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Immunomodulatory potential of bioactive compounds of betel leaf extract targeting COVID-19 immunological human host proteins: An *in silico* study

Fatimawali¹, Marko Jeremia Kalalo¹, Siboantua Broolin Simanjuntak¹, Tri Andira Hebbel¹, Billy Johnson Kepel², Trina Ekawati Tallei^{3*}

¹Pharmacy Study Program, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado, Indonesia.

²Department of Chemistry, Faculty of Medicine, Sam Ratulangi University, Manado, Indonesia.

³Department of Biology, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado, Indonesia.

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ABSTRACT

Forests contain nearly all of the natural resources required by humans. Apart from food, the community makes use of forest products for medicinal purposes. Betel (*Piper betle* L.) is one of the numerous forest plants that thrive in the forests of North Sulawesi. The leaves and fruits are used by indigenous people as anti-inflammatory medications, deodorizing odors, and for maintaining health. Natural medicine has recently been included in clinical trials as immunomodulators in COVID-19 patients. This study aimed to identify novel immunomodulatory compounds derived from betel leaf for the treatment of COVID-19 symptoms, particularly proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1beta, interleukin-6, and nuclear factor kappa B). These cytokines are critical in modulating immune responses. Bioactive compounds from betel leaves were extracted and identified using gas chromatography-mass spectrometry. These compounds were used as ligands for PyRx-based molecular docking. The admetSAR and SwissADME were used to predict ADMET (absorption, distribution, metabolism, excretion, and toxicity) and Lipinski's rule of five parameters of the studied compounds. This study discovered 57 compounds exhibited higher binding energy than the control immunomodulatory agents (β -glucan and thiopurine). Only one of the compounds violated Lipinski's rule of five. ADMET predictions indicated that the compounds possess favorable and safe pharmacokinetic properties, making them suitable for development as drug candidates. The research findings suggest that bioactive compounds derived from betel leaf may prove beneficial in the treatment of COVID-19, particularly in the context of cytokine storms.

INTRODUCTION

Immunomodulatory agents derived from natural materials have emerged as promising candidates for treating COVID-19, which is caused by a highly pathogenic novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Tallei *et al.*, 2021a). SARS-CoV-2 is rapidly spreading and has become the deadliest pandemic, posing significant global

health challenges (Gates, 2020; Rakib *et al.*, 2020). Because of a lack of therapeutic options, mortality rates in intensive care units reached as high as 20% in certain population subsets (Goyal *et al.*, 2020). Globally, as of August 23, 2021, there have been 211,730,035 confirmed cases of COVID-19, including 4,430,697 deaths, reported by the WHO. This figure is growing rapidly in South East Asia, with a reported 47% increase. India, Indonesia, and Sri Lanka had the highest rates of new cases, while Indonesia, India, and Nepal had the highest rates of new deaths. This is exacerbated by the emergence of diverse variants as a result of SARS-CoV-2 mutations that affect infectivity, disease severity, and interactions with host immunity (Harvey *et al.*, 2021). The symptoms of a deadly viral infection can be treated by suppressing the cytokine storm (Ye *et al.*, 2020). Viral infections

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*Corresponding Author

Trina Ekawati Tallei, Department of Biology, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado, Indonesia. E-mail: trina_tallei@unsrat.ac.id

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Table 1. Receptors' grid box dimensions and center.

Receptor	PDB ID	Dimensions	Grid box and center
TNF- α	2AZ5	22.0 \times 16.0 \times 14.0 Å	X: -11.3411; Y: 63.1820; Z: 16.2765
IL-1 β	2NVH	22.0 \times 12.0 \times 16.0 Å	X: 36.2063; Y: 7.4349; Z: 77.9841
IL-6	1ALU	20.0 \times 20.0 \times 20.0 Å	X: -9.1555; Y: -14.4946; Z: 6.3476
NF- κ B p65	1OY3	36.0 \times 38.0 \times 22.0 Å	X: -5.4573; Y: -8.4431; Z: -17.5854

created overactivation of adaptive and innate immune responses such as mitogen-activated protein kinase and nuclear factor kappa B (NF- κ B), causing excessive cytokine, a proinflammatory substance, being released along with chemokines that provoke severe lung alteration (Harisharan *et al.*, 2021; Li *et al.*, 2020; Tang *et al.*, 2020). The overproduction of tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1beta (IL-1 β), as proinflammatory cytokines, created the cytokine storm, prompting a serious problem of multiorgan failure and vascular hyperpermeability (Hu *et al.*, 2021; Jafarzadeh *et al.*, 2020; Sun *et al.*, 2020). There is a crucial need for immunomodulatory agents to overcome this issue by targeting these COVID-19 immunological human host proteins (Henderson *et al.*, 2020; Mehta *et al.*, 2020).

The use of natural components to save lives is required due to the time and cost constraints for which new drug approvals are required during a pandemic. Plants are used indefinitely as a source of medicine due to the presence of specific chemicals/active ingredients that have been empirically demonstrated by indigenous people (Aziz *et al.*, 2018; Pan *et al.*, 2014; Tallei *et al.*, 2019). Plants also contain active compounds that have been scientifically and clinically proven to be used in the treatment of a variety of diseases, both infectious and metabolic (Eddouks *et al.*, 2021; Graf *et al.*, 2010; Kwofie *et al.*, 2021; Silva and Júnior, 2010; Wahab *et al.*, 2021). They are sources of novel drug compounds for antiviral (Khairan *et al.*, 2021; Rakib *et al.*, 2020; Singh *et al.*, 2022; Tallei *et al.*, 2020), as well as immunomodulatory agents (Chakraborty *et al.*, 2021; Jantan *et al.*, 2015; Wen *et al.*, 2012).

To identify potential immunomodulatory agents, preliminary screening of various pharmacological agents derived from medicinal plants is required. Because of its efficiency, the

in silico approach is a promising method for discovering novel compounds as COVID-19 drug candidates (Noor *et al.*, 2021; Pinzi and Rastelli, 2019). In this research, we analyzed medicinal compounds of betel (*Piper betle* L.) leaves using a molecular docking method to obtain promising immunomodulatory agents that could be further utilized for COVID-19 management.

MATERIALS AND METHODS

Ligands' preparations

Our previous study used gas chromatography-mass spectrometry to identify bioactive compounds in betel leaves (Fatimawali *et al.*, 2021). These compounds are used in present studies as ligands. PubChem (<http://pubchem.ncbi.nlm.nih.gov>) was used to find the ligand structures. The three-dimensional (3D) structures of the ligands were saved in .sdf format. The 3D conformations were generated using Avogadro 1.2.0 (Hanwell *et al.*, 2012) and further assembled using AutoDock tools (Morris *et al.*, 2009). Ligands' energy was minimized, and the structures were geometrically optimized. The optimized ligand structures were saved in .pdbqt format and then used for molecular docking.

