Dong G. Research progress of konjac dietary fibre in the prevention and treatment of diabetes. Food Sci Technol. 2022; 42:
7. Safitri AH, Widayati E, Tyagita N.Enhancing Metabolic Parameters: The Impact of Porang Glucomannan on Body Weight, Intraperitoneal Fat, Fasting Blood Glucose, and GLUT-4 Levels in Rats Fed a High-Fat and High-Carbohydrate Diet. Trop J Nat Prod Res. 2023; 7:3198–3202.
8. Suryana EA, Kamsiati E, Usmiati S, Herawati H. Effect of Porang Flour and Low-Calorie Sugar Concentration on the Physico-Chemical Characteristics of Jelly Drinks. IOP Conf Ser Earth Environ Sci. 2022; 985(1):1–8.
9. Zhao Y, Jayachandran M, Xu B. *In vivo* antioxidant and anti-inflammatory effects of soluble dietary fiber Konjac glucomannan in type-2 diabetic rats. Int J Biol Macromol. 2020; 159:1186–1196.
10. Du Q, Liu J, Ding Y. Recent progress in biological activities and health benefits of konjac glucomannan and its derivatives. Bioact Carbohydr Diet Fibre. 2021; 26:100270.
11. Tasakka ACMAR, Iskandar IW, Sulfahri, Suyono EA, Dewi EN, Yuwono M, et al. Molecular docking analysis of selected natural products from Halymenia sp. and Laurencia sp. seaweeds against plasmepsins as antimalarials. IOP Conf Ser Earth Environ Sci. 2022; 1119(1):012048.
12. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. update. Nucleic Acids Res. 2023;51(D1):D1373–80.
13. Dallakyan S and Olson A. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015; 1263:243–250.
14. Si Y, Liu X, Ye K, Bonfini A, Hu XY, Buchon N, et al. Glucomannan hydrolysate promotes gut proliferative homeostasis and extends life span in *Drosophila melanogaster*. J Gerontol - Ser A Biol Sci Med Sci. 2019; 74(10):1549–1556.
15. Ataie-Ashtiani S and Forbes B. A Review of the Biosynthesis and Structural Implications of Insulin Gene Mutations Linked to Human Disease. Cells. 2023; 12(7):1008.
16. Cerón-Rodríguez M, Castillo-García D, Acosta-Rodríguez-Bueno CP, Aguirre-Hernández J, Murillo-Eliosa JR, Valencia-Mayoral P, Sancez E, Loza S. Classic infantile-onset Pompe disease with histopathological neurologic findings linked to a novel GAA gene 4 bp deletion: A case study. Mol Genet Genomic Med. 2022; 10(7):1–9.
17. Gallorini M, Rapino M, Schweikl H, Cataldi A, Amoroso R, Maccallini C. Selective inhibitors of the inducible nitric oxide synthase as modulators of cell responses in LPS-stimulated human monocytes. Molecules. 2021; 26(15):4419.
18. Gusti AMT, Qusti SY, Bahijri SM, Toraih EA, Bokhari S, Attallah SM, Alzahrani A, Alshehri A, Alotaibi H, Fawzy M. Glutathione s-transferase (GSTT1 rs17856199) and nitric oxide synthase (nos2 rs2297518) genotype combination as potential oxidative stress-related molecular markers for type 2 diabetes mellitus. Diabet Metab Syndr Obes. 2021; 14:1385–1403.
19. Huang S, Qin P, Chen Q, Zhang D, Cheng C, Guo C, Li Q, Zhou Q, Tian G, Qie R, Han M, Wu X, Yang X, Feng Y, Li Y, Zhang Y, Wu Y, Liu D, Lu J, Zhang M, Zhao Y, Hu D. Association of FTO gene methylation with incident type 2 diabetes mellitus: A nested case–control study. Gene. 2021; 786:145585.
