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In Silico Study of *Nigella sativa* L. on HMG-CoA Reductase Inhibition as an Anti-Dyslipidemic Agent

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Abstract
Dyslipidemia is a condition of lipid metabolism characterized by an imbalance of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels in the blood. This biosynthesis process can occur through a mechanism modulated by β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase. The most commonly used drug that works by inhibiting this enzyme is simvastatin. However, there are still significant side effects. In this work, *in silico* studies were performed on compounds from black cumin (*Nigella sativa* L.), namely alpha-pinene, p-cymene, nigellimine N-oxide, nigellidine, carvacrol, alpha-hederin, dithymoquinone, thymohydroquinone, thymoquinone, thymol, and nigellicine to predict their activity against HMG-CoA reductase as drug candidates in the treatment of dyslipidemia. The experiments were carried out using computational approaches, such as Lipinski's Rule of Five and ADMET prediction, pharmacophore modeling, and molecular docking simulation. Based on the molecular docking results, there are three compounds that exhibit strong interactions with amino acid residues on HMG-CoA reductase, which have the lowest binding energy values and inhibition constants: nigellicine (-6.84 kcal/mol, 9.71 μM), nigellidine (-6.44 kcal/mol, 19.16 μM), and nigellimine N-oxide (-6.14 kcal/mol, 31.34 μM). These three compounds have potential and can be modified to become candidates for antidyslipidemic drugs with a competitive inhibitor mechanism.

Keywords: antidyslipidemia, black cumin, HMG-CoA reductase, *Nigella sativa* L.

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Studi *In Silico Nigella sativa* L. terhadap Inhibisi HMG-CoA reductase sebagai Anti Dislipidemia

Abstrak
Dislipidemia adalah kondisi gangguan metabolisme lipid yang ditandai dengan ketidakseimbangan kadar kolesterol total, *low-density lipoprotein* (LDL), *high-density lipoprotein* (HDL), dan trigliserida dalam darah. Proses biosintesis ini dapat terjadi melalui mekanisme yang dimodulasi oleh enzim hidroksimetilglutaril-CoA (HMG-CoA) reduktase. Obat yang paling sering digunakan untuk menghambat enzim ini adalah simvastatin. Namun, masih terdapat efek samping yang signifikan. Dalam penelitian ini, studi *in silico* dilakukan pada senyawa dari biji jintan hitam (*Nigella sativa* L.), yaitu alfa-pinen, p-simen, nigellimine N-oxide, nigellidine, carvacrol, alfa-hederin, dithymoquinone, thymohydroquinone, thymoquinone, thymol, dan nigellicine untuk memprediksi aktivitasnya terhadap HMG-CoA reduktase sebagai kandidat obat dalam pengobatan dislipidemia. Eksperimen dilakukan menggunakan pendekatan komputasi, seperti aturan lima Lipinski dan prediksi ADMET, pemodelan farmakofor, dan simulasi penambatan molekuler. Berdasarkan simulasi penambatan molekuler, terdapat tiga senyawa yang menunjukkan interaksi kuat dengan residu asam amino pada HMG-CoA reduktase, yang memiliki nilai energi ikatan terendah dan konstanta inhibisi yaitu nigellicine (-6,84 kkal/mol, 9,71 μM), nigellidine (-6,44 kkal/mol, 19,16 μM), dan nigellimine N-oksida (-6,14 kkal/mol, 31,34 μM). Ketiga senyawa ini memiliki potensi dan dapat dimodifikasi untuk menjadi kandidat obat antidislipidemia dengan mekanisme penghambat secara kompetitif.

Kata Kunci: antidislipidemia, HMG-CoA reduktase, jintan hitam, *Nigella sativa* L.

1. Introduction

Dyslipidemia is a condition of lipid metabolism characterized by an imbalance of total cholesterol, LDL, HDL, and triglyceride levels in the blood. The disease is one of the ten leading causes of morbidity and mortality in Indonesia.[1] Based on data from the National Basic Health Research in 2018, 28.8% of the population in Indonesia over 15 years of age had abnormal total cholesterol levels, 3.4% of the population had very high LDL levels, 24.3% of the population had low HDL, and 0.8% of the population had very high triglyceride levels.[2] A lifestyle with a habit of consuming foods with high fat content, a lack of physical activity, smoking, and obesity can increase the risk of developing dyslipidemia.[3] Therefore, preventive efforts and the latest therapies are needed to reduce the prevalence rate.

