Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Karamunting screening as an antifungal using the In Silico method targeting N-myristoyltransferase

Samsul Hadi[1*], Kunti Nastiti[2]

[1]Department Pharmacy, Universitas Lambung Mangkurat, Banjarbaru, Kalimantan Selatan

[2]Department Pharmacy, Universitas Sari Mulia, Banjarmasin , Kalimantan Selatan

ARTICLE INFO

Article history:

Received Jan 31, 2023
Revised Feb 11, 2023
Accepted Feb 30, 2023

Keywords:

karamunting
N-myristoyltranseferase
PLANTS

ABSTRACT

Karamunting has been empirically used by the community in overcoming itching disorders due to fungi. Therefore the purpose of this study was to screen in silico the content of Karamunting against N-myristoyltranseferase protein. The method used in this study was In Silico screening using PLANTS docking and the materials used were thirteen compounds contained in Karamunting. The results of this study are docking scores from -123.628 to -77.3801 and residues that have similarities with native ligands when interacting with N-myristoyltransferase, namely one to three amino acids, the predicted value using PASSonline ranges from 0.101 to 0.583. The conclusion of this study was obtained three compounds that have the potential as antifungals with the N-myristoyltransferase inhibitor mechanism, these compounds are α-tocopherol-quinone; α-tocopherol A; blumeatin.

Corresponding Author:

Samsul Hadi,
Department pharmacy,
Universitas Lambung Mangkurat,
Jl. Ahmad Yani Km 36, Banjarbaru, 70714, Kalimantan Selatan,
Email: samsul.hadi@ulm.ac.id

INTRODUCTION

Utilization ingredients natural as drug is Thing right can support health Public because own effect side low if compared with drug from ingredients chemistry . Study nutritious substances as antifungal need conducted for find product new potential for hinder or kill resistant fungi with affordable price that is with utilise ingredients nature . One plants that have used by the community is plant karamunting , where in a manner empirical karamunting used by the people of Kalimantan in particular area upstream river middle for treatment itch itch consequence exists mold and allergies . One of the fungi that can causing disturbance this is Candida albicans.

Karamunting is plant shrub that grows wild and abundant in the tropics such as Southeast Asian countries including Indonesia. Karamunting leaves is the most part utilized for treatment , by empirical leaf karamunting utilized the people of Kalimantan for treat wound infection consequence bacteria nor wound burn (Niah & Baharsyah, 2018) . The Dayak tribe uses the leaves for treat sick stomach and thrush (Pradityo et al., 2016) . Not only Public local in Indonesia, society local in Malaysia also take advantage the leaves for treat wounds , acne , hyperpigmentation of the skin , as well prevent formation network scar consequence wound smallpox (Zakaria et al., 2011) .

Studies of cell culture skin mice and humans show that damage skin consequence UV light involves formation species oxygen reactive (ROS) and decrease endogenous antioxidants . For minimize damage caused by ROS , skin own system defense experience ie enzyme antioxidants as catalase (CAT) and superoxide dismutase (SOD). Exposure UV rays and excessive oxidative stress due to ROS causing disturbance skin as aging premature and hyperpigmentation . Besides that well known that ROS plays role urgent in regulation proliferation melanocytes and melanogenesis, so mechanism work inhibiting antioxidants reaction ROS chain capable lower regulation induced hyperpigmentation and melanogenesis UV rays (Kao et al., 2013) . Care main for prevent skin aging due to oxidative stress is usage sunblock or sunscreen products , meanwhile for care secondary is usage product containing antioxidants (Dipahayu et al., 2014) .

