EduChemia
Jurnal Kimia dan Pendidikan

Vol.9, No.1, 2024, p. 60-71
e-ISSN 2502-4787

ANTIDIABETIC ACTIVITIES IN VITRO AND IN SILICO OF NONPOLAR COMPOUNDS IN PATAT LEAVES (*Phrynium capitatum*)

Laras Wijayanti[1], Marvel[2], Samsul Ma'arif[3], Ahmad Fathoni[4*]

[1,3,4]*Department of Chemistry, Faculty of Science and Technology, UIN Syarif Hidayatullah Jakarta, Banten, Indonesia*
[2]*Department of Pharmacy, Faculty of Health Sciences, UIN Syarif Hidayatullah Jakarta, Banten, Indonesia*

*E-mail correspondence: fathoni.ahmad@uinjkt.ac.id

Received: 07 November 2023. Accepted: 9 Mei 2024. Published: 30 Juni 2024

DOI: 10.30870/educhemia.v9i1.21935

Abstract: One form of Indonesian cultural wisdom is the use of leaves as food packaging. In addition to being used as a packaging material, patat leaves are also believed to have antidiabetic benefits. Antidiabetic activity can be assessed through the enzyme α-glucosidase inhibitory activities. In this research, an in vitro and in silico analysis of antidiabetic activity was conducted for the first time on nonpolar extracts of patat leaves. In vitro analysis was conducted using the α-glucosidase enzyme inhibition method, compound analysis was conducted using GC–MS/MS, and an in silico study was conducted via the molecular docking method to the α-glucosidase receptor (PDB: 3W37). The results showed that the nonpolar extract (n-hexane) had very weak antidiabetic activity (with an IC_{50} >> 100 ppm). However, the sample inhibited α-glucosidase enzyme activity by up to 86.91%. GC–MS/MS analysis confirmed the presence of 19 compounds in the nonpolar extract of the patat leaves. Straight-chain hydrocarbons dominate the compounds. The compound with the greatest abundance was Octadecyl 2,2,2-trifluoroacetate (RT 33.908; 9.53% area). An in silico test revealed that the compound with the greatest potential as an antidiabetic agent was γ-methylionone (40.78 μM). On the basis of the results of this theoretical approach, the compound can be further analyzed to validate its activity.

Keywords: α-glucosidase, patat leaf, in silico, in vitro

Abstrak: Salah satu kearifan budaya Indonesia adalah pemanfaatan daun sebagai kemasan makanan. Selain digunakan sebagai bahan kemasan, daun patat juga dipercaya memiliki manfaat antidiabetes. Aktivitas antidiabetes dapat dinilai melalui aktivitas penghambatan enzim α-glukosidase. Pada penelitian ini dilakukan analisis aktivitas antidiabetes secara in vitro dan in silico terhadap ekstrak nonpolar daun patat. Analisis in vitro dilakukan dengan metode penghambatan enzim α-glukosidase, analisis senyawa dilakukan dengan instrumen GC-MS/MS, dan kajian in silico menggunakan metode molekuler docking ke reseptor α-glukosidase (PDB: 3W37). Hasil penelitian menunjukkan bahwa ekstrak nonpolar (n-heksana) mempunyai aktivitas antidiabetik yang sangat lemah (dengan IC50 >> 100 ppm). Namun sampel tersebut mampu menghambat activities enzim α-glukosidase hingga 86,91%.

Analisis GC-MS/MS mengkonfirmasi adanya 19 senyawa dalam ekstrak nonpolar daun patat. Senyawa tersebut didominasi oleh hidrokarbon rantai lurus. Senyawa dengan kelimpahan terbesar adalah Oktadesil 2,2,2-trifluoroasetat (RT 33,908; Area 9,53%). Berdasarkan uji in silico, senyawa yang paling potensial sebagai antidiabetes adalah γ-Methylionone (40,78 μM). Berdasarkan hasil pendekatan teoritis ini, senyawa tersebut dapat untuk dianalisis lebih lanjut memvalidasi aktivitasnya.

