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In Silico Screening and Validation of Natural Components as Novel P-glycoprotein Inhibitors to Enhance the Bioavailability of Cancer Drugs

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Abstract

Background: Multidrug resistance in cancer arises when p-glycoprotein is overexpressed, actively expelling chemotherapeutic agents from cancer cells, thereby lowering their intracellular concentrations and diminishing the effectiveness of conventional therapies. However, *in silico* and docking-based screening of natural compounds offers a promising approach to identify selective, low-toxicity p-glycoprotein inhibitors that could help restore the efficacy of these drugs. **Aim:** The objective of this study was to use an *in silico* approach to study the potential of spice constituents as p-glycoprotein inhibitors, with the possibility that they may increase the bioavailability of co-administered cancer medications by decreasing their efflux from cancer cells. **Methods:** Virtual screening was employed to screen 16 bioactive components from 9 spices for their potential to interact with p-glycoprotein. The binding affinity and binding stability of these interactions were predicted using molecular docking and molecular dynamics simulations in the Biovia Discovery Studio software. **Results:** 7 components were identified with high binding affinities for p-glycoprotein, suggesting their potential as inhibitors. The compounds with the highest binding affinities for p-glycoprotein were hydroxymatairesinol, gingerenone-A, curcumin, and pinoresinol. **Conclusion:** The results of this study have proposed that hydroxymatairesinol from *Sesamum indicum* and gingerenone-A from *Zingiber officinale,* may be considered potential inhibitors of p-glycoprotein.

Major Findings: The *in silico* analysis identified seven spice-derived compounds with strong predicted binding affinities toward p-glycoprotein, with Hydroxymatairesinol (from sesame) and GingerenoneA (from ginger) among the top binders, suggesting they may serve as promising, low-toxicity p-glycoprotein inhibitors to enhance chemotherapeutic drug retention in cancer cells.

Keywords: Anti-cancer Drugs, Efflux Transporter, Molecular Docking, Multidrug Resistance, Spice Components

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1. Introduction

Multidrug Resistance (MDR) is a challenge in oncology, especially regarding the effectiveness of anticarcinogenic medications. MDR is displayed by diseased cells to a variety of chemotherapeutic medicines, resulting in conventional treatment plans being ineffective. Since p-glycoprotein is overexpressed in such cases, anticarcinogenic medicines are actively effluxed from the cells, lowering their intracellular concentrations below therapeutic levels. In addition to being a major obstacle to effective cancer treatment, the advent of MDR raises the morbidity and mortality rates linked to cancer. In order to improve drug bioavailability and restore the efficacy of current therapies, research is being conducted on the inhibition of p-glycoprotein.

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Inhibition of p-glycoprotein can be beneficial when you want to increase systemic or tissue-specific drug levels, particularly for drugs with poor bioavailability and those that face efflux via p-glycoprotein[1].

Recent breakthroughs in drug discovery have focused on the development of new inhibitors with higher selectivity and reduced toxicity. These initiatives include focusing on the nucleotide-binding regions of p-glycoprotein and screening large chemical libraries for possible inhibitors using computational techniques. The present study uses molecular docking and *in silico* screening to find and identify new p-glycoprotein inhibitors from natural product derivatives. The findings will help create less harmful and more effective cancer treatments, ultimately improving patient outcomes[2,3].

2. Materials and Methods

In silico methods can identify novel compounds and predict ligand binding affinity to p-glycoprotein, prioritising compounds for further testing. These investigations successfully prove the principle of specific approaches in identifying p-glycoprotein modulators. The work aimed to investigate, by *in silico* methods, the ability of spice components to act as p-glycoprotein inhibitors, in the anticipation that they would increase the bioavailability of co-administered cancer drugs by reducing their efflux from cancer cells.

