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Original Research Article

Analysis Of *Clerodendrum inerme* Plant Compounds as Anti Diabetes Mellitus Through Network Pharmacology Approach

Ahmad Shobrun Jamil[1*], Fauzan Hilmy[2]

[1]*Department of Pharmacy, Faculty of Health Science, Universitas Muhammadiyah Malang, Indonesia*
[2]*Faculty of Health Science, Universitas Muhammadiyah Malang, Indonesia*

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Abstract

Background: Diabetes mellitus prevalence in Indonesia has surged. In 2021, an estimated 19.5 million people had diabetes, with a 10.6% age-adjusted prevalence. Projections indicate around 9.5 million cases by 2024. Diabetes medications, such as metformin, are commonly used, although these medications have adverse effects. A common choice for chronic diseases like DM is the use of natural medications. A plant known as *Clerodendrum inerme* has the potential to alleviate diabetes, but little is known about its molecular mechanisms.

Objective: The objective of this study was to investigate the chemical compound of Clerodendrum inerme and its molecular mechanism to treat diabetes mellitus.

Methods: The KNApSAcK was used to analyze plant parts of *Clerodendrum inerme* to seek out chemicals present in plants. A screening was done to find compounds by estimating Absorption, Distribution, Metabolism, and Excretion (ADME) parameters using the canonical Simplified molecular-input line-entry system (SMILES) on the SwissADME. On the SwissTargetPrediction tool, predictions of target proteins from compounds that pass the screening are connected to various probable proteins. Utilizing the String-db to show the network between target proteins and associated diseases.

Results: The *Clerodendrum inerme* consists of 24 different compounds. The 24 compounds were screened, and the results showed that 4 of them, specifically (Z)-3-Hexenyl beta-D-glucopyranoside, Rhodioloside, Sammangaoside B, and Clerodermic acid, had the potential to develop into a therapeutic agent. The compound is then analyzed to find the protein target associated with diabetes mellitus and predict its networks. The findings indicate that multiple target proteins, including GSK3B, PPARG, DPP4, and STAT3, are connected to diabetes mellitus.

Conclusion: It has been shown that (Z)-3-Hexenyl beta-D-glucopyranoside, or Clerodermic acid, can attach to the proteins GSK3B, PPARG, DPP4, and STAT3, which are all linked to diabetes mellitus.

Keywords:
Clerodendrum inerme; Diabetes Mellitus; molecular mechanism; potential; therapeutic
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INTRODUCTION

The prevalence of diabetes mellitus in Indonesia has been on the rise over time. In 2021, it was approximated that there were approximately 19.5 million individuals diagnosed with diabetes, which accounts for an age-adjusted comparative prevalence of 10.6%. It is anticipated that by 2024, the diabetic population in Indonesia will reach an estimated 9.5 million individuals.[1]

*Corresponding author:
E-mail: *shobrun@umm.ac.id*
(Ahmad Shobrun Jamil)

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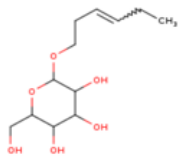
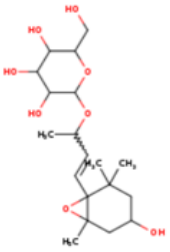
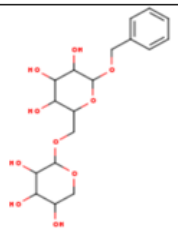
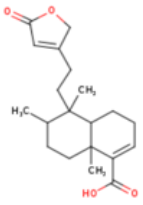
Table 1. List of substances that meet the Lipinski RoF (Rule of Five) for ADME selection. ADME evaluated 24 compounds, and four of them passed. These four substances have the potential to be used for developing novel DM drugs.

Metabolit	Compound Structure	Bioavaibility Diagram	Pubchem CID	Molecule Weight	MLOGP	Bioavability score	BBB permeant
(Z)-3-Hexenyl beta-D-glucopyranoside			5318045	262.3	-1.02	0.55	No
Rhodioloside			159278	388.45	-0.85	0.55	No
Sammangaoside B			102023621	402.39	-2.43	0.55	No
Clerodermic acid			16745295	332.43	3.53	0.85	Yes

Diabetes mellitus (DM) is a chronic metabolic disease or disorder with multiple etiologies characterized by high blood sugar levels and disturbances of carbohydrate, lipid, and protein metabolism as a result of insufficient insulin function.

