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Discovery of Naturally Occurring Flavonoids as Human Cytochrome P450 (CYP3A4) Inhibitors with the Aid of Computational Chemistry

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Human Cytochrome P450 (CYP3A4); Flavonoids; Doxorubicin; Molecular docking; PyRx Virtual Screening Tool.

ABSTRACT: Purpose: The human cytochrome P450 3A4 (CYP3A4) is the biggest individual from the CYP3A subfamily and records for 30–60% of the total for CYP450 adult liver. Hereditary varieties in CYP3A4 are a noteworthy hotspot for inter-patient changeability in plasma concentration, adverse effects and pharmacological response to medications. This research was done to discover naturally occurring novel CYP3A4 inhibitors from flavonoids. Methods: The molecular docking method was used to optimize the inhibiting activity of flavonoids against CYP3A4. PyRx Virtual Screening Tool 0.8 and BIOVIA Discovery Studio 2019 was used for simulation. Results: Flavonoids like Pongamoside A, Pongamoside B, and Pongamoside D have more binding affinity (kcal/mol) i.e. -11.6, -10.9, -10.8 respectively than Doxorubicin which have -10.7 against CYP3A4. Although, Daidzein, Genistein, and Luteolin form more hydrogen bonds than doxorubicin. Conclusion: The rational synthesis of natural analogues in reference to synthetic drugs, could generate drugs with improved therapeutic effect for chemoprevention. CYP3A4 plays a major role in the metabolism of various drugs; by the help of flavonoids, we can control the selective drug metabolism by inhibiting CYP3A4. Despite this, these molecules are not marketed for cancer treatment because of high polarity. If we could overcome this problem, these molecules can acts as effective anticancer agents in the future. Still, if we want to use these compounds clinically, there is a need to generate more scientific evidence and quality data by using *in vivo* and *in vitro* models.

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INTRODUCTION

Flavonoids are a well-known category of polyphenolic compounds. These are the regular dietary materials of the human, as many of the plants contains flavonoids. There are plenty of plants that exerts good pharmacological properties including anticancer activity just because of the presence of flavonoids. Flavonoids are the essential plant shades that act as chemical messengers, physiological controllers, and cell cycle inhibitors [1]. Flavonoids stand out amongst the most tried and broadly distributed substances of plant sources. They are found in natural products, vegetables, leguminous plants and even a few sorts of greenery. The skeleton of flavonoids comprises of 1-benzopyran. It is a C6-C3-C6 framework, in which sweet-smelling rings are associated, shaping a focal pyran or pyron cycle. Contingent upon the position to which ring is associated with the chromane, flavonoids are grouped into isoflavonoids and neoflavonoids [2].

Amongst the different other natural substances, flavonoids hold much consideration because of their noteworthy range of pharmacological activities, such as cell reinforcement, antimutagenic, antibacterial, antiangiogenic, anti-

inflammatory, antiallergic, modulators of enzymatic activities and anti-cancer activity [3]. Apigenin, luteolin, quercetin and kaempferol, the hydroxylated flavonoids are the main constituents of various dietary products and beverages and have been the focus of extensive research over the last years. Apigenin exerts anticancer effects through the modulation of various pathways namely, apoptosis, Reactive oxygen species (ROS) and DNA damage and repair[4].

