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DISRUPTING THE INTERACTION OF IL-1/IL-1 RECEPTOR WITH *Morinda officinalis* BIOACTIVE COMPOUNDS AS STRATEGY TO COMBAT CHRONIC INFLAMMATORY DISEASES: THE INSIGHT FROM *IN SILICO* STUDY

Wira Eka Putra[1,2,*], Sustiprijatno[3], Wa Ode Salma[4], Diana Widiastuti[5]

[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia*
[2]*Department of Biotechnology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia*
[3]*Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development, West Java, Indonesia*
[4]*Department of Nutrition, Faculty of Public Health, Halu Oleo University, Indonesia*
[5]*Departmentof Chemistry, Faculty of Mathematics and Natural Science, Universitas Pakuan, West Java, Indonesia*

*Corresponding author: wira.putra.fmipa@um.ac.id

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Abstract

Chronic inflammatory diseases are serious health problems worldwide. Furthermore, this entity leads to several types of diseases, including cancer, cardiovascular diseases, autoimmune diseases, and diabetes. Many modalities have been proposed to ameliorate chronic inflammatory diseases, including the use of traditional medicine. Recently, the use of herbs as traditional medicine becomes popular in all aspects of society. One of the most plants that are widely used is *Morinda officinalis*. Importantly, *M. officinalis* exerts its medical properties in multiple biological activities, including anti-cancer, anti-inflammatory, and even cardiovascular activity. Thus, in this study, we aimed to evaluate the bioactive compounds of *M. officinalis* through *in silico* approach as an inhibitor of interleukin-1/ interleukin-1 receptor (IL-1/IL-1R) interaction to ameliorate the chronic inflammatory diseases. Molecular docking was used as prediction methods of interaction between the ligands and target protein. In this present study, we found three compounds, namely 1,2-dihydroxy-3-methylanthraquinone, rubiadin, and rubiadin-1-methyl ether, the greatest score of binding affinity (-7.6 kcal/mol) to the target protein. Data visualization also showed a similar interaction pattern, which ensures they have similar binding areas in the target protein, the IL-1R. Therefore, this prediction suggested that these three compounds might provide potential as an inhibitor against the IL-1R. Further research needs to be done to clarify and explore more details about the biological activity of these compounds, especially in chronic inflammatory diseases.

INTRODUCTION

Inflammation is an immune system response as a first-line defense against antigen invasion. However, inflammation action is like a double-edged sword, responsible for antigen elimination. It can promote the worst clinical condition such as cancer, autoimmune diseases, rheumatoid arthritis (RA), and other inflammation chronic diseases [1-3]. Inflammation is a classic sign of chronic inflammation diseases [4,5]. For instance, it has been widely reported that the IL-1/IL-1R is responsible for RA's pathogenesis [6]. The IL-1/IL-1R are unique because these cytokine and receptors are widely associated with innate immunity. The

increasing interaction of IL-1/IL-1R promotes the inflammation cytokines production and induces the inflammation clinically. However, another study showed that blocking IL-1/IL-1R decreased the adverse effect of RA in both clinical and histological view [7]. Discoveries about alternative small molecules or strategies against inflammation-related diseases are important, especially blocking the interaction of IL-1/IL-1R [8]. Nowadays, the use of herbal medicine has become popular in all aspects of society [9]. Herbal medicine offers several benefits compared to current medicine. Herbal medicine can reduce the side effect. More important, herbal medicine more accessible to obtained [9,10].

M. officinalis is a kind of shrub found in the subtropical and tropical regions. This plant has been cultivated for a long time ago due to its traditional uses. Interestingly, the roots part of this plant is usually used for traditional medicine combating several kinds of diseases such as rheumatoid arthritis, depression, osteoporosis, and Alzheimer's diseases [11]. Importantly, *M. officinalis* roots contain several anthraquinones class such as physcion, rubiadin-1-methyl ether, rubiadin, 1-hydroxy-anthraquinone, 1-hydroxy-2-methylanthraquinone, 1,6-dihydroxy-2-methoxyanthraquinone, 2-hydroxy-3-hydroxymethyanthraquinone, tectoquinone (2-Methylanthraquinone), 1,3-dihydroxy-2-methoxyanthraquinone, 1-hydroxy-3-methoxyanthraquinone, 1,2-dihydroxy-3-methylanthraquinone, 1,3,8-trihydroxy-2-methoxy-anthraquinone, 2-methoxyanthraquinone, alizarin-2-methyl ether, digiferruginol, and anthraquinone-2-carboxylic acid [12]. This study aimed to evaluate the bioactive compounds of M. officinalis roots as an inhibitor against inflammation-related diseases from the above explanation.

