IN SILICO STUDY OF INDONESIA MEDICAL PLANTS FOR TUBERCULOSIS THERAPY

THESIS

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BIOLOGY MASTER PROGRAM
DEPARTMENT OF BIOLOGY
FACULTY OF MATHEMATICS AND NATURAL SCIENCES
UNIVERSITY OF BRAWIJAYA
MALANG
2018

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One of the requirements for receiving a Master of Science in Biology

by

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THESIS VALIDITY SHEET

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It was maintained in front of the board examiners
in 26th July 2018
and it was declared to qualify to obtain Master of Science degree in Biology

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BIOGRAPHY

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SUMMARY

In Silico Study of Indonesia Medical Plants for Tuberculosis Therapy

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2018

Tuberculosis is one of the leading infectious diseases in the world. Indonesia is the second highest tuberculosis cases after India. Tuberculosis is commonly infected by *Mycobacterium tuberculosis*, it can rapidly spread via droplet transmission. Malnutrition causes immunodeficiency and therefore it can increase the risk factor for tuberculosis. For a long time, tuberculosis had treated by antimycobacterial drugs like isoniazid, rifampin, and ethambutol inducing *Mycobacterium tuberculosis* resistant, thus it causes difficult to treat. Indonesia is the second highest biodiversity in the world that has more than 30,000 thousand plant species, it consists of 80% medical plants. Not only the biodiversity, Indonesia also has many various ethnics. By the local wisdom and knowledge, medical plants have been used as traditional medicine to treat various diseases, including tuberculosis like *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum. This study is conducted to observe the bioactive compounds that can inhibit the activity of proteins related to tuberculosis development both in human and *Mycobacterium tuberculosis* by *in silico* study. Furthermore, this medicine is expected to be able to cure tuberculosis without causing resistant in mycobacteria.

Briefly, 176 bioactive compounds from *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum were docked with protein targets MMP-1 and Src of human and PknB and KatG of *Mycobacterium tuberculosis* by Patchdock program, then the binding position was observed by LigPlus software. The controls used were doxycycline, saracatinib, mitoxantrone, and isoniazid respectively. The protein docking of Src and PI3K; PknB and FhaA were conducted using Firedock program and visualized by PyMol software. ADME and toxicity of the selected bioactive compounds and controls were done by SwissADME and admetSAR.

According to the docking screening it has been chosen the highest best ten scores of each protein-ligand docking. Seventeen compounds have been selected based on ten highest score from docking result. Each of the compounds had various pattern score while docked with target proteins. Curcumin, demethoxycurcumin, 8-gingerol, phytol, oleic acid, and linoleic acid have been indicated that could bind with four proteins target, whereas according to network analyzing oleic acid, and linoleic acid had interaction with proteins of human and *Mycobacterium tuberculosis.* These compounds might be multitarget compounds could be for tuberculosis therapy. In addition, phytol and oleic acid could alter the position of Src while a bond with PI3K, while phytol also could alter FhaA position while docked with PknB. Moreover, the ADME and toxicity results have been showed that the bioactive compounds were permitted by Lipinski'role and did not lead AMES toxicity. From the result, it might be concluded that *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum have potent for tuberculosis therapy.

FOREWORD

By giving a lot of thanks to Allah SWT, the author can accomplish a master thesis used for receiving Master of Science degree in Biology in Faculty of Mathematics and Natural Sciences, University of Brawijaya. The author also gives thanks to:

1. Prof. Sutiman Bambang Sumitro, SU.,D.Sc, a first supervisor, who gives a lot of suggestions and guidance during whole thesis process and also presents plentiful motivation and wise counsel rendering to always to be a grateful and humble person.
2. Dr. Sri Widyarti, M.Si, a second supervisor, who gives a lot of precious suggestions, guidance, and knowledge during the whole thesis process.
3. Prof. Muhaimin Rifa`i, S.Si., Ph.D.Med.Sc and Prof. Widodo, S.Si., M.Si., Ph.D.Med.Sc as examiner who gives a lot of suggestions and advices for making the thesis better.
4. My lovely family, bapak, ibuk and my twin sisters, who always give numerous pray and motivations to accomplish the thesis.
5. My friends in Nanimonai (Mater of Biology students 2016), Science Complexity working group, and Tazkia IIBS Malang who never stop to give spirit for me to complete the thesis.

The author realizes that this thesis still has plentiful lack, therefore suggestions and good critics are needed to make this scientific work more useful.

Malang, July 2018

Author

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ABBREVIATION LIST

Abbreviation	Annotation
Å	Angstrom
$Å^2$	Angstrom square
ADME	Absorption, distribution, metabolism, and excretion
ADMET	Absorption, distribution, metabolism, excretion and toxicity
adhA	Alcohol dehydrogenase A
adhC	Alcohol dehydrogenase C
alkA	Bifunctional methylated-DNA-protein-cysteine methyltransferase/O-6-methylguanine-DNA transcription regulator
ANGPTL4	Angiopoietin-like 4
APOA1	Apolipoprotein A-I
APOE	Apolipoprotein E
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
CADD	Computer-aided drug design
CCK	Cholecystokinin
CD4+	Cluster of differentiation 4
CHK	CSK-homologous kinase
CSK	C-terminal Src kinase
desA3	Product of *Mycobacterium tuberculosis* H37Rv gene rv3229c, a stearoyl-CoA Δ^9 desaturase
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
ERK	Extracellular Receptor Kinase
FABP4	Fatty acid binding protein 4
FADS2	Fatty acid desaturase 2
fadD6	Long-chain-acyl-CoA synthetase
fadD9	Fatty-acid-CoA ligase
fadD19	Acyl-CoA synthetase

FFAR1	Free fatty acid receptor 1
FhaA	ForkHead Associated A
GI	Gastrointestinal
GCG	Glucagon
HBA	Hydrogen bond acceptor
HBD	Hydrogen bound donor
HIV	Human Immunodeficiency Virus
HTS	High-throughput screening
IFN-γ	Interferon gamma
IL	Interleukin
INH	Isoniazid
JNK	c-Jun N-terminal kinase
KatG	Catalase-peroxidase
LTBI	Latent tuberculosis infection
MDR	Multidrug-resistant tuberculosis
MMP	Matrix metallopeptidase
MT2242	Long-chain-fatty-acid-CoA ligase
MRC	Medical Research Council
NADH	Nicotinamide Adenine Dinucleotide - Hydrogen
NF-κβ	Nuclear factor kappa B
PPARA	Peroxisome proliferator-activated receptor alpha
PI3K	Phosphoinositide 3-Kinase
PknB	Protein Kinase B
RPM	Rifampin
Src	Tyrosine-protein kinase Src
STPK	Ser/Thr protein kinases
TB	Tuberculosis
TDR	Total Drug Resistance
Th1	T helper 1
TNF	Tumor necrosis factor

TPSA	Topology Polar Surface Area
VGEF	Vascular endothelial growth factor
XDR	Extensively drug-resistant

CHAPTER I
INTRODUCTION

1.1 Background

Tuberculosis is a pulmonary infectious disease commonly caused by *Mycobacteria tuberculosis*, an airborne bacterium. Tuberculosis not only causes pulmonary dysfunction but also causes disease in another part of the body. *Mycobacterium tuberculosis* can rapidly spread from a person who has active tuberculosis to others via droplet transmission. In the clinical view, there are two stages of tuberculosis diseases: latent tuberculosis infection (LTBI) and active tuberculosis disease (Pai et al., 2016). LTBI occurs when persons infected with *Mycobacterium tuberculosis* but they cannot transmit the bacteria. In this stage, the bacteria which are in a dormant phase live in the pulmonary granulomas and the patients do not give any symptoms of tuberculosis. Otherwise, active tuberculosis stage, the persons can transmit the bacteria and they show tuberculosis symptoms like fever, fatigue, lack of appetite, weight loss, and coughing up blood (Chinsembu, 2016; Pai et al., 2016). According to the WHO report, tuberculosis is one of the top 10 causing death in the world. In 2015, there were 10.4 million new incidents of tuberculosis in the world and 1.8 million patients tuberculosis death. More than 95% it occurs in low and middle-income countries. Indonesia is in the second highest position of tuberculosis case after India (WHO, 2017). There was an estimated 67-150 thousand mortality caused tuberculosis in Indonesia (WHO, 2015). Poverty causes deployment of TB, the majority through 1) living condition like living in the overcrowded place, slum, and poorly ventilated home 2) prolong delaying checkup 3) malnutrition and/or HIV infection (Marias et al., 2009). These facts match with TB dissemination case in Indonesia, the regions had high TB transmission are the regions which have the highly populated area, high malnutrition cases, and high HIV infection (Suhemi et al., 2013).

Previous studies stated that there was a correlation between tuberculosis with poor nutrition status of the persons (Dargie et al., 2016; Padmapriyadarsini et al., 2016). Insufficient nutrition intake renders immunodeficiency and enhances the tuberculosis risk factor. Based on animal studies, insufficient nutrition intake reduces helper T cell 1 (Th1) cytokine secretion such as IFN γ, IL-2, and TNF α had a role as mycobacteria infection control, reducing NO production and also gaining TGF β production suppressing inflammation cytokine to attack mycobacteria (Cegielski & Mc Murray, 2004).

For a long time, common medicine for treating tuberculosis has been isoniazid, rifampicin, pyrazinamide, and ethambutol (first-line drug). Unfortunately, these drugs cause rapid evolution and result resistant to *Mycobacterium tuberculosis.* Furthermore, this case leads to multidrug-resistant tuberculosis (MDR-TB) and makes tuberculosis more serious and difficult to treat (Nguyen, 2016). WHO stated that in 2015 there were an estimated 480.000 cases of MDR-TB in the world and about 19 – 45 thousand case in Indonesia (WHO, 2015). One of the tuberculosis drug, isoniazid (INH), leads *Mycobacterium tuberculosis* death by disturbing mycolic acid synthesis process. INH can be activated by KatG of *Mycobacterium tuberculosis* to form INH-NAD, then this complex inhibits 2-trans-enoyl-acyl carrier protein reductase (InhA) in the fatty acid synthase type II (FAS II) producing mycolic acid, a component to form mycobacteria envelope (Marrakchi et al., 2000). Currently, it is found that 70-80 % *KatG* and *InhA* are mutated in isoniazid mycobacteria resistance. *KatG* mutation occurs in codon 315, substitution Ser315Thr, therefore it can decrease INH activation. In addition, INH also can alter the expression of *InhA* and mutation in *InhA* ORF is found in *Mycobacterium tuberculosis* INH resistance (Shi et al., 2007). Furthermore, the side effects consuming INH was reported causing psychosis (Prasad et al., 2008; Masood et al., 2011;), toxicity in liver cells (Ramappa & Aithal, 2012), and kidney injury (Chang et al., 2014). From these reasons, it can be concluded tuberculosis therapy focusing only to exterminate bacteria cause mutation and make diseases more severe and hard to cure. Nowadays, for overcoming tuberculosis cases, multiple therapies which can eradicate mycobacteria, improve nutrition, and balance immunity and the human system should be developed.

The advancing of *Mycobacteria tuberculosis* drug resistance, leading researcher to find proper medicine to solve tuberculosis cases. Currently, scientists trying to use herbal medicine to against *Mycobacterium tuberculosis,* bioactive compounds from plants like micromolide and rythromycin may become the framework for developing tuberculosis medicine (Copp & Pearce, 2007). In addition, herbal medicines not only have the ability to eradicate the mycobacteria but also improve the immunity and supply the nutrition. Indonesia one of the tropical country reported that it has 38,000 plants species and there are only 2,039 species used for treating diseases (Zuhud, 2009). It also reported that according to ethnobiological study in various Indonesia ethnics, a lot of Indonesia local plants are potential to against tuberculosis diseases (Indonesia Health Ministry, 2015).

Therefore, this circumstance is so potential by developing medicine treating tuberculosis from Indonesia plants that used Indonesia local people to treat tuberculosis,

Curcuma xanthorrhiza Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum. Some reports have shown that all of these plants had the ability as antimicrobial and immunostimulation (Gharagozloo & Ghaderi, 2001; Kim et al., 2007; Kuru, 2014). For analyzing the effect towards tuberculosis, in silico docking method was used in this study. However, this study emphasizes in reducing drug resistance by inducing defense mechanism and suppressing *Mycobacterium tuberculosis*'s survival, and thus the targets protein selected were both from human such as matrix metallopeptidase 1 (MMP1) and tyrosine-protein kinase Src (Src) and *Mycobacterium tuberculosis* such as protein kinase (PknB) and catalase-peroxidase (KatG) and

1.2 The problem of the research

Do bioactive compounds of *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum. can inhibit the activity of proteins related to tuberculosis progression like PknB and KatG of *Mycobacterium tuberculosis* and also inhibit the protein reducing human defense mechanism and immune systems like MMP-1 and Src?

1.3 The aim of the research

The aim of this research is for knowing bioactive compounds of *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum. can inhibit the activity of proteins related to tuberculosis progression like PknB and KatG of *Mycobacterium tuberculosis* and also inhibit the protein reducing human defense mechanism and immune systems like MMP-1 and Src.

1.4 The benefit of the research

The benefit of this research is to inform the proper design of tuberculosis herbal medicine derived from Indonesia local medical plants for treating tuberculosis.

CHAPTER II

LITERATURE REVIEW

2.1 Tuberculosis (TB)

2.1.1 Latent TB

Clemen von Pirquet, who found tuberculin skin test to detect tuberculosis (TB), first described latent TB. He found a child had positive TB but had no symptoms. People who have latent tuberculosis are infected with *Mycobacterium tuberculosis* but do not have any symptoms of tuberculosis, moreover, they have a high risk to get tuberculosis diseases. The infection process of latent TB is shown in figure 1. In this stage, the bacteria are in dormant phase, latent TB person becomes active TB if the function of cell-mediated immune decreasing, malnutrition, chemotherapy, or treatment using anti-tumor necrosis factor (Druszczyńska et al., 2012).

In the latent TB, granulomas found fewer than in active TB stage. A granuloma is a structural forming of various immune cells like macrophage, T cells, B cells, dendritic cells, neutrophils, natural killer (NK) cells and fibroblast to inhibit bacteria growth and disseminate. It is induced by infected macrophage, releasing proinflammation cytokines to recruit uninfected cells like TNF. Inside the granuloma, the macrophages differentiated into epithelioid or foamy macrophage or fuse to form multinucleated giant cells. Vascular endothelial growth factor (VGEF) is found high in the early stage of developing granuloma. The blood vessels have fettered the lymphocytes indicating to recruit other lymphocytes, macrophages, and dendritic cells. In the granuloma, the bacteria are given stress condition such as hypoxia, nutrient deficiency, acidic pH and inhibition of respiration by nitric oxide, therefore, the bacteria allow in a dormant state (Druszczyńska et al., 2012; Flynn et al., 2011; Russell et al., 2009).

Currently, the treatment for curing latent TB is to control and eradicate the bacteria. The one of the recommendation to treat latent TB is monotherapy with isoniazid (INH) for 9 months. Moreover, for the people resistance with the INH, the other alternatives use rifampin (RPM) for 4 months or in combination with pyrazinamide (PZA) for 2 months. The combination of INH and RPM is also another choice for curing latent TB (Druszczyńska et al., 2012).

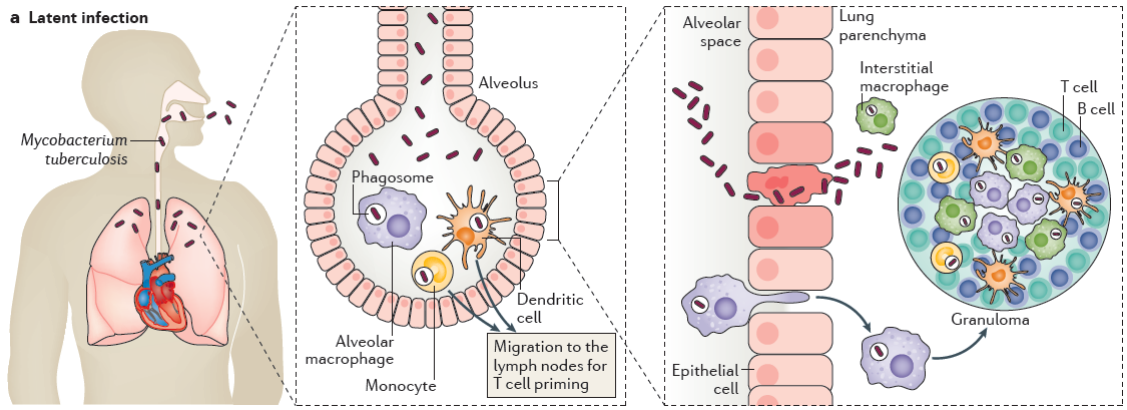


Figure 1 ***Mycobacterium tuberculosis*** **infection in the latent stage.** The bacteria come inside into the lung and reach the alveolar space via inhalation process, then the bacteria encounters epithelial macrophages. If the bacteria breach the first line immune system, the bacteria invade the lung interstitial tissue either by infecting the alveolar epithelium or alveolar macrophage to lung parenchyma. The infected macrophages recruit other uninfected cells to form granuloma (Pai et al., 2016).

2.1.2 Active TB

In latent TB patients, the combination of macrophages, dendritic cells, and T-cell are acceptable to maintain the asymptomatic infection. However, when the subset of the component is not complete the infection can progress into active TB. The progression of active TB is shown in figure 2. The symptoms of active TB include: coughing for 3 weeks or longer, losing weight, poor appetite sweating at night, fever, chills, feeling tired or weak, pain in the chest and coughing up blood or brown-colored. There are three kinds of the people that have a risk of active TB: HIV patients, TNF neutralizing antibodies and inborn errors in immunity. CD4+ T lymphocytes of Th1 is an important cell-mediated immunity for controlling *Mycobacterium tuberculosis* infection. Th1 controlling the infection by producing IFN γ, which it can activate the macrophage to defeat the bacteria through reactive nitrogen and oxygen intermediate and by inducing phagolysosome formation. However, the HIV patients have a depletion of Th1, therefore they susceptible to the infection of *Mycobacterium tuberculosis.* The previous study in the early 1990s demonstrated that the important role of TNF for controlling *Mycobacterium tuberculosis* and it also confirmed that the patients receive anti-TNF-therapy have a risk factor for active TB (Pai et al., 2016; Pawlowski et al., 2012).

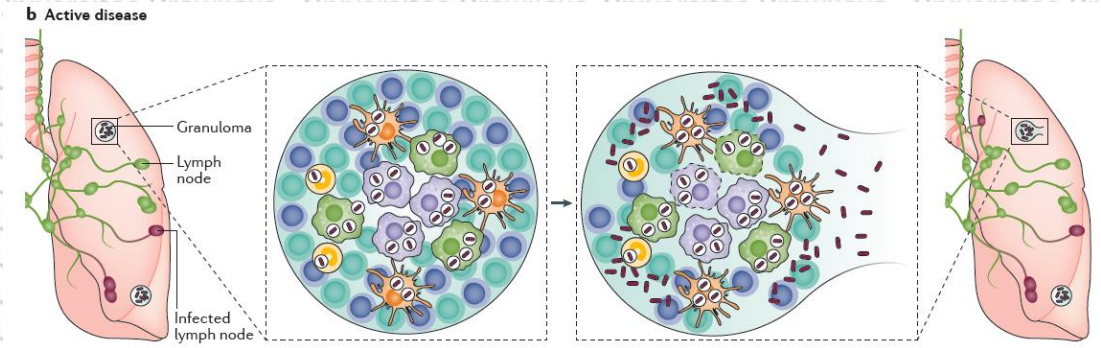


Figure 2 *Mycobacterium tuberculosis* infection in the active stage. The *Mycobacterium tuberculosis* replicate inside the granuloma. If the bacteria load becomes too great and the component of the granuloma cells decrease, the bacteria will disseminate eventually to the other organs. In this phase, the bacteria either can enter the bloodstream or re-enter the respiratory tract and this phase can be said active TB (Pai et al., 2016)

2.1.3 Proteins related in Tuberculosis progression

2.1.3.1 MMP-1

Matrix metalloproteinase (MMP) belongs to subfamily M10A which can degrade extracellular matrix (ECM), extracellular molecules which essential for cellular environments to survive cell. Both fibrous proteins like collagen and elastin and glycoproteins like fibronectin and laminin are the major compounds compiling ECM. MMP is zinc-dependent metalloproteinase which is able to cleave ECM substrate. MMP takes various part to regulate physiological and pathology process such as cell proliferation, cell motility, immune system and host defense. MMP is produced as zymogens, inactive precursor, and it can be active by N-terminal cleavage with other proteins. Commonly the MMP structure consists of a pro-domain, a catalytic domain, a hinge, a hemopexin-like (Hpx) domain, and a stalk region. MMP has 24 members that classified based on the substrate and structure (Arakaki et al., 2009; Itoh, 2015)

MMP-1 is a major member of MMP that most abundant in the body. It is able to degrade collagen type I, II, III, V, and IX. The MMP-1 gene is located in chromosome 11q22. High expression of MMP-1 is related to poor prognosis of some cancers (Arakaki et al., 2009). In tuberculosis case, MMP-1 was also found high expression in tuberculosis patients and it was correlated with the severity of the diseases (Ugarte-Gil et al., 2013). *Mycobacterium tuberculosis* induces phosphorylation of p38 and ERK, the activation of p38 is the major

factor to increase the expression of MMP-1 (Rand et al., 2009). The elevating of MMP activity can break down both the ECM and granuloma in pulmonary.

2.1.3.2 Src

Src tyrosine kinase is a 60-kD protein that belongs to Src family kinase (SFK), and it acts as an important role to transduce signal for regulating proliferation, migration, adhesion, angiogenesis, differentiation and immune system. The structure of Src consists of a unique NH_2 terminal, Src homology domains (SH2 and SH3), and a kinase domain. SH2 and SH3 play a major role in the various cellular process. The upstream signals from growth factor receptors and integrins, or cellular stress cause Src active. Activation of Src needs phosphorylation in the kinase domain segment, the autophosphorylation occurs on Tyr 416. However, inactivation of phosphorylation is on Tyr 527 carried out by C-terminal Src kinase (CSK) or CSK-homologous kinase (CHK). In addition, phosphorylation in C-terminal tail initiate the auto-inphosphorylitation through the assembly of SH2, SH3 and kinase domains (Boggon & Eck, 2004; Lieu & Kopetz, 2011).

Deviation of Src activation has been reported cause breast, lung, colorectal, liver, prostate, pancreatic, and ovarium cancer. In immune system term, the inhibition of Src activation increases IL-12 production and suppress the inflammation with disturbing the NF-Kb activation. Moreover, the suppression of Src activation has been reported decrease the dissemination of *Mycobacteria tuberculosis* (Byeon et al., 2012; Chandra et al., 2013; Lieu & Kopetz, 2011; Wölfl et al., 2013).

2.1.3.3 PknB

Ser/Thr kinase protein family has 11 members involved PknA-PknL, nine of the members are transmembrane receptor protein involved PknB. The PknB structure consists of an extracellular domain, a transmembrane domain, a juxtamembrane region, and a kinase domain. PknB is encoded by *PknB* gene that part of an operon containing *pstP*, *rodA* for controlling cell shape and *pbpA* for synthesizing peptidoglycans. PknB is essential for *Mycobacterium tuberculosis* growth, signal transducer for regulating cell shape and *Mycobacterium tuberculosis* division, and replication regulation. Recently, PknB is used as a target of tuberculosis drug (Chawla et al., 2014; Gupta et al., 2017; Ortega et al., 2014).

2.1.3.4 KatG

KatG is a multifunctional catalase-peroxynitrite and NADH oxidase. *Mycobacterium tuberculosis* needs virulence factor to inhibit the phagosome-lysosome fusion and reduce the pH in phagosome to survive in macrophage that has antibacterial activities. Generating reactive oxidative intermediate (ROI) like hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), single oxygen ($^1O_2$), and hydroxyl radical (•OH) are one of macrophage antibacterial activities. Therefore, *Mycobacterium tuberculosis* has enzymes to inhibit ROI and one of the enzymes is catalase-peroxidase (KatG), a heme enzyme that belongs to Hydroperoxidases I and essentials for reduce hydroxy peroxide (Bartos et al., 2004). Moreover, By the KatG enzyme, INH is changed into INH-NAD which can interfere with activation inhibiting NADH-dependent enoyl-ACP reductase (inhA) in mycolic acid biosynthesis process. Mutation in katG and inhA is associated with isoniazid resistance. Reduction of catalase or peroxidase activity is the result of a KatG mutation which most common mutation is in S315T. In addition mutation in inhA cause resistance to isoniazid and ethionamide. inhA mutation occurs commonly in its promoter region and it associates with monoresistant strains (da Silva & Palomino, 2011).

2.1.4 Drug resistance TB

TB drug resistance first described in 1948, during the early first human trial of TB therapy. Medical Research Council (MRC) TB unit in the United Kingdom launched and conducted the first controlled clinical trial of TB drug, streptomycin. They stated that streptomycin combined with bed rest was good treatment rather than only bed rest. The therapy gave a good outcome in the first 3 months, however, after the therapy, many patients became worse which partly because of streptomycin resistance. In the 1950s, several drugs of TB such as para-amino salicylic acid, isoniazid, pyrazinamide, cycloserine, and kanamycin emerged with different mechanism action, and then various anti-TB drug has developed (Tabel 1) (Pai et al., 2016; Zumla et al., 2013).

Treating by anti-TB drugs induce rapid evolution of *Mycobacterium tuberculosis* and lead multidrug-resistant (MDR), extensively drug-resistant (XDR), and totally drug resistant (TDR) of TB. MDR-TB is defined as a resistant minimum to rifampicin and isoniazid. MDR-TB patients include the persons who get failure treatment after 4 months treatment, persons have recurrent TB, persons infected with drug-resistance TB, or person

Table 1. Main of tuberculosis drugs and the targets (Zumla et al., 2013).

Drug (year of discovery)	Target	Effect
First-line drugs		
Isoniazid (1952)	Enoyl-[acyl-carrier-protein] reductase	Inhibits mycolic acid synthesis
Rifampicin (1963)	RNA polymerase, beta subunit	Inhibits transcription
Pyrazinamide (1954)	S1 component of 30S ribosomal subunit	Inhibits translation and *trans*-translation, acidifies cytoplasm
Ethambutol (1961)	Arabinosyl transferases	Inhibits arabinogalactan biosynthesis
Second-line drug		
Para-amino salicylic acid (1948)	Dihydropteroate synthase	Inhibits folate biosynthesis
Streptomycin (1944)	S12 and 16S rRNA components of 30S ribosomal subunit	Inhibits protein synthesis
Ethionamide (1961)	Enoyl-[acyl-carrier-protein] reductase	Inhibits mycolic acid biosynthesis
Ofloxacin (1980)	DNA gyrase and DNA topoisomerase	Inhibits DNA supercoiling
Capreomycin (1963)	Interbridge B2a between 30S and 50S ribosomal subunits	Inhibits protein synthesis
Kanamycin (1957)	30S ribosomal subunit	Inhibits protein synthesis
Amikacin (1972)	30S ribosomal subunit	Inhibits protein synthesis
Cycloserine (1955)	d-alanine racemase and ligase	Inhibits peptidoglycan synthesis

First line: drugs for treating common TB; second line: drugs for treating MDR-TB

were born in the high prevalent drug resistant-TB countries. Treating common case of TB takes 20 months, while MDR-TB takes 28 months. XDR-TB is described as MDR-TB case and additional resistance with at least one fluoroquinolone like ofloxacin and one second-line

injectable drug like amikacin, kanamycin, capreomycin. Treating XDR-TB takes much time than MDR-TB and needs third-line anti-TB drugs which are very expensive and have more side effects than first-line and second-line drugs. TDR-TB resistance with all first-line and second-line anti-TB drugs (Nguyen, 2016; Wallis et al., 2016; Zumla et al., 2013).

2.1.4.1 Isoniazid resistant

The main medicine for treating TB is Isoniazid (INH). It contains a pyridine ring and a hydrazide group. INH is a pro-drug which can active by enzyme KatG of mycobacteria, it enters the mycobacteria cell via passive diffusion. KatG is a multifunctional catalase-peroxynitritase and NADH oxidase. By the KatG enzyme, INH is changed into INH-NAD which can interfere with activation inhibiting NADH-dependent enoyl-ACP reductase (inhA) in mycolic acid biosynthesis process. Mutation in *katG* and *inhA* is associated with isoniazid resistance. Reduction of catalase or peroxidase activity is the result of a *katG* mutation which most common mutation is in S315T. In addition mutation in *inhA* cause resistance to isoniazid and ethionamide. *inhA* mutation occurs commonly in its promoter region and it associates with monoresistant strains (da Silva & Palomino, 2011).

2.2 Indonesia Medical Plants

Indonesia is the second highest biodiversity in the world, with more than 30,000 plant species (Zuhud, 2009) and it also consists of 80% world medical plants (Elfahmi, et al.,2014). Not only the biodiversity, Indonesia also has plenty of kinds of ethnics, it was reported that Indonesia has 1,086 ethnics with a total population of more than 200 million peoples. Each of the ethnics has local knowledge and wisdom involving traditional medicine. This knowledge is essential to developing herbal medicine because many plant extracts used in modern medicine are discovered from local ethnic knowledge (Indonesia Health Ministry, 2015). Jamu is Indonesia traditional herbal medicine that emerging from the past time and still embedded in the local society culture and mostly it is from plant extracts (Elfahmi, et al.,2014).

According to the previous study, there are 203 kinds of Indonesia plant families that used for medicine. There are 22 kinds of plants families that have more than 20 medicine plant species, whereas other 181 family plants have less than 20 medicine plant species (Zuhud, 2009). Following paragraphs introduce Indonesia medical plants that use as tuberculosis therapy.

2.2.1 *Curcuma xanthorrhiza.* Roxb

Kingdom : Plantae
Division : Spermatophyte
Sub division : Angiospermae
Class : Monocotyledonae
Ordo : Zingiberales
Family : Zingiberaceae
Genus : Curcuma
Spesies : *Curcuma xanthorrhiza* Roxb

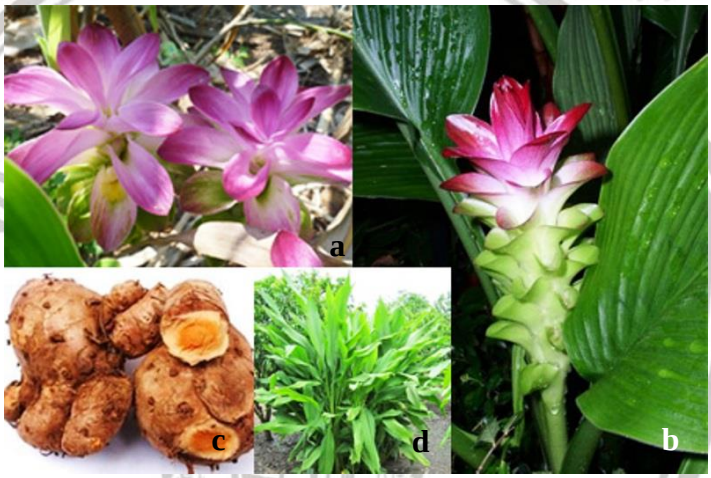


Figure 3 The part of *Curcuma xanthorrhiza.* Roxb. a-b) the flower, c) rhizome, and d) plant (Ulya, 2017).