Kata kunci: α-glucosidase, daun patat, in silico, in vitro

INTRODUCTION

Indonesia is a country with much local wisdom. One is the use of packaging made of leaves (Noviadji, 2014), one of which is the patat (*Phrynium capitatum*) leaf (Figure 1). This plant comes from the *Marantaceae* family and is usually found in wild forests or yards. One plant has 6–7 leaves per adult plant. Patat leaves (*Phyrnium capitatum*) are generally used as rice wrappers. In addition to Indonesia, this plant can be found in Malabar, Sri Lanka, the Eastern Himalayas, and other Malay countries (GBIF, 2019; Tynson *et al*. 2011). In addition, patat leaves are traditionally believed to have antidiabetic abilities (Perme *et al.* 2015). Scientific information about the claims and mechanisms of this activity is still very limited. Among the studies that have been conducted on this topic are in vivo assays of antidiabetic activity conducted by Obet, Rorong, & Fatimah (2020). Alloxan-induced rats treated with Patat leaf ethanol extracts at concentrations of 100, 200, and 300 mg/kg in weight presented decreases in blood sugar concentrations of 29.01, 34.07, and 42.03%, respectively. Plants have diverse phytochemicals that can be extracted via different solvents. Differences in the contents and biological activities of compounds present in extracts, such as the nonpolar *Leucas aspera* (Willd.) extract, which has slightly better antidiabetic activity than polar extracts (Annapandian and Sundaram, 2017; El Hosry *et al.* 2023). Research by Hsieh *et al*. (2012) reported that the nonpolar extract of *Toona sinensis roem* also has antidiabetic activity.

For the first time, this research investigated the in vitro antidiabetic activity of the nonpolar extract of patat leaves. The activity of each compound in this extract needs to be known for its potential antidiabetic activity. A theoretical in silico approach is used for each compound because of its predictive ability and quick analysis of large amounts of data (De *et al.* 2022).

Kingdom	:	Plantae
Divisio	:	Tracheophyta
Class	:	Liliopsida
Ordo	:	Zingiberales
Family	:	Marantaceae
Genus	:	*Phrynium*
Spesies	:	*Phrynium capitatum* Wild

Figure 1. The Taxonomy of the Patat Plant (*Phrynium capitatum*)

METHOD

The materials used in this research were patat leaf (resident's plantation in the Sasak Panjang, Bogor Regency), n-hexane (technical, redistilled), methanol, dimethyl sulfoxide (DMSO), p-nitrophenyl-α-Glucopyranosude (p-NPG), an α-glucosidase enzyme from *Saccharomyces cerevisiae*, sodium hydroxide, potassium dihydrogen phosphate, the ligand structure of the compounds identified in the patat leaf nonpolar extract, and the structure of the antidiabetic receptor (3W37) downloaded from the PDB (Protein Data Bank) (https://www.rcsb.org/).

The tools used include a UV–Vis Spectrophotometer (PerkinElmer), rotary evaporator, GC–MS/MS (QP2010 SE – Shimadzu), and GC–MS/MS (Agilent), computing devices in the form of a personal computer with software ChemDraw Ultra 8.0 (CambridgeSoft, 2006), MarvinSketch 5.2.5.1, Molegro Molecular Viewer 2.5, Autodock 4.2.6 (Morris, 2009), BIOVIA Discovery Studio, Ligplot+ (Roman and Mark, 2011) and several web server programs, such as PdbSum, PreADMET, admetSAR, and RSCB PDB.

The research was conducted experimentally in a chemistry and computational laboratory. The stages of the research conducted in the laboratory include sample preparation via the air-drying method, maceration extraction by changing the solvents three times every 24 hours, and compound identification via GC–MS/MS. The separation system in GC uses reversed-phase chromatography with a DB5-MS UI (phenyl arylene polymer) column with a size of 30 m × 0.25 mm (0.25 m film thickness) (Agilent, 2022). The mobile phase used was helium gas with a flow rate of 1 mL/min. The samples were injected via a split technique to adjust the number of samples that entered the column. The sample was evaporated gradually from 40 °C to the highest temperature of 280 °C. Thus, samples with boiling points above 280 °C were

not analyzed. The compounds analyzed were limited to a retention time range (RT) of 2.30 minutes to 44.00 minutes. The mass–charge ratio (m/z) range was limited to 40.00–550.00.

