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Molecular Docking Extract Ginger Clove Acts As An Antibacterial In Expression Of Tlr2 And Tlr4 Proteins In Recurrent Aphthous Stomatitis (Ras)

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Abstract

Toll-Like Receptors (TLRs) are vital components playing important role in pathogen recognition and natural immunity. TLRs recognize microbial structure and transmit this information into the cell, culminating in an inflammatory cytokine response and in co-stimulatory molecule expression involve in induction of adaptive immunity. This study aims to explore the chemical compounds of ginger and clove as antibacterial. The water molecules and ligands were removed using PyMOL v1.7.4.5 Software (Schrödinger). Molecular docking experiments were performed using the PyRx0.8 software. The expression of TLR2 and TLR4 proteins in Recurrent Aphthous Stomatitis has different ligands and binding affinities. Expression of TLR2 protein with peptidoglycan ligand for microbial sources of gram-positive bacteria, while TLR4 has lipopolysaccharide (LPS) ligand for gram negative bacteria. Lipopolysaccharide (LPS) is a major component of the outer membrane of Gram-negative bacteria. Peptidoglycan (PGN) recognition proteins (PGRPs) are pattern-recognition receptors of the innate immune system that bind and, in some cases, hydrolyze bacterial PGNs. The result showed that quercetin has greater potential as an antibacterial based on its binding affinity and intermolecular interactions. The binding affinity of gingerol eugenol with TLR2 is -5.70, TLR4 protein is -4.60, while binding affinity chlorhexidine (as control) with TLR2 and TLR4 was -7.20. AMES Tests showed that gingeroleugenol is not

potential mutagen and not carcinogens. Druglikeness prediction showed that gingerol and eugenol fulfil the rules of Lipinski, Ghose, Veber, Egan, and Nuegge.

Keywords: Recurrent Aphthous Stomatitis, Ginger, Clove, TLR2, TLR4, lipopolysaccharide, Peptidoglycan

Introduction

Ginger (*Zingiber Officinale*) and Clove (*SyzygiumAromaticum*) are natural ingredients that are often used for seasoning in various dishes. Ginger (*ZingiberofficinaleRosc*) is a plant belonging to the class Monocotyledoneae and the Zingiberaceae family of spices (Mohaddese Mahboubi, 2019). Ginger contains chemical compounds such as (6,8, and 10)- gingerol, (6.8 and 10)-shogaol, paradol, methyl gingerol, gingerdiol, dehydrogingerdion, gingerdion. The main chemical content of cloves is eugenol with a composition of eugenol (81.20%), trans- β -caryophyllene (3.92%), -humulene (0.45%), eugenol acetate (12.43%), caryophyllene oxide (0.25%) and trimetoxycetophenone (0.53%). Ginger is used for the treatment of diseases, including muscle pain, rheumatism, sinusitis, cough, afternoon throat, diarrhea, cramps, indigestion, loss of appetite, fever, flu, and infectious and non-communicable diseases, while Clove has stimulant, anesthetic, carminative, antiemetic, antiseptic and antispasmodic (Mengmeng Zhang, 2020).

Toll-Like Receptors (TLRs) are vital components playing important role in pathogen recognition and natural immunity. TLRs recognize microbial structure and transmit this information into the cell, culminating in an inflammatory cytokine response and in co-stimulatory molecule expression involve in induction of adaptive immunity. Failure of the receptor to recognize pathogen may result in recurrent infection in hosts (Muthukuru M, 2005). Oral mucosal cells such as epithelial cells are thought to act as physical barrier against the invasion of pathogenic organism, but they have an ability to produce inflammatory cytokines and express adhesion molecules. Oral epithelial cells are refractory to many bacterial components although they express TLR/MyD88 (Sugawara S, 2002). Epithelium of oral mucosal is the first line of defense against invading pathogens. TLR4, along with CD14 and other adaptor molecules, recognize pathogen-associated molecular patterns such as lipopolysaccharides (LPS) from gram negative enteric bacteria. TLR2 along with TLR1/TLR6, recognize gram positive peptidoglycans eg. From oral commensal (Dong Z, 2005).

