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Structure-Based Virtual Screening of *Nigella sativa* Compounds as Potential Anti-Lung Cancer Agents Targeting PI3Kα

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Abstract

Background: Lung cancer (LC) is one of the deadliest tumors. Hyperactivation of phosphatidylinositol 3-kinase (PI3K) has been linked to cancer etiology.

Methods: This study computationally screens the *Nigella sativa* compounds and their interactions with PI3Kα to identify potential therapeutic agents for LC. Copanlisib was chosen as the positive control for virtual screening. The LOTUS database was used to produce a library of 132 compounds that represent bioactive components of *N. sativa*. Molecular properties and molecular descriptors of *N. sativa* compounds were obtained from the LOTUS database.

Results: Compounds were ranked based on their binding energy to PI3Kα and interactions with key residues in the PI3Kα binding pocket. The screening identified five compounds as top hits: LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588, which had stronger binding energy than the control Copanlisib. LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 had binding energies of -9.8, -9.6, -9.5, -9.1, and -9.0 kcal/mol, respectively, while the Copanlisib (control) had a binding energy of -8.6 kcal/mol. These compounds interacted with active site residues of PI3Kα. In addition, these compounds have good druglike properties.

Conclusion: The compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 can be used as PI3Kα inhibitors to treat the LC. However, further experimental studies are warranted to validate these compounds as PI3Kα inhibitors.

Introduction

One of the deadliest tumors is lung cancer (LC), which is often detected at an advanced stage because it progresses silently [1,2]. There are two types of LC: primary LC, which begins in the lungs, and secondary LC, which spreads to other body parts. There are two additional classifications for primary LC. The most frequent kind is non-small cell lung cancer (NSCLC) accounting for more than 87 percent of cases. Squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma are all subtypes [3]. Small cell LC is less prevalent than NSCLC and develops more rapidly [4,5].

Alterations in the PI3K/Akt pathway cause uncontrolled cell proliferation. Due to resistance and the negative effects of radiation and chemotherapy, inhibitors targeting this pathway must be developed [6,7]. Phosphoinositide 3-kinases (PI3Ks), which regulate biological activities, are implicated in the PI3K/Akt signaling pathway, which is frequently detected in cancer. PI3Ks are classified into four categories (I–IV) [8-10]. The dysregulation of PI3Ks caused by phosphorylation enhances carcinogenic signaling, emphasizing the need for new enzyme inhibitors [10].

The introduction of computer-aided drug design (CADD) revolutionized drug development [11]. CADD speeds up the design process and increases the accuracy of therapeutic development by simulating and anticipating drug-target interactions, which frequently involve proteins or DNA, using algorithms [12]. The purpose of this study was to identify potential natural PI3Kα inhibitors by virtually screening *Nigella sativa* compounds against PI3Kα.

Methods

Protein preparation

Protein data bank was used to retrieve the 3D structure of PI3Kα (PDB ID: 4JPS). The heteroatoms were removed, and PI3Kα structure was saved in .pdb form.

Nigella sativa compound library preparation

On hundred thirty-two compounds of *N. sativa* were obtained from the LOTUS database. These compounds were first downloaded in sdf format, then energy minimized, and finally converted to pdbqt format. The control Copanlisib (PubChem CID: 135565596) was retrieved from the PubChem database.

Virtual screening

Structure-based virtual screening (VS) docks a group of compounds into the binding site using the biological target's 3D structure. Based on the projected binding energy, a subset of these compounds is selected for further biological analysis [13]. PyRx was used to screen the library of *N. sativa* compounds against PI3Kα. The Discovery Studio visualizer was used to study the interaction between the compound and PI3Kα.

Molecular Properties and Molecular Descriptors

Molecular properties as well as descriptors of *N. sativa* compounds were obtained from the LOTUS database.

Results

To identify a potential PI3Kα inhibitor, docking-based VS was carried out using AutoDock Vina, which was included with the PyRx tool. Compounds were ranked based on their binding energy to PI3K and interactions with key residues in the PI3Kα binding pocket. The screening identified five compounds as top hits: LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588, which had stronger binding energy than the control Copanlisib. The binding energies of the compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 were -9.8, -9.6, -9.5, -9.1, and -9.0 kcal/mol, respectively, whereas the control Copanlisib had a binding energy of -8.6 kcal/mol. The visualization of these 5 compounds alongside Copanlisib revealed that they bind in the same binding pocket of PI3Kα as Copanlisib (Figure 1).

