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Molecular Docking and ADMET Profiling of *Carica papaya* Linn. Seed Phytochemicals: A Computational Approach to Identifying Potential Anticancer

[1]Mansi Chandra and [2]Shruthi Shirur Dakappa
[1]Mount Carmel College, Bengaluru, Karnataka 560052, India
[2]BioEdge Solutions, Bengaluru, Karnataka 560068, India

ABSTRACT

Background and Objective: *Carica papaya* has been traditionally recognized for its therapeutic properties, particularly in developing countries where its extract may be utilized for cancer treatment. The objective of this study is to investigate the phytochemical extract of papaya seeds and evaluate the bioactivity of these compounds through computational methods to identify promising compounds. **Materials and Methods:** Phytochemicals were extracted from *Carica papaya* seeds using aqueous solvents, and 120 compounds were identified using Gas Chromatography-Mass Spectrometry (GC-MS). Molecular docking was performed to investigate the binding affinities of key compounds, including Dovitinib, Diphacinone, and Pyripyropene A, with cancer-related protein receptors, specifically BRAF, MCF-2, and VEGFR-2. An ADMET analysis was carried out to evaluate the absorption, distribution, excretion, and toxicity profiles of the identified compounds, to assess the potential pharmacokinetic properties and bioavailability characteristics. **Results:** Molecular docking results revealed significant binding affinities with target cancer-related proteins, with binding energies of -9.6, -10.6, and -9.5 kcal/mol, respectively. Favorable ADMET profiles suggest potential bioavailability and minimal toxicity. **Conclusion:** This research highlights the presence of phytochemicals with potent anticancer properties, suggesting their suitability for further investigation in preclinical and clinical settings. The findings emphasize the significant role of natural products in the development of cancer therapeutics.

KEYWORDS

Carica papaya, cancer treatment, Gas Chromatography-Mass Spectrometry (GC-MS), molecular docking, Dovitinib, Diphacinone, Pyripyropene A

INTRODUCTION

Natural products have long been integral to traditional medicine and modern drug discovery, with many serving as a foundation for the development of therapeutic agents, including anticancer drugs. Among these, *Carica papaya* Linn., commonly known as papaya or pawpaw, is a tropical fruit from the Caricaceae family, native to Central America and Southern Mexico. It is widely cultivated in countries such as Brazil,

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Mexico, India, and across Asia, Africa, and the Americas[1]. Various parts of the papaya plant, including its fruit, bark, roots, seeds, peel, pulp, and leaves, have been explored for their medicinal properties, with recent studies emphasizing their potential anticancer effects[2].

The seeds and pulp of papaya are particularly rich in benzyl glucosinolate, a precursor to benzyl isothiocyanate, produced through enzymatic breakdown by myrosinase. Benzyl isothiocyanate has been shown to inhibit the proliferation of specific cancer cell lines, highlighting its potential as a therapeutic compound[3,4]. Furthermore, papaya seed extracts have demonstrated significant anticancer activity, particularly against acute promyelocytic leukemia and prostate cancer cells[5]. These findings suggest that papaya seeds could be a valuable resource in the ongoing search for effective anticancer agents. Studies on *Carica papaya* seed extract have shown its efficacy in treating various cancers, including breast, prostate, and colon cancers, as well as acute promyelocytic leukemia[6].

Despite advances in cancer research and clinical evaluation of new therapies, there remains an urgent need for the discovery of safe and effective drugs with minimal side effects. Natural products continue to play a crucial role in this pursuit, with numerous drug discovery programs leveraging their diverse and bioactive compounds[7]. Conventional cancer therapies often come with significant side effects, and there remains a pressing need to identify novel agents with fewer adverse effects and better therapeutic profiles[8].

To further explore its potential, molecular docking has emerged as a valuable tool in natural product-based drug discovery, enabling efficient screening of structurally diverse compounds[9]. This approach aids in predicting interactions between small molecules and drug targets, guiding synthesis decisions and saving time and costs in drug development[10]. Gas Chromatography-Mass Spectrometry (GC-MS) is a powerful analytical technique for identifying bioactive compounds in plant extracts[11,12]. When combined with multivariate data analysis, GC-MS can rapidly identify potential bioactive compounds, improving the efficiency of drug discovery from natural products[11]. The integration of these approaches is crucial for drug discovery, as natural products remain a rich source of novel bioactive compounds, with over 70% of approved drugs between 1981 and 2006 being derived from or structurally similar to nature-based compounds[13].

This study addresses the challenge posed by current cancer treatments by exploring the therapeutic potential of *Carica papaya* Linn. seed extracts. Through molecular docking and ADMET profiling techniques, the research investigates the ability of the phytochemicals to interact with critical cancer-associated proteins, including BRAF, MCF-2, and VEGFR-2.

The primary aim of this study is to thoroughly investigate and identify bioactive compounds extracted from the seeds of *Carica papaya* Linn. that demonstrate strong molecular interactions with cancer-related protein targets. Additionally, this research focuses on assessing the pharmacokinetic properties and toxicological profiles of these compounds to ensure their suitability as drug candidates with optimal therapeutic potential. By integrating computational techniques with the exploration of natural products, the study seeks to pave the way for the development of innovative, plant-based anticancer therapies that combine high efficacy with minimal adverse effects.

MATERIALS AND METHODS

Study area: The experiment was conducted at Bio Edge Solutions in Bangalore, India, over an 8 months period from January to August, 2024.

