PREDICTION OF ANTI-LUNG CANCER POTENTIAL OF TRADITIONAL MEDICINAL PLANT-DERIVED COMPOUNDS: A COMPREHENSIVE *IN SILICO* ANALYSIS

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CANDIDATE'S DECLARATION

We Nikita (2k23/MSCCHE/54) and Manisha Kumari (2k23/MSCCHE/79) hereby certify that the work which is being presented in the dissertation enlightened **"Prediction of Anti-Lung Cancer Potential of Traditional Medicinal Plant-Derived Compounds: A Comprehensive *in Silico* Analysis"** in partial fulfilment of the requirements for the award of the Degree of Master in Science, submitted in the Department of Applied Chemistry, Delhi Technological University is an authentic record of own work carried out during the period from Aug 2024 to May 2025 under the supervision of Prof. Archna Rani.

The matter presented in this dissertation has not been submitted by us for the award of any other degree of this or any other institute.

Manisha Kumari

Nikita

This is to certify that the student has incorporated all the corrections suggested by the examiners in the thesis and the statement made by the candidate is correct to the best of our knowledge.

Signature of Supervisor

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CERTIFICATE

Certified that Nikita (2k23/MSCCHE/54) and Manisha kumari (2k23/MSCCHE/79) has carried out their research work presented in this dissertation entitled **"Prediction of Anti-Lung Cancer Potential of Traditional Medicinal Plant-Derived Compounds: A Comprehensive *In Silico* Analysis"** for the award of Master of Science from the Department of Applied Chemistry, Delhi Technological University, Delhi, under my supervision. The dissertation embodies results of original work, and studies are carried out by the students themself and the contents of the dissertation do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

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ABSTRACT

Lung cancer remains the leading cause of cancer-related deaths worldwide, claiming more lives annually than prostate, breast, and colon cancers combined. Limited resources for prognosis and the rising costs of screening and treatment contribute to this challenge, emphasizing the need for efficient therapeutics. Thus, following a repurposing approach, we investigated the interaction of 108 plant-derived compounds (PDCs) with the lung cancer-associated protein Keap1 (PDB ID: 1X2J). Various analyses—including pkCSM for pharmacokinetic properties, swissADME for ADME profiling, CLC-Pred 2.0 for cytotoxicity assessments, and molecular docking—led to the identification of 15 PDCs as promising candidates for lung cancer therapy. Further, the research highlighted six key ligands—Sesamin, Asiatic acid, Tubulosine, Chrysophanic acid, Bavachinin, and Chrysin—as particularly effective therapeutic agents. These compounds exhibit superior binding affinities compared to the synthetic drugs MSU38225 Gemcitabine and VBQ, with values ranging from -10.4 kcal/mol to -9.3 kcal/mol for the target protein. They also demonstrate notable cytotoxic effects against lung cancer cell lines A549 and A549/TR, strengthening their potential as viable treatment options.

Keywords: Lung cancer; Molecular docking; Pharmacokinetics; Natural compound; Cytotoxicity;

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LIST OF ABBREVIATIONS

Keap1- Kelch-like ECH-associating protein 1

Nrf2- Nuclear factor erythroid 2-related factor 2

PDCs- Plant Derived Compounds

FDA- Food and Drug Administration

MD- Molecular dynamics

VS- Virtual screening

ADME- Absorption, distribution, metabolism, and excretion

Pi- probabilities to be inactive

Pa- probabilities to be active

IAP*- Invariant Accuracy of Prediction

SAR- structure–activity relationship

DMSO- Dimethyl sulfoxide

PDB- Protein Data Bank

Å- Angstrom

BBB- Blood-Brain Barrier

GI - Gastrointestinal tract

CADD- Computer Aided Drug Design

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Lung cancer remains the leading cause of cancer-related deaths worldwide, claiming more lives annually than prostate, breast, and colon cancers combined. In 2020, lung cancer was the most frequent cancer worldwide, accounting for about 2.2 million new cases and 1.8 million recorded deaths, while just 18% of all patients had recovered stage 0, I, and II cancers have a higher probability of recovery, more than 60% of cancer patients still have stage III and IV cancer, which is considered advanced disease and has a low likelihood of recovery[1].When cells in the lung tissue develop abnormally and uncontrollably, lung cancer starts. It's a major health problem. It can undoubtedly cause irreversible death and extremely terrible harm [2]. This is mostly due to the fact that lung cancer typically goes undetected in its early stages, hence it is frequently discovered at an advanced level[3]. Lung cancer may be caused by a variety of factors, such as smoking cigarettes, pipes and cigars actively, or passively (by exposing oneself to second hand smoke), being exposed to radiation, being exposed to indoor and outdoor air pollution, and being exposed to agents like asbestos, nickel, chromium, and arsenic at work. Smoking is the primary risk factor, and men are often more likely than women to develop lung cancer[4].

The development of tumors and chemoresistance is significantly influenced by oxidative stress and dysregulated cellular defense system [5]. The Nrf2/Keap1 pathway is essential for shielding cells from oxidative stress, which is a major factor in the development of cancer[6]. Kelch-like ECH-associating protein 1 (Keap1) is an Neh2-associating protein that negatively regulates Nrf2 activity and plays a crucial role in the cellular defense against both oxidative and electrophilic insults, but in oxidative stress, Nrf2 activates genes that aid in detoxification and antioxidant defense. One possible approach to cancer treatment to target the Keap1-Nrf2 connection [5][6]. By increasing Nrf2 activity, disruption of Keap1–Nrf2 connections may shield cells from oxidative stress; however, in

malignancies, this may also increase tumor survival or resistance to chemotherapy [7]. KEAP1/Nrf2 modulation studies have focused on tumor types such breast, lung, ovarian, and glioblastoma malignancies[8].

While dealing with cancer patients even the most experienced physician may face treatment difficulties. About 90% of patients with lung cancer exhibit symptoms upon diagnosis. A small percentage of patients have local symptoms associated with their initial tumour, while the majority have either nonspecific systemic or metastatic symptoms, according to Van Cleave and Cooley (2004) [9]. Cancer is currently treated primarily with surgery, chemotherapy, radiation, hormones, and immunotherapy, with additional complementary and alternative therapies, including herbal remedies, frequently included. Even though chemotherapy is the most common treatment, there are a number of issues with its use, such as multidrug resistance, extreme toxicity, and limited efficacy[4]. Numerous FDA-approved targeted medications and immune checkpoint inhibitors are utilised in clinical settings; nevertheless, they have a number of harmful side effects, such as rash, nausea, diarrhoea, and even problems with the nervous and cardiac systems. As a result, developing effective treatments is remains challenging yet absolutely crucial[10].

