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Computational study of active compounds of *Citrullus lanatus* Linn peel extract as potential antidiabetics

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ABSTRACT

Diabetes mellitus (DM) is one of the metabolic diseases that have emerged as a global health problem. Type 2 diabetes mellitus (T2DM), which affect 90-95% of DM, is caused by reduced insulin sensitivity and insulin resistance in peripheral tissues. Oral antidiabetics have resulted side effects, prompting an investigation for a natural-based antidiabetic agent as an alternative treatment. Using network pharmacology, we investigated the mechanism of phytochemical substances of *Citrulus lanatus* Linn. peel extract and their interactions with target proteins in the DM pathogenesis pathway. Cytoscape 3.6.1 software has created a network of extract compound-protein targets. Investigation of protein interaction, target gene function enrichment, and signal pathway performed via DAVID, STRING database, and the KEGG pathway database. The computational study identified 90 target proteins associated with T2DM based on protein-protein interactions. In addition, Cytoscape analysis and DAVID enrichment revealed the network of extract compound's target and generated proteins such as INS, TNF-α, IL-6, and AKT2. The KEGG pathway analysis presented the crucial role of insulin resistance and AGE-RAGE signaling pathways. This pathway correlated with lower glucose activity in obesity and hyperglycemia. It indicates that the active constituents of *C. lanatus* Linn peel extract can lower blood sugar levels by interacting with selected proteins. This study's findings will be carried out in further research of *in vitro* trials.

Keywords:
computational study;
KEGG;
PPI;
T2DM;
watermelon peel extract

ABSTRACT

Diabetes melitus (DM) merupakan salah satu penyakit metabolik yang telah menjadi masalah kesehatan global. Diabetes melitus tipe 2 (T2DM), yang menyerang 90-95% penderita DM, disebabkan oleh berkurangnya sensitivitas insulin dan resistensi insulin pada jaringan perifer. Obat antidiabetik oral memiliki efek samping, sehingga mendorong dilakukannya penelitian terhadap agen antidiabetik berbasis bahan alam sebagai pengobatan alternatif. Dengan menggunakan *network pharmacology*, kami meneliti mekanisme senyawa aktif ekstrak kulit buah *Citrulus lanatus* Linn dan interaksinya dengan protein target dalam jalur patogenesis DM. Perangkat lunak Cytoscape 3.6.1 telah membangun jaringan target senyawa ekstrak-protein. Analisis interaksi protein, pengayaan fungsi gen target, dan jalur sinyal dilakukan melalui basis data DAVID, STRING, dan jalur basis data KEGG. Studi komputasional mengidentifikasi 90 protein target yang terkait dengan T2DM berdasarkan interaksi protein-protein. Selain itu, analisis Cytoscape dan pengayaan DAVID mengungkap jaringan target senyawa ekstrak dan protein yang dihasilkan seperti INS, TNF-α, IL-6, dan AKT2. Analisis jalur KEGG menunjukkan peran penting resistensi insulin dan jalur pensinyalan AGE-RAGE. Jalur ini berkorelasi dengan aktivitas glukosa yang lebih rendah pada obesitas dan hiperglikemia. Hal ini menunjukkan bahwa konstituen aktif ekstrak kulit buah *C. lanatus* Linn dapat menurunkan kadar gula darah dengan berinteraksi dengan protein tertentu. Temuan penelitian ini akan dilakukan dalam penelitian lebih lanjut secara *in vitro*.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the metabolic diseases with significant prevalence in the world. According to the International Diabetes Federation (IDF), the global prevalence of T2DM in adults was 536.6 million people (10.5%) in 2021. The global prevalence of T2DM is projected to increase, with a forecast of 7.079 individuals per 100,000 by 2030 and reach 783.2 million people (12.2%) by 2045.[1-3] Most people with diabetes mellitus (DM) undergo T2DM, and over 90% of them are affected by it.[4] Indonesia is among the top 10 countries in Southeast Asia, with the highest prevalence of T2DM at 10.8%. In 2021, the prevalence of DM between the ages of 20-79 yr was 10.6% (19.5 million people).[5] By 2030, it was estimated that 21.3 million people in Indonesia will have diabetes, and it will also be the seventh leading cause of death in the world.[6] A study by the Health Research Association of the Ministry of Health of Republic of Indonesia showed that the prevalence of T2DM in urban areas in Indonesia among 15 yo and above was 5.7%.[7] There are several risk factors for T2DM, including age, genetics, hypertension, dyslipidemia, lack of physical activity, smoking, and stress management. Type-2 DM can be experienced by adults, children, and adolescents aged up to 19 yr.[5]

The primary DM therapy is food treatment by adjusting the patient's diet, while medications can be given when food treatment fails. Sulfonylurea is the most commonly used oral antidiabetic in patients with T2DM.[8] Some undesirable side effects will appear in the long-term use of the drug, including hypoglycemia, lactic acidosis, weight gain, enlargement of the abdomen, and heart toxicity.[9] Therefore, it is necessary to find active compounds derived from natural ingredients as an alternative to diabetes therapy. Indonesia has a wealth of natural plants and potentially a candidate drug based on raw herbal materials. Therefore, a natural ingredients assessment must be conducted to find the active compounds still unknown for pharmacological activity. The World Health Organization (WHO) has also recommended using traditional or herbal medicines to prevent or treat a disease.

