**In silico study of active compounds ADMET Profiling in Curcuma xanthorrhiza Roxb and Tamarindus indica as Tuberculosis Treatment**

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**Keyword**
- Curcuma xanthorrhiza Roxb
- *In silico*
- Pharmacokinetics
- Tamarindus indica L
- Tuberculosis

**ABSTRACT**
Curcuma xanthorrhiza Roxb and *Tamarindus indica* L. have been used for a long time by Indonesia local societies as tuberculosis therapy. This study explores the active compounds of *Curcuma xanthorrhiza* Roxb and *Tamarindus indica* L that important for suppressing the survival of *Mycobacterium tuberculosis* and predicts the pharmacokinetics and toxicity of the compounds. stringApp of Cytoscape 3.6.0 was used for screening the compounds targeting mycobacteria proteins, then computational tools like SwissADME (http://swissadme.ch/) and admetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict/) were applied for estimating absorption, distribution, metabolism, excretion, and toxicity (ADMET) of active compounds. The result has been shown that there were some active compounds could target proteins of *Mycobacterium tuberculosis*. According to the profiling result, these compounds had a various characteristic in gastrointestinal absorption, could pass the blood-brain barrier, and had drug-like properties. In toxicity term, the active compounds did not cause Ames toxicity.

**INTRODUCTION**
Tuberculosis (TB) is a serious public health problem, one of the leading causes of mortality worldwide, infecting about 9 million people, kills approximately 2 million people annually. The global incidence rate for TB is growing each year by approximately 1.1% and the number of cases by about 2.4%. The resistance of anti-TB drugs continued to be recognized as a clinical problem in the 21st century. As a result, multidrug-resistant and extensively drug-resistant TB are now becoming a major threat to health worldwide, accounting for almost 3% of all newly reported cases of TB. Due to the increased drug-resistant strains of bacteria such as *Mycobacterium tuberculosis* and methicillin-resistant *Staphylococcus aureus*, there has been renewed interest in herbal as potential sources of novel antibiotics. The World Health Organization estimated that
annual global use of herbal medicines is about the US $83 billion in 2008, indicating that natural products are important sources of new therapeutics and future medicines (WHO, 2015).

The use of herbal as medicine is well known in rural areas of many developing countries. Most herbal medicines are well tolerated by the patient, with fewer unintended consequences than synthetic medicine. Herbs typically have fewer side effects than synthetic medicine and may be safer to use over time (Cragg & Newman, 2013; Sudjarwo & Koerniasari, 2017). The findings of the new antibacterial compounds in herbal became one of the remarkable alternatives for treatments since they are rich in numerous varieties of secondary metabolites such as alkaloids, flavonoids, tannins, saponin, and phenolic compounds with antibacterial properties (Jyoti & Rajeshwari, 2012). Medicinal plant products have long been used as antibacterial in traditional medicines, for the treatment of many diseases such as TB.

The anti-<i>Mycobacterium tuberculosis</i> of medicinal plant products has become subject to scientific investigations currently worldwide, and their active components provide a potential alternative to conventional anti-<i>Mycobacterium tuberculosis</i>. In this context, the development of medicinal plant product-based drug candidates as anti-<i>Mycobacterium tuberculosis</i> has gained momentum in research studies directed toward the design and discovery of drugs. Absorption, distribution, metabolism, and excretion (ADME) is a term of the pharmacokinetic described character of the drugs or compounds while in the human body. The ADME information gives profile drug candidate and is used to design a drug with effectively and safely. Poor ADME and toxicity information of the compound is one of the major reason for terminating drug design development (Tsaionou et al. 2016).

This study tried to explore by computation study to profile ADME of the active compounds of <i>Curcuma xanthorrhiza</i> Roxb and <i>Tamarindus indica</i> L, which have been used for long time by Indonesia local society to treat tuberculosis (Sa’roni 2009; Sa’roni et al. 2011).

**METHODS**

**Bioactive compounds screening**

55 active compounds of <i>Curcuma xanthorrhiza</i> Roxb and 56 active compounds of <i>Tamarindus indica</i> were used (Jantant et al. 2012; Mary et al. 2012; Ruslay et al. 2007; Sudjaroen et al. Wong, et al. 1998). stringApp of Cytoscape 3.6.0 (Szklarczyk et al. 2017) was used to screen the active compounds targeting <i>Mycobacterium tuberculosis</i> proteins. 4.0 confidence score cutoff was applied to screen the protein targets. This software resulted in network graphics of compounds-proteins with details: proteins and compounds were indicated as nodes and compounds-proteins were shown as edges.

