ASM Sc. J., 20(2), 2025
https://doi.org/10.32802/asmscj.2025.1763

Potential Drug Screening of *Alpinia galanga* (L.) Willd Bioactive Compound against Inhibitor Enoyl-Acyl Carrier Protein Reductase (INHA) *Mycobacterium tuberculosis*

A.M. Rosyada Yusuf[1], W.E. Putra[2]*, H. Susanto[1], D. Widiastuti[3], A. Hidayatullah[4], M.F. Heikal[1] and Sustiprijatno[5]

[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia.*
[2]*Biotechnology Study Program, Department of Applied Sciences, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia.*
[3]*Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Pakuan, West Java, Indonesia.*
[4]*Democratic Governance and Poverty Reduction Unit, United Nations Development Programme, Eijkman-RSCM Building, Jakarta, Indonesia.*
[5]*Research Center for Applied Botany, National Research and Innovation Agency, West Java, Indonesia.*

Tuberculosis is a respiratory disease caused by *Mycobacterium tuberculosis* that has remained a global endemic for decades and is expected to persist as a significant health challenge. Its incidence has been rising worldwide, particularly in Southeast Asia, including Indonesia. The combined treatment of tuberculosis that was carried out did not have significantly different results from that of a separate treatment. This molecular docking study targeted InhA protein with bioactive compounds from *Alpinia galanga*. InhA protein is a protein that has been the target of first-line treatment, namely isoniazid. InhA protein plays a role in synthesising mycolic acid, one of the constituents of *Mycobacterium tuberculosis* cell walls. *Alpinia galanga* has antimicrobial, anti-bacterial and other properties. The docking results showed that four bioactive compounds of *Alpinia galanga*, namely galanal A, pinobanksin, galangin, and alpinone had lower affinity values than the control drug (isoniazid). Based on the amino acid residues, these four compounds showed better hydrogen and hydrophobic bonding than the control drug (isoniazid). Based on literature studies, these four compounds also have antimicrobial and anti-bacterial properties. Therefore, by targeting InhA through NADH inhibition, the elongation of FAS II can potentially be suppressed.

Keywords: *Alpinia galanga;* in silico; InhA protein; medicinal plant; tuberculosis

I. INTRODUCTION

Tuberculosis (TB) is a respiratory disease that has become a global endemic for the past few decades caused by *Mycobacterium tuberculosis*. This disease is estimated to be difficult to eradicate in the next few decades, even though the WHO has declared a tuberculosis-free world by 2020. Until 2020, the majority of tuberculosis cases were concentrated in low-income and developing countries, with approximately 10% classified as multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). Indonesia and other Southeast Asian nations rank among the regions with the highest burden of MDR/RR-TB globally (WHO, 2020; Cohen *et al.*, 2019; Kemenkes RI, 2021). Every year, Indonesia experiences an increase in the number of TB patients with confirmed status by 8060 people and patients undergoing treatment each year by 4557 people (Kemenkes RI, 2021). TB transmission occurs through particulates or airborne droplets that come out of the mouth and nose of an infected person when coughing, talking, or singing (Centers for Disease

Corresponding author's email: wep.cendekia@gmail.com

Control and Prevention, 2016). In another study, it was stated that the risk factors for a person contracting tuberculosis were exposure to drug-resistant TB patients in health facilities and being people with HIV/AIDS (ODHA) (Angelia *et al.*, 2020). TB resistance arises due to multiple factors, including variations in the susceptibility of bacterial strains to drugs, substandard drug management, underlying cardiovascular conditions, HIV/AIDS infection, and alcohol consumption (Safaev *et al.*, 2021).

Currently, tuberculosis treatment involves first-line therapies, second-line therapies, and fixed-dose combinations (FDCs) (Sotgiu *et al.*, 2015; Jilani *et al.*, 2021; Lima *et al.*, 2017). FDCs are pre-formulated combination drugs packaged into a single tablet. According to the WHO Model List of Essential Medicines, FDCs are categorised into three formulations: two-drug combinations (ethambutol + isoniazid or isoniazid + rifampicin), three-drug combinations (ethambutol + isoniazid + rifampicin or ethambutol + pyrazinamide + rifampicin), and four-drug combinations (ethambutol + isoniazid + pyrazinamide + rifampicin) (WHO, 2011). The fixed-dose combination method has advantages in drug supply management, but the FDC formulation is no different from separate drugs, only combining these drugs in one capsule that can be consumed once (Albanna *et al.*, 2013). In a previous study it was demonstrated that there were no significant difference treatments between separate drug formulations using the FDC formulation in TB patients at the end of the intensive phase. Several factors such as the use of co-administered drugs are thought to reduce the effectiveness of the drug (Cesar, 2014).