In vitro antidiabetic activity analysis was performed via the α-glucosidase enzyme inhibition method (Phukhatmuen *et al.*, 2020). The computational experimental (in silico) stage includes drug-likeness screening, pre-ADMET prediction, and molecular docking with the 3W37 receptor (Ahmed *et al.* 2022).

RESULTS AND DISCUSSION

The collected samples were air-dried for seven days to reduce the water content. The maceration method was conducted by soaking a 2144 g air-dried sample with 10 L of n-hexane, and the solvent was changed three times every 24 hours. The total volume of crude extract was ± 28.5 L. The crude extract was evaporated with a rotary evaporator to obtain a solvent-free crude extract, resulting in a yield of 41.43 grams (1.93% w/w).

In vitro analysis was conducted via the α-glucosidase enzyme inhibition method (Phukhatmuen *et al.*, 2020). The concentration series of the sample was used because there was no reference for the same sample. The results show that the sample concentration series used was above 100 ppm (IC_{50} >> 100 ppm). Thus, the antidiabetic activity of the sample was very weak and could not match that of commercial antidiabetic drugs (acarbose) (Phukhatmuen *et al.* 2020). Interestingly, the inhibition of α-glucosidase activity reached a maximum value of 86.91% (Figure 2). This high sample concentration is thought to be related to the sample matrix, which still contains many compounds and not a single compound. Thus, in silico testing is expected to be able to describe the interaction of each compound present in a sample with the enzyme receptor (Angeloni *et al.* 2021).