2.1 Selection of the Protein and its Preparation

The outward-facing, Adenosine Triphosphate (ATP)-bound conformation of human p-glycoprotein was retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) using the PDB ID 6C0V[4]. This conformation of human p-glycoprotein is used in our study due to its ability to represent the critical state where substrates are released into the extracellular space, providing a relevant structural template for understanding drug interactions. Swiss-PdbViewer was used for structural optimisation and energy minimisation. The protein preparation wizard of Discovery Studio was used. Side chain refinement and the cleaning of the protein structure were done using the ChiRotor algorithm prior to docking. The functional binding pockets of p-glycoprotein were recognised by using the automated pocket detection and analysis tool DoG SiteScorer. This conformation, defined by ATP binding and a closed dimer arrangement of the nucleotide-binding domains, provides a basis for identifying potential inhibitors that may modulate p-glycoprotein activity and help counteract MDR in cancer therapy.

2.2 Selection and Preparation of the Ligands

Nine spices were selected for the study, namely: *Sesamum indicum*, *Zingiber officinale*, *Curcuma longa*, *Piper longum*, *Glycyrrhiza glabra*, *Syzygium aromaticum*, *Cichorium intybus*, *Capsicum annuum*, and *Papaver somniferum*. Based on literature mining, 83 bioactive components were identified from them. The 3D chemical structures and unique canonical Simplified Molecular Input Line Entry System (SMILES) strings of the 83 components were identified using the PubChem and ChemSpider databases. Using the Online SMILES Translator tool, all of these canonical SMILES were transformed into aromatic 3D structures in SDF format. The Prepare Ligands protocol in Discovery Studio was used to refine the ligand set by removing duplicate structures and generating possible isomers and tautomers. This ensures accurate and optimised input molecules for subsequent molecular docking and analysis.

2.3 Druglikeness and ADMET profiling

The molecular properties of the selected bioactive compounds were analysed using SwissADME and Molinspiration Cheminformatics software tools. This helped understand that the bioactive components meet the ideal specifications of drug-like molecules. The Molecular Weight (MW), number of Hydrogen Bond Acceptors (nHBA), Molar Refractivity (MR), number of Rotatable Bonds (nRotB), number of Hydrogen Bond Donors (nHBD), Total Polar Surface Area (TPSA) and log of octanol/water partition coefficient (LogP) of all the components were screened. They were also screened for compliance with Lipinski's rule of five, which stipulates that for a drug to be considered orally active it should generally not violate more than one of the following criteria: A molecular mass of less than 500 daltons; A maximum of five hydrogen bond donors; A maximum of ten hydrogen bond acceptors;

and an octanol-water partition coefficient (log P) of no more than five. Using the Pharmacokinetics and Cheminformatics for Small Molecules (PKCSM) tool, the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of all the components that meet Lipinski's Rule of Five were determined.

2.4 Molecular Docking-based Virtual Screening

Protein-ligand docking was performed using Biovia Discovery Studio version 4.5. Following energy minimisation of the protein structure, p-glycoprotein was selected as the receptor molecule, and the binding site sphere was selected. The prepared ligands were docked with p-glycoprotein to get the best pose of each ligand with the lowest binding energy. The CHARMM-based Docker (CDOCKER) algorithm program with a CHARMM-based molecular dynamics simulated annealing approach was used for flexible docking, and the "Analysed Ligand Programme" was employed to analyse the results. Various docking poses were evaluated based on their binding energies.

2.5 Molecular Dynamics Simulations

100-nanosecond Molecular Dynamics (MD) simulations were conducted using Biovia DS software to assess the structural stability and dynamic behaviour of receptor-ligand complexes identified by the lowest binding energies. The simulation process involved solvating the docked complexes in an orthorhombic box with a minimum 1Å distance between ligand atoms and box edges. A CHARMM-based force field was employed for complex preparation. Energy minimisation was performed in two stages: 500 steps of steepest descent followed by 500 steps of conjugate gradient. Following minimisation, the system was heated from 50K to 300K over 4 picoseconds, then equilibrated for 10 picoseconds. Simulation data were recorded every 2 picoseconds. Analysis of the trajectory included computation of geometric properties (distance, angle, torsion, and non-bonded interaction count) and calculation of Root Mean Square Fluctuation (RMSF) values. The binding free energy was estimated using the Molecular Mechanics-Poisson-Boltzmann Surface Area (MMPBSA) method to further evaluate conformational stability.