Preparation of plant material: The sample was washed thoroughly with distilled water and shade-dried for 5 days at room temperature (37°C)[14]. The dried materials were subjected to fine grinding using an electric grinder (Crompton DS 500 BLK 500-Watt Mixer Grinder).

Preparation of aqueous extract: The pulverized plant material, weighing 10 g, was subjected to extraction procedures wherein it was immersed in 100 mL of methanol solvent. This extraction process, conducted at ambient room temperature, spanned a duration of 48 hrs. Importantly, this extraction protocol was iterated twice to enhance the efficacy of compound retrieval from the plant material. Following the extraction process, the methanol filtrate underwent condensation to dryness utilizing a rotary evaporator operating at 40°C. Prior to condensation, the separated extracts were subjected to additional filtration through Whatman No. 1 filter paper. This refinement step facilitated the removal of any particulate matter or impurities present in the extract. Notably, this procedure resulted in the generation of approximately 15-20% of the methanol extract, indicative of the concentration achieved through the condensation process.

GC-MS (Gas Chromatography-Mass Spectrometry) analysis: The GC-MS analysis of aqueous extract of *Carica papaya* Linn. black seeds was performed using GC-MS (Model: Shimadzu GCMS-QP2010 S instrument) adapted with GC-MS solutions software (QP2010 S) and compounds were separated using Rtx-5, capillary column (0.25 mm and 0.25 µm). Then it was further conducted using a split ratio of 1:25 and an injector temperature of 300°C. The column temperature was initially set at 60°C, followed by a temperature ramp to 300°C over 10 min. A sample volume of 1 µL was injected into the column using the split mode[15]. Electron ionization at 70 eV was employed for ionization, with helium serving as the carrier gas at a flow rate of 1 mL/min. Mass scanning was performed within the range of 40–500 m/z.

Crude samples were diluted with an appropriate solvent at a ratio of 1/100 (v/v) and subsequently filtered to remove particles. The particle-free diluted crude extracts (1 µL) were injected into the injector using a split ratio of 30:1. Data collection involved obtaining full-scan mass spectra within the scan range of 40–550 amu. The percentage composition of constituents in the crude extract was determined based on peak area, and identification and characterization of chemical compounds were conducted through GC analysis.

***In silico* experiments**

Protein preparation: The 3D structure of protein targets is labelled BRAF (PDB ID: 6V34), MCF-2 (PDB ID: 6GR2) and Vegf R - beta (PDB ID: 5ABD) was restored from the RCSB Protein Data Bank. These proteins were introduced to Discovery Studios visualizer software to remove water molecules, and ligands and add polar hydrogen atoms. Finally, the protein files are saved as a .pdb file format for docking analysis[16].

Generation of ligand dataset: In this current research, phytochemicals extracted from *Carica papaya* Linn. black seeds were chosen as the ligand molecules. From GC-MS analysis of aqueous extract, 120 compounds were identified. Compounds were analysed[16]. The 3D structure of compounds (SDF files) was retrieved from the PubChem database and used in this study.

Molecular docking study: The present study conducted molecular docking calculations for phytochemicals derived from *Carica papaya* Linn. black seeds with three protein receptors, utilizing Auto Dock Vina implemented in PyRx. The conformation with the minimum binding energy (kcal/mol) was selected as the optimal docking pose[16]. Additionally, Discovery Studio was employed to analyze the interactions between the ligands and proteins[17].

Visualization of protein-ligand complexes: The protein-ligand complexes were visually examined using Discovery Studio Visualizer 20.1 software. This tool enabled the characterization of both polar and hydrophobic interactions between the ligand and the target protein. Furthermore, 2D and 3D illustrations depicting these interactions were generated.

Evaluation of physicochemical and pharmacokinetic characteristics of phytocompounds: The ADMET properties were assessed for the most interacting phytocompounds derived from the aqueous extract of *Carica papaya* Linn. black seeds. Swiss ADME was utilized for this analysis, focusing on Lipophilicity, solubility and hydrophobicity[17]. The evaluation also considered adherence to Lipinski's rule, parameters related to the blood-brain barrier (BBB), human intestinal absorption (HIA), P-glycoprotein, and cytochrome P450 inhibitor isoenzymes. This comprehensive examination provides insights into the pharmacokinetic behaviour and potential bioavailability of the compounds[18].

RESULTS AND DISCUSSION

GC-MS analysis: The GC-MS chromatogram of *Carica papaya* seed aqueous extract shows peaks at 6.96, 11.35, 21.10, and 30.65 min, as listed in Table 1. A sharp rise in signal is observed at 34 min, remaining stable until 40 min, indicating a high abundance of compounds as shown in Fig. 1.

Table 1 reveals a diverse phytochemical composition. Prominent peaks corresponded to Glafenine (RT: 29.26, Area%: 0.13), Propiophenone (RT: 5.29, Area%: 0.22), and Bopindolol (RT: 21.10, Area%: 0.16). These findings underscore the extract's chemical complexity and potential bioactive properties.

The acquired mass spectra were compared with the database provided by the National Institute of Standards and Technology (NIST)[18]. This process involved comparing the spectrum of the unknown components with those of known components stored in the NIST library, supplemented by retention time comparisons. Through this comparative analysis, the names, molecular weights, and structural characteristics of the compounds present in the extracts and formulations were determined. A total of 120 compounds were identified, of which 114 were successfully docked with the target protein. Among these, three compounds exhibited significantly low binding affinity to the target protein[15].

