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Research Article

A Network Pharmacology Analysis of Secondary Metabolites of Noni (*Morinda citrifolia*) as Immunomodulators

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ABSTRACT

Immunomodulators are substances or compounds that can modulate or help increase the activity and function of the immune system. The medicinal use of herbal plants is now increasing again among Indonesian people. Noni (*Morinda citrifolia*) is a plant commonly found in Indonesia that has long been known to have many benefits for treating and preventing various diseases and the secondary metabolites have potential as immunomodulators. This study aimed to determine the protein network associated with the body's immune system, which was activated by the administration of noni. The explorative descriptive research was conducted with *in silico* analysis using a computational model with software, including KNApSAck, Dr. Duke, Pubchem, Swiss ADME, Swiss Target Prediction, Gene Cards, Venny, STRING, and KEGG. Based on the results of pharmacological network analysis, noni contains 128 secondary metabolites, and 83 of them have high bioavailability. Based on pharmacological network analysis, (z,z,z)-8,11,14-eicosatrienoic-acid and 1-5-6-trihydroxy-anthraquinone are important compounds that play a role in the immune system because they are expected to interact with five crucial pathways related to immunomodulators.

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) is the newest of the corona virus groups after Middle Eastern Respiratory Syndrome (MERS)-Cov and Severe Acute Respiratory Syndrome (SARS)-Cov-2 (Ouassou *et al.,* 2020). It was reported that this virus first appeared in Wuhan, China, at the end of December 2019. It spread quickly and reached worldwide concern in just a few months (Botahala, 2021). This disease is caused by SARS-CoV-2 infection (Alkautsar, 2021). This virus can cause respiratory problems and inflammation of the lungs and the clinical symptoms that arise from this disease are very diverse, ranging from the common cold (cough, sore throat, and headaches) to severe complications (pneumonia). (Ouassou *et al.*, 2020). COVID-19 needs to be monitored because its transmission is relatively fast and has a high mortality rate (Saharani *et al.,* 2021). Accordingly, careful efforts are required to maintain a healthy body and proper immune system and response.

Immunomodulators are substances or compounds that can modulate or help increase the activity and function of the immune system. Based on how they work, it is divided into three agents, which are to increase the immune system function (immunostimulator), regulate the immune system (immunoregulator), and inhibit or suppress the immune system (immunosuppressor) (Griana and Kinasih, 2020). The immune system protects the body from various infections by producing antibodies that bind to antigens that occur through a series of interaction mechanisms of the innate immune system and adaptive immunity (Kusnul, 2020). Importantly, maintaining and enhancing the body's immune system can help protect against a variety of diseases, including COVID-19.

The medicinal use of herbal plants is now increasing again among Indonesian people. Several studies have shown that information on herbal use is generally obtained based on information passed down from generation to generation and local culture (Nashrullah *et al.*, 2022). Noni (*Morinda citrifolia*) is a plant commonly found in Indonesia that has long been known to have many benefits for treating and preventing various diseases (Wiradona *et al.*, 2015). Noni has beneficial activity as an antidiabetic (Nerurkar *et al.*, 2015), antioxidant (West *et al.*, 2018), cancer (Kumar *et al.*, 2022), and immunomodulator (Farizal *et al.,* 2020).

However, further information is required to explain this immunomodulatory activity. Therefore, this research was conducted to reveal or demonstrate the processes/molecular and cellular mechanisms that occur in humans when treated with noni with network pharmacology using the *in silico* method. Network pharmacology is a term first used in 2007 (Hopkins, 2007). Network pharmacology provides the basis for complex biological systems in a network perspective. Researchers can understand the health and disease state of the human body by establishing and analyzing the biological network and using it as a target to design effective drug intervention methods (Xin *et al.*, 2021) This method has scientific validity, is relatively new, and has high accuracy (Wen *et al.*, 2016).

