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Melaleuca Leucadendra PHARMACOLOGICAL NETWORK FOR IDENTIFYING POTENTIAL TARGET OF ALCOHOL DEPENDENCE

Risma Ayu Setiawan[1], Ahmad Shobrun Jamil[1*], Siti Rofida[1] and M. Artabah Muchlisin[1]

[1] Department of Pharmacy, Faculty of Health Science, University of Muhammadiyah Malang, Jl. Bendungan Sutami No. 188, Sumbersari, Lowokwaru, Malang, 65145, Indonesia; +628563569655

Email: shobrun@umm.ac.id

Abstract

Melaleuca leucadendra (ML) contains a compound that is potentially a candidate for alcohol dependence. Alcohol dependence is defined by desire, tolerance, anxiety with alcohol, and continuing to drink even though the consequences are dangerous. The study aims to analyze the potential of the ML compound content for alcohol dependence therapy within silico-based pharmacological chain analysis. ML compound data is obtained from the Knapsack database, screening of absorption, distribution, metabolism, and excretion (ADME) of the compounds ML with SwissADME, prediction of the protein of the target compounder ML with the Swiss TargetpPrediction, Gene cards, venny, analysis of the pharmacological network with String-DB and its visualization with Cytoscape version 3.10.0. The pathways correlated with therapy are dopamine receptors, dopamine carriers, serotonin, gamma-aminobutyric acid receptors, and toll-like receptors for known therapeutic target proteins: OPRM1, DRD2, ALDH2, ADH1B, ADH1A, ADH1C, ADH4, SLC6A3, CNR1, POMC, ARRB2, and NCS1. Alcohol-dependent therapies include alpha-Campholenal, Benzaldehyde, trans-Pinocarveol, Borneol, linalool, alfa-Terpineol, (-)-alpha-Bisabolol oxide B, alphaterpine acetate, and Caryophylla-4(148),15-dien-5alphaol.

***Keywords**: Alcohol dependence, In-silico, Melaleuca leucadendra, Network, Pharmacology*

Background

Indonesia is known for its wealth of spices, other natural resources, and biodiversity. With a high level of biodiversity, it can be used as a medicinal plant, becoming a significant ingredient in the production of spices and herbal medicines. The general public widely uses medicinal plants because they have fewer side effects than chemical drugs and help reduce the use of chemicals. *Melaleuca leucadendra* (ML) plants are one of the spices found in Indonesia (Rosnelly & Utama, 2021).

ML, commonly called white wood, is a traditional low-growing plant. This plant can grow to a height of 30 m, but under certain circumstances, it grows into a caterpillar of 1.5–3 m (Ria et al., 2020). ML plants can live on Java Island, East Nusa Tenggara, and Sulawesi Island. The White Tree plant belongs to the Myrtaceae family (Meisarani & Ramadhania, 2016). Almost all parts of this plant (shell, leaves, branches, and whitewood fruit) can be used as medicine. The genus Myrtaceae is one of the most important Essential Oil (EO) producing species in which Essential oil (EO) has a variety of bioactivities, such as antibacterial, antifungal, antioxidant, insecticide, and antiviral (Zhang *et al.*, 2018). The essential oils are obtained from six different ML tissues: young leaves, old leaves, stems, fruits, and ends of branches, with a result of approximately 1%. A total of 104 compounds are identified in the ML essential oil. The primary content of whitewood oil is 1.8-cineol (Eucalyptol), one of the monoterpen compounds. In addition to the predominant range of 1.8-cineol (43.76–60,19%), there are other compounds like α-terpineol (5.93-12.45%), d(+)-limonene (4.45–8.85%), and β-caryophyllene (3.78-7.64%)(Irfan *et al.*, 2022).

Alcohol is a highly addictive substance which many people consume. According to the data of the Central Statistical Agency (2020), the consumption of alcohol by the population aged 15 and over in Indonesia in 2020 was 0.39 liters per capita. In the region, drinking alcohol by the rural population reached 0.61 liters per capita in 2020. Badung and Bali districts have a prevalence of 2.09% of alcoholic drinkers per day, mainly among teenagers (Komang et al., 2023).

Alcohol dependence is defined by desire, tolerance, obsession with alcohol, continuing to drink even though the consequences are dangerous, and the development of physiological withdrawal syndrome when alcohol is suddenly discontinued or consumption is reduced by the International Classification of Diseases (ICD) and by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM). DSM-V's continuum ranges from light to heavy (Hillemacher & Frieling, 2019).

