

4 **Anti-Diabetic Potential of Bitter Melon and Fenugreek Based on**
5 **Centrality Analysis and Molecular Docking against Diabetes**
6 **Mellitus**

7
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19
20 **ABSTRACT**

21 Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by
22 progressive destruction of pancreatic beta cells, resulting in absolute insulin
23 deficiency. Despite advances in insulin therapy, the underlying autoimmune
24 mechanism remains inadequately addressed. Medicinal plants such as *Momordica*
25 *charantia* (bitter melon) and *Trigonella foenum-graecum* (fenugreek) have shown
26 antidiabetic potential, but their therapeutic mechanisms in T1DM remain poorly
27 understood. This study aims to elucidate the molecular mechanisms of bioactive
28 compounds from *M. charantia* and *T. foenum-graecum* in the pathogenesis of T1DM
29 through tissue pharmacology, centrality analysis, and molecular docking. Target
30 proteins associated with T1DM were obtained from the OMIM, MalaCards,
31 GeneCards, and UniProt databases. Bioactive compounds from both plants were
32 collected from IJAH Analytics and KNApSack Family. Protein-protein interaction (PPI)
33 networks were constructed using the STRING database, followed by centrality
34 analysis (degree, betweenness, closeness, and eigenvector centrality) to identify key
35 proteins. The consensus method was applied to select the top 5 hub proteins. Drug-
36 likeness and ADME properties were predicted using SwissADME and Molsoft.
37 Molecular docking was performed using AutoDock Vina to evaluate the binding affinity
38 between bioactive compounds and target proteins. Network pharmacology identified
39 5 DMT1-related proteins and 33 bioactive compounds. Centrality analysis revealed

five hub proteins critically involved in DMT1 pathogenesis. This approach demonstrated that bioactive compounds from *M. charantia* and *T. foenum-graecum* exert therapeutic effects on DMT1 through a multi-target mechanism, providing scientific evidence for their potential as alternative treatments.

Key words: Centrality analysis; Molecular docking; *Momordica charantia*; Tissue pharmacology; *Trigonella foenum-graecum*; Type 1 diabetes mellitus

INTRODUCTION

In 2021, an estimated 8.4 million people worldwide are living with type 1 diabetes (T1D), with a prevalence of 1.5 million (18%) in children and adolescents under the age of 20 [1]. The annual incidence of T1DM in children and adolescents reached 22.0 per 100,000 population, with variations based on age group from 14.6 in children aged 0-4 years to 32.0 in adolescents aged 10-14 years [2]. The prevalence of T1DM has shown a significant increase in recent decades, with projections reaching 13.5-17.4 million cases by 2040, representing a 60-107% increase compared to 2021 [1], [3]. T1DM is a chronic autoimmune disease characterized by the destruction of pancreatic beta cells mediated by autoreactive T cells, leading to absolute insulin deficiency and lifelong dependence on exogenous insulin therapy [4], [5]. This condition contributes to various long-term complications, including diabetic retinopathy, which is the leading cause of blindness in productive age, diabetic nephropathy that can progress to kidney failure, diabetic neuropathy, and an increased risk of cardiovascular disease that significantly increases mortality and morbidity [6], [7], [8]. T1DM occurs due to a complex interaction between genetic factors, particularly human leukocyte antigen (HLA) alleles, and environmental factors such as viral infections that trigger an autoimmune response, in which the immune system mistakenly attacks and destroys insulin-producing cells in the pancreas [4], [9]. The global increase in the incidence of T1DM, especially in younger age groups, and its pathophysiological complexity demand a deeper understanding of autoimmune mechanisms and management strategies to prevent complications and improve the quality of life of patients.