Metabolites contained secondary in extract methanol karamunting including acids _ hexakosanoik , acid gallates , flavonoids, glycosides , phenols , triterpenes , tannins , saponins, and steroids (Joffry et al., 2012) . There is content compound phenols , flavonoids, saponins, and tannins suspected own activity as antifungal (Jeenkeawpieam, 2012) . Research that has been done is that the ethanol extract of 70 karamunting leaves is less effective at inhibiting C.albicans (Megawati, 2016). After fractionation, caramunting leaves have the ability to inhibit the growth of C. albicans (Indriani et al., 2019). Karamunting extract inhibits C. albicans through the mechanism of increasing neutrophils (Hmoteh et al., 2018). Karamunting extract besides having cytotoxic abilities, antioxidants also have antimicrobial (antibacterial and antifungal) abilities (Kusuma et al., 2016). This is what it becomes base thinking eSconducted study activity antifungal from compound karamunting . The protein that becomes the target of antifungals is N -myristoyltransferase . N -myristoyltransferase very important for growth vegetative and survival live C. albicans

RESEARCH METHOD

Material

Equipment used in study this is a laptop with N3700 specifications , 2GB DDR3 and the software used are PLANTS (Korb et al., 2009) , discovery studio (Systèmes, 2020) and Chemaxon (ChemAxon, 2016) . Materials used in study this is protein with 1IYL code (Nichols et al., 2020) and compounds chemical contained in karamunting .

Methods

Study this started with do N- myristoyltranseferase protein search in RCSB, after get the target protein then choose protein A chain with remove other protein chains and different ligands used . Complex between the native ligand and the N- myristoyltransferase protein used as the docking coordinate model for testing compound from karamunting . Next stage there make two dimensional structure from contained compounds in karamunting use Chemaxon . Two dimensional structure next conformation made to 10 for the docking test. Besides do the docking for predict ability compound karamunting as an antifungal use PASSonline (Lagunin et al., 2000) .

Data analysis

Data analysis with count docking score of contained compounds in karamunting compared with native ligands from the N - myristoyltransferase protein complex with equal

$$index = \frac{\text{Docking score compound}}{Docking\ score\ ligand\ native} X100\% \quad (1)$$

RESULTS AND DISCUSSIONS

N -myristoyltransferase is monomeric enzymes that catalyze the transfer of myristic fatty acids from myristoyl -CoA to residue N-terminal glycine from various eukaryotic proteins and viruses. Genetic and biochemical studies has set that N -myristoyltransferase is an interesting target for drug antifungal . N -myristoyltransferase participate in diverse biological processes , incl cascade transduction signaling and apoptosis. Experiment genetics has set that the N - myristoyltransferase gene is very important for growth vegetative and survival live C. albicans and C. neoformans . N - myristoyltransferase C. albicans has 451 residues amino acids, with identity 45% sequence in the enzyme human . Obvious difference in specificity peptide-substrates between N - myristoyltransferases fungals and humans has exploited , and N- myristoyltransferase has identified as a target for chemotherapy potential for agent antifungal (Sogabe et al., 2002) .

Table 1. Results of docking

Name	docking score
Native	-127,031
α-tocopherol-quinone	-123,628
Blumeatin	-102,482
methyl cinnamic	-77.3801
Myricetin	-90.5462
Naringenin	-88.7371
Quercetin	-89.2406
Rhodomyrtone	-94.5339
rhodomyrtosone B	-91.4506
rhodomyrtosone C	-102,266
tetrahydroxyflavanone	-100,272
α-tocopherol A	-112,467
verimol K	-94.3968
watsonianone A	-80.7104

Based on table 1. five scores doking highest is α-tocopherol-quinone (97%); Blumeatin (80%); rhodomyrtosone C (80%); tetrahydroxyflavanone (78%); α-tocopherol A (88%), value percent this is comparative to the native ligand with docking score -127.031, score the more negative this is show bond the more strong (Uzzaman et al., 2019) . This value obtained after conducted validation doking especially formerly to the native ligand, the RMSD value obtained is 1.88 Å, the value below 2 Å , so fulfil condition validation and coordinates obtained _ could used for test compound from karamunting (Rodríguez et al., 1989) . The coordinates used is X:13.4146; Y: 47.7425 ; Z :-1.04137 with a radius of 13.2699 using a 2 Å cluster.

