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Original Research Article

Exploring the Potential of Tamarillo (*Cyphomandra betacea* Cav) Compounds for the Treatment of Type 2 Diabetes Mellitus: A Network Pharmacology Study

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ABSTRACT

The prevalence of diabetes mellitus (DM), especially type 2 DM, has been on the increase with a percentage of 95% in Indonesia. Tamarillo (*Chypomandra betacea* Cav.) can restore adipokine regulation and reduce blood glucose levels which prevents insulin resistance in type 2 DM. Thus, this research aimed to explore the compounds and determine the molecular mechanism of Tamarillo on type 2 DM using a Network Pharmacology approach and compound exploration through a literature review. At the same time, the researchers determined the molecular mechanism using the Network Pharmacology approach: GeneCard, DisGeNET, STRING, Cytoscape, and KEGG database applications. The results showed that the multi-component compounds in Tamarillo had 150 out of 365 target proteins that work in biological processes and signaling pathways of type 2 DM, with 75 target proteins locked and interacting. Among the many molecules in Tamarillo, six bioactive components from the hydroxycinnamic acids group had activity on type 2 DM. These compounds affected biological processes in three types 2 DM signaling pathways: Adipocytokine, Insulin, and Glucagon signaling pathways. With the influence of hydroxycinnamic acid compounds on these three signaling pathways, Tamarillo had the potential to help lower blood glucose levels and prevent insulin resistance in type 2 DM patients. Therefore, Tamarillo fruit can be a safe and natural treatment alternative for patients with type 2 DM.

Keywords: Hydroxycinnamic Acids, Network Pharmacology, Tamarillo, Type 2 DM.

Introduction

Type 2 diabetes mellitus (DM) is a chronic metabolic disease involving various pathogenic processes caused by metabolic abnormalities, namely insulin deficiency in β cells in the pancreas, insulin resistance, or both.[1] Risk factors for type 2 DM can be from a combination of secondary factors, such as obesity, lifestyle, birth weight, stress, and genetic factors.[2] Globally, 422 million adults have diabetes.[3] The prevalence of DM continues to increase in Indonesia. The data from the International Diabetes Federation (2019) estimated an increase in the global prevalence of DM from 9.3% in 2019 to 10.2% in 2030 and 10.9% in 2045. The most common DM is the type 2 DM, with a prevalence of 95% in Indonesia.[4] The federation estimated that at least 629 million people will be affected by 2045. The causes of type 2 DM were unhealthy lifestyles, imbalanced dietary arrangements, and lack of physical activity. Type 2 DM attacks various age groups, with a risk of 36% in the age group <45 years, and the most vulnerable group is age > 45 years, with a risk of 64%.[5] Generally, type 2 DM patients must control their diet with foods that are low in fat and have lots of fibre and avoid those that can increase the glycemic index or sugar levels.[6]

Therefore, Tamarillo is an excellent alternative natural ingredient to fix the issues.

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Tamarillo is a potential food commodity because it has many health benefits that can be explored by the public. Tamarillo (*Cyphomandra betacea Cav*.) is a plant in the eggplant family (*Solanaceae*) originating from New Zealand.[7] The nutritional content of Tamarillo is varied with beneficial health effects, such as vitamin A, vitamin C, and vitamin E.[8] Every 500 mg of Tamarillo fruit contains some complex nutrients such as sugar (0.46), crude fibre (1.98), vitamin C (0.0716), anthocyanin (122.57) and pH (5.9).[9] In addition, based on Putu Anita Devi *et al*. (2018), Tamarillo contained anthocyanin-type flavonoids, an antioxidant source helpful in warding off free radicals and minimizing oxidation reactions.[10] Tamarillo plays a role in reducing blood glucose levels in Type 2 DM patients, mainly because of the content of polyphenols (anthocyanins, flavonoids, phenols) as antioxidants which can restore adipokine regulation, thereby preventing insulin resistance and triglyceride production in adipose tissue.[11]

The network pharmacology approach was used to understand the interactions between active plant compounds and target proteins in the human body.[12] In another research regarding Tamarillo and type 2 DM, this approach was used to discover the molecular mechanisms of the active compounds in Tamarillo fruit with blood glucose levels lowering effects and preventing insulin resistance in type 2 DM.[12] The complex interactions between the active compounds in Tamarillo fruit and target proteins in the human body relates to biological processes and signaling pathways of type 2 DM. This study determined the molecular mechanism of the active compounds in Tamarillo fruit that played a role in lowering blood glucose levels and preventing insulin resistance in type 2 DM.[13] Thus, the network pharmacology approach can help accelerate the development of effective and safe drugs for type 2 DM treatment.

