Original Article

Available online at
www.heca-analitika.com/malacca_pharmaceutics

Malacca Pharmaceutics

Vol. 2, No. 1, 2024

Network Pharmacology Approach to Understanding the Antidiabetic Effects of Pineapple Peel Hexane Extract

Christa Hana Angle Pendong [1], Elly Juliana Suoth [1], Fatimawali Fatimawali [1] and Trina Ekawati Tallei [2,3,*]

[1] Pharmacy Study Program, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado, Indonesia; christahanapendong@gmail.com (C.H.A.P.), ellysuoth@unsrat.ac.id (E.J.S.), fatimawali@unsrat.ac.id (F.F.)
[2] Department of Biology, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado, Indonesia; trina_tallei@unsrat.ac.id (T.E.T.)
[3] Department of Biology, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia

* Correspondence: trina_tallei@unsrat.ac.id

Article History

Received 24 January 2024
Revised 13 March 2024
Accepted 22 March 2024
Available Online 29 March 2024

Keywords:
Network Pharmacology
Pineapple peel
Type 2 Diabetes Melitus
MAPK1

Abstract

The increased interest in exploring alternative treatments for type 2 diabetes mellitus is accompanied by a rise in the prevalence of type 2 diabetes mellitus. Pineapple peel is one of the by-products of pineapple fruit and is known to possess potential for anti-diabetic activity. In this study, the n-hexane extract of pineapple peel was analyzed using network pharmacology methods to ascertain its potential in treating type 2 diabetes mellitus. The GC-MS analysis of the n-hexane extract of pineapple peel revealed the presence of 42 compounds, with 8 of them considered safe as they met the Lipinski Rule of Five criteria for drug-likeness and were classified as safe with toxicity levels in classes IV and V. The pineapple peel extract targeted 55 proteins related to type 2 diabetes mellitus (DMT2), potentially affecting DMT2 through the AGE-RAGE pathway in diabetes complications and insulin resistance. Network pharmacology analysis identified five genes targeted by pineapple peel, namely MAPK1, JAK2, MAPK8, PRKCD, and PPARA. Among these genes, MAPK1 exhibited a higher overall score than the others. Apart from its role in diabetes, MAPK1 is also implicated in cancer.

1. Introduction

Diabetes Mellitus has emerged as a global health threat due to its potential for mortality [1]. Diabetes mellitus is a serious long-term or chronic condition that occurs when there is an increase in blood glucose levels due to the body's inability to produce enough insulin or to use insulin effectively in some cases [2, 3].

Based on its pathogenesis, diabetes mellitus is classified into three types: type 1, type 2, and gestational diabetes mellitus. The most prevalent case of diabetes is type 2 diabetes mellitus, which is a multifactorial disease caused by insulin resistance. It leads not only to hyperinsulinemia and hyperglycemia but also to atherosclerosis, hypertension, and lipid abnormalities [4].

Treatment for individuals with diabetes mellitus is divided into two approaches, including medication therapy involving the consumption of diabetes medication and insulin injections and non-medication therapy aimed at improving lifestyle by consuming nutritious foods and engaging in regular exercise [5]. Medication therapy is administered if non-medication therapy fails or if blood sugar levels cannot be controlled

[6]. However, pharmacological therapy for diabetes with synthetic chemical drugs may potentially induce various side effects when used over the long term. Therefore, safer alternatives for diabetes treatment are needed by harnessing bioactive substances from natural ingredients such as fruits and vegetables [7, 8], one of which is pineapple (*Ananas comosus* L.).

In a study investigating the effects of pineapple peel vinegar, a researcher tested its impact on rats induced by alloxan. The findings indicated reduced blood glucose levels among the tested rats [7]. However, to develop information, it is necessary to analyze with other methods to strengthen information related to its activity against diabetes. Therefore, in-silico tests were conducted to find out what causes pineapple peel to have antidiabetic activity and how strong its potential is. Network pharmacology study is a concept coined by Hopkins in 2007, which states that drugs or compounds act on multiple targets [9]. Based on bioinformatics, biological systems, and biochemistry theories, network pharmacology predicts the mechanism between drug compounds and pharmacological conditions through interactions among multi-components and multi-targets [10, 11].

This study aims to employ network pharmacology to uncover the mechanisms responsible for the antidiabetic effects of pineapple peel vinegar. By integrating principles from bioinformatics, biological systems, and biochemistry, this research aims to elucidate how the bioactive compounds present in pineapple peel vinegar interact with specific targets within the biological pathways relevant to diabetes mellitus. Through a comprehensive analysis of these interactions, including multi-components and multi-targets, the study offers insights into the therapeutic potential of pineapple peel vinegar as a natural remedy for diabetes management. Ultimately, the findings from this investigation aim to advance our understanding of safer and more efficacious treatments for diabetes mellitus, addressing the global health challenge posed by this condition.

2. Materials and Methods

2.1. Profiling of Pineapple Peel Extract

The PubChem website (https://pubchem.ncbi.nlm.nih.gov/) was utilized to retrieve the Simplified Molecular-Input Line-Entry System (SMILES) profiles and three-dimensional (3D) structures of each component identified in the Gas Chromatography-Mass Spectrometry (GC-MS) analysis of n-hexane extract from pineapple peel.

2.2. Prediction of Bioactive Compound Activity

The potential of pineapple peel extract compounds for antidiabetic activity, specifically Type 2 Diabetes Mellitus, is analyzed using the prediction website WAY2DRUG PASS (https://way2drug.com/PassOnline). This website employs Structure Activity Relationship (SAR) analysis to compare input compounds with known compounds that exhibit specific potency. The potential activity of compounds on this website will be indicated by the Pa (Probability active) score. The interpretation of the Pa value is divided into three groups. First, if the Pa value < 0.3, the input compound will likely have almost no biological activity. Second, if the value of 0.3 < Pa < 0.7, it is likely to have a >50% chance of having the expected biological activity. Third, if the Pa value is > 0.7, the possibility of finding activity in the experiment is quite high, according to the results of in vitro and in vivo testing [12, 13].

