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Molecular docking and pharmacokinetic prediction of isoniazid and curcumin compounds against N-acetyltransferase 2 (NAT2) protein

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ABSTRACT: NAT2 serves as the key enzyme responsible for metabolizing the INH compound, with its expression and functional activity significantly contributing to the risk of hepatotoxicity. Due to the possible inhibitory role of curcumin on NAT2, it is important to assess its effect on the metabolic processing of INH and to examine the enzyme-related interactions that may occur between drugs. Molecular docking studies demonstrated that curcumin can localize in the hydrophobic pocket and form a strong bond with NAT2. The aim of this study was to predict the potential interaction of the isoniazid and curcumin compounds against NAT2 protein. In this study, NAT2 protein (PDB ID: 2PFR) was used as a receptor. The results obtained showed the binding energies of native ligand, isoniazid, and curcumin were -5.78, -4.47, -8.35 kcal/mol, respectively. The findings of this research suggest that curcumin is capable of suppressing NAT2 activity, thereby affecting the pharmacokinetics of INH. These results may offer insights into minimizing INH-related liver toxicity and enhancing its effectiveness through co-administration with curcumin.

KEYWORDS: Antituberculosis; curcumin; isoniazid; molecular docking; n-acetyltransferase 2; pharmacokinetic.

INTRODUCTION

Mycobacterium tuberculosis is the bacterium responsible for causing the infectious disease known as tuberculosis (TB). This bacterium can be transmitted through droplets released into the air when sneezing or coughing. TB is one of the most prevalent diseases in Indonesia. In 2019, the WHO estimated that nearly 10 million people suffered from TB [1]. According to a TB prevalence survey, the increase in cases may also be attributed to poor access to treatment and diagnosis. Tuberculosis treatment requires long-term use of anti-tuberculosis drugs (ATBD), which often leads to non-compliance with treatment [2].

Based on the Indonesian tuberculosis treatment guidelines, isoniazid, rifampicin, pyrazinamide, and ethambutol are first-line drugs commonly used in the standard treatment regimen for TB [1], [3]. However, isoniazid is the most commonly used drug in TB treatment. The recommended dose of isoniazid for children, according to the WHO (2010), is 10-15 mg/kgBW, with a maximum dose of 300 mg/day. The level of acetylation, assisted by the NAT2 (N-acetyltransferase 2) genotype, determines the concentration of isoniazid in the blood [2]. N-acetyltransferase (NAT) converts isoniazid (INH) into its acetylated form, N-acetyl isoniazid, through an acetylation process that reduces the drug's potency and produces mild resistance in Mycobacterium tuberculosis. In humans, the NAT2 enzyme carries out a similar acetylation mechanism [4].

The relatively long use of isoniazid, ranging from 8 weeks to 6 months, can produce dangerous side effects on liver function. In addition, antibiotic resistance and co-infection with HIV have contributed to the increase in TB incidence in recent years. Therefore, the development and discovery of new TB drugs to minimize the side effects of isoniazid is crucial. Long-term use of isoniazid may lead to serious side effects, such as hepatotoxicity. Hence, drugs are needed to minimize these side effects. Temulawak (*Curcuma xanthorrhiza* Roxb.) is one of many tropical plants that have benefits and are found in various regions of Indonesia. The major compounds include curcuminoids—such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Many people use ginger as a traditional medicine to treat several conditions, such as

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anti-inflammatory, antioxidant, and hepatoprotective effects, among others. One of the main chemical compounds in ginger that has an anti-inflammatory role is curcumin [5].

Advancements in technology have accelerated the discovery of new drugs, particularly following in silico testing, which serves as the preliminary phase before laboratory experiments. By applying molecular docking simulations, in silico analyses help estimate how drug candidates might bind to their intended molecular targets.

