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Original Research Article

Flavonoids Docked into Several Target Proteins Associated with Cancer: A Molecular Docking Study

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ABSTRACT

The emergence of new drug discovery for cancer treatment is vital and continuously gaining global attention. Although the discovery and development of a new drug takes a long time, the efforts should be retained. Successful findings could be repeated for cancer therapy from natural compounds by investigating flavonoids from molecular docking as the initial study towards the drug development process. Flavonoids derived from plants are believed to have the capability to interact with cancer-related proteins. The present study aims to identify the most favourable cancer-related proteins to be targeted by selected flavonoids through molecular docking simulation. In this study, selected flavonoids from different classes have been docked with several targeted proteins which are involved in cell death, survival, and proliferation, such as death receptors 4 and 5 (DR4 and DR5), epidermal growth factor receptor (EGFR) and farnesyltransferase (FTase). Of all the proteins tested for docking simulation, EGFR protein is among the best-targeted proteins compared to other proteins with the lowest binding energies for each flavonoid, ranging from -9.1 to -8.4 kcalmol^{-1}. Meanwhile, myricetin **(7)** exhibited the strongest binding affinity for three proteins, including EGFR, FTase and DR5. On the other hand, DR4 protein has shown interaction favourably with flavone **(5)** with the binding affinity of -8.0 kcalmol^{-1}. The docking results suggest that the selected flavonoids generally have good binding affinities and interactions with cancer-target proteins, which could be proposed as inhibitors of targeted-proteins in cancer therapy.

***Keywords*:** Flavonoids, Docking, DR4, DR5, EGFR, Farnesyltransferase.

Introduction

Natural flavonoids isolated from the plant kingdom are among the best sources of anticancer drugs. Flavonoids are found in the diet, such as vegetables, fruits, and drinks derived from secondary metabolites.[1] The basic structure of all flavonoids consists of the flavan skeleton, a 15-carbon phenylpropanoid chain (C6-C3-C6 system), which produced two aromatic rings (A and B) and linked by a heterocyclic pyran ring (C).[2] There are six major groups of flavonoids formed, including isoflavonoids, flavanones, flavanols, flavonols, flavones and anthocyanidins. This formation varies based on the degree of oxidation and unsaturation of the flavonoids.[3-5] Previous studies found that flavonoids are potent antioxidants that are beneficial for anticancer drug development. Besides, flavonoids also have the capability to interact with proteins and form protein-flavonoids complexes either soluble or insoluble.[6]

There are four target proteins selected in this study including Tumour Necrosis Factor (TNF)-related apoptosis-inducing ligands (TRAIL)-R1 (DR4) and TRAIL-R2 (DR5), epidermal growth factor receptor (EGFR) and farnesyltransferase (FTase). The DR4 and DR5 are characterized by the presence of the death domain (DD) within the cytoplasmic portion.[7]

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The TRAIL ligands trigger the tumour necrosis factor (TNF) signalling pathway which enable recruitment of Fas-associated protein with death domain (FADD) that eventually cause apoptosis.[8]

These receptors are proposed due to their function in a wide range of physiological mechanisms such as T cell activation and tumorigenesis. In fact, DR4 or DR5 have also been revealed to be more efficient in cancer-targeted studies.[9]

Meanwhile, the EGFR proteins are markedly overexpressed in many solid tumours, including breast, pancreas, head-and-neck, prostate, ovarian, renal, colon, and non-small-cell lung cancer.[10]EGFRsare involved in the proliferation and survival of cancer cells.[11-12]Several immunohistochemical studies also demonstrated that EGFRs expression associated with poor cancer prognosis.[12]

Farnesyltransferase (FTase) is another target protein that gained researchers attention in recent years. This enzyme plays a critical role in the post-translational modification of Ras proteins.[13-14] Ras protein requires FTase to interfere with the signalling cascade, relating to the growth and survival of the cell, proliferation, differentiation, adhesion of cancer cells.[15]The presence of oncogenic forms of Ras proteins can be detected in all forms of neoplasm but is highly present in pancreatic tumours, colon cancer and lung cancer.[16-17] Therefore, this protein is important to be targeted to inhibit Ras protein and thus, avoiding the incidence of cancer.[15]

As the initial approach for the drug discovery process, *in silico* with docking studies was conducted to determine interactions of flavonoids and selected targeted proteins. This docking study is performed to predict the ligand–protein complexes binding and the conformation of target protein upon the ligand binding to its active side.[18]The rationale of the computational modelling study is to select the best small molecule as well as target protein to be experimentally tested for the further drug discovery process. Therefore, this study aims to identify the most favourable proteins which are involved in the cancer pathway

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to be targeted by the selected flavonoids through molecular docking simulation.

