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Antioxidant and Anti-Cancer Insights of Phyla Nodiflora Against Cox-2 Domains Through Conformational Molecular Dynamic Simulations

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ABSTRACT

Cancer is one of the most mortal illnesses in the world. Cancer patients showed elevated levels of COX-2 enzyme and prostaglandin. This points towards the potential target of this enzyme in order to inhibit its enzymatic activity and thus lower prostaglandin. Phyla nodiflora was also reported to trigger apoptosis and cell cycle progression in MCF-7 breast cancer cells with augmented expression of tumorigenesis-inducing transcription factors. The increased antioxidant activity in Ehrlich-Lettre ascites carcinoma (EAC-bearing) mice may be responsible for anticancer activity. We decided to conduct experimental DPPH assays and in silico studies, including molecular docking, molecular dynamic simulation, drug-likeness, ADME, and toxicity, to find therapeutic agents to validate the anticancer and antioxidant activity of the plant. The antioxidant activity of the methanolic extract of the leaf was 42.69% when a 1mg dose of the leaf extract was used, while it increased to 64.49% when the dose of the leaf was increased to 7mg. Molecular docking shows that plant compounds like 8-methoxyluteolin (-8.8 kcal/mol), 8-methoxyapigenin (-8.3 kcal/mol), and 3-methylherbacetin (-9.1 kcal/mol) are ideal possible drug candidates since they have the highest binding affinities and follow Lipinski's rule of five. Molecular dynamic simulation, RMSD, and RMSF values show that they have good binding interaction with the receptor and are stable, hence showing that these compounds may act as novel therapeutic agents against cancers.

Introduction

Cancer is one of the most prevalent illnesses and the second leading cause of death after cardiovascular disease. Antioxidants protect living organisms from damage caused by the uncontrolled generation of reactive oxygen species (ROS). The production of ROS increases, resulting in chronic inflammation that leads to cellular and tissue damage

underlying several neurodegenerative, cardiovascular, and metabolic syndromes. ROS trigger the production of macrophages within the tumour cells through the activation of specific stimuli like TNF- 0 that triggers a rapid release of hydrogen peroxide and free radicals, triggering the subsequent induction of tumour cell apoptosis. Mitochondrial dysfunction is worth discussing when it comes to cancer progression, and it contributes significantly to the initiation of caspase 1 transcription factors and the uptake of Ca 2+ [1] by mitochondria. The discovery of novel drugs using multidrug targets has been an essential approach to cancer treatment[2, 3]. Studies on ligand-receptor docks can aid in the identification of new therapeutic and drug candidates [4]. Cyclooxygenase-2 (COX-2) is the most crucial enzyme and is elevated in patients with cancer[5]. In a study on Phyla nodiflorav breast and lung carcinomas, it was demonstrated that it can induce apoptosis and suppress the proliferation of cancerous cells[6]. Natural drug compounds can be considered as possible arguments to fight various forms of diseases[7]. The rate-limiting enzyme which converts arachidonic acid to prostaglandin is cyclooxygenase (COX) which is present in both COX-1 and COX-2 forms. COX-2 is correlated with human cancer, and its inhibition leads to anti-inflammatory and anti-cancer properties[8]. Many individuals use non-steroidal anti-inflammatory drugs to treat inflammatory diseases. However, these drugs could negatively affect the levels of prostaglandins because they inhibit COX-1 and not COX-2, which in turn leads to the hypermortality of the gastric cancer. COX-2 is a form of COX-1 with major changes, including a small pocket in the midpoint of the active enzyme site. Many drugs, such as rofecoxib and celecoxib, can selectively bind to this pocket. Other drugs, such as meloxicam, can inhibit COX-2 in various ways. It has been demonstrated that genuine COX-2 inhibitors are unable to influence the synthesis of gastric mucosal prostaglandins, do not result in acute harm, and do not cause chronic ulceration in contrast to a placebo [9]. COX-2 is a type of COX-1, which has major alterations, such as a small pocket in the middle of the active enzyme site. Many drugs, such as rofecoxib and celecoxib, are selective based on their interactions with this pocket. Meloxicam and other drugs can suppress COX-2. Studies have indicated that the real COX-2 inhibitors have no influence on the synthesis of gastric mucosal prostaglandins, do not result in acute damage, and do not cause chronic ulceration compared to the placebo [9]. COX-2 is activated by pro-inflammatory cytokines at the site of infection which subsequently induces carcinogenesis and the inhibition of apoptosis and angiogenesis by PGE2, which is among the most essential pathways to disable the immune system [11]. Most cancer cells release PGE2, thereby increasing cancer growth and suppressing the immune system to attack the carcinoma[12].Breast cancer is the 2 nd most frequently cause of death among women. There is a strong correlation between COX-2 expression levels and tumour aggressiveness. Recently, it was shown that the western blot analysis of COX-2 protein expression indicated that non-invasive MCF-7 breast cancer cells had a two-fold increase as opposed to benign MCF-10F breast cells, and a more than four-fold increase in protein COX-2 ($p<0.01$) level in cancerous tissue compared to normal tissue samples. In breast cancer, invasive and ductal carcinoma cases in the North American population, COX-2 had been identified to be increased by 40% among breast cancer patients with invasive and ductal carcinoma [13]. The inhibition of COX-2 has been identified as an effective therapeutic strategy. Therefore, it is among the most significant pharmaceutical treatments [14]. One of the largest components of cancer progression is inflammation[15]. This study aimed to assess the possible bioactive components of Phyla nodiflora in cancer treatment, focusing on the COX-2 enzyme. The plant extract is effective as an antibacterial, antifungal, anti-inflammatory, and antioxidant agent. An in silico study has not yet been conducted to identify new therapeutic drug candidates from the Phyla nodifloramedicinal plant. The plant is anti-inflammatory, and in this regard, it is effective against cancer.

