Elucidating the Pharmacokinetic and Anticancer Properties of Ligands from Common Foods, Spices and Herbs Through Bioinformatics Techniques

ABSTRACT

Background: Cancer is one of the most destructive diseases, claiming millions of lives every year. Oncogenic proteins cause uncontrolled cell growth and potentially result in cancer and are now targets of cancer therapies. The use of *in silico* molecular biology techniques has sped up drug discovery and development.

Methodology: This research investigated the pharmacokinetic and anticancer properties of 60 phytochemicals (ligands) that are found in commonly consumed foods, fruits, vegetables, spices and medicinal plants, through standard *in silico* molecular biology techniques. The ligands were screened for their physicochemical properties, drug-likeness (including the Lipinski's Rule of Five), potential drug-drug interactions, and PAINS and Brenk alerts, using the SwissADME software. Thirteen ligands passed Lipinski's rule and the PAINS and Brenk alert tests. They were therefore used for the anticancer studies. The 13 ligands were docked with 10 oncogenic proteins by using the SwissDock software. Two reference anticancer drugs per oncogenic protein, totaling 20 reference drugs, were used as standard drugs for the anticancer molecular docking study. Selected docked protein ligand complexes were visualized for protein-ligand interactions via the Biovia Discovery Studio Visualizer.

Results: Eight of the ligands (Acetogenin, Annonacin, Annopentocin A, Apigenin, Kaempferol, Muricatonin A, Odoratin, & Scopadulciol) exhibited good dockings (binding energies of less than -6.0 kcal/mol) with at least one of the oncogenic proteins. Visualized protein-ligand interactions included hydrogen bonds, Pi-Alkyl, Pi-Sigma, Pi-Pi T-shaped, Amide-Pi Stacked, and Pi-Sulfur bonds. Many of the ligands exhibited good dockings with several oncogenic proteins. Three ligands (apigenin, kaempferol and scopadulciol) were exceptionally excellent in their dockings with most of the oncogenic proteins and they are recommended for further research, including molecular dynamics simulations and translational research studies. Likewise, the Arg V23, His V27, Leu Y174, Pro Y173, and Pro V28 residues of VEGF, and the Asn A557 residue of FGFR4 exhibited molecular interactions with several ligands tested.

Conclusion: This study has identified potential anticancer agents exhibiting favorable pharmacokinetic properties and minimal toxicity using bioinformatic approaches. Given that most anticancer drugs are associated with adverse effects on healthy cells, resulting in various side effects, the discovery of alternatives with reduced or negligible side effects represents a significant advancement. We recommend that further investigations, including molecular dynamics simulations and translational research studies, be carried out on the eight ligands which have demonstrated promising pharmacokinetic profiles and anticancer activity. Additionally, it is advisable to incorporate foods, spices, and herbs containing these ligands into regular diets, as

they passed pharmacokinetic and toxicity assessments and exhibited notable anticancer properties.

Keywords: Anticancer, Brenk Alert, Cancer, In Silico, Lipinski's Rule, Medicinal Plants, Pharmacokinetics, SwissADME, SwissDock, PAINS Alert.

1.0 INTRODUCTION

Cancer can be referred to as any one of many diseases that are characterized by the development of abnormal cells that divide uncontrollably and could infiltrate and destroy normal body tissue (Chunarkar-Patil et al., 2024). Cancers are among the most devastating diseases affecting humans, causing deaths of millions of people yearly (Upadhyay, 2020). Numerous genetic mutations have been linked to the transformation of normal cells that eventually lead to the development of cancer (Mroz & Rocco, 2017; Ujvari et al., 2018).

There has been a vast amount of data that indicates multiple kinds of physical, chemical, biological, genetic, and environmental factors that lead to the transformation of normal cells to cancerous cells (Upadhyay, 2020). An oncogene is a mutated or overexpressed cellular gene that promotes cancer by enhancing cell growth or inhibiting cell death (Brown, 2021).

Oncogenes encode oncogenic proteins that drive unchecked cell growth, potentially causing cancer. These proteins may be mutated, overexpressed, or fusion forms of normal cellular proteins—such as growth factors, receptors, signaling molecules, and transcription factors. Vascular endothelial growth factor (VEGF) is an oncoprotein which has been implicated in cancers of the breasts, lungs, renal, colorectal, retinoblastoma, pancreatic, prostate, head & neck, etc. (Bendardaf et al., 2017; Kokkotou et al., 2025). Other oncoproteins implicated or overexpressed in various cancers include B-cell lymphoma-2 (BCL-2) protein (Alam et al., 2021), BCL-2-like protein 1 (BCL2L1) (Magouliotis et al., 2022), nuclear factor kappa-B (NF-KB) (Mao et al., 2025), fibroblast growth factor receptor 4 (FGFR4) (Tang et al., 2018), Jak2 Kinase (Perner et al., 2019), epidermal growth factor receptor (EGFR) tyrosine kinase domain (Dickerson et al., 2024), vascular endothelial growth factor receptor 2 (VEGFR-2) (Guo et al., 2010), cyclin dependent kinase 2 (CDK-2) (Knudsen et al., 2025), cyclin dependent kinase 4 (CDK4) (Baker et al., 2022), phosphatidylinositol 3-kinase (PI3K) (Samuels & Waldman, 2010), human epidermal growth factor receptor 2 (HER2) (Cheng, 2024), mammalian target of rapamycin (mTOR) (Petroulakis et al., 2006), among others.

Many oncogenic proteins are targeted in cancer therapy. Targeted therapies work by inhibiting specific proteins involved in cancer progression, but these proteins may also have roles in normal cellular functions, which can result in side effects. The severity and type of side effects depend on the particular targeted therapy and the characteristics of the patient. In addition, many anticancer drugs harm normal cells, leading to serious side effects to the users. This has necessitated the need for safer anticancer drugs with minimal side effects (Du et al, 2021; Fornasier et al., 2018).

Medicinal plants have been used in various communities across the globe in cancer treatment, and many of them have been documented and shown to be promising and effective (Reyaz et al., 2025). In addition, many anticancer drugs have been obtained from medicinal plants. Examples are vincristine, vinblastine, camptothecin, cabazitaxel, and paclitaxel (Cardinali & Nervi, 1968; Dhyani et al., 2022; Sousa-Pimenta et al., 2023). Collectively, accumulating evidence has driven a growing research focus on the anticancer properties of medicinal plants.

Computer-aided drug discovery studies have become increasingly prominent, proving highly effective in complementing and enhancing research conducted in wet laboratories (Ivanova & Karelson, 2022). The application of *in silico* molecular biology methods has accelerated the process of drug discovery and design by uncovering critical insights into the structural and functional properties of nucleic acids, proteins, and prospective drug targets (Magouliotis et al., 2022).

This study used computer-aided drug discovery techniques to evaluate the pharmacokinetic and anticancer potential of 60 ligands from medicinal plants, vegetables, fruits, and spices. *In silico* analyses included ADME (absorption, distribution, metabolism & excretion) and toxicity studies, aiming to identify safe, effective natural anticancer agents for future use.

