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MOLECULAR DOCKING AND *IN SILICO* ANALYSIS OF *ARTEMISIA DRACUNCULUS* PHYTOCOMPOUNDS FOR MUCIN-1 MODULATION IN FIBROSIS

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ABSTRACT

Liver cancer is a disease that may cause morbidity and mortality all over the world. Liver cancer is responsible for over 700,000 fatalities worldwide each year, and the number is rising daily. Numerous studies have demonstrated that herbal remedies can be used to treat a variety of liver conditions, including cancer. *Artemisia dracunculus* is used as a medicinal plant because it possesses alkaloids, phenols and flavonoids. In this study, *A. dracunculus* was extracted using 25 g of powder in 200 mL of ethanol. HPLC analysis of *A. dracunculus* ethanol extract showed the presence of different compounds. The identified lead compounds were docked against liver cancer protein mucin-1 (MUC1) to check their binding affinity. The compounds including myricetin, 1,2,3-oxadiazole, bicyclo [3.3.1] non-2-en-9-ol, and 6-methoxy-2-aminopyridinamine showed good binding energies with docking scores of –6.3, –6.7, –5.7, and –3.8 kcal/mol, respectively. Molecular dynamic simulations were performed to check the structural conformational changes due to the binding affinity of ligands to mucin-1. Various kinds of interactions between mucin-1 and ligand compounds such as bicyclo[3.3.1]non-2-en-9-ol, myricetin and1,2,3-Oxadiazole were demonstrated in this study. Some residues of mucin-1 also developed bonding contacts and produced hydrogen bonds for 60-80 % of the simulation. There are also some intramolecular hydrogen bonds present to indicate the stability of ligands. These compounds were found to have potential activity in curing liver cancer due to their best binding values and simulation patterns. These findings will help researchers to explore more about anticancer compounds from natural sources and new drug design and development. *In vitro* and *in vivo* models of liver cancer that overexpress MUC1 might be used to assess the pharmacokinetics, and absorption of promising drug candidates. In the future, these discoveries might aid researchers in creating novel therapeutic candidates to combat liver cancer.

Keywords: *A. dracunculus*, flavonoids, liver-cancer, mucin-1, molecular docking, molecular dynamic simulation.

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INTRODUCTION

Liver cancer highly affects the rates of death in humans as approximately 830,000 deaths have been recorded per year due to liver cancer (Cancer, 2022). The main cause of cancer is mutations in genes and proteins (Ortega *et al*., 2020) as well as ineffective chemotherapeutic drugs (An *et al*., 2021). Mucin-1 (MUC1) is a transmembrane protein that plays an important role in protecting against normal cells' environmental stress by covering the surface of epithelial cells (Bose & Mukherjee, 2020). Mucin-1 encoding gene, (MUC1) is an oncogene that regulates different steps of cancer onset such as developmental stages and proliferation by participating in the cell signaling mechanisms (Gebregiworgis *et al*., 2017). It may also lead to cancer production by over-expression or mutation. According to previous experimental research, some flavones can either inhibit downstream MUC1 signaling or lower MUC1 expression, which in turn can lower the proliferation in several cancer model and cell lines. These compounds particularly noted for its ability to block pathways that MUC1 interacts. As a result, flavonoid-type phytochemicals that impact MUC1 biology have a molecular precedence (Chen *et al*., 2021). Even in cases where direct MUC1 binding was not always shown, extensively researched polyphenols have been shown to suppress MUC1-dependent programs by reducing tumor cell migration, and sensitizing cells to chemotherapy. They also exhibit pleiotropic anticancer effects such as antioxidant, or apoptosis induction (Marrelli, 2021). Medicinal plants possess many

bioactive compounds that have therapeutic potential to overcome different medical conditions, such as inflammation, abnormal cell growth, infections, and more (Sofowora *et al*., 2013). In the past, almost all medications were consisted of herbal medicinal plants for different diseases. Throughout the annals of history, societies have shared a pragmatic understanding of the beneficial properties of these herbs (Khan, 2014). Biochemical substances produced by plants in their defense mechanism against pathogens, pets, herbivores, and diseases, are also effective in the defense mechanism against a bunch of diseases and other beneficial purposes for humans (Gershenzon & Ullah, 2022). Traditional medicinal plants provide major benefits including economic gains by harvesting and health benefits by consumption (Smith-Hall *et al*., 2012; Ahn, 2017). Plants produce phytochemicals to protect themselves from harmful environmental stresses and herbicides. These compounds are by-products of plant mechanisms (Kumar *et al*., 2023). These medicinal phytochemicals are classified into various major classes such as alkaloids, flavonoids, phenols, saponins, and tannins (Sharma *et al*., 2018) by the possession of different functional groups in their structure (Marrelli, 2021). Among all the classes, phenols are the secondary metabolites possessing one benzene ring with at least one hydroxyl group in their structure (Dai & Mumper, 2010), produced in the shikimic acid pathway (SAP) and pentose phosphate pathway (PPP) (Lin *et al*., 2016). Phenolic compounds play a very basic preventive role against oxidative stress, aging, inflammation, and cardiovascular diseases (Hung *et al*., 2004). The second major class of compounds, flavonoids, polyphenolic metabolites possess a 15-carbon chain with at least 2 phenyl rings and oxygen embedded in one heterocyclic ring in their structure (de Souza Farias *et al*., 2021). Flavonoids have potential roles as anticancer (De Souza *et al*., 2018), anti-oxidants (Di Meo *et al*., 2013), anti-inflammatory, and antibacterial. Phenolic and flavonoid compounds could be novel compounds to check their activity in treating liver cancer. In a study, the *Artemisia dracunculus* plant was investigated to assess its antioxidant potential, and a new drug candidate could be selected for design using natural compounds (Țicolea *et al*., 2024).

In silico studies are the best option to deal with the limitations of experimental research. Virtual screening, and structure based drug designing including molecular docking and molecular dynamic simulation are the best *in silico* approaches to analyze the binding affinities of drug candidates (ligands) with the specific target proteins (Konieczny *et al*., 2023) and the dynamic behavior of the compound bonded with the target protein in the natural system under specific conditions (Tomczak *et al*., 2017), respectively. Lipinski's rule of five is a specified parameter to investigate any compound's nature as a potential drug candidate and its oral availability (Okaecwe, 2019). Solubility and pharmacokinetics (ADMET) analysis used to assess the metabolism, and toxicity parameters of any natural or synthetic drug compound that shown an excellent *in vitro* efficacy (Wang *et al*., 2015). In the current study, *A. dracunculus* plant was investigated to explore the novel anticancer drug candidate(s). In order to ensure reproducibility and scientific credibility, compounds with a documented presence in phytochemical databases (such as PubChem, and ChEMBL) and that had previously been reported in computational cancer research were given priority. Moreover compounds that demonstrated acceptable ADMET profiles and met Lipinski's rule of five were shortlisted in order to ensure pharmacological compatibility that they would be translated into drug-like candidates. Anticancer, and pharmacokinetic properties of the identified phyto-compounds against mucin-1 were predicted in this study using *in silico* methods such as pharmaco-informatics, and molecular dynamics simulations. These methods were used to evaluate the conformational changes, stability, and intermolecular contacts between mucin-1 and the identified lead phytocompounds. In order to battle mucin-1-related cancer in the future, our work seeks to find possible lead phytocompounds from *Artemisia dracunculus* medicinal plant.

MATERIALS AND METHODS

***Collection and identification of the plant*:** *Artemisia dracunculus* was collected from Parachinar which is a small Pashtun town located in capital of Kurram district (province of KPK) in Pakistan, geographically located at 33.8991° N latitude and 70.1006° E longitude. Identification of plant samples was done from the Department of Botany, Government College University, Lahore, Pakistan, and a single specimen was submitted in the herbarium after mounting on a herbarium sheet (Herbarium No. 3838). The plant sample was air dried in the shade. After drying, the plant samples were crushed and ground by an electric grinder by using 40-60 mesh sieve. Finally, the powdered sample was preserved in dry glass jars for future use.

Extraction procedure: Fine powder of plant sample was used for this experimental study. 25 grams of powder was soaked in 200 mL of ethanol at normal room temperature for seven days to enhance the diffusion of compounds. Then the mixture was filtered using Whatman No. 1 filter paper. The rotary evaporator was used to get concentrated ethanol extract under reduced pressure. The plant extract was subjected to further HPLC analysis for identification of phytocompounds.

High-Pressure Liquid Chromatography analysis

Sample preparation: The sample for HPLC was prepared as mentioned above and the extraction was carried out using 2 mL of fermented broth with 50 mL of 95% ethanol under 80 KHz and 45°C in ultrasonic extraction apparatus for 30 min and the procedure was repeated twice. A rotary evaporator was used to dry the filtrate at 50°C and filtered. In 100 milliliters of mobile phases, the dehydrated crude material was dissolved. The extract was injected for HPLC after passing through a 0.45 mm membrane filter (Milipore) and filter paper.

