Molecular Docking Analysis of the Interactions between MMP-9 Protein and Four Coumarin Compounds (Nordentatin, Dentatin, Calusenidin and Xanthoxyletin)

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Abstract

Matrix metalloproteinase-9 (MMP-9) is a noteworthy protease which plays vital roles in many biological activities. MMP-9 is usually overexpressed in inflammatory reactions and malignant disorders. The aim of this research was to study the interaction between the four natural coumarins nordentatin, dentatin, clausenidin, and xanthoxyletin with crystallized MMP-9 (PDB: 2OVX) using molecular docking. Molecular docking was done using AutoDock Vina, AutoDock Tools Version 1.5.4, PyMol, and Discovery Studio Biovia 2019. Molecular docking programs showed binding affinities of nordentatin, dentatin, clausenidin and xanthoxyletin with MMP-9 protein. The optimum binding energy (ΔG) of nordentatin, dentatin, clausenidin and xanthoxyletin against the MMP-9 were found to be -7.8, -7.3, -7.6, and -7.5 kcal/mol, respectively. Some amino acid residues were produced from hydrogen bonds and hydrophobic interactions.

The results showed that nordentatin, dentatin, clausenidin and xanthoxyletin can act as inhibitors for MMP-9. The results indicated that nordentatin, dentatin, clausenidin and xanthoxyletin as inhibitors of MMP-9, could be investigated further for anti-inflammation and anti-cancer properties. Both in vitro and in vivo assays will be necessary to confirm this.

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Introduction

Nordentatin, dentatin, clausenidin and xanthoxyletin are phytochemical compounds in the class of coumarins that can be derived from Clausena excavata plants (sicerek in Indonesian) (Figure 1)[1,2,3]. Various parts of the Clausena excavata plant have been used in traditional medicine throughout the Southeast Asia countries for the treatment of colds, sores, headaches, stomachaches, dysentery, pulmonary tuberculosis, diarrhea, malaria, AIDS, skin diseases, abdominal pain, snake bites, poisoning and also as detoxification agents [4,5]. Recent studies have shown that the plant also has immune-modulator, analgesic, anti-inflammatory, antiviral, anticancer, antioxidant, antimycobacterial, and antifungal activities[5]. Coumarins like those found in Clausena excavata have been found to have anti-inflammatory, anti-bacterial, anti-cholinesterase, anti-oxidant, anti-tumor and anti-cancer properties[5,6].
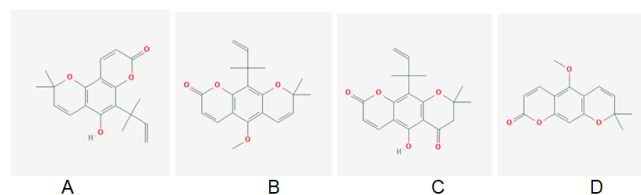

Figure 1. A. Chemical structure of Nordentatin ($C_{19}H_{20}O_4$), B. Dentatin ($C_{20}H_{22}O_4$), C. Clausenidin ($C_{19}H_{20}O_5$), D. Xanthoxyletin ($C_{15}H_{14}O_4$).

Inflammation is the common local vascular response of the immune system to harmful stimuli, such as toxic compounds, damaged cells, pathogens, or irradiation and acts by eliminate destructive stimuli and start the healing process at the tissue level. Signs of inflammation are produced due to the response of immune cells in the form of redness, swelling, heat, pain, and loss of tissue function[7,8]. Changes in permeability of vascular, leukocytes

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recruitment and accumulation, and release of inflammatory mediators all occur during the inflammatory process[8].

Matrix metalloproteinases (MMPs) are a family of extracellular zinc-dependent endopeptidases whose activities are tightly regulated at several stages, including activity, activation, transcription, secretion, and cleansing. MMP-9 plays a role in regulating the pathophysiological processes that involve inflammatory disease[9-11,13-15]. Inflammatory mediators such as macrophages, neutrophils and fibroblasts secrete MMP-9 through stimulation of TGF-β and IL-8. All proteases released from neutrophils promote MMP-9 activation so it is an induced enzyme[7,9-13].