Watermelon fruit (*Citrullus lanatus* Linn) peel extract is known to contain many active compounds that has several pharmacological activity, such as antimicrobial, antioxidant, antidiabetes, anti-inflammatory, hepatoprotector, gastroprotector and anti-cancer.[10-13] El Gizawy *et al.*[13] reported that *C. lanatus* Linn peel extracts have cytotoxic activity in the cancer cell. Syachriyani and Firmansyah[14] that *C. lanatus* Linn peel extracts potentially has *in vitro* antihyperglycemic effects by inhibiting the α-glucosidase. However, the active compound that plays a role in the antihyperglycemic effect has not be discovered, yet. Therefore, it is necessary to conduct preliminary study to identify the active compounds that potentially have antihyperglycemic activity. Network pharmacology helps understand the complexity of herbal compounds, which is essential for developing multicomponent, multitarget therapies that can provide synergistic effects against DM.[15,16] This methodology provides comprehensive mechanistic insights that can lead to the discovery of novel, low toxicity antidiabetic by exploiting the complex interactions between multiple bioactive compounds and disease pathways through the use of high-throughput screening bioinformatics.

Pharmacology networks in herbal antidiabetic research offer significant

benefits in discovering and developing effective new antidiabetics, such as cost-effective, comprehensive mechanism insight and highly predictive approaches to identifying and developing effective targets.[15-17] Therefore, the computational study becomes a method that can be used as an initial step to identify the candidate active compound of an extract that plays a role in a disease.[18,19] This study aimed to identify the active compound of the *C. lanatus* Linn peel extract that potentially acts as an antidiabetic agent.

MATERIAL AND METHODS

This computational study was conducted in the Faculty of Medicine, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta from November 2023 – May 2024. The research flow is presented in FIGURE 1.

Screening and collecting the active compounds of *C. lanatus* Linn peel extract

Various chemical compounds in *C. lanatus* Linn. peel extract was obtained from several previous research journals identifying phytochemical compositions of *C. lanatus* Linn peel extract. Literature searches were performed in PubMed and Google Scholar using the keywords "*Citrullus lanatus* Linn peel extract, *Citrullus lanatus* Linn rind extract and phytochemical study of *Citrullus lanatus* Linn peel extracts". SwissADME determined drug similarity, oral bioavailability, and GI absorption. All chemical compounds in the *C. lanatus* Linn peel extract were screened by SwissADME to obtain drug-likeness according to Lipinski's rules.

Collecting target protein database related to DM

Target proteins associated with DM were collected from DisGeNET, Open Target and CTD. Data collection from DISGeNET (https://www.disgenet.org/search) was performed using the keywords "diabetes mellitus (CUI: C0011849), insulin-dependent (CUI: C0011854), T2DM without complications (CUI: C0494290) in the disease search engine column. The data collected is a summary of disease-related genes, which included 959 genes. The data collected from Open Target (https://www.opentargets.org/) was conducted using the Find Targets for a Given Disease option on the website and used the keyword "Diabetes mellitus, type 2 diabetes mellitus". The summary data retrieved contained 3413 genes. Data was retrieved from CTD (https://ctdbase.org/voc.go?type=disease) using the keyword "Diabetes mellitus, type 2", resulting in 246 genes. Furthermore, the target protein database collected from DisGeNET, open target, and CTD, was subsequently intersected with Venn Bioinformatics (https://www.bioinformatics.org/gvenn/vennresults.php/) and produced 155 target protein related to T2DM.

Constructing target proteins of *C. lanatus* Linn peel active compound

Each active compounds of *C. lanatus* Linn peel extract that fulfilled the Lipinski rules was predicted by using Swiss target prediction program (http://www.swisstargetprediction.ch/predict.php), CTD (https://ctdbase.org/ voc.go?type=chem), and Sea server (https://sea.bkslab.org/). Simplified molecular input line entry specification (SMILES) of the active compounds was filled into the Swiss target prediction website. The data collection was specified in Homo sapiens target proteins. In the CTD website, the keyword "*Citrullus lanata* Linn" was filled in the chemicals search column. Protein IDs were aligned using

UniProt ID to synchronize protein IDs and remove doubly listed proteins. The aligned target protein IDs were compiled in excel format to be imported into Cytoscape 3.7.2, visualized, and analyzed for connectivity levels.

