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Zahabba Patch: Innovation of Gingival Mucoadhesion Patch Combination of Ginger (*Zingiber Officinale*) and Black Cubit (*Nigella Sativa*) as Gingivitis Treatment

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Abstract

Background

The prevalence of periodontal disease in Indonesia reaches 74.1%. Treatment of gingivitis by administering NSAIDs has a side effect of gastritis. Anti-inflammatory and analgesic derived from natural ingredients are known to cause minimal side effects on the patient's body. The active compounds gingerol in ginger (Zingiber officinale) and quercetin in black cumin (Nigella sativa) are known to function as good anti-inflammatory and analgesic agents.

Objectives

This study aims to analyze the effectiveness of gingerol in ginger extract and qurcetin in black cumin as an anti-inflammatory and analgesic packaged in a mucoadhesion patch as a treatment for gingivitis.

Material and Methods

Preparations of gingerol and quercetin were obtained by biocomputation using the PyRx program, the Pymol program, the RCSB PDB website, the Lipinski rule of five page, the PDBSum website, and also the pkCSM website. Physicochemical, pharmacokinetic, toxicity, and molecular docking tests were carried out to determine the biocompatibility of the active ingredients used.

Results

In the physicochemical tests, the compounds glycerol and quercetin can penetrate somatic cell membranes, have good solubility in water, can dissolve easily in the blood, are easily distributed in the body, and can maintain their position and bond strength with the target macro protein. The results of the AMES toxicity, Hepatotoxicity and skin sensitization tests showed negative values for both gingerol and quercetin. In the molecular docking test, the gingerol and quercetin compounds have a tendency to form bonds with COX-1 compared to arachidonic acid without having to increase the dose so that they become competitors to the native ligand.

Conclusion

The active compounds gingerol in ginger extract (Zingiber officinale) and quercetin in black cumin extract (Nigella sativa) contained in Zahabba patch are good anti-inflammatory and analgesic by inhibiting the synthesis of pro-inflammatory cytokines such as PGI2, PGE2, and TXA2 by being competitive inhibitor of the enzyme phospholipase A2 against membrane lipids and the enzyme cyclooxygenase-1 (COX-1) against arachidonic acid.

Keywords: Gingerol, Quercetin, Gingivitis, Muchoadhesive Patch, Human and Health

Introduction

Gingivitis is an inflammation of the gingiva which is usually caused by a bacterial infection that accumulates in plaque. Gingivitis can be characterized by the appearance of inflammation of the gingiva, the presence of periodontal pockets, and gingival recession [1]. According to data reported by the Indonesian Ministry of Health in the 2018 National Basic Health Research Report, the prevalence of periodontal disease reached 74.1% [2].

Dentists can treat gingivitis by scaling and, if necessary, providing pharmacological therapy using analgesics and anti-inflammatories, which are generally classified as NSAIDs. Nevertheless, many cases have been reported that patients who regularly consume anti-inflammatory and analgesic drugs belonging to the NSAIDs class experience side effects of gastritis. According to research conducted by Feyiza, Z. T., *et al* in 2021 showed that 78.8% of patients who regularly take NSAIDs and come to the Paul Millennium College hospital experience side effects of gastritis [3, 4].

Anti-inflammatory and analgesic derived from natural ingredients are known to cause minimal side effects on the patient's body. The active compounds gingerol in ginger (Zingiber officinale) and quercetin in black cumin (Nigella sativa) are known to function as good anti-inflammatory and analgesic [4]. Therefore, researchers took the initiative to create an innovative mucoadhesion patch using ginger and black cumin as a base for the treatment of gingivitis through an in-silico test.

Material and Methods

Gingerol and Quercetin preparations

The materials used in this study were obtained by biocomputation using a computer with Windows 10 64-bit specifications and supported by the PyRx program, the Pymol program, the RCSB PDB page, the Lipinski rule of five page, the PDBSum page, and also the pkCSM page. The materials used in this study were the active compounds gingerol with CID 442793, quercetin with CID 5280343, arachidonic acid with CID 444899, valdecoxib with CID 119607, protein cyclooxygenase-1 (COX-1) with PDB ID 6Y3C, and the enzyme phospholipase A2 with PDB ID 3U8B.

