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Studi molekuler Hesperetin, Diosmin, Tangeretin sebagai co-treatment dengan Cisplatin terhadap proliferasi dan apoptosis sel kanker hati serta pencegahan senescence pada sel normal ginjal
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INTISARI

Angka kejadian kanker hati pada tahun 2022, sekitar 866.136 kasus baru dan 758.725 kematian akibat kanker hati di seluruh dunia. Salah satu agen kemoterapi dalam pengobatan kanker hati adalah cisplatin yang memiliki beberapa efek samping, termasuk nefrotoksisitas. Nefrotoksisitas cisplatin disebabkan oleh peningkatan stres oksidatif akibat akumulasi radikal bebas. Flavonoid citrus pada penelitian ini meliputi hesperetin, diosmin, dan tangeretin memiliki aktivitas antikanker pada perlakuan tunggal maupun *co-treatment* dengan agen kemoterapi, serta bersifat antioksidan sehingga berpotensi sebagai *co-treatment* dengan cisplatin. Penelitian ini bertujuan untuk mengevaluasi potensi masing-masing flavonoid tersebut sebagai *co-treatment* cisplatin pada sel kanker hati HepG2 serta efek sitoprotektifnya terhadap sel normal ginjal Vero.

Studi *in vitro* dilakukan terhadap ketiga flavonoid tersebut, baik secara tunggal maupun masing-masing diberikan secara *co-treatment* dengan cisplatin pada sel HepG2 sebagai model *hepatocellular carcinoma* (HCC) dan sel Vero sebagai model sel normal ginjal. Metode yang digunakan dalam penelitian ini meliputi uji sitotoksisitas (MTT *assay*), pengaruh *senescence* (SA-β-Gal *assay*), pengaruh pembentukan koloni, analisis apoptosis, nekrosis dan siklus sel (*flowcytometry*), serta aktivasi protein regulator proliferasi (ERK1/2, p-ERK1/2), ekspresi cyclin D1 dan ekspresi protein regulator apoptosis (Bax, Bcl-xl, caspase-3) (*capillary Western blot*) terhadap sel HepG2. Perlakuan pada sel normal ginjal Vero, flavonoid citrus serta *co-treatment* dengan cisplatin dievaluasi melalui uji MTT dan *senescence* (SA-β-Gal *assay*) untuk menilai efek sitoprotektif. Keseluruhan data yang diperoleh disajikan sebagai rerata ± SE dan dianalisis secara statistik menggunakan *One-Way* ANOVA dilanjutkan dengan uji Tukey dengan SPSS pada taraf kepercayaan 95%.

Hesperetin, diosmin, tangeretin menunjukkan efek sitotoksik pada sel kanker hati HepG2 dengan nilai IC_{50} masing-masing 258 ± 0,11 µM; 148 ± 1,04 µM; 330 ± 1,84 µM dan IC_{50} cisplatin adalah 5,8 ± 0,34 µM. *Co-treatment* cisplatin (2,8 µM) dengan hesperetin (130 µM), diosmin (74 µM) dan tangeretin (165 µM) secara sinergis menurunkan viabilitas sel dan menghambat pembentukan koloni. Hesperetin (130 µM) dan diosmin (74 µM) sebagai *co-treatment* dengan cisplatin menghambat siklus sel fase G2/M (33,84% dan 37,19%), sedangkan *co-treatment* cisplatin dan tangeretin pada fase S (57,97%). *Co-treatment* hesperetin (130 µM) dan cisplatin (3 µM) paling efektif menginduksi *senescence* (14,7%), apoptosis (17,44%), serta penurunan nekrosis (2,83%), disertai penurunan Bcl-xl, ERK1/2, p-ERK1/2, cyclin D1, serta peningkatan Bax dan caspase-3 dibandingkan dengan cisplatin tunggal. Sebaliknya, *co-treatment* diosmin (74 µM) atau tangeretin (165 µM) dengan cisplatin (3 µM) tidak signifikan terhadap induksi *senescence* maupun apoptosis dibandingkan dengan cisplatin tunggal. Pada sel ginjal Vero, ketiga flavonoid meningkatkan viabilitas sel, dan *co-treatment* dengan cisplatin bersifat antagonis serta anti-*senescence*. Secara keseluruhan, flavonoid citrus hesperetin, diosmin dan tangeretin merupakan *co-treatment* cisplatin yang potensial dalam menghambat proliferasi dan menginduksi apoptosis pada sel HepG2 sekaligus protektif sebagai anti*senescence* terhadap sel Vero.