Alcohol may stimulate an increase in the hypothalamic axis of the pituitary adrenocortical (HPA). HPA axis activation is a significant component of stress response. Several variables, including genotype, gender, and dose parameters, influence this increase. Based on clinical and preclinical studies, HPA axis dysregulation is associated with changes in the activity of the extrahypothalamic stress system in the brain, thus significantly affecting the motivation for alcohol self-administration behavior (Tritama, 2015). Several association studies of the alcohol dependence genome found the result of the ADH gene with the most significant measure of effect with alcohol dependency is ADH1B (Tamara et al., 2014).

The method in silico is a research into the chemical sector beset biology with a computational basis. This method is used to determine the structure of molecules in three dimensions by studying the active side of a particular molecule. The technique explores a compound that acts as a drug candidate and a specific protein in a molecular target (Dona *et al.*, 2019).

In-silico research can explain the molecular and cellular mechanisms that occur when the active compounds found in plants are stimulated. Research related to alcohol dependency control activity by using ML less in providing information related to molecular mechanisms of interaction of ML compounds with the protein chain that regulates alcohol dependence activity. So, this research was done to give a clearer picture of the mechanisms of these interactions in silico. Therefore, this study uses methods of pharmacological grid analysis with in-silico methods. To find out the agents

of the compound in humans, this study can accurately give recommendations for further research that the content of ML can be a drug candidate as a supporter of alcohol dependency awareness. This study was used to visualize the protein networks in the ML related to the relationship of the compound with the protein and the diseases associated with that protein. The benefit of this research is to provide an overview of the mechanisms of the active compounds present in plants and as preliminary data for further research related to the active substance ML. This research will focus on exploring the combination contained in the ML, which can be a candidate drug supporting alcohol consciousness.

This study aims to identify and simulate the molecular pharmacological network of bioactive compounds ML in combating alcohol dependence.

Method of implementation

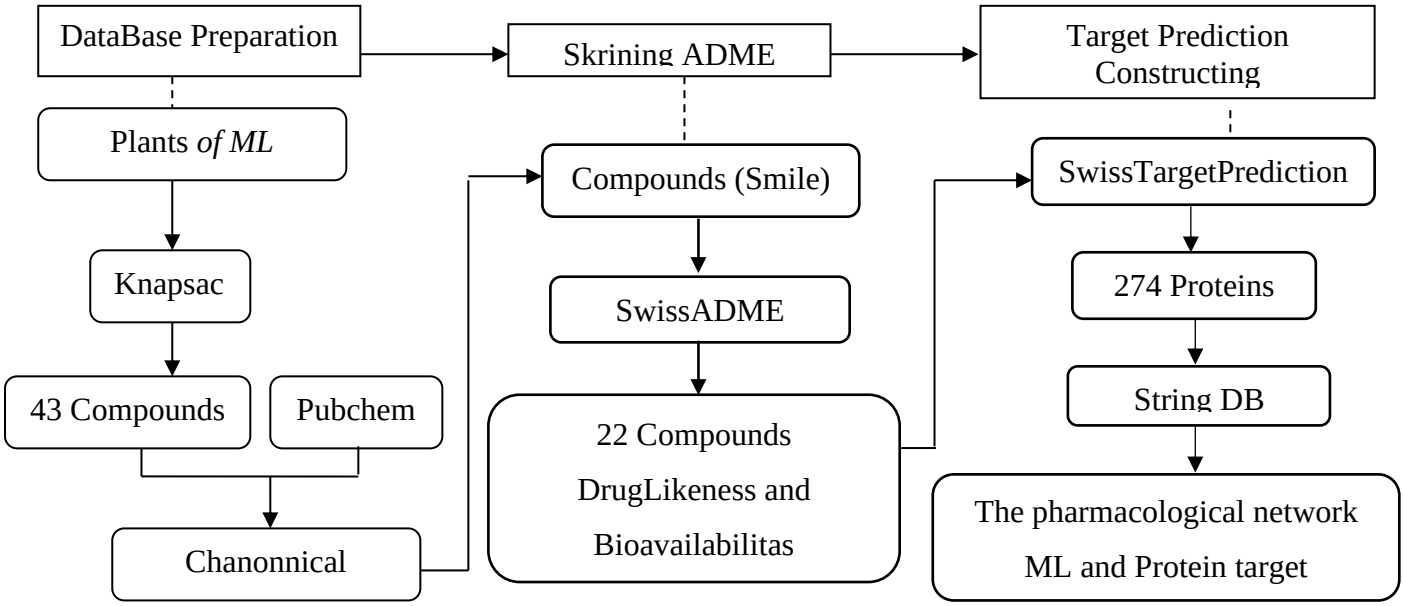


Figure 1. Research Scheme

Materials and Tools

To identify studies eligible for analysis of this pharmacological network, perform computerized searches with Lenovo brand laptops, with Intel(R) Celeron (R) N4100 CPU @ 1.10GHz (4 CPUs), ~+1.1GHz and with RAM 4096 MB. I am using computer analysis with the website operated by Kmapsack Family phytochemical and ethnobotanical Databases (http://www.knapsackfamily.com/), pubchem (https://pubchem.ncbi.nlm.nih.gov), swissADME (http/www.swissadme.ch/), Swiss Target (http / www.swisstargetprediction.ch/, string db (https://string-db.org), Cytoscape and way2drug applications (http // www.way2drugg.com).