Table 1. Drug-likeness properties of the components abiding by Lipinski's rule

Components	MW	HBA	HBD	Log P	No. of violations
	<500 Dalton	<10	<5	<5	<2
Hydroxymatairesinol	374.3	7	3	0.9	0
Gingerenone-A	356.4	5	2	3.3	0
Curcumin	368.3	6	2	2.3	0
Pinoresinol	358.3	6	2	2.5	0
Demethoxycurcumin	338.3	5	2	2.4	0
8-gingerol	322.4	4	2	4.2	0
Licochalcone A	338.4	4	2	4.8	0
Trans Cinnamaldehyde	390.4	7	1	3.1	0
Bisdemethoxycurcumin	308.3	4	2	2.6	0
Piperine	285.3	4	0	3.3	0
10-gingerol	350.5	4	2	5.2	1 (log P)
Pipernonaline	341.4	4	0	5.3	1 (log P)
Lactucopicrin	410.4	7	2	1.1	0
Glabridin	324.3	4	2	4.2	0
Capsazepine	376.9	4	3	3.9	0
Noscapine	413.4	8	0	2.8	0
Doxycycline	444.4	9	6	1.82	1 (HBD)

MW: Molecular weight; HBA: Hydrogen bond acceptors; HBD: Hydrogen Bond donors; Log P: Lipophilicity

3. Results

Out of 83 components, only 16 components passed the screening of the druggability and ADMET properties. These 16 bioactive components also possessed antitumor anticancer proficiency, namely- hydroxymatairesinol (*S. indicum*)[5], gingerenone-A (*Z. officinale*)[6], curcumin (*C. longa*)[7], pinoresinol (*S. indicum*)[8], demethoxycurcumin (*P. longum*)[9], 8-gingerol (*Z. officinale*)[10], licochalcone A (*G. glabra*)[11], trans cinnamaldehyde (*S. aromaticum*)[12], bisdemethoxycurcumin (*P. longum*)[13], piperine (*P. longum*)[14], 10-gingerol (*Z. officinale*)[15], pipernonaline (*P. longum*)[16], lactucopicrin (*C. intybus*)[17], glabridin (*G. glabra*)[18], capsazepine (*C. annuum*)[19] and noscapine (*P. somniferum*)[20].

3.1 Druglikeness and ADMET Prediction

The degree to which a viable drug candidate has characteristics linked to effective drug molecules, such as the right size, shape, solubility, bioavailability and absence of toxicity, is referred to as drug-likeness. The propensity of success for a compound in clinical trials can be predicted partly by looking at its drug-likeness. Depending on Lipinski's rule of five, each component has appropriate drug-like qualities (Table 1).

The ADMET analysis of the selected natural compounds (Table 2) revealed favourable pharmacokinetic properties supporting their potential as P-glycoprotein inhibitors. The Log S values (-4.9 to -3.1) indicated moderate to low aqueous solubility, which is acceptable for lipophilic natural compounds. All compounds showed positive Caco-2 permeability (Log Papp = -0.1 to 1.5) and high predicted intestinal absorption (82.1-100%), suggesting efficient oral uptake and bioavailability. The Log Brain-to-Blood (BB) values (-1.0 to 0.2) suggest limited to moderate blood–brain barrier penetration, which is advantageous for minimising central nervous system side effects while targeting peripheral p-glycoprotein activity. Notably, compounds such as piperine, glabridin, and lactucopicrin exhibited particularly high absorption (>94%). Importantly, all compounds were predicted to be p-glycoprotein inhibitors, indicating their potential to counteract p-glycoprotein-mediated drug efflux and enhance intracellular retention of anticancer agents. Overall, these findings suggest that the screened phytocompounds possess suitable ADMET characteristics, combining high intestinal permeability with p-glycoprotein inhibitory activity, making them

