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THE POTENCY OF BOESENBERGIN A AND BOESENBERGIN B COMPOUNDS FROM *Kaempferia pandurata* AS ANTI-METASTATIS AGENT: *IN SILICO* STUDY

Wira Eka Putra[a,b,*], Wa Ode Salma[c] and Diana Widiastuti[d]

[a]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Indonesia*
[b]*Department of Biotechnology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, Indonesia*
[c]*Department of Nutrition, Faculty of Public Health, Halu Oleo University, Indonesia*
[d]*Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Pakuan, Indonesia*

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

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Abstract

Metastasis is hallmark of the cancer. Recently, targeting molecules that are responsible in promoting metastasis might be one of favorable strategies. In this study, we aimed to evaluate bioactive compounds of *Kaempferia pandurata* rhizome as anti-metastasis against NF-κB. Molecular docking and molecular interaction among ligands and target protein were applied in this study. Importantly, we found the greatest substances which might possible to become inhibitor to NF-κB. Boesenbergin A and B were predicted to have the favorable interaction scores, -8.2 kcal/mol and -7.1 kcal/mol, respectively. More detail, boesenbergin A has certain interaction to residual amino acids such as GLU160, ASP121, THR153, SER113, LYS149, VAL145, HIS144, THR146, TYR60, ALA62, VAL61, HIS112, ALA111, LEU143, ALA156, ARG157. While the boesenbergin B has interaction to residual amino acids such as SER249, PHE310, LEU272, VAL254, HIS307, ARG308, ALA311, ASP274, CYS273, LYS275, LYS244. In the future, further research is necessary to confirm and validate the biological activities of boesenbergin A and B, especially in metastasis incidence.

INTRODUCTION

Globally, cancer becomes the second most death-caused disease after cardiovascular diseases. Interestingly, the incidence of cancer dramatically increases over the years. Numerous reports showed metastasis has become one of the hallmarks of cancer incidences. Metastasis is the condition by which the cancer cells spreading out from their original site to the surrounding tissues or distant organs. Multiple evidences demonstrated that metastasis contributes to poor prognosis of cancer incidence [1,2].

Metastasis is caused by many factors. Recent studies showed the involvement of MMPs (matrix metalloproteinases) family in promoting the tumor progression including invasion, angiogenesis, and metastasis [3-5]. Furthermore, it has been known that MMPs are responsible for matrix remodeling due to their ability in collagen destruction [6]. Targeting MMPs by numerous synthetic small molecules have emerged, however, the recent updates showed failure outcomes, especially in phase III trials [7,8]. As the above explanation, the new strategy to overcome metastasis is crucially necessary. The study conducted by Bond et al. (2001), revealed the inhibition of NF-κB activation can decreases the expression and production of MMPs [6].

Therefore, targeting the NF-κB by small molecules especially from herbal medicine such as *Kaempferia pandurata* rhizome might become the favorable strategy to inhibit the metastasis incidence. It has been reported that *Kaempferia pandurata* rhizome contains several bioactive compounds such as cardamonin, pinostrobin, pinocembrin, 2',6'-dihydroxy-4'-methoxychalcone, boesenbergin A,

boesenbergin B, 5,7-dimethoxyflavone, and 1,8-cineole (eucalyptol) [9]. Therefore, this present study aims to evaluate the bioactive compounds of *Kaempferia pandurate* as an anti-metastatic agent against the NF-κB protein.

MATERIALS AND METHODS

A report by Sukandar et al. (2014) showed that *Kaempferia pandurata* rhizomes contain several pivotal bioactive compounds namely cardamonin, pinostrobin, pinocembrin, 2',6'-dihydroxy-4'-methoxychalcone, boesenbergin A, boesenbergin B, 5,7-dimethoxyflavone, and 1,8-cineole (eucalyptol) [9]. Further, these compounds were set as potential ligands that might have molecular interaction with the target protein (Table 1). The 2D structure of ligands was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Additionally, the 3D structure of NF-κB was obtained from RSCB Protein Data Bank (https://www.rcsb.org/) with protein ID 1SVC.

Table 1. List of bioactive compounds contained in *Kaempferia pandurata* roots and its physical chemistry properties.