Natural substances offer an intriguing treatment option for lung cancer that may be successful and have few adverse effects. Natural chemicals are derived from a variety of sources, such as microbes, plants, and animals, and they offer an intriguing path for cancer treatment medication development. Numerous plants contain natural chemicals, which have been researched since antiquity. Numerous plants have been demonstrated to possess anti-cancer properties through their active phytochemicals[11]. Notably, several newly developed anticancer agents available commercially have been derived from natural sources. These agents have either been produced by modifying the structure of natural compounds or synthesizing novel molecules inspired by natural compounds due to the demanding trend of returning to nature [12][13]. Nutrition is important for human health and has an impact on the development and spread of cancer. Lung cancer prevention and

treatment outcomes are particularly impacted by nutrition. Antioxidant properties of dietary components, particularly plant-based diets, have been discovered. The initiation, development, and failure of treatment of cancer are all impacted by free radicals and oxidative stress when reactive oxygen species (ROS) rise[14]. Flavonoids, terpenes, alkaloids, lignans, saponins, oils, gums, glycosides, minerals, and vitamins are the primary phytochemicals in plants that exhibit anti-cancer properties. It is believed that natural substances have chemotherapeutic activity and could be applied to the treatment of cancer[11]. Several studies have confirmed the chemopreventive potential of natural compounds like curcumin, Epigallocatechin-3-gallate (EGCG), ginsenoside Rg3, resveratrol, β-carotene, lycopene, and sulforaphane that affect the NRF2 pathway. Large natural chemical libraries have yielded novel candidates thanks to virtual screening techniques[14].

Novel medication development is recognised to be a costly and time-consuming procedure [15]. The development of new drugs could be accelerated and made less expensive with the use of computer-aided drug design, or CADD. One of the many CADD tools, molecular docking, has emerged as a crucial method for structural biology and CADD, exceeding conventional drug development techniques in terms of effectiveness[6]. Computational methods are currently being incorporated at practically every stage of drug discovery and development because of the exponential growth in the amount of information on protein structures, small compounds, and genomes. When chemical compounds are logically created using computational techniques, they may have a potentially better affinity for their target given the target molecule's three-dimensional shape[15]. For convenience we have divided the various computing approaches into these two subcategories. **Structure and ligand-based drug discovery** the active site of the macromolecule structure, the presence of particular amino acids in the binding pockets, and the strength of the reacting species' contact are all taken into account during lead identification in structure-based drug design. In order to find the possible hit molecules, structure-based methods such as molecular docking and VS techniques have made it easier to quickly and affordably analyse huge collections of chemical databases. **Virtual**

screening (VS) and molecular dynamics (MD) In the field of drug research, VS has proven useful in screening libraries to find compounds with high binding affinities. By reducing the number of compounds to be assessed in biological assays, this time-efficient method not only assists in handling big datasets but also prevents late-stage drug development failures. MD is crucial for drug development research because it forecasts the molecular and structural alterations of biomolecules caused by intramolecular and intermolecular forces[16].

The study's objective is to investigate anti-lung cancer medications through a repurposing strategy by screening plant-derived compounds (PDCs), which are already known for their wide range of biological activity, utilising a number of computational methods. Out of the 108 test compounds, 15 showed promises as treatment options for lung cancer. Interestingly, across all assessed parameters, six of these compounds - Sesamin, Asiatic acid, Tubulosine, Chrysophanic acid, Bavachinin, and Chrysin—showed superior efficacy in comparison to the synthetic medications MSU38225, Gemcitabine, and VBQ (Fig 2.2). MSU38225 inhibits the growth of human lung cancer cells and makes them more vulnerable to treatment in vitro and in vivo. It is useful in the study of cancer[17]. Gemcitabine is a well-known chemotherapy medication that has FDA approval. It was first created as a nucleoside analogue to treat lung and pancreatic malignancies, but new in silico research indicates it might also bind Keap1, possibly interfering with its interaction with Nrf2. This makes it possible to use gemcitabine for ongoing research[12][19][20]. VBQ is a fluorene-based chemical (2-[(9-oxidanylidenefluoren-4-yl) carbonylamino]ethanoic acid). Its binding of the Keap1 Kelch domain has been validated experimentally. It is able to competitively disrupt the Keap1-Nrf2 interaction by imitating the carboxyl and amide groups that are essential to Nrf2. Its aromatic fluorene core might also facilitate binding by stacking Pi-Pi with the pocket's hydrophobic residues [20].

Chapter 2

MATERIAL AND METHODS

A comprehensive literature review led to the selection and thorough investigation of 108 medicinal plant derived compounds (PDCs) based on a number of criteria, including blood-brain barrier, cytotoxicity profiles, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis, compliance with Lipinski's Rule of Five, drug-likeness characteristics, and binding affinity toward the Keap1 protein (PDB ID: 1X2J). These qualities are essential to look for when evaluating a substance for possible usage as a treatment for lung cancer. Just 15 PDCs have passed the test out of them (Table 2.1).

Table 2.1: 15 Shortlisted plant derived compounds

S.No	Natural Compounds	Plant Source	Reference
1.	Sesamin	*Sesamum indicum L.*	[21]
2.	Asiatic acid	*Centella asiatica*	[22]
3.	Tubulosine	*Alangium cf. longiflorum Merr (Alangiaceae)*	[23][24][25]
4.	Chrysophanic acid	*Dianella longifolia*	[26]
5.	Bavachinin	*Psoralea coralifolia*	[27]
6.	Chrysin	*Passiflora sp.*	[28]
7.	Butin	*Butea monosperma*	[21]
8.	Liriodenine	*Polyalthia longifolia (Sonn.) Thwaites*	[21]
9.	(+)- epieudesmin	*Gmelina arborea Roxb*	[21]
10.	Auraptene	*Aegle marmelos*	[29]
11.	Harmine	*Tribulus terrestris L.*	[21]

12.	6-gingernol	*Zingiber officinale Rosc*	[30][31]
13.	Beta asarone	*Acorus calamus L.*	[21]
14.	Geraniol	*Aeollanthus myrianthus*	[32]
15.	Allicin	*Allium sativum* (Garlic)	[33]

Pharmacokinetics studies

The ADMET properties and pharmacokinetics of these PDCs were determined using a web server known as pkCSM. To aid in drug development, pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction_single/adme_1738603121.71) uses graph-based signatures to build predictive models of important ADMET properties. Additionally, SwissADME (http://www.swissadme.ch/index.php), an online tool, was used to evaluate these compounds' drug-likeness. One well-known guideline to aid in the selection of compounds during the early phases of drug discovery was the Lipinski rule of five (RO5). To evaluate the drug-likeness properties of the substances under investigation, the RO5 criteria were applied. [33] They were also evaluated for drug-likeness using SwissADME. SwissADME was fed the SMILES structures that were retrieved from PubChem [34][35][36].

Cytotoxicity studies

CLC-Pred 2.0 (Cell Line Cytotoxicity Predictor) was used to estimate the likely cytotoxicity of particular medications against the lung cancer cell lines A549 and A549/T. The SMILES notation of each drug was sent to the CLC-Pred 2.0 internet server(https://www.way2drug.com/cell-line/) in order to determine the cytotoxicity score, probability values, and possible targets. The likelihood of cytotoxic activity against the cell line is indicated by Pa. The likelihood that a chemical won't have any cytotoxic effects is indicated by the Pi Chance of Not Being Active[37].