**ADME and toxicity profiling**

PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was applied to get the SMILE structures used for further analysis. SwissADME (http://swissadme.ch/) and admetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict/) were used to obtain pharmacokinetics and toxicity information (Cheng et al. 2012; Daina et al. 2017). The bioactivity prediction was calculated with molinspiration (http://www.molinspiration.com/cgi-bin/properties).

**HASIL DAN PEMBAHASAN**

According to the selection of protein target in <i>Mycobacterium tuberculosis</i> with stringApp of Cytoscape 3.6.0. there were three compounds of <i>Curcuma xanthorrhiza</i> Roxb and five compounds of <i>Tamarindus indica</i> targeting <i>Mycobacterium tuberculosis</i>‘ protein , (Table 1).

The result showed that bisdemethoxycurcumin had interaction with polyketide synthases (PKSs), a large family protein of producing various natural compounds. In <i>Mycobacterium tuberculosis</i> term PKS proteins like Pks 11 and Pks 18 reported had a role in the long-chain α-pyrones synthesis, which is an essential compound in mycobacterium cell wall (Saxena et al. 2003). α-pinene could bind the 20 cytochrome P450 enzymes of <i>Mycobacterium tuberculosis</i>, involved in mycobacterial survival and pathogen in a human cell. Recently, it was reported that cyp144 and cyp130 encoded respectively by Rv1777 and Rv1256c could bind azole (Ouellet et al. 2008, Chenge et al. 2016), an antifungal drug that has anti-TB potent and it has been developing to be multidrug-resistant TB therapy(Gupta et al. 2015). Isoamyl alcohol and furfural were showed that had interaction with alcohol dehydrogenase proteins. Lauric acid had interaction with fas, which plays in fatty acid synthase. Salicylate had interaction with various proteins like : caeA which involved in modifying envelope structure of <i>Mycobacterium</i>
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| Compounds-protein targets | Compounds                  |
|---------------------------|----------------------------|
| The compounds of *Curcuma xanthorrhiza* Roxb | Bisdemethoxycurcumin  
PubChem CID: 5315472 |
|                           | α-pinene                  
PubChem CID: 6654        |
|                           | Nerol acetate; geranyl acetate  
PubChem CID: 1549026     |
| The compounds of *Tamarindus indica*              | 2-Phenylethanol  
PubChem CID: 6054        |
**Tabel 1.** The compounds targeting *Mycobacterium tuberculosis’ protein*

| Compounds-protein targets | Compounds |
|---------------------------|-----------|
| ![](image1) | Isoamyl alcohol; 3-Methylbutanol<br>PubChem CID: 31260 |
| ![](image2) | Furfural<br>PubChem CID: 7362 |
| ![](image3) | Lauric acid<br>PubChem CID: 3893 |
| ![](image4) | Methyl salicylate<br>PubChem CID: 4133 |

Yellow square: active compound; red circle: proteins of *Mycobacterium tuberculosis*; green line: compound-protein interaction; gray line: protein-protein interaction

*tuberculosis* and in protecting mechanism by destructing lipid toxic potential (Lun and Bishai 2007). lpqP is an encoding a membrane-bound lipoprotein, the mutation of lpqP was reported that could alter the morphological colony and cell aggregation, disruption surface motility and biofilm formation and cell division (Nguyen et al. 2010), LipT plays a role as hydrolysing lipids from liposome suspensions, (Fozo and Rucks, 2016), and estB has hydrolase and peroxidase activity. The result of (Table 2) showed the characteristic of the active compounds. According to the (Table 2), all of the bioactive compounds had to vary the value of molecular weight from 308 to 96 g/mol, Increasing molecular weight was associated with poor bioavailability, poor fraction absorbed, higher bound fraction and poor renal clearance (Sakaeda et al. 2001). Polar surface area describes as molecule surface that arises from polar atoms like oxygen, nitrogen or hydrogen attached with oxygen or nitrogen atoms. Molecules had more than 140 Å² were poor absorb into the cell membranes (Clark, 2011; Pajouhesh & Lenz, 2005). The TPSA value showed that bioactive compounds were less than 140 Å². It indicated that active compounds were easy to enter the cells. The
value of Log P of compounds varied from -0.56 to 4.29, the more Log P value the less hydrophilicity of the compounds, and it indicated poor bioavailability (Singh, 2016). The chemical properties of the compounds like molecular weight, TPSA, hydrogen bond acceptor and donor, and log P value determine the compounds druglikeness. The drug-likeness value was shown in (Table 3). Based on these result all of the compounds were allowed by Lipinski, Veber, and Egan. Meanwhile, α-pinene, 2-phenyl ethanol, furfural, and methyl salicylate were not allowed by Ghose, whereas α-pinene, nerol acetate, 2-phenyl ethanol, isoamyl alcohol, furfural and methyl salicylate were not allowed by Muegge.

