Antineuroinflammatory Properties of Compounds from Ethyl Acetate Fraction of *Marsilea crenata* C. Presl. Against Toll-Like Receptor 2 (3A7B) *In Silico*

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Abstract

Parkinson’s disease (PD) can be triggered by overactive TLR2 due to α-synuclein abnormalities and aggregation. *Marsilea crenata* C. Presl. leaves inhibit neuroinflammatory progression. This study aimed to predict the antineuroinflammatory activity of M. crenata leaves with TLR2 (ID 3A7B) in an *in silico* study. The list of chemicals was collected through metabolite profiling with UPLC-QToF MS/MS, then analyzed for physicochemical properties using SwissADME and toxicity using the ProTox II online program. This analysis confirmed the molecule’s safety for therapeutic use. ChemDraw 12.0 was used to build metabolite-profiled compounds. Avogadro 1.2.0 was utilized to optimize geometry, while PyRx 0.8 was used for AutoDock Vina molecular docking. Agonist-TLR2 interactions were examined using docking results from Biovia Discovery Studio 2021. Tethering is valid; the program can be used because the RMSD is less than 2. The results showed that 6 of the 84 metabolite-profiled compounds were antagonistic to 3A7B and shared similar pharmacophore distances and amino acid linkages with N-acetyl-D-glucosamine, a native ligand of 3A7B. By binding to TLR2, the compounds from the ethyl acetate fraction of *M. crenata* leaves may potentially inhibit PD progression.

**Keywords**: *Marsilea crenata* C. Presl., Parkinson disease, neuroinflammation, *in silico*, 3A7B

Background

Neuroinflammation is a natural response of the central nervous system (CNS) to neurotoxic chemicals in order to protect neural tissue. On the other hand, conditions that cause inflammation in the central nervous system (CNS) for a long time can kill hippocampal neuronal cells and reduce cognitive function, which can lead to neurodegenerative diseases (Cherry *et al.*, 2014; Chen *et al.*, 2016; Mizuno, 2015; Ma’arif *et al.*, 2022).
Parkinson's disease (PD) is a neurological illness with a significant prevalence, particularly among geriatrics aged 65 to 70 years (Balestrino & Schapira, 2020; Ma'arif et al., 2021a), marked by tremors, bradykinesia, melancholy, anxiety, sleep disturbances, and dementia (Syamsudin, 2015). The accumulation of Lewy bodies caused by aberrant α-synuclein aggregation is the primary etiology of Parkinson's disease. α-synuclein can promote neuronal cell degeneration and apoptosis as a result of the activation of tool-like receptor 2 (TLR2) on microglia cells, which leads to increased production of proinflammatory cytokines and neuroinflammation. TLR2 is made by microglia cells and helps them recognize pathogens, such as chemicals that are harmful to neurons (Cario, 2008; Borrello et al., 2011).

Semanggi (Marsilea crenata Presl.) is a plant that is used as a particular cuisine for the local community in Surabaya, East Java. In a previous study, M. crenata Presl. was shown to inhibit neuroinflammation progression via the estrogen-receptor (ER) dependent pathway, specifically by decreasing the expression of major histocompatibility complex II (MHCII) and increasing the expression of arginase 1 (Arg1), both of which were caused by phytoestrogen compounds in M. crenata Presl. leaves binding with ER (Ma’arif et al., 2020a; 2020b; 2021b, 2022c; 2022d). This plant also has the effect of increasing locomotor activity in the rotenone-induced parkinsonian zebrafish (Ma’arif et al., 2022e; 2022f).

The goal of this work is to build on prior research that was used in silico to anticipate the antineuroinflammatory action of M. crenata Presl. leave on the TLR2 activation inhibitory pathway (ID 3A7B). In silico research is a computational simulation method that predicts the activity of substances in new drug discovery attempts by employing specific software and web technologies. In silico molecular docking is used to connect small compounds or ligands to macromolecules or receptors (Prieto-Martinez et al., 2018; Makatita et al., 2020).