HPLC conditions: Phytochemicals were analyzed using the reverse phase HPLC (RP-HPLC) system. Shimadzu Corp., Kyoto, consisting of an LC-10ATVp pump, and a loop injector with a loop size of 20 µL. The peak area was calculated by CLASSVP software. Reverse-phase chromatographic analysis was carried out in isocratic conditions using a C-18 reverse phase column (250×4.6 mm i.d., particle size 5 µm, Luna 5 µ C-18; phenomenex, Torrance, CA, USA) at 25°C. The solvent gradients were formed, using a dual pumping system, by varying the proportion of solvent A to solvent B. Solvent B was increased to 50% in 4 minutes and subsequently increased to 80% in 10 min at a flow rate of 1.0 mL/min. The detection wavelength was 280 nm (Karpagasundari and Kulothungan, 2014).

***In silico* studies**

Pharmacokinetics evaluation: All the compounds reported in ethanol extract were analyzed for their ADMET analysis using their smile format to check the compound's oral bioavailability by Swiss ADME (http://www.swissadme.ch/) which involves water solubility, GI absorption, distribution, Lipinski rule of five, drug-likeness, hydrogen bond donors and acceptors (Yousuf *et al*., 2017).

PDB structure retrieval: The complete three-dimensional (3D) structure of selected cancer-causing protein, mucin-1 was obtained from UniProt (https://www.uniprot.org/) with identifier AF-P15941-F1. For the retrieval of 3D structures of selected ligands, the smile formulas were reserved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the 3D structures were downloaded by means of online server, Chemical Sketch Tool (https://www.rcsb.org/chemical-sketch).

Molecular docking: The 3D structure of the target protein Mucin 1 (PDB; P15941) was prepared for molecular docking. The protein preparation was used to arrange the refine structure to progress docking. The binding site was analyzed for all receptors, and protein files were prepared in the AutoDock4 program to save in PDBQT format. The selected compounds were further confirmed by PubChem (https:// pubchem. ncbi.nlm.nih.gov) database. The ligands were transformed into protein data bank (PDB) files. Then ligands were docked against the target protein to check their binding affinities (Yuriev *et al*., 2015) using Autodock Vina (Puthanveedu and Muraleedharan, 2022).

Generation of the grid: The processed protein data files in PDB format were used for docking to identify the active site amino acids. The ligand and receptor grid box was built, the exhaustiveness was set to 34, and the Autodock Vina docking process was executed. The grid box was positioned surrounding the active site. Lamarckian Genetic Algorithm (LGA) technique was used for docking calculations, and the best conformation with the lowermost docked energy was selected.

Swiss-ADME analysis: The Data Warrior program version 4.6.1, Swiss-ADME and pkCSM web server was used to determine the physicochemical features of compounds, including drug-likeness and toxicity. The best candidates for drugs are molecules that follow Lipinski's rule.

Molecular dynamic simulation: To study the dynamic behavior of the protein complex under simulated physiological conditions, molecular dynamics simulations of the protein-ligand (PL) complex were performed using Desmond Schrodinger Maestro (v12.5). The PL complex (atoms) was solvated in a 10 × 10 × 10 Å orthorhombic periodic box built with TIP3P water molecules. The NPT ensemble was implemented with a recording interval of 100 ps, and 100 ns of MDS was performed at 1 atm pressure and 310 K temperature, yielding 1,000 read frames in total. Various parameters of the MDS, such as root mean square fluctuation (RMSF), solvent accessible surface area (SASA), the radius of gyration (rGyr), and dynamic cross-correlation matrix were also investigated to check the stability, structural fluctuations and PL interactions in the solvated system (Kumar *et al*., 2025).

RESULTS

***HPLC analysis*:** A chromatogram of *A. dracunculus* was noted at λ=280 nm and a total of 14 compounds were identified in the ethanol extract (Table 1). Each peak represented the presence of a specific compound with a specific concentration as 1st peak for catechin, 2nd for gallic acid, 3rd for vanillic acid, 4th for caffeic acid, 5th for resveratrol, 6th for myricetin, 7th for kaempferol-glucoside, 8th for kaempferol, 9th for thiopene-2-acetic acid, 10th for phytol, 11th for 1,2,3-oxadiazole, 12th for bicyclo [3.3.1] non-2-en-9-ol, 13th for 6-methoxy-2-aminopyridinamine, and 14th for hexadecenoic acid. Retention times for these phenolic compounds are listed in the table below. By analyzing the retention time, it can be concluded that this method is precise, accurate, and

sensitive enough for quantitatively evaluating phenolic compounds in *A. dracunculus* (Țicolea *et al*., 2024).

Table 1: HPLC analysis of ethanol extract of *A. dracunculus*

No.	RT (min)	Compound	Molecular formula	Molecular weight	Peak area%
1	7.035	Gallic acid	$C_7H_6O_5$	170.12	0.014
2	17.64	Catechin	$C_{15}H_{14}O_6$	290.26	1.68
3	20.14	Vanillic acid	$C_8H_8O_4$	168.14	10.64
4	21.08	Caffeic acid	$C_9H_8O_4$	180.16	1.31
5	36.163	Resveratrol	$C_{14}H_{12}O_3$	228.25	3.13
6	38.525	Myricetin	$C_{15}H_{10}O_8$	318.2351	1.35
7	39.095	Kaempferol-glucoside	$C_{21}H_{20}O_{11}$	448.4	1.35
8	46.13	Kaempferol	$C_{15}H_{10}O_6$	286.23	0.43
9	11.958	Thiophene-2-acetic acid	$C_{18}H_{26}O_2S$	306	0.47
10	18.713	Phytol	$C_{20}H_{40}O$	296	0.68
11	16.683	1,2,3-Oxadiazole	$C_9H_{15}N_3O$	181	0.14
12	22.017	Bicyclo [3.3.1] non-2-en-9-ol	$C_9H_{14}O$	138	0.3
13	23.117	6-methoxy-2-Aminopyridinamine	$C_6H_8N_2O$	124	0.07
14	19.151	Hexadecenoic acid, methyl ester	$C_{17}H_{34}O_2$	270	21.32

In silico studies

Pharmacokinetics evaluation: The present study aims to investigate, design, and develop new inhibitory drug candidates against liver cancer leading proteins for instance mucin-1 using *in silico* screening methods to overcome the leading liver cancer. In the present study, phenolic compounds were investigated as a potential drug candidate by analyzing their biological and physicochemical properties as ADMET analysis which deals with water solubility, membrane permeability, and absorption (Wen *et al*., 2015) in the body with the use of Swiss ADME (Purawarga Matada *et al*., 2022). Physicochemical properties of drug candidates including drug likeness (Lipinski's rule of 5) and drug-likeness are listed in Table 2.

Table 2: Pharmacokinetics and physicochemical properties of lead compounds from ethanol extract of *A. dracunculus*

Sr. No.	Compound	Water solubility	GI absorption	CYP inhibitor	BBB*	Drug-likeness	†Ro5 violations
1	1,2,3-Oxadiazole	Soluble	High	No	No	Yes	1
2	Bicyclo [3.3.1] non-2-en-9-ol	Soluble	High	No	Yes	Yes	1
3	6-methoxy-2-Aminopyridinamine	Soluble	High	No	No	Yes	1
4	Myricetin	Soluble	Low	Yes	Yes	Yes	0

*BBB: blood brain barrier; †Ro5: Lipinski's rule of five

6-Methoxy-2-Aminopyridinamine and Bicyclo [3.3.1] non-2-en-9-ol have optimal physicochemical and ADME properties, which makes them appropriate starting scaffolds for optimizing medicinal chemistry to increase MUC1-targeted efficacy. Myricetin, a biologically active lead compound with excellent safety and potency but requires formulation enhancement to overcome bioavailability limitations. According to the ADMET predictions, most of these phytocompounds from *A. dracunculus* have physicochemical characteristics that are consistent with those of drugs, including low toxicity, tremendous absorption, and metabolic stability. However, drawbacks like moderate permeability emphasize the necessity of optimizing formulations (such as liposomes or nanoemulsions) to improve pharmacokinetic performance (Purawarga Matada *et al*., 2022).

Molecular docking study: MD is a bioinformatics virtual process to check the effectiveness of protein-ligand complexes for drug discovery and development (Mohan *et al*., 2021). The interaction of docked cancer protein mucin-1 and ligands includes hydrogen bonds and other interactions that are important for the activities of proteins (Satpathy, 2020). The docking results were analyzed by Chimera which shows the binding pocket residues as well as hydrogen bonds of ligands with proteins along with bond distance (Butt *et al*., 2020).

Six residues of mucin-1 protein, D1072A, I1073A, E1075A, I1080A, Y1124B, and Y1132B are

detected in the binding pocket forming hydrophobic interactions with 1,2,3-oxadiazole (Fig 1, A). There are nine residues of mucin-1, R1071A, E1075A, Q1079A, I1080A, Y1124B, A1128B, Y1132B, L1134B, and I1136B were present in the binding pocket which formed hydrophobic interactions with 6-methoxy-2-aminopyridinamine (Fig 1B). In the case of ligand "bicyclo[3.3.1]non-2-en-9-ol", F1047A, D1072A, I1073A, E1075A, F1077A, I1080A, F1121B, Y1124B, A1128B, Y1132B, L1134B, and I1136B are the residues in binding pocket of mucin-1 protein forming hydrophobic interactions with compound1 (Fig 1C). Mucin-1 chain A possesses residues, F1054, E1059, P1061, Y1066, K1093, F1094, R1095, and P1096 in the binding pocket, forming two hydrogen bonds (Y1066A and F1094A) with myricetin with the bond distance of 2.252Å and 1.967Å, respectively (Fig 1D).

