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# Molecular Docking and Molecular Dynamics Simulation Study of Anti-Tuberculosis Drug Candidates from Plant-Derived Natural Products against InhA Protein

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**ABSTRACT**

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and is responsible for millions of deaths worldwide every year. Tuberculosis has become a serious public health problem that needs to be eradicated. Current treatments, including first line medication, have unwanted side effects and face the serious problem of multi-drug resistance. Therefore, finding new agents to treat tuberculosis is critically necessary. Thus, in the present study, we aimed to evaluate several plant-derived drug candidates for their anti-tuberculosis activity that work by inhibiting the activity of the Enoyl acyl carrier protein reductase (InhA) enzyme as determined through in silico studies. Drug-likeness and toxicity evaluation, molecular docking, and molecular dynamics simulations were performed to assess new anti-tuberculosis candidates. Plant-derived natural products such as sulcanal, stigmasterol, zambesiacolactone B, coronarin B, zeylenol, galanal B, and galanolactone might have anti-tuberculosis activity according to their binding affinity scores compared to control drugs. The results revealed that sulcanal had the greatest anti-tuberculosis activity by inhibiting InhA compared to other compounds with the most favorable

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binding affinity score and binding interaction properties. Finally, molecular dynamics simulation demonstrated that sulcanal had constant and stable pattern during the initial to terminal stage of the simulation. Finally, we suggest that sulcanal might have the potential for further development as an anti-tuberculosis drug candidate through its InhA inhibition.

**Keywords:** *In silico*; InhA; *Mycobacterium tuberculosis*; Natural products; Tuberculosis

## 1. Introduction

Tuberculosis (Tb) is caused by infection of *Mycobacterium tuberculosis* and remains a serious global health problem [1]. It is estimated that 25% of world's population suffer from Tb at some point. Generally, Tb is transmitted through respiratory droplets which can be spread through coughing, sneezing, talking, and direct inhalation of the Tb bacteria. However, it has been reported that Tb can also spread through the mouth, intestines, and skin [2, 3]. Many public health reports have demonstrated that Tb infection is affected by several risk factors including age, gender, environment, education, and disease burden. For instance, Tb is likely to have higher prevalence in the lower socioeconomic rungs and marginalized sections of society [4]. Additionally, the disease burden is greater in populations such as those living with HIV, who are more easily infected with Tb. Similarly, diabetes mellitus also increases the risk of Tb by 2-3 times [5]. Understanding the main factors that affect Tb incidence may help to determine optimal timing for public health prevention or treatment [6, 7].

Recently, several modalities and techniques have been proposed to treat Tb patients including the recombinant mycobacteriophage technique, high throughput screening, signature tagged mutagenesis, transposon site hybridization, three-dimensional cell culture, as well as the use of first line drugs including isoniazid, rifampicin, ethambutol, and pyrazinamide [8, 9]. However, these are accompanied by the growing challenge of multi-drug-resistant bacteria. It has been reported that nearly five-hundred thousand people are infected with the new multi-drug-resistant Tb [9, 10]. In addition, the first line medication of Tb has unwanted side effects, including liver damage [3]. Unfortunately, new drugs approved for Tb treatment are limited [9]. Therefore, finding new anti-Tb drug candidates is needed.

Medicinal plants have been widely used not only for culinary purposes, but also for treating various ailments [11]. In Indonesia, there exists a commonly prepared herbal medicine known as jamu, which combines a variety of medicinal plants to be taken as a drink. Jamu typically includes *Curcuma xanthorrhiza*, *Curcuma domestica*, *Zingiber aromatica*, *Zingiber officinale*, *Kaempferia pandurata*, and others. These plants contain distinct bioactive compounds that are thought to promote health and address various health conditions. This combination of natural ingredients positions jamu as a holistic and traditional remedy, deeply intertwined with Indonesia's cultural heritage and long-standing practices in herbal medicine [12]. Interestingly, broad studies have demonstrated that plant-derived natural products do have pharmaceutical effects such as anti-inflammation, anti-oxidant, anti-bacteria, anti-virus, and anti-cancer properties [13, 14]. Interestingly, the exploration of plant-derived natural products for anti-tuberculosis treatments is increasing [15, 16]. Therefore, in the present study we aimed to evaluate several plant-derived natural products for their activity as anti-tuberculosis drug candidates that act through Enoyl acyl carrier protein reductase (InhA) enzyme inhibition, as determined through in silico modeling. InhA is widely known as a novel target for anti-tuberculosis activity. The inhibition of InhA activity might result in the disruption of the mycolic acid biosynthesis pathway, which plays an important role in fatty acid metabolism in *M. tuberculosis* [8, 17].