2.0 MATERIALS AND METHODS

2.1 Selection and Retrieval of Oncogenic Proteins

Ten oncogenic proteins were retrieved in their Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) formats from the PDB Data Bank (https://www.rcsb.org/). Table 1 below provides information on the 10 oncogenic proteins, their PDB IDs, and some of the cancers in which they have been implicated.

Table 1

Oncogenic Proteins Used for Molecular Docking

S/N	PROTEIN	RCSB PDB IDs	CANCERS
1	Vascular Endothelial Growth Factor (VEGF)	1FLT	Breast; lung, renal, colorectal, retinoblastoma, pancreatic, prostate, head & neck, etc. (Bendardaf et al., 2017; Kokkotou et al., 2025)
2	Nuclear factor kappa-B (NF-KB)	1SVC	Hepatocellular, breast, colon, prostate. (Mao et al., 2025)
3	Fibroblast growth factor receptor 4 (FGFR4)	4XCU	Hepatocellular, breast, lung, prostate, rhabdomyosarcoma. (Tang et al., 2018)

4	Epidermal Growth Factor Receptor tyrosine kinase domain (EGFRK)	1M17	Non-small cell lung cancer (NSCLC); breast, ovarian and prostate. (Uribe et al., 2021)
5	Anti-apoptotic protein BCL-2	2O2F	Leukemias, lymphomas, and various solid tumors. (Alam et al., 2021)
6	Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2)	4ASD	Breast, ovarian, colon, pancreatic, kidney, liver, leukemia, urothelial, etc. (Guo et al., 2010)
7	Cyclin Dependent Kinase 4 (CDK4)	3G33	Breast; gastrointestinal, small-cell lung. (Baker et al., 2022)
8	Human Epidermal Growth Factor Receptor 2 (HER2), also known as ErbB2	3PP0	Breast (Cheng, 2024)
9	Mammalian target of rapamycin (mTOR)	4JT5	Lung, breast, liver, renal, pancreatic, and prostate. (Petroulakis et al., 2006)
10	Cyclin Dependent Kinase 2 (CDK-2)	6Q4G	Breast, ovarian, lung, and melanoma. (Knudsen et al., 2025)

The oncogenic proteins were selected based on their implications in various cancers, as reported widely in literature.

2.2 Selection and Retrieval of Ligands

Sixty ligands from different medicinal plants, herbs, spices, fruits and vegetables (Appendix 1) were used for the pharmacokinetic and anticancer study, using standard *in silico* molecular biology techniques. Twenty known anticancer drugs were used as reference ligands for the anticancer study. The 3-D structures of the 80 ligands were retrieved from the National Center for Biotechnology Information (NCBI) PubChem database in their Structure Data Format (SDF) (https://pubchem.ncbi.nlm.nih.gov/).

2.3 ADMET Screening

The SwissADME tool (http://www.swissadme.ch/; Daina et al., 2017) was used to perform the ADME (Absorption, Distribution, Metabolism, Excretion) screening. The SMILES (Simplified Molecular Input Line Entry System) notations of the phytochemical ligands were inputted into the SwissADME tool and the output analyzed (Appendix 2). The output predicted the physicochemical properties, drug-likeness (including the Lipinski's Rule of Five), pharmacokinetic parameters, potential drug-drug interactions, and PAIN and Brenk alerts.

Lipinski's Rule of 5 is a set of guidelines in drug discovery used to estimate the likelihood that a chemical compound will have oral activity, based on its physicochemical characteristics. Typically, an orally active drug does not violate more than one of the following criteria: molecular weight below 500, partition coefficient (LogP or CLogP) less than 5, no more than 5

hydrogen bond donors, and no more than 10 hydrogen bond acceptors (Daina et al., 2017). The ligands were screened using several calculated parameters: Drug-Likeness > GI absorption> BBB permeability > Pgp substrate status > involvement as substrates for metabolizing enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). Pain and Brenk alerts (Bisson et al., 2016; Prabha & Ezhilarasi, 2021) were also assessed through the SwissADME software. Ligands that passed the Lipinski's rule of 5 (having 0 or 1 violation), are non-substrates for P-glycoprotein, and have 0 scores for both PAIN and Brenk alerts were used for the *in silico* anti-cancer studies.

2.4 Molecular Docking and Visualizations

Thirteen ligands were selected for the molecular docking experiment, based on their excellent ADMET results. The SMILES formats of the selected ligands were retrieved from the open chemistry database (PUBCHEM) of the National Institutes of Health (NIH) (https://pubchem.ncbi.nlm.nih.gov/). The oncogenic proteins were retrieved in their PDB formats from the RCSB PDB Homepage (https://www.rcsb.org/) as earlier stated.

The ligands' SMILES and the proteins' PDB formats were converted to their pdbqt (Protein Data Bank, Partial Charge, and Atom Type) formats through the online SwissDock AutoDock Vina software (https://www.swissdock.ch/). Each ligand and the corresponding proteins were then subjected to molecular docking using the online SwissDock AutoDock Vina software (Bugnon et al., 2024). The binding energy (kcal/mol) for each ligand-protein docking was noted. Selected docked protein ligand complexes were visualized for protein-ligand interactions via the Biovia Discovery Studio Visualizer ((BIOVIA, San Diego, CA, USA) (Baroroh et al., 2023).

3.0 RESULTS

3.1 ADMET Screening

Sixty ligands were used for the ADMET study, as earlier reported. The results are presented in Appendices 2 and 3. The summary of the results is presented in Table 2. The Molecule column represents the ligands.

Table 2

Summary of ADMET Results

S/N	MOL. #	MOLECULE	LIPINSKI'S VIOLATION	P-gp substrate	PAIN'S ALERT	BRENK'S ALERT	REMARK
1	1	Quercetin	0	No	1	1	
2	2	Odoratin	0	No	0	0	Selected
3	3	Myricetin	1	No	1	1	

4	4	Morindone	0	No	2	1	
5	5	Kaempferol	0	No	0	0	Selected
6	6	Piperine	0	No	0	2	
7	7	Capsaicin	0	No	0	1	
8	8	Allicin	0	No	0	2	
9	9	Alliin	0	No	0	1	
10	10	Curcumin	0	No	0	2	
11	11	Gingerol	0	No	0	0	Selected
12	12	Shogaol	0	No	0	1	
13	13	Harpagoside	2	No	0	1	
14	14	Psoralidin	0	No	0	2	
15	15	Momordicin	1	No	0	1	
16	16	Azadirachtin	2	Yes	0	3	
17	17	Nimbin	1	No	0	2	
18	18	Chasmanthin	0	Yes	0	2	
19	19	Ellagic acid	0	No	1	3	
20	20	Resveratrol	0	No	0	1	
21	21	Lycopene	0	No	0	1	
22	22	Epicatechin	0	Yes	1	1	
23	23	Thymoquinone	0	No	1	1	
24	24	Apigenin	0	No	0	0	Selected
25	25	Limonene	0	No	0	1	
26	26	Vernolic acid	0	No	0	2	
27	27	Anthraquinone	0	No	1	0	
28	28	Mangostin	0	No	0	2	
29	29	Mangiferin	2	No	1	2	
30	30	Beta-Sitosterol	1	No	0	1	
31	31	Lupeol	1	No	0	1	
32	32	Acetogenin	0	No	0	0	Selected
33	33	Annonacin	1	No	0	0	Selected
34	34	Muricatocin A	1	No	0	0	Selected
35	35	Annopentocin A	1	No	0	0	Selected
36	36	Annopentocin B	1	No	0	0	Selected
37	37	Xylopic acid	0	No	0	1	
38	38	Conessine	1	No	0	1	
39	39	Terminaline	0	Yes	0	0	
40	40	Terminalic acid	3	Yes	1	3	
41	41	Cianidanol	0	Yes	1	1	

