"Exploring Apigenin's Potential: Novel Bioactive Molecules for Colon and Lung Cancer Treatment - Insights from Computational and SAR Analysis"

B. Pharm (Honors) Project Report

[In the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

Department of Pharmacy

Faculty of Allied Health Science

Daffodil International University

Submitted By

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Batch: 23rd, Section: B

Department of Pharmacy

Faculty of Allied Health Science

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APPROVAL

This confirms that the research project **"Exploring Apigenin's Potential: Novel Bioactive Molecules for Colon and Lung Cancer Treatment - Insights from Computational and SAR Analysis"** was accepted for partial completion of the requirements for a Bachelor of Pharmacy degree from Daffodil International University's Faculty of Allied Health Science. The project's formats and materials received approval.

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First of all, I want to sincerely thank Allah for his knowledge, physical well-being, perseverance, and spiritual serenity, as well as for guiding me throughout all the challenges I faced to complete this task.

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D E C L A R A T I O N

I, Ruhul Amin, hereby certify that I have completed this project work, "**Exploring Apigenin's Potential: Novel Bioactive Molecules for Colon and Lung Cancer Treatment - Insights from Computational and SAR Analysis**," partially fulfills the requirements for the degree of Bachelor of Pharmacy. I did this under the supervision of **Prof. Dr. Muniruddin Ahmed**, Professor and Head of the Department of Pharmacy, Daffodil International University. In addition, I certify that, other from what is stated above, this work has never before been submitted, in whole or in part, to any other institution or university in hopes of earning another degree or professional certification.

Supervised By

Prof. Dr. Muniruddin Ahmed

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DEDICATION

Dedicated to my parents, who have supported me during my entire B.Pharm journey, and all of my esteemed teachers.

Abstract

Introduction:

Research attempts are still being driven by the need to find successful therapies for lung and colon cancer, with an emphasis on utilizing natural substances. Of them, apigenin has attracted notice due to its intriguing bioactive characteristics. This work investigates the creation of novel bioactive compounds using apigenin and its metabolites for the treatment of lung and colon cancer. It does this by using computational and structure-activity relationship (SAR) methodologies. We are able to learn more about the pharmacological profiles and molecular interactions of these drugs using SAR analysis and computational modeling. The results pave the path for additional laboratory testing and practical application by highlighting the probable use of apigenin and its derivatives as worthwhile candidates for curative option in lung and colon cancer.

Objective:

The objective of this research is to utilize computational and SAR methodologies to develop new bioactive molecules derived from natural apigenin, with the aim of providing effective treatments for colon and lung cancer.

Methodology:

Apigenin and its eight derivatives' physiological and biochemical properties were predicted using the PASS prediction program. Each compound's Pa and Pi values were determined, and eight of them showed encouraging results, indicating that they would make good therapeutic candidates. The molecular structures of the eight variants have been optimized employing resonance frequencies from the DND base and the B3LYP functional, and they were then saved in pdb type for further computer analysis. In addition, the modified substances' ADMET data were evaluated employing the pkCSM tool, and their drug-like qualities were analyzed using the Lipinski rule.

Conclusion

A study involving computational analysis of eight apigenin derivative compounds found nine myricetin derivative compounds with significant inhibitory activity against lung and colon cancer proteins. The compounds were ligands 2, 3, and 6 exhibited promising docking results, with ligand 2 being the most active. They also showed notable efficacy with docking scores of -9.6 and -9.3 kcal/mol. When compared to colon cancer protein PDB: 4UY9, ligands 2 and 6 showed enhanced efficacy with a binding affinity of -8.2 kcal/mol. The binding affinities of ligands 2 and 3 were augmented by -8.0 and -7.3 kcal/mol in lung cancer (PDB: 6MTU).These findings highlight the binding energy and enhanced stabilization of bioactive

apigenin derivatives within the active domain of the experimental proteins associated with lung and colon cancer.

Keywords: Apigenin, Molecular docking, colon cancer, lung cancer, drug design.

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Chapter One

Introduction

1. Introduction

Every biomedical inquiry and new drug development endeavor attempts to find cutting-edge and effective drugs to treat particular diseases. Therefore, it is necessary to carry out the process systematically or step by step to find and create new, powerful drugs. This is because developing new drugs is a labor-intensive, hazardous process that costs a lot of resources and financial investment.

Among the most frequent cancers are lung and colon cancers, which somewhat can occasionally develop simultaneously. Even though the entire medical domain is always evolving and improving, colon and lung cancer continue to be a major incidence that contributes to mortality for millions of people globally each year, following a World Health Organization statement. But up until today, no completely effective remedy has been discovered.

Thus, by deploying the newest reliable CADD techniques, this study has been done to discover new biologically active molecules to treat lung and colon cancer, through apigenin and its analogs. To choose the desired protein, the pass prediction tool was computed at the start of the investigation.

The study found that antiviral, antibacterial, and antifungal drugs have lower active scores than antineoplastic drugs. Carcinogenic proteins were identified in lung and colon cancer, and computer analysis revealed that Apigenin derivatives outperform common chemotherapeutic drugs like carboplatin and epirubicin hydrochloride. The docking score for colon cancer was -6.3 to -8.2 kcal/mol, while for lung cancer it was -7.8 to -9.6 kcal/mol.

Chapter Two

Objective of the Study

2. Objective of the Study

"The purpose of the current investigation is to utilize computational and SAR methodologies to develop new bioactive molecules derived from natural apigenin, with the aim of providing effective treatments for colon and lung cancer. Colon and lung cancer are one of the main reasons many patients are dying due to improper medical treatment option for all class of people. So, find some new compounds which will be easy to produce as well as effective is the main concern of this project"

Chapter Three

Literature review of Apigenin and It's Pharmacological Significance

3. Pharmacological significance of Apigenin

Oranges, celery, parsley, and chamomile tea are just a few examples of fruits, vegetables, and herbs that naturally contain Apigenin, a flavonoid. Numerous studies have been conducted on it, and the results have been published in scientific publications. An outline of its pharmacological relevance is provided below.

