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Molecular Docking Study of *Nigella sativa* Bioactive Compound as E6 Inhibitor Against Human Papillomavirus (HPV) Infection

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ABSTRACT

HPV can trigger cancer cases in the laryngeal, lung, oral, and anogenital. Classification of HPV based on the ability to trigger cancer, HPV is divided into two types consisting of high risk (HR) and low risk (LR). HPV-6 and HPV-11 are low-risk types or only cause precancerous lesions or warts. In the case of lesion progression to intraepithelial malignancies triggered by infection with HPV-16 and HPV-18 types. Previous studies used E6 to target antiviral drug design, the drug works by inhibiting E6 activity and preventing p53 degradation. *Nigella sativa* is widely used as traditional medicine by

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people around the world for generations. This research is important because it is to identify the molecular mechanism of chemical compounds from *Nigella sativa* as a candidate agent for high-risk HPV type of antiviral through inhibition of E6 activity. The inhibition of the E6-p53 complex by the Longifolene compound from *Nigella sativa* causes a decrease in E6 activity and an increase in p53 protein activity, then normal cells will not develop into cancer. Inhibition of the E6-p53 complex will also trigger apoptosis in cells that have been infected with HPV.

Keywords: Bioactive, HPV, Inhibitor, Molecular Docking, *Nigella sativa*

INTRODUCTION

Human Papillomavirus is the causative agent of multiple epithelial lesions and cancer. There are currently about 100 subtypes worldwide[1]. HPV can trigger pathogenesis in humans through the initiation of increased proliferation and immortalization of host cells through the activation of specific oncoproteins. HPV tropism is epithelial cells and basal stem cells[2,3]. HPV is composed of dsDNA and is non-enveloped, the virion has a capsid that is encoded by the L1 & L2 genes, the gene is expressed late[4]. Infectious protein from HPV is activated through early protein (E) consisting of E2, E5, E6, & E7. HPV early protein plays a role in triggering viral replication, protein synthesis, assembly, and increased host cell proliferation[5,6]. Classification of HPV based on the ability to trigger cancer, HPV is divided into two types consisting of high risk (HR) and low risk (LR)[7,8].

HPV can trigger cancer cases in the laryngeal, lung, oral, and anogenital. HPV-6 and HPV-11 are low-risk types or only cause precancerous lesions or warts[9,10]. In the case of lesion progression to intraepithelial malignancies triggered by infection with HPV-16 and HPV-18 types. HPV has specific oncoproteins consisting of E6 & E7, which act to inhibit tumor suppressors such as p53 & pRb, it affects the cell cycle, then triggers cellular transformation into cancer cells[11,12]. E6 plays a crucial role in triggering the inhibitory activity and degradation of p53. E6 will recruit ubiquitin at the E6-p53 complex, it can trigger degradation via the ubiquitin proteasome[13,14]. Previous studies used E6 to target antiviral drug design, the drug works by inhibiting E6 activity and preventing p53 degradation.

Nigella sativa is widely used as traditional medicine by people around the world for generations[15,16]. These medicinal plants also play a therapeutic role in cases of diseases such as diabetes, cancer, and others[17,18]. Other potentials such as antibacterial and antiprotozoa. *Nigella sativa* has activity as an antioxidant, immunomodulator, and a few are used for antiviral[19,20]. This research is important because it is to identify the molecular mechanism of chemical compounds from *Nigella sativa* as a candidate agent for high-risk HPV type of antiviral through inhibition of E6 activity.

METHODS

Ligand-protein retrieval

The chemical compounds of *Nigella sativa* are Thymol (CID 6989), Phenol, 3-(1,1-dimethylethyl)-4-methoxy- (CID 6932), Eicosanoic acid (CID 10467), p-tert-Butyl catechol (CID 7381), & Longifolene (CID 289151), Canonical SMILE, molecular weight, and 3D structures in sdf files were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The target in this study was E6 HPV-16 (PDB ID: 4XR8) obtained from the RCSB PDB database (https://www.rcsb.org/) with pdb files[21,22].

Energy minimization and 3D structure sterilization

The sdf file must be converted to pdb via OpenBabel v2.4.1 software. to obtain a pdb file, the process of changing the format to increase ligand flexibility through energy minimization method, then water molecules and contaminant ligands on the target protein are removed through PyMol v2.5 software to obtain maximum binding energy during docking simulations[23,24,25].

