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Abstract. This study aims to analyze the molecular docking between the active compounds of the *Garcinia mangostana* against the RANKL/RANK/OPG system and its potential as an antiosteoporosis. The research protocol includes the search and modeling of protein and ligand structures and their docking. Software used includes OpenBabel, HEX 8.0, Chimera 1.6.2, Discovery Studio 4.1, LigPlot + and LigandScout 3.1. Tovophillin has the most negative interaction energy with RANKL-OPG (–332.8 Kj/mol) and RANKL-RANK (–298.1 Kj/mol). It was concluded that fourteen active compounds of *Garcinia mangostana* did not interfere with the physiological function of RANKL against RANK. In addition, the active compound will not affect the RANKL-OPG complex. The antiosteoporosis mechanism of *Garcinia mangostana* does not by inhibiting RANKL-RANK interactions.

1. Introduction

Osteoporosis is a systemic skeletal disease characterized by decreased bone mass density and worsening microarchitecture, thereby increasing bone fragility and fracture. The pathophysiology of osteoporosis is very complex, a combination of genetic factors, nutritional factors, and endocrine abnormalities [1-3]. Diabetes mellitus is a metabolic disease characterized by hyperglycemia and has the potential to disrupt bone metabolism and trigger osteoporosis. Specifically, diabetes causes bone microangiopathy and decreased bone formation markers [4]. Diabetes decreases osteoclast activity and interferes with osteoblast activity, resulting in a low bone turnover. This will inhibit osteoclasts and osteoblasts through the induction of oxidative stress, hyperglycemia, and weight loss [5, 6]. Hyperglycemia triggers osteoblast lineage suppression [7], osteoblast apoptosis [8], inhibition of osteoblast-specific factors, and decreased in vitro mineralization [9].

Management of osteoporosis in diabetes mellitus includes lifestyle interventions, optimization of lifestyle control, analysis of the impact of diabetes mellitus treatment on fracture risk, and treatment with antiosteoporosis [10]. Until now, as far as researchers know, the application of herbs in the treatment of osteoporosis due to diabetes mellitus is still rarely done. Hesperidin increases bone turnover markers in serum, including osteopontin, osteocalcin, and decreases alkaline phosphatase in

type 1 diabetes mellitus rats [11]. Green tea has not been able to improve bone mineral content and bone mass in individuals with diabetes mellitus [12]. Anhydroicaritin suppresses osteoclast differentiation and improves bone loss in diabetic rats [13].

The RANKL/RANK/OPG system plays an important role in bone remodeling. RANK is a receptor located on the surface of osteoclasts. RANKL is a RANK ligand that is synthesized and secreted by osteoblasts and bone marrow stromal cells. When the RANKL bond to RANK forms, osteoclast differentiation and bone resorption occur. OPG as a receptor trap against RANKL will block this activity [14, 15]. In type 1 diabetes mellitus found a significant decrease in OPG compared to controls [16]. In ovariectomy model mice suffering from type 1 diabetes mellitus, there was a significant increase in the RANKL / OPG ratio compared to controls [17].

Garcinia mangostana is a fruit plant native to Indonesia. *Garcinia mangostana* contains prenylated and oxygenated xanthone compounds [18]. Various pharmacological actions of *Garcinia mangostana* have been revealed, including as an antioxidant, antimalarial, antiinflammatory, and anticancer [19-22]. Until now, the potential of *Garcinia mangostana* as an antiosteoporosis has not been revealed. Specifically, the effect of *Garcinia mangostana* on the RANKL/RANK/OPG system has also not been revealed. Therefore, this study aims to analyze the interaction in silico between the active compounds of the *Garcinia mangostana* against the RANKL/RANK/OPG system and its potential as an antiosteoporosis.

2. Material and Methods

2.1. Determination of amino acids making up RANKL, RANK, and OPG

The composition of amino acids RANKL (GI: 2612922) RANK (GI: 19924309), and OPG protein (GI: 2072185) was downloaded from the National Center for Biotechnology Information (NCBI), United States National Library of Medicine (NLM), National Institute of Health (NLM) NIH) (http://www.ncbi.nlm.nih.gov). The 3D structure of RANKL, RANKL and OPG will be converted from * .sdf file format, to * .pdb file using OpenBabel software [23].

2.2. Searching and engineering the structure of active components of Garcinia mangostana

The 3D structure of the active compound component *Garcinia mangostana* was obtained from the PubChem Open Chemistry Database. Eleven active compounds were obtained, namely cudraxanthone G (CID426453), 8-deoxygartanin (CID392450), garcimangosone B (CID11143989) (3), garcinone D (CID5495926), garcinone E (CID102985a), gartanin (CID5281633), 1-isomangostin (CID5281641), α-mangostin (CID5281650), γ-mangostin (CID5464078), mangostinone (CID6478778), smeathxanthone A (CID1150950)). For 8-hydroxycudraxanthone G, mangostingone, tovophyllin A was obtained by structural engineering using Discovery Studio 3.5 software [24].

