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Molecular docking analysis of known flavonoids as duel COX-2 inhibitors in the context of cancer

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Abstract:
Cyclooxygenase-2 (COX-2) catalyzed synthesis of prostaglandin E2 and it associates with tumor growth, infiltration, and metastasis in preclinical experiments. Known inhibitors against COX-2 exhibit toxicity. Therefore, it is of interest to screen natural compounds like flavanoids against COX-2. Molecular docking using 12 known flavanoids against COX-2 by FlexX and of ArgusLab were performed. All compounds showed a favourable binding energy of >-10 KJ/mol in FlexX and > -8 kcal/mol in ArgusLab. However, this data requires *in vitro* and *in vivo* verification for further consideration.

Keywords: COX-2, FlexX, ArgusLab, Flavonoids, Cancer.

Background:
More than a century ago, chronic inflammation leads to cancer development by increasing cellular proliferation **[1],** suggested by Virchow et al **[2].** The current innovation of the inducible cyclooxygenase-2 (COX-2) gene has relight attention in the fundamental link between inflammation and cancer, and various models of carcinogenesis have been proposed involving inflammatory stimuli and COX-2 expression **[3].** Cancer development in the presence of chronic inflammation involves the activation of cyclooxygenase-2 (COX-2) and other several transcription factors including NFB alpha, STAT3, activator protein-1, and hypoxia inducible factor 1 alpha **[4-9].** The gene cyclooxygenase encodes two isoenzymes namely COX-1 and its inducible isoform (COX-2). The isoenzyme COX-2 is primarily associated with inflammation **[10, 11].** Under the normal conditions, COX-2 expression is low or not detected in most tissues. Conversely, its overexpression together with activation of cytosolic PLA2 by phosphorylation is a feature of inflammatory reactions. Overexpression of COX-2 occurs in breast, lung, colon, and prostate cancers **[4-6]**. However, recent studies representing the place of COX-2 inhibitors in the prevention of several cancer types such as colon, breast, lung and prostate cancers **[12-16].** In this context, non-steroidal anti-inflammatory drugs (NSAIDs) are widely utilized for the treatment of various inflammatory conditions such as rheumatic fever, rheumatoid arthritis and osteoarthritis. However, because of NSAIDs inhibit both isoforms of cyclooxygenase (COX), their use is often accompanied by gastrointestinal side effects and renal function suppression **[17, 18].** Though celecoxib and rofecoxib are two well-known selective COX-2 inhibitors belong to COXIB's class **[19, 20].** However, the market withdrawal of some COXIBs such as rofecoxib due to increase the risk of heart attack and cardiovascular side effects **[21, 22]**, encourages the researchers to explore new selective COX-2 inhibitors to evaluate their effects and improve the safety profiles.

In current years, several of these reviews touched the general overview for the bioactive aspect for phytochemical compounds **[23-31].** It is also well documented that phyto-compounds have activity against cancer **[32-34]** and COX-2 **[35-38].** Therefore, in our present studies, we focused on the efficacy of natural compounds that may modulate the multistep regulation of COX-2 gene expression, we also discussed their potential as a new generation of selective COX-2 targeting agents alternative to the synthetic COX-2 inhibitors, performed by their binding pattern analysis, which is done by molecular docking analysis **[39]**.