RECEPTOR PREPARATIONS

The 3D structures of the targeted proteins TNF- α (PDB ID: 2AZ5), IL-1 β (PDB ID: 2NVH), IL-6 (PDB ID: 1ALU), and NF- κ B p65 (PDB ID: 1OY3) (Fig. 1) determined by X-ray crystallography were retrieved from Protein Data Bank (<http://www.rcsb.org/pdb>) and used as receptors in this study. The protein structures were optimized with Biovia Discovery Studio Visualizer 2020. Native ligand and water molecules attached to the proteins were removed and then saved in .pdb format.

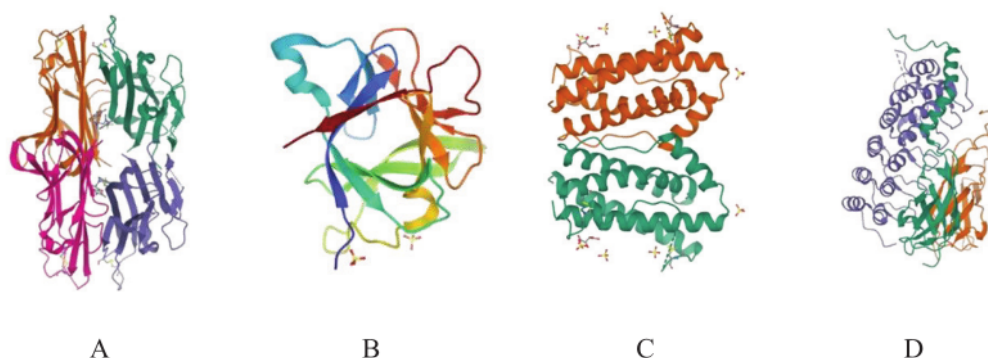


Figure 1. (A) TNF- α (PDB ID: 2AZ5); (B) IL-1 β (PDB ID: 2NVH); (C) IL-6 (PDB ID: 1ALU); and (D) NF- κ B p65 (PDB ID: 1OY3) protein structures.

The proteins were modified by adding polar hydrogen using AutoDock tools. The optimized proteins were saved in .pdbqt format and then further used as receptors for molecular docking.

RECEPTOR-LIGAND DOCKING

The docking procedure was based on our previous research (Sailah *et al.*, 2021; Tumilaar *et al.*, 2021). PyRx 0.8 (Dallakyan and Olson, 2015) was used to carry out molecular docking. Previously optimized ligands and receptors were selected and docked with the Vina wizard feature by using the Run Vina option. Table 1 shows the grid box dimensions and center used in the docking protocol.

ANALYSIS AND VISUALIZATION

Ligand-receptor interactions were visualized in both 2D and 3D structures obtained from the molecular docking output file. The output file was split using the command prompt with command: vinit -input (output file name) .pdbqt. Analysis and visualization of the ligand and receptor interaction were carried

out using Biovia Discovery Studio Visualizer 2020. Interactions of ligand and receptor with the highest binding affinity score were visualized and saved as image files.

DOCKING PROTOCOL VALIDATION

The validation was conducted according to Gupta *et al.* (2021). The control immunomodulatory agents were redocked using AutoDock Vina. The resulting poses were obtained and further analyzed using Pymol. The root mean square error (RMSD) was determined.

ADMET PROPERTIES AND LIPINSKI'S RULE OF FIVE

Ligands with greater binding energy compared to the control were further calculated for their pharmacokinetic characteristic. AdmetSAR 2.0 (Yang *et al.*, 2019) was used to predict the absorption, distribution, metabolism, excretion, and toxicity properties of the compounds, and the number of violations of Lipinski's rule of five was observed using SwissADME (Daina *et al.*, 2017).

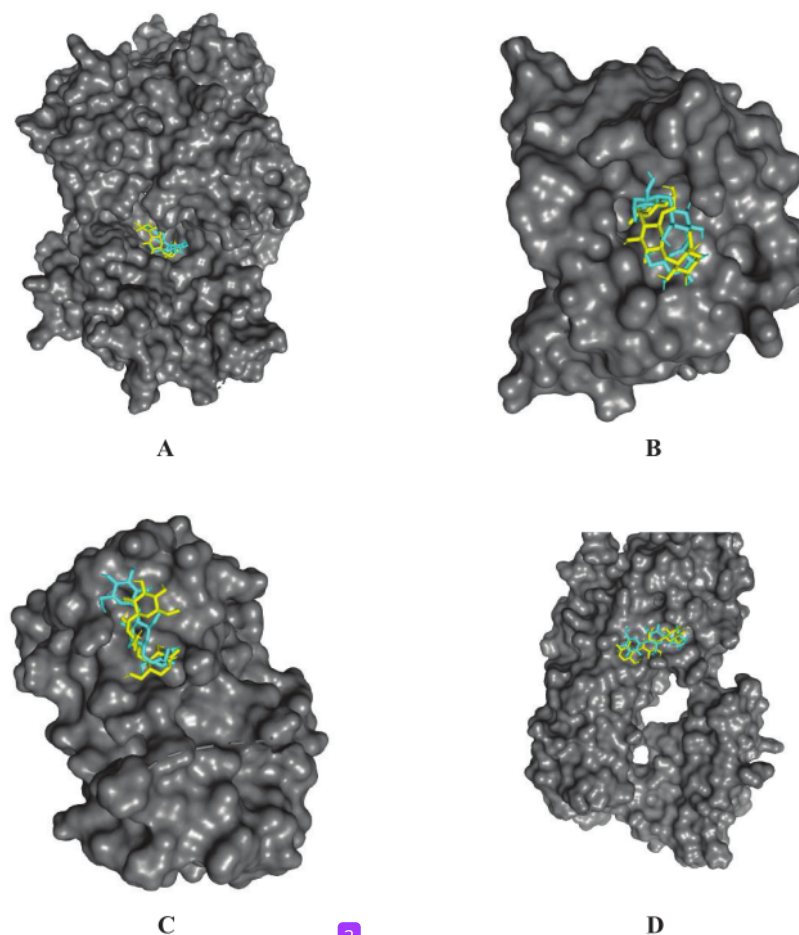


Figure 2. β -Glucan docking validation poses of (A) TNF- α , (B) IL-1 β , (C) IL-6, and (D) NF- κ B p65. The light blue color is the docked result with PyRx, and the yellow color is the redocked result pose using AutoDock Vina.

