International Journal of Chemistry; Vol. 5, No. 3; 2013
ISSN 1916-9698 E-ISSN 1916-9701
Published by Canadian Center of Science and Education

Structure-Based *in Silico* Study of 6-Gingerol, 6-Ghogaol, and 6-Paradol, Active Compounds of Ginger (*Zingiber officinale*) as COX-2 Inhibitors

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Received: February 16, 2013 Accepted: April 15, 2013 Online Published: June 6, 2013

doi:10.5539/ijc.v5n3p12 URL: http://dx.doi.org/10.5539/ijc.v5n3p12

Abstract

Ginger's (*Zingiber officinale*) phenolic compounds, that are 6-gingerol, 6-shogaol, and 6-paradol, have been proven to show anti-inflammatory activity. The purpose of this paper was to discover whether these compounds are potential to be used as COX-2 inhibitors through structure-based *in silico* study, which is based on the character of the receptor. Docking was performed to the binding pockets of both COX-1 and COX-2 enzymes, to examine their selective character on COX-2. The binding pockets used in this project were the sites where flurbiprofen and SC-58, crystallized in the enzymes. The scoring value of the interaction of 6-gingerol, 6-shogaol, and 6-paradol with COX-1 were -7.40, -7.27, and -7.20 kcal/mol, while with COX-2 were -7.97, -8.10, and -7.80 kcal/mol, respectively. K_i value to COX-1 were 3.78, 4.66, and 5.30 μM, while to COX-2 were 1.46, 1.16, and 1.93 μM, respectively. We also calculated the selectivity index value of these compounds to COX-2 and resulted an interval of 0.2 to 0.4, which indicated that all tested compounds could be classified as preferential COX-2 inhibitors. It can be concluded that 6-gingerol, 6-shogaol, and 6-paradol could be developed as COX-2 inhibitors.

Keywords: cyclooxygenase, *in silico* study, 6-gingerol, 6-shogaol, 6-paradol, structure-based drug design

1. Introduction

Cyclooxygenase (COX) enzymes play an important role in inflammatory response, i.e catalyzed the prostaglandins biosynthesis. These enzymes are visualized as homodimers that contain 587 amino acid residues in each chain with molecular weight of 67 230 Daltons. Two isoforms, knows as COX-1 and COX-2, have similar amino acid residues composition and hydrophobic channel as binding pocket (Fabiola et al., 2001). The COX binding pocket contain Val116, Arg120, Val349, Leu352, Tyr355, Leu359, Tyr385, Trp387, Ile523 (for COX-1 or Val523 for COX-2), Gly526, Ser530, and Leu531 (Picot et al., 1994). The most important amino acid residue is Tyr385 that catalyzed the transformation of arachidonic acid to PGG2. COX-2 had larger binding pocket due to the substitution of valine to isoleucine at position 523. COX-1 and COX-2 differ in their distribution and regulatory functions. COX-1 is expressed in cells and normal tissues physiological functions. COX-2 is induced by mediators of inflammation in pathological conditions. Inhibition of both COX-1 and COX-2 with non-selective inhibitors lead to renal and gastrointestinal side effects due to inhibition of COX-1 (Kurumbail et al., 1996).

Ginger (*Zingiber officinale*) contains phenolic compounds that had anti-inflammatory activity, i.e gingerol, shogaol, and paradol (Chung et al., 2001; Ippoushi et al., 2003; Levy et al., 2006). Previous studies showed that gingerol (IC_{50} values is 5.5 μM) inhibited prostaglandins biosynthesis (Kiuchi et al., 1982) and 6-gingerol (50-100 mg/kg) inhibited carrageenan-induced inflammation (Fabiola et al., 2001), 6-shogaol (6.2 mg/kg in 0.2 mL peanut oil) reduced knee inflammation in mice injected by Complete Freund's Adjuvant (Levy et al., 2006). 6-paradol and derivatives inhibited ear edema in mice induced by 12-O-tetradecanoylphorbol-13-acetate (Chung et al., 2001).

In this paper, 6-gingerol, 6-shogaol and 6-paradol were investigated whether these compounds are potential to be used as COX-2 inhibitors through structure-based *in silico* study. Their binding modes were compared with SC-58, a selective COX-2 inhibitor, to determine their selectivity to COX-2. Structure similarity of tested