INTISARI

Indonesia berada pada peringkat pertama penyakit kanker payudara di ASEAN dengan jumlah 65.858 kasus dengan 20%-nya subtipe TNBC. VEGF merupakan protein yang diekspresikan berlebih pada pasien TNBC dan merupakan protein penanda proses angiogenesis. Ekspresi VEGF dimodulasi oleh HGF melalui jalur PI3K-Akt.

Rimpang *Curcuma.mangga* Val. digunakan sebagai antikanker payudara; dan minyak atsirinya bersifat sitotoksik terhadap sel kanker payudara T47D dan MCF-7; namun belum ada penelitian sitotoksisitasnya terhadap sel TNBC. Penelitian ini menguji potensi antikanker TNBC minyak atsiri *C. mangga* Val. melalui anti-angiogenesis dengan target hambatan ekspresi VEGF.

Dilakukan uji sitotoksisitas minyak atsiri *C. mangga* Val. pada sel TNBC-4T1 dengan kontrol positif alpelisib. Uji penghambatan ekspresi VEGF dilakukan secara imunositokimia. Minyak atsiri *C. mangga* Val. diidentifikasi kandungan senyawanya menggunakan GC-MS. Ligan senyawa kandungan diseleksi berbasis *Similarity Index* (SI) $\geq$850 dan persentase kelimpahan relatif $\geq$1%. Penghambatan VEGF dilakukan melalui uji *molecular docking* ligan terseleksi minyak atsiri *C. mangga* Val. pada reseptor PI3K dan Akt dibandingkan terhadap alpelisib.

Dengan destilasi uap air rimpang *C. mangga* Val. dihasilkan minyak atsiri dengan rendemen 0,28% b/b dari simplisia kering. Minyak atsiri yang dihasilkan berwarna kuning dengan BJ 0,953 g/ml. Uji sitotoksisitas menunjukkan: minyak atsiri *C. mangga* Val. sitotoksik terhadap sel 4T1 dengan IC_{50} 91,96 µg/ml; sedangkan IC_{50} alpelisib 32,975 µl/ml. Uji imunositokimia menunjukkan: minyak atsiri *C. mangga* Val. dan alpelisib memiliki efek penghambatan ekspresi VEGF yang sama ($p>0,05$). Uji *redocking* ligan natif pada PI3K (PDB: 4TV3) dan Akt (PDB: 2UW9) dengan metode *Triangle Matcher* menghasilkan RMSD berturut-turut 0,9058Å dan 0,7774Å, sehingga kedua protein dan metode valid untuk digunakan karena RMSD <2Å. Hasil *molecular docking* ligan uji kandungan minyak atsiri rimpang *C. mangga* Val. terhadap reseptor PI3K (PDB: 4TV3) dan Akt (PDB:2UW9) menunjukkan bahwa semua ligan uji mempunyai *docking score* yang lebih lemah daripada ligan natif yaitu ML9 (-8,1290) dan GVP (-7,6835). Ligan uji *m*-camphorene berikatan dengan Lys 802 dan nerolidol berikatan dengan Val 851 pada kinase domain reseptor PI3K sama dengan ligan natif ML9 (dengan Val 851, Lys 802, dan Gln 848). *m*-Camphorene dan nerolidol juga berikatan dengan berturut-turut Ala 232 dan Glu 236 pada kinase domain reseptor Akt sama dengan ligan natif GVP (dengan Glu 236, Glu 230 dan Ala 232). Disimpulkan bahwa minyak atsiri rimpang *C. mangga* Val. berpotensi antikanker payudara *triple negative* melalui penghambatan proses angiogenik.
Kata Kunci: *Curcuma mangga* Val., TNBC, VEGF, 4T1, PI3K/Akt

ABSTRACK

Indonesia was the first rank in ASEAN with 65.858 cases which 20% of the cases was TNBC subtype. VEGF is a protein that is overexpressed in patients with Triple Negative Breast Cancer (TNBC), and is a marker protein in angiogenesis process. The expression of VEGF is modulated by the Hepatocyte growth factor (HGF) through the PI3K-Akt pathway.

Curcuma mangga Val. rhizomes are widely used as an anti-breast cancer; and the oil showed cytotoxic activity on T47D and MCF7 cells; however, there is no research of its cytotoxic activity on TNBC yet. This study was to determine the TNBC-anticancer potency of essential oil C. mangga Val. through anti-angiogenesis with target of VEGF-expression inhibiton.

In the study the cytotoxic activity of C. mangga Val. essential oil was determined towards TNBC-4T1 cells with alpelisib as the positive control. Inhibition of VEGF-protein expression was conducted by immunocytochemical method. C. mangga Val. essential oil was identified using GC-MS. Content ligands were selected based on the Similarity Index (SI) ≥850 and relative abudance percentage ≥1%. The VEGF-expression inhibiton also carried out through molecular docking of the content ligands of C. mangga Val. essential oil on PI3K and Akt receptors compared with alpelisib.

The essential oil of the C. mangga Val *rhizome was resulted from water steam-destillation with yield of 0,28% w/w from dry simplicia. The color of the essential oil obtained was yellow with a specific gravity of 0,953 g/ml. The cytotoxicity test showed that essential oil C. mangga Val. was toxic to 4T1 cells with IC_{50} 91, 96 µg/ml; while the alpelisib's IC_{50} was 32.975 µg/ml. The immunocytochemical test showed that C. mangga Val. oil and alpelisib having the same inhibitor effect on VEGF-expression (p>0,05). Redocking test native ligands to PI3K (PDB: 4TV3) and Akt (PDB: 2UW9) using Triangle Matcher method resulted in RMSDs of 0,9058Å and 0,7774Å which were <2Å; so that the method was valid to use. Molecular docking test results of test ligand to PI3K (PDB: 4TV3)and Akt (PDB:2UW9) showed that all the test ligands had weaker binding than the native ligand ML9 (-81290) and GVP (-7,6835). Test ligands of m-camphorene bound to Lys 802 and nerolidol to Val 851 at the kinase domain of PI3K receptor as that of native ligand ML9 (with Val 851, Lys 802, dan Gln 848). m-Camphorene and nerolidol also bound respectively with Ala 232 dan Glu 236 at the kinase domain of Akt receptor as that of native ligand GVP (with Glu 236, Glu 230 dan Ala 232). It was concluded that C. mangga Val. rhizome's essential oil having anti triple negative breast cancer potency through angiogenic process inhibition.*

Keywords: *Curcuma mangga* Val., TNBC, VEGF, 4T1, PI3K/Akt