Materials and Methods

Materials

The materials used in this study included Tamarillo fruit compounds and GeneCards (https://www.genecards.org), software Cytoscape

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v3.9.1 (https://cytoscape.org), DisGeNET (https://www.disgenet.org), STRING (https://www.string-db.org/), dan Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY (https://www.genome.jp/kegg/pathway.html).

Network Pharmacology Test

Collection and screening of Tamarillo fruit bioactive components

The bioactive components of Tamarillo fruit were obtained based on the results of a literature review of scientific research indexed by Google Scholar with the keyword "*Cyphomandra betacea* compound". The selected components had high levels of dominance based on comparison with literature studies.

Collection and screening of Tamarillo-associated target proteins

Target proteins and genes related to type 2 DM were obtained from GeneCards.[14] Results obtained from GeneCards were limited to targets that had relevance values of ≥10.00, where this value is considered to meet database standards.[12]

Collection and screening of disease-related target proteins and the creation of target networks.

The next step explored target genes associated with type 2 DM using DisGeNET. DisGeNET collected disease target data by tracing a database that collected information about connections between proteins and disease targets.[15] Afterward, creating a target network related to the Tamarillo fruit, which was collected into a target-component network, visualized through a similarity network using Cytoscape v3.9.1.[16] Target proteins and bioactive components of Tamarillo fruit were represented as "nodes" and interactions between the two proteins as "edges". The more essential proteins that were the target of a component, the more these components can be designated as essential components.[12]

Development of a protein interaction network (PPI Network) and enrichment analysis

The (STRING) platform selected active ingredients and disease junction genes for further analysis. The STRING obtained proteins directly and indirectly by neolignans. Meanwhile, in the protein interactions (PPI), the network was built from the genes affected by the Venn diagram.[17] The formation of the PPI network was carried out using common target proteins, with a minimum interaction score of 0.400. This PPI network analysis aimed to investigate biological activity by examining gene ontology (GO), functional annotation, and Kyoto Encyclopedia of Genes and Genomes (KEGG) protein pathway enrichment. The analysis focused on the network's role and function in the signal transduction process.[12]

Results and Discussion

The result obtained from a literature study using the Google Scholar search engine with the keyword "*Cyphomandra betacea* compound" is presented in Table 1. From the collection and screening of target proteins from the GeneCards database with a relevance value of ≥10.00, 365 target proteins were obtained from various compounds (Table 2). From the 365 target proteins, 150 were specific and associated with Type 2 DM (Non-insulin dependent) via DisGeNET. Then, the target network resulting from Cytoscape v3.9.1 visualisation is presented in Figure 1. In the visual target network (Figure 1), six bioactive components of Tamarillo fruit had target proteins associated with type 2 DM disease. Thus, from the six bioactive components (chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, 3-caffeoylquinic acid, and quinic acid), one crucial molecule (hydroxycinnamic acid) with type 2 DM activity was identified. According to Yusuf *et al*. (2021), hydroxycinnamic acid inhibits the activity of the HMG-CoA reductase enzyme in type 2 DM. This inhibitory action was known to stimulate pancreatic cells to increase insulin production.[18] In addition, Tamarillo exhibits type 2 DM benefits by its antioxidant activity and stimulating the multiplication of pancreatic cells to increase insulin production. Based on the Venn diagram (Figure 2) six bioactive components, namely *mitogen-activated protein kinase* 1 (MAPK1), *Nitric oxide synthase* 3 (NOS3), *Mitochondrial inner membrane protein* OXA1L (OXA1L), and *Myeloperoxidase* (MPO) have four identical target genes. This network pharmacology study revealed 75 target proteins associated with type 2 DM, key targets where these proteins were mutually locked and interact (Figure 3).

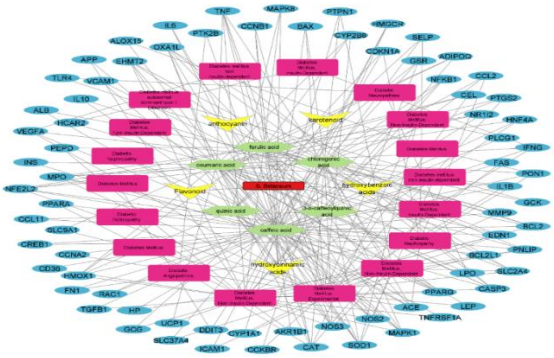

Figure 1: Visual Tamarillo Fruit Network (Red: plant name, Green: compound molecule, Yellow: bioactive component, Pink: Disease, Blue: Target proteins