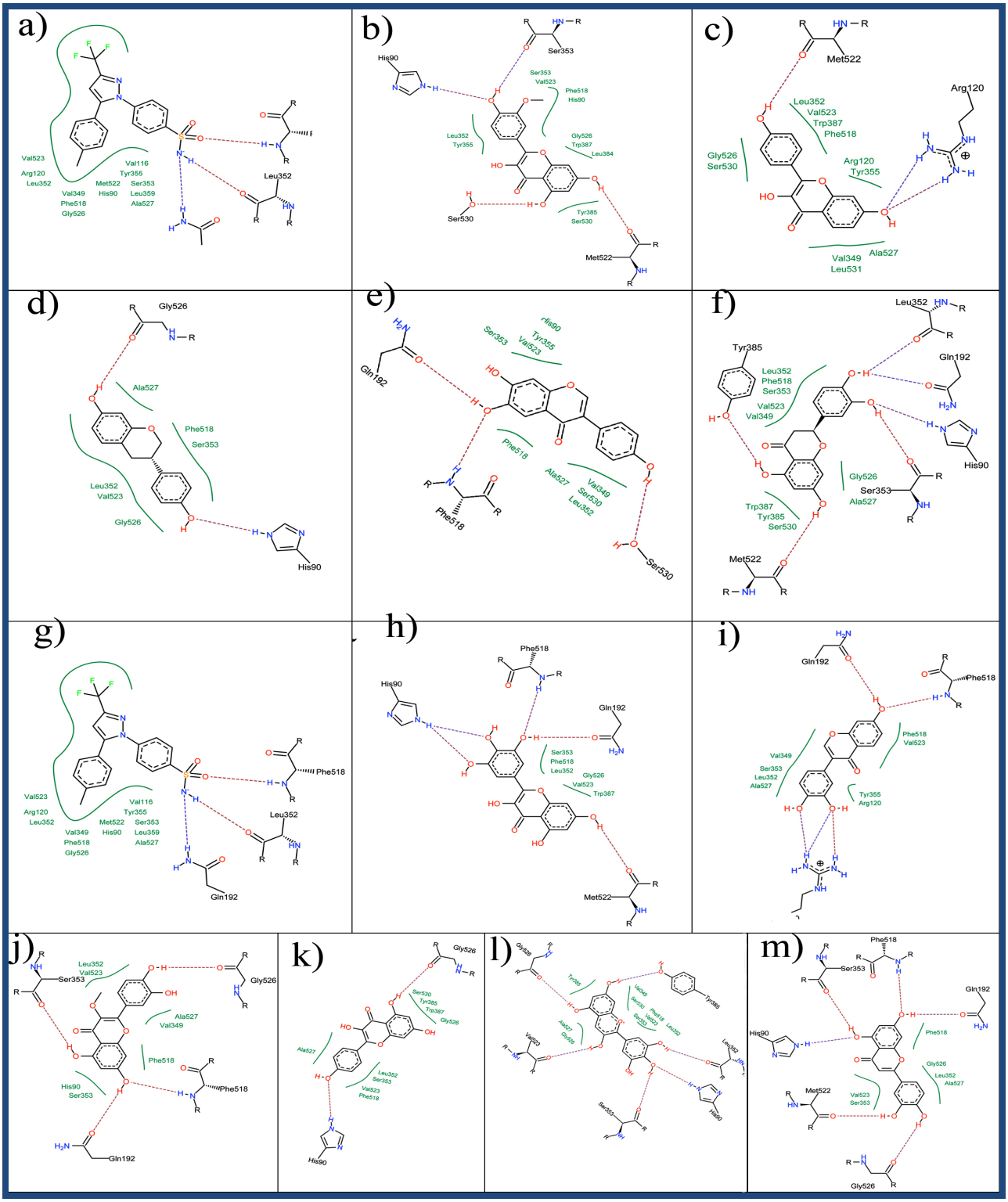

Figure 1: Interaction of COX-2 with **a)** celecoxib; **b)** isorhamnetin; **c)** 5-deoxykaempferol; **d)** equol; **e)** 4', 6, 7-trihydroxyisoflavone; **f)** eriodictyol; **g)** quercetin; **h)** myricetin; **i)** 7, 3, 4'-trihydroxyisoflavone; **j)** quercetin-3-methyl ether; **k)** kaempferol; **l)** delphinidin and **m)** luteolin by FlexX molecular simulation.

Methodology:

Data and Databases

The data from databases used in this study include PDB (Protein Data Bank) **[40]** and PubChem **[41].** PubChem is a public repository of small molecules and their biological properties. Currently, it contains more than 25 million unique chemical structures and 90 million bioactivity outcomes associated with several thousand macromolecular targets **[42].**

Docking Tools

The docking tools used in this study include FlexX (LeadIT 2.1.6) and ArgusLab 4.0.1. FlexX is a fully automated docking program available on LeadIT 2.1.6 package was used to dock compound into the active site of the enzymes. FlexX considers ligand flexibility by changing the conformations of the ligand in the active site, while making the protein rigid **[43]**. ArgusLab offers quite good on-screen molecule-building facilities, with a moderate library of useful molecules.

Ligand Selection and Preparation

For our present studies, we had selected twelve flavonoids having anticancer activity in various models and also a selective COX-2 blocker celecoxib. 3D conformer of all this compounds were downloaded from PubChem data bases in sdf format and converted in to mol2 format by open babel **[44]** software. Details of all compounds used in these studies are represented in the **Table 1 (see supplementary material).**

Protein preparation

The crystal structure of COX-2 (pdb id : 6 COX) enzyme was collected from protein data bank **[40]**. The active site of the enzyme was identified according to the giving information Kurumbail *et al*., 1996 **[45]** protein was prepared by using receptor preparing wizard available in LeadIT 2.1.6 package for FlexX Docking. Docking protocol was maintained in protein preparation for docking in ArgusLab.

