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Original Article

Network Analysis of Indigenous Indonesia Medical Plants for Treating Tuberculosis

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ABSTRACT

Background: Indonesia is the biggest archipelago country with the second biggest biodiversity in the world. A lot of medical plants for treating various diseases can be found in Indonesia, including medical plants for tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis*. **Objective:** The goal of this research is to document the information of Indonesia indigenous medical plants that used various local societies to treat tuberculosis and also analyze active compounds of medical plants with proteins that related to tuberculosis. **Methods and Materials:** The annotation of medical plants for treating tuberculosis was collected from a various source comprising local research papers, theses, and other resources. The information of active compound was taken from Dr. Duke's Phytochemical and Ethnobotanical Databases. A network of active compounds-proteins was analyzed by using Cytoscape 3.6.0. **Results:** The result described that there were twenty-seven species from nineteen families of medical plants used by local societies of Indonesia for tuberculosis therapy, and there were sundry of active compounds from fourteen medical plants had direct interaction with proteins related tuberculosis. **Conclusion:** Most of the active compounds targeted proteins that had a prominent role in immune system. It indicated that medical plants treating tuberculosis through regulating immunity of human body.

Key words: Cytoscape, Immune system, Indonesian medical plants, Network, Tuberculosis.

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INTRODUCTION

Tuberculosis is an airborne infectious disease caused by *Mycobacterium tuberculosis* and it causes approximately 2 million people demise every year. Recently, tuberculosis cases are more developing due to the advancing of tuberculosis therapies that have been used for all this time. Drug-resistant one of the prominent problem of this case. The resistance of tuberculosis drug was recognized in 1947, then it became a sporadic clinical problem in the 1960s until 1980s but only few attention to this problem. Multidrug resistance (MDR) tuberculosis appeared in the early 1990s and it has been still developing until this present time. First line tuberculosis drugs, isoniazid, and rifampicin have been informed that could cause mutation in KatG and RpoB, then it induced MDR tuberculosis.[1-2] Almost 10-19% MDR tuberculosis improves to become extensively drug-resistant (XDR) tuberculosis, which more difficult to treat. It has been reported that in 2008, 55 countries have XDR tuberculosis case. In XDR tuberculosis case, the patients are resistance to fluoroquinolones and injectable second-line tuberculosis drugs like amikacin, kanamycin, and caryomycin.[3-4] Besides, tuberculosis drugs can lead various side effect that induces more severe.[5]

Nature is the source to find appropriate tuberculosis treatment. Various kinds of the medical plant have been reported which could treat tuberculosis and numerous active compounds from plants have been reported had antimycobacterial activity.[6-7] Indonesia, a tropical archipelago country had vast biodiversity both natural and culture. A lot of indigenous medical plants grow in Indonesia, and local societies use it to treat a variety of diseases including tuberculosis. This study collected the information of medical plants used by local society of Indonesia to treat tuberculosis and analyze the involvement of active compounds with proteins related to tuberculosis by network analyzing.

MATERIALS AND METHODS

Data Collection

In this study, various local resources like research papers, theses, and other resources were given ethnobotany information about the medicinal plants that used for treating tuberculosis in local society of Indonesia were collected. The data assembled were consisted of local name, the scientific name of the plants, location (Province), and part of the plants that used. The information of active compounds of the plants was obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/phytochem/search).

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This database provides not only about the active compound of the plants and the biological activity but also the information about the plant that commonly used for treating various diseases from around the world. Even there was a lot of information about ethnobotany in all of the countries, but unfortunately, this website gave limit information about the plant that used for tuberculosis in Indonesia local regions.

Network construction and analysis

Network analysis was used for understanding the effect of medical plants on tuberculosis. The network analyzing active compounds-proteins was constructed with string App of Cytoscape 3.6.0.[8] 18 proteins related tuberculosis was obtained with STRING diseases feature and active compounds-proteins interaction was established with STITCH proteins/compounds feature. 4.0 cutoff score was used to take all of protein-protein and compounds-protein interaction. In the network graphic, proteins and active compounds were presented as nodes, while proteins-proteins and compounds-proteins interaction were presented as edges.

RESULTS AND DISCUSSION

Plants used for treating tuberculosis in Indonesia Provinces

Through the literature retrieval, twenty-seven plants used local societies to treat tuberculosis from various provinces in Indonesia were obtained, as shown in Table 1.