RESULTS AND DISCUSSIONS

COVID-19 continues to spread throughout the world, despite unprecedented social isolation and restrictions. Additionally, various variants of SARS-CoV-2 have begun to emerge, prompting researchers to become even more aggressive in their search for an antidote to this virus. According to Feuillet *et al.* (2021), effective treatments for COVID-19 patients should include a combination of antivirals and immunomodulators. Traditional medicinal plants have been identified as a potentially beneficial source of immunomodulators against COVID-19 (Dutta *et al.*, 2021; Nugraha *et al.*, 2020).

Using a molecular docking approach, we searched for immunomodulatory candidates from betel leaves that have the potential of being developed for COVID-19 management. PyRx was used to carry out the docking. By redocking the control immunomodulatory agents with AutoDock Vina, the docking protocol was validated. The RMSD value of poses was measured to calculate the similarity of poses and coordinate between two molecules. Docking validation poses of β -glucan of TNF- α , IL-1 β , IL-6, and NF- κ B p65 are shown in Figure 2. Docking poses resulting from PyRx (light blue color) were superimposed by the docking poses resulting from Vina (yellow color), and then the RMSD value was calculated. These results showed the similarity of docking pose results from both applications. RMSD value calculates the similarity of the poses quantitatively. The closer the value to zero, the more similar the poses. RMSD value of less than 2Å is acceptable and suggests that the docking protocol used in this study has been carried out successfully (Xiao *et al.*, 2018). The RMSD values of the poses were 1.040, 1.032, 1.310, and 1.930 Å in interactions with receptor TNF- α (PDB ID: 2AZ5), IL-1 β (PDB ID: 2NVH), IL-6 (PDB ID: 1ALU), and NF- κ B p65 (PDB ID: 1OY3), respectively. This indicated that RMSD values were in the acceptable range. Therefore, the present research's docking protocol is valid, and the result is reliable.

Betel leaf bioactive compounds together with β -glucan thiopurine as control immunomodulatory agents were docked to TNF- α , IL-1 β , IL-6 and NF- κ B. The binding energy results are presented in Table 2. Molecular docking has been widely used to design novel components or repurposing drugs (Pinzi and Rastelli, 2019). Molecular docking analyzes binding energy and poses of interactions between ligands and a specific receptor (Ahmed *et al.*, 2019). There are 17 compounds that show lower binding free energy compared to both β -glucan and thiopurine. It suggests that the ligands bind to the proteins with better and stable interactions and are potential as immunomodulatory agents. Androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) has the binding free energy of -8.7, -7.1, -7, and -6.8 kcal/mol for TNF- α , IL-1 β , IL-6, and NF- κ B, respectively. A lower binding free energy indicates that the ligand binds strongly to the receptor and may be capable of inhibiting the protein target's activities.

When compared to the control immunomodulatory agents, 17 compounds had higher binding free energy, particularly with TNF- α . It suggests that most betel leaf bioactive compounds have better immunomodulatory activity than β -glucan and thiopurine due to lower binding free energy and they can inhibit the targeted proteins more steadily and strongly. TNF- α , which was initially identified as an endotoxin-induced glycoprotein, is required for cell proliferation, migration, differentiation, and

death (Ganeshpurkar and Saluja, 2018; Mercogliano *et al.*, 2020). The inflammatory disease may be treated by the use of TNF- α -blocking drugs (Silva *et al.*, 2010).

Various interactions with inflammatory and immune cells are arbitrated by a class of proteins termed interleukins. Interleukins are proteins that help cells grow, differentiate, and activate their functions. IL-1 β (human leukocyte pyrogen/lymphocyte mitogen) and IL-6 are two important interleukins. They are produced by macrophages, T-cells, and bone marrow stromal cells. IL-1 β is an important mediator to evoke an immune response. IL-1 β contributes towards the progression of pain, inflammation, and cell apoptosis (Marchand *et al.*, 2005).

The NF- κ B signaling pathway is regarded the most commonly involved proinflammation pathway (Liu *et al.*, 2017). Several studies have found that NF- κ B regulates a wide range of genes that produce proinflammatory cytokines, adhesion molecules, chemokines, growth factors, and inducible enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Shih *et al.*, 2015).

Amino acid residues that are involved in interactions between proteins and androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) are shown in 2D images. The ligands' binding poses are shown in 3D images (Fig. 3). The interactions are shown to form van der Waals, conventional hydrogen, pi-sigma, alkyl, and pi-alkyl bonds. Binding interactions of the control immunomodulatory agents are shown in 3D and 2D interaction images in Figure 4.

The formation of ligand-receptor complexes is mediated by molecular interactions such as hydrogen bonds, electrostatic interactions, and hydrophobic interactions (Tallei *et al.*, 2021b). Figure 3 shows that androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) forms 10 van der Waals interactions and 2 H-bonds on TNF- α ; 6 van der Waals interactions, 1 pi-sigma bond, 2 pi-alkyl bonds, and 1 H-bond on IL-1 β ; 3 van der Waals interactions, 1 pi-sigma bond, and 3 H-bonds on IL-6; and 6 van der Waals interactions and 1 pi-alkyl bond on NF- κ B p65.

Androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) forms H-bonds with Tyr-151 and Gly-121 on the active site of TNF- α , Leu-80 on polar site of IL-1 β , and Gln-75, Ser-76, and Ser-176 of IL-6. In biological systems, hydrogen bonds have significant roles, particularly in the stabilization of protein structures (Glowacki *et al.*, 2013). Hydrophobic interactions, such as pi-sigma and pi-alkyl bonds, exist in addition to hydrogen bonds (Dai *et al.*, 2019). Pi-sigma bonds are formed with amino acids Phe-133 of IL-1 β and Phe-74 of IL-6, while pi-alkyl bonds are formed with Pro-131 of IL-1 β and Cys-240 of NF- κ B p65. Van der Waals interactions can be found in greater numbers on all target proteins than other bonds. Van der Waals interaction, in combination with hydrogen bonds, contributes to the stability of the formed ligand-protein complexes (He *et al.*, 2005).

