Profil farmakokinetik, potensi ko-kemoterapi dan mekanisme kerja nanokurkumin pada kanker ovarium pada tikus yang diinduksi 7,12-dimethylbenz(a)anthracene (DMBA) = Nanocurcumin pharmacokinetics profile, co-chemotherapy potency and its mechanism in 7,12-dimethylbenz(a)anthracene (DMBA)-induced ovarian cancer rat model

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Abstrak

Latar belakang: Kurkumin memiliki aktivitas antikanker yang poten, namun profil farmakokinetik dan ketersediaan kurkumin di organ target sangat rendah. Nanopartikel kurkumin dibuat untuk meningkatkan aktivitas kurkumin sehingga dapat meningkatkan efek obat pada proses angiogenesis dan proliferasi sel pada tikus model kanker ovarium. Metode: Nanopartikel kurkumin dibuat dengan metode gelasi ionik menggunakan kitosan sebagai polimer. Profil farmakokinetika kurkumin dan nanokurkumin dilakukan pada tikus dengan pemberian dosis oral sebesar 100 mg/kgBB. Sampel darah diambil pada sembilan waktu dan konsentrasi kurkumin dalam plasma dianalisis menggunakan UPLC-MS/MS. Pengujian nanokurkumin sebagai ko-kemoterapi secara in vivo pada kanker ovarium dilakukan pada tikus model kanker ovarium dengan induksi DMBA. Tikus model kanker ovarium diberikan terapi cisplatin atau kombinasi cisplatin dan kurkumin, atau kombinasi cisplatin dan nanokurkumin. Efek antikanker dilihat dari pengukuran marker antiproliferasi (Ki67), marker apoptosis serta jalur sinyal TGF-b/PI3K/Akt dan IL-6/JAK/STAT3.
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Hasil: Diperoleh ukuran partikel nanokurkumin sebesar 19,43±11,24 nm, dengan efisiensi penjerapan 99,97%, dan loading capacity 11,34%. Sifat mukoadhesif nanokurkumin lebih baik dibandingkan dengan kurkumin. Evaluasi profil farmakokinetik pada tikus diperoleh bahwa nanokurkumin meningkatkan AUC, Cmax, Tmax dan menurunkan klirens. Pada uji aktivitas in vivo, pemberian cisplatin dan ko-kemoterapi nanokurkumin menyebabkan penurunan yang signifikan pada volume dan berat ovarium. Penemuan ini sesuai dengan penurunan ekspresi protein TGF-Î², PI3K dan p-Akt/Akt. Efek ko-kemoterapi nanokurkumin juga dapat dapat menurunkan ekspresi protein IL-6, JAK, dan p-STAT3/STAT3. Pemberian cisplatin dan nanokurkumin juga menyebabkan peningkatan marker apoptosis yang signifikan seperti Bax, kaspase-9 dan kaspase-3 serta menurunkan ekspresi Bcl-2.</pre>
Kesimpulan: Nanokurkumin dapat memperbaiki profil farmakokinetika kurkumin, sehingga dapat diaplikasikan pada strategi ko-kemoterapi kanker ovarium dengan menghambat proliferasi melalui penghambatan jalur sinyal PI3K/Akt, JAK/STAT3, peningkatan apoptosis marker Bax, kaspase-3 dan kaspase-9 serta menurunkan ekspresi Bcl-2. Kata kunci: kurkumin, kitosan, nanopartikel, kanker ovarium, PI3K/Akt, JAK/STAT <hr /><pre>
Background: Curcumin has a potent anticancer activity. However, its systemic bioavailability and its concentration in organ is extremely low. The modification of curcumin to curcumin nanoparticles was expected to increase the activity of curcumin on angiogenesis and cell proliferation

process in rat ovarian cancer.</pre>
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Methods: Nanocurcumin were made using ionic gelation methods. The pharmacokinetic profiles of curcumin particles and nanoparticles were then assessed in rats by administering a single oral dose of 100 mg/kg BW. Blood samples were taken from nine predetermined time points, and curcumin plasma concentrations were then analyzed using UPLC-MS/MS. Nanocurcumin was tested as a co-chemotherapy in vivo and was carried out on ovarian cancer animal models, induced with 7,12-dimethylbenz(a)anthracene (DMBA). The ovarian cancer animal models were then treated with cisplatin, or cisplatin and curcumin, or combination of cisplatin with nanocurcumin. The anticancer effect of nanocurcumin as co-chemotherapy was investigated with the measurement of antiproliferation marker (Ki67), apoptotic markers as well as the expression of TGF-b/PI3K/Akt dan IL-6/JAK/STAT3.</pre>
Result: The particle size of the curcumin nanoparticles obtained were 19,43±11,24 nm. Entrapment efficiency (EE) of curcumin nanoparticles were exceeding 99.97%, and drug loading capacity (DLC) was 11.34%. The mucoadhesive properties of the nanoparticles were superior to that of curcumin particles. Pharmacokinetic evaluation in rats revealed that curcumin nanoparticles resulted in an increase of AUC, Cmax, Tmax, and lower Cl. The administration of cisplatin and nanocurcumin co-chemotherapy caused a significant reduction in ovarian volume and weight. These findings followed with decreased protein expression of TGF-Î², PI3K and p-Akt/Akt. The co-chemotherapy effect nanocurcumin is also investigated as a mechanism of action via IL-6, JAK, p-STAT3/STAT3 expressions. Treatments of cisplatin and nanocurcumin resulted in a significant increase in apoptotic markers such as Bax, caspase-9, and caspase-3 expressions and decreased Bcl-2 expression. Conclusion: Nanocurcumin is an effective formulation to improve pharmacokinetics profile. Nanocurcumin as a co-chemotherapy can be considered as a potential co-chemotherapy in ovarian cancer. The improved mechanism of actions are shown by the proliferation inhibition, downregulation of PI3K/Akt, JAK/STAT3 signaling pathways, and Bcl-2 expression and increasing apoptosis through the expression of Bax, caspase-9 and caspase-3. Keywords: curcumin, chitosan, nanoparticles, ovarian cancer, PI3K/Akt, JAK/STAT