## 2. Materials and Methods

### 2.1. Chemical properties and toxicity prediction

Several major bioactive compounds from several medicinal plants such as *Aframomum arundiaceum*, *Aframomum latifolium*, *Aframomum zambesiacum*, *Boesenbergia rotunda*, *Kaempferia marginata*, and *Kaempferia rotunda* were used in this study [18, 19]. The SMILE information of bioactive compounds was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) which included sulcanal (CID. 21604870), stigmasterol (CID. 5280794), zambesiacolactone B (CID. 11624798), coronarin B (CID. 72702906), zeylenol (CID. 10992619), galanal B (CID. 3086504), galanolactone (CID. 11141699), and hemanthidine (CID. 3002914). The chemical information of these bioactive compound were retrieved from SwissADME webserver (http://www.swissadme.ch/). Furthermore, ProTox 3.0. webserver (https://tox.charite.de/protox3/) was employed to perform toxicity level predictions and the determine the probability of these compounds to induce toxicity.

### 2.2. Ligand structure preparation

The chemical structures of the bioactive compounds were retrieved from PubChem database which included sulcanal, stigmasterol, zambesiacolactone B, coronarin B, zeylenol, galanal B, galanolactone, and hemanthidine. Additionally, isoniazid (CID. 3767) and ethionamide (CID. 2761171) were used as control drugs for InhA inhibition [9]. Finally, all chemical structures of the bioactive compounds and control drugs were saved in SDF format for further use in molecular docking.

### 2.3. Target protein preparation

The 3D structure of InhA, the target protein, was obtained from RSCB Protein Data Bank (https://www.rcsb.org/) with PDB ID 2IED. The data was saved in PDB. format for further molecular docking. Cleaning and optimization of the InhA structure was performed using PyMOL software (https://www.pymol.org/).

### 2.4. Molecular docking and visualization

After performing ligand and target protein optimization, molecular docking was conducted using PyRx 0.8 software (https://pyrx.sourceforge.io/). The docking grid was set to cover the entire surface of InhA with the following dimensions: X=75.5359Å, Y= 78.6879Å, dan Z= 85.7672Å. Data analysis and visualization of molecular docking results was done using Discovery Studio software (https://www.3ds.com/).

### 2.5. Molecular dynamics simulation

Molecular dynamics analysis was performed to validate the stability of the protein-ligand complex after molecular docking. Simulation of the protein-ligand complexes was performed using YASARA software (http://www.yasara.org/) for 3500 ps. Some parameters were measured including total energy, Coulomb energy, RMSD, SASA, surface molecule, surface VdW, radius gyration, and H-Bond.

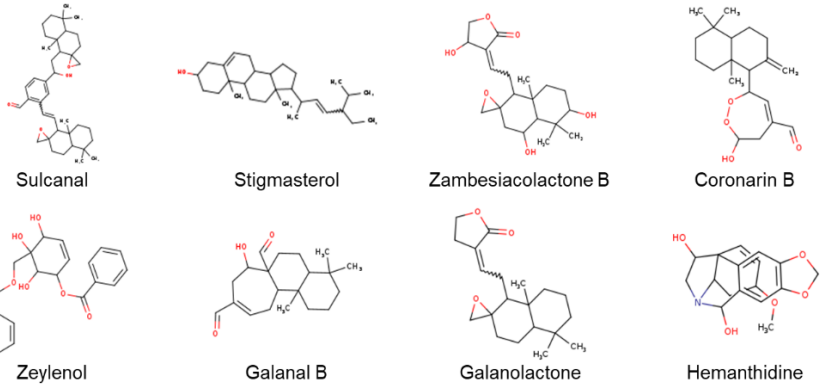
## 3. Results and Discussion

The bioactive compounds used in this study were varied and originated from different types of medicinal plants. Interestingly, many of the bioactive compounds had the common feature of aromatic rings (Fig. 1A). To proceed with the molecular docking process, we evaluated the chemical properties of these bioactive compounds which included the molecular weight, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, and molar refractivity (Fig. 1B). These evaluations were very important to determine the drug-likeness properties of these compounds, which were then used for molecular docking.