Table 2. Residues involved interaction

Name	Residu		
	Hidrogen	electrostatic	hydrofobik
Native	LEU451;ASN392	LEU451	TYR225; TYR354; PHE339; PHE115
α-tocopherol- quinone	TYR225;HIS227	-	ASP110; TYR225; LEU394; LEU415 ; ILE352; VAL390; LEU394; LEU415; LEU394; ILE111; ILE111; HIS227; HIS227; PHE240; PHE339; TYR354;
Blumeatin	TYR225; TYR335; LEU355; ASN392:ND2; CYS393	LEU451	TYR225
metil sinamat	GLN226	TYR225	TYR354; LEU394
myricetin	GLN226; ASN392;:CYS393	-	-
naringenin	TYR335; LEU355; CYS393; ASN392	-	TYR225; TYR354
kuersetin	ASN226; ASN392	-	TYR225
rhodomyrtone	TYR107;TYR225;TYR354; ASN392	-	PHE240; PHE115; LEU350; ILE352; TYR225; PHE240; PHE339; TYR354
rhodomyrtosone B	-	-	LEU394; TYR225; PHE339; TYR354
rhodomyrtosone C	TYR354;TYR225	-	TYR225; VAL108; ILE111; PHE117; PHE240; PHE339;

tetrahydroxyflavanone	TYR335:OH;TYR354:OH; LEU355:N;CYS393:CA	-	-
α-tocopherol A	-	-	TYR225; TYR354; ILE352; LEU394; HIS227; HIS227; PHE339; TYR354
verimol K	ASN392;HIS227	-	TYR225
watsonianone A	TYR107;TYR225;TYR225	-	TYR225; PHE117; LEU394; PHE339

Interacting residues with the protein N - myristoyltransferase served with table 2. Binding cite of N -myristoyltransferase is LEU 451; ASN 392; TYR225; TYR354; PHE339 and PHE115. interacting residues with the Karamunting test ligand next compared with residue bound with ligand native and seen the equation . Equality this ranging from 1 to with 3 residues amino acids. The 3 highest ligands equality interacting residues _ is blumeatin , naringenin, rhodomyrtone, rhodomyrtosone C. blumeatin own the same residue ASN 392; LEU451 and TYR225. Naringenin has the same residue ASN392; TYR225 and TYR354. Rhodomyrtone has the same residue namely ;TYR 225; ASN392 and TYR354.

Tabel 3. Activity prediction

Nama	Pa	Pi
α-tocopherol-quinone	0.454	0.039
blumeatin	0.583	0.02
metil sinamat	0.243	0.029
myricetin	0.508	0.029
naringenin	0.594	0.019
kuersetin	0.49	0.032
rhodomyrtone	0.104	0.055
rhodomyrtosone B	0.109	0.098
rhodomyrtosone C	0.101	0.07
tetrahydroxyflavanone	0.593	0.019
α-tocopherol A	0.372	0.056
verimol K	0.396	0.05
watsonianone A	0.215	0.091

Based on table 3 using passonline value data obtained predict which Pa value is more of 3 is α -tocopherol-quinone; blumeatin ; myricetin; naringenin; quercetin ; tetrahydroxyflavanone ; α-tocopherol A; verimol K. More value of these 3 indicated compound this based on pattern similarity structure antifungal potentially will but not yet proven on a test basis, fine in vitro as well in vivo. If value not enough of 3 then compound the not enough potentially as an antifungal (Alam et al., 2016) .

Based on the docking score , equation interacting residue be compared with native ligand and online pass obtained three derived compounds from potential karamunting as an N - myristoyltransferase inhibitor . the three ligands is α-tocopherol-quinone; α-tocopherol A and blumeatin . About interaction three dimensions Among all three ligands with N - myristoyltransferase could seen in figure 1