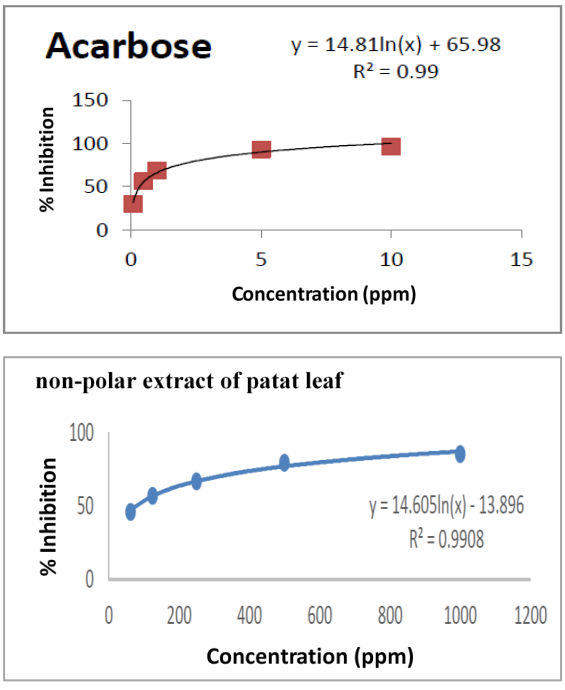

Figure *2* In vitro antidiabetic activity test results

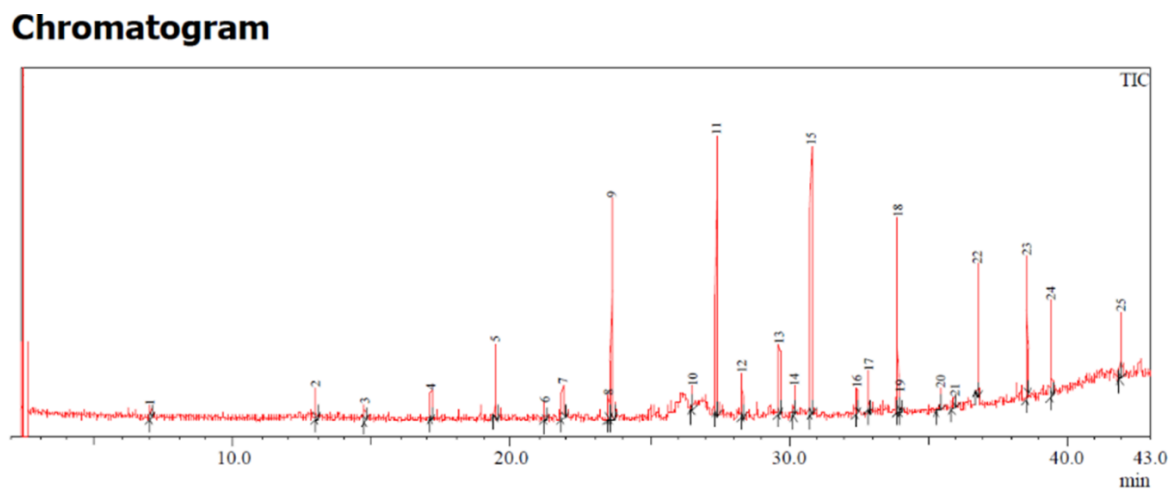

Figure 3 GC–MS chromatogram of the nonpolar extract of a patat leaf

Table 1 Results of the GC–MS spectrum analysis

Peak #	R. Time	Area %	Formula	Mol. Weight	Name	Similarity Index (%)	Status
1	6.984	0.89	$C_{36}H_{38}O_7$	582	D-Glucitol, 1,5-anhydro-1,1-C-[1,2-ethanediylbis(Oxy)]-2,3,4,6-tetrakis-O-(pheny $$	51	Unidentified
2	12.950	1.81	$C_9H_{14}O$	138	Isophorone	91	Identified
3	14.712	1.00	$C_{30}H_{58}O_4S$	514	Didodecyl 3,3′-thiodipropionate	70	Unidentified
4	17.108	1.34	$C_{12}H_{22}O_2$	198	2-tertiobutylcyclohexyl acetate	83	Identified
5	19.417	3.50	$C_{15}H_{30}$	210	trans-7-pentadecene	95	Identified
6	21.192	0.85	$C_{14}H_{22}O$	206	γ-Methylionone	84	Identified
7	21.850	2.38	$C_{14}H_{22}O$	206	2,4-di-tert-butyl-phenol	89	Identified
8	23.492	1.59	$C_{12}H_{14}O_4$	222	Anozol	79	Unidentified
9	23.608	10.23	$C_{15}H_{30}$	210	1-Pentadecene	96	Identified
10	26.533	1.40	$C_{15}H_{20}O$	216	α-Hexylcinnamaldehyde	74	Unidentified
11	27.375	13.14	$C_{18}H_{36}$	252	(5E)-5-Octadecene	95	Identified
12	28.292	3.05	$C_{18}H_{26}O$	258	Galaxolide	90	Identified
13	29.633	3.33	$C_{17}H_{34}O_2$	270	Methyl palmitate	93	Identified
14	30.183	1.52	$C_{16}H_{32}O_2$	256	Palmitic acid	84	Identified
15	30.792	12.83	$C_{20}H_{40}$	280	5-Eicosene, (E)- (CAS)	96	Identified
16	32.442	1.66	$C_{19}H_{36}O_2$	296	Methyl petroselinate	82	Identified
17	32.858	1.73	$C_{19}H_{38}O_2$	298	Methyl stearate	90	Identified
18	33.908	9.53	$C_{20}H_{37}F_3O_2$	366	Octadecyl 2,2,2-trifluoroacetate	95	Identified
19	33.992	0.94	$C_{15}H_{31}DO$	229	Propyl-1-D1 dodecyl ether	72	Unidentified
20	35.450	1.50	$C_{27}H_{56}$	380	Heptacosane	86	Identified
21	35.967	1.12	$C_9H_{13}N_3O_4$	222	Deoxycytidine	64	Unidentified
22	36.775	5.70	$C_{20}H_{40}$	280	Cycloeicosane	94	Identified
23	38.558	6.94	$C_{16}H_{22}O_4$	278	Phthalic acid mono-2-ethylhexyl ester	94	Identified
24	39.425	6.06	$C_{20}H_{37}F_3O_2$	366	Octadecyl 2,2,2-trifluoroacetate	92	Identified
25	41.950	3.90	$C_{23}H_{46}$	322	1-Tricosene	90	Identified
26	43.558	2.06	$C_{14}H_{20}O_2$	220	3,5-Di-tert-butyl-o-benzoquinone	40	Unidentified
		100.00					

The GC–MS chromatograms revealed 26 peaks (Figure 3). At each peak, the spectrum produced by the instrument was analyzed and matched with the spectrum from the library. As a result, 19 of the 26 peaks could be confirmed for their presence and structure, with a percentage of similarity > 80% (Table 1) (Bendik *et al.* 2021). The dominant compound in the nonpolar extract of the patat leaf was *octadecyl 2,2,2-trifluoroacetate* (RT 33,908; 9.53% area). Compounds with known structures were used as ligands in the in silico analysis.