MATERIALS AND METHODS

Plant collection and leaf Extraction

Plant Phyla nodiflora was collected from district Peshawar, KPK, Pakistan, and after drying, the leaves of the plant were converted into powder form. Two different types of solvent, methanol and water, were used for leaf extraction.

Antioxidant Activity

For antioxidant activity, methanol and water extracts of the leaf were used at different concentrations, i.e., 1mg, 3mg, 5mg, and 7mg.

Data Collection

Active constituents of NodifloraHalleridone, 8-methoxyluteolin, 3-methylherbacetin, 8-methoxyapigenin, and Halleron were downloaded from the PubChem database in SDF format, and receptor COX-2 (PDB: 5IKR) was downloaded from the Protein Data Bank in PDB format with the same strategy just like reported in our study (www.pdb.org/pdb)[16].

Protein Preparation

Receptor protein (PDB: 5IKR) was opened using the Discovery Studio software (2021) to remove undesirable molecules (https://discover.3ds.com/discovery-studio-visualizer-download). We removed all hydrogen atoms, water molecules, and associated ligands from the protein. We included hydrogen atoms and stored the protein in PDB format. The same procedure was utilized as in our previous study[16, 17].

Ligand Preparation

The ligands downloaded in PubChem database (https://pubchem.ncbi.nlm.nih.gov) are SDF formatted, hence, they were uploaded into the Open Babel window of PyRx and converted into PDB format, as is the case in our earlier reported work[18].

Molecular Docking

It enabled a molecular docking study, which was conducted on the interactions between the ligand and the protein of five active components of Nodiflora with COX-2 using the PyRx bioinformatics tool [19, 20]. The COX-2 enzyme was transformed into a macromolecule when it was uploaded to PyRx as a receptor protein. The entire ligand molecules were uploaded through the open Babel interface; minimization of energy was performed and pdbqt format obtained. A grad box was generated by the use of the Vina wizard, and then docking was done. Following our previous study [20, 21], Discover Studio 2021 was used to visualize the results, including 2D structures, hydrogen bonds, and lengths of bonds.

Drug-Likeness and ADME

A software named SwissADME online software (http://www.swissadme.ch) was used to determine the drug-likeness and do ADME analysis. ADME is an abbreviation used to denote absorption, distribution, metabolism and excretion. PubChem was used to get canonical SMILEs of ligand compounds that were then entered into swissADME to calculate drug-likeness and ADME parameters, which was consistent with our previously reported study [23].

Toxicity

The canonical SMILES of all ligands were obtained from the PubChem database and input into the Protox-ii online web server (http://tox.charite.de/protox_II), as previously reported [16, 24], and admetSAR (http://lmmd.ecust.edu.cn/admetsar2) for toxicity assessment. Protox-ii online and ADMETSAR were utilized to assess the hepatotoxicity, mutagenicity, cytotoxicity, AMES toxicity, carcinogenicity, and acute oral toxicity of the compounds.

Bioactivities

Drugs to be orally administered must comply with the drug-likeness characteristics to be completed as pharmaceutically consistent with their bioactivity score, hence the reason we used the Molinspiration Toolkit to make the prediction of the chosen compounds, such as in our final report[25] (https://www.molinspiration.com/cgi-bin/properties).

Molecular Dynamics Simulation.

Molecular dynamics (MD) simulation is an effective method of computation that is employed to investigate the conduct and attributes of molecules and substances at the atomic scale. The program Desmond is a software designed by Schrodinger to perform MD simulation of biological systems such as proteins, nucleic acids and membranes. To determine protein-ligand stability, molecular dynamics (MD) simulations were used. The most stable complexes with high binding energies were simulated by MD and analyzed. To determine the dynamic binding behavior and binding stability

of protein-inhibitor complexes in their docked form the Desmond module in the Schrodinger program was used to place MD simulations. The description of the methodology is presented in other sources [26-28].

RESULTS AND DISCUSSION

Antioxidant Activity

The antioxidant activity of leaf extract of *Phyla nodiflora*was analyzed at different concentrations and in three independent experiments. The results (Figure 1) show that when the average absorbance at 517 nm decreases, the scavenging effect of the leaf extracts increases. Figure 1 show that the methanol extract of the leaf is more effective for antioxidant activity, and when the dose of methanol extract is increased, the scavenging effect of the plant extract is noted to be increased. The antioxidant activity of methanol extract is 42.69% when a 1mg dose of the leaf extract is used, while it increases to 64.49% when the dose of leaf extract is increased to 7mg. Antioxidant activity, when ascorbic acid is used, was noted at 95.10%.