Molecular docking

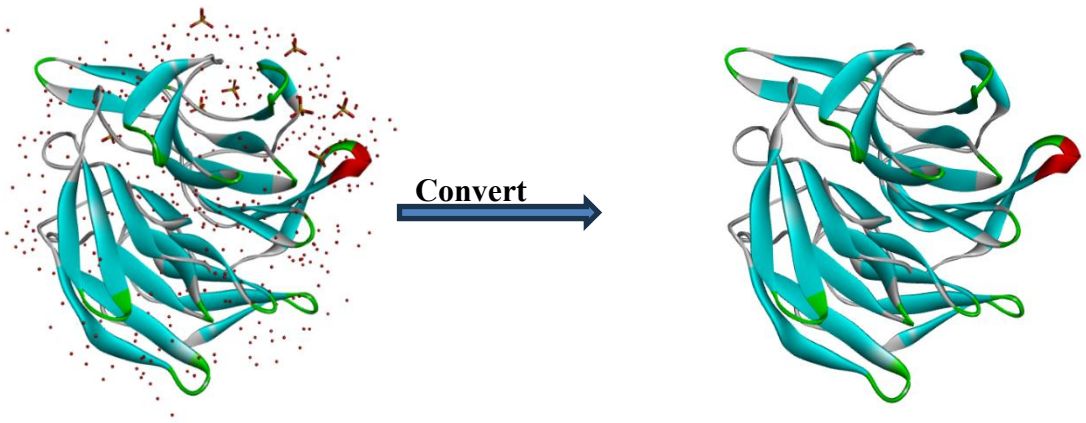
Molecular docking represents a fundamental in silico strategy within the domain of

structure-based drug design, employed to predict the most favorable binding orientation of a ligand within the active site of a target macromolecule, most commonly a protein. The ligand-receptor geometric and physicochemical complementarity is systematically assessed in this method, which is based on the molecular recognition principle. In order to mimic the dynamic interactions, sophisticated computer algorithms provide a variety of ligand orientations and conformations. Each posture is then scored according to the expected binding affinity and interaction stability. Molecular docking makes it possible to effectively screen large libraries of compounds virtually, which speeds up the early phases of drug discovery while drastically lowering the expense and workload of experiments. The structure–activity relationship (SAR) analysis, pharmacologically active drug optimization, and rational lead identification are all made easier by the crucial insights it offers into the molecular drivers of binding. Molecular docking is therefore still a vital tool in contemporary drug development pipelines, particularly when it comes to identifying and ranking new therapeutic compounds.

Protein preparation

The Keap1 Kelch domain's crystal structure (PDB ID: 1X2J, resolution 1.60 Å) was acquired from the RCSB Protein Data Bank. In order to create a minimum receptor appropriate for docking experiments, the file was loaded into BIOVIA Discovery Studio Visualizer, where solvent molecules, DMSO, sulfate ions, and unnecessary chains were eliminated. The structure was standardized using the Prepare Protein protocol (Macromolecules → Prepare Protein). Alternate conformations were resolved, missing heavy atoms and polar hydrogens were added, histidine tautomeric states were assigned for physiological pH, and a brief energy minimization (OPLS/CHARMm) was carried out to relieve steric clashes. Additionally, the framework was modified to include polar charges to improve electrostatic precision during docking. The completed structure was saved in PDBformat for use in subsequent molecular docking investigations[38].

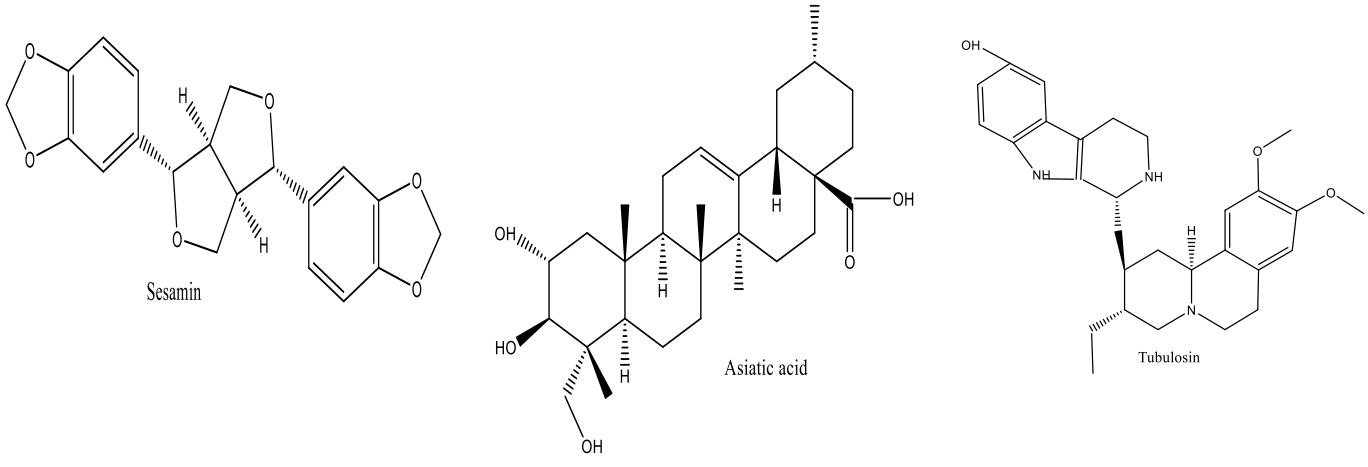
FIG 2.1: Structural Preparation of Keap1 Protein