Methods

Most pharmaceutical substances interact with many or even a few molecular targets in organisms, which determines the complexity of complex biological profiles. Their metabolism in human body values forms one or more metabolites with different physical activity profiles (Dembitsky, 2021). As a result, the development and use of sensible new drugs requires analysis of their biological activity profiles, considering human metabolism. In silico methods are widely used to estimate interactions with new drug-like compounds with therapeutic targets and predict their metabolic transformations (Dona *et al.*, 2019).

Phytochemical Data Warehouse and Phytochemical Data Unification

The first step in this research is the collection of data in the form of a search for the compounds contained in ML plants using a database-based website, namely the Knapsacfamily Database repository page opened at http://www.knapsackfamily.com/. The data was obtained by entering the plant's scientific name in the search engine section and selecting the "knapsack keyword search." The result was copied to the Excel worksheet. The data was then merged by supplementing the identity of the compounds, including canonical smiles, by entering one by one the names of compounds contained in the ML at the data warehouse https://pubchem.ncbi.nlm.nih.gov. The result of this merger is a list of the composition names in the ML, starting from the code of composition, technical smile, and other supporting data.

Prediction of the absorption, distribution, metabolism, and excretion (ADME) of compounds in ML.

The Swiss ADME program (http://www.swissadme.ch/) performs ADME (Absorption, Distribution, Metabolism, and Excrétion) analysis of ML bioactive compounds. This analysis produces results on the bioavailability of bioactive Compounds as described in the form of radar. The absorption and dispersion data of the combination are depicted using the illustration of boiled eggs. In addition, there are molecular weight data, human intestinal absorptions, cerebral blood clots, and TPSA (Daina et al., 2017).

Prediction of the relationship between ML and cell proteins

The existing data was downloaded and sorted using Swiss Target Prediction (http://www.swisstargetprediction.ch/) (Daina et al., 2019). Later, proteins associated with alcohol dependence were collected using GeneCards (Stelzer *et al.*, 2016). I was then looking for a protein slice predicted to bind to a compound from a plant using Venny (Lin *et al.*, 2016). The list of proteins that appear on Venny is then entered into the StringDB database (https://stringdb.org/), and protein tissue analysis related to alcohol dependence is done on the protein target ML plant. That expected outcome is a review of the protein tissue linked to the Alcohol Addiction process (Szklarczyk *et al.*, 2021). After that, a search was conducted to predict protein interactions related to alcohol dependence using the KEGG Pathway method (Kanehisa *et al.*, 2023).

Cytoscape_v3.10.0 software is an open-source environment for large-scale molecular network interaction data integration. Dynamic states of molecules and molecular interactions are dealt with as attributes on nodes and edges. At the same time, static data, such as functional-protein ontology, is supported by annotations. Cytoscape core deals with essential features such as network layout and mapping data attributes to visual display properties (Heath, 2021).

Cytoscape_v3.10.0 software is used to combine bioactive substances with target Alcohol dependence proteins. Way2drug determines the probability to be active (PA) and the possibility to be inactive (PI) activities of each compound. Then, the values of the chances to be activated (PA) and the possibility to be inactivated (PI) activities of the compounds are entered into Excel (Rudik *et al.*, 2018). Cytoscape_v3.10.0 is used to merge ML plant compounds one by one with target proteins.

Results and Discussion

Analysis using SwissADME, Swiss Target, and stringed applications can provide adequate analysis results because it produces valid data. In-silico research using computerized models is on the rise, with increasing numbers of digital data inputs related to testing the activity of drug compounds.

Identification of secondary metabolites ML

The initial step is to identify the metabolite compounds in the ML plant by analyzing the functional interactions of the various proteins involved using the KNApSAcK Family database. Based on the

searches, 43 metabolite compounds in the ML plant were obtained. The analysis results using web knapsack obtained 43 active compounds in the plant ML, 22 of which can be absorbed both by the intestines and able to penetrate the brain's blood vessels in Table 3 and Figure 2.

