Medis: Jurnal Inovasi Kesehatan dan Medika Nusantara
Volume: 1, Nomor: 2, (2026), Juni: 208 - 223
Website: https://ejournal.ojs-lppm.com/index.php/Medis/article/view/317
E-ISSN: 3124-8918

Molecular Docking and Drug-Likeness Prediction of Flavonoid Compounds as COX-2 Inhibitors: An In Silico Study with Celecoxib Re-Docking Validation

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Info Artikel
Received: *02 Juni 2026*
Revised : *10 Juni 2026*
Accepted: *19 Juni 2026*
Published: *28 Juni 2026*

Keywords: *molecular docking, drug-likeness, flavonoid, COX-2 inhibitor, in silico.*

Abstract
Long-term use of NSAIDs is associated with gastrointestinal and cardiovascular adverse effects. That persistent problem has pushed a lot of research toward natural molecules that reduce inflammation with fewer adverse effects. Flavonoids have garnered significant attention because many are active and safe, however, the precise mechanism by which flavonoids interact with cyclooxygenase-2 (COX-2) has not yet been fully elucidated through molecular docking. We selected six of them, quercetin, kaempferol, apigenin, myricetin, luteolin, and genistein, and docked each into the COX-2 crystal structure (PDB ID: 3LN1) using UCSF DOCK6. Celecoxib was the reference. The co-crystallized ligand was re-docked first; the RMSD came out at 0.774 Å. That sits comfortably below the 2.40 Å acceptance limit, so the protocol was reliable for the rest of the work. Quercetin bound tightest: its Grid Score reached –36.36 kcal/mol, roughly 63.4% of the celecoxib score. Kaempferol (–36.25 kcal/mol) and apigenin (–34.69 kcal/mol) were close behind. Inside the active site, quercetin formed five hydrogen bonds, and additional Pi-alkyl plus van der Waals contacts kept it firmly in place. When we checked drug-likeness, all six flavonoids met Lipinski's rule of five except myricetin; its topological polar surface area hit 147.68 Å², causing a single violation. Blood-brain barrier penetration was estimated from PSA values. Quercetin, kaempferol, myricetin, and luteolin all have PSA above 90 Å², so meaningful brain entry is unlikely, precisely what we would consider ideal for a peripheral anti-inflammatory agent. Apigenin and genistein (PSA 86.99 Å²) sit right at the threshold. Quercetin and kaempferol stand out as the strongest leads for peripheral anti-inflammatory therapy, and the next logical steps are in vitro COX-2 inhibition assays followed by preclinical testing.

Kata Kunci*:* penambatan molekul, keserupaan obat, flavonoid, inhibitor COX-2, in silico.

Abstrak
Penggunaan NSAID dalam jangka panjang dikaitkan dengan efek samping gastrointestinal dan kardiovaskular. Masalah yang terus berlanjut ini telah mendorong banyak penelitian terhadap molekul-molekul alami yang mungkin dapat meredakan peradangan tanpa efek samping merugikan yang menyertainya. Flavonoid adalah

salah satu kandidat yang paling sering disebut; aktivitas antiinflamasinya sudah tercatat, dan toksisitasnya rendah. Namun, data tentang bagaimana flavonoid berinteraksi langsung dengan siklooksigenase-2 (COX-2) pada level molekuler masih belum banyak tersedia, terutama hasil penambatan yang membandingkan beberapa flavonoid sekaligus. Dalam simulasi ini, enam flavonoid (quercetin, kaempferol, apigenin, myricetin, luteolin, genistein) ditambatkan ke struktur kristal COX-2 (PDB ID: 3LN1) memakai UCSF DOCK6, dengan celecoxib sebagai pembanding. Protokol diuji dulu dengan menambatkan ulang ligan ko-kristal; Nilai RMSD yang diperoleh adalah 0,774 Å, yang masih berada di bawah ambang batas nilai yang ditetapkan sebesar 2,40 Å. Dengan demikian, protokol penambatan molekuler ini dinyatakan valid dan layak diterapkan. Quercetin keluar sebagai pengikat terkuat, skor Grid –36,36 kkal/mol, sekitar 63,4% dari nilai celecoxib. Kaempferol (–36,25) dan apigenin (–34,69) mengikuti. Di sisi aktif, quercetin dijangkarkan oleh lima ikatan hidrogen, ditambah interaksi Pi-alkil dan van der Waals. Semua flavonoid lolos aturan Lipinski, kecuali myricetin yang melanggar satu parameter karena luas permukaan polar topologisnya tinggi (147,68 Å²). Prediksi penetrasi sawar darah-otak berdasarkan PSA menempatkan quercetin, kaempferol, myricetin, dan luteolin (PSA > 90 Å²) sebagai senyawa yang sulit mencapai otak, keuntungan untuk obat yang kerjanya di perifer. Apigenin dan genistein (86,99 Å²) berada di batas. Melihat seluruh data, quercetin dan kaempferol menonjol sebagai kandidat terkuat untuk terapi anti-inflamasi perifer, dan langkah logis berikutnya adalah uji penghambatan COX-2 secara in vitro, yang kemudian dilanjutkan dengan pengujian praklinis.