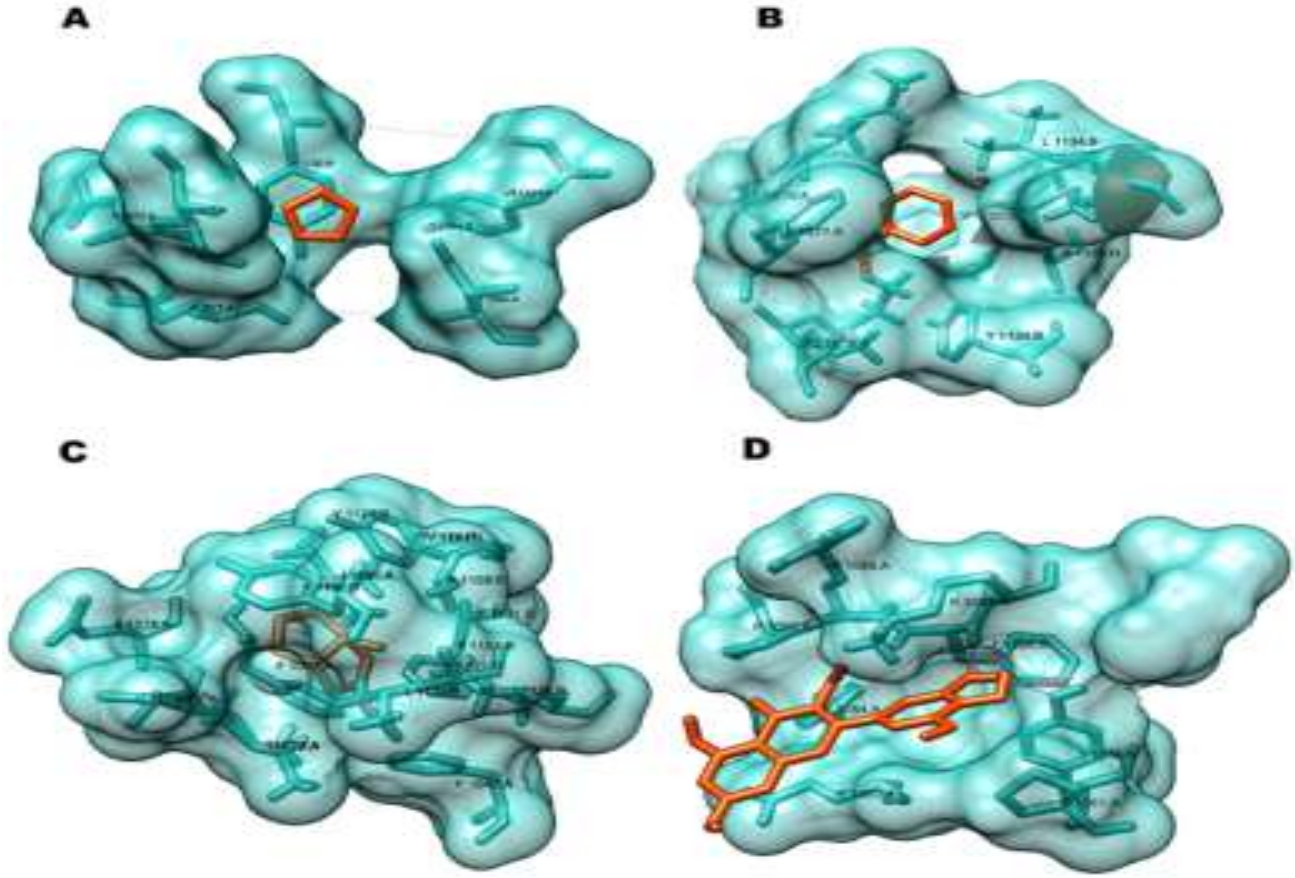

Fig. 1: Binding interactions of mucin-1 (surface, light sea green) with ligands (orange-red) within the active site: (A) 1,2,3-oxadiazole, (B) 6-methoxy-2-aminopyridinamine, (C) bicyclo[3.3.1]non-2-en-9-ol, and (D) myricetin. The docking poses demonstrate the orientation and key intermolecular contacts of each ligand in the MUC1 binding pocket. Myricetin forms two hydrogen bonds, which are shown in pink along with bond distance.

Molecular dynamic simulation: MD simulations for the proteins with ligands were performed for the cancer protein, mucin-1 for a total time duration of 100 ns (Matsuda *et al*., 2018) to evaluate the structural conformational changes caused by the binding of ligands (Bhrdwaj *et al*., 2023) inside the binding pockets of proteins. The four trajectories were analyzed, compared, and examined. Root mean square deviation (RMSD) provides relative dynamic behavior of proteins alone and with ligands (Velázquez-Libera *et al*., 2020). It describes the structural conformational changes in protein ligands before and after complex formation. After an initial increase, the RMSD value of mucin-1 ranges between 1.5 to 3.0Å depending upon the system and remains fairly constant between 60 to 90 ns in blue color representation while in the case of ligand, RMSD value fluctuates in every single nanosecond which means that 1,2,3-oxadiazole is not formed a stable complex with mucin-1, which is showing that after binding the 1,2,3-oxadiazole there is a huge conformational change occurred in protein structure and these range difference is showing that it forms the unstable complex with mucin-1 by forming

unnecessary interactions which are mostly hydrophobic and this unstable complex formation will not produce an inhibitory activity in natural system (Fig 2A). In the case of 6-methoxy-2-aminopyridinamine, protein shows an average RMSD of 1.2 to 2.0Å while in bonded form with ligand, there is a lower RMSD value in the initial 40 ns that represents that ligand is not bonded in first 40 ns after that change in RMSD from value 1.5 to 4.0Å, which is showing that 6-methoxy-2-aminopyridinamine with mucin-1 is not stable (Fig 2B). For ligand, bicyclo[3.3.1]non-2-en-9-ol, the RMSD values ranging from 2.4 to 4.2Å after binding to mucin-1 which is not as much differential range from the native protein's RMSD showing an average RMSD of 3.36Å. The complex is showing a stable conformation before and after binding to the ligand molecule and this complex has the potential to inhibit cancer activity in the natural system (Fig 2C). In section D of Figure 2, RMSD shows a great difference in values before and after binding to a ligand (myricetin) to mucin-1 (Fig 2D).