42	42	Scopadulin	1	Yes	0	0	
43	43	Scoparic acid	1	Yes	0	1	
44	44	Betulinic acid	1	No	0	1	
45	45	Coixol	0	No	0	0	Selected
46	46	Scopadiol	1	Yes	0	1	
47	47	Scopadulciol	1	No	0	0	Selected
48	48	Syringic acid	0	No	0	0	Selected
49	49	Epicatechin	0	Yes	1	1	
50	50	Chlorogenic acid	1	No	1	2	
51	51	Sinapic acid	0	No	0	1	
52	52	Amygdalin	2	No	0	0	
53	53	Neurosporene	2	No	0	0	
54	54	Echitamidine	0	Yes	0	0	
55	55	4-Hydroxylbenzoic acid	0	No	0	0	Selected
56	56	Kolaviron	3	No	0	0	
57	57	Luteolin	0	No	1	1	
58	58	Elaidic acid	1	No	0	1	
59	59	Beta-Amyrin	1	No	0	1	
60	60	Isoflavone glycoside	1	No	1	1	

Table 2 above shows the summary of the ADMET results. Ligands that exhibited drug-likeness (scored 0 or 1 in the Lipinski's violation), non-substrate for p-glycoprotein, no PAIN alert, and no Brenk alert were selected for the molecular docking experiment. As could be seen in Table 2, 13 ligands qualified based on these criteria. They are Odoratin, Kaempferol, Gingerol, Apigenin, Acetogenin, Annonacin, Muricatocin A, Annopentocin A, Annopentocin B, Coixol, Scopadulciol, Syringic acid and 4-Hydroxylbenzoic acid.

3.2 Molecular Docking

The results of the molecular docking of the 13 ligands with the 10 oncogenic proteins are presented in Appendix 4.

Kaempferol, apigenin and scopadulciol had very good dockings with most of the oncogenic proteins while odoratin has good docking with some of the proteins (Appendix 4). Results of molecular dockings of kaempferol, apigenin and scopadulciol are also presented in Figure 1 below.

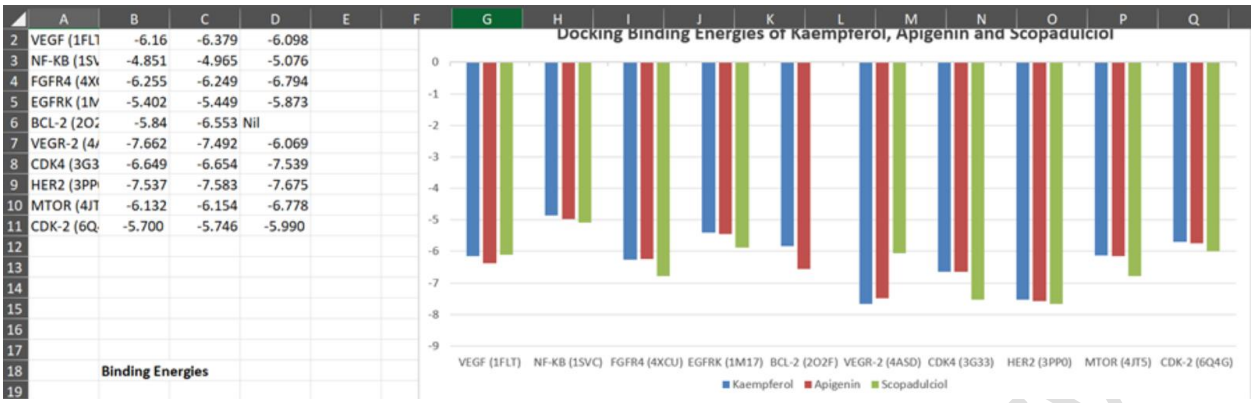

Figure 1: Docking Results for Kaempferol, Apigenin and Scopadulciol

Figure 1 above shows that kaempferol, apigenin and scopadulciol exhibited good binding energies with most of the oncogenic proteins. These three ligands were therefore chosen as the best and their binding energies with most of the proteins were compared with selected anticancer drugs. However, odoratin and coixol were also compared with some selected anticancer drugs regarding their docking with a few of the oncogenic proteins (Table 3).

Table 3 shows the results of the molecular docking of the reference anticancer drugs with their selected oncogenic proteins and compared them with the best three ligand-protein docking results.

Table 3

Molecular Docking Results of Reference Anticancer Drugs with Oncogenic Proteins, as Compared with Selected Ligands.

S/N	PROTEINS	RCSB PDB IDs	LIGAND-1	LIGAND-2	LIGAND-3	REF.-1	REF.-2
1	Vascular Endothelial Growth Factor (VEGF)	1FLT	Kaempferol (-6.160)	Apigenin (-6.379)	Scopadulciol (-6.098)	Sunitinib (-5.742)	Sorafenib (-6.608)
2	Nuclear factor kappa-B (NF-KB)	1SVC	Kaempferol (-4.851)	Apigenin (-4.965)	Scopadulciol (-5.076)	Carfilzomib (-5.262)	BAY 11-7082 (-3.465)
3	Fibroblast growth factor	4XCU	Kampferol (-6.255)	Apigenin (-6.249)	Scopadulciol (-6.794)	Pemigatinib (-5.096)	Erdafitinib (-5.920)

	receptor 4 (FGFR4)						
4	Epidermal growth factor receptor (EGFR) tyrosine kinase domain	1M17	Kaempferol (-5.402)	Apigenin (-5.449)	Scopadulciol (-5.873)	Erlotinib (-4.888)	Gefitinib (-4.985)
5	Apoptosis regulator Bcl-2	2O2F	Kaempferol (-5.840)	Apigenin (-6.553)	Coixol (-4.432)	HA14-1 (-3.160)	Carboplatin (-3.733)
6	Vascular endothelial growth factor receptor 2 (VEGF-2)	4ASD	Kaempferol (-7.662)	Apigenin (-7.492)	Odoratin (-6.596)	Sorafenib (-3.312)	Pazopanib (-5.961)
7	Cyclin Dependent Kinase 4 (CDK4)	3G33	Kaempferol (-6.649)	Apigenin (-6.654)	Scopadulciol (-7.539)	Palbociclib (-7.470)	Ribociclib (-7.388)
8	Human epidermal growth factor receptor 2 (HER2)	3PP0	Kaempferol (-7.537)	Apigenin (-7.583)	Scopadulciol (-7.675)	Neratinib (-7.353)	Tucatinib (-9.025)
9	Mammalian target of rapamycin (mTOR)	4JT5	Kaempferol (-6.132)	Apigenin (-6.154)	Scopadulciol (-6.778)	Dactolisib (-6.638)	β-Elemene (-5.711)
10	Cyclin Dependent Kinase 2 (CDK-2)	6Q4G	Odoratin (-5.750)	Apigenin (-5.746)	Scopadulciol (-5.990)	Tagtociclib (-5.586)	Dinaciclib (-5.525)

