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Molecular Docking Bioactive Compound of Rambutan Peel *(Nephelium lappaceum L)* and NF-Kb in the Context of Cigarette Smoke-Induced Inflammation

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ABSTRACT

Cigarette smoke (CS) is the main activator of highly reactive form of oxygen known as ROS. Increased levels of ROS by cigarette smoke are involved in initiating the inflammatory response of the lungs by triggering the transcription factor NF-κB which causes an increase in the expression of pro-inflammatory cytokines thus initiating chronic obstructive pulmonary disease (COPD). Major phenolic contents of rambutan peel are geraniin, corilagin, ellagic acid and gallic acid which are reported to have significant potential as antioxidants and anti-inflammatories. Currently, in silico drug development has been widely assessed due to the expeditious verdicts. Thus, the study aimed to predict the possibility of geraniin, corilagin, ellagic acid and gallic acid compounds contained in rambutan peel as anti-inflammatory candidates caused by CS with the target binding of NF-κB. Docking simulations were performed by using PyRx 0.8. Data from software and web devices were analyzed descriptively and compared with SC-236 as a control. The docking results showed that all ligands were shown to have binding affinity. Geraniin was a compound with the lowest affinity binding value (-8.6 kcal / mol). Corilagin had the same binding affinity value as the SC-236 control (-7.8 kcal/mol). Then the ellagic acid and gallic acid compounds had a higher binding affinity value than successive controls (-6.9 kcal / mol) and (-5.9 kcal / mol). The overall results showed that corilagin and geraniin compounds were the most suggested anti-inflammatory candidates of rambutan peel for the prevention of chronic inflammation due to CS by inhibiting NF-kB role.

Keywords: Rambutan peel, Cigarette smoke, Anti-inflammatory, Molecular docking.

Introduction

Inflammation is occurred as immune responses for some damaging hazard materials, such as diseases, wounds, contaminants or cells, toxic compounds, or irradiation. The response could be in the form of resilience against the damage by tissue endurance regulation. Inflammation could be caused by chronic or temporal immune reaction.[6] NF-κB transcription factor is a complex signaling pathway with a significance responsibilities in immune system with the focus on inflammation, comprising the production of intermediate molecule in inflammation regulation, bound of the expressed molecule, and lymphocyte stimulation.[2] Persistence symptoms of the response was also instigated in the disease related to cigarette smoke (CS), including pulmonary cancer, chronic obstructive pulmonary disease (COPD), and asthma.[3] COPD is mainly caused by CS due to the abundant number of generated reactive oxygen species (ROS) as long as the respiratory tract. COPD is an illness typified by severe and reversible air path obstruction of the respiratory due to an abnormal growth of tissue as a response to inspired harmful particles while smoking.[14] COPD poses an increasing global health problem with mortality issues.[12] Indecent regulation of antioxidant defense against ROS accumulation throughout smoking or other causes could stimulate cell oxidative stress, with the consequence of proliferated respiratory tissue.[6]

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Increased levels of ROS by cigarette smoke are involved in initiating lung inflamation caused by induction of NF-κB transcription factor[19]. Smoking caused phosphorylation and deprivation of IκBα and causes increased expression of NF-κB regulated pro-inflammatory cytokines.[3] Rambutan (*Nephelium lappaceum L.*) is a kind of tropical fruit of Sapindaceae family. It is common in Southeast Asia, especially in the eastern and southern regions of Thailand. Rambutan peel has substantial capacity caused by the bioactive contents. A reported biological activity of rambutan peels is the antioxidants and anti-inflammatories value due to the phenolic compounds.[21] The main phenolic compounds found in rambutan peel are geraniin, corilagin, ellagic acid and gallic acid.[20]