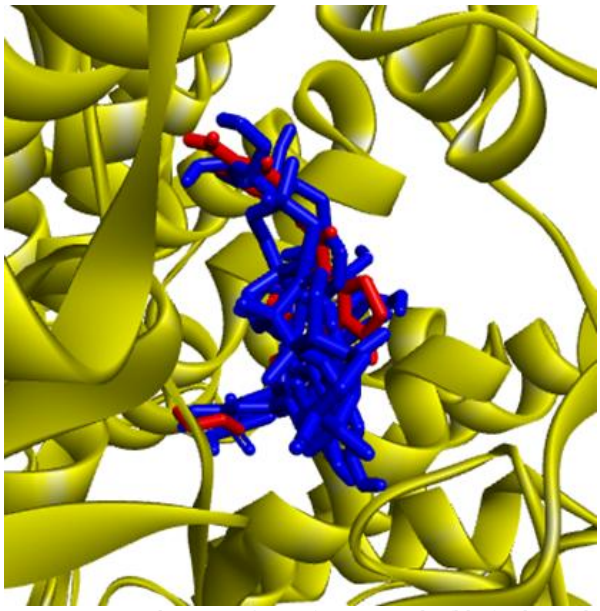

Figure 1: Visualization of top 5 compounds (blue) alongside Copanlisib (red) in the binding pocket of PI3Kα.

The interaction analysis of the compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 with PI3Kα showed that these compounds interacted with several residues of PI3Kα. LTS0117717 interacted with Pro835, Arg818, Gln928, Leu834, Glu849, Val851, Phe794, Arg852, Asn853, Lys924, Arg281, Arg832, Ser275, Leu279, Met278, and Glu821 residues of PI3Kα (Figure 2); while Glu821, Gln825, Met278, Lys271, Arg818, Asn756, Leu755, Phe666, Ser629, Gln630, Glu172, Asn822, Ile819, and Pro835 residues interacted with LTS0169227 (Figure 2). LTS0183019 interacted with Arg662, Asn756, Glu849, Leu755, Cys838, Tyr836, Gly837, Met811, Leu839, Arg818, His670, Ile633, Leu632, Phe666, Ser629, Lys271, and Asn170 residues of PI3Kα (Figure 2). LTS0241372 binds with Gln630, Gln815, Ser629, Asp626, Lys271, Leu814, Cys838, Met811, Ile633, His670, Phe666, Gly837, Leu755, Asn797, Glu849, His759, and Asn756 residues of PI3Kα (Figure 2). LTS0249588 interacted with Glu849, Asn756, Asn170, Arg662, Lys271, Asp626, Ser629, Gln630, Arg818, Met811, Ile633, His670, Phe666, Gly837, Leu755, and His759 residues of PI3Kα (Figure 2). Further, the control Copanlisib interacted with Glu821, Asn822, Ile819, Gln630, His670, Ser629, Arg818, Lys271, Leu839, Gly837, Cys838, Tyr836, Leu814, Gln815, Met811, Ile633, Asn756, Asn170, Gln825, and Met278 residues of PI3Kα (Figure 2).

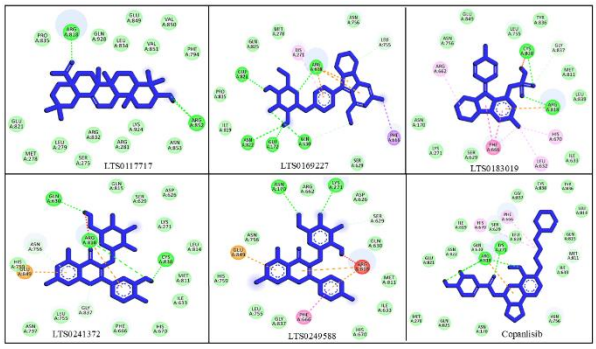

Figure 2: Interacting residues of PI3Kα with the compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588. Compounds have been shown in stick representation.

The compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 exhibited favorable molecular properties (Table 1). These compounds had ratings of 1 or +1, indicating a strong preference for characteristics found in natural products. Furthermore, Lipinski's Rule of Five revealed a comprehensive profile of these compounds, which used the drug's chemical structure to predict oral bioavailability, and they met the criteria (Table 2).

Molecular properties	LTS0117717	LTS0169227	LTS0183019	LTS0241372	LTS0249588
Total atom number	81	65	46	53	52
Heavy atom number	33	34	26	33	32
Bond count	37	38	29	36	35
Number of carbons	30	25	18	21	21
Minimal number of rings	5	5	4	4	4
Maximal number of rings	14	8	7	5	5

Table 1: Molecular properties such as total atom number, heavy atom number, bond count, and carbons number of the selected compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588.