Table 2. ADMET properties of the components

Components	Log S (mol/L)	Log Papp (cm/s)	Intestinal Absorption (%)	Log BB	P-gp I Inhibitor
Hydroxymatairesinol	-3.3	-0.1	-0.1	-1	Yes
Gingerenone-A	-4.3	0.9	91.6	-0.3	Yes
Curcumin	-4	-0	82.1	-0.5	Yes
Pinoresinol	-3.6	1	93.2	-0.4	Yes
Demethoxycurcumin	-3.5	1	91.3	-0.3	Yes
8-gingerol	-4.7	1.4	91.9	-0.2	Yes
Licochalcone a	-4.5	0.6	91.2	-0.1	Yes
Trans- cinnamaldehyde	-4.4	0.9	92.1	-0.7	Yes
Bisdemethoxycurcumin	-3.3	0.9	91.1	0	Yes
Piperine	-3.4	1.5	94.4	-0.1	Yes
10-gingerol	-4.3	0.6	91	-0.8	Yes
Pipernonaline	-4.9	1.3	92.9	-0.1	Yes
Lactucopicrin	-3.1	1	100	-0.4	Yes
Glabridin	-3.6	1.2	94.1	0	Yes
Capsazepine	-3.8	0.9	86.2	0.2	Yes
Noscapine	-3.8	1.1	95.2	-0.5	Yes

Log S: water solubility; Log BB: BBB Permeability; Log Papp: Caco2 permeability; P-gp: P-glycoprotein

promising candidates for improving the bioavailability and efficacy of chemotherapeutic drugs.

3.2 Molecular Docking

The bioactive components were successfully docked in the P-glycoprotein binding pockets by the CDOCKER program. Every bioactive component binds efficiently to the binding site sphere or cavity of the specified receptor molecule. Binding energy is an established parameter to evaluate the binding stability of the protein-ligand complex. Figure 1 shows the binding energy interactions of anticarcinogenic inhibitory components with p-glycoprotein. Hydroxymatairesinol, a component from *S. indicum*, exhibited the lowest binding energy (-117.6 kcal/mol), followed by gingerenone-A (-112.7 kcal/mol) from *Z. officinale* and curcumin (-110 kcal/mol) from *C. longa*. The aforementioned components were found to have binding energies better than those of the established inhibitors of p-glycoprotein, doxycycline (-79.09 kcal/mol) and elacridar (-91.59 kcal/mol).

Hydrogen bonds facilitate the interaction between inhibitors and key amino acid residues within the p-glycoprotein structure, while hydrophobic interactions drive the recognition and transport of amphipathic compounds across membranes, thereby impacting the MDR mechanisms in cancer therapy. Figure 2 shows the hydrogen and hydrophobic interactions of anticarcinogenic inhibitory components with p-glycoprotein. The compound noscapine, which is found in *P. somniferum*, exhibits the highest hydrogen bond interaction with p-glycoprotein (viz. 4), outperforming the control drugs doxycycline (viz. 1) and elacridar (viz. 0). Licochalcone A, a component of *G. glabra*, had the maximum hydrophobic interaction (viz. 7) compared to doxycycline (viz. 3) and elacridar (viz. 2). Figure 3 shows the 2D binding poses of human p-glycoprotein with the best five inhibitory components exhibiting maximal negative binding energy. Table 3 summarises the amino acid residues of p-glycoprotein involved in interaction with the inhibitory components. Figure 4 shows the 3D docked image of human p-glycoprotein with hydroxymatairesinol.