New therapies must be created and found to meet the need for health services, including those for promotion, prevention, treatment, and rehabilitation. Tens or even hundreds of new medications are released into the market each year after going through time-consuming and expensive development processes. DM is a common metabolic condition characterized by persistent hyperglycemia as a result of reduced insulin secretion, impaired glucose utilization, insulin resistance, and increased glucose synthesis.[2] The aim of the treatment of diabetes mellitus is to achieve normal insulin levels in plasma.[3] In network pharmacology approaches, important network proteins are targeted synergistically by two or more drugs acting mechanistically on the same causal signaling disease module.[4]

Diabetes mellitus is classified into two types: type 1 and type 2. Type 1 diabetes causes cell damage, resulting in the inability of the body to produce insulin. Insulin resistance, a condition in which cells fail to respond properly to insulin, is the starting point for type 2 Diabetes.[5] Another type of Diabetes is gestational diabetes. Gestational diabetes mellitus, often called "Type 3 diabetes," emerges during pregnancy, typically vanishing after childbirth. It is characterized by insulin resistance and is linked to factors like interleukin-6 and C-reactive protein. It's essential to monitor and manage to ensure a healthy pregnancy and postpartum period.[6]

When fasting glucose exceeds 120 mg/dL or post-meal levels go beyond 200 mg/dL, it signifies diabetes. For venous blood, fasting levels over 140 mg/dL or post-meal levels over 200 mg/dL indicate diabetes. Impaired glucose tolerance (IGT) falls between 140-200 mg/dL after eating and less than 120-140 mg/dL when fasting. IGT doesn't need treatment but should be monitored.[7]

People are growing increasingly interested in network pharmacology, a brand-new subject based on system biology, bioinformatics, and high-throughput histology.[8] Important network proteins are targeted synergistically by two or more active compounds operating mechanistically on the same signaling disease module in pharmacology methods.[4] Network pharmacology, which recently linked corresponding targets to corresponding diseases and used them as three different types of nodes to construct a "component-target-disease" network, has combined the three active constituents of traditional Chinese medicine[(9).]

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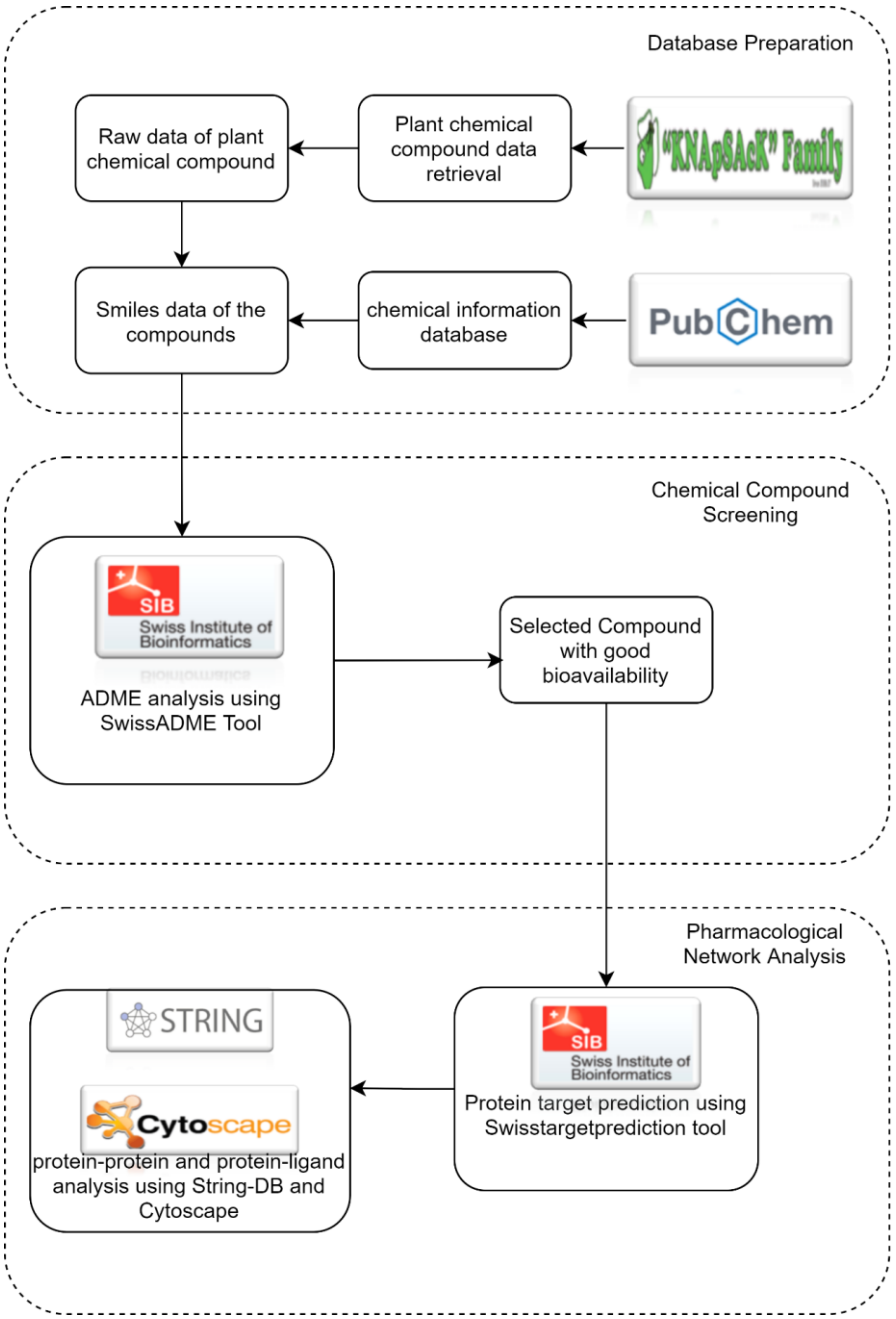

