Science Midwifery, Vol 10, No. 5, December 2022 ISSN 2086-7689 (Print) | 2721-9453 (Online)

Contents lists available at IOCS

Science Midwifery

journal homepage: www.midwifery.iocspublisher.org

Anti-Inflammatory Test Macaranga gigantea with Interleukin Inhibitor approach In Silico

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ARTICLE INFO

Article history:

Received Oct 21, 2022
Revised Oct 28, 2022
Accepted Nov 18, 2022

Keywords:

Docking,
IL1β,
M. gigantea

ABSTRACT (9 PT, Book Antiqua, Ful English)

Inflammation is condition inflammation accompanied by pain and fever . _ In general drug anti-inflammatory work with hinder enzyme cyclooxygenase , both COX-1 and COX-2, which play a role in synthesize inflammatory mediators such as prostaglandins and thromboxane . Various study developed for look for agent more therapy effective and have more risk low good symptom inflammation I or consequence period long from disease inflammation chronic . One of the approach taken is develop IL1β inhibitors. Method used is compound screening active using in silico. Docking software used in study this is autodock 4.2 and visualization interaction using discovery studio , materials used in study this is the compounds contained in M. gigantea. Result of research this is the value of delta G is negative below -4 kcal / mol, so reaction yanga occur between the ligand and the protein will walk spontaneous . Conclusion in study this obtained four ligands with lowest G value that is glycasperin A; broussoflavonol F; 5,7,3 ',4'-Tetrahydroxy-3-methoxy-8,5'-diprenylflavone; meliternatin .

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INTRODUCTION

Inflammation is condition occasional inflammation accompanied by pain and fever. One famous medicine in pioneer treatment is aspirin. Aspirin blocks enzyme cyclooxygenase, both COX-1 and COX-2, which play a role in synthesize inflammatory mediators, namely prostaglandins and thromboxane. Ability for block Prostaglandin and thromboxane production causes aspirin to become agent most therapeutic used in the world. Apart from aspirin , drug nonsteroidal anti-inflammatory drugs (NSAIDs), which target COX-2 in particular prostaglandin synthesis , especially PGE2 (Williams et al., 1999) . Form synthetic cortisol experience (called glucocorticoids) too much used for treat disease inflammation , and release from effect On the other hand , glucocorticoids permanent Becomes mainstay for reduce inflammation . However, still Becomes challenge for researcher for develop more agents effective and low useful risk _ for treat signs and symptoms inflammation I as well as consequence period long from disease inflammation chronic.

COX-2- specific inhibitors have give progress big in treatment pain , especially in patients with osteoarthritis or rheumatoid arthritis. one COX-2 inhibitor development has been by significant reduce effect Gastrointestinal side effects vs with COX-1 inhibitors. However , the use of chronic Several COX -2 specific inhibitors have been linked with enhancement incident cardiovascular as well as cerebrovascular especially in patients with enhancement risk of thrombosis (Hashemi Goradel et al., 2019) . Enhancement risk this possible because subtraction synthesis prostacyclin , which is a blocker experience Activation platelets . In addition to its wide ranging benefits on inflammation joints , COX-2- specific inhibitors are used for reduce development colon cancer in patients risky tall because cell adenocarcinoma of the colon express COX- 2 excessive (Liu et al., 2015) .

Inflammatory mediator PGE2 lowers threshold pain, so PGE2 becomes an attractive target for researched . Main goal of the oral PGE2 inhibitors are for reduce pain. There are two track for synthesize molecule PGE2 inflammation is the constitutive COX-1 pathway and the COX-2 pathway that can induced. While COX-1 contributed level low PGE2 and regulate mechanism homeostasis in health , COX-2 induces at least double more a lot of PGE2 compared with COX-1 and especially related with disease inflammation. COX-2 synthesis is low in individuals healthy but regulated by cytokines proinflammatory such as IL-1 and TNF-α as response to infection or disease inflammation (Saperstein et al., 2009) . There are several step in cascade inflammation cytokine triggered precursors , including recruitment myeloid cells (monocytes and neutrophils) in affected tissue . Product inflammation from oxidation sour Arachidonate (omega-6) including inflammatory prostaglandins (PGE2) and lipoxin (LTB4) is released from infiltrating myeloid cells . On the other hand , product oxidation sour eicosapentanoic (omega-3), PGE3, and LTB5, have anti-inflammatory activity (Saperstein et al., 2009) .

