Studi In Silico dan In vivo Aktivitas Dihydroergochristine sebagai Inhibitor Interleukin-33 pada Hewan Model Penyakit Paru Obstruktif Kronis = In Silico and In Vivo Studies The Activity of Dihydroergocristine as an Inhibitor of Interleukin-33 in Animal Models of Chronic Obstructive Pulmonary Disease

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Abstrak

Penyakit paru obstruktif kronis sebagai penyakit yang ditandai dengan adanya pembatasan aliran udara progresif yang bersifat irreversible terhadap respon inflamasi abnormal dari paru-paru karena adanya partikel atau gas berbahaya. Berdasarkan data Global Initiative for Chronic Obstructive Lung Disease (GOLD) terdapat 65 juta orang menderita penyakit paru obstruktif kronis (PPOK) dan 3 juta orang meninggal setiap tahunnya dan merupakan penyebab utama kematian ketiga di dunia. Penelitian ini menggunakan dua pendekatan studi, pendekatan bioinformatika dan pendekatan in vivo. Pendekatan bioinformatika ini bertujuan untuk mengidentifikasi pathogenesis PPOK menggunakan jejaring farmakologi serta mengidentifikasi kandidat baru senyawa inhibitor ST2/IL-33 menggunakan metode komputasi dengan cara analisis farmakofor, virtual screening dan docking. Hasil pendekatan bioinformatika melalui jejaring farmakologi menunjukan bahwa gen AKT1, TNF, IL-6, ACTB. EGF, VEGFA, STAT3, MAPK3, MYC, JUN, IL10, CCL2 memiliki peranan penting dalam patogenesis penyakit obstruksi kronis yang diinduksi dengan asap rokok elektronik. Hasil farmakofor native ligand (NAG) menunjukkan empat donor ikatan hidrogen dan lima ikatan hidrogen akseptor, dan ligand dihydroergochristine menunjukkan tiga donor ikatan hidrogen dan lima akseptor ikatan hidrogen. Dari hasil analisis docking dihydroergochristine dengan reseptor ST2 menunjukkan energi ikatan yang lebih tinggi (- 10.2 kkal/mol) terhadap reseptor ST2 protein dibandingkan dengan senyawa lain. Pendekatan in vivo menggunakan mencit betina Mus musculus yang dibagi menjadi 6 kelompok: kontrol, kontrol negatif, kontrol positif diberikan inhalasi budesonid 1mg/kg BB/hari, serta 3 kelompok variasi dosis dihydroergochristine 0,0040mg/21gBB mencit/hari; 0,081mg/21gBB mencit/hari; 0,0163mg/21gBB mencit/hari secara inhalasi. Mencit dipaparkan asap rokok elektronik (36 puff sekali sehari selama 8 minggu), kemudian diobati dengan dihydroergochristine atau budesonid selama 3 minggu. Berdasarkan uji statistik pada hasil uji in vivo terdapat beberapa perbedaan bermakna ($p < 0.05$) pada parameter berat badan dan parameter hematologi. Pada parameter histologi persentase sel goblet kelompok kontrol sebesar 3,35 %, kelompok kontrol negatif 51,34 %, kelompok kontrol positif 5,52 %, kelompok D1 30,29 %, kelompok D2 33,94 %, dan kelompok D3 sebesar 16,13 %. Persentase kolagen kelompok kontrol sebesar 7.34 %, kelompok kontrol negatif sebesar 26.44 %, kelompok kontrol positif 8.62 %, kelompok D1 sebesar 23.82 %, kelompok D2 sebesar 21.01 %, dan kelompok D3 sebesar 12.56 %. Persentase penebalan dinding bronkus kelompok kontrol normal sebesar 5.57 %, sedangkan pada kelompok kontrol negatif sebesar 23.25 %, kelompok kontrol positif sebesar 6.28 %, kelompok dosis satu sebesar 17.08 %, kelompok dosis dua sebesar 16.53 %, dan kelompok dosis tiga sebesar 12.93 %. Peningkatan kadar IL-6 pada kelompok kontrol sebesar 4.10 pg/ml, kontrol negatif sebesar 102.39 pg/ml, kelompok kontrol positif mimiliki kadar IL-6 sebesar 23.74 pg/ml, kelompok D1 sebesar 94.08 pg/ml, kelompok D2 sebesar 60.75 pg/ml, dan pada kelompok D3 memiliki kadar IL-66 sebesar 36.18