In silico testing begins with drug-likeness screening by following the Lipinski rule of five (Lipinski *et al.* 2012) and pre-ADMET predictions. The screening results revealed that six compounds met the drug-likeness rules, namely, isophorone, 2-tert-butylcyclohexyl acetate, γ-methylionone, 2,4-di-tert-butylphenol, galaxolide, and phthalic acid mono-2-ethylhexyl ester (Figure 4).

The receptor structure used is the α-glucosidase acid crystal structure in sugar beet α-glucosidase with protein identity 3W37 (Figure 5). The 3W37 receptor is derived from beet seeds and has good specificity for long substrates (Tagami *et al.* 2013; To *et al.* 2021).

The receptor binding analysis used an acarbose native ligand and was validated by the redocking technique. From this validation, the binding affinity value, the RMSD, and the inhibition constant were -6.82 kcal/mol, 1.609 Å, and 9.98 µm, respectively. The value of the redocking results is used as a standard for determining the activity of a compound.

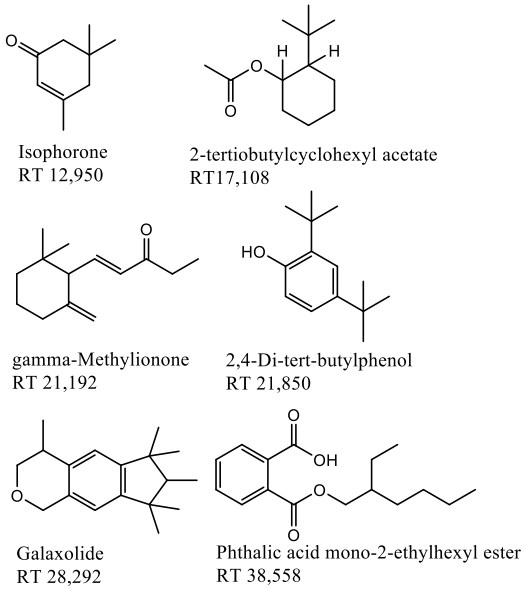

Figure 4 Compounds that meet the drug-likeness parameter

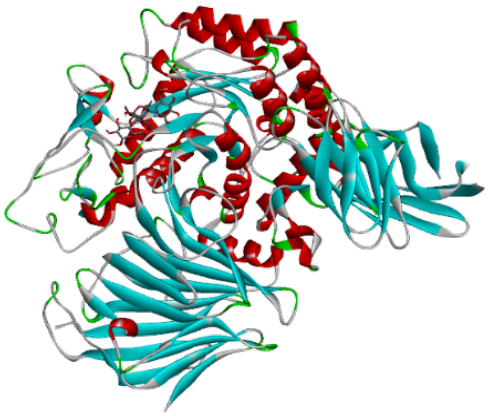

Figure 5 Receptor α-glucosidase and 3W37

Table 2. Molecular docking results

Compound name	Binding Affinity (kcal/mol)	Inhibition Constant
Acarbose	-6.82	9.98 µM
γ-Methylionone	-5.99	40.78 µM
2-tertiobutylcyclohexyl acetate	-5.73	63.32 µM
2,4-di-tert-butyl-phenol	-5.53	88.54 µM
Galaxolide	-5.52	89.46 µM
Isophorone	-5.30	129.86 µM
Phthalic acid mono-2-ethylhexyl ester	-3.91	1.36 mM

