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Interaksi Farmakokinetik Ekstrak Meniran (Phyllanthus niruri) dan Rifampisin: Kajian In Vivo, In Vitro, dan In Silico
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INTISARI

Suplementasi ekstrak meniran (*Phyllanthus niruri*) pada pasien TB menunjukkan perbaikan imunitas dan penurunan virulensi, sehingga penggunaannya mendukung capaian target SDG 3.3 oleh PBB. Namun potensi interaksinya dengan rifampisin belum diketahui. Mengingat efektivitas rifampisin sangat bergantung pada bioavailabilitasnya, maka interaksi farmakokinetik dapat berdampak pada keberhasilan terapi. Penelitian ini bertujuan mengkaji pengaruh ekstrak meniran pada profil farmakokinetik rifampisin serta mengungkap mekanisme interaksinya melalui pendekatan *in vivo*, *in vitro*, dan *in silico*.

Metode penelitian meliputi validasi parsial metode analisis kadar rifampisin dalam plasma, homogenat organ, dan feses, serta untuk uji disolusi menggunakan HPLC-PDA. Studi *in vivo* dilakukan untuk mengevaluasi parameter farmakokinetik, biodistribusi, ekskresi via feses, dan motilitas usus. Uji *in vitro* mencakup analisis profil disolusi, spektrum UV-Vis, dan kromatogram rifampisin pada pH 2 dan pH 6,8. Selanjutnya identifikasi metabolit sekunder ekstrak menggunakan LC-MS/MS, kemudian diikuti dengan penelusuran bioinformatika melalui prediksi ADME, *network pharmacology* dan *molecular docking*.

Validasi yang dilakukan secara parsial menunjukkan bahwa metode terbukti valid dan layak digunakan pada penetapan kadar rifampisin. Pada uji *in vivo*, pemberian ekstrak meniran tidak mempengaruhi AUC, C_{max}, CL/F, V_d/F, biodistribusi rifampisin pada 2 jam pascaperlakuan serta ekskresi rifampisin. Namun terjadi penurunan nilai K_a dari 1,12/jam menjadi 0,24/jam ($P = 0{,}0159$; $p < 0{,}05$) dan memperpanjang T_{max} sebesar 2 kali lipat ($P = 0{,}0132$; $p < 0{,}05$). Hasil *profiling* menunjukan bahwa ekstrak mengandung pyrogallol, ellagic acid, quercetin, hyperin, isoquercitrin, rutin dan corilagin. Penelusuran mekanisme interaksi mengkonfirmasi peningkatan motilitas usus akibat pemberian ekstrak ($P = 0{,}0018$; $p < 0{,}05$) yang secara *in silico* kemungkinan berkorelasi dengan mekanisme antagonis reseptor α_2A-adrenergik. Selanjutnya, pembentukan kompleks non-kovalen pada pH 2 dibuktikan berdasarkan penurunan puncak kromatogram serta hipokromisitas rifampisin pada λ_{max} 334 nm akibat penambahan ekstrak. Kemudian, ekstrak juga menyebabkan peningkatan disolusi rifampisin pada pH 6,8 yang signifikan pada menit ke 20 dan 40 ($P = 0{,}0088$; $p < 0{,}0001$; $p < 0{,}05$). Terakhir, hasil *network pharmacology* mengonfirmasi potensi interaksi melalui kompetisi afinitas pada transporter P-gp antara senyawa dalam ekstrak dan rifampisin. Berdasarkan data tersebut dapat disimpulkan bahwa ekstrak meniran *single dose* memicu interaksi multi-mekanisme yang mengubah kinetika absorpsi tanpa mempengaruhi bioavailabilitas rifampisin.

Kata kunci: Tuberkulosis, kompleks non-kovalen, motilitas usus, kinetika absorpsi, uji disolusi.

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ABSTRACT

Phyllanthus niruri extract has been shown to improve immunity and reduce virulence in TB patients, supporting UN SDG 3.3. However, its interaction with rifampicin has not been established. Because rifampicin's effectiveness depends on bioavailability, any pharmacokinetic interaction could affect treatment success. This study aims to examine the effect of *Phyllanthus niruri* extract on rifampicin pharmacokinetics and to elucidate the mechanism of this interaction through in vivo, in vitro, and in silico approaches.

The research methods included partial validation of the analytical methods for determining rifampicin concentrations in plasma, organ homogenates, and feces, as well as dissolution testing using HPLC-PDA. In vivo studies were conducted to evaluate pharmacokinetic parameters, biodistribution, excretion, and intestinal motility. In vitro tests included analysis of the dissolution profile, UV-Vis spectrum, and rifampicin chromatogram at pH 2 and pH 6.8. Next, secondary metabolites in the extract were identified using LC-MS/MS, followed by bioinformatics analysis through ADME prediction, network pharmacology, and molecular docking.

Partial validation showed that the method was valid and suitable for determining rifampicin concentrations. In in vivo tests, administration of *Phyllanthus niruri* extract did not affect the AUC, C_{max}, CL/F, Vd/F, biodistribution of rifampicin 2 hours after treatment, and rifampicin excretion. However, there was a decrease in the K_a value from 1.12/hour to 0.24/hour ($P = 0{,}0159$; $p < 0.05$) and a two-fold increase in T_{max} ($P = 0{,}0132$; $p < 0.05$). Profiling results showed that the extract contained pyrogallol, ellagic acid, quercetin, hyperin, isoquercitrin, rutin, and corilagin. An investigation of the interaction mechanism confirmed increased intestinal motility following extract administration ($P = 0{,}0018$; $p < 0{,}05$), which, in silico, correlated with an α_2A-adrenergic receptor antagonist mechanism. Furthermore, the formation of a non-covalent complex at pH 2 was demonstrated by a decrease in the chromatogram peak and the hypochromicity of rifampicin at λmax 334 nm following the addition of the extract. Additionally, the extract significantly increased rifampicin dissolution at pH 6.8 at 20 dan 40 minutes ($P = 0{,}0088$; $p < 0{,}0001$; $p < 0{,}05$). Finally, network pharmacology results confirmed the potential for affinity-competitive interactions between compounds in the extract and rifampicin at the P-gp transporter. Based on these data, it can be concluded that a single dose of *Phyllanthus niruri* extract triggers multi-mechanism interactions that alter absorption kinetics without affecting rifampicin bioavailability.

Keyword: Tuberculosis, non-covalent complex, intestinal motility, absorption kinetics, dissolution.