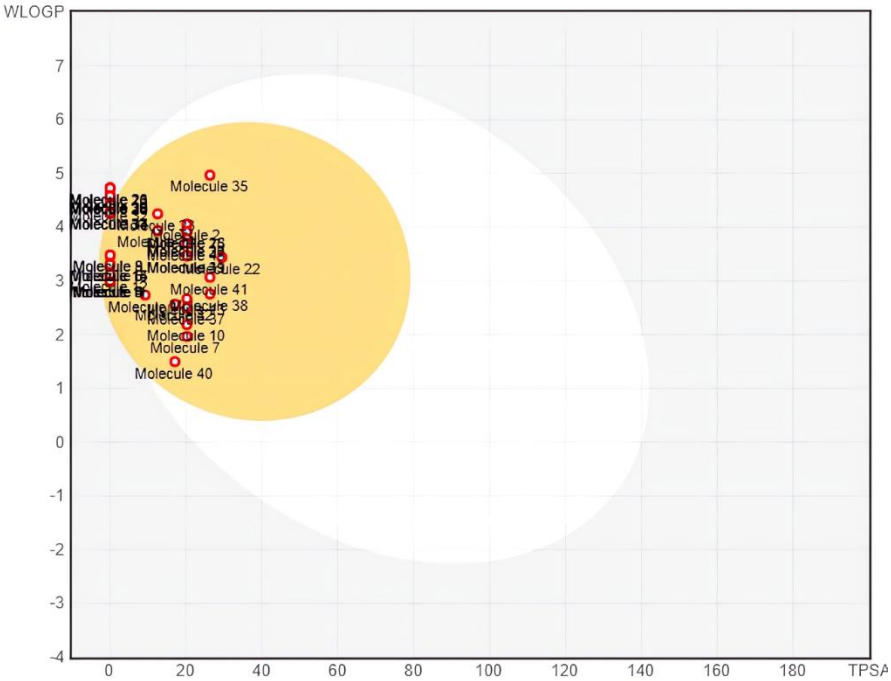


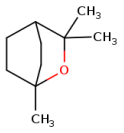
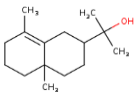
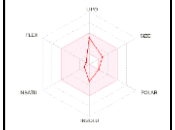
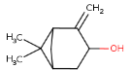
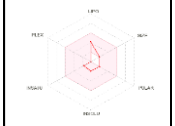
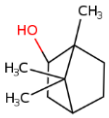
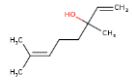
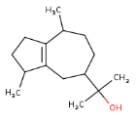
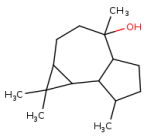
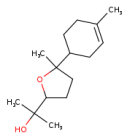
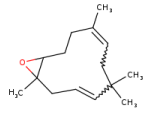
Figure 2. Brain or Intestinal Estimated (Boiled-EGG) ML

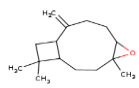
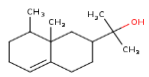
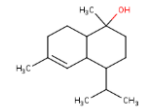
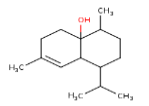
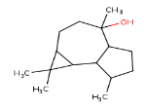
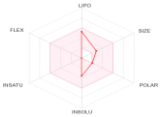
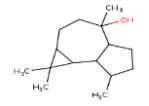
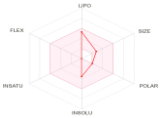
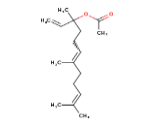
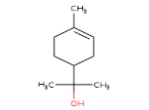
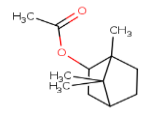
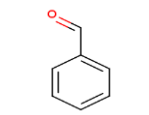
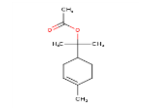
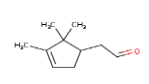
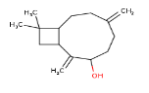
Table 1. Molecule name in BOILED-EGG

No.	Compound Name	Compound Code
1.	1,8-Cineole	Mol 1
2.	gamma-Eudesmol	Mol 2
3.	trans-Pinocarveol	Mol 3
4.	Borneol	Mol 4
5.	Linalool	Mol 5
6.	(-)-Guaiol	Mol 6
7.	Ledol	Mol 7
8.	(-)-alpha-Bisabolol oxide B	Mol 8
9.	Humulene 1,2-epoxide	Mol 9
10.	beta-Caryophyllene oxide	Mol 10
11.	Eremoligenol	Mol 11
12.	alpha-Cadinol	Mol 12
13.	1-epi-Cubenol	Mol 13
14.	(-)-Globulol	Mol 14
15.	Viridiflorol	Mol 15
16.	(E)-Nerolidol acetate	Mol 16
17.	alpha-Terpineol	Mol 17
18.	Borneol acetate	Mol 18
19.	Benzaldehyde	Mol 19
20.	alpha-terpineol acetate	Mol 20
21.	alpha-Campholenal	Mol 21