▪ MATERIALS AND METHODS

Materials

The determination of protein targets in this study was carried out against isoniazid and curcumin compounds. Hardware used is a laptop with the Windows 11 64-bit operating system. Meanwhile, Autodock Tools software from MGLTools 1.5.7, Avogadro 1.2.0, and BIOVIA Discovery Studio 2024. Websites used include RCSB PDB (https://www.rcsb.org/), MolView (https://molview.org/), PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Preparation of macromolecules and ligands

The receptors NAT2 (PDB ID: 2PFR) were identified, which is a web server for compound target prediction. Macromolecules structures downloaded from the PDB (https://www.rcsb.org) in (.pdb) format. Three-dimensional structures of isoniazid and curcumin compounds as ligands were obtained from MolView (https://molview.org/), and then optimized with Avogadro 1.2.0. The preparation is carried out via the AutoDock Tool by separating the original ligand and water molecules, as well as adding hydrogen atom [6].

Validation method

Validation is carried out on the native ligand to determine its correct conformation. The prepared macromolecules are then re-docked with the original ligand. The resulting docking pose is compared to the crystallographic structure of the native ligand using root-mean-square deviation (RMSD). An RMSD value below 2.0 Å indicates that the conformational alignment is acceptable, with lower values closer to zero signifying better structural agreement [6].

Molecular docking

All ligands in the organic molecule library are used to perform molecular docking studies, until molecules are found that have potential for further drug discovery. In the current research, to carry out docking, Autodock Tools 1.5.7 is used. AutoDock applies the Lamarckian Genetic Algorithm (LGA) and operates using an empirical free energy force field model. The docking grid was set manually through protein and grid visualization to achieve appropriate results [7].

Interaction study and visualization of docked complex

The interactive ligand-protein correlation was then visualized using BIOVIA Discovery Studio 2021. The results of the docking of the two molecules were formed into a complex using the AutoDockTools tool (version 1.5.6). The complex was then checked for interactions using BIOVIA Discovery Studio 2021 [8].

Pharmacokinetic prediction of compounds

This procedure was performed using the ADME predictor tool (pkCSM, accessible online at https://biosig.lab.uq.edu.au/pkcsm/prediction). The tool estimates a compound's ADME characteristics based on its SMILES input, after which its pharmacokinetic properties were evaluated.

RESULTS

With technological advancements, the process of discovering new drugs has become significantly faster, particularly due to the use of in silico testing as an initial step before laboratory experiments. Through molecular docking methods in silico tests, potential drug candidates can be predicted to interact with their target molecules [9].

In this study, the NAT2 protein was used as a receptor, obtained from the Protein Data Bank. The compound ligands used are isoniazid and curcumin, compounds found in ginger (*Curcuma xanthorrhiza* Roxb.), with structures taken from PubChem. This research aims to investigate the results of molecular docking for the active compounds in isoniazid and curcumin, focusing on the binding affinity value in kcal/mol. The binding affinity is considered stronger if the value is more negative [10].

Validation of method

Docking validation serves as an initial assessment that should be conducted prior to docking potential ligands. Its primary purpose is to confirm the reliability and appropriateness of the docking methodology [11]. In this phase, the native ligand is re-docked to the NAT2 protein. The initial step in validation involves defining the center of the grid box. This grid represents a spatial framework in which the native ligand or active compound adopts a conformation upon binding to the macromolecule. The grid box establishes the coordinates of the macromolecule's binding or active site. To assess the validity of the docking process, the RMSD between the docked ligand and the ligand's crystallographic position is measured. An RMSD value under 2.0 Å indicates that the docking method is reliable and appropriately validated [12]. The initial step in the molecular docking process is the preparation of a grid box, which functions as the formation of a three-dimensional region on a macromolecule where ligands can tether. The size of the grid box must be adjusted according to the type of docking. The targeted docking method is used, where the area of the grid box is determined with a certain size based on the size of the ligand. After determining the grid box, the file is saved as config.txt, which contains the values of the grid options that have been set [13].

Table 1. Validation of Macromolecule.