The bioavailability of growth factors is maintained by MMP-9 thereby it also encourages cancer proliferation. MMP activity in cell-to-cell adhesion and cell-to-extracellular matrix adhesion plays a fundamental role in tumour progression, including proliferation, angiogenesis, and metastasis[12,14,16,17]. In several studies, MMP-9 levels show an increase in potentially malignant disorders and it is overexpressed in several types of human cancer[12,17]. In oral squamous cell carcinoma, invasion and poor prognosis also correlate with MMP 9 expression[18]. MMP-9 expression has been shown to be a diagnostic marker of oral cancer in the tissue, serum and saliva samples[12]. Because of these properties, MMP-9 is an attractive target for the development of cancer therapy drugs[19, 20].

In silico experimental research with molecular docking computational software has become important for understanding the molecular mechanisms of biological systems, as well as in the search of new therapeutic agents by targeting medically important proteins. Protein-ligand docking is a computational method that can experimentally predict the binding position, orientation, conformation and binding affinity at the atomic level, where ligands (small molecules) can most easily bind to target receptor protein binding sites. The binding strength of the predicted protein-ligand bond is expressed in kilocalories per mole (kcal/mol)[2,21-28].

The effects of the phytochemical compounds nordentatin, dentatin, clausenidin, and xanthoxyletin on MMP-9 have yet to be reported on. This study aims to determine the interactions between nordentatin and dentatin with MMP-9 protein in silico by molecular docking.

Materials and methods

Software and Program

There were several materials used in this docking simulation. The three-dimensional structure of the MMP-9 macromolecule was retrieved from the RCSB Protein Data Bank (http://www.rcsb.org) [PDB: 2OVX]. Then, the molecular formula of the compounds nordentatin, dentatin, clausenidin and xanthoxyletin were downloaded from PubChem (U.S. National Library of Medicine) in the .sdf file format. Software used in this work were: AutoDock Vina, AutoDock Tools version 1.5.4, Biovia Discovery Studio 2019 and Pymol. In this study, AutoDock Vina was used as the main docking program. AutoDock Tools version 1.5.4 was used to preparation of the MMP-9 .pdbqt file and determination of the grid box size. Modifying the structure of receptor and ligands, and post-docking analysis have been carried out using Discovery Studio Biovia 2019 and Pymol.

Ligand Structure Preparation

Ligands used in molecular docking have to follow Lipinski's rule of five, namely: molecular weight <500 grams/mol, having less than 5 hydrogen bond proton donors, less than 10 hydrogen bond acceptors, a calculated octanol/water partition coefficient less than 5 and strong inhibition (>100nM). Lipinski's rule of five is used to determine whether a chemical compound can be used as active drugs orally and have pharmacological and biological properties[29,30]. Molecular Profiles of the Investigated Ligands are shown in Table 1. The chemical structure of the three-dimensional ligand contained in .sdf files was changed to .pdb format using Discovery Studio Biovia 2019. The structure of the ligand in .pdb format was then changed to the .pdbqt format using AutoDock Tools.

Preparation of MMP-9 Macromolecular Structure

In the molecular docking process, MMP-9 macromolecules must be prepared by removing ligands (barbiturates), then stored in a separate pdb file, for further redocking and base virtual screening. Then all the sulfate ions and water molecules contained in the MMP-9 macromolecules were removed. The AutoDock Tools was used to prepare the files needed for

AutoDock Vina and change the format of the protein structure file from .pdb to .pdbqt, adjusting the center and size of the grid box.

Docking Method

Molecular docking has been carried out utilizing AutoDock Vina. Autodock Vina was utilized because of its speed and accuracy[21,31,32]. AutoDock Tools was used to prepare .pdbqt files, set the center and size of the gridbox and then save them, as needed by AutoDock Vina. Then notepad was opened to make the configuration file to run AutoDock Vina. Post docking visualization using Biovia Discovery Studio 2019 and PyMol which shows the mode and conformation of the binding site, interactions of hydrogen bond, interactions of hydrophobic and interactions of electrostatic. The binding process was observed for each protein and ligand interaction that occurred, then characterized.