Mycolic acid is one of the cell wall constituents, and it protects bacteria when in unfavourable conditions (Chiaradia *et al.*, 2017). Mycolic acid synthesis starts from acetyl-CoA carboxylase, which activates malonyl-KOA for fatty acid synthesis I (FAS I) (Goude & Parish, 2008). FAS I has a de novo synthesis of short chain fatty acids and produces hexacosanyl-S-CoA. The FAS II system will extend fatty acids synthesised by FAS I to produce meromycolic acid. In each cycle, fatty acids will elongate by adding two carbon units so that successive activities occur, namely -ketoacyl ACP reductase, trans 2 enoyl ACP reductase, (3R)-hydroxyacyl-ACP dehydrogenase and -ketoacyl ACP synthase (Goude & Parish, 2008). Enoyl acyl carrier protein reductase (InhA) is a protein that plays a role in the mycolic acid biosynthesis process in *M. tuberculosis* in the FAS II stage (He *et al.*, 2007). InhA protein has been the target of first-line treatment, namely isoniazid (PaweŁczyk & Kremer, 2014). In the case of resistance, isoniazid treatment does not work optimally in targeting the InhA protein due to mutations in katG so that this mycolic acid biosynthesis process continues (Duan *et al.*, 2014; Vilchèze *et al.*, 2014). This monofunctional enzyme such as InhA could be a key candidate for new drug targets for developing anti-TB drugs (Vilchèze *et al.*, 2014).

Alpinia galanga (galangal), a member of the Zingiberaceae family, possesses antibacterial properties. Previous studies have demonstrated its use in traditional medicine, particularly for reducing oxygen concentration in latent tuberculosis cases, where bacteria exist in a dormant and non-replicating state (Gupta *et al.*, 2014). Based on this background, a molecular docking study of the active compound of the plant *Alpinia galanga* was conducted against InhA protein which is expected to be a tool in the drug discovery development.

II. MATERIALS AND METHODS

A. Bioactive Compound Data Collection

About 75 structures of bioactive compounds derived from *Alpinia galanga* were obtained from a number of literatures (Samart, 2007; Tungmunnithum *et al.*, 2020; Manse *et al.*, 2017; Morita *et al.*, 1986). The CID number was recorded for validation purposes. The 3D structure of the bioactive compound was obtained from PubChem (https://pubchem.ncbi.mlm.nih.gov). Each compound CID number was recorded for further validation purposes.

B. Lipinski Rule of Five Assessment

All compounds downloaded from PubChem will first be tested using the Lipinski rule of five parameters (https://www.scfbiolitd.res.in/software/drugdesign/lipinski.jsp). Compounds used in oral therapy are generally in the form of small molecules (Goodwin *et al.*, 2017). This test aims to determine whether the bioactive compound can be developed as an oral drug based on its physical and chemical characteristics (Lipinski, 2004).

C. Target Protein Preparation

Enoyl acyl carrier protein reductase (InhA) was used as a target in this study. InhA has been the target of first-line treatment, namely isoniazid and plays a role in the biosynthesis of mycolic acid in *M. tuberculosis* which catalyses the reduction of long-chain *trans 2-enoyl-ACP* in the FAS-II (Fatty acid Synthase - II) pathway (He *et al.*, 2007; PaweŁczyk & Kremer, 2014). The InhA structure (2IED) is downloaded from the RSCB PDB (https://www.rscb.org/) in PDB format. The downloaded protein then purifies the target protein from native ligands and water molecules using PyMol (https://www.pymol.org).

D. Molecular Docking and Visualisation

The docking process uses the PyRx software (https://pyrx.sourceforge.io/). Chemical compounds are minimized and converted to pdbqt format to facilitate docking. InhA is converted to pdbqt format before docking. In this study, the control drug used was isoniazid, which is the first-line drug for tuberculosis and plays a role in inhibiting mycolic acid synthesis (Widodo *et al.*, 2016). The dimensions used in the docking process are X=75.5359Å, Y= 78.6879Å, and Z= 85.7672Å. Two types of visualization are used, namely 2D and 3D visualisation. For 3D visualisation using PyMol (https://www.pymol.org), while for 2D visualisation using LigPlot (https://www.ebi.ac.uk/thronton-srv/software/LigPlus). After that, 4 bioactive compounds with the lowest bond energy values were selected for visualisation.

III. RESULTS AND DISCUSSION

The results of 75 natural compounds from the *Alpinia galanga* plant selected 4 compounds that have binding affinity interactions with the best InhA target protein, namely galanal A (3050416), pinobanksin (73202), galangin (5281616), and alpinone (5317747). These compounds had lower affinity values than the control (Isoniazid; -5.6 kcal/mol), ranging from -8.8 kcal/mol to -8.5 kcal/mol (Table 1).

From the results of visualisation analysis, the natural compound with the best binding affinity compared to other compounds is Galanal A (-8.8 kcal/mol). Galanal A binds to InhA protein, it is found that hydrophobic bond interactions in the Phe97 section; Ile95; Gly14; Ala94; Ile16; Gly40 and hydrogen bond interactions on the Gly96 moiety; Ile15; Phe41. The second compound after Galanal A is Pinobanksin (-8.8 kcal/mol). Pinobanksin binds to the target protein and hydrophobic interactions are found at the Leu 63; Gly40; Ile95; Ile47 as a hydrophobic bond as well as Thr39; Ile15; Gly14 as a hydrogen bond.