Docking with FlexX

FlexX (which is now a part of LeadIT) is a flexible docking method that uses an Incremental Construction (IC) algorithm and a pure empirical scoring function similar to the one developed by Böhm and coworkers to place ligands into the active site **[46].** IC algorithms first dissect each molecule into a set of rigid fragments according to rotatable bonds, and then incrementally assemble the fragments around the binding pocket **[43].** For docking studies, a receptor description file was prepared through the FlexX graphic interface. An active site was defined by selecting the residues of the protein. The active site includes protein residues around 10 Å radius sFre centered on the center of mass of the ligand. Based on energy Values, top ten ranked poses for each ligand in data set were selected for further analysis.

Docking Study with ArgusLab

ArgusLab 4.0.1. is implemented with shape-based search algorithm. Docking has been done using "Lamarckian Genetic Algorithm Docking Engine" exhaustive search docking function of ArgusLab with grid dimension of 65 x 51 x 66. Docking precision was set to "Regular precision" and "Flexible" ligand docking mode was employed for each docking run. The stability of each docked pose was evaluated using ArgusLab energy calculations and the number of hydrogen bonds formed. For each complex, the population size is 50. The number of genes is 10 where, maximum generations are 1000 and the converged when rmsd population fitness < 1 kcal/mol. The best docking model was selected according to the lowest energy calculated by ArgusLab, and the most suitable binding conformation was selected on the basis of hydrogen bond interactions between the ligand and protein near the substrate binding site. The lowest energy poses indicate the highest binding affinity as high energy produces the unstable conformations.

Results & Discussion:

As discussed earlier, COX-2 may play a role in different steps of cancer progression by increasing the proliferation of mutated cells, and thus favoring tumor promotion in addition to by affecting apoptosis, which ultimately affects the efficacy of anticancer therapies **[47-50]**. Natural compounds are proved their potentiality to inhibit the key cell signaling pathways including COX-2, which is gained much attention over the last regarding years, when they are being used alone or perhaps combination with existing chemotherapeutic agents **[51].** Regarding that, we tried to establish the efficacy of some natural flavonoid compounds with known anticancer activity, by analyzing their binding pattern on COX-2 enzyme with two docking routines.

Results from the computations, performed in the present work are described in **Table 2 & Table 3 (see supplementary material),** and their modes of binding patterns are also described below. Here, in this study, we found significant binding affinity of all flavonoids towards the COX-2 enzyme i.e. FlexX (greater than -10 KJ/mol) and ArgusLab (greater than -8 Kcal/mol). The details of protein-ligand bindings, which were generated from ArgusLab are described in **Table 3 (supplementary material)**. The structural basis of COX-2 inhibition was illustrated by Kurumbail *et al.* **[45],** amino acid residues such as H^{90}, R^{120}, Q^{192}, V^{349}, L^{352}, S^{353}, Y^{355}, L^{359}, Y^{385}, W^{387}, R^{513}, A^{516}, F^{518}, V^{523}, G^{526}, A^{527}, L^{531} associated with A chain of COX-2 protein were involved for protein–ligand complementary activity **[52]**. There are several structural features that are considered to be important for efficient COX inhibition: (i) a carboxylate moiety that interacts with the R^{120} side chain; (ii) a carbonyl moiety that interacts via a hydrogen bond with the side chain of S^{530} and (iii) a distal aromatic ring filling a hydrophobic pocket beneath the Y^{385} side chain **[53].** One of the keys to developing COX-2 selective drugs is the larger active site of COX-2 is partly due to a polar hydrophilic side-pocket that forms because of substitution of I^{523}, H^{513} and I^{434} in COX-1 by V^{523}, R^{513} and V^{434} in COX-2. V^{523} is less bulky than I^{523}, which increases the volume of the active site **[54, 55].**

The important consequence of the amino acid changes in COX-2 is to increase the size of the NSAID-binding pocket, allowing this isoenzyme to bind bulky inhibitors more readily than COX-1 **[56]**. As seen in **Figure 1** and **Table 3 (supplementary material)**, all compounds including flavonoids and celecoxib, were formed favorable bindings with COX-2 enzyme. The post docking analysis showed that the compounds taking account of celecoxib, 4', 6, 7-trihydroxyisoflavone, quercetin, quercetin-3-methyl ether, kaempferol, and luteolin formed hydrogen bonds with S^{530} residue. While the other flavonoids including, eridicytol and myricetin formed hydrogen bonding with R^{120}. Moreover, hydrogen bonding between Y^{385} residue of COX-2 and 5-deoxykaemferol was also observed in **Figure 1c.**