22.	Caryophylla-4(14),8(15)-Dien-5alpha-ol	Mol 22

Table 2. ML data based on body absorption, 22 compounds can be well absorbed by the intestine (Gastrointestinal Absorbtion (GI Absorbstion)) and can penetrate the blood vessel of the brain (Blood Brain Barrier permeant (BBB Permeant)).

Metabolit	Compound structure	Bioavailability Radar	Bioavailability Score	MW	BBB Permeant	Lipskin	GI Absorbstion
1,8-Cineole			0,55	154.25 g/mol	Yes	0	High
gamma-Eudesmol			0,55	222.37 g/mol	Yes	0	High
trans-Pinocarveol			0,55	152.23 g/mol	Yes	0	High
Borneol			0,55	154.25 g/mol	Yes	0	High
linalool			0,55	154.25 g/mol	Yes	0	High
(-)-Guaiol			0,55	222.37 g/mol	Yes	0	High
Ledol			0,55	222.37 g/mol	Yes	0	High
(-)-alpha-Bisabolol oxide B			0,55	238.37 g/mol	Yes	0	High
Humulene 1,2-epoxide			0,55	220.35 g/mol	Yes	0	High

beta-Caryophyllene oxide			0,55	220.35 g/mol	Yes	0	High
Eremoligenol			0,55	222.37 g/mol	Yes	0	High
alpha-Cadinol			0,55	222.37 g/mol	Yes	0	High
1-epi-Cubenol			0,55	222.37 g/mol	Yes	0	High
(-)-Globulol			0,55	222.37 g/mol	Yes	0	High
Viridiflorol			0,55	222.37 g/mol	Yes	0	High
(E)-Nerolidol acetate			0,55	264.4 g/mol	Yes	0	High
alpha-Terpineol			0,55	154.25 g/mol	Yes	0	High
Borneol acetate			0,55	196.29 g/mol	Yes	0	High
Benzaldehyde			0,55	106.12 g/mol	Yes	0	High
alpha-terpineol acetate			0,55	196.29 g/mol	Yes	0	High
alpha-Campholenal			0,55	152.23 g/mol	Yes	0	High
Caryophylla-4(14),8(15)-dien-5alpha-ol			0,55	220.35 g/mol	Yes	0	High

Bioavailability prediction of the secondary metabolite of ML

Protein analysis was obtained from SwissADME in Table 2 below using the SwissTarget prediction web server. We got 274 proteins out of 22 active compounds. The protein is a candidate target protein because it has a prediction of the percentage of biological activity (Pa) above 0.0. The results are inserted into venny's web server. Of the 274 proteins, 248 are known to be associated with the alcohol-dependent disease gene. Using the web server string-db, 248 proteins are obtained, 12 proteins that can be candidates for the treatment of alcohol dependence.

