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# Molecular Docking of the Interaction between Citrus amblycarpa Extract Contents and Inflammatory Proteins of Hepatic Steatosis

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# Molecular Docking of the Interaction between *Citrus amblycarpa* Extract Contents and Inflammatory Proteins of Hepatic Steatosis

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## Abstract

*Citrus amblycarpa* possesses various pharmacological activities, such as antioxidant, anticancer, antitumor, hepatoprotective, anti-inflammatory, antidiabetic, antiviral, antibacterial, and antifungal. The main active compounds in *C. amblycarpa* (including gamma (γ)-aminobutyric acid [GABA], hesperidin, naringin, neoeriocitrin, poncirin, quercetin, and rutin) show potential to interact with the inflammatory proteins in hepatic steatosis (such as nuclear factor kappa beta [NF-kB], tumor necrosis alpha [TNF-alpha], interleukin-6 [IL-6], c-Jun NH2-terminal kinase [JNK], and adiponectin). Molecular docking simulations were performed using Swiss Dock (http://www.swissdock.ch/), and analysis and visualization were conducted using Discovery Studio 4.1. Rutin, poncirin, hesperidin, and neoeriocitrin exhibit high affinities to NF-κB, TNF-alpha, IL-6, and adiponectin proteins, respectively. Similar to curcumin–adiponectin complex interaction, neoeriocitrin–adiponectin interaction involves GLY 223, PRO41, and VAL93 residues. Thus, the most potent inhibitor of hepatic sterosis marker was neoeriocitrin.

*Keywords: C. amblycarpa, hepatic steatosis, inflammatory proteins, molecular docking*

## Introduction

Indonesia is facing dual nutrition problems, namely, undernutrition and overnutrition. Overnutrition is caused by a diet high in carbohydrates and fat but low in fiber coupled with reduced physical activity. The excess energy is stored in the body as fat, leading to obesity [1, 2]. In 2018, the prevalence of obesity was 19.52% among adults aged >18 years in South Kalimantan [3]. This phenomenon is attributed to the lifestyle of the South Kalimantan community, especially in major cities such as Banjarmasin where eating out (locally known as “mewarung”) is common.

Obesity can increase the prevalence of various diseases, such as diabetes, dyslipidemia, hypertension, and cardiovascular diseases [4–6]. Fat accumulation in obesity is proinflammatory in nature [7–9] and leads to an increase in the release of free fatty acids [10]. As a consequence, triglyceride accumulates in the liver [11] and induces the adhesion of chemotactic molecules, leading to inflammation and oxidative stress [12].

Inflammation is a series of nonspecific biological processes that occur in response to the entry of foreign substances, tissue damage, or both [13]. During inflammation, a vascular reaction occurs wherein fluids, blood elements, leukocytes, and chemical mediators gather in the tissue to neutralize and eliminate harmful agents and to repair the damaged tissue [14, 15]. The inflammatory mediators in a liver experiencing fatty infiltration include nuclear factor kappa beta (NF-kB), tumor necrosis alpha (TNF-alpha), interleukin-6 (IL-6), c-Jun NH2-terminal kinase (JNK), and adiponectin [16–18]. These molecular markers have docking binding sites to regulate the activities (inhibition or stimulation). NF-kB has cysteine 38 residue in its phosphate backbone binding site [19]. The active site of TNF-alpha is found in the interface dimer, which hinders binding to the receptor and thus blocks signaling pathways including

inflammation [20]. JNK conformation can be affected, particularly on the allosteric site of the enzyme termed the D-recruitment site, thus changing the ATP-binding pocket of JNKs [21]. For adiponectin, the binding site is located in the central cavity of adiponectin receptors, including the neighboring area to the zinc ion [22].

Inflammation can be reduced by blocking these targets using medicinal plant compounds, such as phenols, triterpenes, flavonoids, saponins, tannins, and cinnamic acid [23, 24]. South Kalimantan is home to a distinctive citrus plant, *Citrus amblycarpa*. Phytochemical tests on the ethanol and n-hexane extracts of *C. amblycarpa* revealed the presence of alkaloids, saponins, steroids, triterpenoids, tannins, and flavonoids [25]. The main phenolic compounds in this citrus fruit peel are flavanones (hesperidin, neohesperidin, narirutin, and naringin) and polymethoxylated flavones (nobiletin, sinensetin, and tangeretin). All of these compounds contribute to the various pharmacological activities of *C. amblycarpa*, such as antioxidant, anti-inflammatory, anticancer, antiproliferative, antiviral, and antiplatelet aggregation [26–28].

Flavonoids can inhibit lipid peroxidation and cell fragility [29, 30]. A study found a decrease in the levels of COX-2, ICAM-1, and TNF-alpha in the adipose tissue of obese rat models treated with citrus peel extract containing high flavonoid levels [31]. Furthermore, water extracts from *C. amblycarpa* contain phenolics, quercetin, rutin, and GABA, which can inhibit angiotensin-converting enzyme [32].

This study represents an initial step in investigating the potential of *C. amblycarpa*, the distinctive citrus of South Kalimantan, as a candidate for antiobesity medication. In accordance with ULM's research development roadmap [33], in silico research was conducted on the interaction between the main active compounds of *C. amblycarpa* and obesity markers (Fat mass and *obesity*-associated protein (FTO), leptin, and resistin). Results showed that hesperidin had the lowest binding affinity score when interacting with FTO, leptin, and resistin. Given that obesity can cause inflammation in the liver, an in silico experiment was designed using molecular docking to analyze the interaction between the contents of *C. amblycarpa* extract and inflammation markers in hepatic steatosis.

## Materials and Methods

**Ligand and protein sampling.** The structures of the bioactive compounds of *C. amblycarpa* and the 3D reference ligand structures were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as depicted in Figure 1. The target proteins, namely, NF-KB (PDB 4DN5), TNF-alpha (PDB 1TNF), IL-6 (PDB 1P9M), JNK (PDB 4QTD), and adiponectin (PDB 5LX9), were obtained from the Protein Data Bank (https://www.rcsb.org/) as shown in Figure 2. The ligands' structures were downloaded in .SDF format, and those of the proteins were downloaded in .pdb format [34, 35]. The ligands' pharmacokinetic profiles were analyzed using the SwissADME server (http://www.swissadme.ch/). ADMET profiling was also conducted to obtain information regarding the absorption, distribution, metabolism, excretion, and toxicity of these compounds [36].