2.3. Pharmacokinetic Analysis

Several crucial parameters in the development of new drugs include Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET), which are used to assess how a drug operates within the body, including absorption into the bloodstream, distribution to tissues, metabolism by enzymes, excretion, and potential toxic effects. Lipinski's Rule of 5 (Ro5) serves as a reference todetermine the drug-likeness characteristics of each ligand. The SMILES notation of each ligand functions as input for analysis using the ADMETLab 2.0 database (https://admetmesh.scbdd.com/service/evaluation/index) [14] and the Protox II database (https://comptox.charite.de/protox3/) [15].

2.4. Identification and Analysis of Protein Targets

SwissTargetPrediction (http://www.swisstargetprediction.ch/) and Similarity Ensemble Approach (SEA) (https://sea.bkslab.org/) were used to analyze the target protein of the pineapple peel compound. Prediction results can be obtained by entering the identified SMILES notation. Genes associated with type 2 diabetes mellitus were retrieved from the GeneCards database (https://www.genecards.org/). Then, the disease targets and pineapple peel extract targets were mapped using a Draw Venn Diagram (https://bioinformatics.psb.ugent.be/webtools/Venn/) to determine the intersection of targets. Targets from pineapple peel extract were annotated using the ShinyGO webserver (http://bioinformatics.sdstate.edu/go74/), with a focus on biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

Table 1. GC-MS analysis results and compounds profile of pineapple peel hexane extract from PubChem database.

Code	Chemical Formula	Compound IUPAC Names	SMILES
C1	C_9H_{20}	2,3,4-trimethylhexane	CC(C)CC(C)C(C)C
C2	C_9H_{20}	2,4-dimethylheptane	CCCC(C)CC(C)C
C3	C_9H_{18}	2,4-dimethylhept-1-ene	CCCC(C)CC(=C)C
C4	C_9H_{20}	4-methyloctane	CCCCC(C)CCC
C6	$C_{10}H_{22}$	2,4,6-trimethylheptane	CC(C)CC(C)CC(C)C
C14	$C_{10}H_{22}O$	1-Heptanol, 2-propyl	CCCCCC(CCC)CO
C10	$C_{11}H_{24}$	4-methyldecane	CCCCCCC(C)CCC
C12	$C_{11}H_{24}$	Undecane	CCCCCCCCCCC
C9	$C_{12}H_{14}N_4O_4$	2-vinyl-9-[3-deoxy-β-d-ribofuranosyl] hypoxanthine	C=CC1=NC2=C(C(=O)N1)N=CN2C3C(CC(O3)CO)O
C19	$C_{12}H_{25}Br$	2-Bromo dodecane	CCCCCCCCCCC(C)Br
C22	$C_{12}H_{26}O$	1-Octanol, 2-butyl-	CCCCCCC(CCCC)CO
C29	$C_{12}H_{25}I$	1-Iodo-2-methylundecane	CCCCCCCCCC(C)CI
C7	$C_{13}H_{28}$	2,6,7-trimethyldecane	CCCCC(C)C(C)CCC(C)C
C11	$C_{14}H_{30}O_3S$	Sulfurous acid, nonyl pentyl ester	OS(=O)O
C15	$C_{14}H_{30}$	2,3,5,8-tetramethyldecane	CCC(C)CCC(C)CC(C)C(C)C
C30	$C_{14}H_{30}O$	2-Hexyl-1-octanol	CCCCCCC(CCCCCC)CO
C13	$C_{15}H_{27}F_3O_2$	4-triflouroacetoxytridecane	CCCCCCCCCC(CCC)OC(=O)C(F)(F)F
C20	$C_{15}H_{32}$	2,7,10-trimethyldodecane	CCC(C)CCC(C)CCCCC(C)C
C21	$C_{15}H_{32}$	2,6,11-trimethyldodecane	CC(C)CCCCC(C)CCCC(C)C
C27	$C_{16}H_{34}$	Hexadecane	CCCCCCCCCCCCCCCC
C5	$C_{17}H_{31}F_3O_2$	3-triflouroacetoxypentadecane	CCCCCCCCCC CCC(CC)OC(=O)C(F)(F)F
C16	$C_{17}H_{31}F_3O_2$	3- Trifluoroacetoxypentadecane	CCCCCCCCCCC(CC)OC(=O)C(F)(F)F
C17	$C_{17}H_{31}F_3O_2$	2-Trifluoroacetoxypentadecane	CCCCCCCCCCCCCC(C)OC(=O)C(F)(F)F
C18	$C_{17}H_{36}$	2,6,10-trimethyltetradecane	CCCCC(C)CCCC(C)CCCC(C)C
C23	$C_{17}H_{36}$	Tetradecane, 2,6,10-trimethyl-	CCCCC(C)CCCC(C)CCCC(C)C
C31	$C_{17}H_{36}O$	1-Hexadecanol, 2-methyl-	CCCCCCCCCCCCCCC(C)CO
C37	$C_{17}H_{34}O_2$	Tridecanoic acid, 4,8,12-trimethyl-, methyl ester	CC(C)CCCC(C)CCCC(C)CCC(=O)OC
C24	$C_{18}H_{33}F_3O_2$	4- Trifluoroacetoxyhexadecane	CCCCCCCCCCCCC(CCC)OC(=O)C(F)(F)F
C25	$C_{18}H_{33}Cl_3O_2$	Trichloroacetic acid, hexadecyl ester	CCCCCCCCCCCCCCCCOC(=O)C(Cl)(Cl)Cl
C35	$C_{18}H_{34}O$	15-Octadecenal	CCC=CCCCCCCCCCCCCCC=O
C38	$C_{18}H_{36}O$	Octadecanal	CCCCCCCCCCCCCCCCCC=O
C39	$C_{18}H_{34}O$	10-Octadecenal	CCCCCCCC=CCCCCCCCCC=O
C8	$C_{19}H_{40}$	6-methyloctadecane	CCCCCCCCCCCCC(C)CCCCC
C32	$C_{20}H_{42}O_2$	Ethanol, 2-(octadecyloxy)-	CCCCCCCCCCCCCCCCCCOCCO
C33	$C_{20}H_{42}$	2-methylnonadecane	CCCCCCCCCCCCCCCCCC(C)C
C26	$C_{21}H_{44}$	2,6,10,15-tetramethylheptadecane	CCC(C)CCCCC(C)CCCC(C)CCCC(C)C
C28	$C_{21}H_{44}$	2-methyleicosane	CCCCCCCCCCCCCCCCCCC(C)C
C34	$C_{23}H_{44}O_3$	Carbonic acid, eicosyl vinyl ester	CCCCCCCCCCCCCCCCCCCCOC(=O)OC=C
C36	$C_{26}H_{54}$	7-hexyleicosane	CCCCCCCCCCCCCC(CCCCCC)CCCCCC
C40	$C_{26}H_{54}$	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	CCCCCCCCCCCCCC(CC(CC)CC)CC(CC)CC
C41	$C_{26}H_{44}O_5$	Ethyl iso-allocholate	CCOC(=O)CCC(C)C1CCC2C1(C(CC3C2C(CC4C3(CCC(C4)O)C)O)O)C
C42	$C_{54}H_{108}Br_2$	1,54-dibromotetrapentacontane	C(CCCCCCCCCCCCCCCCCCCCCCCCCCCBr)CCCCCCCCCCCCCCCCCCCCCCCCCCBr