The current drug development revolution uses bioinformatics and computational biology correlated with the science of medical chemistry which is known as in silico. In silico method plays a significant role in the early stages of preclinical to the final stages of clinical development. Not only does it speed up the drug discovery process but it can also prevent late-stage clinical failure thus reducing large costs. Molecular docking is a kind of in silico method, to predict the preferred binding site among molecules which commonly consists of ligand and protein. In this case, the active site of the protein is calculated to analyzed the capability in binding some ligands as an inhibitor or inducer. The analysis and the evaluation is made based on structural conformation and electrostatic properties.[11] The *in silico* technique has been widely reported to be significant in aiding drug design through drug-receptor mechanisms. Based on the above reasons, this study aimed to predict the potential of geraniin, corilagin, ellagic acid and gallic acid compounds contained in rambutan peel as anti-inflammatory candidates caused by cigarette acid with a target of NF-κB *in silico*.

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Materials and Methods

Tools and Materials

Tools: a set of AMD Dual Core Processor A9-9425 bga PC equipped with sofware of BIOVIA Discovery Studio Visualizer and PyRx 0.8, as well as PubChem web servers, Online PASS, and PDB (Protein Data Bank).

Material: 2/3 dimensional structure of bioactive compounds rambutan peel ellagic acid, corilagin, geraniin, and gallic acid as well as control compounds SC-236 and also the structure of the target protein NF-κB CID 1SVC.

Collection of Ligand and Protein Structures

The three-dimensional (3D) or two-dimensional (2D) ligand structures of ellagic acid (CID: 5281855), corilagin (CID: 73568), geraniin (CID: 3001497), and gallic acid (CID: 370) compounds were in the format (*.sdf) and converted to the format (*pdbqt) by using Open Babel. Positive control of NF-κB inhibitors used SC-236 (CID: 9865808). 3D structure NF-κB1 human with PDB ID: 1SVC were in a resolution of 2.60 Å. The crystallized DNA structure alongside the NF-κB1 protein was removed by using biovia Discovery Studio Visualizer software.

Prediction of Anti-Inflammatory Activity of Rambutan Peel Compounds

Predictions were made by using the Online PASS (Prediction of Activity Spectra for Substances) web server through http://www.way2drug.com/passonline/predict.php by entering SMILES ligands obtained from the PubChem database.

Docking and Molecular Visualization

Molecular docking between NF-κB1 receptors with ellagic acid, corilagin, geraniin, and gallic acid as inhibitors was carried out by using Autodock vina software in the PyRx 0.8 program. Biovia Discovery was used to visualize the interaction of ligand-receptor binding in 2D and 3D.

Data analysis

The result of molecular docking was binding affinity and the type of bond formed. Binding affinity shows the value of the bond strength between the ligand and the receptor. The lower the value of binding affinity is, the stronger and more stable the bond will be. The type of bond formed was used to analyze related interaction mechanisms formed.