The bioactive prediction was shown in (Table 4). In this term, score more than 0.0 indicate high activity, 0.0 to -0.5 indicate moderate activity and less than -0.5 indicate inactivity (Paramashivam et al. 2015). According to the result, bisdemethoxycurcumin, α-pinene, nerol acetate, and lauric acid had moderate activity as G protein-coupled receptor ligands. In an ion channel modulator term, nerol acetate indicates high activity followed by bisdemethoxycurcumin, α-pinene, and methyl salicylate that indicate moderate activity. Bisdemethoxycurcumin, a compound that had the moderate capability as a kinase inhibitor, whereas other compounds had inactivity. Bisdemethoxycurcumin has also had the high ability of nuclear receptor ligands, then it was followed by lauric acid and nerol acetate, which had moderate activity score. Bisdemethoxycurcumin and lauric acid were found as protease inhibitor rather than other compounds. Nerol acetate, bisdemethoxycurcumin, and lauric acid had the better ability as enzyme inhibitor than methyl salicylate and α-pinene. From this result, it might be concluded that bisdemethoxycurcumin had good potential in all of these parameters rather than 2-phenyl ethanol, isoamyl alcohol, and furfural that had inactivity score in all parameters.

Based on the pharmacokinetics prediction result (Table 5), all of the compounds had high ability in intestinal absorption (exclude α-pinene), blood-brain-barrier penetration, and none prediction as P-gp substrate. It indicated that all of the compounds could spread through all of the body to suppress the deployment of Mycobacterium tuberculosis when entering the human body. In metabolism of xenobiotics term, most of the compounds had no potential to inhibit P450 proteins. However, bisdemethoxycurcumin could be an inhibitor of CYP1A2, CYP2C9, CYP3A4, and 2-phenyl ethanol as an inhibitor of CYP1A2. According to Flockhart (2007), the inhibition ability of this protein could increase the compounds in the blood plasma and could be decreased in the clearance of substrates. In addition, The toxicity prediction (Table 6) described that all of the compounds could not induce bacteria mutation, thus it might be indicate that all of the compounds did not cause drug resistance.

### Table 2. Chemical Properties

| Compound          | MW (g/mol) | TPSA (Å²) | HBA | HBD | Rotatable Bond | MLogP | Water Solubility |
|-------------------|------------|-----------|-----|-----|----------------|-------|-----------------|
| Bisdemethoxycurcumin | 308.33    | 74.60     | 4   | 2   | 6              | 2.13  | Soluble         |
| α-pinene          | 136.23     | 0.00      | 0   | 0   | 0              | 4.29  | Soluble         |
| Nerol Acetate     | 196.29     | 26.30     | 2   | 0   | 6              | 2.95  | Soluble         |
| 2-phenyl ethanol  | 122.16     | 20.23     | 1   | 1   | 2              | 1.87  | Very soluble    |
| Isoamyl alcohol   | 88.15      | 20.23     | 1   | 1   | 2              | 1.16  | Very soluble    |
| Furfural          | 96.08      | 30.21     | 2   | 0   | 1              | -0.56 | Very soluble    |
| Lauric acid       | 200.32     | 37.30     | 2   | 1   | 10             | 3.51  | Soluble         |
| Methyl salicylate | 152.15     | 46.53     | 3   | 1   | 2              | 1.32  | Soluble         |

MW: molecular weight; TPSA: Topology Polar Surface Area, HBA: Hydrogen bond acceptor; HBD: Hydrogen bound donor; MLogP: partition coefficient
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CONCLUSION

