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# Pharmacological prediction of *Marchantia polymorpha*: GC-MS and molecular docking approaches

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**Abstract**

*Marchantia polymorpha* is the liverworts that can be found abundantly in the Mount Pasang Jember area. The metabolite profiling of *M. polymorpha* has not yet been conducted. The method used in this study was untargeted metabolite profiling using GC-MS, and the results of the metabolite compound profiling were analyzed in silico using bioinformatics-based, namely PASS Online, SwisADME, and Molecular Docking using PyRx 8.0 with AutodockVina. The aims of docking with this protein was adjusted to the PASS Online results, namely alkenylglycerophosphocholine hydrolase inhibitor and antiseborrheic, which are closely related to antifungals. The natural metabolite compounds detected from *M. polymorpha* were fatty acids (20%), terpenoids (16%), and phenolics (10%). Terpenoids-phenolics compounds were analyzed in silico to predict pharmacological potential. Terpenoids showed that the compound with the highest Pa value was 3,7-Cyclodecadiene (Pa=0.920), predicted to be an alkenylglycerophosphocholine hydrolase inhibitor, while the phenolic compound with the highest Pa value was hydroquinone (Pa=0.927), predicted to be an antiseborrheic. Based on SwissADME in silico Druglikeness, five compounds out of a total of six terpenoid and phenolic compounds showed compliance with Lipinski's theory. In addition, the in silico results also showed a bioavailability score of 0.55. Molecular docking was performed on the target protein sterol 14-α-demethylase (CYP51) from *Candida albicans* (PDB ID: 5TZ1). This protein is representative of antifungal agents. The results of molecular docking showed that the compound 3,7-Cyclodecadiene consistently had the strongest binding affinity value of -10.1 kcal/mol with residues ILE A:55, ALA A:62, PHE A:58, and TRP B:5 These results imply that further research on M. polymorpha metabolites should be conducted using comprehensive methods to explore their potential in the field of health.

## Introduction

*Marchantia polymorpha* L. is a liverwort that can grow in tropical regions, including Indonesia. Based on metabolomically, *M. polymorpha* has metabolites that have potential in the field of pharmacology for the future (Farhan et al., 2025; Tran et al., 2020). Research conducted by Stelmasiewicz et al., (2023) indicating potential metabolites of *M. polymorpha* as an antioxidant, antibacterial, and antifungal. However, a screening method or design is needed to detect metabolite compounds found in liverwort. *M. polymorpha*. Methods that can be used to detect metabolite compounds in *M. polymorpha* using chromatography tools by Gas Chromatography-Mass Spectrometry (GC-MS) (Stelmasiewicz et al., 2022).

GC-MS is a chromatography method that can detect the volatile untargeted compound profile in an organism including the plant. Untargeted compounds are metabolomic profiling without specific target compounds, so that compounds will be comprehensively detected in general metabolites (Fiehn, 2017). The principle of this method is the detection of volatile metabolite compounds based on molecular weight (mw), %area, formula, and retention time (Emwas et al., 2015; Ninkuu et al., 2021). Previous research conducted

by Kumar et al., (2016) identify volatile compounds detected in *M. polymorpha* one of them is a terpene compound, namely α-gurjunene, β-chamigrene, 5-Hydroxy-a-Gurjunene, β-himachalene, and cuparene. These compounds have great potential in the pharmacology field, they can be recommended in the future. The results of detection using GC-MS must undergo further analysis in silico based on bioinformatics method. The in silico method that can be recommended as a follow-up analysis of the properties between compounds is molecular docking (MD) (Chikowe et al., 2024; Pan et al., 2019).

MD is a bioinformatics computational method that aims to determine the interaction between a compound's ligand and a target protein in a database including from Protein Data Bank (PDB) (Pagadala et al., 2017; Paggi et al., 2024). MD can be performed as an initial screening to discover bioactive compounds that are candidate drugs for the future (Agu et al., 2023). Research on in silico MD in *M. polymorpha* has been conducted by Singh et al., (2024) The docking results of gallic acid ligand showed an interaction of -6.69763 kcal/mol on the PDB ID: 1GWQ protein. Based on this study, it is recommended as an initial screening for *M. polymorpha* samples from the Mount Pasang, Jember region.

In silico bioinformatics pharmacology predictions can be made using docking as well as bioinformatics websites, namely PASS Online and SwissADME (Desai & Joshi, 2019). Both websites can be combined as an initial profile of metabolite compounds detected in plant samples. PASS Online can predict metabolite compound activity based on the Probability active (Pa) value of a compound, indicated by the Pa score (Druzhilovskiy et al., 2017; Farhan, et al., 2025). The results from in silico PASS Online can be reinforced with a pharmacokinetic design approach using SwissADME (Daina et al., 2017). The use of SwissADME (Absorption, Distribution, Metabolism, Excretion) and druglikeness is widely used in drug candidate development research (Muslikh et al., 2025). The parameters of the bioinformatics website are adjusted according to Lipinski's theory, lipophilicity (LogP), and bioavailability (Daina et al., 2017; Lohidashan et al., 2018).

The methods of GC-MS and bioinformatics-based pharmacological prediction will support the initial profiling of *M. polymorpha* samples. The results of the exploration of *M. polymorpha* can be found abundantly in the Gunung Pasang Jember area at an altitude of 300-900 m. Based on these findings, research on the detection of metabolite compounds and pharmacological prediction in *M. polymorpha* from Jember is novel and will lead to the development of herbal-based research in the future. The aim of this study is to detect untargeted volatile metabolite compounds in *M. polymorpha* and perform in silico pharmacological prediction for initial screening.

## Materials and methods

### 1. Research subject

The subject used in this research was a sample population of liverwort *Marchantia polymorpha*. Samples were collected from the Mount Pasang, Jember, East Java region. Samples 30 gram of *M. polymorpha* were taken from the talus for extraction.