4. Molecular Dynamics Simulation

Using Biovia Discovery Studio software, an all-atom MD simulation analysis was conducted utilising the most stable docked poses to assess the stability of the docked complexes. The simulation analysis was conducted for the two best components with the most negative binding energy in molecular

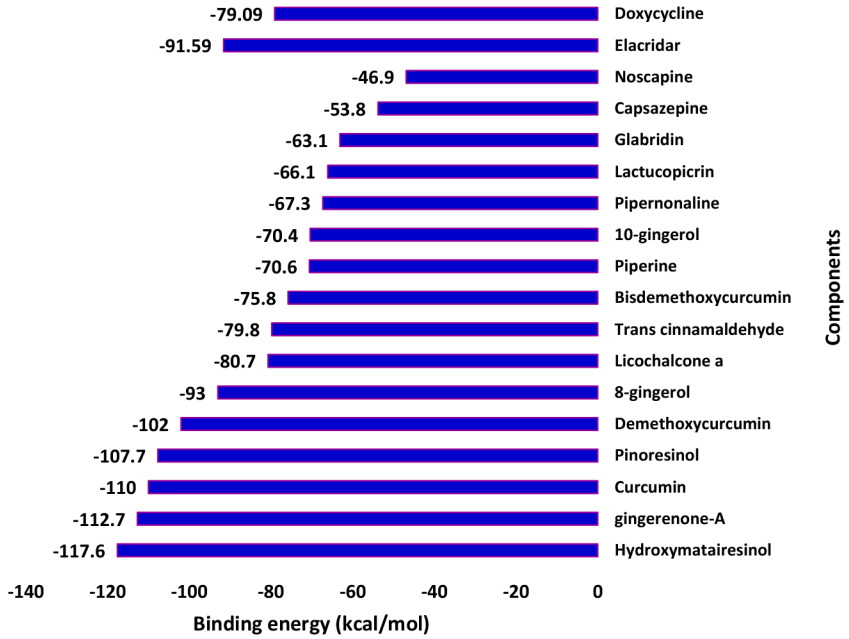


Figure 1. Binding energy interactions (kcal/mol) of anticarcinogenic inhibitory components with the selected target protein, showing Hydroxymatairesinol with the highest binding affinity (-117.6 kcal/mol), followed by Gingerenone-A, Curcumin and Pinoresinol.

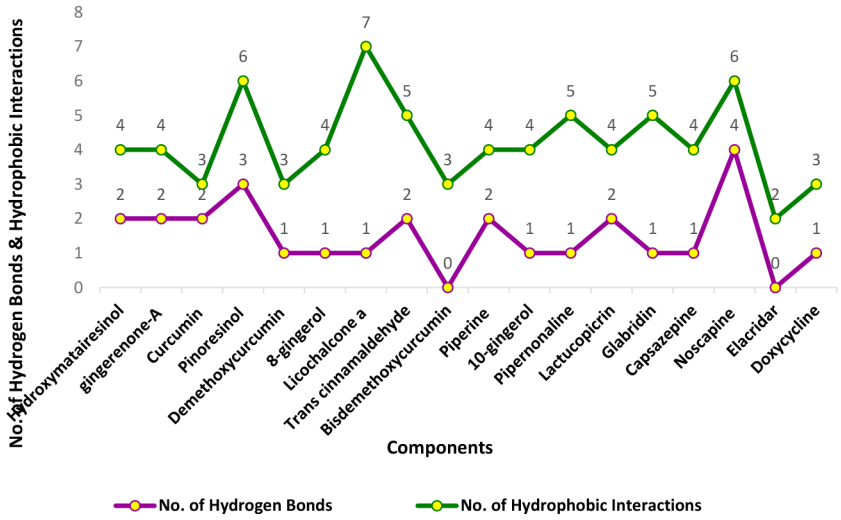


Figure 2. Number of hydrogen bonds and hydrophobic interactions of anticarcinogenic inhibitory components.