pg/ml. Peningkatan kadar karboksihemoglobin pada kelompok kontrol sebesar 18.40 ng/ml, kontrol negatif sebesar 87.53 ng/ml, kelompok kontrol positif memiliki kadar karboksihemoglobin sebesar 22.45 ng/ml, kelompok D1 sebesar 83.57 ng/ml; kelompok D2 sebesar 50.29 ng/ml; dan pada kelompok D3 memiliki kadar IL-66 sebesar 32.36 ng/ml. Berdasarkan hasil penelitian, senyawa dihydroergochristine dapat menurunkan dan memperbaiki inflamasi pada penyakit paru obstruktif kronis
.....Chronic obstructive pulmonary disease as a disease characterized by the presence of progressive irreversible air flow restrictions to abnormal inflammatory responses of the lungs due to the presence of harmful particles or gases. Based on data from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), there are 65 million people suffering from chronic obstructive pulmonary disease (COPD) and 3 million people die every year and is the third leading cause of death in the world. This research uses two study approaches, the bioinformatics approach and the in vivo approach. This bioinformatics approach aims to identify COPD pathogenesis using pharmacological networks and identify new candidates for ST2/IL-33 inhibitor compounds using computational methods using pharmacophore analysis, virtual screening and docking. The results of the bioinformatics approach through pharmacological networks showed that the AKT1, TNF, IL-6, ACTB genes. EGF, VEGFA, STAT3, MAPK3, MYC, JUN, IL10, CCL2 have an important role in the pathogenesis of chronic obstructive disease induced by electronic cigarette smoke. The results of the pharmacophore native ligand (NAG) showed four hydrogen bond donors and five acceptor hydrogen bonds, and the dihydroergochristine ligands showed three hydrogen bond donors and five hydrogen bond acceptors. From the results of the docking analysis of dihydroergochristine with ST2 receptors showed a higher bond energy (-10.2 kcal / mol) to the ST2 receptor protein compared to other compounds. The in vivo approach used female mice Mus musculus which was divided into 6 groups: control, negative control, positive control given budesonid inhalation 1mg/kg BB/day, as well as 3 groups of dihydroergochristine dose variation groups of 0.0040mg/21gBB mice/day; 0.081mg/21gBB mice/day; 0.0163mg/21gBB mice/day inhaled. Mice were exposed to electronic cigarette smoke (36 puffs once a day for 8 weeks), then treated with dihydroergochristine or budesonid for 3 weeks. Based on the statistics analysis in the in vivo test results, there are several significant differences ($p < 0.05$) in weight parameters and hematology parameters. In the histological parameters, the percentage of goblet cells of the control group was 3.35%, the negative control group was 51.34%, the positive control group was 5.52%, the D1 group was 30.29%, the D2 group was 33.94%, and the D3 group was 16.13%. The collagen percentage of the control group was 7.34%, the negative control group was 26.44%, the positive control group was 8.62%, the D1 group was 23.82%, the D2 group was 21.01%, and the D3 group was 12.56%. The percentage of thickening of the bronchi walls of the normal control group was 5.57%, while in the negative control group of 23.25%, the positive control group was 6.28%, the first dose group was 17.08%, the second dose group was 16.53%, and the third dose group was 12.93%. The increase in IL-6 levels in the control group was 4.10 pg/ml, the negative control was 102.39 pg/ml, the positive control group had IL-6 levels of 23.74 pg/ml, the D1 group was 94.08 pg/ml, the D2 group was 60.75 pg/ml, and in the D3 group it had IL-66 levels of 36.18 pg/ml. Increased levels of carboxyhemoglobin in the control group of 18.40 ng/ml, negative control of 87.53 ng/ml, the positive control group had carboxyhemoglobin levels of 22.45 ng/ml, group D1 of 83.57 ng/ml; group D2 of 50.29 ng/ml; and in the D3 group, it had an IL-66 content of 32.36 ng/ml. Based on the results of the study, dihydroergochristine compounds can reduce and improve inflammation in chronic obstructive pulmonary disease.</p>