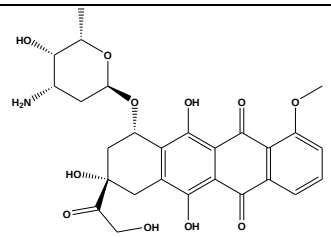
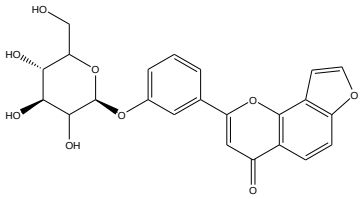
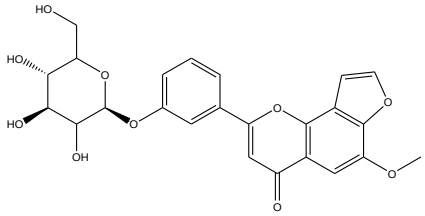
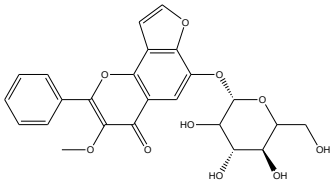
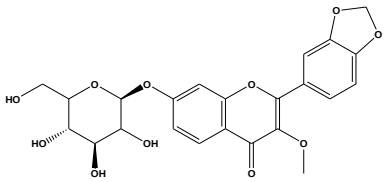
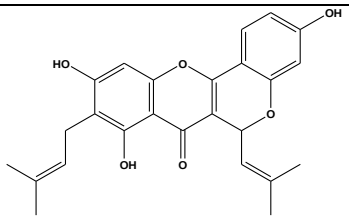
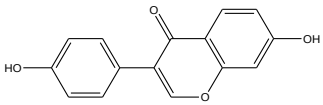
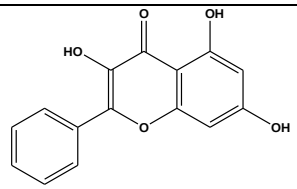
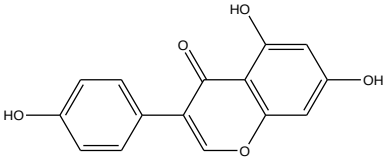
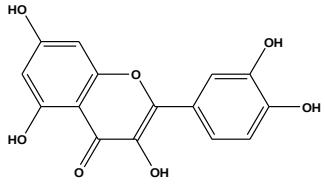
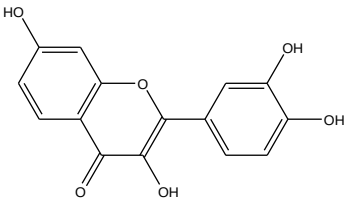
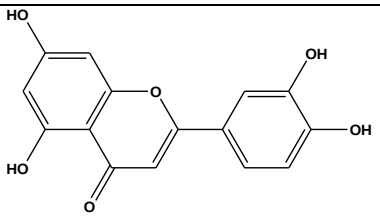
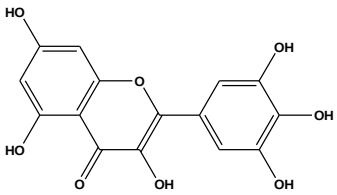
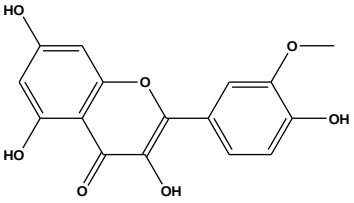
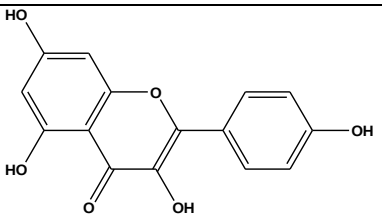
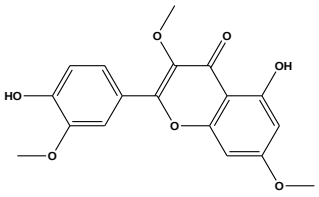
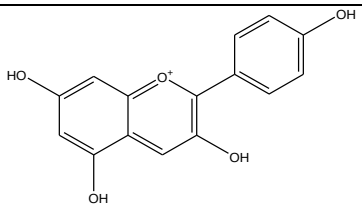
Malignant growth is one of the terrible illnesses caused by unusual cell growth and can attack different tissues. They shape a subset of neoplasms. It speaks of the greatest social insurance issues for humankind and requests a proactive system for cure [5]. It is accounted for the rate of malignancy that has been expanding in developing nations and has turned into the fourth driving reason for death around the world. Chemoprevention by phytoconstituents has advanced as a powerful procedure to control the prevalence of malignant growth. The journey of anticancer agents from plant sources began in the 1950s with the discovery of the vinca alkaloids, vincristine, vinblastine, combretastatin, and colchicine. These Phytochemicals act explicitly on tumor cells without influencing non-cancerous cells. Carcinogenesis is a mind-boggling marvel that includes many signaling cascades. Phytochemicals are viewed as reasonable candidates for anticancer medication advancement due to their pleiotropic activities on target. The examination is in advancement for creating potential competitors (those can square or back off the development of disease cells without any side effects) from these phytochemicals. Numerous phytochemicals and their determined analogs have been distinguished as potential candidates for anticancer treatment. Plants serve as a source of novel compound elements and give a promising line to investigate on malignant growth. The plant and plant metabolites are the reforming sources as these are simple, more secure, easy, quick, and less dangerous as contrasted to traditional treatment methods. There is a positive relationship set up by the epidemiological examinations between expanded utilization of common items with diminished danger of disease. The mechanism responsible for chemoprevention remains essentially unidentified, however, it is likely identified with the closeness of phytochemicals related to plants. Consequently, the search for powerful and more secure natural anticancer agents have attracted the researchers throughout the world. [6,7].

The human cytochrome P450 3A4 (CYP3A4) is the biggest individual from the CYP3A subfamily and records for 30–60% of the total for CYP450 adult liver. The CYP3A4 gene is limited on chromosome 7q21 and up to now, 41 CYP3A4 alleles have been recognized. The human CYP3A locus contains the three CYP3A gene (CYP3A4, CYP3A5, and CYP3A7), three pseudogenes, and a novel CYP3A gene named CYP3A43. Hereditary varieties in CYP3A4 are a noteworthy hotspot for inter-patient changeability in plasma concentration, adverse effects and pharmacological response to medications, for example, paclitaxel, fentanyl, tamoxifen, tacrolimus, and statins. Moreover, existing investigations have announced the role of CYP3A4 inadequate alleles in the disease susceptibility to prostate malignant growth, estrogen receptor-negative breast cancer, and type-2 diabetes [8,9].

Protein-ligand docking is a fundamental part of computer-aided drug design, and it distinguishes the coupling pattern of proteins and ligands by computer simulation. Molecular docking results decide a general binding mode of a ligand. Varieties of compounds from plant sources have been accounted to have significant anticancer properties; in any case, their modes of activity have not been characterized. Molecular docking studies were performed on some flavonoids by using Autodock vina 1.1.2 in PyRx 0.8. [10]. The docking was performed utilizing receptor proteins required with cell cycle, cell development, and DNA replication, i.e., cyclin-subordinate protein kinase 2 (CDK-2), CDK-6, DNA topoisomerases I and II, B-cell lymphoma 2 (Bcl-2), vascular endothelial development factor receptor 2 (VEGFR-2), and the telomere: G-quadruplexes. By molecular docking, the bound confirmations and the coupling attachment among flavonoid and CYP3A4 as the target could be anticipated [11]. Doxorubicin, sold under the brand names adriamycin, used to treat breast malignant growth, bladder cancer, lymphoma, and intense lymphocytic leukemia was utilized for docking studies whose binding interactions were compared with the flavonoids [12].