Materials and Methods

Preparation of ligands and proteins structural files

A total of seven flavonoids from various classes, namely 6-hydroxyflavone**(1)**, apigenin**(2)**, biochanin A**(3)**, fisetin**(4)**, flavone**(5)**, galangin**(6)** and myricetin**(7)**, have been selected as ligands in this study. Their chemical structures were retrieved from the PubChem database as shown in Figure 1.[19] The 3D structures of flavonoids were then prepared in .pdb file, followed by minimization of ligands to obtain the lowest energy conformations using BIOVIA Discovery Studio 2017 R2.[20]

The selection of several proteins in this study was based on the target for anticancer drugs. Crystal structure of four proteins, such as DR4, DR5, EGFR and FTase was obtained from the RCSB Protein Data Bank with PDB ID 5CIR,[21] 1D0G,[22] 3W2S,[23] and 1SA4,[24] respectively and were saved separately in .pdb. These proteins were prepared using BIOVIA Discovery Studio version 17.2, including removing the heteroatoms and water molecules, adding the hydrogen atoms and merging the nonpolar hydrogen atoms. In addition, the Gasteiger charges were added to the protein 3D-structures. All proteins were kept in.pdbqt files.

Docking procedure

Docking simulations were carried out for the flavonoids and target proteins using AutoDock Vina software.[25]All flavonoids were site-directed into protein binding sites based on their reported inhibitors of that particular protein. The grid box was positioned at the identified binding siteof60 × 60 × 60 points with 1 Å spacing centered on DR4, 80 × 80 × 80 points with 1 Å spacing centered on DR5, 20 × 20 × 20 points with 1 Å spacing centered on EGFR and 20 × 20 × 20 points with 1 Å spacing centered on FTase. Docking simulation was set up to 100 exhaustiveness and repeated 10 times. Protein-ligand interactions were characterized using the Discovery Studio Visualizer. The docked protein-ligand complex allows the determination of several interactions, such as polar and hydrophobic interactions between flavonoids and target proteins.

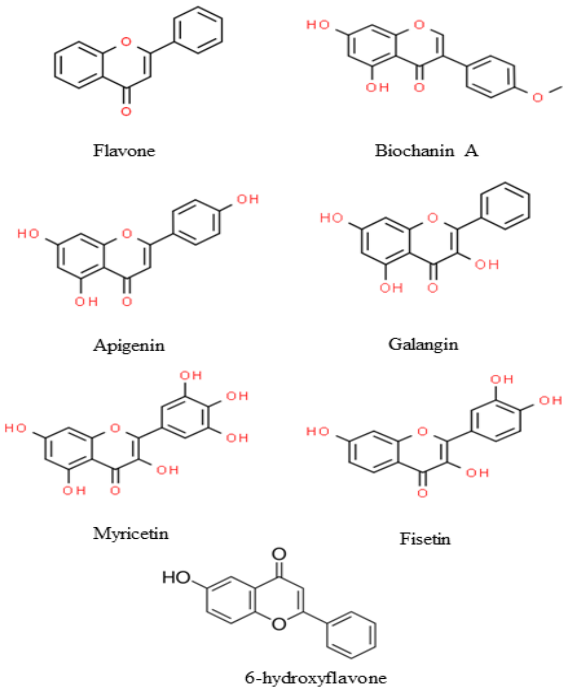

Figure 1: Structures of flavonoids.

Results and Discussion

A total of seven flavonoids were docked into DR4 protein. Table 1 shows the binding affinity of each flavonoid, ranging from -8.0 to -7.2 kcalmol^{-1}. Among them, flavone **(5)** exhibits the strongest binding affinity of -8.0 kcalmol^{-1}. There was not much difference in binding affinity values between DR4-flavonoids. Meanwhile, myricetin **(7)** shows three hydrogen bonds formed at the Gly245, Ser241 and Tyr243of DR4 residues (Table 2 and Figure 2). All flavonoids were seen to interact hydrophobically at two similar residues, namely Tyr243 and Try183 (Table 2). The 3D complex of flavone-DR4 displayed the conformation of its binding (Figure 3).