The drug-likeness screening has been widely occupied in selection and finding new

drug candidate from non-drug compounds. In other words, drug-likeness screening is the process of finding the similarities between drug candidates and established drugs [20]. Drug-likeness screening is very important in drug discovery as it can reduce both the experimental expenditure and the time required for the study [21, 22].

A




B

| Compounds | Formula | Molecular weight | Num. rotatable bonds | Num. H-bond acceptors | Num. H-bond donors | Molar Refractivity |
|---|---|---|---|---|---|---|
| Sulcanal | C39H56O4 | 588.86 g/mol | 6 | 4 | 1 | 175.97 |
| Stigmasterol | C29H48O | 412.69 g/mol | 5 | 1 | 1 | 132.75 |
| Zambesiacolactone B | C20H30O6 | 366.45 g/mol | 2 | 6 | 3 | 94.7 |
| Coronarin B | C20H30O4 | 334.45 g/mol | 2 | 4 | 1 | 93.98 |
| Zeylenol | C21H20O7 | 384.38 g/mol | 7 | 7 | 3 | 98.3 |
| Galanal B | C20H30O3 | 318.45 g/mol | 2 | 3 | 1 | 92.22 |
| Galanolactone | C20H30O3 | 318.45 g/mol | 2 | 3 | 0 | 91.21 |
| Hemanthidine | C17H19NO5 | 317.34 g/mol | 1 | 6 | 2 | 84.18 |

**Fig. 1.** Chemical information of the bioactive compounds used. A). chemical structures of bioactive compounds. B). Physicochemical properties of the bioactive compounds.

After reviewing drug-likeness of the bioactive compounds, toxicity prediction was performed. Toxicity class and $LD_{50}$ prediction, including the probability score of bioactive compounds to induce toxicity, was analyzed. Zambesiacolactone B and zeylenol were predicted to be in toxicity class 5. Sulcanal, stigmasterol, galanal B, and galanolactone were predicted to be in toxicity class 4. Coronarin B and hemanthidine were predicted to be in toxicity class 3 (Fig. 2A). A lower number for the toxicity class indicates the compounds exhibit more toxic activity. For the analysis of probability to induce toxicity, almost all of the compounds were determined to be safe. Several compounds though, such as zambesiacolactone B, galanal B, galanolacton, and hemanthidine, demonstrated potential carcinogenicity or cytotoxicity (Fig. 2B).

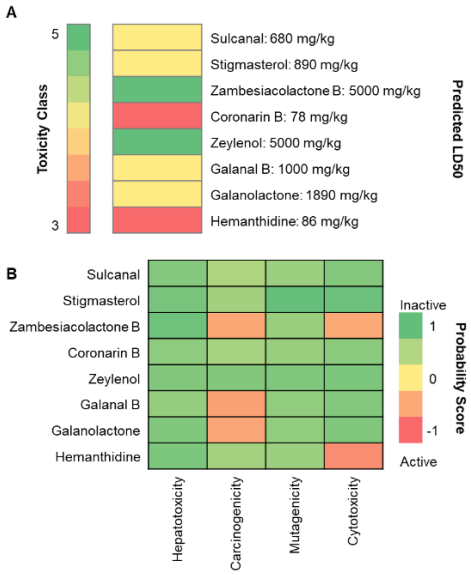



**Fig. 2.** Toxicity prediction of the bioactive compounds. A). Toxicity evaluation based on $LD_{50}$ value, and B). The probability of causing toxicity in some physiological aspects.

Besides the evaluation of chemical structures and properties, toxicity evaluation is also widely used for screening drug candidates. Toxicity prediction offers a possible range of doses for certain compounds and can also predict the possibility of induced toxicity to organs [23, 24]. Importantly, toxicity prediction allows researchers to effectively estimate the number of cells or animal models needed for experiments.