Materials and Methods

Material
The ingredients in this study were 84 compounds from previous studies (Ma’arif, 2020) on the metabolite profiling of the ethyl acetate fraction of M. crenata Presl. leaves using the UPLC-QToF-MS/MS method and TLR2 receptors with ID 3A7B downloaded from www.rcsb.org containing the native ligand N-acetyl-D-glucosamine. This natural ligand stops microglia cells from becoming active, which is what causes neuroinflammation (Hwang et al., 2010).

Physicochemical examination
Compounds identified through metabolite profiling were structured into a simplified molecular-input line-entry system (SMILES) using ChemDraw Ultra 12.0, and the SMILES form was employed so that the compounds could be examined for their physicochemical qualities in the IUPAC name format (Sliwoski et al., 2014). The format is then copied one at a time onto the SwissADME webtool (http://www.swissadme.ch) and run to find the topological polar surface area (TPSA), molecular weight, log P, HBA, HBD, and the statement "Yes" or "No" in meeting Lipinski's five law requirements (Muslikh et al., 2022).

Toxicity testing
A toxicity study was performed by entering the SMILES format into the ProTox II online program (http://tox.charite.de/protox_II/) to predict compound toxicity (LDso) based on the globally harmonized system (GHS).

Preparation of the sample
The Biovia Discovery Studio 2021 program was used to extract receptors from macromolecules and natural ligands. Using ChemDraw Ultra 12.0, the metabolite profiles of the ethyl acetate fraction of M. crenata Presl. leaves were used to make 84 compounds with a 3D structure.
Molecular docking

Compounds that satisfy Lipinski's five law parameters and are non-toxic are geometrically optimized using Avogadro 1.0.1 and the MMFF94 technique. Internal validation of the receptor and native ligand was performed first using AutoDock Vina (PyRx 0.8) to determine the root mean square deviation (RMSD), with an RMSD value of less than 2 indicating that the application is suitable for use (Riwanti et al., 2021). Each drug was docked to the 3A7B receptor using AutoDock Vina (PyRx 0.8), and the interaction was visualized using Biovia Discover Studio 2021 to determine the distance between the pharmacophore and the bound amino acids.

Result and Discussion

A total of 84 compounds from metabolite profiling with UPLC-QToF-MS/MS were screened using SwissADME to see pharmacokinetic and pharmacodynamic properties. The results showed that there were 74 compounds that stated "Yes" in fulfilling Lipinski's five law parameters of molecular weight <500 g/mol, HBD <5, HBA <10, and log p <5, which indicate the compound can be accepted by the body (Ma’arif et al., 2021c). Table 1 A molecular weight of less than 500 g/mol suggests that the molecule is capable of penetrating biological membranes. The log P value shows the compound's capacity to dissolve in the liquid membrane. The hydrogen bonding capacity of the H-acceptor and H-donor is shown, and the higher the value, the more energy is required for the absorption process (Lipinski et al., 1997). The TPSA value is a measure that shows a chemical's capacity to cross the blood-brain barrier when the compound is aimed at the central nervous system (Martin, 2005; Villa et al., 2016; Ma’arif et al., 2022b).

Toxicity studies were performed on 74 substances that matched the Lipinski’s five law parameters. This test was performed to determine the capacity of hazardous chemicals in the ethyl acetate fraction of M. crenata Presl. leaves to be absorbed by the body. The goal of determining the LD50 value is to find a single dose of the test compound that may kill 50% of the experimental animals in one administration so that the potential toxicity of the compound can be determined (Nurmianti & Gusmawarni, 2020). The GHS classification of toxicity levels into six classes. The six toxicity classes are as follows: class I (LD50 ≤5 mg/kg) is fatal if swallowed, class II (5 < LD50 ≤ 50 mg/kg) is toxic if swallowed, class III (50 < LD50 ≤ 300 mg/kg) is toxic if swallowed, class IV (300 < LD50 ≤ 2000 mg/kg) is harmful if swallowed, class V (2000 < LD50 ≤ 5000 mg/kg) may be harmful if swallowed, and class VI (LD50 >5000 mg/kg) (Muslikh et al., 2023). The bigger the LD50 number, the less dangerous the compound is, and vice versa, the greater the value indicated by the LD50, the safer the substance is for the body. The results of this toxicity test show 64 substances with low toxicity in classes 4 and 5 (Supandi et al., 2018), as shown in Table 1.