Inflammation is a dynamic process with cytokines proinflammatory such as tumor necrosis factor TNFα, interleukin (IL)-1β , and vascular endothelial growth factor (VEGF) play a role in role central . Study about various types of targeted inhibitors cytokines , so anticytokine moment this has find the place in treatment disease autoimmune diseases, such as rheumatoid arthritis , colitis , psoriasis, multiple sclerosis, and others. For example is eplizumab , daclizumab, rituximab, ofatumumab, epratuzumab, belimumab. And specific drugs lower TNFα activity was infliximab, adulimumab , golimumab, whereas specific drug IL-1β lowering agents are anakinra, rilonacept, canakinumab, Xoma 052, AMG 108 (Cavalli & Dinarello, 2015) . Use anticytokine this has change life millions patient with disease this . one weakness therapy anticytokine is drop defense immunity body host to infectionand possibility cancer. However so , benefits therapy anticytokine more big than the risks , and the risks could reduced. Compared with consequence treatment glucocorticoids period long for stem inflammation , therapy anticytokine is repair big. Incident rare organ toxicity happen , thing this because therapy anticytokine operate in extracellular than compartment intracellular . However cost drug drug Anticytokines are relatively expensive because drug group this generally is antibody good polyclonal or monoclonal. So it 's needed study anti-inflammatory track anticytokine specifically against IL1β. Plants that have ability anti-inflammatory is macaranga species such *as* M. *pruinose, M. triloba, M. gigantea, and M. tanarius* (Amirta et al., 2017; Joseph, 2014) . *M. peltate* show ability anti-inflammatory at doses of 200 and 400 mg/Kg BW (Gandhimathi, 2013) . It has been successful isolated various type compound from *M. conifera* which has ability inhibits COX1 and COX2 (Jang et al., 2002) . So that one species macaranga that is *M. gigantea* become a target in study insilico , because species this life in Island Kalimantan

RESEARCH METHOD

Materials and tools

Materials used in study this is the compounds contained in *M. gigantea* , IL1β protein crystal with code 5r87 from the RCSB (Berman et al., 2000) . Hardware used is Quad Core Processor N 3700, 2GB DDR3 memory. Software used are Autodock4 (Morris et al., 2009) , marvin bean (ChemAxon, 2016), yasara (Krieger & Vriend, 2014) and discovery studio (Systèmes, 2020) .

Methods

Docking against IL1β begins with protein preparation and preparation of native and contained ligands in M. gigantea . Protein crystals obtained from the RCSB web server. The ligand structure is obtained from Pubchem. After preparation done next make gridbox for docking. In research this use gridbox from the native ligand , namely X:40,439; Y:9.9799; Z;71.27. Gridbox used if the native ligand redocking satisfies condition below 2 then could used for the derived ligand from M. gigantea.

Data analysis

Data obtained from docking using autodock4 is delta G. The value of delta G as description from energy free bond between ligands and interleukin 1 . Second analysis is see distance bond between the ligands and the amino acids of residue using discovery studio

RESULTS AND DISCUSSIONS

Docking against IL1β begins with protein preparation . Preparation this started with disappearance a water molecule and two sulfate ions use yasara (Krieger & Vriend, 2014) . Protein sequences used in study this is chain A, because this A chain bond with native ligands. Native ligands used is there N-phenyl-N'-pyridine-3-γlurea. Autodock4.2 docking using The Lamarckian Genetic Algorithm (LGA). After the docking process is complete Step next is see conformation and energy the lowest that will be used as model validation . Based on the validation process obtained RMSD value 1.0174 so that Fulfill condition validation because value below 2Å (Rodríguez et al., 1989) , because that's the grid box used could used to test against sample . Based on docking test against sample , obtained results some ligands have equality when interact with the IL1β protein. Ligands that have at least 50% equation when interact is glyasperin A, the same residue are Arg4 and Glu105. p-Coumaric acid has equality residues Thr147 and Lys 103. 5,7,3',4'-Tetrahydroxy-3-methoxy-8,5'-diprenylflavone same residue is Lys 103; and Glu105 are shown in Table 1. Residues residue this play a role in the binding of cite ligands to proteins (Nichols et al., 2020) .

