SINTESIS, UJI AKTIVITAS *IN VITRO* DAN STUDI KOMPUTASI HIBRIDA XANTON-ASAM LEMAK SERTA XANTON-SINAMAT SEBAGAI AGEN ANTIKANKER, ANTIMIKROBA, DAN ANTIMALARIA

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INTISARI

Penyakit kanker, infeksi mikroba, dan malaria merupakan tiga penyakit mematikan dengan angka kematian tahunan global yang tinggi. Kondisi ini menjadi semakin serius ketika obat-obatan standar yang digunakan menjadi resisten dan tidak selektif. Tujuan penelitian ini adalah melakukan sintesis, uji aktivitas antikanker, antimikroba dan antimalaria secara *in vitro*, dan studi komputasi meliputi kajian bioinformatika, penambatan molekul dan simulasi dinamika molekul. Empat senyawa hidroksixanton telah berhasil disintesis dari reaksi antara turunan asam salisilat dan fenol dengan persen hasil 6,60%–46,50%. Dari keempat senyawa hidroksixanton, senyawa 3-hidroksixanton memberikan nilai *half-maximal inhibitory concentration* (IC_{50}) paling tinggi terhadap sel normal NIH3T3. Senyawa 3-hidroksixanton direaksikan lebih lanjut untuk menghasilkan lima senyawa hibrida xanton-asam lemak dan tujuh xanton-sinamat dengan persen hasil 77,78%–95,74%. Seluruh senyawa hasil sintesis dikarakterisasi dengan spektroskopi FTIR, MS, ^{1}H- dan ^{13}C-NMR. Aktivitas antikanker *in vitro* seluruh hibrida xanton diuji terhadap sel kanker paru-paru (A549), payudara (T47D), leher rahim (HeLa), dan usus besar (WiDr) sedangkan uji sitotoksisitas dilakukan terhadap sel normal NIH3T3 secara *in vitro* dengan rentang nilai IC_{50} dan indeks selektivitas sebesar 1,54–5784,71 µM dan 0,01–282,08. Di antara 17 senyawa uji, xantil trifluorometilsinamat, xantil oleat, dan xantil klorosinamat merupakan senyawa hibrida yang paling potensial terhadap sel kanker A549, T47D, dan HeLa berturut-turut dengan nilai IC_{50} sebesar 33,37; 8,57; dan 1,54 µM dan indeks selektivitas sebesar 3,07; 9,73; dan 50,46. Xantil trifluorometilsinamat merupakan agen antikanker yang paling potensial terhadap sel kanker WiDr dengan nilai IC_{50} sebesar 45,81 µM dan indeks selektivitas sebesar 2,24. Xantil klorosinamat dan xantil trifluorometilsinamat memberikan aktivitas antimikroba *in vitro* yang paling potensial terhadap mikroba *Staphylococcus aureus*, *Escherichia coli*, dan *Candida albicans* dengan rentang nilai MIC dan MBC sebesar 6,25–12,5 dan 25–50 µg/mL. Xantil nitrosinamat memberikan aktivitas antimalaria *in vitro* paling kuat terhadap *Plasmodium falciparum* strain 3D7 dan FCR-3 dengan rentang nilai IC_{50} dan indeks resistensi sebesar 0,07–0,21 µM dan 2,85. Protein yang mungkin ditarget oleh hibrida xanton telah diidentifikasi melalui kajian bioinformatika sedangkan mode pengikatan dan kestabilan dari hibrida xanton dengan residu asam amino kunci pada situs aktif masing-masing protein telah dikonfirmasi melalui penambatan molekul dan simulasi dinamika molekul. Pendekatan *absorption, distribution, metabolism, excretion, and toxicity* (ADMET) memprediksikan bahwa hibrida xanton memiliki sifat farmakokinetika yang baik dan potensi toksisitas yang rendah. Hasil penelitian ini menunjukkan bahwa hibrida xanton merupakan kandidat obat antikanker, antimikroba dan antimalaria yang memiliki potensi untuk dikembangkan lebih lanjut di masa depan.

Kata kunci: antikanker, antimalaria, antimikroba, hibrida, sintesis, xanton.

SYNTHESES, IN VITRO ACTIVITY ASSAY, AND COMPUTATIONAL STUDIES OF XANTHONE-FATTY ACID AS WELL AS XANTHONE-CINNAMATE HYBRIDS AS ANTICANCER, ANTIMICROBIAL, AND ANTIMALARIAL AGENTS

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ABSTRACT

Cancer, microbial infection, and malaria are three deadly diseases with high mortality cases worldwide. This condition becomes more serious when the used standard drugs are resistant and not selective. This research aims to synthesize, perform *in vitro* anticancer, antimicrobial, and antimalarial activities, and conduct computational studies including bioinformatics, molecular docking, and molecular dynamics simulations. Four hydroxyxanthones have been successfully synthesized from the reaction between salicylic acid and phenolic derivatives in 6.60%–46.50% yield. From these four hydroxyxanthones, 3-hydroxyxanthone compound gave the highest half-maximal inhibitory concentration (IC_{50}) against the NIH3T3 normal cell line. The 3-hydroxyxanthone compound was further reacted to yield five xanthone-fatty acid and seven xanthone-cinnamate hybrid compounds in 77.28%–95.74% yield. All synthesized compounds have been characterized using FTIR, MS, ^{1}H- and ^{13}C-NMR spectroscopies. The *in vitro* anticancer activity of all the xanthone hybrids was tested against lung (A549), breast (T47D), cervixal (HeLa), and colorectal (WiDr) cancer cells while the cytotoxicity assay was performed towards NIH3T3 normal cell with IC_{50} and selectivity index ranging from 1.54–5784.71 μM and 0.01–282.08. Among the 17 tested compounds, xanthyl trifluoromethylcinnamate, xanthyl oleate, and xanthyl chlorocinnamate were the most potential hybrid compounds against A549, T47D, and HeLa cancer cells with IC_{50} values of 33.37, 8.57, and 1.54 μM and selectivity indexes of 3.07, 9.73, and 50.46, respectively. Xanthyl trifluoromethylcinnamate was the most potential anticancer agent against WiDr cancer cells with IC_{50} value of 45.81 μM and selectivity index of 2.24. Xanthyl chlorocinnamate and xanthyl trifluoromethylcinnamate gave the most potential *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* with MIC and MBC values ranging from 6.25–12.5 and 25–50 μg/mL. Xanthyl nitrocinnamate showed the strongest *in vitro* antimalarial activity against *Plasmodium falciparum* strain 3D7 dan FCR-3 with IC_{50} and resistance index values ranging from 0.07–0.21 μM and 2.85. The possible targeted protein by xanthone hybrid was identified using bioinformatical approach while the binding mode and stability of xanthone hybrid with amino acid residues in the active site of each protein was confirmed by molecular docking and molecular dynamics simulations. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) approach predicted that the xanthone hybrid showed good pharmacokinetic properties and low potential toxicities. The results of this research reveal that xanthone hybrids are potential anticancer, antimicrobial, and antimalarial drug candidates, which have the potential to be further developed in the future.

Keywords: anticancer, antimalarial, antimicrobial, hybrid, synthesis, xanthone.