Figure 1. Workflow chart of *Clerodendrum inerme* for the potential treatment of diabetes mellitus based on network pharmacology.

Clerodendrum inerme, often known as Indonesian Gambir Laut, belongs to the Verbenaceae family. Typically, these plants can be found in Australia, Asia, Malaysia, and the Pacific Islands. Clerodendron inerme is traditionally used to halt bleeding and treat asthma, hepatitis, ringworm, and colic. It is also used as a febrifuge, uterine stimulant, pest control agent, and antiseptic.[10] This study aims to determine what compounds in the *Clerodendrum inerme* plant have activity as therapeutic agents for individuals with diabetes mellitus.

This study was carried out utilizing an *in-silico* approach, in which the compounds found in plants were initially searched using a web-based plant database. The compounds that meet the absorption, metabolism, distribution, and excretion (ADME) criteria are then screened based on their ADME properties. It continues with proteins that can bind to compounds, and it will be investigated whether these proteins play a role in the mechanism of diabetes mellitus.

MATERIALS AND METHODS

Plant chemical compound data retrieval

Clerodendrum inerme chemical compound data were retrieved using the KNApSAcK database (accessed on 2023-01-20 at http://www.knapsackfamily.com/knapsack_core/top.php).[11] Then, used the PubChem database (accessed on 2023-01-20 at https://pubchem.ncbi.nlm.nih.gov) to search the compound's canonical Simplified Molecular-Input Line-Entry System (SMILES).[12]