On the other hand, myricetin **(7)** was detected to have a good binding affinity of – 6.5 kcalmol^{-1} against DR5 as compared to flavone **(5)**, with the weakest binding affinity (– 5.7 kcalmol^{-1}). Among all flavonoids, myricetin **(7)** docked with DR5 consists of five hydrogen bonds, which connected at Pro97, Glu98, Asp67, Glu70 and Cys84 residues, resulting in the highest H-bonds formation (Table 2 and Figure 2). In addition, two different interactions, namely hydrophobic and electrostatic were also observed in the complex of DR5-6-hydroxyflavone, DR5-flavone, DR5-galangin and DR5-biochanin A, while the other complex of DR5-flavonoids has interacted only hydrophobically.

Docking results of FTase-flavonoids recorded that myricetin **(7)** again showed the lowest binding energy of -8.2kcalmol^{-1}(Table 1). It was then followed by fisetin **(4)** and flavone **(5)** with the same binding affinity (-8.1 kcalmol^{-1}). Fisetin **(4)** formed three hydrogen bonds and interacted by hydrophobic and electrostatic interactions with FTase residues. A total of seven hydrophobic interactions were detected in the flavone-FTase complex at Arg202, Cys206, Cys254, Gly250, His248, Trp102 and Tyr251 residues. An Arg202 was seen as the most targeted residue of all flavonoids except fisetin **(4)** in FTase protein (Table 2).

Epidermal growth factor receptor (EGFR) exhibited a prominent targeted protein of flavonoids compared to other studied proteins (Table 1). The binding affinities of flavonoids-EGFR were ranged between -9.1 to -8.4 kcalmol^{-1}. The strongest binding affinity was recorded in myricetin **(7)** with -9.1 kcalmol^{-1}. Meanwhile, Table 2 showed that each flavonoid forms electrostatic interaction with Lys745 residue. Mostly, all flavonoids interacted at the same residues of EGFR, such as Leu718, Leu844, Thr790 and Val726 forming hydrophobic interaction between flavonoids and protein.

According to the findings, the ability of flavonoids to exert anticancer activity from various cancer-related proteins have been demonstrated in this study. Although the results are preliminary for simulation work, they can be directed to the identification of the best-targeted protein for the further drug discovery process. Numerous studies have also been reported the capability of flavonoids towards anticancer properties.[2]Among the affected mechanisms in cancer include modulating ROS-scavenging enzyme activities, participating in arresting the cell cycle, inducing apoptosis, autophagy, and suppressing cancer cell proliferation and invasiveness.[26-31]

Table 1: Binding affinities of flavonoids into DR4, DR5, FTase and EFGR

Ligand	Binding Affinities (kcal/mol)			
	DR4	DR5	FTase	EFGR
6-hydroxyflavone**(1)**	-7.9	-5.9	-7.9	-8.4
Apigenin**(2)**	-7.3	-6.2	-7.6	-8.4
Biochanin A**(3)**	-7.1	-6.0	-7.9	-8.6
Fisetin**(4)**	-7.2	-6.2	-8.1	-8.8
Flavone**(5)**	-8.0	-5.7	-8.1	-8.5
Galangin**(6)**	-7.6	-6.2	-7.9	-8.4
Myricetin**(7)**	-7.4	-6.5	-8.2	-9.1