Curcuma xanthorrhiza. Roxb (Figure 3) (local name: temulawak, kong gede,temu latah) is a herbaceous plant that has pseudostem and wide leaves, which each leaf blade is connected with petiole. The height of this plant is about 50-200 cm. *Curcuma xanthorrhiza.* Roxb has a unique compound flower (3-4 flowers) with reddish or yellowish petal color and it has 1.5 – 3cm stem flower. It is mostly found in Java, Kalimantan, Sumatra, and Sulawesi. This plant grows well in fertile soil and belongs to herbaceous that often to flower, harvesting can be done 7-12 months after planting or when the leaves become yellow and fall down. The rhizome has been known as the herbal medicine of Indonesia, many Indonesia local societies have used it as therapy for pain relievers, diabetes, diarrhea, and tumor, it contains saponin, flavonoid, and essential oil that act as antioxidant agents (Hayani, 2006; Prana,

2008). In South Kalimantan, the rhizome *Curcuma xanthorrhiza.* Roxb has been used as tuberculosis therapy (Sa'roni et al, 2011).

2.2.2 *Tamarindus indica* L.

Kingdom : Plantae
Division : Spermatophyta
Sub Division : Magniliophyta
Class : Magnoliopsida
Ordo : Fabales
Family : Fabaceae
Genus : Tamarindus
Species : *Tamarindus indica L.*

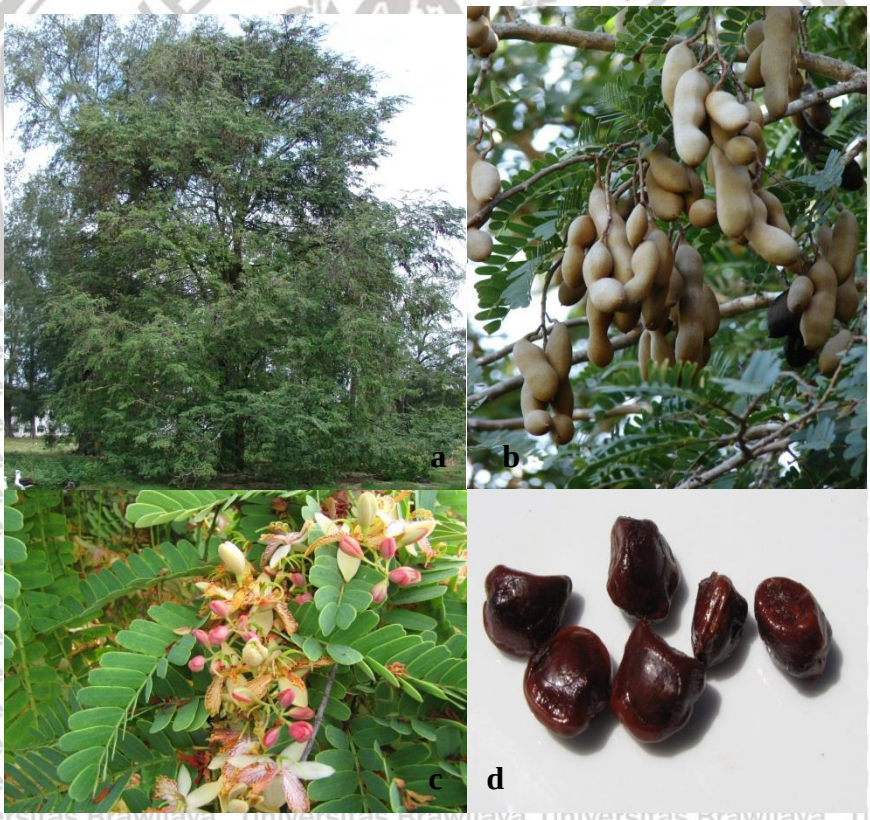


Figure 4 The part of *Tamarindus indica* L. a) The tree, b) fruits, c) flowers and d) seeds **(**Forest and Starr, 2014).

Tamarindus indica L. (Figure 4) (local name: asam Jawa, celagi, asang Jawi) belongs to tropical plant included Family of leguminoceae. This plant is expected from West Africa then

separated to India and South East Asia. Habitus of the plant is an evergreen tree, it has 30 m high and 2 m diameters of the stem. The tree grows well in altitude 1.500 m above sea level 500-1.500 mm with annual average rainfall. It has small alternate leaves with 7.5- 15 cm long, small flower with 4 sepals, and 5 yellowish petals. The fruit has sub-cylindrical straight shape with up to 14 x 4 cm of rounded end and contains 10 seeds, it has brown color exocarp with some strong fibrous. The ripe fruit comprises 40-50% edible pulp and per 100 g contains of 2-3 g protein; 0.6 g fat; 41.1-61.1 g carbohydrate; 0.6 g fiber; 34-78 mg phosphorus; 0.2 - 0.9 mg iron; 0.33 mg thiamin; 0.1 mg riboflavin; 44 mg vitamin C. Fresh seed also comprises 20% protein, 13% water, 59% carbohydrate, and 5.5 % fat. In addition, the stem, leaves, and pulp contains active compounds such as saponins, flavonoids, and tannin (Soemardji, 2007; Utami & Krisnandika, 2016).

For a long time, *Tamarindus indica* L. plant has been utilized as traditional medicine, seasoning, and building materials. Almost all of the plant can be used for the various purpose, so this plant commonly known as a multipurpose plant. The leaves can be used as seasoning, medicine, and cosmetic, the flower is the source of honey bee cultivation, the pulp of the fruit utilize as seasoning, traditional medicine, syrup, ice cream, jam and other food production. In Indonesia local societies, the fruit and leaves are used as a treatment for various diseases such as body pain, asthma, diabetes and soon (Doughari, 2006; Soemardji, 2007). In Bali, the local societies have been used the fruit of *Tamarindus indica* L. for tuberculosis therapy (Sa'roni, 2009).

2.2.3 *Zingiber officinale* var rubrum

Kingdom : Plantae
Division : Spermatophyta
Sub-division : Angiospermae
Class : Monocotyledoneae
Ordo : Zingiberales
Family : Zingiberaceae
Genus : Zingiber
Species : *Zingiber officinale*

Zingiber officinale (Figure 5) (local name: jahe) belongs to Zingiberaceae family that lives in the tropical region and spread in the various region from India to China. Since 551-479 BC, *Zingiber officinale* has been cultivated in India and exported to China. In Asia,

Zingiber officinale is mostly distributed in the wet region. Currently, *Zingiber officinale* has been cultivated in the various region in Indonesia such as North Sumatra, Bengkulu, and in Java. *Zingiber officinale* is a herbaceous plant which has pseudostems with 30-75 cm, narrow leaves like a ribbon with 15-23 cm long and among 2,5 cm wide long and it is arranged two rows alternately. The flower has egg-shaped with approximately 25 cm long and the petal has tube shaped like with narrow strand and has greenish yellow color. *Zingiber officinale* plant can use the rhizome to reproduction (Rukmana 2000; Mikususanti 2008). According to the size and the color of the rhizome, *Zingiber officinale* can be grouped into three varieties *Zingiber officinale* Roscoe (local name: jahe gajah) which has big size rather than others, white-yellowish color, and the taste is not too spicy, *Zingiber officinale* Amarum (local name: jahe emprit) which has small size, white-yellowish color, and the taste is spicy and *Zingiber officinale* Rubrum (local name: jahe merah) which has red color (Styawan, 2002).

Figure 5 The part of *Zingiber officinale* var rubrum. a) The flower, b) plant and c) rhizomes (Zaki6033, 2003).

In Indonesia, *Zingiber officinale* Rubrum has been used in various local societies like Toli-toli, Java, Bugis, Banjar, Madura, Batak, Dayak Bugis, Sunda, and Tionghoa. *Zingiber officinale* Rubrum has been utilized to cure nausea, vomiting, impotence, colds, bloating,

cough and tuberculosis. The strong aroma and spicy taste of the *Zingiber officinale* Rubrum have been believed that it has better efficacy than other varieties, thus inducing people to cultivate this variety. Commonly, *Zingiber officinale* contains 1-2% essential oil, 5-8% resin substances, starch, and sap. The active compound like 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol in *Zingiber officinale* Rubrum are higher than other varieties (Indonesia Health Ministry, 2015; Adnyana & Suciyati, 2017).

2.2.4 *Citrus aurantifolia*

Kingdom : Plantae
Division : Spermatophyta
Sub division : Angiospermae
Class : Dicotyledonae
Ordo : Rutales
Family : Rutaceae
Genus : Citrus
Species : *Citrus aurantiifolia* (Cristm.) Swingle

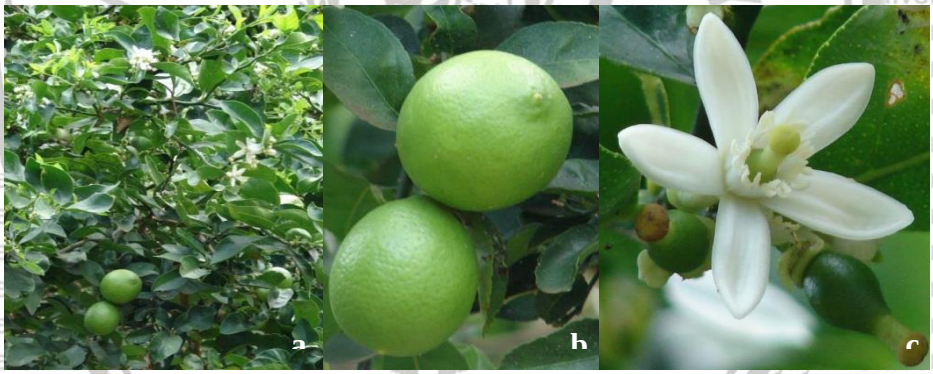


Figure 6 The part of *Citrus aurantiifolia.* a) The plant, b) fruits and c) flowers **(**Forest & Starr, 2008)

Citrus aurantifolia (Figure 6) (local name: jeruk nipis, jeruk pecel) comes from Asia and grow well in the tropical region. It belongs to Rutaceae family and Citrus genus. This plant has 150-350 cm high with spiked dark brown stem, and crenate compound leaves that have ellipse shape, base rounded, and blunt tip. The flowers grow in armpit leaves or on the top of the stem. It has a 4-5 bowl-like shape petals with white-yellowish color. The fruit has round shape with 3.5-5 cm diameters long and thin green fruit peel. *Citrus aurantifolia* is one of the medical plant that is commonly used by local society as seasoning and traditional medicine. In the medical field, *Citrus aurantifolia* has been used as appetite stimulant, antidiarrhea,

antipyretic, anti-inflammatory, and antibacterial. In South Kalimantan, the fruit and flower of *Citrus aurantifolia* have been used by local societies as tuberculosis therapy (Radam et al., 2016). Fruit of *Citrus aurantifolia* contains pectin, enzymes, proteins, fat, pigment (carotene and chlorophyll) and other active compounds like flavonoid, saponin and essential oil such as limonene and citric acid 7% (CCRC, 2014; Prastiwi & Ferdiansyah, 2017).

2.4 *In Silico* drug design

Computational methodology (*in silico*) has been developed and used in many application including for drug design. Drug design using in silico involve a database, quantitative structure-activity relationship, similarity searching, pharmacophore, homology models and another molecular model, machine learning, data mining, network analysis tools and data analysis tools. In recent time, drug design method is difficult, consuming much time and high cost. *In silico* is applied to get the satisfied result by providing valuable predict compound candidates before the research begin. Therefore it makes the cost and time consuming more effective and efficient (Ekins et al., 2007; Liao et al., 2011).

Computer-aided drug design (CADD) has an essential role in the discovery and development of therapeutical. It also a necessary tool in the pharmaceutical industry. CADD methods are classified as structure-based and ligand-based. The structure-based method is similar to high-throughput screening (HTS) both in target and ligand structure, it depends on the knowledge of the target protein structure to calculate interaction energies for all compounds tested and the ability to determine and analyze 3D structures of the biology molecules. The point of this approach is the ability of molecule and specific protein interaction and exert the biological effect of its interaction. Molecules that have favorable interaction will exert similar biological effects. Therefore the new compounds can be explained by using protein's binding site analysis. Researchers have used target protein's binding since the early 1980s. Moreover, the goal of this approach is to design compounds bound tightly to the specific target protein with large free energy and improved ADMET properties, then the results, the candidate compounds, have to be confirmed by in vitro and in vivo research. Structure-based approach contains ligand docking, pharmacophore, and ligand design method. Whereas, the ligand-based method only uses ligand information for predicting activity relying on the similarity or dissimilarity to previous known active ligands. It is used generally when no or little structure information is available. Ligand-based applies a set of references structures collected from compounds know to interact with the target of interest and it is analyzed their 2D and 3D structure. The goal of this approach is representing

the compounds with the physicochemical properties of their interaction. This approach consists of a ligand-based pharmacophore, molecular description and quantitative structure-activity relationship (Sliwoski et al., 2014).

2.5 The conceptual framework of the study

The frame work of the study is shown in figure 7 below.

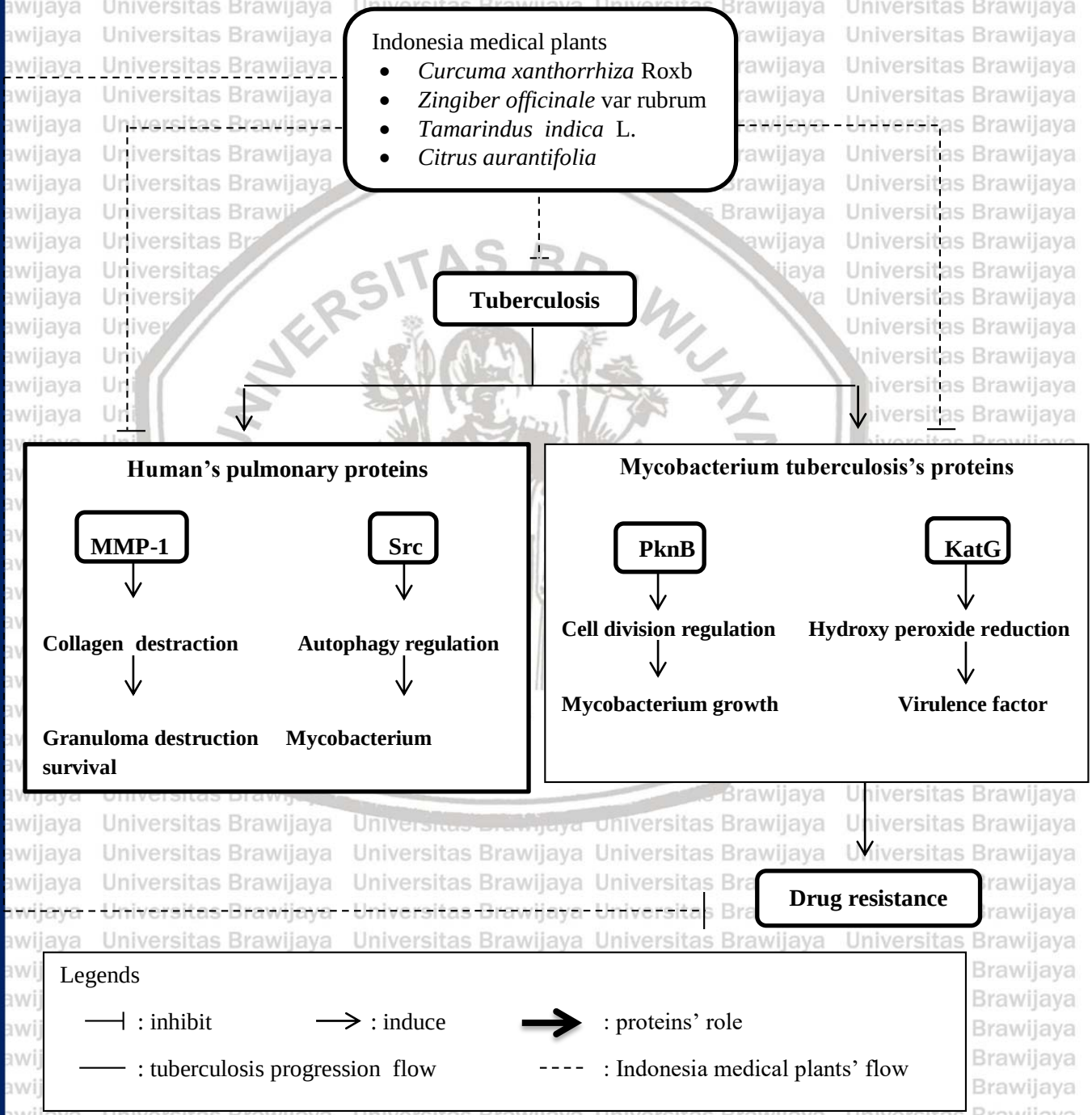


Figure 7. Framework of the study

Tuberculosis is a pulmonary infectious disease that still becomes the world's concern. It is caused by an airborne bacteria, *Mycobacterium tuberculosis.* Indonesia local societies have been used medical plants like *Curcuma xanthorrhiza* Roxb, *Tamarindus indica* L., *Citrus aurantifolia*, and *Zingiber officinale* var rubrum. to treat tuberculosis. This study tries to explore the effect of the those plants' bioactive compounds to the human's protein relating to mycobacteria dissemination such as MMP-1 and Src that take part in granuloma degradation and mycobacteria survival and also the *Mycobacterium tuberculosis*'s proteins like PknB and KatG. Furthermore, these medical plants can reduce the tuberculosis drug resistance.

CHAPTER III
METHODS

3.1 Location and time of the research

This research was conducted in Bioinformatic Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, University of Brawijaya, and it has been held for three months from January 2018 to March 2018.

3.2 Framework of methods

The framework of methods are shown in figure 8 below

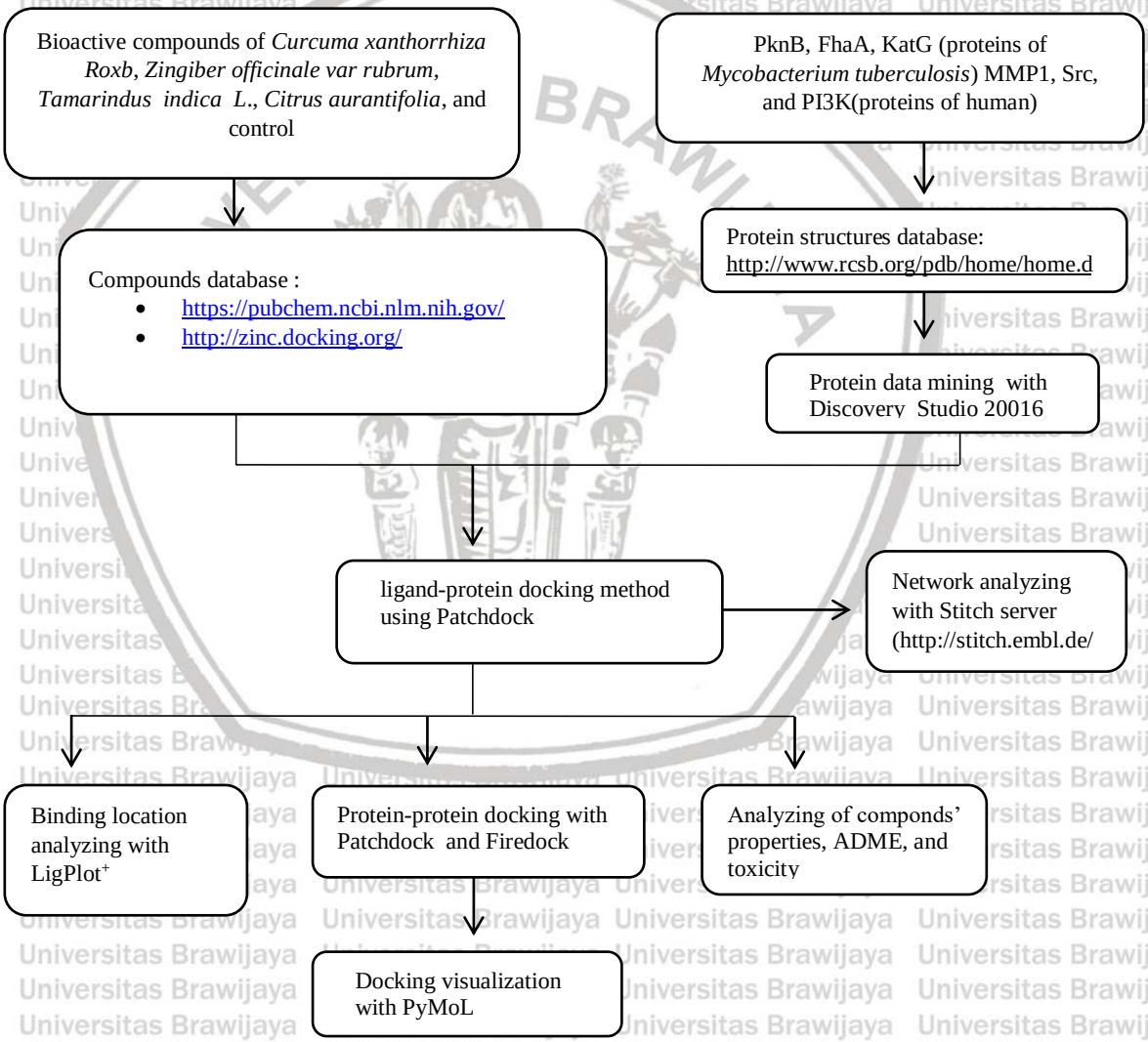


Figure 8. Framework of methods

3.3 Methods

3.3.1 Dataset

Bioactive compounds used consisted of 55 from *Curcuma xanthorrhiza Roxb* (Jantan et al., 2012; Mary et al., 2012; Ruslay et al., 2007), 59 from *Zingiber officinale var Rubrum* (Ghasemzadeh et al, 2016; Sivasothy et al., 2011), and 56 from *Tamarindus indica L.* (Sudjaroen et al., 2005; Wong, et al., 1998), and 53 from *Citrus aurantifolia* (Boussaada & Chemli, 2006; Costa et al., 2014; Phi et al., 2006; Sandoval-Montemayor et al., 2012), all of these compounds were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and ZINC (http://zinc.docking.org/). The controls utilized such as mitoxantrone, isoniazid, doxycycline, and saracatinib were also obtained from PubChem. In addition, target proteins applied in this research were downloaded from RCSB database (http://www.rcsb.org/pdb/home/home.d), *Mycobacterium* tuberculosis's proteins: PknB (2FUM), FhaA (3PO8), and KatG (1SJ2), human's proteins: MMP1 (3SH1), Src (1FKM) and PI3K (3L54). Before conducting to dock, the proteins were prepared to omit water molecules and foreign ligands by Discovery Studio 2016.

3.3.2 Docking

This study consisted of two kinds of docking, ligand-protein docking, and protein-protein docking. Ligand-protein docking was conducted by Patchdock (https://bioinfo3d.cs.tau.ac.il/PatchDock/index.html) with 1.5 RMSD, then the result was observed by LigPlot^{+} (Laskowski & Swindells, 2011) to check the binding location. Protein-protein docking was performed by Patchdock and Firedock (http://bioinfo3d.cs.tau.ac.il/FireDock/refs.html) with 4.0 RMSD. After that, the docking result was visualized by PyMoL.

3.3.3 ADME, and Toxicity

SwissADME (http://swissadme.ch/) was used to obtain absorption, distribution, metabolism, and excretion (ADME) annotation (Daina et al., 2017). admetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict/) was used to get toxicity information of the compounds (Cheng et al., 2012).

3.3.4 Network Analyzing

Search Tool for Interacting Chemicals (STICH), a server used for integrating the interaction of chemical with proteins and small molecules in biological process of living organisms (http://stitch.embl.de/) (Szklarczyk et al., 2016), was used to create target proteins networks The protein database of *Homo sapiens* and *Mycobacterium tuberculosis* H37Rv were used to find the target of compounds.

3.4 Research Design

This study used a descriptive exploratory. An exploratory study is applied when a new case is being investigated or little information about the case. It used to investigate the nature phenomenon completely (Polit et al., 2001). This study explores and describes the effect of bioactive compounds that contained in *Curcuma xanthorrhiza Roxb, Zingiber officinale var Rubrum, Tamarindus indica L.,* and *Citrus aurantifolia* toward the target proteins in human, MMP-1 and Src, and *Mycobacterium tuberculosis,* PknB, and KatG by the computational study.

CHAPTER IV
RESULTS AND DISCUSSION

4.1 Results

4.1.1 Ligand-Proteins Docking

All of the bioactive compounds were docked with target proteins (the results is shown in appendix 1), then the docking score was sorted from the high score. It described that there were some compounds from *Curcuma xanthorrhiza Roxb*, *Zingiber officinale var rubrum*, *Citrus aurantifolia*, and *Tamarindus indica L.* had position in top

Table 2. The ten highest scores of screening result

Plants	Compounds	Class	Binding energy score (kcal/mol)			
			MMP1	Src	PknB	KatG
Curcuma xanthorrhiza Roxb	Curcumin	phenol	5118	5140	5572	5414
Curcuma xanthorrhiza Roxb	Demethoxycurcumin		4802	4920	5108	5692
Curcuma xanthorrhiza Roxb	Bisdemethoxycurcumin		-	5060	-	-
Zingiber officinale var rubrum	8- gingerol		5222	5146	5482	5430
Zingiber officinale var rubrum	8-shogaol		4738	-	5388	5422
Zingiber officinale var rubrum	6-gingerol		-	4892	5002	-
Zingiber officinale var rubrum	6-shogaol		-	-	-	-
Zingiber officinale var rubrum; Citrus aurantifolia	Phytol	terpenoid	4730	4952	5476	5370
Curcuma xanthorrhiza Roxb	Citronellyl pentanoate		-	-	-	5320
Tamarindus indica L;Citrus aurantifolia	Oleic acid	organic acid	4896	5190	5326	5444
Tamarindus indica L ; Citrus urantifolia	Linoleic acid		4560	5156	5216	5660
Tamarindus indica L	Heptadecanoic acid		4896	5038	-	5384
Curcuma xanthorrhiza Roxb	Butyl dodecanoate		4610	-	-	-
Tamarindus indica L	Myristic caid		-	-	-	-
Citrus aurantifolia	Palmitic acid		-	4976	-	-
Tamarindus indica L	Palmitoleic acid		4598	-	5230	5394
Tamarindus indica L ; Citrus aurantifolia	Linolenic acid		-	-	5318	-
	Control	-	4856	6770	5906	3088

ten ranks (Table 2). Four different compounds were in the high score in each target proteins. Phenol compounds like 8-gingerol, curcumin, and demethoxycurcumin were in leading position when it attached with MMP-1, PknB, and KatG, whereas a terpenoid compound, oleic acid, had the highest score when docked with Src. Moreover, some bioactive compounds as curcumin, demethoxycurcumin, 8-gingerol, phytol, and linoleic acid could bind all of the target proteins with good value of binding energy score. It indicated that these compounds might act as a multi-target compound. For more understanding, this case, analyzing the binding position using LigPlot^{+} was conducted.

4.1.1.1 Bioactive compounds-human proteins

In MMP-1 term (Figure 9, Table 3), curcumin and demethoxycurcumin had respectively one hydrogen binding with Tyr210 (2.76 Å) and two hydrogen bindings with Phe149 (2.24 Å) and Arg202 (2.72 Å), these interactions were less than control that had three hydrogen bindings Asp124 (2.97 Å) and Ser142 (2.23 Å, 3.33 Å). Besides, curcumin and demethoxycurcumin also had an external binding respectively with Asn143

Table 3. Binding position and characteristics of selected bioactive compounds-MMP1

Compounds	Hydrogen bond	External binding	Hydrophobic
Curcumin	Tyr210 (2.76 Å)	Asn143	Gln139; Glu199; Pro123; Arg165; Thr145; Thr148; Leu147; Pro177; Arg202; Glu209; Gly178; Glu201; Asp200; Ser142
Demethoxycurcumin	Phe149 (2.24 Å) Arg202 (2.72 Å)	Glu135	Tyr116; Gln139; Leu147; Asp200; Thr145; Glu201; Ser142; Thr148
8- gingerol			Gln139; Pro123; Asn143; Ser142; Arg202; Pro146; Tyr210; Glu209; Pro177; Gly178; Thr145; Asp200; Arg165
Phytol		Thr148	Pro146; Arg202; Thr145; Asp200; Glu201; Pro177; Ser142; Arg165; Asp124; Gku199; Asn143; Gln139; Leu147; Phe149
Oleic acid			Phe149; Glu135; Pro146; Ser142; Thr148; Gln139; Arg202; Arg165; Asn143; Asp200; Glu201; Leu147; Thr145; Phe138
Linoleic acid			Tyr210; Glu209; Pro146; Pro177; Asp200; Thr148; Arg165; Asn143; Ser142; Glu201; Thr145; Arg202
Control	Asp124 (2.97 Å) Ser142 (2.23 Å; 3.33 Å		Pro146; Leu147; Arg202; Glu199; Asp200; Glu201; Gln139; Arg165; Asn143; Thr148; Pro177

and Gln135. In addition, phytol also had an external binding with Thr148. However, 8-gingerol, oleic acid, and linoleic acid only had hydrophobic interaction with MMP1. Overall, curcumin, demethoxycurcumin, 8-gingerol, oleic acid, and linoleic acid could bind with a catalityc domain of MMP1 in 106-261 residues (Bertini et al., 2012).

According to the ligand-Src docking result (Figure 10, Table 4), control and phenol compounds like curcumin, demethoxycurcumin bound with the SH3 domain (83-142) and SH3-SH2 interaction domain (142-146) of Src protein (Mak et al., 1996; Xu, Harrison, & Eck, 1997). Even though these compounds had a same binding position, but it had different interactions. Curcumin, demethoxycurcumin, and 8-gingerol had one hydrogen binding successively in Lys104 (2.07 Å), Val339 (3.19 Å), and Thr247 (3.02 Å) and one external binding successively in Tyr149 and Val 339. In another side, phytol and organic compounds like oleic acid and linoleic acid had a same binding position in Asn391, Leu273, Ser345, Asp404, and Asp348. Nevertheless, these compounds had different interaction, phytol, and linoleic acid were in the hydrophobic state while interacting with Src, while oleic acid created a hydrogen interaction with Asp386 (2.97 Å).