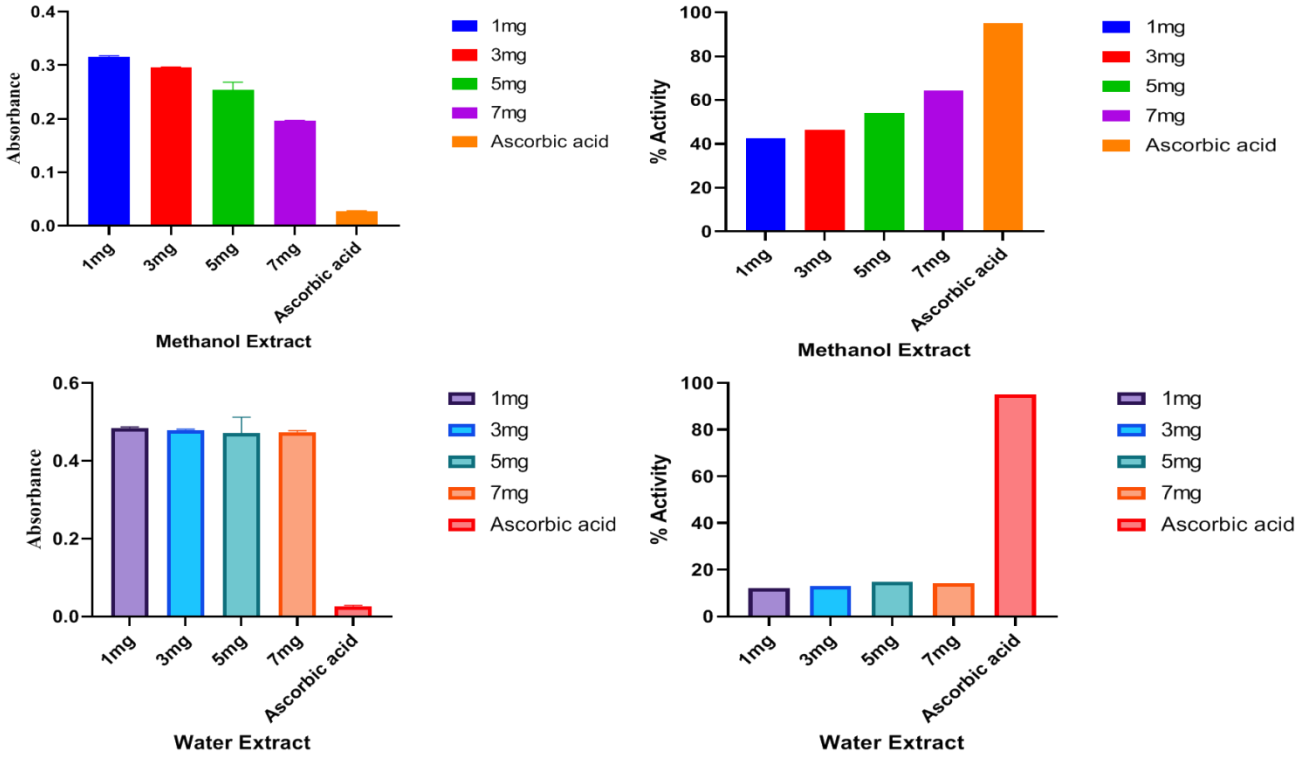


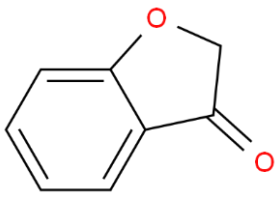
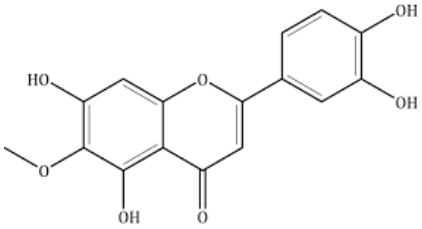
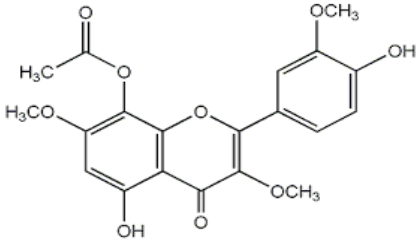
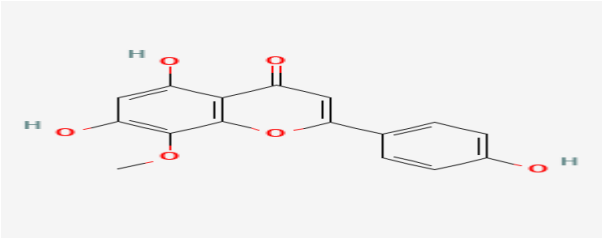
Figure .1 Antioxidant potential with absorbance and percent activity of methanol and water extract of *Phyla nodiflora*leafat different concentrations at OD=517 nm.

Molecular Docking

Molecular docking for five bioactive constituents was carried out against the COX-2 enzyme to evaluate their role as anti-cancer agents. In contemporary drug development, molecular docking plays a crucial role in ligand-protein and protein-protein interactions as well as the binding sites of receptors that ligand molecules bind to [29]. Table 2 indicates that four of the five selected compounds exhibit high binding affinity and low binding energy, demonstrating their strong interaction with the receptor protein COX-2.