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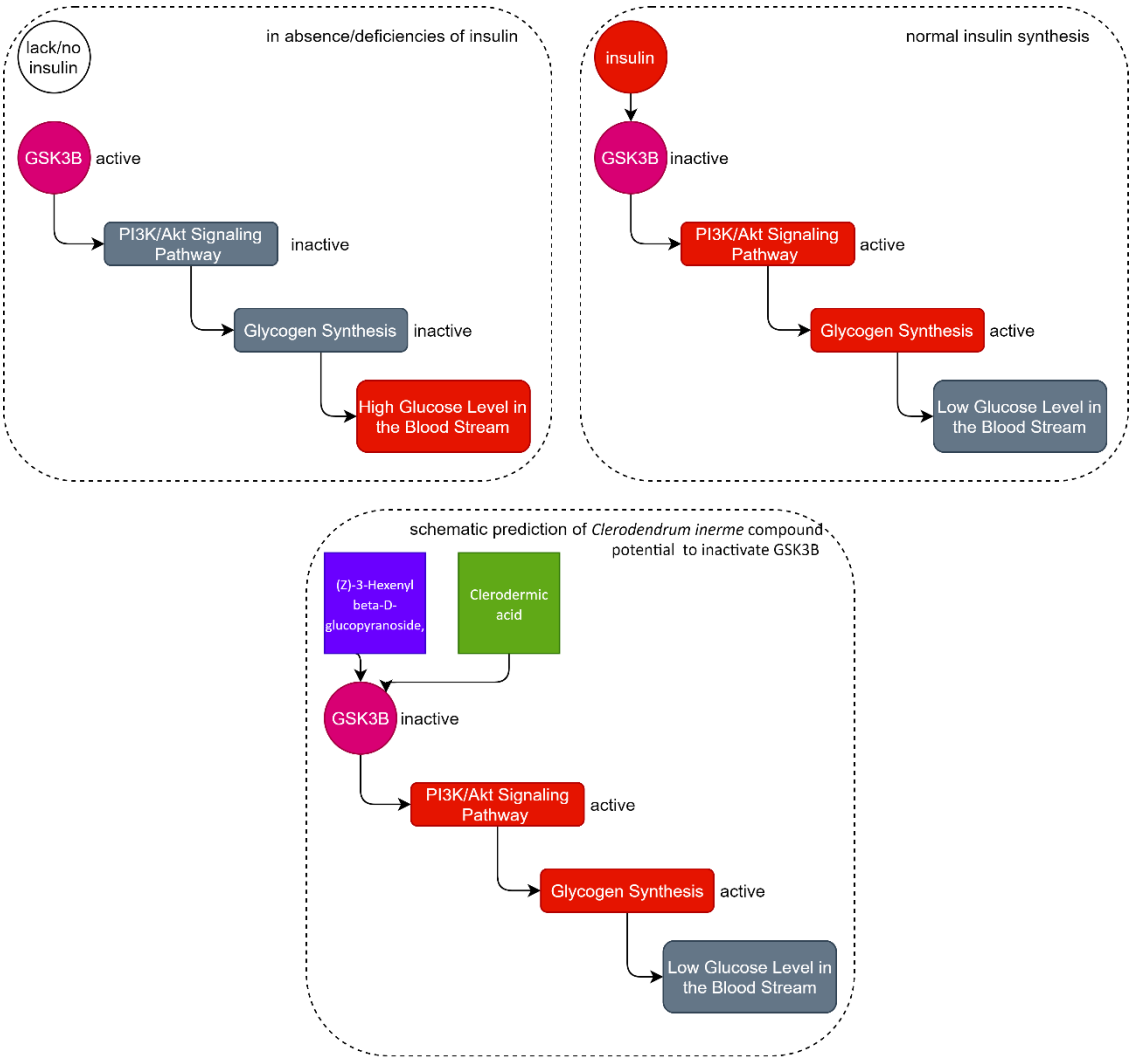

Figure 2. Predictive scheme for potential bioactive compounds in Clerodendrum inerme as candidates for diabetes mellitus treatment. GSK3B is a crucial protein in blood sugar regulation. The first scheme (top left) shows that with low or no insulin binding to GSK3B, glycogen synthesis is inactive. The second scheme (top right), with insulin binding to GSK3B, makes this protein inactive, activating glycogen synthesis and reducing blood glucose levels. The third scheme (bottom) suggests two compounds from C. inerme, (Z)-3-Hexenyl beta-D-glucopyranoside and Clerodermic acid, may potentially replace insulin's role by inhibiting GSK3B activity and activating the glycogen synthesis pathway, thus lowering blood glucose levels.

Chemical Compound Screening

Chemical compound screening is used to find compounds that do not cause toxicity by predicting ADME characteristics, pharmacokinetic properties, drug-like qualities, and chemical friendliness of pharmaceuticals from one or more small molecules to aid in drug discovery using SwissADME tool (http://www.swissadme.ch/index.php, accessed on 2023-01-20).[13]

Protein Target Prediction

Protein targets were predicted using the SwissTargetPrediction tool (http://www.swisstargetprediction.ch, accessed on 2023-01-20).[14] This tool estimates the most likely macromolecular targets of a small molecule that is thought to be bioactive. The prediction is based on a mix of 2D and 3D similarity with a library of 370,000 known actives on over 3000 distinct proteins from three different species.[14]

Construction of target protein network and analysis

The following stage is to investigate functions and correlations between protein targets after discovering the protein targets for chemical compounds in plants. Utilizing String-DB and Cytoscape tools, it was possible to determine the link between the protein target and the chemical composition of plants. The online platform String-DB and the Cytoscape software version 3.1.1.9 can be utilized to perform direct (physical) and indirect (functional) connections related to this interaction.[15,16] The results of the correlation are built based on (1) Interaction between plant compounds and protein targets and (2) Interaction between protein targets and disease.