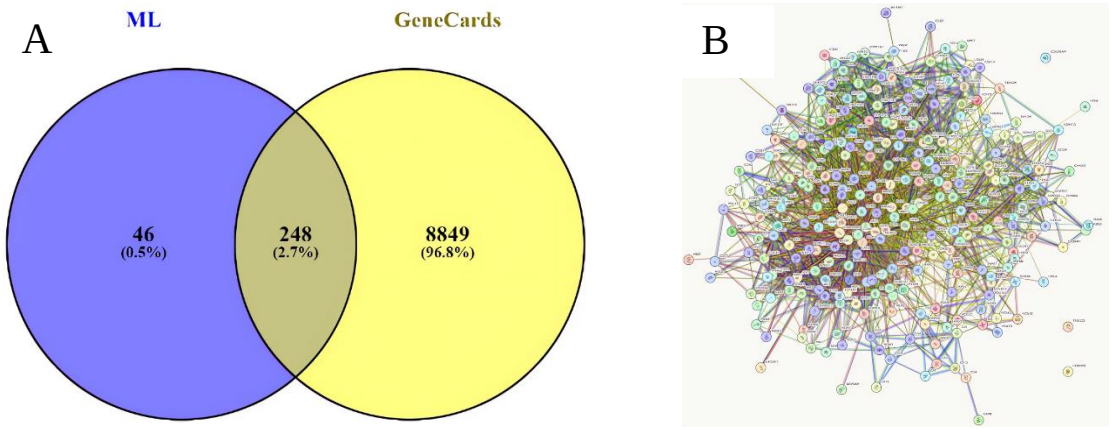


Figure 3. (A). Venn diagram (https://bioinfogp.cnb.csic.es/tools/venny/) tools venny the number of proteins involved in congenital alcohol dependence with the keyword entered in the gene card database (https://www.genecards.org/) "genetic alcohol dependence in blue circles. Target proteins interacting with ML were obtained from analysis using Swissstargetprediction (http://www.swisstarget Prediction.ch/) in yellow circles. The iris are old yellow and contain 248 target proteins that interact with the content of the ML compound. (B). Network 248 targets ML proteins related to DB string software (https://string-db.org/).

Alcohol dependence is linked to a secondary metabolite ML.

Protein obtained from the Venn diagram cuts was further analyzed using StringDB, which aims to create a network of interactions between the secondary metabolite and the selected target protein. It seeks to discover the relationship between the selected proteins and analyze the biological pathways of alcohol dependence affected by these proteins. (Figure 3A). StringDB is a database of known and predicted protein-protein interactions integrating functional relationship data from various sources, including >9 million proteins (Kanehisa *et al.*, 2023). StringDB collects biological sources, such as biochemical experiments, text mining, and co-expression studies, to create integrated scores. It provides a straightforward and fast way to see if there is a functionally related gene/protein group (Heath, 2021).

After that, a KEGG analysis was carried out. From the results of the analysis, the path related to alcohol dependence was searched, and there were four tracks with the highest strength values selected. (Figure 4A). Kyoto Encyclopedia of Genes and Genome (KEGG) is a collection of manually drawn path maps representing our knowledge of molecular interactions and reaction networks. It determines the molecular mechanisms of compounds in plants interacting with target proteins to assess their role in the immune system. KEGG is used for research and education in bioinformatics, including data analysis in genomics, metagenomics, metabolomics, and other omics studies, modeling and simulation in system biology, and translation research in drug development

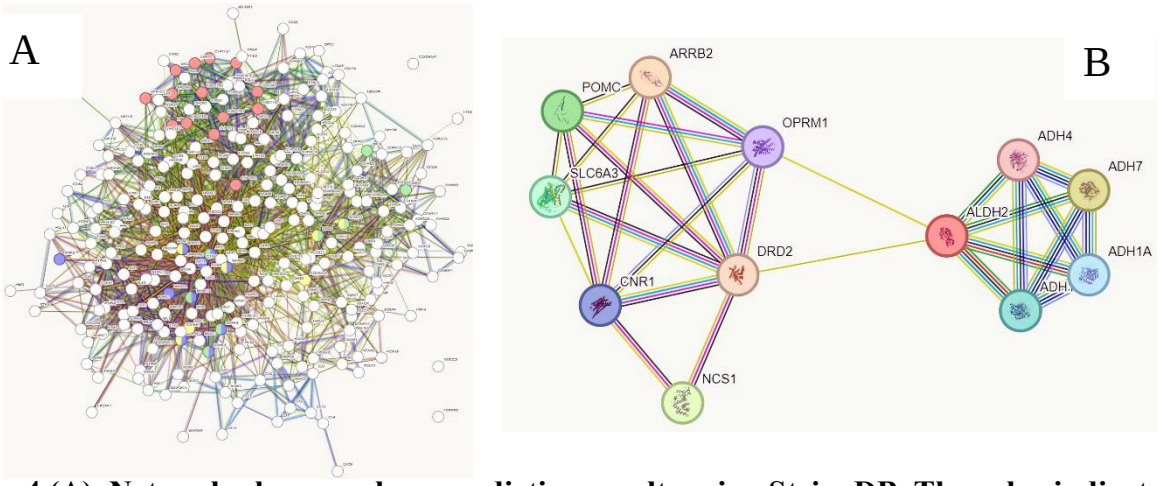


Figure 4.(A). Network pharmacology prediction results using StringDB. The color indicates which path is related to the protein. Signal pathway Steroid hormone biosynthesis (red); Toll-like receptor signaling pathway (blue); Dopaminergic synapse (green); Alcoholism (kuning). (B). The network of proteins associated with alcohol dependence results in analysis using string-db.