Minute amounts of LPS released from infecting pathogens can initiate potent innate immune responses that prime the immune system against further infection. However, when the LPS response is not properly controlled it can lead to fatal septic shock syndrome. The common structural pattern of LPS in diverse bacterial species is recognized by a cascade of LPS receptors and accessory proteins,

LPS binding protein (LBP) and the Toll-like receptor4 (TLR4) complex (Rongjin Guan, 2004). One recent study indicates that both TLR2 and TLR4 positive cells infiltrate the oral mucosa in mucosal health and disease., but very little is understood about the overall expression pattern of PRRs in the human oral mucosal health and in Recurrent Aphthous Stomatitis and how they regulate local immune responsiveness (Ortega Cava, 2003).

Recurrent Aphthous Stomatitis (RAS) are the most common oral disease characterized by repeated development of painful ulcers. The etiology of RAS is still unknown. Many local and systemic factors such as viral or bacterial infection, food hypersensitivity, genetic factors, and systemic disease could be involved in the pathogenesis of RAS. Previous study have also suggested that this inflammatory disease is a result of abnormal immune response directed towards the oral mucosal. The Innate immune system also plays a role in several human diseases. The primary function of Toll Like receptors (TLRs) is to recognized pathogens (DiahSavitriErnawati, 2016).

Ginger and cloves are herbal plants that are used to treat diseases such as muscle pain, rheumatism, sinusitis, cough, sore throat, diarrhea, cramps, indigestion, loss of appetite, fever, flu, and infectious and non-communicable diseases such as mouth disease (RAS). Ginger Clove has stimulant, anesthetic, carminative, antiemetic, antiseptic and antispasmodic properties so that it is feasible to be used as an extract that is useful for human health in general and dental and oral health in particular (Kawiji, 2016).

Based on this background, researchers are interested in conducting "molecular docking" of the active compound in clove ginger as an antibacterial in the expression of TLR2 and TLR4 proteins in RAS patients.

Materials and Methods

Tools and Materials

Laptop with Intel® Core™ specifications, 4 GB RAM and graphics card. The software used is the Windows 10 operating system, the Autodock Tools package (The Scripps Research Institute), Open Babel 2.3.3, Autodock Vina, and PyMOL. The hardware device used is an Acer Aspire E Laptop with OS specifications: Windows 8.1, Processor AMD A-Series Quad Core Processor A10-7300 (4 MB L2 cache, RAM 16 GB DDR3L SDRAM). The software uses applications, namely PyMOL, PyRX. The materials used are protein data bank website (<https://www.rcsb.org>), PubChem

(<https://pubchem.ncbi.nlm.nih.gov>), Toxicity Test (<http://lmmmd.ecust.edu.cn>) and Druglikeness Test (<http://www.swissadme.ch>)

Preparation

Preparation of compounds in Dayak onion plants to be used as ligands was obtained through the PubChem website and then downloaded in 3D SDF format. Preparations of TLR2 and TLR4 receptor proteins were obtained through the PDB website (Protein Data Bank), then downloaded in PDB format. Next, open the PyMOL application to clean the water molecules contained in the target protein that are still dirty to be used as pure target protein.

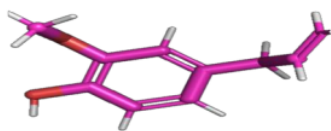
Research Procedure

The molecular docking process uses the Autodock tools application and Autodock vina on the PyRx application. The receptor and ligand structures that have been optimized are separately stored in the same folder. By opening the application, click the file, click load the target protein molecule that has been cleaned. For ligands click file then click import and select sdf format and enter the ligands that have been downloaded in PubChem previously. Then click on Autodock Vina click start and select molecular and ligand then click forward after it appears click maximise then click forward again until running is complete after that the docking result number appears and select the smallest number then save with sdf format. Furthermore, the saved sdf file is entered into the PyMOL application to see the visualization of the docking results of the target ligand and protein.

