

The Potential of ZICURMA Herbal Supplement in Inhibiting Pro-Inflammatory Cytokines as Therapeutic Agents in SARS-CoV2 Infection

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Received: 12 May 2022, Revised: 5 July 2022, Accepted: 15 July 2022, Published: 2 December 2022

Abstract

nSARS-CoV2 causes pneumonia and acute respiratory distress syndrome that involves exacerbated pro-inflammatory cytokines hyperproduction. ZICURMA, zing-curcuma is a tonic developed from ginger, turmeric, and curcuma that may be adequate to remedy nSARS-CoV2 infections. Therefore, this study aims to predict the effectiveness and possible inhibition of potentially bioactive compounds in ZICURMA against pro-inflammatory cytokines through a molecular docking approach. Three bioactive compounds were identified and extracted from KnapSackFamily, namely bisacumol, curcumin and desmethoxycurcumin; then, the 3D structures were generated from PubChem. The protein targets were prepared using an open babel program integrated into PyRx 0.8; there were TN- α , IL-6 / IL-6R, and IL-1 / IL-1R, respectively. The results showed that the ligands had moderate to solid binding affinity with values ranging from -5.0 kcal/mol to -9.0 kcal/mol. However, it offers a mismatch of bonds, including between curcumin compounds and IL-6, IL-6R, IL-1R and IL-1 β . In silico simulation proves that the bioactive compound in ZICURMA does not allow binding to IL-6, IL-6R, IL-1R and IL-1 β proteins. However, it cannot be used as a standard reference to determine the feasibility of bisacumol, desmethoxycurcumin, and curcumin as an anti-viral candidate. Further in-vitro researches should be conducted to validate the potency of ZICURMA as an anti-viral infection.

Keywords: COVID-19, Curcuma, Ginger, In silico, Turmeric

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was first discovered in Wuhan, China, and has widespread to more than 224 countries. Around 6 million deaths and more than 546 million COVID-19 cases have been reported globally by the end of June 2022, however it increases continuously [1]. Meanwhile, there are more than 6 million COVID-19 cases with a death rate of 2.6 % has been reported in Indonesia [2]. Even though it has low fatality rate compared to SARS-CoV in 2004 and MERS-CoV in 2012 [3], the COVID-19 fatality rate has increased in the elderly or people with comorbidities [4].

SARS-CoV2 infection causes lung inflammation process that produces cytokines massively, and induces a systemic fatality immune disorder [5-7]. The unstable activity of the cytokines aggressively destructs multi-organ that aggravating patient conditions with comorbidities. Several studies show that about 20 % of COVID-19 patients experiencing a long-COVID syndrome that decrease their immune respond [8]. Most hospitalized patients with severe COVID-19 symptoms report long-term symptoms, including fatigue and shortness of breath [9].

SARS-CoV2 triggers systemic immune catastrophe and induces inflammation that attacks internal organ. It is difficult to prescribe exact medicine to kills the virus and stop infection. The current COVID-19 treatment process only focuses on the symptoms that appear and improving the immune system [10,11]. Administration of inappropriate long-term medication potentially causes tissue damage or organ failure.

Therefore, increasing immune system stability in one of the prominent alternative solution preventing severe viral infection. For example, consuming herbals or traditional medicine may improve health condition during the disease, because it has a potential bioactive compound as immunomodulators [12,13]. Medicinal plants such as ginger (*Zingiber officinale* Roscoe) contain zingiberin, which is efficacious controlling macrophage activity in various types of infections [14]. In addition, turmeric (*Curcuma domestica* L) and curcuma (*Curcuma xanthorrhiza* ROXB) contain curcumin which is preventing oxidative stress during viral infections [15-17]. Hence, the use of ginger, curcuma and turmeric (ZICURMA) potentially developed as immunomodulatory supplements for COVID-19 patients. However, the effectiveness of ZICURMA as an immunomodulator, especially in stopping pro-inflammatory cytokines in COVID-19 cases, still needs to be studied a lot.

Simulation of the interaction between proinflammatory cytokines and bioactive compounds ZICURMA using in silico technique can overview the immune system control pathways in viral infections. In silico analysis using molecular docking helps shorten the time and streamline research before applying to animals or humans. Molecular docking is a process carried out to predict the ligand-receptor interactions that occur. In this process, all ligands are maximally able to interact with the receptors based on the developed algorithm. Therefore, the visualization process is needed to validate the ligand-receptor interactions that occur. Therefore, this study aims to predict the potential of compounds in ZICURMA to inhibit proinflammatory cytokines through an in-silico approach.

Materials and methods

Retrieval and preparation of ligands structure

The ligand structures were selected by screening and extracting common bioactive compounds contained in *Z. officinale*, *C. domestica* and *C. xanthorrhiza* ROXB) from http://www.knapsackfamily.com/knapsack_core/top.php. Based on these results, 13 active compounds was found from the 3 herbal species. The 3D structure of 13 active compounds was downloaded from the PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) in .sdf format. The 3 ligands were prepared using the Open Babel 2.4.0 program [18] integrated in PyRx 0.8. Azithromycin, chloroquine, and anakinra were used for control in inhibiting TNF alpha, IL-6 / IL-6R and IL-1 / IL-1R, respectively [19,20].

Table 1 The same active compounds in ginger, turmeric and curcuma based on KnapSack data.