Table 3. Target compounds and proteins that can be drug-supported alcohol dependency awareness

No.	Senyawa	Protein target
1.	alpha-Campholenal	ADH4, ADH1A, ADH1B, ADH1C, CNR1
2.	Benzaldehyde	ADH1B, ADH1A,
3.	trans-Pinocarveol	DRD2
4.	Borneol	DRD2
5.	Linalool	DRD2, OPRM1, SLC6A3
6.	alpha-Terpineol	DRD2, SLC6A3
7.	(-)-alpha-Bisabolol oxide B	OPRM1, CNR1
8.	alpha-terpineol acetate	ALDH2, CNR1, SLC6A3
9.	Caryophylla-4(14),8(15)-dien-5alpha-ol	SLC6A3

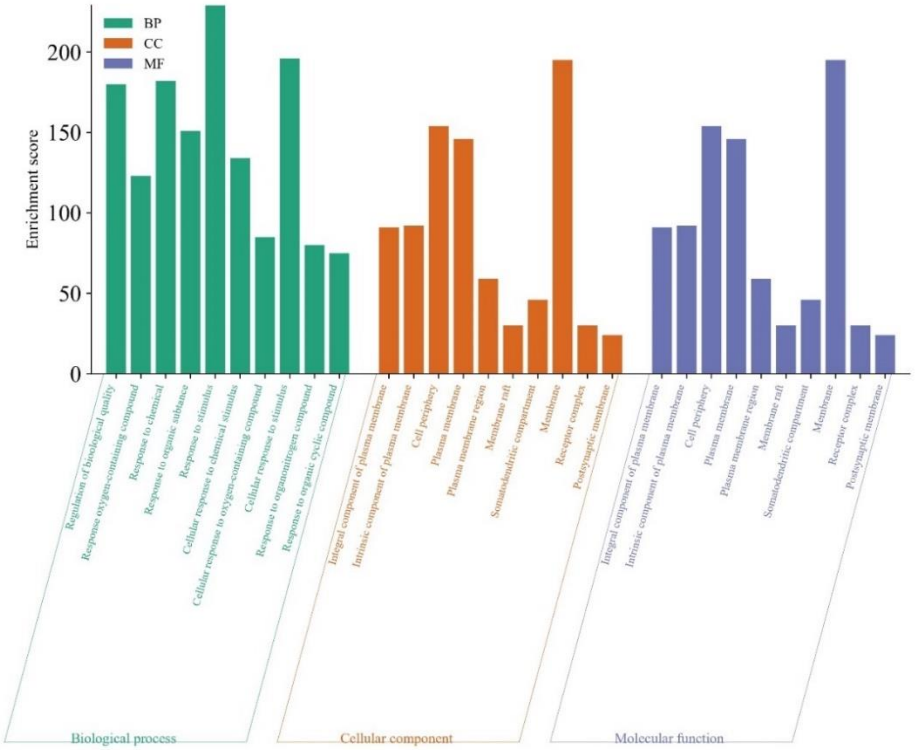


Figure 5. Column diagram 10 enriched terms in each category Biological process (BP), Cellular Component (CC), Molecular Function (MF)

Figure 6 is a network of target proteins with bioactive compounds using Cytoscape applications. Green-dyed hexagon is a bioactive compound found in ML plants. Yellow-dyed circles are target proteins associated with a natural alcohol addiction drug containing 12 proteins. In the link between bioactive compounds and proteins in the pharmacological chain results below (Figure 6), the target protein in the active combination obtained is bound to the protein in that bioactive composition.

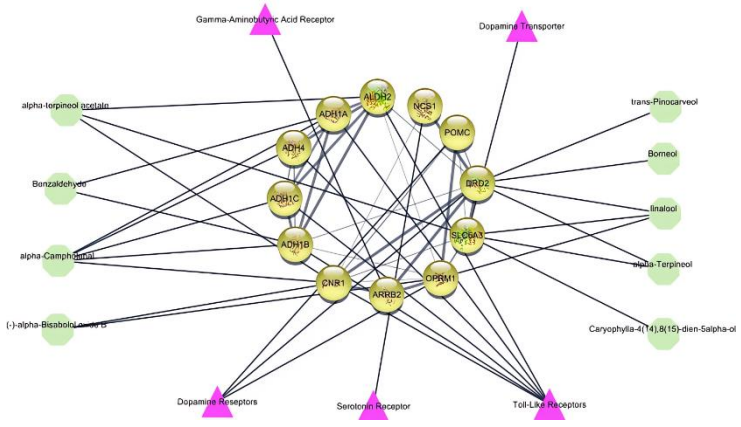


Figure 6. A network of interactions between 9 active compounds in ML (green) and alcohol dependence target proteins (yellow). ML contains nine active substances that are known to interact with 12 target proteins from 5 alcohol dependency signaling paths. (pink).

Figure 7. Biological Activity Percentage (Pa) specifically related to alcohol dependence of compounds contained in ML extract using Way2Drug PASS Online Database analysis.