2.3. Structural modeling and molecular docking

The 3D structure of the target proteins is predicted using the SWISS-MODEL webserver with the homology modeling method. The 3D structure of the protein was then validated using Ramachandran plot analysis [24, 25]. HEX 8.0 software is a device for simulating docking between active compounds of *Garcinia mangostana* and target proteins [26]. The docking protocol consists of three stages of visualization, namely minimization of rigid-body energy, semi-flexible repairs, and finishing refinement in explicit solvents. The docking results are then visualized with Chimera 1.6.2 software and Discovery Studio 4.1. The docking analysis results are visualized using Discovery Studio 4.1, LigPlot + and LigandScout 3.1 software [27, 28]. Analysis of the interaction between proteins and ligands is done to see the number and type of bonds formed.

3. Results

The interaction energy between the RANKL-OP complex, tovophyllin A has the most negative interaction energy (–332.8 Kj/mol). The interaction energies of other active compounds in sequence include mangostingone (–331.2 Kj/mol), garcinone E (–309.8 Kj/mol), cudraxanthone G (–306.2

Kj/mol), 8-hydroxycudraxanthone G (−305.7 Kj/mol) , 1-isomangostin (−290.7 Kj/mol), α-mangostin (−285.1 Kj /mol), γ-mangostin (−284.6 Kj/mol), garcinone D (−282.6 Kj/mol), mangostinone (−277.4 Kj/mol) mol), 8-deoxygartanin (−274.0 Kj/mol), smeathxanthone A (−273.1 Kj/mol), gartanin (−268.8 Kj/mol), and garcimangosone B (−264.6 Kj/mol).

The interaction energy between the RANKL-RANK complex, of the fourteen active compounds *Garcinia mangostana*, tovophyllin A has the most negative interaction energy (−298.1 Kj/mol). Other interaction energy of active compounds include mangostingone (−283.8 Kj/mol), garcinone E (−274.7 Kj/mol), smeathxanthone A (−272.5 Kj/mol), α-mangostin (−265.4 Kj/mol), γ-mangostin (− 258.2 Kj/mol), gartanin (−254.7 Kj/mol), cudraxanthone G (−250.4 Kj/mol), 8-hydroxycudraxanthone G (−249.6 Kj/mol), 1-isomangostin (−248.9 Kj/mol), garcimangosone B (−248.4 Kj/mol), garcinone D (−246.1 Kj/mol), 8-deoxygartanin (−245.5 Kj/mol), and mangostinone (−243.7 Kj/mol).

4. Discussion

First, we simulate an interaction model between fourteen active compounds of *Garcinia mangostana* and the RANKL-OPG complex. Tovophyllin A is an active compound that is the most easily interacted with this complex compared to other compounds. However, the active compound will not affect the RANKL-OPG complex. Our previous study analyzed the interaction between RANKL-OPG and obtained an interaction energy of −584.74 Kj/mol [29]. This indicates that OPG will continue to work as a decoy against RANKL in the context of regulating the balance of bone formation and resorption.

For the second model, we simulate the interaction between the active ingredient *Garcinia mangostana* and the RANKL-RANK complex. The interaction energy of the RANKL-RANK complex is −660.95 Kj/mol [29]. All active compounds of *Garcinia mangostana* have more positive energy interactions with RANKL-RANK. That is, the fourteenth active compound *Garcinia mangostana* has no potential to inhibit RANKL-RANK signals. This has two meanings. First, in physiological views, this indicates that the active compound will not interfere with RANKL-RANK interactions. RANKL is expressed in various tissues, including mammary gland epithelial cells, prostate, pancreas, skeletal muscle, thymus, liver, colon, small intestine, adrenal gland, and osteoblasts [30]. RANKL−RANK interactions are involved in the formation of mammary and lymph node tissue, and temperature regulation [31]. Second, in the osteoporosis pathway, the RANKL-RANK complex is a signal of osteoclast activation and bone resorption. The Antiosteoporosis mechanism of these compounds does not go through the anti - resorption activity. This study extends previous finding that *Garcinia mangostana* can reduce bone resorption activity, through decreasing TRAP markers [32]. In addition, garcinol is able to inhibit bone resorption induced by RANKL [33].

It was concluded that fourteen active compounds of *Garcinia mangostana* did not interfere with the physiological function of RANKL against RANK. In addition, the active compound will not affect the RANKL-OPG complex. The antiosteoporosis mechanism of *Garcinia mangostana* does not by inhibiting RANKL-RANK interactions.

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