Table 4. Binding position and characteristics of selected bioactive compounds-Src

Compounds	Hydrogen bond	External binding	Hydrophobic
Curcumin	Lys104 (2.07 Å)	Tyr149	Thr247; Cys245; Glu147; Phe150; Gln144; Asn135; Val137; Ser134; Ala138; Phe86; Pro139; Leu89
Demethoxycurcumin	Lys321 (3.19 Å)	Val399	Leu89; Glu146; Tyr149; Gln144; Phe150; Tyr90; Glu320; Glu157; Arg160; Thr247; Glu147;
8- gingerol	Thr247 (3.02 Å)		Ala145; Leu89; Glu147; Leu161; Ile153; Phe150; Tyr90; Glu146
Phytol			Asp348; Gly274; Leu273; Asp404; Ser345; Leu393; Val281; Asn391; Lys295; Arg388; Gly276; Gln275; Cys277; Ala390; Leu347
Oleic acid	Asp386 (2.97 Å)		Phe278; Asn391; Asp404; Val281; Asp348; Ser345; Leu273; Gly274; Gln275; Arg388
Linoleic acid			Gly276; Phe278; Lys295; Asp404; Val281; Leu273; Asp348; Ser345; Asn391
Control	Asn397 (2.84 Å)		Thr247; Phe150; Leu161; Ile153; Glu396; Val399; Ser342; Tyr340; Met341; Lys401; Glu339; Glu320; Pro250; Ser248

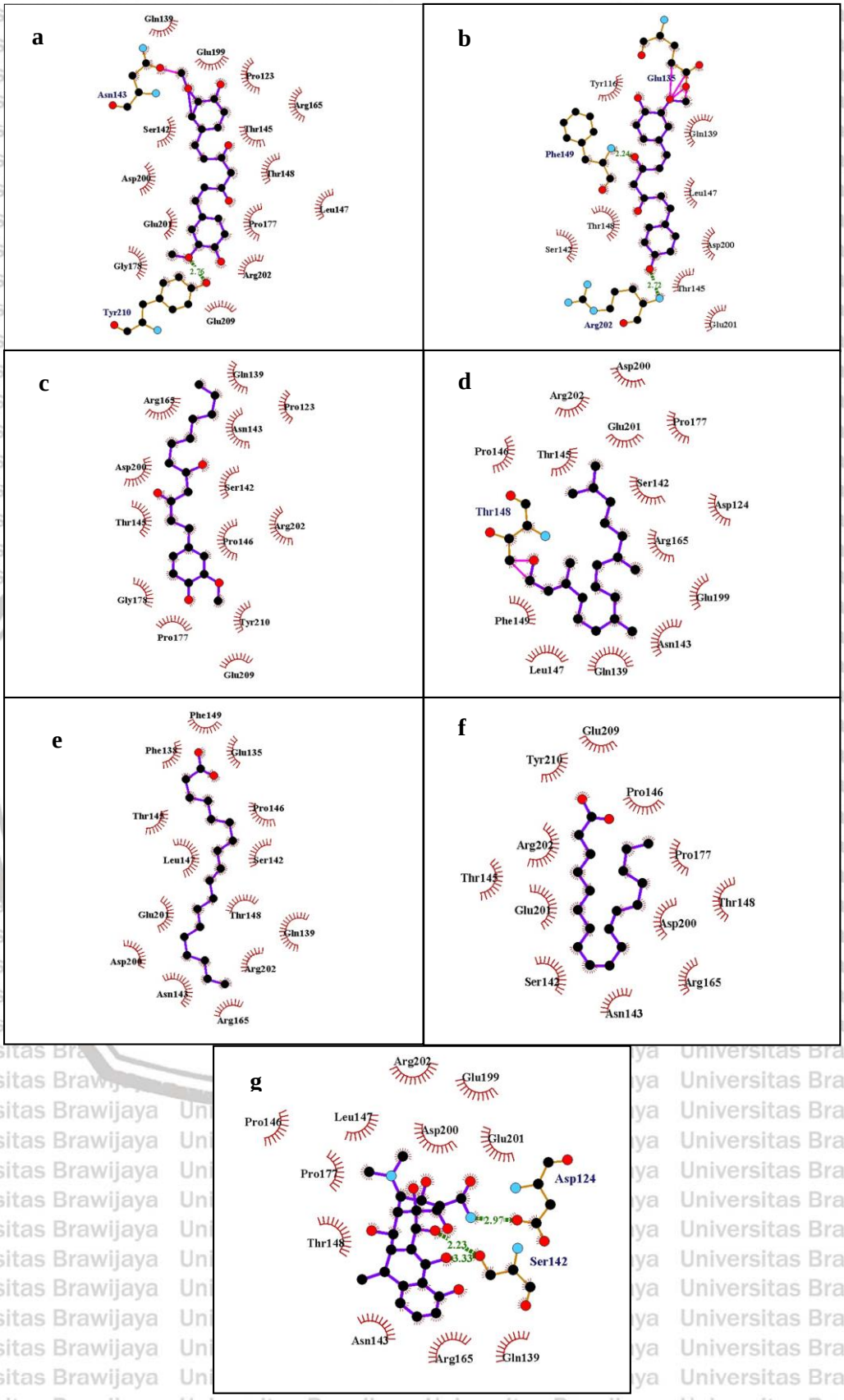


Figure 9. MMP1- bioactive compounds (a) curcumin (b) demethoxycurcumin (c) 8-gingerol (d) phytol (e) oleic acid (f) linoleic acid (g) control.

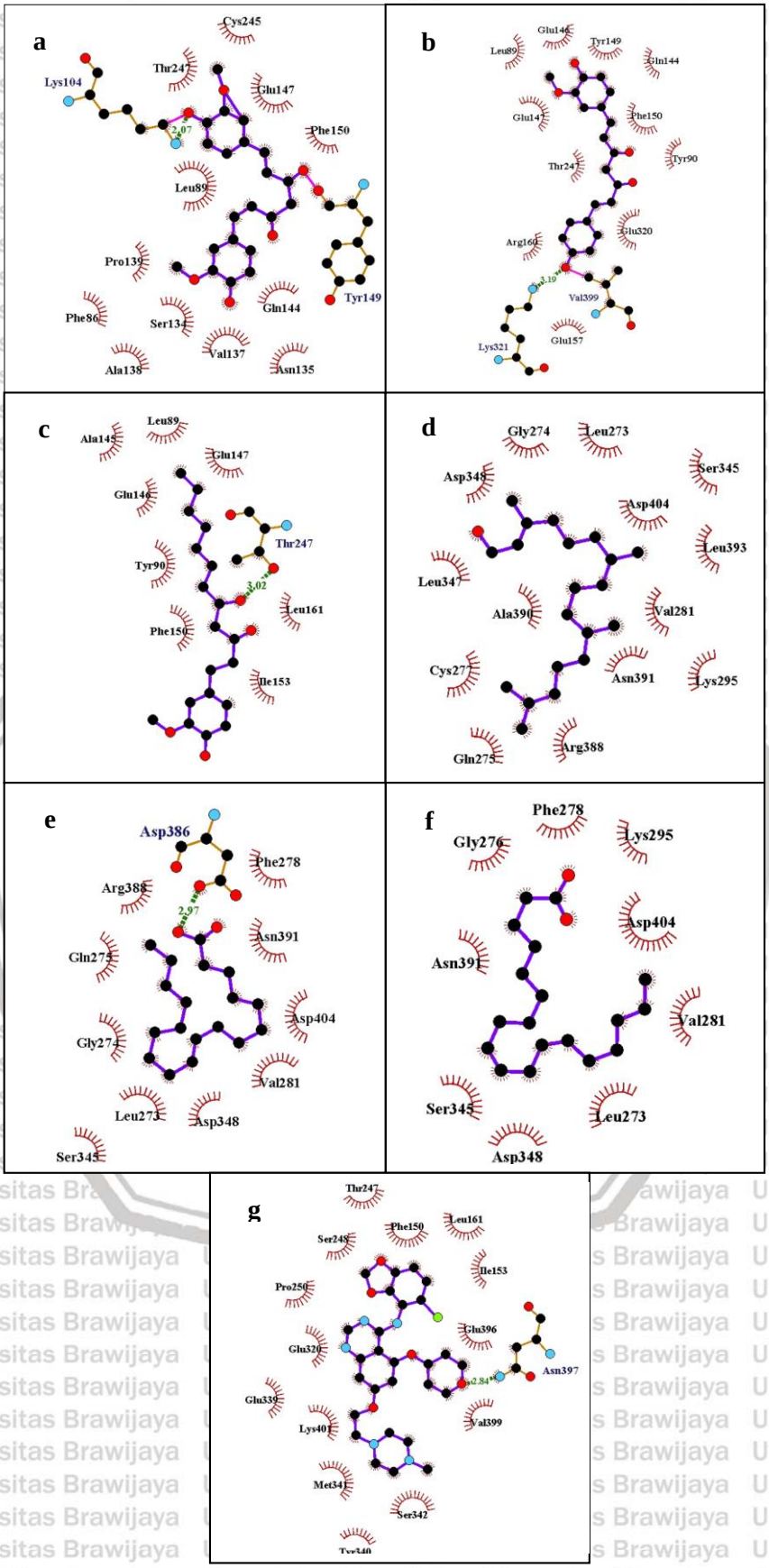


Figure 10. Src-bioactive compounds (a) curcumin (b) demethoxycurcumin (c) 8-gingerol (d) phytol (e) oleic acid (f) linoleic acid (g) control.

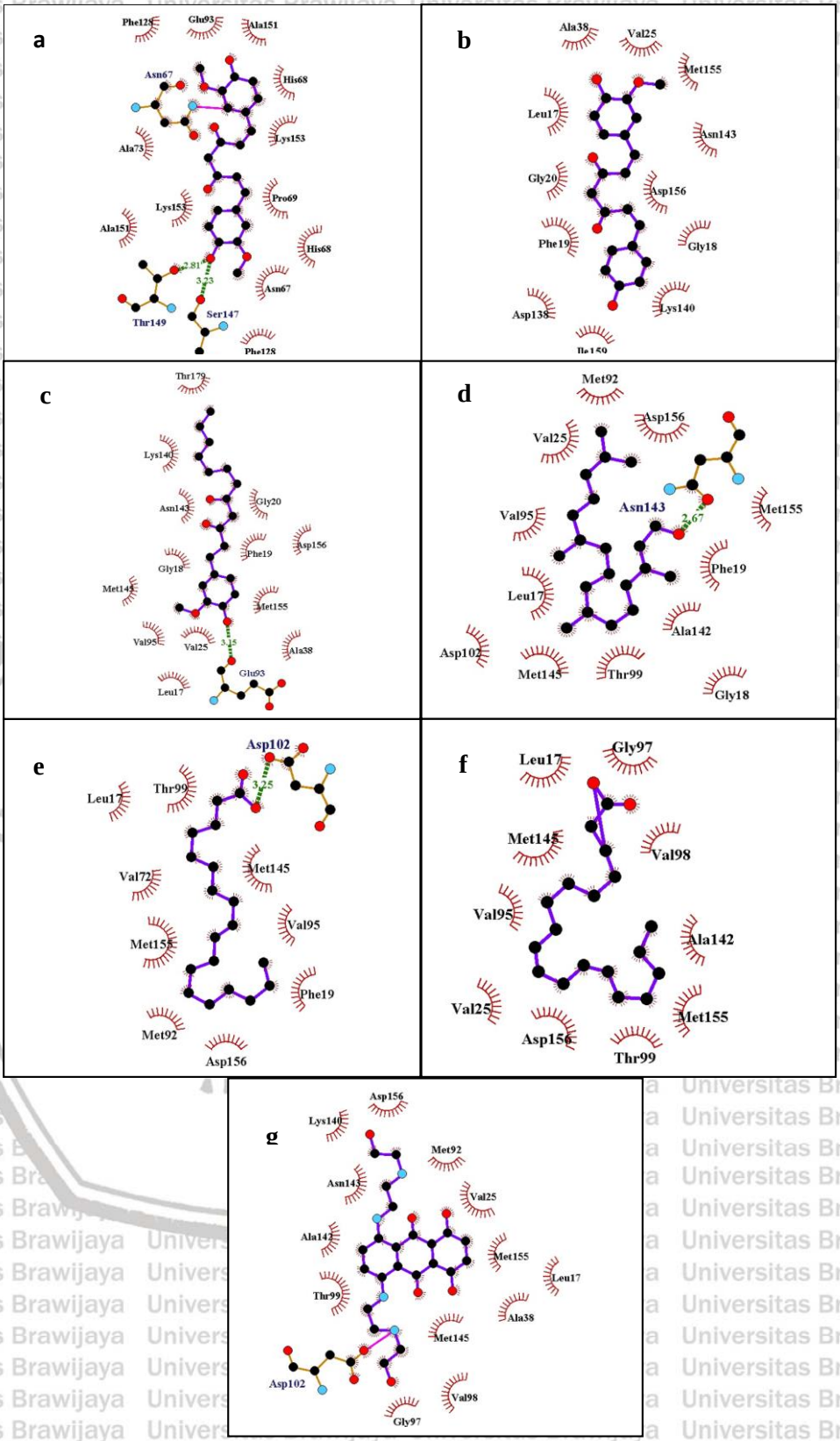


Figure 11. PknB- bioactive compounds (a) curcumin (b) demethoxycurcumin (c) 8-gingerol (d) phytol (e) oleic acid (f) linoleic acid (g) control.

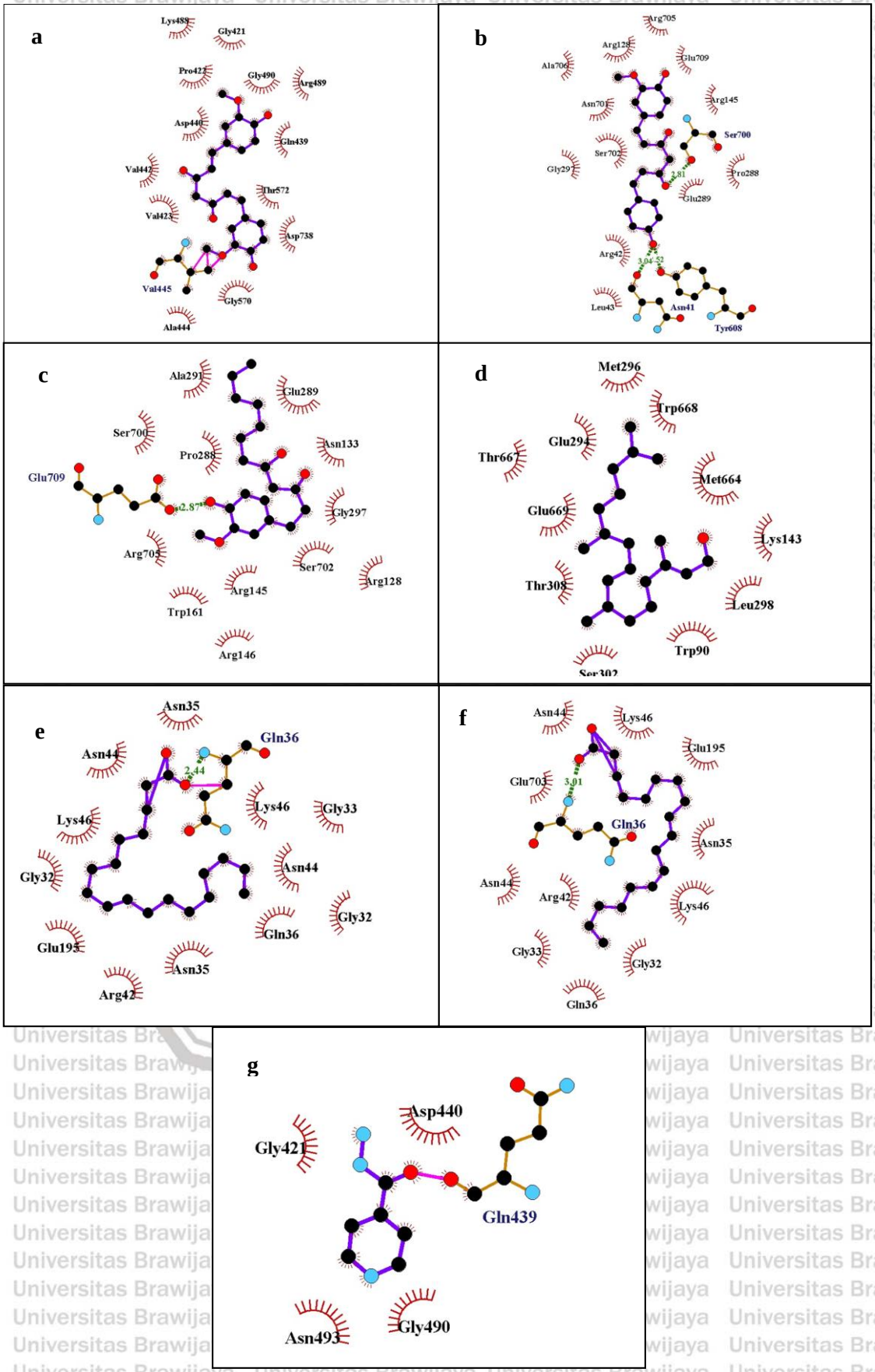


Figure 12. KatG- bioactive compounds (a) curcumin (b) demethoxycurcumin (c) 8-gingerol (d) phytol (e) oleic acid (f) linoleic acid (g) control.

4.1.1.2 Bioactive compounds - *Mycobacterium tuberculosis'* proteins

The result of PknB – bioactive compounds docking showed (Figure 11, Table 5) that curcumin had two interaction of hydrogen bindings, Thr149 (2.81 Å) and Ser147(3.23 Å), whereas, 8-gingerol, phytol, and oleic acid only had a hydrogen binding successively in Glu93 (3.15 Å), Asn143 (2.67 Å), and Asp102 (3.25 Å). Meanwhile, control had one external binding with Asp126 and linoleic tended to be hydrophobic when interacted with PknB. In addition, all of the compounds had a same binding position, this compound bound with PknB N-terminal lobes residues, Leu17, Gly18, Val25, Ala38, Met92, Glu93, and Val95, and C-terminal of PknB lobes (exclude curcumin), Met145 and Met155. According to the previous study, when the ligand bound in this position, it could suppress the activity of PknB (Wehenkel et al., 2006).

Table 5. Binding position and characteristics of selected bioactive compounds-PknB

Compounds	Hydrogen bond	External binding	Hydrophobic
Curcumin	Thr149 (2.81 Å) Ser147 (3.23 Å)	Asn67	Phe128; Glu93; Ala151; His68; Lys153; Pro69; His68; Asn67; Phe128; Ala151; Lys153; Ala73
Demethoxycurcumin			Ala38; Val25; Met155; Asn143; Asp156; Gly18; Lys140; Ile159; Asp138; Phe19; Gly20; Leu17
8- gingerol	Glu93 (3.15 Å)		Thr179; Gly20; Phe19; Asp156; Met155; Ala38; Leu17; Val25; Val95; Met145; Gly18; Asn143; Lys140
Phytol	Asn143 (2.67 Å)		Met92; Asp156; Met155; Phe19; Ala142; Gly18; Thr99; Met145; Asp102; Leu17; Val95; Val25
Oleic acid	Asp102 (3.25 Å)		Leu17; Thr99; Met145; Val95; Phe19; Asp156; Met92; Met155; Val72;
Linoleic acid			Leu17; Gly97; Val98; Ala142; Met155; Thr99; Asp156; Val25; Val95; Met145
Control		Asp102	Asp156; Met92; Val25; Met155; Leu17; Ala38; Met145; Val98; Gly97; Thr99; Ala142; Asn143; Lys140

Based on the result of KatG docking term (Figure 12), all of the compounds had a distinct binding location. Curcumin and control had same hydrophobic interaction in Gly421, Asp440, Gln439 and Gly, demethoxycurcumin and 8-gingerol in Glu 709, Arg 705, Arg 145, Arg 128, Gly 297, and Glu 289, while oleic and linoleic acid in Asn 44,

Lys 46, Glu 195, Asn 35, Gly 32, Gln 36, Gly 33, and Arg 42. Demethoxycurcumin had three hydrogen bindings with Ser 700 (2.81 Å), Asn 41 (3.04 Å) Tyr 608 (2.52 Å), whereas 8-gingerol, oleic acid, and linoleic acid had a hydrogen bindings, respectively with Glu 709 (2.87 Å), Gln 36 (2.44 Å), and Gln 36 (3.01Å).

Table 6. Binding position and characteristics of selected bioactive compounds-KatG

Compounds	Hydrogen bond	External binding	Hydrophobic
Curcumin		Val445	Lys488; Gly421; Gly490; Arg489; Gln439; Thr572; Asp738; Gly570; Ala444; Val423; Val442; Asp440; Pro422
Demethoxycurcumin	Ser700 (2.81 Å) Try608 (2.52 Å) Asn41 (3.04 Å)		Ala706; Arg128; Arg705; Glu709; Arg145; Pro288; Glu289; Leu43; Arg42; Gly297; Ser702; Asn701
8- gingerol	Glu709 (2.87 Å)		Ser700; Ala291; Pro288; Glu289; Asn133; Gly297; Arg128; Ser702; Arg145; Arg146; Trp161; Arg705;
Phytol			Met296; Trp668; Met664; Lys143; Leu298; Trp90; Ser302; Thr308; Glu669; Thr667; Glu294
Oleic acid	Gln36 (2.44 Å)		Asn35; Lys46; Gly33; Asn44; Gln36; Gly32; Asn35; Arg42; Glu195; Gly32; Lys46; Asn44
Linoleic acid	Gln36 (3.01 Å)		Glu703; Asn44; Lys46; Glu195; Asn35; Lys46; Gly32; Gln36; Gly33; Arg42; Asn44
Control		Gln439	Asp440; Gly490; Asn493; Gly421

4.1.2 Protein-protein docking

According to the ligand-protein docking results (Table 2), control had a higher score when interacted with Src and PknB rather than bioactive compounds, for exploring this case, protein-protein docking was carried out. In this term, Src was docked with phosphatidylinositide 3-kinases (PI3K), a protein signal transducer taking part to phosphorylate inositol group. The complex of Src-PI3K activates the AKT/mTOR pathway that had a role as autophagy negative regulator. Based on the previous studies, compounds inhibit Src-PI3K complex obviously can suppress the survival of *Mycobacterium tuberculosis* (Chandra, et al., 2013; Karim et al., 2011). In another side, PknB was complexed with ForkHead Associated A (FhaA), a protein substrate of

Ser/Thr protein kinases (STPKs). The interaction of PknB and FhaA involve growing process of *Mycobacterium tuberculosis* (Grundner et al., 2005).

Table 7. Protein-protein docking by Patchdock and Firedock

Compounds	Global Energy (kcal/mol)	Attractive VdW	Repulsive VdW	ACE	HB
(Src-curcumin)-PI3K	-43.44	-29.21	3.78	3.89	-4.77
(Src-demethoxycurcumin)-PI3K	-45.16	-35.56	13.61	5.67	-6.19
(Src-8-gingerol)- PI3K	-45.16	-35.56	13.61	5.67	-6.19
(Src-phytol)- PI3K	-36.43	-35.92	22.70	6.81	-10.75
(Src-oleic acid)- PI3K	-38.88	-36.67	15.32	2.49	-6.51
(Src-linoleic acid)- PI3K	-43.67	-38.65	23.70	5.77	-7.30
(Src-control)- PI3K	**-41.29**	**-40.88**	**28.87**	**6.73**	**-7.53**
Src- PI3K	**-43.67**	**-38.65**	**23.70**	**5.77**	**-7.30**
(PknB-curcumin)-FhaA	-46.84	-29.90	14.47	2.99	-8.55
(PknB-demethoxycurcumin)- FhaA	-46.84	-29.90	14.47	2.99	-8.55
(PknB-8-gingerol)- FhaA	-46.84	-29.90	14.47	2.99	-8.55
(PknB-phytol)- FhaA	-47.75	-44.47	24.38	-3.40	-10.64
(PknB-oleic acid)- FhaA	-46.84	-29.90	14.47	2.99	-8.55
(PknB-linoleic acid)- FhaA	-46.84	-29.90	14.47	2.99	-8.55
(PknB-control)- FhaA	**-46.84**	**-29.90**	**14.47**	**2.99**	**-8.55**
PknB- FhaA	**-46.84**	**-29.90**	**14.47**	**2.99**	**-8.55**

Based on the protein-protein docking result (Table 7), the global energy of complex of Src-phytol-PI3K and Src-oleic acid-PI3K were higher global energy than control. It indicates that when phytol and oleic acid bound with Src, it might be harder to bind with PI3K than when Src complexed with control. The visualization of the complex protein shown (appendix 2) that phytol and oleic acid could change the binding position of Src while complex with PI3K (Figure 13). Moreover, the result of PknB complex shown that all of the compounds had the same value of global energy with control, no compound attached. Nevertheless PknB-phytol-FhaA complex had a lower score with others, then when it was checked with PyMoL, phytol also could change the binding position of PknB while it docked with FhaA (Figure 14). From this results, it might be concluded that

phytol and oleic acid had uniqe mechanisme while complex with PknB-FhaA and Src-PI3K.

4.1.3 ADME and Toxicity result

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 (Tsaioun et al., 2016). The ADME and toxicity of the selected compounds (to ten high docking score) were shown in Table 8.

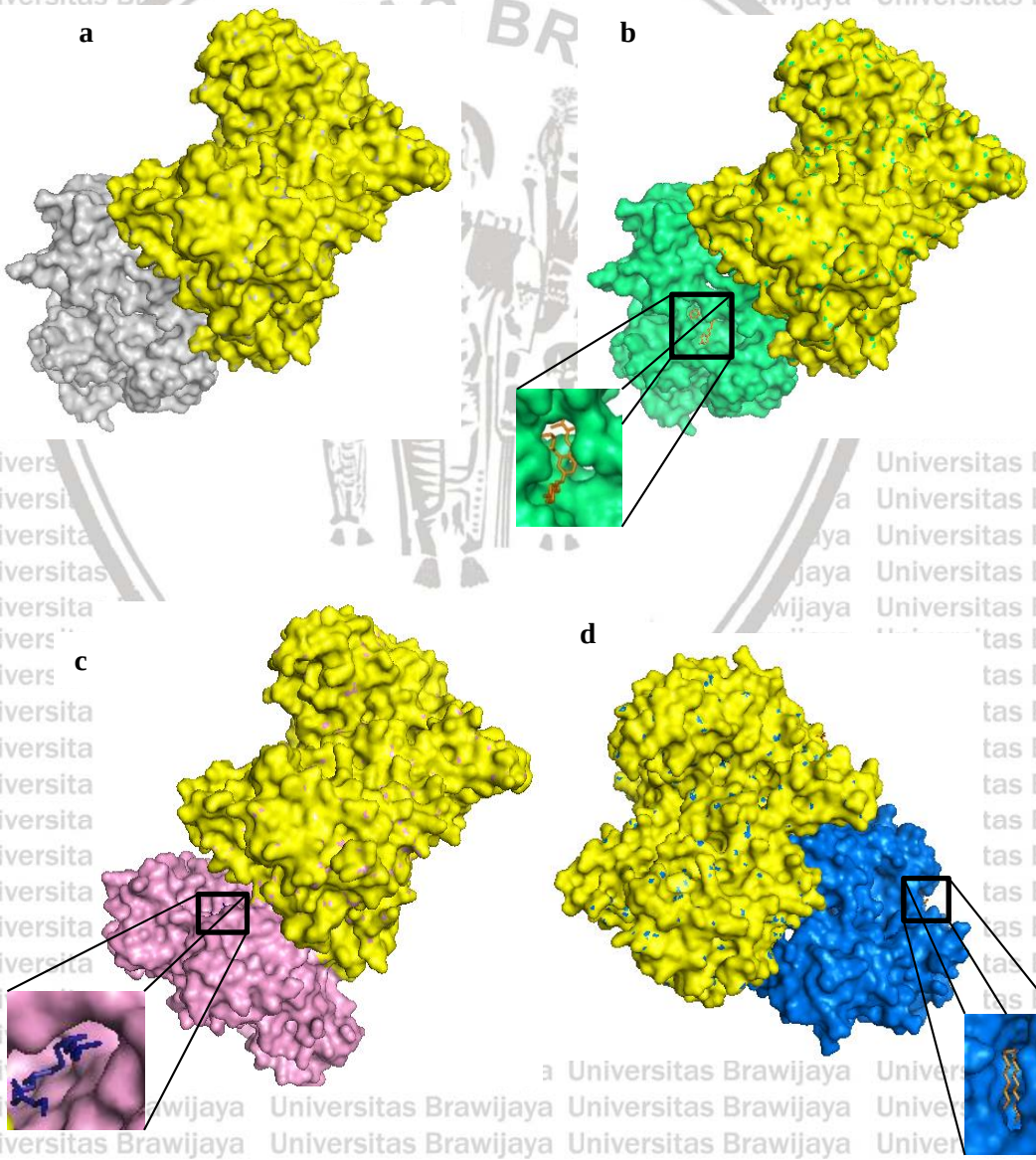


Figure 13 Src complex (a) Src-PI3K (b) (Src-control)-PI3K c) (SCR-phytol)-PI3K d (Src-oleic acid)-PI3K. Gray structure: Src wildtype protein; yellow structure: PI3K: green structure: Src-sacaratinib complex; pink structure: Src-phytol; blue structure: Src-oleic complex.

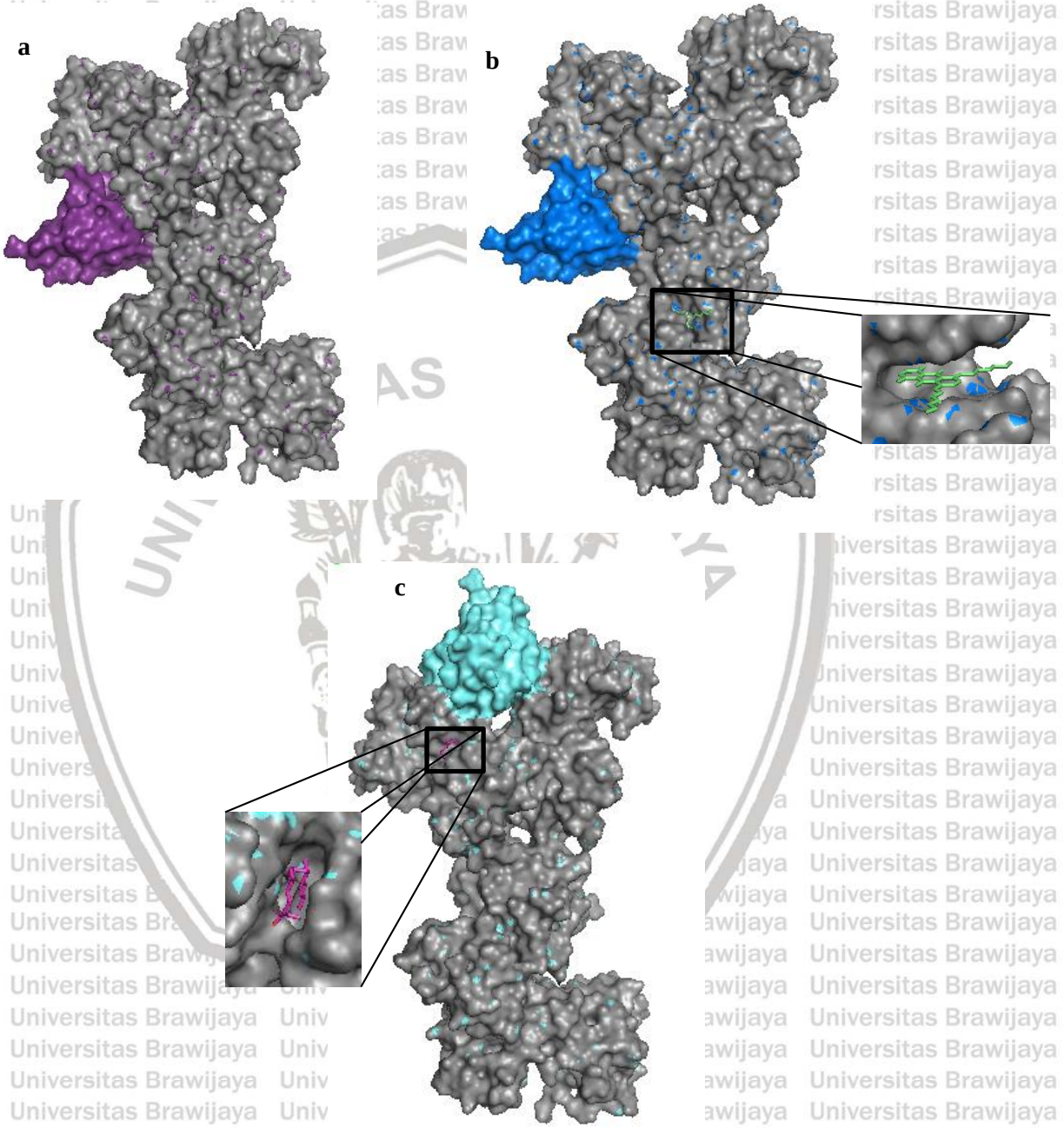


Figure 14 PknB complex (**a)** PknB-FhaA (**b) (**PknB -control)- FhaA (**c)** (PknB -phytol)-FhaA Gray structure: PknB; purple: FhaA in PknB-FhaA complex; dark blue: FhaA in PknB -(PknB -mitoxantrone)- FhaA complex; light blue: FhaA in PknB -(PknB -phytol)- FhaA complex.