Results and Discussion

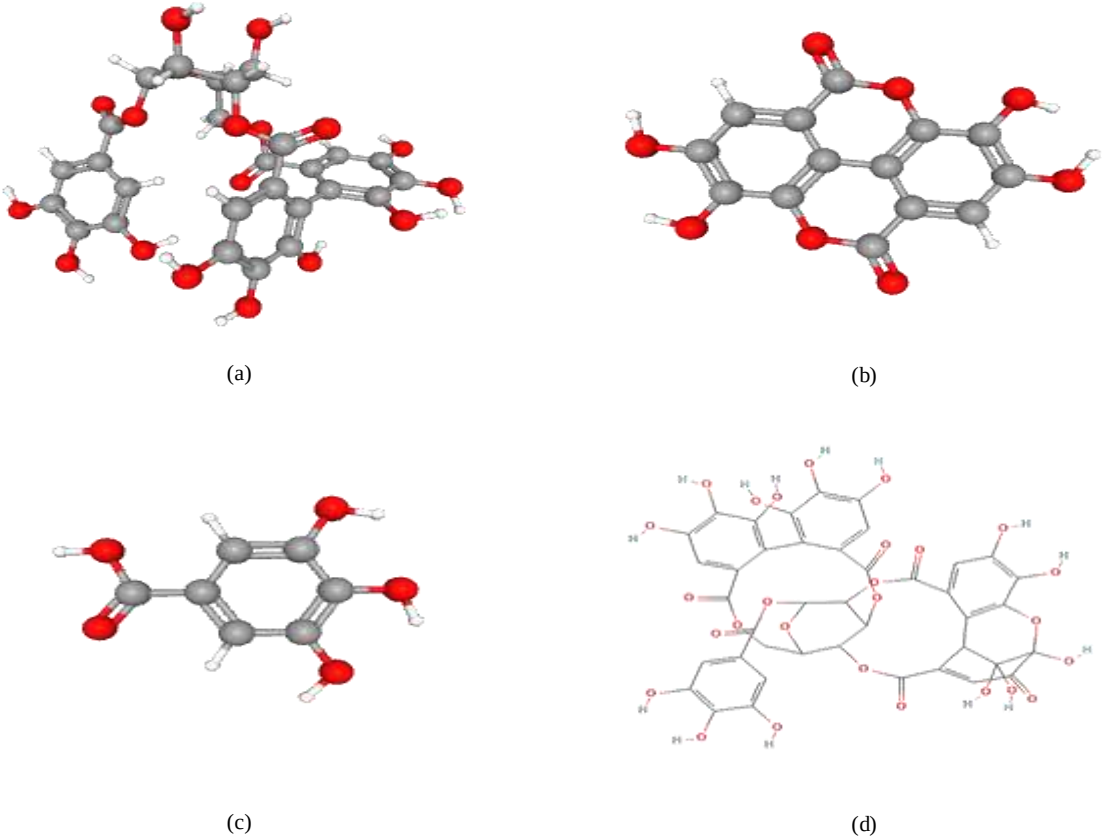
Collection of Ligand and Protein Structures

The 2D/3D structure of ligand compounds was obtained from the PubChem database in the Sybil Data Files (*.sdf) format and protein receptors were obtained from the PDB database in the Protein Data Bank (*.pdb) format. Test ligands include ellagic acid, corilagin, geraniin, and gallic acid (Figure 1). The test ligands were then compared to the comparative ligand which is SC-236 in the capability in binding receptor protein which is NF-κB1 (Figure 2). The structure of 3D receptor proteins which is NF-κB1 human with PDB ID: 1SVC. The receptors that had been downloaded from the RCSB still attach to water molecule as well as other solvents attached to the original conformation. Therefore, they must be removed so as not to hinder the tethering of other ligands on the binding side (Figure 3).

Prediction of Anti-Inflammatory Activity of Bioactive Compounds of Rambutan Peel

Screening of bioactive compounds of rambutan peel aimed to determine the potential bioactivity of compounds as anti-inflammatories. Screening was carried out by using the PASS (Prediction of Activity Spectra for Substances) Online database, which is a web server-based application that predicts the spectrum of biological activity of a compound based on its structure, based on the principle that the biological activity of a compound is correspondent to its structure.[16]

The predicted results of probability to be active (Pa) of ellagic acid, corilagin, and geraniin compounds were more than 0.7 (Pa > 0.7) (Table 1).



(a) (b) (c) (d)

Figure 1: 2D/3D structure of test ligands (a) 3D Corilagin, (b) 3D Ellagic acid, (c) 3D Gallic acid, (d) 2D Geraniin.

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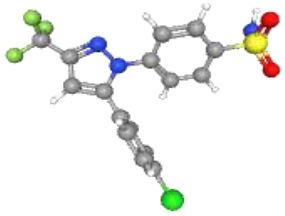

Figure 2: Comparator ligand 3D structure of SC-236

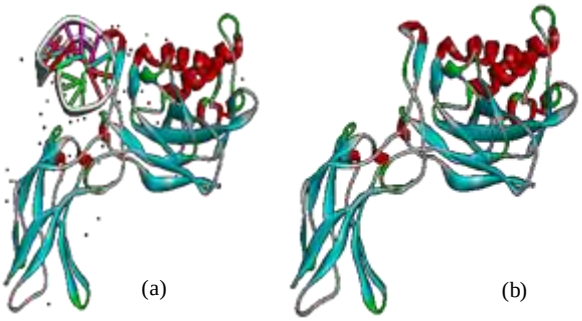

Figure 3: The 3D structure of the NF-κB1 receptor (a) NF-κB1 crystallized alongside DNA and other solvents (b) NF-κB1 preparation results.