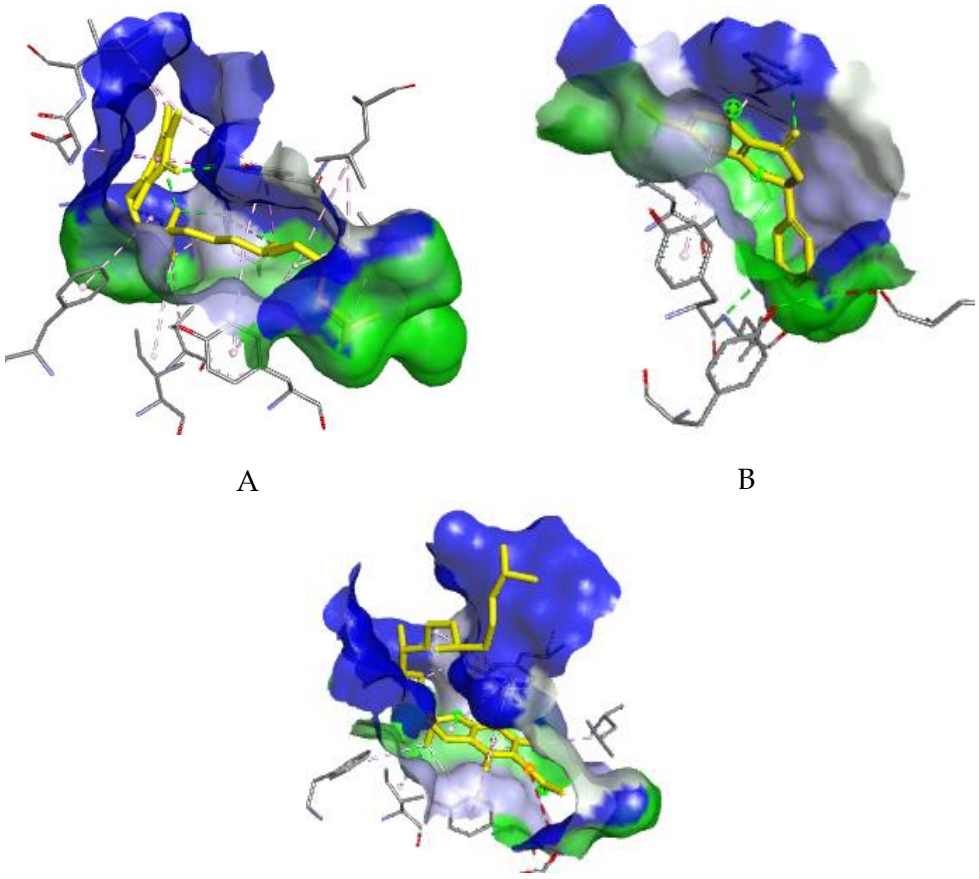

Figure 1. Visualization three potential compounds _ as an N - myristoyltransferase inhibitor . Yellow color is a ligand. A α-tocopherol-quinone; B. α-tocopherol A; C. blumeatin

Bluematin Besides found in Karamunting compound this works too isolated from Blumea balsamifera, compound this potentially in hinder increasing Blumea balsamifera and triglycerides from in heart (Xu et al., 1993) . Isolated bluematin Dodonaea viscose have ability in lower blood fat after 8 day gift (Zhang et al., 2012) . Compound this is also found with Vitex agnus-castus with own activity in inhibit GLUT4 which plays a role in blood sugar regulation (Chen et al., 2011) . α-tocopherol-quinone and α-tocopherol are antioxidants which late in the fat involved in overcome lipid peroxidase in development disease disturbance kidney chronic , besides that compound this role in resolve inflammation , immune system disorders and disease cardiovascular (Galli et al., 2022) .

CONCLUSION

Based on in silico antifungal screening with N -myristoyltransferase targets to contained compounds in karamunting obtained three potential compounds , compounds compound this is α-tocopherol-quinone; α-tocopherol A ; blumeatin ; with indicators of docking scores above 80% against native ligands and predictions activity use PASSonline above 0.3. So that these three compounds can be used as a reference for further research, either in vitro or in vivo in preclinical tests on the antifungal C.albicans, because an in silico screening process has been carried out, so further research is not carried out on all the compounds contained in caramunting.

ACKNOWLEDGEMENTS

The researcher would like to thank Lambung Mangkurat University for providing the opportunity for this research.

