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Research Article

Molecular Docking Analysis of Flavonoids from *Syzygium cumini* (L.) Skeels: Proapoptotic Potential as an Anticancer Mechanism

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Abstract

Non-small cell lung cancer (NSCLC) presents a significant global health challenge, with its prevalence and mortality rates rising steadily. In Indonesia, *Syzygium cumini* (L.) Skeels, known for its flavonoid richness, has a long history in traditional medicine. However, its specific mechanisms of action against cancer, particularly in inducing apoptosis in NSCLC, have not been fully elucidated. This study utilized an *in silico* approach to evaluate the pro-apoptotic potential of *S. cumini* flavonoids against NSCLC by targeting key proteins: Bcl-2, Bax, and Caspase-3. We retrieved flavonoid structures from PubChem and protein data from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The drug-likeness of these compounds was assessed using Swiss ADME, adhering to Lipinski's rule of five, while their anti-NSCLC probability was predicted using PASS Online. Molecular docking and screening were performed with PyRx, and the results were visualized using Discovery Studio. Our findings identified epigallocatechin 3-O-gallate and ellagic acid as the most promising anti-NSCLC candidates. Ellagic acid demonstrated the strongest binding affinity to Caspase-3, suggesting a potent pro-apoptotic effect. Epigallocatechin 3-O-gallate, on the other hand, exhibited the lowest binding energy across multiple target proteins, particularly Bcl-2 and Bax, indicating its broad pro-apoptotic potential. These results collectively suggest that flavonoids from *S. cumini* may hold significant promise as a source of novel anti-NSCLC agents, warranting further *in vitro* and *in vivo* investigations.

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INTRODUCTION

Lung cancer remains a leading cause of death globally, with the World Health Organization (WHO) reporting an estimated 2.21 million new cases in 2020 alone[1,2]. Common symptoms include cough, hemoptysis, chest pain, and shortness of breath[3]. The disease is broadly classified into two types: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC)[4-6]. Accounting for roughly 85% of all cases, NSCLC has a poor prognosis, with a five-year survival rate of only 10–15%[7-10]. Current treatment strategies, such as surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, often lead to palliative outcomes, severe adverse reactions, and the development of drug resistance, significantly reducing a patient's quality of life[11-13].

At the molecular level, apoptosis, or programmed cell death, is a crucial process for eliminating malignant cells. This pathway is tightly regulated by the Bcl-2 gene family on the mitochondrial outer membrane[14]. The Bcl-2 family includes both pro- and anti-apoptotic regulators[15]. In healthy cells, the pro-apoptotic protein Bax forms a heterodimer with the anti-apoptotic protein Bcl-2, which prevents the activation of Caspase-3 and, consequently, apoptosis[16,17]. However, in NSCLC, a heightened Bax/Bcl-2 interaction and a reduced Bax-to-Bcl-2 ratio block the initiation of this critical cell death pathway[18].

Syzygium cumini (L.) Skeels, a plant native to South Asia, has a rich history of traditional medicinal use and is known for its high concentration of flavonoids, secondary metabolites with established anticancer properties[19-25]. The anticancer potential of *S. cumini* has been demonstrated in previous studies, with its seed extract showing efficacy against ovarian cancer cells[26] and its fruit methanol extract suppressing lung cancer cell proliferation[27]. Despite these promising findings, no studies have specifically investigated the pro-apoptotic activity of *S. cumini* against NSCLC. Given that the therapeutic potential of natural compounds can be initially assessed through virtual screening and *in silico* approaches[28], this study aims to determine the potential of *S. cumini* flavonoids as pro-apoptotic agents in NSCLC by targeting the key proteins Bcl-2, Bax, and Caspase-3.

