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Preliminary Study of The Structure of Hesperidin and Neohesperidin as a Potential Inhibitor of SARS-CoV-2 by using The DFT Method

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Abstract

The discovery of drugs as COVID-19 antivirals has been intensively carried out by researchers as an effort to reduce the number of victims of the COVID-19 pandemic in 2020. The discovery of main protease (Mpro) which plays a role in protein replication and transcription helped researchers identify virus inhibitors. This research has examined the potency of the bioflavonoid compounds hesperidin and the flavanon glycosides neohesperidin and their structural stability as potential inhibitors of SARS-CoV-2 by DFT computation. The first method used is the calculation of density functional theory (DFT) on hesperidin and neohesperidin molecules to optimize the geometry of the molecular structure, analysis of frontier molecular orbitals (FMO), chemical reactivity index, and map electrostatic potential (MEP).

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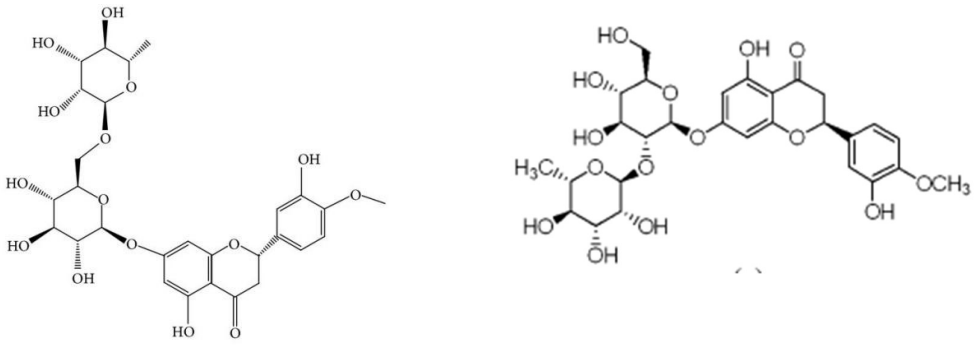
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory virus that attacks the respiratory system that caused the global COVID-19 pandemic in early 2020. Efforts to find drugs are still being carried out today. In this era, invention technology using simulation methods using computers is widely used because it does not require much time and the results are accurate. The crystal structure of SARS-CoV-2 that has been found can help identify inhibitors of the virus. The crystal structure of SARS-CoV-2 found from the results of X-ray diffraction is Mpro or 3Clpro. Mpro plays a role in protein replication and transcription. Inhibition carried out on Mpro or 3CLpro can cause death in the virus because the process of transcription and replication in the virus is disrupted. Humans do not have an enzyme that resembles Mpro so that the death of the virus will not have a toxic effect on the body (Zhang et al., 2020). Research on Mpro as a drug target has been carried out previously by Ullrich and Nitsche (2020). This study used the N3 compound as a ligand which was obtained through high-speed virtual drug screening. In another study, research by Jin, et al. (2020), the N3 ligand is able to inhibit Mpro in coronaviruses such as SARS-CoV and MERS-CoV.

In this study, the potency of the bioflavonoid compounds hesperidin and the flavanon glycosides neohesperidin and their interactions with Mpro compared with the N3 ligand will be investigated. Compounds included in the flavonoids include hesperidin and neohesperidin. Hesperidin is reported to have pharmacological activities such as anti-inflammatory, antioxidant, and antiviral (Kanaze et al., 2009). The chemical structure of the hesperidin and neohesperidin molecules is shown in Figure 1 (Srilatha et al., 2013; Lee et al., 2009).