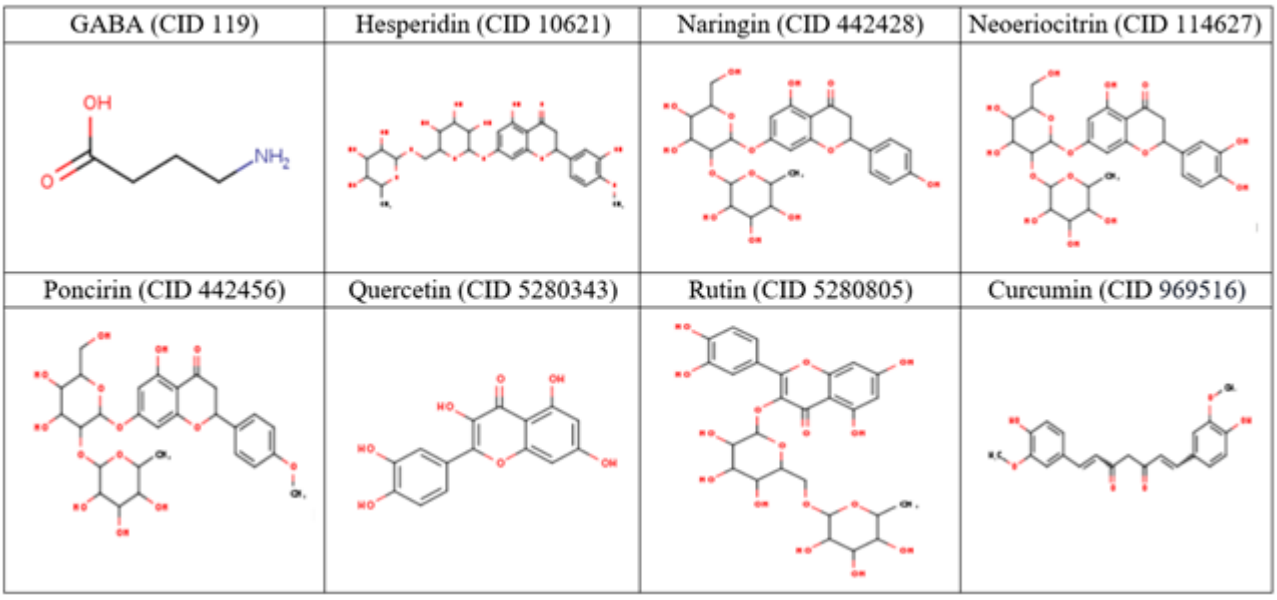


**Figure 1. Chemical Compounds Found in *C. amblycarpa* Peel and Curcumin**

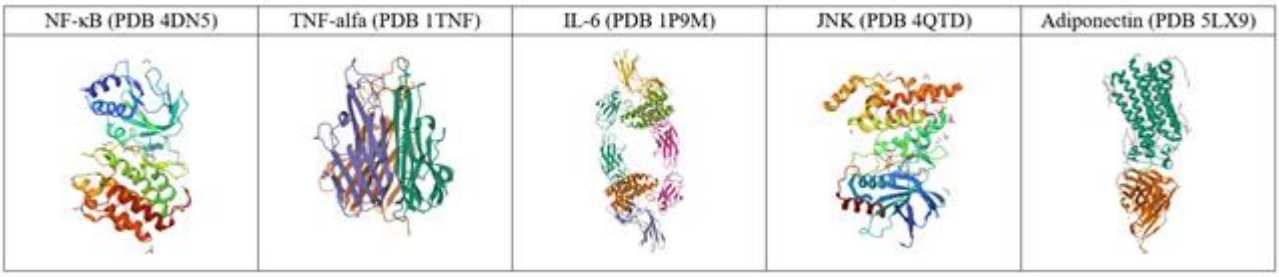


**Figure 2. Inflammatory Protein Mediators in Hepatic Steatosis**

**Docking method validation.** The docking method was validated by redocking using a natural ligand for each receptor. In this validation, the root mean square deviation (RSMD) was used as a parameter describing how much the protein–ligand interaction changes during docking to determine the deviation value. If the RMSD is ≤2 Å, then the docking method is valid and can be used to dock the test compound [34]. Glycerol is a native ligand for NF-κB with an RMSD of approximately 0.031 Å.

Magnesium is native ligand for TNF-alpha with an RMSD of 0.125 Å. Tartaric acid–IL-6, phosphoamino acid–JNK, Oleic acid–adiponectin present RMSD values <2 Å, that is, 0.121, 0.083, and 0.070 Å, respectively. The validation results of the native ligands for each receptor showed that their RMSD values meet the criteria.

**Protein and ligand preparation.** This study utilized the seven main chemical compounds in *C. amblycarpa* peel: GABA (CID 119), hesperidin (CID 10621), naringin (CID 442428), neoeriocitrin (CID 114627), poncirin (CID 442456), quercetin (CID 5280343), and rutin (CID 5280805). One reference drug compound, curcumin (CID 969516), was employed as a reference ligand. The ligands were prepared using Chimera 1.6.2 to minimize their energy and convert them to mol2 format. Meanwhile, the target proteins were prepared using Discovery Studio 4.1 [34].

**Docking and visualization.** The protein–ligand complexes obtained from the docking simulations between ligands and target proteins were docked and visualized using the Swiss Dock link (http://www.swissdock.ch/) [36]. The docking method involved four crucial stages, namely, visualization, rigid-body energy minimization, semi-flexible refinement, and final refinement in explicit solvent. The docking results were evaluated and visualized with Discovery Studio 4.1 software. Through this analysis, the interactions between proteins and ligands were explored to gain insights into the types and number of formed bonds [35].

## Results and Discussion

Molecular docking was conducted to predict the interactions between the active compounds of *C. amblycarpa* (GABA, hesperidin, naringin, neoeriocitrin, poncirin, quercetin, and rutin) and the inflammatory marker proteins of hepatic steatosis (NF-kB, TNF-alpha, IL-6, JNK, and adiponectin) and between the control compound (curcumin) and the same inflammatory proteins. Analysis of the bioavailability of *C. amblycarpa* active compounds and curcumin using the SwissADME software revealed their various properties such as lipophilicity, molecular weight, polarity, and water solubility as shown in Figure 3.

For NF-kB, rutin exhibited the highest affinity with a score of −9.63 kcal/mol, followed by neoeriocitrin with a score of −9.27 kcal/mol and poncirin with a score of −8.77 kcal/mol. These results indicate that rutin is the best potential compound to act as an NF-kB inhibitor. For TNF-alpha, poncirin demonstrates the highest affinity with a score of −9.09 kcal/mol, followed by naringin with a score of −8.95 kcal/mol and neoeriocitrin with a score of −8.85 kcal/mol. This finding suggests the potential of poncirin as a TNF-alpha inhibitor. For IL-6 protein, hesperidin exhibits the highest affinity with a score of −9.49 kcal/mol, followed by rutin with a score of −8.77 kcal/mol and poncirin with a score of −8.51 kcal/mol. These results indicate the potential of hesperidin, rutin, and poncirin as IL-6 inhibitors. For JNK, curcumin still has the best binding affinity of −9.2 kcal/mol, followed by hesperidin with a score of −7.9 kcal/mol, neoeriocitrin with a score of −7.89 kcal/mol, and rutin with a score of −7.81 kcal/mol. Lastly, for adiponectin, neoeriocitrin exhibits the highest affinity with a score of −8.98 kcal/mol, followed by reference ligand, curcumin, with −8.08 kcal/mol, hesperidin with −8.07 kcal/mol, and naringin with −8.05 kcal/mol. These findings indicate that neoeriocitrin is the best inhibitor for adiponectin. As a reference, curcumin demonstrates favorable affinities to all the target proteins.