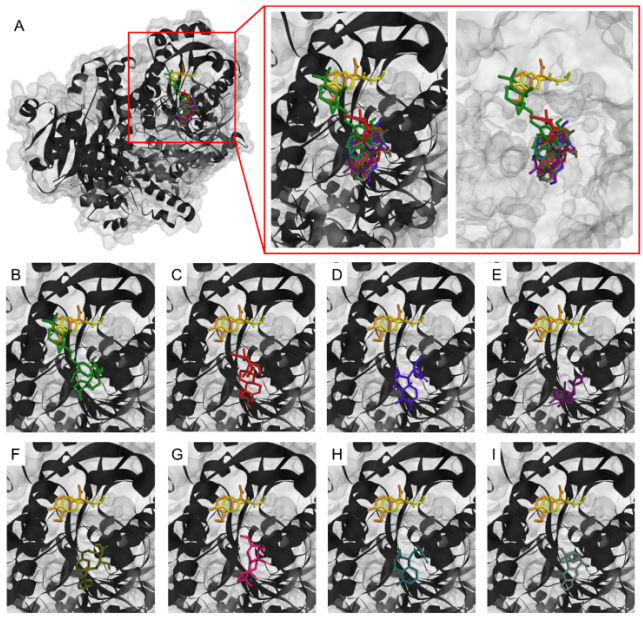



**Fig. 3.** The 3D structure visualization of bioactive compounds and control drugs toward InhA (A). Single view of compound and control drugs including sulcanal (B); stigmasterol (C); zambesiacolactone B (D); coronarin B (E); zeylenol (F); galanal B (G); galanolactone (H); and hemanthidine (I) binds to InhA. The control drugs are represented in yellow and orange.

According to molecular docking, the bioactive compounds in this study demonstrated competitive inhibitory activity. The 3D visualization showed that the bioactive compounds have a similar binding area to the control drugs used in this study (Fig. 3). In addition, the binding interactions, such as H-bonding and Van der Waals interaction are formed between the protein-ligand (Fig. 4, Fig. 5). These indicate that the bioactive compounds might contribute to changes in InhA bioactivity.

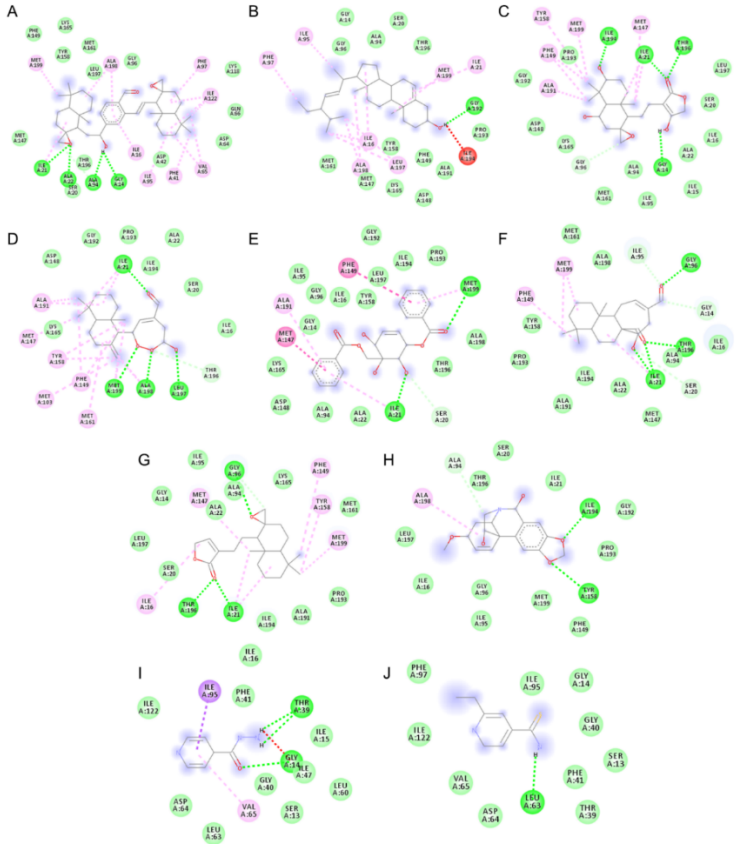



**Fig. 4.** The 2D structure and interaction visualization of sulcanal (A); stigmasterol (B); zambesiacolactone B (C); coronarin B (D); zeylenol (E); galanal B (F); galanolactone (G); hemanthidine (H); isoniazid (I); and ethionamide (J) bound to InhA.