In recent years, the immune system and pancreatic beta cells have become the main focus in studies of the pathogenesis of type 1 diabetes mellitus due to their significant role in the interaction between genetic, environmental, and autoimmune factors and the destruction of insulin-producing cells [4], [10], [11]. Pancreatic beta cells also play a crucial role in regulating blood glucose levels, insulin secretion, and metabolic homeostasis [12], [13], [14]. There are two main phases in the pathogenesis

of T1DM: the presymptomatic phase, characterized by positive autoantibodies but preserved beta cell function (Stages 1 and 2), and the symptomatic phase, with clinical manifestations due to extensive beta cell destruction (Stage 3) [15], [16]. The presymptomatic phase is characterized by the infiltration of autoreactive lymphocytes into the islets of Langerhans (insulinitis), while the symptomatic phase is characterized by absolute insulin deficiency and dependence on exogenous insulin therapy [17], [18]. T1DM can cause beta cell dysfunction in insulin secretion due to an autoimmune response mediated by cytotoxic CD8⁺ T cells and helper CD4⁺ T cells that release proinflammatory cytokines [19], [20]. Beta cell destruction occurs through an apoptotic mechanism triggered by proinflammatory cytokines such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) released by infiltrating immune cells [21], [22]. Massive beta cell destruction in T1DM leads to loss of glycemic control and an increased risk of microvascular and macrovascular complications, significantly increasing morbidity and mortality [7]. Additionally, absolute insulin deficiency in T1DM triggers increased lipolysis and ketogenesis, which can progress to diabetic ketoacidosis, a life-threatening acute condition characterized by the accumulation of ketone bodies (β -hydroxybutyrate and acetoacetate) in the blood [23].

The network pharmacology approach has been widely used to explore the potential of bioactive compounds from herbal plants and determine their therapeutic capabilities in type 1 diabetes mellitus and other autoimmune diseases [24], [25]. This method allows the identification of molecular targets relevant to the pathogenesis of T1DM, including inflammatory pathways, beta cell apoptosis, and immune response modulation [26]. In addition to the use of a network pharmacology approach, one of the contributions of this study is the application of centrality analysis, a technique used in the identification of key nodes in complex biological networks, to the domain of protein-protein interaction (PPI) networks, particularly in the selection of target proteins that play a central role in the pathogenesis of T1DM [27]. Centrality analysis, which includes degree centrality (measuring the number of direct connections of a protein), betweenness centrality (measuring the frequency of a protein as a bridge in the shortest path), and closeness centrality (measuring the average proximity of a protein to all other proteins), has been proven effective in identifying potential therapeutic targets in various complex diseases, including diabetes [27], [28], [29]. Proteins with high centrality values tend to play a crucial role in cellular function and are more effective drug target candidates than ordinary proteins [29], [30]. The use of centrality

methods in the context of DMT1 allows the identification of key proteins that can be modulated by herbal bioactive compounds to inhibit the progression of autoimmunity and protect pancreatic beta cells [24], [27].

In the context of exploring bioactive compounds for T1DM, this study focused on two herbal plants with significant therapeutic potential, namely bitter melon (*Momordica charantia*) and fenugreek (*Trigonella foenum-graecum*). Bitter melon is a herbal plant originating from Africa and later spread widely to Asia, South America, India, East Asia, and the Caribbean, with major domestication occurring in eastern India and southern China [31]. This plant has various pharmacological activities, including antidiabetic effects through insulin secretion modulation and GLUT4 translocation [32], [33], antioxidant and anti-inflammatory effects, and pancreatic beta cell protection through NF- κ B and JNK pathway modulation [33]. *M. charantia* has been reported to contain cucurbitane-type triterpenoids such as charantin, momordicin, and momordicoside [34], p-insulin-like polypeptides [33], saponins, flavonoids, alkaloids, and galactomannans [32]. Kelabat is a plant native to the Middle East and Asia, which has spread to India, Nepal, Africa, and is widely cultivated in Asia and Africa [35]. This plant has diverse pharmacological activities, including antidiabetic effects through increased GLUT4 translocation, hexokinase activity, and α -amylase inhibition [36], [37], antioxidant, anti-inflammatory, antihyperlipidemic, and GLP-1 modulation and DPP-IV inhibition effects [36]. *T. foenum-graecum* is reported to contain soluble galactomannan fiber (approximately 50% of the seeds) that plays a role in glycemic control [35], [36], alkaloids such as trigonelline, steroid saponins such as diosgenin and protodioscin, flavonoids such as quercetin, apigenin, and luteolin, the amino acid 4-hydroxyisoleucine which has insulinotropic activity [37], and phenolic compounds [36].