According to the Table 4, all of the bioactive compounds had to vary the value of molecular weight from 228 to 368 g/mol, whereas the control compounds had bigger value than active compounds, more than 368 g/mol (except isoniazid 137.14 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 Å^2 are poor absorb into the cell membranes (Clark, 2011; Pajouhesh & Lenz, 2005). The TPSA value showed that bioactive compounds were less than 140 Å^2 and otherwise for the control compounds like doxycycline and mitoxantrone. It indicated that bioactive compounds were easy to enter the cells rather than control (except sacaratinib and isoniazid). In addition, based on the previous study, the flexibility of molecule could be measured some criteria 1) no more than 10 rotatable bonds 2) the value of the Polar surface area is no more than 140 Å^2 or no more than 12 hydrogen bond acceptors and donors (Veber et al., 2002). The bioactive compounds had more than 10 rotatable bound evenly rather than the control, whereas doxycycline and mitoxantrone had 12 hydrogen bond acceptors and donors. The value of Log P of bioactive compounds varied from 1.47 to 5.25, yet the controls had a lower value than bioactive compounds. The more Log P value the less hydrophilicity of the compounds, and it indicated poor bioavailability (Singh, 2016). However, the value of the molecular weight, hydrogen bond and acceptors, and Log P determine the result of Lipinski's rule. Lipinski's rule is the rule of evaluating the compounds with certain chemical and physical properties which can predict the absorption or permeation of the compounds thus give important information for drug design. This rule explains that if the compound has more than 5 hydrogen bond donors, 10 hydrogens bound acceptors, the value of molecular weight more than 500 and the calculation of MlogP more than 4.15, the compound indicate poor bioavailability (Lipinski et al.,1997). All of the compounds were allowed based on the Lipinski's rule, even though have one violation. In water solubility term, 8-shogaol, phytol and all of the organic compounds were moderate solubility, whereas isoniazid as control was very soluble in water.

Table 8. ADME and Toxicity result

Compounds	Mw (g/mol)	TPSA (Å²)	HBA	HBD	Rotatable bound	MLog P	Water solubility	Lipinski role	GI absorption	BBB permeant	Toxicity	
											AMES Toxicity	Probability
Curcumin	368.38	93.06	6	2	8	1.47	Soluble	Yes; 0 violation	High	No	Non AMES toxic	0.9132
Demethoxycurcumin	338.35	83.83	5	2	7	1.80	Soluble	Yes; 0 violation	High	No	Non AMES toxic	0.7747
Bisdemethoxycurcumin	308.33	74.60	4	2	6	2.31	Soluble	Yes; 0 violation	High	yes	Non AMES toxic	0.7802
8- gingerol	322.44	66.76	4	2	12	2.61	Soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.7697
8-shogaol	304.42	46.53	3	1	11	3.37	Moderately soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.7896
6-gingerol	294.39	66.76	4	2	10	2.14	Soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.7697
6-shogaol	276.37	46.53	3	1	9	2.90	Soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.7896
Phytol	296.53	20.23	1	1	13	5.25	Moderately soluble	Yes; 1 violation: MLOGP>4.15	Low	No	Non AMES toxic	0.9132
Citronellyl pentanoate	240.38	26.38	2	0	10	3.84	Soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.9281
Oleic acid	284.46	37.30	2	1	15	4.57	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	No	Non AMES toxic	0.6568
Linoleic acid	280.45	37.30	2	1	14	4.47	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	Yes	Non AMES toxic	0.6568
Heptadecanoic acid	270.45	37.30	2	1	15	4.44	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	Yes	Non AMES toxic	0.6452
Butyl dodecanoate	256.42	26.30	2	0	14	4.19	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	Yes	Non AMES toxic	0.9627
Myristic caid	228.37	37.30	2	1	12	3.69	Moderately soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.9865
Palmitic acid	256.42	37.30	2	1	14	4.19	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	Yes	Non AMES toxic	0.9865

Compounds	Mw (g/mol)	TPSA (Å²)	HBA	HBD	Rotatable bound	MLog P	Water solubility	Lipinski role	GI absorption	BBB permeant	Toxicity	
											AMES Toxicity	Probability
Palmitoleic acid	254.41	37.30	2	1	13	4.09	Moderately soluble	Yes; 0 violation	High	Yes	Non AMES toxic	0.9674
Linolenic acid	278.43	37.30	2	1	13	4.38	Moderately soluble	Yes; 1 violation: MLOGP>4.15	High	Yes	Non AMES toxic	0.9132
Sacaratinib	542.03	90.44	10	1	8	2.07	Moderately soluble	Yes; 1 violation: MW>500	High	No	Non AMES toxic	0.5
Deoxycycilin	444.43	181.62	10	7	2	-2.08	Soluble	Yes; 1 violation: NHorOH>5	Low	No	Non AMES toxic	0.9132
Mitoxantrone	444.48	163.18	10	8	12	-1.69	Soluble	Yes; 1 violation: NHorOH>5	Low	No	AMES Toxic	0.9108
Isoniazid	137.14	68.01	4	3	2	-0.47	Very soluble	Yes; 0 violation	High	No	AMES toxic	0.8557

Mw: Molecular weight; TPSA: Topology Polar Surface Area; HBA: Hydrogen bond acceptor; HBD: Hydrogen bound donor; GI absorption: gastrointestinal absorption; BBB permeant: Blood-Brain-Barrier permeant

Based on the annotation of gastrointestinal absorption, most of the compounds had high ability to absorb into the intestine, yet phytol, doxycycline, and mitoxantrone had low ability to absorb. The blood-brain barrier (BBB) is a selective semipermeable membrane separating the blood circulation from the brain and extracellular fluid in the central nervous system. If the compound has the capability to permeate into BBB it indicates that the compound can easily separate in the central nervous, and it was like most of the bioactive compounds that had a high ability to permeant into BBB. In another side, the controls were difficult to permeant. AMES toxicity can identify the compounds caused by mutation in an organism. The result was showed that mitoxantrone and isoniazid can induce DNA mutation, and last studies were explained that the mutation effect of these compounds (Frei et al., 1992; Seifert, Catanzaro, Catanzaro, & Rodwell, 2015).

4.1.4 Network Analyzing

The result of the network analysis are shown in Figure 15 and 16. According to Gene Ontology (GO) biological process, the figure 15 described that oleic acid and linoleic acid

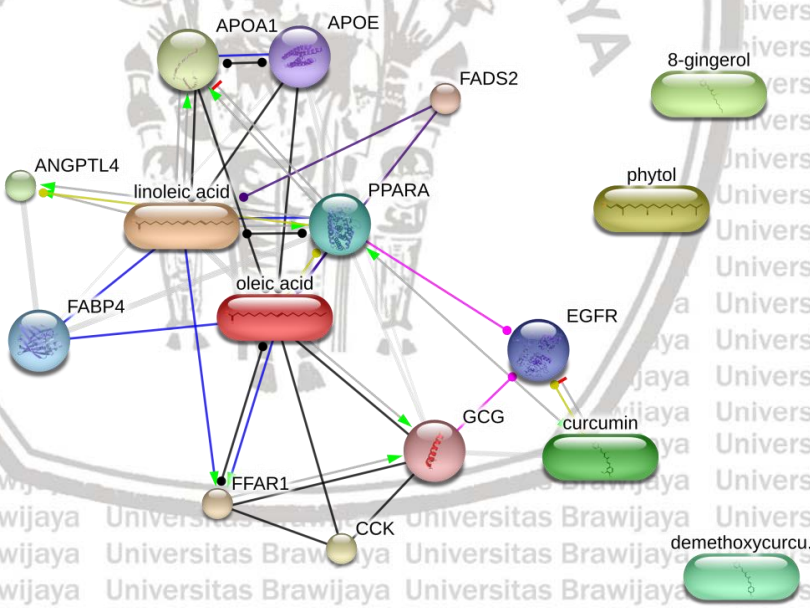
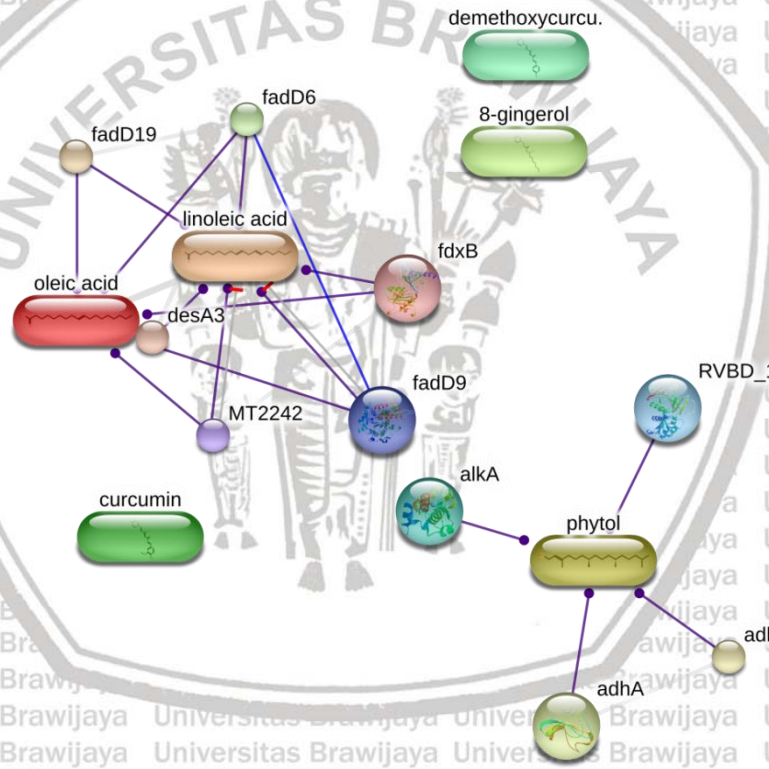


Figure 15. Network interaction of bioactive compounds and human proteins. Magenta line: posttranslational modification; yellow line: transcriptional regulation; black line: reaction; blue line: binding; purple line: catalysis; circle end: unspecified; arrowhead end: positive regulation; line end: negative regulation, big circle: protein; small circle: small molecule.

had interaction with proteins related with negative regulation of appetite (CCK, GCG, PPARA), negative regulation of response to external stimulus (APOA1, APOE, PPARA,

GCG, and CCK), and lipid homeostasis (APOA1, APOE, FABP4, and ANGPTL4). However, in negative regulation of response to external stimulus term, APOE and APOA1 have a rule as negative regulation of inflammation according to the Gene Ontology Annotations database (http://www.informatics.jax.org/). The suppression of inflammation is essential to reduce the over inflammation effect caused by T-cell immunity to mycobacterial infection. In addition, chronic inflammation has been shown that could induce defect signaling of T-cell and abnormality in immune effector functions (Zumla et al., 2015). Oleic acid also had interaction with FFAR1 that take a part in glucose homeostasis. Meanwhile, in another side, curcumin had negative interaction with EGFR that has important role for growth and development. A study shown that curcumin could inhibit EGFR in kinase domain, and it could be lead into novel anticancer therapy (Starok et al., 2015).



. **Figure 16. Network interaction of bioactive compounds and *Mycobacterium tuberculosis's* proteins.** Purple line: catalysis; blue line: binding; circle end: unspecified; line end: negative regulation, big circle: protein; small circle: small molecule.

The result of network analyzing has shown that oleic acid and linoleic acid had interaction with small molecules: fadD19, desA3, and MT2242, which essential for the long-chain fatty acid metabolic process in *Mycobacterium tuberculosis*. The cell envelope

structure of the bacteria consist of various plentiful lipid involved long chain fatty acid, and it is also important in virulence factor, inherent drug resistance and ability to replication in macrophage, and thus, lipid synthesis is a target to present drug of tuberculosis (Clifton et al., 2007). Moreover, linoleic acid also had interaction with fadD9 and fadD6 that had ligase activity function, and fdxB involved in electron transfer. Phytol has been shown had interaction with alkA which it takes a part in transcription regulation, alcohol dehydrogenase such as adhA and adhC, and RVbd 1409 known as RibD which is an important protein to synthesise riboflavin.

4.2 Discussion

Based on the result above, the bioactive compounds from *Curcuma xanthorrhiza* Roxb, *Zingiber officinale* var rubrum, *Tamarindus indica* L., and *Citrus aurantifolia* had higher docking score to block the activation of human proteins like MMP-1, which take part to degrade collagen constructing granuloma, and Src, that can inhibit autophagy process, and also block *Mycobacterium tuberculosis* proteins like PknB, which can induce mycobacteria grow and KatG, that reduce reactive oxygen species in mycobacteria. These medical plants not only used by Indonesia local people for tuberculosis therapy but also some local societies from other countries such as Uganda and Brazil (Leitão et al., 2013; Tabuti et al., 2010). Besides, these plants have reported that the compound constituted could inhibit mycobacteria activity (Sandoval-Montemayor et al., 2012; Siddiqui et al.,2012; Ngadino et al, 2018). Oleic acid and linoleic acid bioactive compounds from *Tamarindus indica* L. and *Citrus aurantifolia* had been reported that could be a selective inhibitor of enoyl-acyl carrier protein reductase (FabI) which takes apart in fatty acid synthesis in bacteria (Zheng et al., 2005). Curcumin, a major polyphenolic pigment contained in Curcuma genus, has been reported could induce the activation of JNK pathway to activate apoptosis in macrophage (Li et al., 2014). 8-gingerol from Zingiberaceae family could inhibit mycobacteria survival through it lipophilicity characteristic (Hiserodt et al., 1998). Phytol has been also shown that could suppress the infection *Mycobacteria tuberculosis* (Rajab et al., 1998). Moreover, All of this compounds were shown to attach in the catalytic domain of MMP-1, these indicated disturbed catalytic activity of MMP-1 to break collagen which is constituting granuloma. Curcumin, linoleic acid, oleic acid, and phytol have been evaluated that could also suppress the expression of MMP-1 gene (Bastiaansen-Jenniskens et al., 2013; Kim et al., 2005; Mun et al., 2009). In Src inhibition, all of the compounds had a various effect toward the Src-PI3K

complex. Curcumin has been reported that could suppress the activation signaling Src/PI3K pathway for inducing apoptosis (Shakibaei et al., 2013). In addition, based on the network analyzing result above, linoleic acid and oleic acid had interaction with proteins both human and *Mycobacterium tuberculosis.* It might be concluded that this study described some compounds such as curcumin, demethoxycurcumin, phytol, oleic acid, and linoleic acid could act as multitarget compounds, inhibiting target proteins both human and *Mycobacterium tuberculosis.*

Polypharmacology or multi-target compound refers to one compound can target many proteins. Polypharmacology applies multiple drugs acting in dissimilar targets, that are involved in the various physiological response. It has emerged as a new drug discovery paradigm. Recently, the concept of one compound or drug one target receptor evidently more effective as expected, and less various side effect has arisen (Medina-Franco et al., 2013; Reddy & Zhang, 2013). Three types of polypharmacology that can be designed for infectious therapy: (1) series inhibitor, which can inhibit proteins in the same metabolic pathway (2) parallel inhibitor, which can inhibit proteins unrelated mechanism (3) network inhibitor, which combination of series inhibitor and parallel inhibitor (Oldfield & Feng, 2014). Currently, scientists design SQ109 as new multitarget inhibitor for tuberculosis. It could transporter proteins, MmpL3, menaquinone biosynthesis and ATP synthesis (Li et al., 2014). Nevertheless, it will not effective when the compound only target virulence factor, otherwise, development of mycobacteria dissemination is also caused by imbalance immune system or other human mechanisms (Orme et al., 2015; Vyas & Goswami, 2017).

However, tuberculosis is an infectious disease that related to nutrition. It has been presented that malnutrition related to tuberculosis and associated with worse outcomes. Malnutrition also effects in immune development, the nutrition status of the tuberculosis patients and healthy persons significantly different. Several studies reported that tuberculosis patients had a low level of serum albumin (< 35g/L), these case might reflect the presence of inflammation rather than protein deficient state (USAID, 2008). Micronutrient deficiency is associated with immunodeficiency and lead susceptible to *Mycobacterium tuberculosis* infection. TB patients were reported had a depletion of some nutrients like vitamin A, C, iron, zinc, copper, selenium, cholesterol, and polyunsaturated fatty acid. Vitamin A is important for the immune system, it is needed for normal activity of T cell, B cell, macrophage, and antibody production. Deficiency of vitamin A increases bacteria infection to epithelial cells of respiratory (Gupta et al., 2009). Zinc is one of micronutrient which is necessary for normal

function of T cell, the activity of cytokines and macrophage migration (Cegielski & McMurray, 2004).

In addition, *Curcuma xanthorrhiza* Roxb, *Zingiber officinale* var rubrum, *Tamarindus indica* L., and *Citrus aurantifolia* not only contain active compounds that can use inhibit mycobacteria deployment but also contain nutrients that needed by tuberculosis patients. According to nutrition fact database (https://www.nutritionvalue.org/) these plants contains various macronutrients like amino acids, fatty acids, sugars, fibers, vitamin A, C, B, E, K and minerals such as zinc, calcium, copper, magnesium, manganese, phosphorus, potassium, and sodium. Thus, consuming *Curcuma xanthorrhiza* Roxb, *Zingiber officinale* var rubrum, *Tamarindus indica* L., and *Citrus aurantifolia* not only inhibit mycobacteria but also can improve immunity and complete nutrients.

In the ligands-protein docking result, it has shown that the compounds had a different trait of the hydrogen bond, external binding, and hydrophobic. A hydrogen bond is a weak interaction constituted by an attraction of hydrogen atom with the more electronegative atoms like oxygen, fluorine, and hydrogen. A hydrogen bond is one of the important bindings in biomolecular. Hydrogen bonds are essential to stabilize the structure of the proteins and nucleic acid and can take a role as biomolecular recognition. A study has described that weak (3.2-4.0 Å) and strong (2.2-2.5 Å) hydrogen bonds are found ubiquitously in ligand-protein recognition (Panigrahi, 2008). Similarly, hydrophobic, an effect of aggregation of non-polar substance in aqueous solution, was also influence the drug recognition to the target proteins. According to a previous study, hydrogen bonds and hydrophobic interaction can affect the stability of the ligand in the receptor and change the binding affinity and drug efficacy (Varma et al., 2010).

CHAPTER V
CONCLUSIONS AND SUGGESTIONS

5.1 Conclusions

The novel formulation of jamu from *Curcuma xanthorrhiza* Roxb, *Zingiber officinale* var rubrum, *Tamarindus indica* L., and *Citrus aurantifolia* for tuberculosis therapy contained six compounds, curcumin, demethoxycurcumin, 8-gingerol, phytol, oleic acid, and linoleic acid could act as polypharmacology, binding all of the target proteins both in human and *Mycobacterium tuberculosis* to suppress the mycobacteria grow and deployment. However, based on the network analyzing only linoleic and oleic acid had interaction with proteins of human and *Mycobacterium tuberculosis.* According to docking complex, phytol and oleic acid could change the position of Src while a bond with PI3K, and in addition, phytol also could change FhaA position while docked with PknB. Moreover, all of the bioactive compounds contained in medical plants were allowed by Lipinski'role and did not induce AMES toxicity, thus could not make DNA mutation and resistance. Based on the results, this novel formulation could be a candidate for tuberculosis medication.

5.2 Suggestions

This study used in silico docking method as the major method, therefore for it should be conducted laboratory experiment to prove the effect of medical plants toward tuberculosis and need to do clinical trial experiments when it utilizes in tuberculosis patients. For more analyzing the position binding change, this study is needed to be continued with molecular dynamic docking that can give a lot of information alteration or protein characteristic when docked with another protein or ligand. Moreover, because of the massive bioactive compounds that are contained in the medical plants, this study should be continued with exploring other bioactive compounds, thus it can give more explanation about the effect of these medicinal plants. Because the shortage of the in silico method, this study focuses on reducing drug mechanism by suppressing selected proteins, while for solving tuberculosis complex solutions are needed. Therefore, further studies are expected to more investigate the aspect of the immune system and nutrition for overcoming tuberculosis case. In addition, The plants selected in the study can be used as novel formula herbal therapy for tuberculosis.

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Appendix 1 Docking result of bioactive compounds-protein targets

Docking of bioactive compounds-KatG *Mycobacterium tuberculosis*

No	Plants	Compound name	Score	Area	ACE	Transformation
1	*Curcuma xanthorrhiza* Roxb	curcumin	5414	701.60	-289.19	0.54 -0.09 -0.83 60.57 50.86 28.59
2	*Curcuma xanthorrhiza* Roxb	Bisdemethoxycurcumin	5266	597.70	-155.79	-0.29 -0.15 -1.86 66.60 21.04 51.94
3	*Curcuma xanthorrhiza* Roxb	Demethoxycurcumin	5692	640.70	-180.66	0.33 -0.07 -1.75 66.02 20.81 51.86
4	*Curcuma xanthorrhiza* Roxb	Xanthorrhizol	4644	488.70	-115.61	0.08 0.02 -1.11 65.65 28.71 21.57
5	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Ar-Curcumene	4648	499.70	-121.66	0.59 -0.17 -0.53 45.64 5.76 53.11
6	*Curcuma xanthorrhiza* Roxb	β-Curcumene	4584	503.60	-119.86	-2.90 -0.06 -1.03 66.19 29.07 21.25
7	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*;*	Camphor	3206	340.80	-88.77	2.39 0.38 1.83 57.01 36.90 5.34
8	*Curcuma xanthorrhiza* Roxb	Ar-Turmerone	4562	503.70	-136.74	-2.69 0.36 2.88 45.76 4.25 53.05
9	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Zingiberene ; α-Zingiberene	4740	510.00	-101.57	-1.62 0.60 2.92 47.21 4.86 52.58
10	*Curcuma xanthorrhiza* Roxb	Zerumbone	4434	479.70	-104.70	-2.91 -1.23 -1.08 47.63 4.73 52.63
11	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Geranyl acetate	4362	489.90	-124.89	3.04 0.01 3.08 45.24 4.95 53.69
12	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	α-Pinene	3362	384.20	-45.74	1.63 -0.12 -1.23 67.40 27.39 52.81
13	*Curcuma xanthorrhiza* Roxb	α-thujene	3552	372.10	-42.24	-1.80 -0.49 -1.39 67.66 27.25 52.96
14	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Camphene	3232	358.00	-110.64	0.82 -0.86 -2.25 42.17 11.73 70.59
15	*Curcuma xanthorrhiza Roxb; Zingiber officinale* var rubrum*; Citrus*	β-Pinene	3250	370.00	-49.60	-0.08 -0.07 2.20 67.44 27.38 52.75

No	Plants	Compound name	Score	Area	ACE	Transformation
	aurantifolia					
16	*Curcuma xanthorrhiza* Roxb	Cis-Pinane	3338	349.60	-56.08	0.45 -0.26 -0.46 43.03 8.75 22.07
17	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia ;*	Myrcene ; β-Myrcene	3612	403.30	-54.49	-2.08 0.33 1.74 66.56 27.31 52.83
18	*Curcuma xanthorrhiza* Roxb	α-Terpinene	3656	401.80	-56.31	-2.52 -0.32 -1.31 67.34 27.23 52.71
19	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*;*	1,8-Cineole	3420	387.60	-38.97	0.65 0.03 2.12 67.23 27.14 52.64
20	*Curcuma xanthorrhiza* Roxb *Citrus aurantifolia*	(Z)-β-Ocimene	3666	440.10	-146.60	3.03 0.65 1.23 62.81 47.92 27.38
21	*Curcuma xanthorrhiza* Roxb *Citrus aurantifolia*	α-Terpineol	3592	396.30	-50.88	-2.74 -0.48 -1.42 67.58 27.21 52.58
22	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Tamarindus indica* L. *; Citrus aurantifolia*	Terpinen-4-ol	3592	396.30	-50.88	-2.74 -0.48 -1.42 67.58 27.21 52.58
23	*Curcuma xanthorrhiza* Roxb	Ethyl-4E-octenoate	3780	462.50	-79.25	2.62 -0.11 -1.64 67.17 23.67 52.08
24	*Curcuma xanthorrhiza* Roxb	Dihydro citronellol acetate	4374	483.40	-89.23	2.85 -0.12 2.95 46.62 5.33 53.22
25	*Curcuma xanthorrhiza* Roxb	α-Cubebene	4420	473.00	-166.40	3.10 -0.02 3.11 45.17 5.10 53.56
26	*Curcuma xanthorrhiza* Roxb	(Z)-β-Damascenone	4254	446.60	-139.05	1.41 1.19 -0.10 41.79 11.28 70.69
27	*Curcuma xanthorrhiza* Roxb	Methyl perillate	3866	447.60	-75.38	-0.12 0.17 1.66 68.14 26.01 52.23
28	*Curcuma xanthorrhiza* Roxb	(Z)-Isoeugenol	3876	449.70	-150.66	2.40 0.32 1.61 63.84 46.88 27.42
29	*Curcuma xanthorrhiza* Roxb	α-Cis-bergamotene	4690	491.80	-132.77	-0.18 0.12 1.73 65.81 29.44 21.45
30	*Curcuma xanthorrhiza* Roxb	Methyl undecanoate	4306	499.30	-103.33	2.02 -0.06 -1.59 67.38 23.08 52.22
31	*Curcuma xanthorrhiza* Roxb	β-Humulene	4464	483.10	-104.22	0.83 0.25 -1.20 66.15 28.68 22.05
32	*Curcuma xanthorrhiza* Roxb	(Z)-β-Farnesene	4948	545.40	-129.92	0.29 0.03 -1.02 66.04 29.49 21.42
33	*Curcuma xanthorrhiza* Roxb	(E)-caryophyllene	4312	475.90	-91.69	2.11 0.95 2.69 47.55 4.64 52.10
34	*Curcuma xanthorrhiza* Roxb	γ-elemene	4554	472.70	-79.82	-1.68 0.60 -0.88 66.26 28.01 22.19
35	*Curcuma xanthorrhiza* Roxb	(E)-β-farnesene	4710	530.10	-134.07	2.55 -0.39 2.08 66.57 28.96 21.72

No	Plants	Compound name	Score	Area	ACE	Transformation
36	*Curcuma xanthorrhiza* Roxb	γ-Curcumene	4514	499.70	-149.91	-2.69 0.54 2.69 45.17 4.75 52.72
37	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	β-Bisabolene	4748	502.00	-130.77	-0.68 0.11 -1.25 66.08 29.94 22.03
38	*Curcuma xanthorrhiza* Roxb	(Z)-γ-Bisabolene	4660	513.30	-103.73	1.47 0.52 2.92 47.20 5.09 52.53
39	*Curcuma xanthorrhiza* Roxb	β-sesquiphellandrene	4618	530.80	-129.63	1.04 -0.42 0.06 46.45 4.77 52.56
40	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Caryophyllene oxide	4278	467.80	-165.94	-0.63 -1.05 -2.28 41.48 12.27 70.54
41	*Curcuma xanthorrhiza* Roxb	Citronellyl pentanoate	5320	560.60	-134.91	3.08 0.17 2.59 46.13 5.26 53.69
42	*Curcuma xanthorrhiza* Roxb	Cis-cadin-4-en-7-ol	4338	476.40	-128.35	2.95 0.09 2.43 65.75 30.27 21.68
43	*Curcuma xanthorrhiza* Roxb	Cubenol	4468	468.40	-146.50	2.96 0.34 1.53 65.48 30.40 21.42
44	*Curcuma xanthorrhiza* Roxb	α-Eudesmol	4362	452.30	-142.54	-0.45 -0.06 2.53 44.91 5.83 53.73
45	*Curcuma xanthorrhiza* Roxb	(E)-Amyl cinnamic alcohol	4366	524.20	-174.22	2.60 0.62 1.92 62.18 48.74 27.89
46	*Curcuma xanthorrhiza* Roxb	(E)-citronellyl tiglate	4998	552.70	-129.97	-1.05 0.80 -3.02 47.28 4.72 52.66
47	*Curcuma xanthorrhiza* Roxb	β-Bisabolol	4752	507.40	-104.98	1.02 -0.25 1.95 66.32 28.84 22.07
48	*Curcuma xanthorrhiza* Roxb	Ar-Curcumen-15-al	4642	496.70	-126.72	-2.76 0.12 -0.97 65.69 29.61 21.41
49	*Curcuma xanthorrhiza* Roxb	Chamazulene	4090	480.50	-204.49	-0.85 0.69 2.28 28.57 8.90 50.48
50	*Curcuma xanthorrhiza* Roxb	(E, Z)-Farnesol	4872	514.20	-107.44	0.14 0.75 -1.01 66.18 28.42 22.06
51	*Curcuma xanthorrhiza* Roxb	Butyl dodecanoate	4740	633.20	-215.85	-2.98 -0.71 -2.19 65.30 52.54 31.10
52	*Curcuma xanthorrhiza* Roxb; *Zingiber officinale* var rubrum*; Citrus aurantifolia*	Linalool	3772	424.40	-129.63	3.00 -0.22 2.70 27.08 11.06 51.52
53	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	α-Phellandrene	3670	394.50	-56.24	2.43 0.18 1.83 67.82 27.48 52.74
54	*Curcuma xanthorrhiza* Roxb	(E)-Ethyl cinnamate	3934	461.60	-169.01	-3.12 0.46 1.32 63.34 48.43 27.54
55	*Curcuma xanthorrhiza* Roxb	Thujopsan-2-α-ol	4248	472.10	-132.25	-2.20 1.45 -0.98 56.92 37.37 5.57

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56	*Zingiber officinale* var rubrum	2-Heptanol	3376	350.30	-96.74	-1.62 -0.91 -1.14 29.73 8.41 50.03
57	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Sabinene	3516	373.90	-60.22	-2.01 0.16 -0.54 43.46 8.92 22.45
58	*Zingiber officinale* var rubrum	δ-3-Carene	3408	363.90	-43.26	-0.70 -0.01 -0.21 43.29 9.31 22.26
59	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	p-Cymene	3594	393.40	-47.75	-2.93 0.18 1.78 66.97 27.10 52.42
60	*Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Limonene	3548	405.60	-143.76	0.40 -0.68 -1.86 62.77 47.89 26.88
61	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	β-Phellandrene	3598	376.40	-53.12	-2.77 -0.04 -0.34 43.19 9.13 22.39
62	*Zingiber officinale* var rubrum	2-Heptyl acetate	3896	431.30	-44.65	0.54 -0.32 -1.38 67.48 26.65 52.87
63	*Zingiber officinale* var rubrum	Trans-β-ocimene	3666	440.10	-146.60	3.03 0.65 1.23 62.81 47.92 27.38
64	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	γ-Terpinene	3674	385.00	-54.48	2.54 -0.28 -1.47 67.41 27.11 52.52
65	*Zingiber officinale* var rubrum	Terpinolene ; alpha terpinolene	3520	407.00	-130.03	-0.78 0.87 1.49 63.34 46.64 26.84
66	*Zingiber officinale* var rubrum	2-Nonanone	3568	424.10	-134.57	-0.41 0.59 1.27 63.12 48.79 27.59
67	*Zingiber officinale* var rubrum	Trans-sabinene hydrate	3622	394.90	-46.33	-2.38 0.35 1.93 67.59 27.00 52.61
68	*Zingiber officinale* var rubrum	Camphene hydrate	3330	353.70	-39.90	-2.81 -0.18 2.96 43.47 9.24 22.38
69	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Citronellal	3902	467.00	-136.99	2.64 0.59 1.81 62.61 48.21 27.85
70	*Zingiber officinale* var rubrum*;*	Isoborneol ; Borneol	3184	370.80	-115.72	-2.48 -0.37 -3.11 41.65 11.92 70.47
71	*Zingiber officinale* var rubrum	Myrtenal	3348	366.30	-46.47	0.78 -0.02 -0.59 67.13 26.68 52.24
72	*Zingiber officinale* var rubrum	Linalyl formate	3934	417.40	-138.14	-3.01 0.13 1.31 64.44 30.98 21.25
73	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	β-Citronellol	3750	454.30	-132.90	-0.81 0.65 1.56 62.93 47.21 26.86
74	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Geraniol	3690	382.80	-114.24	-0.55 0.02 2.94 44.63 6.44 54.13