Constructing of protein-protein interaction related with T2DM

The search tool for the retrieval of interacting genes/proteins (STRING) was used to identify functional relationships between important targets with a combined score greater than 0.4. The STRING website (https://string-db.org/) was used to identify possible gene target related to diabetes mellitus pathway. Protein-protein interactions (PPI) are generated by inserting all target proteins obtained from previous steps into the STRING database (https://string-db.org/). The interaction score was set to the greatest confidence (0.900) with Homo sapiens as the single organism. Using Venn bioinformatics, the intersection was conducted between PPI data, target proteins from active compounds, and the top 7 target proteins associated with T2DM. The PPI networks were further analyzed with Cytoscape 3.7.2 software to find a protein significance rating based on connectivity scores.

Gene ontology and pathway enrichment

Gene ontology is one of the most important sources of biological information since it defines specific protein functions. The database for annotation, visualization, and integrated discovery (DAVID, https://david.ncifcrf.gov/) provides systematic and comprehensive bio-functional annotation for a large number of genes or proteins, allowing for the identification of biological annotations that are significant. Protein targets obtained from previous steps are entered into DAVID using the parameters listed below: “Select identifier” is changed to “OFFICIAL GENE SYMBOL”, “List type” is changed to “Gene list,” and the species is changed to “Homo sapiens”. Gene ontology and KEGG pathway analysis were assessed in previous gene target results. Several essential parameters exist, including biological process (BP), cellular component (CC), and molecular function. The KEGG score was obtained with a p value < 0.05.

RESULTS

Target protein of *C. lanatus* Linn peel extract active compound

The active compounds of *C. lanatus* Linn peel extract was obtained from literature studies in previous research journals. A total of 12 active compounds of *C. lanatus* Linn peel extract was identified (TABLE 1). Drug-likeness of active compounds was assessed based on Lipinski’s rule of five. The SwissADME tool obtained the 12 active compounds’ drug-likeness, oral bioavailability, and GI absorption. The results showed that only three active compounds (protocatechuic acid, phloroglucinol, and L-citruline) met the criteria of Lipinski rules. These active compounds also showed oral bioavailability >30% and high GI absorption. Meanwhile, the other nine active compounds had violations in Lipinski rules of 1-3 violation. The chance of poor absorption usually increases with the number of violation rules. The most active compounds that broke the Lipinski rules of 5 have low GI absorption (TABLE 1). The Swiss target prediction, sea server, and CTD were used to identify target proteins from 3 active compounds obtained, resulting in 241 target proteins (FIGURE 2).

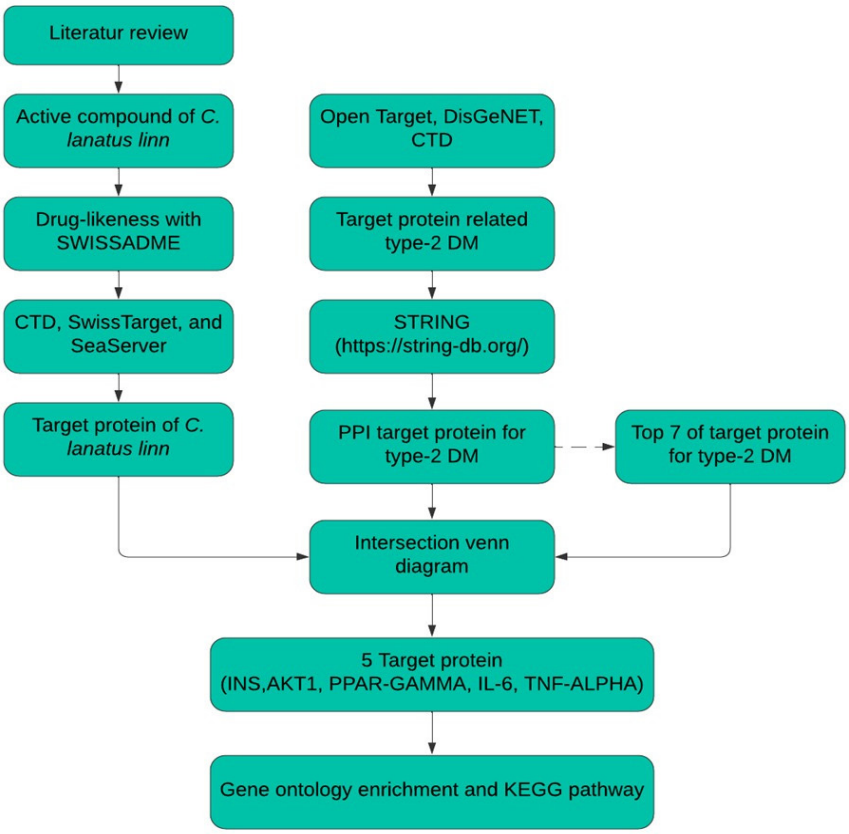


FIGURE 1. The research flow

TABLE 1. General characteristics of active compounds *C. lanatus* Linn peel extract