MATERIALS AND METHODS

In this present study, the anthraquinones constituent from *M. officinalis* were used as ligands against the IL-1R. The compounds of anthraquinones class were consist of physcion, rubiadin-1-methyl ether, rubiadin, 1-hydroxy-anthraquinone, 1-hydroxy-2-methylanthraquinone, 1,6-dihydroxy-2-methoxyanthraquinone, 2-hydroxy-3-hydroxymethyanthraquinone, tectoquinone (2-Methylanthraquinone), 1,3-dihydroxy-2-methoxyanthraquinone, 1-hydroxy-3-methoxyanthraquinone, 1,2-dihydroxy-3-methylanthraquinone, 1,3,8-trihydroxy-2-methoxy-anthraquinone, 2-methoxyanthraquinone, alizarin-2-methyl ether, digiferruginol, and anthraquinone-2-carboxylic acid. The 2D structure of these compounds was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Further physicochemical properties of each compound based on the Lipinski's rule of five [13] can be seen in Table 1.

On the other hand, the 3D structure of IL-1R protein was built through SWISS-Model (https://swissmodel.expasy.org/) after retrieved the protein sequences from the UniProt database (https://www.uniprot.org/). Further steps such as ligands and protein preparation were done to optimize the molecular docking processes. Molecular docking and data visualization proceeded as similar protocol as previous studies [14-16].

Table 1. The list of bioactive compounds from *M. officinalis* and its physicochemical properties according to Lipinski's rule [13].

No.	Bioactive Compounds	CID	Molecular Mass (Dalton)	Hydrogen Bond Donor	Hydrogen Bond Acceptors	High Lipophilicity (LogP)	Molar Refractivity
1.	Physcion	10639	284	2	5	1.81	67.94
2.	Rubiadin-1-methyl ether	96191	268	1	4	2.15	66.40
3.	Rubiadin	124062	254	2	4	1.66	61.13
4.	1-hydroxy-anthraquinone	8512	224	1	3	1.69	54.12
5.	1-hydroxy-2-methylanthraquinone	160817	238	1	3	1.96	60.25
6.	1,6-dihydroxy-2-methoxyanthraquinone	132521	270	2	5	1.33	61.81
7.	2-hydroxy-3-hydroxymethyanthraquinone	44445519	254	2	4	1.66	61.13
8.	Tectoquinone (2-Methylanthraquinone)	6773	222	0	2	2.26	59.37
9.	1,3-dihydroxy-2-methoxyanthraquinone	146101	270	2	5	1.54	61.82
10.	1-hydroxy-3-methoxyanthraquinone	13412786	254	1	4	1.88	60.28
11.	1,2-dihydroxy-3-methylanthraquinone	429241	254	2	4	1.66	61.13
12.	1,3,8-trihydroxy-2-methoxy-anthraquinone	25202463	286	3	6	1.21	63.35
13.	2-methoxyanthraquinone	18646	238	0	3	2.18	59.40
14.	Alizarin-2-methyl ether	80103	254	1	4	1.88	60.28

15.	Digiferruginol	32209	254	2	4	1.66	61.13
16.	Anthraquinone-2-carboxylic acid	67030	252	1	4	1.44	58.05

RESULTS AND DISCUSSION

In developing countries, society still depends on traditional based medicine. *M. officinalis* is a type of plant that is widely used as medicinal plants in Asia [12,17]. *M. officinalis* roots contain rich compounds such as saccharides, organic acid, anthraquinones, and volatile oils. Many reports demonstrated that *M. officinalis* has therapeutic potencies such as antibacterial, anti-tubercular, anti-cancer, anti-oxidant, anti-inflammatory, and cardiovascular action [17]. Several reports on the chemical properties showed the *M. officinalis* components are distributed in several tissues and organs. Further, the study on acute toxicity and genotoxicity suggests that *M. officinalis* is nontoxic [18]. Thus, this suggested that the *M. officinalis* constituents have big potencies as drug candidates.