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INTRODUCTION

Osteoarthritis, rheumatoid arthritis, and several cancers collectively affect millions of adults worldwide with chronic pain and disability, and persistent low-grade inflammation is increasingly recognized as a shared pathogenic mechanism underlying all three conditions [1]. In rheumatoid arthritis, joint damage occurs in addition to inflammation, which causes many chronic health problems, including lymphoma and osteoporosis [1]. Chronic inflammation has started to be recognized as a mechanism for cancer. COX-2, which is an enzyme that causes the inflammatory and painful prostaglandins, is an important player in this mechanism [1], [2].

For rheumatoid arthritis and pain associated with osteoarthritis, Non-selective NSAIDs have been the mainstay of therapy. COX-2 and COX-1 are both inhibited [3]. COX-1 is the constitutive enzyme that protects the gastrointestinal lining. Multiple NSAIDs have caused gastrointestinal bleeding due to ulcers [3]. To mitigate gastrointestinal problems of COX-1, COX-2 inhibitors, or

coxibs, were developed [2], [4]; however, they also cause cardiovascular problems, leading to the withdrawal of Rofecoxib in 2004 and the requirement of cardiovascular safety studies for celecoxib [5]. This contrast with COX-1 and COX-2 remains and highlights the need for new anti-inflammatories with different mechanisms [3], [5]. One class that shows promise is flavonoids. Several studies found that traditional NSAIDs tend to inhibit both COX-1 and COX-2 non-selectively, rather than selectively targeting COX-2 [3]. Acute toxicity data indicate that the oral LD50 of these flavonoids is more than 2000 mg/kg, the threshold used by the OECD to classify a product as low risk [6]. When administered in single doses up to dietary levels, repeated dose studies showed no significant adverse effects [6]. By suppressing COX-2-mediated prostaglandin synthesis, downregulating the 5-lipoxygenase (5-LOX) pathway, and preventing the production of pro-inflammatory cytokines, flavonoids reduce inflammation through complementary molecular targets without the full enzymatic blockade associated with traditional NSAIDs [2].

Although this can happen, some in silico studies of the interaction of flavonoids with COX-2 employed low-resolution COX-2 crystal structures and did not mention a re-docking validation step [7], [8]. In many cases, these studies restricted themselves to the evaluation of binding affinity while avoiding the assessment of the drug-likeness and toxicological profiles, which restricted the biological plausibility of their assumptions [7], [8]. To fill these gaps, a high-resolution COX-2 crystal structure (PDB ID: 3LN1, 2.40 Å) was used [9], celecoxib was used as a control and the docking procedure was confirmed with a re-docking (RMSD, 2.4 Å) approach. The grid based DOCK6 algorithm was used to perform a validation step on the in silico docking of COX-2 and the concurrent prediction of the toxicological and drug-likeness profiles of six flavonoids. This study aimed to identify flavonoid candidates with favorable COX-2 binding affinity, acceptable drug-likeness, and low predicted toxicity through a rigorously validated molecular docking protocol employing celecoxib re-docking as a methodological benchmark [7], [8].

COMPUTATIONAL METHOD

Materials and Software

The three-dimensional structure of the cyclooxygenase-2 (COX-2) protein target (PDB ID: 3LN1, resolution 2.40 Å) was selected as it provides a high-resolution crystal complex with its selective inhibitor, celecoxib, which is suitable for docking protocol validation. The structure was

downloaded from the Protein Data Bank (https://www.rcsb.org). The 3D structures of six flavonoid ligands—quercetin (CID: 5280343), kaempferol (CID: 5280863), apigenin (CID: 5280443), myricetin (CID: 5281672), luteolin (CID: 5280445), and genistein (CID: 5280961)—along with celecoxib (CID: 2662, used as internal reference) were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Structure preparation was performed using UCSF Chimera v1.18. Docking simulations were conducted using UCSF DOCK6 v13.1. Molecular visualization, generation of 2D and 3D structural poses, and property predictions were performed using Discovery Studio Visualizer v4.5 and Open Babel v3.1.1 [8], [14].

Preparation and Docking Protocol

Chain A of the COX-2 crystal structure was used for the docking study. The protein was prepared by removing all water molecules, ions, and unbound heteroatoms. The native co-crystallized celecoxib was temporarily retained to define the active site coordinates before being removed prior to the docking run. Protonation states of the amino acid residues were adjusted to physiological pH (7.4). Hydrogen atoms were added, and AMBER ff14SB force field atom types with standard partial atomic charges were assigned for protein preparation. Docking scoring employed the AMBER parm99 van der Waals parameter set as implemented in DOCK6. All ligands were processed using Open Babel v3.1.1 by converting SDF files to MOL2 format, assigning Gasteiger partial charges, and performing local energy minimization (MMFF94x). The docking grid was centered on the coordinates of the native co-crystallized celecoxib. The grid box was set to 40 × 40 × 40 Å with a 0.3 Å spacing using DOCK6.