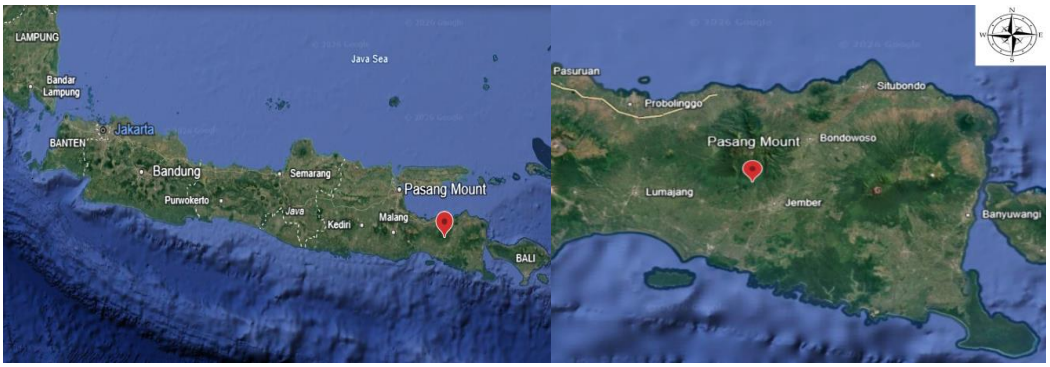



**Figure 1. Utilizing Google Earth to identify sampling locations at Mount Pasang, Jember, East Java (8°05'44.53"S 113°37'35.95"E), with an elevation of 443.83 m**

### 2. Method and research design

A 30-gram samples of *M. polymorpha* with 300 mL of methanol for three days was macerated. The macerated sample was processed in a rotary evaporator at 30°C, producing a crude extract ready for injection into the GC-MS. The working principle of MS detector temperature was 280°C an the column used was a Restek Rtx®-50 column (Crossbond® 5% phenyl-50% methyl polysiloxane). The carrier gas used in this GC-MS was helium at a pressure of 64.1 kPa (Ilmiah et al., 2025). The results from GC-MS were chromatographic peaks and bioinformatic analysis was performed based on the Wiley9.LIB and NIST databases (Farhan et al., 2025; Setyati et al., 2024).

The results of metabolite compound detection were used for pharmacological prediction using bioinformatics with Way2drug PASS Online and SwissADME. In silico PASS Online provides the Probability of Activity value of a compound based on SMILES (Pubchem) with parameters if the Pa value is > 0.7, the compound has very strong biological activity and can proceed to the laboratory experiment stage, while if the Pa value is < 0.7, the compound has weak biological activity (Lohidashan et al., 2018). SwissADME in silico was performed based on SMILES (Pubchem), and analysis was conducted according to Lipinski's theory with the following criteria: Molecuar Weight ≤ 500, LogP ≤ 5, H-bond Donor (HBD) ≤ 5, H-bond Acceptor (HBA) ≤ 5, dan Violation ≤ 1 (Rauf et al., 2023).

The results of profiling metabolite compound were performed using Molecular Docking (MD) with PyRx 0.8 with Autodockvina software (http://pyrx.sourceforge.net/). Ligands were collected based on PubChem (SDF) and converted to PDB format using Open Babel version 2.2.3 (www.openbabel.org) (Ayodele et al., 2023; Zubair et al., 2023). Receptors were used in this research is PDB ID 5TZ1 (https://www.rcsb.org/) the receptor recommended as an antifungal (Tamaian et al., 2023). The docking results collection was visualized using Biovia Discovery Studio 2025 software (https://discover.3ds.com/discovery-studio-visualizer-download) (Baroroh et al., 2023).

## Results and discussion

### 1. Untargeted Metabolite Profiling of *M. polymorpha*

The results of untargeted metabolites profiling using GC-MS showed from the *M. polymorpha* sample were fatty acids (20%), terpenoids (16%), and phenolics (10%) (Table 1). The results were also shown by chromatographic peaks (Figure 2). A total of 50 untargeted compounds were detected. All compounds were detected based on their molecular weight at a specific retention time. Based on the chromatogram, the compound formula was analyzed using a database. Figure 2 and Table 1 show the results of untargeted compound detection in *M. polymorpha.*

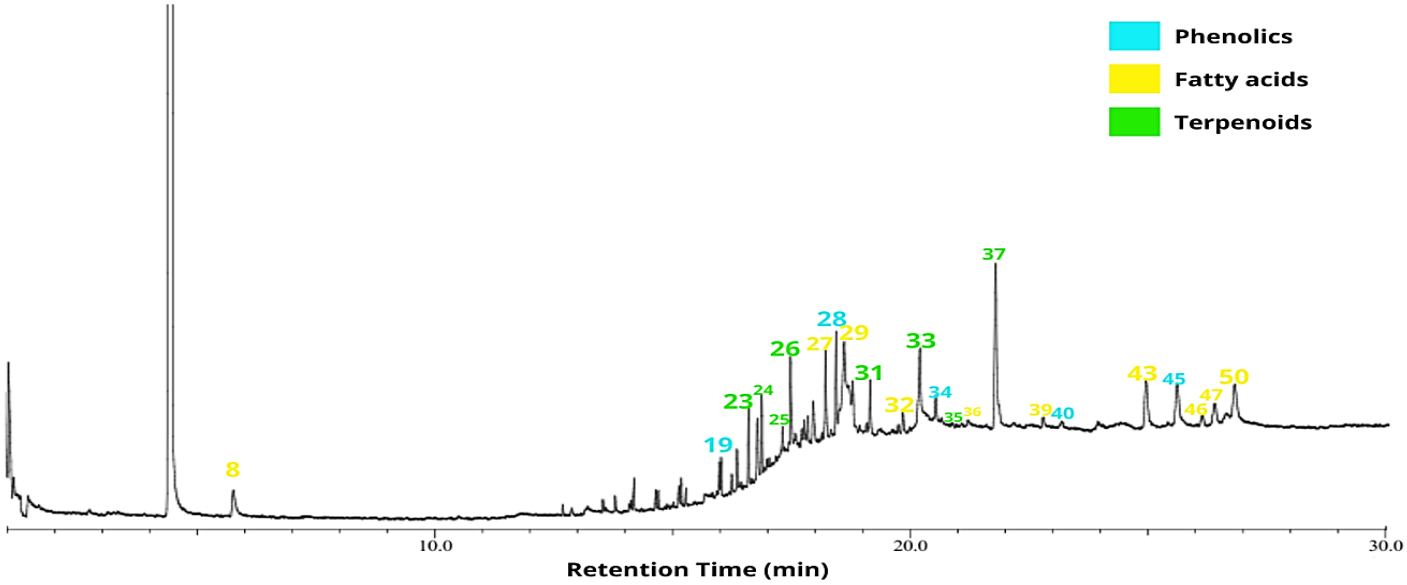



**Figure 2. GC-MS chromatogram of *M. polymorpha* extract**

GC-MS chromatography in Figure 2 shows several metabolite compounds that were successfully detected. The x-axis shows the retention time, which is the optimal time for a compound to be detected at a certain peak, while the y-axis shows the chromatography peak, which is the peak of the compound that can be detected in the mass spectrum, and is adjusted to the database. Based on this output, a total of 50 compounds can be identified in 30 minutes of GC-MS running. Table 1 below provides information on the names of the metabolite compounds, along with their scores and optimal RT for the detection of these compounds.