Molecular docking studies: Ligand and receptor structures were imported into PyRx for molecular docking studies. The receptor was prepared by defining the binding site and configuring the grid box dimensions to cover the active site. Docking simulations were executed using AutoDock Vina within PyRx. The docking data were assessed by analyzing binding affinity scores and visually inspecting the binding poses to evaluate the ligand-receptor interactions[17]. The molecular docking analysis identified that the

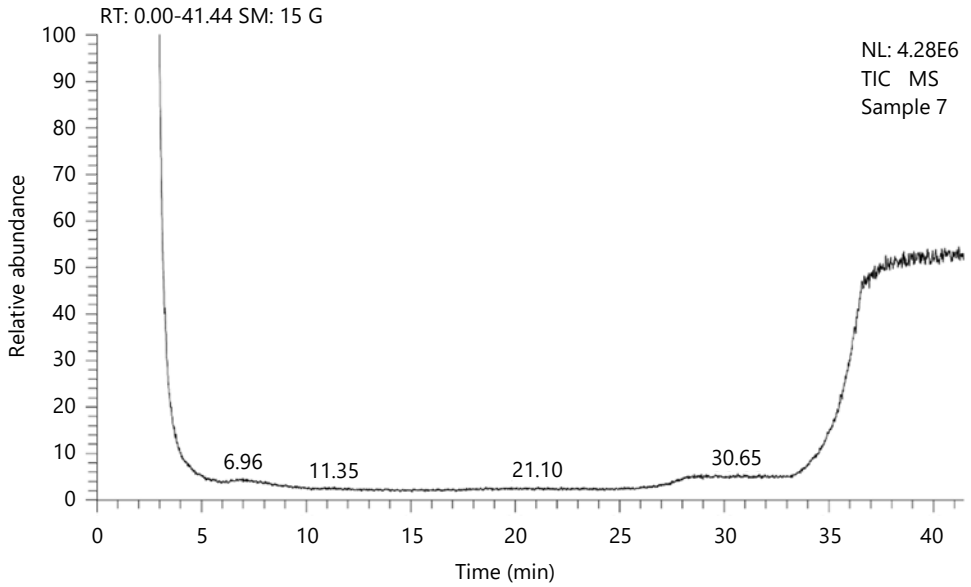


Fig. 1: GC-MS chromatogram of *Carica papaya* seed aqueous extract

Table 1: GC-MS analysis of the aqueous extract of *Carica papaya* seeds

Compound name	Retention time	Probability	Case number	Area (%)
Propiophenone	5.29	30.04	5350-97-0	0.22
Apraclonidine	9.46	7.28	66711-21-5	0.18
2-Phenethylamine	8.8	10.15	NA	0.04
Thebaine	8.04	22.01	115-37-7	0.19
Octadecane	9.92	4.73	55282-12-7	0.09
Bi-2,4,6-cycloheptatrien-1-yl	12.19	14.81	831-18-5	0.04
Diatrizoic acid	12.78	4.81	117-96-4	0.15
Dovitinib	19.09	5.87	405169-16-6	0.18
Pipemidic acid	13.17	11.48	51940-44-4	0.07
Nitralin	13.17	10.59	4726-14-1	0.07
15-Hydroxy-5Z,8Z,11Z,13E-eicosatetraenoic acid	13.93	35.19	73836-87-0	0.22
5,6-Dihydroxy-8Z,11Z,14Z-eicosatrienoic acid	13.93	7.42	213382-49-1	0.22
2-Phenylethanethiol	14.47	10.4	14856-80-5	0.12
6,9,12-Octadecatrienoic acid	14.96	4.88	77509-03-06	0.17
Diphacinone	17.81	5.69	82-66-6	0.16
Clotrimazole	15.19	17.94	23593-75-1	0.13
Propanal, (2,4-dinitrophenyl) hydrazone	15.66	9.78	725-00-8	0.08
14-O-Acetyldaunomycinone	32.09	6.34	29984-41-6	0.18
Buflomedil	15.66	3.57	55837-25-7	0.08
Benzeneethanamine	15.97	6.29	582-22-9	0.06
Bergenin	16.3	8.58	477-90-7	0.07
Propenoic acid	16.35	7.78	346612-92-8	0.09
Naphthalene	16.46	5.21	0493-04-09	0.03
1-(2-Nitrophenyl)-1,2-ethanediol	17.28	5.92	51673-59-7	0.05
2-Butanone, (2,4-dinitrophenyl) hydrazone	17.52	3.9	958-60-1	0.09
2'-Hydroxy-2,4,5,6'-tetramethoxychalcone	17.69	15.41	1435452-19-9	0.11
Corydaldine	29.57	6.23	493-49-2	0.11
Quinine	17.69	3.56	130-95-0	0.14
Glafenin	29.26	71.69	3820-67-5	0.13
Norfluoxetine	18.4	4.76	56161-73-0	0.06
2,4-Dinitro-1,3-dimethyl-benzene	19.41	3.64	0603-02-01	0.17
Pyripyropene A	19.47	5.48	147444-03-9	0.06
Piperidine, 3-phenyl-	20.24	8.68	3973-62-4	0.14
3-Nitrophthalhydrazide	20.24	5	3682-15-3	0.14
Bopindolol	21.1	77.32	62658-63-3	0.16
2,4-Dimethoxycinnamic acid	28.69	5.85	6972-61-8	0.11
Phenol, 4-chloro-2-(4-nitrobenzylidenamino)-	21.55	7.6	64073-87-6	0.08
Benzenemethanol	21.83	13.21	56750-76-6	0.06
2,4-Imidazolidinedione	28.37	8.02	55517-85-6	0.1
N-(4-Isopropylbenzyl)-3-phenylpropionamide	22.67	8.41	300862-83-3	0.04
4-Hydroxy-2',4',6'-trichlorobiphenyl	22.77	20.15	14962-28-8	0.05
Hydrazinecarboxamide, N-(2,6-dichloro-4-pyridinyl)-2-[1,3-dimethyl -4-(1-methylethyl)-1H-pyrazolo[3,4-b] pyridin-6-yl]-	23.28	6.09	383150-41-2	0.14
1H-Benzotriazole-1-methanamine, N-phenyl-	23.28	5.15	62001-29-0	0.14
Resodiacetophenone	24.38	5.97	2161-85-5	0.13
Diatrizoic acid	25.27	1.74	117-96-4	0.03
Heptanal, (2,4-dinitrophenyl) hydrazone	25.35	10.4	2074-05-07	0.12
Thieno[2,3-c] furan-3-carbonitrile, 2-amino-4,6-dihydro-4,4,6,6-tetramethyl-	26.82	6.88	447412-24-0	0.08
3,5-Dimethoxycinnamic acid	30.15	5.14	16909-11-8	0.2
Thymol	27.4	6.97	330455-64-6	0.09
1,4-Benzenediol, 2,6-bis(1,1-dimethylethyl)-	31.61	12.96	2444-28-2	0.12