Galangin (-8.5 kcal/mol) is the third compound after pinobanksin. Galangin binds to InhA proteins at the Ala94, Ile95 moieties; Thr196; Ile21; Tyr158; Gly192; Phe149; Pro193 with hydrophobic bonds and bound to the Gly96 moiety; met199; Ile194; Ala198; Leu197 with hydrogen bonds. The fourth compound after galangin is Alpinone (-8.5 kcal/mol) which has the same binding affinity as galangin. Alpinone only has hydrogen bonds when it binds to the InhA protein. Alpinone binding to the target protein is at the Pro193; Phe149; met199; Tyr158; Gly192; Ile194; Ile21; met147; Ser20; Gly14; Ala94; Leu197; Thr196; Ile16.

Table 1. Docking results from 5 bioactive compounds in *Alpinia galanga*

No	Compound	Affinity (kcal/mol)	Amino Acid	Interaction
1	Galanal A	**−8.8**	Phe97; **Ile95**; **Gly14**; Ala94; Ile16; Gly40	**Hydrophobic interactions**
			Gly96	**Hydrogen bond** (3.15)
			Ile15	**Hydrogen bond** (3.06)
			Phe41	**Hydrogen bond** (2.98)
2	Pinobanksin	**−8.6**	Leu 63; Gly40; **Ile95**; Ile47	**Hydrophobic interactions**
			Thr39	**Hydrogen bond** (2.98)
			Ile15	**Hydrogen bond** (3.01 and 3,31)
			Gly14	**Hydrogen bond** (3.06)
3	Galangin	**−8.5**	Ala94, **Ile95**; **Thr196**; **Ile21**; Tyr158; Gly192; **Phe149**; Pro193	**Hydrophobic interactions**
			Gly96	**Hydrogen bond** (3,18 and 2.82)
			Met199	**Hydrogen bond** (3.18)
			Ile194	**Hydrogen bond** (3.01)
			Ala198	**Hydrogen bond** (2.88)
			Leu197	**Hydrogen bond** (2.79)
4	Alpinone	**−8.5**	Pro193; **Phe149**; Met199; Tyr158; Gly192; **Ile194**; **Ile21**; Met147; **Ser20**; **Gly14**; Ala94; **Leu197**; **Thr196**; Ile16	**Hydrophobic interactions**
5	Isoniazid	**−5.6**	Leu63; **Ile95**; Ile47; Ile15; Gly40	**Hydrophobic interactions**
			Gly14	**Hydrogen bond** (3.06 and 3.31)
			Thr39	**Hydrogen bond** (2.98)

* Note: the bold mark represents the amino acid NADH binding site residues

Mycobacterium tuberculosis has a complex cell wall composed of long-chain mycolic acids, a cross-linked peptidoglycan network, and arabinogalactan (Bhat *et al*., 2017). The enoyl-acyl carrier protein reductase (InhA) is a key enzyme involved in mycolic acid biosynthesis and serves as a critical target for tuberculosis treatment (He *et al*., 2007). In this study, isoniazid, a first-line anti-tuberculosis drug, was selected as a control due to its ability to target the InhA protein (Marrakchi *et al*., 2000). As a prodrug, isoniazid inhibits mycolic acid synthesis by activating catalase/peroxidase enzymes (KatG) and $MnCl_2$, leading to the formation of isonicotinoyl anions (radicals). These radicals covalently bind to the NADH active site of InhA, thereby inhibiting its function (Palomino *et al*., 2014; Jena *et al*., 2014).

The docking results of 75 active compounds of *Alpinia galanga* contained 4 compounds that showed the results with the best binding affinity values compared to the control drug isoniazid seen from the parameters of affinity values and amino acid residues (Table 1). These four natural compounds from *Alpinia galanga* showed that they could bind stably compared to the control. The binding affinity value indicates the compound's ability to bind to the target protein (Thafar *et al*., 2019). The lower the binding affinity value, the more reactive the molecule is, and it is predicted to interact and bind to the target protein spontaneously (Damayanti *et al*., 2017).

In molecular docking studies, amino acid residue parameters are used to assess the strength of interactions between a compound and its target protein, particularly through hydrogen bonding. The ability of a compound to bind to the same amino acid residues at the active site is a key factor in evaluating its potential as an inhibitor (Fajar *et al*., 2021). Hydrogen bonds facilitate substrate interactions with the target protein by forming new bonds within the protein-ligand complex (Bégué *et al*., 2008; Zhao *et al*., 2011). The four analysed compounds are associated with a crucial NADH-binding residue, suggesting their potential to inhibit NADH function. Inhibition of NADH can inhibit enzymatic activation because NADH binds to InhA so that it will

inactivate the fatty acid-II (FAS-II) elongation pathway thereby inhibiting the synthesis of mycolic acid as one of the building blocks of cell walls (Vögeli *et al*., 2018; Takayama *et al*., 2005). The four compounds from the *Alpinia galanga* plant have a range of hydrogen bond distance values between 2.79 – 3.15 Å. According to Jeffrey, there are three categories of hydrogen bonds: the strong category when the value of the donor-acceptor distance is between 2.2 – 2.5 Å, the medium category is between 2.5 – 3.2 Å, and the weak category is 3.2 – 4.0 Å. Based on this, the categories of the four compounds are included in the medium category (Jeffreya & George, 1997).