Docking simulations were conducted with 5,000 orientations for quercetin and myricetin (due to their conformational flexibility) and 1,000 orientations for the remaining compounds [6]. To validate the docking protocol, celecoxib was re-docked into the COX-2 active site. The root-mean-square deviation (RMSD) between the docked and crystallographic poses was calculated using the obrms tool from Open Babel. The validation was successful, yielding an RMSD value of 0.774 Å, which is well within the acceptable criterion of < 2.40 Å [8], [14].

Interaction Analysis

Molecular interactions between the compounds and COX-2 were analyzed using Discovery Studio Visualizer v4.5. Both 2D interaction diagrams and 3D structural poses were generated to identify key interacting residues, focusing on specific interactions such as hydrogen bonds, Pi-Alkyl,

and van der Waals interactions within the active site. To complement this, to complement this, the structures of the selected compounds were prepared and optimized, with file format conversions executed using Open Babel software.

Critical pharmacokinetic parameters, including gastrointestinal absorption, blood-brain barrier (BBB) permeability, cytochrome P450 inhibition, and organ toxicity, were rigorously evaluated. This in silico screening was performed to verify the drug-likeness and safety compliance of the potential COX-2 inhibitors [8].

Drug-Likeness and Physicochemical Property Prediction

Physicochemical parameters including molecular weight (MW), LogP (lipophilicity), polar surface area (PSA), hydrogen bond acceptors (HBA), and hydrogen bond donors (HBD) were calculated using Open Babel. Drug-likeness was evaluated with Lipinski's rule of five. Blood-brain barrier (BBB) permeability was predicted using the rule that compounds with PSA $\leq$ 90 Å^2 are generally expected to cross the BBB, whereas compounds with PSA > 90 Å^2 are predicted as less likely to cross the BBB [11]. Toxicological potential and general ADMET properties were predicted using ProTox-II and SwissADME web servers [8], [9].

RESULTS AND DISCUSSION

Method Validation

Validation of the molecular docking protocol is essential to ensure the accuracy and reliability of results in predicting the correct docked conformation of ligands into the target's active site. The RMSD value between the docked conformation of celecoxib and its native crystallographic pose was found to be 0.774 Å. Since this value is well within the threshold of 2.40 Å [9], the developed docking protocol was considered valid and capable of generating reliable results for binding analyses of various flavonoids against the COX-2 active site.

The low RMSD value confirms that both protein and ligand preparations, as well as the docking parameters, are appropriate for screening these flavonoids. Furthermore, the high resolution (2.40 Å) of the 3LN1 structure provides a clear three-dimensional representation (Figure 1), enabling the docking protocol to identify active sites and fit ligands properly [10], [12].

Binding Affinity

The docking simulations yielded quantitative insights into how flavonoids bind to the COX-2

active site. The docking scores obtained for each compound are listed in Table 1. Among the tested flavonoids, quercetin displayed the most favorable predicted binding against COX-2 with a Grid Score of -36.36 kcal/mol, followed by kaempferol (-36.25 kcal/mol) and apigenin (-34.69 kcal/mol). More negative Grid Score values indicate stronger binding of ligands to the target protein [7], [11].

The affinity difference between quercetin and kaempferol was very small (0.11 kcal/mol), suggesting that both compounds possess nearly equivalent binding capabilities. Quercetin still ranked first because it forms more hydrogen bonds, which add extra stability to the complex. Myricetin has more hydroxyl groups but displayed weaker affinity. Its higher PSA (147.68 Å^2) likely restricts conformational flexibility and raises internal strain, reducing binding strength.

These results are consistent with previous studies identifying quercetin as a potent COX-2 inhibitor [10], [12] Quercetin's five hydroxyl groups allow it to interact extensively with active-site residues [6]. In LPS-stimulated cells, quercetin reduces COX-2 protein expression more effectively than acetylsalicylic acid [13]. Recent docking and molecular dynamics studies also confirm that hydroxylated flavonoids bind strongly to COX-2 [14].

Residue Interactions

Detailed analysis of molecular interactions, including conventional hydrogen bonds, carbon-hydrogen bonds, Pi-Alkyl, and van der Waals forces, was performed for the three ligands with the most favorable docking scores, namely quercetin, kaempferol, and apigenin (Table 2 and Figure 2). Quercetin formed four conventional hydrogen bonds, one carbon-hydrogen bond, Pi-Alkyl interactions, and van der Waals interactions with residues including Ser119, Val350, and Trp387. It also showed one unfavorable donor-donor interaction with Tyr385 and a Pi-cation interaction with Ser530 (distance ~4.0 Å).

In comparison, kaempferol generated only one conventional hydrogen bond and one carbon–hydrogen bond with Ser119, together with Pi-Alkyl, Pi-cation, and van der Waals interactions. Apigenin formed only a single conventional hydrogen bond with Ser119 while relying predominantly on hydrophobic contacts. The lower number of polar interactions observed for both ligands is consistent with their slightly weaker binding affinities than quercetin, suggesting that hydrogen bonding, together with complementary hydrophobic interactions, contributes to stabilizing the ligand–COX-2 complex rather than acting as the sole determinant of binding affinity. [8], [11].