Molecular descriptors	LTS0117717	LTS0169227	LTS0183019	LTS0241372	LTS0249588
NP-likeness score	1.18	1.02	1	1	1
Alogp	6.42	1.25	2.09	0.59	0.86
Alogp2	41.24	1.56	4.38	0.35	0.73
Apol	87.2121	72.4846	53.4591	59.9199	59.1179
Bpol	53.4319	42.2774	31.8029	28.5701	28.5701
Eccentric Connectivity Index Descriptor	673	893	444	666	645
Fmf Descriptor	0.6667	0.7647	0.7308	0.697	0.7188
Fsp3	0.9	0.48	0.3333	0.2857	0.2857
Fragment Complexity Descriptor	6169.03	3639.09	1654.08	2080.12	2033.11
Petitjean Number	0.5	0.4667	0.5	0.5	0.5
Lipinski's Rule (Failures)	1	0	0	1	1
Wiener Path Number	2660	3528	1467	2914	2698
Xlogp	9.052	1.135	0.114	1.711	1.956
Zagreb Index	204	188	146	180	174
TopoPSA	57.53	105.86	98.69	210.51	190.28

Table 2: Molecular descriptors such as NP-likeness, Fmf Descriptor, and Lipinski's Rule of the selected compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588.
NP = natural product

Discussion

LC is the leading cause of cancer-related death worldwide, with a 5-year survival rate of around 15% [14]. Despite advancements, it remains a significant health burden, with incidence expected to climb in many places by 2035 [15]. Symptoms include prolonged cough, chest pain, and shortness of breath, emphasizing the importance of early medical action. Hyperactivation of phosphatidylinositol 3-kinase (PI3K) has been linked to cancer aetiology. Emerging therapies, such as PI3K/mTOR inhibitors, show promise for inducing apoptosis and reducing tumor cell proliferation. Enhanced therapy procedures and research are required to address this issue [16]. The study screened *N. sativa* compounds against PI3Kα to identify potential natural PI3Kα inhibitors.

A high negative binding energy between ligand-protein complex indicates that ligand has strong binding to the target protein [17,18]. Interestingly, compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 exhibited stronger

binding energy than the control Copanlisib, indicating stronger binding of these compounds with PI3Kα.

Copanlisib is a pan-class I PI3K inhibitor that primarily targets the α- and δ-isoforms [19] and has been used as positive control in this study. Glu821, Asn822, Ile819, Gln630, His670, Ser629, Arg818, Lys271, Leu839, Gly837, Cys838, Tyr836, Leu814, Gln815, Met811, Ile633, Asn756, Asn170, Gln825, and Met278 residues of PI3Kα were involved in the binding with Copanlisib. Interestingly, the compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 were also observed to bind with most of these PI3Kα residues, indicating that these compounds bind at the same pocket of PI3Kα as does the control Copanlisib.

H-bonding has an important role in the stability of compounds with target protein [20,21]. The compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 form several H-bonds with PI3Kα. LTS0117717 was H-bonded with Arg818 and Arg852 residues of PI3Kα; while Glu821, Arg818, Gln630, Glu172, and Asn822 residues were H-bonded with LTS0169227. LTS0183019 was H-bonded with Cys838, and Arg818 residues of PI3Kα. LTS0241372 was H-bonded with Gln630, and Arg818 residues of PI3Kα. Furthermore, Asn170, and Lys271 residues of PI3Kα were H-bonded with LTS0249588.

N. sativa (black cumin) is a well-known medicinal herb in traditional medicine, with numerous therapeutic applications. *N. sativa* seeds and seed oil are used to treat a variety of conditions. This plant and its bioactive components display a variety of biological actions, including anti-diabetic, anticancer, antibacterial, and anti-inflammatory properties [22-24]. In this study, the identified *N. sativa* compounds LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 showed strong binding with PI3Kα and can be used as anticancer agents.

This study in silico screened the bioactive compounds of *N. sativa* against PI3Kα. LTS0117717, LTS0169227, LTS0183019, LTS0241372, and LTS0249588 were identified as five hits with a stronger affinity than Copanlisib. These compounds exhibit good drug-like properties, making them potential PI3Kα inhibitors for LC management.

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Conflicts of Interest

No conflict of interest.

Generative AI Statement

The author declares that Generative AI tools including Grammarly, and QuillBot were used to enhance the language and clarity of this work. I take full responsibility for the accuracy and integrity of the content.

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