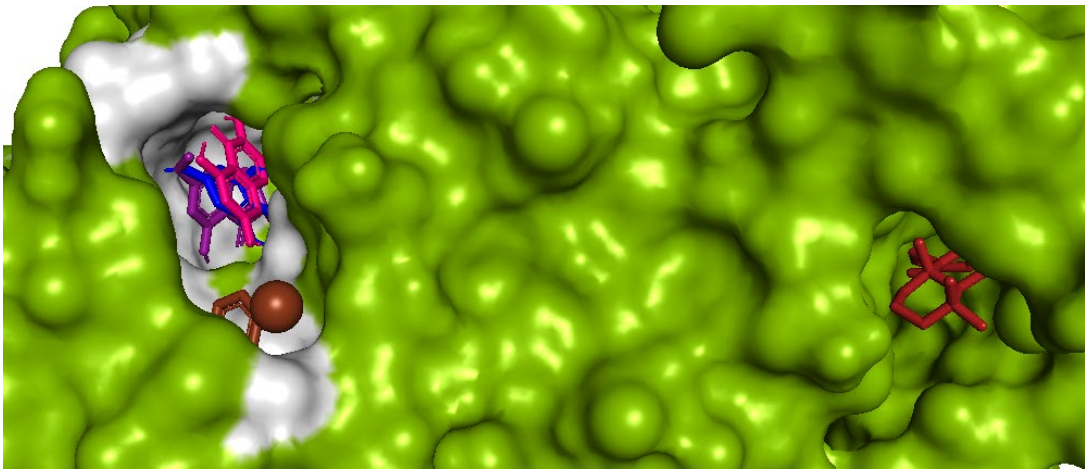

Figure 1. 3D visualisation results of bioactive compounds and drug controls with InhA protein

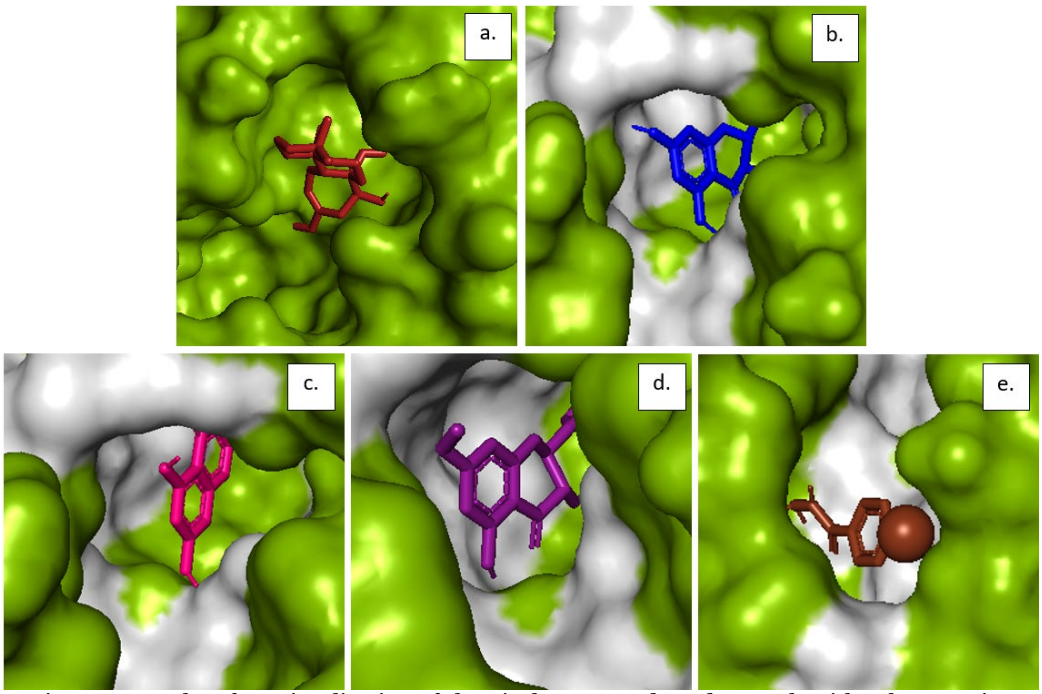

Figure 2. Results of 3D visualisation of chemical compounds and controls with InhA protein.
a. galanal A b. pinobanksin c. galangin d. alpinone e. isoniazid (control drug)