The ligand is stabilized within the active site through a combination of polar and non-polar

interactions, contributing to both binding affinity and binding specificity. Hydrophobic residues, including Ala390, Val350, Val532, Leu531, and Tyr355, primarily mediate the non-polar interactions that anchor the ligand. Meanwhile, polar amino acid residues further stabilize the ligand by forming polar interactions, enhancing the overall ligand–protein complex stability. [5], [11]

In previous studies, binding residues Arg120, Tyr355, and Ser530 of COX-2 were frequently reported. In our study, Arg120 was absent in all interactions, while Tyr355 and Ser530 were observed in certain cases. Due to numbering variations within different PDB coordinates, exact interaction details cannot be directly compared. Nevertheless, the calculated total interactions demonstrate the potential of these molecules in forming stable complexes with the COX-2 active site (Figure 3). These results are consistent with published studies showing that stability of inhibitor-COX-2 interactions is attributed not only to the number of hydrogen bonds but also to synergistic effects involving various forces such as carbon-hydrogen bonds, Pi-Alkyl, Pi-Pi, and van der Waals interactions. These comprehensive interactions are thought to impart biological activity [16].

Drug-Likeness and Physicochemical Properties

Drug-likeness and physicochemical property evaluation was conducted to assess the initial pharmacokinetic feasibility of the flavonoid compounds as oral COX-2 inhibitor candidates. Based on the prediction results, six of the seven compounds met all Lipinski criteria without violations, while Myricetin showed one violation. These results indicate that most of the tested flavonoids possess physicochemical characteristics that support their development as oral drug candidates. In this study, the evaluation was limited to drug-likeness and physicochemical parameters, including molecular weight, LogP, PSA, HBA, HBD, and compliance with Lipinski's rule of five, which are commonly used as preliminary indicators of oral drug candidate suitability [15].

Quercetin and Kaempferol, which showed the best binding affinity in the docking analysis, also had good drug-likeness profiles. Quercetin has a molecular weight of 302.24 Da, LogP of 1.78, and PSA of 127.45 Å², while Kaempferol has a molecular weight of 286.24 Da, LogP of 2.07, and PSA of 107.22 Å². In contrast, Myricetin exhibited the highest PSA value (147.68 Å²), reflecting its greater molecular polarity. High PSA values are generally associated with lower membrane permeability and reduced oral absorption. This characteristic may contribute to its lower binding affinity compared to Quercetin and Kaempferol despite possessing a higher number of hydroxyl groups [15].

In addition, all flavonoids had relatively low LogP values (1.48–2.19) compared to Celecoxib (5.30), indicating a balance between hydrophilic and hydrophobic properties that potentially support the solubility of the compounds. Overall, the analysis results showed that Quercetin and Kaempferol had the best combination of binding affinity and physicochemical characteristics, making them the most prospective flavonoid candidates for further development as COX-2 inhibitors [15].

Limitation

Although this study successfully identified the potential of several flavonoid compounds as COX-2 inhibitors through molecular docking and ADMET prediction approaches, several limitations need to be considered when interpreting the results. First, all analyses were conducted in silico, so the results are still predictive and cannot directly describe the compounds' biological activity in real biological systems. Therefore, validation through in vitro and in vivo testing is necessary to confirm the predicted anti-inflammatory activity [16].

The second limitation stems from the use of the rigid receptor approach in molecular docking, where the protein structure is assumed to be static during the simulation. In reality, proteins are dynamic and can undergo conformational changes when interacting with ligands. This potentially results in some biologically feasible interactions not being fully accommodated in the docking simulations [16].

Furthermore, the solvation model used is still simplistic and does not fully represent complex physiological environmental conditions. The influence of water molecules, ions, and other biological system dynamics can contribute to the stability of the ligand-protein complex, which is not fully reflected in docking calculations. Therefore, further research using molecular dynamics simulation approaches and binding free energy calculations is needed to obtain a more comprehensive picture of the complex stability and potential anti-inflammatory activity of flavonoid compounds against COX-2. Limitations related to protein flexibility, representation of the solvent environment, and the predictive nature of molecular docking are aspects that have been widely discussed in structure-based drug design strategies because they can affect the accuracy of ligand-protein interaction predictions during the drug discovery stage [16].

CONCLUSIONS

This study successfully demonstrated that the molecular docking protocol using DOCK6 is valid, as confirmed by an RMSD value of 0.774 Å from the celecoxib re-docking validation. Among the six flavonoid compounds tested, quercetin and kaempferol emerged as the most promising COX-2 inhibitor candidates, with binding affinities of approximately 63% relative to celecoxib. Quercetin's superiority is attributed to the formation of five hydrogen bonds within the COX-2 active site, supported by optimal hydrophobic and van der Waals interactions. Physicochemical property analysis revealed that six of seven compounds complied with Lipinski's rule of five. BBB prediction indicated that quercetin, kaempferol, myricetin, and luteolin (PSA > 90 Å²) are unlikely to cross the blood-brain barrier, while apigenin and genistein (PSA = 86.99 Å²) are borderline. This profile supports the development of these flavonoids for peripheral inflammation with potentially reduced central side effects. Based on these findings, quercetin is recommended as a lead candidate for further in vitro validation through COX-2 inhibition assays.