Table 1. The value of free energy for each compounds and residues involved _ in bond hydrogen

Compound	G		Residue
native ligands	-	6,960	Lys103; Thr147; Glu105; Leu110
Glyasperin A	-	6,656	Arg4; Glu105; Lys103; met148
Broussoflavonol F	-	6,448	Glu105; Lys103; asn53
Apigenin	-	5,747	Lys103; Arg4
Ferulic acid	-	4,592	Lys103; asn108
p-Coumaric acid	-	4,470	met148; Thr147; Asn53; Lys103
5,7,3',4'-Tetrahydroxy-3-methoxy-8,5'-diprenylflavone	-	5,972	Lys103; Asn53; Glu105
4'-O-Methyl-8-prenylnaringenin	-	5.071	met148; Lys103; Asn53; Phe150
4'-O-methyl-5,7,4'-trihydroxyflavone	-	5,760	Asn53; Lys103
Meliternatin	-	5,831	Arg4; Lys103; met148

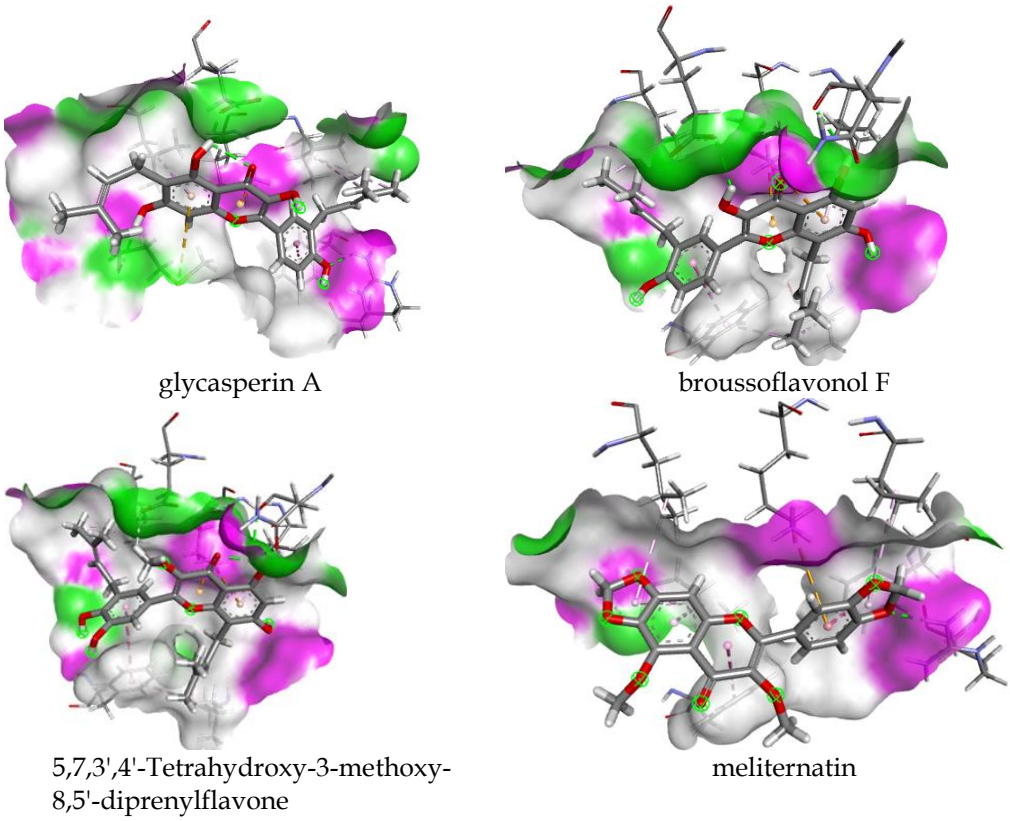

Figure 1. 3 dimensional interaction from four ligands that have energy Lowest

Based on 3 dimensional structure on inform bond hydrogen between ligands and good protein as danor hydrogen or acceptor hydrogen . glyasperin A who swim as a hydrogen donor to Arg4 residue ; Glu105; Lys103; met148. broussoflavonol F plays a role as H donor to Glu105; Lys103; asn53. 5,7,3',4'-Tetrahydroxy-3-methoxy-8,5'- diprenylflavone as a hydrogen donor against Lys103; Asn53; Glu105. Meliternatin play a role as Hydrogen donor to Arg4; Lys103; met148. Beside Bond hydrogen that happens between ligands with IL1β and distance below 3 , happens bond type another . Bond this is bond hydrophobic Among glyasperin A with Phe46 with distance bond 5.001 , Ile 56 - 5,226 , Leu110 – 4,954 . Broussoflavonol F with Phe150 at a distance of 5.122 , Leu6 – 5,283 , Leu110 – 4,681 , Ile56 – 4,719 . 5,7,3',4'-Tetrahydroxy-3-methoxy-8,5'-diprenylflavone binds with Phe150 at a distance of 5.163 , Leu6 - 4.084 , Ile56 at a distance of 4.648 . Meliternatin bond with Phe46 with distance 5,155 , Phe 150 - 4,944 , Leu 110 – 5,038 , Ile56 – 4,587 .

Cytokines that play a role in lower threshold pain and damage network one _ presence of interleukin-1. Therapy The use of IL-1 inhibitors can reduce level severity , increase recovery vision , hearing and repair of organs affected by mediation trade . So that The use of IL-1 inhibitors can help condition fail kidney set it Infraction , Obay already _ proven as IL-1 inhibitors are anakinra ®, rilonacept ® and canakinumab ® (Bachove & Chang, 2014) .