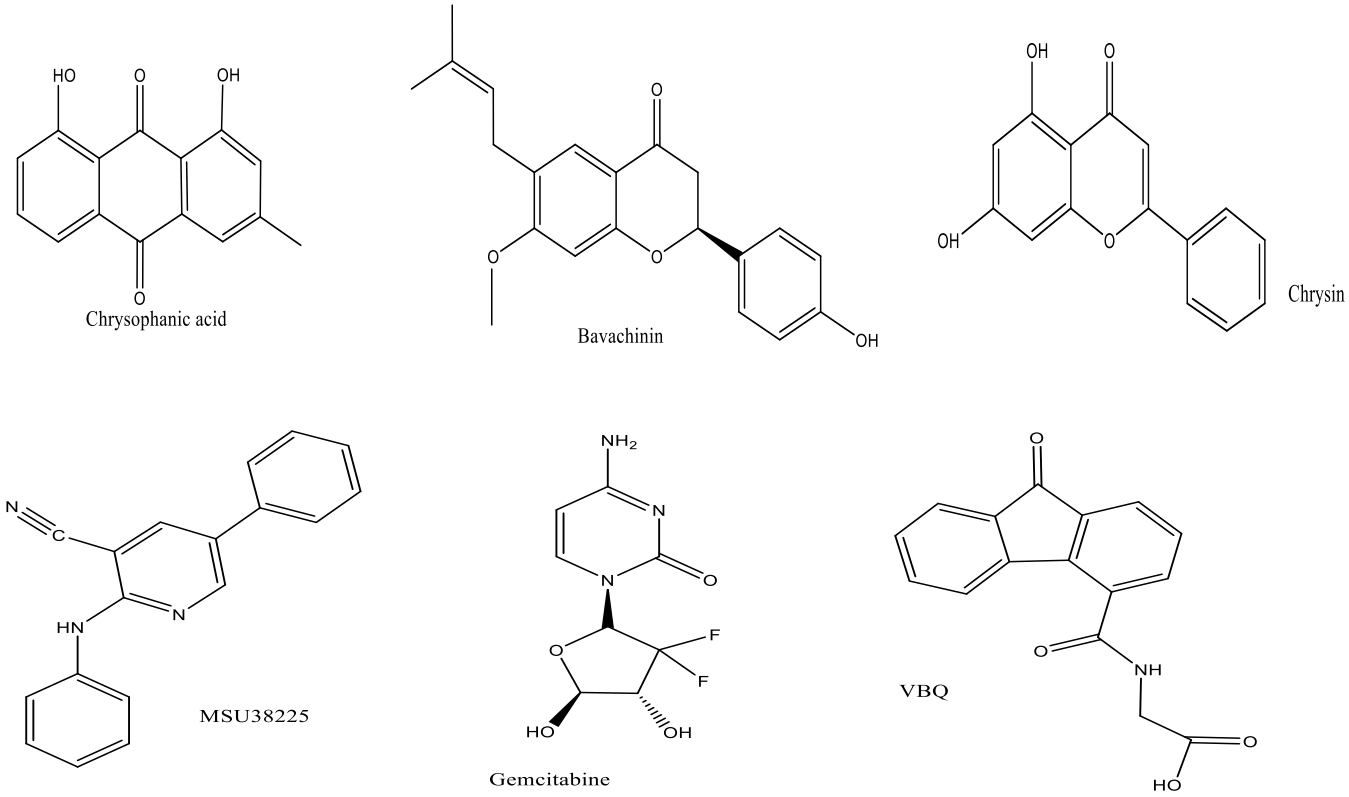


Ligand preparation

The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) provided the ligand structures in.sdf format upon request. Using the Universal Force Field (UFF) and Open Babel (version 2.4.1) (https://sourceforge.net/projects/openbabel/files/openbabel/2.4.1/), ligands were imported using PyRx (version 0.8) and energy was minimized. All ligands were subjected to the PDBQT format after reduction. PDBQT files were completed and used for molecular docking studies[39][40] .

FIG 2.2 : Structures of Plant-Derived and Synthetic Ligands





Docking

Molecular docking was performed using AutoDock Vina, a docking engine included in PyRx (version 0.8)(https://pyrx.sourceforge.io/). As the receptor, the generated protein in PDBQT format was utilized, while the ligand input was the previously reduced and transformed ligand. The grid box was set up by defining the docking search space by providing the dimensions (size X: 57.5063 Å, size Y: 48.2386 Å, size Z:55.1662 Å) and center coordinates (X:24.8023 Å, Y:61.1659 Å, Z:39.4251 Å). Docking was conducted with the exhaustiveness parameter set to 8 and the number of binding modes set to 9. The top-ranked pose from the docking data was chosen for additional interaction analysis and visualization based on binding affinity (kcal/mol).

2D & 3D Visualisation

The BIOVIA Discovery Studio Visualizer from Dassault Systèmes (version v24.1.023298) was used to display and evaluate the docked complexes and their interactions. The PyRx-acquired protein–ligand complex was imported using the pdb format. Molecular docking research was followed by the visualization of the ligand-protein interactions using the Biovia Discovery Studio visualizer (https://discover.3ds.com/)discovery-studio-visualizer-download. The docked complexes were examined using the Biovia Discovery Studio program's 3-D visualization features and 2-D interaction tool. This allowed the ligand-protein interactions to be thoroughly examined in both two- and three-dimensional representations[41].

Chapter 3

RESULTS AND DISCUSSION

Among the 15 compounds listed in Table 2.1, six PDCs demonstrated molecular docking scores exceeding those of the reference synthetic medications MSU38225, Gemcitabine and VBQ. These six compounds are comprehensively discussed in this section.

3.1 Pharmacokinetic studies

All PDCs meet the ADME requirements effectively. The ADME profile analysis revealed bioavailability scores of 0.55 and 0.56 for each PDC, as indicated in Table 3.1a. All the 6 PDCs cross the Blood-brain barrier (BBB) except asiatic acid(Table3.1b). It's interesting to note that every compound adhered to Lipinski's criterion, druglikeness (Table3.1a).

3.2 Cytotoxicity studies

In Silico prediction of Cytotoxic Potential in PDCs against Lung Cancer Cells the CLC-Pred 2.0 [37] program employed PASS (Cell Line Cytotoxicity Predictor) algorithms to evaluate the likelihood of activity (Pa) and inactivity (Pi) against particular human cancer cell lines in order to forecast the cytotoxic potential of six PDCs. With a projected cytotoxicity of 0.839 and a Pi of 0.009 against the human lung cancer cell line A549(Table3.2), Sesamin outperformed the other drugs examined, suggesting a high likelihood of action. Asiatic acid and Tubulosine likewise demonstrated moderate expected cytotoxic potential against A549 cells, with respective Pa values of 0.428 and 0.543(Table3.2). For lung carcinoma, all these three PDCs showed the same Inhibition Activity Probability (IAP*) values of 0.856, indicating a consistent potential for anti-cancer activity. The projected activity of Chrysophanic acid, Bavachinin, and Chrysin, A549/TR, a potential cisplatin-resistant kind of lung cancer, was used to evaluate the results. While the values for Bavachinin and Chrysin were 0.092 and 0.081, respectively, Chrysophanic acid had a Pi of 0.007 and a Pa of 0.148(Table3.2). Even though these three

drugs' Pa scores were lower than those of compounds evaluated on A549 cells, they showed higher IAP* values of 0.959, which suggests a larger anticipated inhibitory capability against the resistant adenocarcinoma phenotype. These findings imply that while Chysophanic acid, Bavachinin, and Chrysin may have the ability to overcome medication resistance in lung adenocarcinoma, Sesamin may be a suitable candidate for treating conventional lung cancer.

3.3 MOLECULAR DOCKING

Molecular docking is a popular and reliable in silico method that is essential in the early phases of logical drug development since it can predict the binding orientation and affinity of bioactive chemicals within the target protein's active site. Molecular docking was used in this study to assess the binding affinities of 6 PDCs— Sesamin, Asiatic acid, Tubulosin, Chrysophanic acid, Bavachinin, and Chrysin against test protein and their docking scores were compared with three reference molecules (MSU38225, Gemcitabine and VBQ) that are known to be active against targets related to lung cancer. The docking scores of the reference compounds, which show a gradient of binding efficacy from moderate to low, were MSU38225 (-9.3 kcal/mol) Gemcitabine (-8.1 kcal/mol), and VBQ (-7.4 kcal/mol). All six PDCs showed higher anticipated binding affinities in contrast. A docking score of – 10.4 kcal/mol showed that Sesamin had the greatest interaction, surpassing all reference compounds. Chrysin matched MSU38225 score of -9.3 kcal/mol, but Bavachinin (-9.4 kcal/mol), Asiatic acid (-9.9 kcal/mol), and Tubulosin and Chrysophanic acid (-9.7 kcal/mol each) all outperformed it. Compared to Gemcitabine and VBQ, all test substances performed noticeably better. These results show that these natural substances have the potential to be excellent lead candidates for additional pharmacological research and development in the treatment of lung cancer. Their value in the context of drug development based on natural products is highlighted by their superior or equivalent binding characteristics in comparison to the reference standards.