phytochemical Dovitinib, derived from *Carica papaya* seeds, exhibits significant binding affinity toward the target proteins 6v34, 6gr2, and VEGFR, with binding energies of -9.6, -9.5, and -6.8 kcal/mol, respectively[17]. Additionally, the phytochemicals Diphacinone and Pyripyropene A also demonstrated strong binding affinities, with Diphacinone showing binding energies of -10.6, -8.7, and -6.5 kcal/mol, and Pyripyropene A exhibits binding energies of -9.5, -8.8, and -6.6 kcal/mol. The low binding energies suggest robust molecular interactions between these phytochemicals and the target proteins, indicating their

potential as bioactive compounds[19]. For the Discovery Studios analysis, the best position of ligand and receptor molecules were imported. Discovery Studios provided a detailed analysis of the ligand-receptor interactions, offering scoring functions and advanced visualizations of the binding modes (Fig. 2a-r). This enabled an in-depth investigation of the interactions, revealing specific amino acid residues involved and offering a three-dimensional view of the ligand-receptor complex. Detailed results of the docking studies, including the number of bonds formed, interacting amino acid residues of the target proteins, and bond lengths, are summarized in Table 1[20].

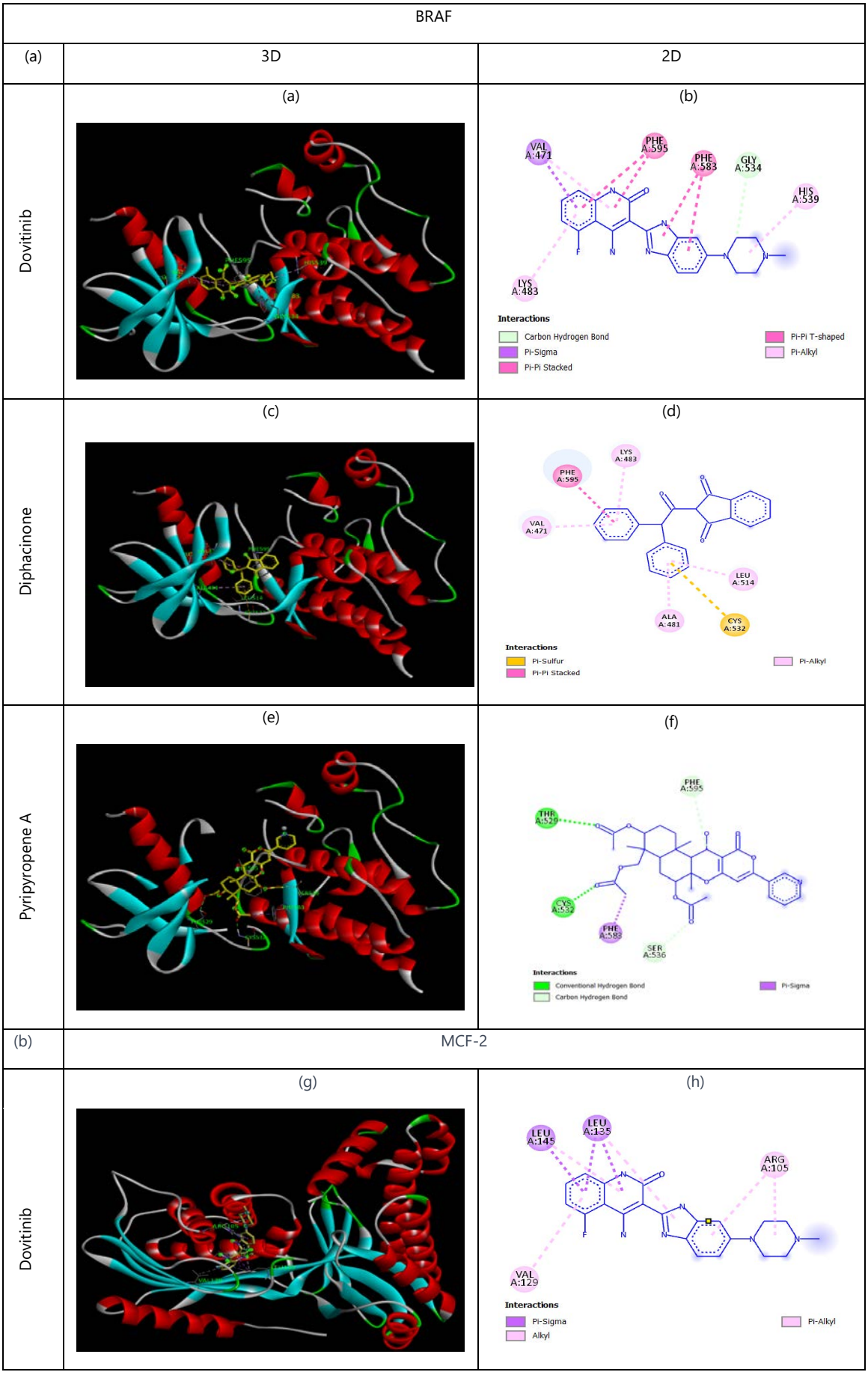
In this study, molecular docking analysis of BRAF (PDB ID: 6V34) with the compounds Dovitinib, Diphacinone, and Pyripyropene A revealed that Dovitinib formed six hydrogen bonds with the amino acid residues VAL471, LYS483, GLY534, HIS539, PHE583, and PHE595. Diphacinone also established six hydrogen bonds with the residues VAL471, ALA481, LYS483, LEU514, CYS532, and PHE595. Similarly, Pyripyropene A formed six hydrogen bonds involving the residues THR529, CYS532, SER536, PHE583, and PHE595 (Fig. 2)[21].