MATERIALS AND METHODS

Materials

The flavonoids from *S. cumini* used in this study were identified based on existing literature[21] and retrieved from the PubChem database. The specific compounds and their corresponding CID numbers were vanillic acid (8468), ellagic acid (5281855), chlorogenic acid (1794427), ferulic acid (445858), gallic acid (370), syringic acid (10742), 3,4-dihydroxybenzoic acid (72), catechin (9064), epicatechin (72276), epigallocatechin (72277), laricitrin 3-O-glucoside (101682256), myricetin (5281672), myricetin 3-O-pentoside (21477996), myricetin 3-O-rhamnoside (5281673), quercetin (5280343), rutin (5280805), syringetin-3-galactoside (20056941), syringetin-3-glucoside (20056942), myricitrin (5281673), kaempferol (5280863), myricetin 3-glucuronide (5487413), liquiritigenin (114829), gallocatechin (65084), epigallocatechin 3-O-gallate (65054), gallocatechin gallate (5276890), and isoquercetin (5280804). The 3D conformers of these compounds were downloaded from PubChem and converted to Protein Data Bank (PDB) format using the Open Babel module within PyRx, where energy minimization was also performed using the universal force field (UPF)[29]. The three target proteins—Bcl-2 (PDB: 1GJH), Bax (PDB: 1F16), and Caspase-3 (PDB: 3DEI)—were obtained from the RCSB PDB database. Prior to docking, the protein files were prepared by removing all water molecules using AutoDock and Notepad++ to optimize the binding site for ligand interaction. Ligand minimization was also conducted using PyRx[17].

Methods

Drug-likeness analysis

The pharmacological properties and drug-likeness of the flavonoids were analyzed using the SwissADME online platform. The Lipinski's rule of five, which guides the evaluation of a compound's oral bioavailability, was applied. A compound was considered to have a positive prediction for drug-likeness if it met at least two of the following criteria: molecular weight (MW) <500 Da, hydrogen bond donors (HBD) <5, hydrogen bond acceptors (HBA) <10, a high lipophilicity (LogP) <5, and molar refractivity (MR) of 40-130[30,31].

Anticancer probability prediction

To predict the biological activity, PASS Online was used, with a focus on anticancer properties. A compound was considered active if its probability of activity (Pa) exceeded both its probability of inactivity (Pi) and a threshold of 0.3, a criterion favored as a preliminary indicator for molecular docking[17]. The specific bioactivities assessed included anticarcinogenic, antioxidant, antimutagenic, antineoplastic, apoptosis agonist, free radical scavenger, and stimulators of Caspase-3 and Caspase-8, as well as TP53 inhibition.

Virtual screening and visualization

Molecular docking was performed using the highly accurate software PyRx[32]. The docking procedure was specifically configured to target only the protein's lock residue, as detailed in **Table I**, to ensure high specificity in predicting binding interactions[33]. The binding affinity was determined by the magnitude of the energy affinity, with more negative values indicating a more stable and favorable interaction[34]. The compound with the most negative binding affinity was selected for further analysis. The resulting ligand-protein complexes and their interactions were visualized in detail using Discovery Studio[35,36].

Table I. Active site reference of NSCLC target proteins.

Proteins	PDB	Active Site	Grid		References
			Center	Dimension	
Bcl-2	1GJH	Glu100 (hydrogen bond), Tyr105 (hydrogen bond), Glu143 (hydrogen bond)	X: 3.5702 Y: -4.2149 Z: 2.1695	X: 30.1345 Y: 30.1345 Z: 30.1345	**37**
Bax	1F16	Cys21 (hydrogen bond), Gln28 (hydrogen bond), Gln32 (hydrogen bond), Glu131 (hydrogen bond), Arg134 (hydrogen bond)	X: 20.5808 Y: -0.11783 Z: 16.3104	X: 38.9892 Y: 38.9892 Z: 38.9892	38
Caspase-3	3DEI	His121 (hydrophobic interaction), Cys163 (hydrogen bond)	X: -41.8984 Y: 6.8576 Z: 0.0000	X: 60.7095 Y: 64.0438 Z: 4.1856	**39**

Data analysis

The stability of the molecular docking results was validated through molecular dynamics (MD) simulations by assessing the root mean square fluctuation (RMSF)[36]. This procedure was carried out using CABS-flex 3.0 with default parameters. A compound was considered to have a stable fluctuation if its RMSF value was between 1 and 3 Å, thereby confirming the reliability of the docked pose[40].