2.5. Network Pharmacology Analysis

The protein target data originating from pineapple peel, along with the intersecting proteins related to DMT2, including the insulin receptor (INSR), were uploaded to the STRING Version 11.5 database (a search tool for retrieving interacting genes/proteins) to analyze their interactions. The organism chosen for analysis was Homo sapiens (human). The analysis data generated, presented in TSV format from the STRING database, were further processed using CytoScape Version 3.10.

3. Results and Discussion

3.1. Pineapple Peel Hexane Extract Profile

The GC-MS analysis of n-hexane extract from pineapple peel yielded 42 compounds, and the corresponding SMILES data have been compiled (Table 1). The SMILES information retrieved from the PubChem database is essential for the subsequent phase.

Nearly all compounds demonstrate insulin promoter potential (Figure 1), so their potential as insulin promoters is the primary foundation for the treatment of type 2 diabetes mellitus. Among these compounds, 26

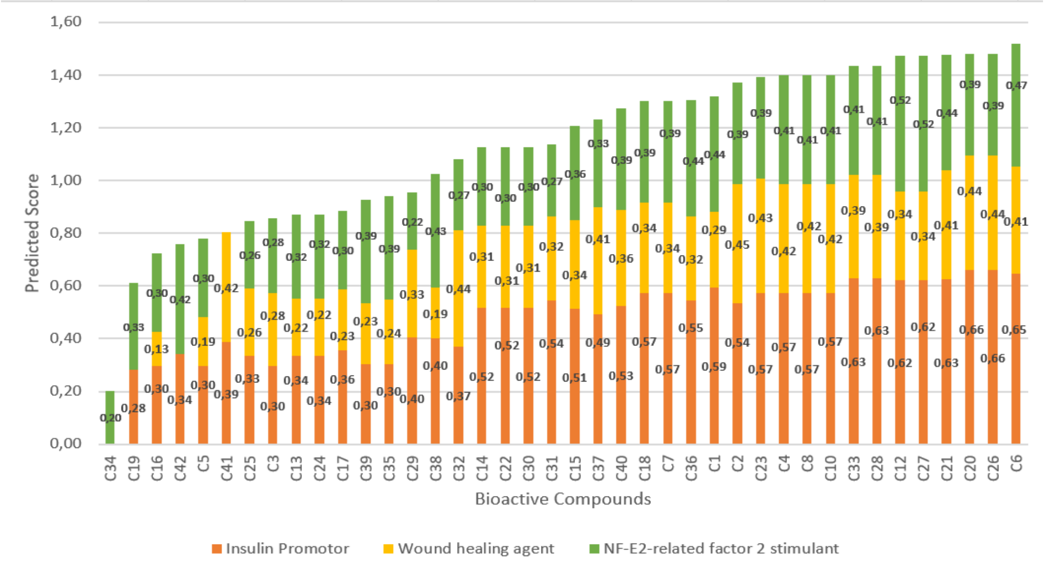


Figure 1. Cumulative predictive score of pineapple peel extract for treating T2DM based on Structure-Activity-Relationship (SAR) using the WAY2DRUG website. This assessment includes the impact as an insulin promoter, wound healing agent, and Nrf2 stimulant.