The therapy used to regulate blood cholesterol levels necessitates the administration of cholesterol-lowering drugs. Various types of drugs can be used for this purpose, but the most common and often found in the market are drugs from the statin group, which include atorvastatin, lovastatin, pravastatin, and simvastatin.[4] However, the use of this therapy is limited due to its side effects that can cause myopathy, worsen kidney function to kidney failure, and hepatotoxicity.[5] The mechanism of action of the drug simvastatin works as an HMG-CoA reductase inhibitor that reduces cholesterol levels in the blood.[6]

The β-Hydroxy β-methylglutaryl-CoA or HMG-CoA reductase is an enzyme that functions to convert HMG-CoA into mevalonate, the main precursor in cholesterol biosynthesis, which is a rate-limiting enzyme in the mevalonate pathway. This enzyme activity increases due to the increased expression of SREBP-2, mediated by Sp1, especially when a high-fat diet is given, and is the therapeutic target of statin drugs.[7] HMG-CoA reductase plays a crucial role in regulating the synthesis of non-sterol isoprenoid derivatives and cholesterol. Regulation of this enzyme occurs through two mechanisms, namely short-term and long-term. Long-term regulation depends on the rate of gene transcription, while short-term regulation occurs when cellular energy levels are low and involves phosphorylation-dephosphorylation and proteolysis processes mediated by the endoplasmic reticulum (ER).[8] Certain compounds from natural materials can be developed into pharmaceutical agents with minimal side effects and intrinsic toxicity.[9] There are several medicinal plants in the treatment of dyslipidemia, such as cinnamon bark, chrysanthemum flowers, gardenia fruit, and mori leaves. However, these plants are rarely used in Indonesia as they are commonly used in China as medicinal and food plants.[10]

Black cumin (*Nigella sativa* L.) is a natural ingredient commonly used in the Middle East, Asia, and southern Europe as a traditional medicinal remedy. Black cumin exhibits various therapeutic activities, particularly in the area of antidyslipidemia, which can reduce total and LDL cholesterol levels while increasing HDL cholesterol levels.[11,12] Black cumin contains many chemical compounds, namely thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellicine, nigellimine N-oxide, nigellidine, and alpha-hederin.[13] The synergistic action of various components in black cumin mediates the lipid-lowering mechanism.

In silico methods, which involve computational modeling or simulation, are considered quite effective due to their fast processing times and low costs. *In silico* studies require a validated process to accurately identify potential interactions between ligand compounds and receptors. *In silico* studies are also helpful in identifying natural compounds that target specific proteins.[14] Until now, there has been no research on *in silico* examination of black cumin extract compounds against HMG-CoA reductase as an anti-dyslipidemia agent. This study was conducted on the black cumin plant using computational approaches, including Lipinski's rule and ADMET prediction, pharmacophore modeling, and molecular docking simulation. This study aims to examine the interaction and affinity of 11 selected bioactive compounds contained in black cumin, namely thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellicine, nigellimine N-oxide, nigellidine, alpha-pinene, p-cymene, and alpha-hederin, as well as simvastatin as a control compound against HMG-CoA reductase receptors, to determine the potential of these compounds as anti-dyslipidemia agents.

2. Materials and methods

2.1. Materials

This study was conducted on a laptop equipped with a Windows 11 64-bit operating system, an Intel Core i5-1135G7 CPU, and 8 GB of DDR4 RAM. Some software, including ChemDraw 49 and Chem3D 20.1.1, was used to create 2D and 3D ligand structures. LigandScout 4.4.5 was used for pharmacophore analysis. AutoDock 4.2.6, along with the GUI AutoDock Tools 1.5.7, were used for molecular docking. BIOVIA Discovery Studio Visualizer V21.1.0.20298 was used to visualize 3D structures and interactions between receptors and ligands.