According to the Table 1, four species belong to Zingiberaceae, two species belong to Apiaceae, Malvaceae, Piperaceae, Euphorbitaceae and Rubiaceae, and one species respectively from Myrtaceae, Malvaceae, Fabaceae, Plantaginaceae, Piperaceae, Petiveriaceae, Lamiaceae, Rubiaceae, Verbenaceae, Euphorbiaceae, Apiaceae, Rutaceae, Moraceae, Acanthaceae, Bromeliaceae, Asphodelaceae, Asteraceae, and Araceae. According to Figure 1, *Lantana camara* L. and *Curcuma domestica* are precious tuberculosis medical plants for many local societies in Indonesia, followed by *Centella asiatica, Hibiscus rosa sinensis,* and *Artocarpus elasticus. Lantana camara L* is used extensively from west until east Indonesia provinces (map of Indonesia provinces is shown in Figure 2),[41] includes Lampung, Central Java West Sulawesi, and South Sulawesi, while

Table 1: Medical plants used in local society of Indonesia for treating tuberculosis.

No	Local Name	Family	Species	Province	Part of plant	Ref.
1	Jahe	Zingiberaceae	*Zingiber officinallis Rosc.*	Central Sulawesi	Rhizome	9
2	Jamblang	Myrtaceae	*Syzygium cumini (L.) Skeels*	Madura	Barks; Fruits; Seeds	10
3	Sidaguri	Malvaceae	*Sida rhombifolia*	Central Java	Leaves	11-12
4	Asam Jawa	Fabaceae	*Tamarindus indicia L*	Bali; Central Sulawesi	Fruits	13,9
5	Ki urat; Daun sendok	Plantaginaceae	*Plantago major L*	South Borneo, Bali	Leaves	14-15
6	Sirih	Piperaceae	*Piper betle*	West Sumatra	Leaves	14
7	Singolawang	Petiveriaceae	*Petiveria alliacea*	West Java	Leaves	16
8	Selasih	Lamiaceae	*Ocimum basillicum L*	South Borneo; West Sumatra	Seeds; Leaves	14-15
9	Rumput gelong; Suruhan	Piperaceae	*Peperomia pellucida*	Bengkulu	Not mention	17
10	Mengkudu	Rubiaceae	*Morinda citrifolia*	Center Celebes	Leaves	18
11	Bunga Tahi Ayam; Tembelekang; gala gala bassi	Verbenaceae	*Lantana camara L.*	West Celebes; South Celebes; Lampung; Central Java	Flowers; Leaves; Fruit	12,19-23
12	Kencur	Zingiberaceae	*Kaempferia galanga L.*	Bali	Rhizome	13
13	Tukudan	Euphorbiaceae	*Jatropha gossypifolia*	North Celebes	All of the part	24
14	Kembang sepatu	Malvaceae	*Hibiscus rosa sinensis L*	Riau; South Sumatera; Bengkulu	Flower; Leaves	25-26
15	Adas	Apiaceae	*Foenoculum vulgare*	East Java	Seeds	27
16	Patikan kebo	Euphorbiaceae	*Euphorbia hirta L*	South Borneo	Herbs	15
17	Kunyit Putih	Zingiberaceae	*Curcuma zedoaria*	South East Celebes; East Kalimantan	Rhizome; Tuber	15,28
18	Kunyit	Zingiberaceae	*Curcuma domestica*	East Java; Central Sulawesi; South Sulawesi; East Kalimantan	Rhizome	27-29
19	Kopi	Rubiaceae	*Coffea Arabica*	East Java	Seeds; Leaves	27
20	Jeruk nipis	Rutaceae	*Citrus aurantifolia*	South Borneo; Central Sulwesi	Fruit; Flower	9,30-31
21	Pegagan	Apiaceae	*Centella asiatica*	Central Java; South east celebes; South Sulawesi	All of the part	11,29,32-33
22	Benda/ terap	Moraceae	*Artocarpus elasticus*	West Java; East java; Riau	Bark; leaves; sap; all of the part	34-36
23	Sambiloto	Acanthaceae	*Andrographis paniculata*	East Java	Herbs	27,37
24	Nanas Putih	Bromeliaceae	*Ananas comosus Merr*	South East Celebes	Fruit	15
25	Lidah buaya	Asphodelaceae	*Aloe vera*	North Sumatra; Banten	Stem; Leaves	38-39
26	Bandotan	Asteraceae	*Ageratum conyzoides L*	South East Celebes	Herbs	15
27	Dringu	Araceae	*Acorus calamus L.*	East Java	Leaf; Rhizome	40