**Table 1. Untargeted metabolite compounds profiling in methanol extracts of *M. polymorpha***

| Peak# | RT (min) | Similarity Score | Compound | Group |
|---|---|---|---|---|
| 1 | 1.269 | 98 | Carbamic acid, monoammonium salt | Amonia/nitrogen |
| 2 | 1.453 | 87 | 2-Formylhistamine | Amina |
| 3 | 1.533 | 82 | N,N'-Bis(2-methyl-2-nitrosobutan-3-one) | Contamination |
| 4 | 1.749 | 83 | Cystine | Amino acid |
| 5 | 1.98 | 85 | 1-Butanol | Alcohol |
| 6 | 3.03 | 90 | Pyrazine, methyl- | Nitrogen |
| 7 | 4.721 | 97 | Ethanol, 2-butoxy- | Solvent |
| 8 | 6.012 | 95 | Acetic acid | Fatty acid |
| 9 | 12.85 | 92 | Cyclooctasiloxane, hexadecamethyl- | Siloxane |
| 10 | 13.035 | 93 | Cyclohexane, 1-ethenyl-1-methyl-2-(1-methyle | Siloxane |
| 11 | 13.681 | 91 | Acetamide | Amino acid |
| 12 | 13.936 | 95 | Ethanol, 2-(2-butoxyethoxy)- | Solvent |
| 13 | 14.775 | 93 | 1-Propanol, 2-(2-hydroxypropoxy)- | Solvent |
| 14 | 14.833 | 95 | 1-Propanol, 2-(2-hydroxypropoxy)- | Solvent |
| 15 | 15.016 | 90 | 1-Propanol, 2-(2-hydroxypropoxy)- | Solvent |
| 16 | 15.254 | 92 | 2-Propenamide | Amida |
| 17 | 15.31 | 84 | Cyclodecasiloxane, eicosamethyl- | Siloxane |
| 18 | 15.404 | 88 | Ethyl tetradecyl ether | Solvent |
| 19 | 15.8 | 87 | Phosphonic acid, (p-hydroxyphenyl)- | Phenolic |
| 20 | 16.051 | 84 | 2-Pyrrolidinone | Nitrogen |
| 21 | 16.136 | 85 | Cyclooctasiloxane, hexadecamethyl- | Siloxane |
| 22 | 16.36 | 82 | Cyclononanone | Ketone |
| 23 | 16.466 | 84 | Ledol | Terpenoid |
| 24 | 16.544 | 85 | 1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7 | Terpenoid |
| 25 | 16.705 | 85 | 3,7-Cyclodecadiene-1-methanol, .alpha.,.alpha | Terpenoid |
| 26 | 16.977 | 80 | 1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7 | Terpenoid |
| 27 | 17.081 | 87 | Isopropyl palmitate | Fatty acid |
| 28 | 17.412 | 93 | 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6 | Phenolic |
| 29 | 17.81 | 87 | 1-Hexadecanol | Fatty acid |
| 30 | 17.933 | 95 | Diethyl Phthalate | Contammination |
| 31 | 18.046 | 92 | Benzofuran, 2,3-dihydro- | Terpenoid |
| 32 | 18.414 | 87 | Dodecanoic acid | Fatty acid |
| 33 | 18.523 | 84 | 9,19-Cyclolanostan-24-one, 3-acetoxy-25-met | Terpenoid |
| 34 | 18.785 | 81 | 1,3-Benzenediol, 5-pentyl- | Phenolic |
| 35 | 18.868 | 81 | 6-Octenal, 3,7-dimethyl-, (R)- | Terpenoid |
| 36 | 19.011 | 92 | n-Nonadecanol-1 | Fatty acid |
| 37 | 19.154 | 86 | 1,1,4,7-Tetramethyldecahydro-1H-cyclopropa[ | Terpenoid |
| 38 | 19.226 | 86 | Tetracosamethyl-cyclododecasiloxane | Siloxane |
| 39 | 19.816 | 91 | Tetradecanoic acid | Fatty acid |
| 40 | 19.911 | 91 | 3-Methoxy-5-propylphenol | Phenolic |
| 41 | 20.049 | 88 | Dibutyl phthalate | Contammination |
| 42 | 20.591 | 87 | Tetracosamethyl-cyclododecasiloxane | Siloxane |
| 43 | 21.831 | 93 | n-Hexadecanoic acid | Fatty acid |
| 44 | 22.817 | 85 | Tetracosamethyl-cyclododecasiloxane | Siloxane |
| 45 | 23.959 | 85 | Hydroquinone | Phenolic |
| 46 | 24.954 | 90 | Octadecanoic acid | Fatty acid |
| 47 | 25.603 | 90 | 9-Octadecenoic acid, (E)- | Fatty acid |
| 48 | 26.132 | 91 | Bis(2-ethylhexyl) phthalate | Contammination |
| 49 | 26.377 | 93 | Caffeine | Alkaloid |
| 50 | 26.794 | 91 | 9,12-Octadecadienoic acid (Z,Z)- | Fatty acid |

*M. polymorpha* extract detected a total of 50 untargeted compounds in 30 minutes running time, including fatty acids (20%), terpenoids (16%), phenolics (10%), and others (54%). These results show that several groups of compounds were detected, namely primary metabolites, secondary metabolites, and contaminations/artifacts. The primary metabolites detected in the *M. polymorpha* sample were fatty acids. In general, fatty acids are very easy to detect using GC-MS because, although they have low volatility, they

have non-polar properties that can be extracted by methanol by binding (–COOH) (Kamatou & Viljoen, 2017). Based on physiological structural lipids of membranes and energy storage lipids in plants, including liverworts, are chemically (Pannu et al., 2024; Soriano et al., 2022). Liverwort is capable of producing fatty acids, namely saturated and unsaturated fats. This production is closely related to several enzymes found in *M. polymorpha*, namely elongase and desaturase enzymes. These two enzymes are specifically capable of lengthening and multiplying fatty acid chains. In addition to being closely related to enzymes in fatty acid production, genes play a very important role in this production. *M. polymorpha* has the FAE3 and ELO2 genes that play an active role in fatty acid elongation, thus reinforcing the reason for the abundance of fatty acids in *M. polymorpha* samples (Kajikawa et al., 2003; Takemura et al., 2012).