3.1 Anti-inflammatory Effect:

By blocking pro-inflammatory cytokines and enzymes including lipoxygenase (LOX) and cyclooxygenase (COX), apelin has shown strong anti-inflammatory effects. It's possible uses as medicine in inflammatory diseases are facilitated by this action [18][19].

3.2 Antioxidant Action:

Apigenin is a strong antioxidant that scavenges free radicals to lessen oxidative stress and shield cells from harm. Numerous health advantages, which include protection of the nervous system and cardiac wellness have been scientifically correlated to its antioxidant qualities [20][21].

3.3 Anticancer Properties:

Apigenin's potential for cancer therapy and protection has been the subject of numerous investigations. In numerous cancer types, especially breast, colon, prostate, and skin cancer, it is being demonstrated to cause apoptosis—programmed cell death—inhibit angiogenesis—blood vessel development necessary for cancer proliferation—and restrict the development of cancerous cells [22][23].

3.4 Neuroprotective benefits:

The antioxidant and anti-inflammatory properties of apigenin contribute to its neuroprotective benefits. It may lessen the effects of neurodegenerative illnesses including Parkinson's and Alzheimer's by lowering reactive oxygen species and inflammation of the neurons, according to research [24].[25].

3.5 Anxiolytic and Sedative Properties:

Preliminary research on apigenin has revealed sedative and anxiolytic (anxiety-reducing) characteristics. Like benzodiazepines, it functions as a positive allosteric modulator of GABA-A receptors, which suggests that it may be used to treat disorders such as insomnia and anxiety. [26][27]

Chapter Four

Materials and methods

4. Materials and methods

4.1 Computational method and working procedure

4.1.1 PASS prediction

To quantify the pass prediction, the online tool has been implemented. With an acceptance percentage of more than 95% for chemicals that resemble drugs, this online platform forecasts the physiological and biochemical features for approximately 4,000 groups of organic elements centered on their structural compositions. The values of Pa and Pi stand for it. According to Lagunanin et al. (2000), the Pa and Pi values often have a maximum of 1 [6].

4.1.2 Preparation of Ligand and molecular optimization

First, Chemdraw Professional was used to draw each and every chemical structure. To complete the algorithmic operation associated with these elements, vibrational pitches from the semi-core pseudo-potentials and DND basis (diffused basis set) operational are being implemented. Ultimately, the refined structures of molecules were saved in PDB format for subsequent computation, including ADMET, drug-likeness, pass prediction, and molecular docking.

4.1.3 Determination of the data of ADMET

The ADMET forecast is regarded as a crucial study for the creation and identification of novel medicinal compounds. When assessing the characteristics and in silico pharmacokinetic parameters of the compounds under consideration, the ADMET attributes are the most useful. This makes it possible to assess ADMET properties quickly and provisionally prior to the substances are thoroughly assessed in vitro, as newly produced molecules could be toxic or have negative effects on the body. Consequently, ADMET facts has been projected employing the online program pkCSM (http://biosig.unimelb.edu.au/pkCSM/prediction) [7]. The chemical characteristics and molecular structures provide the basis for the calculation and measurement of the aforementioned ADMET data.

4.1.4 Determination of Lipinski rule

Another crucial factor in computer-based medication creation is the Lipinski rule. The "rule of five" is a tool used to calculate how much a chemical will bind to its lipid bilayers in the body and how much of it will bleed through. Lipinski's "rule of five" is used to evaluate these attributes; If a ligand meets each of the following five requirements, it is deemed drug-like. [8]

- There is less than 500 g/mol of molecular weight.
- The water/octanol partition coefficient that was computed is less than five (logP 5).
- There are just a few less than five donors of hydrogen bonds.
- There are no more than ten hydrogen bond acceptors, mainly N and O atoms.

4.1.5 Protein preparation and molecular docking

When assessing drug interactions with proteins, one of the most effective and suitable methods is to use molecular docking.

Therefore, new protein needs to be produced prior to the docking assessments. In the beginning the 3D protein's crystal form was gathered from the Protein Data Bank at https://www.rcsb.org. Following uploading of this protein to the Biovia discovery studio 2021 application, all surplus and undesirable materials—such as pharmaceuticals or heteroatoms—were reduced. After that, it was imported to the PyRx program for ligand-based molecular interactions. And stored in PDB format. The protein crystal framework and the corresponding information that comes with it are provided as follows.