The results show that 3-methylherbacetin, 8-methoxyluteolin, 8-methoxyapigenin, and Halleridone have binding affinities of -9.1, -8.8, -8.3, and -6.1, respectively. Generally for active drug compounds, -6.00 kcal/mol is considered as potential binding energy[30]. Hydrogen bond and bond distance were also analyzed for all the ligands interacting with the receptor protein COX-2. A molecular docking study of COX-2 reported that sesame oil is considered a traditional medicine with a -6.0 to -8.4 kcal/mol binding affinity[31]. Another study conducted to explore potential inhibitors of COX-2 shows that xanthoxyletin, having an -8.9 kcal/mol binding affinity, is a potential agent to inhibit COX-2 expression [32]. Curcumin was found to interact with Gln192, Asp347, Arg513, Leu351, Leu383, Leu357, Arg120, and Glu524 residues of the COX-2 enzyme [33].It is evident from Table 2 and figures (2, 3, and 4) that Gln461, Trp139 (2), Asp229, Arg333 (2), Leu238 (2), Asn144, Cys36, Glu140, Arg376 (2), and Asn375 residues of the COX-2 enzyme have bond lengths of 2.16 Å, 2.92 Å, 2.51 Å, 2.70 Å, 2.42 Å, 2.61 Å, 2.68 Å, 2.97 Å, 2.22 Å, 2.38 Å, 2.20 Å, 2.29 Å, and 2.15 Å, respectively, interacting with our selected bioactive constituents of *Phyla nodiflora*. The bioactive molecule 8-methoxyluteolin makes the most stable complex with receptor protein due to a high number of hydrogen bonds. The hydrophobic interaction in the binding site of COX-2 is driven by Tyr385 and Tyr387[34].

Table .1 List of five selected bioactive constituents with compound name and structure depiction of Nodiflora.

S.NO	Compound names	Structure Depiction
1	Halleridone	
2	8-methoxyluteolin	
3	3-methylherbacetin	
4	8-methoxyapigenin	

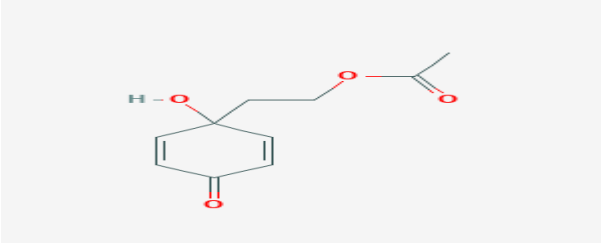
5	Halleron	

Table .2 Molecular docking results of selected bioactive compounds of *Nodiflora* medicinal plant.

S.No	Compounds	Binding Affinity (Kcal/mol)	Hydrogen Bond	Bond Distance (Å)
1	Halleridone	-6.1	GLN A:461	2.16
2	8-methoxyluteolin	-8.8	TRP B:139, ASP A:229, ARG A:333, LEU A:238, ASN B:144	2.51, 2.70, 2.42, 2.68, 2.22
3	8-methoxyapigenin	-8.3	ARG A:333, GLU B:140, LEU A:238	2.61, 2.20, 2.97
4	Halleron	-5.6	ARG B:376, ASN A:375, ARG A:376	2.29, 1.83, 2.15
5	3-methylherbacetin	-9.1	CYS B:36	2.38

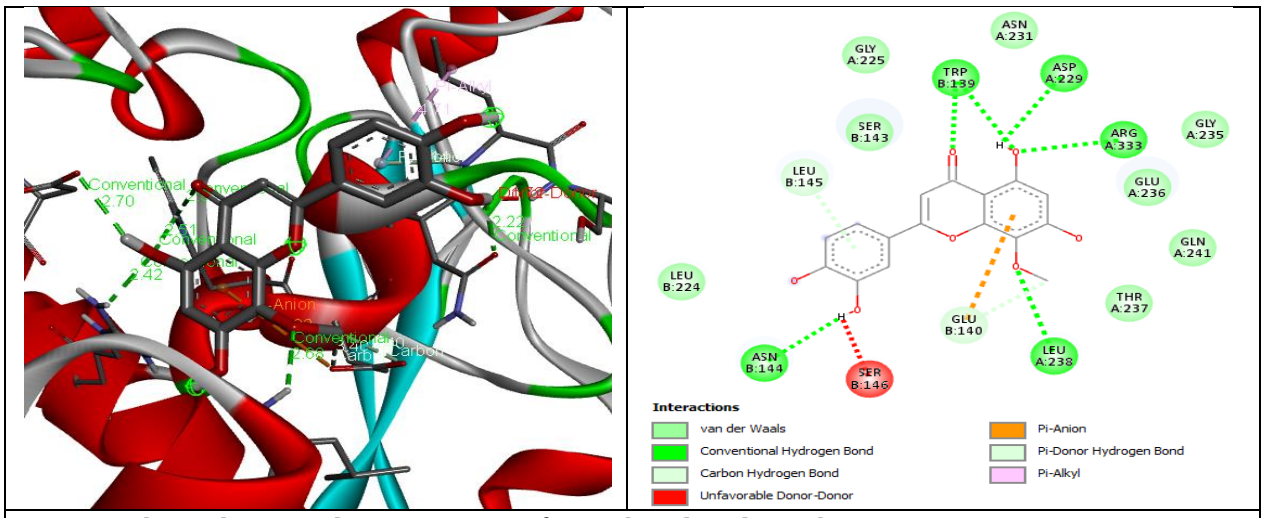


Figure .2shows the 2D and 3D interaction of 8-methoxyluteolin with receptor protein COX-2.