Furthermore, all compounds were found to having hydrophobic interactions with V^{523} and mostly with pi-alkyl and pi-sigma bonding, except delphinidin **(Table 2 in in supplementary material).** However, delphinidin formed pi-cation interaction with R^{120} residue and hydrogen bonding with V^{523} **(Figure 1).** Generally, it is often necessary to determine, as a first step of computational drug design and discovery, the binding of a ligand to a targeted protein. The computational arrangement for predicting ligand binding occurrence, affinity, and orientation is usually denoted to as "molecular docking", which has been a matter of rigorous research for periods **[57].**

The progress of a molecular docking tool typically starts with an efficient search algorithm, which places the ligand in the active site of the targeted protein in various different positions, orientations, and in flexible docking, conformations **[58, 59].** However, in our study, we tried to find out the positions and orientations of flavonoids and in the active site of COX-2 enzymes. Moreover many of flavonoids compound have already proved their ability to reduce the COX-2 expressions in various cancer models **(Table 1 in supplementary material).** As discussed in **Table 1 (supplementary material),** isorhamnetin, 5-deoxykaempferol are widely present in fruit and vegetable, has the ability to suppress the UVB-induced expression of cyclooxygenase-2 (COX-2) in skin cancer **[60, 61]**. Another important flavonoid, quercetin belongs to the flavonoids family and consists of 3 rings and 5 hydroxyl groups found in many fruits, vegetables, leaves and grains. Early studies in various literatures suggested it has the aptitude in reducing COX-2 expression in cancer **[62-66]** or noncancerous cell **[67, 68].** Myricetin is a widely distributed flavonol that is found in many plants, including tea, berries, fruits, vegetables, and medicinal herbs attenuated the COX-2 expression UVB-induced skin cancer **[69-71].**

In previously published report, it was shown that 7, 3', 4'-trihydroxyisoflavone (7, 3', 4'-THIF) suppressed UVB-induced COX-2 expression in skin cancer **[72].** It was also well known that, kaemferol inhibits COX-2 expression in inflammatory condition in both normal and cancer cells **[73-75].** Furthemore delphinidin is an anthocyanidin, a primary plant pigment, already probed its ability to reduce COX-2 expression particularly in skin cancer **[76,77].** Luteolin is a common flavonoid that exists in many types of plants including fruits, vegetables, and medicinal herbs **[78].** Recent studies recommended that luteolin supress the COX-2 expression in cancer **[79, 80]** also in non-cancerous cell **[81].** Henceforth, with concerning to the low toxicity of the flavonoids toward normal cells **[82, 83]** Our studies are in favor of a potential use of flavonoids in adjuvant chemotherapy and COX-2 inhibition in many cancer.

Conclusion:

Flavonoid modulation of COX-2 transcription may therefore be an important mechanism in anti-carcinogenesis. In the present study, docking results revealed the binding interactions between the COX-2 protein and the 12 natural flavonoids compound along with a synthetic compound where, in different docking routines, all showed a favorable binding energy greater than 10 kj/mol (FlexX) and in ArgusLab, binding energy is greater than -8 kcal/mol. However, polyphenols are a broad class of compounds with antioxidant and other health benefits. The efficacy of phytochemicals on human health is influenced by on several factors. The molecular structures of phytochemicals influence the extent to which they are altered by cooking processes and the methods by which they are fascinated by the gastrointestinal tract. Numerous actions are shared among different flavone ring-bearing molecules and their action in the complex biochemical machinery of the cell requests to be further clarified.

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Supplementary material:

Table 1: Flavonoids and selective COX-2 blocker having anticancer activities.

Flavonoids	Pubchem id	Organ or tissue type	References
Delphinidin	CID 128853	Skin cancer	**[84, 85]**
Quercetin	CID 5280343	Skin cancer	**[86, 87]**
Myricetin	CID 5281672	Skin cancer	**[88-92]**
Equol	CID 91469	Skin cancer, Prostate cancer, Breast Cancer	**[93, 94]**
Isorhamnetin	CID 5281654	**Article I.** Skin cancer, Colon cancer, Colorectal cancer	**[95-97]**
Quercetin-3-methyl ether	CID 5280681	**Article II.** Skin cancer, Breast cancer, Leukaemia	**[98-100]**
Kaempferol	CID 5280863	Skin cancer, Colon cancer	**[101-103]**
Eriodictyol	CID 440735	Skin cancer, Breast Cancer	**[104, 105]**
Luteolin	CID 5280445	Skin cancer, Lung cancer, Prostate cancer, Colon cancer.	**[106-110]**
5-deoxykaempferol	CID 5281611	Skin cancer	**[111]**
7,3',4'-Trihydroxyisoflavone	CID 5284648	Skin cancer	**[72]**
4',6,7-trihydroxyisoflavone	CID 5284649	Colon cancer	**[112]**
Celocoxib	CID 2662	Cyclooxygenase-2 inhibitor in cancer	**[113, 114]**