Molecular docking results revealed several compounds with high and low affinities to NF-kB, which triggers hepatic inflammation [37]. The compounds with high affinities, such as rutin, neoeriocitrin, poncirin, and naringin, demonstrate strong potential to inhibit NF-kB activation. Their mechanisms involve suppressing IκBα phosphorylation, IκBα degradation, and NF-kB translocation into the cell nucleus [38]. By inhibiting the

NF-kB activation pathway, these compounds can reduce the production of proinflammatory cytokines that contribute to hepatic inflammation [39]. Meanwhile, the compounds with low affinities, such as GABA and quercetin, may have a limited effect in inhibiting NF-kB activation. The molecular docking results of the active compounds from *C. amblycarpa* against NF-kB, TNF-alpha, IL-6, JNK, and adiponectin are presented in Table 1, and the 2D interactions are shown in Table 2 and Figure 4. Similar interactions with binding site residues indicate that these compounds may exhibit inhibitory activity against the inflammatory proteins involved in hepatic steatosis.

Compounds with high affinities to TNF-alpha have strong potential in inhibiting its activity and influencing the pathomechanism of hepatic inflammation [40]. As the compounds with the highest affinities, poncirin, naringin, and neoeriocitrin could have adequate effects on preventing hepatic inflammation. The mechanisms of these compounds involve several steps. First, they inhibit TNF-alpha production, thereby reducing the amount of proinflammatory cytokines released [41]. Second, they suppress TNF-alpha signaling transduction, thus disrupting the signal pathways required for inflammation activation and amplification [42]. Meanwhile, the compounds with low affinities, such as GABA and quercetin, may have a limited effect on TNF-alpha activity. Although they can influence TNF-alpha production, their low affinities might result in their weak impact on controlling hepatic inflammation.

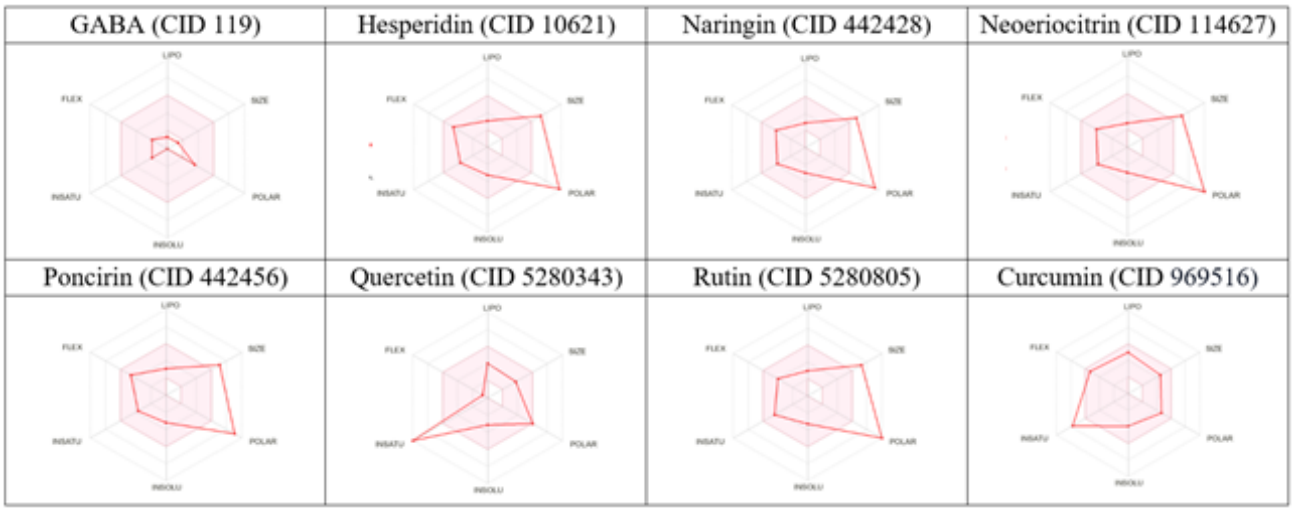


**Figure 3. Bioavailability Analysis of Active Compounds from *C. amblycarpa* and Curcumin Using Swiss ADME Software Bottom of Form**

**Table 1. Binding Affinity Score of Active Compounds of *C. amblycarpa* and Curcumin against Hepatic Steatosis Inflammatory Proteins**

| Parameters | | Protein | | | | |
|---|---|---|---|---|---|---|
| | | NF-κB | TNF-alpha | IL-6 | JNK | Adiponectin |
| **Binding Affinity (kcal/mol)** | GABA | −6.64 | −6.38 | −6.44 | −5.97 | −5.88 |
| | Hesperidin | −7.73 | −8.67 | −9.49 | −7.9 | −8.07 |
| | Naringin | −8.24 | −8.95 | −8.48 | −7.66 | −8.05 |
| | Neoeriocitrin | −9.27 | −8.85 | −8.37 | −7.89 | −8.98 |
| | Poncirin | −8.77 | −9.09 | −8.51 | −7.53 | −7.93 |
| | Quercetin | −7.35 | −7.24 | −7.14 | −6.74 | −6.91 |
| | Rutin | −9.63 | −8.44 | −8.77 | −7.81 | −7.38 |
| | Curcumin | −9.06 | −7.61 | −7.93 | −9.2 | −8.08 |