METHODS

Materials and Tools

This research utilized the online database to gather and process the data. KNApSAck Family (http://www.knapsackfamily.com/) and Dr. Duke's Phytochemicals and Ethnobotanical Database (https://phytochem.nal.usda.gov/) were used to collect the secondary metabolites of noni. SwissADME (http://www.swissadme.ch/) was used to predict the bioavailability of the secondary metabolites of noni. Swiss Target Prediction (http://www.swisstargetprediction.ch/) was used to predict target proteins related to plant secondary metabolite compounds. GeneCards (https://www.genecards.org/) collected target proteins associated with immunomodulation. StringDB (https://string-db.org/) was used to gather, assess and integrate all existing information on protein-protein interactions.

Methods

dentification of secondary metabolites of noni was obtained using the KNApSAck Family and Dr. Duke's Phytochemicals (Afendi *et al.*, 2012) and Ethnobotanical databases (U.S. Department of Agriculture, Agricultural Research Service, 1992-2016). Then, the prediction of bioavailability was done using SwissADME and the BOILED-Egg method (Daina *et al.*, 2017; Daina and Zoete, 2016). Only compounds that enter the BOILED-Egg area were selected for the next step.

SwissTargetPrediction was used to collect target proteins predicted to interact with secondary metabolites (Daina *et al.*, 2019). Then, proteins that related to immunomodulators were collected using GeneCards (Stelzer *et al.*, 2016). The next step looks for the intersection of proteins that are predicted to bind to compounds from plants using Venny (Oliveros, 2007-2015). The list of proteins that appeared on Venny was then entered into the StringDB database for further processing (Szklarczyk *et al.*, 2021). After that, predictions of protein interaction related to the immune system were searched using the KEGG Pathway method (Kanehisa *et al.*, 2023).

Data analysis

Data analysis focused on what pathways play the most significant role in the network. Then, the analysis focused on which protein interacts the most with the pathway. Finally, the secondary metabolites of noni which interact with these proteins, were researched.

RESULTS AND DISCUSSION

Identification of secondary metabolites of noni

Secondary metabolites of noni were obtained using the KNApSAck Family and Dr. Duke’s Phytochemicals and Ethnobotanical Databases. There are several compounds in both databases. Compounds from the group of inorganic and long-chain fatty acid compounds were removed for further processing. There are 128 total identified compounds, with 108 compounds identified in KNaPSaCK Family and 20 compounds identified in Dr. Duke's Phytochemicals and Ethnobotanical Database (Table 1).

Bioavailability Predictions

The bioavailability of a drug is an essential parameter in determining the amount and speed of drug absorption in the body. Therefore, the determination of this bioavailability is crucial in this study. The bioavailability prediction of noni's secondary metabolites was conducted using the BOILED-Egg method with Swiss ADME. This method aims to visually describe the prediction of the ability of a compound to be absorbed. The method can predict areas with

Table 1. List of Secondary Metabolites of Noni from Dr. Duke's Phytochemicals and Ethnobotanical Databases and KNApSAcK Family