RESULTS AND DISCUSSION

The flavonoids were initially evaluated for their pharmacological suitability based on Lipinski's rule of five, a standard for assessing drug-likeness[41,42]. Our analysis revealed that all 26 flavonoids examined satisfied at least two of the required criteria, indicating their potential as viable pharmaceutical compounds (**Table II**). Following this, an in-depth anticancer probability analysis was performed using PASS Online. The results showed that epigallocatechin and gallocatechin possessed the highest total Pa scores (**Figure 1**), suggesting a stronger likelihood of exhibiting anticancer properties compared to other compounds[43]. Consequently, these two compounds were prioritized for further bioinformatics investigation. However, it is crucial to note that these *in silico* predictions must be validated through subsequent *in vitro* and *in vivo* studies. Compounds selected for molecular docking against the NSCLC-apoptosis pathway targeted proteins were those that not only adhered to Lipinski's rule of five but also demonstrated high anticancer potential in the PASS Online analysis.

Molecular docking analysis, conducted with PyRx and visualized using Discovery Studio, identified the most favorable ligand-receptor complexes. The results, presented in **Table III** and **Figure 2**, demonstrate that the three most promising flavonoid compounds exhibited binding affinities of less than -5 kcal/mol against all three target proteins. Furthermore, the Root Mean Square Deviation (RMSD) values for all of these compounds were 0, indicating a perfect alignment and a high degree of stability between the docked ligands and the target proteins. These highly negative binding energies, coupled with the zero RMSD values, provide strong evidence of the compounds' potent inhibitory activity and stable interaction with

each target. The exceptional stability of these complexes, as indicated by the RMSD values, is crucial as it suggests a high probability of maintaining a stable interaction in a biological context[3,44].

Table II. Lipinski's rule of five selected flavonoids from *S. cumini*.

Flavonoids	MW (g/mol)	HBD	HBA	LogP	MR (cm³/mol)
Vanillic acid	161.15	2	4	1.08	41.92
Ellagic acid	302.19	4	8	1	75.31
Chlorogenic acid	354.31	6	9	-0.38	83.5
Ferulic acid	194.18	3	4	1.36	51.63
Gallic acid	170.12	4	5	0.21	39.47
Syringic acid	198.17	2	5	0.99	48.41
3,4-dihydroxybenzoic acid	154.12	3	4	0.65	37.45
Catechin	290.27	5	6	0.85	74.33
Epicatechin	290.27	5	6	0.85	74.33
Epigallocatechin	306.27	6	7	0.42	76.36
Laritricin 3-O-glucoside	494.40	8	13	-0.45	116.65
Myricetin	318.24	6	8	0.79	80.06
Myricetin 3-O-pentoside	450.36	8	12	-0.48	106.21
Myricetin 3-O-rhamnoside	464.38	8	12	0.09	111.02
Quercetin	302.24	5	7	1.23	78.03
Rutin	610.52	10	16	-1.29	141.38
Syringetin-3-galactosidase	508.43	7	13	-0.19	121.12
Syringetin-3-glucosidase	508.43	7	13	-0.19	121.12
Myricitrin	464.38	8	12	-0.23	111.02
Kaempferol	286.24	4	6	1.58	76.01
Myricetin 3-O-glucoronide	494.36	9	14	-0.86	112.79
Liquiritigenin	256.2	2	4	2.07	69.55
Gallocatechin	306.27	6	7	0.42	76.36
Epigallocatechin 3-O-gallate	442.37	7	10	1.25	110.14
Gallocatechin gallate	458.37	8	11	1.01	112.06
Isoquercetin	464.38	8	12	-0.25	110.16

Note: The red color indicates a violation of Lipinski's rule of five.