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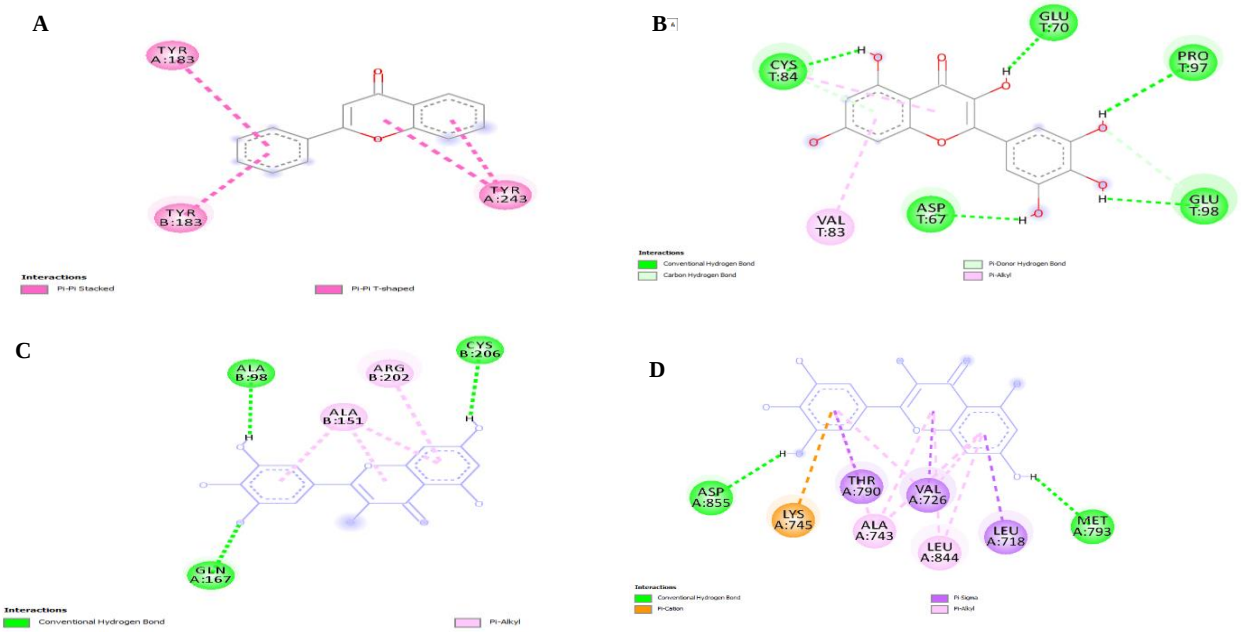

Figure 2: Two-dimensionalmolecular docking interactions of the strongest binding affinities of flavonoids into DR4, DR5, FTase and EGFR. a) flavone-DR4 complex, b) myricetin-DR5 complex, c) myricetin-FTase complex, d) myricetin-EGFR complex. Each interaction is depicted in different dashed lines for ligands and protein residues.