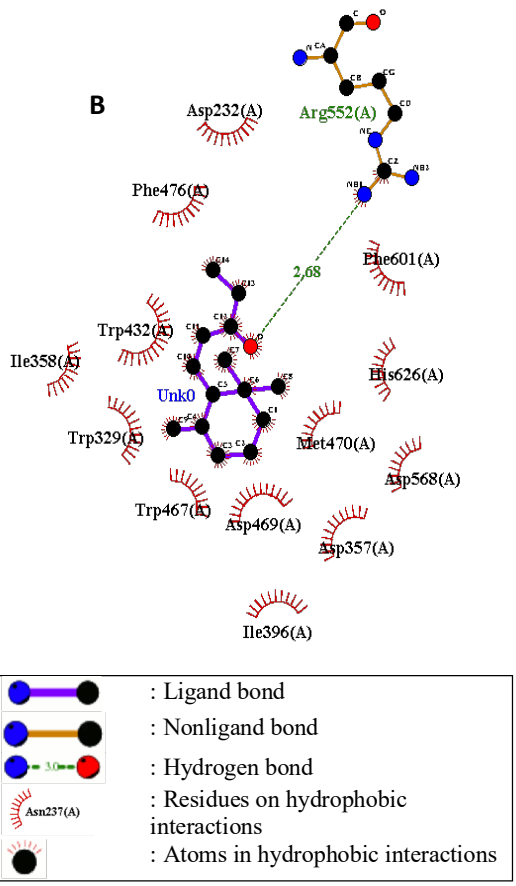

Figure 6. Molecular docking visualization (2D) of γ-methylionone with the α-glucosidase receptor 3W37

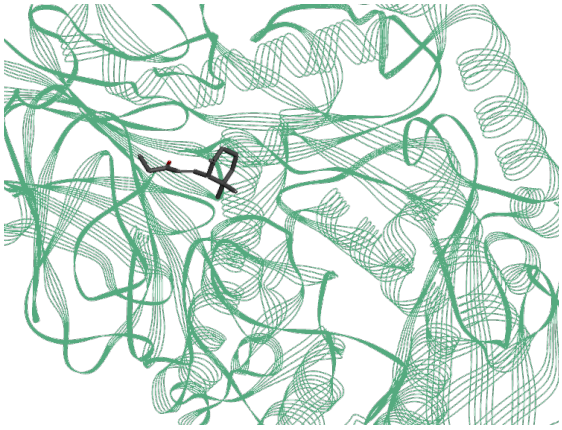

Figure 7. Molecular docking visualization (3D) of γ-methylionone with the α-glucosidase receptor.

The compound γ-methylionone (-5.99 kcal/mol) had the most stable binding affinity when it was docked with the receptor. The inhibition constant of γ-methylionone (40.78 µM) showed that this compound was the most potent inhibitor of the action of the α-glucosidase enzyme. In silico test data from six compounds that met the drug-likeness rules can be found in Table 2.

Two-dimensional visualization of the binding of the γ-methylionone compound to the α-glucosidase receptor revealed the presence of hydrogen bonds and hydrophobic interactions. The hydrogen bond is indicated by a green dotted line, and the surrounding hydrophobic interactions are marked with a red line with different numbers of residues. The results of hydrogen bonding and hydrophobic interactions involve amino acids. The residue on the

hydrogen bond formed in the γ-methylionone compound is Arg552, which has a distance of 2.68 Å. The hydrophobic interactions formed indicate that there are residues in the form of amino acids such as Phe601, His626, Met470, Asp568, Asp357, Ile396, Asp469, Trp467, Trp329, Ile358, Trp432, Phe476, and Asp232 (Figure 6). The results of three-dimensional visualization of γ-methylionone compounds with α-glucosidase receptors revealed that the ligand is in the active site so that the ligand can bind to the right position on the α-glucosidase receptor (Figure 7). The active area of the receptor or binding site is the area where the receptor binds to the ligand, which affects the conformation and function of the receptor. Binding sites include amino acid residues that play a role in forming interactions between macromolecules and ligands, such as hydrogen bonds and hydrophobic bonds (Arwansyah, Ambarsari and Sumaryada, 2014).

γ-Methylionone is a synonym for α-isomethylionone, which is an additional component in cosmetics (National Center for Biotechnology Information, 2023) and can be obtained as a pure compound from various chemical vendors. In nature, γ-methylionone is found in many essential oil components and is thought to be the result of the conversion of carotenoid compounds (Yamazaki *et al.* 1988); one such plant is *Fagopyrum tataricum Gaertn.* (Shi *et al.* 2021). Oxime compounds that have a γ-methylionone building block are known to have potential as antimicrobial agents, as studied previously Surowiak et al. (2022).