Research on neohesperidin compounds conducted by Denaro, et al. (2020) in vitro showed that the neohesperidin compound could inhibit the induced injury to alveolar epithelial cells. Meanwhile Cheng, et al. (2021), Through docking simulations, Hesperidin (HD) and Hesperetin (HT) have demonstrated their potential to bind to two cellular proteins: transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2), which are required for cellular entry of SARS-CoV-2. Neohesperidin (NeoHD) is a flavanone glycoside found in citrus fruits. It is the 7-O-neohesperidose derivative of hesperetin (HT), which in turn is the 4'-methoxy derivative of eriodictyol. Hesperetin is a flavanone. Hesperetin's 7-O-glycoside, as a Hesperidin (HD), is a naturally occurring flavanon-glycoside, the main flavonoid in lemons and sweet oranges (Rouseff et al., 1987). Therefore, it is necessary to carry out further studies to determine the potential of the compounds hesperidin and neohesperidin as inhibitors SARS-CoV-2. Are the results obtained better or not when compared with the N3 ligand.

Research in drug discovery can be carried out in several ways, including DFT (Density Functional Theory), molecular docking and molecular dynamics with molecular mechanics studies. poisson-Boltzmann surface area. DFT works based on the Schrödinger equation. DFT used for geometry optimization to produce the lowest energy of the molecule so that during the simulation the molecule is in a stable state. The DFT simulation requires a basis set and functional type. In this study the basis set used is the 6-31G gaussian basis set and the functional type used is a combination of hybrid Becke three parameters and the Lee-Yang-Parr correlation function (B3LYP).



(a) (b)

Figure 1. Chemical structure of the molecule (a) Hesperidin and (b) Neohesperidin

METHOD

The DFT simulation was carried out as an optimization of the molecular structure. The simulation was carried out using GaussView 6.0 and Gaussian 09W software. The simulation was carried out using the 6-31G base set and the B3YLP functional type. The simulation is carried out in two steps, namely geometry optimization and data analysis. Simulation Methods, Conditions and Parameters.

The data used in this study were secondary data in the form of molecular structures obtained from PubChem ID: 10621 for hesperidin and ID: 442439 for neohesperidin. Accessed via the web address https://pubchem.ncbi.nlm.nih.gov/. PubChem is a website that provides a database of chemical molecular structures. The structure of the ligand used as a comparison was obtained from a docking study conducted by Yasin et al. (2020). Structure downloaded from PDB (Protein data bank) with ID: 6LU7. The ligand structure obtained is a complex protein, so it must be separated first to be simulated.

Preparation starts with downloading the required molecular structure and protein structure. 3D molecular structure obtained through PubChem with .mol format. The ligand structure of the N3 inhibitor was obtained from PDB ID: 6LU7. Inhibitor ligands are downloaded beforehand by separating the ligands and their receptors using the AutodockTools software.

RESULTS AND DISCUSSION

Geometry Optimization

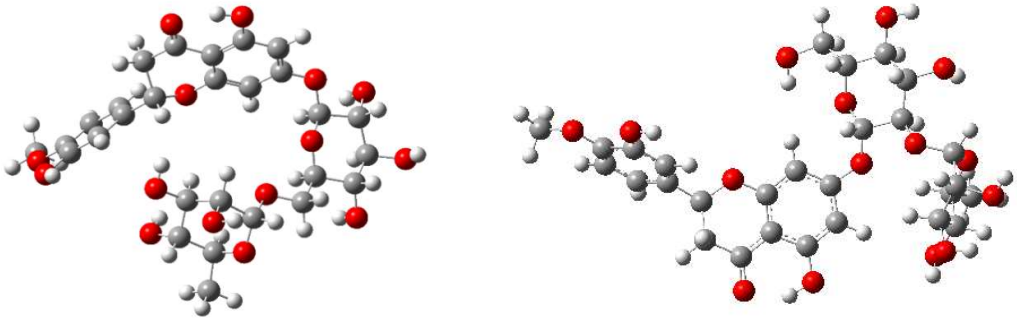
These results of the DFT simulation are geometry optimization and analysis of frontier molecular orbitals, electrostatic potentials map, and chemical reactivity index. Data from the results of geometric optimization carried out. From the data generated, hesperidin and neohesperidin have reached a state of convergence. The two compounds are hesperidin and neohesperidin, have a total negative energy. Energy optimization simulation results of geometry can be seen in Table 1.