RESULTS

Clerodendrum inerme compound

The search for compounds contained in the *Clerodendrum inerme* plant was carried out through a database available on the KNApSAcK website. Found 24 metabolite compounds and then carried out the next stage, namely the selection of compounds based on

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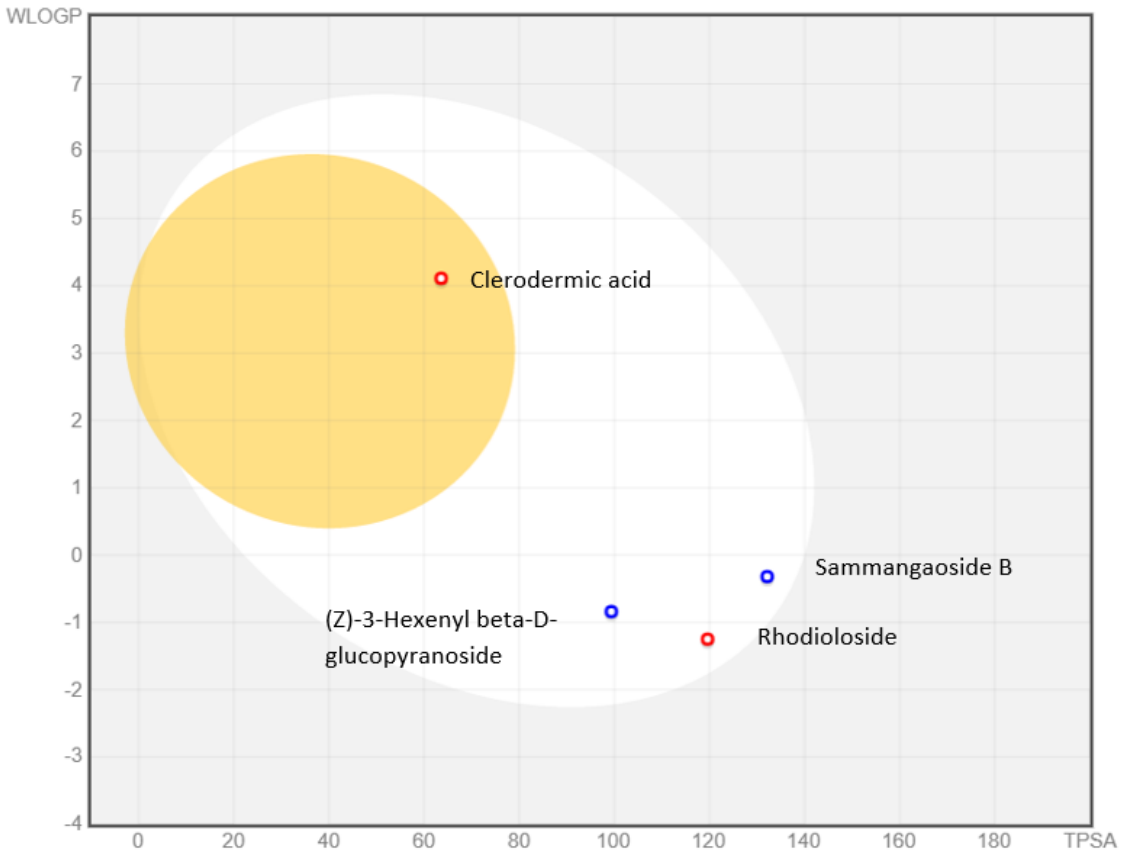

Figure 3. Distribution of plant compounds using the BOILED-Egg visualization, to determine the lipophilicity of these compounds. There is one compound that can penetrate the blood-brain barrier, namely Clerodermic acid. The other 3 compounds cannot penetrate the blood-brain barrier.