The materials used include 3D structures of native ligand simvastatin acid (C25H40O6), the crystal structure of HMG-CoA reductase catalytic domain

in complex with compound 7g (PDB ID: 3CCW), reference compounds simvastatin, and all the tested bioactive compounds have been minimized in energy.

2.2. Methods

2.2.1. Lipinski's Rule of Five Prediction

Lipinski's Rule of Five (RO5) prediction was conducted by obtaining the canonical SMILES of both the reference and test compounds via the PubChem website (https://pubchem.ncbi.nlm.nih.gov/) and subsequently analyzed using the SwissADME website (http://www.swissadme.ch/). The parameters assessed included molecular weight, LogP, the number of hydrogen bond donors, and hydrogen bond acceptors.

2.2.2. ADMET Prediction

ADMET prediction was performed using the PreADMET website (https://preadmet.webservice.bmdrc.org/) by selecting both ADME Prediction and Toxicity Prediction modules. The .mol files of each compound were uploaded to generate ADMET values, including %HIA (human intestinal absorption), CaCo-2 permeability, PPB (plasma protein binding), BBB (blood-brain barrier penetration), Ames test, and carcinogenicity.

2.2.3. Pharmacophore Screening

An active and decoy compound database was constructed using the HMG-CoA reductase receptor, which was downloaded from the DUDE database (https://dude.docking.org/targets) with the ID 3CCW. A total of ten pharmacophore models were generated and validated. The active and decoy databases were uploaded by selecting the load screening database feature. The screening process was initiated by clicking the "Perform Screening" button. Receiver Operating Characteristic (ROC) curves were generated by selecting the plot function, and all resulting ROC images were saved. The best model was selected based on the highest Area Under the Curve (AUC) value, with an AUC greater than 0.5 considered acceptable for validation.

Pharmacophore screening of the test compound was conducted by uploading it to the screening perspective feature. The best pharmacophore model was transferred to the screening perspective, and a screening approach was selected from a ligand-based standpoint. After the process was completed, the hit compound was displayed along with its pharmacophore match score (fit score).

2.2.4. Preparation of Receptors and Test Compounds

The HMG-CoA reductase receptor protein with ID 3CCW was downloaded from the RCSB Protein Data Bank (www.rcsb.org). The receptor structure was imported into BIOVIA Discovery Studio software for ligand and receptor separation, then saved in .pdb format. The receptor and the test compound ligands were prepared using AutoDock Tools software. Hydrogen atoms and Kollman charges were added to the receptor, while the test compounds were processed with Gasteiger charges and torsion settings. The prepared files were saved in .pdbqt format.

2.2.5. Molecular Docking Validation

Molecular docking validation was performed using AutoDock Tools and AutoDock 4.2.6. The ligand and receptor files were loaded, grid and docking parameters were generated, and the configurations were saved in .dpf format. The root-mean-square deviation (RMSD) value was evaluated, with a threshold of 2 Å or less accepted for validation.

2.2.6. Molecular Docking

Molecular docking results were visualized in both 2D and 3D formats using AutoDock Tools and BIOVIA Discovery Studio Visualizer. The resulting visualizations were saved in .jpg format for further analysis.

3. Result

3.1. Lipinski's Rule of Five Prediction

The test results are listed in Table 1. There are 10 black cumin (*Nigella sativa* L.) compounds that have molecular weight <500 Da, hydrogen bond donor (<5) acceptor (<10), and 11 compounds have partition coefficient (LogP) <5, so that 10 compounds such as alpha-pinene, p-cymene, nigellimine N-oxide, nigellidine, carvacrol, alpha-hederin, dithymoquinone, thymoquinone, thymol, and nigellicine can be said to qualify the Lipinski's Rule of Five parameters so that they can be given oral administration.