Furthermore, the docking analysis of MCF-2 (PDB ID: 6GR2) with the same compounds showed that Dovitinib established five hydrogen bonds with the residues ARG105, VAL129, LEU135, LEU145, and GLY136. Diphacinone formed six hydrogen bonds with the residues ARG105, LEU135, SER141, LEU145, GLU174, and MET180. Pyripyropene A, on the other hand, formed eight hydrogen bonds with the residues ARG37, TYR109, GLY136, SER142, MET180, CYS182, ASP186, and TYR236 (Fig. 2)[21].

Lastly, molecular docking of human VEGF receptor-beta (PDB ID: 5ABD) with Dovitinib, Diphacinone, and Pyripyropene A demonstrated that Dovitinib formed six hydrogen bonds with GLU153, LEU154, VAL155, PRO157, ARG189, and LYS190. Diphacinone established four hydrogen bonds with the residues LYS170, PHE172, LEU204, and LYS217, while Pyripyropene A formed four hydrogen bonds with TYR139, SER140, ILE145, and HIS147 (Fig. 2)[21].

Evaluation of physicochemical and pharmacokinetic characteristics of phytocompounds: Drug-likeness and medicinal chemistry properties of the test compounds were assessed using Swiss ADMET. This tool evaluates the potential of a molecule to be an oral drug concerning its bioavailability[14]. The drug-likeness prediction results are summarized in Table 3. The identified compounds had molecular weights below 500 g/mol, except for Pyripyropene A, which had a molecular weight of 583.63 g/mol[17]. Dovitinib exhibited a lower Clog P value compared to both Diphacinone and Pyripyropene A, suggesting better hydrophilicity and consequently, favorable absorption and permeation characteristics. Solubility, indicated by the log S value, shows that a higher log S corresponds to lower solubility, which could hinder absorption[14]. Based on these criteria, Dovitinib is more soluble in blood than Diphacinone and Pyripyropene A.

Additionally, a lower topological polar surface area (TPSA) correlates with enhanced membrane permeability, making it a desirable trait for drug-likeness[20]. According to Lipinski's rule of five, TPSA should range between 0-Pyripyropene A. Notably, Dovitinib and Diphacinone did not violate any of Lipinski's criteria regarding molecular weight, TPSA, the number of rotatable bonds, H-bond acceptors, and H-bond donors, while Pyripyropene A had two violations[14]. The bioavailability score predicted by Swiss ADME estimates 140 $Å^2$, and the evaluated compounds fall within this acceptable range, with Dovitinib having a lower TPSA than the likelihood of a compound achieving at least 10% oral bioavailability in rats or having measurable Caco-2 permeability, factoring in total charge, TPSA, and Lipinski rule violations[14]. Both Dovitinib and Diphacinone demonstrated favorable and comparable bioavailability scores, unlike Pyripyropene A shown in Table 2 and Fig. 3.