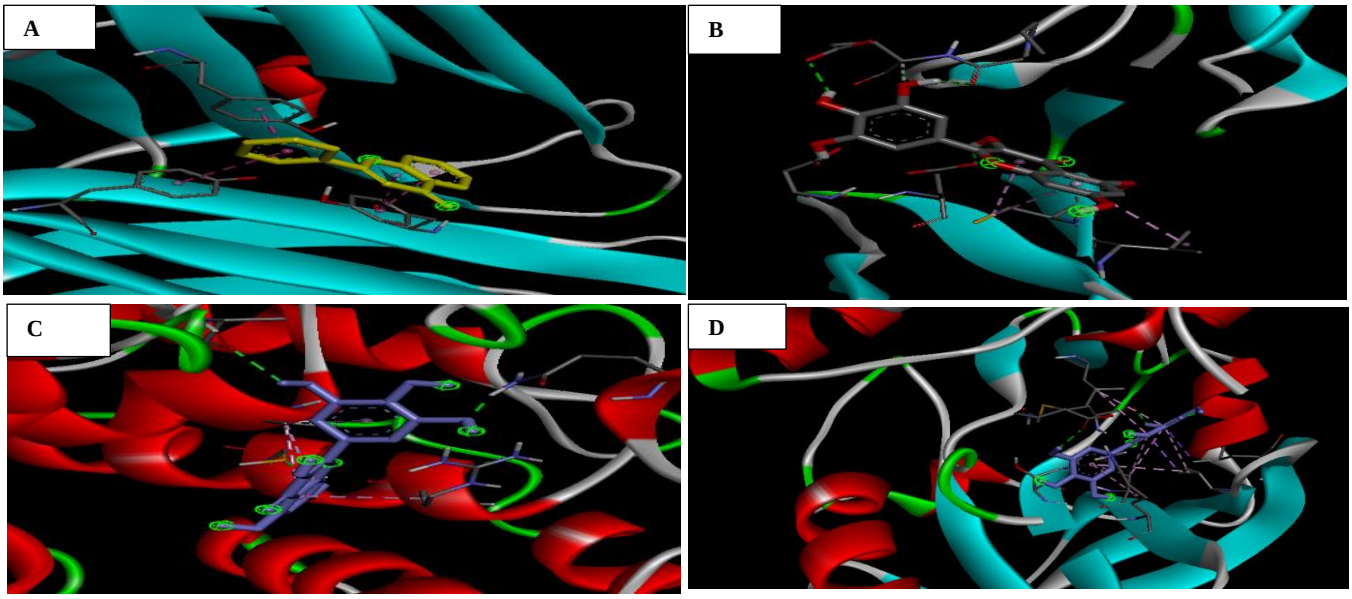

Figure 3: Three-dimensionalmolecular docking interactions of the strongest binding affinities of flavonoids into DR4, DR5, FTase and EGFR. a) flavone-DR4 complex, b) myricetin-DR5 complex, c) myricetin-FTase complex, d) myricetin-EGFR complex. Each interaction is depicted in different dashed lines for ligands and protein residues.

The flavonoids structure, which comprise 15 carbons and is linked to two benzene rings, contribute to their excellent pharmacological properties. As shown in Table 1, each flavonoid has the capability in interfering with the growth and proliferation signalling cascades in cancer cells, involving DR4, DR5, EFGR and FTase proteins. EGFR protein revealed the best-targeted protein with the strongest binding affinities of all flavonoids (Table 1).

Of all flavonoids, myricetin **(7)** exhibited the highest binding affinity at three proteins, including EGFR, FTase and DR5. These proteins play critical roles in the survival, proliferation and apoptosis of the cells. Myricetin **(7)** is a polyhydroxyflavonol compound reported in multiple studies to possess strong anticancer effects against several cancers through various mechanisms.[32] The present findings from the study of myricetin **(7)** in several targeted proteins could anticipate the affected mechanism in cancer cells experimentally. A previously reported study found that the hydroxyl group of the myricetin formed hydrogen bond at the side chain of EGFR residues (Asp800, Cys797, Met793 and Gln791).[32] Meanwhile, Lys745 residue of EGFR interacted at the carbonyl group of myricetin **(7)** was also shown in the present study (Table 2 and Figure 2).

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Table 2: Binding interactions profile of complex of flavonoids with DR4, DR5, FTase and EFGR .1

Ligand	DR4			DR5			FTase			EFGR		
	Hydrogen bonding	**Hydrophobic interaction**	**Electrostatic interaction**	**Hydrogen bonding**	**Hydrophobic interaction**	**Electrostatic interaction**	**Hydrogen bonding**	**Hydrophobic interaction**	**Electrostatic interaction**	**Hydrogen bonding**	**Hydrophobic interaction**	**Electrostatic interaction**
6hydroxy flavone	-	A:TYR243 B:TYR183 A:TYR183	-	T:GLN48 T:CYS60	T:PHE59	T:ARG62 T:ASP49	B:HIS248	B:ARG202 B:CYS206 B:CYS254 B:GLY250 B:TRP102 B:TYR251	-	A:MET793 A:GLY796	A:VAL726 A:THR790 A:LEU844 A:ALA743 A:LEU718	A:LYS745
Apigenin	B:SER241 A:TYR243	B:TYR243	-	T:ARG92 T:GLU98 T:CYS84	T:CYS84	-	B:CYS206 B:ARG202 B:HIS248	B:TRP303 B:TYR251 B:CYS254	-	A:MET793	A:LEU718 A:THR790 A:VAL726 A:ALA743 A:LEU844	A:LYS745
Biochanin A	-	A:TYR243 B:TYR183	-	T:HIS33 T:GLN48 T:ARG62	T:CYS60 T:LYS45	T:ASP49	B:ARG202	B:TYR154 B:TRP303	-	A:LEU788	A:VAL726 A:THR790 A:ALA743 A:LEU718 A:LEU844	A:LYS745
Fisetin	B:GLN244	A:TYR243 B:TYR183 A:TYR183	-	T:TRP120 T:CYS84	T:ARG92 T:VAL83	-	B:HIS248 B:LYS294 B:ASP297	B:TYR300	B:ARG291	A:LYS745 A:ALA743	A:LEU718 A:LEU844 A:THR790 A:VAL726	A:LYS745
Flavone	-	A:TYR243 B:TYR183 A:TYR183	-	T:HIS33 T:GLN48 T:CYS60	T:LYS45	T:ASP49	-	B:ARG202 B:CYS206 B:CYS254 B:GLY250 B:HIS248 B:TRP102 B:TYR251	-	-	A:ALA743 A:LEU718 A:LEU844 A:THR790 A:VAL726	A:LYS745
Galangin	-	A:TYR243 B:TYR183 A:TYR183	-	T:GLN48 T:CYS44	T:ARG62 T:ASP49	T:PHE59 T:CYS60	A:GLN167 B:TRP102 B:ALA98	B:ALA151 B:ARG202 B:HIS149	-	A:ASP855 A:MET793	A:ALA743 A:LEU718 A:LEU844 A:THR790 A:VAL726	A:LYS745
Myricetin	B:GLY245 B:SER241 A:TYR243	B:TYR243	-	T:PRO97 T:GLU98 T:ASP67 T:GLU70 T:CYS84	T:VAL83	-	A:GLN167 B:ALA98 B:CYS206	B:ARG202 B:ALA151	-	A:ASP855 A:MET793	A:ALA743 A:LEU718 A:LEU844 A:THR790 A:VAL726	A:LYS745