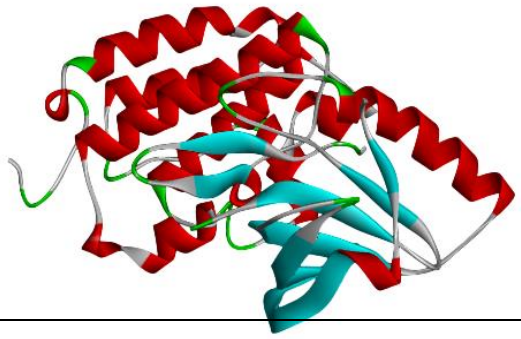
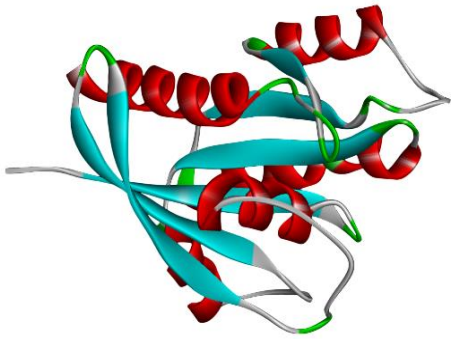
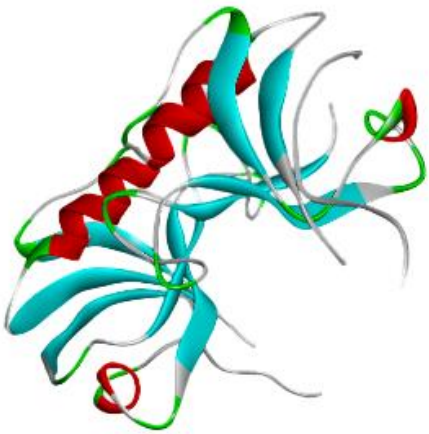
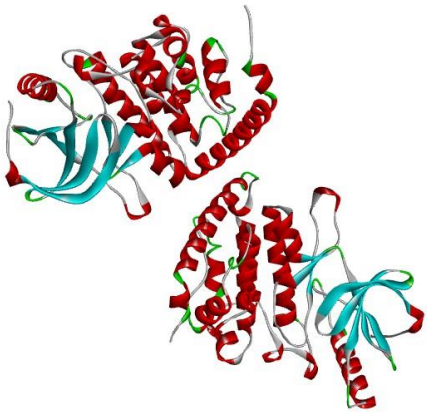
Title	Lung Cancer Protein PDB: 8A27	Lung Cancer Protein PDB: 8ONV
Organism	Homo sapiens	Homo sapiens
Resolution	1.07 Å	1.01 Å
three-dimensional structure of Lung cancer		
References		
Title	Colon Cancer Protein PDB: 6MTU	Colon Cancer Protein PDB: 4UY9
Organism	Homo sapiens	Homo sapiens
Resolution	2.14 Å	2.81 Å
three-dimensional structure of Colon cancer		
References		

Figure 1: Three-dimensional protein structure of lung and colon cancer

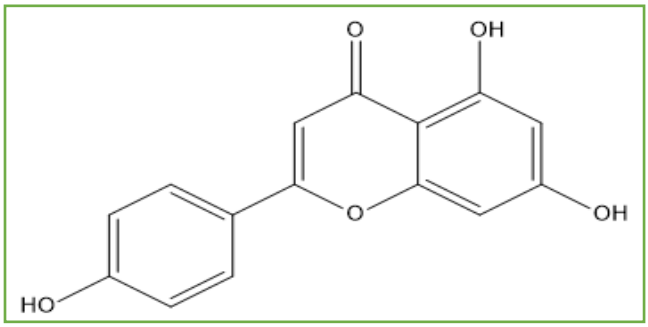
Chapter Five

Result and discussion

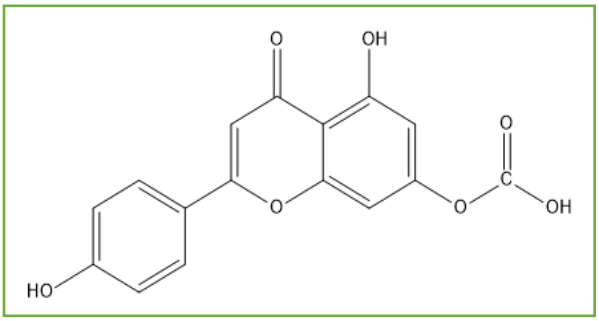
5. Result and discussion

5.1 Structure-activity relationship

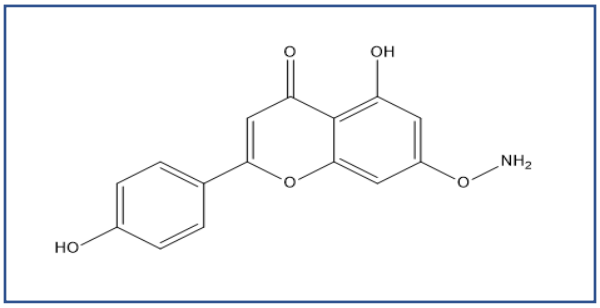
The structural–activity relationship (SAR) can be employed to forecast the intended biological processes compared to the molecular framework. There is a relationship between pharmaceuticals and chemical development. This cutting-edge method aids in the biosynthesis of innovative, appealing molecules and helps to describe existing substances, both of which are important goals in the drug development cycle. Apigenin was the main chemical in our study. To test Apigenin's effectiveness against lung and colon cancer, we replaced strong functional groups at various stages of the drug's development. The chemical composition is displayed below.