Compounds	Formula	MW (g/mol)	Lipinski Violation	GI abs	PubChem CID
Lycopene	$C_{40}H_{56}$	536.9	2	low	446925
Beta-Carotenes	$C_{40}H_{56}$	536.9	2	low	5280489
Xanthophylls	$C_{40}H_{56}O_2$	568.871	2	low	5281243
Protocatechuic acid	$C_7H_6O_4$	154.12	0	high	528594
Phloroglucinol	$C_6H_6O_3$	126.11	0	high	359
Cucurbitacin B	$C_{32}H_{46}O_8$	558.7	1	low	5281316
Cucurbitane	$C_{30}H_{54}$	414.7	1	low	71306377
L-citruline	$C_6H_{13}N_3O_3$	175.19	0	high	9750
Cucurbitacin C	$C_{32}H_{48}O_8$	560.7	1	low	5281317
Cucurbitacin E	$C_{32}H_{44}O_8$	556.7	1	low	5281319
Cucurbitacin D	$C_{30}H_{44}O_7$	516.7	1	high	5281318
Cucurbitacin E 2-O-beta-D-glucopyranoside	$C_{38}H_{54}O_{13}$	718.8	3	low	CHEBI:68916

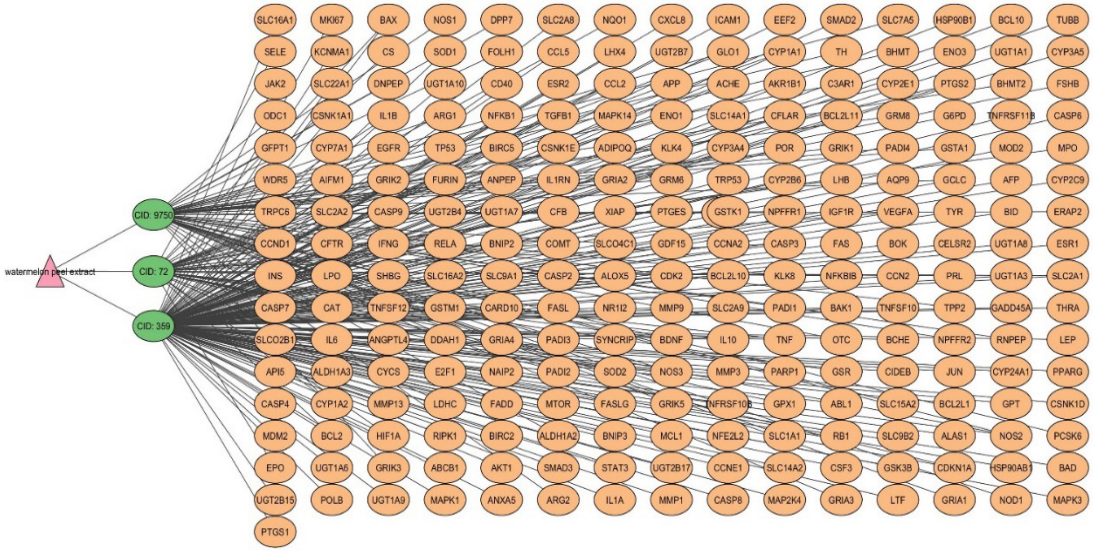


FIGURE 2. Visualization target protein of *C. lanatus* Linn peel extract

Target proteins related to T2DM

The identification of target proteins related to the pathogenesis of T2DM using DisGeNET, open target, and CTD yielded the following results: 959, 3413, and 246 target proteins respectively. The target protein results from the three sources were intersected with Venn Bioinformatics (FIGURE 3), resulting in 155 target proteins that have a relationship with the pathogenesis of T2DM. All targets were identified for their interactions using the STRING database. These interactions were used to build a protein-protein interaction (PPI) network, which was then analyzed using Cytoscape 3.7.2 software to determine the degree of connectivity.

FIGURE 4a presents the intersection results between the target proteins of the PPI, the target proteins of the *C. lanatus* Linn peel extract, and the target proteins with high degree rankings, resulting in 5 target proteins (INS, PPAR-γ, TNF-α, AKT1, IL-6). We identified 28 target proteins that may be involved in the pathogenesis of T2DM resulting from the intersection of target protein related to T2DM and target protein of the active compounds of *C. lanatus* Linn extract. In addition, the intersection results were submitted to Cytoscape to build a target network of the active compounds of the *C. lanatus* Linn that play a role in the pathogenesis of T2DM (FIGURE 4b). Green colors represent the active compounds of *C. lanatus* Linn extract; orange colors represent protein targets, and connecting lines represent compound-target interactions.