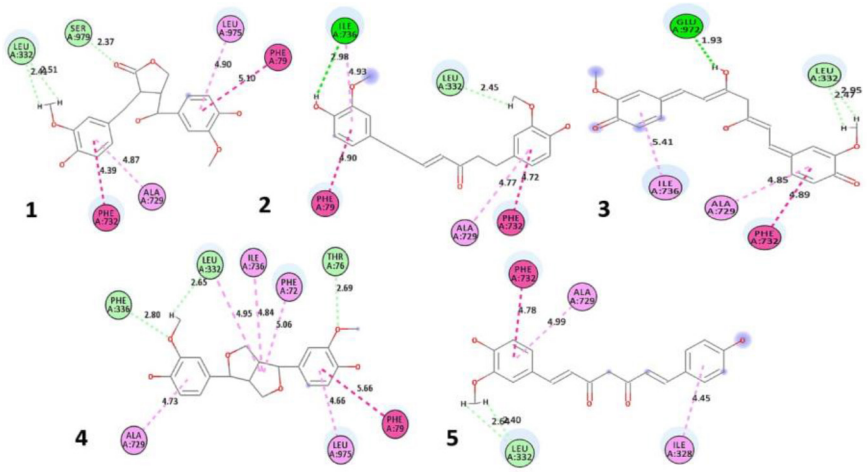


Figure 3. 2D interaction diagrams illustrating the docking poses of the top five inhibitory phytocompounds with P-glycoprotein. The interactions are depicted as follows: light green dotted lines indicate carbon-hydrogen bonds, dark green dotted lines indicate conventional hydrogen bonds, light pink dotted lines indicate π-alkyl interactions, and dark pink dotted lines indicate π-π T-shaped interactions. The components shown are (**1**) Hydroxymatairesinol, (**2**) Gingerenone-A, (**3**) Curcumin, (**4**) Pinoresinol, and (**5**) Demethoxycurcumin.

docking, hydroxymatairesinol and gingerenone-A. In a molecular dynamics simulation, when the ligand and receptor have a negative binding energy, it means that their energy is less than that of the unbound state, which is stable and energetically favourable. Hydroxymatairesinol possesses a binding energy of -20.5 kcal/mol and gingerenone-A possesses -26.3 kcal/mol for MD simulation analysis. Hydroxymatairesinol exhibited an interaction energy of -99.49 kcal/mol and a van der Waals energy of 7,777.78 kcal/mol, indicating a strong and stable binding interaction. Gingerenone-A, on the other hand, showed a less negative interaction energy of -30.70 kcal/mol, but a slightly higher van der Waals energy of 8,022.68 kcal/mol.

The stability of a protein or molecule can be evaluated using RMSF, which can also be used to pinpoint the flexible areas crucial to biological activity. For the p-glycoprotein and hydroxymatairesinol MD simulation system, the residues Serine at position 35 (SER35), Threonine at position 202 (THR202), Aspartate at position 77 (ASP77), Arginine at position 41 (ARG41), Glycine at position 203 (GLY203), Serine at position 43 (SER43), Phenylalanine at position 204 (PHE204), Valine at position 206 (VAL206),

Table 3. Summary of amino acid residues of P-glycoprotein involved in interaction with the inhibitory components

Components	Amino acids involved in hydrogen bonds	Amino acids involved in hydrophobic interactions
Hydroxymatairesinol	LEU332, SER979	PHE79, ALA729, PHE732, LEU975
Gingerenone-A	LEU332, ILE736	PHE79, ALA729, PHE732, ILE736
Curcumin	LEU332, GLU972	ALA729, PHE732, ILE736
Pinoresinol	THR76, LEU332, PHE336	PHE72, PHE79, LEU332, ALA729, ILE736, LEU975
Demethoxycurcumin	LEU332	ILE328, ALA729, PHE732
8-Gingerol	LEU332	ILE328, PHE336, ALA729, PHE732
Licochalcone A	GLU972	PHE72, LEU332, PHE336, PHE732, ILE736, LEU975, LEU976
Trans Cinnamaldehyde	LEU332, ALA729	PHE72, PHE79, LEU332, PHE732, ILE736
Bisdemethoxycurcumin	0	ILE328, LEU332, PHE732
Piperine	MET75, THR76	PHE79, PHE336, PHE732, LEU975
10-Gingerol	GLU972	PHE79, PHE336, PHE732, ILE736
Pipernonaline	SER979	PHE79, ILE328, PHE336, ALA729, PHE732
Lactucopicrin	PHE336, SER979	ILE328, LEU332, PHE732, ILE736
Glabridin	SER979	PHE72, PHE79, LEU332, PHE732, ILE736
Capsazepine	PHE336	PHE72, LEU332, PHE732, ILE736
Noscapine	THR76, LEU332, LEU975, SER979	PHE72, ALA729, PHE732, ILE736, LEU975, LEU976
Elacridar	0	PHE79, ILE328
Doxycycline	LEU976	LEU332, ILE736, PHE732