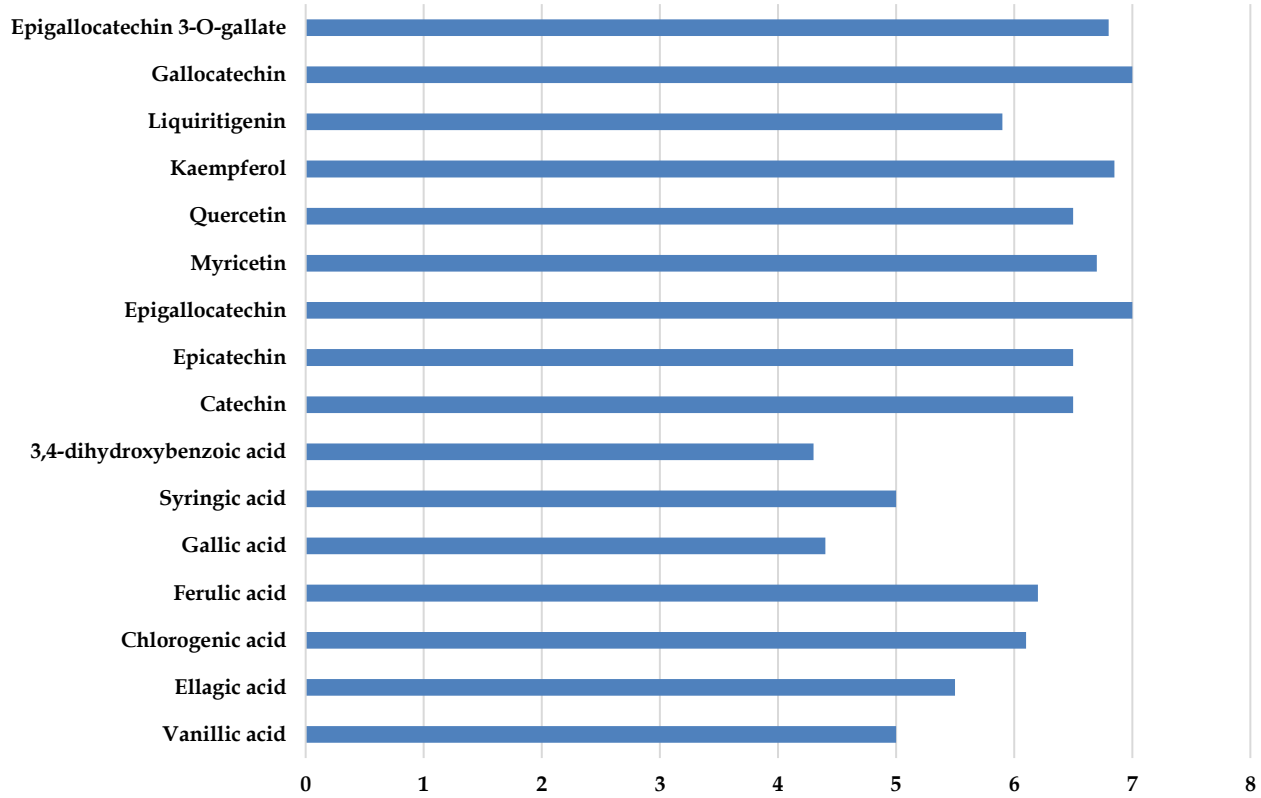

Figure 1. Total anticancer probability score of *S. cumini* flavonoids against NSCLC.

Table III. Docking analysis of selected flavonoids from *S. cumini* against target proteins based on binding affinity scores.

Compounds	Bcl-2	Bax	Caspase-3
Vanillic acid	-5.3	-5.8	-6.6
Ellagic acid	-6.8	-8.4	-9.4
Chlorogenic acid	-6.6	-7.4	-9.2
Ferulic acid	-5.9	-6.4	-6
Gallic acid	-5.1	-6	-7
Syringic acid	-5.3	-6.1	-6.4
3,4-dihydroxybenzoic acid	-5.2	-5.7	-4.7
Catechin	-6.5	-7.7	-7.7
Epicatechin	-6.5	-7.5	-7.8
Epigallocatechin	-6.4	-7.3	-7.8
Myricetin	-6.5	-7.6	-8.2
Quercetin	-6.5	-7.8	-8
Kaempferol	-6.3	-7.8	-7.5
Liquiritigenin	-6.5	-7.8	-7.7
Gallocatechin	-6.4	-7.7	-7.8
Epigallocatechin 3-O-gallate	-7.1	-8.9	-8.6