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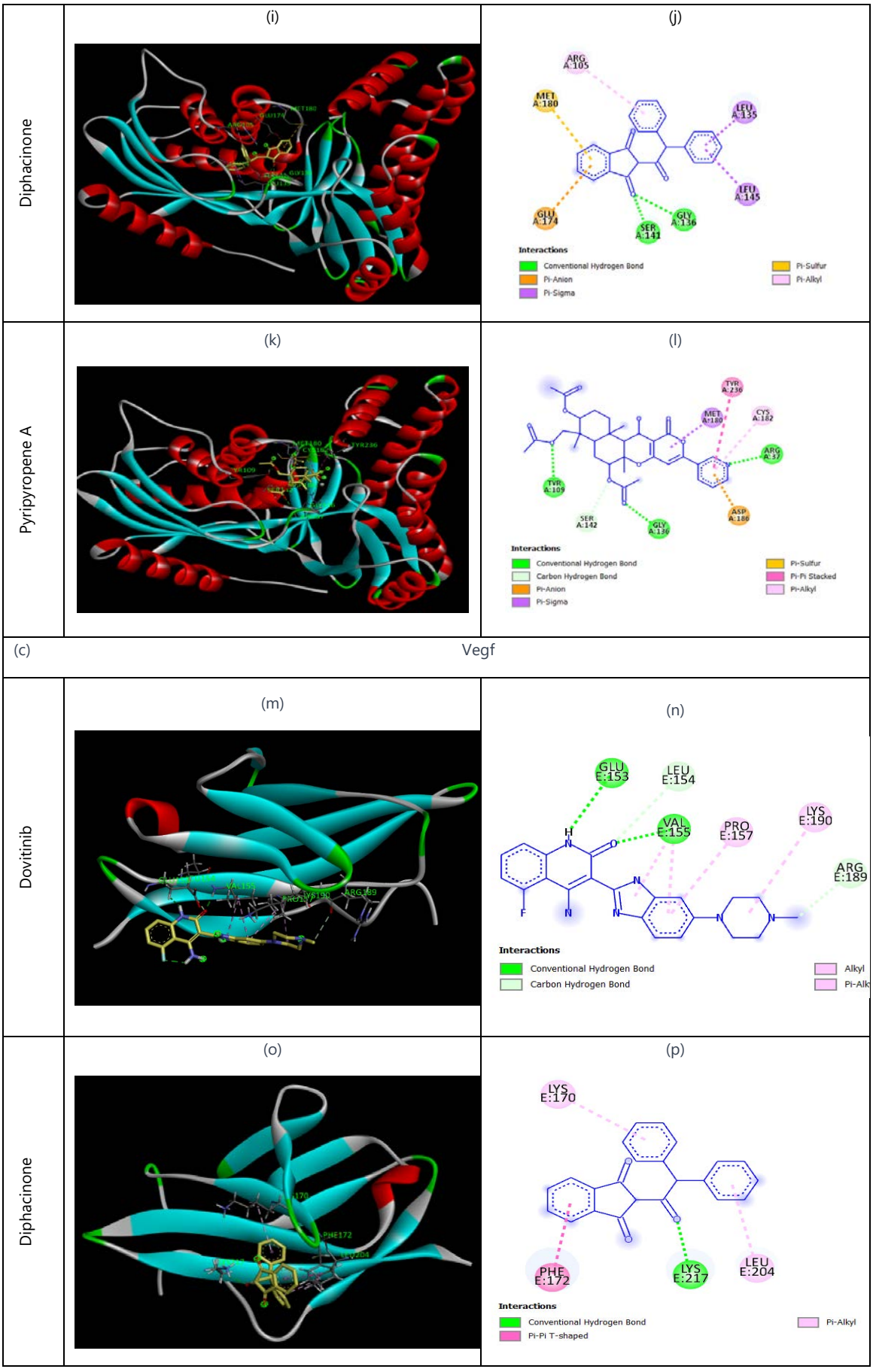

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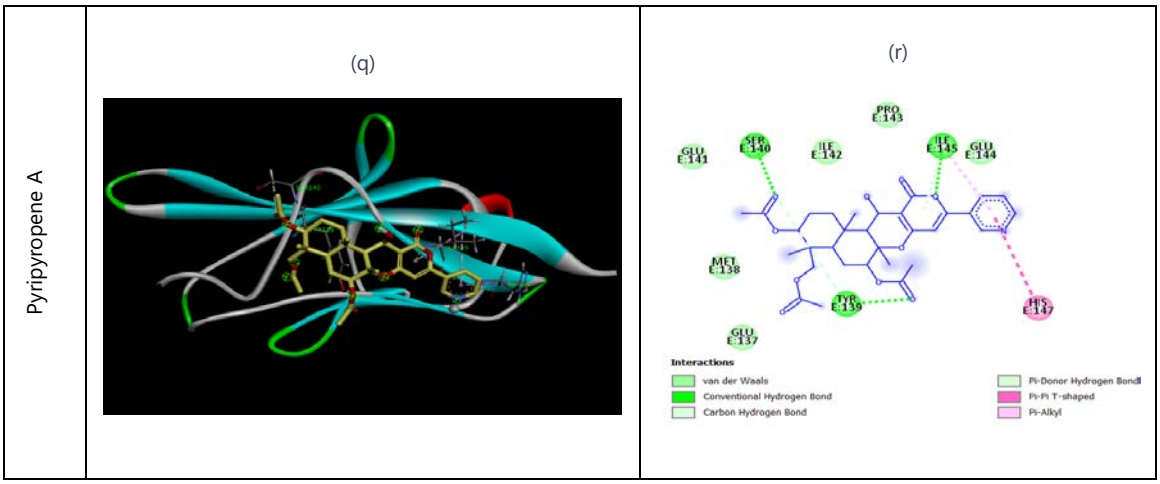