Interestingly, of all the bioactive compounds, sulcanal demonstrated the most favorable binding affinity, with a ΔG value of -12.7 kcal/mol, indicating its strong interaction potential with the target protein. Following sulcanal, stigmasterol showed a notable binding affinity of -10.0 kcal/mol, making it the second most promising candidate. Compounds such as zambesiacolactone B (-9.8 kcal/mol), coronarin B (-9.5 kcal/mol), zeylenol (-9.3 kcal/mol), and galanal B (-9.3 kcal/mol) also exhibited strong binding interactions, albeit slightly less potent than sulcanal and stigmasterol. Galanolactone (-9.2 kcal/mol) and hemanthidine (-9.0 kcal/mol) followed closely, maintaining significant binding potential (Table 1). In comparison, isoniazid and ethionamide both displayed much weaker binding affinities, with ΔG values of -5.6 kcal/mol. These findings suggest that the bioactive compounds, particularly sulcanal, offer favorable binding capabilities compared to the control drugs, underscoring their potential as effective therapeutic candidates for further molecular and pharmacological studies.

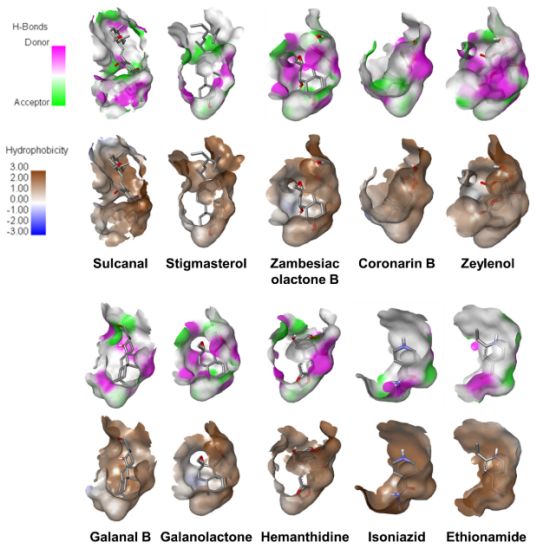



**Fig. 5.** The physicochemical properties of bioactive compounds and control drug toward InhA, including aromatic properties, interpolated charge, hydrophobicity, ionizability, and SAS properties.

**Table 1.** List of binding affinity values, chemical interactions, and amino acid residues of the bioactive compounds and control drugs toward InhA.