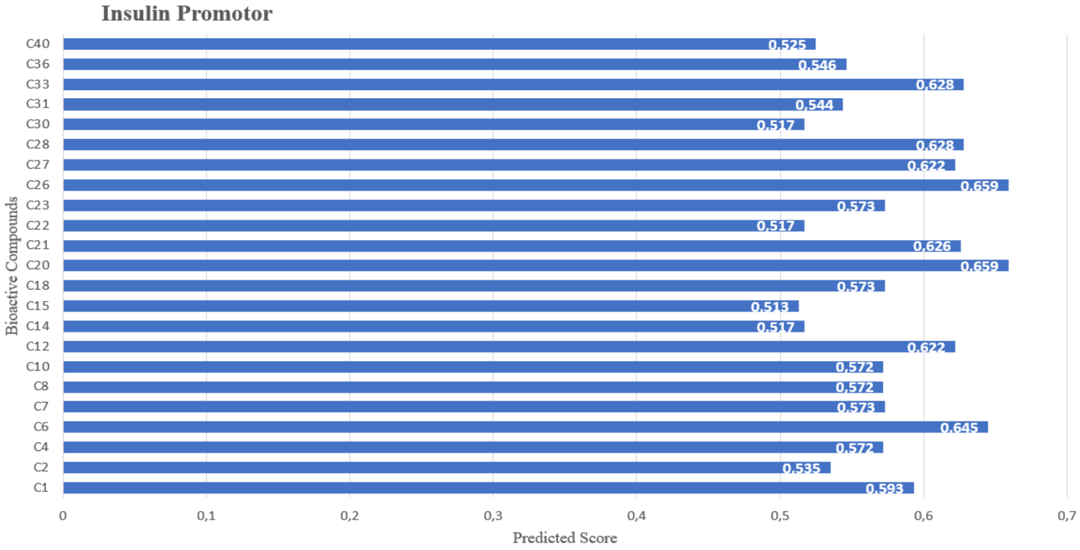


Figure 2. SAR prediction of the potential of pineapple peel for treating T2DM, especially its potential as an insulin promoter. Compounds C20 and C26 have the highest predictive value as insulin promoters with a Pa score of 0.659.

were found with an insulin promoter Pa score > 0.4 (Figure 2).

3.2. Potential of Pineapple Peel Extract in the Treatment of Type 2 Diabetes Mellitus

Diabetes results from elevated blood glucose levels. Individuals with diabetes face the risk of developing wounds, referred to as diabetic ulcers, necessitating the use of wound-healing agents to facilitate the healing process [16]. In addition, Nrf2 (Nuclear-factor erythroid 2 (NF-E2)-related factor) is a transcription protein that regulates genes involved in antioxidant and anti-inflammatory responses. Its association with type 2 diabetes mellitus is due to its protective mechanism against oxidative damage and inflammation that can worsen diabetic conditions. In the study of Sireesh et al. [17], impaired insulin secretion in pancreatic β cells caused by cytokine stress can be restored by Nrf2 activation, as assessed by glucose-stimulated insulin secretion (GSIS). Oxidative stress is a common pathogenic factor thought to cause insulin resistance, impaired glucose tolerance, and β-cell dysfunction [18]. Thus, the Nrf2 pathway may also play a role in treating widespread oxidative damage, such as pancreatic damage, insulin resistance, and a spectrum of diabetic complications. Therefore, activation of Nrf2 can enhance antioxidant defense and reduce oxidative stress. Additionally, insulin promoters are one of the factors whose function is to increase the production and release of insulin by pancreatic beta cells. Under normal

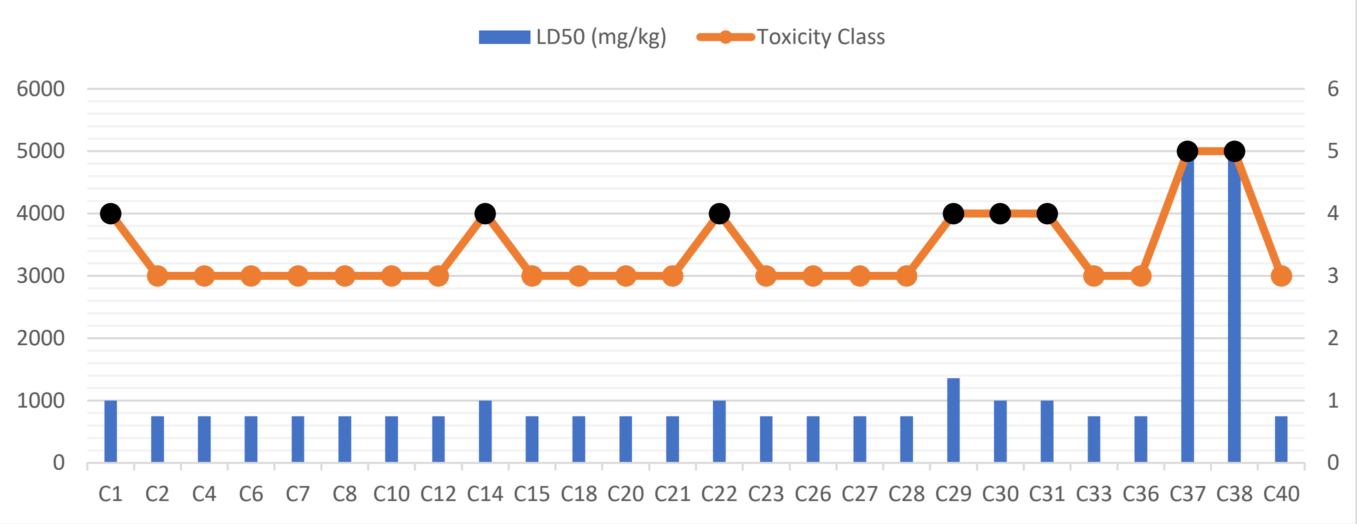
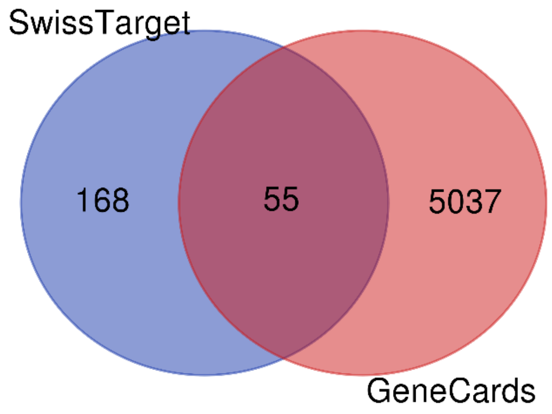


Figure 3. Toxicity prediction based on the LD_{50} and toxicity classes of each compound detected in pineapple peel. Black dots indicate the presence of eight compounds that are the focus of further analysis, namely C1, C14, C22, C29, C30, C37, and C38.