When the docking results of the best three ligands for each protein were compared with those of selected anticancer drugs, the ligands were seen to have similar or better docking results than the anticancer drugs (Table 3). For instance, while sorafenib (-6.608 kcal/mol) had the best docking with VEGF, the phytochemical ligands had similar dockings: kaempferol (-6.160kcal/mol), apigenin (-6.379 kcal/mol), scopadulciol (-6.098), and they all had better dockings than the other reference anticancer drug, sunitinib (-5.742). All the three best phytochemical ligands for

fibroblast growth factor receptor 4 (FGFR4): kampferol (-6.255 kcal/mol), apigenin (-6.249 kcal/mol), and scopadulciol (-6.794) had better dockings than the two reference drugs, pemigatinib (-5.096 kcal/mol) and erdafitinib (-5.920 kcal/mol) (Table 3).

3.3 Biovia Discovery Studio Visualization

Table 4 below shows the interactions of apigenin, kaempferol, and scopadulciol with selected oncogenic proteins through the Biovia discovery studio visualization technique. The types of chemical interactions, e.g., hydrogen bonds, are indicated.

Table 4

Interactions between Selected Ligands and the Oncogenic Proteins

Ligand	Oncogenic Protein	Interactions
Apigenin	1FLT (VEGF)	Arg V23 (H Bond), His V27 (Pi-Pi T- shaped), Leu Y174 (Pi Sigma), Pro Y173 (Pi-Alkyl), Pro V28 (Pi-Alkyl)
Apigenin	4XCU (FGFR4)	Asn A557 (H Bond), Asn A617 (Pi-Alkyl), Arg A616 (Pi-Alkyl)
Kaempferol	1FLT (VEGF)	Arg V23 (H Bond), Cys V102 (H Bond), His V27 (Pi-Pi T-shaped), Phe Y172 (Pi-Pi T-shaped), Leu Y174 (Pi-Sigma), Pro V28 (Pi-Alkyl), Pro Y173 (Pi-Alkyl)
Kaempferol	1SVC (NF-KB)	Asn P103 (H Bond), Asn P103 (Amide-Pi Stacked), Asp P209 (Pi-Anion)
Kaempferol	4XCU (FGFR4)	Asn A557 (H Bond), Lys A644 (H Bond),
Scopadulciol	1FLT (VEGF)	His V27 (Pi-Sigma), Arg V23 (Pi-Alkyl), Ile V29 (Pi-Alkyl), Met V55 (Pi-Sulfur)

Table 4 above shows the interactions between the selected ligands and the amino acid residues of the selected oncogenic proteins (VEGF, FGFR4, & NF-KB). As could been seen, the interactions included hydrogen bonds, Pi-Pi T-shaped bonds, Pi-Alkyl bonds, Pi-Sigma bonds, Pi-Sulfur bond, Amide-Pi Stacked, Halogen (Fluorine) bond, and Pi-Anion bond.

Some of the protein-ligand interaction visualizations are displayed in Figures 2-6.

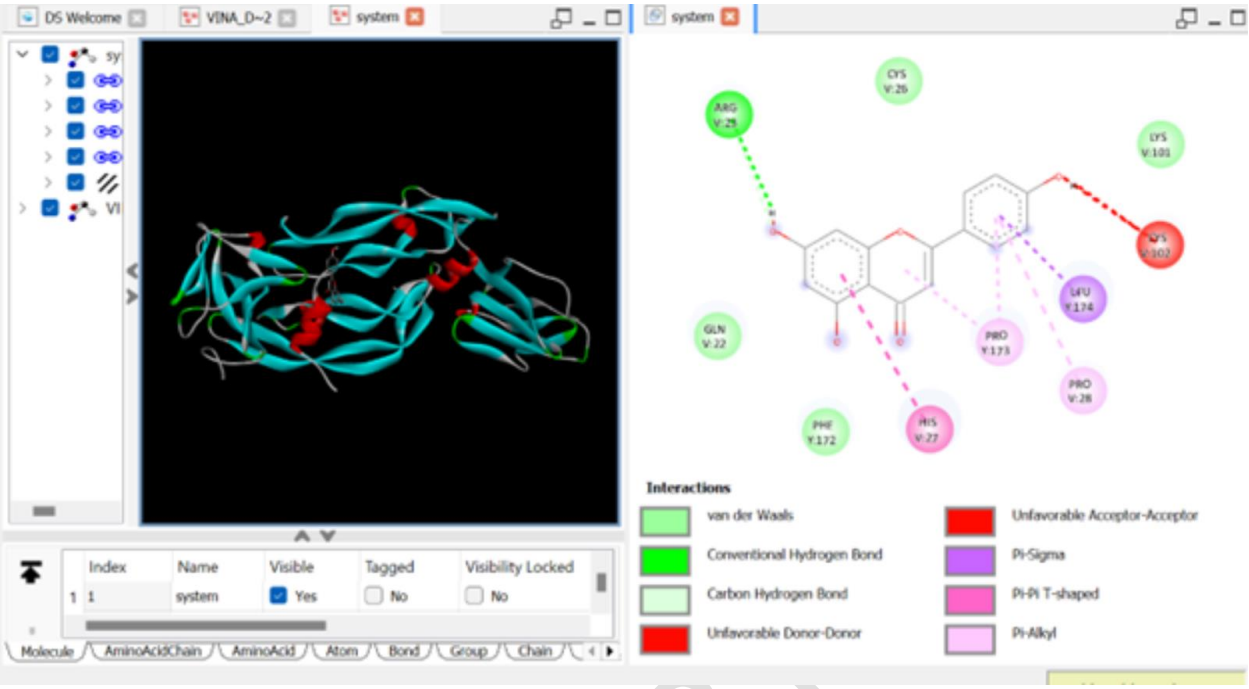

Figure 2. Biovia Discovery Studio Visualization Results for Apigenin with VEGF (1FLT)

