

# Potensi nanokurkumin dalam mencegah epithelial mesenchymal transition pada sel lestari kanker payudara MCF-7 yang dipaparkan endoksifen dan estradiol = Potency of nanocurcumin for the prevention of epithelial mesenchymal transition in endoxifen and estradiol treated MCF-7 breast cancer cell line / Paramita

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## Abstrak

### <b>ABSTRAK</b>

Latar Belakang: Endoksifen merupakan terapi baru pada pengobatan sel kanker payudara yang responsif terhadap endokrin. Studi terdahulu menunjukkan bahwa paparan endoksifen jangka panjang dapat menyebabkan resistensi melalui mekanisme Epithelial-Mesenchymal Transition (EMT). EMT adalah sebuah proses dimana suatu sel epithelial berubah menjadi sel mesenkimal. Proses EMT ditandai dengan adanya modulasi marker-marker epithelial seperti E-cadherin, vimentin dan TGF- $\beta$ 1. Berbagai penelitian telah menunjukkan bahwa paparan singkat kurkumin dapat memperbaiki marker-marker EMT. Namun, kurkumin memiliki keterbatasan karena bioavailabilitasnya yang rendah. Oleh karena itu, pada penelitian ini kami menggunakan nanokurkumin untuk mencegah jalur EMT.

Metode: ini merupakan penelitian in vitro menggunakan sel MCF-7. Kami membagi sel menjadi beberapa kelompok yaitu: Endoksifen 1000 nM+ $\beta$ -estradiol 1 nM, Endoksifen 1000 nM+ $\beta$ -estradiol 1 nM + nanokurkumin (8.5  $\mu$ M dan 17  $\mu$ M), Endoksifen 1000 nM+ $\beta$ -estradiol 1 nM+kurkumin 17  $\mu$ M dan DMSO selama 8 minggu. Sel kemudian dipanen dan dihitung setiap minggu. Setelah minggu ke-4 dan ke-8 paparan, ekspresi E-cadherin, TGF- $\beta$ 1 dan vimentin diukur menggunakan two-step qRT PCR. Pada minggu ke-8, kadar protein TGF- $\beta$ 1 diukur dengan ELISA, sementara morfologi sel MCF-7 diamati menggunakan mikroskop konfokal.

Hasil: Terdapat peningkatan viabilitas sel pada kelompok Endoksifen 1000 nM+ $\beta$ -estradiol 1 nM. Viabilitas sel menurun secara signifikan pada kelompok nanokurkumin dan kurkumin 17  $\mu$ M, tetapi tidak pada kelompok nanokurkumin 8.5  $\mu$ M. Analisis marker EMT pada minggu ke-8 menunjukkan terdapat peningkatan ekspresi mRNA vimentin dan TGF- $\beta$ 1 sementara ekspresi mRNA E-cadherin dan kadar protein TGF- $\beta$ 1 tampak menurun. Hasil menunjukkan bahwa pemberian nanokurkumin pada semua dosis tidak mampu memperbaiki ekspresi vimentin, TGF- $\beta$ 1, dan E-cadherin. Tidak tampak perbedaan yang signifikan antara nanokurkumin dan kurkumin terhadap modulasi marker-marker EMT pada sel kanker payudara yang dipaparkan endoksifen berulang. Pengamatan morfologi menggunakan mikroskop konfokal menunjukkan adanya sel mesenkimal baik pada kelompok endoksifen+ $\beta$ -estradiol maupun kelompok yang mendapat nanokurkumin/kurkumin.

Kesimpulan: nanokurkumin tidak mampu mencegah aktivasi EMT walaupun dapat menurunkan viabilitas sel pada penggunaan jangka panjang. Meskipun nanokurkumin lebih terakumulasi di dalam sel. tidak tampak perbedaan potensi dibandingkan dengan kurkumin dalam menurunkan marker EMT.

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**ABSTRACT**

**Background:** Endoxifen is a novel therapy in the treatment of endocrine responsive type of breast cancer. Previous study showed that long-term exposure of endoxifen may lead to resistance through the mechanism of Epithelial-Mesenchymal Transition (EMT). EMT is a process where epithelial cells turn into mesenchymal cells. EMT is characterized by the modulation of epithelial markers such as E-cadherin, vimentin and TGF- $\beta$ . Various studies have shown that short term treatment with curcumin may improve EMT markers. However, the efficacy of curcumin is limited by its low bioavailability. In this study, we use nanocurcumin to prevent the activation of EMT.

**Methods:** This is an in vitro study in MCF-7. We exposed the cells to several groups, which are: endoxifen 1000nM +  $\beta$ -estradiol 1 nM, endoxifen 1000nM +  $\beta$ -estradiol 1 nM + nanocurcumin (8.5  $\mu$ M and 17  $\mu$ M), endoxifen 1000nM +  $\beta$ -estradiol 1 nM + curcumin 17  $\mu$ M and DMSO, for 8 consecutive weeks. Cells were then harvested and counted weekly. After 4 and 8 weeks of treatments, E-cadherin, TGF- $\beta$  and vimentin expressions were measured using a two-step qRT PCR. At week 8, protein level of TGF- $\beta$ 1 was measured by ELISA, while MCF-7 cell morphology was observed using confocal microscope.

**Results:** MCF-7 cell viability was increased in endoxifen +  $\beta$ -estradiol group. Cell viability was significantly decreased in nanocurcumin and curcumin 17  $\mu$ M, but not in nanocurcumin 8.5  $\mu$ M group. Analysis of EMT markers at week 8 indicates that there were increase in vimentin and TGF- $\beta$ ; mRNA expressions, while E-cadherin mRNA expressions and TGF- $\beta$ 1 protein concentrations were shown to decrease. The results showed that administration of nanocurcumin in all the dose administered were incapable improving the expressions of vimentin, TGF- $\beta$ 1 and E-cadherin. There were no significant differences between nanocurcumin and curcumin on the modulation of EMT's markers in breast cancer cells exposed to repeated endoxifen and estradiol. Morphological observation using confocal microscope showed the presence of mesenchymal cells both in the endoxifen+ $\beta$ -estradiol group and the group given nanocurcumin/curcumin.

**Conclusion:** nanocurcumin is incapable to prevent the activation of EMT, although it may reduce cell viability on a long-term use. Although nanocurcumin are more accumulated in the cells, they show no difference in efficacy compared with curcumin in reducing EMT markers.