Although *M. charantia* and *T. foenum-graecum* have been extensively studied as antidiabetic agents in type 2 diabetes mellitus, there has been no comprehensive study exploring their mechanism of action as therapeutic agents for type 1 diabetes mellitus using a network pharmacology approach with centrality analysis and in silico validation. This study aims to answer these questions by investigating the mechanisms of the active compounds found in *M. charantia* and *T. foenum-graecum* using a centrality-based network pharmacology approach, as well as screening for target proteins associated with the pathogenesis of T1DM through protein-protein interaction

network analysis. The results of the study were validated using molecular docking to predict the binding affinity of target compounds and proteins.

MATERIALS AND METHODS

Network Pharmacology

Screening of protein targets. Target proteins were identified based on diseases and active compounds from *Momordica charantia* and *Fenugreek*. Target proteins related to Type 1 Diabetes Mellitus were obtained from the OMIM database (<https://www.omim.org/>) [38], IJAH Analytics (<http://ijah.apps.cs.ipb.ac.id/>), MalaCards (<https://www.malacards.org/>) [39], GeneCards (<https://www.genecards.org/>) [40], and UniProt (<https://www.uniprot.org/>) [41]. The keyword used was “Type 1 Diabetes Mellitus”.

Target proteins associated with active compounds were collected from (<http://ijah.apps.cs.ipb.ac.id/>) and Knapsackfamily (https://www.knapsackfamily.com/knapsack_core/top.php) [42] using the keywords “*Momordica Charantia*” and “*Fenugreek*” as search inputs.

The final data on plant proteins and disease proteins, after removing duplicates, were entered into Venny, yielding an intersection containing data on the sets of plant and disease proteins that are mutually related.

Protein-protein interaction (PPI) network. The targets obtained from the intersection in Venny were previously analyzed using the STRING database (<https://string-db.org/>) [43] with the Multiple Proteins feature and the “Organism” section selected as *Homo Sapiens*. The parameters used to search for PPI data were the full STRING network type and a medium confidence score of 0.400. The results were exported as PNG images and downloaded as .TSV files.

Centrality Analysis. The .TSV files from StringDB were converted into an Adjacency Matrix, then the values for Degree Centrality, Betweenness Centrality, Closeness Centrality, and Eigenvector Centrality were calculated [27], [28], [29]. All calculations were performed using the Python programming language.

Consensus Method. Selection of the top 5 from the previous Centrality results. Proteins recorded in the four Centrality criteria will be filtered. The results of the filtering will be calculated as the average for each remaining protein, then the top 5 largest will be selected based on the average results of each.

Drug-likeness and ADME prediction

Duplicates in the plant active compound data obtained will be removed using Venny (<https://bioinfogp.cnb.csic.es/tools/venny/>). After that, the data will be filtered using the parameters Bioavailability Score ≥ 0.5 and Drug Likeness > 0 . The SwissAdme website (<http://www.swissadme.ch/>) [44] will be used to find the bioavailability score and the Molsoft website (<https://molsoft.com/mprop/>) to find drug likeness. The plant active compounds that meet the criteria will be predicted for their target proteins using SwissTargetPrediction (<https://www.swisstargetprediction.ch/>) [45].

Molecular Docking

The top 5 receptor structures were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>) [46] and selected using parameters of resolution below 2.50 Å and wwPDB validation values where all lines leaned more towards blue. The 3D structure of the ligand was obtained through PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) [47]. Proteins and ligands were prepared using AutoDockTools [48], For the receptor, water was deleted, the ligand carried by the receptor was removed (which can be checked via the web (<https://proteins.plus/>) [49]), add hydrogens (*Polar Only*), add *Kollman Charges*, then Macromolecule and Choose receptor were selected, after which it was saved as .PDBQT. For the ligand, import the PDB file and select the output to save as .PDBQT. The location of the binding site is determined based on the ligand, so in the Grid Box, make sure to select Center On Ligand. Molecular docking was performed using AutoDock Vina 1.2.7 [50] in AutoDockTools. The docking results are visualized using PyMOL (<https://pymol.org/2/>) for 3D visualization.