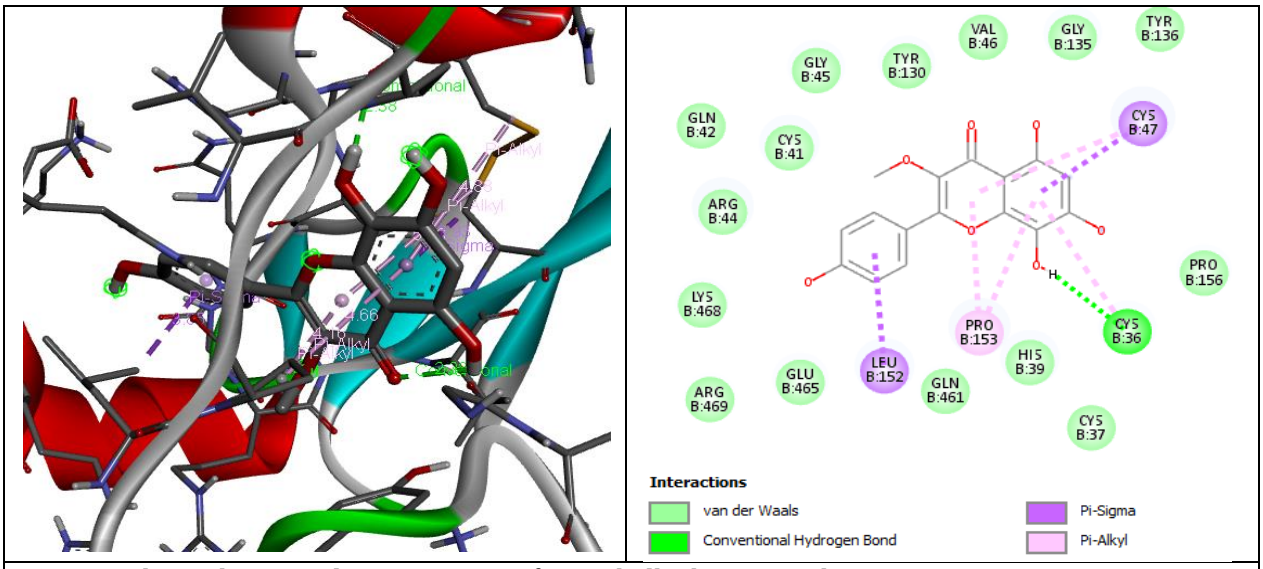


Figure .3shows the 2D and 3Dinteraction of 3-methylherbacetin with receptor protein COX-2.

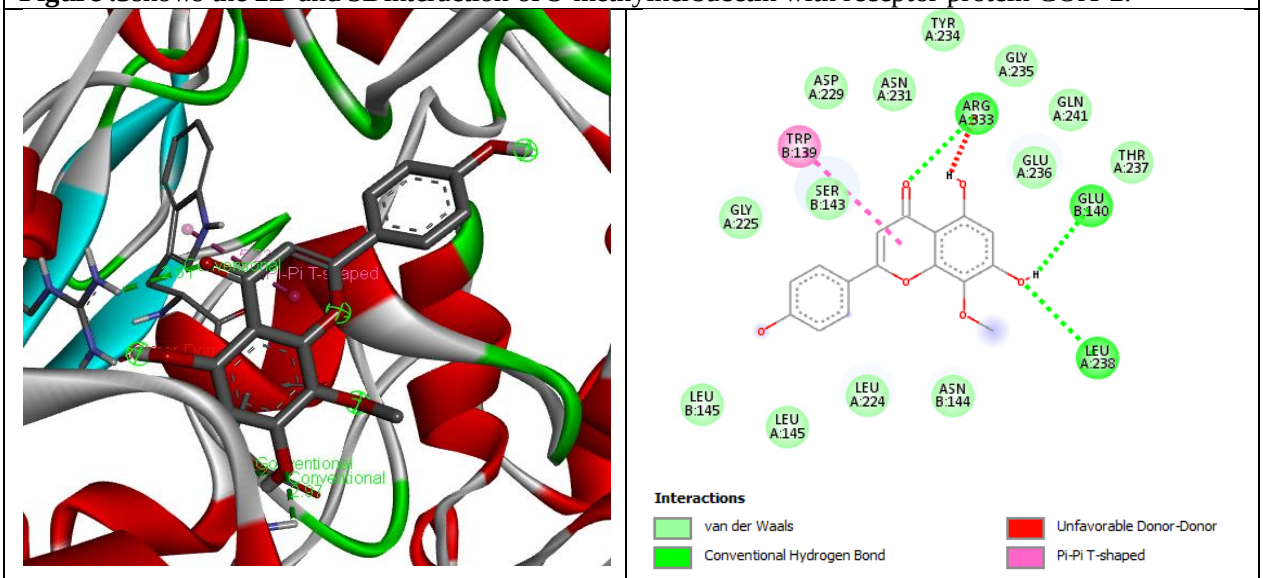


Figure .4shows the2D and 3D interaction of 8-methoxyapigenin with receptor protein COX-2.