Several fatty acids that were successfully detected in the *M. polymorpha* sample were 1-Hexadecanol, Octadecanoic acid, n-Hexadecanoic acid, 9-Octadecenoic acid. These results are consistent with Pannu et al., (2024) which successfully detected the compound in the same species, *M. polymorpha*. This compound can be further developed in the field of pharmacology, as previous research on *M. polymorpha*, which contains fatty acids, has demonstrated its antioxidant, anti-inflammatory, and antifungal properties. The GC-MS results not only provide information on fatty acid profiling but can also be recommended for further research as a fundamental pharmacology study based on bioactive natural compounds derived from *M. polymorpha* (Cai et al., 2022; Singh et al., 2024).

Terpenoids are a group of secondary metabolites that are abundant in liverworts, especially in the oil body. Terpene synthesis in *M. polymorpha* is similar to that in other plants, namely through mevalonate (MVA) and non-mevalonate (MEP) pathways (Takizawa et al., 2021). There are several terpenoids that are often detected using GC-MS, one of which is sesquiterpenes. Several previous studies have mentioned that sesquiterpenes in plants have great potential as antioxidants and even anticancer agents (Nowaczyński et al., 2025; Stelmasiewicz et al., 2022). In this research, several terpenoid compounds were successfully profiling, including Ledol, 6-Octenal, 3,7-dimethyl-, (R)-, Benzofuran, 2,3-dihydro-, 1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7, and others. Previous studies have reported that ledol and azulane compounds are found in *M. polymorpha*, which function as defense and chemosystematics (Nowaczyński et al., 2025). While benzofuran compounds, volatile aromatic compounds that are difficult to detect in liverworts and are commonly detected in plants of the genus *Lepidium*, need to be further developed because previous reports indicate that these compounds have potential as anticancer, antibacterial, and antifungal agents (Hussein, 2016).

Phenolics are a group of secondary metabolites that are commonly detected using GC-MS, including in *M. polymorpha* samples. Phenolics are synthesized, as is generally the case, through the phenylpropanoid pathway with a specific enzyme, phenylalanine ammonia-lyase (PAL). Several phenolic compounds were detected in *M. polymorpha*, namely phosphonic acid, (p-hydroxyphenyl)-,4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6, 1,3-Benzenediol, 5-pentyl-, 3-Methoxy-5-propylphenol, and Hydroquinone. These compounds are simple and substituted phenolic groups that are predicted to have pharmacological activity in the future (Son et al., 2020). Previous studies have reported that phenolic compounds in *M. polymorpha* have potential as antioxidants, antibacterials, and anticancer agents (Tran et al., 2020; Zhang et al., 2022).

The GC-MS detection results found compounds outside the fatty acids, terpenoids, and phenolics groups. Other compounds are contaminants and artifacts commonly found in GC-MS detection. Contamination in this GC-MS detection is siloxane compounds, siloxane is a compound that should be contained in plastic. The detection of siloxane in the *M. polymorpha* sample originated from equipment made from silicone (Piechota, 2021). The trigger for this contamination is that during the GC stationary phase, the temperature will increase dramatically so that the detector will automatically detect it as a compound based on the chromatogram peak (Arata et al., 2021; Frolova et al., 2025; Sauerschnig et al., 2018). In addition to contamination, GC-MS detection results also contained artifacts, namely residues caused by the solvents used. One of the artifacts detected in this study was ethanol, 2-butoxy- (peak-7) with the highest peak reading (Verpoorte et al., 2022). For this research, there was a deficiency in other detections, namely peak-49, which was read as caffeine (alkaloid group). This compound is very uncommon in liverworts, as caffeine is a compound typically found in coffee. Calibration and instrument cleaning factors greatly influenced the reading of this compound (Lemos et al., 2022; Rocha et al., 2023).

## *2.* Prediction pharmacology of secondary metabolites *M. polymorpha*

Pharmacological predictions of *M. polymorpha* as an initial screening focused on detected secondary metabolite compounds, including terpenoids and phenolics (primary metabolites for further). This evaluation approach is based on the fact that secondary metabolites have more complex structures and functional groups, making them more likely to exhibit specific biological activities that are pharmacologically relevant (Nowaczyński et al., 2025; Son et al., 2020). Based on, previous studies According to earlier research, *M. polymorpha* metabolites particularly terpenoids and phenolics, have shown general pharmacological potential such as antioxidants, antibacterials, and antifungals (Nowaczyński et al., 2025; Spinedi et al., 2021). Evaluation of bioactive property predictions (PASS Online) and druglikeness (SwissADME) provides a more efficient and rational in silico approach to analyze the early stages of metabolite compounds as drug candidates (Rauf et al., 2023). Table 2 shows the results of bioactive predictions using PASS Online for secondary metabolites (terpenoids and phenolics) in *M. polymorpha.*

**Table 2. Prediction bioactive of Terpenoids and Phenolics *M. polymorpha***

| Group | Compound | Prediction | Pa |
|---|---|---|---|
| Terpenoids (SM) | Ledol | Antiseborrheic | 0.788 |
| | 1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7 | Apoptosis agonist | 0.667 |
| | 3,7-Cyclodecadiene-1-methanol, .alpha.,.alpha | Alkenylglycerophosphocholine hydrolase inhibitor | 0.920 |
| | 1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7 | Apoptosis agonist | 0.667 |
| | Benzofuran, 2,3-dihydro- | Antidyskinetic | 0.738 |
| | 9,19-Cyclolanostan-24-one, 3-acetoxy-25-met | Apoptosis agonist | 0.792 |
| | 6-Octenal, 3,7-dimethyl-, (R)- | Antisecretoric | 0.772 |
| | 1,1,4,7-Tetramethyldecahydro-1H-cyclopropa | Antiseborrheic | 0.821 |
| Phenolics (SM) | Phosphonic acid, (p-hydroxyphenyl)- | Antiseborrheic | 0.722 |
| | 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6 | Antiinflammatory | 0.800 |
| | 1,3-Benzenediol, 5-pentyl- | Antiseborrheic | 0.869 |
| | 3-Methoxy-5-propylphenol | Antiseborrheic | 0.909 |
| | Hydroquinone | Antiseborrheic | 0.927 |

The results of bioactive predictions on terpenoid compounds show that the compound with the highest Pa value is 3,7-cyclodecadiene (Pa=0.920), predicted to be an alkenylglycerophosphocholine hydrolase inhibitor, while the compound with the highest Pa value among phenolic compounds is hydroquinone (Pa=0.927), predicted as an antiseborrheic agent. These results indicate biological activity that can be considered as a candidate for future drugs. The terpenoid compound 3,7-cyclodecadiene is predicted to be an alkenylglycerophosphocholine hydrolase inhibitor, a compound that can inhibit alkenylglycerophosphocholine hydrolase, which plays a role in plasmalogen hydrolysis. Plasmalogens are ether phospholipids that have a vinyl-ether bond at the sn-1 position of glycerol and are commonly found in the cell membranes of nerve tissue, the heart, and immune cells (Bozelli et al., 2021; Yergaliyeva et al., 2022). Pharmacologically, compounds related to plasmalogens are considered therapeutic candidates for neurodegenerative diseases such as Alzheimer's (Dorninger et al., 2022).