Parameters	
Macromolecule	**N-acetyltransferase 2**
Grid Center	X = 9.746 Y = 36.281 Z = 67.032
Grid Box	43x45x36
Binding Energy	-5.78 kcal/mol
RMSD	1.97 Å

Note: RMSD: Root Mean Square Deviation

Based on Table 1, the re-docking results produced an RMSD of 1.97 Å and a minimum binding free energy of -5.78 kcal/mol, indicating that the applied docking method is both valid and reliable. In the Autodock evaluation program Energy calculations are carried out in two stages. In the first step, intramolecular energy evaluated transition from previous state tethering to a complex state afterward. In the second step, the energy between molecules docking evaluated ligands and proteins (macromolecules) in their form after docking is physically bound (bound conformation). In the autodock program Gibbs energy of binding is obtained, namely the amount of several energies, which include Van der Waals energy, hydrogen, electrostatics and desolvation. Van der Waals energy is the energy of attraction between two carbon atoms. Energy hydrogen is the interactive energy between oxygen atoms. Electrostatic energy is energy that resulting from opposite charges in each molecules and desolvation energy, are binding energy between macromolecules and ligands in solution [14].

Molecular docking

Table 2. Results of docked compounds.

Ligand	Binding Energy (kcal/mol)
Coenzyme A (Native ligand)	-5.78
Isoniazid	-4.47
Curcumin	-8.35

Note: RMSD: Root Mean Square Deviation

Based on the results of method validation in Table 2, the binding energy of Coenzyme A (native ligand) against the NAT2 protein was found to be -5.78 kcal/mol. From the molecular docking results, once the target was achieved, the binding energies of isoniazid and curcumin compounds were obtained with binding energy values of -4.47 kcal/mol and -8.35 kcal/mol, respectively. Based on this, curcumin has the lowest binding energy value and is considered the most potent of the two ligands.

Visualization of the docked complex

Visualization in molecular docking creates graphical representations of molecular structures and interactions, enhancing the understanding of biomolecular relationships and the outcomes of docking simulations [15]. Visualization can help prioritize promising candidates and provide insights into drug mechanisms and disease pathology [16].