55 protein targets of pineapple peel active compound

NOS2, CDK8, SHBG, CCR3, ASAH1, CYP19A1, PDGFRB, SHH, JAK2, GCGR, QRFPR, PRKCD, POLA1, ACHE, BRD1, PTPN1, IGF1R, IL6ST, CIT, AR, MDM4, FABP5, CTSK, ESR1, PDE4D, HMGCR, HMOX1, MC4R, FLT1, GLRA1, CA4, MAPK1, TYK2, MAPK8, PHF8, CYP17A1, PRKCQ, MAP3K11, KDM5C, PPARG, NR3C1, PFKFB3, RARA, PDE2A, PPARA, RORA, RASGRP1, AVPR1A, SLC9A1, OPRM1, SLC5A2, DDR1, ABHD6, CYP24A1, PNPLA2.

Figure 4. Mapping results between pineapple peel target proteins and type 2 diabetes mellitus disease proteins.

conditions, pancreatic beta cells will secrete insulin after eating or after the release of hormones such as catecholamines and glucagon. Disruptions in the body's production or response to insulin can lead to diabetes, so the involvement of insulin promoters is important [19]. Consequently, these activities—Nrf2, insulin promotion, and wound healing—are indispensable in supporting diabetes treatment.

3.3. Pharmacokinetic Analysis and Drug-Likeness Assessment

A total of 26 analyzed compounds exhibited adherence to the Ro5 and demonstrated drug-like properties. Meanwhile, ADMET analysis results indicated that several compounds possessed favorable pharmacodynamic and pharmacokinetic characteristics. Among the 26 bioactive compounds, C1, C14, C22, C29, C30, C31, C37, and C38 were taken for further analysis (Figure 3). The eight compounds have bioactive activity with Class IV and V toxicity, which are predicted to have low toxicity and are classified as safe. Generally, the results of the assessment of bioactive compounds show low toxicity if they are in classes IV and V. However, it is excluded for certain compounds that require attention because they have the potential to cause human hepatotoxicity (H-HT), drug-induced liver injury (DILI), mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity when in the form of single compounds [14].

3.4. Potential Protein Targets and Biological Pathways

Eight compounds were selected after passing pharmacodynamic, pharmacokinetic, toxicity, drug-likeness, and Lipinski's Rule of Five tests. Subsequently, they proceeded to the identification stage of protein target targets. Data on the compounds' protein targets were obtained from SwissTarget and disease protein targets from GeneCards. These databases were then inputted into the Draw Venn Diagram website. The results indicated 55 interrelated protein targets between the compound protein targets in pineapple peel and the type 2 diabetes mellitus disease protein targets (Figure 4).

The analysis results utilizing the KEGG pathway (Figure 5) indicate that the significant pathway related to DMT2 among pineapple peel targets is the AGE-RAGE signaling pathway in diabetes complications. Four genes are involved in this pathway, namely Janus kinase 2 (JAK2), mitogen-activated protein kinase 1 (MAPK1), mitogen-

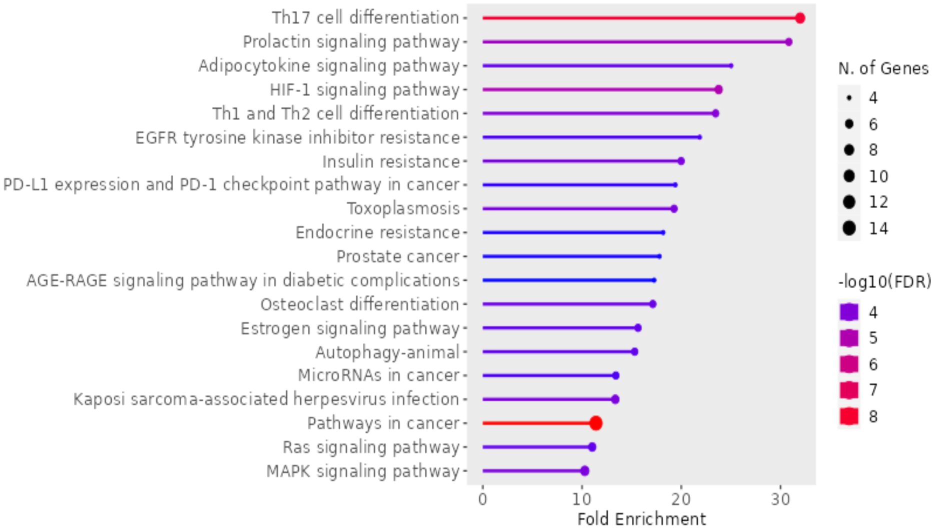


Figure 5. Annotation of the top 20 KEGG pathways targeted by pineapple peel using the ShinyGO website.