Table 1 .The total energy of the optimization of the molecule

Compound	Total energy ($x10^6$ kJ/mol)
Hesperidin	-5.819313372
Neohesperidin	-5.819321251

The hesperidin molecule and the neohesperidin molecule in Figure 2 have an atomic number of 77 atoms and 81 bonds. The number of atoms and bonds did not change before and after optimization. The molecular weight of hesperidin before and after optimization did not change, namely 610.561 g/mol. The dipole moment before optimization is 3.565 and after optimization is 4.261. Molecular energy before and after optimization changes. The molecular energy before optimization is 0 kJ/mol, while the molecular energy after optimization is -5.819313372$x10^6$ kJ/mol.

Optimization results on the neohesperidin molecule also experienced several changes, namely the dipole moment and molecular energy. The dipole moment before optimization is 6.497 and after optimization is 2.047. The molecular weight after optimization is 0 kJ/mol and after optimization is -5.819321251 $x10^6$ kJ/mol.



(a) (b)

Figure 2. Molecular chemical structure optimization (a) Hesperidin and (b) Neohesperidin

Frontier Molecular Orbitals

The results of the analysis of the frontier molecular orbitals show the HOMO-LUMO side of both molecules, the Frontier Molecular Orbital is a parameter to explain the mechanism of organic reactions in the interaction between the ligand and its receptor protein. In the hesperidin molecule the HOMO side is shown on the benzene ring (C28-C36), while in the neohesperidin molecule on the functional group side -CH3OH, and -OH. The LUMO site on the hesperidin molecule is shown on the side of the benzene ring and the -CH3OH, and -OH functional groups. In the neohesperidin molecule the LUMO site is shown on the benzene ring (C28-C36).

The energy gap is the difference between E_{LUMO} and E_{HOMO}. The assessment of energy gaps helps characterize electron molecular transport and chemical reactivity. Molecules with low energy gaps are generally associated with high chemical reactivity and low molecular stability, and vice versa (Hegazy et al., 2013). The gap energy value in Figure 3 shows the reactivity of a molecule. The gap energy value produced by hesperidin (ΔE = 0.11798 eV) is smaller than that of neohesperidin (ΔE =

0.14438 eV). This shows that the hesperidin molecule is more reactive when compared to neohesperidin.

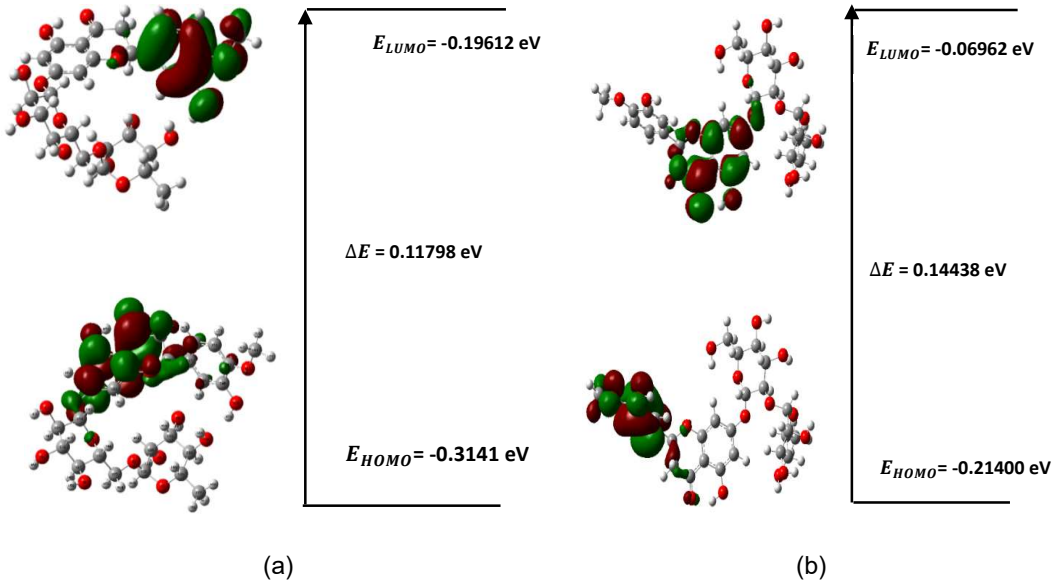


Figure 3. Atomic orbital composition of HOMO-LUMO (a) Hesperidin and (b) Neohesperidin