Active Compounds	PubChem ID	Molecular Weight (g/mol)	Molecular Formula
Alpha terpineol	17100	154.25	C ₁₀ H ₁₈ O
Bisacumol	5315469	218.33	C ₁₅ H ₂₂ O
Borneol	64685	154.25	C ₁₀ H ₁₈ O
Camphene	6616	136.23	C ₁₀ H ₁₆
Camphor	2537	152.23	C ₁₀ H ₁₆ O
Curcumin	969516	368.40	C ₂₁ H ₂₀ O ₆
Desmethoxycurcumin	146723	338.40	C ₂₀ H ₁₈ O ₅
P-cymene	7463	134.22	C ₁₀ H ₁₄
Terpinolene	11463	136.23	C ₁₀ H ₁₆
1,8 cineole	2758	154.25	C ₁₀ H ₁₈ O
4-terpineol	11230	154.25	C ₁₀ H ₁₈ O
(+)-alpha-pinene	82227	136.23	C ₁₀ H ₁₆
(+)-beta-pinene	10290825	136.23	C ₁₀ H ₁₆
Inhibitors commercial			
Anakinra	139595263	509.60	C ₂₀ H ₂₃ N ₅ O ₇ S ₂
Azithromycin	447043	749.00	C ₃₈ H ₇₂ N ₂ O ₁₂
Chloroquinne	2719	319.90	C ₁₈ H ₂₆ ClN ₃

Retrieval and preparation of protein preparation

The 3D structures of the 3 cytokines, including TNF- α (2AZ5), IL-6 / IL-6R (1P9M) and IL-1 β / IL-1R (1ITB) were retrieved from the RCSB PDB web server (<https://www.rcsb.org/>). The cytokines were then prepared to remove water molecules and ligands using BIOVIA Discovery Studio 16.1 for Windows system (<http://www.Accelrys.com>).

Molecular docking analysis and interaction prediction

Molecular docking analysis was performed to determine ligands-receptor interactions using AutoDock Vina v1.2.0 [21,22], which is integrated into PyRx 0.8. In this study, specific docking was carried out by forming a grid box based on the active site of the receptor [23,24]. The binding energies resulting from the ligand-receptor interactions were compared, and the same binding site analysis was performed with the control compound. The ligand-receptor interaction with the smallest binding energy was visualized using Discovery Studio 16.1 to determine the amino acid residues and the bonds formed. The docking stability was verified by calculating the Root Mean Square Deviation (RMSD) scored less than 3 Å and the root-mean-square fluctuation (RMSF) indicating that there was no amino acid fluctuation in the amino acid during docking.

Results and discussion

Molecular docking simulation examines the conformation of ligands that bind proteins by measuring the binding energy based on various potential bonds and interactions between atoms. The interactions formed between ligands and proteins, electrons are involved in the formation of ionic and covalent bonds [25]. As evidence, this study used bisacumol, curcumin, and desmethoxycurcumin as ligands and TNF- α , IL-6, IL-6R, IL-1 β , IL-1R as the targets. Docking analysis results in this study showed that bisacumol, curcumin and desmethoxycurcumin were the 3 active compounds with the lowest binding energy. Desmethoxycurcumin has the lowest binding energy for its interaction with TNF- α and IL-6R, while Bisacumol and Curcumin have the lowest binding energy for their interaction with IL-6 and IL-1R (Table 2).

Table 2 Affinity binding energy between ligand (bioactive compounds) and targeted proteins.

Active Compounds	PubChem CID	Binding Energy (Kcal/mol)				
		TNF- α	IL-6	IL-6R	IL-1 β	IL-1R
Bisacumol	5315469	-6.4	-7.0	-5.9	-5.5	-6.2
Curcumin	969516	-7.5	-6.4	-6.0	-6.0	-6.9
Desmethoxycurcumin	146723	-7.7	-6.4	-6.4	-6.0	-6.8
Inhibitors commercial						
Anakinra	139595263	n/d	n/d	n/d	-6.7	-6.8
Azithromycin	447043	-7.7	-5.4	-6.6	n/d	n/d
Chloroquine	2719	-6.6	-4.9	-4.7	n/d	n/d

The low binding energy (kcal) indicates that the interaction between bioactive can easily bind to the target protein. However, the size of the binding efficiency between the ligands with the protein is determined by the characteristics and properties of the compounds being tested, especially the size of the compounds required to obtain a high binding affinity to the target protein [26]. The calculation of the ability of bioactive to bind and affect cytokines through the combination of the efficiency of the size of the compound to attach to the receptor site must be considered in silico simulations and physicochemical characteristics [27]. Based on the analysis results, the average affinity of the ligand to the receptor is 5.0 - 7.0 kcal/mol, which indicates the form of interaction between the bioactive compound and the target cytokine, the correlation is moderate and tends to be high.

In general, a low-affinity bond energy score is often used as a reference for selecting the most potent ligand after the in silico screening process [28]. This is because the low-affinity energy indicates less effort is used to form a stable bond between the ligand and target protein. However, this quantitative measure cannot be used as the only criterion to assess the effectiveness of bioactive compounds in influencing proteins for in vivo treatment. Because the bioactive may undergo metabolic processes into intermediate compounds that are more related to inhibition of cell signaling pathways. Therefore, drugs such as anakinra, azithromycin and chloroquine were used as a reference for determining the threshold for feasibility of ligand-protein complex interactions [24]. It can be said that predominantly, the value of binding energy between the target protein and the ligand of the bioactive compound ZICURMA is higher than that of the control ligand.