TNF- α is a powerful proinflammatory molecule that controls a variety of macrophage functions (Parameswaran and Patial, 2010). Trauma and infection cause a continuous release of TNF- α , resulting in its highest bioavailability in the early stages of tissue inflammation. One of the most important functions is to regulate the production of the proinflammatory cytokine cascade (Ye *et al.*, 2020). TNF- α regulates the formation of a proinflammatory cytokine cascade through molecular interactions (Liu *et al.*, 2016). Tyr-59, Tyr-151, and Tyr-119 are active amino acids that play a

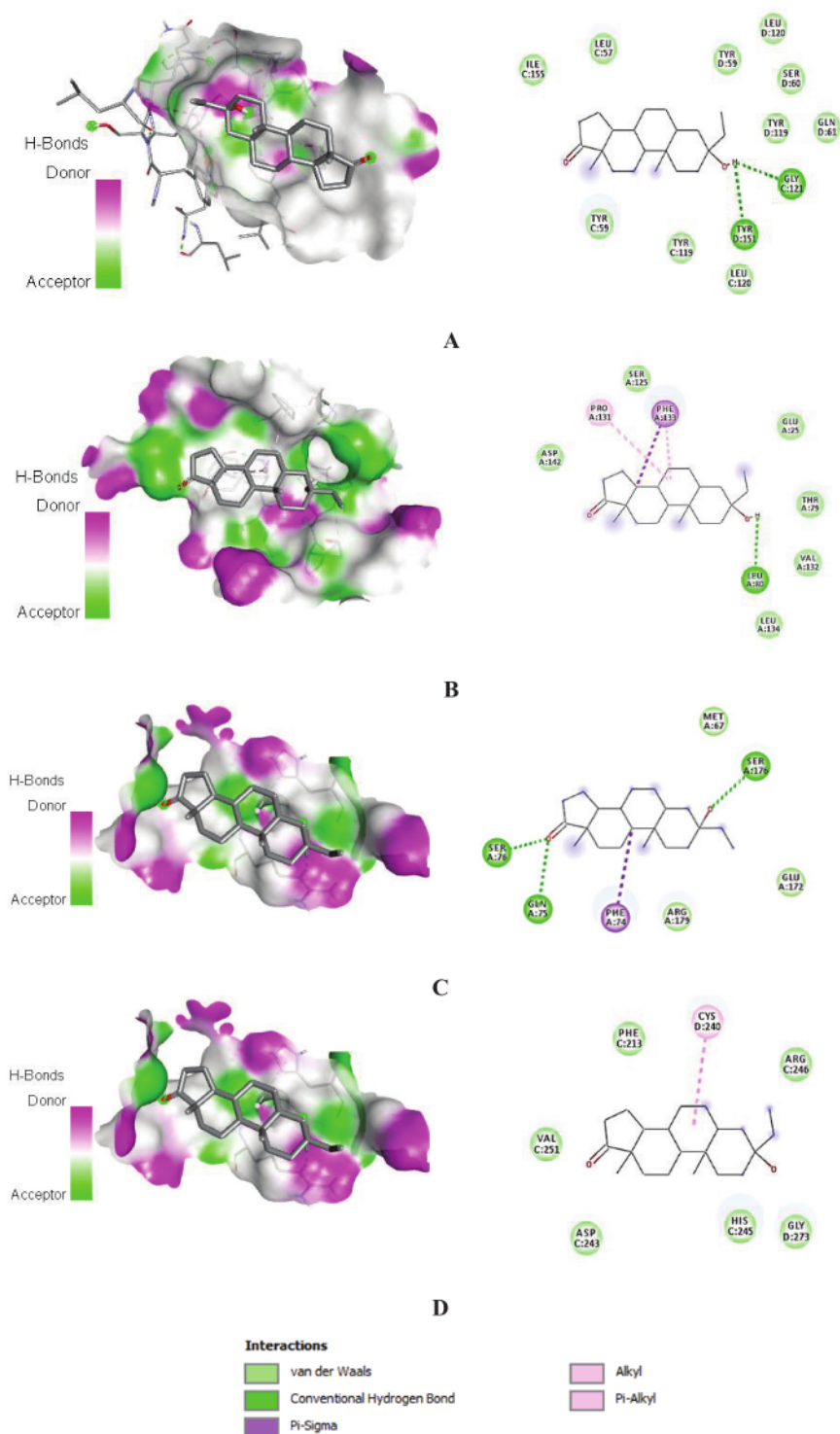
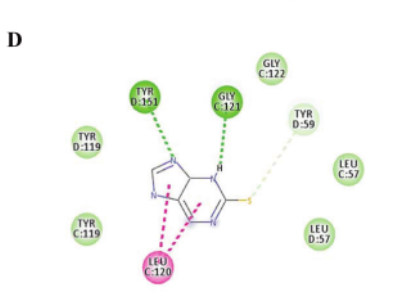
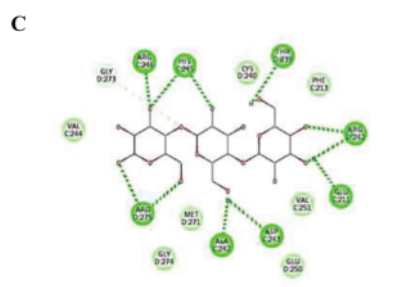
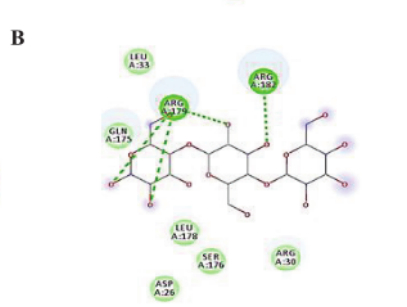
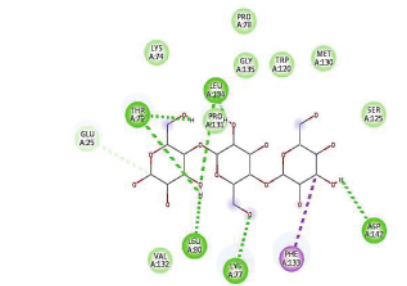
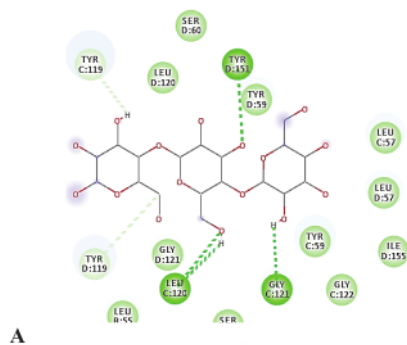
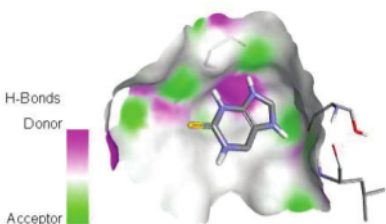
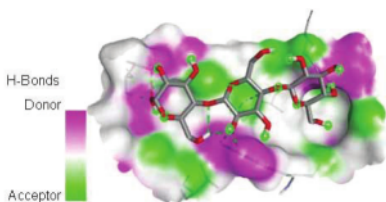
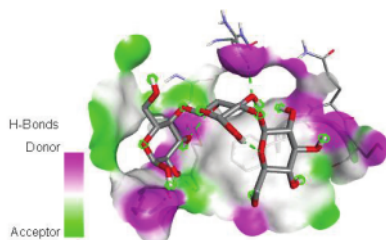
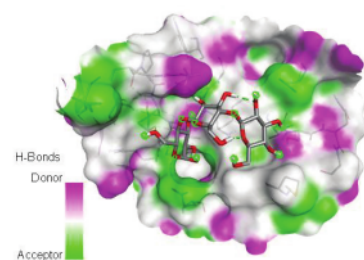
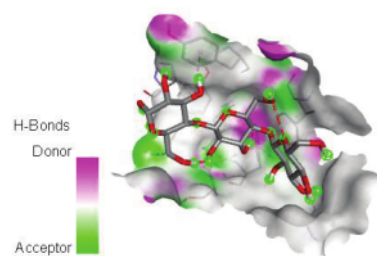