3.4 The 2D & 3D visualization

To understand the interactions at the molecular level between 1X2Jand six plant-derived compounds (sesamin, Asiatic acid, Tubulosine, Chrysophanic acid, Bavachinin, and Chrysin)—which demonstrated higher molecular docking scores than the standard synthetic drug—2D and 3D visualizations were performed using Biovia Discovery Studio. The Biovia Discovery Studio program's 2-D interaction tool has shown the following interaction

Sesamin is a lignan compound primarily found in sesame seeds and sesame oil possessing antioxidant, anti inflammatory and anti cancer properties[42]. It manifested high-affinity with target protein showing multiple intractions stabilizing the ligand within the binding pocket. The key intraction hydrogen bond with residue VAL A:418 along with carbon hydrogen bond with residues GLY A:364, GLY A:462 and GLY A:509, the diverse interaction profile suggest a strong binding affinity of the compound to the active site. (Fig 1)

Asiatic acid (AA) is mostly found in *Centella asiatica*, a traditional medicinal herb. *C. asiatica* is primarily composed of pentacyclic triterpenoid saponins[22]. AA demonstrated conventional hydrogen bond of ligand with residues VAL A:465 and VAL A:561 . These interactions indicate strong binding affinity and potential anti cancer activity of this PDC. (Fig 2)

Tubulosine is an alkaloid that occurs naturally. 2D & 3D visualization revealed multiple interactions of Tubulosine with 1X2J stabilizing the ligand within the binding pocket. Key conventional hydrogen bonds are observed with residues VAL A:418, VAL A:465, and VAL A:606. Hydrophobic interactions, including alkyl and pi-alkyl, were identified with ALA A:366 , CYS A:368 , VAL A:420 , VAL:467, and LEU A:468. The diverse interaction profile suggests a strong binding affinity of the compound to the active site. (Fig 3)

Chrysophanic acid, a naturally occurring anthraquinone (chrysophanol), has been extracted from a variety of biological sources, such as microorganisms, lichens, and plants[26]. Its 2D & 3D visualization with protein (PDB ID: 1X2J) revealed key

interactions that stabilize the ligand within the binding pocket . Key conventional hydrogen bonds were observed with residues LEU A:365, VAL A: 465, and VAL A:512. while carbon hydrogen bonds formed with residues ALA A:366, GLY A: 464 and GLY A: 605 were identified, contributing additional stability to the ligand–protein complex. An unfavourable acceptor – acceptor interaction with VAL A:606 was noted, potentially indicating steric or electronic repulsion with the binding site. These interactions collectively provide insight into the binding mechanism and suggest that the molecule has notable binding potential with the target protein. (Fig 4)

Bavachinin is a naturally occurring bioactive flavanone present in the dried seeds of *Psoralea corylifolia*[43]. Important interactions that support the stability of its binding with the target protein were revealed by the molecular docking with the protein. Conventional hydrogen bonds with VAL A:465 and ARG A:415 were found. Alkyl and pi-alkyl hydrophobic interactions were observed, such as those between ARG A:415 and ALA A:556. Furthermore, the ligand stabilizes the binding pocket by a pi-sigma bond interaction with ALA A:556. These interactions suggest that the chemical has a high binding affinity and may have biological activity (Fig 5).

Chrysin (5,7-dihydroxyflavone), a naturally occurring polyphenol, is present in propolis, honey, and a number of different plants[44]. 2D & 3D visualization revealed that in addition to carbon-hydrogen interactions with residue GLY A: 464, which indicated polar contact, a typical hydrogen bond was seen with residues such as VAL A: 606, GLY: 367, VAL A: 465, and VAL: 512. The residues ALA A:366, ALA A:566, and ARG A:415 showed hydrophobic interaction. These interactions imply that the drug has a good chance of interacting to the protein of interest (Fig 6).

The docking studies showed that MSU38225 had a high affinity for binding to the 1X2J protein. This suggests a stable interaction between the ligand and the protein, indicating keap1 inhibitory potential. The molecular docking analysis of MSU38225 with protein showed key interactions that contribute to its binding stability, van der Waals interactions with amino acid residues like ILE A:416 and Val A: 418.Hydrophobic interactions,

including alkyl and Pi-alkyl interactions, were identified with ALA A:366, CYSA:368, VAL A:369, VAL A:420 and ALA A:607 contribute to the total binding affinity by encouraging the ligand to fit snugly (Fig 7).

Gemcitabine is a synthetic medication that is currently used for lung cancer treatment. The docking studies showed that Gemcitabine had a high affinity for binding to the 1X2J protein. This suggests a stable interaction between the ligand and the protein, indicating keap1 inhibitory potential. The molecular docking analysis of Gemcitabine residues GLY A:367, VAL A:465, and VAL A:512 Through hydrophobic interactions, carbon–hydrogen bonds with LEU A:365, GLY A:417, and GLY A:464 were found, further stabilizing the ligand. The residues VAL A:463 and ALA A:510 were found to exhibit halogen bonding interactions, suggesting that halogen moieties contribute to improved specificity. Further supporting the overall binding conformation was a Pi- Sigma interaction between the ligand's aromatic ring and ALA A:366 aliphatic side chain (Fig 8).

A good binding profile within the active site was shown by VBQ in the docking analysis with the 1X2J protein. GLY A:364, SER A:508, and ALA A:556 all formed three hydrogen bonds with the molecule, enabling strong polar interactions that are necessary for ligand stability. Furthermore, SER A:363, GLY A:509, and GLY A:603 were shown to form carbon–hydrogen bonds, which helped to stabilize hydrophobic compounds by means of van der Waals forces. A prominent Pi-Pi T-shaped interaction occurred between the aromatic framework of VBQ and the phenolic ring of TYR A:334, promoting stereoelectronic complementarity and aiding in the precise positioning of the ligand within the binding pocket. Additionally, a hydrophobic Pi–alkyl interaction between the aromatic segment of VBQ and the aliphatic side chain of ARG A:415 contributed to the non-polar environment, thereby enhancing the binding strength and structural stability of the ligand–protein complex (Fig 9).

TABLE 3.1a The drug-likeness properties of the 6 shortlisted PDCs using swissADME

S. No	Natural Compounds	No. Of Lipinski violations	Druglikeness	MLOGP	GI absorption	Bioavailability Score	Water Solubility LOGS (ESOL) CLASS	No. of H-bond acceptor	No. of H-bond donor
1.	Sesamin	0	Yes	1.98	High	0.55	-3.93 Soluble	6	0
2.	Asiatic acid	0	Yes	4.14	High	0.56	-6.33 Less soluble	5	4
3.	Tubulosin	0	Yes	2.88	High	0.55	-5.68 Moderately souluble	5	3
4.	Chrysophanic Acid	0	Yes	0.92	High	0.55	-4.11 Moderately souluble	4	2
5.	Bavachinin	0	Yes	2.61	High	0.55	-4.83 Moderately souluble	4	1
6.	Chrysin	0	Yes	1.08	High	0.55	-4.19 Moderately souluble	4	2
X.	MSU38225	0	Yes	3.44	High	0.55	-5.50 Moderately souluble	2	1
Y.	Gemcitabine	0	Yes	1.22	High	0.56	-0.67 Very soulubl	7	3

							e		
Z.	VBQ	0	Yes	1.22	High	0.56	-2.96 soluble	4	2

TABLE 3.1b The obtained values of ADMET properties of the 6 shortlisted PDCs using pkCSM