ACKNOWLEDGEMENT

We thank the Department of Nanotechnology Engineering, Faculty of Advanced Technology and Multidiscipline, Universitas Airlangga, and the Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga for the facilities and academic support during this research. We also appreciate the PUI-PT Research Center for Biomolecular Engineering (BIOME), Universitas Airlangga, for the collaborative research environment. This study received no specific grant from any funding agency; the Article Processing Charge was covered by the corresponding author. All authors have read and approved the final manuscript.

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TABLE

Table 1. *Grid Score Results*

No	Compound	Grid_Score (kcal/mol)	Relative to Celecoxib (%)
1	Celecoxib	-57.38	100%
2	Quercetin	-36.36	63.4%
3	Kaempferol	-36.25	63.2%
4	Apigenin	-34.69	60.5%
5	Myricetin	-32.97	57.5%
6	Genistein	-25.60	44.6%
7	Luteolin	-24.89	43.4%

Table 2. *Interactions Summary*

Ligand	H-bonds (conventional + carbon)	Unfavorable	Pi-Alkyl	van der Waals
Quercetin	5 (4 conv + 1 C-H)	1 (TYR)	5	Multiple
Kaempfetrol	2 (1 conv + 1 C-H)	1 (TYR)	5	Multiple
Apigenin	1 (conv)	0	5	Multiple

Table 3. *Physicochemical Properties and Lipinski Compliance*

No	Compound	MW (DA)	LogP	PSA (Å²)	HBA	HBD	Lipinski
1	Quercetin	302.24	1.78	127.45	7	5	Pass
2	Kaempferol	286.24	2.07	107.22	6	4	Pass
3	Apigenin	270.24	2.19	86.99	5	3	Pass
4	Myricetin	318.24	1.48	147.68	8	6	Warning*
5	Luteolin	286.24	1.89	107.22	6	4	Pass
6	Genistein	270.24	2.08	86.99	5	3	Pass
7	Celecoxib	381.37	5.30	86.36	4	2	Pass

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GAMBAR DAN KETERANGANNYA

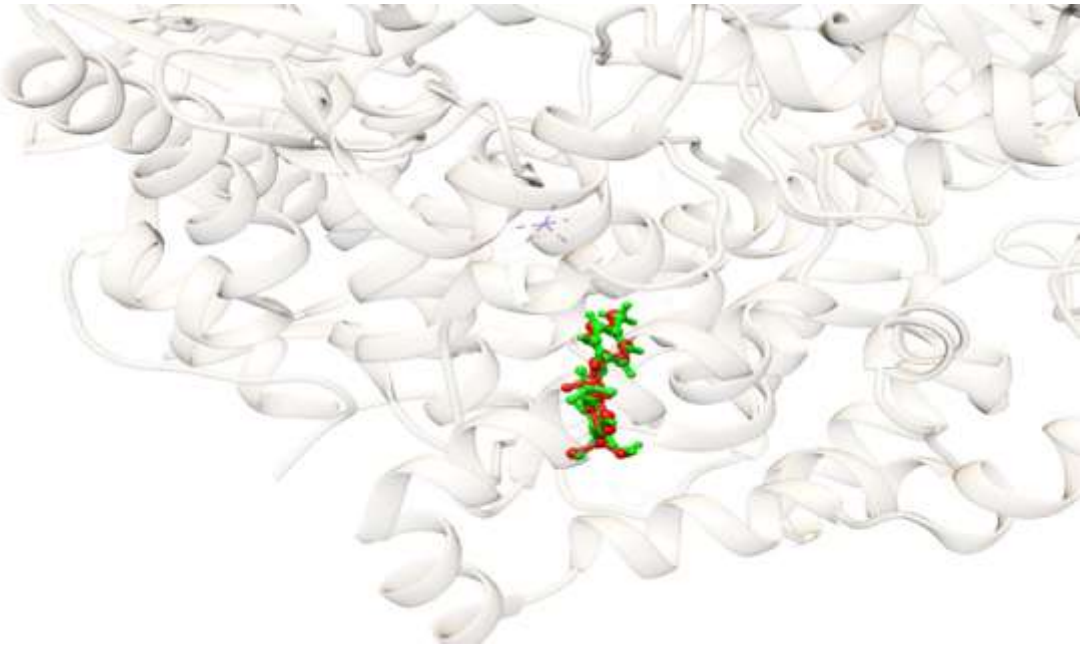
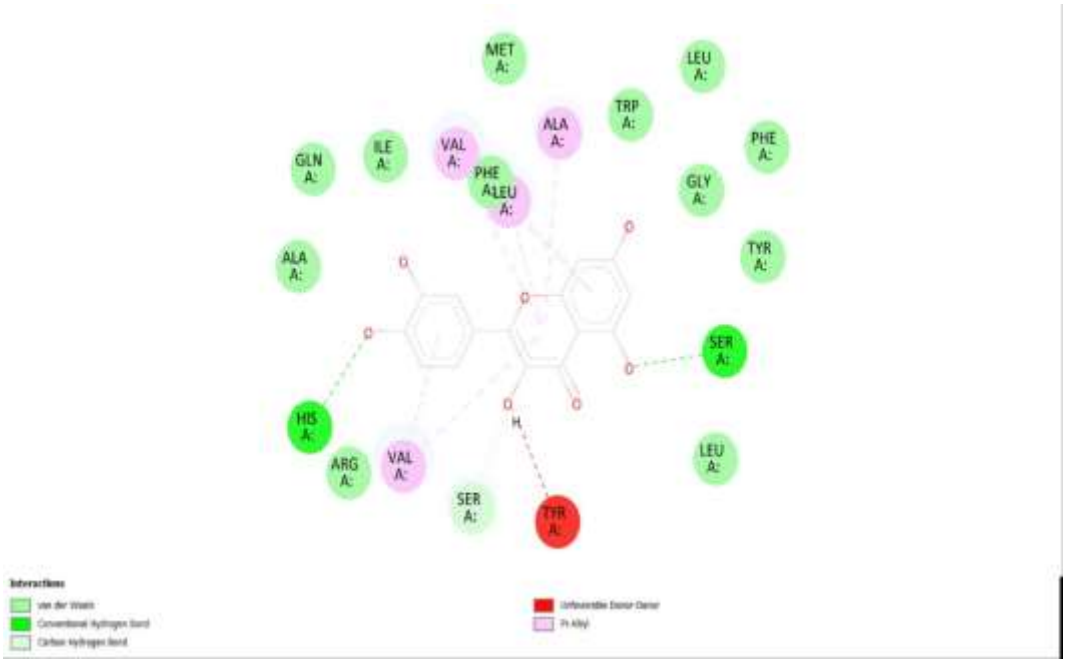


