ABSTRAK

Latar Belakang: *Hepatic ischemia-reperfusion injury* (H IRI) merupakan kondisi berhentinya aliran darah (iskemia) menuju hepar diikuti kembalinya aliran darah (reperfusi). Kondisi ini mendominasi penyebab kematian setelah transplantasi hepar, tetapi belum terdapat pengobatan standar. H IRI dimulai saat iskemia lokal dilanjut fase reperfusi yang terjadi peningkatan *reactive oxygen species* (ROS) sehingga akan mengarah pada inflamasi dan apoptosis. Pada penelitian sebelumnya, *Piper betle* (sirih) berpotensi menghambat ROS.

Tujuan: Penelitian ini bertujuan untuk mengkaji pengaruh pemberian ekstrak *P. betle* terhadap fungsi hepar melalui kadar AST, ekspresi mRNA CD68, tampakan imunohistokimia p53, dan tampakan apoptosis hematoksilin-eosin pada model H IRI.

Metode: Ekstrak *Piper betle* dilarutkan menggunakan *ultrasonic-assisted extraction* dengan etanol 80%. Sebagai kontrol, digunakan kelompok *sham operation* dan kelompok H IRI. H IRI dimodelkan pada tikus wistar jantan (2 bulan, 130-200 gram) dengan menjepit trias portal menggunakan *atraumatic clamp* selama 60 menit diikuti dengan reperfusi 3 hari. Kelompok SR-100, SR-200, dan SR-400 diberikan perlakuan H IRI dan diberi ekstrak *P. betle* berturut-turut 100 mg/kg, 200 mg/kg, dan 400 mg/kg secara oral sekali sehari selama 3 hari. Fungsi hepar dinilai dengan kadar serum *aspartat aminotransferase* (AST). Ekspresi mRNA CD68 diuji dengan RT-PCR. Tampakan apoptosis hepar dilihat dari imunohistokimia protein p53 dan tampakan cedera hepar ditunjukkan dengan pewarnaan hematoksilin-eosin melalui adanya ketidakteraturan sel hepar dan vakuolisasi sel.

Hasil: Pemberian ekstrak *Piper betle* terutama dosis 400 mg/kg dibanding kelompok H IRI memiliki kadar AST yang lebih rendah (p=0,002), ekspresi mRNA CD68 yang lebih rendah (p=0,014), tidak dijumpai tampakan protein p53, dan perbaikan struktur jaringan hepar melalui keteraturan sel dan tidak adanya vakuolisasi sel.

Kesimpulan: Ekstrak *P. betle* memiliki potensi untuk memperbaiki fungsi hepar, menekan inflamasi dan apoptosis, serta perbaikan struktur hepatosit model H IRI.

Kata Kunci: *Hepatic ischemia-reperfusion injury*, *Piper betle,* Inflamasi, Apoptosis

ABSTRACT

Background: Hepatic ischemia-reperfusion injury (H IRI) is a condition where blood flow stops (ischemia) to the liver followed by the return of blood flow (reperfusion). This condition dominates the cause of death after liver transplantation, but there is no standard treatment. H IRI begins during local ischemia followed by a reperfusion phase where there is an increase in reactive oxygen species (ROS) so that it will continue to apoptosis and inflammation. In previous research, *Piper betle* has the potential to inhibit ROS.

Objective: This study aims to examine the effect of administration of *P. betle* extract on liver function through AST levels, CD68 mRNA expression, p53 immunohistochemical appearance, and hematoxylin-eosin apoptosis appearance in the H IRI model.

Method: *Piper betle* extract was dissolved using ultrasonic-assisted extraction with 80% ethanol. As controls, the sham operation group and the H IRI group were used. H IRI was modeled in male Wistar rats (2 months, 130-200 grams) by clamping the portal triad using an atraumatic clamp for 60 minutes followed by 3 days of reperfusion. The SR-100, SR-200, and SR-400 groups were given H IRI treatment and given *P. betle* extract respectively 100 mg/kg, 200 mg/kg, and 400 mg/kg orally once a day during reperfusion. Liver function was measured by serum aspartate aminotransferase (AST) levels. CD68 mRNA expressions were tested by RT-PCR. The appearance of liver apoptosis was seen from p53 protein immunohistochemistry. The appearance of liver injury was shown by hematoxylin-eosin staining through liver cell irregularities and cell vacuolization.

Results: Administration of *Piper betle* extract, especially at a dose of 400 mg/kg compared to the H IRI group, had lower AST levels (p=0.002), lower CD68 mRNA expression (p=0.014), no p53 protein appearance, and improved liver tissue structure through cell regularity and the absence of cell vacuolization

Conclusion: *P. betle* extract has the potential to improve liver function, suppress inflammation and apoptosis, and improve the structure of hepatocytes in the H IRI model.

Keywords: Liver ischemia-reperfusion injury, *Piper betle*, Inflammation, Apoptosis