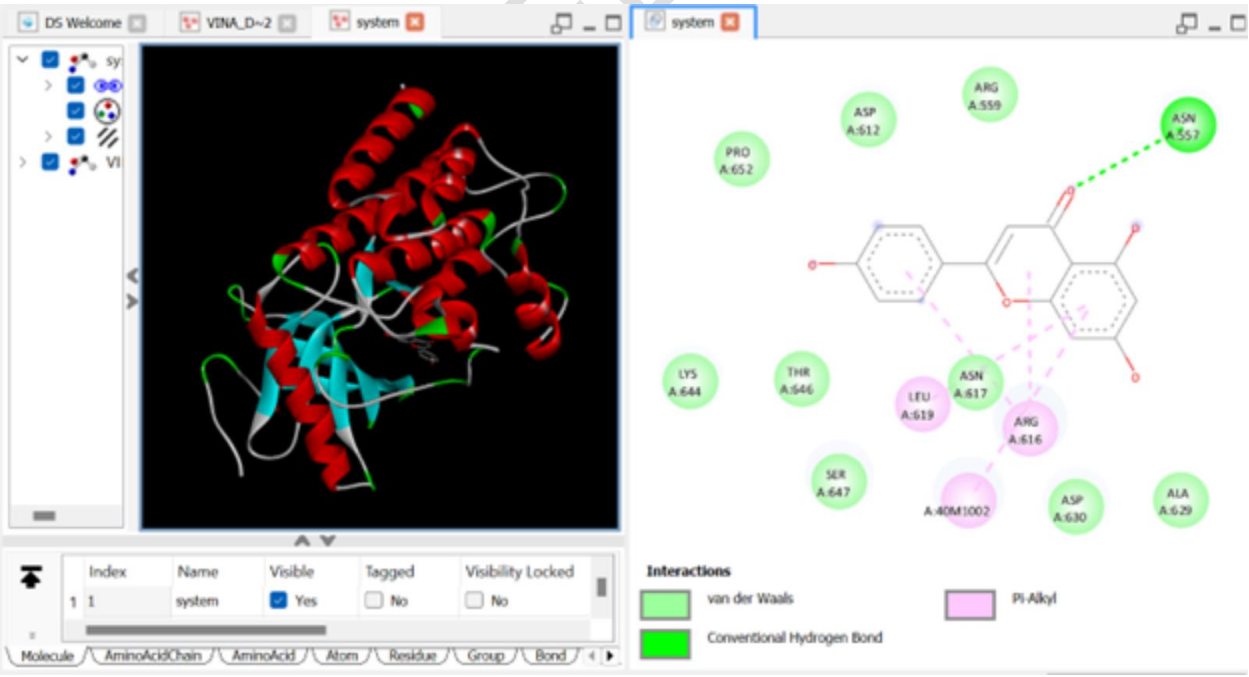

Figure 3. Biovia Discovery Studio Visualization Results for Apigenin with FGFR4 (4XCU)

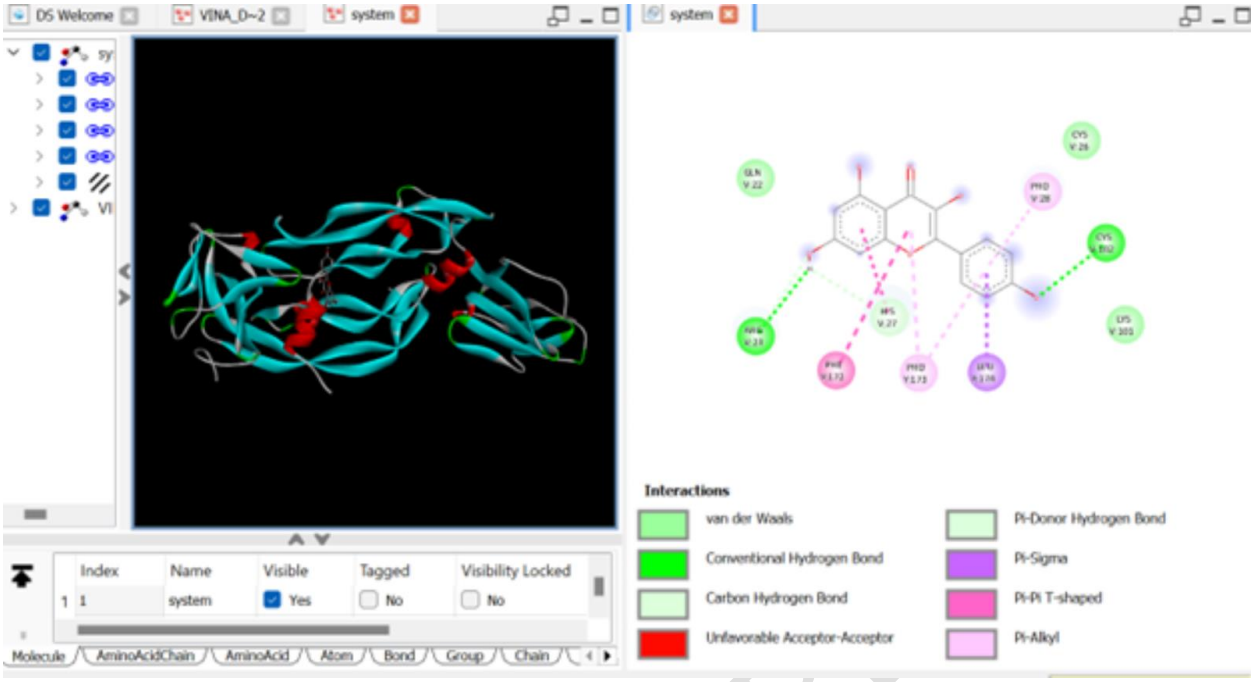

Figure 4. Biovia Discovery Studio Visualization Results for Kaempferol with VEGF (1FLT)