Table 2: Summary of FlexX docking results with COX-2 and ligands.

Flavonoids	Score	Match	Lipo	Ambig	Clash	Rot	□G Kj/mol	Ligand Efficiency
Celocoxib	-26.85	-21.15	-14.73	-7.33	6.77	4.2	-29	0.27
Isorhamnetin	-20.93	-22.32	-11.21	-8.56	8.76	7.0	-30	0.31
5-deoxykaempferol	-19.26	-15.65	-11.83	-5.77	4.40	4.2	-29	0.35
Equol	-21.94	-17.43	-12.88	-5.71	4.48	4.2	-27	0.36
4',6,7-trihydroxyisoflavone	-20.61	-17.03	-10.03	-6.17	3.89	4.2	-26	0.31
Eriodictyol	-24.63	-24.97	-11.21	-7.43	6.58	7.0	-23	0.26
Quercetin	-21.66	-24.06	-11.19	-6.85	8.05	7.0	-20	0.21
Myricetin	-21.59	-23.18	-12.27	-7.26	7.38	8.4	-19	0.20
7,3',4'-Trihydroxyisoflavone	-26.25	-23.85	-11.82	-6.92	6.75	4.2	-18	0.22
Quercetin-3-methyl ether	-24.88	-25.55	-10.48	-7.76	6.51	7.0	-16	0.16
Kaempferol	-20.92	-17.93	-13.00	-7.33	6.35	5.6	-15	0.17
Delphinidin	-18.41	-23.92	-11.55	-7.36	10.36	8.4	-15	0.16
Luteolin	-27.67	-26.93	-10.23	-7.25	5.75	5.6	-13	0.14

Table 3: Type of interactions and interacting amino acid residues of COX-2 protein with selected ligands, generated from ArgusLab.

Flavonoids	Binding Energy kcal/mol	H-Bonding	Hydrophobic Bonding			Pi-Cation
			Pi - Alkyl	Pi-Pi	Pi-Sigma	
Celecoxib	-9.35	Q^{192}, R^{120}, L^{531},S^{530}	V^{523},A^{527},L^{352}, F^{198}	-	V^{349}, Y^{348}	-
Isorhamnetin	-8.25	-	V^{349}, L^{352}, V^{523}.	-	S^{353},A^{527}, V^{523}	-
5-deoxykaempferol	-9.14	-	V^{523}, I^{517}, A^{516}	Y^{355}	V^{349}	-
Equol	-9.92	Q^{192}, F^{518}	V^{523}, V^{349}, L^{352},L^{531},A^{527}	-	-	-
4',6,7-trihydroxyisoflavone	-9.89	S^{530}	V^{523}, A^{527}, L^{352}, L^{531}	-	V^{349}	-
Eriodictyol	-9.50	F^{518}, R^{120}	-	-	A^{527}, V^{349}, V^{523}	-
Quercetin	-8.94	R^{513}, R^{120}, Q^{192}	V^{523}, V^{349}, L^{352}	-	V^{523}, A^{527}	-
Myricetin	-8.91	R^{120}	V^{349}, V^{523}	-	A^{527}, V^{523}	-
7,3',4'-Trihydroxyisoflavone	-9.86	-	A^{527}, V^{523}, L^{531}, L^{352}	-	S^{353}, V^{349}	-
Quercetin-3-methyl ether	-8.26	$H^{90,}$ S^{530}	A^{527}, V^{349}, L^{352}	-	V^{349}, V^{523}	-
Kaempferol	-10.64	W^{385}, S^{530}	V^{349}, L^{352}	-	L^{352}, V^{523}, A^{516}	
Delphinidin	-8.94	E^{524}	V^{89}, V^{116}, I^{112}	Y^{355}	L^{93}	R^{120}
Luteolin	-10.72	S^{530}	A^{516}, L^{352}, V^{349}	-	V^{523}	-