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Ethyl p-methoxycinnamamate from *Kaempferia galanga* inhibits angiogenesis through tyrosine kinase

Juni Ekowati*, Suko Hardjono*, and Iwan Sahrial Hamid**

ABSTRACT

**BACKGROUND**
Many tumors express on their receptor tyrosine kinases vascular endothelial growth factor activity associated with angiogenesis. Inhibition of angiogenesis through reduction of tyrosine kinase activity is a promising strategy for cancer therapy. The present study aimed to determine the mechanism and potency of ethyl p-methoxycinnamamate (EPMC) isolated from *Kaempferia galanga* as angiogenesis inhibitor.

**METHODS**
A laboratory experimental study was conducted using chorio-allantoic membranes (CAMs) of nine-day old chicken eggs induced by 60ng basic fibroblast growth factor (bFGF). Ethyl p-methoxycinnamamate (EPMC) potency was determined at dosages of 30, 60, 90 and 120 μg and compared with celecoxib 60 μg as reference drug and one negative bFGF-induced control group. Neovascularization and endothelial cell count in CAM blood vessels were evaluated. To predict the antiangiogenic mechanism of EPMC, a docking study was performed with the Molegro Virtual Docker program on tyrosine kinase as receptor (PDB 1XKK).

**RESULTS**
Angiogenesis stimulation by bFGF was prevented significantly (p<0.05) by EPMC at dosages of 30, 60, 90 and 120 μg and this activity was dose dependent. Molecular docking showed interaction between EPMC functional groups and tyrosine kinase amino acids at Met766, Met793, Thr854, Thr790, Gln791 and Ala743. There was an association between EPMC antiangiogenic activity and docking study results.

**CONCLUSIONS**
Ethyl p-methoxycinnamamate is a potential new angiogenesis inhibitor through interaction with tyrosine kinase. EPMC could be a promising therapeutic agent for treatment of angiogenesis-related diseases.

**Keywords:** Ethyl p-methoxycinnamamate, chorio-allantoic membrane, angiogenesis, tyrosine kinase

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Univ Med 2015;34:43-51
DOI: 10.18051/UnivMed.2015.v34.043

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Etil p-metoksinsinamat dari Kaempferia galanga menghambat angiogenesis melalui interaksi dengan tirosin kinase

ABSTRAK

LATAR BELAKANG
Banyak tumor menunjukkan pada reseptor tirosin kinase mereka ekspresi vascular endothelial growth factor yang berhubungan dengan angiogenesis. Hambatan angiogenesis melalui pengurangan aktivitas tirosin kinase adalah strategi yang menjanjikan untuk terapi kanker. Penelitian ini bertujuan untuk menentukan mekanisme dan potensi etil p-metoksinsinamat (EPMC) sebagai penghambat angiogenesis.

METODE
Sebuah studi eksperimental laboratorium dilakukan menggunakan chorio-allantoic membrane (CAM) telur ayam tertutup berumur sembilan hari, yang diinduksi dengan basic fibroblast growth factor (bFGF) 60pg. Potensi EPMC didistribusikan pada dosis 30, 60, 90 dan 120 μg; dibandingkan dengan celecoxib 60 μg sebagai obat refeensi dan satu grup tanpa perlakuan. Neovaskularisasi dan sel endotiel pembuluh darah daru dari CAM dibendung dan dievaluasi. Untuk prediksi mekanisme antiangiogenesis EPMC, dilakukan studi docking pada reseptor tirosin kinase (PDB 1XKK) menggunakan program Molegro Virtual Docking v.5.5

HASIL
Stimulasi angiogenesis oleh bFGF pada CAM dibandingkan secara signifikan (p< 0.05) oleh EPMC pada dosis 30, 60, 90 and 120 μg dan bersifat dose dependent. Celecoxib dan EPMC tersebut menyebabkan terjadinya lisis sel endotiel daru dari CAM. Studi docking menunjukkan adanya interaksi antara gugus fungsi pada EPMC dengan residu asam amonio tirosin kinase pada Met766, Met793, Thr834, Thr790, Gln791 dan Ala743. Studi docking dan aktifitas antiangiogenesis EPMC tersebut menunjukkan hasil yang berhubungan.

KESIMPULAN
Etil p-metoksinsinamat merupakan senyawa yang berpotensi sebagai angiogenesis inhibitor melalui hambatan pada tirosin kinase.

Kata kunci : Etil p-metoksinsinamat, korio allantois membran, angiogenesis, tirosin kinase

INTRODUCTION

Tyrosine kinase receptors of many tumors express vascular endothelial growth factor (VEGF) activity connected with angiogenesis.1 In the last decade, angiogenesis has been explored in depth as an interesting cancer therapeutic target, since angiogenesis is an important step in tumor growth and cancer metastasis.1,2

Drug resistance, increased tumor progression, and signs of drug toxicity such as bleeding, fatigue, hypertension and gastrointestinal perforation are the main clinical problems that occur in patients treated with angiogenesis inhibitors.1 Thus, the use of natural herbal alternative agents to constrain angiogenesis is quite crucial in cancer treatment. Ethyl p-methoxycinnamate (EPMC), a major constituent of Kaempferia galanga Linn. (local name: kencur, Fam. Zingiberaceae) has been used as sunscreen,14 analgesic 5 and anti-inflammatory.6,7 agent, as cyclooxygenase-2 (COX-2) inhibitor, and to treat fibrosarcoma in mice.5 It is has been established that PGE2 production in preclinical breast and colon cancer