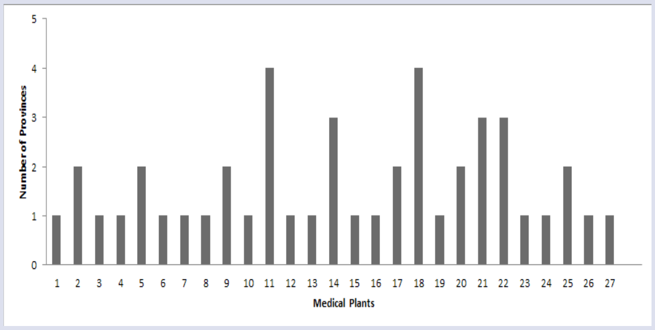

Figure 1: Distribution of medical plants utilization used for tuberculosis.

Figure 2: Map of Indonesia provinces.

Table 2: Active compounds from the database.

Active compounds of Medical Plants For Tuberculosis					
10-shogaol[1]	Plantigoside[5]	Apiole[9,15]	Isopimpinellin[15,20]	Allantoin[19]	Terpinolene[1,20,27]
8-shogaol[1]	Scutellarin[5]	Asperuloside[10]	β- pinene[1,4,8,15,18,20,21,27,26]	Caffeol[19]	Ocimene[15,20]
10-shogaol[1]	Hispidulin[5]	Gentisic acid[10,15]	Ascorbic acid [2-4, 6,8-10,15,20-22, 24,25]	Amyrin[16]	Terpinen-4-ol[1,4,8,15,20,27]
12-gingerol[1]	Caffesterol[19]	Caffein[19]	Riboflavin[1-4,6,8-10,14,15,18-20,22,24,25]	Hydroxycinnamic acid[5]	Asiaticoside[21]
6-gingerol[1]	Benzoic acid[5]	Lantadene B[11]	α- phellandrene[1,15,18,20,21]	Androgapholide[23]	Madacasic acid[21]
Paradol[1]	Asparagine[6]	Icterogenin[11]	1,8-cineole[1,6,8,11,15,1718,20,27]	Neoandrogapholide[23]	Madecassoside[21]
Zingerone[1,18]	Ornithine[6]	Cadinol[11]	Tannin[2,3,6,7,12,19,21,22]	Linalool[1,8,11,18,20,24,27]	Asiatic acid[21]
Zingiberene[1,17]	Shikimic acid[15,16]	1-triacontarol[11]	Niacin[1-4,6,8,9,14,15,18-20,22,24,25]	Phytosterol[15,24]	6-gingerodione[1]
Xanthorrhizol[1]	Hydrochavicol[6]	Lantalonic acid[11]	α-pinene[1,4,8,11,15,17,18,20,21,26]	Palmitate[1,4,7,8,20,21]	Rhamnose[16]
Acoardin[27]	Estragole[6,8,15]	Borneol[1,8,12,17,18,20]	Palmitoleic acid[1,4,20]	Petroselinic acid[15]	Acerone[27]
Azulene[25,27]	Curcumin[17,18]	Aloin[25]	Vanillic acid[8,15]	α- terpinene[1,8,15,18,26,27]	10-gingerodione[1]
Betulinic acid[2]	Eugenol[6]	Carene[12,15]	Caryophyllene[8,9,11,20,27,26]	Sabinene[1,8,15,18,20,27]	Baicalein[5]
Marmesin[15]	Isocurcumenol[17]	Ethyl cinnamate[4,12]	Beta sitosterol [4,8,12,18,19,21,26]	Limonene[1,4,8,15,18,20,27]	Nonadecanoic acid[7]
Scoparone[15]	Curcumenol[17]	Nerol[1,4,20]	Caffeic acid[1,8,15,16,19]	α- terpineol[1,4,11,15,18,20,24]	Estrageole[6,8,15]
Osthenol[15]	Rutin[15,8]	P-methoxy styrene[11]	Ethyl-P-Methoxycinnamate[12]	α- thujene[1,15,20]	Imperatorin[15]
Quinic acid[4,15]	Turmerone[18]	Jatrophole[13]	Linoleic acid[1,4,8,15,16,19-21,24]	β- phellandrene[1,4,11,15,20]	Quercetrin[15,16,18, 21,26]
Sinapic acid[15]	Curcumadiol[17]	Jatrophone[13]	Oleic acid[1,4,8,15,16,19-21]	Malic acid[4,15,24,20]	Allantoic acid[19]
Isoquercetrin[15]	Catalpol[5]	Isovitexin[13]	Camphene[1,8,12,15,17-18,21,26]	Syringic acid[15]	Methoxy cinnamate[12]
Scoporetin[15]	Nonanal[1,20]	Vitexin[13]	Rhamnetin[16]	Citric acid[1,4,15,19,20]	Aucubin[5]
Tartaric acid[4]	Planteose[8]	Cyanidin[14]	Eugenol methyl ether[6]	Citronellal[1,20]	Campesterol[9,16,18,2425]
Succinic acid[4]	Esculin[8]	Ceryl alchohol[15]	Bisdemethoxycurcumin[17,18]	Germacrene[20]	γ- tocotrienol[15]
Safrole[4,8]	Aesculetin[8]	Fenchone[15]	Demethoxycurcumin[17,18]	Myrcene[1,8,15,20]	Ar turmerone[18]
Apigenin[5,12]	Eriodictyol[8]	Ferulic acid[15]	Curcumene[18]	Myristic acid[1,4,19,20]	Curcumanolide-A[17]
Luteolin[5]	Neral[1,4,8,20]	Curcumanolide-B[17]	Curcumenone[17,18]	Isocurzerenone[17]	Ellagic acid[16]