Docking of the small molecule into the binding site of a receptor and guessing the binding interaction of the complex is a noteworthy part of the structure-based drug design process. By molecular docking, the bound conformations and the binding affinity between Flavonoids and human cytochrome P450 3A4 as the target could be predicted [13]. **Table 1** represents the names and structures of doxorubicin and the flavonoids used for molecular docking. The structures of all the compounds were generated by using ChemDraw Ultra 8.0 with the help of IUPAC name took from the official website of U.S. National Library of Medicine PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Table 1. Name and Structures of compounds used for molecular docking

Doxorubicin	Pongamoside A	Pongamoside B
		
Pongamoside C	**Pongamoside D**	**Cyclocommunin**
		
Daidzein	**Galangin**	**Genistein**
		
Quercetin	**Fisetin**	**Luteolin**
		
Myricetin	**Isorhamnetin**	**Kaempferol**
		
Pachypodol	**Pelargonidin**	
		

MATERIALS AND METHODS

System used for Molecular docking

Molecular docking was performed on Lenovo ThinkPad with 64-bit operating system, Processor: Intel(R) Core(TM) i5-4300M CPU @2.60 GHz 2.59 GHz, RAM: 4GB by using PyRx-Virtual Screening Tool.

Ligand Preparation

The Structures of all the compounds (SDF File) were downloaded from the official website of the U.S. National Library of Medicine PubChem (https://pubchem.ncbi.nlm.nih.gov/). Structures then imported into PyRx 0.8 using open bable tool and energy minimization

(optimization) was performed by considering fundamental parameters based on the element, its hybridization, and connectivity i.e. by Universal Force Field (UFF)[16]. These ligands were then converted to AutoDock Ligand format (PDBQT).

Macromolecule Preparation

Autodock vina 1.1.2 in PyRx 0.8 was used to perform the docking studies of all the compounds against the crystal structure of human cytochrome P450 3A4 (CYP3A4). The crystal structure of CYP3A4 was obtained from the RCSB Protein Data Bank (PDB) with PDB ID-4K9T (http://www.rcsb.org/structure/4K9T) with Homo sapiens organism and Escherichia coli expression system. The CYP3A4 crystal structure was optimized, purified and prepared for docking with the help of Discovery Studio Visualizer 2019 by removing unwanted water molecules, bound ligands from protein structure and saved again in PDB file format to the same folder[17].

Molecular Docking Procedure

The purified CYP3A4 crystal structure file was loaded to docking software PyRx 0.8 using a load molecule option from the File toolbar. Chain-A was used to perform the docking, as it contains the active site which confirmed by checking interactions of native ligand present in the crystal structure (http://www.rcsb.org/3d-view/4K9T?preset=ligandInteraction&sele=1RD). The CYP3A4 crystal structure was then converted to Autodock macromolecule (pdbqt format) by using the right-click option. Binding affinity studies were performed by using Vina Wizard Tool in PyRx 0.8. All the ligand molecules (PDBQT Files), and target (CYP3A4) were selected for docking study. For molecular docking simulation, the three-dimensional grid box (size_x = 18.5286782874Ao; size_y = 26.047226475Ao; size_z = -9.59195798998Ao) was designed using Autodock tool 1.5.6 with exhaustiveness value of 8. After selecting molecules, the active amino acid residues were selected to define the cavity with the help of Toggle Selection Spheres option given in PyRx[18]. To occupy all the active binding sites and essential residues, the grid box was aligned properly. All the ligands and CYP3A4 then subjected for docking to get the finding affinities.

Identification of Cavity and Active Amino Acid Residues

The active amino acid residues in the protein were identified and noted using BIOVIA Discovery Studio Visualizer (version-19.1.0.18287)[17]. The selection of the amino acids in the active site was used to analyze the grid box and to define the cavity. All the docking poses, ligand and protein interactions were studies by importing output files into Discovery Studio which enables us to identify the types of interactions. Discovery Studio is an offline life sciences software that offers tools to study drug-receptor interaction, docking poses visualization and macromolecule preparations. The chosen cavity was the binding site of the native ligand in PDB 4K9T.

RESULTS AND DISCUSSION

All the flavonoids and doxorubicin successfully docked on CYP3A4. Binding energy is released when a drug molecule associates with a target, leading to a lowering of the overall energy of the complex [14]. Molecular formula, Lipinski's rule of five, binding affinity (kcal/mol), and active amino acid residues are presented in Table 1. Lipinski's rule of five plays an important role in molecule screening and validation. Here, Pongamosides i.e. Pongamoside A, Pongamoside B, and Pongamoside D have shown better binding affinity than doxorubicin.

Table 2 represents 3D- & 2D-images of docking poses along with no. of hydrogen bonds involved in the interaction. The 2D-docking pose also shows the chemical structure of the ligands which enables us to predict groups and/or atoms involved in the bond formation with CYP3A4.

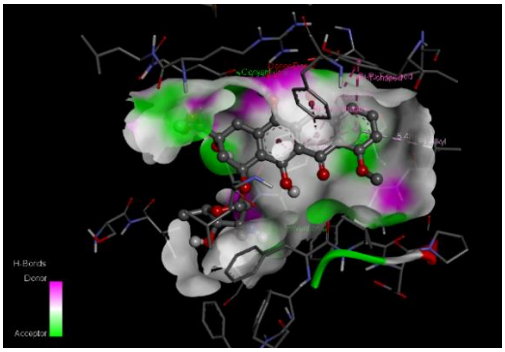
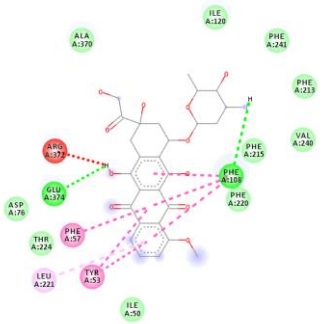
Table 2. Properties, Lipinski's rule of five, binding affinity and active amino acid residues.