On the other hand, examining the interaction model through a visualized model comparing the quality of the interaction between the ligands of bioactive compounds and the cytokines targeted in this study.

Visualization using PyMol aims to determine the ligand-binding site of each receptor used in this study. The results showed that the 3 active and control compounds had the same binding position on TNF- α and IL-1R, respectively. In IL-6 interaction, bisacumol and desmethoxycurcumin have the same binding site as Azithromycin, while curcumin has the same binding site as chloroquine (**Figure 1**).

Although the docking simulation results for bisacumol, curcumin and desmethoxycurcumin showed an interaction with the target protein, the fit-transfiguration between the compounds was strongly influenced by the binding position with the ligand pose. Further analysis was used to determine the types of amino acids formed from ligand-receptor interactions. The interaction between bisacumol, curcumin and desmethoxycurcumin with TNF- α performs the same binding site with the azithromycin and chloroquine.

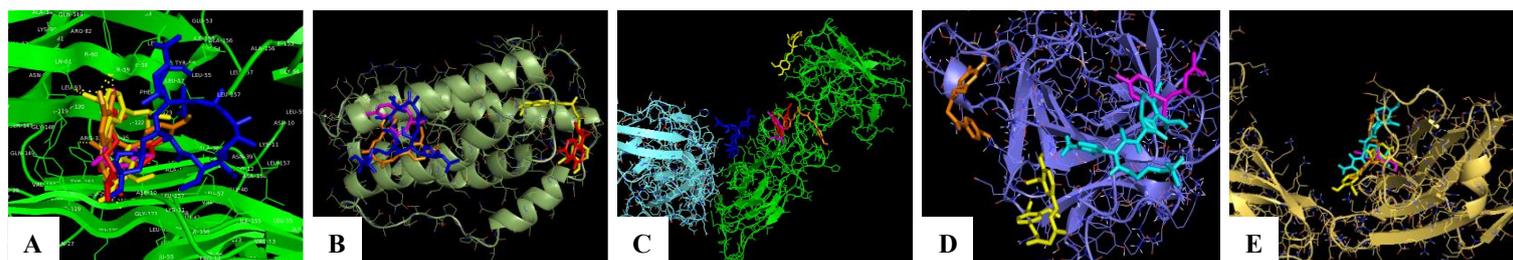
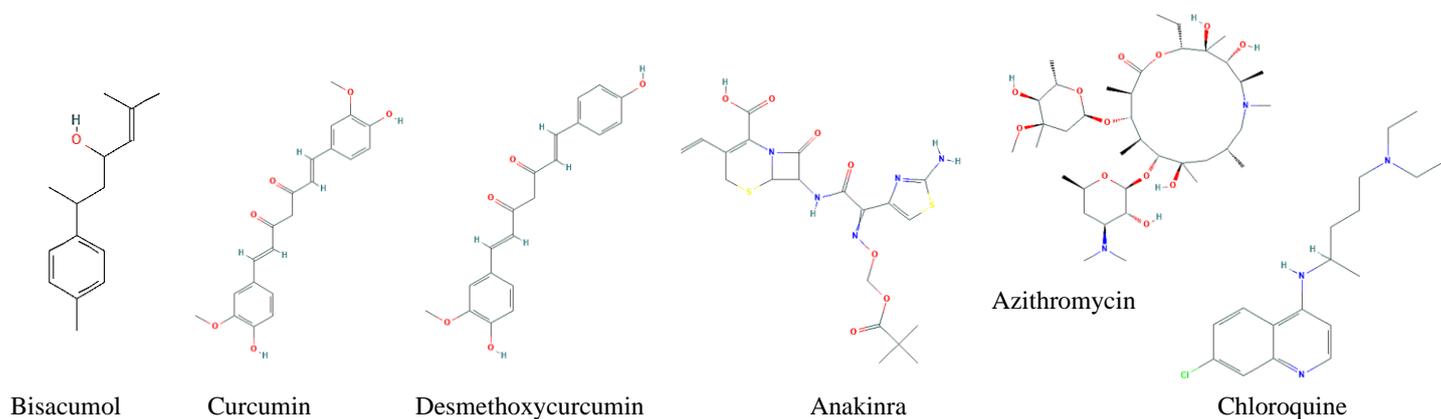


Figure 1 The ligand-binding sites on pro-inflammatory cytokines: (A) TNF- α , (B) IL-6, (C) IL-6R, (D) IL-1 β and (E) IL-1R. Pro-inflammatory cytokines presented in flat ribbon structure with ligands presents as colored stick. Azithromycin as blue stick, Chloroquine as red stick, Anakinra as cyan stick, Bisacumol as magenta stick, Curcumin as yellow stick, and Desmethoxycurcumin as orange stick.

The similarity of the binding site between the ZICURMA bioactive compound and the control compound (azithromycin and chloroquine) was found in the Leu-57, Tyr-59 and Tyr-120 residues, where the dominant interactions at the binding site were dominated by the amino acids: Leucine, tyrosine and glycine. The interaction of ligands with bioactive compounds is dominated by conventional hydrogen bonds with the hydroxyl end of the group and weak van der Waals bonds (**Figure 2**). In addition, stacking interactions were observed in the docking simulation between the ligand and TNF- α protein, which showed an interesting noncovalent interaction between the Tyr aromatic ring and the cyclic ends of bisacumol, curcumin and desmethoxycurcumin. The docking simulation also showed that despite the similarity of the curcumin chain to desmethoxycurcumin, the resulting interaction with the TNF-protein was different, which resulted in an inverted configuration.