Table 1: Tamarillo fruit bioactive components

Name of Compound	Molecular Type	Pubchem CID	Reference
keracyanin, pelargonidin 3-rutinoside, tulipanin, Delphinidin 3-O-*α*-l-rhamnosyl-(1-5,25)-*β*-d-glucoside	Anthocyanins	29231, 44256626, 5492231, 443650	[30], [31], [32], [33]
chlorogenic acid, caffeic acid, coumaric acid, ferulic acid, 3-o-caffeoylquinic acid, quinic acid	hydroxycinnamic acids	1794427, 689043, 124202751, 445858, 1794427, 6508	[30], [34]
β-carotene, *β*-cryptoxanthin, zeaxanthin	carotenoids	5280489, 5281235, 5280899	[35], [33], [31]
Kaempferol-3-rutinoside, kaempferol 8-C-*β*-d-galactoside, katekin, epikatekin	Flavonoids	5318767, 14345562, 163184559	[30], [36], [37], [32], [34]
gallic, ellagic	hydroxybenzoic acids	370, 5281855	[30], [31], [36], [37], [38]

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Table 2: Target protein screening results

Compound Type	Number of Gene Targets	Gifts Range	Relevance Range
chlorogenic acid	52	43-61	10-34
Caffeic Acid	151	21-62	10-41
Coumaric Acid	76	45-61	10-39
Feluric Acid	64	43-62	10-39
Quinic Acid	21	45-59	11-24
caffeoylquinic acid	1	52	11