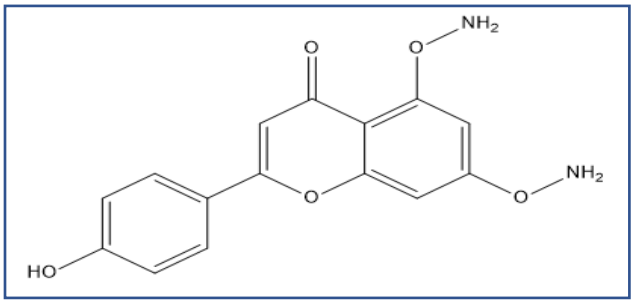
Ligand 1



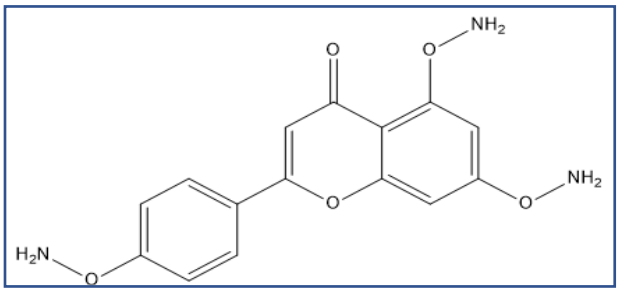
Ligand 2



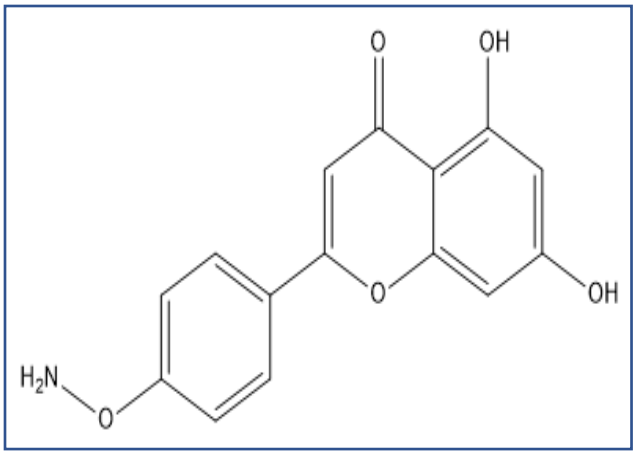
Ligand 3



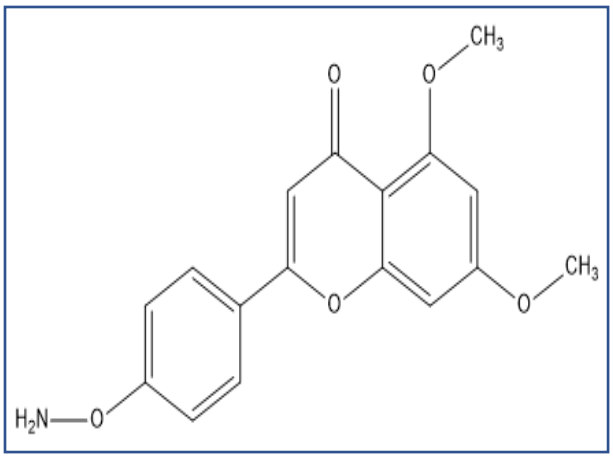
Ligand 4



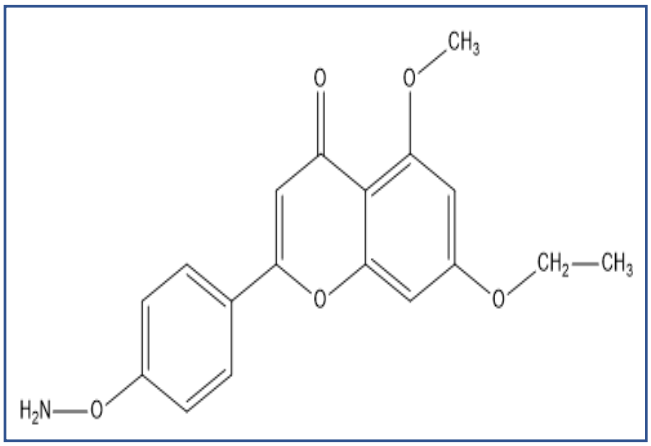
Ligand 5



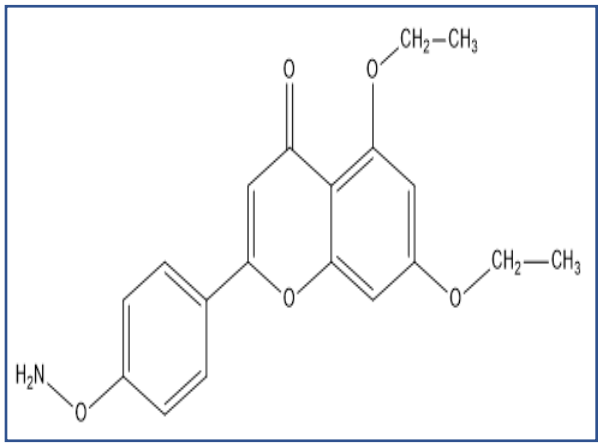
Ligand 6



Ligand 7



Ligand 8



Ligand 9

Figure 2: Chemical structure of Apigenin(Ligand-1) and its derivatives (Ligand 2-9)

5.2 PASS prediction spectrum and analysis

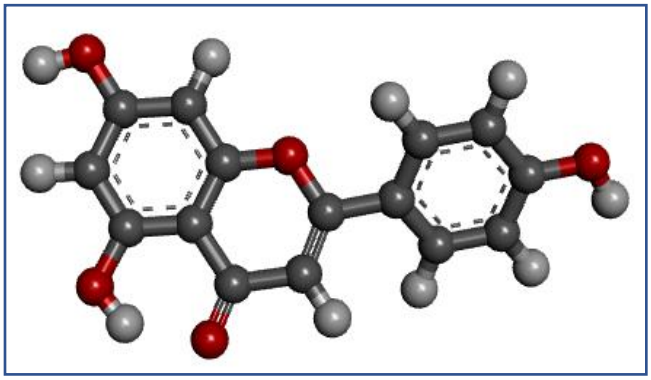
Using a web-based program called The Activity Profiles for chemicals (PASS) data on the antimicrobial, anti-fungal, and antineoplastic characteristics of the chemicals found through SAR research was gathered. The collected pass spectrum numbers that underwent scrutinized revealed Pa scores of 0,324–0,469 for antiviral, 0,183–0,391 for antibacterial, 0,195–0,524 for antifungal, and 0,768–0,942 for antineoplastic. This showcases the prospect of being antineoplastic or having a higher Pa score. As a result, the diseases to be addressed are lung and colon malignancies, and additional pertinent research has been conducted.