The study used an in silico method with an active compound from a whitewood plant (Melaleuca leucadendra) with a target protein correlated with the ADH1B gene. There are 43 active

compounds found in Melaleuca leucadendra. This data can be downloaded in Excel file format through the knapsack family. However, in the bioavailability analysis of compounds using Swiss ADME, 22 active substances have ADME criteria shown through Boiled-EGG (Figure 2) that can be absorbed both by the intestines and can penetrate the blood vessels of the brain (Indarwati et al., 2019). In the analysis of the target protein, Melaleuca leucadendra had 274 target proteins with a probability value of more than 0, which indicates that the protein has good activity(Szklarczyk *et al.*, 2021). Of the 274 proteins, there are 248 that interact with the ML protein with alcohol dependency. Of the 248 proteins, they are placed in the DB string, and the result is 12 proteins that are influential in the treatment of alcohol dependence. The proteins involved are OPRM1, DRD2, ALDH2, ADH1B, ADH1A, ADH1C, ADH4, SLC6A3, CNR1, POMC, ARRB2, and NCS1.

PPI (Protein-Protein Interaction) tissue construction through STRING aims at predicting protein interactions that contribute to the Alcohol dependency pathway. There are 12 target proteins OPRM1, DRD2, ALDH2, ADH1B, ADH1A, ADH1, ADH4 and SLC6A3,CNR1,POMC,ARRB2,NCS1 that form this receptor (Figure 3B).OPRM1 (micro-opioid receptor) is the gene code for the MOP receptor, coupled with G-proteins that are capable of altering the function of MOP Receptors so that the G variant binds beta-endorphins three times more strongly than the A variant, potentially also affecting the availability of MOP receptors (Szentkereszty *et al.*, 2019). DRD2 and POMC play a role in helping to create D2-type dopamine receptors, and if paired with the G-receptor protein, they will inhibit adenyl cyclase activity (Weiland et al., 2020); (Campus, 2014). ALDH2 is needed to produce ethanol derivative acetate in the brain that is useful to control the effects of production, cellular, and behavior of alcohol metabolites in a specific way region of the brain (Chen et al., 2019). ADH1B, ADH1A, ADh1C, and ADH4 have been identified as a grouping in the long arm of chromosome 4 that acts as the enzyme that metabolizes alcohol in the liver (Wall et al., 2016). SLC6A3 is a transport protein that relies on the Na+/Cl− 12-membrane domain, with responsibility for the extra-cellular synaptic dopamine re-absorption into the parsnips neurons, and with this the cessation of dopaminergic neurotransmission, thus the receptor protein SLC7A3 was a potential candidate in clinical studies of alcohol dependence (Xu *et al.*, 2017). CNR1 can enhance endocannabinoid functions and can restore affective homeostasis without the presence of alcohol, thereby reducing or eliminating the incentive to consume alcohol because of its negative strengthening properties (Rodr et al., 2023). ARRB2 (β-arrestin2), which influences the function of dopamine two receptors (D2R) as an intracellular signal and release of Gamma-Aminobutyric Acid (GABA) (Lyoo *et al.*, 2014). NCS1 can regulate nerve growth channels and neurite extensions (Bandura & Feng, 2019).

Interactions between grids and target proteins focus on proteins with minimum interaction scores > 0; the higher the interaction score on a protein, the more biologically meaningful it will be. In this study, Cytoscape was used against 12 target proteins, namely OPRM1, DRD2, ALDH2, ADH1B, ADH1, ADH4, SLC6A3, CNR1, POMC, ARRB2, and NCS1. The results of the Cytoscape can be seen in the table of percentage values of biological activity (Pa) (Daina et al., 2019). The higher the PA value, the stronger it can be said that the bond is strong (Agahi *et al.*, 2020). It can be seen in Figure 6 that the PA values obtained are so high that they can be made as a recommendation of compounds in supporting consciousness of alcohol dependence on whitewood plants. Therefore, this research can be helpful as an advanced laboratory experimental research, namely in silico testing of ML as a consciousness of alcohol dependence.

Conclusion

ML has activity associated with alcohol dependence disease. Based on the analysis of pharmacological chains, it is known that the bioactive compound ML can be used as a candidate therapeutic ingredient for alcohol dependence. Nevertheless, this research needs to be continued

with in vitro and in vivo pre-clinical and clinical studies to provide more accurate results for alcohol-dependent disease. The study, using the in-silico method with several websites and software, found that the entire section of the ML plant contains 43 bioactive compounds, 22 bioactive substances have high bioavailability and nine bioactive chemicals with 12 target proteins that can be used as new drug ingredients from alcohol dependence.

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