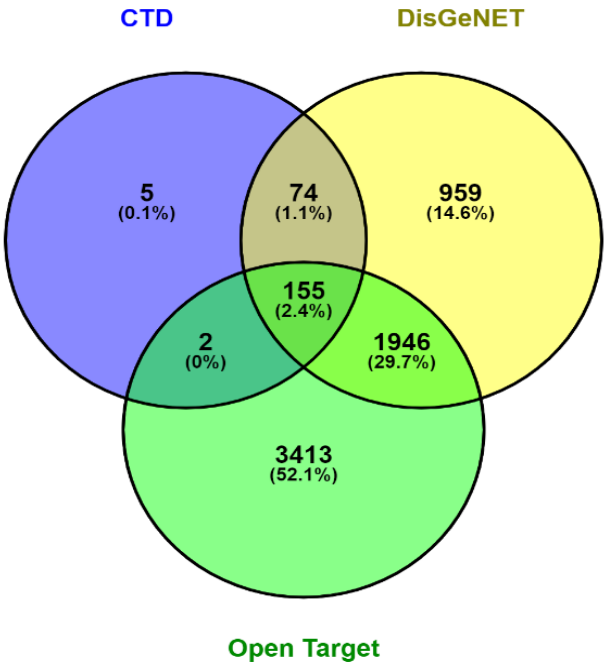
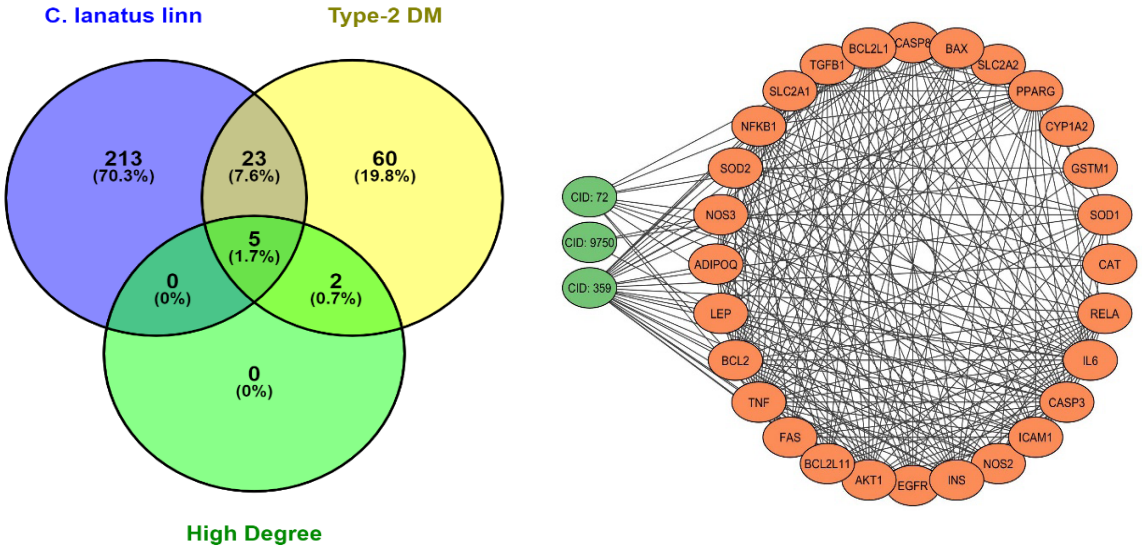


FIGURE 3. Intersection venn diagram of target proteins related to T2DM



a b

FIGURE 4. (a) intersection Venn diagram between target protein of *C. lanatus* Linn, target protein associated T2DM, and target protein with high degree ranking, (b) active compounds-target network of *C. lanatus* Linn peel extract associated to T2DM pathogenesis.

