INTISARI

Herb-Drug Interactions (HDIs) pada fase farmakokinetika khususnya metabolisme dapat mempengaruhi aktivitas farmakologi. Ekstrak etanol sambiloto (*Andrographis paniculata* (Burm.f.) Nees dan senyawa metabolit utamanya andrografolida diketahui bersifat induktor/inhibitor enzim CYP450 dan *UDP-glucoronosyltransferase* (UGTs). Penelitian ini bertujuan untuk mengkaji mekanisme interaksi antara ekstrak sambiloto dan andrografolida dengan glipizid melalui kajian farmakokinetika dan pengaruhnya terhadap aktivitas farmakologi antidiabetes (farmakodinamika).

Tahapan penelitian terdiri dari uji *in silico docking* molekuler menggunakan software MOE® dan uji simulasi dinamika molekul menggunakan Gromacs 2016 untuk menentukan energi dan stabilitas ikatan antara senyawa dari sambiloto termasuk andrografolida terhadap reseptor CAR (PDB ID 1XVP) dan PXR (PDB ID 1SKX). Studi *in vitro* pada sel HepG2 dilakukan untuk mengukur ekspresi gen CAR,PXR,CYP2C9, dan UGT1A1. Studi *in vivo* dilakukan dengan mengukur parameter farmakokinetika glipizid pada tikus normal dan diabetes menggunakan metode HPLC yang optimal dan tervalidasi. Uji aktivitas farmakologi dilakukan pada tikus diabetes (induksi STZ/NA) dengan parameter penurunan kadar glukosa darah (%PKGD), morfologi insula Langerhans, dan ekspresi *pancreatic* insulin serta ekspresi CAR, PXR, CYP2C9, dan UGT1A1 dari organ hepar tikus menggunakan qRT -PCR.

Hasil pengukuran kadar glipizid pada plasma dan perhitungan profil farmakokinetika glipizid model non kompatemen dengan analisis *PK solver* menunjukkan adanya kenaikan beberapa parameter farmakokinetika seperti nilai C_{max} dan $AUC0_{-t}/AUC_{0-\infty}$ glipizid pada tikus normal (p>0,05) dan secara signifikan pada tikus diabetes (*P<0,05*) setelah diberikan bersama ekstrak sambiloto dan berdampak pada naiknya efek penurunan kadar glukosa darah hingga 53,99%. Sedangkan kombinasi dengan andrografolida terjadi penurunan kadar glipizid pada tikus diabetes yang diikuti turunnya nilai C_{max}, $AUC_{0-t}/AUC_{0-\infty}$, secara signifikan (*P<0,05*) dan menyebabkan aktivitas antidiabetes menurun. Mekanisme interaksi tersebut diprediksi melalui jalur ekspresi CAR dan PXR yang ditunjukkan dari hasil *docking*, dinamika molekul, dan peningkatan ekspresi pada sel HepG2 dan organ hepar tikus. Ekstrak sambiloto diprediksi bersifat inhibitor ekspresi enzim CYP2C9 sehingga menyebabkan peningkatan kadar glipizid utuh dalam plasma. Sedangkan peningkatan ekspresi CYP2C9 dan turunnya UGT1A1 oleh andrografolida secara signifikan menyebabkan metabolisme glipizid dipercepat. Kesimpulan dari penelitian ini adalah pemberian ekstrak sambiloto dan andrografolida mampu berinteraksi dengan glipizid dengan merubah parameter farmakokinetika glipizid melalui perubahan ekspresi CAR, PXR, CYP2C9, dan UGT1A1 yang sejalan dengan aktivitas farmakologi antidiabetes. Adanya interaksi tersebut dapat dijadikan perhatian potensial HDIs yang berdampak pada efek farmakologi glipizid, dan penggunaan bersama keduanya untuk terapi diabetes mellitus perlu dikaji lebih lanjut.

Kata Kunci: *Andrographis paniculata*, andrografolida, glipizid, HDIs

ABSTRACT

Herb-Drug Interactions (HDIs) during the pharmacokinetic phase, particularly metabolism, can affect pharmacological activity. It is known that the ethanolic extract of sambiloto (Andrographis paniculata (Burm. f.) Nees *and its major metabolite andrographolides are inductors/inhibitors of CYP450 and UDP-glucuronosyltransferase (UGTs) enzymes. This study examines the interaction mechanism between Sambiloto extract, andrographolide, and glipizide by studying pharmacokinetics and their effect on antidiabetic pharmacological activity (pharmacodynamics).*

The procedures for the study included in silico molecular docking studies with MOE® software and molecular dynamics simulation simulations with Gromacs 2016 to investigate the energy and stability of the binding between chemicals from Sambiloto, such as andrographolide on CAR receptors (PDB ID 1XVP) and PXR receptors (PDB ID 1SKX). The CAR, PXR, CYP2C9, and UGT1A1 gene expression levels in HepG2 cells were measured in vitro. In measuring the pharmacokinetic parameters of glipizide in normal and diabetic rats using the optimized and validated HPLC method, in vivo studies, were performed. On diabetic rats (STZ/NA-induced), a pharmacological activity test was conducted with the parameters of decreased blood glucose levels (%PKGD), the morphology of Langerhans insula, and expression of pancreatic insulin, as well as expression of CAR, PXR, CYP2C9, and UGT1A1 from rat liver organs using qRT-PCR.

The test findings for measuring glipizide levels in plasma were used to arrange the glipizide pharmacokinetic profile of the non-compartment analysis (NCA) model using PK solver analysis. Several pharmacokinetic parameters, such as the value of Cmax and AUC0–t/AUC0–∞ glipizide, increased in normal rats ($p>0.05$) and significantly in diabetic rats (P0.05) following administration of Sambiloto extract, resulting in a 53.99% increase in the effect of lowered blood glucose levels. While the combination with andrographolide decreased glipizide levels in diabetic rats, significant decreases in Cmax, AUC0–t/AUC0–∞, and antidiabetic activity was also observed. Docking, molecular dynamics, and enhanced expression in HepG2 cells and rat liver tissues demonstrated the CAR and PXR expression pathways utilized to anticipate the interaction mechanism. It is projected that Sambiloto extract will inhibit the CYP2C9 enzyme, resulting in a rise in plasma levels of intact glipizide. Moreover, it is projected that an increase in CYP2C9 expression and a considerable decrease in UGT1A1 by andrographolide will speed up glipizide metabolism. This study concludes that the administration of Sambiloto extract and andrographolide affected glipizide's pharmacokinetics through changes in the expression of CAR, PXR, CYP2C9, and UGT1A1 which are in line with antidiabetic activity. This interaction may cause concern for HDIs that influence the pharmacological effects of glipizide, necessitating more research into their application in treating diabetes mellitus.

Keywords: Andrographis paniculata, andrographolide, glipizide, HDIs