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75	*Zingiber officinale* var rubrum	Trans-2-decenal	3792	435.50	-72.70	2.92 0.20 1.64 67.27 24.38 51.93
76	*Zingiber officinale* var rubrum *Citrus aurantifolia*	Geranial	3740	382.30	-115.25	2.15 0.87 0.50 41.11 12.01 70.50
77	*Zingiber officinale* var rubrum	Bornyl acetate	3928	431.50	-53.33	-0.64 0.96 2.85 47.65 4.86 52.22
78	*Zingiber officinale* var rubrum	2-Undecanone	3934	470.20	-167.62	-2.68 0.61 1.11 64.55 51.02 29.63
79	*Zingiber officinale* var rubrum	Myrtenyl acetate	4006	488.50	-171.14	0.50 -0.41 -1.45 63.12 47.40 27.29
80	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Neryl acetate	4376	510.60	-159.13	1.10 -0.39 -0.82 28.36 10.01 50.93
81	*Zingiber officinale* var rubrum	α-Copaene	4196	440.20	-155.01	-2.78 -0.03 -0.82 44.45 5.89 53.83
82	*Zingiber officinale* var rubrum	β-Elemene	4528	485.70	-75.15	-2.22 -1.16 -0.49 47.91 4.70 51.87
83	*Zingiber officinale* var rubrum	Isocaryophyllene	4324	467.00	-188.06	1.11 0.81 0.20 41.37 12.06 70.50
84	*Zingiber officinale* var rubrum	α-Humulene	4372	467.20	-93.58	-0.41 -0.66 2.14 66.50 28.15 22.49
85	*Zingiber officinale* var rubrum	Allo-aromadendrene	4168	437.20	-124.39	3.04 0.18 1.53 66.05 28.88 21.44
86	*Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Germacrene D	4344	476.50	-176.34	-1.81 0.38 0.14 41.91 11.46 70.82
87	*Zingiber officinale* var rubrum	α-Selinene	4264	471.20	-103.42	2.41 -0.51 2.02 65.90 28.57 21.86
88	*Zingiber officinale* var rubrum	α-Muurolene	4328	478.70	-138.08	0.76 1.15 0.26 42.18 12.02 71.60
89	*Zingiber officinale* var rubrum	Trans,trans-α-farnesene	4730	518.50	-133.97	0.56 -0.25 -0.52 45.82 5.71 53.21
90	*Zingiber officinale* var rubrum	δ-Cadinene	4328	468.60	-120.80	0.65 -0.17 -2.26 66.58 28.46 22.08
91	*Zingiber officinale* var rubrum	γ-Eudesmol	4470	460.70	-132.43	2.93 0.23 1.79 64.94 30.43 21.73
92	*Zingiber officinale* var rubrum	β-Eudesmol	4456	474.80	-117.42	0.75 -0.10 -0.35 45.80 5.45 53.37
93	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	α-Bisabolol	4694	505.30	-164.72	-0.10 0.18 1.61 65.79 29.96 21.27
94	*Zingiber officinale* var rubrum	Cis,cis-farnesol	4736	529.70	-118.71	2.37 -0.33 2.31 66.23 29.09 22.10
95	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Trans,trans-farnesol ; Farnesol	4770	499.30	-128.76	-2.94 -0.28 -1.75 65.95 29.44 21.26
96	*Zingiber officinale* var rubrum	Trans,trans-farnesal	4770	499.30	-128.76	-2.94 -0.28 -1.75 65.95 29.44 21.26

No	Plants	Compound name	Score	Area	ACE	Transformation
97	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Phytol	5370	640.20	-108.87	-2.76 0.31 2.85 75.37 20.64 62.22
98	*Zingiber officinale* var rubrum	6-gingerol	5010	604.90	-135.02	-0.12 -0.16 -1.57 67.27 24.77 52.14
99	*Zingiber officinale* var rubrum	8-gingerol	5430	628.00	-151.11	-1.66 -0.06 -1.58 67.07 22.77 52.42
100	*Zingiber officinale* var rubrum	6-shogaol	4906	553.00	-149.53	-3.04 0.09 2.62 45.25 4.55 53.35
101	*Zingiber officinale* var rubrum	8-shogaol	5422	645.30	-171.85	-2.99 0.13 2.01 66.96 29.45 21.26
102	*Tamarindus indica* L.	3-methyl-2-butanone	2620	275.30	-94.30	-1.56 0.01 1.92 54.13 4.01 36.75
103	*Tamarindus indica* L.	1 –penten-3-one	2582	293.50	-9.34	-2.43 0.12 -0.37 43.21 9.45 22.27
104	*Tamarindus indica* L.	(E)-2-butenal	2262	235.30	-83.03	-0.95 0.45 2.51 69.68 19.10 35.60
105	*Tamarindus indica* L.	hexanale	3038	330.00	-78.82	-0.13 0.91 1.85 30.10 8.17 49.95
106	*Tamarindus indica* L.	(E)-2-pentenal	2686	285.20	-107.15	2.74 -0.43 2.20 53.16 4.83 37.29
107	*Tamarindus indica* L.	3-methylbutanol	2596	286.40	-93.13	-0.71 0.13 -0.72 54.02 4.93 37.34
108	*Tamarindus indica* L.	hydroxyacetone	2096	212.80	-34.79	-2.75 -0.94 0.94 35.01 18.63 28.62
109	*Tamarindus indica* L.	5-methyl-2(3H)-furanone	2484	257.40	-104.20	2.27 -0.92 -3.03 70.41 19.23 36.35
110	*Tamarindus indica* L. *; Citrus aurantifolia*	trans-linalool oxide (furanoid)	3856	421.20	-41.82	2.54 0.41 1.76 67.22 27.33 52.50
111	*Tamarindus indica* L.	acetic acid	1704	173.30	-48.20	-2.02 0.17 -0.41 45.30 -1.87 38.98
112	*Tamarindus indica* L.	furfural	2494	270.30	-98.20	1.70 0.66 -0.99 53.81 4.60 37.21
113	*Tamarindus indica* L.	2-acetylfuran	2774	324.80	-95.00	2.05 0.31 1.65 62.95 46.95 27.24
114	*Tamarindus indica* L.	pyrrole	2122	213.60	-111.44	-1.84 -0.22 0.03 69.56 19.41 34.84
115	*Tamarindus indica* L.	octanol	3416	409.40	-115.09	-0.24 -0.64 -1.64 62.83 48.13 27.32
116	*Tamarindus indica* L.	5-methylfurfural	2798	303.40	-19.04	2.36 0.09 2.57 43.26 8.78 21.94
117	*Tamarindus indica* L.	isomaltol	2850	320.30	-69.37	-1.86 0.96 -0.59 62.91 46.08 26.55
118	*Tamarindus indica* L.	γ-butyrolactone	2196	235.40	-39.86	-1.85 0.68 -0.96 30.04 9.91 52.70
119	*Tamarindus indica* L.	phenylacetaldehyde	3188	355.00	-32.72	0.66 -0.22 -0.93 66.73 27.59 52.75
120	*Tamarindus indica* L.	2-methylbutyric acid	2674	282.10	-105.46	1.23 0.06 2.65 54.42 4.47 37.36

No	Plants	Compound name	Score	Area	ACE	Transformation
121	*Tamarindus indica* L.	2,3-dimethylmaleic anhydride	2830	295.00	-122.79	1.60 0.66 -0.83 54.15 4.50 36.87
122	*Tamarindus indica* L.	methyl salicylate	3406	355.30	-19.96	0.57 -0.06 -0.56 42.88 8.99 22.47
123	*Tamarindus indica* L.	β-damascenone	4034	419.20	-133.02	3.04 0.36 2.04 65.23 30.98 21.43
124	*Tamarindus indica* L.	hexanoic acid	3056	325.70	-80.70	0.24 -0.94 -1.46 29.87 8.53 50.50
125	*Tamarindus indica* L.	geranylacetone	4538	488.50	-102.29	1.76 0.28 2.83 46.07 4.91 52.25
126	*Tamarindus indica* L.	guaiacol	2950	326.10	-97.91	-0.88 0.97 0.89 62.94 47.02 27.00
127	*Tamarindus indica* L.	benzyl alcohol	2818	304.60	-90.64	0.41 -0.99 -1.76 29.62 9.73 51.61
128	*Tamarindus indica* L.	2-phenylethanol	3132	331.00	-33.43	2.84 0.11 2.61 43.00 8.99 22.12
129	*Tamarindus indica* L.	maltol	2724	311.70	-13.22	2.36 -0.20 2.22 68.03 26.87 52.69
130	*Tamarindus indica* L.	2-(hydroxyacetyl)furan	2860	312.00	-10.53	0.91 0.06 -0.48 43.14 8.92 21.83
131	*Tamarindus indica* L.	pyrrole-2-carboxaldehyde	2404	266.50	-98.76	-1.97 -0.28 2.42 53.59 5.09 36.96
132	*Tamarindus indica* L.	octanoic acid	3502	417.40	-120.57	-0.69 0.67 1.46 63.18 47.33 27.01
133	*Tamarindus indica* L.	eugenol	3752	406.40	-62.02	-2.77 0.18 -0.66 67.44 26.41 52.48
134	*Tamarindus indica* L.	nonanoic acid	3696	426.40	-118.32	-1.51 0.67 1.93 61.68 48.91 28.14
135	*Tamarindus indica* L.	p-vinylguaiacol	3556	375.00	-35.10	-2.65 0.08 -0.66 43.26 9.71 22.20
136	*Tamarindus indica* L.	decanoic acid	3836	429.50	-112.55	-2.30 -0.71 -1.11 61.59 49.72 28.70
137	*Tamarindus indica* L.	dihydroactinidiolide	3716	386.70	-154.45	2.03 -0.31 3.03 41.27 11.74 69.85
138	*Tamarindus indica* L.	p-vinylphenol	3108	334.10	-30.67	2.45 0.19 2.68 43.43 8.94 22.21
139	*Tamarindus indica* L.	benzoic acid	2846	315.40	-19.26	0.05 -0.12 -0.71 43.53 8.79 22.37
140	*Tamarindus indica* L.	lauric acid	4356	532.50	-45.41	-1.65 0.77 -1.82 49.14 4.25 49.54
141	*Tamarindus indica* L.	vanillin	3484	370.00	-29.29	-2.83 -0.22 -1.36 43.01 9.60 22.52
142	*Tamarindus indica* L.	myristic acid	4704	548.50	-132.09	-1.95 -0.11 -1.97 66.47 20.97 52.27
143	*Tamarindus indica* L.	pentadecanoic acid	4712	605.70	-214.41	-0.38 0.69 1.05 66.04 52.91 32.01
144	*Tamarindus indica* L. *; Citrus*	palmitic acid	5268	636.20	-193.00	-0.27 0.65 1.12 65.13 52.29 30.77

No	Plants	Compound name	Score	Area	ACE	Transformation
	aurantifolia					
145	*Tamarindus indica* L.	palmitoleic acid	5394	603.20	-94.46	-2.57 -0.59 -1.10 62.08 34.04 36.59
146	*Tamarindus indica* L.	heptadecanoic acid	5384	657.20	-199.38	2.99 -0.63 -2.02 65.61 53.10 31.20
147	*Tamarindus indica* L. *; Citrus aurantifolia*	oleic acid	5444	619.00	18.90	-1.87 -0.72 -2.11 59.23 16.14 37.58
148	*Tamarindus indica* L. *; Citrus aurantifolia*	linoleic acid	5660	629.60	19.20	-1.51 0.79 0.98 59.04 16.39 37.95
149	*Tamarindus indica* L.	linolenic acid	5198	606.20	-103.89	-0.61 -0.09 -0.64 47.45 3.55 10.93
150	*Tamarindus indica* L.	(+)-Catechin	4494	493.10	-124.78	2.36 0.16 -0.98 66.45 30.50 22.48
151	*Tamarindus indica* L.	(-)-Epicatechin	4318	478.40	-86.37	2.68 0.32 -1.09 66.57 29.32 22.53
152	*Tamarindus indica* L.	Taxifolin	4430	477.40	-111.96	1.99 -0.21 -0.59 45.57 5.37 52.88
153	*Tamarindus indica* L.	Apigenin	4476	475.20	-95.05	1.58 -0.12 2.02 66.57 29.54 22.29
154	*Tamarindus indica* L.	Eriodictyol	4350	528.80	-208.16	1.34 -0.41 -1.29 62.57 48.11 27.77
155	*Tamarindus indica* L.	Luteolin	4502	523.40	-225.00	-2.87 -0.71 -1.37 62.33 48.88 28.32
156	*Tamarindus indica* L.	Naringenin	4434	487.40	-100.77	1.77 -0.32 -0.44 45.98 5.41 52.61
157	*Citrus aurantifolia*	cis-Verbenol	3266	380.80	-120.64	0.45 0.84 -0.59 41.64 11.71 70.67
158	*Citrus aurantifolia*	Nerol	3772	391.30	-120.32	2.41 -0.78 -2.61 41.29 11.92 69.79
159	*Citrus aurantifolia*	Neral	3802	447.80	-130.10	-1.90 -0.19 -1.13 62.61 47.14 27.05
160	*Citrus aurantifolia*	Germacrene B	4410	472.40	-133.70	0.64 0.02 -0.23 45.80 5.44 53.33
161	*Citrus aurantifolia*	Octanal	3490	403.30	-98.61	1.25 -0.81 -1.25 62.08 47.63 27.06
162	*Citrus aurantifolia*	Nonanal	3632	415.10	-106.85	-1.67 0.77 1.91 61.85 48.10 27.49
163	*Citrus aurantifolia*	(E)-Limonene oxide	3614	376.40	-48.38	-3.07 0.04 2.84 43.50 9.28 22.26
164	*Citrus aurantifolia*	δ-Elemene	4686	494.90	-137.14	0.05 -0.17 -1.43 65.81 29.88 21.36
165	*Citrus aurantifolia*	Decanal	3794	452.10	-135.78	-2.79 -0.81 -1.52 62.74 48.34 27.98
166	*Citrus aurantifolia*	l-Carvone	3584	399.40	-45.79	-0.85 0.09 2.01 66.87 27.39 52.74
167	*Citrus aurantifolia*	Cumin aldehyde	3632	397.30	-50.08	2.57 0.33 1.71 67.56 26.97 52.45
168	*Citrus aurantifolia*	Perillaldehyde	3566	376.50	-49.81	0.98 0.28 1.64 67.37 27.05 52.61

No	Plants	Compound name	Score	Area	ACE	Transformation
169	*Citrus aurantifolia*	Tridecanal	4392	536.70	-79.04	3.03 0.61 -1.82 49.42 2.81 49.94
170	*Citrus aurantifolia*	Dodecyl acetate	4578	514.60	-52.02	2.20 0.61 -0.57 59.74 10.70 36.33
171	*Citrus aurantifolia*	Tetradecanal	4518	534.50	-184.88	-1.77 0.74 1.24 64.20 50.37 29.35
172	*Citrus aurantifolia*	Perillyl alcohol	3514	422.80	-152.99	2.83 0.52 1.55 63.14 47.90 27.52
173	*Citrus aurantifolia*	Pentadecanal	4744	581.30	-202.62	-2.29 -0.65 -2.05 64.73 51.61 30.72
174	*Citrus aurantifolia*	Cedryl acetate	4990	536.90	-145.03	-0.43 0.15 2.61 45.49 5.63 53.40
175	*Citrus aurantifolia*	Cinnamyl alcohol	3354	388.60	-133.23	2.77 0.80 1.22 62.88 47.34 27.28
176	*Citrus aurantifolia*	(E)-Nerolidol	4816	517.80	-162.87	-3.10 0.36 1.62 65.51 30.52 21.59
177	Control	Isoniazid	3088	352.30	-120.54	-2.63 0.72 -0.36 63.75 46.08 27.21

Docking of bioactive compounds-PknB *Mycobacterium tuberculosis*

No	Plants	Compound	Score	Area	ACE	Transformation
1	*Curcuma xanthorrhiza* Roxb	curcumin	5572	704.00	-98.03	1.73054 -0.11526 0.35131 74.80515 -60.85315 -31.74717
2	*Curcuma xanthorrhiza* Roxb	Bisdemethoxycurcumin	4860	541.00	-153.18	-3.00830 0.46001 1.43673 71.78940 -80.71504 -29.08508
3	*Curcuma xanthorrhiza* Roxb	Demethoxycurcumin	5108	556.40	-112.81	-1.26243 -0.92430 0.89033 57.70208 -4.07941 -59.27636
4	*Curcuma xanthorrhiza* Roxb	Xanthorrhizol	4168	469.80	-172.67	2.00918 -1.34320 0.85019 56.06771 -5.50860 -56.27259
5	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Ar-Curcumene	4506	488.90	-169.3	-3.04855 -0.23322 -1.11842 73.63405 -78.07151 -27.42886
6	*Curcuma xanthorrhiza* Roxb	β-Curcumene	4352	507.70	-192.44	-0.90050 0.71538 0.29395 75.95713 -60.81458 -29.93626
7	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*;*	Camphor	3510	370.30	-58.24	-0.90050 0.71538 0.29395 75.95713 -60.81458 -29.93626
8	*Curcuma xanthorrhiza* Roxb	Ar-Turmerone	4402	495.30	-161.88	0.54682 0.32904 1.80115 81.54003 -45.63297 -25.54608
9	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Zingiberene ; α-Zingiberene	4366	479.10	-81.38	2.05730 -0.71047 -2.57545 65.29815 -21.45944 -35.65498
10	*Curcuma xanthorrhiza* Roxb	Zerumbone	4136	451.10	-191.19	-1.71613 0.32695 1.26505 61.82315 1.71394 -25.96040
11	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Geranyl acetate	4232	447.4	-46.37	0.63941 0.98369 1.20553 65.74840 -21.13020 -35.94845
12	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus*	α-Pinene	3486	380	-68.15	1.01484 0.05308 -2.29087 75.62720 -61.47801 -30.26229

No	Plants	Compound	Score	Area	ACE	Transformation
	aurantifolia ;					
13	*Curcuma xanthorrhiza* Roxb	α-thujene	3480	377.30	-58.51	-2.12059 0.53561 0.49556 75.59946 -61.46442 -29.53613
14	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Camphene	3454	366.20	-68,18	-0.11344 -0.04342 -2.73530 75.47235 -61.39101 -30.26109
15	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	β-Pinene	3514	377.20	-72.64	-0.44058 0.51838 0.79375 55.78677 0.90255 -40.26990
16	*Curcuma xanthorrhiza* Roxb	Cis-Pinane	3548	380.50	-73.99	0.15713 0.66850 0.69280 55.77500 0.81773 -40.16998
17	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia ;*	Myrcene ; β-Myrcene	3542	406.40	-67.83	2.19283 0.17991 0.50495 75.79764 -60.88663 -30.28010
18	*Curcuma xanthorrhiza* Roxb	α-Terpinene	3292	381.40	-61.51	-2.58372 -0.09917 0.57332 75.55878 -61.07605 -30.55971
19	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*;*	1,8-Cineole	3592	387.80	-59.14	0.42643 0.15273 -2.05873 75.46514 -61.24878 -29.76541
20	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	(Z)-β-Ocimene	3412	376.10	-123.54	0.33917 -1.25853 1.36529 56.07013 -5.81487 -55.48573
21	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	α-Terpineol	3394	391.70	-54,320	1.20643 -0.22203 -2.81946 75.54778 -61.26009 -29.78897
22	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Tamarindus indica* L. *; Citrus aurantifolia*	Terpinen-4-ol	3368	399.40	-48.82	2.47211 0.06635 0.52508 75.42278 -61.72739 -29.96914
23	*Curcuma xanthorrhiza* Roxb	Ethyl-4E-octenoate	3716	409.70	-96.72	-2.56107 -0.30433 -1.09882 81.24664 -44.55763 -25.37002

No	Plants	Compound	Score	Area	ACE	Transformation
24	*Curcuma xanthorrhiza* Roxb	Dihydro citronellol acetate	4182	455.80	-178.52	1.30230 1.02172 1.73275 61.85746 2.30486 -25.99268
25	*Curcuma xanthorrhiza* Roxb	α-Cubebene	4208	449.90	-173.92	-1.83650 0.87468 1.42229 61.84811 2.49063 -25.33356
26	*Curcuma xanthorrhiza* Roxb	(Z)-β-Damascenone	3770	462.00	-76.43	-1.79555 -0.32956 -2.69993 76.13713 -61.16061 -30.59731
27	*Curcuma xanthorrhiza* Roxb	Methyl perillate	3710	390.00	-140.67	0.07908 -1.33670 1.58478 56.82999 -5.69599 -54.82912
28	*Curcuma xanthorrhiza* Roxb	(Z)-Isoeugenol	3510	407.50	-46.58	-1.63782 -0.16162 -2.65955 75.31855 -61.61216 -30.70146
29	*Curcuma xanthorrhiza* Roxb	α-Cis-bergamotene	4452	481.10	-94.67	1.75562 0.99353 1.04954 65.27973 -21.56450 -36.00691
30	*Curcuma xanthorrhiza* Roxb	Methyl undecanoate	4192	486.60	-77.33	0.31311 0.14279 0.13982 70.78616 -62.53261 -31.01515
31	*Curcuma xanthorrhiza* Roxb	β-Humulene	4048	432.50	-69.65	2.03578 -1.01989 -2.40295 65.59906 -21.17876 -35.38853
32	*Curcuma xanthorrhiza* Roxb	(Z)-β-Farnesene	4474	476.70	-189.64	-1.72239 0.83761 1.49579 61.88008 2.68265 -25.31179
33	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	(E)-caryophyllene	4008	434.80	-193.31	-1.68286 -0.57363 -1.81376 61.71558 1.68276 -26.12435
34	*Curcuma xanthorrhiza* Roxb	γ-elemene	4292	466.70	-188.77	2.52245 1.33004 -0.58593 55.45662 -6.10262 -55.55812
35	*Curcuma xanthorrhiza* Roxb	(E)-β-farnesene	4620	505.60	-84.77	3.06989 -0.87298 -2.37996 66.13049 -21.60139 -35.81467
36	*Curcuma xanthorrhiza* Roxb	γ-Curcumene	4308	522.40	-99.62	-1.12490 0.09434 0.42861 74.99264 -61.31233 -31.01545
37	*Curcuma xanthorrhiza* Roxb *; Citrus aurantifolia*	β-Bisabolene	4340	512.10	-137.65	-0.04984 -0.35639 -1.15124 81.32891 -44.23291 -25.39935
38	*Curcuma xanthorrhiza* Roxb	(Z)-γ-Bisabolene	4378	465.90	-75.33	-1.64326 0.81943 1.10320 66.15282 -21.39875 -35.81994

No	Plants	Compound	Score	Area	ACE	Transformation
39	*Curcuma xanthorrhiza* Roxb	β-sesquiphellandrene	4064	453.30	-191.80	-1.44676 1.24851 -2.42808 55.82135 -5.50512 -54.92228
40	*Curcuma xanthorrhiza* Roxb; *Zingiber officinale* var rubrum*; Citrus aurantifolia*	Caryophyllene oxide	3986	432.00	-72.28	-0.63019 0.37105 -2.76157 65.92902 -21.30384 -36.70514
41	*Curcuma xanthorrhiza* Roxb	Citronellyl pentanoate	4610	502.90	-176.65	1.36848 -1.09910 -3.03783 55.26216 -5.86389 -55.07546
42	*Curcuma xanthorrhiza* Roxb	Cis-cadin-4-en-7-ol	4060	450.90	-114.28	0.61899 -0.47100 -0.11448 65.42283 -21.68729 -37.48719
43	*Curcuma xanthorrhiza* Roxb	Cubenol	4172	440.90	-170.99	-1.85328 0.80542 1.50262 61.69920 1.64600 -25.62002
44	*Curcuma xanthorrhiza* Roxb	α-Eudesmol	3990	431.50	-75.85	0.30689 0.61268 0.87526 65.72794 -21.56185 -36.01114
45	*Curcuma xanthorrhiza* Roxb	(E)-Amyl cinnamic alcohol	4352	502.90	-69.80	-3.04733 0.15992 0.40273 71.49664 -62.14687 -30.65556
46	*Curcuma xanthorrhiza* Roxb	(E)-citronellyl tiglate	4838	523.10	-188.67	-2.90484 -1.29508 1.98904 54.85875 -5.56894 -55.74699
47	*Curcuma xanthorrhiza* Roxb	β-Bisabolol	4086	439.60	-184.47	1.49586 1.40342 -1.30968 55.50925 -5.80329 -55.80011
48	*Curcuma xanthorrhiza* Roxb	Ar-Curcumen-15-al	4370	478.30	-90.09	-1.59407 -0.87912 -2.62024 65.63703 -21.18151 -36.56214
49	*Curcuma xanthorrhiza* Roxb	Chamazulene	4000	423.60	-192.52	2.55598 -1.50108 -1.00630 62.02021 1.75861 -26.39058
50	*Curcuma xanthorrhiza* Roxb	(E, Z)-Farnesol	4562	513.80	-115.87	-0.16789 0.96965 0.87610 65.79773 -22.04175 -35.85286
51	*Curcuma xanthorrhiza* Roxb	Butyl dodecanoate	4644	578.10	-110.70	-1.82735 -0.06287 0.51316 69.84122 -64.68240 -29.95786
52	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Linalool	3664	425.50	-54.98	2.39695 0.41923 0.51863 74.87190 -61.04383 -30.48233

No	Plants	Compound	Score	Area	ACE	Transformation
53	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	α-Phellandrene	3376	377.00	-132.77	2.48898 0.01150 -1.34542 81.94843 -47.55289 -26.32446
54	*Curcuma xanthorrhiza* Roxb	(E)-Ethyl cinnamate	3676	402.00	-116.18	-0.18441 -1.26034 1.03164 56.77119 -5.33526 -55.78843
55	*Curcuma xanthorrhiza* Roxb	Thujopsan-2-α-ol	3446	396.50	-56.37	-0.32299 -0.02534 0.47910 75.16469 -61.47400 -30.00543
56	*Zingiber officinale* var rubrum	2-Heptanol	2952	326.70	-35.84	0.87256 0.38374 0.17104 74.26810 -62.26354 -30.41857
57	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Sabinene	3330	386.20	-68.42	-2.55622 -0.22687 -2.69744 56.05904 1.29611 -39.97158
58	*Zingiber officinale* var rubrum	δ-3-Carene	3308	385.70	-71.83	0.31601 -0.49362 -1.95271 55.62617 1.24950 -40.17619
59	*Zingiber officinale* var rubrum *Citrus aurantifolia*	p-Cymene	3446	396.50	-56.37	-0.32299 -0.02534 0.47910 75.16469 -61.47400 -30.00543
60	*Zingiber officinale* var rubrum *Citrus aurantifolia*	Limonene	3342	388.80	-131.22	-2.71364 -0.19849 1.31043 82.75155 -47.13527 -26.31455
61	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	β-Phellandrene	3278	368.90	-139.61	-2.61973 -0.30831 1.34955 82.75710 -47.47434 -26.85973
62	*Zingiber officinale* var rubrum	2-Heptyl acetate	3736	421.10	-35.72	1.48698 -0.24577 -2.51857 74.34858 -61.11443 -30.52552
63	*Zingiber officinale* var rubrum	Trans-β-ocimene	3350	369.50	-141.79	0.64405 0.21027 -1.82279 61.51903 1.53008 -27.28574
64	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	γ-Terpinene	3282	378.70	-60.83	0.24334 0.01228 -2.81371 74.97392 -61.67831 -30.50674
65	*Zingiber officinale* var rubrum	Terpinolene ; alpha terpinolene	3652	387.30	-54.26	-0.95809 0.42508 0.69486 75.49215 -61.35582 -29.72626
66	*Zingiber officinale* var rubrum	2-Nonanone	3320	382.70	-43.03	2.61847 -0.21058 -2.70586 73.46008 -61.85863 -31.11094
67	*Zingiber officinale* var rubrum	Trans-sabinene hydrate	3652	387.30	54.26	-0.95809 0.42508 0.69486 75.49215 -61.35582 -29.72626
68	*Zingiber officinale* var	Camphene hydrate	3360	383.50	-58.28	-0.20289 0.88063 -0.35056 75.87087 -61.37527 -29.91103

No	Plants	Compound	Score	Area	ACE	Transformation
	rubrum					
69	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Citronellal	3548	394.00	-119.48	-0.82 0.48 -2.24 83.50 -46.58 -27.14
70	Zingiber officinale var rubrum;	Isoborneol ; Borneol	3452	370.10	-56.40	1.52734 -1.04124 1.67875 76.07586 -61.29983 -29.57159
71	*Zingiber officinale* var rubrum	Myrtenal	3416	388.90	-59.07	1.63489 -0.17602 0.70620 75.79958 -61.32861 -30.32963
72	*Zingiber officinale* var rubrum	Linalyl formate	3956	430.50	-69.31	0.00859 -0.83325 -2.42977 64.71511 -21.57842 -35.70227
73	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	β-Citronellol	3494	412.30	-52.48	0.85736 -0.30870 -2.66369 75.71384 -61.14519 -29.44126
74	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Geraniol	3482	401.90	-141.91	-0.13143 -0.12367 -1.77506 81.96708 -47.16856 -26.07382
75	*Zingiber officinale* var rubrum	Trans-2-decenal	3576	403.20	-94.48	-1.88613 0.37345 2.09061 81.34143 -45.24941 -25.18208
76	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Geranial	3540	427.90	-51.63	1.49350 -0.20631 0.66944 76.22247 -61.56172 -30.29697
77	*Zingiber officinale* var rubrum	Bornyl acetate	3862	434.00	-60.53	-0.33123 0.27136 0.34176 75.07570 -61.98554 -29.95848
78	*Zingiber officinale* var rubrum	2-Undecanone	3756	438.40	-75.2	0.46690 0.25366 0.12393 71.83150 -62.17765 -31.42161
79	*Zingiber officinale* var rubrum	Myrtenyl acetate	4004	471.80	-61.54	-1.37716 0.14644 0.22403 75.24425 -61.61906 -30.11100
80	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Neryl acetate	4298	481.00	-148.66	-0.77821 -0.10693 -1.28879 82.46730 -46.00322 -26.29502
81	*Zingiber officinale* var rubrum	α-Copaene	4104	440.70	-90.65	2.05102 -0.96316 -1.84126 65.34227 -21.41584 -36.22525
82	*Zingiber officinale* var rubrum	β-Elemene	4380	475.20	-64.78	0.69944 1.10868 1.70258 65.97718 -21.48362 -35.96002
83	*Zingiber officinale* var rubrum	Isocaryophyllene	4140	446.4	-196.75	1.47893 0.62530 1.26156 61.80707 2.56566 -26.13729