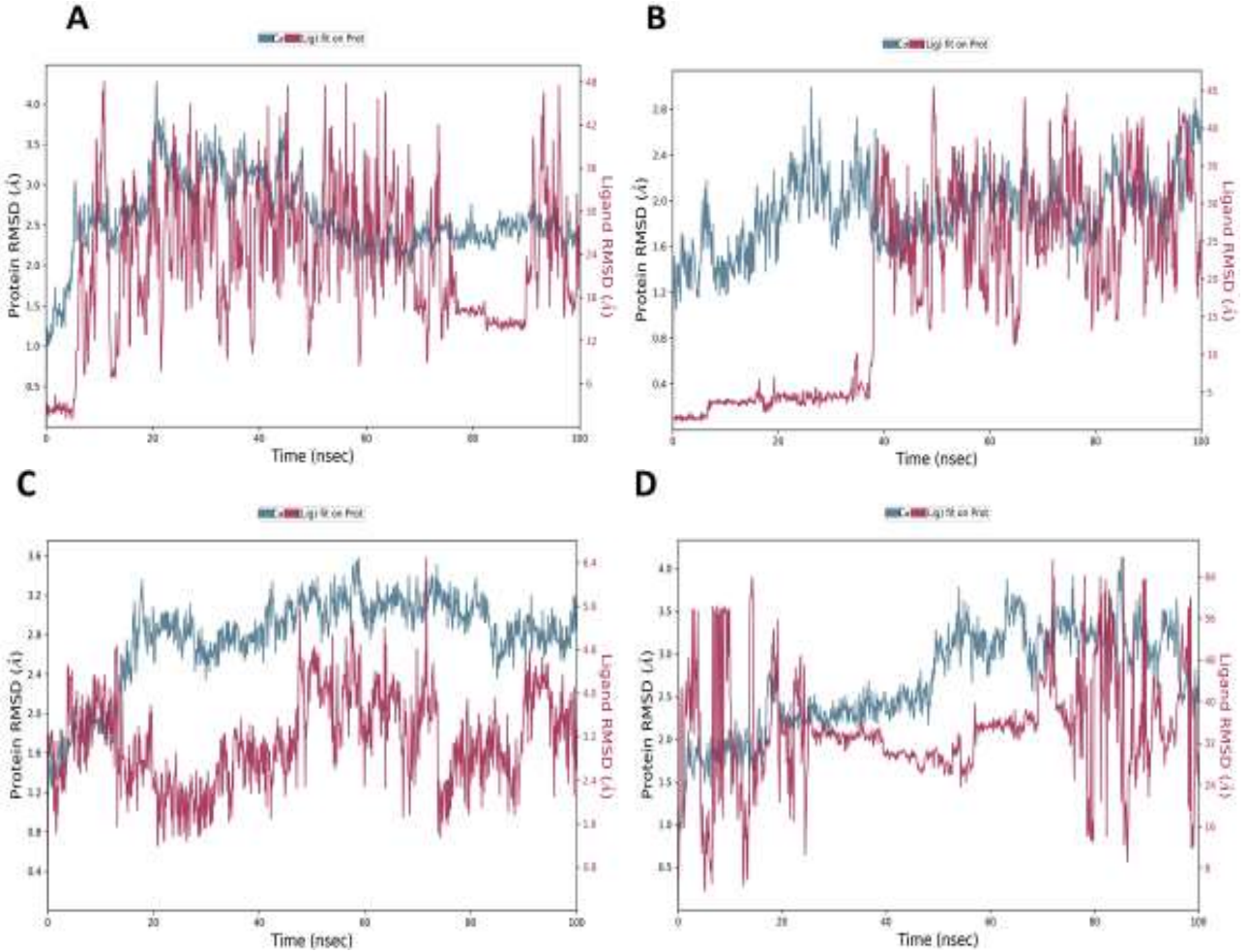

Fig. 2: RMSD analysis of mucin 1–ligand complexes during a 100 ns molecular dynamics simulation. The RMSD trajectories of MUC1 (blue) and respective ligands (red) are shown for (A) 1,2,3-oxadiazole, (B) 6-methoxy-2-aminopyridinamine, (C) bicyclo[3.3.1]non-2-en-9-ol, and (D) myricetin. The plots illustrate the time-dependent conformational stability of the protein backbone and the corresponding ligand within the binding pocket, reflecting overall complex stability and dynamic equilibrium throughout the simulation.

Root means square fluctuation (RMSF) is a parameter to investigate the flexibility of protein backbone to change its conformation to bind a ligand perfectly in its binding pocket to perform potential activity. In Figure 3, graph show the specific residues to which ligands bind. These residues are mostly the binding pocket residues that show flexibility for the ligand. The average vales of RMSF in these four complexes are between 1.0 to 2.0 Å which show that proteins have good flexibility to adjust the ligand and perform activity (Agarwal *et al*., 2020).

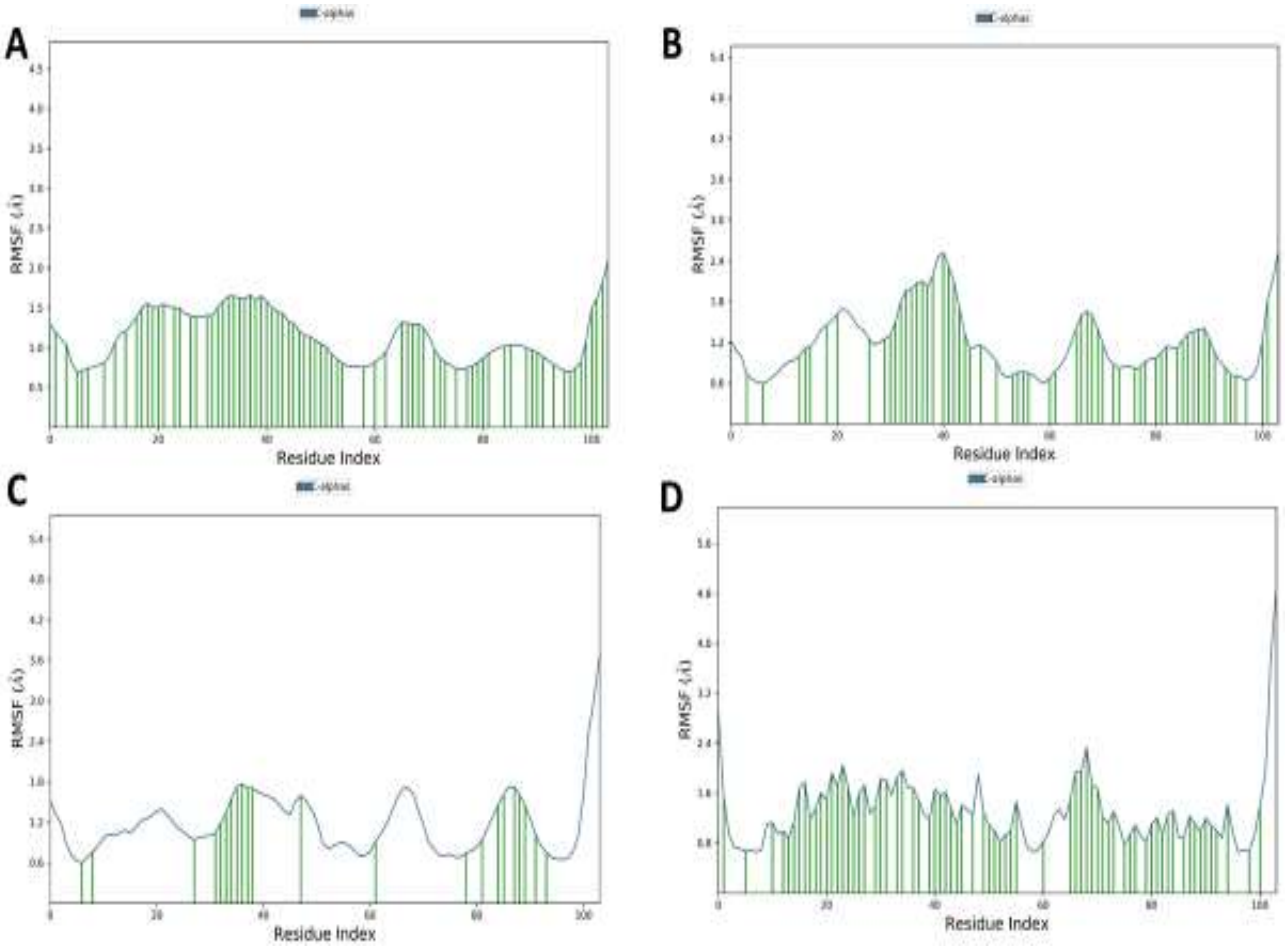

Fig. 3: RMSF analysis of the mucin-1 protein with ligand molecules. (A) 1,2,3-oxadiazole, (B) 6-methoxy-2-aminopyridinamine, (C) bicyclo[3.3.1]non-2-en-9-ol, and (D) Myricetin during the 100 ns simulation period.

To determine the effect of a ligand on whole protein, six properties demonstrate the strength of ligands within binding pocket of protein (mucin-1). These properties involved specific ligand RMSD, which is the measurement of deviation of ligand from the reference conformation of the protein (Naveed *et al*., 2024). The second parameter is the radius of gyration (rGyr) which indicates the movement of ligands around a specific axis. PSA is the polar surface area of a ligand that is accessible to the nitrogen and oxygen atoms in receptors (Veeramachaneni *et al*., 2021). Solvent accessible surface area is the molecular surface that remains in contact with water molecules of the natural system (Dasari *et al*., 2017). These are the six properties that indicate the whole dynamic behavior of ligands on a receptor protein in its complex form. In the case of 1,2,3-oxadiazole, RMSD values ranged between 0.2 to 0.3Å which indicate fluctuation in structural conformation after binding to the protein, rGyr (1.30Å) is showing the stability of the complex. There is no intramolecular hydrogen bond inside the ligand and fluctuations in the surface area indicate minor changes in conformation throughout the simulation of 100 ns (Fig 4). For 6-methoxy-2-aminopyridinamine, its polar atoms help to form hydrogen-bond with important polar residues of MUC1, and its stiff heterocyclic structure helps to minimize conformational entropy loss upon binding. The RMSD convergence and the favorable docking energy both show this stability. Higher RMSD of bicyclo[3.3.1] indicated that during simulation, this tiny, nonpolar bicyclic alcohol may have briefly detached from the active pocket and experienced weaker stabilizing interactions, primarily hydrophobic contacts. Lower binding affinity and less conformational restriction within the pocket are indicated by the ligand's drift, even if the protein's structure remained steady. These slight RMSD changes in myricetin imply that the chemical maintained a stable binding site association while allowing for some flexibility of its tiny heterocyclic ring. These kinds of variations are common for low-molecular-weight ligands, which can move or rotate a little bit inside a bigger binding cavity without losing important interactions. A strong and energetically advantageous complex between myricetin and MUC1 was produced, as evidenced by the

stable RMSD plateau and persistent hydrogen-bond interactions. With important aromatic residues, the planar structure and numerous hydroxyl groups probably facilitate its great binding affinity by facilitating regular hydrogen bonding.