Gingerol and Quercetin preparations

Preparation of gingerol, quercetin, protein COX-1, and protein phospholipase A2 is the first step before carrying out a series of molecular docking tests. By utilizing the PubChem data base and the Protein Data Bank, the compounds to be prepared can be searched using the keywords gingerol, quercetin, COX-1 protein, and protein phospholipase A2 regullatin arachidonic acid.

Physicochemical Test

The physicochemical test was carried out by entering the SMILE arrangement of the 2D gingerol and quercetin compounds on the Lipinski Rule of Five page.

Pharmacokinetic Test

Pharmacokinetic tests were carried out using the SMILE sequence of gingerol and quercetin compounds on the pkCSM online tools page. By entering the SMILE sequence of citral compounds, numerical results will be obtained from the aspects of water solubility, skin permeability, and human fraction unbound which will be further analyzed in the discussion.

Toxicity Test

Toxicity test aims to determine the toxicity of a compound. Therefore, this test needs to be done. The test was carried out by entering the SMILE of the citral compound on the pkCSM online tools page by reviewing several parameters such as AMES toxicity, human maximum tolerated dose, hepatotoxicity, and skin sensitization.

Molecular Docking Test

The gingerol and quercetin test compounds will go through the docking stage with the native ligand on the active chain of the COX-1 protein and the phospholipase A2 enzyme using the PyRx application. The results of this docking process will show the binding affinity value which will be used as material for further data analysis.

Data analysis

Data analysis was performed using data binding affinity resulting from molecular docking procedures. The interactions that occur between the gingerol, quercetin, and native ligand compounds on the active chain of COX-1 protein and the phospholipase A2 enzyme can be seen by comparing their binding affinity values.

Library Studies

Literature studies from this research are sourced from websites that have proven their credibility, such as PubMed, Research Gate, and NCBI. By including a combination of the keyword's "analgesic", "ginger", "anti-inflammatory", "black cumin", and "gingivitis" in order to obtain journals with good credibility and validity that can be accounted for.

Result

Table 1: Physicochemical Test Results for the Active Compounds Gingerol and Quercetin Using the Lipinski Rule of Five

Parameter	Standar	Gingerol	Quercetin
Molecular mass (Da)	≤ 500	294	302
Hydrogen Bond Donor	≤ 5	2	5
Hydrogen Bond Acceptor	≤ 10	4	7
Log P	≤ 5	3,58	0,52
Molar Refractive	40-130	86,13	64,37

Both gingerol and quercetin compounds have a molecular mass value of less than 500 daltons or 294 daltons and 302 daltons respectively. -respectively of 4 and 7. This Log P value reflects the polarity of a compound to oil, if a compound has a Log P value of more than 5, it will also be more difficult for the compound to dissociate and dissolve in the body. The results of physicochemical tests using bioinformatics showed that gingerol and quercetin compounds had log P values of 3.58 and 0.52, respectively. Molar refractivity is a value that reflects the ability of the tested drug compound to maintain its position and bond strength with the tested target macro protein. The gingerol and quercetin compounds have molar refractivity values between 40-13, respectively 86.13 and 64.37.

Table 2: The Results of Pharmacokinetic Test for Active Compounds Gingerol and Quercetin

Parameter	Gingerol	Quercetin
Water solubility	-3,164	-2.925
Skin permeability	-2,817	-2.735
Human fraction unbound	0,258	0.206

The gingerol and quercetin compounds have water solubility values of -3.164 and -2.925, respectively. Then for the skin permeability value of the gingerol compound it has a value of 2.817 and quercetin has a value of -2.375. From the results of pharmacokinetic testing regarding fraction unbound, the active compounds gingerol and quercetin had FU values of 0.258 or 25.8% and 0.206 or 20.6%,

respectively.

Table 3: The Results of Toxicity Test of Active Compounds Gingerol and Quercetin

Parameter	Gingerol	Quercetin
AMES *toxicity*	None	None
Human maximum tolerated dose	0,635	0.499
Hepatotoxicity	None	None
Skin sensitization	None	None

From the results of the pkCSM test, it was found that the gingerol and quercetin compounds gave negative results for AMES toxicity. In the human maximum dose parameter, gingerol shows the maximum dose value that is tolerated in Log yield units (mg/KgBW) is 0.635 or when converted to units of mg/KgBW is 4.31 mg/KgBW. The quercetin compound shows the maximum tolerated dose value in Log yield units (mg/KgBW) is 0.499 or when converted to units of mg/KgBW is 3.16 mg/KgBW. Through the pkCSM test, gingerol and quercetin compounds can be seen that these compounds do not cause hepatotoxicity. From the results of the toxicity test, the gingerol and quercetin compounds were negative for skin sensitization.