Table 1: Pass prediction spectra analysis

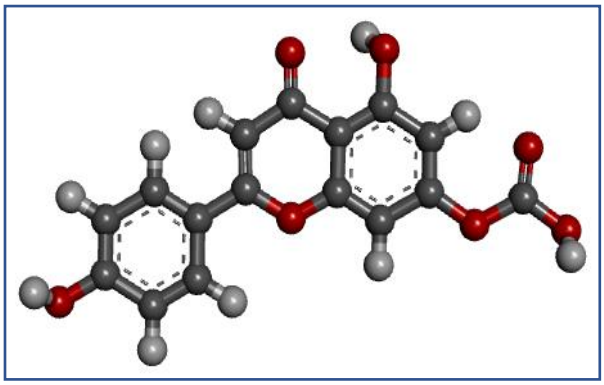
Ligand	Antiviral (Herpes)		Antibacterial		Antifungal		Antineoplastic	
No	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
01	0,469	0,014	0,391	0,032	0,524	0,027	0,774	0,015
02	0,406	0,033	0,364	0,039	0,373	0,056	0,768	0,016
03	0,409	0,032	0,291	0,064	0,319	0,074	0,902	0,005
04	0,381	0,044	0,225	0,098	0,252	0,105	0,922	0,005
05	0,348	0,061	0,189	0,129	0,195	0,140	0,942	0,004
06	0,409	0,032	0,291	0,064	0,319	0,074	0,902	0,005
07	0,333	0,070	0,183	0,134	0,207	0,132	0,893	0,005
08	0,324	0,075	*	*	0,199	0,137	0,825	0,009
09	0,350	0,060	*	*	0,212	0,129	0,832	0,008

5.3 Optimized Structure of the Tested Ligand

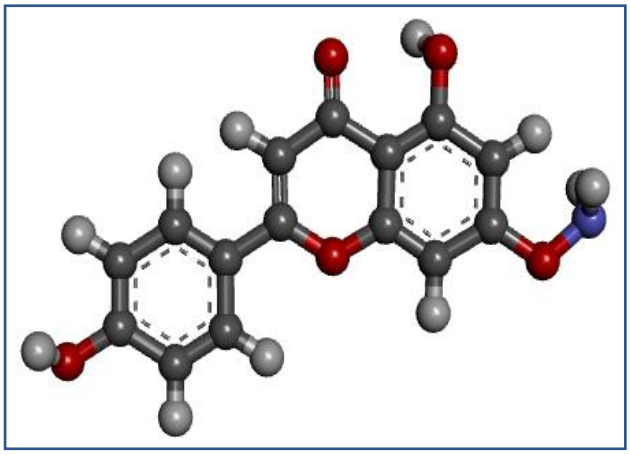
With the goal to generate an optimally robust structure with the lowest possible ground-state energy, structure adjustment is accomplished by changing a molecule's atoms. It is most widespread in computer-assisted chemistry to use this method [9]. To obtain appropriate insights, all investigated ligands ought to be tuned in prior to molecular docking. Figure 5 shows the chemical figures that have been modified.