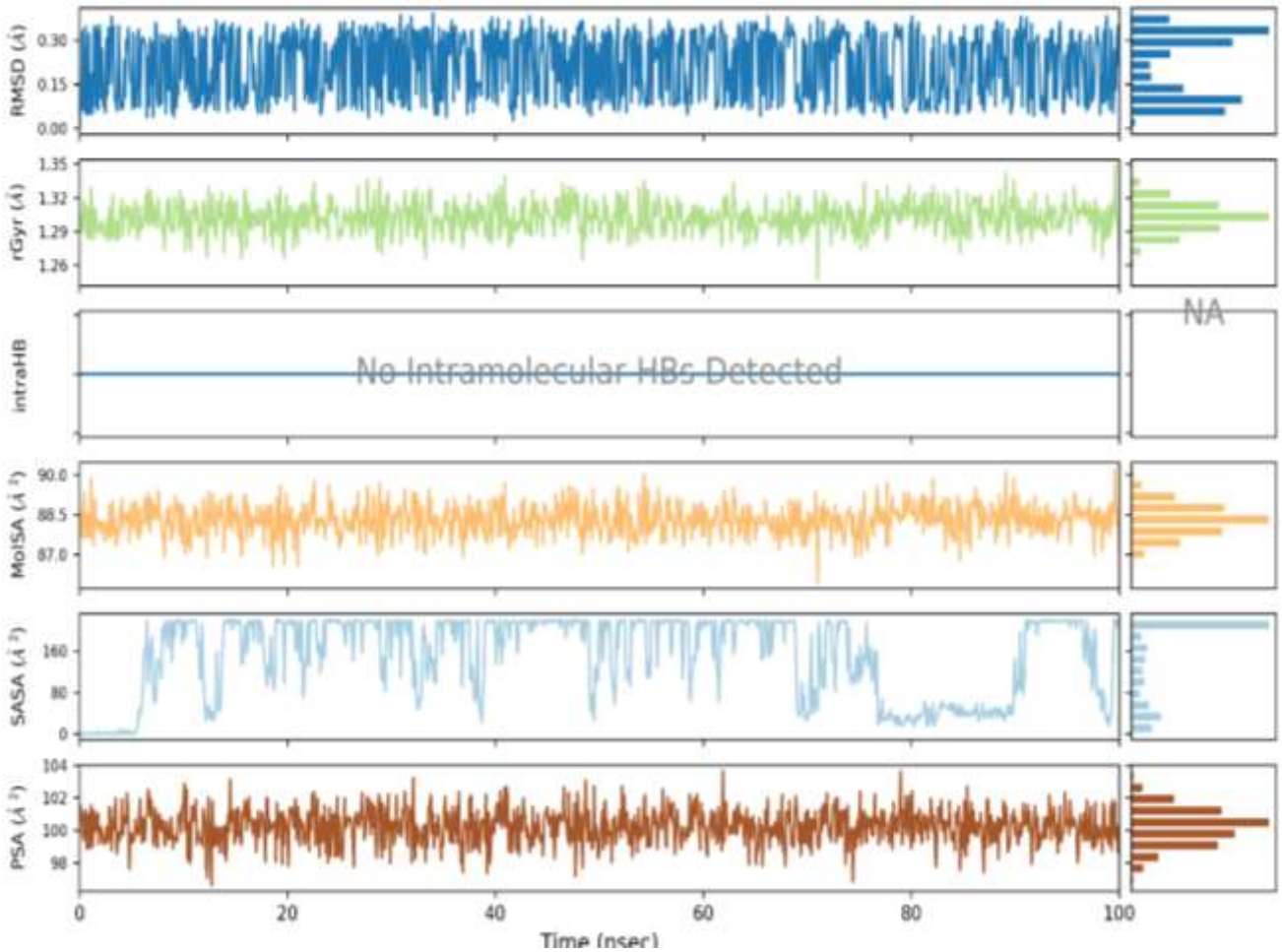

Fig. 4: Molecular simulation parameters of 1,2,3-oxadiazole in the docked complex with mucin-1 during 100 ns simulation.

In case of 6-methoxy-2-aminopyridinamine, RMSD values ranged between 0.2 to 0.4Å which indicates fluctuation in structural conformation after binding to the protein, rGyr (2.06Å) shows the stability of the complex. There is no intramolecular hydrogen bond inside the ligand and fluctuations in the surface area (MolSA and PSA) indicate minor changes in conformation throughout the simulation of 100 ns. SASA plot indicates no stable contact with water in the first 40 ns and for the remaining duration of the simulation it changes towards stable contact with water molecules (Fig 5).

In case of bicycle [3.3.1] non-2-en-9-ol, an average RMSD value is 0.12Å which indicates minor fluctuation in structural conformation after binding to protein, and an average rGyr is 1.9625Å shows the compactness of the complex. There is no intramolecular hydrogen bond inside the ligand and fluctuations in the surface area (MolSA and PSA) indicate minor changes in conformation throughout the simulation of 100 ns. SASA plot indicates the stable contact with water in the first 15 ns and then again stabilizes the contact in the second half duration of the simulation (Fig 6).

Myricetin RMSD value is 1.45Å throughout the simulation to indicate the stable complex conformation. The radius of gyration shows the stable compactness of the complex.

There are intramolecular hydrogen bonds present to indicate the stability of ligands and fluctuation in surface area properties (SASA, MolSA, and PSA) represent the contact of surface area to different molecules like water, nitrogen or oxygen, and polar surfaces to stabilize the complex of protein and ligand (Fig 7).

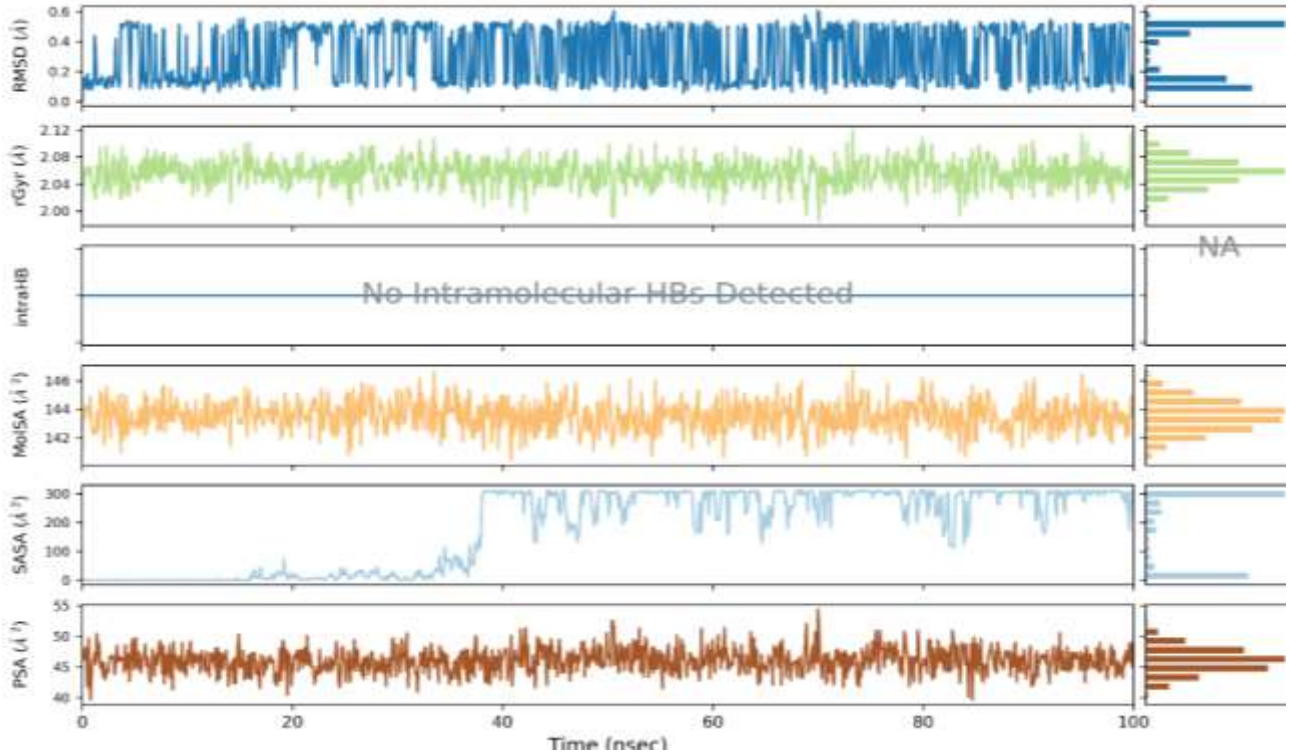

Fig. 5: Molecular simulation parameters of 6-methoxy-2-aminopyridinamine in the docked complex with mucin-1 during 100 ns simulation.