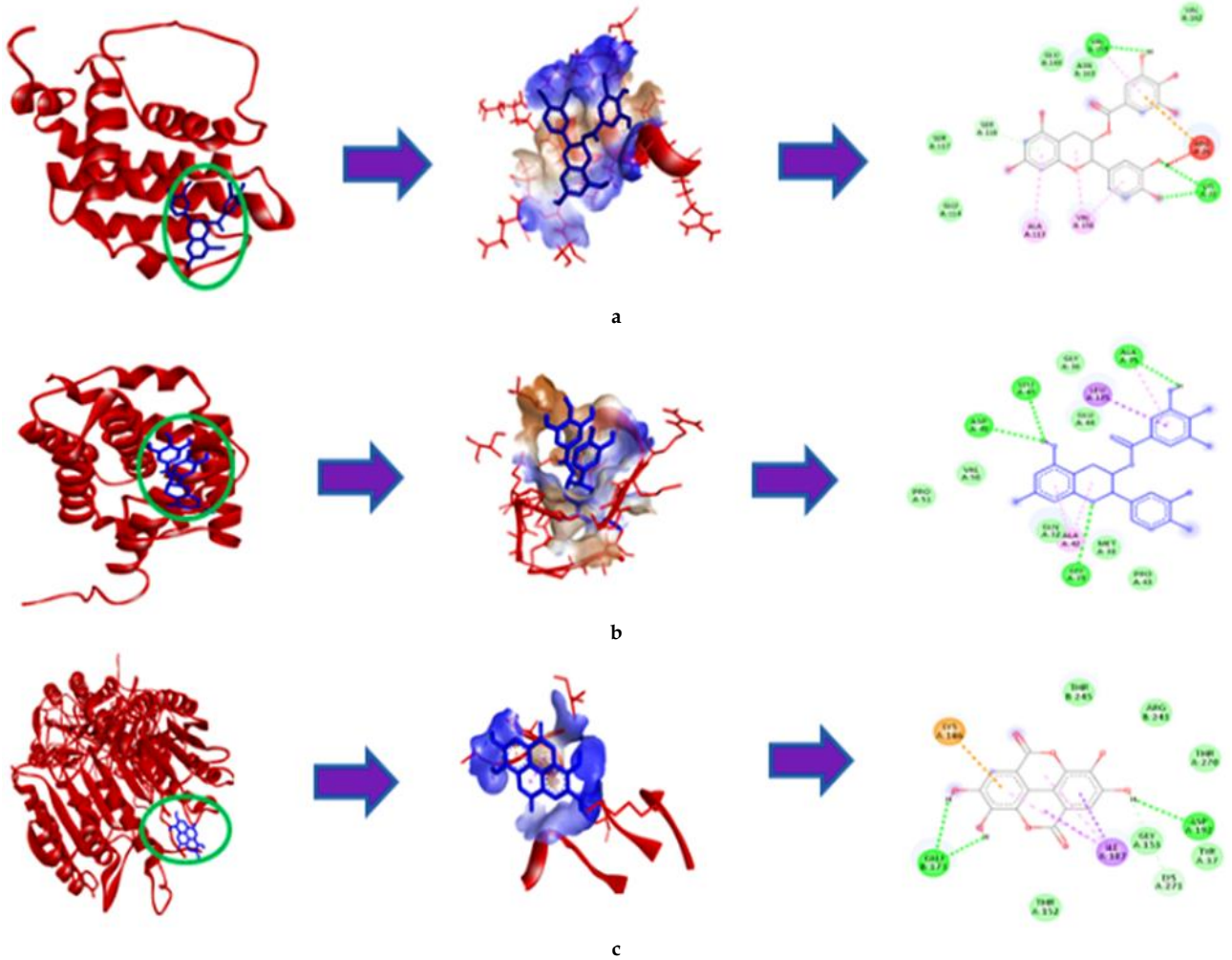

Figure 2. Visualization of ligand-targeted protein binding: (**a**) epigallocatechin 3-O-gallate to Bcl-2, (**b**) epigallocatechin 3-O-gallate to Bax, and (**c**) ellagic acid to Caspase-3. Note: (**left**) 3D interaction, (**middle**) hydrophobicity, and (**right**) 2D visualization of ligand-targeted proteins.

The molecular docking analysis revealed that epigallocatechin 3-O-gallate exhibited the strongest binding affinity to Bcl-2 with an affinity energy of -7.1 kcal/mol. This interaction was stabilized by three hydrogen bonds with Lys22 and Val159 residues, as well as a variety of hydrophobic bonds including van der Waals, pi-cation, pi-donor hydrogen, alkyl, and pi-alkyl bonds. The formation of pi-alkyl bonds, in particular, is crucial for inhibiting Bcl-2 activity and subsequently promoting apoptosis[44-46]. However, an unexpected and less favorable bond to Arg26 resulted in a slightly more positive affinity value. This type of interaction is often considered less ideal in docking simulations due to its potential for induced-fit bonds,

irrelevant binding modes, or unpredictable behavior at other sites. Crucially, the interaction between epigallocatechin 3-O-gallate and Bcl-2 did not involve the catalytic residues Glu100, Tyr105, and Glu143[32], suggesting a less stable interaction compared to the drug-protein interactions with the Bax protein.

In contrast, epigallocatechin 3-O-gallate demonstrated a significantly more negative binding affinity for Bax at -8.9 kcal/mol. This robust interaction was stabilized by four hydrogen bonds and eleven hydrophobic bonds, including van der Waals, alkyl, pi-alkyl, and pi-sigma interactions[47]. A notable van der Waals bond to the catalytic residue Gln32 of Bax further supports the potential for accelerated proteolysis and maturation of the protein[35,48]. The relationship between the anti-apoptotic Bcl-2 and pro-apoptotic Bax proteins is a critical, antagonistic one. In NSCLC cells, an imbalance in