Other predictions of terpenoid compounds with the highest scores are 1,1,4,7-tetramethyldecahydro as an antiseborrheic (Pa=0.821) and 9,19-Cyclolanostan as an apoptosis agonist (Pa=0.729). Antiseborrheic is a bioactive property that refers to the skin's control over increased sebum caused by *Malassezia* fungi (Filatov et al., 2023b). Other studies reinforce that terpenoid compounds are highly effective in treating chronic symptoms caused by oily skin and inflammation (Filatov et al., 2023a; Triviño et al., 2025). In phenolic compounds, the three compounds with the highest bioactivity scores were also predicted to be antiseborrheic. These results can be used as a pharmacological basis for future research on compounds isolated from *M. polymorpha*. This finding is also consistent with previous studies which indicate that the metabolite compounds in *M. polymorpha* are predicted to be antifungal (Poveda, 2024; Singh et al., 2023).

Based on the PASS Online results, further predictions were made using SwissADME to profile druglikeness in accordance with Lipinski's theory. Pharmacological predictions with SwissADME focused on terpenoids and phenolics with the three highest Pa scores, namely 3,7-Cyclodecadiene-1-methanol, 9,19-Cyclolanostan, Tetramethyldecahydro-1H-cyclopropa, Hydroquinone, 3-Methoxy-5-propylphenol, and 1,3-Benzenediol, 5-pentyl-. The SwissADME in silico results can be seen in Table 3. These results will be screened and continued in the molecular docking stage.

**Table 3. Druglikeness prediction of terpenoids and phenolics *M. polymorpha* using SwissADME (Lipinski rules)**

| Compound | Lipinski rule's | | | | Bioavailability Score | Druglikeness |
|---|---|---|---|---|---|---|
| | MW (g/mol) | Nu.of HBA | Nu.of HBD | LogP | | |
| 3,7-Cyclodecadiene-1-methanol, .alpha.,.alpha | 152.23 | 1 | 1 | 2.31 | 0.55 | 0 violation |
| 9,19-Cyclolanostan-24-one, 3-acetoxy-25-met | 412.73 | 0 | 0 | 5.51 | 0.55 | 1 violation MLOGP>4.15 |
| 1,1,4,7-Tetramethyldecahydro-1H-cyclopropa | 140.22 | 1 | 0 | 2.25 | 0.55 | 0 violation |
| Hydroquinone | 110.11 | 2 | 2 | 0.92 | 0.55 | 0 violation |
| 3-Methoxy-5-propylphenol | 166.22 | 2 | 1 | 2.19 | 0.55 | 0 violation |
| 1,3-Benzenediol, 5-pentyl- | 180.24 | 2 | 2 | 2.04 | 0.55 | 0 violation |

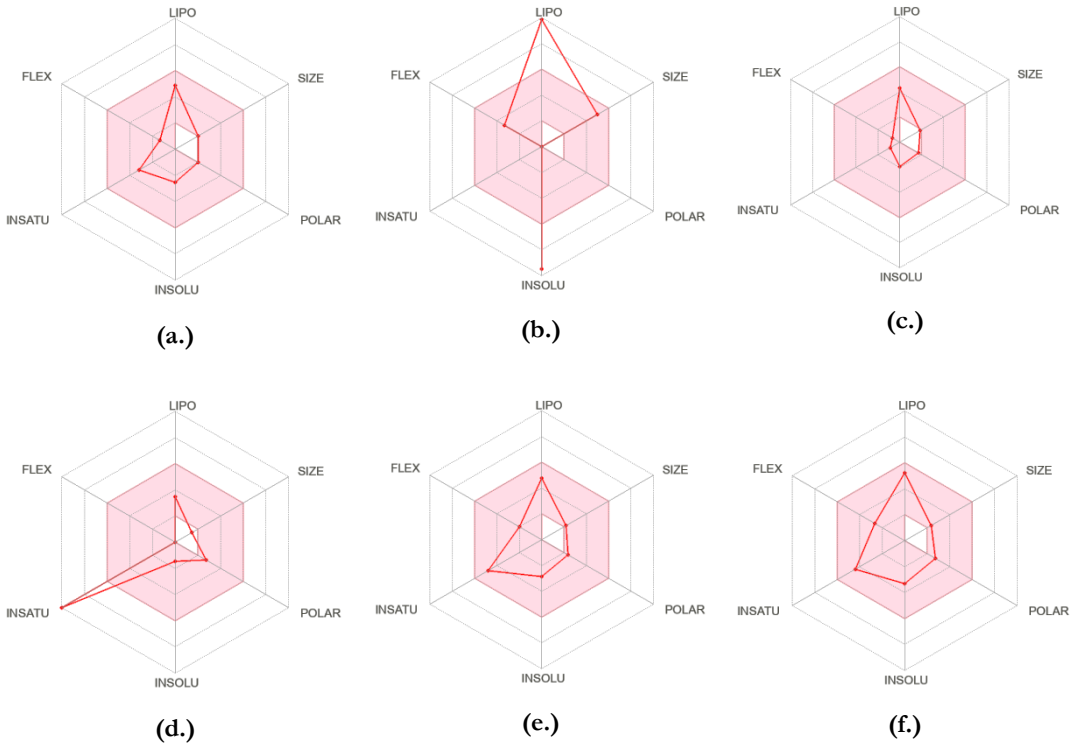
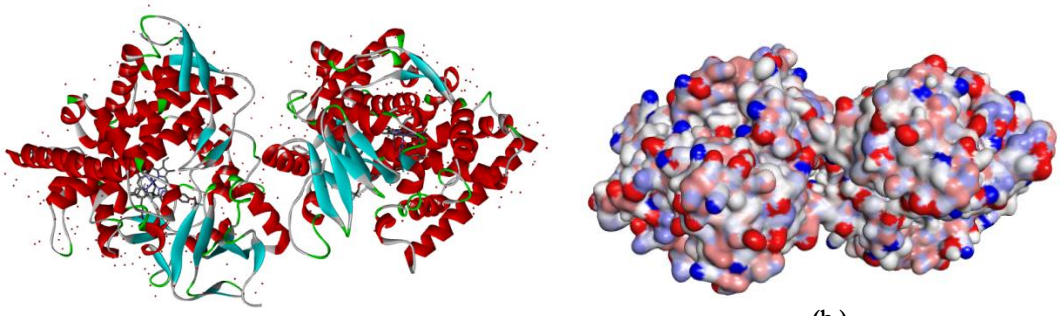