Owing to the wide use of γ-methylionone in industry and the possibility that the compound may originate as a contaminant, it is necessary to confirm the presence of this compound in the sample. To ensure that, compound confirmation was conducted via a different GC–MS instrument (Agilent). The GC–MS/MS system used was previously described by Fathoni (2021). γ-Methylionone was detected at 10.167 min, confirming that these compounds were derived from the sample rather than from the contaminating matrix introduced during sample preparation.

CONCLUSION

The nonpolar extract (n-hexane) had very weak antidiabetic activity (with an IC_{50} >> 100 ppm). However, the sample inhibited α-glucosidase enzyme activity by up to 86.91%. A total of 19 compound structures were confirmed in

the nonpolar extract of plant leaves. Straight-chain hydrocarbons dominate the compound. The compound with the greatest abundance was Octadecyl 2,2,2-trifluoroacetate (RT 33.908; 9.53% area). The in silico test revealed that the compound with the greatest potential as an antidiabetic agent was 40.78 μM γ-methylionone (3W37). This test confirmed that the compound was indeed contained in the sample. On the basis of the results of this theoretical approach, the compound can be further analyzed to validate its activity.

ACKNOWLEDGMENT

The research entitled In Vitro and In Silico Antidiabetic Analysis of Nonpolar Compounds in Patat Leaves (Phrynium capitatum) was carried out with the assistance of the LP2M-Puslitpen grant with the contract number B-302/LP2M-PUSLITPEN/TL.03/2022.

REFERENCES

Agilent. (2022). *DB-5ms Columns*, *Agilent Product*, Accessed: 1 July 2022. From https://www.agilent.com/en/product/gc-columns/low-bleed-gc-ms-columns/db-5ms-columns .

Ahmed, S., Ali, M. C., Ruma, R. A., Mahmud, S., Paul, G. K., Saleh, M. A., ... & Islam, M. R. (2022). Molecular docking and dynamics simulation of natural compounds from betel leaves (Piper betle L.) for investigating the potential inhibition of alpha-amylase and alpha-glucosidase of type 2 diabetes. *Molecules*, *27*(14), 1–19. https://doi.org/10.3390/molecules27144526.

Angeloni, S., Spinozzi, E., Maggi, F., Sagratini, G., Caprioli, G., Borsetta, G., ... & Ricciutelli, M. (2021). Phytochemical profile and biological activities of crude and purified Leonurus cardiaca extracts. *Plants*, *10*(2), 1–15. https://doi.org/10.3390/plants10020195.

Annapandian, V.M. and Sundaram, R.S. (2017). In vitro Antidiabetic Activity of Polar and Nonpolar Solvent Extracts from Leucas aspera (Willd.) Link Leaves. *Pharmacognosy Research*, *9*, 261–265. https://doi.org/10.4103/pr.pr.

Arwansyah, A., Ambarsari, L. and Sumaryada, T.I. (2014). Simulasi *Docking* Senyawa Kurkumin dan

Analognya Sebagai Inhibitor Reseptor Androgen pada Kanker Prostat. *Current Biochemistry*, *1*(1), 11–19. https://doi.org/10.29244/cb.1.1.11-19.

Bendik, J., Kalia, R., Sukumaran, J., Richardot, W. H., Hoh, E., & Kelley, S. T. (2021). Automated high confidence compound identification of electron ionization mass spectra for nontargeted analysis. *Journal of Chromatography A*, *1660*, 462656. https://doi.org/10.1016/j.chroma.2021.462656.

CambridgeSoft. (2006). *Chem & Bio Draw*. Cambridge Scientific Computing, Inc.

De, P., Bhayye, S., Kumar, V., & Roy, K. (2022). In silico modeling for quick prediction of inhibitory activity against 3CLpro enzyme in SARS CoV diseases. *Journal of Biomolecular Structure and Dynamics*, *40*(3), 1010-1036. https://doi.org/10.1080/07391102.2020.1821779.