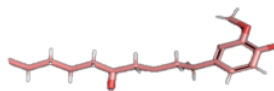
Results and Discussion

In this study, to obtain a ligand as a candidate drug to be developed, the criteria for a good drug must follow ¹⁴³ Lipinski's Rule of Five developed by Christopher A. Lipinski (Tallei TE, 2020). Prior to molecular docking, it is necessary to check the nature of the ligand used, whether it meets the rules.

Eugenol



Gingerol



Control Ligand: Chlorhexidine

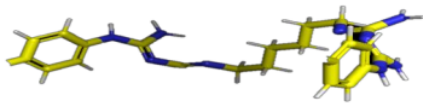


Figure 1. Visualization 3D Eugenol, Gingerol and Chlorhexidine 3D compounds

With water molecules

Without water molecules



Figure 2. Visualization 3D Target Proteins TLR2 (Ligand Peptidoglycan)

With water molecules

Without water molecules



Figure 3. Visualization 3D Target Proteins TLR2 (Ligand LPS)

The results of visualization of molecular docking gingerol and eugenol have vander Waals bonds and conventional hydrogen bonds for eugenol, gingerols have conventional hydrogen bonds found in the molecular docking results. Visualization of molecular docking results for eugenol compounds, gingerols with main protein receptors TLR2 and TLR4 in 3D and 2D forms, on residual gingerol and eugenol compounds that act on the active site, namely the van der Waals bond.

Based on the results obtained, gingerol and eugenol showed activity as an antibacterial agent for SAR with the mechanism of inhibition of the SAR protease through the formation of hydrogen bonds with negative affinity.