ADME ANALYSIS and Drug-Likeness

An ADME investigation was performed using Swiss ADME to determine various characteristics, including physical properties, lipophilicity, adherence to Lipinski's rule, and the solubility of bioactive compounds [35]. ADME is a significant factor in drug development, as numerous medication candidates fail to succeed in clinical trials. Orally administered drug candidates may have a maximum of two infractions [36]. We applied Lipinski's rule of five (≤5 hydrogen bond donors, ≤10 hydrogen bond acceptors, molecular weight ≤500 Da, molar refractivity 40–130, and ≤logP) to select compounds for potential medicinal efficacy. Table 3 indicates that all selected bioactive compounds adhere to the Lipinski rule of five without violating any criteria. Lead likeness indicates that Halleridone and Halleron each possess a single violation, while all other compounds exhibit none. All compounds exhibit high solubility as indicated by the gastrointestinal absorption and solubility classification. Logarithmic values for water solubility span from -10 to 0. There are multiple levels of solubility: -10 indicates insoluble, -6 denotes poorly soluble, -4 signifies soluble, -2 represents very soluble, and 0 corresponds to highly soluble [35]. Table 3 indicates that all selected compounds are soluble, with none exhibiting insolubility.

The five compounds were solely selected on the basis of wet analysis provided in the literature. Although the aqueous extract was prepared, the DPPH assay demonstrated that the antioxidant activity is more pronounced in the ethanolic extract as compared to the aqueous.

Table .3 ADME analysis and drug-likeness results of selected bioactive constituents of *PhylaNodiflora*.

Properties	**Features**	**Halleridone**	**8-methoxyluteolin**	**3-methylherbacetin**	**8-methoxyapigenin**	**Halleron**
Physiochemical	MW(g/mol)	154.16	316.26	316.26	300.26	196.2
Properties						
	H.B Donor	1	4	4	3	1
	H.B Acceptor	3	7	7	6	4
	MR	38.35	82.5	82.5	80.48	49.81
	Arom. Heavy Atom	0	16	16	16	0
	Rotatable Bonds	0	2	2	2	4
	TPSA	46.53	120.36	120.36	100.13	63.6
Lipophilicity	logP(SILICOS-IT)	0.95	2.06	2.06	2.55	0.88
Water Solubility	Logs(SILICOS-IT)	-0.43	-3.94	-3.94	-4.52	-0.8
Pharmacokinetics	GI Absorption	High	High	High	High	High
Drug-likeness	Lipinski	Yes: 0 Violation	Yes: 0 Violation	Yes: 0 Violation	Yes: 0 Violation	Yes: 0 violation
Lead likeness		Yes: 1 Violation	Yes: 0 Violation	Yes: 0 Violation	Yes: 0 Violation	Yes:1 violation

Toxicity Predictions

The Protox-II server was employed to assess potential medication candidates for adverse effects, including hepatotoxicity, mutagenicity, and cytotoxicity. Table 4 demonstrates that Halleridone, 8-methoxyluteolin, 3-methylherbacetin, and 8-methoxyapigenin possess non-toxic characteristics and may be suitable for medicinal applications, as they adhere to Lipinski's rules and exhibit no harmful effects. ADMETSAR was employed to evaluate and confirm the toxicity of the chosen compounds. The analysis reveals that all candidates examined are categorized as AMES non-toxic and non-carcinogenic (Table 5). All compounds demonstrated weak inhibition of the human ether-a-go-go-related gene (hERG) and displayed acute toxicity in rats, with a median maximum lethal dose (LD50) of 2.63 mol/kg. The results can be compared to those of cisplatin, which is classified as a carcinogen, is AMES hazardous, functions as a mild hERG inhibitor, and has a rat acute toxicity of 2.24[38]. All substances are categorized as "class III" according to expected acute oral toxicity. Compounds in this category demonstrate LD50 values under 5000 mg/kg and are typically regarded as potential candidates for pharmacological use. The examination of the reported compound relies on clinical trials[39].

Table .4 Toxicity results of five selected bioactive constituents of Phylanodiflora medicinal plant.

Compound Name	Hepatotoxicity	Mutagenicity	Cytotoxicity
Halleridone	Inactive	Inactive	Inactive
8-methoxyluteolin	Inactive	Inactive	Inactive
3-methylherbacetin	Inactive	Inactive	Inactive
8-methoxyapigenin	Inactive	Inactive	Inactive

Table .5 Toxicity profiling of four selected compounds (with high binding affinity) using admetSAR server.