Ligand interactions with proteins IL-6 have fewer amino acid residues in the coordination complex than TNF- (**Figure 3**), whereas IL-6R has fewer ligand interactions (**Figure 4**). The interaction between bisacumol and the receptor at the IL-6 binding site is formed by 5 residues, including Phe-229, Glu-277, Glu-278, Phe-279 and Arg-231. Although the binding-affinity value shows a relatively high number, the docking simulation shows the opposite result. The interaction between curcumin and IL-6 results in an unfavorable donor-donor interaction, representing a mismatch in the binding position between the ligand and the receptor. In this study, protein flexibility was not considered in the docking protocol, thus allowing

in-silico interaction of the ligand with the receptor. This is because of the effect of induced fit, which computationally will take into account the suitability and match of the ligand with the simulated protein [29]. Unfavorable donors also indicate the possibility that the target protein has an unexpected mode of action or a different binding site from the simulation results. The unfavorable donor-donor interaction may be kinetically unfavorable as it increases the unbinding site or unintegrated part between the ligand and protein, contributing to the high energy cost of twisting in the binding cavity [30]. Therefore, even though the binding affinity value is close to -9 kcal/mol, the simulation shows a mismatch between the curcumin ligand and IL-6 protein interactions.

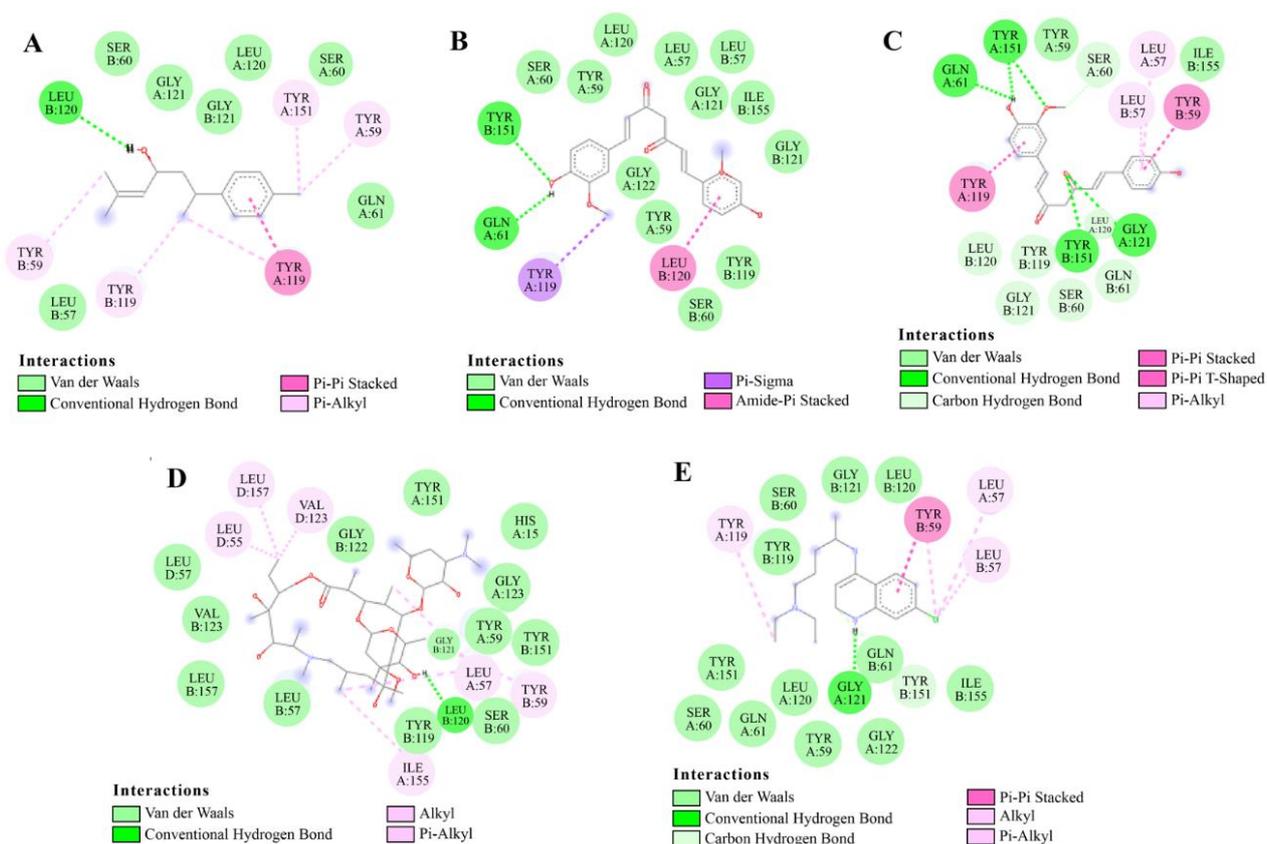


Figure 2 Amino acid residues that formed based on ligands-TNF- α interaction: (A) bisacumol, (B) curcumin, (C) dezmethoxycurcumin, (D) azithromycin and (E) chloroquine.