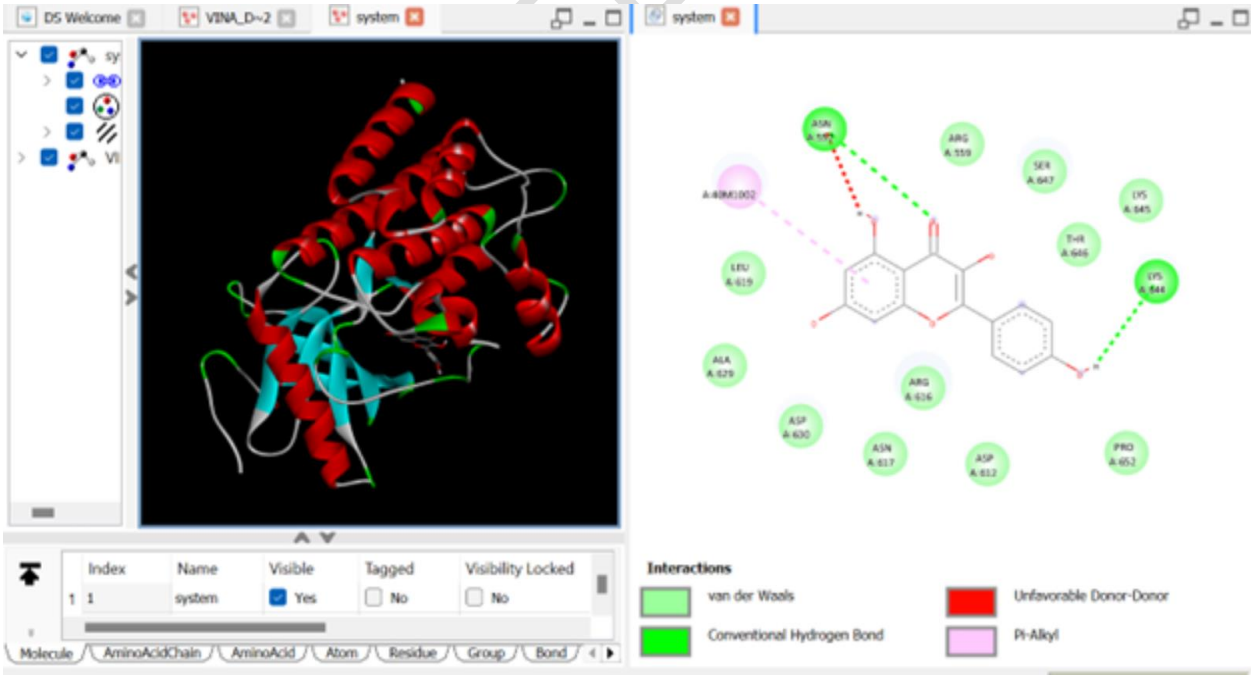

Figure 5. Biovia Discovery Studio Visualization Results for Kaempferol with FGFR4 (4XCU)

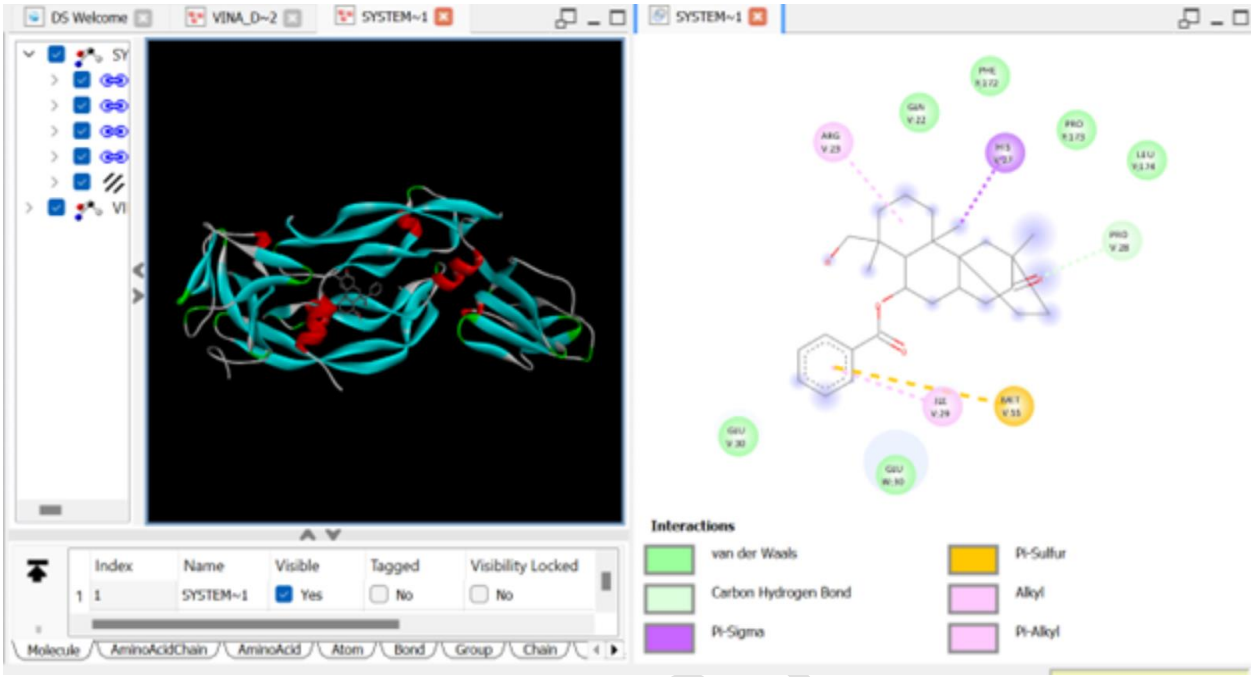

Figure 6. Biovia Discovery Studio Visualization Results for Scopadulciol with VEGF (1FLT)

Figures 2-6 above display the different interactions between the amino acid residues of selected oncogenic proteins with some of the ligands; these complement the information provided in Table 5 above. Table 5 and Figures 2-6 indicate that specific amino acid residues are much involved in the interaction of the proteins with the specific ligands. For instance, Arg V23, His V27, Leu Y174, Pro Y173 of 1FLT (VEGF) were all involved in interacting with apigenin, kaempferol and scopadulciol. Pro V28 of 1FLT also interacted with apigenin and kaempferol. Similarly, Asn A557 residue of 4XCU (FGFR4) interacted with both apigenin and kaempferol (Table 5 & Figure 2).

4.0 DISCUSSION

4.1 Pharmacokinetic Properties of Ligands

The goal of this research is to identify ligands with promising pharmacokinetic properties with little or no toxic effects which would serve as potential anticancer drugs. Therefore, we decided to identify and select ligands that passed Lipinski's rule of 5, are non-substrates to P-glycoprotein, and have no PAINS and Brenk alerts.

As indicated in Table 2, 13 ligands out of a total of 60 used for the pharmacokinetic screening passed these tests and were there subjected to the anticancer screenings, together with selected

reference anticancer drugs. Eight of the selected ligands have no Lipinski's violation while five have one violation each, which is acceptable (Table 2; Appendices 1 & 2). All 13 ligands were non-substrates of P-glycoprotein, and they had no PAINS and Brenk alerts.

Lipinski's Rule of Five is a guideline used in drug discovery to predict if a molecule is likely to have good oral bioavailability. An orally active drug is expected to have no more than one violation of four criteria: molecular weight < 500 Da, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and an octanol-water partition coefficient (LogP) < 5. It is a rule of thumb for pre-clinical screening to assess a compound's "druglikeness" (Benet et al., 2016; Lipinski et al., 2001).

P-glycoprotein is an ATP-binding cassette (ABC) transporter that expels toxins and xenobiotics from cells, acting as a biological barrier by extruding toxins and xenobiotics out of cells. Studies show it significantly affects drug absorption and disposition, mainly by restricting drug entry into the brain and intestinal cells rather than promoting drug excretion from the liver and kidneys (Lin & Yamazaki, 2003). Being a non-substrate for the P-glycoprotein is therefore a desirable property of any potential drug.

PAINS (Pan-Assay Interference Compounds) are chemical entities known to frequently produce false-positive outcomes in various biological screening assays, presenting a notable obstacle in the field of drug discovery (Baell & Walters, 2014). Bioinformatics tools like SwissADME are used in virtual screening and library design to identify problematic compounds, helping researchers focus on likely drug candidates and avoid false positives. Hence, the incorporation of this parameter in our study is desirable (Daina et al, 2017).