Figure 3. 3D and 2D configuration of interaction between androstan-17-one,3-ethyl-3-hydroxy-(5.alpha.) and (A) TNF- α , (B) IL-1 β , (C) IL-6, and (D) NF- κ B p65.



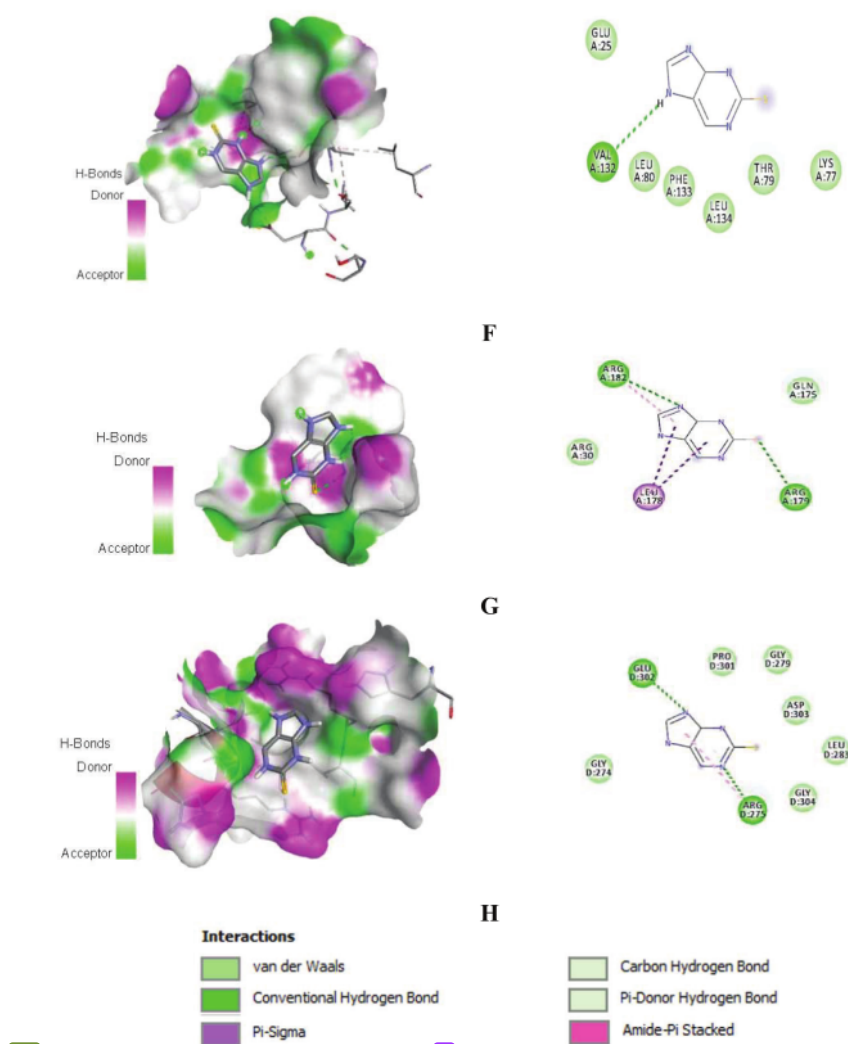


Figure 4. 3D and 2D interactions of **39** can binding to (A) TNF- α , (B) IL-1 **83** IL-6, and (D) NF- κ B p65. 3D and 2D interactions of thiopurine binding to (E) TNF- α , (F) IL-1 β , (G) IL-6, and (H) NF- κ B p65.

crucial role in TNF- α function. By binding to this amino acid, the inhibitor can significantly impair its function (Parves *et al.*, 2021). In addition to the active residue of tyrosine, the TNF- α binding site is composed of Leu-57, Ser-60, Gln-61, Leu-120, Gly-121, and Gly-122, so that binding to these amino acids can cause inhibition of their biological activity (He *et al.*, 2005). The binding free energy of androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) is low, implying the formation of a stable complex with TNF- α . This compound has a van der Waals interaction with the amino acids Tyr-59, Tyr-151, and Tyr-119, which are active amino acids of TNF- α , so that this binding will cause the potential for TNF- α inactivation. Interactions also occur with the amino acids Leu-57, Ser-60, Gln-61, Leu-120, Gly-121, Gly-122, and Ile-155, which indicates that this compound binds to the binding site or around the active side of TNF- α . Wang *et al.* (2020) used the Molecular

Operating Environment (MOE)-site Finder in determining the TNF- α binding site (PDB ID: 2AZ5) and found that the binding site was located around the amino acids Tyr-119, Leu-57, Tyr-59, Ser-60, Leu-120, Gly-121, Gly-122, and Tyr151. These findings corroborate the findings of this investigation and may attest to the validity of the binding sites chosen for molecular docking. Apart from functioning as proinflammatory cytokines, TNF- α also enhances the signaling of mediators of lipid transduction, such as prostaglandins and platelet-activating factors (Vassalli, 1992). Based on its roles, TNF- α plays a central role in the activation of inflammatory cells (Yang *et al.*, 2018).