ADME. The requirements used are lipinski. Lipinski's Rule Of Five (RoF) is that the molecular weight is lower than 500 Da, the number of hydrogen bond donors is less than 5, the number of hydrogen bond acceptors is less than 10, and *x* log *P* is lower than 5.[17] Detailed result can be found in table 1.

The 4 compounds were examined for their lipophilicity using the Brain or Intestinal EstimateD Permeation (BOILED-Egg) method. For this purpose, BOILED-Egg is proposed as an accurate predictive model that works by calculating the lipophilicity and polarity of small molecules.[18] From these results, it was found that 1 compound could penetrate the Blood-brain barrier, that is Clerodermic Acid. For full details, it can be seen in Figure 2.

Correlation between compounds and protein targets

The four compounds that passed ADME will be tested to see if they can bind to any protein target associated with diabetes. The String-DB database is used to perform data mining. String-DB intends to prioritize scope (applying thousands of genome-sequenced organisms), evidence source richness (including automated text mining), and usability features (such as customization, enrichment detection, and programmatic access).[15] The target protein that have a probability to bind to protein target is shown in figure 3. The predicted targets of the four compounds include several proteins relevant to diabetes mellitus. They include GSK3B, PPARG, STAT3, ACE, and DPP4.

Apart from diabetes mellitus, other diseases were found that had a relationship with protein targets predicted from plant compounds that can be seen in figure 4. So, there is potential as a drug candidate apart from diabetes mellitus. In diabetes mellitus, there are 2 metabolites from the *Clerodendrum inerme* plant that are predicted to bind to target proteins, it is (Z)-3-Hexenyl beta-D-glucopyranoside (PubChem ID: 5318045) and Clerodermic acid (PubChem ID: 16745295).

Correlation between protein targets and diabetes mellitus

Figures 2 and 3 reveal a relationship between the substance (Z)-3-Hexenyl beta-D-glucopyranoside and the proteins GSK3B, PPARG, DPP4, and STAT3 that have a role in controlling diabetes mellitus. Clerodermic acid appears to interact with PPARG and GSK3B.

DISCUSSION

GSK3B, also known as glycogen synthase kinase-3, is a proline-directed serine-threonine kinase that has been linked to the phosphorylation and inactivation of glycogen synthase, insulin signaling, glycogen synthesis, neurotrophic factor signaling, Wnt signaling, neurotransmitter signaling, and microtubule dynamics. microtubule dynamics, neurotrophic factor, Wnt, neurotransmitter signaling, and insulin and glycogen synthesis.[19] GSK3B is important in the treatment of diabetes. In insulin-related signaling pathways, GSK3B is considered a negative regulator, and phosphorylation renders GSK3B inactive. One of the major downstream targets of AKT signaling is GSK3B. Figure 5 shows