Compound	hERG inhibition	Rat(LD50,mol/kg)	AMES	Carcinogen	Actute oral toxicity	Carcinogenesity (class 3)
Halleridone	Weak	1.7272	Non	Non	III	Non-required
8-methoxyluteolin	Weak	2.6388	Non	Non	III	Non-required
3-methylherbacetin	Weak	2.6388	Non	Non	III	Non-required
8-methoxyapigenin	Weak	2.7192	Non	Non	III	Non-required
Cisplatin	Weak	2.2490	Yes	Yes	II	Non-required

Bioactivity Prediction

Molinspiration serves as a significant tool for evaluating the bioactivity scores of natural chemicals in relation to therapeutic targets, as illustrated in Table 6. The probability of a compound exhibiting significant biological activity is contingent upon its bioactivity score. Compounds exhibiting bioactivity values exceeding 0.00 are generally considered significant, whereas those with scores ranging from -0.50 to 0.00 demonstrate moderate activity, and compounds with scores below -0.50 are classified as inactive [23]. The analysis indicates that multiple pathways may be involved in the physiological effects of the chemical compounds. Interactions with nuclear receptor ligands, GPCR ligands, ion channel modulator ligands, enzyme inhibitors, and protease inhibitors may also contribute to its onset**.**

The results of bioactivity scores show that all selected compounds are highly active to act as ligands of enzyme inhibitors; 8-methoxyapigenin, 8-methoxyluteolin, and 3-methylherbacetin are highly active to act as ligands of nuclear receptors and kinase inhibitors, while 8-methoxyapigenin can bind as a ligand of ion channel modulator. The result shows that 8-methoxyapigenin, 8-methoxyluteolin, and 3-methylherbacetin are moderately dynamic toward GPCR and protease inhibitors. The overall finding reveals that our selected ligand molecules are associated with all pharmacological targets.

Table .6

Bioactivity score of selected bioactive compounds according to Molinspirationcheminformatics software.

Bioactivities	Halleridone	8-methoxyluteolin	3-Methylherbacetin	8-methoxyapigenin
GPCR ligand	-0.77	-0.10	-0.11	-0.09
Ion channel modulator	-0.52	-0.01	-0.17	0.01
Kinase inhibitor	-1.62	0.17	0.21	0.17
Nuclear receptor	-0.52	0.19	0.21	0.22

ligand				
Protease inhibitor	-0.73	-0.25	-0.28	-0.26
Enzyme inhibitor	0.04	0.22	0.25	0.23

Molecular Dynamic Simulation

Molecular dynamics simulations were performed on the top candidates demonstrating increased binding energies. The anticipated conformational changes from the initial structure were quantified using root mean square deviation (RMSD) during the simulation period. Furthermore, structural stability, atomic mobility, and residue flexibility in protein interactions were assessed through root mean square fluctuation (RMSF) values. The peaks of the RMSF graph represent the protein's fluctuations throughout the simulation[25]. The N- and C-terminals demonstrate increased variability relative to other regions of the protein.

The alpha helices and beta strands tend to exhibit lesser fluctuation since they are firmer than the unstructured section of the protein the loop portion. The 8-methoxyapigenin complex RMSD deviated slightly by a range of 2.4 to 4.2 A to nearly 30 and 45 ns; and then the system became equilibrated after 75 ns. This represents the stability of the protein-protein binding (Figure 5). The 8-methoxyluteolin complex RMSD showed a slight change at the beginning. After 50 ns, the system stabilized and attained balance during the rest of the experiment (Figure 5). A displacement of the 3-methylherbacetin complex was observed between 40 and 65ns, and after that the system became stationary (Figure 5).

Root Mean Square Fluctuation (RMSF) is an effective method of describing protein chain variations. The peaks denote those parts of the proteins which are the most variable during the RMSF simulation. Protein N- and C-terminals have an increased tendency to be modified than any other part of the protein structure. Alpha helices tend to be less flexible and rigid than the unstructured part of the protein, and the beta strands tend to be the same. The MD trajectories show that the highest peaks are in the loop regions, or in the N-terminal and C-terminal zones of the residue [40]. It was found that there was no alteration of RMSF at the contacts between the ligands and the receptor (represented by green lines), which indicates that ligands have high binding affinity to receptor proteins (Figure 6).