S.No	Natural Compounds	Intestinal absorption (human)	BBB permeability	DISTRIBUTION (Log BB) CNS Per (LogPs)	EXCRETION Total clearance	AMES Toxicity
1.	Sesamin	97.81	Yes, -0.862	-2.939	-0.126	Yes
2.	Asiatic acid	62.8555	No, 0.646	-1.984	0.202	No
3.	Tubulosin	91.521	Yes, -0.815	-1.897	1.082	No
4.	Chrysophanic Acid	96.558	Yes,0.212	-2.111	0.02	Yes
6.	Bavachinin	93.672	Yes, -0.36	-1.878	0.073	No
7.	Chrysin	93.761	Yes ,0.403	-1.912	0.405	No
X.	MSU38225	92.613	Yes, -0.361	-1.324	0.523	Yes
Y.	Gemcitabine	68.491	No, -0.878	-3.61	0.415	No
Z.	VBQ	95.307	No, -0.285	-2.486	0.287	No

TABLE 3.2: Cytotoxicity of shortlisted PDCs Against Human Cancer Cell Lines.

S. No	Natural Compounds	Pa	Pi	Cell-line	Description	Tissue/Organ	Type	IAP*
1.	Sesamin	0.839	0.009	A549	Lung carcinoma	Lung	Carcinoma	0.856
2.	Asiatic acid	0.428	0.094	A549	Lung carcinoma	Lung	Carcinoma	0.856
3.	Tubulosin	0.543	0.057	A549	Lung carcinoma	Lung	Carcinoma	0.856
4.	Chrysophanic Acid	0.148	0.007	A549/TR	Putative Cisplatin-resistant lung adenocarcinoma	Lung	Adenocarcinoma	0.959
5.	Bavachini	0.0	0.0	A549/	Putative	Lung	Adenocarci	0.9

	n	92	37	TR	Cisplatin-resistant lung adenocarcinoma		noma	59
6.	Chrysin	0.081	0.058	A549/TR	Putative Cisplatin-resistant lung adenocarcinoma	Lung	Adenocarcinoma	0.959
X.	MSU38225	0.097	0.031	A549/TR	Putative Cisplatin-resistant lung adenocarcinoma	Lung	Adenocarcinoma	0.959
Y.	Gemcitabine	0.511	0.065	A549	Lung carcinoma	Lung	Carcinoma	0.856
Z.	VBQ	0.206	0.184	A427	Lung carcinoma	Lung	Carcinoma	0.872

TABLE3.3: Molecular Docking Scores of the 6 PDC's with Protein (PDB ID: 1X2J)

S.No	Natural Compounds	PUBCHEM ID	Molecular Formula	Molecular Weight g/mol	Docking **Score** Kcal/mol	3D&2D vis
1.	Sesamin	72307	$C_{20}H_{18}O_6$	354.4	-10.4	Fig 1
2.	Asiatic acid	119034	$C_{30}H_{48}O_5$	488.7	-9.9	Fig 2
3.	Tubulosin	72341	$C_{29}H_{37}N_3O_3$	475.62	-9.7	Fig 3
4.	Chrysophanic acid	10208	$C_{15}H_{10}O_4$	254.24	-9.7	Fig 4
5.	Bavachinin	10337211	$C_{21}H_{22}O_4$	338.4	-9.4	Fig 5
6.	Chrysin	5281607	$C_{15}H_{10}O_4$	254.24	-9.3	Fig 6
X.	MSU38225	102125878	$C_{21}H_{19}N_3$	313.4	-9.3	Fig 7
Y.	Gemcitabine	60750	$C_9H_{11}F_2N_3O_4$	263.2	-8.1	Fig 8
Z.	VBQ	165416264	$C_{16}H_{11}NO_4$	281.26	-7.4	Fig 9