IL-1 is a proinflammatory cytokine that is released when the innate pathogen-sensing pathway is activated during microbial infection (Browne, 2015). Excessive release of proinflammatory cytokines, on the other hand, causes a cytokine storm, which causes

widespread tissue damage and multiorgan failure, which is fatal, resulting in death. In COVID-19 patients, targeting cytokines can improve survival rates and reduce mortality (Ragab *et al.*, 2020). The poses of interaction between betel fruit bioactive compounds and IL-1 β were analyzed. The interaction occurs with the amino acids Glu-25, Thr-79, Leu-80, Ser-125, Pro-131, Val-132, Phe-133, Leu-134, and Asp-142 of IL-1 β . Quillin *et al.* (2006) found cavity 4 and cavity 5 of IL-1 β , with amino acids in cavity 4 being Lys-16, Ala-127, Met-130, Ser-125, Thr-48, Pro-131, and Ala-28, and in cavity 5 being Leu-10, Val-132, Leu-18, Leu-26, Phe-42, Leu-69, and Ile-122. Cavity 4 is the more polar side and has a small volume (16 Å³), while the cavity is the central apolar side and has a volume of 39 Å³. These amino acids also play a role in the kaurenoic acid-IL-1 β and ibuprofen-IL-1 β complexes (Karmakar *et al.*, 2019). IL-1 β is an inflammatory mediator that causes various biological responses ranging from the central nervous system, hematologically and metabolically (Dinarello, 2011). An excessive inflammatory response, on the other hand, can result in tissue damage and disease (Wallach *et al.*, 2014).

IL-6 is the most important immune response and inflammatory mediator induced by infection or injury. More than half of the COVID-19 patients have elevated IL-6 levels (Zhang *et al.*, 2020). In COVID-19 patients, IL-6 levels are linked to an inflammatory response, respiratory failure, and mortality (Herold *et al.*, 2020; Zhang *et al.*, 2020). According to Grifoni *et al.* (2020), anti-IL-6 drugs can be used to manage cytokine storms caused by SARS-CoV-2, which could be a treatment option for COVID-19. In its interaction with IL-6, androstan-17-one, 3-ethyl-3-hydroxy-, (5.alpha.) molecularly binds to Met-67 which is a hydrophobic side chain, with Phe-74, which is part of the disulfide (Cys73-Cys83), with Gln-75 and Ser-76m, which are part of type II β turn (Gln75-Phe78), and with Glu-172, Ser-176, and Arg-179, which are part of the D helix (Gln156-Arg182) of IL-6. Previous studies have shown that changes to Arg-179, Gln-175, Phe-74, and Gly-35 could significantly reduce IL-6 activity. On IL-6, the compound interacts with amino acids on sites 1 and 2, which play a role in mediating IL-6 binding to IL-6r and gp130, respectively. Androstan-17-one, 3-ethyl-3-hydroxy-, (5.alpha.), which binds to IL-6 in this study, is predicted to decrease or stop its activity by blocking IL-6 binding to IL-6r and gp130 in signal transduction. 26

NF- κ B proteins are critical regulators of innate and adaptive immune responses, including proliferation, apoptosis inhibition, cell migration and invasion, and angiogenesis and metastasis (Park and Hong, 2020). NF- κ B is activated continuously or transiently in response to viral and bacterial infections, necrotic cell products, DNA damage, oxidative stress, and proinflammatory cytokines (Karin and Greten, 2005; Taniguchi and Karin, 2018). NF- κ B p65 (along with p50 in the heterodimer form) is the most commonly occurring form of NF- κ B activated through the regulated pathway concerning pathological stimuli. The principal point for the discovery and development of new drugs was the NF- κ B p6a signaling path (Grancieri *et al.*, 2019). On the basis of a docking study of NF- κ B p65, Grancieri *et al.* (2019) found that the active site was around the amino acid Lys-221, His-245, Arg-246, Gly-273, Gly-274, Arg-275, Leu-282, Leu-283, Pro-285, and Gly-304. The present study also found that androstan-17-one, 3-ethyl-3-hydroxy-, (5.alpha.) interacts with NF- κ B p65 in the same binding region, namely the amino

acids Phe-213, Cys-240, Asp-243, His-245, Arg-246, Val-251, and Gly-273. This binding site contains amino acids that are involved in the pharmacological activity; thus, binding to or inhibiting this site can result in a decrease in NF- κ B p65 activity. NF- κ B is a transcription factor that regulates a variety of functions of the innate and adaptive immune systems and plays a critical role in inflammatory responses. NF- κ B promotes the expression of a wide range of proinflammatory genes, among them, are those encoding cytokines and chemokines, both of which are involved in the regulation of inflammation. Inhibition of this protein is predicted to reduce cytokine production and alleviate cytokine storms (Liu *et al.*, 2017).

The present study demonstrates that bioactive compounds from betel leaves have a significantly higher binding free energy to all of the targeted proteins compared to controls. A study conducted by Johnson *et al.* (2020) docked a total of 43 compounds from *Phyllanthus nivosus* leaves on TNF- α using PyRx. The binding free energies were found to range from the highest -2 kcal/mol to the lowest 6.3 kcal/mol. This is a significantly lower value than the one obtained in the current study. Kaempferol and chlorogenic acid were studied for their binding free energy against IL-1 β and IL-6 using PyRx by Karmakar *et al.* (2019). The binding free energies of -7.0 and -6.8 kcal/mol were found in chlorogenic acid and kaempferol, respectively, to IL-1 β , while the binding with IL-6 showed -7.1 and -7.7 kcal/mol.

A total of 17 compounds were subjected to additional pharmacokinetic analysis. Lipinski's Ro5 criteria of β -glucan, thiopurine, and several of the betel leaf bioactive compounds are presented in Table 3. β -Glucan was found to violate five out of six criteria, suggesting that there will be a major drug system delivery development for the drug. Sixteen of the 17 best betel leaf compounds have been shown to conform to Lipinski's Ro5 (Lipinski *et al.*, 2001). This indicates that the possible immunomodulatory compounds in betel leaf extract are orally active.

ADMET profiles of β -glucan, thiopurine, and some of the betel leaf bioactive compounds are presented in Table 4. The potential immunomodulatory compounds in betel leaf extract were predicted to have good *in vitro* activities due to their high binding affinity with the target proteins. The binding free energy value, when combined with the ADMET profile, can be used to predict the safety and efficacy of betel leaf bioactive compounds in *in vivo* and clinical settings.