Results

Docking Validation

In molecular docking, the coordinate center and size of grid box must be validated to make sure that the ligands bind to the binding site at the right conformation[32]. In this study, validation of docking was done by redocking the crystal pyrimidine-2,4,6-trione at the binding site with grid box size x = 14, y = 18, z = 14 and center: x = 27.012, y = 8.884, z = 50.083 with a distance 1.000 Å. The best redocking results showed a binding energy of -12 kcal/mol (Figure 2).
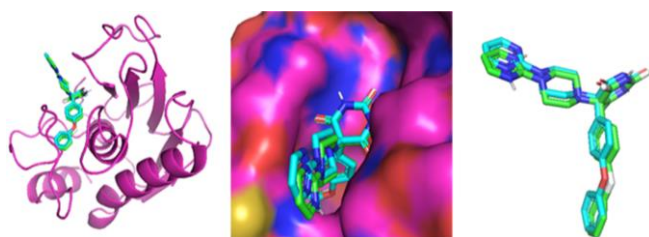

Figure 2. Redocking co-crystal pyrimidine-2,4,6-trione into MMP-9 binding site (PDB: 2OVX). Crystal ligand conformation shown in blue carbons. The best redocked conformation of pyrimidine-2,4,6-trione is indicated in green carbons.

Inhibitors bound to MMP-9 binding site

The four compounds showed strong affinities for the binding site of MMP-9;

nordentatin with a binding energy (ΔG) of -7.8 kcal/mol and dentatin -7.3 kcal/mol, clausenidin -7.6 kcal/mol and xanthoxyletin -7.5 kcal/mol. Nordentatin showed the strongest affinity of the four compounds (Table 2). The best mode conformations of nordentatin, dentatin, clausenidin, xanthoxyletin and redocked pyrimidine-2,4,6-trione with MMP-9 macromolecules are visualized in Figure 3.

Ligands	PubChem CID	Molecular Formula	Molecular Weight (g mol⁻¹)	Hydrogen bond acceptors	Hydrogen bond donors	Log P	Rotatable bond count
Nordentatin	5320206	$C_{19}H_{20}O_4$	312.365	4	1	4.4	2
Dentatin	342801	$C_{20}H_{22}O_4$	326.4	4	0	4.7	3
Clausenidin	5315947	$C_{19}H_{20}O_5$	328.4	5	1	4.1	2
Xanthoxyletin	66548	$C_{15}H_{14}O_4$	258.27	4	0	2.8	1

Table 1. Physicochemical properties of the candidate ligands based on Lipinski's Rule of Five.

Ligands	The binding energy (binding affinity) value generated in each conformation, ΔG (kcal/mol)								
	1	2	3	4	5	6	7	8	9
Nordentatin	-7.8	-7.7	-7.1	-6.7	-6.7	-6.7	-6.7	-6.6	-6.6
Dentatin	-7.3	-7.2	-6.9	-6.6	-6.6	-6.6	-6.5	-6.5	-6.3
Clausenidin	-7.6	-7.5	-7.3	-7.1	-6.9	-6.8	-6.5	-6.4	-6.4
Xanthoxyletin	-7.5	-7.3	-7.2	-7.1	-7.0	-7.0	-6.8	-6.7	-6.6

Table 2. The binding energy of nordentatin, dentatin, clausenidin and Xanthoxyletin at the binding site of MMP-9.
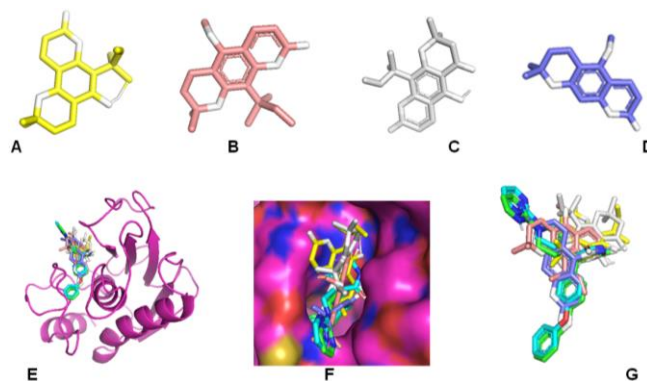