No	Compound Name	Compound Code	Source
1	(e)-6-dodeceno-gamma-lactone	Mol1	(1)
2	(z)-6-dodeceno-gamma-lactone	Mol2	(1)
3	(z,z)-2,5-undecadien-1-ol	Mol3	(1)
4	(z,z,z)-8,11,14-eicosatrienoic-acid	Mol4	(1)
5	1-5-6-trihydroxy-anthraquinone	Mol5	(1)
6	1-butanol	Mol6	(1)
7	1-hexanol	Mol7	(1)
8	2,6-di-o-(beta-d-glucopyranosyl)-1-o-octanoyl-beta-d-glucopyranose	Mol8	(1)
9	2-heptanone	Mol9	(1)
10	2-hydroxy-1-methoxy-7-methyl-anthraquinone	Mol10	(1)
11	2-methyl-3-methylthio-propanoate	Mol11	(1)
12	2-methyl-butanoic-acid	Mol12	(1)
13	2-methyl-hexanoate	Mol13	(1)
14	2-methyl-propanoic-acid	Mol14	(1)
15	3-5-6-trihydroxy-2-methyl-anthraquinone	Mol15	(1)
16	3-hydroxy-2-butanone	Mol16	(1)
17	3-hydroxy-morindone	Mol17	(1)
18	3-methyl-2-buten-1-ol	Mol18	(1)
19	3-methyl-3-buten-1-ol	Mol19	(1)
20	3-methyl-thiopropanoic-acid	Mol20	(1)
21	Methyl pheophorbide a	Mol21	(2)
22	(-)-pinoresinol	Mol22	(2)
23	Pteryxin	Mol23	(2)
24	Scopoletin	Mol24	(2)
25	Vanillin	Mol25	(2)
26	Coniferaldehyde	Mol26	(2)
27	Alizarin	Mol27	(2)
28	1-hydroxy-2-methoxyanthraquinone	Mol28	(2)
29	Anthragallol	Mol29	(2)
30	Lucidin	Mol30	(2)
31	Morindone	Mol31	(2)
32	Rubiadin	Mol32	(2)
33	2-methylanthraquinone	Mol33	(2)
34	Asperuloside	Mol34	(2)
35	Aucubin	Mol35	(2)
36	Monotropein	Mol36	(2)
37	6beta-hydroxygeniposide	Mol37	(2)
38	Phytol	Mol38	(2)
39	Ursolic acid	Mol39	(2)
40	(-)-beta-sitosterol	Mol40	(2)
41	Jaceosidin	Mol41	(2)
42	Apigenin 5,7-dimethyl ether 4'-galactoside	Mol42	(2)
43	Kaempferol	Mol43	(2)
44	Nicotiflorin	Mol44	(2)
45	Quercitrin	Mol45	(2)
46	Rutin	Mol46	(2)
47	Isorhamnetin 3-o-rutinoside	Mol47	(2)
48	Oleanolic acid	Mol48	(2)
49	3-o-beta-d-glucopyranosyl sitosterol	Mol49	(2)
50	Physcion	Mol50	(2)
51	Peucedanocoumarin iii	Mol51	(2)
52	(6s,9r)-roseoside	Mol52	(2)
53	13-epi-phaeophorbide a methyl ester	Mol53	(2)

54	3,4'-dihydroxy-3'-methoxypropiophenone	Mol54	(2)
55	3-o-acetylpomolic acid	Mol55	(2)
56	5,15-dimethylmorindol	Mol56	(2)