References

Alam, M., Khan, A., Wadood, A., Khan, A., Bashird, S., Amane, A., Jan, abdul K., Rauf, A., & Farooq, U. (2016). Bioassay-Guided Isolation of Sesquiterpene Coumarins from Ferula narthex Bioss: A New Anticancer Agent. *Frontiers in Pharmacology*, *7*. https://doi.org/10.3389/fphar.2016.00026

ChemAxon. (2016). ChemAxon - Software Solutions and Services for Chemistry and Biology. In *MarvinSketch, Version 16.10.31*. https://chemaxon.com/

Chen, S.-N., Friesen, J. B., Webster, D., Nikolic, D., van Breemen, R. B., Wang, Z. J., Fong, H. H. S., Farnsworth, N. R., & Pauli, G. F. (2011). Phytoconstituents from Vitex agnus-castus fruits. *Fitoterapia*, *82*(4), 528–533. https://doi.org/https://doi.org/10.1016/j.fitote.2010.12.003

Dipahayu, D., Soeratri, W., & Agil, M. (2014). Formulasi Krim Antioksidan Ekstrak Etanol Daun Ubi Jalar Ungu (Ipomoea Batatas (L.) Lamk) Sebagai Anti Aging. *Pharmaceutical Sciences and Research*, *3*(1), 166–179. https://doi.org/https://scholarhub.ui.ac.id/psr/vol1/iss3/3/

Galli, F., Bonomini, M., Bartolini, D., Zatini, L., Reboldi, G., Marcantonini, G., Gentile, G., Sirolli, V., & Di Pietro, N. (2022). Vitamin E (Alpha-Tocopherol) Metabolism and Nutrition in Chronic Kidney Disease. In *Antioxidants* (Vol. 11, Issue 5). https://doi.org/10.3390/antiox11050989

Hmoteh, J., Musthafa, K. S., & Voravuthikunchai, S. P. (2018). Effects of Rhodomyrtus tomentosa extract on virulence factors of Candida albicans and human neutrophil function. *Archives of Oral Biology*, *87*, 35–42. https://doi.org/10.1016/j.archoralbio.2017.11.007

Indriani, O., Fatiqin, A., & Oktarina, T. (2019). Pengaruh Ekstrak Dan Fraksi Daun Karamunting (Rhodomyrtus Tomentosa (Aiton) Hassk.) Terhadap Pertumbuhan Bakteri Eschericia Coli. *Jurnal Aisyiyaah Medika*, *4*(1). https://doi.org/https://doi.org/10.36729/jam.v4i1

Jeenkeawpieam, J. (2012). Antifungal activity and molecular identification of endophytic fungi from the angiosperm Rhodomyrtus tomentosa. *AFRICAN JOURNAL OF BIOTECHNOLOGY*, *11*. https://doi.org/10.5897/AJB11.3962

Joffry, S. M., Yob, N. J., Rofiee, M. S., Affandi, M. M. R. M. M., Suhaili, Z., Othman, F., Akim, A. M., Desa, M. N. M., & Zakaria, Z. A. (2012). *Melastoma malabathricum* (L.) Smith Ethnomedicinal Uses, Chemical Constituents, and Pharmacological Properties: A Review. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 258434. https://doi.org/10.1155/2012/258434

Kao, Y.-Y., Chuang, T.-F., Chao, S.-H., Yang, J.-H., Lin, Y.-C., & Huang, H.-Y. (2013). Evaluation of the Antioxidant and Melanogenesis Inhibitory Properties of Pracparatum Mungo (Lu-Do Huang). *Journal of Traditional and Complementary Medicine*, *3*(3), 163–170. https://doi.org/https://doi.org/10.4103/2225-4110.113443

Korb, O., Stützle, T., & Exner, T. E. (2009). Empirical scoring functions for advanced Protein-Ligand docking with PLANTS. *Journal of Chemical Information and Modeling*, *49*(1), 84–96. https://doi.org/10.1021/ci800298z

Kusuma, I. W., Ainiyati, N., & Suwinarti, W. (2016). Search for biological activities from an invasive shrub species rosemyrtle (Rhodomyrtus tomentosa). *Nusantara Bioscience*, *8*(1).

Lagunin, A., Stepanchikova, A., Filimonov, D., & Poroikov, V. (2000). PASS: prediction of activity spectra for biologically active substances. *Bioinformatics (Oxford, England)*, *16*(8), 747–748. https://doi.org/10.1093/bioinformatics/16.8.747

Megawati, E. P. (2016). Uji Aktivitas Antifungi Ekstrak Etanol Daun Karamunting (Rhodomyrtus Tomentosa (Aiton) Hassk) Terhadap Pertumbuhan Candida Albicans Secara in Vitro. *Jurnal Mahasiswa Fakultas Kedokteran Untan*, *2*(4).