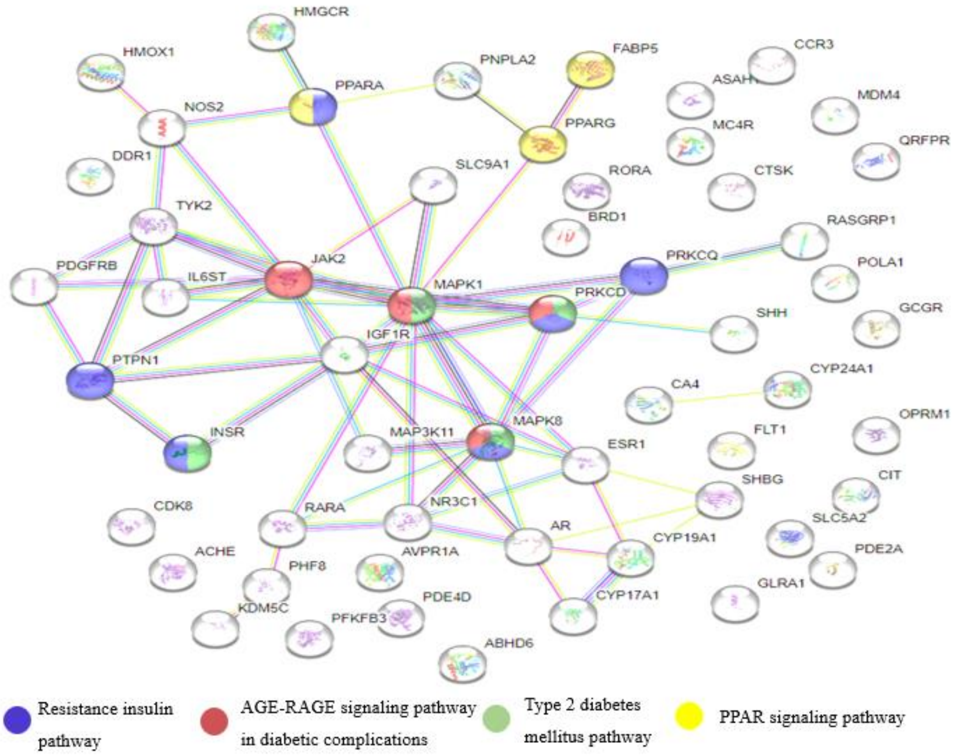


Figure 6. The analysis results using STRING version 11.5 with an interaction score of 0.700 (high confidence).

ativated protein kinase 8 (MAPK8), and protein kinase C delta (PRKCD).

The activity of pineapple peel indicated in Figure 5 is highest in the cancer pathway, marked by red lines and dots. Several proteins involved in this pathway include NOS2, ESR1, JAK2, MAPK1, HMOX1, MAPK8, CCND1, PDGFRB, CDK2, RARA, PPARG, IL6ST, IGF1R, CASP3, SHH, AR, and RASGRP1. However, the results from ShinyGO also indicate that pineapple peel has potential targets in the pathway for type 2 diabetes mellitus therapy. Among these pathways is the AGE-RAGE signaling pathway in diabetes complications and insulin resistance. Proteins involved in this pathway include JAK2, MAPK1, MAPK8, CCND1, PRKCD, CASP3, PRKCQ, PPARA, and PTPN1.

3.5. Network Pharmacology Analysis

STRING analysis focused on proteins with an interaction score of 0.700 (high confidence). This value means the higher the interaction score, the more biologically meaningful the interaction is [12]. Through network pharmacology analysis, nine potential proteins besides INSR are involved in several diabetes-related pathways,

Figure 7. Visualization of Protein-Protein Interaction (PPI) targeting pineapple peel bioactive compounds on T2DM using Cytoscape 3.10 with a confidence value of 0.7. Proteins that have binding networks with INSR include PTPN1. Meanwhile, MAPK1 is highlighted in dark red as it has the highest degree value.

Table 2. Top five results of Protein-Protein Interaction (PPI) related to type 2 diabetes mellitus.

Proteins	Degree	Betweenness Centrality	Closeness Centrality	Overall Score	Pathway
MAPK1	13	0.48	0.6	14.08	AGE-RAGE signaling pathway in T2DM diabetic complications
JAK2	10	0.15	0.5	10.65	AGE-RAGE signaling pathway in diabetic complications
MAPK8	8	0.10	0.48	8.58	AGE-RAGE signaling pathway in diabetic complications, insulin resistance, T2DM
PTPN1	5	0.01	0.37	5.38	Insulin resistence
PPARA	4	0.11	0.42	4.53	Insulin resistance, PPAR signaling pathway

including MAPK1, MAPK8, PRKCD, JAK2, PPARA, PRKCQ, PPARG, PTPN1, and FABP5 (Figure 6). Based on degree, betweenness centrality, and closeness centrality, there are five potential protein targets from pineapple peel, namely MAPK1, JAK2, MAPK8, PTPN1, and PPARA.

Degree, closeness centrality, and betweenness centrality are classical centrality metrics used to analyze proteins that play crucial roles in biological networks. Degree is the number of neighbors each node has. Closeness centrality measures how quickly impact or information flows from one node to another [20]. In addition, Closeness centrality is meant to measure the total distance from one node to all other nodes in the network [21].

In this study, the genes involved in the AGE-RAGE signaling pathway in diabetic complications are MAPK1, JAK2, and MAPK8. Based on data from the KEGG website, the AGE-RAGE signaling triggers the activation of several intracellular signaling pathways involving NADPH oxidase, protein kinase C, and MAPK, also resulting in NF-kappaB activity. NF-kappaB activity induces the expression of proinflammatory cytokines such as RAGE. Another study also reported inhibiting the AGE-RAGE signaling pathway in diabetes can ameliorate diabetes-induced retinal damage [22].

MAPK1, JAK2, and MAPK8 are among the top three protein targets from pineapple peels associated with the AGE-RAGE signaling pathway in diabetes complications. At the same time, PTPN1 and PPARA are identified as protein targets in the insulin resistance pathway (Table 2). MAPK1 is highlighted as a target of active compounds associated with the anti-inflammatory pathway [23]. According to Sukmanadi et al. [24], MAPK1 is also a target in anticancer pathways due to its apoptosis-related activities. The involvement of JAK2 in diabetes is also depicted in Figure 7. Gurzov et al. [25] suggest that JAK2 regulates the functions of muscle, liver, brain, pancreas, fat, and immune system under normal homeostatic conditions and in obesity and diabetes. MAPK1 and MAPK8 play roles in glucose metabolism, obesity, hyperglycemia, and hyperinsulinemia [26, 27]. Activation of PPARA reduces weight gain and improves insulin sensitivity in obese mice [28].

4. Conclusions

This study concludes that pineapple peel targets proteins associated with the AGE-RAGE signaling pathway in diabetes complications and insulin resistance, comprising five genes: MAPK1, JAK2, MAPK8, PTPN1, and PPARA. However, the ShinyGO analysis suggests that pineapple peel may be more significant in cancer diseases beyond its association with diabetes. Therefore, this research could pave the way for exploring pineapple peel activity in cancer therapy.