1=*Zingiber officinallis Rosc.*; 2= *Syzygium cumini (L.) Skeels*; 3= *Sida rhombifolia*; 4= *Tamarindus indica L*; 5= *Plantago major L*; 6= *Piper betle*; 7= *Petiveria alliacea*; 8= *Ocimum basillicum L*; 9= *Peperomia pellucida*; 10= *Morinda citrifolia*; 11= *Lantana camara L.*; 12= *Kaempferia galanga L.*; 13= *Jatropha gossypifolia*; 14= *Hibiscus rosa sinensis*; 15= *Foeniculum vulgare*; 16= *Euphorbia hirta L*; 17= *Curcuma zedoaria* 18= *Curcuma domestica*; 19= *Coffea arabica*; 20= *Citrus aurantifolia*; 21= *Centella asiatica*; 22= *Artocarpus elasticus*; 23= *Andrographis paniculata*; 24= *Ananas comosus Merr*; 25= *Aloe vera*; 26= *Ageratum conyzoides L*; 27= *Acorus calamus L.*

Curcuma domestica is most used only in East Indonesia Province such as East Java, Central Sulawesi, South Sulawesi, and East Kalimantan.

Some of this medical plants not only in Indonesia but also in other countries also use it to treat tuberculosis. Leaves of *Lantana camara* L are used by local societies of Uganda to inhibit the activity of mycobacterial.[42] *Sida rhombifolia* and *Aloe vera* belong to important plant that stated in Ayurvedic medicines in India for treating tuberculosis.[43-44] Mexican people use *Citrus aurantifolia* traditional medicine for tuberculosis, and moreover, it was already proved that *Citrus aurantifolia* peel could against multi-drug resistant *Mycobacterium tuberculosis*.[45] Traditional China medicine plant, *Zingiber officinallis* Rosc. and *Curcuma domestica* are reported could medicate tuberculosis through isocitrate lyase and macrophage activity.[46] Bangladesh and Indonesia have similarity in medical plants for tuberculosis, it is reported that *Andrographis paniculata*, *Centella asiatica*, *Aloe vera*, and *Hibiscus rosa sinensis* are used to treat *Mycobacterium tuberculosis* infection.[47]

Analysis of active compounds target network

Through Dr. Duke's Phytochemical and Ethnobotanical Databases active compounds of the medical plants were obtained from the database. In this study only selected active compounds were used, as shown in Table 2.