All 17 compounds were found to have a high rate of intestinal absorption in humans, indicating that they are well absorbed and can enter the body orally. The blood-brain barrier's permeability and subcellular localization were used to characterize the compounds' distribution. A high blood-brain barrier's permeability demonstrated that the ligands could penetrate and distribute throughout the brain. The subcellular localization of the compounds predicted their ability to distribute and penetrate at the subcellular level (Daneman and Prat, 2015; Soni *et al.*, 2016). The results of the present study showed that betel leaf bioactive compounds can be distributed and penetrate in mitochondria, lysosomes, and plasma membrane. All of the compounds were not CYP2D6 substrates, indicating that they are poorly metabolized in the body. However, metabolism has the potential to change a drug's effectiveness in the body (Lee *et al.*, 2019).

Hepatotoxicity and acute oral toxicity were chosen as the toxicity parameters for this study. Hepatotoxicity is a proxy for organ toxicity, whereas acute oral toxicity is a proxy for the maximum dose of the studied compounds that the body can tolerate. The findings that the selected compounds are hypothetically nontoxic to the liver imply that the bioactive compounds in

betel leaf are unlikely to cause liver damage. The compounds were classified as toxicity class III ($500 < LD_{50} \leq 5,000$ mg/kg), implying that the body can tolerate a dose of up to 500 mg/kg. As a result, it is recommended that these compounds be developed as drugs within that range (Cheng *et al.*, 2011; Gadaleta *et al.*, 2019; Li *et al.*, 2014; Yang *et al.*, 2017).

Table 2. β -Glucan, thiopurine, and betel leaf bioactive compounds binding free energy.

Ligands	Molecular formula	PubChem CID	Binding free energy (kcal/mol)			
			2AZ5 (TNF- α)	2NVH (IL-1 β)	1ALU (IL-6)	1OY3 (NF- κ B p65)
β -Glucan	C ₁₈ H ₃₂ O ₁₆	439262	-6	-5.1	-3.3	-7
Thiopurine	C ₅ H ₄ N ₄ S	3015569	-4.7	-4.1	-3.6	-4.8
Androstan-17-one,3-ethyl-3-hydroxy-(5.alpha.)	C ₂₁ H ₃₄ O ₂	14681481	-8.7	-7.1	-7.3	-6.8
alpha-Longipinene	C ₁₅ H ₂₄	520957	-8.1	-5.3	-5.3	-5.5
alpha-Cadinol	C ₁₅ H ₂₆ O	6431302	-7.3	-6	-5.4	-5.8
t-Muurolol	C ₁₅ H ₂₆ O	3084331	-7.2	-5.4	-5.2	-5.8
delta-Cadinene	C ₁₅ H ₂₄	441005	-7.2	-6	-5.6	-5.6
Epiglobulol	C ₁₅ H ₂₆ O	11858788	-7.2	-5.3	-5.3	-5.7
27 Juniper camphor	C ₁₅ H ₂₆ O	521214	-7.2	-4.9	-5	-5.6
Naphthalene, 1,2,3,4-tetrahydro-1,6-dimethyl-4-(1-methylethyl)-, (1S-cis)-(calamenene)	C ₁₅ H ₂₂	6429077	-7.1	-5.8	-5.8	-5.9
beta-Cadinene	C ₁₅ H ₂₄	10657	-7.1	-5.6	-5.6	-5.8
Cedrene	C ₁₅ H ₂₄	521207	-7.1	-5.1	-5.6	-5.7
delta-Cadinol	C ₁₅ H ₂₆ O	6431456	-7	-5.2	-5	-5.8
alpha-Amorphene	C ₁₅ H ₂₄	12306052	-6.9	-5.1	-5.4	-5.9
Longipinocarveol, trans	C ₁₅ H ₂₄ O	534645	-6.9	-5.3	-5	-5.5
64 Germacrene D	C ₁₅ H ₂₄	91723653	-6.8	-4.9	-4.9	-5.6
43 Phenol, 2,4-bis(1,1-dimethylethyl)	C ₁₄ H ₂₂ O	7311	-6.4	-5.6	-5.2	-5.3
7,10,13-Hexadecatrienoic acid, methyl ester	C ₁₇ H ₂₈ O ₂	5367325	-6.1	-4.5	-4.9	-4.7
11,14,17-Eicosatrienoic acid, methyl ester	C ₂₁ H ₃₆ O ₂	5367326	-6.1	-4.9	-4.8	-4.3
17 Benzoic acid, 2,4-dimethyl	C ₉ H ₁₀ O ₂	11897	-6	-4.8	-4.9	-5.4
Phenol, 2-methoxy-4-(2-propenyl)-, acetate (acetyluugenol)	C ₁₀ H ₁₂ O ₃	7136	-6	-4.9	-5	-4.8
17 Allyl-6-methoxyphenol	C ₁₀ H ₁₂ O ₂	596375	-6	-4.6	-4.7	-4
Benzoic acid, 3,5-dimethyl	C ₉ H ₁₀ O ₂	10356	-6	-5	-4.8	-5.2
Phenol, 2-methoxy-4-(2-propenyl)	C ₁₀ H ₁₂ O ₂	3314	-5.9	-4.7	-4.4	-5
Benzoic acid, 2,6-dimethyl	C ₉ H ₁₀ O ₂	12439	-5.8	-4.9	-3.8	-5.2
Phytol 55	C ₂₀ H ₄₀ O	5280435	-5.7	-4.1	-4	-4.2
8,11-Octadecadienoic acid, methyl ester	C ₁₉ H ₃₄ O ₂	5319737	-5.6	-4.8	-5	-4.5
Phenol, 2-methoxy-3-(2-propenyl)	C ₁₀ H ₁₂ O ₂	596373	-5.6	-4	-4.3	-5.1
4,7-Octadecadienoic acid, methyl ester	C ₁₉ H ₃₀ O ₂	569159	-5.5	-4.3	-3.8	-4
Tricosane	C ₂₃ H ₄₈	12534	-5.5	-4.4	-4	-3.8
37 Ethyl oleate	C ₂₀ H ₃₈ O ₂	5363269	-5.5	-4.3	-4.5	-3.6
9,12-Octadecadienoic acid (Z,Z)-, methyl ester	C ₁₉ H ₃₄ O ₂	5284421	-5.4	-4.1	-4.8	-4
Hexadecanoic acid, ethyl ester	C ₁₇ H ₃₄ O ₂	12366	-5.4	-4.1	-4.1	-4.2