Kata Kunci: hesperetin, tangeretin, diosmin, proliferasi, apoptosis

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ABSTRACT

Liver cancer remains a major global health burden, with approximately 866,136 new cases and 758,725 deaths reported worldwide in 2022. Cisplatin is one of the chemotherapeutic agents commonly used for the treatment of liver cancer; however, its clinical application is limited by several adverse effects, particularly nephrotoxicity. Cisplatin-induced nephrotoxicity is primarily associated with increased oxidative stress caused by the excessive accumulation of free radicals. Citrus flavonoids investigated in this study, including hesperetin, diosmin, and tangeretin, have demonstrated anticancer activity both as single agents and in co-treatment with chemotherapeutic drugs. In addition, their antioxidant properties suggest their potential as co-treatment agents with cisplatin. Therefore, this study aimed to evaluate the potential of these citrus flavonoids as co-treatment with cisplatin in HepG2 liver cancer cells and to investigate their cytoprotective effects on normal kidney Vero cells.

An in vitro study was conducted using hesperetin, diosmin, and tangeretin, either as single treatments or in co-treatment with cisplatin, in HepG2 cells as a hepatocellular carcinoma (HCC) model and Vero cells as a normal kidney cell model. The experimental methods included cytotoxicity assessment using the MTT assay, cellular senescence analysis using the senescence-associated β-galactosidase assay, colony formation assay, apoptosis, necrosis, and cell cycle analyses by flow cytometry, as well as the evaluation of proliferation-related proteins (ERK1/2 and p-ERK1/2), cyclin D1 expression, and apoptosis-regulating proteins (Bax, Bcl-xL, and caspase-3) using capillary Western Blot analysis in HepG2 cells. In normal kidney Vero cells, the cytoprotective effects of citrus flavonoids, either alone or in combination with cisplatin, were evaluated using the MTT assay and SA-β-Gal assay. All data were expressed as the mean ± standard error (SE) and statistically analyzed using one-way analysis of variance (ANOVA) with SPSS software at a 95% confidence level.

Hesperetin, diosmin, and tangeretin exhibited cytotoxic effects on HepG2 liver cancer cells, with IC_{50} values of 258 ± 0.11 μM, 148 ± 1.04 μM, and 330 ± 1.84 μM, respectively, while the IC_{50} of cisplatin was 5.8 ± 0.34 μM. Co-treatment of cisplatin (2.8 μM) with hesperetin (130 μM), diosmin (74 μM), and tangeretin (165 μM) synergistically reduced cell viability and inhibited colony formation. Co-treatment of hesperetin (130 μM) and diosmin (74 μM) with cisplatin inhibited the cell cycle at the G2/M phase (33.84% and 37.19%), whereas co-treatment of cisplatin and tangeretin induced arrest at the S phase (57.97%). Co-treatment of hesperetin (130 μM) and cisplatin (3 μM) was the most effective in inducing senescence (14.7%) and apoptosis (17.44%), while reducing necrosis (2.83%), accompanied by decreased expression of Bcl-xL, ERK1/2, p-ERK1/2, and cyclin D1, as well as increased expression of Bax and caspase-3 compared to single cisplatin. In contrast, co-treatment with diosmin (74 μM) or tangeretin (165 μM) and cisplatin (3 μM) did not significantly induce senescence or apoptosis compared with single cisplatin. In Vero kidney cells, all three flavonoids increased cell viability, and their co-treatment with cisplatin showed antagonistic and anti-senescence effects. Overall, citrus flavonoids hesperetin, diosmin, and tangeretin demonstrate potential as co-treatment agents with cisplatin in inhibiting proliferation and inducing apoptosis in HepG2 cells, while also providing protective anti-senescence effects on Vero cells.

Keywords: hesperetin, tangeretin, diosmin, proliferation, apoptosis