Based on the visualisation of the docking results, the amino acid residues of the three compounds except alpinone have interactions on hydrogen bonds, namely Gly96 and Gly14. This is in line with previous research that hydrogen bonds are formed in the InhA-NADH structure, which occurs at the amino acid residues Gly14, Asp64, Val65, and Gly96 (Kumar & Sobhia, 2015). The similarity of interactions on amino acid residues is predicted to inhibit the development of NADH by inactivating InhA. The results of 2D visualisation of the four compounds not only interact through hydrogen bonds, but there are also other factors such as hydrophobic bonds. Hydrophobic bonds combine non-polar regions between compound molecules and biological receptors to affect the conformational stability between ligands and

macromolecules (Saleh, 2015). From these results, these four compounds showed better hydrophobic bonding than the control drug (isoniazid).

Compounds derived from *Alpinia galanga* show potential as natural products for tuberculosis prevention. One such compound, galanal A, is a diterpene found in *Alpinia galanga* (Morita *et al.*, 1986). Labdane diterpenes, including galanal A, exhibit various biological activities, such as antifungal, antiviral, cytotoxic, radical-scavenging, anti-hypertensive, hepatoprotective, anti-inflammatory, and antibacterial properties (Haraguchi *et al.*, 1996; Abe *et al.*, 2014; Alajmi *et al.*, 2018). In a previous study, galanal A from Myoga (*Zingiber mioga* Roscoe) demonstrated antibacterial activity against gram-positive bacteria, including *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, at concentrations of 25–125 µg/mL, while its activity against gram-negative bacteria was observed at concentrations exceeding 1000 µg/mL (Abe *et al.*, 2014).

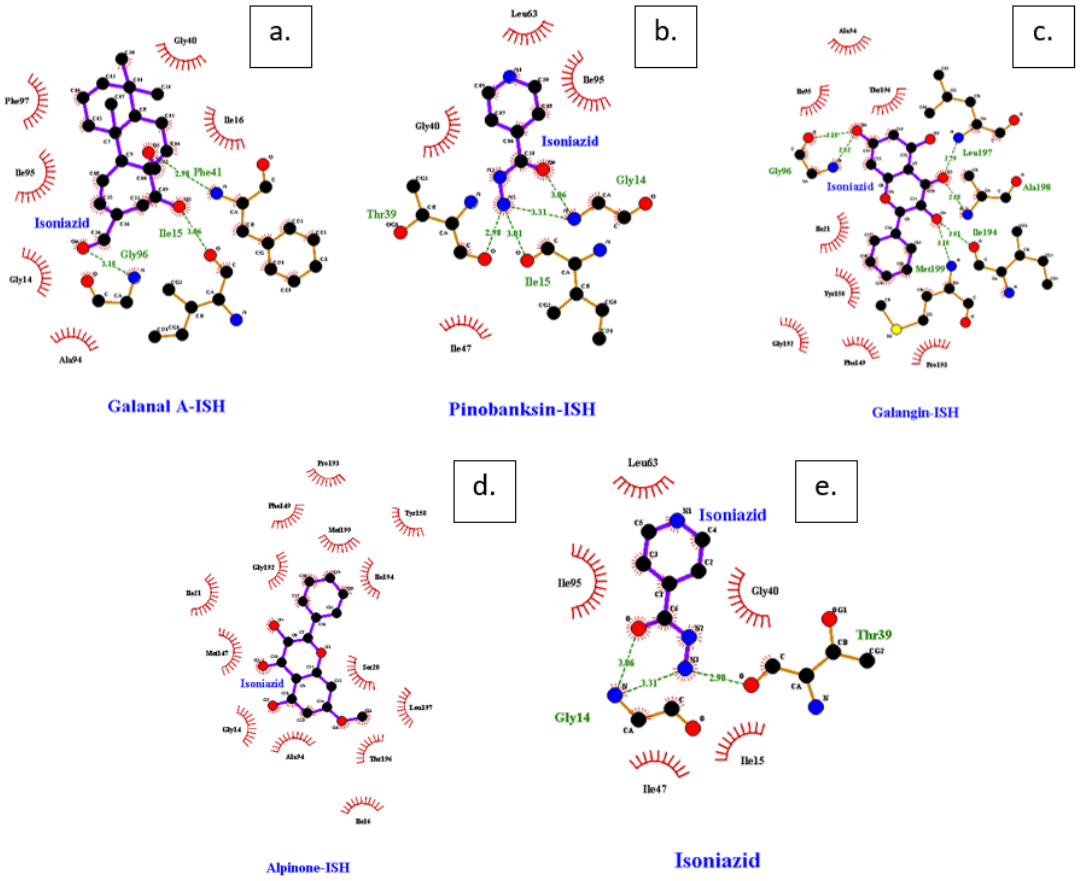

Figure 3. Results of 2D visualisation of chemical compounds and controls with InhA protein.
a. galanal A b. pinobanksin c. galangin d. alpinone e. isoniazid (control drug)