**Table 2. Chemical Interaction Results of Molecular Docking**

| Protein | Ligand | Chemical Interactions |
|---|---|---|
| NF-κB | GABA | **attractive charge** : GLU501, ARG451 |
| | Hesperidin | **pi-cation** : GLN403, GLN403, LEU404<br>**pi-alkyl** : ALA400 |
| | Naringin | **conventional hydrogen bond** : ARG405<br>**carbon hydrogen bond** : THR401<br>**metal-acceptor** : HSE415<br>**pi-cation** : LEU404, GLN403<br>**pi-donor hydrogen bond** : THR401<br>**pi-alkyl** : ALA400 |
| | Neoeriocitrin | **conventional hydrogen bond** : GLN403<br>**carbon hydrogen bond** : GLN403, THR401<br>**pi-cation** : LEU404<br>**pi-donor hydrogen bond** : GLN403, THR401<br>**pi-alkyl** : ARG405 |
| | Poncirin | **conventional hydrogen bond** : LEU404<br>**carbon hydrogen bond** : THR401<br>**metal-acceptor** : LEU404<br>**unfavorable acceptor-acceptor** : THR401<br>**pi-cation** : GLN403, LEU404<br>**amide-pi stacked** : GLN403<br>**alkyl and pi-alkyl**: ARG405, LEU404 |
| | Quercetin | **conventional hydrogen bond** : GLY602<br>**metal-acceptor** : LEU604<br>**pi-cation** : LYS373, ARG601, GLY602<br>**pi-alkyl** : ARG601, LEU604 |
| | Rutin | **conventional hydrogen bond** : THR401, GLN403<br>**carbon hydrogen bond** : GLN403, THR401<br>**metal-acceptor** : HSE415<br>**pi-cation and pi-anion** : LEU404, THR401, GLU396<br>**alkyl and pi-alkyl** : LEU404, ALA400, ARG405 |
| | Curcumin | **conventional hydrogen bond** : LEU472<br>**metal-acceptor** : MG1<br>**pi-cation** : LEU406<br>**alkyl and pi-alkyl** : ALA427, VAL414, LEU522 |
| TNF-alpha | GABA | **conventional hydrogen bond** : ASN92<br>**carbon hydrogen bond** : ASN34 |
| | Hesperidin | **carbon hydrogen bond** : THR105<br>**pi-cation** : THR105 |
| | Naringin | **conventional hydrogen bond** : ARG103, GLY108, GLU104<br>**carbon hydrogen bond** : ARG103, GLU104<br>**pi-anion** : GLU104<br>**pi-alkyl** : ARG103 |
| | Neoeriocitrin | **conventional hydrogen bond** : SER9<br>**carbon hydrogen bond** : ALA35, ARG32<br>**metal-acceptor** : ASN39<br>**pi-cation** : ALA38<br>**alkyl and pi-alkyl** : **LEU36**, PRO8 |
| | Poncirin | **conventional hydrogen bond** : GLN102<br>**carbon hydrogen bond** : GLU104, ARG103<br>**pi-cation** : GLU104 |
| | Quercetin | **pi-alkyl** : PRO12, ALA156 |
| | Rutin | **conventional hydrogen bond** : TYR87, ALA35<br>**carbon hydrogen bond** : ALA35<br>**unfavorable donor-donor** : SER86<br>**pi-cation** : **ALA33**<br>**alkyl and pi-alkyl** : ARG6 |

**Table 2.** ***Continue***

| Protein | Ligand | Chemical Interactions |
|---|---|---|
| TNF-alpha | Curcumin | **conventional hydrogen bond** : **ALA33**<br>**metal-acceptor** : ASN39<br>**pi-cation** : PRO8<br>**alkyl and pi-alkyl** : PRO8, ALA38, **LEU36** |
| IL-6 | GABA | **conventional hydrogen bond** : ASP134<br>**carbon hydrogen bond** : ALA135 |
| | Hesperidin | **carbon hydrogen bond** : **THR134**, PHE 136<br>**alkyl and pi-alkyl** : PRO157, VAL15, ALA181 |
| | Naringin | **conventional hydrogen bond** : LYS146, LYS120<br>**pi-anion** : GLU95<br>**pi-pi T-shaped** : PHE147<br>**pi-alkyl** : LYS120 |
| | Neoeriocitrin | **pi-cation** : MET250<br>**pi-donor hydrogen bond** : MET250<br>**pi-alkyl** : MET250 |
| | Poncirin | **carbon hydrogen bond** : TRP247<br>**pi-cation** : PRO251, GLN249, SER248<br>**pi-donor hydrogen bond** : TRP247<br>**pi-alkyl** : GLN249 |
| | Quercetin | **conventional hydrogen bond** : ASP149<br>**unfavorable acceptor-acceptor** : ASP149<br>**pi-cation** : CYS150, LYS151, THR161, LYS153<br>**pi-donor hydrogen bond** : LYS151, THR161<br>**pi-lone pair** : THR161<br>**pi-alkyl** : CYS160, CYS150 |
| | Rutin | **conventional hydrogen bond** : THR130, **THR134**, HSD131, ASP155<br>**carbon hydrogen bond** : LEU132, THR130<br>**pi-cation** : ARG154<br>**pi-lone pair** : ARG154<br>**pi-alkyl** : ARG154 |
| | Curcumin | **carbon hydrogen bond** : GLY126, GLY127, THR156, ALA152<br>**pi-cation** : GLY126, **THR134**<br>**pi-donor hydrogen bond** : GLY126, GLY127, THR156, ALA152<br>**alkyl** : ALA152 |
| JNK | GABA | **carbon hydrogen bond** : GLU109 |
| | Hesperidin | **metal-acceptor** : LEU224 |
| | Naringin | **conventional hydrogen bond** : LEU274<br>**pi-cation** : LYS273<br>**pi–pi T-shaped** : TYR269<br>**pi-alkyl** : TYR269 |
| | Neoeriocitrin | **conventional hydrogen bond** : SER161, LYS160<br>**pi-cation** : **SER161** |
| | Poncirin | **conventional hydrogen bond** : LYS160<br>**pi-cation** : SER161 |
| | Quercetin | **pi-cation** : SER161<br>**pi-alkyl** : ALA113, CYS163 |
| | Rutin | **conventional hydrogen bond** : LYS160<br>**carbon hydrogen bond** : LYS160<br>**pi-cation** : SER161 |
| | Curcumin | **metal-acceptor** : MG426<br>**unfavorable donor-donor** : MET111<br>**alkyl** : CYS116, VAL40, LEU168, ALA53, VAL158, ILE32<br>**pi-alkyl** : CYS116, VAL40, LEU168, ALA53, VAL158, ILE32 |