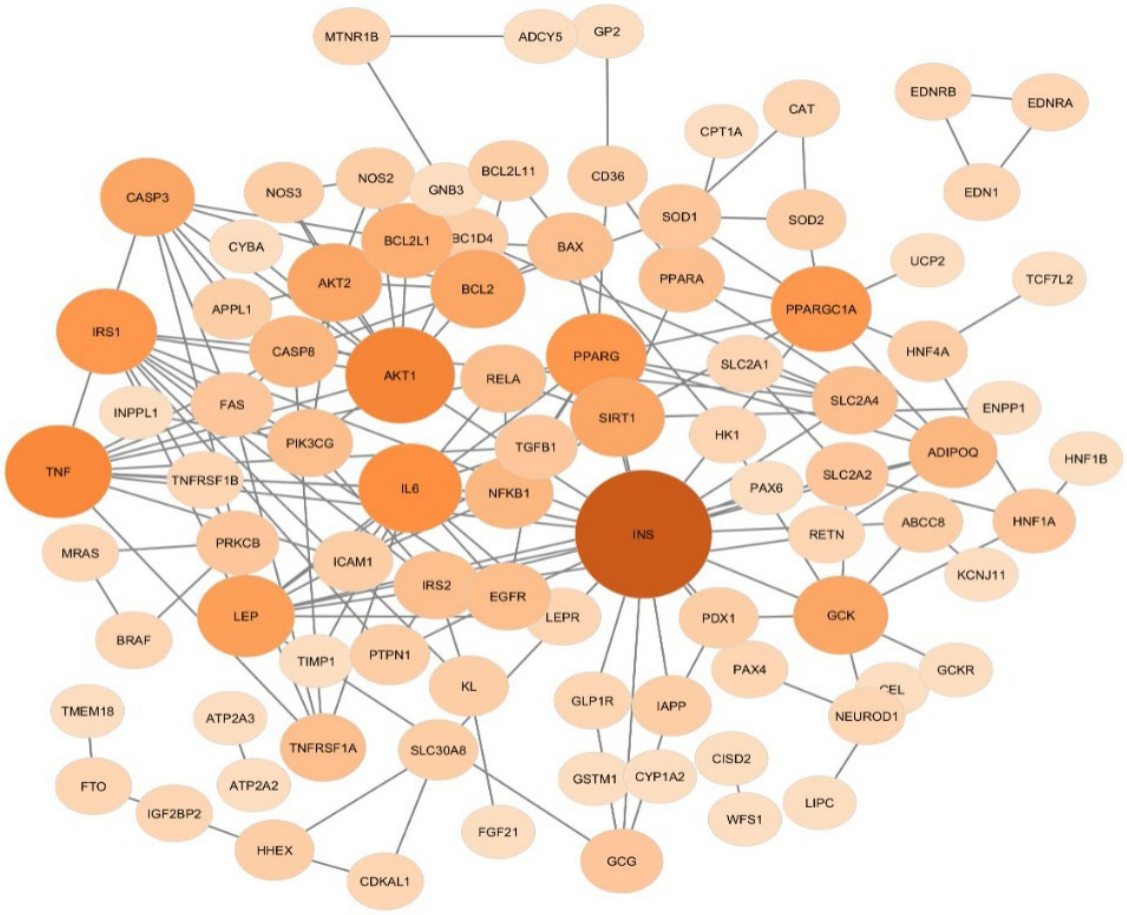


FIGURE 5. PPI network of protein related T2DM in homo sapiens.

The PPI network of proteins associated with T2DM in homo sapiens is shown in FIGURE 5, graded from light to dark orange. A darker orange color indicates a higher degree of the protein in the tissue. The higher degree value indicates that the protein plays a more significant role in the pathogenesis of T2DM. In addition, larger nodes also indicate a higher degree of the protein in the network. We performed the KEGG pathway analysis in 5 target proteins (INS, PPAR-γ, TNF-α, AKT1, IL-6) and obtained 72 pathways ($p<0.05$). These results represented insulin resistance and the AGE-RAGE pathway in diabetic complications associated with glucose-lowering activity (FIGURE 6). The KEGG analysis results also showed that IL6, AKT1, TNF-α and INS were involved in the insulin resistance pathway. In addition, IL6, AKT1 and TNF-α also played a role in the AGE-RAGE signaling pathway in diabetic complications.

Gene ontology (GO) functional enrichment analysis of the five target proteins was conducted by DAVID, resulting in 80 GO in terms of biological function, 3 GO in cellular component, and 5 GO in molecular function. These results showed glucose homeostasis's role in the biological process of target protein that promotes the active compounds of *C. lanatus* Linn as a potential candidate of antidiabetic. The target proteins were spread over cellular components in extracellular space, ER lumen, and extracellular region. The molecular function results correspond to the target gene of the protein being analyzed (FIGURE 7).

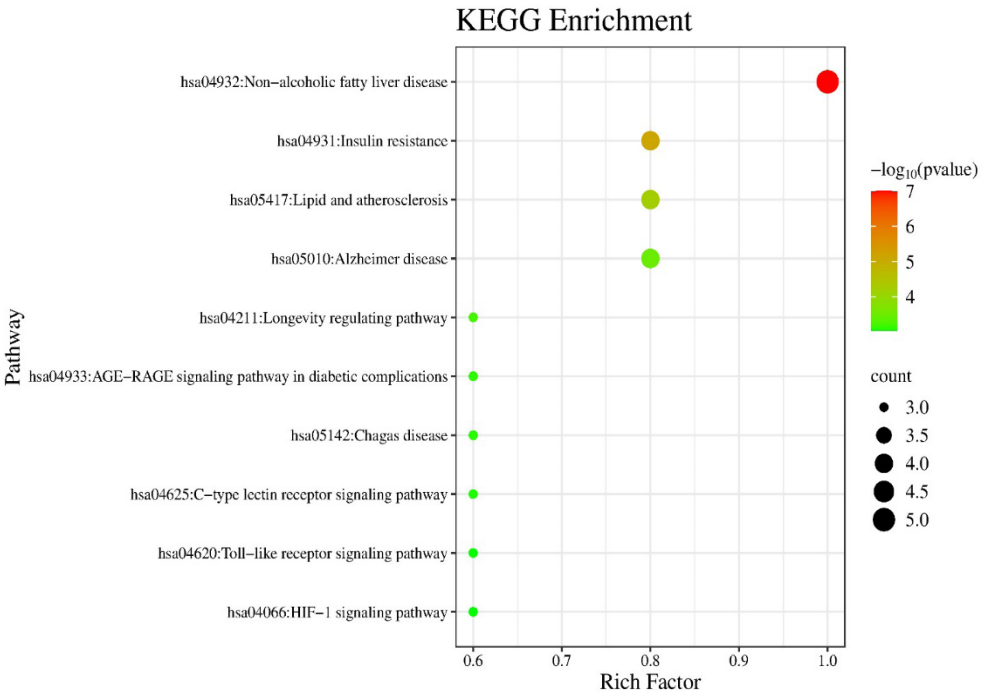


FIGURE 6. KEGG enrichment analysis results by DAVID.