Most human diseases are caused by chronic inflammation resulting in loss of function in joints, blood vessels, or entire organs. In some organs, such as the heart and brain, acute inflammation can be fatal (Murray et al., 2015). Interleukin-1 (IL-1) is a major cytokine of local and systemic inflammation, and the availability of IL-1-specific targeting agents has revealed the pathological role of IL-1-mediated inflammation. IL-1α and IL-1β are two types of IL-1 derived from IL1A and IL1B (Dinarello, 2018). Each interleukin binds to the surface receptor of each cell when they are activated. Once activated, it triggers inflammatory mediators, chemokines and

various other cytokines. Symptoms that arise when IL-1A or IL-1B binds to the receptor are symptoms of fever, loss of appetite, joint and muscle pain, digestive and sleep disturbances, fatigue and hypotension (Rothman et al., 2020). So the use of IL1β inhibitors is needed to overcome this disorder. Use of IL1β inhibitors in atherosclerosis. The role of IL-1β is closely correlated with its signal transduction. Thus, inhibition of its signal transduction is a way to alleviate atherosclerosis. There are several molecules that can inhibit IL-1β and IL-1Rα signal transduction. IL-1Rα can competitively bind to IL-1R1 when it will bind to IL-1β or IL-1α. Antagonists can bind IL-1R1 strongly but cannot recruit IL-1Racp (IL-1R3) to form TIR dimers. It is thus unable to mediate the appropriate intracellular signaling. IL-1R2 is a receptor that binds to IL-1α or IL-1β and can recruit IL-1R3, which is structurally similar to IL-1R1 but lacks an intracellular domain and therefore cannot form TIR dimers (Teufel et al., 2022) .

CONCLUSION

Based on the research that has been done, compounds that have the potential as interleukin 1β inhibitors with the lowest free energy value indicators are glyaperin A (-6.656 kcal/mol); broussoflavonol F (-6,448 kcal/mol); 5,7,3',4'-Tetrahydroxy-3-methoxy-8,5'-diprenylflavone (-5,972 kcal/mol); Meliternatin (- 5,831 kcal/mol), these compounds have in common with the native ligand, which is bound to the amino acid residue lysine 103.

ACKNOWLEDGEMENTS

Researcher say thanks to the Universitas Lambung Mangkurat who has give opportunity in study this

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