In this study, we tried to evaluate several compounds from the anthraquinones group. The compounds from anthraquinone family have a wide spectrum of action related to medical properties, such as anti-arthritic, anti-inflammatory, anti-oxidant, and hepatoprotective activity. Furthermore, the 1,2-dihydroxy-3-methylanthraquinone and rubiadin-1-methyl ether extracted from *M. officinalis* were reported to have anti-ageing, anti-inflammation, anti-tumor, and anti-osteoporotic activity, which control and regulated the osteoblast [17,19]. Many research showed that *M. officinalis* extracts have anti-inflammatory effects. However, the mechanism of action from its constituents is on minimal data.

Table 2. The result of binding affinity value among the target protein, IL-1R and multiple bioactive compounds of *M. oficinalis*

No	Ligands	Target Protein	Binding Affinity
1.	1,2-dihydroxy-3-methylanthraquinone	IL-1R	-7.6 kcal/mol
2.	Rubiadin	IL-1R	-7.6 kcal/mol
3.	Rubiadin-1-methyl ether	IL-1R	-7.6 kcal/mol
4.	2-hydroxy-3-hydroxymethyanthraquinone	IL-1R	-7.5 kcal/mol
5.	1,6-dihydroxy-2-methoxyanthraquinone	IL-1R	-7.3 kcal/mol
6.	1-hydroxy-2-methylanthraquinone	IL-1R	-7.3 kcal/mol
7.	Physcion	IL-1R	-7.3 kcal/mol
8.	Anthraquinone-2-carboxylic acid	IL-1R	-7.3 kcal/mol
9.	Tectoquinone (2-Methylanthraquinone)	IL-1R	-7.2 kcal/mol
10.	Digiferruginol	IL-1R	-7.0 kcal/mol
11.	1,3,8-trihydroxy-2-methoxy-anthraquinone	IL-1R	-7.0 kcal/mol
12.	1,3-dihydroxy-2-methoxyanthraquinone	IL-1R	-7.0 kcal/mol
13.	1-hydroxy-anthraquinone	IL-1R	-7.0 kcal/mol
14.	Alizarin-2-methyl ether	IL-1R	-6.9 kcal/mol
15.	1-hydroxy-3-methoxyanthraquinone	IL-1R	-6.9 kcal/mol
16.	2-methoxyanthraquinone	IL-1R	-6.8 kcal/mol

According to our simulation through molecular docking, we found the top three compounds with favorable binding affinity scores, namely 1,2-dihydroxy-3-methylanthraquinone, rubiadin, and rubiadin-1-methyl ether (Table 2). These three compounds have similar binding affinity scores, -7.6 kcal/mol, and become the highest score compared to others. The data visualization also demonstrated that these compounds are located in similar positions, which means the compounds bind to a similar coordinate (Figure 1). The lower or negative binding affinity scores, the greatest and favorable interaction between ligands and protein will be formed [20,21]. Furthermore, we also noted the interaction of the top three ligands with the highest binding affinity scores and residual amino acid were 1,2-dihydroxy-3-methylanthraquinone – IL-1R (TYR144, PHE128, ILE213, GLN130, VAL141, LEU140, GLY139, LEU132, PRO133, VAL134, PRO143), Rubiadin – IL-1R (LYS131, LEU132, VAL134, PRO133, GLY139, LEU140, VAL141, GLN130, ILE213, PHE128, PRO143, TYR144), and Rubiadin-1-methyl ether – IL-1R (PRO143, LEU132, VAL134, PRO133, LEU140, GLY139, VAL141, GLN130, ILE213, PHE128, A144) (Table 3).

Interestingly, we showed a similar pattern on residual amino acids from these interactions: PRO143, LEU132, VAL134, PRO133, LEU140, GLY139, VAL141 GLN130, ILE213, PHE128, TYR144. These similar patterns ensure that the three ligands bind in the similar binding area of the target protein, IL-1R.

Table 3. List of residual amino acids of target protein that interact with the ligands

No	Ligand-Protein Complex	Amino Acid Residues
1.	1,2-dihydroxy-3-methylanthraquinone – IL-1R	TYR144, PHE128, ILE213, GLN130, VAL141, LEU140, GLY139, LEU132, PRO133, VAL134, PRO143
2.	Rubiadin – IL-1R	LYS131, LEU132, VAL134, PRO133, GLY139, LEU140, VAL141, GLN130, ILE213, PHE128, PRO143, TYR144
3.	Rubiadin-1-methyl ether – IL-1R	PRO143, LEU132, VAL134, PRO133, LEU140, GLY139, VAL141, GLN130, ILE213, PHE128, TYR144