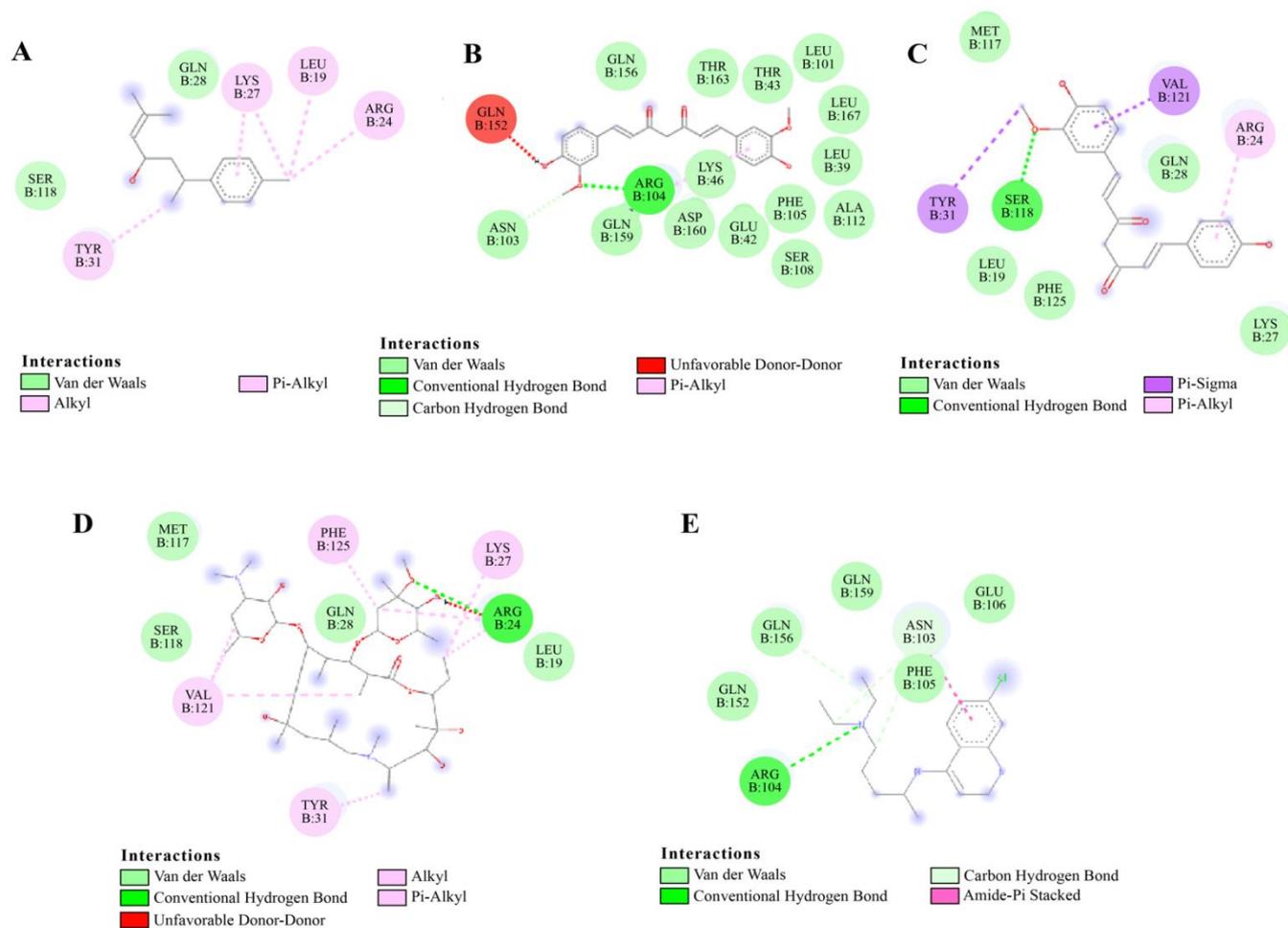


Figure 3 Amino acid residues that formed based on ligands-IL-6 interaction. At the top is ligands-IL-6 interaction: (A) bisacumol, (B) curcumin, (C) dezmethoxycurcumin, (D) azithromycin and (E) chloroquine.