Table 1. Pharmacokinetic and pharmacodynamic analysis from ethyl acetate fraction of M. crenata Presl. leaves antagonistic to 3A7B

<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds</th>
<th>Parameters of Lipinski's Five Laws</th>
<th>Lipinski’s Five Laws</th>
<th>TPSA (Å²)</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Molecular Weight ≤ 500 g/mol</td>
<td>HBA ≤10</td>
<td>HBD ≤5</td>
<td>Log P ≤5</td>
</tr>
<tr>
<td>1.</td>
<td>Valinol</td>
<td>103.16</td>
<td>2</td>
<td>2</td>
<td>0.28</td>
</tr>
<tr>
<td>2.</td>
<td>3,3’-[(1E)-3-Ethyl-1-triazene-1,5- diyl]bis(4-methoxy-1,2,5- oxadiazole)</td>
<td>269.22</td>
<td>10</td>
<td>0</td>
<td>1.38</td>
</tr>
<tr>
<td>3.</td>
<td>11-Aminoundecanoic acid</td>
<td>201.31</td>
<td>3</td>
<td>2</td>
<td>1.62</td>
</tr>
<tr>
<td>4.</td>
<td>Diethofencarb</td>
<td>267.32</td>
<td>4</td>
<td>1</td>
<td>2.75</td>
</tr>
<tr>
<td>5.</td>
<td>N,N’-1,4-Phenylenediacetamide</td>
<td>192.21</td>
<td>2</td>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>6.</td>
<td>2,2’-[(6-Amino-5-nitro-2,4- pyrimidinediyl)dimino]diethanol</td>
<td>258.23</td>
<td>6</td>
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<td>-1.04</td>
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<tr>
<td>7.</td>
<td>Phenpropamate</td>
<td>179.22</td>
<td>2</td>
<td>1</td>
<td>1.80</td>
</tr>
<tr>
<td>8.</td>
<td>N-(2-Oxododecanoyl)-L-homoserine</td>
<td>315.41</td>
<td>5</td>
<td>3</td>
<td>2.19</td>
</tr>
<tr>
<td>No.</td>
<td>Compounds</td>
<td>Molecular Weight ≤ 500 g/mol</td>
<td>HBA ≤ 10</td>
<td>HBD ≤ 5</td>
<td>Log P ≤ 5</td>
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<td>-----</td>
<td>-----------</td>
<td>-----------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>9</td>
<td>3-(4-Carboxamidoyl-1-piperazinyl)-2-hydroxy-1-propanesulfonic acid</td>
<td>266.32</td>
<td>6</td>
<td>4</td>
<td>-2.17</td>
</tr>
<tr>
<td>10</td>
<td>N,N,N′-Trimethyl-6-[3-(methylsulfonyl)-1H,1,2,4-triazol-1-yl]-1,3,5-triazine-2,4-diamine</td>
<td>266.33</td>
<td>5</td>
<td>1</td>
<td>0.75</td>
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<tr>
<td>11</td>
<td>Dopaamine</td>
<td>315.41</td>
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<td>12</td>
<td>DMCM</td>
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<td>1.72</td>
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<td>Propazone</td>
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<td>0.22</td>
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<td>15</td>
<td>N-Ethyl-N(2-thienylmethyl)-L-methioninamide hydrochloride</td>
<td>308.89</td>
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<td>16</td>
<td>2-Methyl-2-propanyl 4-oxo-1-piperidinecarboxylate</td>
<td>199.25</td>
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<td>0</td>
<td>1.19</td>
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<tr>
<td>17</td>
<td>1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxyl]-2-propanol (2E)-2-butenedioate (1:1)</td>
<td>383.44</td>
<td>8</td>
<td>4</td>
<td>1.49</td>
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<tr>
<td>18</td>
<td>Periloryne</td>
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<td>19</td>
<td>Tetradecasphinganine</td>
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<td>C16 phytophosphosine</td>
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<td>4</td>
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<tr>
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<td>(1-Oxo-4-phenyl-2(1H)-phthalazinyl)acetic acid</td>
<td>280.28</td>
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<td>22</td>
<td>1,1′-(Decylimino)dio(2-propanol)</td>
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<td>3</td>
<td>2</td>
<td>3.58</td>
</tr>
<tr>
<td>23</td>
<td>Phytophosphosine</td>
<td>317.51</td>
<td>4</td>
<td>4</td>
<td>3.60</td>
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<tr>
<td>24</td>
<td>(2S,3R)-2-Amino-1,3-heptadecanediol</td>
<td>287.48</td>
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<td>3</td>
<td>4.08</td>
</tr>
<tr>
<td>25</td>
<td>Pentadecylamine</td>
<td>227.43</td>
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<td>1</td>
<td>4.21</td>
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<td>Safingol</td>
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<td>3-(Hexadecylamino)-1,2-propanediol</td>
<td>315.53</td>
<td>3</td>
<td>3</td>
<td>4.81</td>
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<td>28</td>
<td>N'-[4,6-Di(4-morpholinyl)-1,3,5-triazin-2-yl]-N'-methyl-2-(4-morpholinyl)propanehydrazide</td>
<td>436.51</td>
<td>8</td>
<td>1</td>
<td>-0.13</td>