Pinobanksin, galangin and alpinone compounds are derivatives of flavonoid compounds from *Alpinia galanga* (Samart, 2007; Tungmunnithum *et al.*, 2020). Flavonoid compounds in *Alpinia galanga* also have antimicrobial, anti-fungal, anti-inflammatory, anti-diabetic, antioxidant, anti-ulcer, and anti-tumour activities (Alajmi *et al.*, 2018; Chouni & Paul, 2018). Flavonoid compounds such as pinobanksin have anti-proliferative properties and inhibit gram-positive bacteria (Catchpole *et al.*, 2015; Biva *et al.*, 2016). In a previous study, using bacterial culture and phytochemical screening methods, flavonoid compounds in *Alpinia galanga* have antimicrobial activity against isoniazid resistance strains by observing oxygen concentrations through Axenic assay (Gupta *et al.*, 2014). In an in vitro study by Cao and colleagues, flavonoid compounds showed direct antibacterial activity on *M. tuberculosis* bacteria by reducing *M. tuberculosis* survival, aggregation, increased cell density and granuloma formation (Cao *et al.*, 2019). Based on this, it is predicted that this bioactive compound from *Alpinia galanga* can inhibit *M. tuberculosis* by disrupting mycolic acid synthesis through inhibition of NADH so that InhA which plays a role in mycolic acid synthesis is stopped.

IV. CONCLUSION

Galanal A (-8.8 kcal/mol) had the lowest binding affinity value and was followed by pinobanksin (-8.8 kcal/mol), galangin and alpine (-8.5 kcal/mol). The four compounds had better affinity values than the control (Isoniazid: -5.6 kcal/mol). The *enoyl-acyl carrier protein reductase* (InhA) inhibitor is a protein that plays a role in the mycolic acid biosynthesis process in *Mycobacterium tuberculosis*. One treatment targeting the InhA protein isoniazid, which can inhibit mycolic acid synthesis. The distance between the hydrogen bonds indicates that the donor and receptor bonds are pretty strong/moderate with a range of 2.79-3.15 Å., which indicates a value between 2.5 – 3.2 Å. The most common amino acid residues in hydrogen bonding are Gly96 and Gly 14. Based on this, it is predicted that this bioactive compound from *Alpinia galanga* can inhibit *M. tuberculosis* by interfering with mycolic acid synthesis through inhibition of NADH so that InhA plays a role in mycolic acid synthesis stopped.

V. ACKNOWLEDGEMENT

Authors thank to Universitas Negeri Malang for support this study.

VI. REFERENCES

Abe, M, Ozawa, Y, Uda, Y, Yamada, F, Morimitsu, Y, Nakamura, Y & Osawa, T 2014, 'Antimicrobial Activities of Diterpene Dialdehydes, Constituents from Myoga (*Zingiber mioga* Roscoe), and their Quantitative Analysis, OUP, vol. 68, no. 7, pp. 1601–1604.

Alajmi, MF, Mothana, RA, Al-Rehaily, AJ & Khaled, JM 2018, 'Antimycobacterial Activity and Safety Profile Assessment of *Alpinia galanga* and *Tinospora cordifolia*', Evidence-Based Complementary and Alternative Medicine, 2018.

Albanna, AS, Smith, BM, Cowan, D & Menzies, D 2013, 'Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis', European Respiratory Journal, vol. 42, no. 3, pp. 721–732.

Angelia, A, Doda, DVD & Manampiring, AE 2020, 'Prevalensi Tuberkulosis Laten Dan Evaluasi Kebijakan Rumah Sakit Berdasarkan Persepsi Tenaga Kesehatan Terhadap Pencegahan Tuberkulosis', Jurnal Biomedik: JBM, vol. 12, no. 3, pp. 192–199.

Bégué, JP & Bonnet-Delpon, DG 2008, 'Biological Impacts of Fluorination: Pharmaceuticals Based on Natural Products', Fluorine and Health, pp. 553–622.

Bhat, ZS, Rather, MA, Maqbool, M, Lah, HU, Yousuf, SK & Ahmad, Z 2017, 'Cell wall: A versatile fountain of drug targets in *Mycobacterium tuberculosis*', Biomedicine & Pharmacotherapy, vol. 95, pp. 1520–1534.

Biva, IJ, Ndi, CP, Griesser, HJ & Semple, SJ 2016, 'Antibacterial constituents of *Eremophila alternifolia*: An Australian aboriginal traditional medicinal plant', Journal of Ethnopharmacology, vol. 182, pp. 1–9.

Cao, R, Teskey, G, Islamoglu, H, Gutierrez, M, Salaiz, O, Munjal, S, Fraix, MP, Sathananthan, A, Nieman, DC & Venketaraman, V 2019, 'Flavonoid Mixture Inhibits *Mycobacterium tuberculosis* Survival and Infectivity', Molecules 2019, vol. 24, no. 5, p. 851.