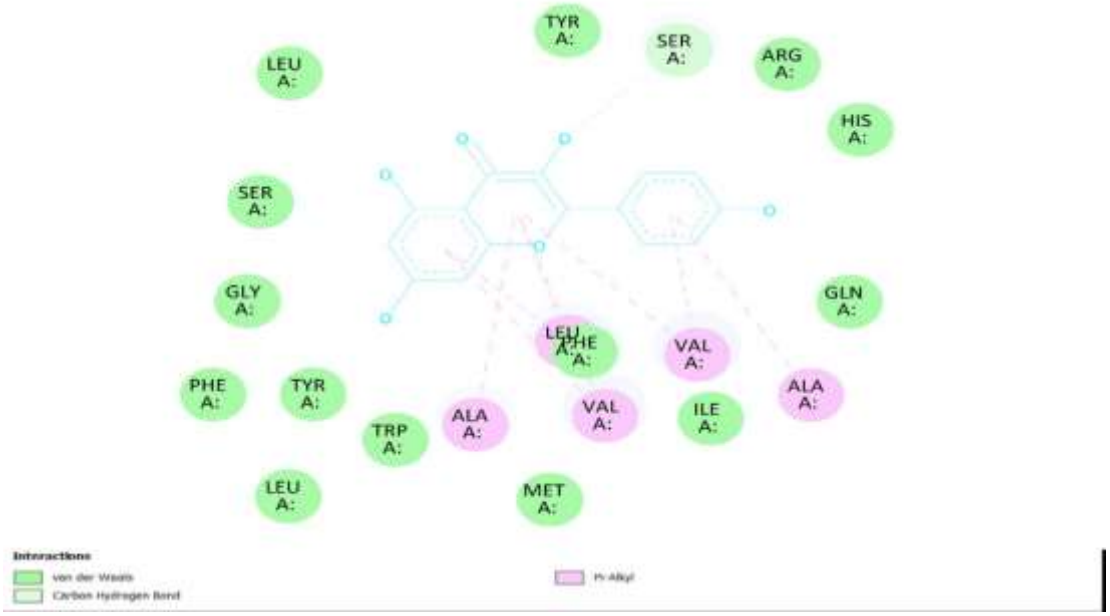
Figure 1. *Overlay of the celecoxib re-docking pose (green) with the crystal pose from PDB 3LN1 (red). RMSD = 0.774 Å (< 2.40 Å, valid)*

(a)



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(b)



(c)