Fig. 2(a-r): 2D and 3D interaction of compounds, (a) 3D interaction of Dovitinib with the BRAF (PDB ID: 6V34), (b) 2D interaction diagram of Dovitinib, highlighting key hydrogen bonds (Gly) and other ligand interactions with active site residues, (c) 3D interaction of Diphacinone with the BRAF, (d) 2D interaction diagram of Diphacinone, highlighting key interactions with active site residues, (e) 3D interaction of Pyripyropene A with the BRAF, (f) 2D interaction diagram of Pyripyropene A, highlighting key hydrogen bonds (Thr, Cys) and other ligand interactions with active site residues, (g) 3D interaction of Dovitinib with the MCF2 (PDB ID: 6GR2), (h) 2D interaction diagram of Dovitinib, highlighting key interactions with active site residues, (i) 3D interaction of Diphacinone with the MCF2, (j) 2D interaction diagram of Diphacinone, highlighting key hydrogen bonds (Gly, Ser) and other ligand interactions with active site residues, (k) 3D interaction of Pyripyropene A with the MCF2, (l) 2D interaction diagram of Pyripyropene A, highlighting key hydrogen bonds (Tyr, Gly, Arg) and other ligand interactions with active site residues, (m) 3D interaction of Dovitinib with the VEGFR-2 (PDB ID: 5ABD), (n) 2D interaction diagram of Dovitinib, highlighting key hydrogen bonds (Glu, Val) and other ligand interactions with active site residues, (o) 3D interaction of Diphacinone with the VEGFR-2, (p) 2D interaction diagram of Diphacinone, highlighting key hydrogen bonds (Lys) and other ligand interactions with active site residues, (q) 3D interaction of Pyripyropene A with the VEGFR-2, and (r) 2D interaction diagram of Pyripyropene A, highlighting key hydrogen bonds (Tyr, Ser, Ile) and other ligand interactions with active site residues

ADMET properties: The ADMET properties of the test compounds were evaluated using ADMET SAR, accessed August (8/8/2024), with the results summarized in Fig. 3 and Table 2.

Table 2 compares key physicochemical properties and drug-likeness parameters of Dovitinib, Diphacinone, and Pyripyropene A. Dovitinib and Diphacinone meet Lipinski's rule of five with no violations, while Pyripyropene A shows two violations, likely due to its higher molecular weight (583.63 g/mol) and increased number of hydrogen bond acceptors[11]. Diphacinone has the lowest surface area (51.21 $Å^2$) and synthetic accessibility score (2.61), suggesting simpler synthesis compared to Dovitinib (3.2) and Pyripyropene A (6.56). Pyripyropene A exhibits the highest molar refractivity (149.19) and surface area (151.46 $Å^2$), but its bioavailability score (0.17) is significantly lower than Dovitinib and Diphacinone (both 0.55). These differences highlight the variations in molecular complexity, drug-likeness, and synthetic feasibility among the compounds.

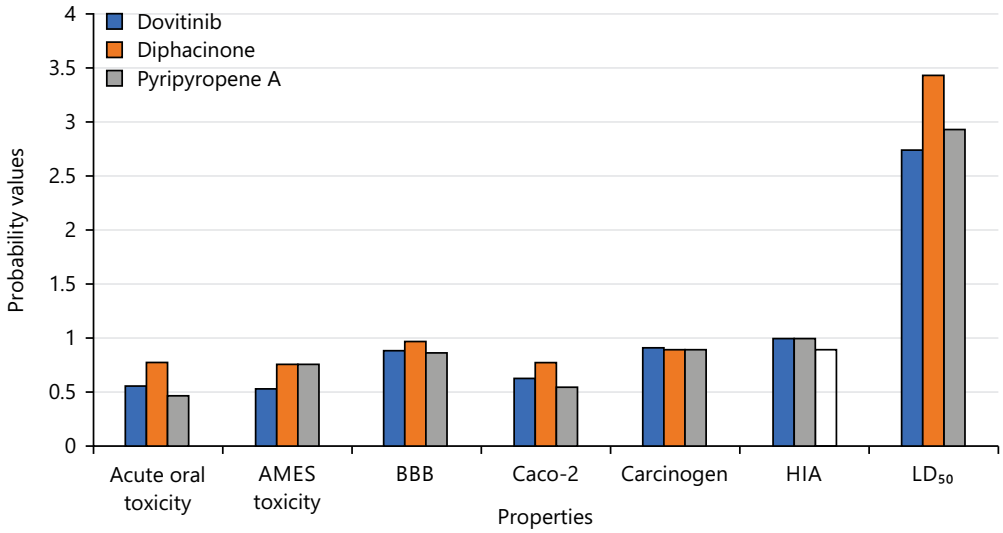

Fig. 3: ADMET profiles of three compounds: Dovitinib, Diphacinone, and Pyripyropene A

Table 2: Comparison of drug-likeness and medicinal chemistry properties using swiss ADMET

Indicator	Dovitinib	Diphacinone	Pyripyropene A
Molecular weight (g/mol)	392.43	340.37	583.63
Formula	$C_{21}H_{21}FN_6O$	$C_{23}H_{16}O_3$	$C_{31}H_{37}NO_{10}$
Number of rotatable bonds	2	4	8
Number of H-bond acceptors	4	3	11
Number of H-bond donors	3	0	1
Molar refractivity	120.28	98.7	149.19
Surface area 94.04 Å^2 (TPSA)	94.04 Å^2	51.21 Å^2	151.46 Å^2
Clog p	2.26	3.75	3.01
Solubility log S	-3.66	-4.89	-4.69
Lipinski rule	Yes; 0 violation	Yes; 0 violation	No, 2 violations
Bioavailability Score	0.55	0.55	0.17
Synthetic accessibility	3.2	2.61	6.56