Tabel 4: The results of Molecular Docking Test of Active Compounds Gingerol, Quercetin, Arachidonic Acid, and Valdecoxib Against Protein COX-1 and Enzyme Phospholipase A2

Target proteins	Test compound	*Binding affinity* (kcal/mol)	Mode	RMSD *lower and upper bound*
Protein COX-1 with PDB ID 6Y3C	*Arachidonic acid*	-5,2	0	0
	Gingerol	-6,8	0	0
	Quercetin	-9,1	0	0
Protein *phospholipase* A2 with PDB ID 3U8B	Valdecoxib	-6,4	0	0
	Gingerol	-5,9	0	0
	Quercetin	-6,3	0	0

From the results of the molecular docking test, the docking results were obtained between the COX-1 protein and 3 test ligands, one of which was a native ligand. The results of the molecular docking test between arachidonic acid and COX-1 protein have a binding affinity of -5.2 kcal/mol. These results became a comparison in the group tested against COX-1. The gingerol and quercetin compounds have a binding affinity value of -6.8 kcal/mold and -9.1 kcal/mol, respectively, both of which have a lower binding affinity value compared to the bond formed between COX-1 and arachidonic acid. The results of the next test, the results of the reaction of the enzyme phospholipase A2 with two ligands and one native ligand. The binding affinity value between the valdecoxib compound and the phospholipase A2 enzyme is -6.4 kcal/mol. Meanwhile, the binding affinity values between the gingerol and quercetin compounds for the phospholipase A2 enzyme were -5.9 kcal/mold and -6.3 kcal/mol, respectively.

After going through the molecular docking process, the docking results will be visualized using the Biovia application to position the bond between the ligand and the target protein. The following is a visualization of the compound's arachidonic acid, gingerol, and quercetin with COX-1 protein.