Based on the STITCH and STRING pathway analysis, it shows that several compounds from *Euphorbia hirta, Foeniculum vulgare, Ocimum basillicum, Zingiber officinallis Rosc, Curcuma domestica, Plantago major, Curcuma zedoaria, Centella asiatica, Coffea arabica, Ageratum conyzoides L, Tamarindus indica, Citrus aurantifolia, Petiveria alliacea* and *Lantana camara* L interact with protein related tuberculosis. The network constructed with Cytoscape is shown in Figure 3. Most of the active compounds targets are protein implicated in immune systems like IL-4, Tumor Necrosis Factor (TNF), IL-1B, CCL-2, and TLR4. It indicates that active compound treats tuberculosis through immunity balancing system. Tuberculosis therapies targeting immunity balancing can improve the treatment outcome and also well-regulated immune system may prevent reactivation of latent tuberculosis.[48] The network describes some of the active compounds include ellagic acid, α-pinene, myristic acid, asiaticoside, aucubin, rutin, and esculin have direct interaction with protein related tuberculosis mechanism, while other compounds have indirect interaction.

Ellagic acid has direct interaction with IL-4, a cytokine produced by a variety of immune cells. In tuberculosis case, IL-4 has a role as an anti-inflammatory.[49] However, The increasement of IL-4 was reported that could inhibit mycobacteria eradication through depletion of IFN-γ production.[50] Ellagic acid, a phenolic compound found in a variety of plants including *Euphorbia hirta*. A previous study showed that ellagic acid could reduce the IL-4 level in eosinophilic inflammation case. Besides interacting with IL-4, ellagic acid also has interaction with Epigallocatechin gallate (EGCG) and NOS3 had a direct correlation with IL-4. In addition, Scoparone another active compound from *Foeniculum vulgare* is also targeting nitric oxide synthase 3 (NOS3), a macrophage enzyme produced nitric oxide that against microbial. NOS3 exhibit NO when *Mycobacterium tuberculosis* infects macrophage.[51]

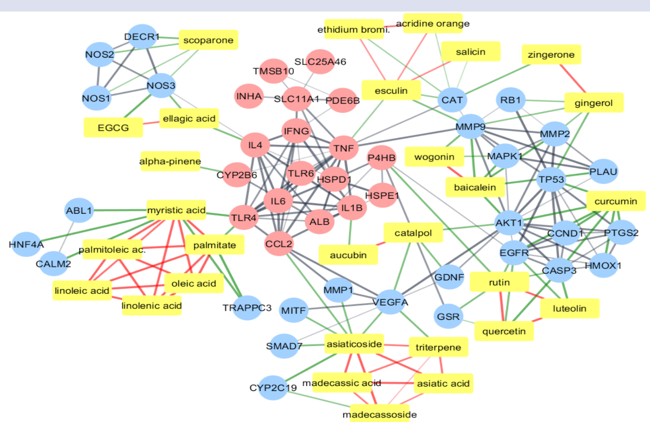

Figure 3: Active compound-protein related tuberculosis pathway network. The red circle represents protein involved tuberculosis disease mechanism. The blue circle represents proteins which are not involved in tuberculosis mechanism. The yellow rectangular represent active compounds from medical plants. The green line represents active compound-protein interaction. The red line represents active compound-active compound interaction. The Grey line represent protein-protein interaction.

Esculin, one of an active compound found in Ocimum basillicum shows that interact directly with TNF, catalase (CAT) and Matrix metallopeptidase 9 (MMP9). It has been informed that TNF-α and MMP-9 had tuberculosis pathogenesis role. Mycobacterium tuberculosis through ERK pathway can elevate TNF-α and induce the production of MMP9.[52] Esculin has been reported that could reduce high expression of TNF-α and inhibit MMP9 expression.[53-54] Not only esculin but also gingerol, baicalein, and wogonin, another active compound interacted with baicelein, have interaction with MMP9 and TNF-α and moreover, some studies have been approved these compounds' effect toward MMP9 and TNF-α.[55-57] In tuberculosis treatment, it may be suggested that esculin, gingerol, wogonin, and baicelin reduce the level of TNF-α and MMP9. Furthermore, zingerone found in *Zingiber officinallis* Rosc also have interaction with TNF-α through catalase. Catalase was stated that could induce apoptosis via TNF-α, which apoptosis for macrophage was an important mechanism to against mycobacterial infection.[58-59]

Prolyl 4-hydroxylase subunit beta (P4HB) is an enzyme catalyzing disulfide bonds that can increase Th-2 cells migration.[60] P4HB is one of protein-related tuberculosis which targeted by rutin directly, whereas having indirect interaction with quercetin, luteolin, and curcumin through epidermal growth factor receptor (EGFR). In addition, IL-1B and CCL-2 are chemokine taking apart to form granuloma which can containment or eradicate mycobacteria.[61-62] In the network, the active compound of *Plantago major* and *Centella asiatica,* aucubin and asiaticoside, respectively can interact directly with IL-1B and CCL-2.