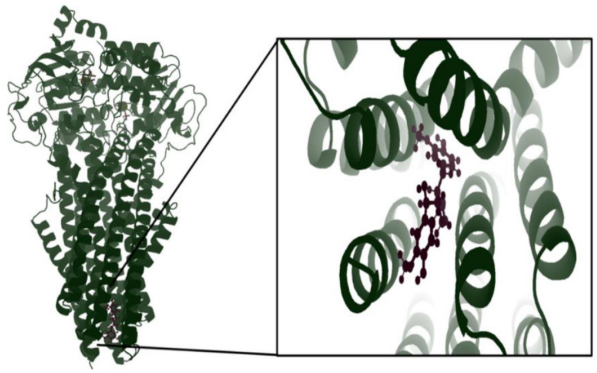


Figure 4. Docked complex of human p-glycoprotein and hydroxymatairesinol and the zoomed image of hydroxymatairesinol, accommodated in the active site of human p-glycoprotein. Graphics created by the 3D structural visualisation program PyMOL.

Phenylalanine at position 208 (PHE208), Glycine (GLY207) possess low RMSF values ranging from 0.37Å to 0.91Å (Figure 5). For the p-glycoprotein and gingerenone-A MD simulation system, the residues Arginine at position 210 (ARG210), Threonine at position 55 (THR55), Tryptophan at position 212 (TRP212), Methionine at position 51 (MET51), Lysine at position 213 (LYS213), Threonine at position 215 (THR215), Valine at position 217 (VAL217), and Leucine at position 216 (LEU216) possess low RMSF values ranging from 0.37Å to 0.93Å. These lower RMSF values indicate stable proteins or molecules with fewer motile atoms, reducing the risk of conformational changes that could affect biological function. The radius of gyration for hydroxymatairesinol and gingerenone-A

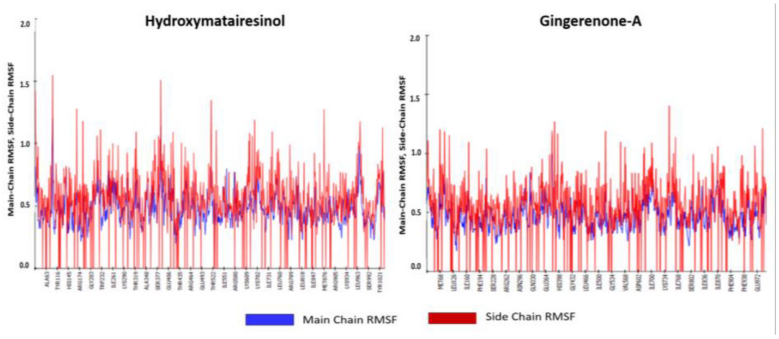


Figure 5. RMSF analysis of the p-glycoprotein backbone and side-chain residues in complex with Hydroxymatairesinol (left) and Gingerenone-A (right), where blue lines represent main-chain RMSF and red lines represent side-chain RMSF.

was 48Å and 47.9Å respectively, which demonstrates that during simulation, the complex structures were compact. The results demonstrate that the stability of the protein-ligand complexes was maintained during MD simulations.