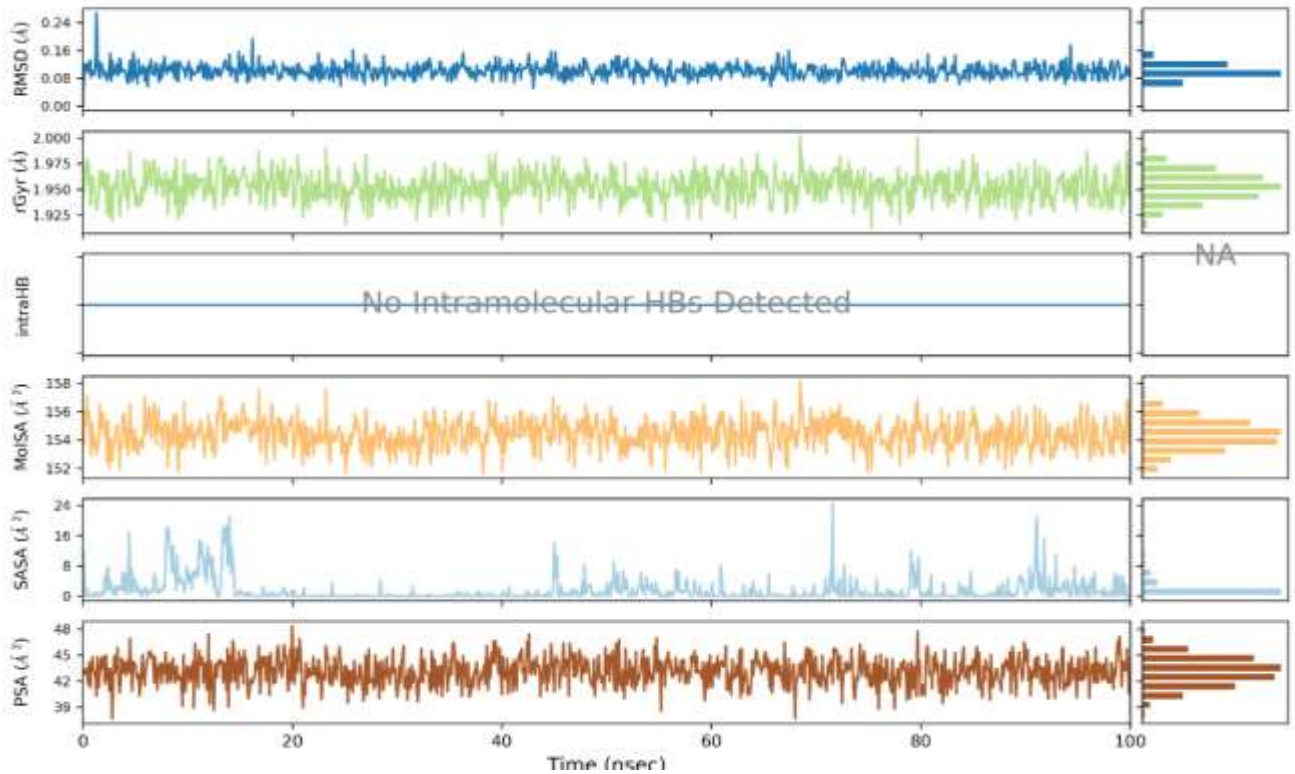

Fig. 6: Molecular simulation parameters of bicyclo[3.3.1]non-2-en-9-ol in the docked complex with mucin-1 during 100 ns simulation.

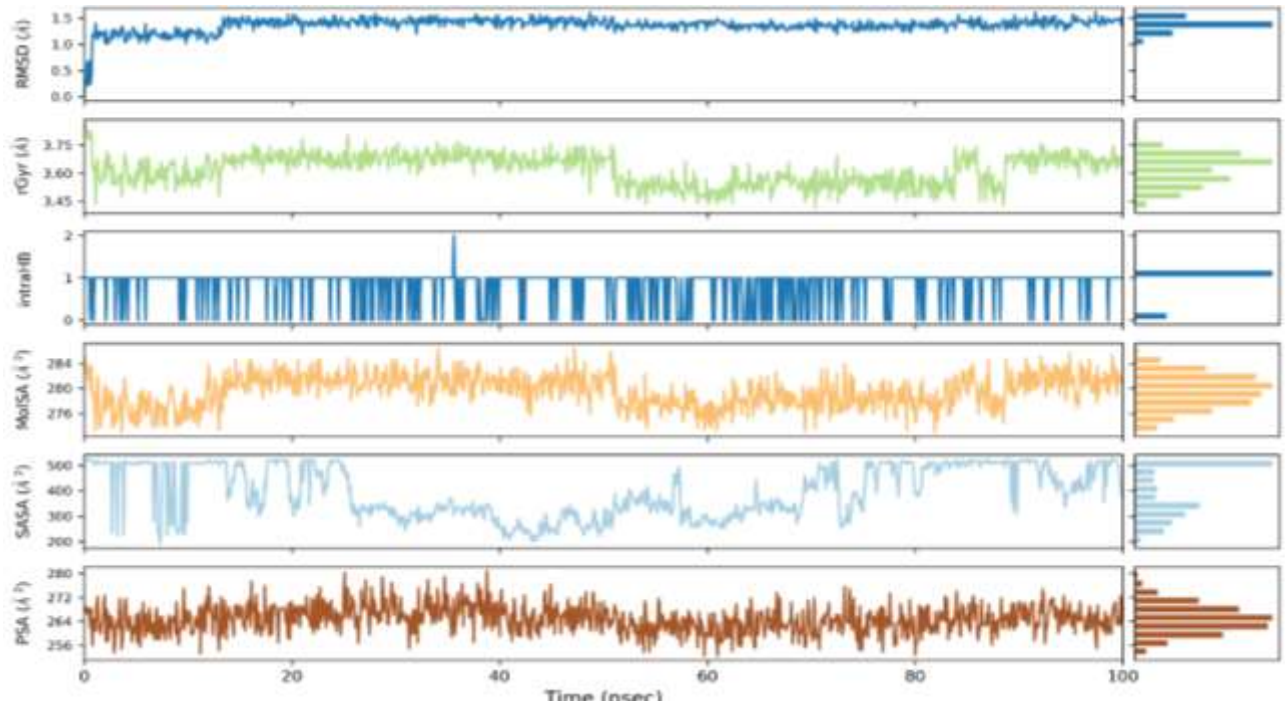

Fig. 7: Molecular simulation parameters of myricetin in the docked complex with mucin-1 during 100 ns simulation.

Protein interactions with the ligand can be examined throughout the simulation analysis. Protein-ligand contacts are categorized into hydrogen bonds, hydrophobic, ionic, and water bridges. A value of 0.6 suggests that 60% of the simulation time the specific interaction (Water Bridge) is sustained as shown in Figure 8. Values over 1.0 are possible as some protein residue may make multiple contacts of the same subtype with the ligand. A maximum of 35% of hydrogen bonds were formed during the simulation with ligand 1,2,3-oxadiazole as shown in the green bar in Fig 8. No ionic interaction was observed in the complex of mucin-1 with 1,2,3-oxadiazole (Fig 8).

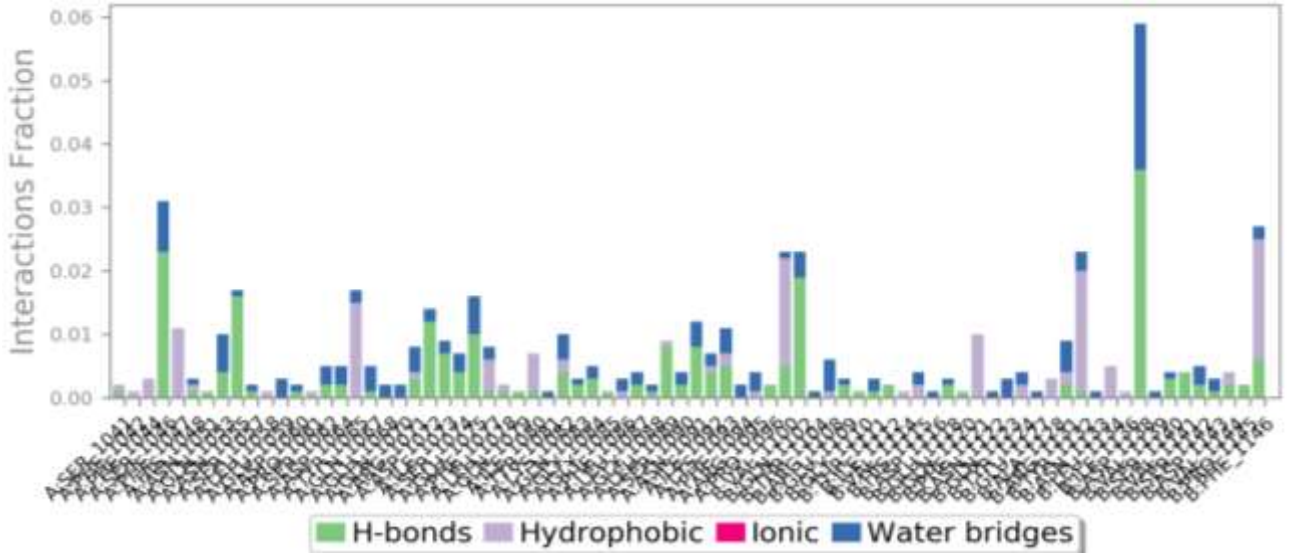

Fig. 8: Interaction profile of the mucin-1 protein with 1,2,3-oxadiazole within the binding pocket. The diagram illustrates various non-covalent interactions, including ionic bonds and water-mediated hydrogen bridges, stabilizing the ligand–protein complex. The interaction map highlights key amino acid residues involved in binding, demonstrating the contribution of electrostatic and solvent-assisted contacts to the overall affinity and structural stability of the mucin-1–1,2,3-oxadiazole complex.