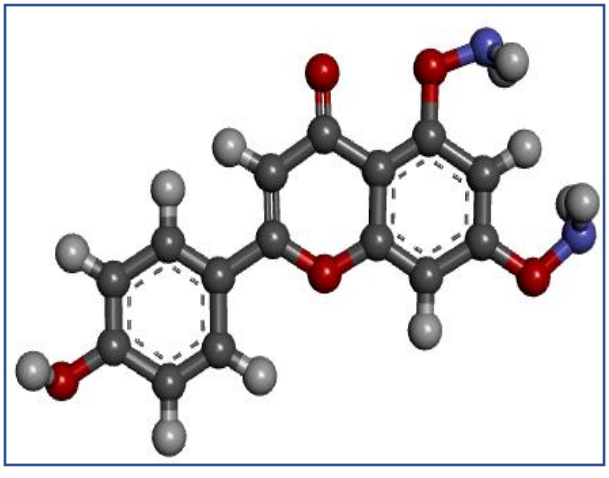
Ligand 1



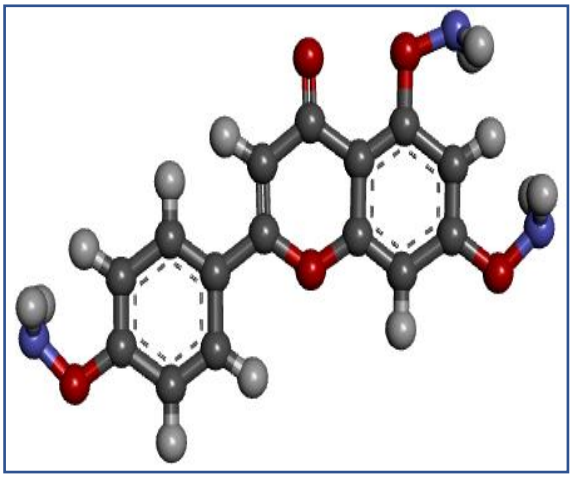
Ligand 2



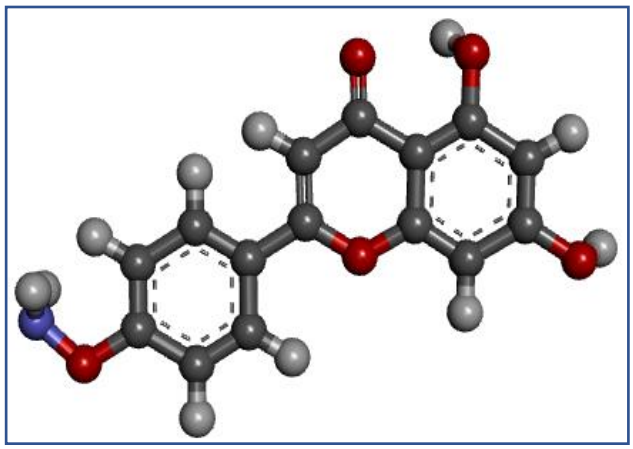
Ligand 3



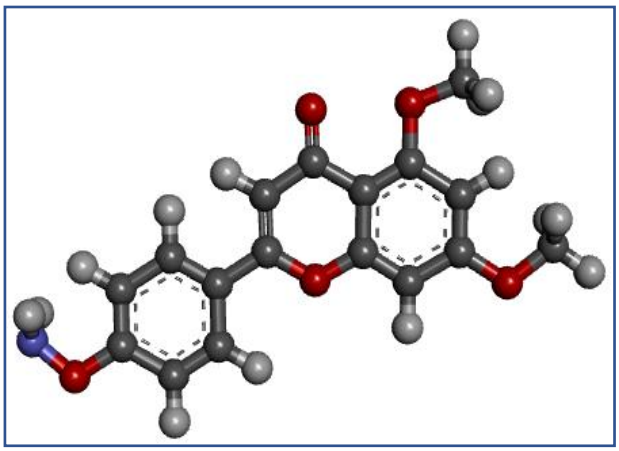
Ligand 4



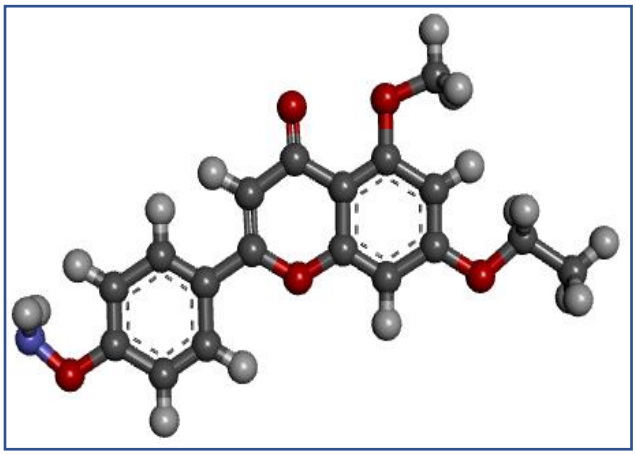
Ligand 5



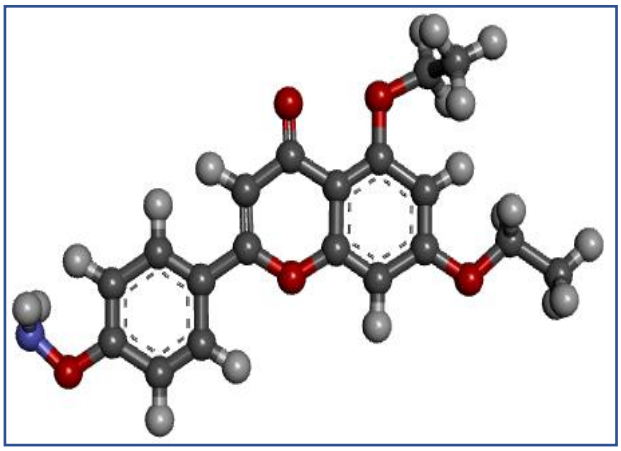
Ligand 6



Ligand 7



Ligand 8



Ligand 9

Figure 3: Optimized structure of the tested

5.4 Lipinski rule, pharmacokinetics, and drug-likeness

A major factor in why possible medications don't work and don't get to the target place is their low and insufficient bioavailability. Computational approaches for assessing drug-likeness, like the Lipinski rule, might drastically minimize these issues. To qualify as a viable and efficient orally bioactive compound and to give a specific physiochemical or biological productivity, every bioactive compound must conform to the Lipinski rule. Following identifying and validating the Lipinski rule for the molecules of interest that were disclosed, it was observed that every designed bioactive molecule actively adheres to the rule, with no violation of the rule.[10][8]

Furthermore, all molecules except ligand 2 have a bioavailability score of roughly 0.55, whereas the molecular weight value is determined at 270.24–341.36. Last but not least, the gastrointestinal system absorbs a large amount of all the bioactive compounds.

Table 2: Data on Lipinski rule, pharmacokinetics, and drug-likeness

Ligand No	Molecular weight	Number of rotatable bonds	Hydrogen bond acceptor	Hydrogen bond donor	Topological polar surface area Å²	Lipinski rule		Bioavailability Score	GI absorption
						Result	violation		
01	270.24	1	5	3	90.90	Yes	0	0.55	High
02	314.25	3	7	3	117.20	Yes	0	0.56	High
03	285.25	2	6	3	105.92	Yes	0	0.55	High
04	300.27	3	7	3	120.94	Yes	0	0.55	High
05	315.28	4	8	3	135.96	Yes	0	0.55	High
06	285.25	2	6	3	105.92	Yes	0	0.55	High
07	313.30	4	6	1	83.92	Yes	0	0.55	High
08	327.33	5	6	1	83.92	Yes	0	0.55	High
09	341.36	6	6	1	83.92	Yes	0	0.55	High

5.5 Molecular docking and interaction analysis

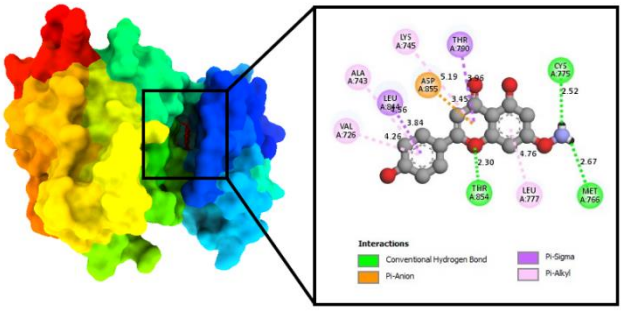
The table (3) shows the binding affinity of nine ligands (01-09) against two lung cancer proteins (PDB: 8A27 and PDB: 80NV) and two colon cancer proteins (PDB: 4UY9 and PDB: 6MTU). Binding affinity is measured in negative log units (kcal/mol), so higher values indicate stronger binding [11].