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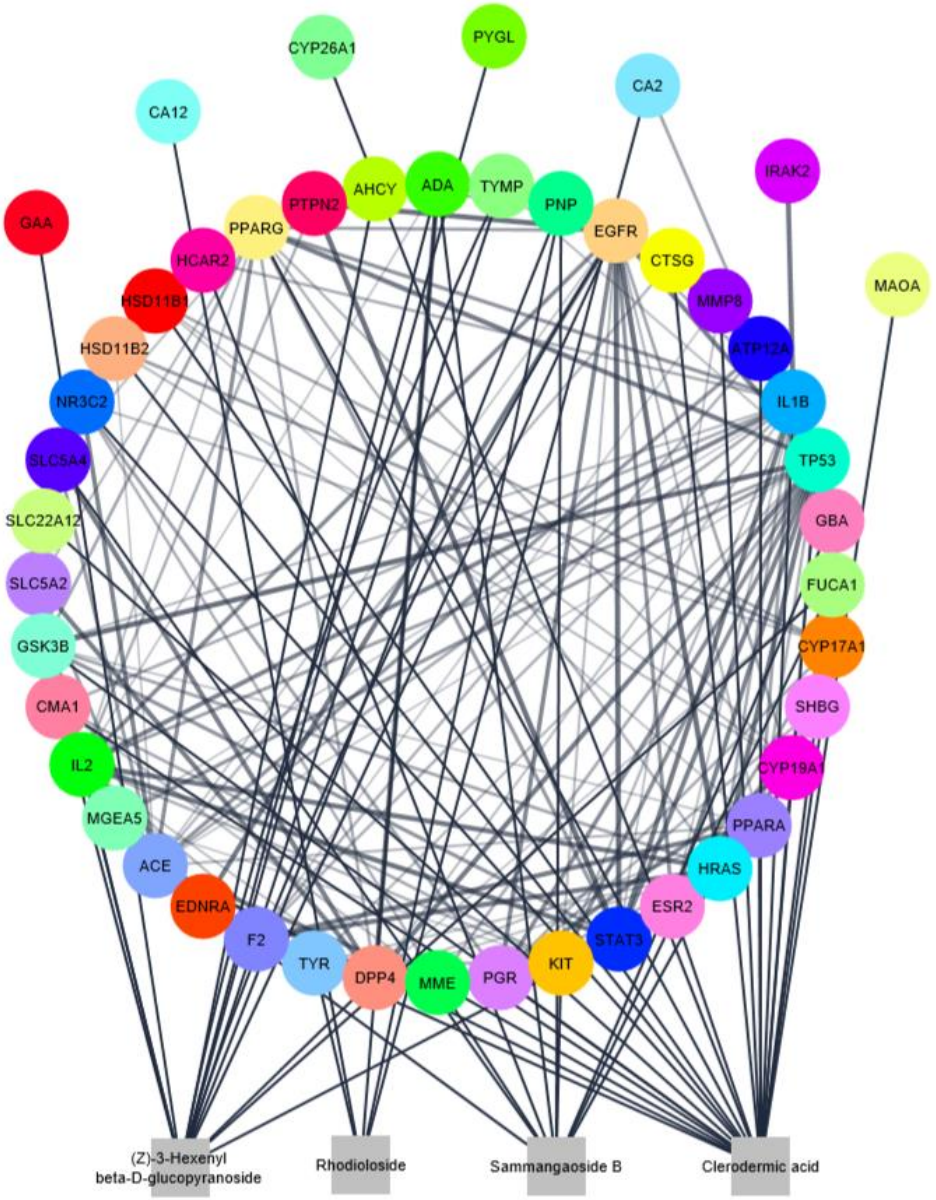

Figure 4. The correlation between *Clerodendrum inerme* metabolites and protein targets, which are shown in gray are plant metabolites called (Z)-3-Hexenyl beta-D-glucopyranoside, Rhodioloside, Sammangaoside B, Clerodermic acid. The colors of the rainbow are the target protein resulting from the prediction of the protein target.

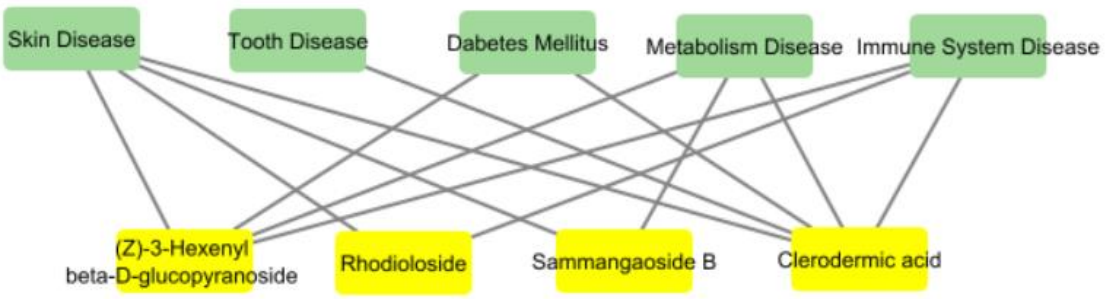

Figure 5. Correlation between disease and metabolites of *Clerodendrum inerme.*

diabetes influences cell death through disruption of insulin signaling pathways.[20] Compounds from the *Clerodendrum inerme* plant will act as inhibitors on GSK3B so that the glycogen protein synthase is not inhibited and there is no decrease in glycogen synthesis.