3.2. ADMET Prediction

ADMET determination was carried out on 10 compounds that had fulfilled Lipinski's previous predictions, with the results listed in Table 2. In the absorption parameter, the % HIA was obtained with a good category in all test compounds, and the Caco-2 value with a moderate category. In the distribution parameter, of the 10 test compounds, only nigellimine N-oxide, and nigellicine had PPB values < 90% and none of the compounds were poor in penetrating the brain barrier. In terms of parameters, most of the test

Table 1. Lipinski's Rule of Five Prediction Results

No.	Compound Name	Molecular Weight	LogP (<5)	Hydrogen Bonding		Meet RO5 Criteria
				(<500 Da)	Acceptor (<10)	
1.	Alpha-pinene	136.2336	2.9987	0	0	Yes
2.	p-cymene	134.2177	3.1884	0	0	Yes
3.	Nigellimine N-oxide	219.2359	2.5939	0	3	Yes
4.	Nigellidine	294.3469	3.2294	1	4	Yes
5.	Carvacrol	150.2171	2.8240	1	1	Yes
6.	Alpha-hederin	750.9538	3.5211	7	12	No
7.	Dithymoquinone	328.4010	2.7134	0	4	Yes
8.	Thymohydroquinone	166.2164	2.5296	2	2	Yes
9.	Thymoquinone	164.2005	1.6669	0	2	Yes
10.	Thymol	150.2171	2.8240	1	1	Yes
11.	Nigellicine	246.2614	1.5550	1	5	Yes

compounds showed mutagenic properties, with the exception of alpha-hederin which was predicted to be a non-mutagenic agent, and carvacrol and thymol showed negative carcinogenic results in mice and rats while the other compounds showed mixed results.

3.3. Pharmacophore Screening

If the AUC-ROC value of the pharmacophore model is greater than 0.50, it can be considered valid.[15] Out of the 10 pharmacophore models, the best model is Model 1 with an AUC-ROC value of 1.00, as shown in Figure 1. Following this, a screening of test compounds was conducted, resulting in the identification of 3 compounds namely thymohydroquinone, nigellicine, and carvacrol. Their visualization is shown in Figure 2.

3.4. Molecular Docking Validation

Validation showed that the RMSD of the dimeric form of HMG-CoA reductase, subunits of chains C and D, was 1.861 Å. This result indicates that the molecular docking method met the validation criteria.

3.5. Molecular Docking

The molecular docking results are shown in Table 3. The binding energies and inhibition constants of simvastatin and the test compounds were obtained through Autodock. Molecular docking results are available in Table 3 and Figure 3.

4. Discussion

The Lipinski's Rule of Five is a rule used to evaluate whether a chemical compound with certain pharmacological or biological activities can be used as an oral drug preparation in humans.[16] Some conditions become the parameters of the Lipinski's Rule of Five, namely molecular weight < 500 Da, logP < 5, hydrogen bond donor < 5, and hydrogen bond acceptor < 10.[17] In the molecular weight parameter, 10 of the 11 black cumin plant compounds (*Nigella sativa* L.) such as alpha-pinene, p-cymene, nigellimine N-oxide,

Table 2. ADMET Prediction Results

No.	Compound Name	Absorption		Distribution		Mutagens	Toxicity	
							Carcinogens	
		HIA (%)	Caco-2 (nm/sec)	PPB (%)	BBB		Mice	Rat
1.	Alpha-pinene	100	23.63	100	5.53	Mutagen	-	+
2.	p-cymene	100	23.43	100	4.96	Mutagen	+	-
3.	Nigellimine N-oxide	98.15	10.60	42.79	1.04	Mutagen	-	+
4.	Nigellidine	95.71	46.51	93.01	0.64	Mutagen	+	-
5.	Carvacrol	100	38.01	100	6.38	Mutagen	-	-
6.	Alpha-hederin	59.91	20.67	87.67	0.09	Non-mutagen	+	-
7.	Dithymoquinone	98.32	19.66	97.96	1.80	Mutagen	+	+
8.	Thymohydroquinone	89.19	20.39	100	4.97	Mutagen	-	+
9.	Thymoquinone	99.28	23.03	100	1.78	Mutagen	+	+
10.	Thymol	100	38.01	100	6.38	Mutagen	-	-
11.	Nigellicine	96.68	20.69	71.86	0.63	Mutagen	+	-