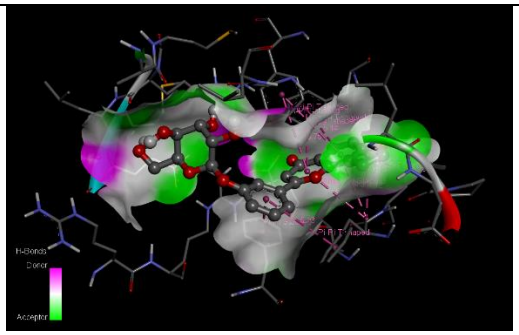
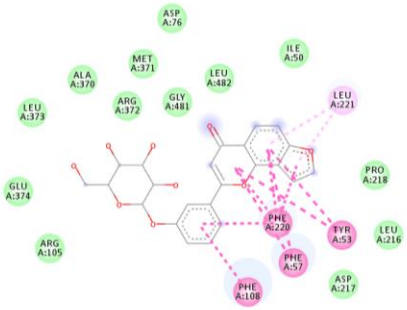
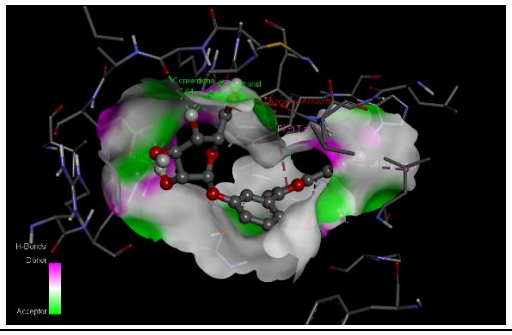
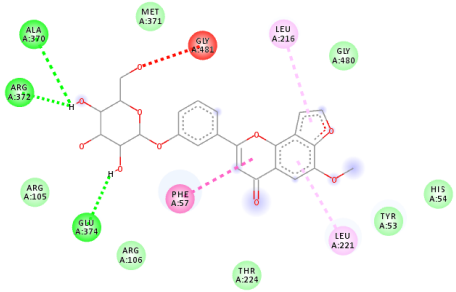
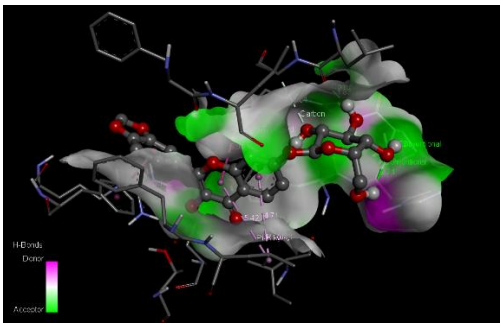
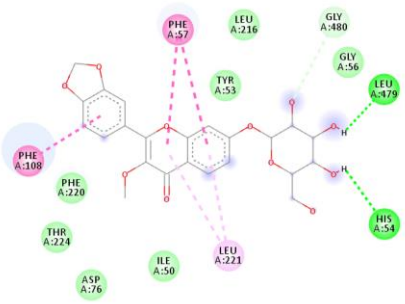
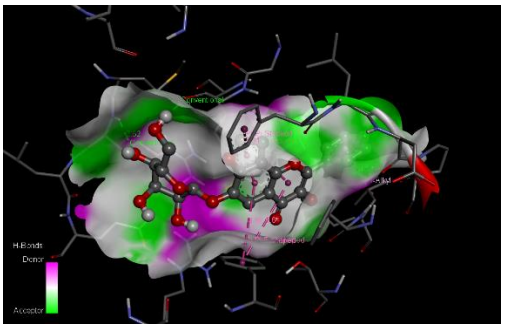
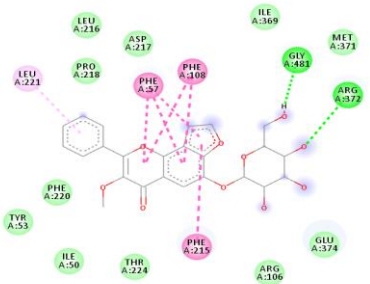
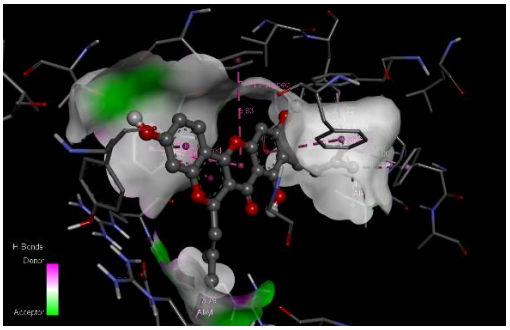
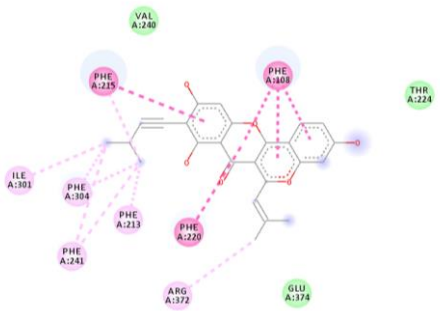
Name of Compound	Molecular Formula	Lipinski's rule of five		Binding affinity (kcal/mol)	Active amino acid residues
Doxorubicin	$C_{27}H_{29}NO_{11}$	Molecular weight (<500 DA)	543.5	-10.7	Ala370, Ile120, Phe241, Phe213, Val240, Phe215, Phe108, Phe220, Ile50, Tyr53, Leu221, Phe57, Thr224, Asp76, Glu374 (Forms unfavourable bond with Arg372)
		XLogP (<5)	1.3		
		H-Bond donor (5)	6		
		H-bond acceptor (<10)	12		
Pongamoside A	$C_{23}H_{20}O_9$	Molecular weight (<500 DA)	440.4	-11.6	Leu373, Ala370, Arg372,