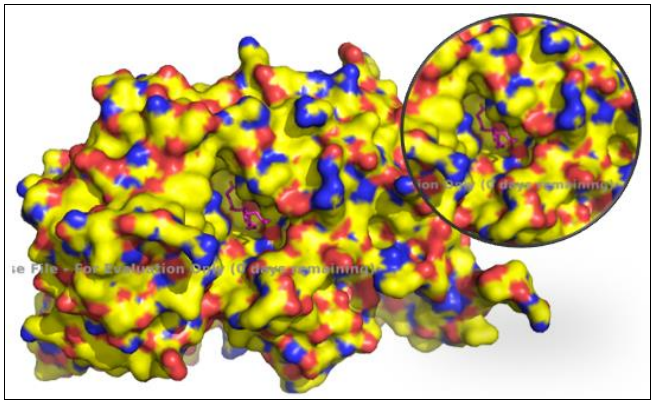

Fig 1: Visualization between arachidonic acid compounds and COX-1 proteins

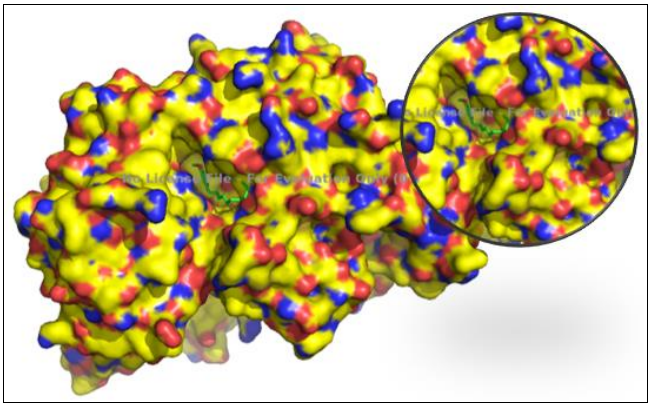

Fig 2: Visualization between gingerol compounds and COX-1 protein

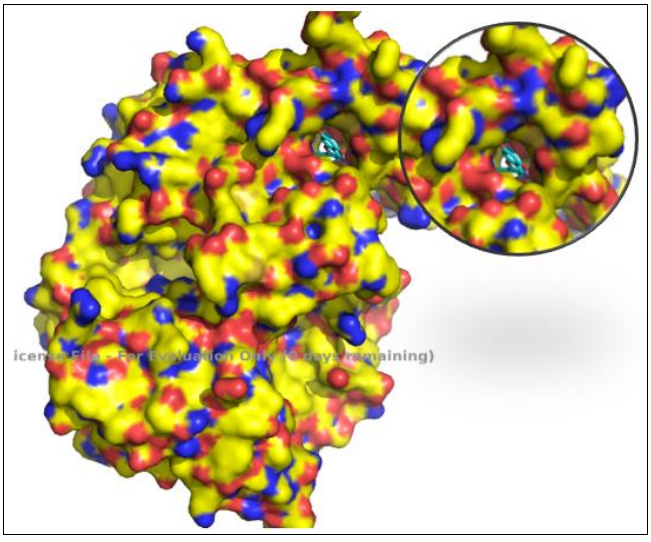

Fig 3: Visualization between quercetin compounds and COX-1 proteins

From the picture above, it can be visualized the compounds arachidonic acid, gingerol, and quercetin on COX-1 protein. In the figure it can also be visually analyzed that the gingerol and quercetin test compounds can bind to the COX-1 protein. After visualizing the arachidonic acid, gingerol, and quercetin ligands against COX-1, visualization was also carried out in the test group of valdecoxib, gingerol, and quercetin ligands against the phospholipase A2 enzyme. The

following is a visualization of valdecoxib, gingerol, and quercetin for phospholipase A2.

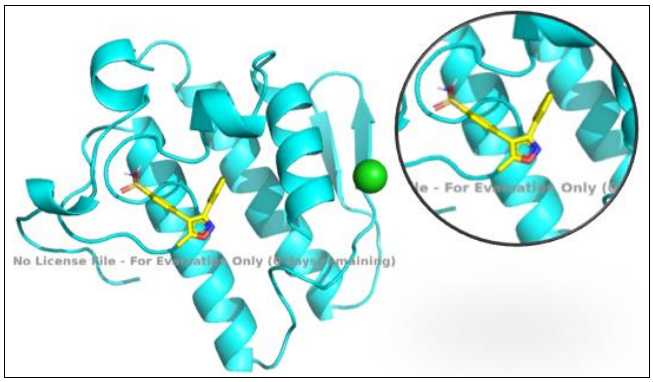

Fig 4: Visualization between valdecoxib compound and phospholipase A2 enzyme

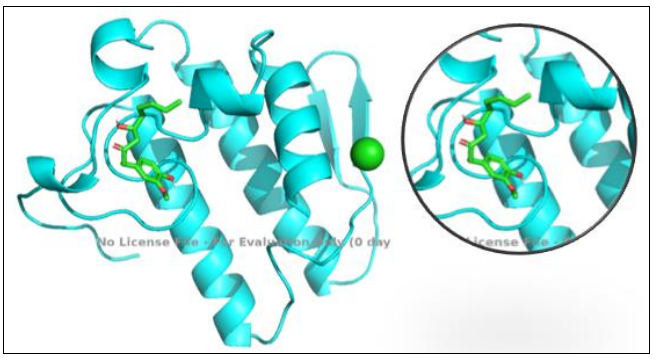

Fig 5: Visualization between gingerol compounds and phospholipase A2 enzymes

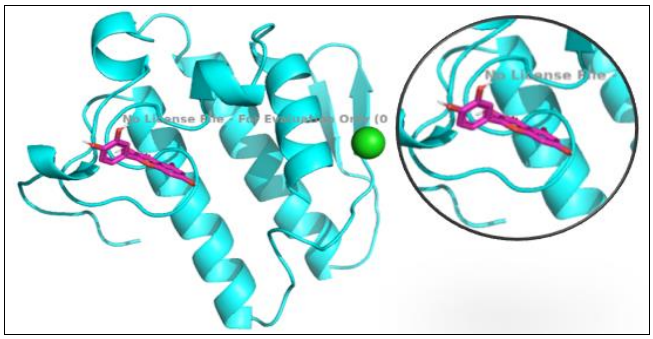

Fig 6: Visualization between the quercetin compound and the phospholipase A2 enzyme