RESULTS AND DISCUSSION

Network Pharmacology

There are 5 T1DM target proteins obtained from OMIM, 90 from UniProt, 162 from MalaCards, and 392 from GeneCards. After removing duplicates, the final result of type 1 diabetes mellitus target proteins was 571 proteins. Active compounds from plants were also searched for in IJAH and KnapsackFamily. For Pare, 191 compounds were found, and for Kelabat, 75 compounds were found.

Drug-likeness of the compounds

The bioavailability score and drug likeness of the compounds obtained previously from both Pare and Kelabat were calculated and selected using the parameters Bioavailability Score ≥ 0.5 and Drug Likeness > 0 . The results were 66 compounds from 191 compounds for Pare, while for Kelabat, 15 compounds were obtained from 75 compounds.

ADME Prediction

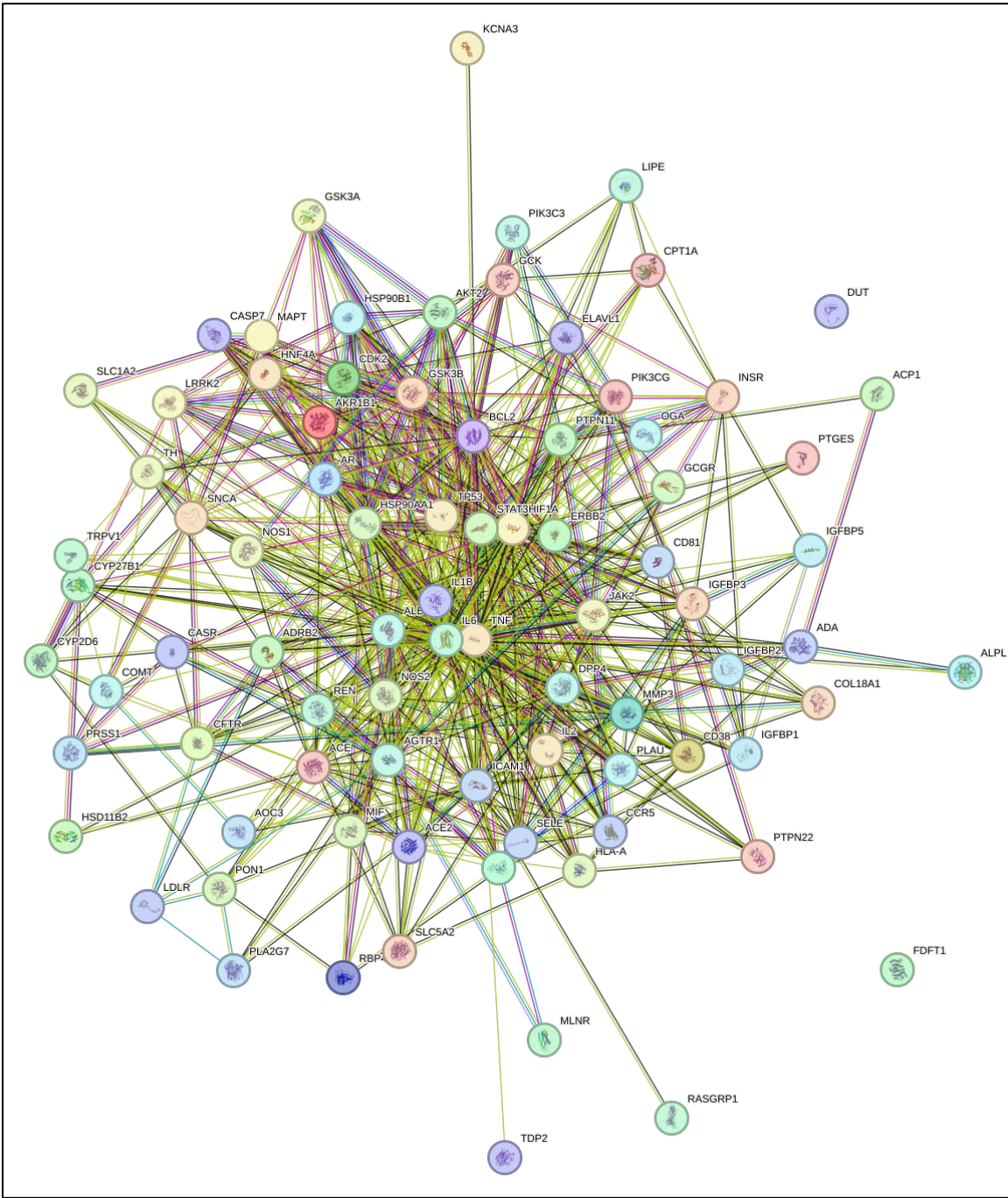
All compounds from Pare and Kelabat after selection will be predicted for proteins related to those compounds using SwissTargetpPrediction. 66 Pare compounds produced 6540 protein data, after removing duplicates, 819 proteins were found. 15 Kelabat compounds produced 1300 protein data, after removing duplicates, 560 proteins were found.