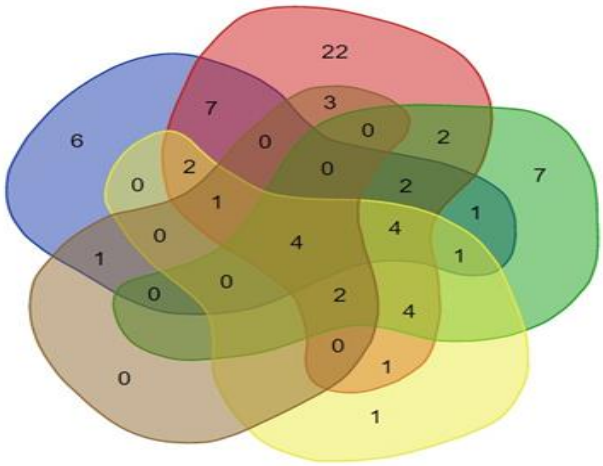

Figure 2: Venn diagram of 150 Tamarillo fruit target proteins against type 2 DM

Tamarillo fruit contains multiple components that interact with multiple targets through various mechanisms of action. The mechanism of action of the Tamarillo fruit phytoconstituents can be explained at the molecular level in a more comprehensive manner from upstream to downstream in the signaling pathway using network pharmacology studies. The results of the analysis from KEGG identified several target genes. The target genes most associated with the data, were mitogen-activated protein kinase 1 (MAPK1), mitogen-activated protein kinase 8 (MAPK8), Tumor Necrosis Factor (TNF), Insulin (INS), Adiponectin (ADIPOQ), and Solute Carrier Family 2 Member 4 (SLC2A4). KEGG analysis showed that the hydroxycinnamic acids in Tamarillo affected three signaling pathways related to blood sugar regulation and metabolism in type 2 DM. The three signaling pathways were the Adipocytokine signaling pathway (hsa04920), the Insulin signaling pathway (hsa04910), and the Glucagon Signaling Pathway (hsa04922) (Table 3, Figure 4). The adipocytokine signaling pathway is associated with the production and regulation of adipokines, i.e. hormones produced by fat cells, and plays a role in regulating metabolism and insulin resistance.[19] The hydroxycinnamic acids in Tamarillo affected this signaling pathway by interacting with the target protein ADIPOQ (Adiponectin), an adipokine important in regulating glucose and insulin metabolism.[20] Adipokines have significant effects in controlling fat metabolism and insulin response, with direct anti-diabetic, anti-atherogenic, and anti-inflammatory properties. These adipokines stimulate phosphorylation, activate AMPK in the liver and skeletal muscle, increase glucose utilisation, and support fatty acid metabolism.[21] On the other hand, Adiponectin played a role in increasing insulin sensitivity by increasing glucose absorption and reducing the process of gluconeogenesis in the liver. In addition, adiponectin has a suppressive effect on proinflammatory mediators such as IL-6 and TNF-α.[22] Normally, adiponectin is secreted by adipocytes in several isoforms, including multimeric forms, monomeric forms containing full-length and globular subforms, and some oligomers. Adiponectin increases insulin sensitivity in various tissues, including the liver, skeletal muscle, adipose tissue, ectopic, and cardiac tissue, indicating its capacity to provide protection.[23] The insulin signaling pathway is related to cells response to insulin, a crucial hormone that regulates blood glucose levels.[24] Insulin naturally interacts with particular receptors on the surface of cells, and its effects play a significant role in controlling glycaemia or blood sugar levels.[25] These receptors react with intracellular glucose metabolism and deactivates insulin to stimulate glucose uptake by the tissue, resulting in glucose intolerance, which occurs slowly and progressively leading to diabetes mellitus going undetected.[26] Insulin (INS) contributed to a decrease in blood glucose concentration by increasing cell permeability to monosaccharides, amino acids, and fatty acids. Moreover, insulin accelerates the process of glycolysis, the pentose phosphate cycle, and glycogen synthesis in the liver.[27] The hydroxycinnamic acids in Tamarillo also influenced this signaling pathway by interacting with the INS (Insulin) target protein, thereby helping to optimise cell response to insulin. The glucagon signaling pathway was associated with the regulation of glucagon, a hormone that plays a role in increasing blood sugar levels in the body. Tumor Necrosis Factor Alpha (TNF-α) is a cytokine produced by inflammatory and adipocyte cells in response to chronic inflammation, such as that which occurs in type 2 DM.[1] TNF-α is a major proinflammatory cytokine that plays a vital role in the development of insulin resistance. TNF-α decreases the expression of the Insulin-Regulated Glucose Transporter Type 4 (GLUT4), mainly located in adipocytes, bone, and heart muscle. In addition, through induction of serine phosphorylation of the insulin receptor substrate-1, TNF-α acts as an inhibitor of peripheral insulin function, ultimately leading to insulin resistance.[28] In individuals with type 2 DM, TNF-α levels in the blood tend to be high, causing chronic inflammation and interfering with insulin function.[29] TNF increases metabolic activity, suggesting that several adipocyte-derived factors were related to insulin resistance.[2] The hydroxycinnamic acids in Tamarillo also affect this signaling pathway by interacting with the TNF (Tumor Necrosis Factor) target protein, an inflammatory factor in regulating glucagon and glucose metabolism. By the influence of hydroxycinnamic acid on these three signaling pathways, Tamarillo has the potential to help lower blood sugar levels and prevent insulin resistance in people with type 2 diabetes mellitus. An approach to tissue pharmacology is crucial to understanding this compound's molecular mechanisms in treating type 2 diabetes mellitus of type 2 DM.

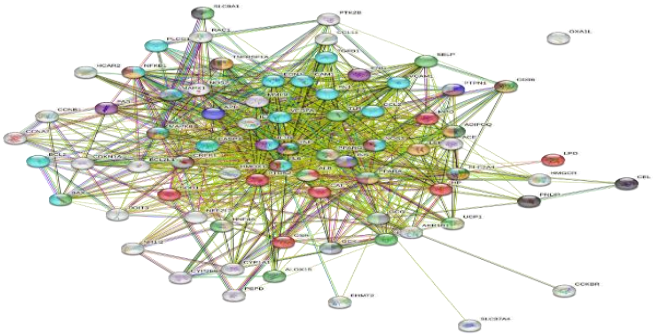

Figure 3: Interaction network of 150 core proteins from the STRING database (75 nodes, 988 edges, PPI enrichment p-value: < 1.0e-16

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Table 3: Result of the KEGG gene interaction analysis of Tamarillo

Pathway	Description	Count in network	Strength	False Discovery Rate	Gene Ontology
Hsa04933	AGE-RAGE signaling pathway in diabetic complications	18 of 98	1.68	4.70e-22	Insulin receptor binding (GO:0005158)
hsa04930	Type II diabetes mellitus	7 of 46	1.6	8.70e-09	Antioxidant activity (GO: 0016209)
hsa04920	Adipocytokine signaling pathway	9 of 69	1.53	2.01e-10	Fatty acid binding (GO:0005504)
hsa04940	Type I diabetes mellitus	5 of 39	1.52	3.20e-06	Lipid binding (GO:0008289)
hsa04931	Insulin resistance	12 of 107	1.47	6.31e-13	
hsa04911	Insulin secretion	4 of 82	1.1	0.00099	
hsa04910	Insulin signaling pathway	6 of 133	1.07	6.10e-05	
hsa04922	Glucagon Signaling Pathway	4 of 101	1.01	0.0020	