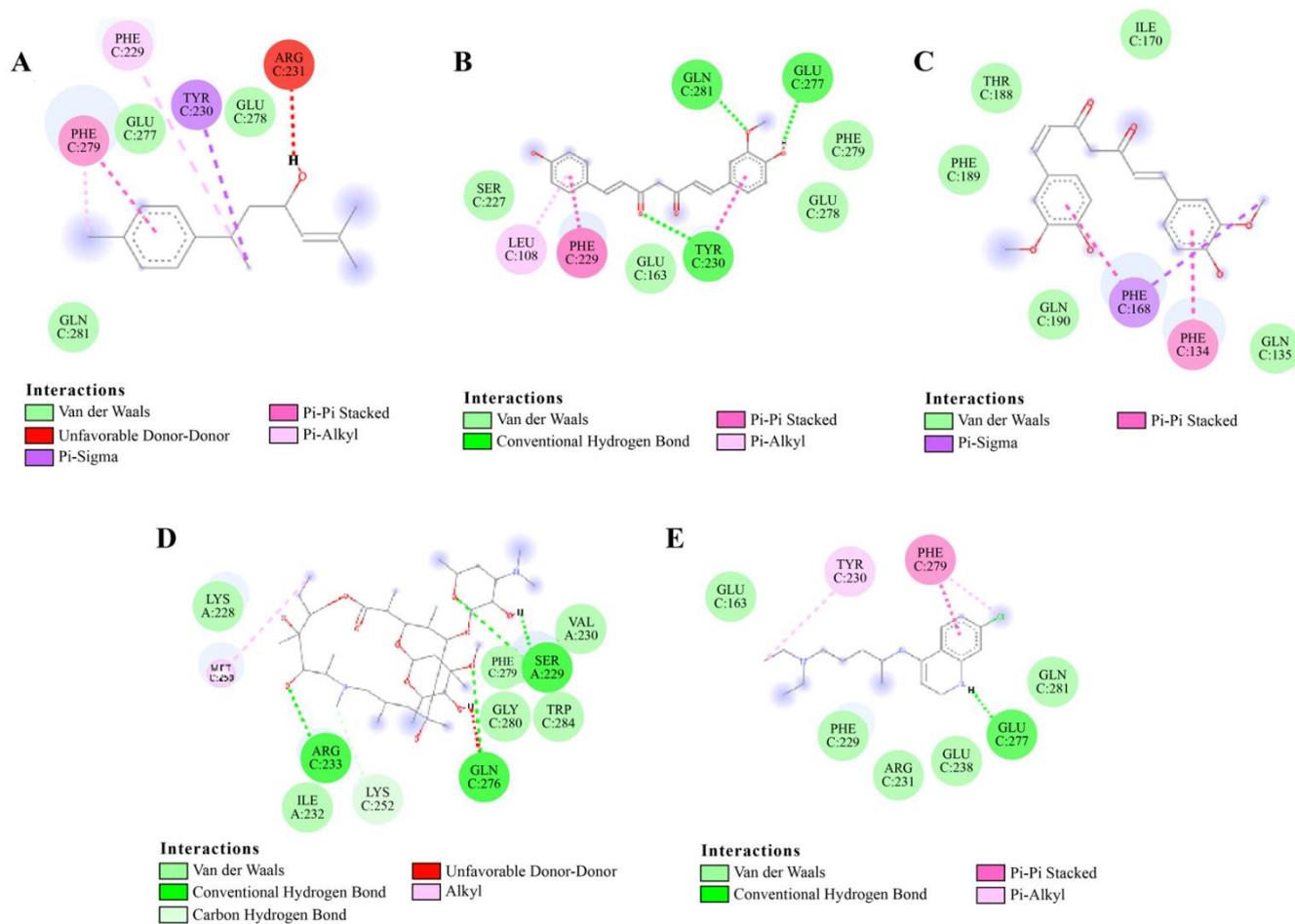


Figure 4 Amino acid residues that formed based on ligands-IL-6R interaction. At the top is ligands-IL-6 interaction: (A) bisacumol, (B) curcumin, (C) dezmethoxycurcumin, (D) azithromycin and (E) chloroquine.