No	Plants	Compound	Score	Area	ACE	Transformation
84	*Zingiber officinale* var rubrum	α-Humulene	4068	439.4	-133.71	-0.20072 0.24865 -2.14230 65.74873 -22.08846 -37.37175
85	*Zingiber officinale* var rubrum	Allo-aromadendrene	4012	431.5	-117.58	0.28908 -0.13664 0.67657 65.36835 -21.97774 -37.03199
86	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Germacrene D	4074	442.8	-67.06	2.17833 -1.10385 -1.89706 65.87020 -20.96918 -36.32537
87	*Zingiber officinale* var rubrum	α-Selinene	3948	457.6	-208.01	-2.49200 -0.37869 1.16518 83.07304 -47.49533 -26.71819
88	*Zingiber officinale* var rubrum	α-Muurolene	4112	438.00	-96.92	-1.66402 -0.50143 -1.90560 65.83181 -21.74421 -36.47391
89	*Zingiber officinale* var rubrum	Trans,trans-α-farnesene	4546	505.70	-70.49	1.39078 0.75594 0.32314 66.01479 -20.96833 -34.81386
90	*Zingiber officinale* var rubrum	δ-Cadinene	4120	454.60	-194.64	-1.62114 -1.05001 1.37674 61.74405 2.00040 -25.83080
91	*Zingiber officinale* var rubrum	γ-Eudesmol	4186	462.60	-163.26	-0.84267 1.34036 -0.44897 55.07932 -5.92239 -55.82665
92	*Zingiber officinale* var rubrum	β-Eudesmol	4182	457.30	-42.93	1.90 -0.81 -2.79 66.50 -20.81 -35.75
93	*Zingiber officinale var rubrum; Citrus aurantifolia*	α-Bisabolol	4270	466.00	-189.85	-0.44065 0.49944 -2.30137 83.82129 -46.46309 -27.63310
94	*Zingiber officinale var rubrum*	Cis,cis-farnesol	4434	492.20	-197.04	1.23826 -0.94033 0.93973 61.79446 3.24531 -25.74361
95	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Trans,trans-farnesol ; Farnesol	4558	480.60	-176.97	1.35 -1.09 -1.93 61.50 1.39 -25.79
96	*Zingiber officinale* var rubrum	Trans,trans-farnesal	4558	480.60	-176.97	1.34509 -1.08542 -1.93269 61.50193 1.38986 -25.79444
97	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Phytol	5476	580.60	-188.04	1.74841 -0.58052 -1.75207 61.90836 3.23592 -23.84459
98	*Zingiber officinale* var rubrum	6-gingerol	5002	591.70	-83.03	0.88 -0.28 -2.94 73.28 -61.46 -31.20
99	*Zingiber officinale* var rubrum	8-gingerol	5482	615.90	-153.87	-3.13 -1.14 1.38 56.65 -4.34 -58.17

No	Plants	Compound	Score	Area	ACE	Transformation
100	*Zingiber officinale* var rubrum	6-shogaol	4768	531.30	-56.91	-2.22 -0.44 0.02 66.37 -20.89 -36.45
101	*Zingiber officinale* var rubrum	8-shogaol	5388	610.70	-77.75	0.77 0.70 0.60 66.58 -21.42 -35.80
102	*Tamarindus indica* L.	3-methyl-2-butanone	2470	274.00	-27.15	2.80612 -0.00168 0.90081 75.52959 -61.90015 -29.98020
103	*Tamarindus indica* L.	1 –penten-3-one	2372	267.70	-26.39	-2.35536 -0.24876 -2.83099 55.82699 0.38986 -40.53526
104	*Tamarindus indica* L.	(E)-2-butenal	2128	236.50	-23,38	-0.95331 1.08775 1.32888 55.97104 0.71118 -40.53978
105	*Tamarindus indica* L.	hexanale	4074	442.80	-67.06	2.17833 -1.10385 -1.89706 65.87020 -20.96918 -36.32537
106	*Tamarindus indica* L.	(E)-2-pentenal	2434	262.80	-75.27	1.64863 -0.31040 0.16964 56.58281 -5.93114 -52.81157
107	*Tamarindus indica* L.	3-methylbutanol	2526	292.80	-30.86	0.34550 0.54790 0.54388 55.70017 1.00421 -39.82095
108	*Tamarindus indica* L.	hydroxyacetone	1966	210.20	-65.77	-1.18158 -0.16892 0.24182 72.18111 -74.15220 -26.47381
109	*Tamarindus indica* L.	5-methyl-2(3H)-furanone	2284	253.70	-24.71	1.35177 1.12036 -0.65502 56.85353 0.58978 -41.57494
110	*Tamarindus indica* L. ; *Citrus aurantifolia*	trans-linalool oxide (furanoid)	3616	422.70	-49.58	-1.35991 -0.09489 0.59152 75.12057 -61.13771 -29.90247
111	*Tamarindus indica* L.	acetic acid	1558	172.10	-53.93	1.22161 0.41632 -2.77790 73.12228 -73.95331 -26.13236
112	*Tamarindus indica* L.	furfural	2402	243.90	-97.65	0.48614 0.11002 2.92637 72.46613 -74.42106 -26.21177
113	*Tamarindus indica* L.	2-acetylfuran	2698	308.40	-23.46	-1.92250 0.07531 -2.51727 75.55399 -61.42574 -29.64661
114	*Tamarindus indica* L.	pyrrole	2036	221.80	-85.73	-0.58830 0.46203 3.10514 72.63079 -74.24357 -26.46786
115	*Tamarindus indica* L.	octanol	3122	354.30	-30.57	-0.38578 0.29965 0.29354 73.39061 -62.47798 -30.36213
116	*Tamarindus indica* L.	5-methylfurfural	2642	283.40	-100.20	-2.18422 0.11322 0.51824 55.35466 -6.08217 -52.86245
117	*Tamarindus indica* L.	isomaltol	2636	294.10	-16.05	-1.54987 -0.30398 -2.72820 75.55730 -61.71568 -29.30229
118	*Tamarindus indica* L.	γ-butyrolactone	2062	219.20	-82.59	0.95553 -0.33659 0.32258 73.00735 -74.22955 -26.75616
119	*Tamarindus indica* L.	phenylacetaldehyde	3052	328.70	-46.07	2.83743 -0.22548 -2.50343 75.57465 -61.33487 -29.99709
120	*Tamarindus indica* L.	2-methylbutyric acid	2520	278.40	-27.36	2.33384 0.81866 -2.02698 76.11864 -60.75897 -30.26714
121	*Tamarindus indica* L.	2,3-dimethylmaleic anhydride	2638	273.80	-121.81	-2.76677 -0.20232 0.32450 72.2-0096 -74.24866 -26.31726
122	*Tamarindus indica* L.	methyl salicylate	3084	321.90	-111.32	1.63298 -0.63056 1.32827 61.49682 0.29888 -26.99393

No	Plants	Compound	Score	Area	ACE	Transformation
123	*Tamarindus indica* L.	β-damascenone	3790	427.60	-152.00	-2.46830 -0.07190 3.13859 64.43449 -22.70316 -37.62991
124	*Tamarindus indica* L.	hexanoic acid	2720	294.40	-106.65	0.91271 0.13952 -1.74199 82.38513 -47.22072 -26.36307
125	*Tamarindus indica* L.	geranylacetone	4284	510.10	-66.68	0.96187 -0.38038 -2.83685 73.74036 -62.04398 -31.27710
126	*Tamarindus indica* L.	guaiacol	2858	312.40	-4.49	-0.54 -0.29 3.10 75.87 -61.14 -29.96
127	*Tamarindus indica* L.	benzyl alcohol	2832	308.70	-39.03	2.98135 -0.40283 -2.57582 75.75050 -61.17422 -29.89937
128	*Tamarindus indica* L.	2-phenylethanol	3084	333.50	-44.92	2.70743 -0.24717 -2.68999 75.42840 -61.23454 -29.92387
129	*Tamarindus indica* L.	maltol	2710	312.40	-37.38	-0.69267 -0.39201 -2.98101 55.64068 0.61379 -40.43470
130	*Tamarindus indica* L.	2-(hydroxyacetyl)furan	2256	241.70	-94.79	0.69153 -0.39608 -0.08343 56.51119 -6.09230 -52.52032
131	*Tamarindus indica* L.	pyrrole-2-carboxaldehyde	2256	241.70	-94.79	0.69 -0.40 -0.08 56.51 -6.09 -52.52
132	*Tamarindus indica* L.	octanoic acid	3164	350.90	-111.36	-2.26551 -0.41951 1.15445 82.55638 -47.35723 -26.69725
133	*Tamarindus indica* L.	eugenol	3540	370.90	-148.70	1.79551 0.26677 1.28430 61.76202 2.30817 -26.80914
134	*Tamarindus indica* L.	nonanoic acid	3478	373.10	-117.43	-2.51380 0.10758 -1.63099 81.85415 -46.56377 -26.38947
135	*Tamarindus indica* L.	p-vinylguaiacol	3156	330.70	-123.77	-1.81404 0.40108 1.36965 61.45225 0.96623 -27.04287
136	*Tamarindus indica* L.	decanoic acid	3726	411.90	-50.24	2.81733 -0.22273 -2.93164 73.04098 -62.39943 -30.76438
137	*Tamarindus indica* L.	dihydroactinidiolide	3546	402.20	-64.3	2.30648 0.02952 -2.38126 75.03331 -61.42455 -30.12393
138	*Tamarindus indica* L.	p-vinylphenol	3016	328.00	-41.19	-0.28469 -0.32708 -2.84111 76.04004 -61.41295 -29.67166
139	*Tamarindus indica* L.	benzoic acid	2808	298.00	-35.71	-1.60752 -0.87954 -2.00902 55.63969 0.78844 -40.42256
140	*Tamarindus indica* L.	lauric acid	4084	452.90	-86.44	1.40844 -0.56844 -0.67552 81.12660 -44.22525 -25.20032
141	*Tamarindus indica* L.	vanillin	3040	362.00	-30.33	1.88878 0.28593 0.43119 76.11629 -60.92742 -30.22611
142	*Tamarindus indica* L.	myristic acid	4352	534.90	-96.84	-0.82991 -0.80836 0.53078 79.69970 -59.37694 -34.04034
143	*Tamarindus indica* L.	pentadecanoic acid	4692	522.00	-110.37	1.47890 -0.52979 -0.59881 83.39999 -45.55746 -27.13624
144	*Tamarindus indica* L. ; *Citrus aurantifolia*	palmitic acid	4758	546.20	-74.92	0.71817 0.26033 -2.54354 74.34032 -61.34433 -31.03214
145	*Tamarindus indica* L.	palmitoleic acid	5230	621.90	-89.71	-1.85103 0.54491 -2.46461 76.43344 -60.21536 -32.23916
146	*Tamarindus indica* L.	heptadecanoic acid	4980	568.20	-115.44	1.12607 -0.51339 -0.67149 83.23730 -45.66655 -27.28998
147	*Tamarindus indica* L. ;	oleic acid	5326	563.40	563.40	-1.63120 0.75770 1.41039 61.72168 3.71433 -24.38448

No	Plants	Compound	Score	Area	ACE	Transformation
	Citrus aurantifolia					
148	*Tamarindus indica* L. ; *Citrus aurantifolia*	linoleic acid	5216	569.60	-212.73	-1.25087 -0.04959 -1.92831 62.22537 4.09054 -25.41938
149	*Tamarindus indica* L.	linolenic acid	5318	566.80	-218.19	-1.48896 -0.51984 -1.88271 61.93917 3.43670 -25.16034
150	*Tamarindus indica* L.	(+)-Catechin	4314	493.50	-170,05	2.52342 -0.26793 -1.18926 81.44847 -45.64879 -25.59374
151	*Tamarindus indica* L.	(-)-Epicatechin	4240	494.60	-206,41	2.73514 -0.42195 -1.17147 81.69072 -45.96360 -25.37605
152	*Tamarindus indica* L.	Taxifolin	4334	501.70	-151.00	-0.84441 -0.40015 -1.18946 80.92615 -45.56788 -25.60113
153	*Tamarindus indica* L.	Apigenin	4308	462.30	-182.05	0.28360 -0.28501 -1.18412 73.50027 -77.79710 -27.64388
154	*Tamarindus indica* L.	Eriodictyol	4338	473.60	-175.57	-0.13067 0.27645 2.00900 73.83414 -77.94629 -27.30945
155	*Tamarindus indica* L.	Luteolin	4296	464.50	-178.00	0.39037 -0.20542 -1.15241 73.75452 -78.08430 -27.55035
156	*Tamarindus indica* L.	Naringenin	4112	454.00	-201.92	1.26022 1.19421 -2.38459 56.25637 -5.36763 -54.71371
157	*Citrus aurantifolia*	cis-Verbenol	3498	387.40	-63.91	1.56709 0.03593 -2.52104 75.72050 -60.93698 -29.94912
158	*Citrus aurantifolia*	Nerol	3518	421.60	-55.99	-0.60057 -0.11916 0.97751 75.62833 -61.19974 -30.27835
159	*Citrus aurantifolia*	Neral	3546	366.30	-98.40	0.12753 0.17646 -2.15137 65.65507 -22.28247 -37.80056
160	*Citrus aurantifolia*	Germacrene B	4190	448.40	-120.83	-0.15023 0.30397 -2.62831 65.77496 -21.65719 -37.60332
161	*Citrus aurantifolia*	Octanal	3086	323.70	-104.14	1.16809 -1.29130 0.47568 56.18903 -5.98264 -55.48609
162	*Citrus aurantifolia*	Nonanal	3336	346.60	-101.65	-0.32477 1.21072 -1.91518 56.03639 -5.13686 -56.12661
163	*Citrus aurantifolia*	(E)-Limonene oxide	3278	337.60	-143.11	2.91776 -1.26758 1.59491 61.57132 0.76542 -26.12746
164	*Citrus aurantifolia*	δ-Elemene	4346	473.70	-67.33	2.55234 -0.88117 -1.96405 65.74617 -21.48631 -35.95942
165	*Citrus aurantifolia*	Decanal	3544	399.50	-65.03	-0.92810 0.25163 2.12772 80.35020 -44.04426 -25.14658
166	*Citrus aurantifolia*	l-Carvone	3324	384.80	-129.28	-0.36644 0.37732 -1.76525 82.71780 -47.33337 -26.40178
167	*Citrus aurantifolia*	Cumin aldehyde	3354	389.30	-61.57	0.69391 0.16965 0.54930 74.92587 -61.31624 -30.41119
168	*Citrus aurantifolia*	Perillaldehyde	3384	386.20	-54.11	0.75745 0.27603 0.22240 74.94984 -61.36803 -30.24214
169	*Citrus aurantifolia*	Tridecanal	4180	472.80	-92.56	-1.35905 0.50704 2.58807 82.15607 -44.90604 -25.93841
170	*Citrus aurantifolia*	Dodecyl acetate	4434	486.10	-87.60	-0.98658 0.51793 2.48287 81.32077 -43.96859 -26.06277
171	*Citrus aurantifolia*	Tetradecanal	4706	535.10	-96.62	2.45043 -0.22838 -2.96966 70.54794 -62.56279 -31.26732
172	*Citrus aurantifolia*	Perillyl alcohol	3272	375.60	-137.87	-2.35881 -0.34182 1.44979 81.90120 -47.57963 -26.16042

No	Plants	Compound	Score	Area	ACE	Transformation
173	*Citrus aurantifolia*	Pentadecanal	4702	499.90	-95.88	1.53961 -0.50477 -0.57840 82.50827 -44.33303 -26.77592
174	*Citrus aurantifolia*	Cedryl acetate	4000	423.60	-192.52	2.55598 -1.50108 -1.00630 62.02021 1.75861 -26.39058
175	*Citrus aurantifolia*	Cinnamyl alcohol	3088	357.10	-49.72	0.30647 -0.26560 -2.50638 75.17155 -61.60339 -30.41187
176	*Citrus aurantifolia*	(E)-Nerolidol	4796	511.70	-95.88	-0.59773 1.00017 0.80230 65.78826 -21.53468 -35.50107
177	Control	mitoxantrone	5906	674.00	-219.74	2.84 -0.74 -0.18 82.05 -44.92 -26.58

Docking of bioactive compounds- Src human

No	Plants	Compound	Score	Area	ACE	Transformation
1	*Curcuma xanthorrhiza* Roxb	curcumin	5140	606.40	-298.85	2.91 -0.61 2.76 -13.34 -3.17 27.78
2	*Curcuma xanthorrhiza* Roxb	Bisdemethoxycurcumin	5060	589.10	-127.42	-1.55 0.21 -0.06 3.89 -5.37 0.70
3	*Curcuma xanthorrhiza* Roxb	Demethoxycurcumin	4920	558.70	-151.35	1.83 -0.85 0.52 -12.15 0.41 22.26
4	*Curcuma xanthorrhiza* Roxb	Xanthorrhizol	4224	492.20	-43.32	1.55 0.00 0.05 5.24 -4.88 0.48
5	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Ar-Curcumene	4140	474.00	-54.36	-1.44 -0.21 -3.11 4.19 -4.96 0.32
6	*Curcuma xanthorrhiza* Roxb	β-Curcumene	4188	459.30	-57.29	-1.77 0.05 -3.10 4.12 -4.47 0.09
7	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Camphor	2936	318.70	-15.66	-1.48 -0.58 0.25 6.36 -5.37 0.68
8	*Curcuma xanthorrhiza* Roxb	Ar-Turmerone	4132	452.50	-67.93	1.62 -0.47 2.89 6.34 -4.69 -0.20
9	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	Zingiberene ; α-Zingiberene	4148	461.00	-91.42	1.06 0.08 -2.99 3.21 -4.78 -0.45
10	*Curcuma xanthorrhiza* Roxb	Zerumbone	3656	418.10	-56.48	-0.96 -0.05 0.00 5.16 -5.05 -0.20
11	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Geranyl acetate	3672	401.90	-58.69	1.94 0.04 -0.08 2.25 -4.70 -0.08
12	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale var rubrum; Citrus aurantifolia*	α-Pinene	2958	322.70	-6.64	0.29 -0.48 2.46 6.53 -4.78 0.65
13	*Curcuma xanthorrhiza* Roxb	α-thujene	3040	357.00	-26.06	-1.83 0.71 0.16 7.27 -5.70 1.09
14	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Camphene	3000	318.90	-2.72	0.00 0.19 -0.02 6.32 -4.83 0.41
15	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	β-Pinene	3068	335.90	-23.78	0.44 0.68 -0.80 7.12 -5.32 0.58
16	*Curcuma xanthorrhiza* Roxb	Cis-Pinane	2970	321.00	-12.58	-0.74 -0.46 0.54 7.03 -5.14 0.74
17	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	Myrcene ; β-Myrcene	3350	350.30	-27.91	-0.29 -0.46 3.01 5.00 -4.75 0.02

No	Plants	Compound	Score	Area	ACE	Transformation
18	*Curcuma xanthorrhiza* Roxb	α-Terpinene	3130	352.00	-32.92	1.21 -0.46 1.25 2.45 -12.19 22.69
19	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*;*	1,8-Cineole	3134	339.50	-13.01	-1.81 0.35 -0.20 6.24 -5.40 0.67
20	*Curcuma xanthorrhiza* Roxb; *Citrus aurantifolia*	(Z)-β-Ocimene	3460	383.50	-114.75	-0.94 0.68 0.15 -16.91 -2.15 24.66
21	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	α-Terpineol	3186	350.00	-123.59	0.75 -0.62 -2.95 -16.29 -2.28 25.12
22	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Tamarindus indica* L. *; Citrus aurantifolia*	Terpinen-4-ol	3156	355.50	-34.90	-1.14 0.23 -1.71 2.40 -12.63 22.90
23	*Curcuma xanthorrhiza* Roxb	Ethyl-4E-octenoate	3864	430.90	-44.41	-1.36 0.04 0.01 2.10 -5.03 0.51
24	*Curcuma xanthorrhiza* Roxb	Dihydro citronellol acetate	3816	412.60	-63.08	1.93 0.08 0.05 1.83 -4.53 -0.76
25	*Curcuma xanthorrhiza* Roxb	α-Cubebene	3888	459.80	-77.29	-0.42 -0.70 -2.38 -8.11 16.35 -3.18
26	*Curcuma xanthorrhiza* Roxb	(Z)-β-Damascenone	3444	391.50	-42.97	1.92 0.18 -0.29 4.30 -4.90 0.12
27	*Curcuma xanthorrhiza* Roxb	Methyl perillate	3456	386.70	-22.11	2.00 0.84 -1.80 2.72 -13.24 23.62
28	*Curcuma xanthorrhiza* Roxb	(Z)-Isoeugenol	3340	377.60	-52.65	1.81 0.55 0.01 7.24 -5.79 0.83
29	*Curcuma xanthorrhiza* Roxb	α-Cis-bergamotene	3970	456.20	-199.01	1.59 -0.67 -3.14 -16.55 -1.61 24.62
30	*Curcuma xanthorrhiza* Roxb	Methyl undecanoate	4262	457.50	-55.91	-1.97 0.30 -0.08 3.64 -5.09 0.47
31	*Curcuma xanthorrhiza* Roxb	β-Humulene	3716	424.50	-58.26	2.25 -0.10 -0.08 3.78 -4.73 -0.15
32	*Curcuma xanthorrhiza* Roxb	(Z)-β-Farnesene	4190	480.10	-89.49	1.85 0.08 -3.13 3.30 -5.17 -0.25
33	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia;*	(E)-caryophyllene	3572	404.60	-54.02	-1.61 -0.25 2.66 4.47 -4.51 -0.34
34	*Curcuma xanthorrhiza* Roxb	γ-elemene	3748	423.70	-105.56	-2.02 0.57 -2.76 0.47 -4.08 -0.50
35	*Curcuma xanthorrhiza* Roxb	(E)-β-farnesene	4170	477.40	-68.97	-0.99 0.02 0.16 4.01 -4.42 -0.51
36	*Curcuma xanthorrhiza* Roxb	γ-Curcumene	4194	458.50	-61.29	1.41 -0.05 3.03 4.00 -4.48 0.08
37	*Curcuma xanthorrhiza* Roxb*; Citrus aurantifolia*	β-Bisabolene	4412	475.30	-66.10	-0.95 0.00 0.00 3.62 -4.71 0.34
38	*Curcuma xanthorrhiza* Roxb	(Z)-γ-Bisabolene	3998	469.60	-65.01	-1.75 -0.33 2.95 5.88 -5.20 0.41

No	Plants	Compound	Score	Area	ACE	Transformation
39	*Curcuma xanthorrhiza* Roxb	β-sesquiphellandrene	3932	444.80	-76.85	-0.98 -0.03 3.08 4.35 -4.80 -0.29
40	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Caryophyllene oxide	3582	382.70	-93.70	-0.99 -0.25 -0.03 1.38 -4.44 -0.63
41	*Curcuma xanthorrhiza* Roxb	Citronellyl pentanoate	4324	473.50	-101.31	1.29 -1.22 -2.37 -10.55 0.91 19.25
42	*Curcuma xanthorrhiza* Roxb	Cis-cadin-4-en-7-ol	3740	440.80	-29.54	1.63 0.41 -0.22 6.36 -4.63 0.66
43	*Curcuma xanthorrhiza* Roxb	Cubenol	3858	434.10	-114.74	2.41 0.51 -0.61 -0.19 -4.48 0.04
44	*Curcuma xanthorrhiza* Roxb	α-Eudesmol	3760	402.80	-93.39	0.92 0.22 -2.87 1.76 -4.36 -0.63
45	*Curcuma xanthorrhiza* Roxb	(E)-Amyl cinnamic alcohol	4398	489.20	-77.60	-0.68 0.06 3.11 3.65 -5.46 0.85
46	*Curcuma xanthorrhiza* Roxb	(E)-citronellyl tiglate	4330	501.30	-133.97	2.98 -1.16 1.56 0.23 -5.49 1.99
47	*Curcuma xanthorrhiza* Roxb	β-Bisabolol	4426	484.90	-84.09	2.36 -0.08 -0.18 3.93 -5.00 0.60
48	*Curcuma xanthorrhiza* Roxb	Ar-Curcumen-15-al	4402	493.10	-87.24	-1.22 -0.24 2.97 5.42 -5.09 0.35
49	*Curcuma xanthorrhiza* Roxb	Chamazulene	3676	406.10	-31.10	1.70 0.06 -1.67 25.48 14.36 2.25
50	*Curcuma xanthorrhiza* Roxb	(E, Z)-Farnesol	4102	445.00	-122.27	-2.16 0.39 -2.89 -0.06 -4.23 -1.17
51	*Curcuma xanthorrhiza* Roxb	Butyl dodecanoate	4842	532.70	-160.24	1.13 0.46 -2.52 -14.17 -0.84 24.62
52	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Linalool	3506	408.60	-56.72	0.80 -0.06 0.37 -8.18 16.82 -2.99
53	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum	α-Phellandrene	3116	348.20	-152.33	-2.13 -0.77 -2.65 -15.73 -1.40 25.53
54	*Curcuma xanthorrhiza* Roxb	(E)-Ethyl cinnamate	3596	395.00	-38.84	-0.49 0.06 3.03 3.70 -5.14 1.31
55	*Curcuma xanthorrhiza* Roxb	Thujopsan-2-α-ol	3630	430.60	-64.48	-0.57 -0.63 3.07 6.65 -5.16 0.27
56	*Zingiber officinale* var rubrum	2-Heptanol	2968	346.10	-102.07	-2.00 -0.84 -2.95 2.62 -6.72 7.95
57	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Sabinene	3072	365.70	-27.32	-1.25 0.52 -0.13 7.41 -5.65 1.33
58	*Zingiber officinale* var rubrum	δ-3-Carene	2922	312.00	-18.06	-1.89 -0.11 -0.07 5.74 -4.89 0.26
59	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	p-Cymene	3124	338.30	-38.65	0.99 0.04 -1.73 2.59 -12.90 22.70
60	*Zingiber officinale* var rubrum *Citrus aurantifolia ;*	Limonene	3154	346.00	-138.80	-0.70 0.64 0.12 -16.27 -1.70 25.53

No	Plants	Compound	Score	Area	ACE	Transformation
61	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	β-Phellandrene	3200	347.00	-139.74	-0.85 0.63 0.26 -16.36 -1.51 25.13
62	*Zingiber officinale* var rubrum	2-Heptyl acetate	3532	374.70	-125.51	1.08 -0.70 -2.90 -16.44 -1.38 24.66
63	*Zingiber officinale* var rubrum	Trans-β-ocimene	3236	349.40	-19.49	0.07 -0.01 3.10 4.13 -4.42 0.55
64	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	γ-Terpinene	3138	345.40	-52.98	-1.77 -0.22 1.53 2.41 -12.37 21.66
65	*Zingiber officinale* var rubrum	Terpinolene ; alpha terpinolene	3236	350.10	-130.77	-2.37 -0.65 -2.90 -17.03 -1.60 24.65
66	*Zingiber officinale* var rubrum	2-Nonanone	3310	410.10	-139.21	-0.18 -0.73 3.01 3.05 -6.60 8.31
67	*Zingiber officinale* var rubrum	Trans-sabinene hydrate	3098	347.60	-21.09	1.96 0.31 -1.69 2.41 -11.76 22.22
68	*Zingiber officinale* var rubrum	Camphene hydrate	2868	315.50	-12.94	-2.70 -0.03 -0.12 6.65 -5.02 0.47
69	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Citronellal	3446	377.60	-25.98	0.33 0.17 3.11 4.37 -4.74 0.80
70	*Zingiber officinale* var rubrum	Isoborneol ; Borneol	2916	325.10	-17.63	0.90 0.43 -2.87 7.49 -5.18 0.75
71	*Zingiber officinale* var rubrum	Myrtenal	2872	329.20	-24.27	-2.62 -0.50 2.88 7.49 -5.62 1.33
72	*Zingiber officinale* var rubrum	Linalyl formate	3706	405.00	-52.69	-3.12 -0.02 3.08 3.26 -5.00 0.04
73	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	β-Citronellol	3512	387.70	-131.46	1.19 -0.84 3.02 -17.28 -1.74 24.40
74	*Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Geraniol	3332	423.30	-142.90	-1.32 -0.61 -3.05 2.96 -6.96 7.45
75	*Zingiber officinale* var rubrum	Trans-2-decenal	3628	405.70	-34.51	-1.41 -0.11 3.13 5.01 -5.24 1.48
76	*Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Geranial	3446	390.10	-26.63	-0.76 -0.37 2.83 6.86 -4.91 1.02
77	*Zingiber officinale* var rubrum	Bornyl acetate	3506	415.50	-44.99	-2.15 -0.84 2.97 7.74 -5.32 0.63
78	*Zingiber officinale* var rubrum	2-Undecanone	3748	402.80	-41.98	0.20 -0.14 3.10 1.35 -4.52 0.62
79	*Zingiber officinale* var rubrum	Myrtenyl acetate	3730	431.30	-22.28	0.20 -0.61 2.90 7.62 -5.04 1.23
80	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Neryl acetate	3990	461.60	-137.53	2.82 0.64 -0.12 -18.17 -2.06 24.50
81	*Zingiber officinale* var rubrum	α-Copaene	3918	430.40	-36.26	1.97 0.13 -0.21 6.02 -4.94 0.59

No	Plants	Compound	Score	Area	ACE	Transformation
82	*Zingiber officinale* var rubrum	β-Elemene	3896	439.20	-34.79	-0.96 0.47 -0.42 5.86 -4.37 -0.16
83	*Zingiber officinale* var rubrum	Isocaryophyllene	3752	422.20	-112.02	-1.21 0.24 -0.15 -0.16 -4.58 0.11
84	*Zingiber officinale* var rubrum	α-Humulene	3672	453.80	-92.93	2.03 0.43 -1.85 -6.11 19.59 -2.59
85	*Zingiber officinale* var rubrum	Allo-aromadendrene	3556	387.90	-112.64	3.01 -0.98 1.53 -0.55 -4.10 -0.48
86	*Zingiber officinale* var rubrum*; Citrus aurantifolia ;*	Germacrene D	3612	406.70	-55.50	-1.10 -0.35 -0.06 5.01 -4.48 -0.61
87	*Zingiber officinale* var rubrum	α-Selinene	3762	422.50	-73.79	1.53 -0.12 -3.13 3.63 -5.00 -0.16
88	*Zingiber officinale* var rubrum	α-Muurolene	3826	416.80	-49.53	-1.46 -0.03 -0.20 4.57 -4.79 0.09
89	*Zingiber officinale* var rubrum	Trans,trans-α-farnesene	4368	484.70	-60.41	1.37 -0.30 2.96 3.12 -4.71 0.15
90	*Zingiber officinale* var rubrum	δ-Cadinene	3802	469.10	-63.43	2.57 -0.70 -2.23 -8.10 16.31 -3.50
91	*Zingiber officinale* var rubrum	γ-Eudesmol	3906	469.10	-141.82	-0.78 0.39 0.27 -18.03 -2.55 24.83
92	*Zingiber officinale* var rubrum	β-Eudesmol	3888	422.60	-77.65	2.35 -0.36 0.24 2.12 -4.26 -0.06
93	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	α-Bisabolol	4122	464.70	-53.46	1.05 -0.95 1.29 2.48 -13.21 24.35
94	*Zingiber officinale* var rubrum	Cis,cis-farnesol	4166	461.90	-90.65	2.30 -0.37 0.23 1.11 -4.00 -0.62
95	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Trans,trans-farnesol ; Farnesol	4000	452.50	-98.41	1.97 0.07 0.05 0.71 -4.39 -0.55
96	*Zingiber officinale* var rubrum	Trans,trans-farnesal	4000	452.50	-98.41	1.97 0.07 0.05 0.71 -4.39 -0.55
97	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Phytol	4952	565.70	-96.68	-1.06 -0.42 0.10 2.17 -4.05 -1.00
98	*Zingiber officinale* var rubrum	6-gingerol	4892	552.00	-74.66	0.97 -0.01 -3.14 2.79 -4.55 -0.01
99	*Zingiber officinale* var rubrum	6-shogaol	4278	471.60	-51.68	2.13 -0.89 -1.50 -9.76 1.19 18.76
100	*Zingiber officinale* var rubrum	8-shogaol	4592	520.70	-110.69	-2.47 0.18 -2.94 1.41 -3.80 -1.25
101	*Zingiber officinale* var rubrum	8-gingerol	5146	601.30	-159.29	-3.04 0.43 -2.64 -10.95 0.95 23.02
102	*Tamarindus indica* L.	3-methyl-2-butanone	2344	267.30	-93.87	-2.78 0.68 0.58 4.80 -6.79 9.46
103	*Tamarindus indica* L.	1 –penten-3-one	2376	265.90	-74.94	-0.53 -0.20 1.13 5.06 16.13 -7.09
104	*Tamarindus indica* L.	(E)-2-butenal	2074	230.30	-77.13	-1.25 0.54 -0.59 4.66 -6.13 9.54