No.	Bioactive Compounds	CID	Molecular Mass (Dalton)	Hydrogen Bond Donor	Hydrogen Bond Acceptors	High Lipophilicity (Logp)	Molar Refractivity
1.	Cardamonin	641785	270	2	4	2.12	66.67
2.	Pinostrobin	73201	270	1	4	2.46	67.25
3.	Pinocembrin	68071	256	2	4	1.76	61.97
4.	2',6'-Dihydroxy-4'-Methoxychalcone	5316793	270	2	4	2.30	67.33
5.	Boesenbergin A	6313827	404	1	4	4.90	114.97
6.	Boesenbergin B	23643133	404	1	4	4.90	114.97
7.	5,7-Dimethoxyflavone	88881	282	0	4	2.77	69.58
8.	1,8-Cineole (Eucalyptol)	2758	154	0	1	2.85	51.48

Ligands preparation was performed by considering several indicators such as molecular mass, hydrogen bond donor, hydrogen bond acceptors, high lipophilicity, and molar refractivity, which all of them are considered as the Lipinski rule of five (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) and energy minimization for ligands [10]. Moreover, protein optimization was done by cleaning another unwanted ligand and arrange the hydrophobicity of the protein structure. Molecular docking was performed via PyRx Software [11] by similar protocol as our previous study [12-14]. In this present study, molecular docking dimension was set as follow; X axis= 62.3071, Y axis= 44.1579, and Z axis= 49.4279. Furthermore, the number of amino acid residues and interaction affinity values among ligands and protein were evaluated. Data analysis and visualization were accomplished through software developed by the Biovia Dassault system.

RESULTS AND DISCUSSION

The interaction bond between the ligand and protein is important because it regulates many biological activities. In this present study, we attempt to evaluate several bioactive compounds of *Kaempferia pandurata* rhizome against NF-κB protein. The NF-κB is known as a master of regulator which activates many signaling for transcription [15-18]. Previously, other reports showed that MMPs were regulated by NF-κB. In the study about breast cancer conducted by Bond et al., (2001) demonstrated that inhibiting the NF-κB can reduce the production of MMPs [6]. Therefore we hypothesized the interaction between ligands from *Kaempferia pandurata* rhizome might disrupt the biological activity of NF-κB (Figure 1), which in turn resulting in the regulation of MMPs expression.