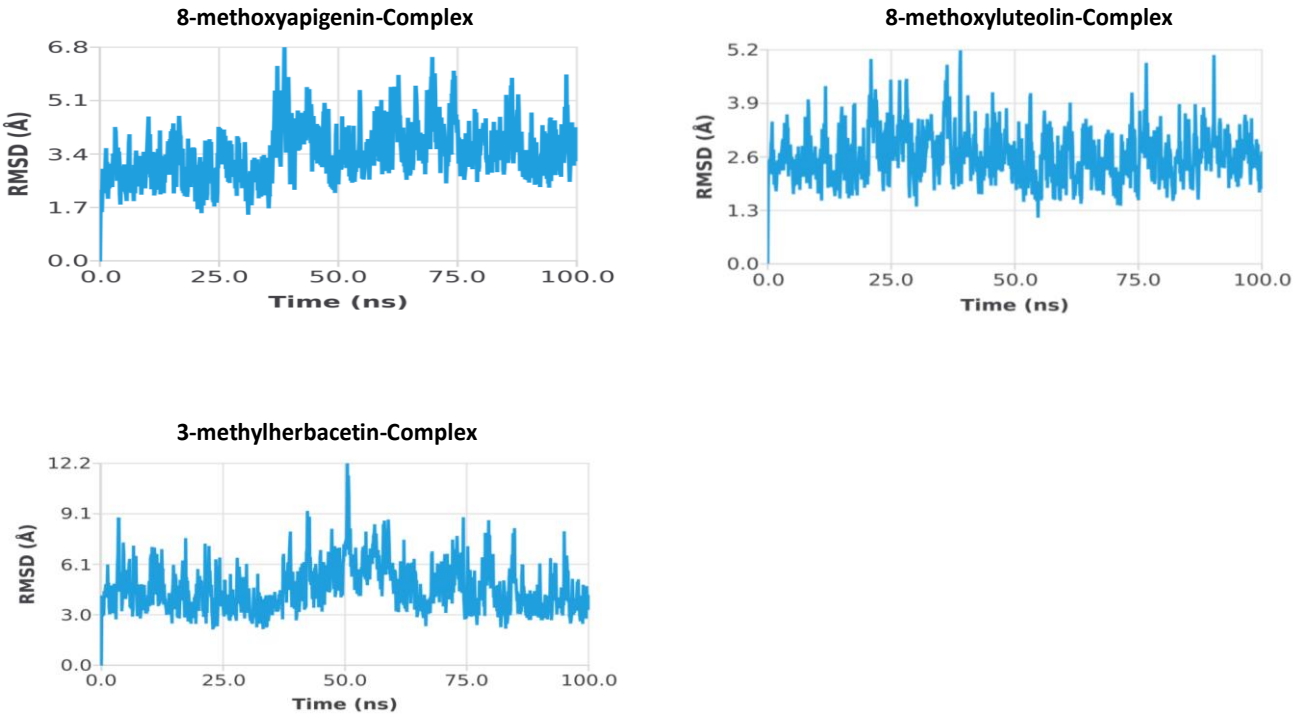


Figure 5: Root Mean Square Deviation (RMSD) plot of8-methoxyapigenin,8-methoxyluteolin and 3-methylherbacetin complexes.

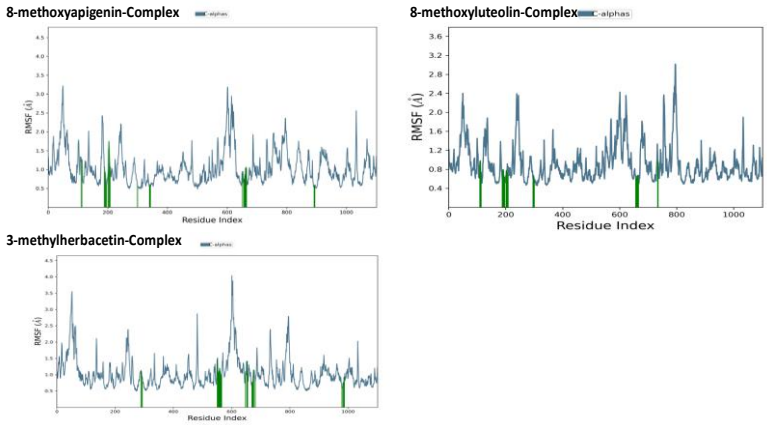


Figure 6: Root Mean Square Fluctuation plot of8-methoxyapigenin,8-methoxyluteolinand 3-methylherbacetin complexes.

Herbal remedies known as flavonoids have a variety of medicinal activities, including antioxidant, anti-inflammatory, analgesic, anti-carcinogenic, anti-bacterial infection, anti-fungal, and antiviral effects[41]. The leaves and stems of *Phyla nodiflora*have anti-proliferative and apoptotic effects on human breast cancer cell lines when they are extracted in methanol and ethyl acetate. Through apoptosis, the extracts at 90–120 µg/ml might stop the proliferation of cancer cells[42]. The anticancer effect in breast cancer for the methanol extract of *Phyla nodiflora*was evaluated using the MCF7 cell line and the MTT assay, which shows that the plant extract has potential for inhibition of MCF7 cells with IC_{50} ranges from 90 to 120µg/ml. Another in vitro anticancer study of plant extracts using NCI-H450 cell lines for human lung cancer shows the potential effect as anti-proliferative for tested cell lines with an IC_{50} value of 10 µg/ml. Increased antioxidant activity in EAC-bearing mice may be responsible for the anticancer effect [6]. Halleridone and Hallerone isolated from nodiflora show anticancer, anti-tumor, and antifungal properties. 8-methoxyluteolin and 8-methoxyapigenin, methanol extract of A. *Judaica* medicinal plant, exhibit significant bioactivities including anti-inflammatory, hepatoprotective, anti-diabetic, and antioxidant activities [43]. Herbacetin demonstrated anti-carcinogenic and anticancer effects in vitro against

SK-MEL-5 melanoma and A431 cutaneous squamous cell carcinoma at 10 and 20 M doses. According to three different assays, i.e., the AKT kinase assay, the Insilico assay, and the ex vivo pull-down assay, Herbacetin suppresses the activity of AKT and associated signaling pathways like GSK3 and RSK2 by directly binding to AKT [44].

CONCLUSIONS

It is concluded hereby that *Phyla nodiflora*bioactive compounds have a great role as antioxidant and anti-cancer agents. The study shows that three compounds that are docked against the COX-2 enzyme have a high binding affinity score, and molecular dynamic simulation, RMSD, and RMSF value also support the strong binding of the compounds with COX-2, obey all guidelines of Lipinski, and are biologically active, hence showing that these compounds, 8-methoxyluteolin, 3-methylherbacetin, and 8-methoxyapigenin, may act as novel therapeutic agents for the treatment of cancers.

Statements and Declarations

Conflicts of Interest : The authors declare no conflict of interest.

Data Availability Statement: Not applicable

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