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<tr>
<td>29</td>
<td>Gloeosolactone</td>
<td>292.41</td>
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<td>0</td>
<td>4.09</td>
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<td>30</td>
<td>Docetyl phthalate</td>
<td>390.56</td>
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<td>6.30</td>
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<td>31</td>
<td>Eucamidine</td>
<td>337.58</td>
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<td>1</td>
<td>6.76</td>
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<td>32</td>
<td>(2E,4E)-N-Isobutyl-2,4-icosadienamide</td>
<td>363.62</td>
<td>1</td>
<td>1</td>
<td>7.27</td>
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<td>33</td>
<td>1-Hydroxy-2,2,6,6-tetramethyl-4-piperidinyl stearate</td>
<td>439.71</td>
<td>4</td>
<td>1</td>
<td>7.37</td>
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<td>34</td>
<td>2-Deoxy-2-(diethylamino)hexopyranose</td>
<td>235.28</td>
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<td>3,4,5-Trin(1,2,4-triazin-3-yl)-2-pyridinecarboxamide</td>
<td>359.31</td>
<td>11</td>
<td>1</td>
<td>-0.67</td>
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<td>36</td>
<td>Dimethylsulfoxide (DMSO)</td>
<td>78.13</td>
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<td>Picolinamide</td>
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<td>0.31</td>
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<tr>
<td>38</td>
<td>Chlorogenic acid</td>
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<td>6</td>
<td>-0.39</td>
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<td>39</td>
<td>Clovamide</td>
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<td>Deoxyclovamide</td>
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<td>1.59</td>
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<td>3,4,5-Trimethoxy-N-(4-pyridindimethyl)benzamide</td>
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<td>1.79</td>
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<td>7-methoxy-4-(aminomethyl)coumarin</td>
<td>205.21</td>
<td>4</td>
<td>1</td>
<td>1.31</td>
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<tr>
<td>43</td>
<td>6-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-4-oxo-1-phenylbutyl]-3,4-dihydro-2H-pyran-2-one</td>
<td>465.37</td>
<td>3</td>
<td>0</td>
<td>6.24</td>
</tr>
<tr>
<td>44</td>
<td>Kamprerol</td>
<td>286.24</td>
<td>6</td>
<td>4</td>
<td>1.58</td>
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<tr>
<td>45</td>
<td>1,3,5-Trinitro-2,4,6-tripropoxybenzene</td>
<td>387.34</td>
<td>9</td>
<td>0</td>
<td>1.41</td>
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<tr>
<td>46</td>
<td>2-Chloro-4-(1H-imidazol-1-yl)-6-(1-piperidinyl)-1,3,5-triazine</td>
<td>264.71</td>
<td>4</td>
<td>0</td>
<td>1.67</td>
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<td>47</td>
<td>Alidrene</td>
<td>289.41</td>
<td>3</td>
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<td>2.98</td>
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<td>48</td>
<td>Piperidolate</td>
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<td>49</td>
<td>Aspirin Arginine</td>
<td>354.36</td>
<td>8</td>
<td>6</td>
<td>-1.03</td>
</tr>
<tr>
<td>50</td>
<td>2,2-Dimethyl-4,13-dioxo-3,8,11,17,20-pentaaza-5,14-diazadocosan-22-oic acid</td>
<td>408.44</td>
<td>9</td>
<td>3</td>
<td>0.37</td>
</tr>
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<td>51</td>
<td>Jasmonate</td>
<td>180.24</td>
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<td>1.89</td>
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<tr>
<td>52</td>
<td>CB-13</td>
<td>368.47</td>
<td>2</td>
<td>0</td>
<td>6.08</td>
</tr>
<tr>
<td>53</td>
<td>Asparaginylcysteinyhtreomine</td>
<td>336.36</td>
<td>7</td>
<td>6</td>
<td>-2.78</td>
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</tbody>
</table>
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The RMSD of the validation technique using receptor and native ligand binding using AutoDock Vina (PyRx 0.8) was 1.761 Å. RMSD of less than 2 implies that the application is appropriate for molecular anchoring techniques that provide near-experimental outcomes (Nursamsiar et al., 2020; Ma’arif et al., 2021d). The receptor 3A7B and 64 metabolite-profiled molecules were then re-tethered with AutoDock Vina (PyRx 0.8). In addition, Biovia Discovery Studio 2021 was used to determine the amino acids produced, the pharmacophore distance, and the type of bond. The results of molecular docking showed that six molecules were bad for 3A7B. They are all listed in Table 2.