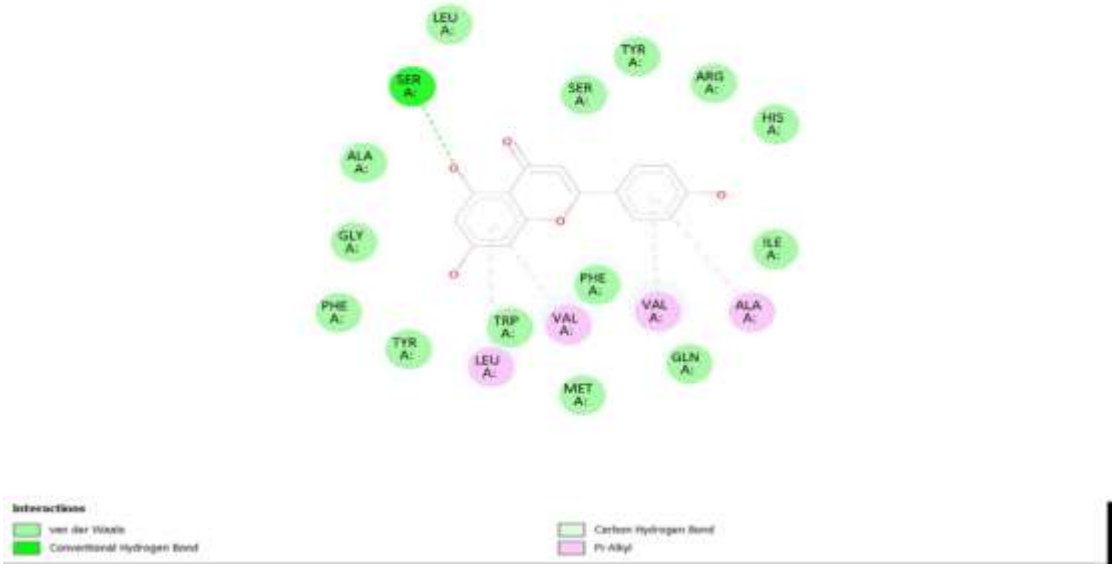
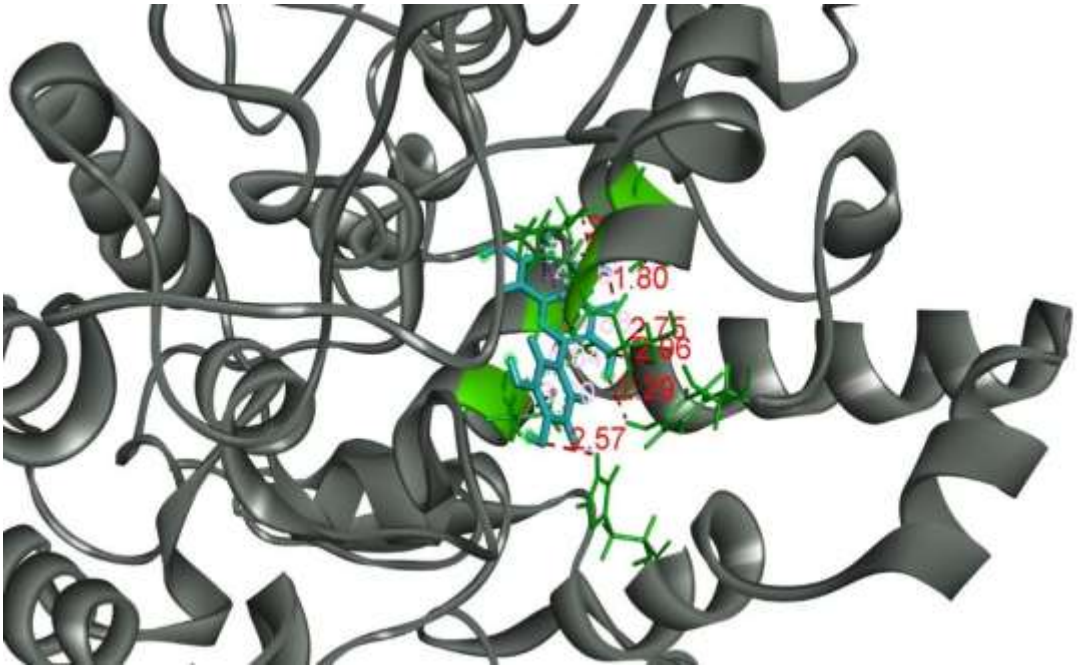