Chemical Reactivity Index

The chemical reactivity index shows the resistance of a chemical system to changes in the electronic distribution that occur within a molecule. The chemical reactivity indices calculated in this study were band gap (ΔE), electronegativity (X) , hardness (η), softness (σ), electrophilicity (ω) , and E_{LUMO}. E_{HOMO}, and E_{LUMO} shows predictions of ionization potential ($I = -E_{HOMO}$) and electron affinity ($A = -E_{LUMO}$). The results of the calculation of the chemical reactivity index resulting from molecular optimization are shown in Table 2.

Hardness and softness values Hardness or hardness index indicates the resistance of an atom to transfer charge while softness indicates the polarizability of electrons to describe the capacity of an atom to accept electrons. The hardness index value for hesperidin was 0.05899 eV, lower than that for neohesperidin, which was 0.07219 eV. Meanwhile, the hesperidin softness index value was 16.9520 eV^{-1}, higher than that of neohesperidin, 13.8523 eV^{-1}. This shows that the hesperidin molecule which is softness is easier to react and forms bonds so that it can be used as an inhibitor. This is in accordance with what was reported by Pearson (1988) that molecules that have a higher hardness index value tend to be difficult to react with the surface, conversely if the molecule has a higher softness index it tends to interact easily with the surface.

Furthermore, the HOMO (E_{HOMO}) energy value of the hesperidin molecule is -0.3141 eV, lower than that of the neohesperidin molecule -0.2140 eV. This shows that the neohesperidin molecule is more easily absorbed on the surface. Meanwhile, the LUMO (E_{LUMO}) energy of hesperidin is -0.19612 eV, higher than that of the neohesperidin molecule, which is -0.06962 eV. This shows that the ability of the neohesperidin acceptor is greater to accept lone pairs of electrons. By comparing the values of and of the two molecules, it can be seen that neohesperidin has a better inhibitory efficiency compared to hesperidin. This is in accordance with the statement submitted by Gece & Bilgiç (2017) that the higher the value and the lower the value indicates that the molecule has a high inhibition efficiency.

Gap band (ΔE) of hesperidin is 0.11798 eV and neohesperidin is 0.14438 eV. Hesperidin has a lower band gap (ΔE) value when compared to the neohesperidin molecule. This shows that hesperidin is adsorbed more effectively when compared to neohesperidin. This is in accordance with what was conveyed by Ebenso, et al., (2010) that the lower the band gap (ΔE) value of a molecule, the better the inhibition efficiency (Ebenso at al., 2010). ΔE The ionization potential of the hesperidin molecule is 0.3141 eV and the neohesperidin molecule is 0.2140 eV, larger than neohesperidin. The hesperidin molecule has a higher ionization potential value when compared to the neohesperidin molecule. The lower neohesperidin value indicates that neohesperidin is more reactive compared to hesperidin. This is in accordance with the statement of Chakraborty, et al., (2010) that a reactive molecule is a molecule that has a low ionization potential value (Chakraborty et al., 2010).

The next is electronegativity, the hesperidin molecule has an electronegativity value of 0.25511 eV and the neohesperidin molecule has 0.14438 eV. The hesperidin molecule has a greater electronegativity value when compared to the neohesperidin molecule. This shows that hesperidin has a higher electron-withdrawing ability when compared to neohesperidin. This is in accordance with what was reported by Udowo (2018) that molecules that have a large electronegativity value more easily attract electrons so that they are easier to adsorb (Udowo., 2018).

