

## ABSTRAK

Efek genotoksik merupakan efek kerusakan *deoxyribonucleic acid* (DNA) akibat paparan agen, di antaranya obat sitostatik. Salah satu obat sitostatik yang dapat termetabolisme menjadi metabolit toksiknya oleh CYP 3A4 (*family* CYP 450) dan menimbulkan *adverse drug reaction* (ADR) berupa efek genotoksik adalah siklofosfamid (SIF). Salah satu strategi pengatasannya adalah aplikasi agen antigenotoksik berupa ekstrak etanolik daun pepaya (*Carica papaya* L.) (EEDP) yang mengandung *quercetin*. Penelitian ini bertujuan untuk mengetahui efek antigenotoksik EEDP serta interaksi *quercetin* dengan CYP3A4.

EEDP diperoleh melalui maserasi menggunakan etanol 70% dengan rendemen sebesar 24,94%. Analisis kualitatif kandungan senyawa EEDP dilakukan melalui kromatografi lapis tipis. Evaluasi aktivitas antigenotoksik EEDP dilakukan melalui *mammalian in vivo micronucleus test* menggunakan 42 ekor mencit betina galur Swiss terinduksi siklofosfamid dengan parameter jumlah *micronucleated polychromatic erythrocyte* (MNPCE)/ 1000 PCE dan % *polychromatic erythrocyte* (PCE)/ (PCE+ *normochromatic erythrocyte* (NCE)). Pengamatan interaksi *quercetin* pada CYP3A4 dilakukan melalui *molecular docking* menggunakan *software* PLANTS dengan parameter *docking score*.

Hasil penelitian menunjukkan bahwa EEDP 250; 500; 1000 mg/kgBB secara signifikan ( $p < 0,05$ ) menurunkan jumlah MNPCE/ 1000 PCE sebesar 2,06; 2,25; dan 2,80 kali dibandingkan dengan SIF yang menunjukkan bahwa EEDP berefek antigenotoksik. EEDP juga meningkatkan %PCE/ (PCE+NCE) sebesar 1,83; 1,98 ; dan 2,19 kali yang menunjukkan bahwa EEDP tidak toksik pada dosis uji. *Docking score* menunjukan *quercetin* (-74,48) lebih poten berinteraksi dengan CYP 3A4 daripada SIF (-70,83) dan memiliki situs ikat sama (Ile 369). Secara keseluruhan, EEDP berpotensi sebagai agen antigenotoksik melalui mekanisme interaksi *quercetin* pada CYP 3A4.

Kata kunci : antigenotoksik, *Carica papaya* L., MNPCE, *in vivo*

## ABSTRACT

Genotoxic effect is the deoxyribonucleic acid (DNA) damage caused by agent exposure, such as cytostatic drug. One of the cytostatic drug which can be metabolized into its toxic metabolite by CYP 3A4 (family of CYP 450) and causes genotoxic effect as its adverse drug reaction (ADR) is cyclophosphamide. The effective strategy for that problem is antigenotoxic agent application by papaya leaf (*Carica papaya* L.) ethanolic extract (PLEE) which contains quercetin. The aim of this study is to investigate the antigenotoxic effect of PLEE and also the interaction between quercetin and CYP 3A4.

PLEE was extracted using 70% etanol with 24,94% rendemen. Qualitative analysis of PLEE content was conducted by thin layer chromatography. The antigenotoxic effect of PLEE was conducted by mammalian in vivo micronucleus test using 42 female Swiss mice induced by cyclophosphamide with the parameters of micronucleated polychromatic erythrocyte (MNPCE)/1000 polychromatic erythrocyte (PCE) and %PCE/(PCE+normochromatic erythrocyte (NCE)). The observation of quercetin and CYP 3A4 interaction was conducted by molecular docking using PLANTS software with the parameter of docking score.

The result of this study showed that PLEE with the dose of 250; 500; 1000 mg/kgBW decreased the MNPCE/1000 PCE parameter in the ammount of 2,06; 2,25; and 2,80 times significantly ( $p<0,05$ ) compared with cyclophosphamide control, which is showed that PLEE has antigenotoxic effect. PLEE of the three doses was also increased %PCE/(PCE+NCE) parameter in the ammount of 1,83; 1,98; and 2,19 times significantly ( $p<0,05$ ) compared with cyclophosphamide control, which is showed that PLEE is not toxic in treatment doses. The docking score showed that quercetin (-74,48) is more potent to interact with CYP 3A4 than cyclophosphamide (-70,83), and also has the same binding site (Ile 369). Overall, PLEE has potential antigenotoxic effect through quercetin interaction on CYP 3A4 mechanism.

**Keywords:** antigenotoxic, *Carica papaya* L., MNPCE, in vivo