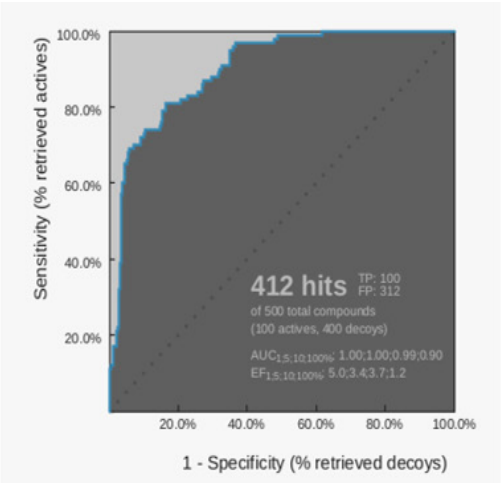

Figure 1. AUC-ROC Model 1 Pharmacophore

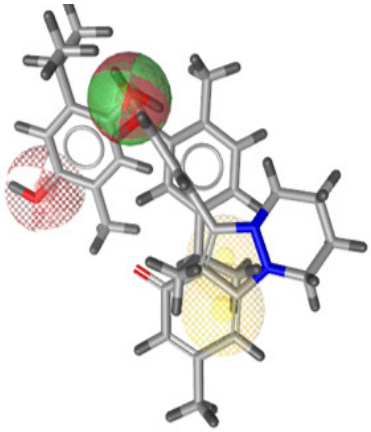

Figure 2. Pharmacophore Visualization of thymohydroquinone, nigellicine, and carvacrol.

nigellidine, carvacrol, alpha-hederin, dithymoquinone, thymoquinone, thymol, and nigellicine have a molecular weight <500 Dalton, which means that the distribution process to penetrate the cell membrane through the diffusion process is good because the smaller the molecular weight the easier it is to penetrate the cell membrane.[18] The compound also has high permeability and distribution because it has donor hydrogen bonds <5 and acceptor hydrogen bonds <10.[19] An increased number of hydrogen bond donors and acceptors is associated with higher energy requirements for absorption, whereas a lower number promotes more efficient membrane permeability.[20] While in the partition coefficient parameter (LogP), all compounds, including alpha-hederin, have hydrophilic properties that enable the compound to easily penetrate the lipid bilayer membrane and are not strongly bound to the membrane, so that it is easy to recognize the target and has no toxic effects.[21]

In this study, the predictions made were Intestinal Absorption (HIA) and Caco-2 cell permeability as absorption parameters, Plasma Protein Binding (PPB) and blood-brain barrier (BBB) as distribution parameters, and Ames Test and carcinogenicity as toxicity parameters. This prediction was made on 10 compounds that fulfill the Lipinski's Rule of Five. Human Intestinal Absorption (HIA) predicts the absorption rate in the human gut with 70–100% indicating good absorption.[22] Meanwhile, Caco-2 is used to predict the permeability of Caco-2 cells with multiple transportation routes through the intestinal epithelium.[23] Based on the test results, all test compounds are in the range of 70-100% so that they have a % HIA with a good category. For the Caco-2 parameter, all compounds are categorized as having medium permeability, which falls within the range of 4-70 nm/s.

The PPB parameter predicts compounds that can be bound to blood plasma, where the PPB value is greater than 90%.[22] Based on the test results eight compounds can be bound to blood plasma where the PPB value is> 90%. Blood-brain barrier predicts the ability of compounds to cross the blood-brain barrier.