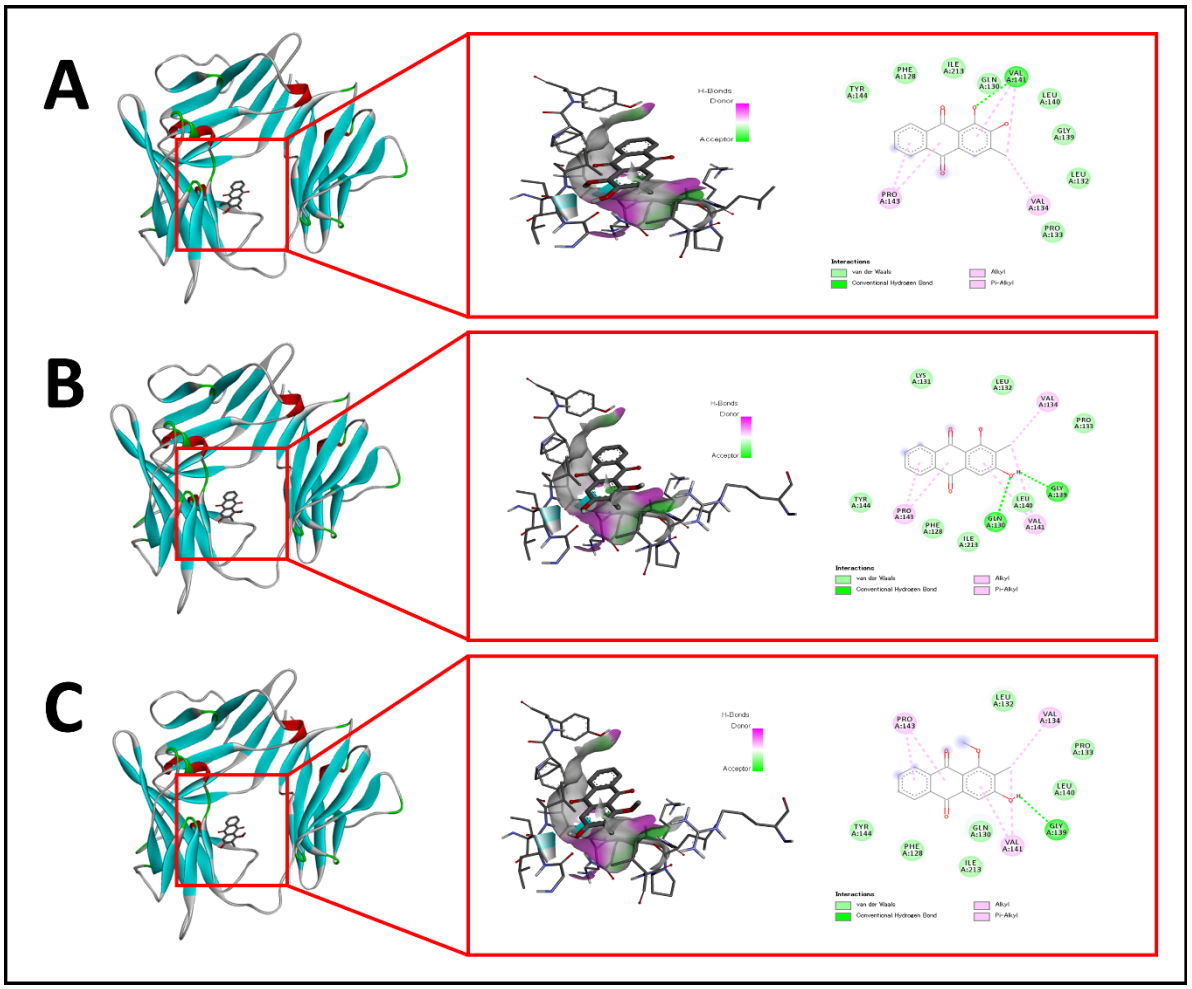

Figure 1. Data visualization from molecular docking simulation of IL-1R protein and top three ligands with the greatest binding affinity.

CONCLUSION

This study predicts three compounds of *M. officinalis* roots that have the greatest binding affinity against IL-1R, namely 1,2-dihydroxy-3-methylanthraquinone, rubiadin and rubiadin-1-methyl ether. Thus, these compounds might be possible to apply as inhibitor agent candidates for ameliorating chronic inflammation diseases. However, further research needs to be done to clarify and explore the biological activities of these compounds.

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CONFLICT OF INTEREST

The authors declare there is no competing interest in this study.

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