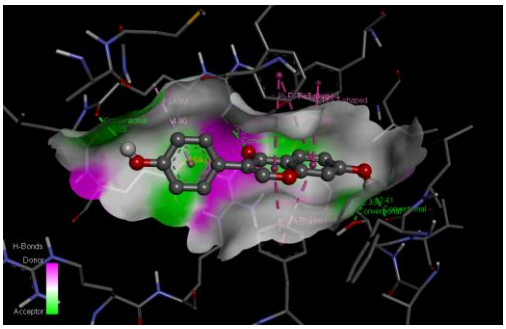
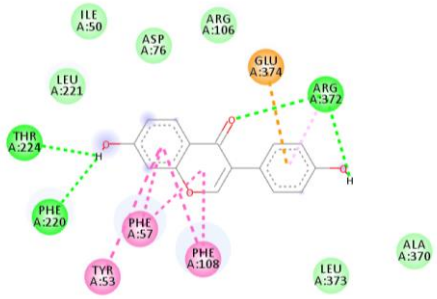
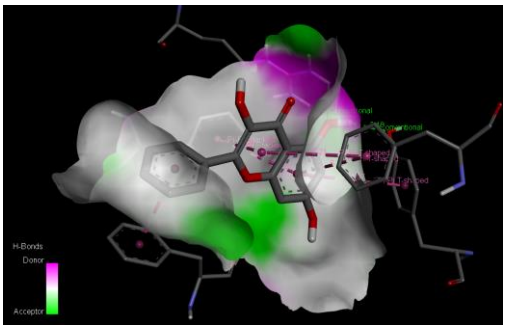
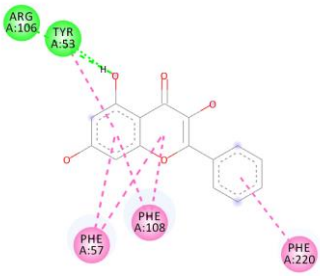
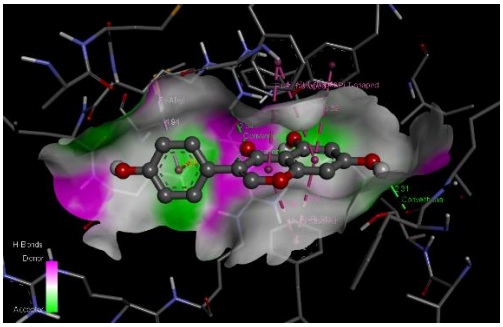
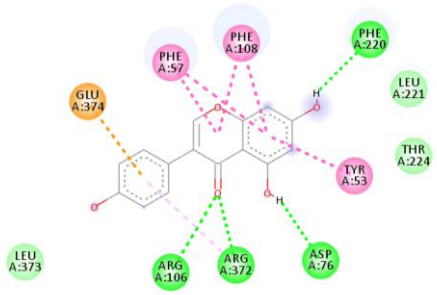
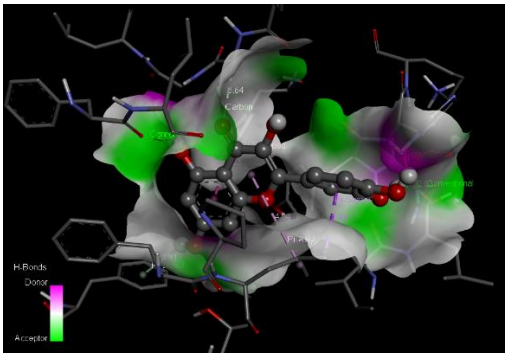
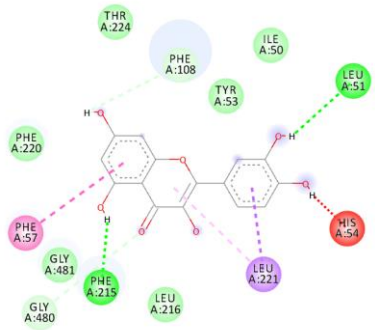
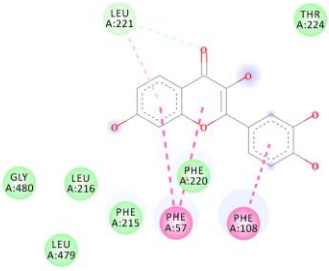
		XLogP (<5)	1.4		Met371, Gly481, Asp76, Leu482, Ile50, Leu221, Pro218, Leu216, Tyr53, Phe57, Phe220, Phe108, Arg105, Glu374
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	9		
Pongamoside B	$C_{24}H_{22}O_{10}$	Molecular weight (<500 DA)	470.4	-10.9	Arg372, Ala370, Met371, Leu216, Gly480, His54, Tyr53, Leu221, Thr224, Phe57, Arg106, Glu374, Arg105 (Forms unfavourable bond with Gly481)
		XLogP (<5)	1.4		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	10		
Pongamoside D	$C_{23}H_{22}O_{11}$	Molecular weight (<500 DA)	474.4	-10.8	Phe57, Leu216, Tyr53, Gly480, Gly56, Leu479, His54, Leu221, Ile50, Asp76, Thr224, Phe220, Phe108
		XLogP (<5)	1		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	11		
Pongamoside C	$C_{24}H_{22}O_{10}$	Molecular weight (<500 DA)	470.4	-10.6	Leu221, Pro218, Leu216, Asp217, Phe57, Phe108, Ile369, Gly481, Met371, Arg372, Glu374, Arg106, Phe215, Thr224, Ile50, Tyr53, Phe220
		XLogP (<5)	1.6		
		H-Bond donor (5)	2		
		H-bond acceptor (<10)	10		
Cyclocommunin	$C_{25}H_{24}O_6$	Molecular weight (<500 DA)	420.4	-10.1	Phe215, Val240, Phe108, Thr224, Glu374, Arg372, Phe220, Phe213, Phe241, Phe304, Ile301