Figure 3. The best mode conformations of four compunds inside the binding site of MMP-9 (A) Nordentatin is indicated in yellow carbons. (B) Dentatin is indicated in salmon carbons. (C) Clausenidin is indicated in gray carbons. (D) Xanthoxyletin is indicated in blue carbons. (E, F, G) Superimposition of redocked pyrimidine-2,4,6-trione compounds, nordentatin, dentatin, clausenidin and xanthoxyletin. Redocked of pyrimidine-2,4,6-trione compounds is indicated in green carbon. Crystal ligand conformation shown in cyan.
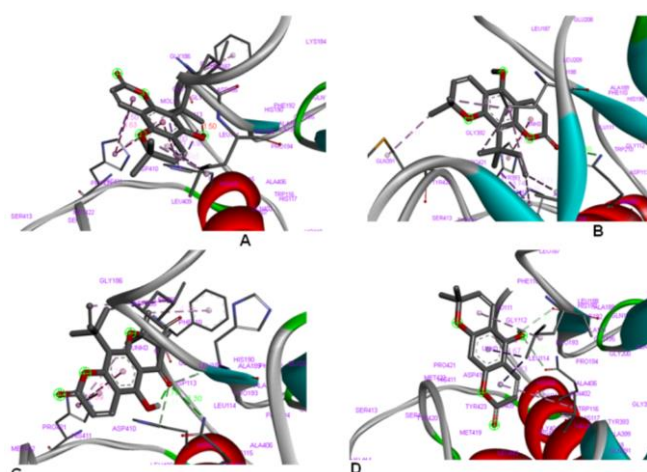
Figure 4. Amino acids were produced in the interactions between ligands and receptors. (A) Nordentatin and MMP-9 interaction. (B) Interaction of dentatin and MMP-9 (C) Interaction of clausenidin and MMP-9. (D) Interaction of xanthoxyletin and MMP-9.

Ligands	Binding energy, ΔG (kcal/mol)	Residues of amino acid involved in interactions and distance (Å)		
		Interactions of Hydrogen bond	Interactions of Hydrophobic	Interactions of Electrostatic
Nordentatin	-7.8	-	His405 (3.99), His405 (4.00), His411 (3.59), His405 (5.82), His411 (4.62), His411 (5.02), Leu188 (3.99), Leu187 (4.86), Leu188 (5.45), Phe110 (4.66), His411 (4.50)	-
Dentatin	-7.3	Gln402 (3.30)	His401 (3.74), His411 (5.46), Leu188 (4.05), Met422 (4.11), Leu188 (4.46), Leu188 (4.88), Val398 (3.71), His401 (4.36)	-
Clausenidin	-7.6	Gln402 (3.30), His190 (3.57), His405 (3.11)	His411 (5.59), His411 (5.16), Leu187 (4.61), Leu187 (4.25), Phe110 (4.39), His411 (5.17)	-
Xanthoxyletin	-7.5	Ala189 (2.94), Gln402 (3.35)	Leu188 (3.83), Leu188 (3.67), Leu188 (4.95), Val398 (4.83)	

Table 3. The residues of amino acid involved in receptor-ligand interactions at the active sites.

Hydrophobic interactions occurred between nordentatin and MMP-9 forming eleven amino acid residues His405 (3.99 Å), His405 (4.00 Å), His411 (3.59 Å), His405 (5.82 Å), His411 (4.62 Å), His411 (5.02 Å), Leu188 (3.99 Å), Leu187 (4.86 Å), Leu188 (5.45 Å), Phe110 (4.66 Å), His411 (4.50 Å). No amino acid residues were produced from hydrogen bonds and electrostatic interactions (Figure 4, Table 3).

Hydrogen bonds from dentatin compounds formed one amino acid residue Gln402 (3.30 Å). Hydrophobic interactions between dentatin compounds with MMP-9 formed eight amino acid residues His401 (3.74 Å), His411 (5.46 Å), Leu188 (4.05 Å), Met422 (4.11 Å), Leu188 (4.46 Å), Leu188 (4.88 Å), Val398 (3.71 Å), His401 (4.36 Å). There were no amino acid residues produced from electrostatic interactions (Figure 4, Table 3).

Hydrogen bonds from clausenidin compounds formed three residues of amino acid Gln402 (3.30 Å), His190 (3.57 Å), His405 (3.11 Å). Hydrophobic interactions between clausenidin compounds with MMP-9 formed six amino acid residues His411 (5.59 Å), His411 (5.16) Å, Leu187 (4.61 Å), Leu187 (4.25 Å), Phe110 (4.39 Å), His411 (5.17 Å). There were no amino acid residues produced from electrostatic interactions (Figure 4, Table 3).

Hydrogen bonds with xanthoxyletin formed two residues of amino acid Ala189 (2.94 Å) and Gln402 (3.35 Å) from MMP-9. Interaction of hydrophobic occurred between xanthoxyletin and MMP-9 forming four residues of amino acid Leu188 (3.83 Å), Leu188 (3.67 Å), Leu188 (4.95 Å), and Val398 (4.83 Å). No amino acid residues were produced from electrostatic interactions (Figure 4, Table 3).