Molecular docking simulation

Molecular docking simulation in this study aims to identify compounds from *Nigella sativa* as inhibitors of HPV-16 E6 protein activity. The simulation was carried out using PyRx v0.9.9 software with an autogrid covering the entire surface of target. The activity level of the query compound refers to the binding affinity score formed, the more negative it is, the stronger the possibility of ligand binding to the specific domain of the target protein. The docked molecular complexes are displayed on sticks, cartoons, and transparent surfaces through PyMol v2.5 software through the structural selection method[26,27,28].

Ligand-protein Interaction

Weak bonds play a role in ligands to produce an activity response to proteins. The ligand-protein interactions formed are weak bonds, weak bonds such as hydrogen, electrostatic, alkyl, van der Waals, and hydrophobic. The Discovery Studio 2016 software version was used in this study to identify the weak bonds formed in molecular complexes[29].

Structural Visualization

Molecular visualization of the ligand-protein complex was carried out using PyMol v2.5 software through staining and structural selection methods. The 3D structure shown consists of cartoons, surfaces, and sticks, staining is done on the protein constituent chains[30].

RESULT AND DISCUSSION

Revealing of inhibitor molecular mechanism from *Nigella sativa* compound

Nigella sativa in people's lives around the world is used for traditional medicine such as anti-inflammatory, antiviral, preventing free radicals, and others[31]. *Nigella sativa* was identified to have chemical compounds consisting of Thymol, Phenol, 3-(1,1-dimethylethyl)-4-methoxy-, Eicosanoic acid, p-tert-Butyl catechol, & Longifolene (Table 1). This study used a chemical compound from *Nigella sativa* to identify candidate antiviral drugs against HPV by inhibiting the activity of oncoprotein E6 by molecular docking simulation with autogrid positions are center (Å) X: -54.007 Y: -3.836 Z: -14.773 dimensions (Å) X: 66.209 Y: 50.535 Z: 54.869.

Table 1. *Nigella sativa* chemical compound from PubChem

Compound	CID	Formula	SMILE Canonical
Thymol	6989	$C_{10}H_{14}O$	CC1=CC(=C(C=C1)C(C)C)O
Phenol, 3-(1,1-dimethylethyl)-4-methoxy-	6932	$C_{11}H_{16}O2$	C11H16O2 CC(C)(C)C1=C(C=CC(=C1)O)OC
Eicosanoic acid	10467	$C_{20}H_{40}O_2$	CCCCCCCCCCCCCCCCCCCC(=O)O
p-tert-Butyl catechol	7381	$C_{10}H_{14}O_2$	CC(C)(C)C1=CC(=C(C=C1)O)O
Longifolene	289151	$C_{15}H_{24}$	CC1(CCCC2(C3C1C(C2=C)CC3)C)C

Longifolene has a binding affinity of -6.4 kcal/mol more negative than other compounds when it binds to E6 protein (Table 2), Longifolene is predicted to inhibit the activity of E6 protein in HPV because it has more negative binding than other compounds. The molecular docking simulation aims to determine the activity of the ligand binding on the protein domain by referring to the binding affinity value. The binding affinity value indicates the inhibitory ability of a ligand on the activity of the target protein[32]. Visualization of docking results is displayed through cartoons structure and sticks with selected coloring (Figure 1).

Table 2. The comparison of compound binding affinity

Compound	Molecular Weight (g/mol)	Minimize Energy (kcal/mol)	Binding Affinity (kcal/mol)
Thymol	150.22	+120.83	-5.4
Phenol, 3-(1,1-dimethylethyl)-4-methoxy-	180.24	+247.37	-5.1
Eicosanoic acid	312.5	+3394.99	-4.7
p-tert-Butyl catechol	166.22	+106.31	-5.6
Longifolene	204.35	+534.45	-6.4