Fig 1: Sesamin

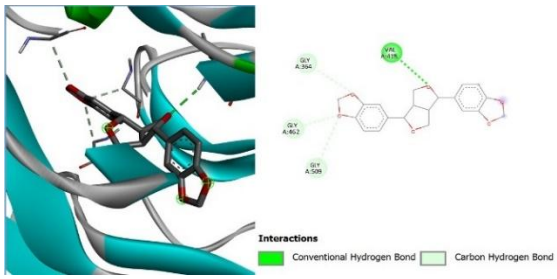


Fig 2: Asiatic acid

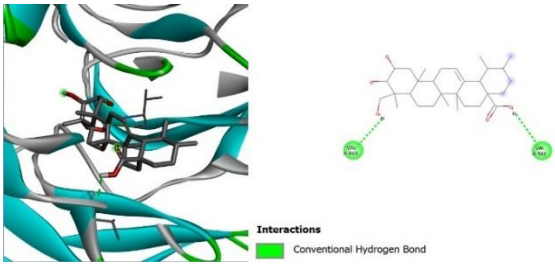


Fig 3: Tubulosin

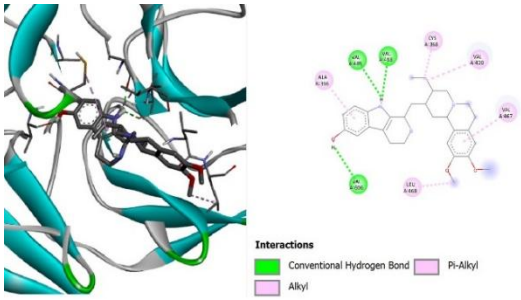


Fig 4: Chrysophanic acid

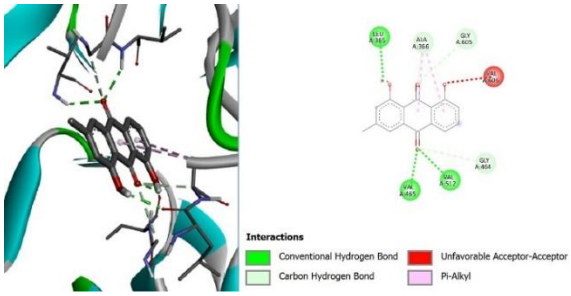


Fig 5: Bavachinin

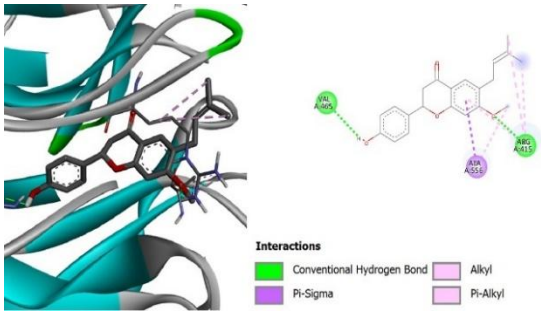


Fig 6: Chrysin

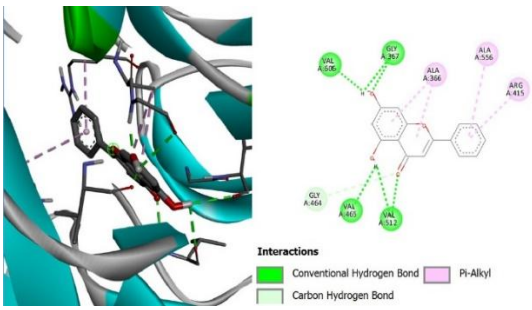


Fig 7: MSU38225

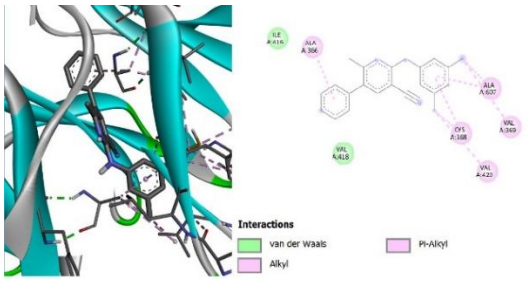


Fig 8: Gemcitabine

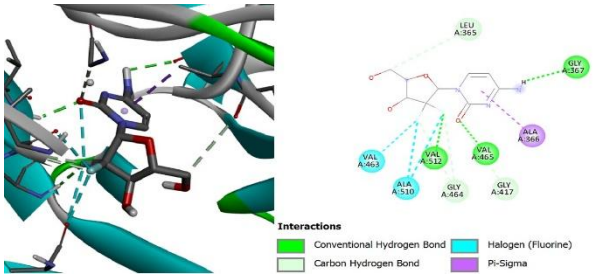
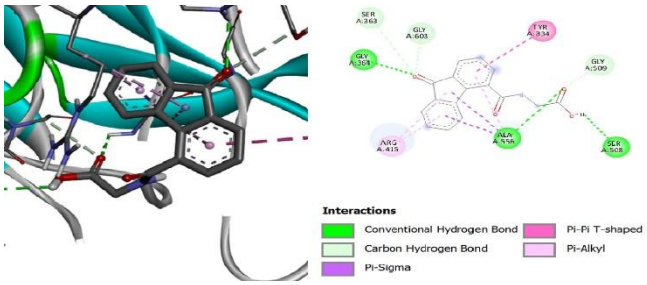


Fig 9: VBQ



CHAPTER 4

CONCLUSIONS

A balance between ROS and antioxidants is necessary for the human body's cells and tissues to operate properly. Oxidative stress is the result of this balance being upset and ROS production being above normal. Direct inhibition of Keap1 has emerged as a promising strategy to combat oxidative stress-related diseases, including lung cancer. The synthetic lung cancer drugs are associated with significant side effects. Therefore, PDCs are being explored as therapeutic agents. This study highlights the potential of natural small molecules as Keap1 inhibitors, paving the way for the development of targeted lung cancer treatments. Among 108 selected PDCs, fifteen were found to possess favorable characteristics for drug development. Further, Sesamin with PubChem ID: 72307, has shown the best docking score and fulfilled other requirements as well. Sesamin is an active compound found in sesame seeds. In East Asia, Sesamum indicum L. seeds are utilized as a traditional meal, and its oil is used in Chinese and Indian naturopathic medicine to prevent aging and increase vitality. It concludes that Sesamin has the strong potential to be used in developing a novel therapeutic drug for lung cancer treatment. Its natural origin and absence of side effects, in contrast to synthetic drugs, make it an appealing candidate for further drug development and clinical evaluation.

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SUSTAINABLE DEVELOPMENT GOALS THAT CAN ALIGN WITH THIS RESEARCH

SDG 1: No Poverty

The study may potentially lower the cost of cancer care by creating low-cost remedies from locally accessible plants, which would lessen healthcare-related poverty in regions that are already at risk.

SDG 3: Good Health and Well Being

This research promotes the discovery of possible anti-lung cancer chemicals. In order to help with early identification, therapy development, and prevention methods for lung cancer—one of the most prevalent non-communicable diseases. Promoting easily available and reasonably priced healthcare options, especially in poor nations, is consistent with the use of traditional medicinal herbs.

SDG 9: Industry, Innovation and Infrastructure

Innovative methods in biotechnology and health sciences are demonstrated by the application of in silico analysis and computational drug discovery.
It facilitates quick and inexpensive screening of bioactive chemicals, increasing the effectiveness and scalability of drug development.

SDG 15: Life on Land

By concentrating on traditional medicinal plants, the study emphasises the importance of indigenous knowledge and biodiversity.
It can promote the sustainable use of natural resources for medical purposes as well as the protection of plant species.

SDG 17: Partnership for the Goals

Collaborations between practitioners of traditional medicine, biomedical researchers, and computational scientists are encouraged by this type of multidisciplinary study. The publication might encourage international collaborations in the areas of cancer research and treatment development.

LIST OF PUBLICATIONS

1. Conference Details

1.1 Poster presentation by Nikita

Presented Poster titled **"The investigation of keap1 inhibition through molecular docking and cytotoxicity studies of naturally derived compounds in lung cancer therapy"** in the International conference on **"Current Advances in Drug Design and Translational Science" (CADDTS-2025)** organized by Department of Chemistry, Jamia Milia Islamia, New Delhi held on 26th-28th February 2025.

1.2 Poster presentation by Manisha Kumari

Presented Poster titled **"Molecular Docking and Cytotoxicity evaluation of protein target plant derived compound for lung cancer therapy"** in the International conference on **"Ecosystem functioning and sustainability in changing environment" (ESCE-2025)** organized by Department of Botany, Institute of Science, Banaras Hindu University held on 6th-8th February 2025.

2. Certificates

International Conference on
Ecosystem Functioning and Sustainability in Changing Environment
ESCE - 2025
Organized by
Department of Botany, Institute of Science
Banaras Hindu University, Varanasi-221005, INDIA

Certificate

This is to certify that Dr./Mr./Ms. Manisha Kumari, Delhi Technological University has been awarded Young Scientist/Women Scientist/best oral/ best poster presentation award during the **International Conference on "Ecosystem Functioning and Sustainability in Changing Environment" (ESCE-2025)** held from February 6-8, 2025, at the Department of Botany, Banaras Hindu University, Varanasi, India. The title of the work presented was Molecular docking and cytotoxicity evaluation of Protein target plant derived compounds for lung cancer therapy

Prof. R Sagar
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Prof. Satheeshkumar PK
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INTERNATIONAL CONFERENCE ON CURRENT ADVANCES IN DRUG DESIGN AND TRANSLATIONAL SCIENCE (CADDTS-2025)

(UNDER THE AEGIS OF SPARC PROGRAM)

26th – 28th February 2025

CERTIFICATE OF PRESENTATION

This is to certify that Dr./Mr./Ms. Nikita of Delhi Technological University has successfully presented oral/poster titled "The investigation of Keap1 inhibition through molecular docking and cytotoxicity studies of naturally derived compounds in lung cancer therapy" in the international conference on "Current Advances in Drug Discovery and Translational Science", organized by the Department of Chemistry, Jamia Millia Islamia, New Delhi, held on 26th – 28th February 2025.