57	6alpha-hydroxyadoxoside	Mol57	(2)
58	Acetylursolic acid	Mol58	(2)
59	Asperulosidic acid	Mol59	(2)
60	Barbinervic acid	Mol60	(2)
61	Citrifoside	Mol61	(2)
62	Clethric acid	Mol62	(2)
63	Damnacanthol	Mol63	(2)
64	Deacetyl asperuloside	Mol64	(2)
65	Deacetylasperulosidic acid	Mol65	(2)
66	Hederagenin	Mol66	(2)
67	Rotungenic acid	Mol67	(2)
68	Rubiadin-1-methyl ether	Mol68	(2)
69	Lucidin 3-methyl ether	Mol69	(2)
70	1-hydroxy-2-methyl-9,10-anthraquinone	Mol70	(2)
71	2-methyl-1,3,6-trihydroxyanthraquinone	Mol71	(2)
72	Alizarin 1-methyl ether	Mol72	(2)
73	Americanin	Mol73	(2)
74	Anthragallol 1,3-dimethyl ether	Mol74	(2)
75	Anthragallol 2-methyl ether	Mol75	(2)
76	Citrifolinin a	Mol76	(2)
77	Yopaaoside a	Mol77	(2)
78	Morenone 1	Mol78	(2)
79	Morenone 2	Mol79	(2)
80	Morindacin	Mol80	(2)
81	Morindone-5-methyl ether	Mol81	(2)
82	Nordamnacanthal	Mol82	(2)
83	Yopaaoside b	Mol83	(2)
84	Americanol a	Mol84	(2)
85	(-)-balanophonin	Mol85	(2)
86	7-hydroxy-8-methoxy-2-methylanthraquinone	Mol86	(2)
87	1,3,8-trihydroxy-2-methoxyanthraquinone	Mol87	(2)
88	1-hydroxyanthraquinone	Mol88	(2)
89	2-hydroxy-3-(hydroxymethyl)anthraquinone	Mol89	(2)
90	Isoscopoletin	Mol90	(2)
91	Morintrifolin a	Mol91	(2)
92	Morintrifolin b	Mol92	(2)
93	Soranjidiol	Mol93	(2)
94	2,3-dihydroxypropyl hexadecanoate	Mol94	(2)
95	Citrifolinin b epimer a	Mol95	(2)
96	Citrifolinin b epimer b	Mol96	(2)
97	Cytidine	Mol97	(2)
98	Dehydromethoxygaertneroside	Mol98	(2)
99	D-glucose	Mol99	(2)
100	Methyl beta-d-fructofuranoside	Mol100	(2)
101	Damnacanthal	Mol101	(2)
102	1-methoxy-2-methylanthraquinone	Mol102	(2)
103	Dide-o-methyltanegool	Mol103	(2)
104	Damnacanthol 11-primeveroside	Mol104	(2)
105	Americanoic acid a	Mol105	(2)
106	Americanin d	Mol106	(2)
107	9,10-dihydro-1-hydroxy-9,10-dioxo-2-anthracenecarboxaldehyde	Mol107	(2)
108	Citrifolinin b	Mol108	(2)
109	Digiferruginol omega-primeveroside	Mol109	(2)
110	Isoamericanoic acid a	Mol110	(2)