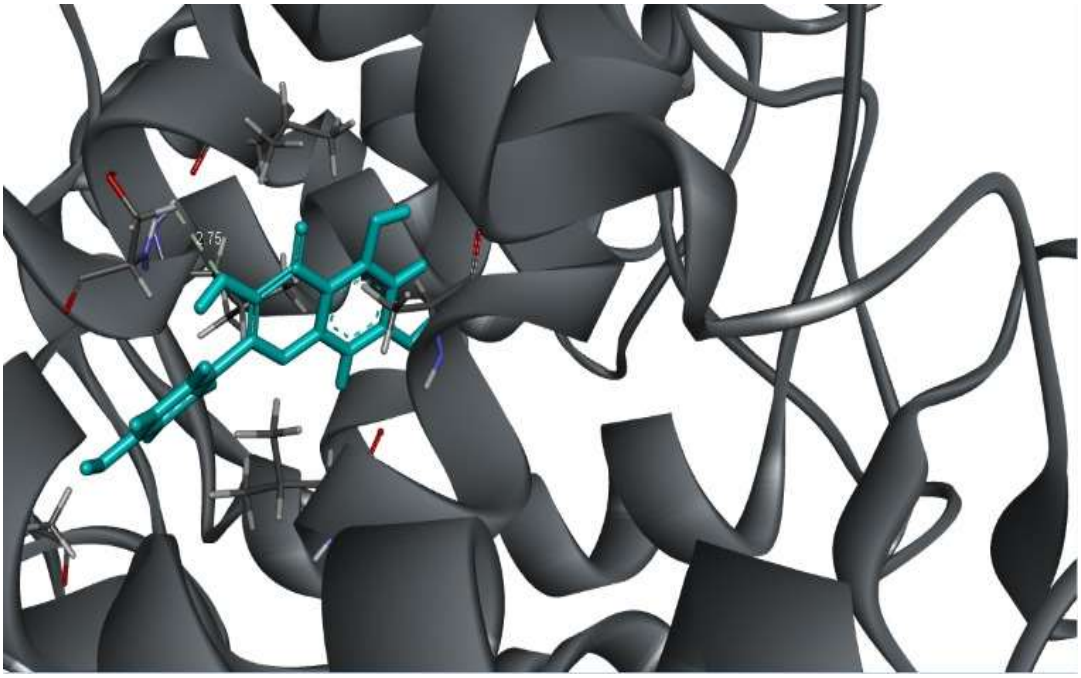
Figure 2. *2D interaction diagram of flavonoids with COX-2. (a) Quercetin; (b) Kaempferol; (c) Apigenin.*

Farhan Nur Huda [1], Nabila Widya Artha Ramadhani [2], Georgean Hugo Firmando [3], Matthew Aric Christoper Alecia [4], Jamie Fransisco Purba [5], Wahyu Rama Iswara [6], Mughni Ghatsa Pramudiwiyanto [7], Noctorio Arry Athallah [8], Muhammad Adriansyach Ramadhani [9], Imam Siswanto [10]

(a)



(b)



Farhan Nur Huda [1], Nabila Widya Artha Ramadhani [2], Georgean Hugo Firmando [3], Matthew Aric Christoper Alecia [4], Jamie Fransisco Purba [5], Wahyu Rama Iswara [6], Mughni Ghatsa Pramudiwiyanto [7], Noctorio Arry Athallah [8], Muhammad Adriansyach Ramadhani [9], Imam Siswanto [10]

(c)

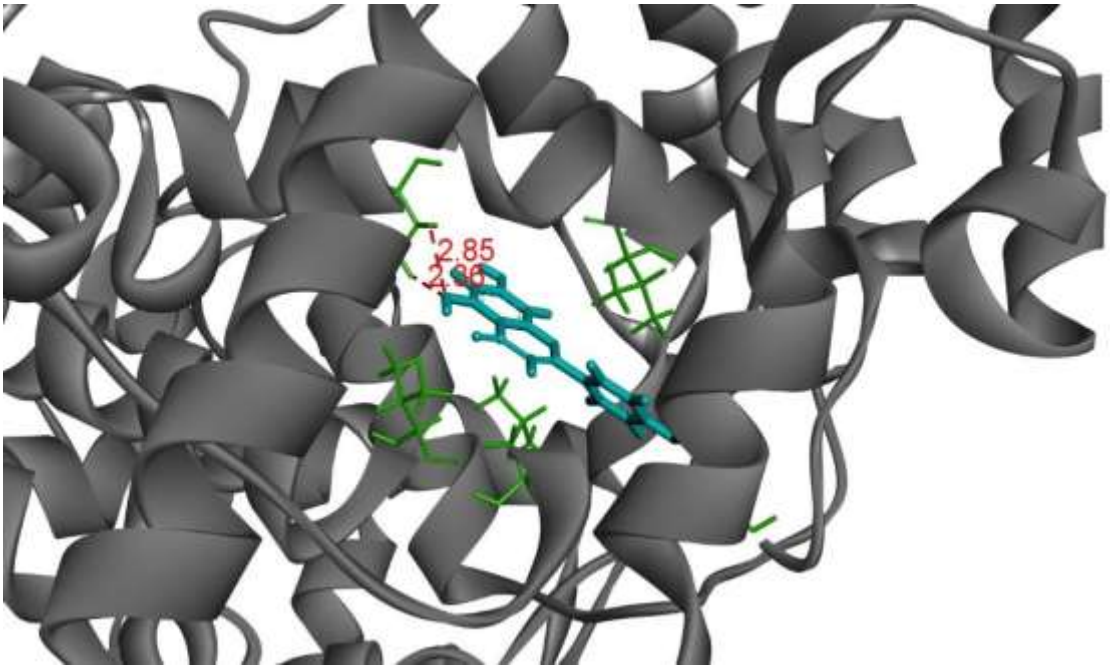


Figure 3. *3D docking poses in the COX-2 active site. (a) Quercetin; (b) Kaempferol; (c) Apigenin.*