A **Brenk alert** is a structural warning in medicinal chemistry that flags chemical fragments likely to be toxic, reactive, unstable, or cause poor pharmacokinetics. The system lists 105 problematic fragments identified by Brenk et al. (2008), and tools like SwissADME trigger an alert when these are found in a compound, prompting further review before considering it as a drug candidate. These alerts help researchers focus on compounds with better safety and efficacy prospects early in drug discovery (Daina et al., 2017).

The 13 ligands that passed the Lipinski's rule, P-glycoprotein non-substrate and PAINS and Brenk alert tests are components of many commonly consumed foods, herbs and spices, and no wonder, these food materials are consumed safely for nutritional and medicinal purposes in different parts of the world. For example, odoratin is a component of *Eupatorium odoratum* leaves that are traditionally used for wound healing, treating diarrhea, sore throats, and as an insect repellent. Studies confirm their antimicrobial, anti-inflammatory, and antioxidant effects (Sirinthipaporn & Jiraungkoorskul, 2017).

Kaempferol is a phytochemical found in plants such as *Moringa oleifera* and *Sutherlandia frutescens*, plants used widely for medicinal purposes. *Moringa oleifera* is a nutrient-dense plant valued for its protein, vitamins (C, A, B), minerals (calcium, iron, potassium, zinc), and

phytochemicals such as kaempferol. Traditionally, its parts are used to treat asthma, high blood sugar, infections, inflammation, and may support heart health and antioxidant activity (Anwar et al., 2007). *Sutherlandia frutescens* is mainly valued for its potent medicinal properties, especially its antioxidant and anti-inflammatory effects, due to key bioactive compounds rather than nutritional content. It supports traditional use as an adaptogenic tonic (Aboyade et al., 2014).

The same is true for the rest of the ligands: gingerol (found in ginger, *Zingiber officinale*), apigenin (found in parsley, chamomile, and celery), scopadulciol (found in licorice weed), annonacin (found in Annona muricata, soursop), muricatocin A (found in soursop), annopentocin A (found in soursop), annopentocin B (found in soursop), acetogenin (found in avocado, pawpaw, sugar apple, & soursop), coixol (found in *Coix lacryma-jobi* or adlay, & *Scoparia dulcis* or licorice weed), syringic acid (found in pineapples, olives, grapes, dates, & pumpkin), and 4-Hydroxylbenzoic acid (found in *Gongronema latifolium*). These plants are used extensively for nutritional and/or medicinal purposes across global communities, and nutritional and health benefits of these plants and their phytochemicals have been documented (Anh et al., 2020; Kong et al., 2021; Kooti & Daraei, 2017; Morebise, 2015; Mutakin et al., 2022; Rahmani et al., 2014 Seenak et al., 2021).

4.2 Anticancer Properties

The 13 ligands exhibited varying binding energies (in kcal/mol) when docked with the 10 oncogenic proteins (Appendix 4). There isn't a universal minimum binding energy threshold since it depends on the protein target and docking software used. However, generally, a binding energy below −6.0 kcal/mol is considered favorable, whereas around −4.0 kcal/mol indicates weaker binding (Ivanova & Karelson, 2022).

Eight of the ligands (Acetogenin, Annonacin, Annopentocin A, Apigenin, Kaempferol, Muricatonin A, Odoratin, & Scopadulciol) exhibited docking energies of lower than -6.0 kcal/.mol with at least one oncogenic protein, with some of them having docking energies of less than -6.0 kcal/mol with multiple oncogenic proteins. For instance, kaempferol had a binding energy of -7.662 kcal/mol against VEGR-2, -7.537 kcal/mol against HER2, -6.649 kcal/mol against CDK4, -6.132 kcal/mol against mTOR, -6.255 kcal/mol against FGFR4, and -6.160 kcal/mol against VEGF. The anticancer properties of these eight ligands have been documented through various lab studies: Acetogenin (Jacobo-Herrera et al, 2019), Annonacin (Xiao et al., 2025), Annopentocin A (Rovik et al., 2025), Apigenin (Rahmani et al., 2022), Kaempferol (Kaur et al., 2024), Muricatocin A (Ilango et al., 2022), Odoratin (Omoboyowa et al., 2022), and Scopadulciol (Hasnawati et al., 2023). Three of these ligands (apigenin, kaempferol & scopaldulciol) were exceptionally remarkable in their docking properties, as they exhibited good dockings with most of the oncogenic proteins (Table 3).

4.2.1 Apigenin

Apigenin (4′,5,7-Trihydroxyflavone) belongs to a broad category of plant-based polyphenols known as flavonoids (Abid et al., 2022). Its anticancer effects stem from its ability to arrest angiogenesis, stimulate programmed cell death, antagonize cell proliferation, limit metastasis, activate the immune system, mitigate inflammation (Naponelli et al., 2024; Yan et al., 2017), and enhance the efficacy of chemotherapy (Nozhat et al, 2021).

Apigenin has been reported to downregulate antiapoptotic factors such as BCL2 (2O2F), decrease NF-kB (1SVC) signaling [Naponelli et al., 2024], degrade human epidermal growth factor receptor 2, HER2 (3PP0) (Way et al., 2004) inhibit the mammalian target of rapamycin, mTOR (4JT5) pathway (Yang et al., 2018), and decrease epidermal growth factor receptor (1M17) (Sharma et al., 2022), as part of the mechanisms of its anticancer actions. Our study shows that apigenin had good binding energies with the proteins reported by these authors.

Our study shows that apigenin interacted with the Arg V23 of VEGF via hydrogen bond (H bond). It also interacted with the His V27 (Pi-Pi-T shaped), Leu Y174 (Pi Sigma), Pro Y173 (Pi-Alkyl) and Pro V28 (Pi-Alkyl) residues of VEGF (Figure 1; Table 5). Likewise, apigenin interacted with the Asn A557 (H bond), Asn A617 (Pi-Alkyl) and Arg A616 (Pi-Alkyl) residues of FGR4 (Figure 2; Table 5). These interactions might be part of the molecular mechanisms through which apigenin exhibits its anticancer activities against these proteins.

Further investigation reveals that the binding energies of apigenin with these proteins were comparable, and in some cases, better than those of the reference anticancer drugs used for the study (Table 4). For instance, while apigenin had a binding energy of -7.583 with 3PP0 (HER2), that of Neratinib was -7.353 kcal/mol and that of Tucatinib was -9.025 kcal/mol. Apigenin's binding energy with mTOR (4JTF) was -6.154 kcal/mol, a value very close to that of Dactolisib (-6.638 kcal/mol) and better than that of the other reference drug, β- Elemene (-5.711 kcal/mol). Similarly, apigenin's docking binding energy value with VEGF (1FLT) was comparable to that of sorafenib (reference drug-1) and better than that of sunitinib (reference drug-2). Similar results could be seen with the other proteins (Table 3).