Here are some observations from the table:

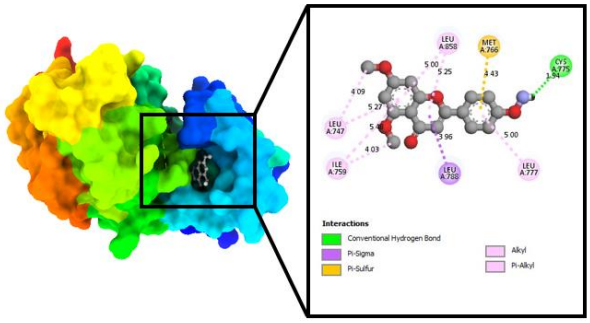
- For all ligands, the binding affinity is stronger against the lung cancer proteins than the colon cancer proteins. This suggests that the ligands may be more selective for lung cancer cells.
- Ligand 02 has the strongest binding affinity for both lung cancer proteins (PDB: 8A27 and PDB: 80NV), with values of -9.1 and -9.6 kcal/mol, respectively.
- Ligand 07 has the weakest binding affinity for both lung cancer proteins, with values of -8.1 and -8.5 kcal/mol, respectively.

Table 3: Binding affinity against lung and Colon cancer protein.

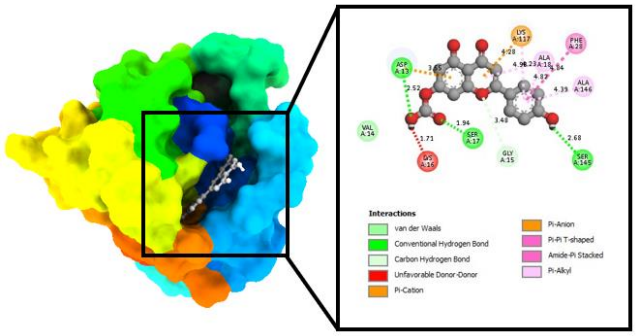
Ligand No	Lung Cancer Protein PDB: 8A27	Lung Cancer Protein PDB: 8ONV	Colon Cancer Protein PDB: 6MTU	Colon Cancer Protein PDB: 4UY9
01	-8.7	-9.1	-7.6	-8.1
02	-8.1	-9.6	-8.0	-8.2
03	-8.5	-8.8	-7.3	-7.8
04	-8	-8.8	-7.2	-8.0
05	-7.8	-9.1	-7.2	-7.7
06	-8.1	-9.3	-6.7	-8.2
07	-8.1	-8.5	-6.3	-7.9
08	-7.8	-8.6	-7.3	-6.6
09	-7.8	-8.2	-6.8	-7.6



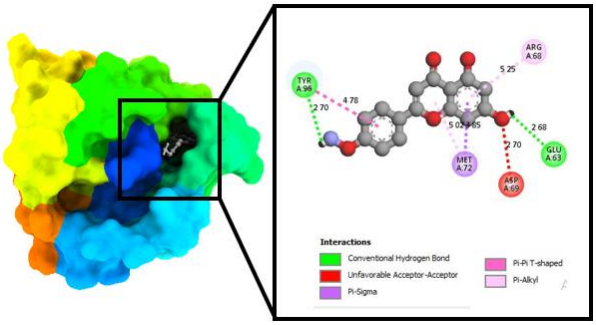
Molecular docking poses of 8a27 (EGFR) and Ligand 03



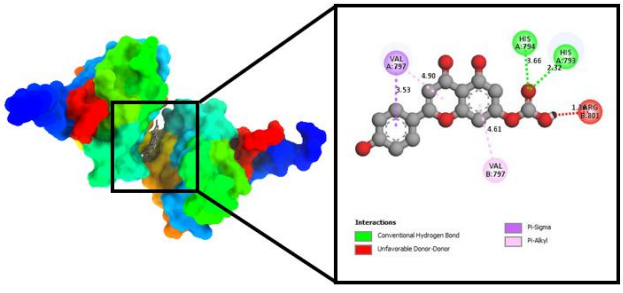
Molecular docking poses of 8a27 (EGFR) and Ligand 07



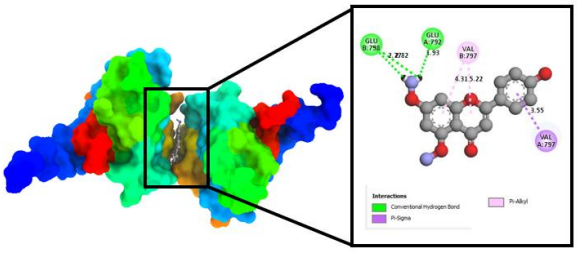
Molecular docking poses of 8ONV and Ligand 02



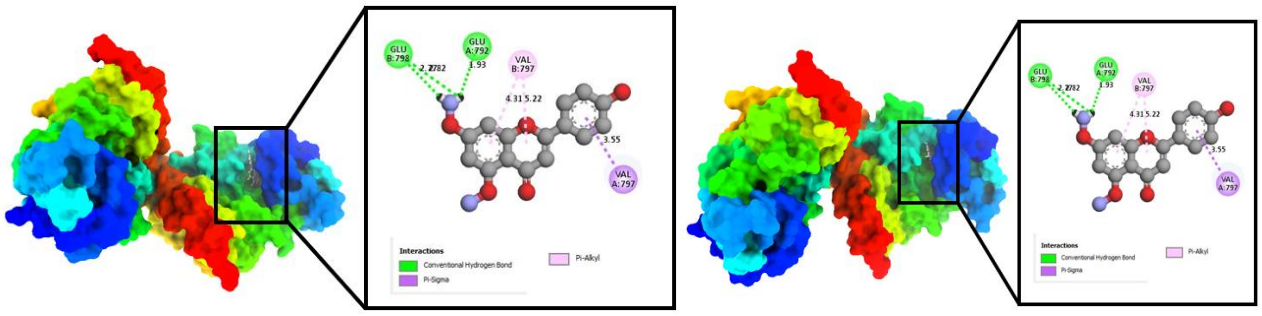
Molecular docking poses of 8ONV and Ligand 06