Table 1: Anti-inflammatory activity of bioactive compounds rambutan peel

Compounds	Canonical SMILE	Pa	Activity
Ellagic acid	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	0.749	Anti-inflammatory
Corilagin	C1C2C(C(C(C(O2)OC(=O)C3=CC(=C(C(=C3)O)O)O)O)OC(=O)C4=CC(=C(C(=C4C5=C(C(=C(C=C5C(=O)O1)O)O)O)O)O)O)O	0.7	Anti-inflammatory
Geraniin	C1C2C3C(C(C(O2)OC(=O)C4=CC(=C(C(=C4)O)O)O)OC(=O)C5=CC(=C(C6=C5C7C(=CC(=O)C(C7(O)O)(O6)O)C(=O)O3)O)O)OC(=O)C8=CC(=C(C(=C8C9=C(C(=C(C=C9C(=O)O1)O)O)O)O)O)O	0.808	Anti-inflammatory
Gallic acid	C1=C(C=C(C(=C1O)O)O)C(=O)O	0.548	Anti-inflammatory

The Pa value which is higher than 0.7 means that the molecule expected to bind and activate or inhibit the protein[5]. Thus, these compounds have very high probability to become anti-inflammatory. Further research of the compound in a laboratory scale could enhance the development of new drug. Gallic acid compounds have a Pa value of more than 0.5 but less than 0.7 ($0.5 < Pa < 0.7$) (Table 1), indicating that the compound has a potential as an anti-inflammatory but not as high as the previous compounds.

Docking and Molecular Visualization

The results of molecular docking between the test ligand and the control ligand with the NF-κB1 receptor protein were shown to have binding affinity. Based on the docking results, the lowest affinity binding value was a geraniin of -8.6 kcal/mol. Corilagin compounds had the lowest binding affinity value after geraniin which was -7.8 kcal / mol. Then, it was followed by ellagic acid compounds, -6.9 kcal / mol, and the highest is gallic acid compounds -5.9 kcal / mol. The control ligand is used as a comparison has a binding affinity of -7.8 kcal/mol (Figure 4). Binding affinity indicates the value of the strength of the interaction between two or more reversible binding molecules. The lower the binding affinity value between the ligand and the target molecule is, the stronger and more stable the binding will be.[10] The magnitude of the binding affinity value obtained is influenced by the interaction formed between the ligand and the NF-κB1 receptor. Such interactions can be van der waal's bonds, hydrophobic bonds, and hydrogen bonds to different amino acid residues (Table 2).

Visualization was performed to see the binding amino acid residues. The presence of amino acid interactions involved allowed contact between ligands and NF-κB1 receptors so that they had inhibitory activity. Hydrogen bonds are the most important specific interactions in biological processes contributing to the affinity of the molecule for the target protein, thereby forming electrostatic interactions (hydrogen donors and acceptors).[4] The presence of hydrogen bonds provided conformational stability in ligands with NF-κB1 receptors which contributed to a decrease in the value of binding affinity. In addition to the relationship between hydrogen bonds and binding affinity values, there were still many influencing factors such as van der waal's and hydrophobic interactions. Based on the visualization results of sc-236 drug compounds on the NF-κB1 protein, it can form a hydrophobic bond of alkyl bond with amino acid residues Phe220, Tyr166 and carbon hydrogen bonds with amino acid residues Thr229, Ala181, as well as hydrogen bonds with amino acid residues Lys95, Arg164, Glu160. These results were used as a reference to compare amino acid residues that bind to test ligands, namely rambutan peel bioactive compounds in inhibiting the NF-κB1 target protein. Corilagin compounds in NF-κB1 proteins can form hydrophobic bonds of alkyl bonds with amino acid residues Pro71 and carbon hydrogen bonds with amino acid residues Gly55, Phe56, His67, as well as hydrogen bonds formed in amino acid residues Arg59, Arg57, Asn250 with a distance of < 2Å which indicated a stronger bond was formed. Although corilagin had the same binding affinity value as the SC-236 control compound, which was-7.8 kcal / mol, in the visualization results there is no similarity of amino acid residues with controls at the binding site which is the area of protein binding to ligands that will affect the conformation and function of proteins.[1] This showed that the binding area of corilagin compounds in the NF-κB1 protein was different from that of control compounds. This is because a ligand will look for the most stable conformation on the active side of the target protein.