**Table 2.** ***Continue***

| Protein | Ligand | Chemical Interactions |
|---|---|---|
| Adiponectin | GABA | **conventional hydrogen bond** : TYR236, TYR240<br>**carbon hydrogen bond** : PHE239, TYR236<br>**pi-donor hydrogen bond** : PHE239, TYR236 |
| | Hesperidin | **alkyl and pi-alkyl** : LEU250, VAL232, LEU225, LEU189, ILE261 |
| | Naringin | **conventional hydrogen bond** : GLY163<br>**metal-acceptor** : LEU178<br>**pi-cation** : GLY185<br>**alkyl and pi-alkyl** : PHE168, MET167 |
| | Neoeriocitrin | **conventional hydrogen bond** : LYS178, **GLY223,** LEU243<br>**pi-cation** : **PRO41**, GLN179<br>**pi-alkyl** : **VAL93** |
| | Poncirin | **carbon hydrogen bond** : TYR240<br>**pi–pi T-shaped** : TYR236<br>**pi-alkyl** : VAL232, LEU186, CYS246 |
| | Quercetin | **conventional hydrogen bond** : TYR236, GLY378<br>**pi–pi T-shaped** : TYR240<br>**pi-alkyl** : CYS246, CYS380 |
| | Rutin | **conventional hydrogen bond** : LEU186<br>**carbon hydrogen bond** : LEU186<br>**alkyl and pi-alkyl** : LEU250, LEU189, LEU193 |
| | Curcumin | **conventional hydrogen bond** : GLY180<br>**pi-cation** : **GLY223**<br>**amide-pi stacked** : **GLY223**<br>**alkyl and pi-alkyl** : **PRO41**, LYS242, PHE222, **VAL93** |

*Bold font indicated similar residue resulted by molecular interaction

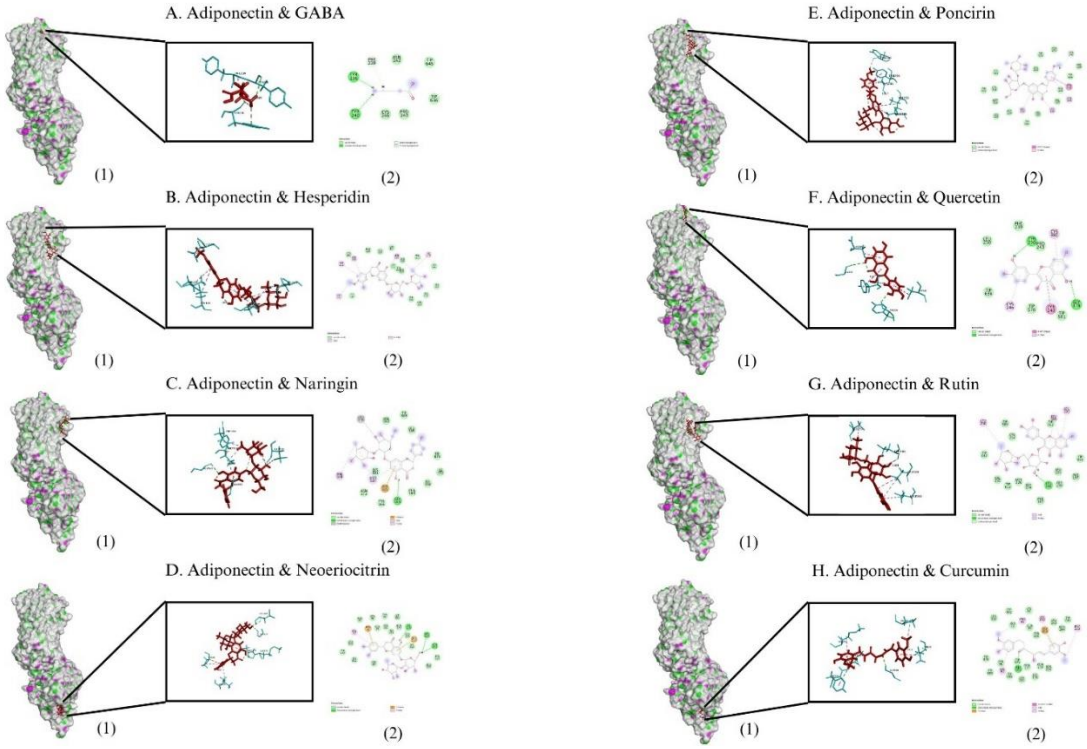


**Figure 4. Interactions between Ligands and Adiponectin Visualized using Discovery Studio 4.1 (A–H); 3D Structures (1) and 2D Structures (2) of the Interaction between *Citrus amblycarpa* Compounds and Adiponectin; Molecular Docking Performed using Swiss Dock Software and Visualization by the Discovery Studio Visualizer v19.1.0.18287 Program**

In terms of affinities to IL-6, significant differences were observed among the bioactive compounds (Figure 5). Compounds with high affinities to IL-6 exhibit strong interactions with this protein and have the potential to become effective agents in preventing hepatic inflammation [43]. For instance, hesperidin, rutin, and poncirin are the compounds with high affinities to IL-6. They form strong bonds with target protein residues through van der Waals forces, hydrogen bonding, and pi-cation bonding. These strong interactions allow these compounds to effectively inhibit IL-6 activity [44]. By strongly interacting with this protein, these compounds can hinder the signal pathways involving IL-6, reduce the production of inflammatory mediators, and slow down inflammation in the liver [45]. Some compounds have low affinities to IL-6, such as GABA and quercetin. Although they can still interact with the protein, their interactions tend to be weak and not as robust as that of compounds with high affinities. As a consequence, their impact in inhibiting IL-6 activity and alleviating hepatic inflammation might be limited.

With regard to the pathomechanism, JNK also plays a crucial role in the inflammation and oxidative stress pathways [46]. During hepatic inflammation, excessive JNK activation can trigger the production of various inflammatory mediators and stimulate cellular damage [47]. Compounds with high affinities to JNK can directly inhibit its activation or modulate the involved pathways. By strongly interacting with this protein, these compounds inhibit JNK activation and reduce the production of inflammatory mediators [48]. Hesperidin exhibits a high affinity to JNK. Its strong interaction with JNK can effectively hinder the latter's function, making the former a promising option for preventing hepatic inflammation. Compounds such as neoeriocitrin, rutin, and naringin also show sufficiently high affinities to JNK (Figure 6). Although their affinities may slightly differ, these compounds still have the potential to interact with this protein and inhibit its activity. They form various types of bonds, including van der Waals, hydrogen bonds, and pi-cation interactions, allowing them to effectively bind to JNK. However, compounds such as GABA and quercetin display relatively low affinities to JNK. Despite their ability to interact with this protein, their ability to inhibit JNK activity might not be as strong as that of compounds with high affinities.