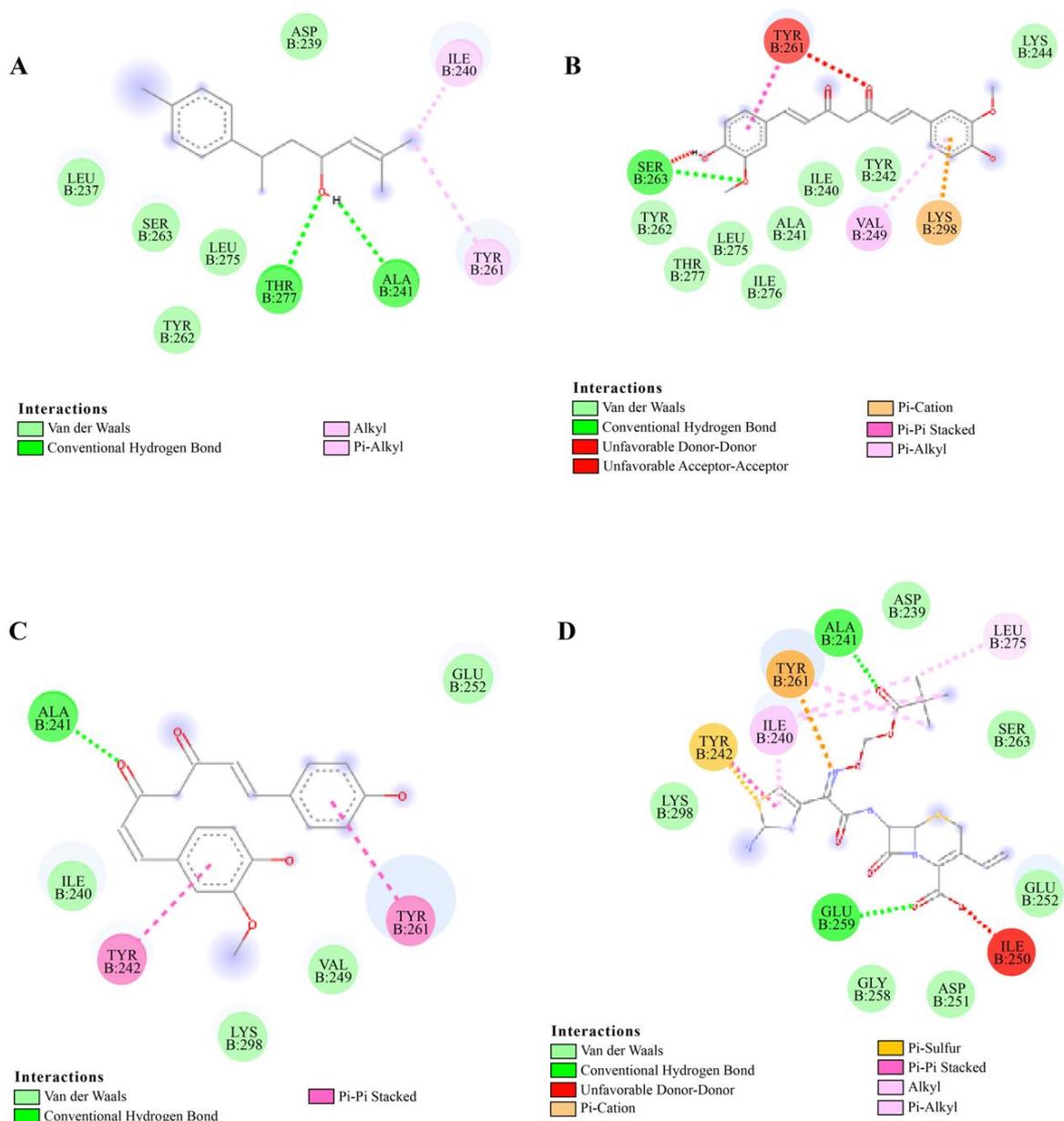


Figure 5 Amino acid residues that formed based on ligands-IL-1R interaction: (A) bisacumol, (B) curcumin, (C) dezmethoxycurcumin and (D) anakinra.

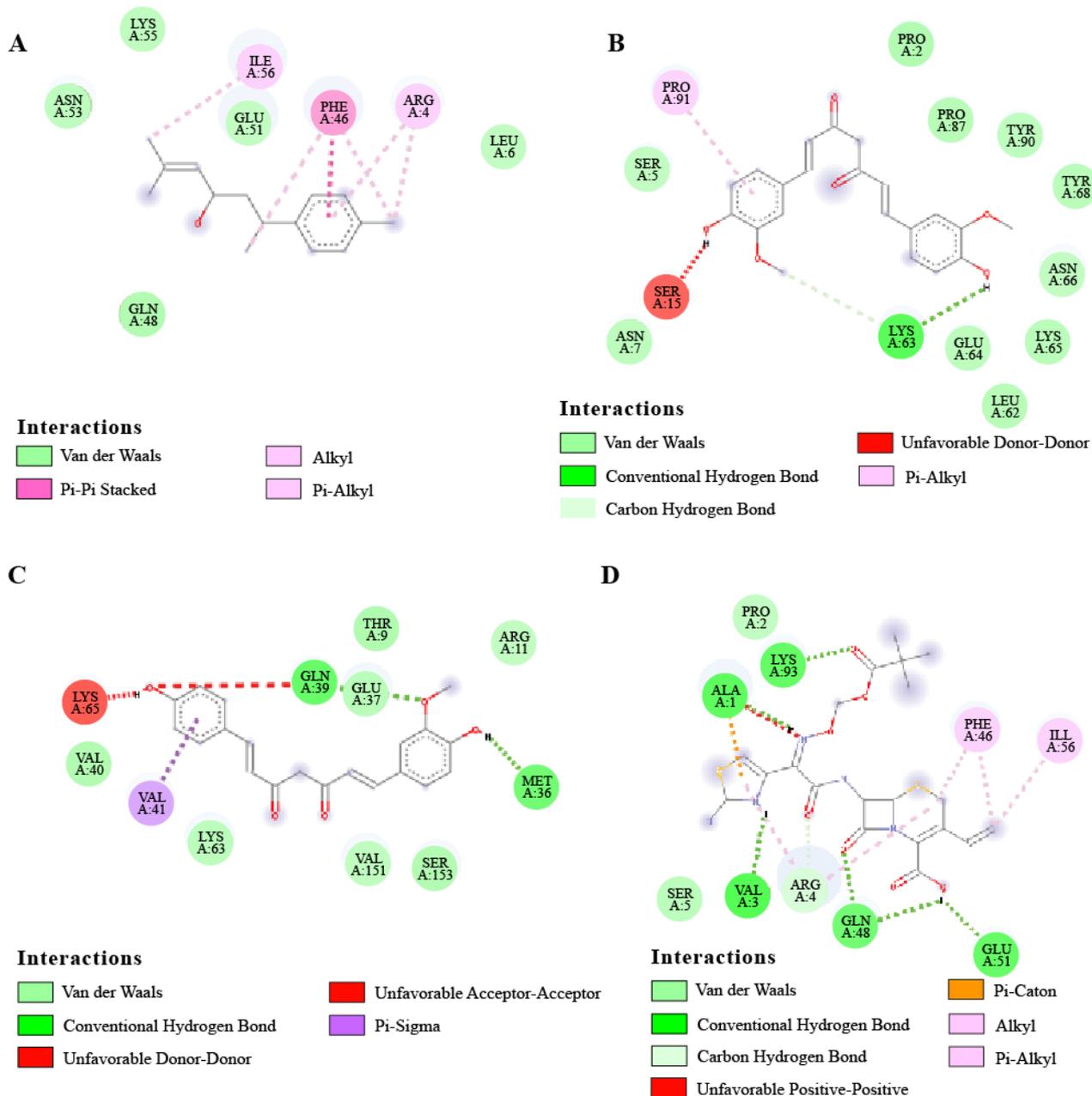


Figure 6 Amino acid residues that formed based on ligands-IL-1 β interaction: (A) bisacumol, (B) curcumin, (C) dezmethoxycurcumin and (D) anakinra.