Protein Target

In Venny, 819 Pare proteins and 560 Kelabat proteins were removed, resulting in 949 proteins. After that, 571 type 1 diabetes mellitus proteins were compared with 949 plant proteins, resulting in a total of 85 related proteins.

Protein-protein Interaction

In the STRING section Multiple Proteins, 85 slice proteins that had been obtained were entered. Then the results of the images of the nodes between proteins were given as follows,



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84 nodes were generated. From this, a .TSV file was obtained containing the values between these nodes, which were then used to create the following adjacency matrix

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	ACE	ACE2	ACP1	ADA	ADR2	AGTR1	AKR1B1	AKT2	ALB	ALPL	AOC3	AR	BCL2	CASP7	CASR	CCR5	CD38	CD81	
2	ACE	0	0,956	0	0	0,552	0,974	0,481	0	0,912	0	0	0	0,403	0	0	0,401	0	0
3	ACE2	0,956	0	0	0	0	0,996	0	0	0,862	0	0	0,418	0	0	0	0,526	0	0
4	ACP1	0	0	0	0,432	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	ADA	0	0	0,432	0	0	0	0	0	0,576	0,451	0	0	0	0	0	0	0,401	0
6	ADR2	0,552	0	0	0	0	0,873	0	0	0,432	0	0	0	0	0	0	0	0	0
7	AGTR1	0,974	0	0	0	0	0	0	0	0,665	0	0	0	0	0	0,511	0	0	0
8	AKR1B1	0,481	0	0	0	0	0	0	0	0,503	0	0	0	0	0	0	0	0	0
9	AKT2	0	0	0	0	0	0	0	0	0	0	0	0	0,95	0	0	0	0	0
10	ALB	0,912	0	0	0	0	0	0	0	0	0,404	0,506	0,534	0,748	0,423	0,46	0,497	0,554	0,586
11	ALPL	0	0	0	0,451	0	0	0	0	0,404	0	0	0	0	0	0	0	0	0
12	AOC3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	AR	0	0	0	0	0	0	0	0	0	0	0	0	0,623	0	0	0	0	0
14	BCL2	0,403	0	0	0	0	0	0	0,95	0	0	0	0	0	0,857	0	0,411	0,724	0
15	CASP7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	CASR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	CCR5	0,401	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,693	0
18	CD38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,691
19	CD81	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	CDK2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

This adjacency matrix will be analyzed using a Python script with Centrality Analysis, and the top 10 results from 84 nodes based on Betweenness, Closeness, Degree, and Eigenvector are as follows:

Top 10 nodes by Eigenvector Centrality:		Top 10 nodes by Betweenness Centrality:		Top 10 nodes by Closeness Centrality:		Top 10 nodes by Degree Centrality:	
Eigenvector Centrality		Betweenness Centrality		Closeness Centrality		Degree Centrality	
IL6	0.26435	TNF	0.13117	IL6	0.835052	IL6	0.802469
TNF	0.258701	ALB	0.12803	TNF	0.818182	TNF	0.777778
IL1B	0.247604	IL6	0.126724	ALB	0.794118	ALB	0.740741
ALB	0.247293	IL1B	0.078047	IL1B	0.771429	IL1B	0.703704
TP53	0.212936	BCL2	0.058458	TP53	0.692308	TP53	0.567901
STAT3	0.208253	TP53	0.050582	STAT3	0.663934	BCL2	0.518519
BCL2	0.201839	ICAM1	0.038537	BCL2	0.663934	STAT3	0.493827
HIF1A	0.198352	AGTR1	0.031268	HIF1A	0.658537	HIF1A	0.481481
HSP90AA1	0.17547	HIF1A	0.024541	ICAM1	0.623077	HSP90AA1	0.419753
ICAM1	0.17134	ACE	0.022938	HSP90AA1	0.618321	ICAM1	0.407407

Consensus was reached on the table above to find which proteins were found in the four categories marked in bold. Then, the average for each protein was calculated to determine the top 5 as follows

AVERAGE	
IL6	0.50714875
TNF	0.49645775

IL1B	0.450196
ALB	0.4775455
TP53	0.38093175
BCL2	0.3606875
HIF1A	0.34072775
ICAM1	0.31009025

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244 So, the top 5 target proteins are IL6, TNF, IL1B, ALB, and TP53. From these five, find
 245 each compound that has these proteins in the SwissTargetPrediction results table.

246 Molecular Docking

247 There are 5 receptors and 33 ligands used for molecular docking using
 248 AutoDock Vina. The binding affinity result is -9.097 kcal/mol for receptor 7X7X against
 249 the ligand (3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one,
 250 also known as ergosta-5,6-epoxide. Not only in 7X7X, ergosta-5,6-epoxide also has
 251 the highest binding affinity value in other receptors, such as -8.336 kcal/mol in 4NI7, -
 252 7.416 kcal/mol in 5M2J, and -3.752 kcal/mol in 8RCI. In second place is Decortinone,
 253 which has binding affinity values of -8.155, -7.997, and -6.629 for 7X7X, 4NI7, and
 254 5M2J, respectively.

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4NI7		
No.	Compound/Ligand	Binding Affinity (kcal/mol)
1	(3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one	-8.336
2	Decortinone	-7.997
3	(-)-beta-Sitosterol	-7.164

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5M2J

No.	Compound/Ligand	Binding Affinity (kcal/mol)
1	(3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one	-7.416
2	Decortinone	-6.629
3	Apigenin 7-O-beta-D-glucopyranoside	-5.627

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7X7X		
No.	Compound/Ligand	Binding Affinity (kcal/mol)
1	(3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one	-9.097
2	Decortinone	-8.155
3	Momordicine I	-6.616

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8C3U		
No.	Compound/Ligand	Binding Affinity (kcal/mol)
1	13beta,28-Epoxy-11-ursen-3-one	-3.863
2	(-)-beta-Sitosterol	-3.826
3	Biochanin A	-3.744

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8RCI		
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No.	Compound/Ligand	Binding Affinity (kcal/mol)
1	(3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one	-3.752
2	Kuguacin B	-3.75
3	13beta,28-Epoxy-11-ursen-3-one	-3.733

CONCLUSION

In this study, we demonstrate the potential of bitter melon and fenugreek in the treatment and management of type 1 diabetes mellitus based on a network pharmacology approach using Centrality Analysis. We integrated network pharmacology and molecular docking to identify the possible mechanisms of action of these compounds.

The application of Centrality Analysis and Consensus revealed five main targets, namely IL6, TNF, IL1B, ALB, and TP53, which have the potential to be targets in overcoming type 1 diabetes mellitus. We identified 33 potential compounds from the combination of Pare and Kelabat and then performed molecular docking. The molecular docking study results showed good binding between the receptor protein and the ligand. This was demonstrated by the evidence of binding affinity from docking, which was quite large in (3beta,5alpha,6alpha,22E)-5,6-Epoxy-3-hydroxyergosta-8,22-dien-7-one against 4NI7, 5M2J, 7X7X, and 8RCI.

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ETHICAL STATEMENT

287 Not applicable.

288 CONFLICT OF INTEREST

289 The authors declare no conflict of interest.

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