### Table 2. Pharmacokinetic and pharmacodynamic analysis from ethyl acetate fraction of *M. crenata* Presl. leaves antagonistic to 3A7B

<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds</th>
<th>Binding Affinity (kcal/mol)</th>
<th>Amino Acids (Types of Bonds)</th>
<th>Pharmacophore Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Native Ligand</td>
<td>-2.4</td>
<td>Pro387 (Hydrogen)</td>
<td>3.437</td>
</tr>
<tr>
<td>2</td>
<td>Valinol</td>
<td>-2</td>
<td>Pro387 (Hydrogen)</td>
<td>2.925</td>
</tr>
<tr>
<td>3</td>
<td>3,3’-[(1E)-3-Ethyl-1-triazene-1,3-diyl]bis(4-methoxy-1,2,5-oxadiazole)</td>
<td>-2.27</td>
<td>Pro387 (Hydrogen)</td>
<td>2.536</td>
</tr>
<tr>
<td>4</td>
<td>Phenprobamate</td>
<td>-2.37</td>
<td>Pro387 (Hydrogen Donor)</td>
<td>2.575</td>
</tr>
<tr>
<td>5</td>
<td>Propazone</td>
<td>-2.3</td>
<td>Pro387 (Hydrogen)</td>
<td>2.640</td>
</tr>
<tr>
<td>6</td>
<td>Tetradecasphinganine</td>
<td>-1.33</td>
<td>Pro387 (Hydrogen)</td>
<td>3.781</td>
</tr>
<tr>
<td>7</td>
<td>2-Deoxy-2-(diethylamino)hexopyranose</td>
<td>-1.8</td>
<td>Pro387 (Carbon Hydrogen)</td>
<td>3.597</td>
</tr>
</tbody>
</table>
The native ligand N-Acetyl-D-Glucosamine is antagonistic and inhibits TLR2 activation by binding to amino acids in the form of Pro 387 and Asn 414 and a pharmacophore distance of 3.437 Å, each of which is in the form of hydrogen bonds. Compounds are said to be antagonists if they bind to the same amino acid as the native ligand (Figure 1). The more similar the amino acids bound by the compounds in M. crenata Presl. leaves are to native ligands, the more similar the types of interactions that occur (Ekins et al., 2007; Suhud et al., 2015). Also, the similarity of the pharmacophore distance determines how similar the activities are (source). The resulting binding affinity shows a negative value, which explains the strong and stable bond formed (Syahputra et al., 2014). The results of the analysis of agonist compounds in Biovia Discovery Studio 2021 can be seen in Figures 2 to 7.
Figure 3. Visualization of 3,3’-[(1E)-3-ethyl-1-triazene-1,3-diyl]bis(4-methoxy-1,2,5-oxadiazole) compounds with TLR2. A: 2D; B: 3D