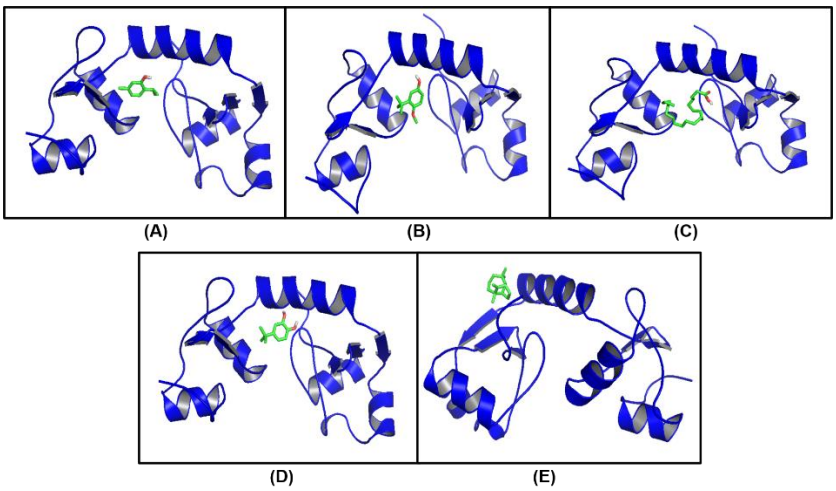

Figure 1. 3D Visualization from the docking results. (A) E6_Thymol (B) E6_Phenol, 3-(1,1-dimethylethyl)-4-methoxy- (C) E6_Eicosanoic acid (D) E6_p-tert-Butyl catechol (E) E6_Longifolene.

Molecular interaction at E6 protein

Chemical bond interactions in molecular complexes are identified to determine the type of bond and position[33,35]. All ligands have the same interaction position at Leu74, Tyr39, Val60, Val38, Phe52, Gln114, Val69, and Leu57, this position allows them to act as potential domains to lead inhibitory activity at E6 (Table 2). Weak bond interactions such as van der Waals, hydrogen, and alkyl are also formed in all ligands, Longifolene has more hydrogen bond interactions than other compounds and this can strengthen the prediction that Longifolene can act as a good drug candidate. Weak bond interactions consisting of hydrogen, hydrophobic, and alkyl can play a role in triggering the response of biological activity on the target protein[36,37]. The number of hydrogen bonds can be used as an indicator of the stability of a drug candidate molecule[38,39]. Thus, Longifolene is predicted to become a drug molecule because it can affect the activity of E6 protein through weak bonds and has the highest number of hydrogen bonds.

Table 2. Chemical interaction on E6 pocket binding domain

Compounds	Molecular Interaction
Longifolene	**van der Waals**: Val38, Val60, Ala68, Leu74, Tyr39, Gln114, Leu107, Phe52 **Hydrogen**: Tyr77, Cys58 **Alkyl**: Val69, Leu57
Phenol, 3-(1,1-dimethylethyl)-4-methoxy-	**van der Waals**: Phe52, Ser81, Tyr77, Gln114, Val60 **Alkyl**: Leu57, Val38, Leu74, Tyr39, Val69,
Eicosanoic acid	**van der Waals**: Tyr39, Ala68, Gln114, **Alkyl**: Val69, Val60, Val38, Phe52, Leu74, Leu57
p-tert-Butyl catechol	**van der Waals**: Ala68, Gln114, Arg109, Tyr39 **Alkyl**: Leu57, Val69, Val38, Val60, Phe52, Leu74, Cys58
Thymol	**van der Waals**: Phe52, Ala68, Tyr39, Gln114 **Alkyl**: Val60, Val69, Val38, Leu74, Leu57, Cys58,

Nigella sativa is an HPV antiviral candidate to prevent the development of cervical cancer through the binding of Longifolene to the E6 domain. Longifolene compounds can produce a more negative binding affinity than others and produce weak binding interactions to trigger an E6 inhibitor response through the Leu74, Tyr39, Val60, Val38, Phe52, Gln114, Val69, and Leu57 domains. The inhibition of the E6-p53 complex by the Longifolene compound causes a decrease in E6 activity and an increase in p53 protein activity, then normal cells will not develop into cancer[40]. Inhibition of the E6-p53 complex will also trigger apoptosis in cells that have been infected with HPV.

CONCLUSION

Nigella sativa can act as an antiviral through the binding activity of Longifolene compounds in preventing the E6-p53 complex through the specific domains the Leu74, Tyr39, Val60, Val38, Phe52, Gln114, Val69, and Leu57 through weak bond interactions and are stable because Longifolene have a large number of hydrogen bonds. We recommend the E6-binding domain for further research as a target for HPV drug design and the results of this study are yet to be verified through wet lab testing.

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