The compounds of *Curcuma xanthorrhiza* Roxb such as bisdemethoxycurcumin, α-pinene, and nerol acetate, and 2-phenyl ethanol, isoamyl alcohol, furfural, lauric acid, and methyl salicylate of *Tamarindus indica* targeted proteins of *Mycobacterium tuberculosis* that had potential as anti-tuberculosis. According to the ADME profiling, all of these compounds had various chemical characteristics and bioactivity. However, all of the compounds were allowed by Lipinski, Veber, Egan’s rule, and it could be easier to absorb in the blood-brain-barrier system. In toxicity term, all of the compounds had non-ames toxicity, thus it will not cause resistance in order to avoid multi-drug resistance TB. In this study did not mention the possible interaction with other molecules and also the interaction of active compounds with human proteins related with the immune system and

| Compound                        | Lipinski | Ghose | Veber | Egan | Muegge | Bioavailability Score |
|----------------------------------|----------|-------|-------|------|--------|-----------------------|
| Bisdemethoxycurcumin             | Yes      | Yes   | Yes   | Yes  | Yes    | 0.55                  |
| α-pinene                         | Yes      | No    | Yes   | No   | No     | 0.55                  |
| Nerol Acetate                    | Yes      | Yes   | Yes   | Yes  | No     | 0.55                  |
| 2-phenyl ethanol                 | Yes      | No    | Yes   | No   | Yes    | 0.55                  |
| Isoamyl alcohol                  | Yes      | No    | Yes   | No   | Yes    | 0.55                  |
| Furfural                         | Yes      | No    | Yes   | No   | Yes    | 0.55                  |
| Lauric acid                      | Yes      | Yes   | Yes   | Yes  | Yes    | 0.56                  |
| Methyl salicylate                | Yes      | No    | Yes   | No   | Yes    | 0.55                  |

Table 3. Druglikeness of the compounds

| Compound                        | GPCR    | ICM    | KI     | NRL    | PI     | EI     |
|----------------------------------|---------|--------|--------|--------|--------|--------|
| Bisdemethoxycurcumin             | 0.00    | -0.14  | -0.26  | 0.25   | -0.08  | 0.15   |
| α-pinene                         | -0.48   | -0.43  | -1.50  | -0.62  | -0.85  | -0.34  |
| Nerol Acetate                    | -0.50   | 0.04   | -1.11  | -0.12  | -0.80  | 0.21   |
| 2-phenyl ethanol                 | -2.00   | -1.28  | -2.11  | -2.08  | -2.08  | -1.38  |
| Isoamyl alcohol                  | -3.58   | -3.53  | -3.69  | -3.55  | -3.38  | -3.52  |
| Furfural                         | -3.76   | -3.78  | -3.86  | -3.81  | -3.92  | -3.80  |
| Lauric acid                      | -0.27   | -0.04  | -0.75  | -0.24  | -0.36  | 0.04   |
| Methyl salicylate                | -1.14   | -0.55  | -1.22  | -1.03  | -1.27  | -0.62  |

Table 4. Bioactivity prediction

| Compound                        | GI       | BBB     | P-gp    | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|----------------------------------|----------|---------|---------|------------------|------------------|------------------|------------------|------------------|
| Bisdemethoxycurcumin             | High     | Yes     | No      | Yes              | No               | Yes              | No               | Yes              |
| α-pinene                         | Low      | Yes     | No      | No               | No               | Yes              | No               | No               |
| Nerol Acetate                    | High     | Yes     | No      | No               | No               | No               | No               | No               |
| 2-phenyl ethanol                 | High     | Yes     | No      | Yes              | No               | No               | No               | No               |
| Isoamyl alcohol                  | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Furfural                         | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Lauric acid                      | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Methyl salicylate                | High     | Yes     | No      | No               | No               | No               | No               | No               |

Table 5. Pharmacokinetics prediction

| Compound                        | GI       | BBB     | P-gp    | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|----------------------------------|----------|---------|---------|------------------|------------------|------------------|------------------|------------------|
| Bisdemethoxycurcumin             | High     | Yes     | No      | Yes              | No               | Yes              | No               | Yes              |
| α-pinene                         | Low      | Yes     | No      | No               | No               | Yes              | No               | No               |
| Nerol Acetate                    | High     | Yes     | No      | No               | No               | No               | No               | No               |
| 2-phenyl ethanol                 | High     | Yes     | No      | Yes              | No               | No               | No               | No               |
| Isoamyl alcohol                  | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Furfural                         | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Lauric acid                      | High     | Yes     | No      | No               | No               | No               | No               | No               |
| Methyl salicylate                | High     | Yes     | No      | No               | No               | No               | No               | No               |

GPCR: G protein-coupled receptor ligands; ICM: ion channel modulators; KI: kinase inhibitor; NRL: nuclear receptor ligands; PI: protease inhibitor; EI: enzyme inhibitor

GI absorption: gastrointestinal absorption; BBB permeant: Blood-Brain-Barrier permeant; P-gp: permeability glycoprotein substrate
energy distribution mechanism to suppress the dissemination of *Mycobacterium tuberculosis* in the human body, therefore further investigations and laboratory works are needed to overcome TB problems.

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