Ellagic acid compounds in NF-κB1 proteins can form van der waal's bonds with amino acid residues Gly185, Ile163, Gly184, Glu182, Gly183, Thr229, Phe228, pi bond, hydrophobic bonds on Arg164 amino acid residues, and hydrogen bonds on amino acid residues Tyr166, Lys95, Ala181. The result of the binding affinity value of ellagic acid compounds was -6.9 kcal / mol, greater than that of control compounds which showed that the bonds of ellagic acid compounds in NF-κB1 were not stronger and more stable than those of controls. However, in the visualization results there were similarities in amino acid residues Tyr166, Lys95, Ala181, Thr229, Arg164. This showed that ellagic acid compounds had a tethering position that was almost similar to control compounds whose mechanism of action was as an inhibitor of NF-κB1although only a few amino acids can interact in the binding site area. Therefore, it was possible that ellagic acid compounds had inhibitory activity in NF-κB1 even though their inhibitory activity was not as strong as that of control compounds.

Gallic acid compounds in NF-κB1 proteins can form van der waal's bonds with amino acid residues His108, Asn106, Gly104, Asn103, Asp209, Gln204, pi bond hydrophobic bonds with amino acid residues Thr102 and Met208, as well as hydrogen bonds formed in the amino acid residues Glu207. The binding affinity value of gallic acid compounds, which was greater than the control, was -5.9 kcal / mol, indicating that gallic acid compounds had a low potential as inhibitors of NF-κB1 proteins.

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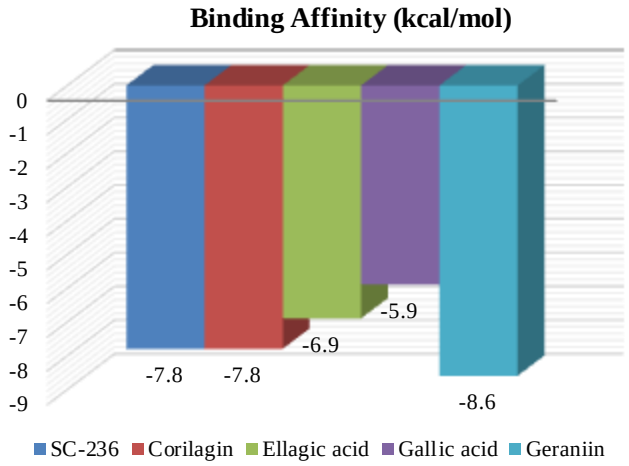

Figure 4: Bond affinity values result from docking of rambutan peel bioactive compounds with NF-κB1 receptors.