Catchpole, O, Mitchell, K, Bloor, S, Davis, P & Suddes, A 2015, 'Antiproliferative activity of New Zealand propolis and phenolic compounds vs human colorectal adenocarcinoma cells', Fitoterapia, vol. 106, pp. 167–174.

Centers for Disease Control and Prevention 2016, 'How TB Spreads | Basic TB Facts | TB | CDC', <https://www.cdc.gov/tb/topic/basics/howtbspreads.htm>.

Cesar, MD 2014, 'Perbedaan Efek Obat Anti Tuberkulosis Kombinasi Dosis Tetap Dibanding Lepasan Terhadap Konversi Sputum Basil Tahan Asam Saat Akhir Fase Intensif Pada Pasien Tuberkulosis Dewasa di Balai Besar Kesehatan Paru Masyarakat Surakarta', Doctoral dissertation, Universitas Muhammadiyah Surakarta.

Chiaradia, L, Lefebvre, C, Parra, J, Marcoux, J, Burlet-Schiltz, O, Etienne, G, Tropis, M & Daffé, M 2017, 'Dissecting the mycobacterial cell envelope and defining the composition of the native mycomembrane', Scientific Reports 2017 7:1, vol. 7, no. 1, pp. 1–12.

Chouni, A & Paul, S 2018, 'A review on phytochemical and pharmacological potential of *Alpinia galanga*', Pharmacognosy Journal, vol. 10, no. 1, pp. 9–15.

Cohen, A, Mathiasen, VD, Schön, T & Wejse, C 2019, 'The global prevalence of latent tuberculosis: a systematic review and meta-analysis', European Respiratory Journal, vol. 54, no. 3.

Damayanti, DS, Utomo, DH & Kusuma, C 2017, 'Revealing the potency of *Annona muricata* leaves extract as FOXO1

inhibitor for diabetes mellitus treatment through computational study', in Silico Pharmacology, vol. 5, no. 1.

Duan, X, Xiang, X & Xie, J 2014, 'Crucial components of mycobacterium type II fatty acid biosynthesis (Fas-II) and their inhibitors', FEMS Microbiology Letters, vol. 360, no. 2, pp. 87–99.

Fajar, R, Asshiddiq, I, Yahya, A, Risandiansyah, R & Ked, S 2021, 'Potensi Antiadhesi Senyawa Aktif *Hibiscus sabdariffa* L pada Penghambatan Protein Target IcsA *Shigella flexneri* melalui Studi in Silico Molecular Docking', Jurnal Kedokteran Komunitas, vol. 9, no. 2.

Goodwin, RJA, Bunch, J & McGinnity, DF 2017, 'Mass Spectrometry Imaging in Oncology Drug Discovery', in Advances in Cancer Research (1st ed.), vol. 134.

Goude, R & Parish, T 2008, 'The genetics of cell wall biosynthesis in *Mycobacterium tuberculosis*', Future Microbiology, vol. 3, no. 3, pp. 299–313.

Gupta, P, Bhatter, P, D'souza, D, Tolani, M, Daswani, P, Tetali, P & Birdi, T 2014, 'Evaluating the anti-*Mycobacterium tuberculosis* activity of *Alpinia galanga* (L.) Willd. axenically under reducing oxygen conditions and in intracellular assays', BMC Complementary and Alternative Medicine 2014 14:1, vol. 14, no. 1, pp. 1–8.

Haraguchi, H, Kuwata, Y, Inada, K, Shingu, K, Miyahara, K, Nagao, M & Yagi, A 1996, 'Antifungal activity from *Alpinia galanga* and the competition for incorporation of unsaturated fatty acids in cell growth', Planta Medica, vol. 62, no. 4, pp. 308–313.

He, X, Alian, A & Ortiz De Montellano, PR 2007, 'Inhibition of the *Mycobacterium tuberculosis* enoyl acyl carrier protein reductase InhA by arylamides', Bioorganic & Medicinal Chemistry, vol. 15, no. 21, pp. 6649–6658.

Jeffrey, George A 1997, 'An introduction to hydrogen bonding', Oxford University Press.

Jena, L, Waghmare, P, Kashikar, S, Kumar, S & Harinath, BC 2014, 'Computational approach to understanding the mechanism of action of isoniazid, an anti-TB drug', International Journal of Mycobacteriology, vol. 3, no. 4, pp. 276–282.

Jilani, TN, Avula, A, Gondal, AZ & Siddiqui, AH 2021, 'Active Tuberculosis', StatPearls.

Kemenkes RI 2021, Dashboard TB - TBC Indonesia, <https://tbindonesia.or.id/pustaka-tbc/dashboard-tb/>.

Kumar, V & Sobhia, ME 2015, 'Molecular Dynamics Assisted Mechanistic Study of Isoniazid-Resistance against Mycobacterium tuberculosis InhA', PLOS ONE, vol. 10, no. 12, p. e0144635.