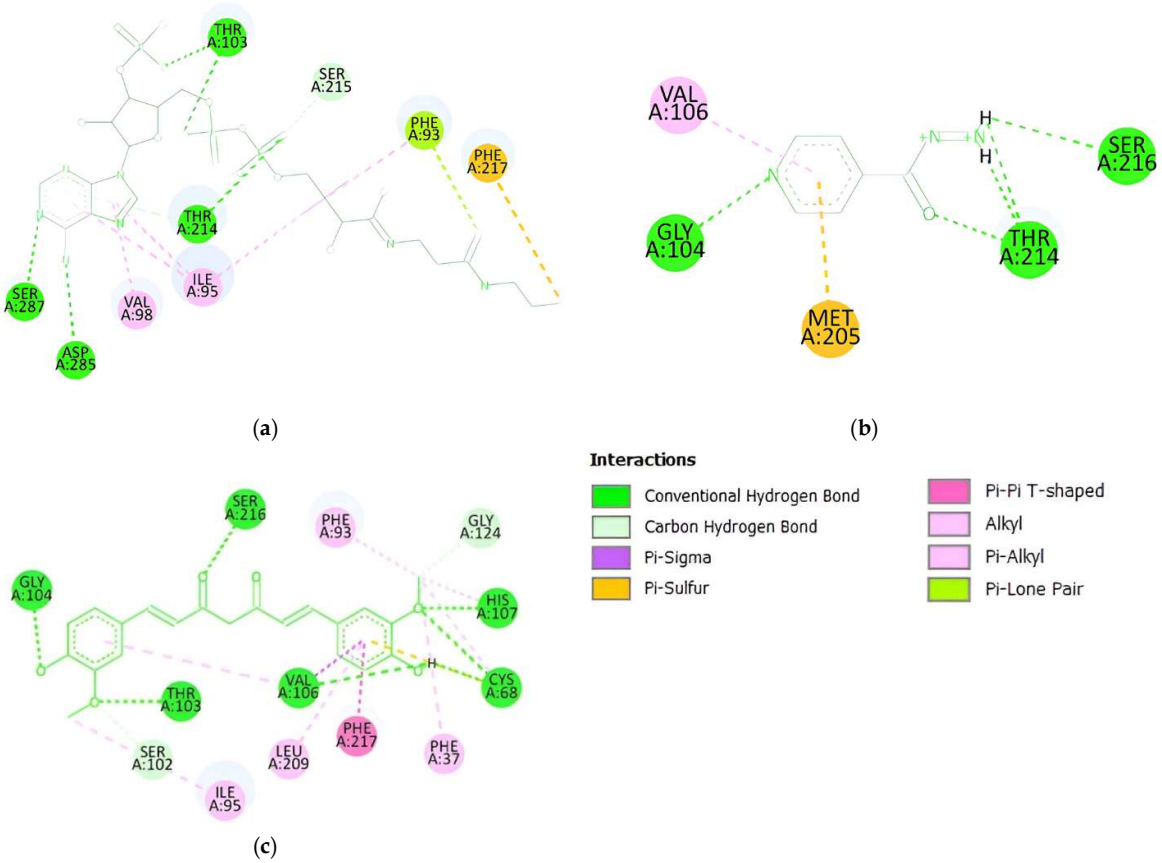

Figure 1. Two-dimensional (2D) visual representations of molecular docking interactions between ligands and the NAT2 protein (PDB ID: 2PFR) are shown for: (**a**) the native ligand, (**b**) the isoniazid compound, and (**c**) the curcumin compound.

Based on the visualization results in Table 3, it can be concluded that the curcumin compound has the shortest bond distance compared to isoniazid compound, which is 1.80775 Å. According to information from

the literature, the bond distance indicates the stability and strength of a bond's ability to bind with a protein; the shorter the distance, the stronger and more stable the bond is for protein binding [17]. Hydrogen bonds form when there is interaction between a hydrogen atom and fluorine (F), nitrogen (N), or oxygen (O) atoms [18].

Table 3. Interactions of ligands with the NAT2 Protein.

Ligand	Bond Distance (Å)	Bond Type	Amino Acid Residue	Ratio of Identical Residue	Percentage (%)
Coenzyme A (Native ligand)	1.63433	Conventional Hydrogen Bond	**PHE93**; VAL95; VAL98; **THR103**; **THR214**; SER215; **PHE217**; ASP285; SER287	9/9	100
Isoniazid	1.91561	Conventional Hydrogen Bond	GLY104; VAL106; MET205; **THR214**; SER216	1/5	20
Curcumin	1.80775	Conventional Hydrogen Bond	PHE37; CYS68; **PHE93**; ILE95; SER102; **THR103**; GLY104; HIS107; VAL106; GLY124; LEU209; SER216; **PHE217**	3/13	23

Note: PHE: Phenylalanine; VAL: Valine; THR: Threonine; SER: Serine; ASP: Asparagine; GLY: Glycine; MET: Methionine; CYS: Cysteine; ILE: Isoleucine; HIS: Histidine; LEU: Leucine

Pharmacokinetic prediction

The selection of ADME predictions, which absorption, distribution, metabolism, and excretion, was carried out. Drug candidates with a good oral pharmacokinetic profile are determined by the following parameters: high GI absorption, pharmacokinetic properties (GI absorption, Substrate Pgp, Log P, VDss, inhibitor CYP1A2, CYP2C19, CYP2D6, CYP3A4, and Clt), which are presented in Table 4.

Table 4. Predicted Pharmacokinetic Parameters.