the Bax/Bcl-2 ratio leads to tumor survival and proliferation due to blocked apoptosis[49,50]. Therefore, a strong interaction with Bax, which promotes its pro-apoptotic function, is highly desirable as it could lead to the release of cytochrome c and the activation of caspases, thereby initiating apoptosis[18,34].

Molecular docking analysis indicated that ellagic acid had the highest binding affinity for Caspase-3, with an affinity energy of -9.1 kcal/mol. This interaction was mediated by three hydrogen bonds with Glu173 and Asp192, and eleven hydrophobic bonds involving residues such as Lys186, Ile187, and Thr245. However, none of these interactions engaged with the catalytic dyad of Caspase-3 (His121 and Cys163)[36], a critical step for its pre-activation and subsequent folding and maturation[50-52]. Despite this, the presence of hydrogen and hydrophobic bonds is known to reduce bond energy and promote stable ligand-protein complexes[54-56], which could potentially initiate caspase activation and apoptosis in NSCLC cells[18,34].

Molecular dynamics simulations confirmed the stability of the epigallocatechin 3-O-gallate-Bcl-2 complex, as indicated by a root mean square flexibility (RMSF) value below 3 Å (40). However, the epigallocatechin 3-O-gallate-Bax and ellagic acid-Caspase-3 complexes showed significant fluctuations, with RMSF values exceeding 3 Å in several residues. Nevertheless, a focused analysis revealed that the active sites of each protein maintained stable fluctuations, even when they did not show significant interactions in the initial molecular docking (**Figure 3**). This discrepancy between the docking and dynamics results suggests that while the computational predictions are promising, they are not entirely conclusive. The lack of interaction with key catalytic residues and the fluctuating nature of the complexes with Bax and Caspase-3 indicate that further validation through *in vitro* and *in vivo* experiments is necessary to confirm their therapeutic potential.