4.2.2 Kaempferol

Kaempferol, a flavonoid found in numerous foods and medicinal plants, inhibits cancer cell growth, triggers apoptosis, and reduces metastasis by disrupting cell signaling and affecting the tumor microenvironment. Studies suggest it may help treat breast, liver, and lung cancers and boost chemotherapy effectiveness (Amjad et al., 2022; Imran et al., 2019). Kaempferol has been reported to inhibit cancer by suppressing angiogenesis through downregulation of VEGF expression and its signaling pathways. It reduces both mRNA and protein levels of VEGF in various cancer cells, including ovarian and colon cancers, and blocks VEGFR-2 protein expression and kinase activity, limiting new blood vessel formation for tumor growth (Luo et al., 2012; Yu et.al, 2022).

Luo et al. (2009) reported that kaempferol exhibits minimal cytotoxicity while effectively inhibiting angiogenesis and VEGF expression in human ovarian cancer cells. Kaempferol has been shown to inhibit FGFR4 by binding to its kinase domain, specifically interacting with the ATP-binding pocket. This prevents activation and phosphorylation by fibroblast growth factor (FGF), blocking downstream pathways such as RSK2, PI3K/Akt, and ERK/p38 MAPK. Inhibiting these pathways disrupts cell proliferation, migration, and survival, resulting in anti-cancer effects like apoptosis and cell cycle arrest (Coleman et al., 2014; Zheng et al., 2022).

Our molecular docking and visualization results show that kaempferol interacted with VEGF through the following amino acid residues of the protein: Arg V23 (H bond), Cys V102 (H bond), His V27 (Pi-Pi T-shaped), Phe Y172 (Pi-Pi T-shaped), Leu Y174 (Pi Sigma), Pro V28 (Pi-Alkyl), and Pro Y173 (Pi-Alkyl) (Figure 3; Table 5). Kaempferol also interacted with FGFR4 through the following amino acid residues of the protein: Asn A557 (H bond) and Lys A644 (H bond) (Figure 4; Table 5). This indicates that kaempferol may have a direct inhibitory effect on these proteins and binding to the amino acid residues indicated may be part of the mechanisms for the inhibitory effect.

Our study shows that kaempferol exhibited binding energy of -6.160 kcal/mol when docked with VEGF. This is close to the binding energy of the reference drug sorafenib (-6.608 kcal/mol) and better than that of the other reference drug, sunitinib (-5.742 kcal/mol). (Table 4). Kaempferol also exhibited a better binding energy when docked with FGFR4 (-6.255 kcal/mol) compared with the two reference drugs: pemigatinib (-5.096 kcal/mol) and erdafitinib (-5.920) (Table 5). Kaempferol also exhibited a better binding energy (-7.537 kcal/mol) than the reference drug neratinib (-7.353 kcal/mol) when docked with HER2, though the second reference drug, tucatinib, had a better docking binding energy (-9.025 kcal/mol) (Table 4). Similar results are also seen for the binding of kaempferol with mTOR when the binding energy is compared to those of the reference drugs (Table 3).

4.2.3 Scopadulciol

Laboratory research indicates that scopadulciol (also called dulcinol), a diterpenoid derived from the plant *Scoparia dulcis (*Licorice weed), demonstrates strong anticancer and cytotoxic effects against several cancer cell lines, mainly based on in vitro and animal experiments). Research has demonstrated its cytotoxic and antiproliferative activities against various cancer cell types, including gastric, prostatic, and HeLa (cervical) cell lines (Hasnawati et al., 2023).

Our study shows that scopadulciol had good docking binding energies with most of the oncogenic proteins and compared well or even better than the reference drugs (Tables 3 & 4). For instance, scopadulciol had better binding energies of -7.539 kcal/mol with CDK4 when compared with the two reference drugs (Palbociclib, -7.470 kcal/mol; Ribociclib, -7.388 kcal/mol). While previous research reports did not link the anticancer effect of scopadulciol to its direct inhibition of the oncogenic proteins, our *in silico* study shows a good docking binding

energy of scopadulciol with the proteins. Therefore, this is an area that may be investigated in future research studies.

5.0 CONCLUSION

This study has demonstrated the pharmacokinetic and toxicity profiles of 60 ligands found in commonly consumed foods, spices, herbs and medicinal plants through *in silico* molecular biology techniques. Thirteen of the ligands passed the Lipinski's rule, P-glycoprotein non-substrate and PAINS and Brenk alert tests and were used for anticancer tests. Results of their docking with ten oncogenic proteins showed that most of them exhibited excellent dockings which compared well with reference anticancer drugs while some even had better docking than the reference drugs.

Acetogenin, Annonacin, Annopentocin A, Apigenin, Kaempferol, Muricatonin A, Odoratin, and Scopadulciol demonstrated docking energies below -6.0 kcal/mol with at least one oncogenic protein. Notably, several of these compounds exhibited docking energies below -6.0 kcal/mol with multiple oncogenic proteins. Apigenin, kaempferol, and scopaldulciol showed strong docking with most oncogenic proteins. Our study supports earlier reports by different authors on the inhibitory effects of apigenin on VEGF, mTOR and BCL2, and the inhibitory effects of kaempferol on VEGF and FGFR4. Thus, blocking these proteins may be part of the mechanisms of anticancer properties of these ligands.

The following amino acid residues of VEGF (1FLT): Arg V23, His V27, Leu Y174, Pro Y173, and Pro V28, and the Asn A557 of FGFR4 (4XCU) are of interest because they exhibited molecular interactions with several of the ligands. They should therefore be investigated further in both wet and in silico research as possible targets for anticancer drugs.

The anticancer mechanisms of scopadulciol have been documented by various authors. While direct inhibition of the oncogenic proteins investigated here were not among the popularly reported mechanisms of scopadulciol's anticancer activity, our study has shown good docking of this ligand with most of the oncogenic proteins. Thus, it is recommended that more wet lab research works in this area should be conducted to ascertain the direct inhibitory effects of scopadulciol on these oncogenic proteins.

Plant materials which are rich sources of the 13 ligands used for the anticancer study are consumed traditionally for both nutritional and medicinal purposes with little or no reports of harm, and our study has supported their uses for these purposes. Since most anticancer drugs exhibit toxic effects on normal cells thus leading to various side effects, identifying alternatives with minimal or no side effects is a step in a positive direction. We hereby recommend that further research, including molecular dynamics simulations and translational research studies, should be conducted on the eight ligands (acetogenin, annonacin, annopentocin A, apigenin, kaempferol, muricatonin A, odoratin, & scopadulciol) that have demonstrated good pharmacokinetic profiles and promising anticancer activities. We also recommend that the foods,

spices and herbs that contain these ligands that passed the pharmacokinetic and toxicity tests and exhibited good anticancer docking should be incorporated into regular diets owing to their anticancer properties.

LIMITATIONS

This research work is limited to *in silico* research studies; hence, there is the need for confirmatory wet lab studies. While the anticancer properties of several of the ligands have been confirmed through wet lab studies (as indicated in the Discussion section of this paper), there is the need for confirmation of their protein-ligand interactions as well as the pharmacokinetic properties of the ligands through animal models, *in-vitro* studies, and/or clinical studies. This present study could therefore be a guide to researchers as the findings may serve as a foundation for future *in-vitro* and *in-vivo* experimental validation and translational research.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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