Compound	Pharmacokinetic Parameters									
	Abs. GI (%)	Subs. Pgp	Log P	VDss (L/kg)	Inh. CYP 1A2	Inh. CYP 2C19	Inh. CYP 2C9	Inh. CYP 2D6	Inh. CYP 3A4	Clt (mL/min/kg)
Isoniazid	92.601	No	-0.3149	0.484	No	No	No	No	No	5.272
Curcumin	82.190	Yes	3.3699	0.609	Yes	Yes	Yes	No	Yes	0.995

Note: Abs. GI: Absorption in Gastrointestinal; Subs. Pgp: P-glycoprotein substrate; VDss: Steady State Volume of Distribution; Inh: Inhibitor; Clt: Total Clearance

DISCUSSION

Molecular docking is a computational technique used to predict interactions between ligands and receptors. This method is categorized into two main types: blind docking and targeted (or oriented) docking. Oriented docking is a process docking where the location of the active side is known from the receptor, while blind docking is the docking process that is carried out without knowing the location of the active side or receptor docking site. This study is done by blind docking ligand to the receptor, because it doesn't know the correct grid box parameters from isoniazid and curcumin Donor compounds hydrogen bonds no more than 5. Acceptor hydrogen bonds no more than 1, log P no more than 5 [19]. The interactions that can be observed in the image are mainly hydrogen bond interactions, donor-donor interactions and Pi-Pi stacking. In general, the value of ΔG is related to the number of H-bond interactions. The more H-bonds, the lower the binding affinity value, so the better it is at inhibiting targeting the receptor [20].

In molecular docking validation, the root mean square deviation (RMSD) is used to evaluate the accuracy of the docking protocol by comparing the predicted ligand pose with its experimentally determined crystallographic conformation. An RMSD value of less than 2.0 Å is generally considered acceptable, as it indicates that the docking method can reproduce the native binding orientation of the ligand with high reliability. This threshold is widely adopted because deviations below 2 Å are within the typical resolution range of X-ray crystallography and reflect minimal structural discrepancy between the predicted and experimental poses. Therefore, when the RMSD obtained from re-docking the co-crystallized ligand is below this limit, the docking parameters and scoring function are regarded as valid for further virtual screening studies [21].

The docking approach was verified by determining the Root Mean Square Deviation (RMSD) between the target protein and its original ligand. Docking simulations were conducted with both the compound ligand and the reference ligands against the target protein. RMSD serves as a key metric to assess how closely the docked ligands resemble the crystallographic structures. RMSD measures the distance between the docked ligand's position on the protein and its original binding location in the native crystal structure [22]. This RMSD value is also referred to as the binding distance. RMSD is used to determine how specific the docking combination is. The docking method is considered valid if the RMSD value is ≤ 2 Å [23]. The RMSD value obtained in this study is 1.97 Å, which means that the molecular docking method used has been validated and produced specific and positive results. The lower the RMSD value, the better the prediction of the current ligand position approaching the original conformation [24].

Residue-ligand interactions refer to the contacts or relationships between amino acid residues and the ligand molecule bond. In this process, amino acid residues within the protein binding pocket interact with atoms and groups on the ligand molecule. This interaction is used to understand in detail how the ligand interacts with its target protein at the atomic level. The ligand-residue interactions of coenzyme A with the 2PFR receptor are shown in Figure (a).

The residue-ligand bonds in the isoniazid compound with the 2PFR receptor have 5 bonds with 3 hydrogen bonds and 2 hydrogen bonds, VAL and MET. The docking process of isoniazid with the 2PFR receptor can also be said to be successful because it fulfills Lipinski's rules namely hydrogen bonds less than 10. Furthermore, the binding of the curcumin ligand residues with the 2PFR receptor is shown in figure c the following.

The residue-ligand bonds of curcumin with the 2PFR receptor consist of 13 bonds: 6 conventional hydrogen bonds, 2 carbon-hydrogen bonds, and 5 bonds with ILE, LEU, and PHE. The docking of curcumin against the 2PFR receptor can also be considered successful because it fulfills Lipinski's rules, specifically that the number of hydrogen bonds is less than 10. The interactions between the curcumin ligand and the 2PFR receptor include the highest number of ligand interactions with residues compared to the previous two ligands.

