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Potensi Antibakteri Fungi Endofit Brotowali (Tinospora crispa (L.) Hook.f. & Thomson.) terhadap Bakteri Multidrug-Resistant (MDR) melalui Integrasi Analisis Metabolomik dan Genomik
Zahrotin Saleha, Wahyu Aristyaning Putri, S.Si., M.Sc., Ph.D ; Prof. Rina Sri Kasiamdari, S.Si, Ph.D.
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POTENSI ANTIBAKTERI FUNGI ENDOFIT BROTOWALI (*Tinospora crispa* (L.) Hook.f. & Thomson.) TERHADAP BAKTERI *MULTIDRUG-RESISTANT* (MDR) MELALUI INTEGRASI ANALISIS METABOLOMIK DAN GENOMIK

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INTISARI

Peningkatan kasus resistensi antibiotik dalam beberapa tahun terakhir telah menjadikan masalah ini sebagai ancaman kesehatan global. Hal ini mendorong upaya pencarian alternatif agen antibakteri yang lebih efektif dan aman. Penelitian ini bertujuan untuk mengeksplorasi potensi fungi endofit dari tanaman Brotowali (*Tinospora crispa* (L.) Hook.f. & Thomson.) terhadap bakteri *multidrug-resistant* (MDR) melalui pendekatan integratif metabolomik dan genomik. Fungi endofit diisolasi dari jaringan akar, batang, dan daun *T. crispa*, menghasilkan 38 isolat dengan karakter morfologi yang beragam. Skrining awal antibakteri menggunakan metode *agar plug* menunjukkan sebagian besar isolat memiliki aktivitas antibakteri terhadap MDR *Escherichia coli*, MDR *Klebsiella pneumoniae*, dan MDR *Staphylococcus aureus*, dengan isolat A22 sebagai kandidat paling potensial. Metabolit sekunder A22 diekstraksi menggunakan metode maserasi dan pelarut etil asetat. *Minimum Inhibitory Concentration* (MIC) ekstrak sebesar 25 mg/mL terhadap ketiga bakteri uji. Deteksi metabolit ekstrak A22 menggunakan LC-HRMS mendeteksi 633 fitur, seleksi akhir menyisakan 65 senyawa metabolit sekunder potensial, didominasi golongan alkaloid, terpenoid, poliketida, dan fenolik. Senyawa utama yang terdeteksi meliputi caryophyllene oxide, 5,7-dihydroxy-4-methylcoumarin, dan 5-hydroxymethyl-2-furaldehyde yang berpotensi sebagai antibakteri. Identifikasi molekuler berbasis ITS rDNA menunjukkan bahwa isolat A22 memiliki tingkat kemiripan 98% dengan *Preussia persica*. Analisis *Whole Genome Sequencing* (WGS) menggunakan platform *Oxford Nanopore Technology* (ONT) menghasilkan genom berukuran ±34,2 Mb dengan kualitas tinggi (BUSCO 98,7%). Analisis genom mengungkap 41 *biosynthetic gene clusters* (BGCs) yang berpotensi terlibat dalam biosintesis metabolit sekunder, termasuk *cluster* NRPS, PKS, terpenoid, dan indole, yang mendukung temuan metabolomik pada LC-HRMS. Penelitian ini menunjukkan bahwa fungi endofit *P. persica* dari *T. crispa* memiliki potensi besar sebagai sumber senyawa antibakteri baru terhadap bakteri MDR. Integrasi analisis metabolomik dan genomik memberikan dasar kuat untuk eksplorasi biosintesis metabolit sekunder serta pengembangan kandidat obat berbasis mikroba endofit.

Kata Kunci: Resistensi antibiotik; antibakteri MDR; fungi endofit; *Tinospora crispa*; *Preussia persica*; metabolomik; genomik; *biosynthetic gene clusters.*

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ANTIBACTERIAL POTENTIAL OF ENDOPHYTIC FUNGI FROM BROTOWALI *(Tinospora crispa (L.) Hook.f. & Thomson.)* AGAINST MULTIDRUG-RESISTANT (MDR) BACTERIA THROUGH INTEGRATED METABOLOMIC AND GENOMIC ANALYSIS

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ABSTRACT

Bacterial resistance to various antibiotics is now a global problem due to a significant increase in cases. This has prompted efforts to find alternative antibacterial agents that are more effective and safer. This study aims to explore the potential of endophytic fungi from the Brotowali plant (*Tinospora crispa* (L.) Hook.f. & Thomson.) against multidrug-resistant (MDR) bacteria through an integrative metabolomic and genomic approach. Endophytic fungi were isolated from the root, stem, and leaf tissues of *T. crispa*, yielding 38 isolates with diverse morphological characteristics. Initial antibacterial screening using the agar plug showed that most isolates exhibited antibacterial activity against MDR *Escherichia coli, Klebsiella pneumoniae*, and *Staphylococcus aureus,* with isolate A22 identified as the most promising candidate. Secondary metabolites from A22 were extracted using maceration and ethyl acetate. The minimum Inhibitory Concentration (MIC) of the extract was 25 mg/mL against all three test bacteria. LC-HRMS analysis of the A22 extract detected 633 features, of which were identified as potential secondary metabolites, predominantly alkaloids, terpenoids, polyketides, and phenolics. The major compounds included caryophyllene oxide, 5,7-dihydroxy-4-methylcoumarin, and 5-hydroxymethyl-2-furaldehyde, which have been reported to possess potential antibacterial activity. Molecular identification based on ITS rDNA showed that isolate A22 has a similarity of 98% with *Preussia persica*. Whole Genome Sequencing (WGS) using the *Oxford Nanopore Technology* (ONT) platform yielded a genome of approximately 34.2 Mb with high quality (BUSCO 98.7%). Genomic analysis revealed 41 biosynthetic gene clusters (BGCs) potentially involved in the biosynthesis of secondary metabolites, including NRPS, PKS, terpenoid, and indole clusters, which support the metabolomic findings from LC-HRMS. This study demonstrated that the endophytic fungus *P. persica* from *T. crispa* possessed great potential as a source of new antibacterial compounds against MDR bacteria. The integration of metabolomic and genomic analyses provided a strong foundation for the exploration of secondary metabolite biosynthesis and facilitated the development of endophytic microbe-based drug candidates.

Keywords: Antibiotic resistance; MDR antibacterial agents; endophytic fungi; *Tinospora crispa*; *Preussia persica*; metabolomics; genomics; biosynthetic gene clusters.