Natural Flavonoids for the treatment of Hyperuricemia, Molecular Docking studies

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Abstract— **Hyperuricemia is a condition where high level of uric acid is present in the blood. One of the factors contributing to this is the overproduction of uric acid by hydroxylation of xanthine which is catalyzed by Xanthine Oxidase (XO). Flavonoids have been shown to possess high activity for inhibition toward xanthine oxidase, and found to have the ability to decrease uric acid levels in serum. In this study, we perform molecular docking for more than 100 natural flavonoids onto XO, using Auto Dock 3.0.5 software. The result showed that ErysubinF, an isoflavone, has a superior inhibition activity compared to others flavonoids with a very low docked energy (docked energy = -12.82 Kcal/mol). Analysis using both Ligplot and InsightII showed that the main interaction between ErysubinF and the enzyme's active site involves only hydrophobic interaction due to the presence of two isopentene side chains.**

Keywords— **Flavonoids, Hyperuricemia, Xanthine oxidase.**

I. Introduction

Hyperuricemia lead to many complications such as gout and kidney stones and may also be associated with renal insufficiency and cardiovascular diseases [1]. Hyperuricemia is defined as when the uric acid concentration rises to ≥7 mg/dl for men and ≥6 mg/dl for women [2]. This condition is usually treated using allopurinol (4-hydroxypyrazolo [3,4-d] pyrimidine), an analogue of hypoxanthine, which is a specific potent inhibitor and substrate for xanthine oxidase [3]. Allopurinol is slowly oxidized to oxypurinol, a xanthine analogue, which is a more potent xanthine oxidase inhibitor [3].

The most common adverse effects of allopurinol include hypersensitivity reactions, skin rashes and gastrointestinal distress. However, these effects almost always occur in individuals with reduced glumerular filtration. Syndromes of allopurinol toxicity include rashes, fever, worsening of renal insufficiency, vasculities, easinophilia and death have also been reported [4]. These syndromes appear to be more common in the elderly patients with renal insufficiency. Safety in children and during pregnancy has not been establish [5]. Due to these adverse effects, therefore, there is a need for an alternative anti-hyperuricemia agent without the side-effects such as those associated with allopurinol.

Xanthine Oxidase (EC 1.17.3.2, XO) plays a key physiological role in the metabolism of purines by catalyzing the hydroxylation reaction of hypoxanthine to xanthine which further results in the formation of uric acid [5, 8]. XO, together with its interconvertible form, Xanthine Dehydrogenase (EC 1.17.1.4, XDH), are called Xanthine Oxidoreductase (XOR) [5]. The crystal structure revealed that both enzymes are homodimer of 145 kDa subunits, which consist of a 20-kDa N-terminal domain containing two iron-sulfur centers, a 40-kDa middle domain containing flavin adenine dinucleotide (FAD), and an 85-kDa C-terminal containing the molybdopterin cofactor [5, 9, 10]. The monomer can be divided into three domains; the small N-domain starts from residue 1 to 165, and contains both iron/sulfur cofactors that is connected to the second domain (FAD-binding domain) residues 226 to 531 by residues 166 to 225. FAD is also connected to the third domain by another linker composed of residues 532 to 589, with some residues missing (532 to 536). The large third domain (residues 590 to 1,332) also contain molybdopterin cofactor [11]. The Molybdenum and the FAD centers can accept two electrons each, while iron-sulphur clusters can accept one electron each [10]. The oxidation of xanthine takes place at the molybdopterin cofactor and the electrons are distributed to other centers by intramolecular electron transfer [11].

Flavonoids are a class of low molecular weight phenolic compounds that are widely distributed in the plant kingdom [15]. Many flavonoids are easily recognized as flower pigments in most angiosperm families. However, their occurrence is not restricted to flowers as they are also present all parts of plant. The chemical structure of flavonoids are based on a C15 skeleton with two phenolic rings connected together by three carbon units, and grouped according to the presence of different substituents on the rings and the degree of ring saturation. They frequently attached with sugars moiety to increase their water solubility [16, 17] (Fig. 1).

In this study, we performed molecular docking for more than 100 natural flavonoids onto Xanthine oxidase (XO), in order to screen for the activity of these compounds against XO.