Pengaruh nanopartikel kurkumin terhadap hepatotoksisitas cisplatin pada terapi kanker ovarium tikus melalui modulasi jalur persinyalan antioksidan Nrf2/Keap1 = Effects of nanocurcumin on cisplatin-induced hepatotoxicity in rat ovarian cancer model by modulation of the Nrf2/Keap1 antioxidant signaling pathway

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Abstrak

Latar Belakang: Cisplatin, agen kemoterapi pilihan untuk kanker ovarium, bersifat hepatotoksik dengan menginduksi stres oksidatif. Kurkumin adalah agonis jalur Nrf2/Keap1 yang penting dalam respons terhadap stres oksidatif, namun bioavailabilitasnya buruk. Pemberian kurkumin dalam bentuk nanopartikel meningkatkan bioavailabilitasnya dalam tubuh dan distribusinya ke organ target. Penelitian ini bertujuan untuk mengetahui pengaruh nanopartikel kurkumin terhadap hepatotoksisitas cisplatin melalui modulasi jalur Nrf2/Keap1 dilihat dari kadar MDA dan ekspresi gen jalur Nrf2/Keap1.
Metode: 25 ekor tikus Wistar betina dikelompokkan menjadi 5 kelompok yaitu kelompok normal, 4 kelompok model kanker ovarium yang diinduksi DMBA yang dibagi menjadi kelompok tanpa terapi, monoterapi cisplatin 4 mg/KgBB intraperitoneal, ko-kemoterapi cisplatin dan kurkumin konvensional 100 mg/KgBB per oral, serta ko-kemoterapi cisplatin dan nanopartikel kurkumin dalam kitosan 100mg/KgBB per oral selama 1 bulan. Tikus dikorbankan dan hepar disimpan beku. Pengukuran MDA dilakukan dengan metode spektrofotometri, sementara analisis gen jalur Nrf2/Keap1 dilakukan dengan prosedur qRT-PCR.
Hasil: Uji parametrik ANOVA dan post-hoc Tukey menunjukkan adanya penurunan kadar MDA hepar secara bermakna antara kelompok ko-kemoterapi kurkumin konvensional dan ko-kemoterapi nanokurkumin dengan kelompok monoterapi cisplatin (p=0,000 dan p=0,005). Tidak ada perbedaan bermakna antarkelompok pada ekspresi relatif mRNA Keap1 (p=0,190). Tidak ada perbedaan bermakna antara kelompok ko-kemoterapi kurkumin konvensional dengan nanokurkumin terkait ekspresi relatif Nrf2 (p=0,990), HO-1 (p=0,513), dan NQO-1 (p=1,000).
Kesimpulan: Pemberian kurkumin menurunkan kadar MDA jaringan hepar dibanding kelompok monoterapi cisplatin. Tidak ada perbedaan bermakna antara kurkumin konvensional dan nanokurkumin dalam melemahkan hepatotoksisitas cisplatin dilihat dari MDA dan ekspresi gen jalur Nrf2/Keap1.
.....Introduction: Cisplatin induces hepatotoxicity by oxidative stress-related mechanism. Curcumin activates the Nrf2/Keap1 pathway, modulating cellular response to oxidative stress, but its bioavailability is poor. The administration of curcumin in nanoparticles may increase the bioavailability and distribution of curcumin into tissues. This research aimed to assess the attenuation of cisplatin- induced hepatotoxicity through the modulation of Nrf2/Keap1 pathway by nanocurcumin.
Methods: 25 female Wistar rats were divided into a normal group and four ovarian cancer models by DMBA induction (further classified into a no treatment group, cisplatin monotherapy [4 mg/KgBW i.p.], co-administration of cisplatin and conventional curcumin [100 mg/KgBW p.o.], and co-administration of cisplatin and curcumin-loaded chitosan nanoparticles [100mg/KgBW p.o.]) for a month. The livers of the sacrificed animals were frozen. MDA level was measured by spectrophotometry, while the analysis of Nrf2/Keap1 pathway was done using qRT-PCR.

Results: The ANOVA parametric test showed significant differences between groups in hepatic MDA level ((p<0,001). MDA level was markedly reduced in groups receiving conventional (p<0,001) and nanocurcumin (p=0,005), though there were no significant differences between the administration of conventional and nanocurcumin in MDA level (p=0,277). There were no significant differences between groups in Keap1 relative mRNA expression (p=0,190). No statistically significant differences were observed between groups receiving conventional curcumin and nanocurcumin in the relative gene expression Nrf2 (p=0,990), HO-1 (p=0,513), and NQO-1 (p=1,000) mRNAs.
Conclusion: Curcumin did attenuate cisplatin-induced hepatotoxicity, but no significant differences were observed in hepatic MDA level and relative expression of genes in the Nrf2/Keap1 pathway between conventional curcumin and nanocurcumin administration.