As for the visualization results, there was also no similarity of amino acid residues at the binding site with control compounds. Geraniin compounds in nf-κB1 proteins can form van der waal's bonds with amino acid residues Ser75, Pro51, Ala73, Gln53, Arg335, Glu341, Arg284, Tyr286, Pro345, alkyl bond hydrophobic bonds with amino acid residues Leu340, hydrophobic bonds of carbon hydrogen bonds with amino acid residues Lys52, and hydrogen bonds with amino acid residues Arg54, Thr342, Gln333, Glu344 were formed. Although geraniin had a smaller binding affinity value compared to the SC-236 control compound of -8.6 kcal / mol, in the visualization results there was no similarity of amino acid residues with controls at the binding site. The results of the visualization in three dimensions (3D) and two-dimensional (2D) can be seen in Figure 5. Based on the results obtained, corilagin and geraniin compounds had a fairly high potential for anti-inflammatory activity through a fairly high affinity binding ratio formed between corilagin and geraniin with NF-kB1 target proteins to affinity binding between SC-236 drug compounds with NF-kB1 target proteins. The compounds of ellagic acid and gallic acid had a low anti-inflammatory potential because the tethering of ellagic acid and gallic acid compounds with the NF-kB1 target protein was not stronger and more stable than the tethering of the SC-236 drug compound with the NF-kB1 target protein.

Table 2: Amino acid residues of NF-κB1 ligands-receptors

Number	Ligand-Macromolecular Names	Van der Waal's Interaction	Hydrophobic Bond			Hydrogen Bond
			Pi bond	Alkyl bond	Carbon Hydrogen bond	Residue/Distance
1.	Corilagin – NF-κB1	-	-	Pro71	Gly55 Phe56 His67	Arg59 (N – HN)/1,02022 Å Arg57 (N – HN)/1,02022 Å Asn250 (N – HN)/1,0204 Å
2.	Ellagic acid – NF-κB1	Gly185 Ile163 Gly184 Glu182 Gly183 Thr229 Phe228	Arg164	-	-	Tyr166 (N – HN)/1,02024 Å Lys95 (N – HN)/1,01989 Å Ala181 (N – HN)/1,01985 Å
3.	Gallic acid – NF-κB1	His108 Asn106 Gly104 Asn103 Asp209 Gln204	Thr102 Met208	-	-	Glu207 (N – HN)/ 1,01977 Å
4.	Geranin – NF-κB1	Ser75 Pro51 Ala73 Gln53 Arg335 Glu341 Arg284 Tyr286 Pro345	-	Leu340	Lys52	Arg54 (N – HN)/1,02017 Å Thr342 (N – HN)/1,01973 Å Gln333 (N – HN)/1,02001 Å Glu344 (N – HN)/1,02023 Å
5.	SC-236 – NF-κB1	-	-	Phe220 Tyr166	Thr229 Ala181	Lys95 (N – HN)/1,01989 Å Arg164 (N – HN)/ 1,01941 Å Glu160 (N – HN)/ 1,0205 Å