The analysis includes a range of parameters: Blood-brain barrier (BBB) penetration, human intestinal absorption (HIA), acute oral toxicity, carcinogenicity, Caco-2 cell permeability, AMES toxicity, and lethal dose 50 (LD50), among others. A BBB and HIA value approaching 1 is indicative of optimal permeability and absorption, reflecting the compounds' ability to effectively cross the blood-brain barrier and be absorbed in the intestine. The results reveal that all three test compounds exhibit high levels of intestinal absorption and BBB permeability, suggesting their potential efficacy in targeting the central nervous system and effective systemic absorption. In terms of safety and toxicity, the AMES toxicity and carcinogenicity assessments are crucial for identifying any potential mutagenic or cancer-causing effects. Additionally, the LD50 values provide insight into the dosage required to achieve a 50% mortality rate in test organisms, serving as an indicator of the compound's acute toxicity[19]. Both test compounds are characterized as non-carcinogenic and demonstrate favorable LD50 values, underscoring their safety profile in terms of carcinogenic risk and acute toxicity. In Fig. 3 Diphacinone shows the highest likelihood of toxicity and carcinogenicity. Dovitinib exhibits potential for brain penetration and absorption, but also a risk of liver toxicity. All three compounds have significantly higher LD50 values compared to the other two, suggesting that they are less likely to cause acute toxicity (fatal effects) at lower doses.

The current study has successfully identified and evaluated the anticancer potential of phytochemicals derived from the black seeds of *Carica papaya* Linn. Using molecular docking techniques, demonstrated that compounds such as Dovitinib, Diphacinone, and Pyripyropene A have significant binding affinities to crucial cancer-related proteins, including BRAF, MCF-2, and VEGFR-2. These findings highlight the therapeutic potential of these compounds as inhibitors that may effectively disrupt cancer pathways.

The lower binding energies observed indicate strong interactions, which are essential for the effective inhibition of target proteins. Such results are consistent with existing literature that supports the efficacy of natural products in cancer treatment. Additionally, the ADMET analysis provides a comprehensive overview of the pharmacokinetic properties of these compounds, suggesting their favorable absorption, distribution, metabolism, and excretion profiles, as well as minimal toxicity. This indicates the potential for good bioavailability and safety in therapeutic applications.

Previous research, including studies by Gowtham *et al.*[17] and Saravanan *et al.*[18] demonstrated the effectiveness of natural products in molecular docking, identifying potential anticancer compounds. Similarly, Al-Seadi *et al.*[20] analyzed papaya leaf extracts using GC-MS. However, this study focuses on papaya seeds, seeking to discover their distinct bioactive compounds and therapeutic properties, thus adding to the increasing body of evidence supporting the role of natural products in drug development. While Taghizadeh *et al.*[16] targeted the MCL-1 protein in breast cancer, this study focuses on BRAF, MCF-2, and VEGFR-2 proteins, emphasizing a distinct set of targets in cancer research.

Earlier research has highlighted the anticancer potential of *Carica papaya*, with Mahrous and Noseer[6] observing its effects on colon cancer cells and Alotaibi *et al.*[5] on prostate cancer. In contrast, this study broadens these findings by investigating papaya seed compounds' interactions with proteins related to breast cancer and other cancers. Similarly, Muhammad *et al.*[19] performed molecular docking, drug-likeness, and ADMET assessments on potential inhibitors from Carica papaya against SARS-CoV-2, emphasizing the critical role of ADMET studies in determining the pharmacokinetics and safety of natural compounds. This research will also integrate ADMET analysis to evaluate the drug-like characteristics of Diphacinone, ensuring its safety and effectiveness in cancer treatment.

Although the results are promising, there are limitations to consider. The use of in silico methods without experimental validation calls for careful interpretation of the findings. Future studies should aim to validate these computational results through *in vitro* and *in vivo* experiments to confirm their anticancer potential. Additionally, exploring the combined effects of these compounds with current cancer treatments could improve their therapeutic efficacy.

Investigating the synergistic effects of the identified compounds in combination with current cancer therapies could enhance treatment efficacy and improve patient outcomes. In addition, exploring the pharmacokinetics and biodistribution of these compounds in vivo will provide valuable insights into their ADME profiles, guiding future therapeutic development.

Expanding the study to include a broader range of cancer types could reveal more specific or universal therapeutic applications of papaya seed compounds. This approach may lead to the development of papaya-based natural products as adjuncts to traditional treatments. Ultimately, integrating experimental validation with molecular docking predictions will help refine and advance cancer treatment strategies.

CONCLUSION

The study presents compelling evidence for the anticancer potential of phytochemicals found in the seeds of *Carica papaya* Linn. The identified compounds, Dovitinib, Diphacinone, and Pyripyropene A, exhibit strong molecular interactions with cancer-related proteins, suggesting their potential as therapeutic agents. The favorable ADMET profiles further support their viability for development into cancer treatments. This research underscores the value of natural products in drug discovery and reinforces the potential of *Carica papaya* as a source of novel anticancer agents. Future research should focus on validating these findings through experimental studies and exploring the broader applications of these compounds in cancer therapy. The integration of traditional knowledge and modern technology offers a promising approach to the development of effective, natural treatments for cancer.

SIGNIFICANCE STATEMENT

This study explores the anticancer potential of phytochemicals derived from carica papaya seeds; they provide diverse therapeutic properties. Unlike synthetic drugs, which often lead to many side effects. This research investigates on how compounds like Dovitinib, Diphacinone, and Pyripyropene A can interact with cancer-related proteins. Through molecular docking and ADMET studies, that identifies compounds with low binding affinities, minimum toxicity, and good bioavailability. By the results, it can be concluded that these phytochemicals can offer safer, reduced side effects, and enhanced precision.

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