Electrophilicity value athesperidin is greater than the electrophilicity of the neohesperidin molecule. The electrophilicity value of the hesperidin molecule was 0.55163 eV and that of the neohesperidin molecule was 0.13929 eV. The high electrophilicity value indicates that the molecule tends to be difficult to bond. From these values it can be seen that the neohesperidin molecule tends to bind easily when compared to the hesperidin molecule.

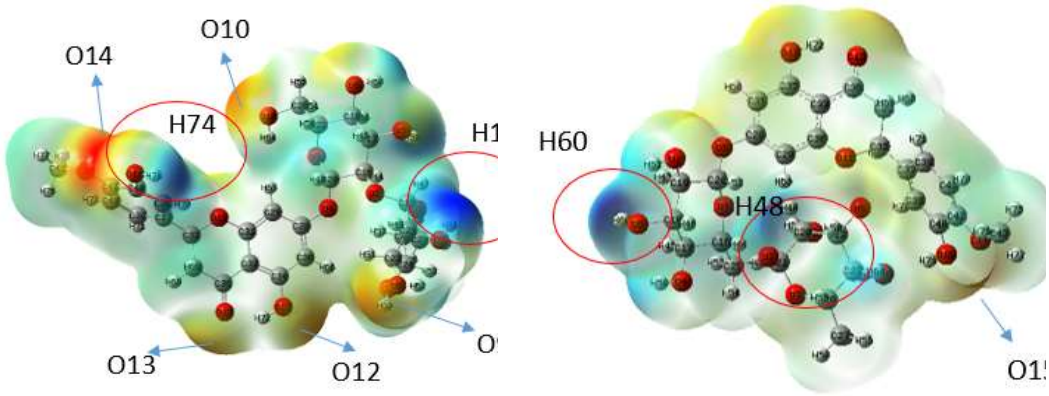
Table 2. Index of Chemical Reactivity of Hesperidin and Neohesperidin Compounds

Parameter	Hesperidin	Neohesperidin
E_{HOMO}(eV)	-0.3141	-0.2140
E_{LUMO}(eV)	-0.19612	-0.06962
band gaps (ΔE)	0.11798	0.14438
Electronegativity (eV)/ χ	0.25511	0.14181
Chemical potential (eV)/ μ	-0.25511	-0.14181
Hardness(eV)/ η	0.05899	0.07219
Softness(eV-1)/ σ	16.9520	13.8523
Electrophilicity (D2/eV)/ ω	0.55163	0.13929
Ionization Potential (eV)/ I	0.3141	0.2140
Electron Affinity (eV)/ A	0.19612	0.06962

Electrostatic Potential (MEP)

The Electrostatic Potential map shows the polarity of a molecule and the nature of the charges indicated by different colors. Electrophile and nucleophile indications are marked with red and blue polarity colors. The visualization results of the molecular polarity of hesperidin and neohesperidin are shown in Figure 4. The red color indicates that the side is an electrophilic side, that is, accepts electron pairs, while the blue color indicates a nucleophilic side that donates electron pairs. The results of the simulation show the nucleophile and nucleophile sides. The nucleophilic side of hesperidin is indicated by a blue surface on the H16 and H74 atoms, whereas in neohesperidin H60 and H48. The electrophile

sites on the hesperidin molecule are shown at O9, 010, 012, O13, and O14 atoms. Whereas in the neohesperidin molecule the electrophile side is indicated by the O15 atom. Based on the images generated from the simulation, hesperidin has more electrophile sides when compared to neohesperidin.



(a) (b)

Figure 4. Map of the electrostatic potential of the (a) Hesperidin and (b) Neohesperidin molecule

CONCLUSIONS

Based on the overall results of the DFT simulation analysis, it shows that hesperidin and neohesperidin still have the potential to be developed for drugs, especially as COVID-19 antivirals. DFT can be used to simulate the FOMO, Chemical Reactivity Index, and MEP of these potential antiviral drug candidates. The simulation results show that in general the neohesperidin molecule has the potential to be a better inhibitor or drug than Hesperidin. However, this research still needs to be continued with docking simulations and molecular dynamics to see its potential as an antiviral drug for COVID-19.

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