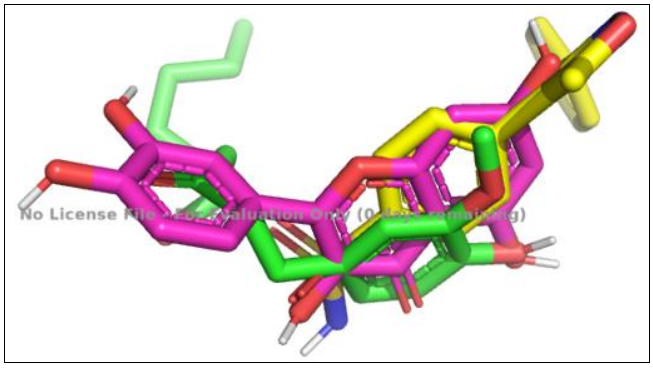

Fig 7: Visualization of valdecoxib, gingerol, and quercetin ligands against phospholipase A2

Ligands valdecoxib, gingerol, and quercetin to phospholipase A2. Visualization can also describe the position of the ligand that binds to phospholipase A2. Based on the visualization results, the three compounds, namely valdecoxib, gingerol, and quercetin, all have the same binding site for phospholipase A2.

Discussion

The physicochemical test is one of a series of in silico tests that aim to predict the ability of a drug to cross a cell membrane in the body by biocomputation. One of the biocomputations that can be used to predict is the Lipinski test. The Lipinski test can use the Lipinski rule of five. This test takes five aspects that are used as parameters, each parameter has its own conditions that must be met by a compound to be tested[5]. This test is considered important because ligands that enter the body must be able to pass through the cell membrane. It is said to be able to pass through the cell membrane, a compound must meet the requirements of the Lipinski rule of five test [5].

A compound can be said to be able to penetrate the cell membrane if it has a molecular mass of less than 500 Daltons. Both gingerol and quercetin compounds have molecular mass values of less than 500 daltons or 294 daltons and 302 daltons respectively. This indicates that gingerol and quercetin compounds can penetrate somatic cell membranes [6]. The second parameter is regarding donor hydrogen bonds. A compound can be said to have good solubility if it has a value of acceptor hydrogen bonds that is less than or equal to 5 and the number of acceptor hydrogen bonds is less than or equal to 10. This is related to the ability of the compound to undergo passive diffusion by assessing the number of donor hydrogen bonds. as well as acceptors. The gingerol and quercetin compounds have the same number of donor hydrogen bonds of 2 and 5, and the number of acceptor hydrogen bonds of 4 and 7 respectively. gingerol, both of which have good water solubility so they can be easily distributed and easy to penetrate cell membranes [6].

Another parameter is the Log P value, which reflects the polarity of compounds in the blood. This Log P value reflects the polarity of a compound to oil, if a compound has a Log P value of more than 5, it will be more difficult for the compound to dissociate and dissolve in the body. The results of physicochemical tests using bioinformatics showed that gingerol and quercetin compounds had log P values of 3.58 and 0.52, respectively. This indicates that both gingerol and quercetin compounds are polar compounds that can dissolve easily in the blood and are easily distributed in the body. The last parameter of the physicochemical test is the molar refractivity value. Molar refractivity is a value that reflects the ability of the tested drug compound to maintain its position and bond strength with the tested target macro protein. A compound can be said to be able to maintain its position and bond strength with the target macro protein if it has a yield value between 40-130. Both gingerol and quercetin compounds have molar refractivity values between 40-13, respectively 86.13 and 64.37. This indicates that both gingerol and quercetin compounds can maintain their position and bond strength with the target macro protein [7].

One of the recommended methods for testing herbal compounds that are appointed as drug candidates must be through pharmacokinetic tests, because this test is considered important because the drug compounds to be administered orally or parenterally must be known. Through this test it is useful to map the ability of compounds in distribution, absorption, excretion, and metabolism when they are in the body. One way to determine pharmacokinetic properties is through the application of pkCSM [8]. The following are the results of the pharmacokinetic test of the genistein compound using the pkCSM online tools biocomputation. The gingerol and quercetin compounds have water solubility values of -3.164 and -2.925, respectively. Then for the skin permeability value of the gingerol compound it has a value of 2.817 and quercetin has a value of -2.375. From the results of pharmacokinetic testing regarding fraction unbound, the active compounds gingerol and quercetin had FU values of 0.258 or 25.8% and 0.206 or 20.6%, respectively.