Niah, R., & Baharsyah, R. N. (2018). Potensi Ekstrak Daun Tanaman Karamunting (Melastoma Malabathricum L.) di Daerah Kalimantan sebagai Antibakteri Staphylococcus Aureus. *Jurnal Ilmiah Manuntung*, *4*(1), 36–30. https://doi.org/https://doi.org/10.51352/jim.v4i1.138

Nichols, C., Ng, J., Keshu, A., Kelly, G., Conte, M. R., Marber, M. S., Fraternali, F., & De Nicola, G. F. (2020). Mining the PDB for Tractable Cases Where X-ray Crystallography Combined with Fragment Screens Can Be Used to Systematically Design Protein-Protein Inhibitors: Two Test Cases Illustrated by IL1β-IL1R and p38α-TAB1 Complexes. *Journal of Medicinal Chemistry*, *63*(14), 7559–7568.

https://doi.org/10.1021/acs.jmedchem.0c00403

Pradityo, T., Santoso, N., Ervizal, A., & Zuhud, M. (2016). Etnobotani di Kebun Tembawang Suku Dayak Iban, Desa Sungai Mawang, Kalimantan Barat. *Media Konservasi*, *21*(2), 183–198. https://doi.org/https://doi.org/10.29244/medkon.21.2.183- 198

Rodríguez, E., Arqués, J. L., Rodríguez, R., Nuñez, M., Medina, M., Talarico, T. L., Casas, I. A., Chung, T. C., Dobrogosz, W. J., Axelsson, L., Lindgren, S. E., Dobrogosz, W. J., Kerkeni, L., Ruano, P., Delgado, L. L., Picco, S., Villegas, L., Tonelli, F., Merlo, M., … Masuelli, M. (1989). Protein-Protein and Protein-Ligand Docking. *Intech*, *32*(tourism), 137–144. https://www.intechopen.com/books/advanced-biometric-technologies/liveness-detection-in-biometrics

Sogabe, S., Masubuchi, M., Sakata, K., Fukami, T. A., Morikami, K., Shiratori, Y., Ebiike, H., Kawasaki, K., Aoki, Y., Shimma, N., D'Arcy, A., Winkler, F. K., Banner, D. W., & Ohtsuka, T. (2002). Crystal structures of Candida albicans N-myristoyltransferase with two distinct inhibitors. *Chemistry & Biology*, *9*(10), 1119–1128. https://doi.org/10.1016/s1074-5521(02)00240-5

Systèmes, D. (2020). *Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes*. https://discover.3ds.com/discovery-studio-visualizer-download#_ga=2.4935860.685747970.1587999055-a5d1c1c0-3176-11e9-a86f-e302515d21c8

Uzzaman, M., Chowdhury, M., & Hossen, M. (2019). Thermochemical, Molecular docking and ADMET studies of Aspirin metabolites. *Frontiers in Drug, Chemistry and Clinical Research*, *2*. https://doi.org/10.15761/FDCCR.1000130

Xu, S. B., Chen, W. F., Liang, H. Q., Lin, Y. C., Deng, Y. J., & Long, K. H. (1993). [Protective action of blumeatin against experimental liver injuries]. *Zhongguo yao li xue bao = Acta pharmacologica Sinica*, *14*(4), 376–378.

Zakaria, Z. A., Rofiee, M. S., Mohamed, A. M., Teh, L. K., & Salleh, M. Z. (2011). In vitro antiproliferative and antioxidant activities and total phenolic contents of the extracts of Melastoma malabathricum leaves. *Journal of Acupuncture and Meridian Studies*, *4*(4), 248–256. https://doi.org/10.1016/j.jams.2011.09.016

Zhang, L.-B., Ji, J., Lei, C., Wang, H.-Y., Zhao, Q.-S., & Hou, A.-J. (2012). Isoprenylated flavonoid and adipogenesis-promoting constituents of Dodonaea viscosa. *Journal of Natural Products*, *75*(4), 699–706. https://doi.org/10.1021/np2009797