Figure 4. Visualization of phenprobamate with TLR2. A: 2D; B: 3D

Figure 5. Visualization of propazone with TLR2. A: 2D; B: 3D
Figure 6. Visualization of tetradecasphanganine with TLR2. A: 2D; B: 3D

Figure 7. Visualization of 2-deoxy-2-(diethylamino)hexopyranose with TLR2. A: 2D; B: 3D

Compounds that match Lipinski’s five law requirements, have a high potential as antineuroinflammatory agents. Six chemicals are "yes" and have low toxicity: valinol; 3,3’-[(1E)-3-ethyl-1-triazene-1,3-diyl]bis(4-methoxy-1,2,5-oxadiazole); phenprobamate; propazone; tetradecasphanganine; and 2-deoxy-2-(diethylamino)hexopyranose. These chemicals are expected to be powerful enough to bind TLR2, hence suppressing their activity. Blocking the TLR2 pathway could be the basis of future treatments for neuroinflammation (Dzamko et al., 2017).

The abnormal aggregation of α-synuclein is harmful to dopaminergic neuron cells and plays a significant role in the etiology of Parkinson’s disease (Yulianti et al., 2015). TLR2 is involved in the stimulation of the inflammatory response in microglia cells as a result of α-synuclein abnormalities in Parkinson’s disease (Dzamko et al., 2017). Gene mutations can result in α-synuclein disorders such aggregation and degeneration, which are the major components of Lewy bodies (Lewis & Spillane, 2018). Because excessive activation leads the generation of proinflammatory cytokines, microglia cells will be the first to respond to this α-synuclein abnormalities (Gelosa et al., 2017). Marsilea crenata Presl. is an alternative for treating inflammation in Parkinson’s disease sufferers, which primarily affects the elderly. Marsilea crenata Presl. leaves anti-neuroinflammatory activity was tested in silico using the molecular docking approach. Molecular docking is beneficial for predicting the conformation of the ligand when it binds to the target and looking for connections between receptors and ligands (Ferreira et
al., 2015). When the ligand (drug) comes in contact with the receptor, the shape of the macromolecule’s changes, which leads to a biological response (Siswandono, 2015). Pathogens or anomalies that attack the body will be met with self-defense by the immune system, in this example by the TLR. Over-activation of TLRs, on the other hand, can alter brain homeostasis due to excessive synthesis of proinflammatory cytokines, resulting in a variety of illnesses (Gao et al., 2017). TLR2 activation enhances NF-κB translocation from the cytoplasm to the nucleus, where it binds to DNA and initiates the transcription process. This causes microglia cells to respond to M1 polarity circumstances and activates proinflammatory molecules (Penn, 2002; Engler-Chiurazzi et al., 2017). Compounds from M. crenata Presl. suppress TLR activation, causing microglia activity to shift from M1 polarity to M2 polarity, transforming it into an antineuroinflammatory drug (Cui et al., 2013). Furthermore, suppressing TLR2 activation can diminish α-synuclein aggregation. As a result, M. crenata Presl. can act as a neuroprotector, reducing neuroinflammation and improving cognitive performance (Villa et al., 2016; Kwon et al., 2019).

Conclusion

The results showed that 6 of the 84 metabolite-profiled compounds were antagonistic to 3A7B and shared similar pharmacophore distances and amino acid linkages with N-acetyl-D-glucosamine, a native ligand of 3A7B. By binding to TLR2, the compounds from the ethyl acetate fraction of M. crenata leaves may have the potential to inhibit PD progression with an anti-inflammatory mechanism.

References


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