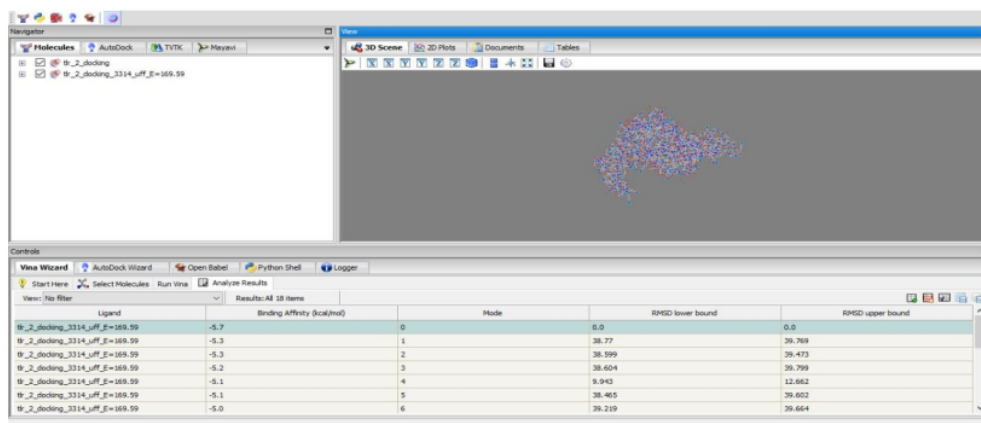


Figure 4. Vina Autodocking Process Gingerol compound with TLR2 protein

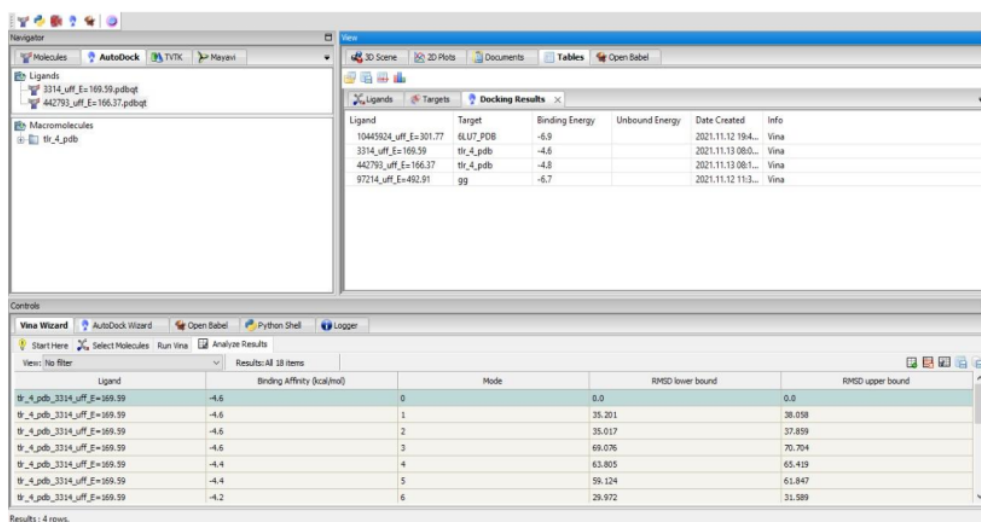


Figure 5. Vina Autodocking Process Eugenol compound with TLR4 protein

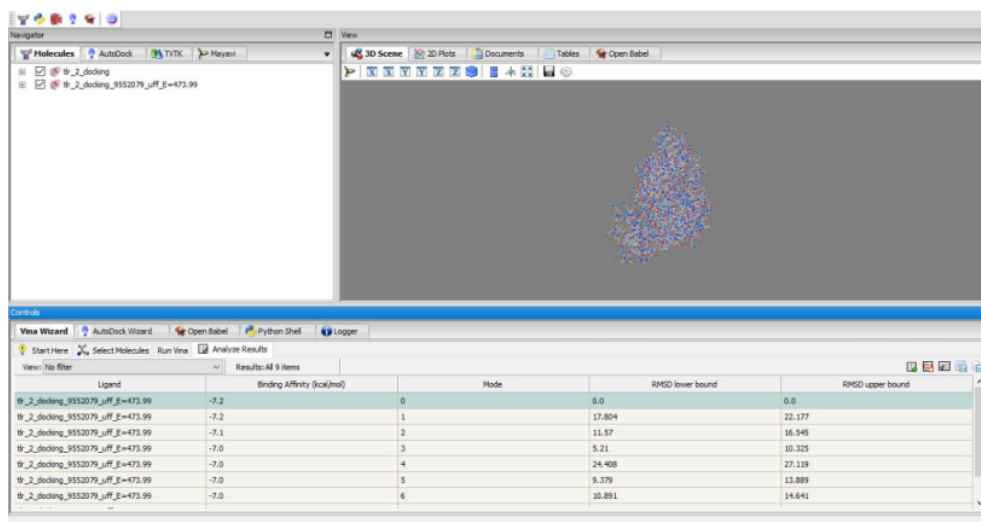


Figure 6. VINA Autodocking Process of Chlorhexidine Compound with TLR2 protein

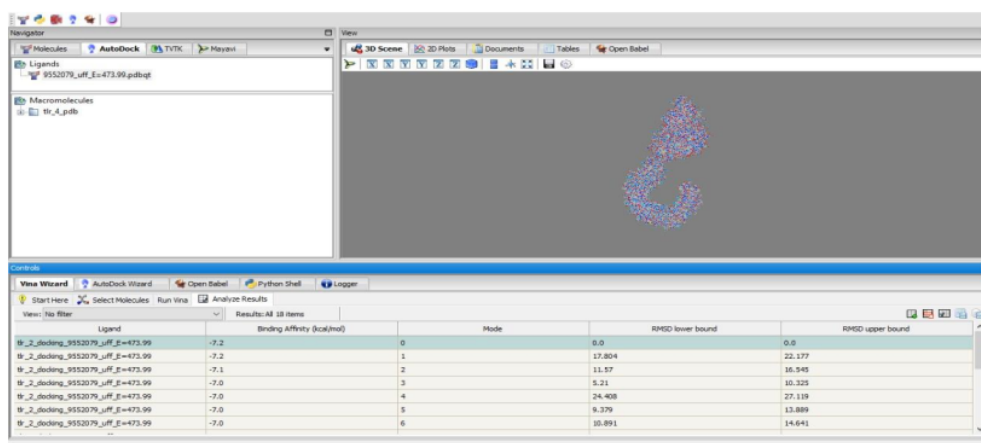


Figure 7. VINA Autodocking Process of Chlorhexidine Compound with TLR4 protein



Figure 8. Visualization 3D TLR2 and TLR4 With Test Compound

Toxicity Test

In the toxicity test, the results were obtained for Peptidoglycan, LPS and Chlorhexidine compounds with nonAMES Toxic and Non Carcinogens results.