Table 3. Molecular Docking Results

No.	Compound Name	Cluster	Binding Energy (kcal/mol)	Konstanta Inhibition Ki (μM)	Interaction with Amino Acids		
					Hydrogen Bonding	Van der Waals Bonding	Miscellaneous
1.	Nigellicine	2	-6.84	9.71	-4.80	-7.44	-2.63
2.	Nigellidine	3	-6.44	19.16	-6.95	-7.03	-0.08
3.	Nigellimine N-oxide	4	-6.14	31.34	-6.2	-7.04	-0.84
4.	Dithymoquinone	3	-6.11	33.16	-6.35	-6.71	-0.36
5.	Simvastatin Acid	8	-5.43	104.62	-10.87	-13.78	-2.92
6.	Thymoquinone	1	-5.13	173.09	-5.11	-5.43	-0.32
7.	Carvacrol	3	-5.09	184.65	-5.24	-5.69	-0.45
8.	Thymol	4	-4.88	266.27	-5.17	-5.47	-0.31
9.	Thymohydroquinone	4	-4.85	278.66	-5.15	-5.74	-0.60
10.	Alpha-pinene	2	-4.53	476.68	-4.52	-4.53	-0.01
11.	p-cymene	2	-4.03	1100	-4.33	-4.33	-0.00

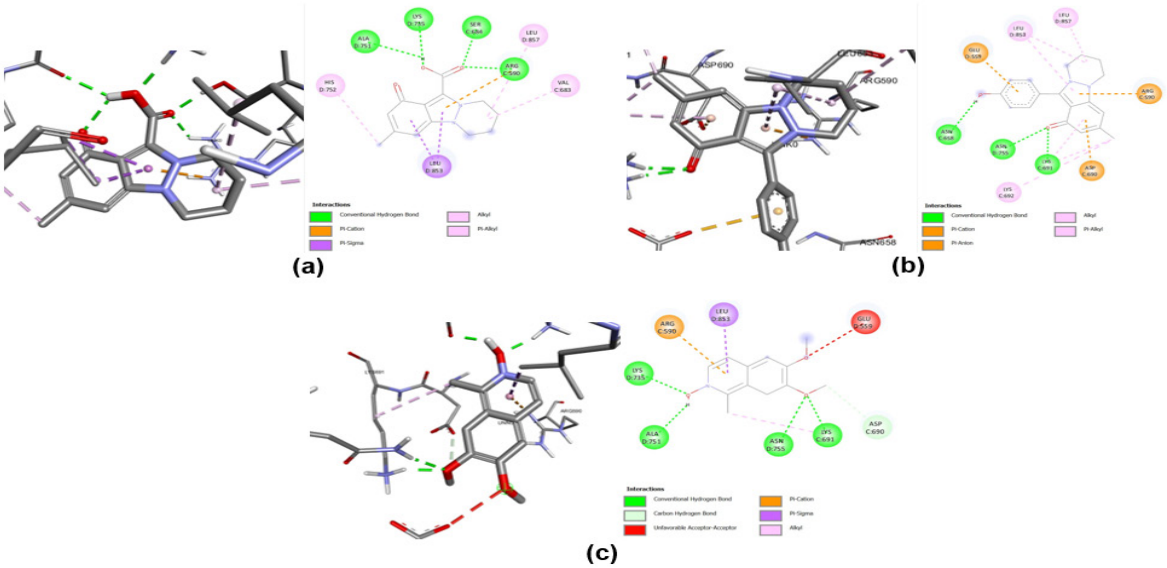

Figure 3. Visualization of Molecular Docking Simulation of (a) Nigellicine, (b) Nigellidine, and (c) Nigellimine N-oxide.

Drugs that are not neuroactive do not cross the blood-brain barrier to avoid psychotropic side effects.[24] Nigellidine, nigellimine N-oxide, dithymoquinone, and thymoquinone have a low ability to pass through the blood-brain barrier, making them suitable as targets for dyslipidemia therapy.

Toxicity prediction helps identify safe drug candidates, as over 30% fail due to toxicity.[25] The Ames test is used to predict whether the compound under study is a mutagen. Meanwhile, carcinogens are substances that can cause the development of malignant tumors or cancerous genetic changes.[26] Based on the results of the study, compounds with ideal pharmacokinetics include nigellidine, thymol, carvacrol, thymoquinone, and dithymoquinone.