4. Discussion

Natural substances are promising as p-glycoprotein inhibitors, improving cancer medication bioavailability and mitigating MDR mechanisms. These compounds work well with traditional treatments and are being explored for their potential in drug transport and cancer treatment. Researchers are developing adjuvant components and innovative pharmaceutical formulations to address MDR in cancer cells[21,22]. In cell lines with elevated p-glycoprotein expression, curcumin (from turmeric) at concentrations of 30-60μM and 6-gingerol (from ginger) at 100-500μM were shown to impede the transport driven by p-glycoprotein of the drug digoxin, demonstrating their inhibitory effects in both *in vitro* and *in vivo* studies[23,24]. Natural compounds like curcumin, ginsenosides, piperine, and some green tea catechins from milk thistle impede p-glycoprotein, while others promote drug transport through p-glycoprotein[25]. Flavonoids like Tangeretin, sinensetin, isosinensetin, sciadopitysin, and oroxylin significantly inhibited p-glycoprotein in Multi Drug Resistance 1 (MDR1)-Madin-Darby Canine Kidney II (MDCKII) cells, reducing paraquat and taxol efflux and enhancing cytotoxicity[26]. Piperine, a P-glycoprotein inhibitor, significantly enhanced rhodamine-123 retention in doxorubicin-resistant National Cancer Institute/ Adriyamycin- Resistant (NCI/ADR-RES) cells, potentiating cytotoxicity and inhibiting orthovanadate-sensitive ATPase activity in human ovarian cancer cells[27]. Studies show phylloquinone, kutkin, and atisine prevent drug efflux, while natural p-glycoprotein inhibitors like magnoflorine, diayangambin, curcumin, withanone, and embelin enhance allopathic medication bioavailability in target cells[28]. Moreover, several spice compounds, in particular pandamarilactone-31, were identified as possible natural inhibitors of p-glycoprotein and thus could improve drug absorption and therapeutic efficacy[29]. Recent research focuses on p-glycoprotein-mediated MDR and a decrease in tumour cell p-glycoprotein expression. Natural components have been studied to inhibit p-glycoprotein and prevent drug efflux. These inhibitors may be more toxic-free and selective, making them better for clinical use. Analysing the ADMET profile and binding affinities, molecular dynamics analysis revealed stability and bioavailability.

Based on our current study findings, we may assume that using hydroxymatairesinol and gingerenone-A together to deliver anticarcinogenic treatment may help prevent MDR caused by drug efflux. The binding energies of hydroxymatairesinol and gingerenone-A were -117.6 kcal/mol and -112.7 kcal/mol, respectively, which are more negative than the binding energy of doxycycline (-79.09 kcal/mol) and elacridar (-91.59 kcal/mol), a known P-glycoprotein inhibitor. Hydroxymatairesinol and gingerenone-A showed improved binding mechanisms. Hydroxymatairesinol possessed two hydrogen bonds with amino acids LEU332 and SER979 and four hydrophobic interactions with amino acids PHE79, ALA729, PHE732 and LEU975. Gingerenone-A also possessed two hydrogen bonds with amino acids LEU332 and ILE736 and four hydrophobic interactions with amino acids PHE79, ALA729, PHE732 and ILE736. Due to their greater binding affinities and stronger interactions than doxycycline, hydroxymatairesinol and gingerenone-A, which are active ingredients of *S. indicum* and *Z. officinale*, may be regarded as the key components in preventing p-glycoprotein-mediated cancer drug efflux.

5. Conclusion

Overall, the findings highlight the significant potential of natural compounds as effective p-glycoprotein inhibitors that can enhance drug bioavailability and counteract MDR in cancer therapy. Among the compounds studied, hydroxymatairesinol and gingerenone- A demonstrated particularly strong binding affinities and stable interactions with key amino acids involved in p-glycoprotein function, surpassing known inhibitors such as doxycycline and elacridar. These results suggest that combining hydroxymatairesinol and gingerenone-A could offer a promising, low-toxicity strategy to improve the efficacy of anticancer treatments by reducing drug efflux. Further in-depth experimental and clinical studies are

warranted to validate their therapeutic potential and optimise their application in cancer pharmacotherapy.

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Author Contribution

Swagata Mukhopadhyay contributed to the methodology, data collection, data analysis, and original draft writing. Sayak Ganguli contributed to the conceptualisation, methodology, data analysis, and data visualisation. Pratiti Ghosh contributed to the conceptualisation, methodology, writing, data analysis, data visualisation, supervision, and project administration. All authors have read and agreed to the published version of the manuscript.