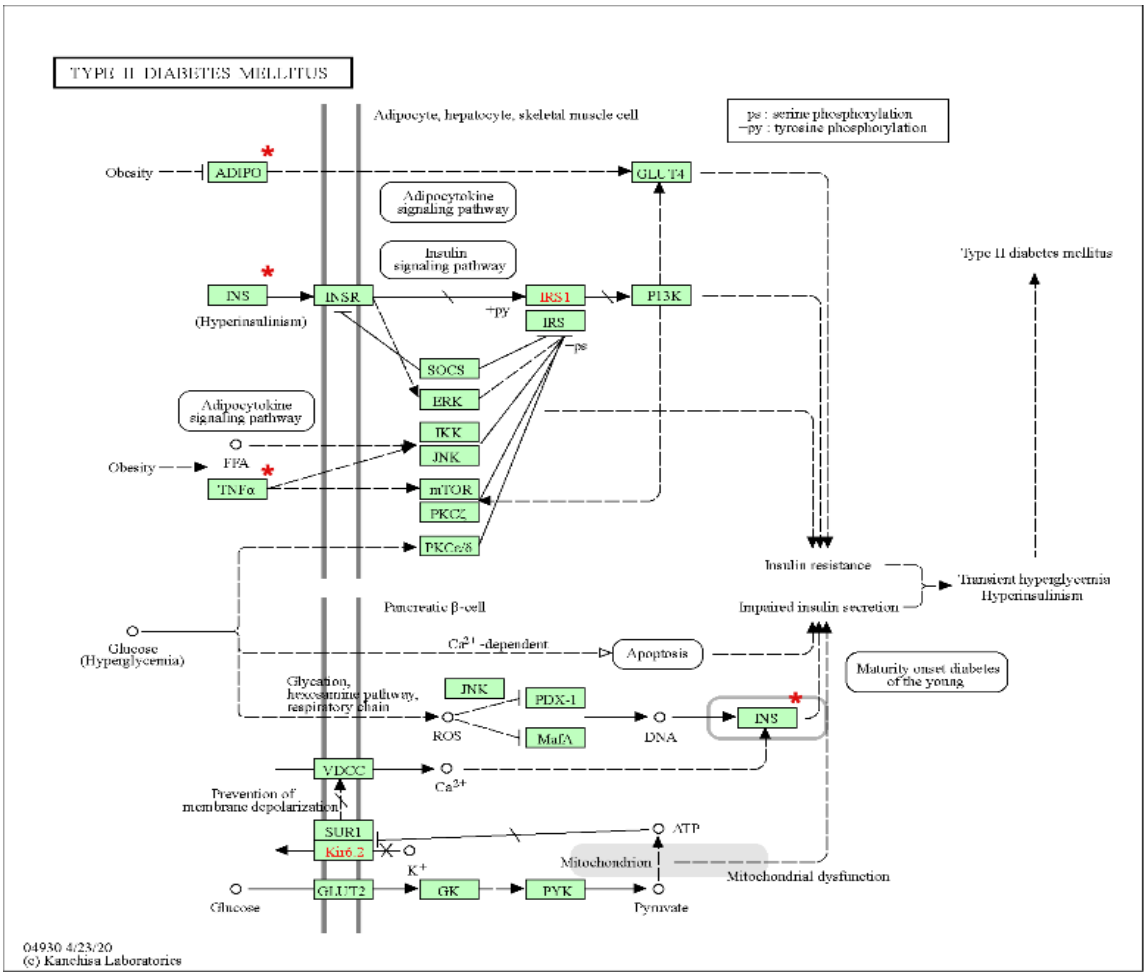

Figure 4: Type II DM signaling pathway (KEGG:04930)

Conclusion

In conclusion, Network Pharmacology analysis revealed a total of 365 target proteins associated with tamarillo fruit, of which 150 were involved in biological processes and signaling pathways associated with type 2 DM. 75 of these target proteins had unique roles and were locked, interacting in the disease context. The target proteins most associated with type 2 DM in the data were MAPK1, MAPK8, TNF, INS, ADIPOQ, and SLC2A4. Also, six bioactive components from the hydroxycinnamic acid group with activity in type 2 DM were identified in Tamarillo fruit. These compounds affected biological processes and signaling pathways in type 2 DM, namely the Adipocytokine, Insulin, and glucagon Signaling Pathways. Therefore, Tamarillo fruit can be a safe and natural treatment alternative for patients with type 2 DM.

Conflict of Interest

The authors declare no conflict of interest.

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.

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