Adiponectin regulates inflammatory responses and metabolism [49]. Compounds with high affinities to adiponectin, such as neoeriocitrin, hesperidin, and naringin, form strong interactions with this protein, including van der Waals forces, hydrogen bonds, and pi-alkyl interactions. These bonds enable the inhibition of adiponectin activity [50]. In the pathomechanism of hepatic inflammation, these compounds can inhibit the signal pathways involving adiponectin, reduce the production of inflammatory mediators, and alleviate

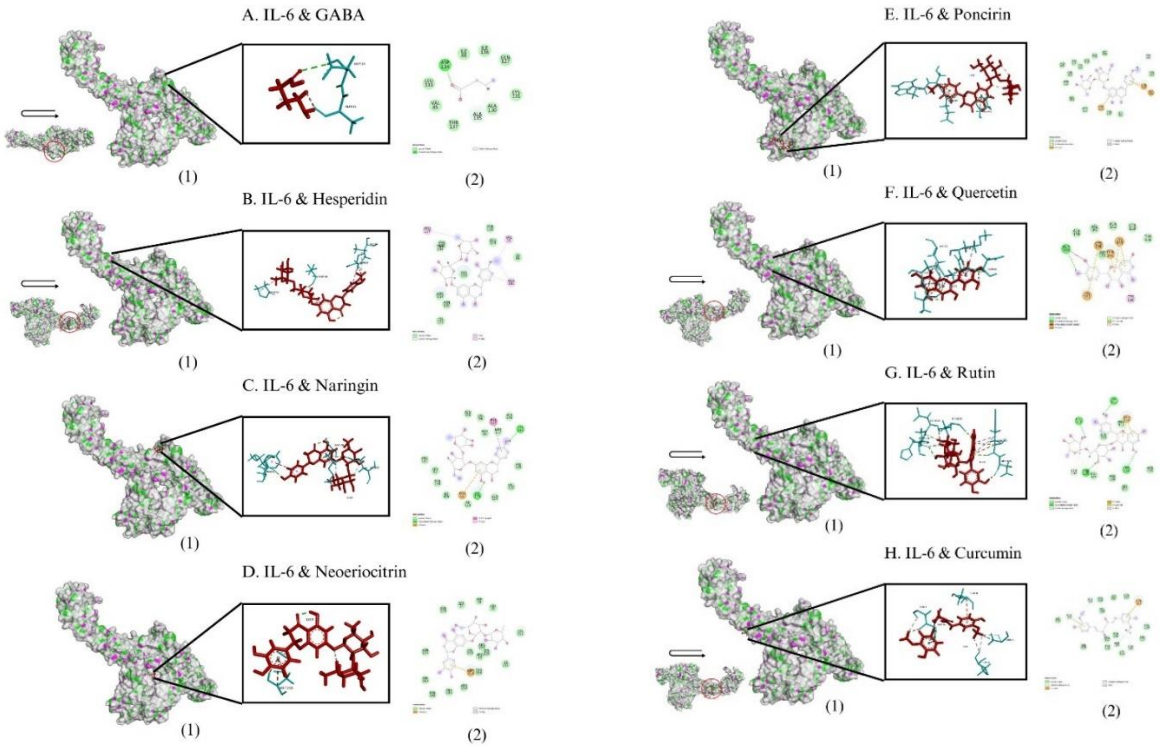


**Figure 5. Interactions between Ligands and IL-6 Visualized using Discovery Studio 4.1 (A–H); 3D Structures (1) and 2D Structures (2) of the Interaction between *Citrus amblycarpa* Compounds and IL-6; Molecular Docking Performed using Swiss Dock Software and Visualization by the Discovery Studio Visualizer v19.1.0.18287 Program**

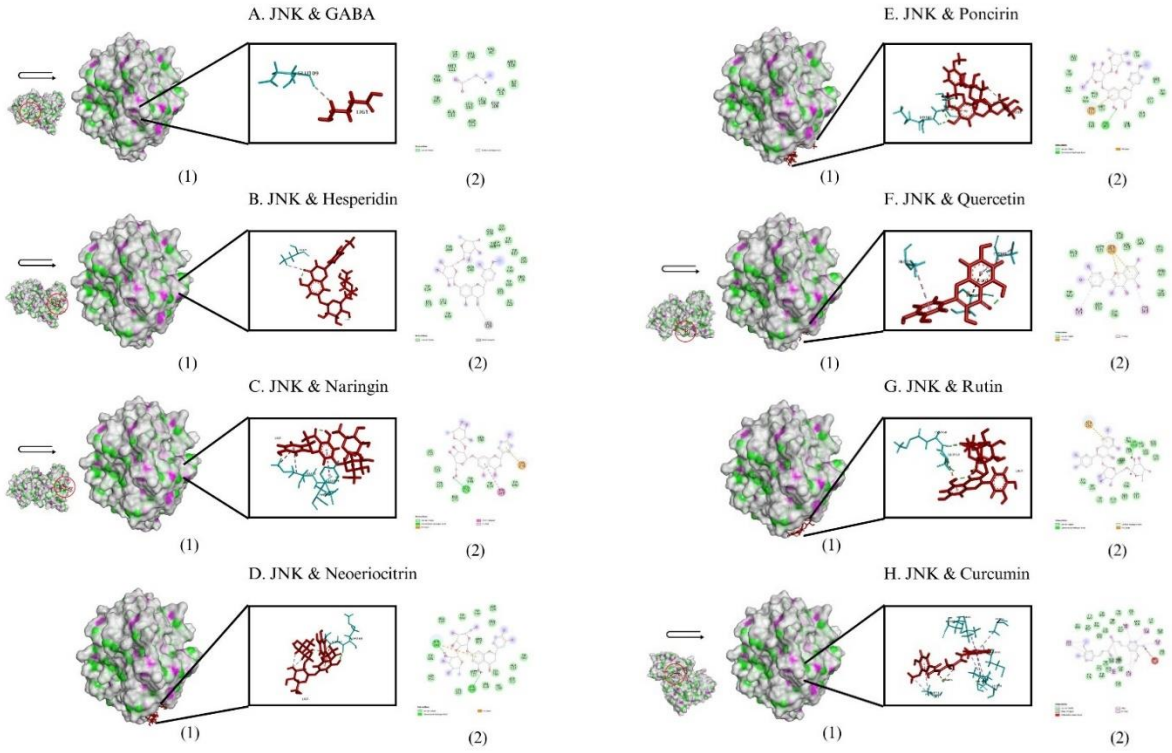


**Figure 6. Interactions between Ligands and JNK Visualized using Discovery Studio 4.1 (A–H); 3D Structures (1) and 2D Structures (2) of the Interaction between *Citrus amblycarpa* Compounds and JNK; Molecular Docking Performed using Swiss Dock Software and Visualization by the Discovery Studio Visualizer v19.1.0.18287 Program**

inflammation in the liver [51]. Compounds with low affinities to adiponectin, such as GABA and quercetin, have weak interactions with this protein. Although some van der Waals force and hydrogen bonds may be present, their low affinities to adiponectin might reduce their effectiveness in inhibiting this protein's activity. Therefore, these compounds might not have a significant impact on reducing hepatic inflammation.