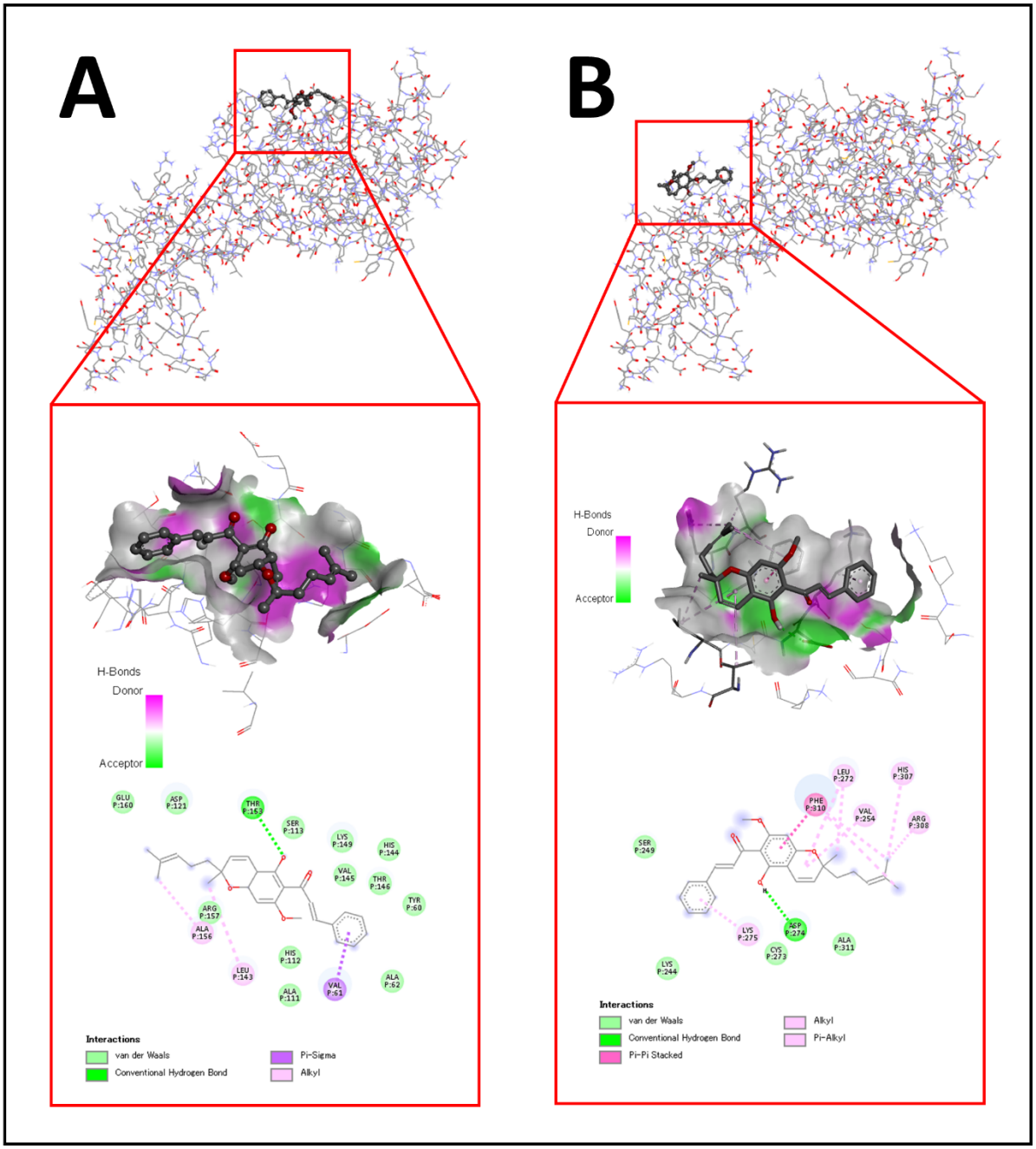

Figure 1. Visualization of ligand-receptor complex interaction. A). Interaction prediction of boesenbergin A to the NF-κB protein. B). Interaction prediction of boesenbergin B to the NF-κB protein.

Accordingly, the predicted computational results showed that boesenbergin A (-8.1 kcal/mol) and boesenbergin B (-7.2 kcal/mol) have the greatest score of binding affinity to the target protein, NF-κB (Table 2). Precisely, the binding affinity score showed how the ligands can interact with the target protein. The lowest score means the ligand has the greatest possibility to have stable interaction [12,19]. Furthermore, the molecular interaction visualization also showed several hydrogen binding among ligands and residual amino acids including boesenbergin A - NF-κB interaction (GLU160, ASP121, THR153, SER113, LYS149, VAL145, HIS144, THR146, TYR60, ALA62, VAL61, HIS112, ALA111, LEU143, ALA156, and ARG157) and boesenbergin B - NF-κB interaction (SER249, PHE310, LEU272, VAL254, HIS307, ARG308, ALA311, ASP274, CYS273, LYS275, and LYS244) (Table 3).

Table 2. Binding affinity prediction of each ligand toward the target protein, NF-κB.

No	Ligand	Target Protein	Binding Affinity
1.	Boesenbergin A	NF-κB	-8.1 kcal/mol
2.	Boesenbergin B	NF-κB	-7.2 kcal/mol
3.	Pinocembrin	NF-κB	-6.7 kcal/mol
4.	Pinostrobin	NF-κB	-6.6 kcal/mol
5.	5,7-dimethoxyflavone	NF-κB	-6.5 kcal/mol
6.	2',6'-dihydroxy-4'-methoxychalcone	NF-κB	-6.5 kcal/mol
7.	Cardamonin	NF-κB	-6.4 kcal/mol
8.	1,8-cineole (eucalyptol)	NF-κB	-4.8 kcal/mol

According to the binding motive of both boesenbergin A or B to the amino acid residues (Table 3), it showed that each compound has a different binding coordinate (Figure 1). Hydrogen bond between ligand and protein plays a pivotal role especially to keep the interaction stable [12,19]. Several experiments also showed the bioactivity of boesenbergin as anti-cancer and anti-inflammatory. This compound promotes the apoptosis signaling, upregulates the number of ROS in cancer cells, and controlling the cell cycle arrest [20]. These results then strengthen the role and possibility of boesenbergin A and B which may potentially as anti-metastasis agents.

Table 3. Residual amino acids of NF-κB that interact to each ligand, Boesenbergin A or Boesenbergin B.

No	Ligand-Protein Complex	Amino Acid Residues
1.	Boesenbergin A - NF-κB	GLU160, ASP121, THR153, SER113, LYS149, VAL145, HIS144, THR146, TYR60, ALA62, VAL61, HIS112, ALA111, LEU143, ALA156, ARG157
2.	Boesenbergin B - NF-κB	SER249, PHE310, LEU272, VAL254, HIS307, ARG308, ALA311, ASP274, CYS273, LYS275, LYS244

CONCLUSION

According to computational prediction, boesenbergin A and boesenbergin B that can be found in *Kaempferia pandurata* rhizome may have potential as anti-metastasis by inhibiting and disrupting NF-κB to activate the MMPs family.

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CONFLICT OF INTEREST

There is no conflict of interest in this present study.

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