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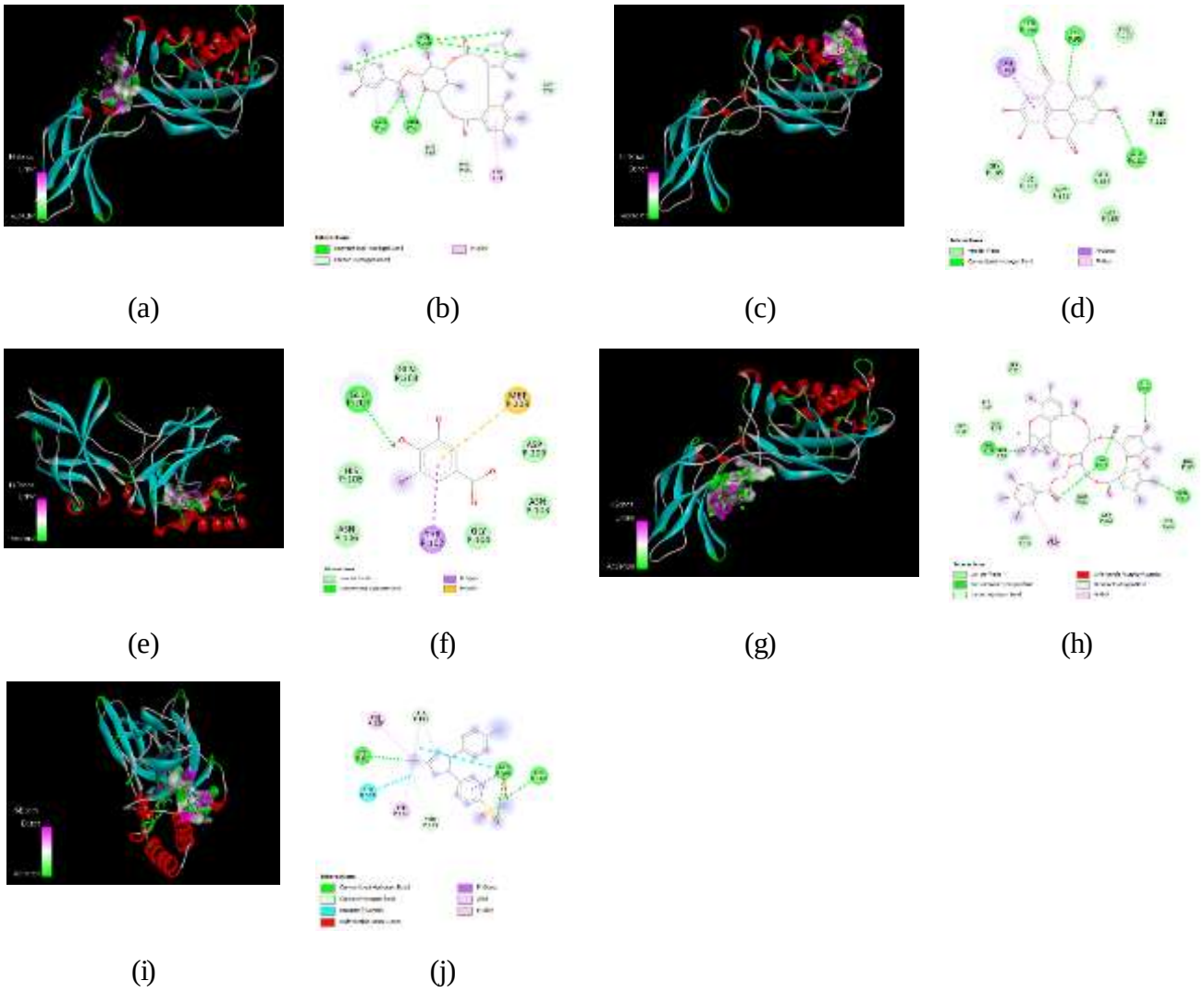

Figure 5: 2D Visualization & 3D (a) 3D Corilagin & NF-κB1 (b) 2D Corilagin & NF-κB1 (c) 3D Ellagic acid & NFκB1 (d) 2D Ellagic acid & NF-κB1 (e) 3D Gallic acid & NF-κB1 (f) 2D Gallic acid & NF-κB1 (g) 3D Geraniin & NF-κB1 (h) 2D Geraniin & NF-κB1 (i) 3D Control & NF-κB1 (j) 2D SC-236 & NF-κB1 (Control).

The anti-inflammatory potential of the test compound existed because it had an affinity to the NF-kB1 protein. The affinity that occurred between the test compounds to the NF-κB1 protein was able to inhibit transcriptions from pro-inflammatory genes induced by cigarette smoke condensate. As a result, expression increase of NF-κB regulated pro-inflammatory gene products can be suppressed, so as to prevent the occurrence of chronic inflammation associated with the initiation of lung cancer, chronic obstructive pulmonary disease (COPD), and asthma.

Conclusion

Based on the results of research that has been carried out, it can be concluded that corilagin and geraniin compounds have a high potential to be used as anti-inflammatory drug candidates through the NF-kB1 inhibition mechanism while ellagic acid and gallic acid compounds have a low potential if they are used as anti-inflammatory drug candidates through the NF-kB1 inhibition mechanism for the prevention of chronic inflammation induced by cigarette smoke.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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