Myristic acid and palmitate target TLR 4 which is related to tuberculosis pathogen. Toll-like receptor including TLR1, TKR2, TLR3, and TLR4, play a necessary part in the innate immune system. These receptors express in macrophage and dendritic cell to recognize mycobacterial. The recognition of TLR2 and TLR4 with *Mycobacterium tuberculosis* could induce macrophage apoptosis. In addition, palmitate can act as a TLR4 ligand on dendritic cells and induce IL-1B secretion.[63] This may be specified that palmitate is a natural compound becoming a candidate for tuberculosis drug.

CYP2B6 is one of cytochrome P450 enzyme involved in the transformation of drug and other xenobiotics, CYP2B6 polymorphism can be an indicator for tuberculosis treatment.[64] α- pinene, a terpenoid compound, shows had direct interaction with CYP2B6. Even though other plants are not included in the network, but some previous studies reported the evidenced effect of tuberculosis. The ethyl-p-methoxycinnamate of *Kaempferia galanga* L can inhibit the activity of a variety of *Mycobacterium tuberculosis* strains including MDR strain.[65] The extracts of *Andrographis paniculata, Petiveria alliacea, Morinda citrifolia, Acorus calamus* L.,*Aloe vera, Kaempferia galanga* L., and *Syzygium cumini (*L.*) Skeels* were also reported that had the ability to suppress the activity of *Mycobacterium tuberculosis*.[66-71]

CONCLUSION

There are twenty-seven medical plants reported to treat tuberculosis disease in Indonesia local society. After being observed by network tuberculosis pathway analysis, there are some active compounds including ellagic acid, scoparone, esculin, zingerone, gingerol, baicalein, curcumin, rutin, quercetin, luteolin, asiaticoside, medacassoside, myristic acid, palmitate and α-pinene from fourteen plants such as *Euphorbia hirta, Foeniculum vulgare, Ocimum basillicum, Zingiber officinallis* Rosc, *Curcuma domestica, Plantago major, Curcuma zedoaria*, *Centella asiatica*, *Coffea arabica, Ageratum conyzoides* L, *Tamarindus indica, Citrus aurantifolia, Petiveria alliacea* and *Lantana camara* L that interact with protein related tuberculosis both directly and indirectly. Most of the active compounds target proteins involved in the immune system and it can be indicated that these compounds treat tuberculosis diseases through immune stability in the patient body. These plants may be a candidate to make a formulation for tuberculosis therapy and should be conducted in a real experiment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict interest

ABBREVIATIONS

IL-4: Interleukin 4; **TLR:** Toll-like receptor; **CCL-2:** Chemokine (C-C motif) Ligand 2; **CYB2B6:** Cytochrome P450 2B6; **IL-1B**: Interleukin 1 beta.

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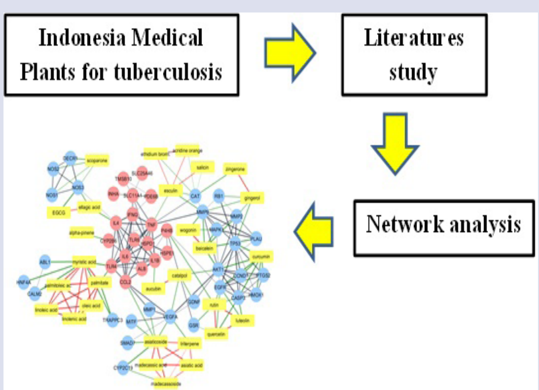
GRAPHICAL ABSTRACT



SUMMARY

- Tuberculosis is a respiratory infectious disease caused by *Mycobacterium tuberculosis*. For a long time, Indonesia local societies have been used medical plants for tuberculosis therapy. By using network analysis study, the active compounds of medical plants can modulate human immunity to treat tuberculosis.

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