The results of molecular interaction analysis of NF-kB, TNF-alpha, IL-6, JNK, and adiponectin with GABA, hesperidin, quercetin, poncirin, neoeriocitrin, rutin, naringin, and curcumin are depicted in Table 2. For NF-kB, it exhibits complex interactions with various ligands. In particular, hydrogen bond is dominant in the interaction between NF-kB and rutin involving THR401 and GLN403 (Figure 7). NF-kB interacts with GABA through attractive charges on amino acid residues GLU501 and ARG451. Hesperidin forms pi-cation bonding with GLN403 and LEU404 and pi-alkyl interactions with ALA400. Naringin interacts with the ARG405 residue through conventional hydrogen bonding and forms carbon hydrogen bonding with THR401 and metal acceptor interactions with HSE415. Neoeriocitrin engages in conventional hydrogen bonding with the GLN403 residue and carbon hydrogen bonding with GLN403 and THR401. It also interacts through pi-cation bonding with LEU404 and pi-donor interactions with GLN403 and THR401. Poncirin forms conventional hydrogen bonding with LEU404, carbon hydrogen bonding with THR401, and metal acceptor interactions with LEU404. Unfavorable interactions also occur between the metal acceptor and THR401, as along with pi-cation bonding with GLN403 and LEU404 and amide pi–pi stack interactions with GLN403. Quercetin interacts with the GLY602 residue through hydrogen bonding and forms metal acceptor interactions with LEU604. It also interacts through pi-cation bonding with LYS373, ARG601, and GLY602 and pi-alkyl interactions with ARG601 and LEU604. However, all the tested ligands did not involve any of the residues in the reference ligand–receptor interaction (Figure 4).

Neoeriocitrin, poncirin, quercetin, and rutin have the same amino acid residue, SER 161, when docked with JNK (Figure 6). However, they do not share any residue with curcumin. When reacted with adiponectin, neoeriocitrin shows three amino acid residues in common with curcumin, namely, GLY 223, PRO41, and VAL93 (Figure 4). For TNF-alpha, it involves the same key amino acid residues as curcumin, namely, LEU36 when interacting with neoeriocitrin and ALA33 when interacting with rutin (Figure 8). GABA forms conventional hydrogen bonds with the ASN92 residue and carbon hydrogen bonds with ASN34. Hesperidin interacts through carbon hydrogen bonds and pi-cation

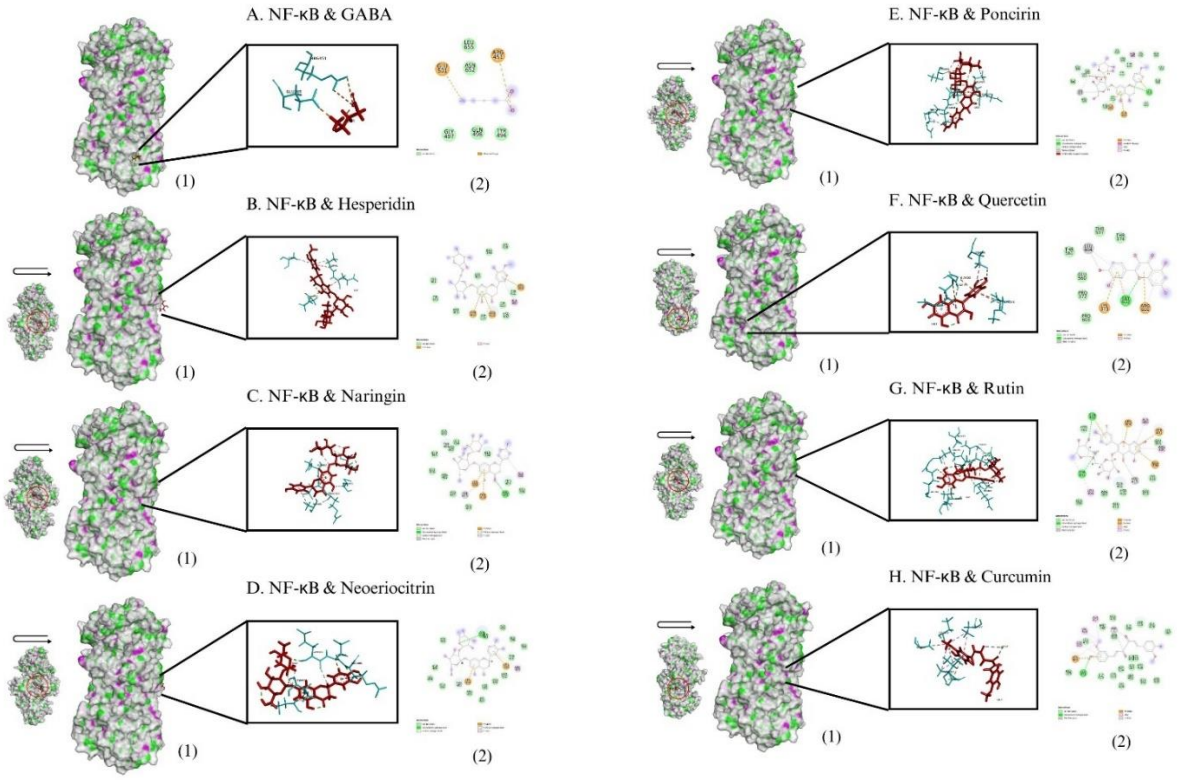


**Figure 7. Interactions between Ligands and NF-kβ Visualized using Discovery Studio 4.1 (A–H); 3D Structures (1) and 2D Structures (2) of the Interaction between *Citrus amblycarpa* Compounds and NF-kβ; Molecular Docking Performed using Swiss Dock Software and Visualization by the Discovery Studio Visualizer v19.1.0.18287 Program**