Unfavorable donor-donor interactions were also shown between the bisacumol ligand in the C-9 free hydroxyl group and the Arg-231 residue at IL-6R. Furthermore, unfavorable donor-donor interactions were also found in the curcumin ligand docking simulation with IL-1R and IL-1 β . In addition, another form of interaction that indicates a mismatch of binding forms that may be generated is the emergence of an unfavorable acceptor-acceptor interaction between curcumin and Tyr-261 on the IL-1R protein. This further confirms that interaction between the ligands, bisacumol, curcumin and desmethoxycurcumin, with inflammatory cytokines, is also not possible *in vivo*.

Other forms of interaction such as pi-alkyl, pi-pi T shape, and pi-sulfur are non-covalent interactions. The pi-alkyl interaction in the docking simulation in this study shows the pi-electron interaction of the alkyl group of protein residues above the aromatic ligand group. At the same time, the pi-pi interaction T shape shows the pi-electron interaction between the 2 aromatic groups perpendicular to form the letter T [31].

This is due to the affinity caused by sideways ligand ring electrons interacting with electrons on the ringside of protein residues [32]. For example, the interaction formed on the aromatic group of curcumin with residues Tyr-59 and Tyr-119 TNF-. Whereas in the pi-sulfur interaction, the pi electrons of the aromatic ligand ring interact with the lone pair of electrons on the S atom at the serine residue.

In all molecular dynamic simulations, the interactions between ligands and target proteins are dominated by conventional hydrogen bonds, van der Waals and pi stacked. Hydrogen bonding is one of the fundamental bonds by which the complex coordination structure between the ligand and the target protein is formed. The participation of the residue group in the binding is a determining factor in the feasibility of ligand inhibition on the performance of the target protein. Several amino acid residues can form H-bonds through their side chains, namely side chains containing hydroxyl (Ser and Thr), amides (Asn and Gln), or charged residues such as Lys, Arg, and Asp, and Glu. Also known to participate in H-bonding are aromatic amino acids, such as His, Tyr and Trp. Most attention has been focused on the ability of these residues to form conventional H-bonds of the OH, O or NHO type. Although in this study, the dominance of conventional H-bonds is expected to represent the strongest type of interaction, the presence of unfavorable donor-donor and unfavorable acceptor-acceptor interactions should be noted as a possible interaction incompatibility. This is because proteins have a mechanism for folding and forming the most optimal quaternary structure in interacting with ligands [33].

The rhizomes of ginger, turmeric, and curcuma, used as the main ingredients for making ZICURMA are herbs belonging to the Zingiberaceae, which contain compounds that have potential as an anti-viral anti-inflammatory, including bisacumol [34], curcumin [35,36] and desmethoxycurcumin [37]. The results of preclinical studies using animal models show that curcumin regulates the expression of genes related to pro and anti-inflammatory factors such as IL-6, IL-8, IL-10 and COX-2. The administration of *C. domestica* rhizome extract was also shown to increase polymorphonuclear neutrophil apoptosis (PMNs) associated with pulmonary edema, resulting in damage to the alveolar-capillary membrane. Furthermore, the bioactive compounds in Zingiberaceae species are able to bind radical oxygen species (ROS) that exacerbate the inflammatory response. These studies are evidence that supports the bioactive compound in ZICURMA as a therapeutic agent against pneumonia in humans due to infection with the SARS-CoV2 virus [38].

Conclusions

ZICURMA's bioactive compounds, bisacumol, curcumin and desmethoxycurcumin, had a moderate binding affinity and tended to be firm with bond values ranging from -5.0 kcal/mol to -9.0 kcal/mol. The strongest binding affinity level was discovered between TNF- α and desmethoxycurcumin followed by curcumin, up to -7.7 kcal/mol and -7.5 kcal/mol, respectively, while the lowest was observed between bisacumol and IL-1 β interaction. However, this affinity value cannot be used as a complete reference in determining the feasibility of desmethoxycurcumin and curcumin as main candidates for anti-viral compounds. The simulation of the interactions formed shows a mismatch of bonds, including between curcumin compounds and IL-6, IL-6R, IL-1R and IL-1 β . Therefore, further analysis to test the efficacy of the bioactive compounds in ZICURMA as anti-inflammatory needs to be studied more deeply through in-vivo and in-vitro studies. Furthermore, a docking analysis was carried out to strengthen the justification for the positive effect of ZICURMA in the computational treatment of viral infections. This is because it is necessary to consider biological characteristics, especially in these compounds' metabolic processes and bioavailability.

Acknowledgment

The acknowledgment is delivered to the Ministry of Education, Culture, and Higher Education for funding the research through the Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) Scheme and Pusat Unggulan Ilmu Pengetahuan Teknologi Pangan Fungsional, Research and Community Service Institute of Universitas Negeri Semarang (UNNES), Indonesia.

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