| Compound | Amino Acids Residue | Interaction |
|---|---|---|
| **Sulcanal** | Ile21(A); Ala22(A); Ala94(A); Gly14(A) | H-bond |
| ΔG: -12.7 kcal/mol | Thr196(A); Ser20(A); Met147(A); Phe149(A); Tyr158(A); Lys165(A); Met161(A); Leu197(A); Gly96(A); Lys118(A); Gln66(A); Asp64(A); Asp42(A) | Van der Waals |
| *Aframomum latifolium* | | |
| **Stigmasterol** | Gly192(A) | Hydrogen Bond |
| ΔG: -10.0 kcal/mol | Pro193(A); Ala191(A); Asp148(A); Phe149(A); Lys165(A); Tyr158(A); Met147(A); Met161(A); Gly96(A); Gly14(A); Ala94(A); Ser20(A); Thr196(A) | Van der Waals |
| *Kaempferia marginata* | | |
| **Zambesiacolactone B** | Ile94(A); Ile21(A); Thr196(A); Gly14(A) | Hydrogen Bond |
| ΔG: -9.8 kcal/mol | Leu197(A); Ser20(A); Ile16(A); Ala22(A); Ile15(A); Ala94(A); Ile95(A); Met161(A); Gly96(A); Lys165(A); Asp148(A); Gly192(A); Pro193(A) | Van der Waals |
| *Aframomum zambesiacum* | | |
| **Coronarin B** | Ile21(A); Leu197(A); Ala198(A); Met199(A) | Hydrogen Bond |
| ΔG: -9.5 kcal/mol | Thr196(A); Lys165(A); Asp148(A); Gly192(A); Pro193(A); Ala22(A); Ile194(A); Ser20(A); Ile16(A) | Van der Waals |
| *Aframomum latifolium* | | |
| **Zeylenol** | Met199(A); Ile21(A) | Hydrogen Bond |
| ΔG: -9.3 kcal/mol | Ala198(A); Thr196(A); Ser20(A); Ala22(A); Ala94(A); Asp148(A); Lys165(A); Gly14(A); Ile95(A); Gly96(A); Ile16(A); Tyr158(A); Leu197(A); Ile194(A); | Van der Waals |
| *Kaempferia rotunda* | Gly192(A); Pro193(A) | |
| **Galanal B** | Gly96(A); Thr196(A); Ile21(A) | Hydrogen Bond |
| ΔG: -9.3 kcal/mol | Gly14(A); Ile16(A); Ala94(A); Ser20(A); Met147(A); Ala22(A); Ile194(A); Ala191(A); Pro193(A); Tyr158(A); Met161(A); Ala198(A); Ile95(A) | Van der Waals |
| *Aframomum latifolium* | | |
| **Galanolactone** | Gly96(A); Ile21(A); Thr196(A) | Hydrogen Bond |
| ΔG: -9.2 kcal/mol | Met161(A); Pro193(A); Ala191(A); Ile194(A); Ser20(A); Leu197(A); Ala22(A); Gly14(A); Ala94(A); Ile95(A); Lys165(A) | Van der Waals |
| *Aframomum arundiaceum* | | |
| **Hemanthidine** | Ile194(A); Tyr158(A) | Hydrogen Bond |
| ΔG: -9.0 kcal/mol | Gly192(A); Pro193(A); Phe149(A); Met199(A); Gly96(A); Ile95(A); Ile16(A); Leu197(A); Thr196(A); Ala94(A); Ser20(A); Ile21(A) | Van der Waals |
| *Boesenbergia rotunda* | | |
| **Isoniazid** | Thr39(A); Gly14(A) | Hydrogen Bond |
| ΔG: -5.6 kcal/mol | Ile15(A); Ile47(A); Leu60(A); Ser13(A); Gly40(A); Leu63(A); Asp64(A); Ile122(A); Ile16(A); Phe41(A) | Van der Waals |
| **Ethionamide** | Leu63(A) | Hydrogen Bond |
| ΔG: -5.6 kcal/mol | Ile95(A); Gly14(A); Gly40(A); Ser13(A); Phe41(A); Thr39(A); Asp64(A); Val65(A); Phe97(A); Ile122(A) | Van der Waals |