111	3-methyl-3-butenyl glucoside	Mol111	(2)
112	Hydyotanthraquinone	Mol112	(2)
113	Morinaphthalene	Mol113	(2)
114	Nonioside b	Mol114	(2)
115	1-o-octanoylgentiobiose	Mol115	(2)
116	Nonioside d	Mol116	(2)
117	Nonioside a	Mol117	(2)
118	Physcihydrone	Mol118	(2)
119	1-o-octanoylsophorose	Mol119	(2)
120	Nonioside e	Mol120	(2)
121	Nonioside f	Mol121	(2)
122	Nonioside g	Mol122	(2)
123	Morindicone	Mol123	(2)
124	Morinthone	Mol124	(2)
125	Morinaphthalenone	Mol125	(2)
126	1,3,5-trihydroxy-2-methoxy-6-(methoxymethyl)anthraquinone	Mol126	(2)
127	1,1',5-tri-o-methylmorindol	Mol127	(2)
128	2-methyl-1,3,6-trihydroxyanthraquinone	Mol28	(2)

Note: (1) Dr. Duke's Phytochemicals and Ethnobotanical Databases; (2) KNApSAcK Family.

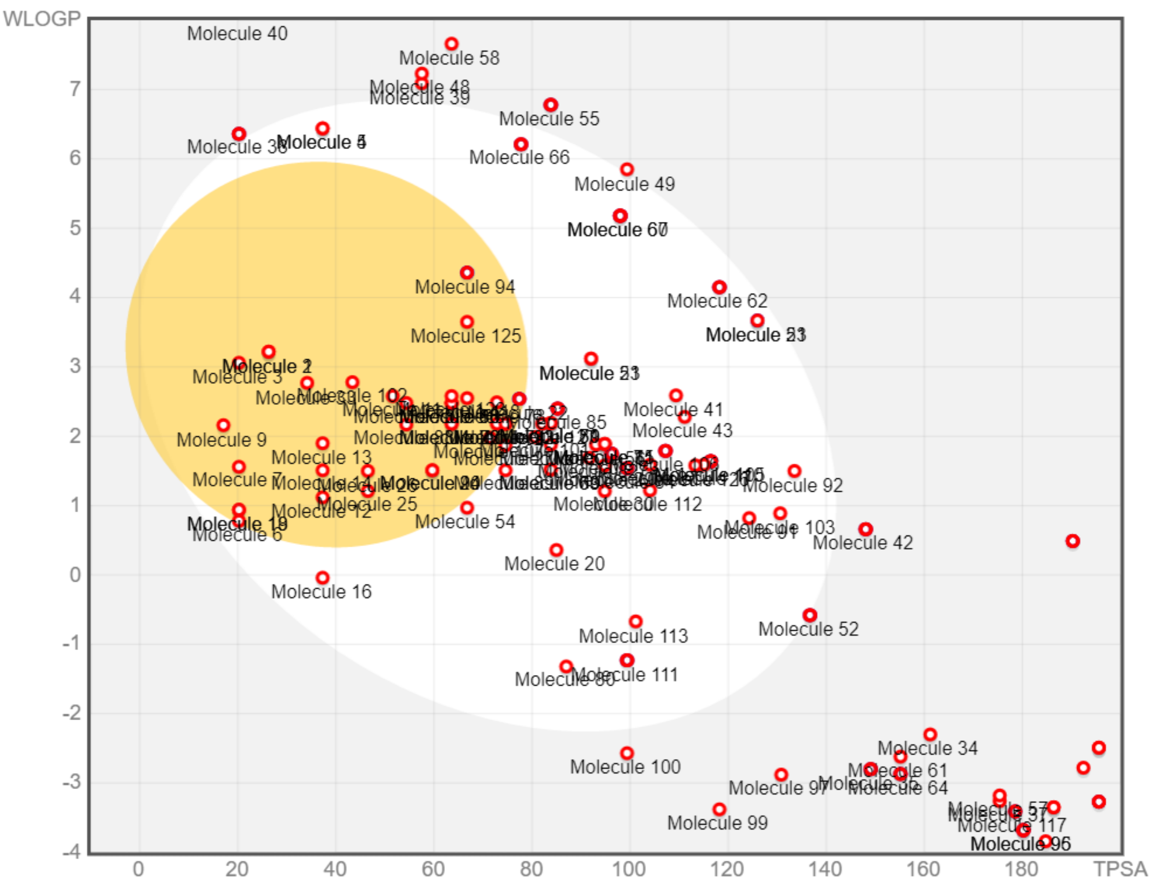

Figure 1. Results of analysis of secondary metabolites of noni using BOILED-Egg.

good gastrointestinal absorption that has physicochemical properties that enter the BOILED-Egg area. This method can make accurate predictions by calculating the lipophilicity and polarity of the compounds using an image model (Figure 1) to classify the absorption of compounds. The white egg area in the figure shows the ability of a compound to be absorbed into the digestive tract. In contrast, the yolk area shows the ability of a compound to penetrate the blood-brain barrier based on WLogP and TPSA, which describe the lipophilicity and polarity of a compound (Daina and Ziote, 2019). This study showed 83 secondary metabolite compounds had high bioavailability (Table 2).

Immunomodulators-related Proteins that are Predictable to Interact with Noni's Secondary Metabolites

SwissTargetPrediction analysis aims to predict the interaction of compounds with proteins targeted in research. Based on the results of the investigation, it was found that 1040 proteins were predicted to interact with noni's secondary metabolites. Furthermore, the search for target proteins from immunomodulators was done using GeneCards. The results showed that there were 1337 proteins related to immunomodulators. Subsequently, Venny was used to determine the interaction between proteins predicted to interact with noni's secondary metabolites with immunomodulators-related proteins. From the interaction results, 267 immunomodulator-related proteins were predicted to interact with noni's secondary metabolites (Figure 2).

Table 2. Bioavailability prediction of the secondary metabolite of noni using BOILED-Egg method