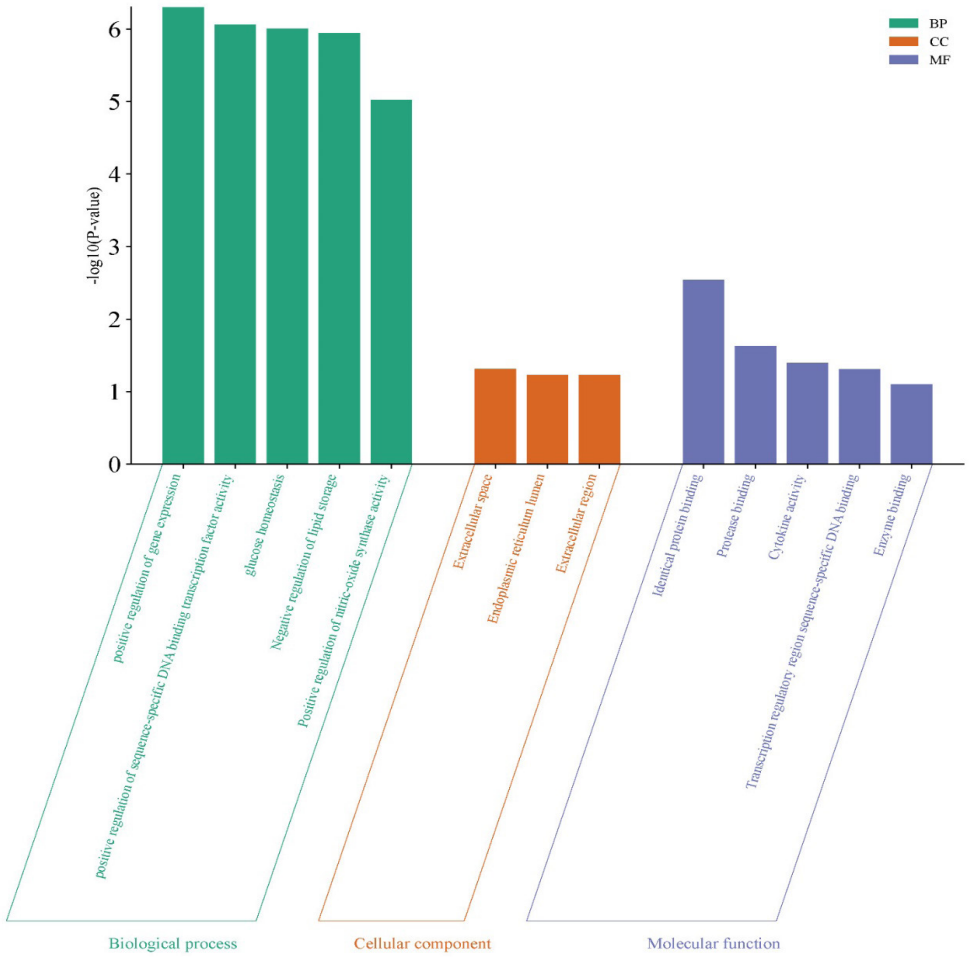


FIGURE 7. GO functional enrichment analysis in term of biological process, cellular component, and molecular function.

DISCUSSION

The ADME (absorption, distribution, metabolism, and excretion) profile plays a critical role in drug discovery and development by optimizing properties of drug candidate or a compound, predicting drug efficacy and safety. The ADME profile also essential to understand drug bioavailability and ensure that different drug formulations have the same therapeutic and adverse effects. Therefore, oral bioavailability become a critical factor in drug development, determining the rate and extent to which the active components of an oral drug are absorbed and reach the systemic circulation.[20] In addition, drug-likeness also an important consideration in the selection of compounds with desirable bioavailability during the early phases of drug discovery and development.

Drug-likeness refers to an active compound's similarity to a known drug and potential to become a drug. The biological activity of the drug is usually better with higher oral bioavailability and drug-likeness values.[21,22] Computational studies play a crucial role in evaluating drug-likeness by predicting the physicochemical, pharmacokinetic, and toxicological properties of compounds.[23] These studies can be used to guide the design of new compounds with improved ADME properties and to optimize the properties of existing compounds for better drug development outcomes.[24,25]

Computational studies and network pharmacology have been applied to studying medicinal plants to understand their therapeutic effects and potential for drug development. These approaches can help screen and identify medicinal plants' active compounds, predict their targets for specific diseases, predict potential therapeutic effects, and explore pathways to understand the underlying mechanisms of action and biological processes.[26,27] Therefore, computational approaches are currently in use for the development of drugs from natural sources. *Citrullus lanatus* Linn peel extract has been found to possess anti-hyperglycemic and anti-DM properties. However, the active compounds responsible for these effects have not yet been identified. The ADME properties of the active compounds were obtained through these computational studies.