Author Contributions: Conceptualization, C.H.A.P. and T.E.T.; methodology, C.H.A.P.; software, E.J.S. and F.F.; validation, T.E.T., E.J.S. and F.F.; formal analysis, C.H.A.P. and T.E.T.; investigation, C.H.A.P.; resources, T.E.T.; data curation, C.H.A.P.; writing—original draft preparation, C.H.A.P., T.E.T., E.JS.; writing—review and editing, C.H.A.P., T.E.T., E.J.S..; visualization, C.H.A.P.; supervision, T.E.T., E.J.S., F.F.; project administration, T.E.T.; funding acquisition, C.H.A.P. All authors have read and agreed to the published version of the manuscript.

Funding: This study does not receive external funding.

Ethical Clearance: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting this study's findings are available upon request from the corresponding author.

Conflicts of Interest: All the authors declare that there are no conflicts of interest.

References

1. Tan, S. Y., Mei Wong, J. L., Sim, Y. J., Wong, S. S., Mohamed Elhassan, S. A., Tan, S. H., Ling Lim, G. P., Rong Tay, N. W., Annan, N. C., Bhattamisra, S. K., and Candasamy, M. (2019). Type 1 and 2 Diabetes Mellitus: A Review on Current Treatment Approach and Gene Therapy As Potential Intervention, *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, Vol. 13, No. 1, 364–372. doi:10.1016/j.dsx.2018.10.008.
2. International Diabetes Federation. (2021). *IDF Diabetes Atlas* (10th ed.), International Diabetes Federation.
3. Maulana, A., Faisal, F. R., Noviandy, T. R., Rizkia, T., Idroes, G. M., Tallei, T. E., El-Shazly, M., and Idroes, R. (2023). Machine Learning Approach for Diabetes Detection Using Fine-Tuned XGBoost Algorithm, *Infolitika Journal of Data Science*, Vol. 1, No. 1, 1–7. doi:10.60084/ijds.v1i1.72.
4. Selvaraj, D. J. (2018). Identification of New Antidiabetic Agents Targeting GLUT4 Protein Using In Silico Analysis, *International Journal of Green Pharmacy*, Vol. 12, No. 04. doi:10.22377/ijgp.v12i04.2269.
5. Lestari, L., and Zulkarnain, Z. (2021). Diabetes Melitus: Review Etiologi, Patofisiologi, Gejala, Penyebab, Cara Pemeriksaan, Cara Pengobatan dan Cara Pencegahan, *Prosiding Seminar Nasional Biologi* (Vol. 7), 237–241.
6. Hamzah, D. F. (2019). Analisis Penggunaan Obat Herbal Pasien Diabetes Mellitus Tipe Ii Di Kota Langsa, *JUMANTIK (Jurnal Ilmiah Penelitian Kesehatan)*, Vol. 4, No. 2, 168–177.
7. Purba, E. C. (2020). Kelor (Moringa oleifera Lam.): Pemanfaatan dan Bioaktifitas, *Pro-Life*, Vol. 7, No. 1, 1–12. doi:10.33541/jpvol6Iss2pp102.
8. Abas, A. H., Tallei, T. E., Idroes, R., and Fatimawali, F. (2023). Ficus minahassae (Teijsm. & de Vriese) Miq.: A Fig Full of Health Benefits from North Sulawesi, Indonesia: A Mini Review, *Malacca Pharmaceutics*, Vol. 1, No. 1, 1–7. doi:10.60084/mp.v1i1.24.
9. Hopkins, A. L. (2007). Network Pharmacology, *Nature Biotechnology*, Vol. 25, No. 10, 1110–1111. doi:10.1038/nbt1007-1110.
10. Syahruni, R., Umar, A. H., Rahman, H. N., and Kusuma, W. A. (2023). Exploration of Annona muricata (Annonaceae) in the Treatment of Hyperlipidemia through Network Pharmacology and Molecular Docking, *Sains Malaysiana*, Vol. 52, No. 3, 899–939. doi:10.17576/jsm-2023-5203-17.
11. Tang, Y., Su, H., Wang, H., Lu, F., Nie, K., Wang, Z., Huang, W., and Dong, H. (2021). The Effect and Mechanism of Jiao-Tai-Wan in the Treatment of Diabetes Mellitus with Depression Based on Network Pharmacology and Experimental Analysis, *Molecular Medicine*, Vol. 27, No. 1, 154. doi:10.1186/s10020-021-00414-z.
12. Firzannida, F., Bagaskara, S., Savira, S. S., Fadnurrahim, A., and Rofida, S. (2022). Network Pharmacology of Black Cumin (Nigella sativa L.) as a Candidate of OMAI in Colorectal Cancer: In Silico Study, *Indonesian Journal of Biotechnology*, Vol. 27, No. 2, 87. doi:10.22146/ijbiotech.70699.
13. Raihan, A., Illahi, A. K., Rokhimah, S., Elisa, T. P. P., and Maliza, R. (2023). Identification of Bioactive Solutions of Corn Silk (Zea mays L.) Extract and Biological Activity Test By Bioinformatics, *Jurnal Biologi Tropis*, Vol. 23, No. 1, 245–250. doi:10.29303/jbt.v23i1.5846.
14. Fatimawali, Tallei, T. E., Kepel, B. J., Bodhi, W., Manampiring, A. E., and Nainu, F. (2023). Molecular Insight into the Pharmacological Potential of Clerodendrum minahassae Leaf Extract for Type-2 Diabetes Management Using the Network Pharmacology Approach, *Medicina*, Vol. 59, No. 11, 1899. doi:10.3390/medicina59111899.
15. Tania, A. D., Kalalo, M. J., Kepel, B. J., Niode, N. J., Kusumawaty, D., and Idroes, R. (2022). Evaluation of the Potential for Immunomodulatory and Anti-inflammatory Properties of Phytoconstituents Derived from Pineapple [Ananas comosus (L.) Merr.] Peel Extract Using an In Silico Approach, *Philippine Journal of Science*, Vol. 151, No. 1, 397–410.
16. Apolinário, P. P., Zanchetta, F. C., Breder, J. S. C., Adams, G., Consonni, S. R., Gillis, R., Saad, M. J. A., and Lima, M. H. M. (2023). Anti-Inflammatory, Procollagen, and Wound Repair Properties of Topical Insulin Gel, *Brazilian Journal of Medical and Biological Research*, Vol. 56. doi:10.1590/1414-431x2023e12640.
17. Sireesh, D., Dhamodharan, U., Ezhilarasi, K., Vijay, V., and Ramkumar, K. M. (2018). Association of NF-E2 Related Factor 2 (Nrf2) and inflammatory cytokines in recent onset Type 2 Diabetes Mellitus, *Scientific Reports*, Vol. 8, No. 1, 5126. doi:10.1038/s41598-018-22913-6.
18. Harkin, C., Cobice, D., Watt, J., Kurth, M. J., Brockbank, S., Bolton, S., Johnston, F., Strzelecka, A., Lamont, J. V., Moore, T., Fitzgerald, P., and Ruddock, M. W. (2023). Analysis of Reactive Aldehydes in Urine and Plasma of Type-2 Diabetes Mellitus Patients through Liquid Chromatography-Mass Spectrometry: Reactive Aldehydes As Potential Markers of Diabetic Nephropathy, *Frontiers in Nutrition*, Vol. 9. doi:10.3389/fnut.2022.997015.
19. Tanase, D. M., Gosav, E. M., Costea, C. F., Ciocoiu, M., Lacatusu, C. M., Maranduca, M. A., Ouatu, A., and Floria, M. (2020). The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease

(NAFLD), *Journal of Diabetes Research*, Vol. 2020, 1–16. doi:10.1155/2020/3920196.

20. Evans, T. S., and Chen, B. (2022). Linking the Network Centrality Measures Closeness and Degree, *Communications Physics*, Vol. 5, No. 1, 172. doi:10.1038/s42005-022-00949-5.

21. Zhang, J., and Luo, Y. (2017). Degree Centrality, Betweenness Centrality, and Closeness Centrality in Social Network, *Proceedings of the 2017 2nd International Conference on Modelling, Simulation and Applied Mathematics (MSAM2017)*, Atlantis Press, Paris, France. doi:10.2991/msam-17.2017.68.

22. Xie, T., Chen, X., Chen, W., Huang, S., Peng, X., Tian, L., Wu, X., and Huang, Y. (2021). Curcumin is a Potential Adjuvant to Alleviates Diabetic Retinal Injury via Reducing Oxidative Stress and Maintaining Nrf2 Pathway Homeostasis, *Frontiers in Pharmacology*, Vol. 12. doi:10.3389/fphar.2021.796565.

23. Tallei, T. E., Fatimawali, Adam, A. A., Ekatanti, D., Celik, I., Fatriani, R., Nainu, F., Kusuma, W. A., Rabaan, A. A., and Idroes, R. (2024). Molecular Insights into the Anti-Inflammatory Activity of Fermented Pineapple Juice Using Multimodal Computational Studies, *Archiv Der Pharmazie*, Vol. 357, No. 1. doi:10.1002/ardp.202300422.

24. Sukmanadi, M., Sudjarwo, S. A., and Effendi, M. H. (2020). Molecular Mechanism of Capsaicin from (Capsicum Annuum L.) on Expression of MAPK1 and AKT1 Protein as Candidate of Anticancer Drugs: In silico Study, *Pharmacognosy Journal*, Vol. 12, No. 4, 916–919. doi:10.5530/pj.2020.12.130.

25. Gurzov, E. N., Stanley, W. J., Pappas, E. G., Thomas, H. E., and Gough, D. J. (2016). The Pathway in Obesity and Diabetes, *The FEBS Journal*, Vol. 283, No. 16, 3002–3015. doi:10.1111/febs.13709.

26. Hayashi, Y., Toyomasu, Y., Saravanaperumal, S. A., Bardsley, M. R., Smestad, J. A., Lorincz, A., Eisenman, S. T., Cipriani, G., Nelson Holte, M. H., Al Khazal, F. J., Syed, S. A., Gajdos, G. B., Choi, K. M., Stoltz, G. J., Miller, K. E., Kendrick, M. L., Rubin, B. P., Gibbons, S. J., Bharucha, A. E., Linden, D. R., Maher, L. J., Farrugia, G., and Ordog, T. (2017). Hyperglycemia Increases Interstitial Cells of Cajal via MAPK1 and MAPK3 Signaling to ETV1 and KIT, Leading to Rapid Gastric Emptying, *Gastroenterology*, Vol. 153, No. 2, 521-535.e20. doi:10.1053/j.gastro.2017.04.020.

27. Ganugula, R., Nuthalapati, N. K., Dwivedi, S., Zou, D., Arora, M., Friend, R., Sheikh-Hamad, D., Basu, R., and Kumar, M. N. V. R. (2023). Nanocurcumin Combined with Insulin Alleviates Diabetic Kidney Disease through P38/P53 Signaling Axis, *Journal of Controlled Release*, Vol. 353, 621–633. doi:10.1016/j.jconrel.2022.12.012.

28. Lee, D., Shin, Y., Roh, J. S., Ahn, J., Jeoong, S., Shin, S. S., and Yoon, M. (2020). Lemon Balm Extract ALS-L1023 Regulates Obesity and Improves Insulin Sensitivity via Activation of Hepatic PPARα in High-Fat Diet-Fed Obese C57BL/6J Mice, *International Journal of Molecular Sciences*, Vol. 21, No. 12, 4256. doi:10.3390/ijms21124256.