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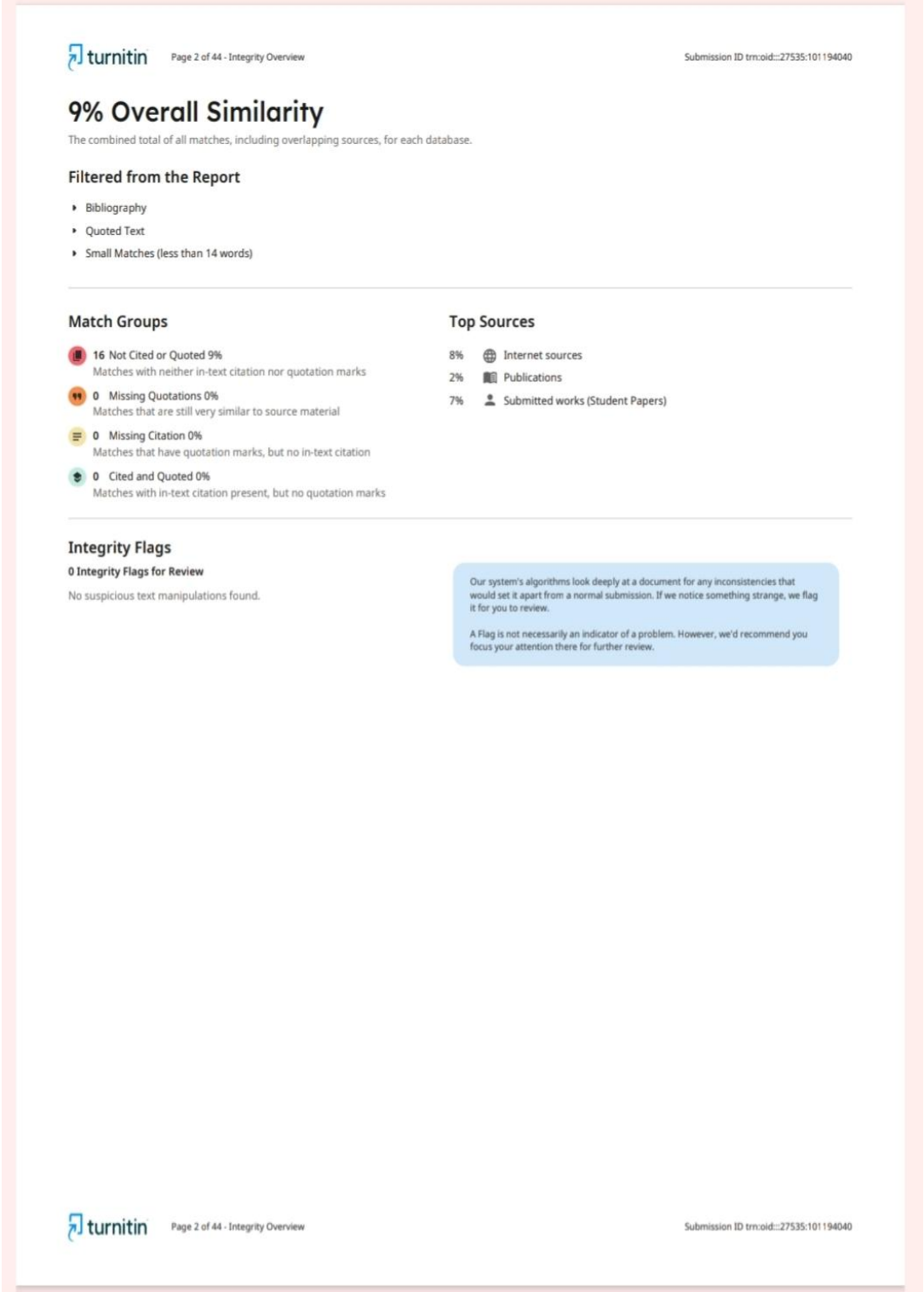

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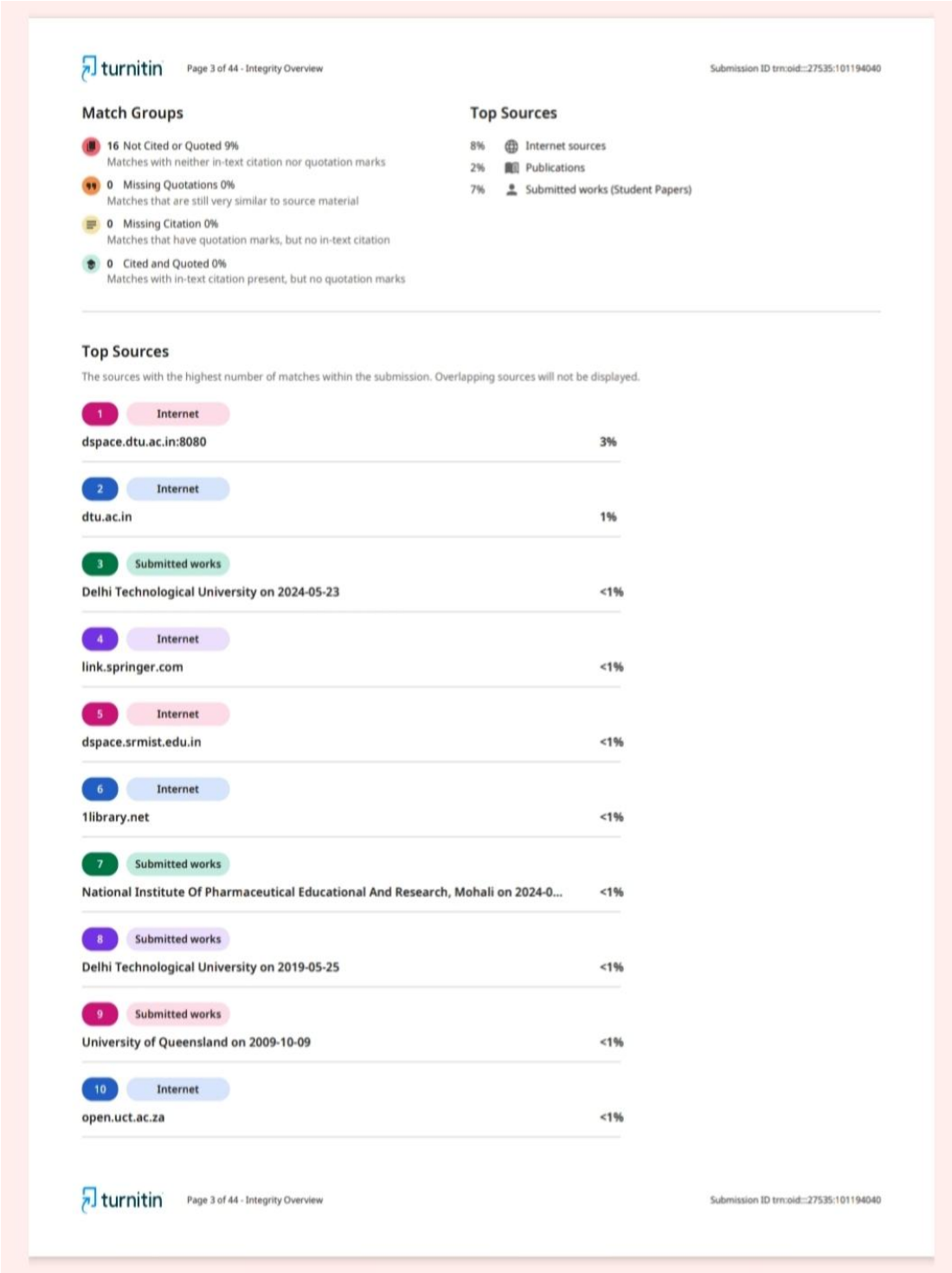

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