This study serves a preliminary screening of bioactive compounds in *C. lanatus* Linn peel extract and as a novel therapeutic approach to identify the compound that responsible in pharmacological effects and identify the biochemical pathway of *C. lanatus* Linn in the treatment of T2DM. We evaluated the drug-likeness of the 12 bioactive compounds in *C. lanatus* Linn peel extract based on Lipinski rules of five. We identified three bioactive compounds (protocatechuic acid, phloroglucinol, and L-citruline) that fulfilled the Lipinski and discovered 241 protein targets of these bioactive compounds that connected to pathogenesis of T2DM. We also identified 155 protein targets connected to pathogenesis of T2DM and 28 proteins were found as protein target of these bioactive. This finding strength the possibility of *C. lanatus* Linn peel extracts as an alternative agent for T2DM therapy.

According to our intersection analysis, we discovered 5 target proteins (INS, PPAR-γ, TNF-α, AKT1, IL-6) of *C. lanatus* Linn that related to pathogenesis of T2DM. The KEGG pathway analysis of these target protein were involved in insulin resistance and AGE-RAGE pathway in diabetic complications associated with glucose-lowering activity. Those signaling pathways had direct relationship with glucose-lowering activity through the regulation of glucose homeostasis, gene expression, cytokine activity, and nitric-oxide synthase activity. This finding can be supported the anti-hyperglycemia effect of *C. lanatus* Linn peel extract that

reported by Syachriyani *et al*.,[14] Another *in vitro* study from Balogun found that watermelon rind can potentially reduce the onset of T2DM through inhibition of intestinal carbohydrate hydrolyzing enzymes.[28] In addition, Ajiboye *et al*.,[29] reported that watermelon juice has anti-hyperglycemia, antioxidant, and anti-inflammatory activities in diabetic rats. Jibril *et al*.,[30] also reported that watermelon leaf extract has anti-diabetic activities in diabetic rats and has better effect than metformin. According to KEGG analysis, other pathways closely connected to T2DM pathogenesis were non-alcoholic fatty liver disease, lipid and atherosclerosis, and the HIF-1 signaling pathway.

Insulin signaling pathway involved the PI3K/Akt pathway that roles in regulation of glucose metabolism. We predicted that *C. lanatus* Linn bioactive compounds would have antidiabetic activity through up-regulation of gene expression encoding insulin and inhibition of cytokine activity. Those will activate the PI3K/Akt pathway and induces glycogen synthesis, increases glucose uptake into the muscle cell, and reduces blood glucose levels. We indicated that our proteins target (INS, IL-6, and TNF-alpha) were involved in the activity of PI3K/Akt pathway. The variation of these protein could cause disturbance the insulin signaling pathway. Similar study from Olowosoke suggested that the bioactive compound from Citrullus lanatus linn could bind to DPPIV, SGLT2, and PPAR-γ by the in-silico study.[31] The PI3K/Akt pathway and PPAR-γ signaling pathways may interact to enhance insulin sensitivity. The activated Akt can phosphorylate and activate transcription factors that regulate PPAR-γ expression or activity, thereby enhancing their effects on glucose metabolism.

The bioactive compounds in the herbal extract may have worked synergistically to produce the pharmacological effect. Wink *et al*.,[32] study also stated that bioactive compound in herbal medicine works through synergistic interaction each other to produce pharmacological effect. Targeting the protein that cause disruption in insulin signaling pathway may prevent the disease progression. We proposed that our key proteins target, namely INS, TNF-α, AKT1, IL-6 were involved mainly in insulin resistance and non-alcoholic fatty liver disease (NAFLD) pathway. In addition, our key proteins target also involved in several pathway that connected direct or indirect with T2DM pathogenesis. Alteration of these protein expression may disrupt the associated pathway T2DM resulting in progressive disease. The target genes of the active compounds are also enriched in several inflammatory conditions suggesting that they may act on various anti-inflammatory cytokines and influence T2DM. However, *in vitro* and *in vivo* study still needs to be conduct to validate our computational study findings. A comprehensive approach from computational to *in vivo* studies will be used to discover drugs targeting the pathogenesis of T2DM.

CONCLUSION

In conclusion, 3 active compounds of *C. lanatus* Linn extract based on Lipinski's rules including protocatechuic acid, phloroglucinol, and L-citruline that connected to target protein in T2DM pathogenesis are discovered. The intersection study presents protein target related to T2DM pathogenesis were INS, TNF-α, AKT1, and IL-6 through insulin resistance and AGE-RAGE pathway in diabetic complications associated with glucose-lowering activity. These pathway roles in regulation of glucose homeostasis, gene expression, cytokine activity, and nitric-oxide synthase activity.

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