		XLogP (<5)	4.1		
		H-Bond donor (5)	3		
		H-bond acceptor (<10)	3		
Daidzein	$C_{15}H_{10}O_4$	Molecular weight (<500 DA)	254.2	-9.3	Leu221, Ile50, Asp76, Arg106, Glu374, Arg372, Ala370, Leu373, Phe108, Phe57, Tyr53, Phe220, Thr224
		XLogP (<5)	2.5		
		H-Bond donor (5)	2		
		H-bond acceptor (<10)	4		
Galangin	$C_{15}H_{10}O_5$	Molecular weight (<500 DA)	270.2	-9.3	Arg106, Tyr53, Phe220, Phe108, Phe57
		XLogP (<5)	2.3		
		H-Bond donor (5)	3		
		H-bond acceptor (<10)	5		
Genistein	$C_{15}H_{10}O_5$	Molecular weight (<500 DA)	270.2	-9.1	Glu374, Phe57, Phe108, Phe220, Leu221, Thr224, Tyr53, Asp76, Arg372, Arg106, Leu373
		XLogP (<5)	2.7		
		H-Bond donor (5)	3		
		H-bond acceptor (<10)	5		
Quercetin	$C_{15}H_{10}O_7$	Molecular weight (<500 DA)	302.2	-8.7	Thr224, Phe108, Tyr53, Ile50, Leu51, Leu221, Leu216, Phe215, Gly481, Gly480, Phe57, Phe220 (Forms unfavourable bond with His54)
		XLogP (<5)	1.5		
		H-Bond donor (5)	5		
		H-bond acceptor (<10)	7		
Fisetin	$C_{15}H_{10}O_6$	Molecular weight (<500 DA)	286.2	-8.7	Leu221, Thr224, Phe108, Phe220, Phe57, Phe215, Leu479, Leu216, Gly480
		XLogP (<5)	2		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	6		
Luteolin	$C_{15}H_{10}O_6$	Molecular weight (<500 DA)	286.2	-8.6	Phe215, Leu221, Phe57, Leu479, Gly56, His54, Ile50, Phe108, Thr225, Phe220
		XLogP (<5)	1.4		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	6		