Peroxisome proliferator-activated receptor gamma (PPARγ- or PPARG) is a type II nuclear receptor that acts as a transcription factor and is encoded by the PPARG gene in humans. It is also known as glitazone reverse insulin resistance receptor or NR1C3 (nuclear receptor

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subfamily 1, group C, member 3).[21] Several lines of evidence have shown that the SNPs of the PPARG (nuclear receptor) have an important role in controlling lipid and glucose metabolism.[22] PPARG promotes adiponectin collection from fat cells, increases fatty acid storage in fat cells (reduces lipotoxicity), induces FGF21, and enhances nicotinic acid adenine dinucleotide phosphate synthesis by increasing the CD38 enzyme.[23] The role of plant compounds in PPARG is as a ligand on PPARG (receptor). Once activated by the plant compound *Clerodendrum inerme*, the nuclear receptor binds to DNA-specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. Hence, it controls the peroxisome beta-oxidation pathway of fatty acids.

The STAT3 gene encodes signal transducers and activators of transcription that mediate cellular responses to growth factors such as interleukins, KITLG/SCF, LEP, and others. Coactivators such as NCOA1 or MED1 to the promoter region of target genes upon activation. According to research, the JAK2/STAT3/SOCS-1 signaling pathway is activated to cause hepatic insulin resistance and is also involved in the treatment of T2DM and insulin resistance.[24] Studies showing that activation or loss of STAT3 leads to insulin resistance, loss of muscle mass, or increased satellite cell repair depending on STAT3 stimulation and penning length are proof of this. In the framework of myotubes made from people with impaired glucose tolerance, IL-6 causes insulin resistance. Insulin sensitivity is increased and muscle regeneration is facilitated by STAT3 inhibition in muscles.[25]

Adenosine Deaminase Complexing Protein-2 and T cell CD26 antigen are related to dipeptidyl peptidase 4, commonly referred to as Gen DPP4. This is a type II intrinsic glycoprotein transmembrane enzyme that breaks down the protein X-proline from the N polypeptide's starting codon. Dipeptidyl peptidase 4 plays a significant role in the metabolism of glucose and insulin as well as the immune system. The surface cell receptor glycoprotein found in synaptic vesicles is essential for mediating cell-to-cell receptor activation (TCR). Acts as a positive regulator of T-cell coactivation by binding to at least ADA, CAV1, IGF2R, and PTPRC. The connection between CAV1 and CARD11 promotes T cell proliferation and NF-kappa-B activation in T cell receptors/caras that are concentrated on CD3. Interaction with ADA also changes the adhesion of the limfosit-epitel adhesion. Compounds in the Clerodendrum inerme plant function as DPP4 inhibitors, so increasing or prolonging GLP-1 levels can potentiate insulin secretion by the pancreas. In addition, inhibition of DPP4 can reduce the production of α cells, so that glucagon and glucose in plasma also decrease.[26]

From the extensive elucidation of cellular molecular mechanisms related to the interaction between bioactive compounds in C. inerme and target proteins, particularly in the context of diseases like diabetes mellitus, it's important to understand that this research is *in-silico* or computationally predictive, utilizing artificial intelligence. Subsequent in vitro and in vivo studies are imperative to confirm and bolster the evidence presented by this research.

In vitro and in vivo research are essential to corroborate *in-silico* findings. While *in-silico* provides valuable predictions, in vitro and in vivo studies validate these predictions in real biological systems. They offer insights into how substances or interventions affect living organisms, their safety, and potential side effects. In vivo research, in particular, is crucial for testing therapies' effectiveness on experimental animals or humans, providing a deeper understanding of their therapeutic potential. By combining data from these three research approaches, we gain a more comprehensive understanding, reduce errors, and support the development of safer and more effective treatments.

CONCLUSION

Compounds contained in the *Clerodendrum inerme* plant, that are (Z)-3-Hexenyl beta-D-glucopyranoside, Clerodermic acid can bind to proteins associated with diabetes mellitus (GSK3B, PPARG, DPP4, STAT3). These compounds bind by inhibiting or activating the function of the target protein. So the *Clerodendrum inerme* plant has potential as a diabetic drug candidate.

The use of computer models, which may oversimplify complicated biological processes, is one restriction of *in-silico* research. It doesn't account for real-world unpredictability and could produce inaccurate predictions. Additionally, data quality and model validation are significant challenges that need additional experimental validation to produce reliable results. Recommend strengthening *in-silico* research through model complexity enhancement, actual variability involvement, and robust experimental accuracy validation through in vitro and in vivo research.

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