Fathoni, A. (2021). Characterization of Phytochemicals and Chemical Compounds of Patat Leaves (Phrynium capitatum) as Wrapping Materials for Pesor Doclang. *EduChemia (Jurnal Kimia dan Pendidikan)*, *6*(1), 13–25. https://doi.org/10.30870/educhemia.v6i1.9189.

El Hosry, L., Al Ayash, S., Matar Boumosleh, J., & Bou-Maroun, E. (2023). Chemical Composition, Antioxidant, and Anti-Diabetic Activities of Scorzonera phaeopappa Boiss. *Stresses*, *3*(4), 773-784. https://doi.org/10.3390/stresses3040053.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews*, *64*, 4-17. https://doi.org/10.1016/j.addr.2012.09.019.

Morris, G.M. (2009). AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility', *Wiley InterScience*, *7*. https://doi.org/10.1002/jcc.

National Center for Biotechnology Information. (2023). *PubChem Compound Summary for CID 5356787, alpha-Isomethylionone.*, *PubChem*, Accessed: 26 April 2023, https://pubchem.ncbi.nlm.nih.gov/compound/alpha-Isomethylionone

Noviadji, B.R. (2014). Desain Kemasan Tradisional Dalam Konteks Kekinian. *Jurnal Fakultas Desain*, *1*(1), 10–21.

Obet, O., Rorong, J.A. and Fatimah, F. (2020). Skrining Fitokimia dan Aktivitas Antidiabetes dalam Ekstrak Daun Nasi (Phrynium capitatum). *Jambura Journal of Chemistry,* *2*(2), 53–61. https://doi.org/10.34312/jambchem.v2i2.7083.

Perme, N., Choudhury, S. N., Choudhury, R., Natung, T., & De, B. (2015). Medicinal plants in traditional use at Arunachal Pradesh, India. *International Journal of Phytopharmacy*, *5*(5), 86-98. https://doi.org/10.7439/ijpp.

Phukhatmuen, P., Raksat, A., Laphookhieo, S., Charoensup, R., Duangyod, T., & Maneerat, W. (2020). Bioassay-guided isolation and identification of antidiabetic compounds from Garcinia cowa leaf extract. *Heliyon*, *6*(4), e03625. https://doi.org/10.1016/j.heliyon.2020.e03625.

Roman, L. and Mark, S. (2011). LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. *Journal of Chemical Information and Modeling*, *51*, 2778–2786.

Shi, J., Tong, G., Yang, Q., Huang, M., Ye, H., Liu, Y., ... & Zhao, D. (2021). Characterization of key aroma compounds in tartary buckwheat (Fagopyrum tataricum Gaertn.) by means of sensory-directed flavor analysis. *Journal of agricultural and food chemistry*, *69*(38), 11361-11371. https://doi.org/10.1021/acs.jafc.1c03708

Surowiak, A. K., Sowała, M., Talma, M., Groborz, K., Balcerzak, L., Lochyński, S., & Strub, D. J. (2022). Cytotoxicity, early safety screening, and antimicrobial potential of minor oxime constituents of essential oils and aromatic extracts. *Scientific Reports*, *12*(1), 5319. https://doi.org/10.1038/s41598-022-09210-z.

Tagami, T., Yamashita, K., Okuyama, M., Mori, H., Yao, M., & Kimura, A. (2013). Molecular basis for the recognition of long-chain substrates by plant α-glucosidases. *Journal of Biological Chemistry*, *288*(26), 19296-19303. https://doi.org/10.1074/jbc.M113.465211.

To, D. C., Bui, T. Q., Nhung, N. T. A., Tran, Q. T., Do, T. T., Tran, M. H.,

... & Nguyen, P. H. (2021). On the inhibitability of natural products isolated from Tetradium ruticarpum towards tyrosine phosphatase 1B (PTP1B) and α-glucosidase (3W37): An in vitro and in silico study. *Molecules*, *26*(12), 3691. https://doi.org/10.3390/molecules26123691.

Yamazaki, Y., Hayashi, Y., Arita, M., Hieda, T., & Mikami, Y. (1988). Microbial conversion of α-ionone, α-methylionone, and α-isomethylionone. *Applied and environmental microbiology*, *54*(10), 2354-2360.