20. Velazquez-Roman J, Angulo-Zamudio UA, León-Sicairos N, Medina-Serrano J, DeLira-Bustillos N, Villamil-Ramírez, H, Medina-Serrano J, DeLira-Bustillos N, Villamil-Ramírez H, Canizales-Quinteros S, Macías-Kauffer L, Campos-Romero A, Alcántar-Fernández J, Canizalez-Roman A. Association of FTO, ABCA1, ADRB3, and PPARG variants with obesity, type 2 diabetes, and metabolic syndrome in a Northwest Mexican adult population. J Diabet Complic. 2021; 35(11):108025.
21. Sabourdy F, Labauge P, Stensland HMFR, Nieto M, Garcés VL, Renard D, Castelnovo G, de Champfleur N, Levade T. A MANBA mutation resulting in residual beta-mannosidase activity associated with severe leukoencephalopathy: A possible pseudodeficiency variant. BMC Med Genet. 2009; 10:84.
22. Wang L and Suzuki T. Dual functions for cytosolic α-mannosidase (Man2C1) its down-regulation causes mitochondria-dependent apoptosis independently of its α-mannosidase activity. J Biol Chem. 2013; 288(17):11887–11896.
23. Ding S, Xu S, Ma Y, Liu G, Jang H, Fang J. Modulatory mechanisms of the NLRP3 inflammasomes in diabetes. Biomol. 2019; 9(12):1–15.
24. Shin D and Lee KW. Dietary carbohydrates interacts with AMY1 polymorphisms to influence the incidence of type 2 diabetes in Korean adults. Sci Rep. 2021; 11(1):1–8.
25. Zia F, Zia KM, Zuber M, Ahmad HB, Muneer MI. Glucomannan based polyurethanes: A critical short review of recent advances and future perspectives. Int J Biol Macromol. 2016; 87:229-236.
26. Chua M, Baldwin TC, Hocking TJ, Chan K. Traditional uses and potential health benefits of Amorphophallus konjac K. Koch ex N.E.Br. J Ethnopharmacol. 2010; 128(2):268–278.
27. Crampon K, Giorkallos A, Deldossi M, Baud S, Steffenel LA. Machine-learning methods for ligand–protein molecular docking. Drug Discov Today. 2022; 27(1):151–164.
28. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20:13384–13421.
29. Yin B, Bi YM, Fan GJ, Xia YQ. Molecular mechanism of the effect of Huanglian Jiedu decoction on type 2 diabetes mellitus based on network pharmacology and molecular docking. J Diabet Res. 2020; 2020:5273914.
30. Gaillard T. Evaluation of AutoDock and AutoDock Vina on the CASF-2013 Benchmark. J Chem Inf Model. 2018; 58(8):1697–1706.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

31. Singh G. *In silico* screening and pharmacokinetic properties of phytoconstituents from Ferula asafoetida H.Karst. (Heeng) as potential inhibitors of α-amylase and α-glucosidase for Type 2 Diabetes Mellitus. J Diabet Metab Disord. 2022; 21(2):1339-1347.
32. Ibrahim SRM, Mohamed GA, Khayat MTA, Ahmed S, Abo-Haded H. α-Amylase inhibition of xanthones from Garcinia mangostana pericarps and their possible use for the treatment of diabetes with molecular docking studies. J Food Biochem. 2019; 43(5):1–10.
33. Proença C, Freitas M, Ribeiro D, Oliveira EFT, Sousa JLC, Tomé SM, Ramos M, Silva A, Fernandes P, Fernandes E. α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. J Enzyme Inhib Med Chem. 2017; 32(1):1216-1228.
34. Assefa ST, Yang E young, Chae S young, Song M, Lee J, Cho MC, Jang S. Alpha Glucosidase Inhibitory Activities of Plants with Focus on Common Vegetables. Plants (Basel). 2019; 9(1):2.
35. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, Stein TI, Nudel R, Lieder I, Mazor Y, Kaplan S, Dahary D, Warshawsky D, Guan-Golan Y, Kohn A, Rappaport N, Safran M, Lancet D. The GeneCards suite: From gene data mining to disease genome sequence analyses. Curr Protoc Bioinforma. 2016; 54:1.30.1-1.30.33.
36. Mpo CO and Summary UND. National Center for Biotechnology Information (2023) PubChem CID 24892726 Structure. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Glucomannan