In the case of 6-methoxy-2-aminopyridinamine, mostly hydrophobic interactions were formed. Only a few of the residues formed hydrogen bonds with 6-methoxy-2-aminopyridinamine during the whole simulation (green bars). These bars show that protein did not form a very stable complex with 6-methoxy-2-aminopyridinamine during the whole simulation (Fig 9).

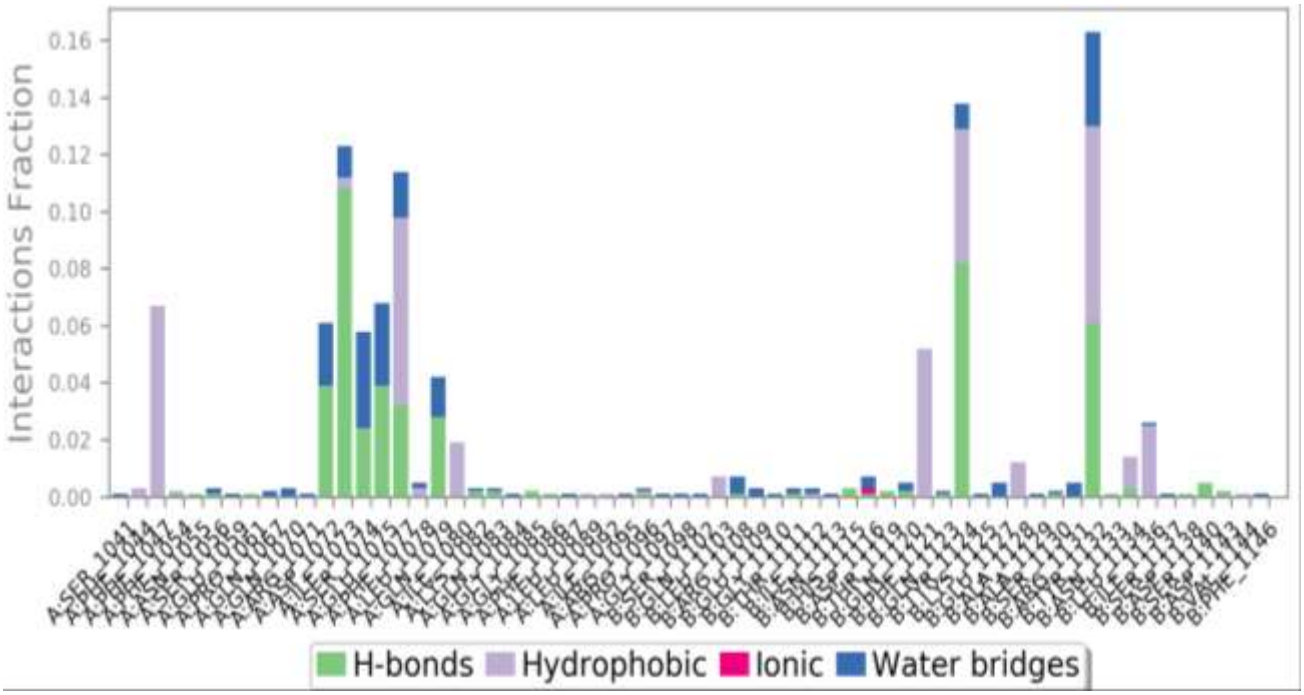

Fig. 9: Interaction map of the mucin-1 protein with 6-methoxy-2-aminopyridinamine complex, showing ionic bonds and water-bridge interactions between the ligand and key residues within the binding pocket.

In Fig 10, different types of interactions of mucin-1 with bicyclo [3.3.1] non-2-en-9-ol are shown. There is a smaller number of residues of mucin-1 that formed bonding interactions with bicyclo[3.3.1]non-2-en-9-ol and Tyr1132 formed hydrogen bonding during the 60%-time duration of the simulation which showed that it formed interaction at least for 60 ns of time, during 100 ns simulation.

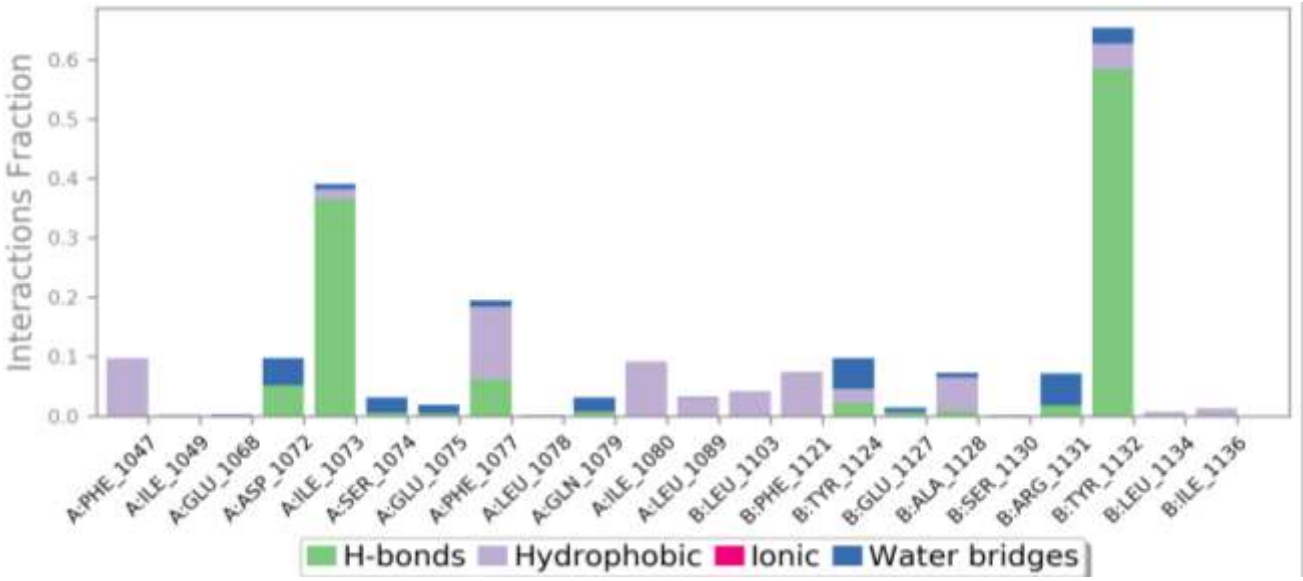

Fig. 10: Interaction map of the mucin-1 protein with bicyclo[3.3.1]non-2-en-9-ol complex, showing ionic bonds and water-bridge interactions between the ligand and key residues within the binding pocket.

Myricetin formed water bridge interaction most of the time of simulation as shown in the blue bars. There are 1-2% ionic interactions observed by 2-3 residues of mucin-1 with myricetin. Some residues formed hydrogen bonds for most of the simulation time as shown in Fig. 11, residue number 1113-1116 in green bars. The formation of hydrogen bonds is the indication of the stability of the complex of protein and ligand.

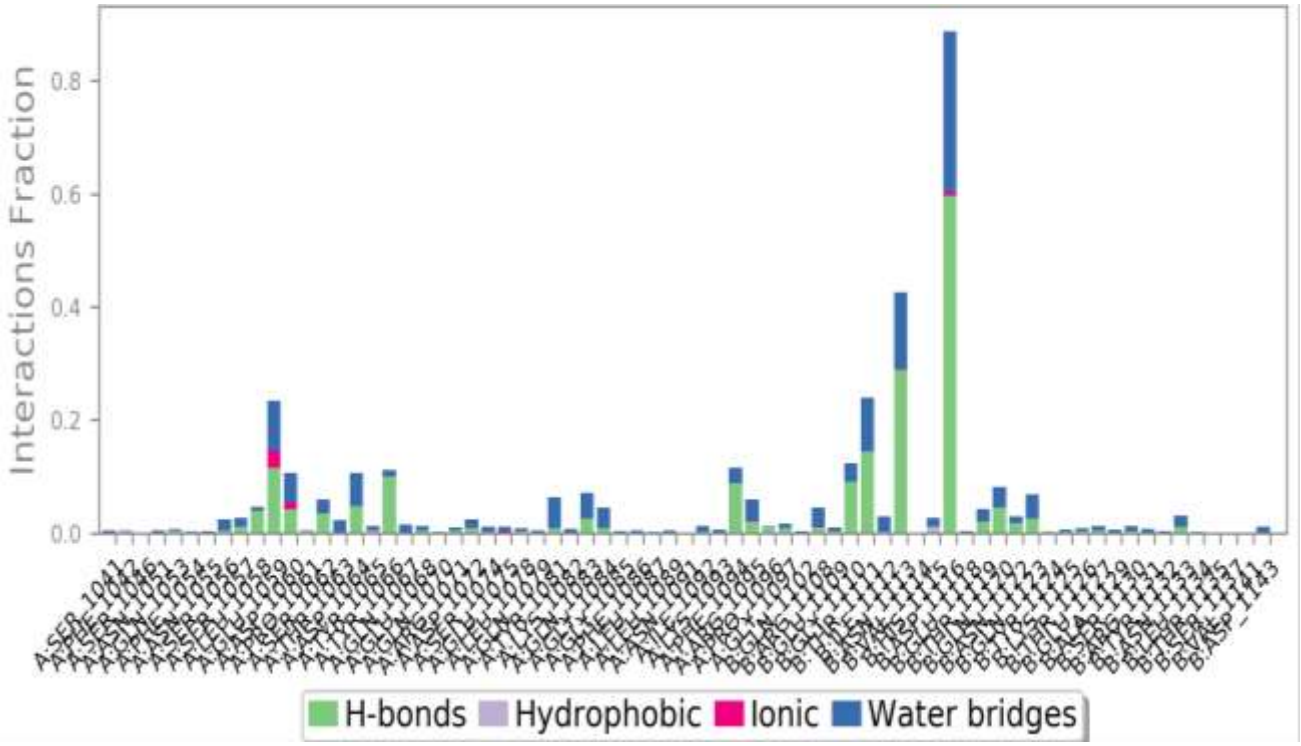

Fig. 11: Interaction map of the mucin-1 protein with myricetin complex, showing ionic bonds and water-bridge interactions between the ligand and key residues within the binding pocket.