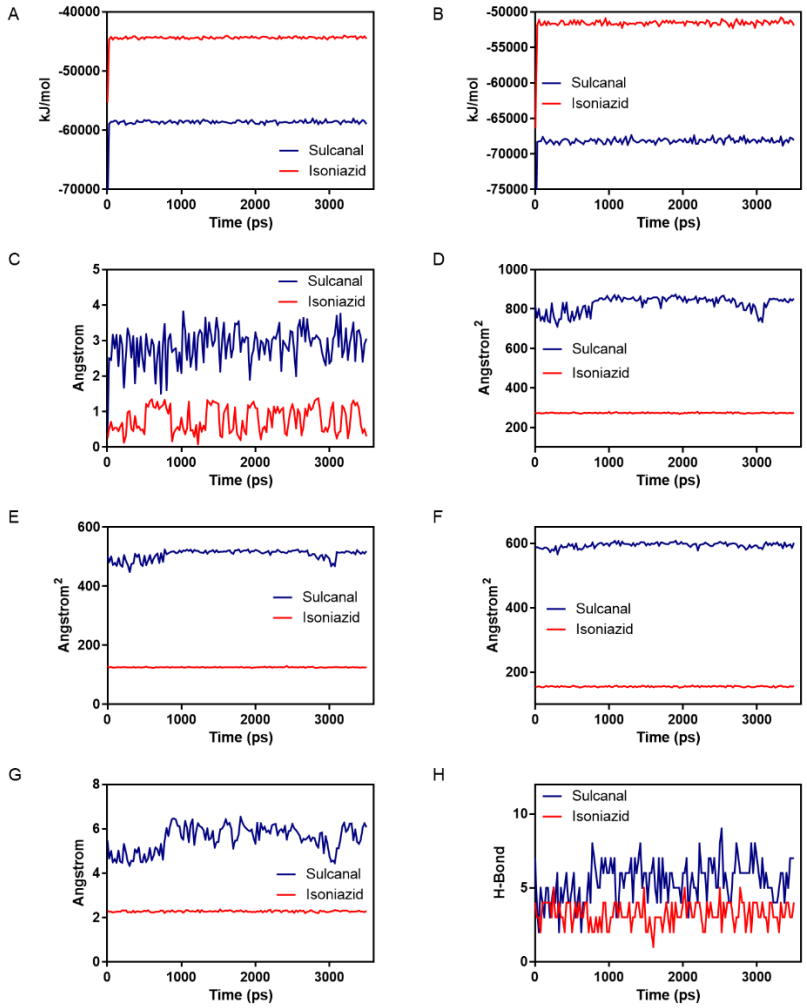



**Fig. 6.** Molecular dynamic simulations of InhA - sulcanal and InhA– isoniazid complexes. A). Total energy, B). Coulomb energy, C). RMSD, D). SASA, E). Surface molecule, F). Surface VdW, G). Radius gyration, and H). H-Bond.

Molecular docking is a widely used technique in drug discovery research. Molecular docking helps researchers to identify binding affinity and the interactions formed between the ligand and target protein. The interactions formed between the ligand and target protein thus enable researchers not only to explore the properties of the ligand in the binding area, but also to define the basic biochemical activity within the interaction [25, 26].

Molecular docking provides the prediction of binding affinity scores which estimates binding conformation between the ligand and target protein [27-29]. Furthermore, molecular docking also provides the prediction of chemical interactions formed between the ligand and target protein. H-bond and hydrophobic interactions play a crucial role in maintaining interaction stability. More than that, hydrophobic interactions have been demonstrated to be involved in many chemical and biological phenomena, such as molecular recognition, protein folding, biological membranes, surfactant aggregation, and more [30].

Molecular dynamic simulations play an important role in determining the stability of protein-ligand complex interactions. During the time-dependent simulation, we could monitor how the ligand behaves toward the target protein, whether it maintains its interaction or it disassociates. A favorable drug candidate should have consistent and stable interactions with the target protein, therefore their therapeutic benefit toward the target protein could optimized. According to our molecular dynamics simulations, we found almost all parameters, including total energy, Coulomb energy, RMSD, SASA, surface molecule, surface VdW, radius gyration, and H-Bond, had constant values for both sulcanal and isoniazid against InhA. However, in all parameters except H-bonding, the values between sulcanal and isoniazid against InhA were different (Fig. 6).

Molecular dynamics simulations could predict protein behavior or ligand stability during time-dependent simulations. The simulation could provide insight into several biomolecular processes including conformational change, ligand binding, and protein structure stability. The results from molecular dynamics simulations enables researchers to optimize the compounds for getting the best performance and stability during interaction with the target proteins [31-33].

The present study faced some limitations. First, using web-based tools with diverse algorithms can result in inconsistent outcomes. Furthermore, when conducting docking studies, it is critical to focus on specific binding sites in order to more accurately predict the biological activity of the drugs. A further limitation is the instrument-constrained short simulation time of less than 10 ns. Future studies should strive to extend the simulation period to obtain more precise results. Finally, conducting experimental assessments, including in vitro and in vivo studies, is crucial for evaluating the potency of compounds against InhA as potential anti-TB drug candidates. These studies are crucial for validating the efficacy and therapeutic potential of the compounds.

## 4. Conclusion

Plant-derived natural products such as sulcanal, stigmasterol, zambesiacolactone B, coronarin B, zeylenol, galanal B, and galanolactone might have anti-tuberculosis activity. To a greater extent, in silico analysis including toxicity predictions and molecular docking indicated sulcanal to have the greatest favorability as an anti-tuberculosis drug candidate through InhA inhibition, as compared to other tested compounds, including the control drugs. Finally, molecular dynamics simulations indicated sulcanal has a constant and stable pattern of interaction during the initial to terminal stage of simulations.

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