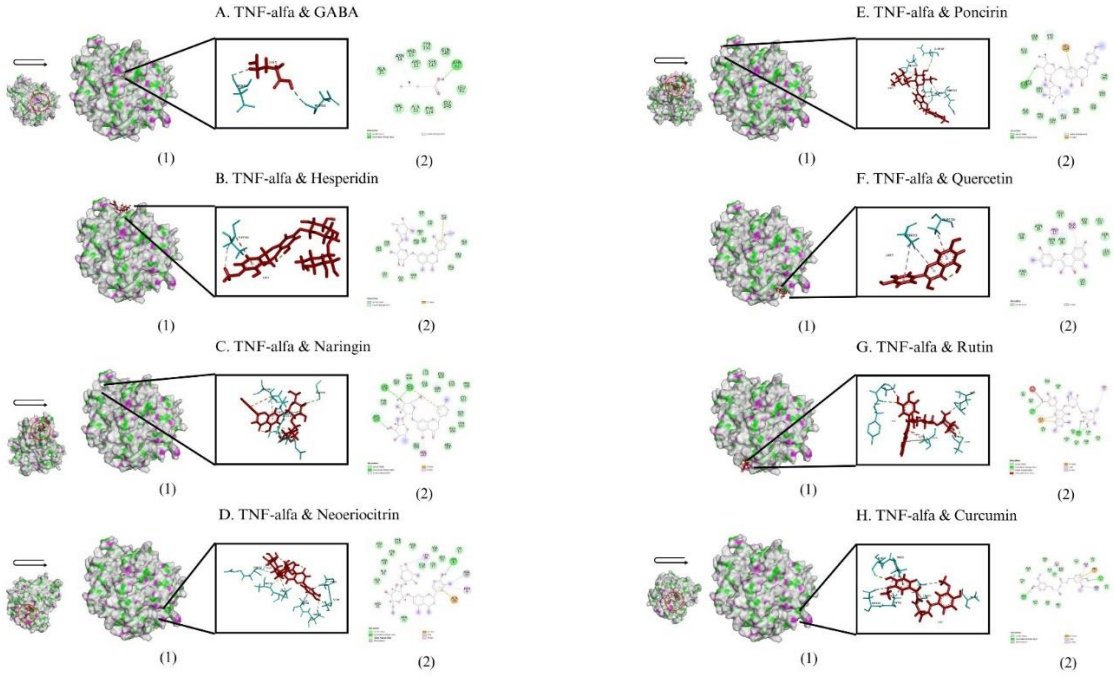


**Figure 8. Interactions between Ligands and TNF-alpha Visualized using Discovery Studio 4.1 (A–H); 3D Structures (1) and 2D Structures (2) of the Interaction between *Citrus amblycarpa* Compounds and TNF-alpha; Molecular Docking Performed using Swiss Dock Software and Visualization by the Discovery Studio Visualizer v19.1.0.18287 Program**

interactions with the THR105 residue. Naringin forms conventional hydrogen bonds with the ARG103, GLY108, and GLU104 residues; carbon hydrogen bonds with ARG103 and GLU104; pi-anion interaction with GLU104; and pi-alkyl interaction with ARG103. Neoeriocitrin interacts through conventional hydrogen bonds with the SER9 residue; carbon hydrogen bonds with ALA35 and ARG32; metal acceptor interactions with the ASN39 residue; pi-cation bonding with ALA38; and alkyl and pi-alkyl interactions with LEU36 and PRO8. Poncirin forms conventional hydrogen bonds with the GLN102 residue, carbon hydrogen bonds with GLU104 and ARG103, and pi-cation interaction with GLU104. Quercetin interacts through pi-alkyl bonding with PRO12 and ALA156. Rutin forms conventional hydrogen bonds with the TYR87 and ALA35 residues. An unfavorable interaction also occurs between donors and SER86. Moreover, this ligand interacts through pi-cation bonding with ALA33 and alkyl and pi-alkyl interactions with ARG6.

For IL-6, GABA forms conventional hydrogen bonds with the ASP134 residue and carbon hydrogen bonds with ALA135 (Figure 5). Hesperidin interacts through carbon hydrogen bonds with THR134 and PHE136 and alkyl and pi-alkyl interactions with PRO157, VAL15, and ALA181. Naringin forms conventional hydrogen bonds with LYS146 and LYS120, pi-anion interaction with GLU95, and a pi–pi T-shaped interaction with PHE147. Neoeriocitrin interacts through pi-cation and pi-donor hydrogen bonds with MET250 and pi-alkyl interactions with MET250. Poncirin forms carbon hydrogen bonds with TRP247; pi-cation bonds with PRO251, GLN249, and SER248; a pi-donor hydrogen bond with TRP247; and a pi-alkyl interaction with GLN249. Quercetin interacts through conventional hydrogen bonds with ASP149 and unfavorable acceptor interactions with ASP149. Pi-cation interactions also occur with CYS150, LYS151, THR161, and LYS153, pi-donor hydrogen bonds with LYS151 and THR161, and pi-lone pair interactions with THR161. This ligand also interacts through alkyl and pi-alkyl interactions with CYS160 and CYS150. Rutin forms conventional hydrogen bonds with THR130, THR134, HSD131, and ASP155 and carbon hydrogen bonds with LEU132 and THR130. It also exhibits pi-cation, pi–pi T-shaped, and pi-alkyl interactions with ARG154.

Adiponectin displays complex interactions with various ligands through numerous different amino acid residues. It interacts with GABA through conventional hydrogen bonds with TYR236 and TYR240 residues and carbon hydrogen bonds with PHE239 and TYR236 residues. Hesperidin interacts through alkyl and pi-alkyl interactions with LEU250, VAL232, LEU225, LEU189, and ILE261 residues. Naringin forms conventional hydrogen bonds with GLY163 residue and interacts through metal acceptor interactions with LEU178, pi-cation interactions with GLY185, and alkyl and pi-alkyl interactions with PHE168 and MET167. Neoeriocitrin interacts through conventional hydrogen bonds with LYS178, GLY223, and LEU243; pi-cation bonding with PRO41 and GLN179; and pi-alkyl interaction with VAL93. Poncirin forms carbon hydrogen bonds with TYR240 and interacts through pi–pi T-shaped interactions with TYR236 and pi-alkyl interactions with VAL232, LEU186, and CYS246. Quercetin interacts through conventional hydrogen bonds with TYR236 and GLY378, pi–pi T-shaped interactions with TYR240, and pi-alkyl interactions with CYS246 and CYS380. Rutin forms conventional hydrogen bonds with LEU186, carbon hydrogen bonds with LEU186, and alkyl and pi-alkyl interactions with LEU250, LEU189, and LEU193.

Neoeriocitrin, poncirin, quercetin, and rutin involve various amino acid residues when docked with JNK, but none are the same as those for curcumin (Figure 5). Their overlapping residue is SER161. Neoeriocitrin and adiponectin interaction has three amino acid residues in common with curcumin, namely, GLY 223, PRO41 and VAL93. This study reveals a variety of binding affinities and interaction types between compounds and proteins involved in hepatic inflammation. These proteins can inhibit hepatic inflammation caused by lipid accumulation, which peaks under certain circumstances. The findings have significant implications for the development of treatment strategies to address hepatic inflammation due to lipid accumulation in the future.

## Conclusion

Rutin, poncirin, hesperidin, and neoeriocitrin presented high affinities to NF-κB, TNF-alpha, IL-6, and adiponectin proteins, respectively. The neoeriocitrin–adiponectin interaction involved GLY 223, PRO41, and VAL93 residues, which were similar to those in curcumin–adiponectin complex interaction. Thus, the most potential inhibitor of hepatic sterosis inflammation was neoeriocitrin. This study showed that *C. Amblycarpa* compound could be a candidate drug against hepatic inflammation. Further research is needed to comprehensively understand the mechanisms of these compounds and validate their potential in the development of anti-inflammatory hepatic therapies.

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