Molecular docking poses of 6MTU and Ligand 02



Molecular docking poses of 6MTU and Ligand 04



Molecular docking poses of 4UY9 and Ligand 02

Molecular docking poses of 4UY9 and Ligand 06

Figure 4: Docking interactions between the proposed compound and colon–lung cancer, hydrogen bonding, and 2D picture of the active sites

5.6 ADMET prediction and ADME features analysis

The development of efficient bioactive compounds necessitates the use of ADMET because drugs can have limitations, such as insufficient or toxic ADMET properties [13]. As a result, it is believed that estimating ADMET properties is essential to lowering the potential that complications could pop up in the aftermath of innovation and throughout clinical or preclinical treatment options [14].

Employing pkCSM [7],[12] and SwissADME [15], ADMET properties are anticipated for the described new Apigenin compounds. Furthermore, a logarithm (mol/L) is used to describe solubility in water [17]; insoluble <-10, weakly <-6, mildly <-4, soluble <-2, and extremely soluble <0) [16]. The observed log-scale derivatives of apigenin range from -3.179 to -3.707, which is between -3 and -4. This indicates that the chemical derivatives of apigenin are soluble in a water-based media.

Depending upon their positive LogP values, ligands 1, 6, and 7 exhibits the most desirable outcomes for distribution. The partition coefficient, or logP, describes how a molecule is distributed between water and fat. Higher distribution into tissues is indicated by positive values. Renal excretion of all substances is anticipated (OCT2 substrate).

Table 4: Computation of ADME features

Ligand No	Absorption		Distribution		Metabolism		Excretion	
	Water solubility, log S	Caco-2 permeability (10- 6 cm/s)	VDss (human) (log L/kg)	BBB permeability	CYP450 1A2 inhibitor	CYP450 2C9 inhibitor	Total clearance (ml/min/kg)	Renal OCT2 substrate
01	-3.329	1.007	0.822	-0.734	Yes	No	0.566	No
02	-3.75	0.845	-0.56	-1.331	Yes	No	0.706	No
03	-3.179	0.918	-0.093	-0.944	Yes	No	0.77	No
04	-3.246	-0.147	-0.183	-0.935	Yes	No	0.794	No
05	-3.205	-0.149	-0.017	-0.845	Yes	No	0.775	No
06	-3.129	1.028	-0.182	-1.015	Yes	Yes	0.757	No
07	-3.707	1.406	-0.077	-0.596	Yes	No	0.876	No
08	-3.893	1.389	0.019	-0.62	Yes	Yes	0.924	No
09	-4.145	1.387	0.033	-0.628	Yes	Yes	0.974	No

5.7 Aquatic and non-aquatic toxicity value analysis

Toxicology is another element affecting the safety and effectiveness of drugs. Hepatic damage dermal sensitivity, highest permissible dose, and AMES toxicities are the metrics used for forecasting aquatic and non-aquatic toxicity. Except 3, practically all ligands were found to be below the AMES toxicity threshold. The range of the greatest dose that may be tolerated was 0.328–0.913 mg/kg/day. Patients with scores of 2.45–3.488 mol/kg for oral rat acute toxicity and 1.254–2.582 mg/kg/day for oral rat chronic toxicity should receive a maximum of 0.913 mg/kg/day. Lastly, hepatotoxicity or skin sensitivity cannot be caused by any medication.

Table 5: Toxicity value prediction

Ligand No	AMES toxicity	Maximum tolerated dose (human), mg/kg/day	Oral rat acute toxicity (LD50), (mol/kg)	Oral rat chronic toxicity (mg/kg/day)	Hepatotoxicity	Skin Sensitization
01	No	0.328	2.45	2.298	No	No
02	No	0.858	2.476	1.817	No	No
03	Yes	0.76	3.165	1.748	No	No
04	No	0.913	3.242	1.988	No	No
05	No	0.559	3.262	2.582	No	No
06	No	0.803	3.145	1.7	No	No
07	No	0.714	3.484	1.254	No	No
08	No	0.743	3.488	1.261	No	No
09	No	0.814	3.459	1.327	No	No

Chapter Six

Conclusion

6. Conclusion

To create innovative, potent treatments against lung and colon cancer, several apigenin derivative compounds were exposed to computational research, including drug-likeness, pass perdition, ADMET, and molecular docking tests. Our research allowed us to pinpoint 8 Apigenin derivative substances with significant suppressive action. The docking results for ligands 2 and 3 showed the lowest score of -8.1 and -8.5 kcal/mol, correspondingly, whereas ligand 9 towards the lung cancer protein PDB: 8ONV had the highest score of -8.2 kcal/mol. Of the two addressed proteins, ligand 2 is the most effective ligand. The molecular docking scores are -9.6 and -9.3 kcal/mol in ligands 2 and 6, consequently. Additionally, at -8.2 kcal/mol, ligands 2 and 6 have increased in efficacy in comparison to colon cancer PDB 4UY9. likewise, the binding affinities of ligands 2 and 3 have increased by -8.0 and -7.3 in lung cancer (PDB 6MTU). Consequently, the crystal structures of lung and colon cancer as well as the suggested bioactive apigenin derivatives demonstrated that each molecule had some great and reasonable binding energy and enhanced stabilization in the the experimental protein's active domain.

Chapter Seven

References

7. References

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