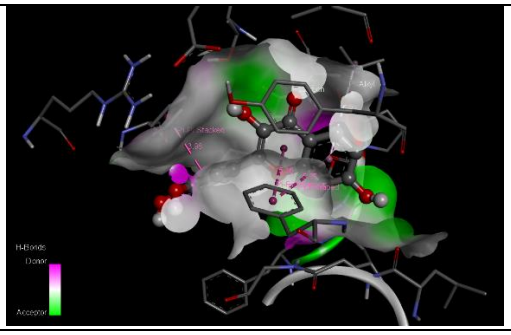
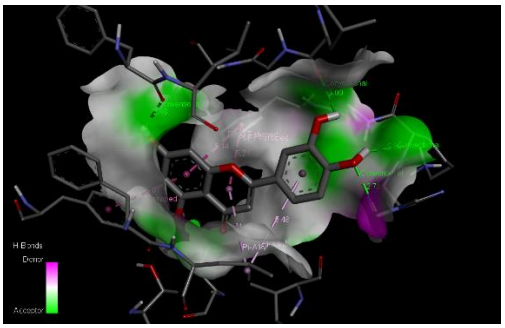
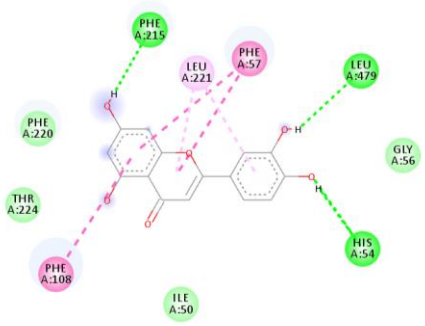
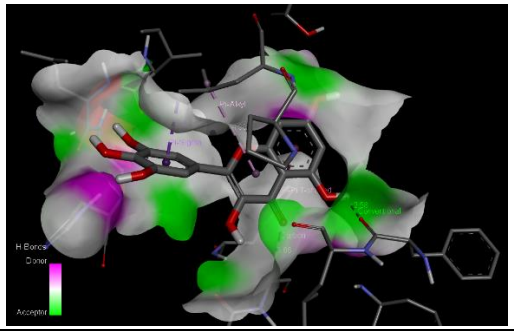
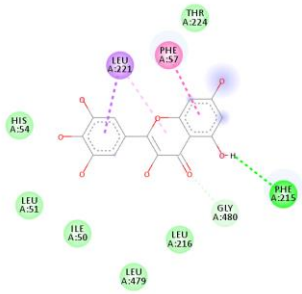
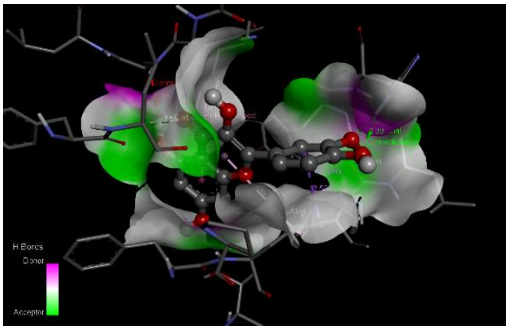
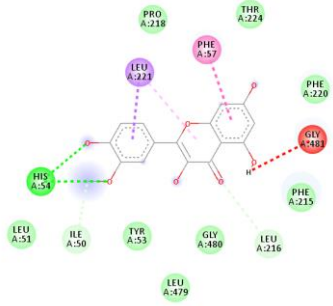
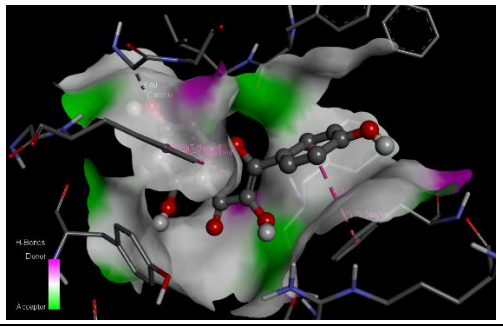
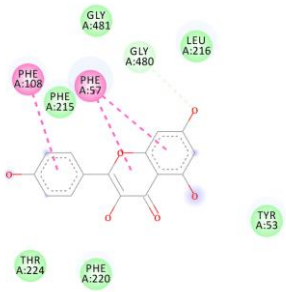
Myricetin	$C_{15}H_{10}O_8$	Molecular weight (<500 DA)	318.2	-8.6	Leu221, Phe57, Thr224, Phe215, Gly480, Leu216, Leu479, Ile50, Leu51, His54
		XLogP (<5)	1.2		
		H-Bond donor (5)	6		
		H-bond acceptor (<10)	8		
Isorhamnetin	$C_{16}H_{12}O_7$	Molecular weight (<500 DA)	316.2	-8.4	Leu221, Pro218, Phe57, Thr224, Phe220, Phe215, Leu216, Gly480, Leu479, Tyr53, Ile50, Leu51, His54 (Forms unfavourable bond with Gly481)
		XLogP (<5)	1.9		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	7		
Kaempferol	$C_{15}H_{10}O_6$	Molecular weight (<500 DA)	286.2	-8.4	Phe108, Phe215, Phe57, Gly481, Gly480, Leu216, Tyr53, Phe220, Thr224
		XLogP (<5)	9.8		
		H-Bond donor (5)	1		
		H-bond acceptor (<10)	1		
Pachypodol	$C_{18}H_{16}O_7$	Molecular weight (<500 DA)	344.3	-8.3	Leu221, Pro218, Leu479, Gly480, Phe215, Leu216, Phe220, Thr224, Phe108, Phe57, Tyr53, His54, Ile50, Leu51
		XLogP (<5)	3.1		
		H-Bond donor (5)	2		
		H-bond acceptor (<10)	7		
Pelargonidin	$C_{15}H_{11}O_5^+$	Molecular weight (<500 DA)	271.2	-8.2	Tyr53, Phe215, Gly481, Phe220, Phe108, Leu221, Phe57, Thr224, Ile50
		XLogP (<5)	2.1		
		H-Bond donor (5)	4		
		H-bond acceptor (<10)	1		