Lima, GC, Silva, EV, Magalhães, P de O & Naves, JS 2017, 'Efficacy and safety of a four-drug fixed-dose combination regimen versus separate drugs for treatment of pulmonary tuberculosis: a systematic review and meta-analysis', Brazilian Journal of Microbiology, vol. 48, no. 2, pp. 198–207.

Lipinski, CA 2004, 'Lead- and Drug-like Compounds: The rule-of-five revolution', Drug Discovery Today: Technologies, vol. 1, no. 4, pp. 337–341.

Manse, Y, Ninomiya, K, Nishi, R, Hashimoto, Y, Chaipech, S, Muraoka, O & Morikawa, T 2017, 'Labdane-Type Diterpenes, Galangalditerpenes A–C, with Melanogenesis Inhibitory Activity from the Fruit of *Alpinia galanga*', Molecules 2017, vol. 22, no. 12, p. 2279.

Marrakchi, H, Lanéelle, G & Quémard, A 2000, 'InhA, a target of the antituberculous drug isoniazid, is involved in a mycobacterial fatty acid elongation system, FAS-II', Microbiology, vol. 146, no. 2, pp. 289–296.

Morita, H & Itokawa, H 1986, 'New Diterpenes from *Alpinia galanga* WILD, vol. 15, no. 7, pp. 1205-1208, <http://Dx.Doi.Org/10.1246/Cl.1986.1205>.

Palomino, JC & Martin, A 2014, 'Drug Resistance Mechanisms in Mycobacterium tuberculosis', Antibiotics, vol. 3, no. 3, p. 317.

PaweŁczyk, J & Kremer, L 2014, 'The Molecular Genetics of Mycolic Acid Biosynthesis', Microbiology Spectrum, vol. 2, no. 4.

Safaev, K, Parpieva, N, Liverko, I, Yuldashev, S, Dumchev, K, Gadoev, J, Korotych, O & Harries, AD 2021, 'Trends, Characteristics and Treatment Outcomes of Patients with Drug-Resistant Tuberculosis in Uzbekistan: 2013–2018', International Journal of Environmental Research and Public Health 2021, vol. 18, no. 9, p. 4663.

Saleh, W 2015, 'Studi Hubungan Kuantitatif Struktur-Aktivitas Anti-tuberkulosis Senyawa Amidasi Etil p-metoksisinamat dengan Pendekatan Hansch dan Penambatan Molekuler pada Enzim Inh A, UIN Syarif Hidayatullah.

Samart, N 2007, 'Isolation and identification of galangin and other compounds from *Alpinia galanga* linnaeus willd and *Alpinia officinarum* hance, <http://sutir.sut.ac.th:8080/jspui/handle/123456789/2868>.

Sotgiu, G, Centis, R, D'ambrosio, L & Migliori, GB 2015, 'Tuberculosis Treatment and Drug Regimens', Cold Spring Harbor Perspectives in Medicine, vol. 5, no. 5.

Takayama, K, Wang, C & Besra, GS 2005, 'Pathway to Synthesis and Processing of Mycolic Acids in Mycobacterium tuberculosis', Clinical Microbiology Reviews, vol. 18, no. 1, p. 81.

Thafar, M, Raies, A Bin, Albaradei, S, Essack, M & Bajic, VB 2019, 'Comparison Study of Computational Prediction Tools for Drug-Target Binding Affinities', Frontiers in Chemistry, vol. 7, p. 782.

Tungmunnithum, D, Tanaka, N, Uehara, A & Iwashina, T 2020, 'Flavonoids Profile, Taxonomic Data, History of Cosmetic Uses, Antioxidant and Anti-Aging Potential of *Alpinia galanga* (L.) Willd', Cosmetics 2020, vol. 7, no. 4, p. 89.

Vilchèze, C, Jacobs, WR & JR 2014, 'Resistance to Isoniazid and Ethionamide in Mycobacterium tuberculosis: Genes, Mutations, and Causalities', Microbiology Spectrum, vol. 2, no. 4, MGM2.

Vögeli, B, Rosenthal, RG, Stoffel, GMM, Wagner, T, Kiefer, P, Cortina, NS, Shima, S & Erb, TJ 2018, 'InhA, the enoyl-thioester reductase from *Mycobacterium tuberculosis* forms a covalent adduct during catalysis', The Journal of Biological Chemistry, vol. 293, no. 44, p. 17200.

Widodo, Irianto, A & Pramono, H 2016, 'Karakteristik Morfologi *Mycobacterium tuberculosis* yang Terpapar Obat Anti TB Isoniazid (INH) secara Morfologi', Majalah Ilmiah Biologi BIOSFERA: A Scientific Journal, vol. 33, no. 3, pp. 109–115.

World Health Organization 2011, WHO model list of essential medicines: 17th list.

World Health Organization 2020, 'Global Tuberculosis Report 2020', <http://apps.who.int/bookorders>.

Zhao, H & Huang, D 2011, 'Hydrogen Bonding Penalty upon Ligand Binding', PLoS ONE, vol. 6, no. 6.