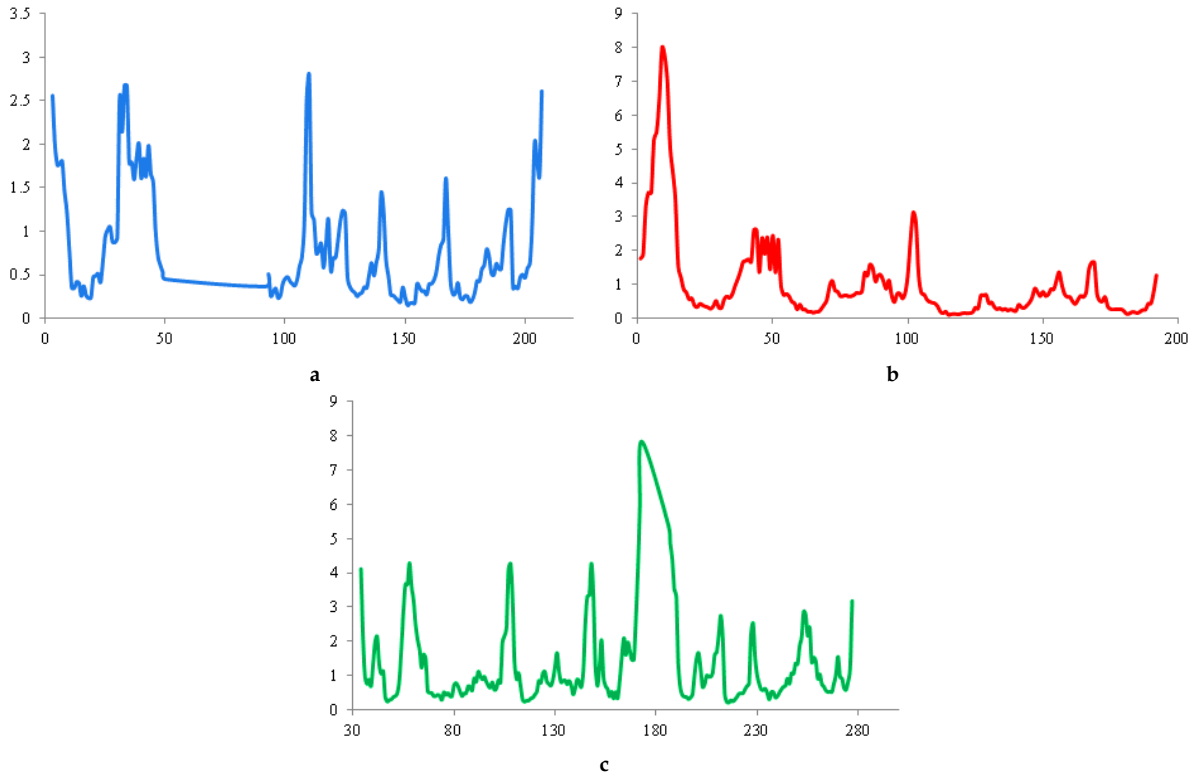

Figure 3. RMSF results from: (**a**) epigallocatechin 3-O-gallate-Bcl-2; (**b**) epigallocatechin 3-O-gallate-Bax; and (**c**) ellagic acid-Caspase-3 complex.

CONCLUSION

This study demonstrated the potential of *S. cumini* flavonoids as pro-apoptotic agents against NSCLC through a computational approach. Molecular docking results indicate that epigallocatechin 3-O-gallate and ellagic acid are promising candidates, showing strong binding affinities to the pro-apoptotic proteins Bcl-2/Bax and Caspase-3, respectively. However, with the exception of the epigallocatechin 3-O-gallate-Bcl-2 complex, the flavonoids did not consistently occupy the active sites and lacked stable molecular dynamics. These findings highlight the need for further *in vitro* and *in vivo* research to validate the therapeutic potential of these compounds and advance them toward clinical application.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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