A pharmacophore is a part of the structure of a drug compound that triggers a biological response and ensures interaction with a biological target. The results are hydrophobic bonds, hydrogen bonds, aromatics, and positive and negative ionization.[27] This pharmacophore modeling and screening have the aim of knowing which functional groups have interactions with the target receptor so that modifications can be made to other functional groups to increase or improve the activity of a compound that is a drug candidate, as well as knowing which compounds have activity similar to their natural ligands.[28]

Based on the validation results by 10 groups of 10 compounds in Figure 1, the model showed excellent ability of predicting with an AUC value near 1.0, and it was able to recognize all of the 100 true active compounds in the test set. This indicated that the model was robust and predictive for the screening of HMG-CoA Reductase inhibitors. According to the literature, an AUC value of nearly 1 is considered a good indicator, so Model 1 is selected as the best compound for this screening. One of the top hits from the screening is shown in Figure 2. Although it is a distinct score from the known potent drug, its close alignment further strongly suggests that this hit compound does, in fact, possess the fundamental molecular criteria for occupancy. The compound is envisioned to satisfy all three essential pharmacophoric points, as depicted: a hydrophobic region by its isopropyl group, a hydrogen bond acceptor on the phenolic oxygen, and a positively ionizable center on the heterocyclic nitrogen. This well-fitted implies the promising potential of this newly led compound for further development. Although they had lower scores than the potent drug Simvastatin, their high score strongly confirms that they possess these major molecular features that are required to bind to the HMG-CoA Reductase at the active site.[29]

Molecular docking is a computational method used to describe the interaction of ligands and receptors or proteins.[29] Molecular docking began with validation of the receptor's natural ligand, the HMG-CoA reductase receptor, with its native ligand, simvastatin. From the validation of natural ligands carried out, the results with the lowest bond energy are obtained at -5.43 kcal/mol. The validation parameters for molecular docking results are determined by the Root Mean Square Deviation (RMSD) value. This parameter indicates that a smaller RMSD value corresponds to a more accurate calculation result, resulting from a more minor error or deviation in the calculation. Conversely, a larger RMSD value means a larger deviation in the calculation. The expected RMSD value is less than 2 Å.[26] The RMSD value of 1.861 Å (<2 Å) indicates a similarity between the redocked ligand and the original ligand, making the molecular docking method suitable

for use on standard and test compounds. An RMSD value of <2 Å suggests that AutoDock's parameters, scoring functions, and search algorithms are working correctly. A high RMSD, on the other hand, (over 3 Å, or even 2 Å in some situations), could mean that the docking process was not able to replicate the binding pose precisely and is consequently seen as less reliable.[31]

Furthermore, testing was conducted on 10 compounds that had been selected, and the results are presented in Table 3. The smaller Gibbs free energy indicates that the bond between the ligand and the receptor is more stable. The inhibition constant is used to determine how the ligand inhibits receptor activity. The smaller inhibition constant indicates that the ligand concentration inhibits the smaller receptor activity.[32] Based on the test, it is known that Nigellicine has the smallest Gibbs free energy value and inhibition constant with visualization as in Figure 3 where the amino acid residue interacts with the HMG-CoA reductase receptor to form a conventional hydrogen bond in ALA D:751, LYS D:735, SER C:684, and ARG C:590; pi-cation bond on ARG C:590; pi-sigma bond on LEU D:853; alkyl bonds at HIS D: 752, LEU D:854, and VAL C:683. Therefore, nigellicine was selected as the best compound out of 10 compounds that were considered to have the most potential as antidyslipidemic drug candidates because nigellicine interacts with the active site of HMG-CoA reductase.

5. Conclusion

Based on in silico studies and analyses conducted through Lipinski's Rule of Five prediction tests, ADME-Tox, pharmacophore screening, and molecular docking of 10 black cumin bioactive compounds, it is known that molecularly, nigellicine, nigellidine, and nigellimine N-oxide have potential and can be modified to become candidates for antidyslipidemic drugs with a competitive inhibitor mechanism, based on their interactions with amino acid residues in HMG-CoA reductase, exhibiting the lowest binding energy values and inhibition constants. Further studies can be conducted by analyzing the interactions of nigellicine, nigellidine, and nigellimine N-oxide with the HMG-CoA reductase receptor.

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Conflict of Interest

The authors declare no conflicts of interest.

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