No	Bioavailability Prediction	Amount	Compound Code
1	High	83	Mol1, Mol2, Mol3, Mol4, Mol5, Mol6, Mol7, Mol9, Mol10, Mol11, Mol12, Mol13, Mol14, Mol15, Mol16, Mol17, Mol18, Mol19, Mol20, Mol21, Mol22, Mol23, Mol24, Mol25, Mol26, Mol27, Mol28, Mol29, Mol30, Mol31, Mol32, Mol33, Mol41, Mol43, Mol50, Mol51, Mol54, Mol56, Mol60, Mol62, Mol63, Mol66, Mol67, Mol68, Mol69, Mol70, Mol71, Mol72, Mol73, Mol74, Mol75, Mol78, Mol79, Mol80, Mol81, Mol82, Mol83, Mol84, Mol85, Mol86, Mol87, Mol88, Mol89, Mol90, Mol91, Mol92, Mol93, Mol94, Mol101, Mol102, Mol103, Mol105, Mol106, Mol107, Mol110, Mol111, Mol112, Mol113, Mol118, Mol123, Mol127, Mol128
2	Low	45	Mol8, Mol34, Mol35, Mol36, Mol37, Mol38, Mol39, Mol40, Mol42, Mol44, Mol45, Mol46, Mol47, Mol48, Mol49, Mol52, Mol53, Mol55, Mol57, Mol58, Mol59, Mol61, Mol64, Mol65, Mol76, Mol77, Mol95, Mol96, Mol97, Mol98, Mol99, Mol100, Mol104, Mol108, Mol109, Mol114, Mol115, Mol116, Mol117, Mol119, Mol120, Mol121, Mol122, Mol124, Mol125, Mol126

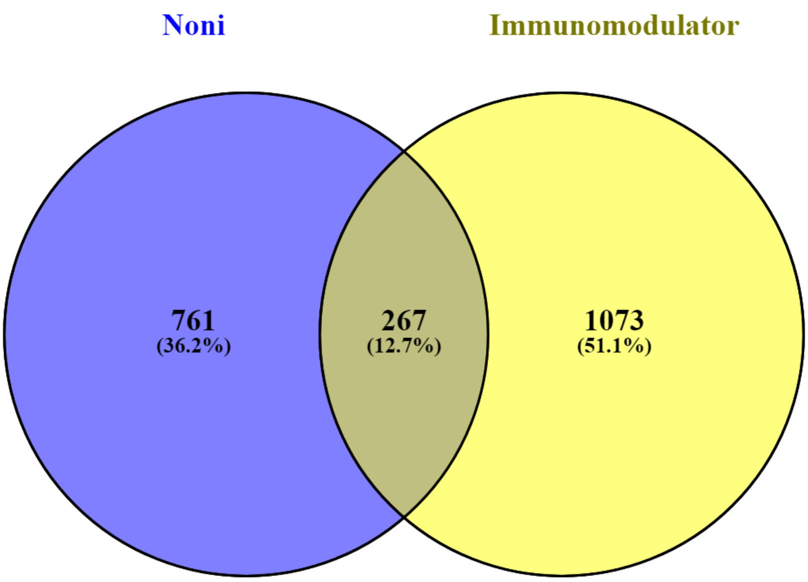

Figure 2. Venn diagram of protein that predicted noni and immunomodulator-linked.

Pharmacology Network

StringDB analysis is used to create interaction networks between secondary metabolites and selected target proteins. This step aims to determine the relationship between the selected proteins and the compounds contained in the noni plant and to analyze the immunostimulating biological pathways affected by these proteins (Figure 3). KEGG enrichment analysis is to determine the molecular mechanism of compounds contained in plants in interacting with target proteins in order to determine their role in the body's immune system (Figure 4). The pathways associated with the immunomodulator were searched, and five pathways with the highest strength values were selected (Table 3). The five pathways consist of the Programmed Cell Death-Ligand 1 (PD-L1) expression and PD-1 checkpoint pathway in cancer, T-Helper 17 (Th17) cell differentiation, Interleukin-17 (IL-17) signaling pathway, Tumor Necrosis Factor (TNF) signaling pathway, and Fc epsilon RI signaling pathway.