Discussion

In molecular docking studies, the binding affinity of protein-ligand complexes is determined based on the concept of free energy. Binding affinity is the strength of the interaction between two (or more than two) molecules that bind reversibly (interact). Strong binding affinity are indicated by free energy that has a negative or low value, in this case, within the protein-ligand complex and indicates that the ligand is in a favourable conformation[27, 32, 36-38].

The AutoDock Vina scoring function can be used to calculate the prediction of the strength of binding affinity (kcal / mol) between protein-ligand complexes. The AutoDock Vina scoring function can divided into two parts: i) The amount of intramolecular and intermolecular contributions, including steric, interactions of hydrophobic and hydrogen bonding, is a part that conformation-dependent. and ii) The number of rotatable bonds that between heavy atoms in a ligand is a part of independent-conformation. In the AutoDock Vina scoring function, each contribution (the number of rotatable bonds, steric, hydrogen bonding, and hydrophobic interaction) is given a different weight[21,32]. A good

drug shows the stability of the binding with the receptor molecule, so that it has a negative binding energy[27].

The strong interaction between the interacting subunits establish the stability of the protein-ligand complex. Formerly, hydrophobic energies were considered as the main energy that drove the formation of stable protein complexes. However, other parameters (such as free energy, enthalpy, entropy, changes in heat capacity, interactions of Van-der-Waals, salt bridges and hydrogen bonds) are also involved in the stable complexe formation. So, hydrophobic interactions alone cannot determine the stability of protein complexes[39]. Analysis of large amounts of experimental data has shown that hydrophobic interactions and hydrogen bonds contribute greatly to the stability of protein folding[40]. A protein-ligand complex is only stable when changes in the free energy of the system are negative[35].

In the assessments using AutoDock Vina, nordentatin showed the best binding affinity than the other three coumarin compounds, but all showed strong binding affinity for the MMP-9 protein. Nordentatin, dentatin, clausenidin and xanthoxyletin compounds also comply with Lipinsky's rule of five indicating they could be well absorbed and metabolized by the body[29,30,41].

Nordentatin has been shown to exhibit strong cytotoxicity against NCI-H187 and KB cell lines[42]. Dentatin has been shown to induce apoptosis in MCF-7 cells[43]. Studies conducted by Jantamat et al., (2019) showed xanthoxyletin compound, which has a relatively low cytotoxicity, can cause the death of HepG2 cells with a higher apoptosis percentage and lower necrosis percentage than three other types of coumarin (clausarin, dentatin and nordentatin)[44]. Clausenidin has been found to have a potential cytotoxic effect and can also stimulate apoptosis in HT-29 cancer cells[45].

Apoptosis is a programmed cell death mechanism involved in the elimination of cancer cells, which leads to the success of therapy. Loss of apoptosis is commonly found in most cancers. Hence, the goal of any cancer therapy is the induction of apoptosis in the target cancer cells[44]. MMP plays a role in pro-apoptotic and anti-apoptotic activities, in almost all the main stages of cancer development: escape from apoptosis and immune surveillance, invasion and migration of tumor cells, metastasis, and angiogenesis.

MMP-9 functions to release several extracellular matrix factors, which encourage the proliferation and migration of endothelial cells involved in angiogenesis and tumor growth. For this reason, the inhibition of MMP-9 activity potentially has a very significant role in treatment of cancer development[17,46].

As MMP-9 protein is often overexpressed in an inflammatory reaction and in malignant progression of cancers such as oral epithelial malignant transformation generation of MMP-9 inhibitors with increased selectivity is one step in the production of potential drugs to address these problems[10,18]. This study indicates that nordentatin, dentatin, clausenidin and xanthoxyletin can act as such inhibitors for MMP-9, so they could well reduce MMP-9 expression in vivo.

Conclusions

From the present study, it can be concluded that nordentatin, dentatin, clausenidin and xanthoxyletin have potential as inhibitors of the MMP-9 protein. Four species of coumarin nordentatin, dentatin, clausenidin and xanthoxyletin could have prospective use in anti-inflammation and anticancer therapy through the inhibition of MMP-9. But further research will have to explore the stability of protein-ligand complex by molecular dynamic simulation. Experimental studies by in vitro and in vivo are needed to validate this hypothesis.

Declaration of Interest

The authors report no conflict of interest.

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