No	Plants	Compound	Score	Area	ACE	Transformation
105	*Tamarindus indica* L.	hexanale	2562	317.60	-95.27	0.90 -0.73 -2.97 3.66 -6.93 8.40
106	*Tamarindus indica* L.	(E)-2-pentenal	2428	270.20	-77.22	-0.46 0.33 -1.62 5.00 16.09 -6.88
107	*Tamarindus indica* L.	3-methylbutanol	2340	258.40	-64.87	-0.89 -0.69 1.49 4.80 15.98 -6.89
108	*Tamarindus indica* L.	hydroxyacetone	2076	213.20	-73.93	-1.86 -0.52 -0.65 4.97 -6.53 10.15
109	*Tamarindus indica* L.	5-methyl-2(3H)-furanone	2304	249.90	-83.04	1.15 -1.05 -2.32 5.76 17.54 -6.37
110	*Tamarindus indica* L.; *Citrus aurantifolia*	trans-linalool oxide (furanoid)	3250	371.50	2.21	-2.47 -0.52 2.70 6.77 -4.73 0.29
111	*Tamarindus indica* L.	acetic acid	1686	185.10	-61.20	-1.09 -0.63 0.09 5.08 -6.58 10.63
112	*Tamarindus indica* L.	furfural	2232	250.40	-88.98	-0.30 0.38 -2.10 5.85 16.00 -6.81
113	*Tamarindus indica* L.	2-acetylfuran	2462	264.90	-94.79	-0.83 0.39 0.87 -15.95 -1.74 25.57
114	*Tamarindus indica* L.	pyrrole	2070	215.60	-102.98	1.84 -0.26 -0.47 5.08 -6.04 10.28
115	*Tamarindus indica* L.	octanol	3174	381.20	-110.13	-0.27 0.86 -0.18 3.13 -6.85 7.98
116	*Tamarindus indica* L.	5-methylfurfural	2488	271.90	-77.13	-1.27 0.01 0.66 -15.85 -1.55 25.02
117	*Tamarindus indica* L.	isomaltol	2508	270.40	-115.28	-1.61 -0.51 0.64 -15.32 -1.25 26.28
118	*Tamarindus indica* L.	γ-butyrolactone	2122	222.20	-100.88	0.63 -0.34 -0.80 5.16 -6.73 10.04
119	*Tamarindus indica* L.	phenylacetaldehyde	2728	311.00	-119.29	-1.65 0.06 1.16 5.27 15.56 -7.37
120	*Tamarindus indica* L.	2-methylbutyric acid	2368	250.30	-18.11	-2.18 0.84 1.31 7.36 -5.80 0.33
121	*Tamarindus indica* L.	2,3-dimethylmaleic anhydride	2454	272.60	-102.07	1.40 1.02 -2.38 -16.32 -1.67 25.58
122	*Tamarindus indica* L.	methyl salicylate	2890	357.30	-47.22	0.41 -1.05 -0.21 -6.39 16.98 -3.05
123	*Tamarindus indica* L.	β-damascenone	3638	422.90	-40.71	-0.31 0.43 -0.29 5.75 -4.82 0.06
124	*Tamarindus indica* L.	hexanoic acid	2620	292.20	-8.17	-2.18 0.29 -1.82 2.39 -11.15 22.06
125	*Tamarindus indica* L.	geranylacetone	4232	470.80	-25.12	-1.70 0.24 0.01 5.21 -4.74 0.99
126	*Tamarindus indica* L.	guaiacol	2724	306.20	-11.18	0.67 0.62 -0.48 7.92 -5.62 1.66
127	*Tamarindus indica* L.	benzyl alcohol	2698	278.90	-109.54	-2.55 0.36 -1.91 5.10 15.92 -6.78
128	*Tamarindus indica* L.	2-phenylethanol	2700	296.90	-117.67	-1.52 0.34 0.43 -16.06 -1.83 25.64
129	*Tamarindus indica* L.	maltol	2482	299.50	-47.19	0.96 0.30 1.18 -6.94 17.00 -2.01
130	*Tamarindus indica* L.	2-(hydroxyacetyl)furan	2538	280.20	-112.31	-3.00 0.23 -1.48 5.59 16.00 -6.76

No	Plants	Compound	Score	Area	ACE	Transformation
131	*Tamarindus indica* L.	pyrrole-2-carboxaldehyde	2152	265.40	-41.95	-3.10 -0.80 -0.36 -5.76 17.08 -2.56
132	*Tamarindus indica* L.	octanoic acid	3176	386.40	-123.67	-2.36 -0.82 -3.01 3.53 -6.10 8.43
133	*Tamarindus indica* L.	eugenol	3364	364.00	6.69	-1.12 -0.34 1.28 3.21 -11.30 22.84
134	*Tamarindus indica* L.	nonanoic acid	3388	412.40	-146.76	-2.86 0.72 0.09 3.58 -6.92 8.34
135	*Tamarindus indica* L.	p-vinylguaiacol	2952	325.50	-129.55	1.50 -0.09 -2.62 -14.73 -1.02 25.29
136	*Tamarindus indica* L.	decanoic acid	3672	417.90	-53.69	0.56 -0.11 -0.01 3.03 -5.20 1.00
137	*Tamarindus indica* L.	dihydroactinidiolide	3302	351.20	-43.85	-2.35 -0.56 3.13 6.14 -5.15 -0.41
138	*Tamarindus indica* L.	p-vinylphenol	2696	296.20	-116.40	-1.90 -0.34 -2.56 -15.04 -1.07 25.54
139	*Tamarindus indica* L.	benzoic acid	2526	283.70	-24.39	0.39 0.68 0.07 8.85 -5.50 2.57
140	*Tamarindus indica* L.	lauric acid	4310	516.40	-161.41	1.57 -0.85 3.00 1.60 -6.37 6.09
141	*Tamarindus indica* L.	vanillin	2772	294.90	-1.31	-0.26 -0.38 -2.86 6.43 -5.42 1.00
142	*Tamarindus indica* L.	myristic acid	4664	547.90	-178.67	1.56 -0.85 2.99 0.71 -6.16 5.17
143	*Tamarindus indica* L.	pentadecanoic acid	4824	547.90	-83.75	2.87 0.18 -0.09 3.56 -4.77 1.47
144	*Tamarindus indica* L.*; Citrus aurantifolia*	palmitic acid	4976	540.40	-150.19	1.50 0.51 -2.49 -13.78 -0.65 24.21
145	*Tamarindus indica* L.	palmitoleic acid	4810	561.90	-173.64	-2.01 -0.16 0.64 -15.86 -2.98 24.12
146	*Tamarindus indica* L.	heptadecanoic acid	5038	572.20	-115.80	-2.34 0.18 -0.09 2.63 -5.11 1.04
147	*Tamarindus indica* L.*; Citrus aurantifolia*	oleic acid	5190	555.70	-77.58	1.84 0.17 -0.03 2.59 -4.70 -0.75
148	*Tamarindus indica* L.*; Citrus aurantifolia*	linoleic acid	5156	577.80	-83.21	-2.09 -0.27 2.99 1.65 -4.34 -0.70
149	*Tamarindus indica* L.	linolenic acid	4562	520.80	-77.21	-0.91 0.30 -0.12 1.22 -4.04 -0.13
150	*Tamarindus indica* L.	(+)-Catechin	4134	458.30	-101.16	2.82 -0.15 0.02 2.73 -4.68 -0.27
151	*Tamarindus indica* L.	(-)-Epicatechin	4136	463.40	-64.19	1.63 0.04 3.03 4.05 -5.20 0.63
152	*Tamarindus indica* L.	Taxifolin	4134	467.00	-88.67	-0.14 -0.10 0.07 2.38 -4.60 -0.02
153	*Tamarindus indica* L.	Apigenin	3968	433.20	-64.02	1.14 -0.01 0.07 4.01 -4.95 0.25
154	*Tamarindus indica* L.	Eriodictyol	4136	461.00	-46.27	-2.23 0.03 -0.26 5.09 -4.90 1.14
155	*Tamarindus indica* L.	Luteolin	4044	456.00	-74.43	1.36 0.02 -0.04 2.65 -5.14 0.57
156	*Tamarindus indica* L.	Naringenin	4072	449.60	-66.20	-1.30 -0.04 -3.14 2.85 -5.00 0.36

No	Plants	Compound	Score	Area	ACE	Transformation
157	*Citrus aurantifolia*	cis-Verbenol	2984	332.20	-41.52	-1.24 -0.00 0.06 7.54 -5.35 0.55
158	*Citrus aurantifolia*	Nerol	3178	366.00	-44.41	1.93 -0.10 2.81 6.14 -5.12 0.30
159	*Citrus aurantifolia*	Neral	3296	379.10	-58.61	-0.59 0.61 -1.88 2.47 -13.51 22.79
160	*Citrus aurantifolia*	Germacrene B	3746	426.80	-58.08	-2.01 -0.51 2.96 5.57 -4.94 -0.19
161	*Citrus aurantifolia*	Octanal	3048	328.70	-103.18	-0.99 0.71 -0.16 -16.98 -1.64 24.73
162	*Citrus aurantifolia*	Nonanal	3292	371.60	-38.98	-0.76 -0.08 -0.00 2.88 -5.30 0.94
163	*Citrus aurantifolia*	(E)-Limonene oxide	3090	356.40	-123.86	1.46 -0.84 -2.73 -17.18 -1.91 24.35
164	*Citrus aurantifolia*	δ-Elemene	3792	438.50	-76.38	2.18 0.01 2.95 4.23 -4.85 0.11
165	*Citrus aurantifolia*	Decanal	3604	393.70	-56.91	0.74 0.10 -3.04 1.54 -5.10 0.72
166	*Citrus aurantifolia*	l-Carvone	3188	360.20	-134.63	2.54 0.85 0.08 -16.44 -1.90 24.86
167	*Citrus aurantifolia ;*	Cumin aldehyde	3082	346.40	-152.77	-1.88 -0.74 -2.69 -15.45 -1.43 25.94
168	*Citrus aurantifolia*	Perillaldehyde	3156	357.70	-157.65	1.14 -0.92 -2.91 -16.38 -1.36 25.36
169	*Citrus aurantifolia*	Tridecanal	4352	531.80	-164.71	-0.66 0.86 -0.20 1.75 -6.00 5.89
170	*Citrus aurantifolia*	Dodecyl acetate	4638	555.60	-109.59	0.86 -0.02 -0.06 6.57 -5.48 0.53
171	*Citrus aurantifolia*	Tetradecanal	4538	553.90	-164.12	-1.71 -0.88 3.02 0.73 -5.98 4.60
172	*Citrus aurantifolia*	Perillyl alcohol	3092	360.50	-42.65	1.82 0.21 -1.94 2.82 -12.70 22.46
173	*Citrus aurantifolia*	Pentadecanal	4692	563.50	-117.19	-2.54 0.05 3.08 5.32 -5.34 0.63
174	*Citrus aurantifolia*	Cedryl acetate	3910	455.40	-139.08	-1.48 0.01 -3.04 0.47 -4.90 0.05
175	*Citrus aurantifolia*	Cinnamyl alcohol	2866	321.90	-38.65	-1.64 0.38 -1.83 2.14 -12.56 22.11
176	*Citrus aurantifolia*	(E)-Nerolidol	4246	459.30	-44.22	-1.23 0.28 -0.09 4.34 -4.36 -0.14
177	Control	Saracatinib	6770	775,0	-57.22	-2.22 -1.10 -1.56 -9.72 -0.52 15.56

Docking of bioactive compounds-MMP-1human

No	Plants	Compounds	Score	Area	ACE	Transformation
1	*Curcuma xanthorrhiza* Roxb	curcumin	5118	627.00	-152.91	-1.35 -0.35 2.09 33.20 -26.91 9.83
2	*Curcuma xanthorrhiza* Roxb	Bisdemethoxycurcumin	4474	508.80	-135.62	-1.61 1.09 -3.00 3.61 -16.49 -10.69
3	*Curcuma xanthorrhiza* Roxb	Demethoxycurcumin	4802	550.90	-194.05	-1.64 0.85 -0.99 30.82 -24.02 2.80
4	*Curcuma xanthorrhiza* Roxb	Xanthorrhizol	4126	459.60	-130.53	-2.30 1.02 -2.64 4.09 -16.40 -13.46
5	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum	Ar-Curcumene	4034	422.80	-139.48	-0.39 0.37 1.78 7.35 -30.21 -0.48
6	*Curcuma xanthorrhiza* Roxb	β-Curcumene	3964	479.30	-165.04	-1.70 -0.95 0.05 2.89 -16.57 -11.11
7	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum*;*	Camphor	3036	323.00	-109.45	-0.21 0.14 -0.33 3.32 -16.58 -12.49
8	*Curcuma xanthorrhiza* Roxb	Ar-Turmerone	4064	483.60	-200.40	1.23 1.04 -2.92 2.67 -17.31 -9.78
9	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum	Zingiberene ; α-Zingiberene	3842	436.70	-153.63	0.88 0.11 0.78 43.30 -26.49 22.56
10	*Curcuma xanthorrhiza* Rox*b*	Zerumbone	3780	426.80	-127.74	1.69 -1.01 0.15 3.07 -16.60 -13.27
11	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum*;* *Citrus aurantifolia*	Geranyl acetate	3848	456.70	-124.62	-2.13 -0.43 0.02 3.77 -16.72 -12.42
12	*Curcuma xanthorrhiza Roxb;* *Zingiber officinale* var rubrum*;* *Citrus aurantifolia*	α-Pinene	3054	333.00	-119.66	1.74 -0.45 0.49 4.11 -16.47 -12.17
13	*Curcuma xanthorrhiza* Roxb	α-thujene	3312	371.50	-120.96	1.29 0.35 -2.59 3.15 -16.86 -11.85
14	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum*;* *Citrus aurantifolia*	Camphene	3016	321.40	-102.43	1.32 0.58 -2.69 3.40 -16.80 -12.47
15	*Curcuma xanthorrhiza* Roxb*;* *Zingiber officinale* var rubrum*;* *Citrus aurantifolia*	β-Pinene	2968	316.00	-88.05	1.99 -0.02 0.42 3.77 -16.44 -12.99
16	*Curcuma xanthorrhiza* Roxb	Cis-Pinane	3072	323.20	-104.37	2.49 -0.78 0.22 3.77 -16.55 -12.49
17	*Curcuma xanthorrhiza* Roxb*;*	Myrcene ; β-Myrcene	3556	382.60	-123.20	2.08 0.21 -2.94 3.16 -16.68 -11.92

No	Plants	Compounds	Score	Area	ACE	Transformation
	Citrus aurantifolia					
18	*Curcuma xanthorrhiza* Roxb	α-Terpinene	3170	366.90	-126.55	-1.86 -0.60 0.44 3.23 -17.02 -11.45
19	*Curcuma xanthorrhiza* Roxb; *Zingiber officinale* var rubrum	1,8-Cineole	3230	339.80	-108.49	2.55 0.05 -2.79 3.53 -16.70 -12.55
20	*Curcuma xanthorrhiza* Roxb; *Citrus aurantifolia*	(Z)-β-Ocimene	3300	379.50	-119.94	-2.20 0.50 3.14 4.14 -16.44 -11.80
21	*Curcuma xanthorrhiza* Roxb; *Citrus aurantifolia*	α-Terpineol	3206	348.80	-118.10	0.76 0.30 1.93 32.54 -26.45 7.95
22	*Curcuma xanthorrhiza* Roxb; *Zingiber officinale* var rubrum; *Tamarindus indica* L. ; *Citrus aurantifolia*	Terpinen-4-ol	3304	368.10	-135.22	1.88 -0.33 0.23 3.37 -16.60 -11.33
23	*Curcuma xanthorrhiza* Roxb	Ethyl-4E-octenoate	3504	412.40	-112.20	-0.12 -1.17 -2.19 12.40 -9.54 -13.48
24	*Curcuma xanthorrhiza* Roxb	Dihydro citronellol acetate	4022	444.00	-132.81	1.56 -0.08 1.90 32.81 -26.94 8.44
25	*Curcuma xanthorrhiza* Roxb	α-Cubebene	3866	419.30	-113.56	-2.22 0.25 0.94 2.81 -17.56 -13.21
26	*Curcuma xanthorrhiza* Roxb	(Z)-β-Damascenone	3686	434.80	-144.26	1.65 -0.59 0.08 2.92 -17.10 -11.17
27	*Curcuma xanthorrhiza* Roxb	Methyl perillate	3504	399.20	-129.15	1.56 -0.95 0.37 2.89 -16.85 -11.58
28	*Curcuma xanthorrhiza* Roxb	(Z)-Isoeugenol	3356	387.10	-139.50	-1.41 -0.21 0.04 2.41 -16.30 -11.75
29	*Curcuma xanthorrhiza* Roxb	α-Cis-bergamotene	4076	459.70	-114.92	-1.95 0.90 -3.11 3.66 -16.85 -12.98
30	*Curcuma xanthorrhiza* Roxb	Methyl undecanoate	3838	414.00	-123.02	0.47 1.23 -2.39 3.11 -16.68 -10.89
31	*Curcuma xanthorrhiza* Roxb	β-Humulene	3854	458.40	-145.28	1.11 -1.01 0.04 3.54 -16.92 -11.77
32	*Curcuma xanthorrhiza* Roxb	(Z)-β-Farnesene	4194	481.40	-164.00	-0.77 -1.02 0.67 2.75 -16.33 -12.86
33	*Curcuma xanthorrhiza* Roxb; *Zingiber officinale* var rubrum; *Citrus aurantifolia*	(E)-caryophyllene	3740	421.40	-178.22	1.51 -0.47 1.85 32.74 -26.44 8.24
34	*Curcuma xanthorrhiza* Roxb	γ-elemene	3790	451.00	-152.49	2.31 -0.20 -2.38 2.61 -17.39 -12.46
35	*Curcuma xanthorrhiza* Roxb	(E)-β-farnesene	4066	466.30	-151.97	-1.52 -0.31 2.09 33.08 -26.62 7.76
36	*Curcuma xanthorrhiza* Roxb	γ-Curcumene	4064	493.70	-179.73	1.31 1.07 -2.77 2.62 -17.20 -10.52
37	*Curcuma xanthorrhiza* Roxb;	β-Bisabolene	4206	496.50	-182.71	-1.19 -1.10 0.18 2.44 -17.05 -9.69

No	Plants	Compounds	Score	Area	ACE	Transformation
	Citrus aurantifolia					
38	*Curcuma xanthorrhiza* Roxb	(Z)-γ-Bisabolene	3914	415.50	-120.10	-2.95 0.43 2.95 3.56 10.27 -19.13
39	*Curcuma xanthorrhiza* Roxb	β-sesquiphellandrene	4070	482.90	-161.36	-1.28 0.76 -3.04 2.77 -17.02 -11.20
40	*Curcuma xanthorrhiza* Roxb*; Zingiber officinale* var rubrum*; Citrus aurantifolia*	Caryophyllene oxide	3734	440.80	-131.36	-1.24 -0.17 0.12 3.25 -16.75 -12.72
41	*Curcuma xanthorrhiza* Roxb	Citronellyl pentanoate	4398	506.20	-125.66	1.48 1.23 -2.74 2.93 -16.87 -11.95
42	*Curcuma xanthorrhiza* Roxb	Cis-cadin-4-en-7-ol	3790	455.50	-157.98	-1.32 -0.01 -0.20 3.53 -16.43 -12.62
43	*Curcuma xanthorrhiza* Roxb	Cubenol	3808	442.20	-141.80	-1.97 -0.71 -0.08 2.63 -17.49 -11.93
44	*Curcuma xanthorrhiza* Roxb	α-Eudesmol	3844	454.20	-136.45	1.23 0.22 -3.03 3.04 -16.65 -12.75
45	*Curcuma xanthorrhiza* Roxb	(E)-Amyl cinnamic alcohol	4152	449.60	-150.25	-2.78 1.19 -2.65 2.97 -16.92 -9.63
46	*Curcuma xanthorrhiza* Roxb	(E)-citronellyl tiglate	4074	436.00	-93.61	0.92 1.07 -2.33 3.69 -16.38 -14.71
47	*Curcuma xanthorrhiza* Roxb	β-Bisabolol	4032	467.00	-176.09	2.02 0.43 -1.17 33.40 -28.16 9.87
48	*Curcuma xanthorrhiza* Roxb	Ar-Curcumen-15-al	4078	471.60	-184.51	-1.19 -0.96 0.12 2.45 -16.85 -9.83
49	*Curcuma xanthorrhiza* Roxb	Chamazulene	3698	425.80	-187.11	-1.79 0.04 -3.14 2.59 -16.29 -11.76
50	*Curcuma xanthorrhiza* Roxb	(E, Z)-Farnesol	4138	483.70	-140.13	-1.37 1.23 2.91 3.17 -16.90 -12.39
51	*Curcuma xanthorrhiza* Roxb	Butyl dodecanoate	4610	514.10	-183.04	-1.82 -0.90 2.19 32.77 -27.17 6.14
52	*Curcuma xanthorrhiza Roxb; Zingiber officinale var rubrum; Citrus aurantifolia*	Linalool	3362	369.50	-115.58	1.93 0.08 -1.11 32.73 -26.49 8.81
53	*Curcuma xanthorrhiza Roxb; Zingiber officinale* var rubrum	α-Phellandrene	3244	353.00	-107.02	-1.10 -0.87 0.05 3.66 -16.73 -11.99
54	*Curcuma xanthorrhiza* Roxb	(E)-Ethyl cinnamate	3432	370.20	-138.99	1.27 0.57 -1.11 32.86 -27.92 9.25
55	*Curcuma xanthorrhiza* Roxb	Thujopsan-2-α-ol	3682	410.80	-163.67	1.63 -0.35 -1.16 32.63 -25.92 8.33
56	*Zingiber officinale* var rubrum	2-Heptanol	2882	310.50	-87.88	-2.17 0.10 1.92 32.39 -26.49 8.64
57	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Sabinene	3192	360.60	-114.96	1.65 -0.41 0.57 3.67 -16.65 -12.03
58	*Zingiber officinale* var rubrum	δ-3-Carene	3168	336.90	-104.01	-2.82 -0.42 -0.12 4.10 -16.72 -12.44

No	Plants	Compounds	Score	Area	ACE	Transformation
59	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	p-Cymene	3226	367.30	-129.03	0.70 0.71 -3.12 3.10 -16.65 -11.36
60	*Zingiber officinale* var rubrum; *Citrus aurantifolia ;*	Limonene	3182	367.40	-108.87	-1.38 -0.49 -0.00 3.51 -16.52 -12.06
61	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	β-Phellandrene	3250	363.20	-107.14	-1.97 -0.29 0.25 2.95 -17.08 -11.95
62	*Zingiber officinale* var rubrum	2-Heptyl acetate	3554	394.10	-118.20	2.28 -0.95 -2.52 12.70 -9.02 -13.40
63	*Zingiber officinale* var rubrum	Trans-β-ocimene	3326	386.00	-90.87	1.78 -0.76 -0.13 3.39 -16.78 -12.66
64	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	γ-Terpinene	3240	367.30	-111.53	1.97 -0.48 0.33 3.82 -16.60 -12.07
65	*Zingiber officinale* var rubrum	Terpinolene ; alpha terpinolene	3234	350.00	-95.55	1.12 -0.71 0.05 4.31 -16.98 -12.14
66	*Zingiber officinale* var rubrum	2-Nonanone	3238	376.00	-130.05	1.73 -1.22 -2.29 12.16 -9.00 -12.99
67	*Zingiber officinale* var rubrum	Trans-sabinene hydrate	3144	357.40	-95.41	-0.96 0.95 2.82 3.60 -17.14 -12.43
68	*Zingiber officinale* var rubrum	Camphene hydrate	3082	329.20	-120.27	2.56 -0.25 -0.03 3.58 -16.51 -12.12
69	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	Citronellal	3428	403.40	-121.05	-1.93 0.46 -3.13 2.49 -16.40 -11.25
70	*Zingiber officinale* var rubrum	Isoborneol ; Borneol	2956	318.60	-96.77	-1.56 -0.30 -3.11 3.85 -16.77 -12.32
71	*Zingiber officinale* var rubrum	Myrtenal	3040	333.30	-141.72	1.83 0.54 0.37 13.10 -8.38 -12.25
72	*Zingiber officinale* var rubrum	Linalyl formate	3692	443.50	-118.62	-0.77 0.54 -3.06 3.46 -16.73 -11.91
73	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	β-Citronellol	3570	393.20	-102.71	1.08 0.61 -3.05 3.85 -16.97 -11.70
74	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	Geraniol	3354	371.50	-110.45	2.06 -0.35 -1.09 33.18 -26.86 7.95
75	*Zingiber officinale* var rubrum	Trans-2-decenal	3390	377.20	-141.49	1.43 0.88 0.79 12.95 -7.37 -10.57
76	*Zingiber officinale* var rubrum; *Citrus aurantifolia*	Geranial	3342	373.80	-83.59	0.71 0.88 -2.46 4.20 -16.51 -13.05
77	*Zingiber officinale* var rubrum	Bornyl acetate	3672	415.40	-123.50	-1.42 -0.75 0.37 3.44 -16.92 -11.98
78	*Zingiber officinale* var rubrum	2-Undecanone	3536	400.70	-81.33	-1.14 -0.85 0.21 4.38 -16.18 -13.67
79	*Zingiber officinale* var rubrum	Myrtenyl acetate	3648	415.90	-116.11	-2.10 0.82 -3.03 4.14 -16.62 -12.67

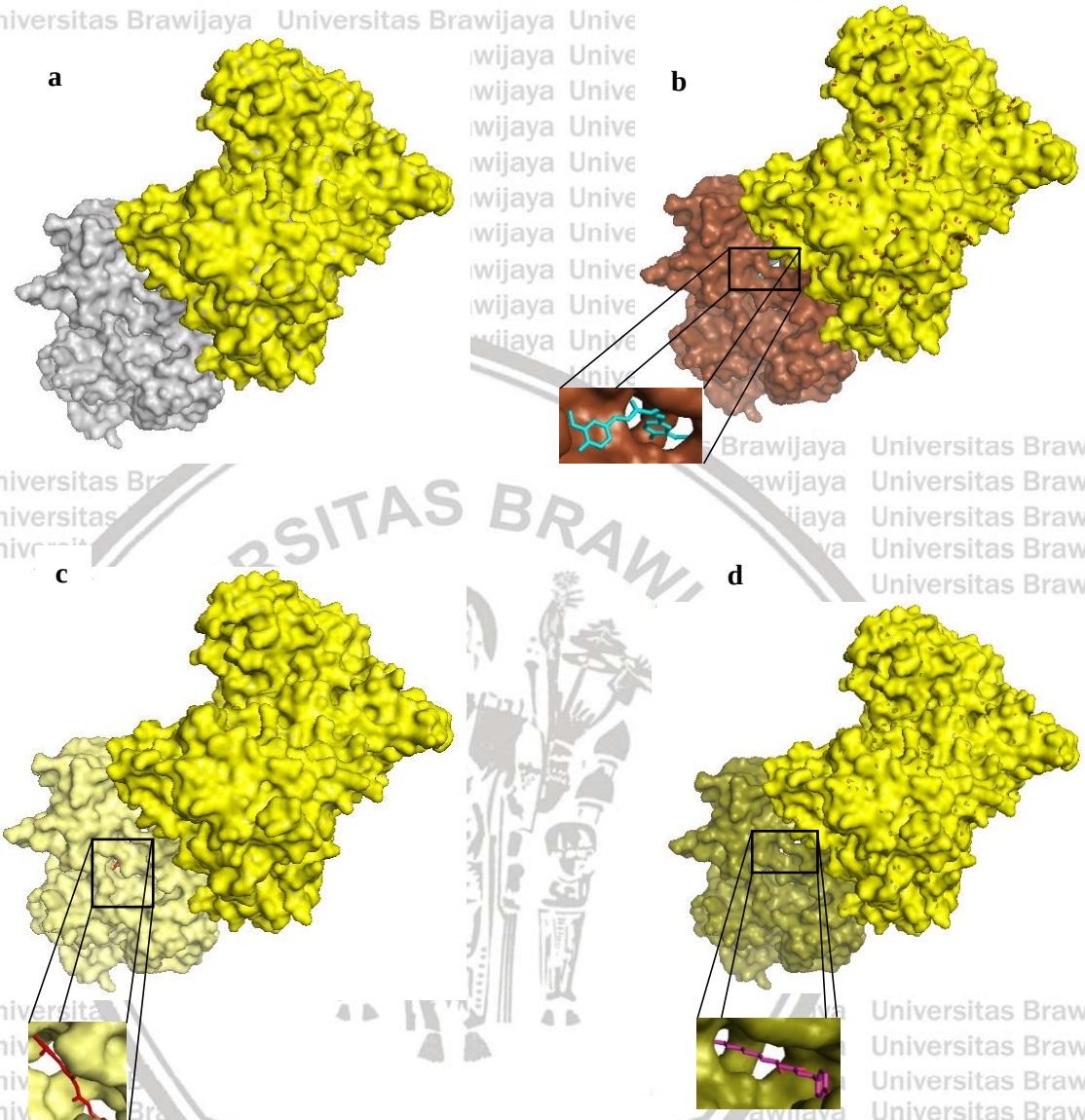
No	Plants	Compounds	Score	Area	ACE	Transformation
80	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Neryl acetate	4130	479.30	-147.52	-2.01 -1.24 -0.03 2.49 -17.21 -9.67
81	*Zingiber officinale* var rubrum	α-Copaene	3818	420.30	-132.22	-2.32 -1.31 -0.62 2.85 -17.18 -12.44
82	*Zingiber officinale* var rubrum	β-Elemene	3916	465.40	-145.54	1.67 1.10 -2.90 2.55 -16.93 -12.28
83	*Zingiber officinale* var rubrum	Isocaryophyllene	3766	428.80	-140.04	-1.32 0.29 -2.87 2.66 -16.99 -12.64
84	*Zingiber officinale* var rubrum	α-Humulene	3728	442.20	-125.47	-1.91 -0.69 0.31 2.88 -17.23 -12.67
85	*Zingiber officinale* var rubrum	Allo-aromadendrene	3668	423.20	-115.91	-1.37 -0.02 -2.95 3.49 -16.98 -13.12
86	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Germacrene D	3750	439.00	-121.34	-0.95 0.39 -2.89 2.92 -17.50 -12.95
87	*Zingiber officinale* var rubrum	α-Selinene	3848	457.90	-142.76	1.87 0.44 -2.84 3.20 -17.09 -12.42
88	*Zingiber officinale* var rubrum	α-Muurolene	3832	448.90	-153.02	-2.48 -0.80 0.16 2.93 -17.01 -12.30
89	*Zingiber officinale* var rubrum	Trans,trans-α-farnesene	4110	478.30	-173.12	-0.65 0.78 0.69 14.06 -7.17 -10.67
90	*Zingiber officinale* var rubrum	δ-Cadinene	3894	454.10	-172.72	-1.24 0.86 -3.10 3.23 -17.19 -10.95
91	*Zingiber officinale* var rubrum	γ-Eudesmol	3904	454.30	-108.71	-2.52 -0.45 0.08 3.83 -17.17 -13.01
92	*Zingiber officinale* var rubrum	β-Eudesmol	3874	448.80	-143.25	-2.21 -0.23 0.27 2.85 -17.40 -12.30
93	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	α-Bisabolol	4068	458.30	-161.52	-2.23 0.75 -0.82 31.80 -25.47 7.27
94	*Zingiber officinale* var rubrum	Cis,cis-farnesol	4150	459.60	-147.67	-1.55 -0.51 2.03 32.40 -25.99 7.29
95	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Trans,trans-farnesol ; Farnesol	4094	454.00	-125.11	-0.94 1.15 -0.29 3.49 -16.51 -13.30
96	*Zingiber officinale* var rubrum	Trans,trans-farnesal	4094	454.00	-125.11	-0.94 1.15 -0.29 3.49 -16.51 -13.30
97	*Zingiber officinale* var rubrum*; Citrus aurantifolia*	Phytol	4730	555.50	-161.87	-1.64 0.52 -1.11 31.82 -24.80 6.18
98	*Zingiber officinale* var rubrum	6-gingerol	4494	521.80	-208.01	2.62 -0.82 2.11 33.04 -29.27 9.05
99	*Zingiber officinale* var rubrum	8-gingerol	5222	590.40	-142.79	-1.59 -0.98 0.29 3.54 -16.63 -10.35.
100	*Zingiber officinale* var rubrum	6-shogaol	4122	457.40	-109.18	-2.78 -1.03 1.00 32.75 -24.81 7.03
101	*Zingiber officinale* var rubrum	8-shogaol	4738	549.30	-140.54	1.43 0.48 -3.06 3.06 -16.43 -14.05
102	*Tamarindus indica* L.	3-methyl-2-butanone	2488	263.20	-82.05	2.57 0.75 0.48 12.04 -9.07 -12.25