Toxicity testing is one of the procedures that must be passed by a drug candidate. The purpose of testing for toxicity is to expect that a drug consumed by humans does not cause toxic effects in the body. In general, toxicity tests are carried out on test animals in a laboratory. However, this requires quite a long time and costs are relatively more expensive. Therefore, biocomputational toxicity testing is an efficient choice in drug candidate testing procedures [9].

In addition to the advantages in terms of cost and time, biocomputational toxicity testing has the advantage of being an easier testing method. The test was carried out using pkCSM which can predict a secondary metabolite compound present in the human body with the various test components requested. However, the focus on toxicity tests only includes the AMES toxicity test components, human maximum tolerated dose, hepatotoxicity, and skin sensitization. Following are the results of the genistein compound toxicity test using pkCSM. From the results of the pkCSM test, it was found that the gingerol and quercetin compounds gave negative results for AMES toxicity. AMES toxicity is a cellular mutation condition caused by chemical activity in the body. This first discovery was made by a researcher named Bruce Ames in 1973. If a compound is said to be positive for AMES toxicity, then those 13 compounds when consumed and in the body will become mutation factors and trigger mutations [10].

The next parameter is the human maximum dose. Dosage is the quantity of a compound that researchers use to become medicine and will eventually be consumed by humans. The benefit of knowing the dose threshold is to determine the therapeutic dose of a drug compound so that it does not become a toxic dose for the body. The gingerol compound shows the maximum tolerated dose value in Log yield units (mg/KgBW) is 0.635 or when converted to units of mg/KgBW is 4.31 mg/KgBW. The quercetin compound shows the maximum tolerated dose value in Log yield units (mg/KgBW) is 0.499 or when converted to units of mg/KgBW is 3.16 mg/KgBW. From this information, it will be the basis for determining therapeutic doses and drug use doses prior to *in vitro* and *in vivo* testing [11].

The next component is hepatotoxicity. Through the pkCSM test, gingerol and quercetin compounds can be seen that these compounds do not cause hepatotoxicity. Hepatotoxicity is a condition in which liver cells are damaged by toxic chemicals. Several drugs have been conclusively documented to cause liver injury in numerous case reports and case series. Many such drugs have a known clinical sign (phenotype) of liver injury and causality has been further documented by positive re-challenge examples. This test component is considered necessary because a drug that enters the body will later be metabolized in the liver, so testing for hepatotoxicity is necessary [12].

The parameter of the toxicity test is the skin sensitization test. Skin sensitization or skin allergy testing is a key end point for safety assessment, especially for chemicals in cosmetic products and personal care drugs. Skin sensitization is an immune reaction to exogenous reactive haptens or prohaptens, which react with skin proteins and make them immunogenic. The whole process can be broadly divided into sensitization and elicitation phases. In the sensitization phase, chemical agents react with skin proteins, and dendritic cells process modified proteins and present antigens to naive T cells in local lymph nodes, leading to the expansion of antigen-specific T cell clones. On subsequent exposure to the same sensitizer, a specific T cell-mediated immune response can be elicited (elicitation phase). Skin sensitization resulting in allergic contact dermatitis is a common occupational health and environmental problem. As with all forms of allergic disease, contact allergy develops in two phases and is dependent by definition on the stimulation of an immune response. The first phase – or induction phase – begins when an inherently susceptible individual is exposed (usually on the skin surface) to an amount of contact allergen sufficient to trigger a skin immune response resulting in immunological priming [13].

Subjects who have acquired skin sensitization now have the ability to mount a faster and more aggressive secondary immune response if contact is made with the same allergen again on the same or distant skin site. This second phase – or elicitation phase – is associated with a local skin inflammatory reaction at the site of skin exposure that is characterized clinically as allergic contact dermatitis. From the results of the toxicity test, the gingerol and quercetin compounds were negative for skin sensitization. So it can be concluded that gingerol and quercetin compounds do not cause contact dermatitis due to treatment using pharmaceutical mucoadhesion patches [13].

Molecular docking is done by preparing the components to be tested. These components are prepared beforehand. The preparations carried out included the deletion of the H2O molecule present in the COX-1 protein and the phospholipase A2 enzyme, and the deletion of non-sense ligands. The compounds arachidonic acid and valdecoxib here act as a comparison between the strengths formed by native ligands with the test ligands, namely gingerol and quercetin against COX-1 and the enzyme phospholipase A2[14]. After preparing the ligand and protein, molecular docking tests were carried out using the PyRx application. The principle of molecular docking is to simulate reactions in the body between ligands and proteins in biocomputation [14].