**Figure 3. Bioavailability radar plots of selected metabolites (terpenoids and phenolics) from *M. polymorpha* obtained from Mount Pasang. Each radar map visualization six important physicochemical factors that influence oral drug-likeness: lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU), and molecular flexibility (FLEX); (a.) 3,7-Cyclodecadiene-1-methanol, .alpha.,.alpha; (b.) 9,19-Cyclolanostan-24-one, 3-acetoxy-25-met; (c.) 1,1,4,7-Tetramethyldecahydro-1H-cyclopropa; (d.) Hydroquinone; (e.) 3-Methoxy-5-propylphenol; (f.) 1,3-Benzenediol, 5-pentyl-**

Based on the SwissADME in silico Druglikeness Table 3, five compounds out of a total of six terpenoid and phenolic compounds showed compliance with Lipinski's theory. In addition, the in silico results also showed a bioavailability score of 0.55, according to Daina et al., (2017) these results indicate moderate to good potential for oral absorption. Small compounds < 500 (g/mol) have limited hydrogen bonding ability and excellent membrane permeability, making them suitable as lead compounds. One compound had 1 violation, namely 9,19-Cyclolanostan. This case should be considered for further screening because it has the potential for very low solubility and is predicted to have a decrease in bioavailability score (Daina & Zoete, 2019; Riyadi et al., 2021; Sardar, 2023).

As seen in Figure 3, the radar visualization of bioavailability from SwissADME, panel (b.) shows deviations from the optimal zone. This deviation is predicted to have an impact on excessive lipophilicity, as indicated by the panel pointing excessively towards LIPO (panel b.). The compounds in panel B have excessive LIPO patterns (LogP 5.51), compounds with excessively high LIPO values result in limited water solubility and oral bioavailability, so they are eliminated in the subsequent pharmacological bioinformatics process. Recent research strongly supports these findings, with in silico SwissADME being used as an initial screening of drug candidate compounds based on Lipinski's rules, including in the evaluation of lipophilicity, solubility, and bioavailability (Deshmukh et al., 2025; Rafi et al., 2025). In addition, the SwissADME principle based on Lipinski's theory has been applied to plants that are already used as herbs in Indonesia. One example is Curcuma extract, which shows compliance with Lipinski's principle and indicates potential for oral absorption (Sumardi & Suprianto, 2024). The SwissADME in silico results, the phenolic and terpenoid compounds were then subjected to molecular docking, with the hope of providing more offensive pharmacological predictions. Molecular docking was performed on the best compounds from SwissADME, namely compounds that had no violations.

Compound *M. polymorpha* was docked against the antifungal receptor, as PASS Online results showed antiseborrheic properties with Druglikeness in accordance with Lipinski rules. Docking in this research only focused on the binding affinity values obtained and then correlated them with other relevant studies. Docking was performed against the target protein PDB ID 5TZ1, namely sterol 14-α-demethylase, cytochrome P450 (CYP51) enzyme (Figure 3) derived from *Candida albicans* (Jadhav et al., 2020; Warfield et al., 2014). This protein is considered to be effective in killing fungal growth through the mechanism of lanosterol methylation, resulting in damage to the fungal cell membrane. The structure of sterol 14- α -demethylase has previously been studied with antifungal drugs including posaconazole and VT-1161 (Hargrove et al., 2017). PDB ID 5TZ1 is increasingly reinforced by pharmacological predictions as an antifungal protein after several research developments related to 5TZ1 antifungal inhibition (Antypenko et al., 2023; Shah et al., 2025; Upadhyay et al., 2024).



**(a.)** **(b.)**

**Figure 4. 3D visualization of the crystal structure of the target protein sterol 14- α -demethylase (CYP51) from *Candida albicans* with potential docking as an antifungal (PDB ID: 5TZ1); (a.) 3D visualization representation of the primary and secondary protein domain structures; (b.) Representation of surface area and surface or cavity as ligand binding target locations.**

The ligands used against the 5TZ1 protein are 3,7-Cyclodecadiene, 1,1,4,7-Tetramethyldecahydro, Hydroquinone, 3-Methoxy-5-propylphenol, and 1,3-Benzenediol. The compound was selected based on PASS Online scoring results showing biological activity related to antifungal and SwissADME (no violation). Overall docking of the ligands to 5TZ1 resulted in an interaction, marked by the attachment of

the ligands to the structure of the target protein area as a receptor (Figure 4). All compounds showed attachment orientation in different areas, but remained within the active structure of the target protein (Figure 4). Figure 4. Visualization of ligand attachment to the active area of the target protein.