No	Plants	Compounds	Score	Area	ACE	Transformation
103	*Tamarindus indica* L.	1 –penten-3-one	2402	263.90	-82.03	0.31 -1.16 -2.26 11.96 -8.74 -12.48
104	*Tamarindus indica* L.	(E)-2-butenal	2012	237.40	-78.93	-2.64 1.04 -1.69 22.40 -22.25 11.51
105	*Tamarindus indica* L.	hexanale	2636	295.90	-95.45	1.30 -0.94 -2.14 11.82 -8.93 -12.63
106	*Tamarindus indica* L.	(E)-2-pentenal	2436	256.70	-92.03	0.34 0.88 -0.23 12.39 -9.08 -11.87
107	*Tamarindus indica* L.	3-methylbutanol	2324	283.40	-100.95	-0.63 0.93 2.34 21.19 -22.65 13.33
108	*Tamarindus indica* L.	hydroxyacetone	1902	218.10	-74.90	2.44 0.87 1.00 21.65 -23.40 13.16
109	*Tamarindus indica* L.	5-methyl-2(3H)-furanone	2292	277.20	-110.37	-1.93 0.22 0.82 20.59 -23.20 13.83
110	*Tamarindus indica* L. *; Citrus aurantifolia*	trans-linalool oxide (furanoid)	3324	376.30	-116.87	-0.13 -0.09 -1.11 32.75 -26.14 8.45
111	*Tamarindus indica* L.	acetic acid	1494	161.40	-11.19	-2.41 -1.25 -0.23 -4.80 -8.68 -31.06
112	*Tamarindus indica* L.	furfural	2268	279.10	-99.16	-2.24 -0.97 0.55 21.38 -21.87 12.71
113	*Tamarindus indica* L.	2-acetylfuran	2546	270.90	-106.36	-0.90 -0.55 2.72 12.35 -8.90 -12.07
114	*Tamarindus indica* L.	pyrrole	2058	235.60	-100.64	0.62 1.11 -0.24 21.49 -22.85 13.51
115	*Tamarindus indica* L.	octanol	3032	372.70	-123.10	-0.65 1.07 -2.10 22.44 -21.43 10.76
116	*Tamarindus indica* L.	5-methylfurfural	2576	281.00	-98.96	-1.28 0.49 0.78 12.75 -8.04 -11.83
117	*Tamarindus indica* L.	isomaltol	2578	285.40	-110.22	-2.21 -0.66 -2.21 12.45 -8.90 -11.30
118	*Tamarindus indica* L.	γ-butyrolactone	2096	259.20	-83.85	-0.84 0.35 -2.65 21.09 -22.19 13.49
119	*Tamarindus indica* L.	phenylacetaldehyde	2800	313.20	-125.48	-0.46 0.45 1.18 12.96 -8.55 -12.00
120	*Tamarindus indica* L.	2-methylbutyric acid	2448	256.80	-93.00	2.42 -0.90 2.80 12.32 -9.13 -11.69
121	*Tamarindus indica* L.	2,3-dimethylmaleic anhydride	2458	257.40	-81.57	2.96 -0.95 -0.17 14.71 3.08 -16.44
122	*Tamarindus indica* L.	methyl salicylate	2930	328.20	-87.12	-0.93 0.70 -3.12 3.47 -16.79 -11.64
123	*Tamarindus indica* L.	β-damascenone	3698	440.90	-157.31	1.18 -0.22 0.21 2.47 -16.93 -11.84
124	*Tamarindus indica* L.	hexanoic acid	2652	300.10	-108.19	0.64 -0.88 -2.33 12.22 -8.25 -11.79
125	*Tamarindus indica* L.	geranylacetone	3940	478.20	-145.67	2.19 0.21 -2.34 2.21 -18.04 -11.66
126	*Tamarindus indica* L.	guaiacol	2732	320.40	-138.28	-0.39 -0.92 -0.84 21.16 -22.48 13.43
127	*Tamarindus indica* L.	benzyl alcohol	2688	285.30	-109.71	0.06 -0.97 -2.51 12.36 -8.67 -12.51
128	*Tamarindus indica* L.	2-phenylethanol	2890	310.90	-122.46	0.28 -0.98 -2.30 12.55 -8.63 -12.31

No	Plants	Compounds	Score	Area	ACE	Transformation
129	*Tamarindus indica* L.	maltol	2636	314.30	-121.34	-2.35 -0.33 1.94 21.34 -22.29 12.86
130	*Tamarindus indica* L.	2-(hydroxyacetyl)furan	2604	282.60	-111.18	-1.72 -0.41 -2.36 12.35 -8.26 -11.75
131	*Tamarindus indica* L.	pyrrole-2-carboxaldehyde	2220	244.70	-92.04	1.03 -0.78 -2.27 12.14 -8.48 -12.12
132	*Tamarindus indica* L.	octanoic acid	3030	360.90	-124.24	0.99 -1.05 -2.36 12.02 -8.82 -12.46
133	*Tamarindus indica* L.	eugenol	3270	379.70	-126.67	-1.54 0.24 -2.92 3.05 -17.12 -11.20
134	*Tamarindus indica* L.	nonanoic acid	3326	376.60	-118.56	-1.37 1.12 1.23 11.75 -9.01 -13.90
135	*Tamarindus indica* L.	p-vinylguaiacol	3026	324.80	-80.40	2.01 -0.21 -2.79 4.26 -16.81 -12.09
136	*Tamarindus indica* L.	decanoic acid	3490	427.90	-126.37	-1.47 1.28 0.73 12.29 -8.65 -10.69
137	*Tamarindus indica* L.	dihydroactinidiolide	3326	380.00	-118.04	-0.80 1.29 3.14 2.98 -17.20 -11.89
138	*Tamarindus indica* L.	p-vinylphenol	2748	299.90	-122.08	-2.16 -0.73 -2.81 13.18 -7.85 -11.17
139	*Tamarindus indica* L.	benzoic acid	2594	284.90	-112.01	0.41 -0.71 -2.22 12.23 -8.94 -12.07
140	*Tamarindus indica* L.	lauric acid	3846	424.70	-102.72	-0.92 -0.34 2.08 32.73 -26.33 9.61
141	*Tamarindus indica* L.	vanillin	2820	290.70	-111.18	-1.59 -0.41 1.81 14.77 2.31 -15.57
142	*Tamarindus indica* L.	myristic acid	4410	472.70	-182.71	1.59 0.90 -0.93 31.30 -25.60 4.83
143	*Tamarindus indica* L.	pentadecanoic acid	4326	482.10	-186.71	0.52 -0.86 2.26 32.23 -26.55 5.39
144	*Tamarindus indica* L. *; Citrus aurantifolia*	palmitic acid	4432	518.10	-207.04	-2.77 -0.94 2.31 31.58 -26.02 4.73
145	*Tamarindus indica* L.	palmitoleic acid	4598	562.30	-153.76	1.73 0.77 -2.46 13.86 -7.76 -17.25
146	*Tamarindus indica* L.	heptadecanoic acid	4896	555.60	-207.60	-1.51 -0.84 2.23 31.08 -25.67 4.56
147	*Tamarindus indica* L. *; Citrus aurantifolia*	oleic acid	4896	574.40	-202.73	0.58 -1.11 1.91 2.80 -14.90 -15.37
148	*Tamarindus indica* L. *; Citrus aurantifolia*	linoleic acid	4560	545.90	-156.30	0.89 -1.47 -0.48 2.05 -16.80 -10.51
149	*Tamarindus indica* L.	linolenic acid	4536	553.20	-209.60	-2.45 -1.03 2.40 2.18 -15.91 -13.69
150	*Tamarindus indica* L.	(+)-Catechin	3952	461.60	-197.69	2.20 -1.19 0.50 3.10 -16.38 -9.91
151	*Tamarindus indica* L.	(-)-Epicatechin	3944	449.30	-194.67	2.47 -1.07 0.45 3.18 -16.71 -9.98
152	*Tamarindus indica* L.	Taxifolin	3904	459.50	-180.38	-0.84 -1.10 0.45 2.98 -16.90 -10.49

No	Plants	Compounds	Score	Area	ACE	Transformation
153	*Tamarindus indica* L.	Apigenin	3876	436.10	-176.35	1.13 1.16 -2.93 3.22 -16.63 -10.53
154	*Tamarindus indica* L.	Eriodictyol	4094	448.80	-172.14	-1.55 -0.57 1.99 33.64 -29.15 9.90
155	*Tamarindus indica* L.	Luteolin	3908	439.00	-88.68	-0.80 -1.08 0.42 4.92 -16.14 -13.90
156	*Tamarindus indica* L.	Naringenin	3982	437.40	-193.04	-1.62 -0.58 1.97 33.16 -28.47 10.03
157	*Citrus aurantifolia*	cis-Verbenol	2990	324.60	-100.32	-1.85 -1.34 1.05 3.45 -17.00 -12.54
158	*Citrus aurantifolia*	Nerol	3344	390.20	-114.29	1.33 -0.58 0.06 2.66 -16.87 -11.50
159	*Citrus aurantifolia*	Neral	3358	387.30	-119.75	0.95 0.52 3.09 3.48 -16.19 -11.75
160	*Citrus aurantifolia*	Germacrene B	3876	443.30	-149.63	1.28 -0.65 0.20 2.68 -17.05 -12.06
161	*Citrus aurantifolia*	Octanal	2938	352.80	-145.48	-3.12 0.99 -1.81 22.34 -22.23 11.16
162	*Citrus aurantifolia*	Nonanal	3268	374.60	-109.64	0.60 -1.12 -2.06 11.43 -9.72 -14.36
163	*Citrus aurantifolia*	(E)-Limonene oxide	3172	369.30	-98.55	-1.87 -0.53 0.36 2.87 -16.97 -12.46
164	*Citrus aurantifolia*	δ-Elemene	3848	425.00	-116.95	1.95 -0.36 1.99 32.17 -24.78 7.86
165	*Citrus aurantifolia*	Decanal	3426	400.70	-124.97	-1.66 1.18 1.00 11.63 -9.15 -14.39
166	*Citrus aurantifolia*	l-Carvone	3194	341.90	-117.19	0.43 0.24 2.07 32.86 -26.45 8.75
167	*Citrus aurantifolia*	Cumin aldehyde	3218	360.60	-89.40	1.00 0.52 -2.98 4.22 -16.38 -12.60
168	*Citrus aurantifolia*	Perillaldehyde	3166	366.30	-103.79	2.32 0.41 -2.92 3.92 -16.72 -12.07
169	*Citrus aurantifolia*	Tridecanal	3838	417.30	-162.19	-1.25 -0.92 2.17 32.70 -27.64 7.21
170	*Citrus aurantifolia*	Dodecyl acetate	4104	520.50	-109.47	1.75 -1.11 -2.17 11.93 -9.90 -15.66
171	*Citrus aurantifolia*	Tetradecanal	4080	447.70	-179.80	1.21 0.76 -0.87 32.32 -26.98 6.93
172	*Citrus aurantifolia*	Perillyl alcohol	3206	372.60	-100.04	-0.91 -0.61 0.33 4.15 -16.64 -11.90
173	*Citrus aurantifolia*	Pentadecanal	4252	525.20	-136.47	0.86 -1.24 -2.35 12.63 -8.36 -10.51
174	*Citrus aurantifolia*	Cedryl acetate	4030	469.90	-162.59	1.41 0.31 3.11 2.78 -16.73 -12.76
175	*Citrus aurantifolia*	Cinnamyl alcohol	2968	320.90	-111.92	1.78 0.23 1.91 32.51 -26.23 8.57
176	*Citrus aurantifolia*	Farnesene	4110	478.30	-173.12	-0.65 0.78 0.69 14.06 -7.17 -10.67
177	Control	Deoxyciclin	4856	521.50	-90.64	-2.33 -1.34 -0.51 3.95 -16.94 -14.65

Appendix 2 The result of complex proteins docking (SRC- compound)-PI3K



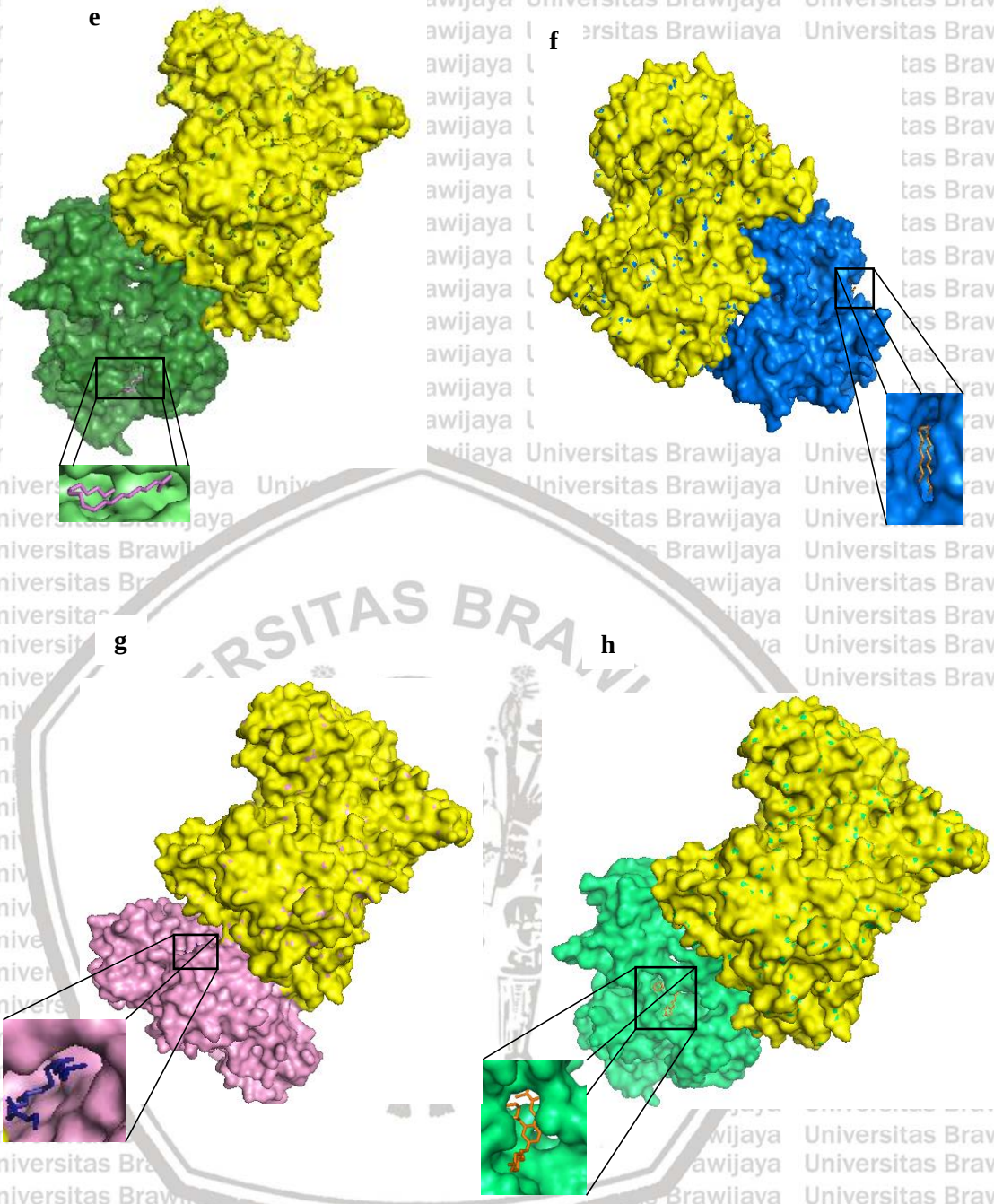
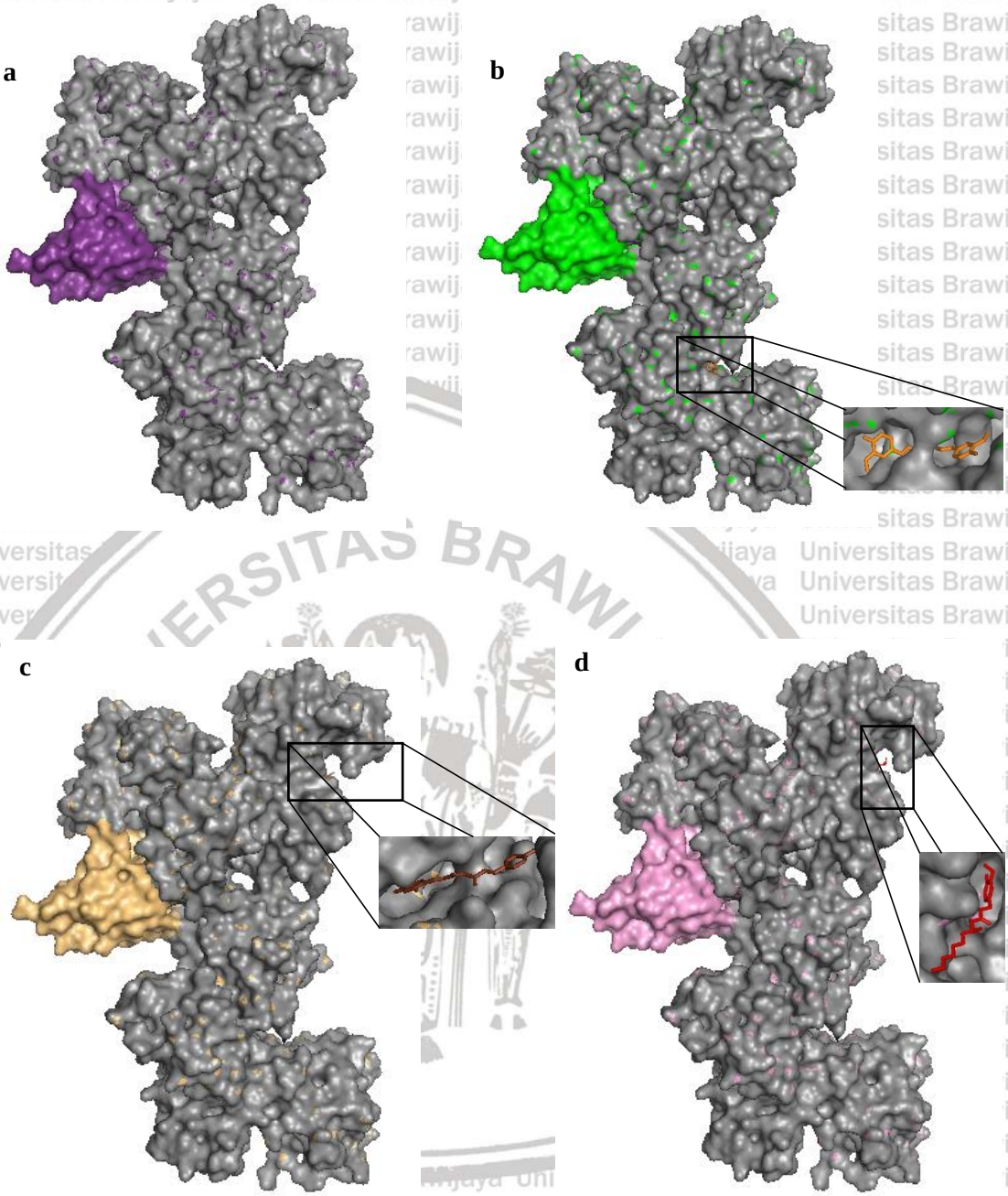


Figure A 17. Src complex docking. a) Src PI3K b) (Src-curcumin)-PI3K c) (Src-demethoxycurcumin)-PI3K d) (Src-8-gingerol)-PI3K e) (Src-linoleic acid)-PI3K f) (Src-oleic acid)-PI3K g) (Src-phytol)-PI3K h) (Src-saracatinib)-PI3K; Gray structure: Src wildtype protein; yellow structure: PI3K; brown structre: Src-curcumin complex; light yellow structure: Src-demethoxycurcumin complex; dark yellow: Src- 8-gingerol complex; light green structure: Src-linoleic acid complex; blue structure: Src-oleic complex; pink structure: Src-phytol; Src-saracatinib complex

(PknB- compound)-FhaA



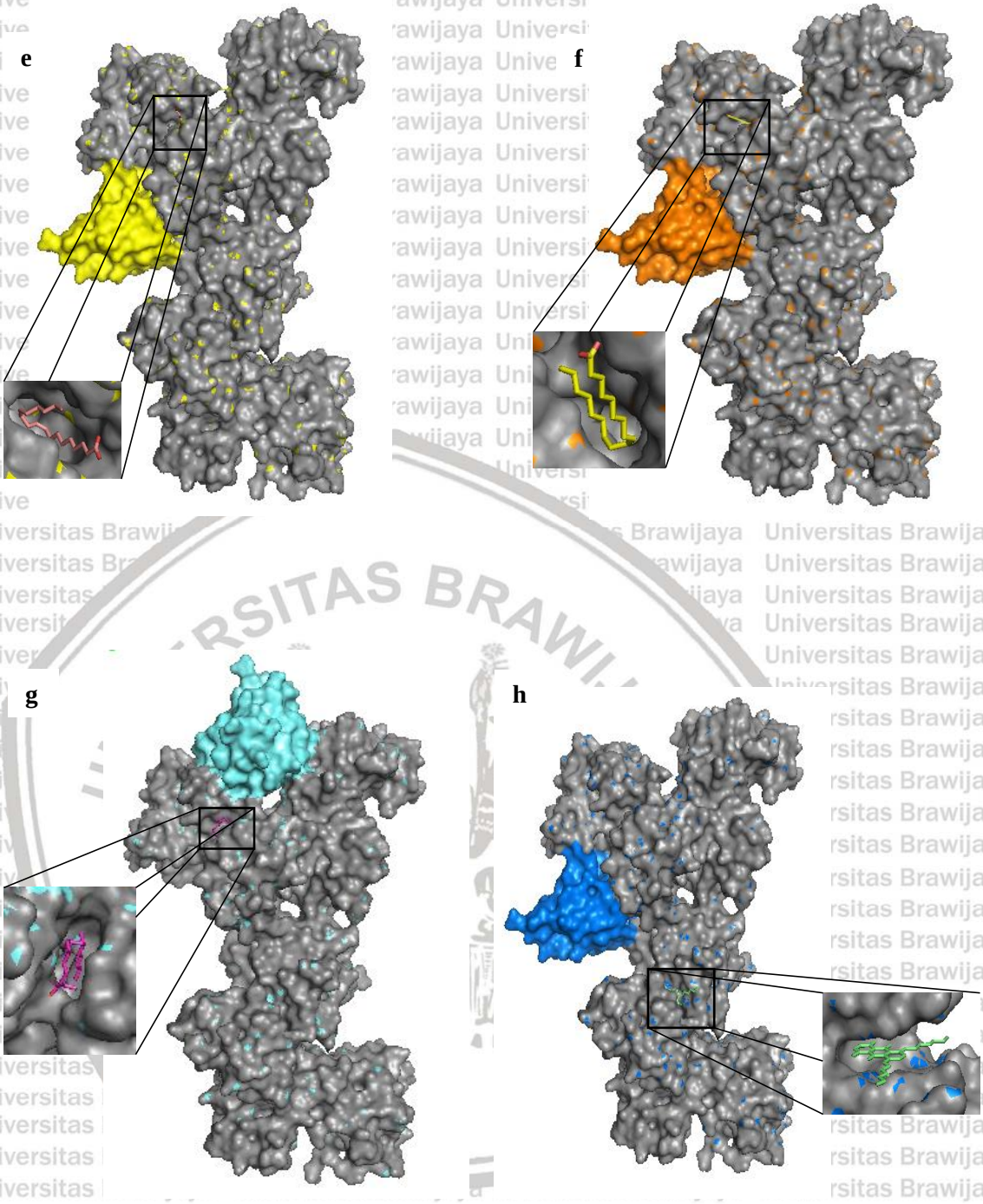


Figure A 18. PknB complex docking. a) PknB-FhaA b) (PknB-curcumin)-FhaA c) (PknB-demethoxycurcumin)-FhaA d) (PknB -8-gingerol)- FhaA e) (PknB -linoleic acid)- FhaA f) (PknB -oleic acid)- FhaA g) (PknB -phytol)- FhaA h) (PknB -saracatinib)- FhaA; Gray structure: PknB; purple: FhaA on PknB-FhaA complex; green : FhaA on PknB-curcumin complex; light brown: FhaA on PknB-demethoxycurcumin complex; pink: FhaA on PknB-8-gingerol complex; yellow: FhaA on PknB-linoleic acid complex; orange: FhaA on PknB-oleic complexl; light blue: FhaA on PknB-phytol complex; dark blue: FhaA on PknB-mitoxantrone complex

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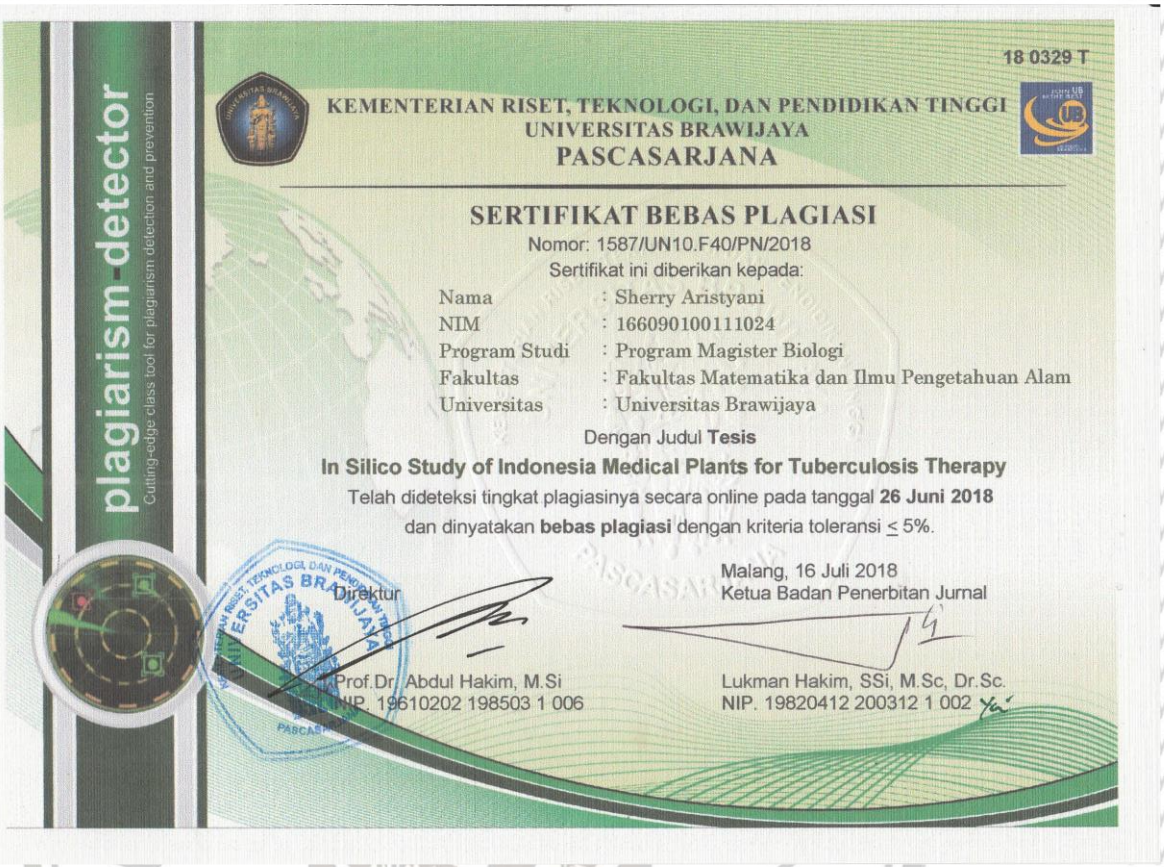

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Pharmacogn J. 2018; 10(5): xx-xx
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Original Article

Network Analysis of Indigenous Indonesia Medical Plants for Treating Tuberculosis

Sherry Aristyani, Sri Widyarti, Sutiman Bambang Sumitro*

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 Material:** 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. **Conclusions:** 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, Indonesia medical plants, Network, Tuberculosis.

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History

- Submission Date: xx-xx-xxxx;
- Review completed: xx-xx-xxxx;
- Accepted Date: xx-xx-xxxx

DOI : 10.5530/pj.2017.4.x

Article Available online
http://www.phcogj.com/v10/i5

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).

Cite this article: Aristyani S, Widyarti S, Sumitro SB. Network Analysis of Indigenous Indonesia Medical Plants for Treating Tuberculosis. Pharmacog J. 2018;10(5):x-x.

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 stringApp 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 specvies 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

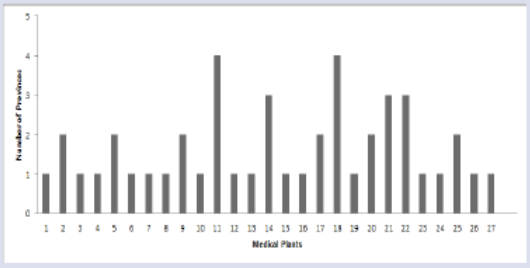

Figure 1: Distribution of medical plants utilization used for tuberculosis.

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]

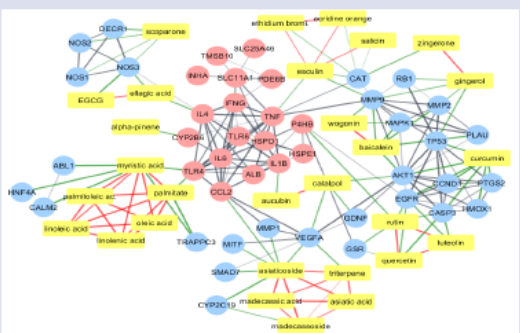

Figure 3: Active compound-protein related tuberculosis pathway network. The red circle represents protein involved tuberculosis disease mechanism. The blue circle represents proteins which are not involved in tuberculosis mechanism. The yellow rectangular represent active compounds from medical plants.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

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.

ACKNOWLEDGMENT

The authors are thankful to Wulida Khoirunnisa and other members of Science complexity working group, Department of Biology, University of Brawijaya for providing a lot of knowledge to support this research.

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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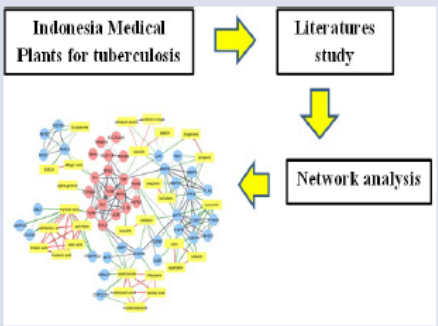
GRAPHICAL ABSTRACT



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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Cite this article: Aristyani S, Widyarti S, Sumitro SB. Network Analysis of Indigenous Indonesia Medical Plants for Treating Tuberculosis. Pharmacog J. 2018;10(5):x-x.