DISCUSSION

New developments in computer-aided drug discovery enable the search for possible inhibitors by examining natural product libraries. Researchers employ molecular docking simulations, a crucial method in computer-aided drug development, to mimic the interactions between target proteins and small compounds in order to identify possible inhibitors. Chemicals derived from plants have inhibitory effect against a variety of fibrotic enzymes and proteins (Konieczny *et al*., 2023). Natural flavonoids and polyphenols have been shown in a number of recent studies to reduce MUC1 expression and activity in cancer models. Biological therapy is the possibility for small molecules and phytochemicals to affect downstream signaling of mucin as seen by some flavonoids that blocking MUC1-dependent pathways (Ekiert *et al*., 2021). The behavior of small compounds that bind a protein core can vary between isoforms, human cancers, and preclinical models. MUC1 may even partially suppress tumor cells, making them more sensitive to current treatments. Adjuvants made from natural substances could lower the effective dosages of harmful cancer medications (Marrelli, 2021). Similarly immunomodulatory effects of phytochemicals are common such as cytokine releasing or TAM (tumor associated macrophages) polarization. By altering the cytokine/chemokine milieu or decreasing MUC1-driven immune evasion, these substances may improve antitumor immunity or work in concert with immune checkpoint inhibitors (Kumar *et al*., 2023).

In the current study, *A. dracunculus* showed a significant amount of phenols and flavonoids to exhibit several biological activities like antioxidant, antitumor, anti-inflammatory, antimicrobial, antidepressant, and many others (Ekiert *et al*., 2021). Literature findings proved that the investigated plant exhibited anti-tumor and antioxidant activities (Navarro-Salcedo *et al*., 2017). Because *Artemisia dracunculus* contains flavonoids and phenols and utilized as a medicinal plant and phytocompounds from *Artemisia dracunculus* may interact with MUC1 and affect fibrogenesis-related pathways due to the plant's varied chemical makeup (Kumar *et al*., 2023). MUC1 is a transmembrane glycoprotein that is overexpressed in a number of epithelial malignancies, such as breast, pancreatic, and hepatocellular carcinomas (Marrelli, 2021). The *in silico* results of this study offer a useful basis for the early-stage

drug discovery process that targets this protein. Strong binding affinities and advantageous ADMET profiles have been found in phytocompounds from *A. dracunculus*, indicating that they may be used as lead candidates for the creation of low-toxicity, natural medicines or as adjuvants in cancer treatment. *A. dracunculus* ethanol extract HPLC examination revealed the presence of many phyto-compounds. Molecular docking, and pharmacoinformatics, were among the *in silico* techniques used in this investigation to predict the anticancer and pharmacokinetic properties of the discovered phytocompounds against mucin-1 (Ekiert *et al*., 2021). Mucin-1 (MUC1) is a transmembrane glycoprotein that is important for immunological control, tissue defense, and cellular communication. Numerous epithelial tissues produce MUC1, which is involved in barrier function, cell adhesion, and defense against external toxins. MUC1 has been demonstrated to control fibroblast activity, adjust inflammatory responses, and affect extracellular matrix remodeling in the context of fibrosis (Marrelli, 2021). After a thorough examination of the HPLC data and available literature, phytocompounds were selected to determine anti-cancer potential using molecular docking analysis and molecular dynamic simulations that targeted the mucin 1 protein. The comprehensive computer analysis might provide strong support for a trustworthy framework that could help scientists create and refine new molecules (Kandeel *et al.*, 2023).

The structural stability, flexibility, and interactions within the mucin 1 and ligand complex are all thoroughly understood thanks to the combined studies of this study. Different binding affinities were found when pharmaceutical drugs were molecularly docked against MUC1. Various kinds of interactions between mucin-1 and bicyclo[3.3.1]non-2-en-9-ol were demonstrated in this study. Fewer residues of mucin-1 developed bonding contacts with bicyclo[3.3.1]non-2-en-9-ol, whereas Tyr1132 produced hydrogen bonds for 60% of the simulation, indicating that a minimum of 60 ns of interaction occurred during simulation. In order to reduce nuclear translocation and transcriptional activation of fibrotic genes, polyhydroxylated flavonols frequently insert into shallow protein pockets and form H-bonds with side chains and the backbone. According to reported studies these phytocompounds may prevent MUC1-mediated fibrogenesi by a variety of complimentary ways. Myricetin and other compounds have the ability to directly bind MUC1 interfaces kinase signaling (STAT3, or NF-κB), which suppresses the release of paracrine TGF-β transcription factors that activate hepatic stellate cells. MUC1 dimerization and nuclear translocation may be inhibited by smaller scaffolds (such as 6-methoxy-2-aminopyridinamine and bicyclo[3.3.1]non-2-en-9-ol) that provide fragment-like PPI inhibition (Ekiert *et al*., 2021). Myricetin may bind the cytoplasmic tail of MUC1-C or the adjacent interface, sterically preventing the recruitment of STAT3 or import machinery (Marrelli, 2021). These kinds of findings are crucial for drug development and discovery because they clarify the intricate molecular activity that affects how well possible mucin1 inhibitors work (Tomczak *et al*., 2017). As it was demonstrated that flavonoids and phenolic compounds may bind to the extracellular domain of MUC1 and alter its signaling, according to docking studies, potentially providing therapeutic benefits in fibrotic disorders (Marrelli, 2021). Their potential as MUC1 modulators has been rationalized by these investigations, which have revealed important amino acids in the MUC1 binding pocket that are involved in the interaction with plant-derived chemicals. This thorough analysis not only supports possible therapeutic uses but also directs future studies to maximize interactions for better pharmacological results. Protein dynamics and *in vivo* cellular activities that may change chemical action are just a few examples of the intricate biological systems that computational models cannot accurately represent and these are also limitations of present research study. *In vivo* models of malignancies that overexpress MUC1 should be used to evaluate promising drugs' safety characteristics, bioavailability, and therapeutic efficacy. In order to understand synergistic pathways and therapeutic activity, future research may look at *Artemisia dracunculus's* bioactive compounds, their quantitative analysis and their multi-target effects on pertinent cancer-associated proteins.

Conclusion: Different bioactive compounds are identified in ethanol extract of *A. dracunculus* and selected for *in silico* and ADMET analysis to identify specific compounds with positive medicinal chemistry and drug likeness. Molecular docking of medicinal compounds against MUC1 showed different binding affinities such as 2-6-methoxy-2-aminopyridinamine with affinity value -3.8 kcal/mol, 3-bicyclo [3.3.1] non-2-en-9-ol with -5.7 kcal/mol, myricetin with -6.3 kcal/mol, and 1,2,3-oxadiazole with -6.7 kcal/mol. These phytocompounds' anticipated binding affinities, pharmacological activity, and possible lethal effects were not verified by any *in vitro* or *in vivo* tests. As a few of phytochemicals identified from *A. dracunculus* were employed in the study, which may have left out some other bioactive compounds with more complementary anti-MUC1 properties. Further quantitative, *in vitro* and *in vivo* pharmacokinetic parameters must be examined in accordance with the dependability of molecular dynamics simulation results, which further demonstrates the accuracy of docking results. These findings may help researchers to develop new drug candidates against liver cancer in future.

Declarations and Acknowledgements

Availability of data and materials: We declare that all the data generated are included in this study.

Ethical approval: This study was previously approved by Institution of Molecular Biology and Biotechnology, Bioethical, Biosafety and Biosecurity Committee of Department of Molecular Biology and Biotechnology, University of Lahore with reference number CRiMM/23/Research/83 and is in accordance with research guidelines of IMBB, TUOL.

Declaration of Competing Interest: The author declares that there is no conflict of interest.

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Consent to Participate: All authors are equally participated in preparation and submission of original draft of this research paper.

Consent to publish: All authors gave their consent to publish this article

Data availability: No data generated during this review article study

Conflict of interest: The authors declare that they have no conflict of interest.

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