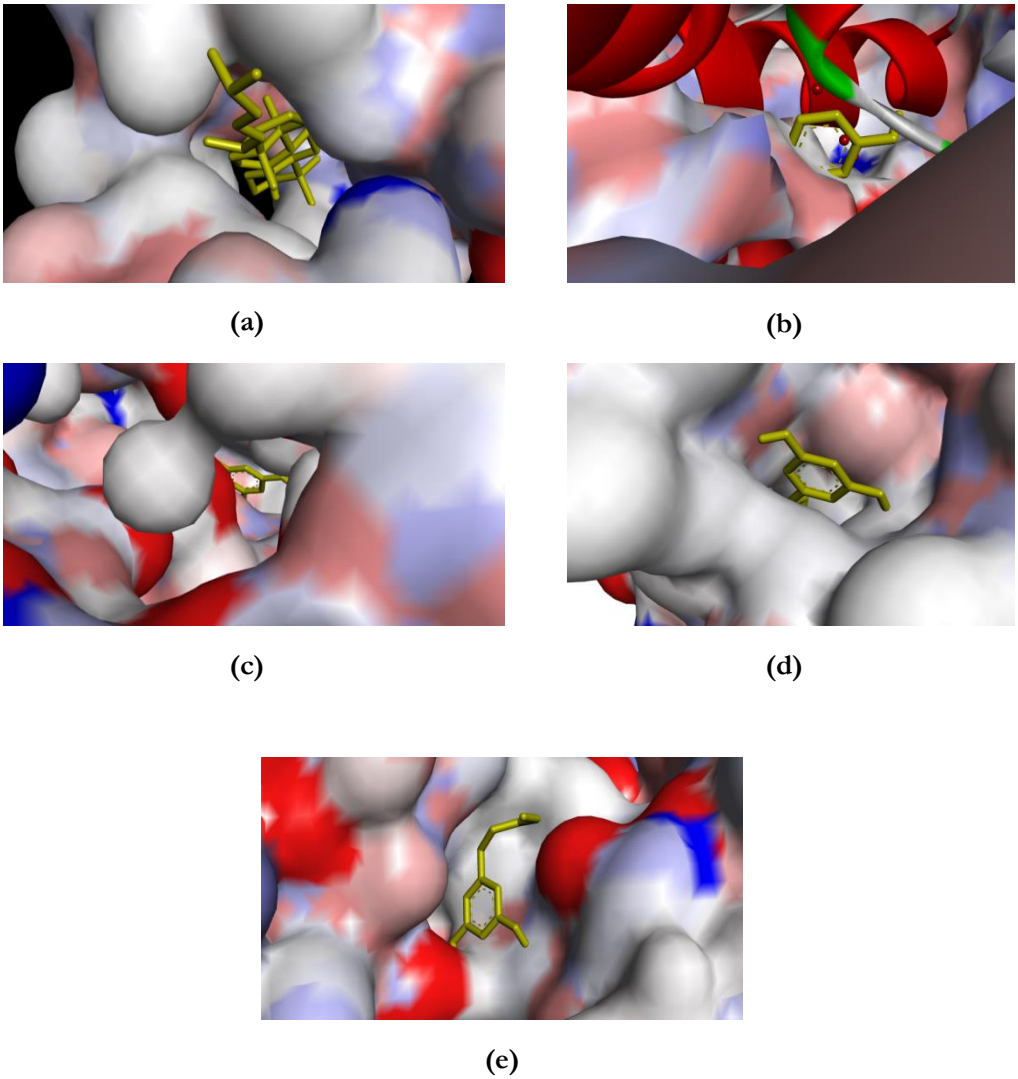



**Figure 5. 3D visualization of the Ligand-Protein complex resulting from molecular docking against the target protein sterol 14-α-demethylase (CYP51) from *Candida albicans* as an antifungal agent; (a.) 3,7-Cyclodecadiene; (b.) 1,1,4,7-Tetramethyldecahydro; (c.) Hydroquinone; (d.) 3-Methoxy-5-propylphenol; (e.) 1,3-Benzenediol, 5-pentyl-. Parts (a-e) show the visualization of ligand binding to the active site of the protein in the top-ranked pose.**

The molecular docking that has been carried out produces binding affinity and RMSD values, which are parameters of the success of in silico MD (Table 4). Based on these results, interpretation was then carried out with visualization to determine the resulting residue interactions (Figure 5).

**Table 4. Binding affinity score from ligand metabolite compounds of *M. polymorpha* molecular docking-based**

| Compound | Binding affinity Score kcal/mol | RMSD |
|---|---|---|
| 3,7-Cyclodecadiene-1-methanol, .alpha.,.alpha | -10.1 | 0 |
| 1,1,4,7-Tetramethyldecahydro-1H-cyclopropa | -4.9 | 0 |
| Hydroquinone | -6 | 0 |
| 3-Methoxy-5-propylphenol | -7 | 0 |
| 1,3-Benzenediol, 5-pentyl- | -6 | 0 |