Continued

Ligands	Molecular formula	PubChem CID	Binding free energy (kcal/mol)			
			2AZ5 (TNF- α)	2NVH (IL-1 β)	1ALU (IL-6)	1OY3 (NF- κ B p65)
80 Methyl linolenate	C ₁₉ H ₃₂ O ₂	5319706	-5.3	-4.6	-4.7	-4.5
Pentadecanoic acid, 14-methyl-, methyl ester	C ₁₇ H ₃₄ O ₂	21205	-5.3	-4.1	-4.9	-3.7
Ethyl linoleate	C ₂₀ H ₃₆ O ₂	5282184	-5.2	-4.4	-4	-3.9
31 Hexacosane	C ₂₆ H ₅₄	12407	-5.2	-4	-4.9	-3.6
11-Octadecenoic acid, methyl ester	C ₁₉ H ₃₆ O ₂	5364432	-5.2	-4.2	-4.7	-3.7
8-Octadecenoic acid, methyl ester	C ₁₉ H ₃₆ O ₂	5364422	-5.1	-4.7	-4	-3.9
P + B14:B50entadecanoic acid, ethyl ester	C ₁₇ H ₃₄ O ₂	38762	-5.1	-4.1	-4.4	-4.1
41 Ethyl octadec-9-enoate	C ₂₀ H ₃₈ O ₂	8123	-5	-4.1	-4.9	-3.8
9-Octadecenoic acid, methyl ester	C ₁₉ H ₃₆ O ₂	5280590	-4.9	-4.2	-3.8	-3.9
Tetradecanoic acid, ethyl ester	C ₁₇ H ₃₄ O ₂	31283	-4.9	-4.5	-4.5	-3.8
Hexadecanoic acid, methyl ester	C ₁₇ H ₃₄ O ₂	8181	-4.6	-4.3	-4.4	-3.7
Torreyol	C ₁₅ H ₂₆ O	3084311	-4.2	-6.1	-5.5	-6.5
d-Nerolidol (peruvicol)	C ₁₅ H ₂₆ O	5356544	-4	-4.8	-5.2	-4.8

Table 3. Analysis of Lipinski's Ro5 of β -glucan, thiopurine, and some of the betel leaf bioactive compounds

PubChem CID	Molecular Weight (≤ 500 g/mol)	Rotatable Bonds (<10)	Hydrogen Bond Acceptors (≤ 10)	Hydrogen Bond Donors (≤ 5)	Log P (≤ 5)	Topological Polar Surface Area (≤ 140 Å)	Violation (<2)	Lipinski's Rules of Five
439262	504.44	7	16	11	-6.15	268.68	5	No
3015569	152.18	0	2	2	-0.75	89.45	0	Yes
14681481	318.49	1	2	1	4.15	37.30	0	Yes
520957	204.35	0	0	0	5.65	0	0	Yes
6431302	222.37	1	1	1	3.67	20.23	0	Yes
3084331	222.38	1	1	1	3.67	20.23	0	Yes
441005	204.35	1	0	0	4.63	0	0	Yes
11858788	222.37	0	1	1	3.81	20.23	0	Yes
521214	222.38	0	1	1	3.67	20.24	0	Yes
6429077	202.34	1	0	0	5.45	0	1	Yes
10657	204.35	1	0	0	4.63	0	0	Yes
521207	204.35	0	0	0	5.65	0	1	Yes
6431456	222.37	1	1	1	3.67	20.23	0	Yes
12306052	204.35	1	0	0	4.63	0	0	Yes
534645	220.35	0	1	1	3.67	20.23	0	Yes
91723653	204.35	1	0	0	4.53	0	0	Yes
7311	206.33	0	1	1	3.99	93.14	0	Yes
5367325	264.40	12	2	0	4.14	26.30	1	Yes
5367326	320.51	16	2	0	5.06	26.30	2	No

Table 4. ADMET prediction of β -glucan, thiopurine, and selected betel leaf bioactive compounds

PubChem CID	Human Intestinal Absorption	Blood-brain Barrier Permeability	Subcellular Localization	Cytochrome P450 2D6 Substrate	Hepato-toxicity	Acute Oral Toxicity
439262	No	No	Mitochondria	No	No	IV
3015569	Yes	Yes	Lysosomes	No	Yes	III
14681481	Yes	Yes	Mitochondria	No	No	III
520957	Yes	Yes	Lysosomes	No	No	III
6431302	Yes	Yes	Lysosomes	No	No	III
3084331	Yes	Yes	Lysosomes	No	No	III
441005	Yes	Yes	Lysosomes	No	No	III
11858788	Yes	Yes	Lysosomes	No	No	III
521214	Yes	Yes	Lysosomes	No	No	III
6429077	Yes	Yes	Lysosomes	No	No	III
10657	Yes	Yes	Lysosomes	No	No	III
521207	Yes	Yes	Lysosomes	No	No	III
6431456	Yes	Yes	Lysosomes	No	No	III
12306052	Yes	Yes	Lysosomes	No	No	III
534645	Yes	Yes	Lysosomes	No	No	III
91723653	Yes	Yes	Lysosomes	No	No	III
7311	Yes	Yes	Mitochondria	No	No	III
5367325	Yes	Yes	Plasma membrane	No	No	III
5367326	Yes	Yes	Plasma membrane	No	No	III

CONCLUSION

The betel leaf bioactive compounds have the potential to inhibit the COVID-19 host immunological proteins due to their high affinity with all the targeted proteins. The compound binding free energies ranged from -4 to -8.7 kcal/mol, -4 to -10 kcal/mol, -3.8 to -7.3 kcal/mol, and -3.6 to -6.8 kcal/mol for TNF- α , IL-1 β , IL-6, and NF- κ B, respectively. Seventeen ligands showed higher binding energy than the control immunological agents. Androstan-17-one,3-ethyl-3-hydroxy-,(5.alpha.) has binding free energy of -8.7 , -7.1 , -7 , and -6.8 kcal/mol for TNF- α , IL-1 β , IL-6, and NF- κ B p65, respectively. When compared to previous studies, this study discovered that the betel leaf bioactive compounds have a significantly higher binding free energy to all of the targeted proteins. Lipinski's Ro5 analysis demonstrates that majority of the compounds comply with the criteria and are predicted to be active when administered orally as drugs. The ADMET prediction of the compounds indicates that the ligands have favorable pharmacokinetic properties, implying that they have the potential to be developed as drugs. Hence, betel leaf bioactive compounds have the potential to treat COVID-19 because of having immunomodulatory effects and suppressing the cytokine storm, and they have the potential to be developed as drugs because of their good and safe ADMET profile.

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AUTHOR CONTRIBUTIONS

5 All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

15 The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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