Similarly, other flavonoids interacted at the same residue (Lys745) through electrostatic interaction.

The docking results of myricetin **(7)** into EGFR could lead to phosphorylation of key tyrosine residues within the carboxy-terminal portion of EGFR.[33]This specific binding site initiates an intracellular signalling pathway which also leads to apoptosis.[34-39] On the other hand, FTase is found to be myricetin **(7)** targeted protein as compared to other flavonoids with the highest binding affinity (-8.2 $kcalmol^{-1}$). FTase, a heterodimer of two subunits α and β, is an enzyme that contains its active center divalent zinc (Zn^{2+}) to bind to the CAAX fragment.[40]As reported by Ashok *et al*. (2020), the FTase ligand is based on the CAAX site, containing methionine or serine residues located in the β-subunit of FTase.[41] Meanwhile, the α-subunit restores the enzyme activity, after farnesyl transfer is phosphorylated.[42]

Flavone **(5)**, a basic structure of flavones, exhibited the strongest binding affinity of DR4 protein (Table 1). As compared to other flavonoids, flavone **(5)** with no functional group in the phenyl ring B could be the reason for its action. It was then followed by 6-hydroxyflavone **(1)** and galangin **(6)** with the same characteristic in ring B. In contrast, the presence of the methoxy group in the phenyl ring B of biochanin A **(3)** resulted in its binding affinity in DR4 protein to increase the value (Table 1). Interestingly, the virtual action of all flavonoids reversed their action in DR5 protein compared to DR4 protein. Binding affinity was increased for flavone **(5)** and other flavonoids with no functional group attached at ring B. The other structure of flavonoids had also shown that phenyl ring A contributes to the good binding affinity with the presence of hydroxyl group at position C-7.

Both DR4 and DR5 proteins initiate an extrinsic apoptotic pathway in cells.[43]Flavonoids could activate the extrinsic pathway,which mimics the action of agonists of DR4 and DR5 to induce apoptosis of cancer cells.[44] Current findings can exploit the mechanism of action knowledge to understand flavonoids interactions with several cancer-targeted proteins. Also, the docking results predicted that binding of flavonoids-target complexes might further be elucidated for their complex stability as well as in the experimental approach. The findings reported the binding affinities and the complex interactions of selected flavonoids with cancer-related proteins that can be used to develop promising new anticancer drugs with a low molecular weight, which allows them to absorb in the outer membrane of cancer cells.[45]

Conclusion

Molecular docking provides a comprehensive understanding of the binding of lead molecules with target proteins. The results predicted a good binding affinity of all flavonoids into cancer-related protein. Among them, EGFR is the most favourable protein to be targeted by all tested flavonoids which could later inhibit the proliferation and survival of cancer cells. Different classes of flavonoids in this study exhibit almost comparable interaction, suggesting any of them could be the lead molecule of developing new drugs. However, this preliminary study needed further validation on the complex stability based on the strongest binding affinity, especially from EGFR as part of the extensive simulation findings prior to the next experimental stage *in vitro* and *in vivo* studies.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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