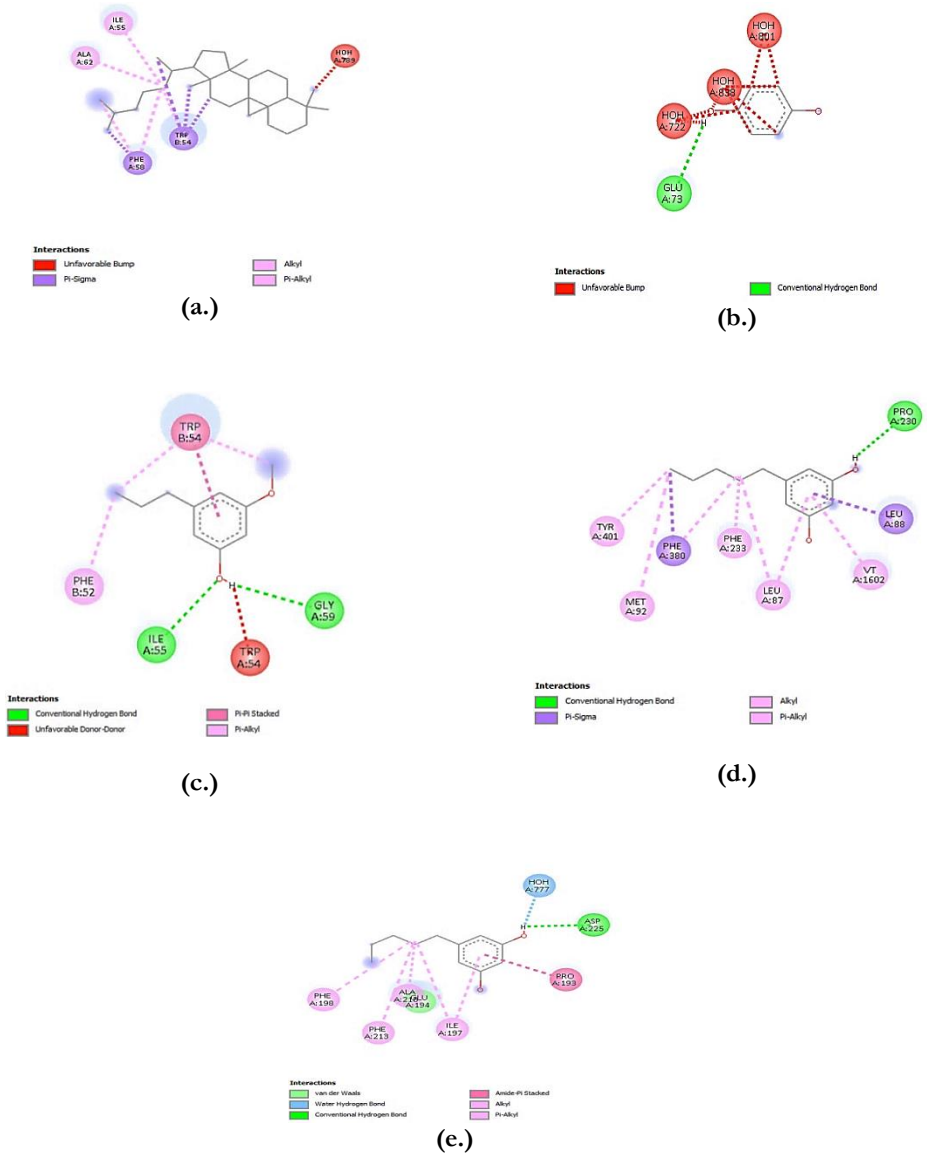



**Figure 6. Show 2D visualization of ligand interaction for sterol 14-α-demethylase (CYP51) (a.) 3,7-Cyclodecadiene; (b.) 1,1,4,7-Tetramethyldecahydro; (c.) Hydroquinone; (d.) 3-Methoxy-5-propylphenol; (e.) 1,3-Benzenediol, 5-pentyl-**

Based on the MD results, compound 3,7-Cyclodecadiene has the strongest binding affinity score of -10.1 kcal/mol with residues ILE A:55, ALA A:62, PHE A:58, and TRP B:5 (Figure 6a). A low affinity value indicates that the compound has more effective antifungal inhibition compared to other compounds in principle docking. This is in line with previous studies that the basic principle of binding or interaction is that the more negative the value, the stronger the ligand-receptor interaction (Elsaman et al., 2025). Compounds obtained with the best interaction results can be recommended as drugs or antifungal agents. This theory is based on previous research conducted by Fawwaz et al., (2024), I-RMFZ can be highly selective against target docking toxicity, as indicated by the highest interaction. Another compound, 3-Methoxy-5-propylphenol, obtained an affinity score of -7 kcal/mol, which can be categorized as good because it is still relatively low and has significant interaction potential with active protein residues. Meanwhile, Hydroquinone and 1,3-Benzenediol compounds have the same affinity value of -6 kcal/mol.

Previous research on CYP51 has been conducted, showing an optimal value of −8.7 kcal/mol for potential antifungal ligands (Rahman et al., 2025).

Further validation of the docking results showing that the 3,7-Cyclodecadiene compound is the best docking result in this study is reviewed from the 3D visualization of aromatic conditions, H-Bonds, and hydrophobicity (Figure 7). The visualization of the aromatic edge/face (Figure 7a) shows that the ligand fills/interacts with the active protein with a non-polar orientation, while the H-bond (Figure 7b) is located at a polar point, although not too dominant. This condition will greatly assist the ligand in interacting with the receptor without reducing the level of hydrophobicity (Ahmmed et al., 2023).

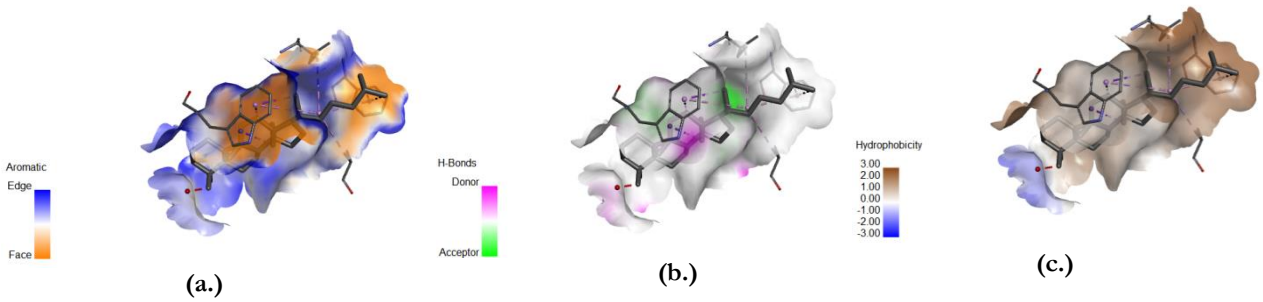



**Figure 7. 3D visualization of the interaction between the 3,7-Cyclodecadiene ligand and the target protein; (a.) Aromatic visualization showing the interaction between the aromatic ring of the ligand and the active surface area of the protein (edge/face); (b.) Visualization of hydrogen bond donors and acceptors showing interactions between the ligand and protein residues; (c.) Visualization of hydrophobicity shows that the dominance of nonpolar areas on the active protein surface, a hydrophobic condition, can stabilize the protein complex.**

## Conclusion

The untargeted metabolites profiled in *M. polymorpha* in this study were fatty acids (20%), terpenoids (16%), and phenolics (10%). All of these compounds are highly volatile, making them easily detectable by GC-MS. Bioinformatics-based pharmacological predictions focused on secondary metabolites as an initial screening. The PASS Online in silico results for terpenoids showed that the compound with the highest Pa value was 3,7-Cyclodecadienem (Pa=0.920), predicted to be an alkenylglycerophosphocholine hydrolase inhibitor, while for phenolics, the compound with the highest Pa value was hydroquinone (Pa=0.927), predicted to be an antiseborrheic. Meanwhile, in druglikeness using SwissADME, five compounds out of a total of six terpenoid and phenolic compounds showed compliance with Lipinski's theory. In addition, the in silico results also showed a bioavailability score of 0.55. In silico molecular docking was performed on five metabolite compounds that had successfully passed screening in the previous method. The molecular docking results showed that the 3,7-Cyclodecadiene compound had the strongest binding affinity value of -10.1 kcal/mol. Based on these results, the compound 3,7-Cyclodecadiene *M. polymorpha* can be recommended for further clinical research and can be used as implications for further research in the biomedical field.

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**Author's contributions:** All contributions were made individually by Abdillah Maulana Farhan, including conceptualization, methodology, analysis, and writing of the manuscript, and approved the final version

**Generative AI:** The use of artificial intelligence in the preparation of manuscripts is limited to language translation tools to improve clarity and language quality, without affecting the scientific substance, data analysis, or interpretation of research results. This study used bioinformatics applications and websites,

including software for molecular docking analysis, PASS Online, and SwissADME, as part of the data analysis method.

**Data availability:** Supporting data for this research comes from journals, proceedings, books, and freely accessible bioinformatics tools.

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