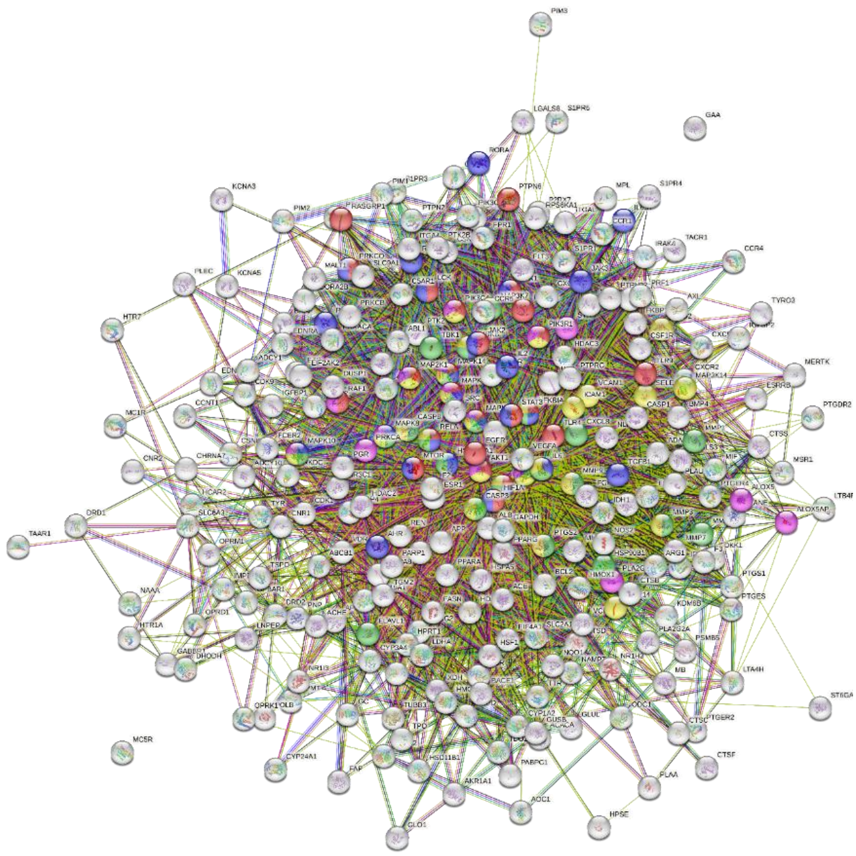

Figure 3. Network Pharmacology prediction results using StringDB. The color indicates which pathway is associated with the protein. Fc epsilon RI signaling pathway (red); PD-L1 expression and PD-1 checkpoint pathway in cancer (blue); Th17 cell differentiation (green); TNF signaling pathway (purple); IL-17 signaling pathway (yellow).

Table 3. Five important pathways that related with immunomodulator by KEGG enrichment

No.	Pathway	Strength
1.	PD-L1 expression and PD-1 checkpoint pathway in cancer	1.32
2.	Th17 cell differentiation	1.28
3.	IL-17 signaling pathway	1.28
4.	TNF Signaling pathway	1.25
5.	Fc epsilon RI signaling pathway	1.25

Table 4. Protein and secondary metabolite of noni that related with immunomodulator

No.	Pathway	Strength
1.	MAPK1	Mol1, Mol2, Mol4, Mol5, Mol7, Mol10, Mol21, Mol22, Mol23, Mol25, Mol27, Mol62, Mol74, Mol79, Mol84, Mol85, Mol86, Mol101, Mol107, Mol111, Mol113
2.	MAPK3	Mol1, Mol2, Mol4, Mol5, Mol66, Mol79, Mol84, Mol85
3.	MAPK14	Mol4, Mol5, Mol21, Mol87, Mol123

Based on the analysis performed, there are three proteins that have interactions with the five important pathways in the immunomodulatory system (Table 4). The next step was to identify the secondary metabolites that were predicted to interact with these proteins. Based on the analyzed result, two molecules could interact with these proteins, namely Mol4 ((z,z,z)-8,11,14-eicosatrienoic-acid) and Mol5 (1-5-6-trihydroxy-anthraquinone).

Therefore, noni has the potential to be further explored and developed as a promising immunomodulating agent. These findings are in accordance with research by Farizal *et al.* (2020), which revealed that noni plants have great potential as an immunomodulatory agent. *In vitro* and *in vivo* studies can be conducted to prove the immunomodulating activity of plants, especially the content of immunomodulating compounds which have an important role, as predicted in the pharmacological network study in this study.

CONCLUSIONS

Based on the results of pharmacological network analysis, (z,z,z)-8,11,14-eicosatrienoic-acid and 1-5-6-trihydroxy-anthraquinone are predicted to be important compounds that play a role in the immune system because they are known to interact with five important pathways that are associated with immunomodulators.

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