The bond types obtained from the visualization are primarily conventional hydrogen bonds, which play a role in the stability of conformational changes in the NAT2 protein and serve as inhibitors in hepatotoxicity. The hydrogen and hydrophobic bond interactions between the ligand and receptor both play crucial roles in the stability of the ligand [25]. According to the literature, a protein is likely to undergo stable conformational changes between the ligand (as an inhibitor) and the target protein if many hydrogen bonds are formed [26]. This is further supported by the fact that the presence of hydrogen bonds can facilitate electrostatic interactions, which are crucial for the compound's affinity with the target protein [27].

Furthermore, the amino acid residues obtained and compared to the native ligand (Coenzyme A) showed that curcumin is more similar to it than isoniazid, with a similarity percentage of 23%. Amino acid residues are crucial in determining the similarity of a compound's activity, especially within the active site of the target protein's macromolecular structure [28]. According to the literature, a compound is predicted to have similar activity if it shares amino acid residues; the more residues that match, the more similar the activity will be, in this case, as an inhibitor of the NAT2 protein [29].

The intestine is typically the main location where a drug is absorbed following oral administration. Based on Table 4, the predicted absorption for isoniazid and curcumin were 92.60% and 82.19%, respectively. This indicates that the compounds isoniazid and curcumin are predicted to be mostly absorbed in the

gastrointestinal tract, which is consistent with the literature stating that isoniazid has a bioavailability of 93% [30], while curcumin has a bioavailability of 60% [31].

A p-glycoprotein (Pgp) substrate is a substance that relies on the P-glycoprotein transporter for various functions, such as drug absorption, excretion, and other key processes, which can result in alterations within the body or affect the impact of other drugs on the body [32],[33]. The results of this study show that isoniazid is unlikely to be a Pgp substrate, while curcumin can be, as it can significantly inhibit P-gp activity [34].

Compounds with good permeability can be analyzed using Lipinski's Rule of Five, one of which is the Log P value. This rule states that a compound will have good permeability if its Log P value is <5. The results for isoniazid and curcumin show that the two modified ligands meet Lipinski's rule, meaning it can be predicted that these structural modifications will have good permeability in the body. The literature reports that the Log P value of isoniazid is −0.64, while curcumin's Log P value is between 2.3 and 3.2 [35], [36].

The steady-state volume of distribution (VDss) refers to a theoretical volume in which a drug must be evenly distributed to produce the same concentration as observed in blood plasma. A VDss is considered low if it is below 0.71 L/kg (log VDss < -0.15), and high if it is greater than 2.81 L/kg (log VDss > 0.45). Based on this criterion, isoniazid and curcumin are expected to exhibit low VDss values [37].

Cytochrome P450 is a key enzyme involved in detoxification, predominantly located in the liver, which functions to oxidize xenobiotic compounds and support their elimination during drug metabolism. It is divided into CYP1A2 (metabolizing endogenous compounds), CYP2C19 (metabolizing at least 10 percent of commonly prescribed drugs, such as clopidogrel), CYP2C9 (metabolizing steroid hormones and fatty acids), CYP2D6 (metabolizing several drugs, such as antidepressants), and CYP3A4 (metabolizing bile acids) [38]. The study results predicted that isoniazid does not have the ability to inhibit the enzymes mentioned above, while the curcumin compound can inhibit all except CYP2D6.

Total clearance (Clt) represents the overall capacity of the organism (a combination of organs and tissues) to irreversibly eliminate a specific chemical, without specifying which organs or elimination routes are involved. The organism's total ability to eliminate a drug is the sum of hepatic clearance, renal clearance (the primary sites for drug removal), and clearance by other tissues [39]. The literature reports that the total clearance of the isoniazid compound is 7.833 mL/min/kg [40], while the total clearance of curcumin is 81.833±15.6 mL/min/kg for oral administration [41].

▪ CONCLUSION

The results of this study indicate that curcumin pretreatment can improve the distribution of isoniazid by inhibiting NAT2 activity. Additionally, curcumin markedly reduces systemic exposure to acetylisoniazid, a harmful metabolite of isoniazid associated with isoniazid-induced hepatotoxicity. This study provides important evidence suggesting that curcumin can protect against liver injury caused by isoniazid and enhance its therapeutic effect through inhibition of NAT2 activity.

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