After the molecular docking process was carried out, the binding affinity results were obtained as follows: After carrying out the molecular docking simulation test, the binding affinity, mode, and RMSD results were obtained. Each of these test results has its own meaning and reflection. Mode is a value that indicates the difference in the location of the binding site and the conformation formed. After that, there is the RMSD parameter. RMSD is a reflection of

stability formed by a ligand-protein bound complex. The closer to zero the RMSD value is, the more stable or the most stable the stability that is built between the ligand-protein bond. The last thing obtained from the molecular docking test is binding affinity. Binding affinity is a parameter that determines the amount of energy needed for a compound to bind to proteins [15].

From the results of the molecular docking test, the docking results were obtained between the COX-1 protein and 3 test ligands, one of which was a native ligand. The results of the molecular docking test between arachidonic acid and COX-1 protein have a binding affinity of -5.2 kcal/mol. These results became a comparison in the group tested against COX-1. The gingerol and quercetin compounds have a binding affinity value of -6.8 kcal/mold and -9.1 kcal/mol, respectively, both of which have a lower binding affinity value compared to the bond formed between COX-1 and arachidonic acid. This shows that biocomputationally, gingerol and quercetin compounds have a tendency to form bonds with COX-1 compared to arachidonic acid without having to increase the dose so that they become competitors to the native ligand.

The results of the next test, the results of the reaction of the enzyme phospholipase A2 with two ligands and one native ligand. The binding affinity value between the valdecoxib compound and the phospholipase A2 enzyme is -6.4 kcal/mol. Meanwhile, the binding affinity values between the gingerol and quercetin compounds for the phospholipase A2 enzyme were -5.9 kcal/mold and -6.3 kcal/mol, respectively. This value indicates that the gingerol and quercetin compounds have a lower binding affinity value but not too much. The distance between the binding affinity values of gingerol and valdecoxib is 0.5 kcal/mol, while the binding affinity values between quercetin and valdecoxib are 0.1 kcal/mol. This linkage provides biocomputational results that the compounds gingerol and quercetin have a lower tendency compared to valdecoxib to bind to the phospholipase A2 enzyme. This does not mean that gingerol and quercetin compounds cannot replace valdecoxib to inhibit phospholipase A2 enzymes, but gingerol and quercetin compounds can replace valdecoxib provided that the dose given must exceed the spike in lipid conversion by phospholipase A2 in order to replace valdecoxib to inhibit the lipid conversion process by phospholipase A2 [15].

After going through the molecular docking process, the docking results will be visualized using the Biovia application to position the bond between the ligand and the target protein. The following is a visualization of the compounds arachidonic acid, gingerol, and quercetin with COX-1 protein. From the picture above, it can be visualized the compounds arachidonic acid, gingerol, and quercetin on COX-1 protein. In the figure it can also be visually analyzed that the gingerol and quercetin test compounds can bind to the COX-1 protein. After visualizing the arachidonic acid, gingerol, and quercetin ligands against COX-1, visualization was also carried out in the test group of valdecoxib, gingerol, and quercetin ligands against the phospholipase A2 enzyme. The following is a visualization of valdecoxib, gingerol, and quercetin for phospholipase A2,

From the visualization results, we get an overview of the bond location between the valdecoxib, gingerol, and quercetin ligands on phospholipase A2. Visualization can also describe the position of the ligand that binds to phospholipase A2. Based on the visualization results, the three compounds, namely valdecoxib, gingerol, and quercetin, all have the same binding site for phospholipase A2. So that it can give an idea that gingerol and quercetin compounds can replace the role of valdecoxib as an inhibitor of phospholipase A2 [15].

Conclusion

The active compounds gingerol in ginger extract (Zingiber officinale) and quercetin in black cumin extract (Nigella sativa) contained in Zahabba patches can work by inhibiting the synthesis of pro-inflammatory cytokines such as PGI2, PGE2, and TXA2 by being a competitive inhibitor of the enzyme phospholipase A2 against lipids membranes and cyclooxygenase-1 (COX-1) enzymes against arachidonic acid. Gingerol and quercetin have better effectiveness than the native ligands valdecoxib and arachidonic acid as evidenced by the binding affinity value that must be supported and the therapeutic dose calculated so that they can become competitive inhibitors that are effective but do not cause lethal doses.

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Conflict of Interest

The author declares no conflict of interest.

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