Table 1. Toxicity Test Results of Gingerol and Eugenol Compounds

Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.6699
AMES Toxicity	Non-AMES toxic	0.6199
Carcinogens	Non-carcinogens	0.8605
Fish Toxicity	High FHMT	0.9677
Tetrahymena Pyriformis Toxicity	High TPT	0.9983
Honey Bee Toxicity	Low HBT	0.8089
Biodegradation	Not ready biodegradable	0.9963
Acute Oral Toxicity	III	0.3911
Carcinogenicity (Three-class)	Non-required	0.6172

ADMET Predicted Profile --- Regression

Druglikeness Test

Lipinski's rule states that a molecule can be continued with docking simulations if (1) the molecular weight is less than 500 Da, (2) the logpvalue is less than 5, (3) the number of hydrogen bond donors is less than 5, and (4) the number of hydrogen bond acceptors is less than 10. (5). In the druglikeness test (lipinski) it was found that the compound eugenol, gingerol and chlorhexidine, the result of lipinski was Yes, which means that molecular docking can be continued.

Table 2. Bioavailability Score Compounds Gingerol and Eugenol

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Table 3. The result of Binding Affinity

Ligand	Binding Affinity
	TLR2
Peptidoglycan	-5.70
	TLR4
LPS	-4.60
Chlorhexidine (Control)	-7.20

Most of the extracts from herbs such as ginger (gingerol) dan cloves (eugenol), are intended to treat some chronic diseases that exist in the oral cavity such as RAS. Thus, drug concentrations must be consistent if used as antibacterial therapy. Side effects of gingerol and eugenol compounds for the body have been observed, evaluated and associated with cell permeability and good metabolic processes, as the results of this study indicate that gingerol and eugenol are not potential mutagens and are not carcinogens.

Ligands are considered to have the potential to enter cell membranes and be absorbed by the body if they meet Lipinski's rules. After that, look at the lowest binding affinity value because the smaller the binding affinity value, the stronger the binding ability between the ligand used and the receptor (Masula AF, 2018).

Eugenol (4-allyl-2-methoxyphenol) is a major phenolic constituent of essential oils extracted from clove, nutmeg, and cinnamon. It exhibits antimicrobial, anti-inflammatory, and antioxidative properties (Rathinam P, 2017). It has also been widely used in flavoring, as well as in the cosmetic, pharmaceutical, and dentistry industries (MohammadiNejad S, 2017). Nowadays, the application of eugenol in the agricultural industry, such as in animal feeds, is increasing. Previous studies have reported that the administration of eugenol improved the health status and growth performance (Compiani R, 2013).

Additionally, eugenol showed antimicrobial activity against pig gut flora (Marchese A, 2017). Moreover, eugenol has been found to possess anti-inflammatory properties by decreasing the production of proinflammatory cytokines through regulating inflammation and redox status in lipopolysaccharide (LPS)-induced inflammation in acute lung injury (Huang X, 2015). Eugenol suppressed cyclooxygenase-2 expression in LPS-stimulated mouse macrophage RAW264 cells. Therefore, eugenol has the potential to be an alternative to AGP, by preventing and alleviating the inflammatory gut diseases caused by weaning stress (Blavi L, 2015). Additionally, the flavor of eugenol in feeds positively affects postweaning performance and feeding behavior of piglets, which helped piglets adapt to a novel solid food from liquid (Qianruhui, 2020).

Based on the results of molecular docking of gingerol and eugenol compounds to TLR2 and TLR4, van der Waals bonds and hydrogen bonds were found in both docking results. Both of these bonds play an important role in the docking results.

Conclusion

This research proves that gingerol and eugenol have the potential as antibacterial based on their binding affinity with -5.70 TLR2 protein and -4.60 TLR4 protein so that intermolecular interactions occur. This can also be seen from the control used, namely chlorhexidine with a binding affinity of -7.20.

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Conflict of Interest.

The authors declare that there is no conflict of interest.

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