Table 3. 3D- & 2D-images of docking poses along with no. of hydrogen bonds involved.

Name of Compound	3D-docking pose	2D-docking pose	No. of hydrogen bonds involved
Doxorubicin			02
Pongamoside A			00

			
Pongamoside B			02
Pongamoside D			02
Pongamoside C			02
Cyclocommuni n			00

Daidzein			04
Galangin			02
Genistein			04
Quercetin			02
Fisetin			00

			
Luteolin			03
Myricetin			01
Isorhamnetin			02
Kaempferol			00

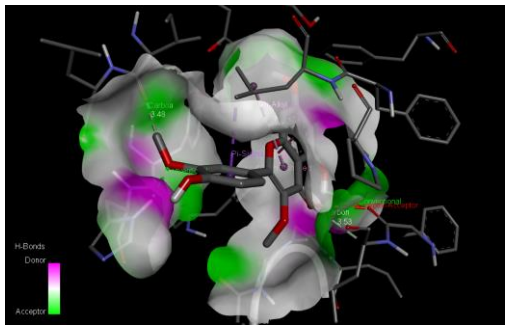
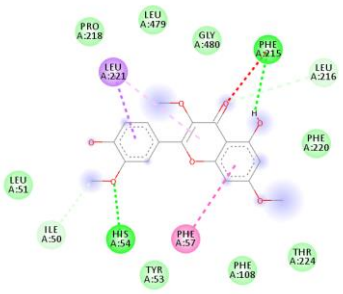
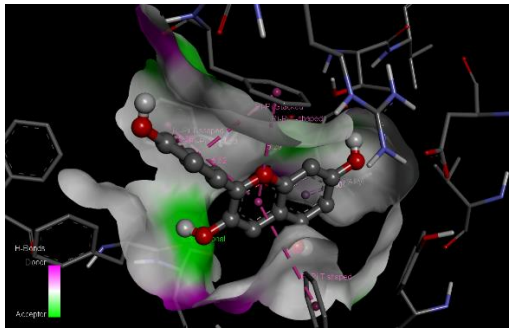
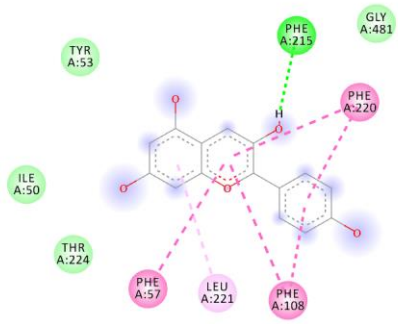
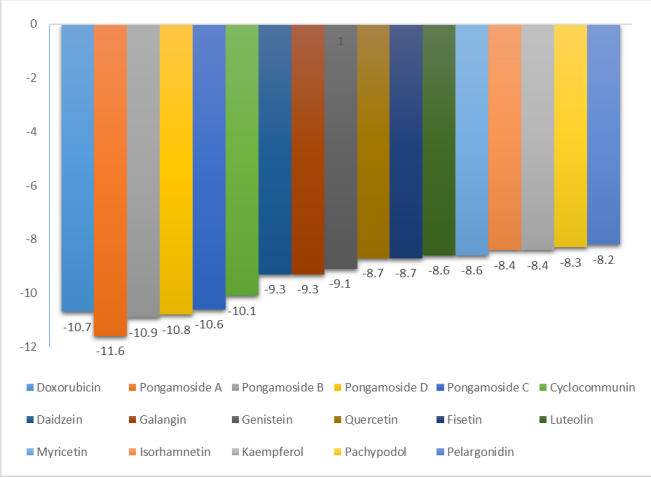
Pachypodol			02
Pelargonidin			01

Figure 1 represents the comparative binding affinities (kcal/mol) of doxorubicin and flavonoids. Many of the flavonoids have shown better binding affinity than doxorubicin.

Figure 1. Comparative binding affinities of the compounds (Graphical presentation)



As we have represented docking data along with 2D- & 3D-docking poses including no. hydrogen bonds involved in the interactions in Table 2. The formation of a hydrogen bond with the target molecule always results in inhibition of the receptor. Sadhna Sinha et al reported the Molecular docking of flavones at the colchicines binding pocket which revealed that the compounds bind at a–b interfacial site of tubulin, correlating binding interactions with probable inhibition mechanism. The study reveals important observations to generate improved flavonoids that leads to cell apoptosis [15]. In case of Pongamoside A, it forms zero hydrogen bonds but still its binding affinity i.e. -11.6 kcal/mol is best because Pongamoside A forms van der Waals force attraction, Pi-Pi Stacked bonds, Pi-Pi T-shaped bonds, Amide-Pi stacked bonds and Pi alkyl bonds with more amino acid residues than doxorubicin i.e. -10.7 kcal/mol which forms two hydrogen bonds with CYP3A4. Pongamoside B and Pongamoside D have binding affinities (kcal/mol) -10.9 and -10.8 with the formation of 2-2 hydrogen bonds each with CYP3A4. This can be sufficient scientific evidence showing more potency of these flavonoids in terms of inhibition of CYP3A4 than the approved drug, doxorubicin. Although, Pongamoside C, Galangin, Quercetin, Isorhamnetin, Pachypodol forms 2-2 hydrogen bonds each with binding affinities -10.6, -9.3, -8.7, -8.4 and -8.3 kcal/mol respectively. Surprisingly Daidzein and Genistein formed 4 hydrogen bonds each with CYP3A4 with a docking score of -9.3 and -9.1 kcal/mol respectively which is much enough to inhibit the activity of CYP3A4. Luteolin has formed 3 hydrogen bonds with -8.6 kcal/mol binding affinity. The amino acid residues in the cavity involved in the interactions are represented in **Table 1**.

CONCLUSION

It is well known that natural compounds have proven to have a safe biological window as compared to molecules from a synthetic source. In present work, molecular docking studies disclosed, that flavonoids Pongamoside A, Pongamoside B,

and Pongamoside D have a better binding affinity towards CYP3A4 than doxorubicin. Although, if we talk about the formation of hydrogen bonds with target macromolecule, Daidzein, Genistein, and Luteolin form more hydrogen bonds than doxorubicin. In conclusion, the above docking study disclosed that rational synthesis of natural analogues in reference to synthetic drugs could generate drugs with improved therapeutic effects for chemoprevention. CYP3A4 plays a major role in the metabolism of various drugs; by the help of flavonoids, we can control the selective drug metabolism by inhibiting CYP3A4. Despite this, these molecules are not marketed for cancer treatment because of their high polarity. If we could overcome this problem, these molecules can acts as effective anticancer agents in the future. Still, if we want to use these compounds clinically, there is a need to generate more scientific evidence and quality data by using *in vivo* and *in vitro* models.

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None

CONFLICTS OF INTEREST
None.

DATA AVAILABILITY
Not declared.

FUNDING SOURCE
Not declared

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