IDENTIFICATION OF USNIC ACID DERIVATIVES AS NEW ANTIVIRAL AGENTS VIA VIRTUAL SCREENING ON DENGUE, INFLUENZA A AND AVIAN INFLUENZA A

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ABSTRAK

Jangkitan virus yang muncul terus menimbulkan ancaman besar terhadap kesihatan awam secara global dalam beberapa tahun terakhir. Penyakit virus seperti Denggi, Influenza (H1N1), dan Avian Influenza telah menyebabkan cabaran yang besar kepada sistem penjagaan kesihatan, pertumbuhan dan perkembangan ekonomi. Walaupun ubat antivirus baru dikembangkan dan diluluskan setiap tahun, isu kos dan pencemaran alam sekitar tetap menjadi cabaran utama bagi para saintis. Pendekatan inovatif baru yang melibatkan teknologi pengkomputeran perlu digunakan dalam pengembangan dan penemuan ubat. Oleh itu, kajian ini bertujuan untuk mencari sebatian antivirus baru yang berpotensi dengan menggunakan pangkalan data terbitan asid usnic melalui saringan maya melalui pelbagai pendekatan *in silico* seperti penapisan farmakofor, pemeriksaan dok molekul, dan ramalan farmakokinetik. Terdapat tiga bahagian utama yang dibincangkan; Bahagian A: Penemuan sebatian pelopor anti-DENV, Bahagian B: Penemuan sebatian pelopor anti-Influenza A dan Bahagian C: Penemuan sebatian pelopor anti-selesema burung A. Pengkalan data telah dihasilkan daripada empat ratus dua puluh lapan sebatian terbitan asid usnik yang diambil dari pelbagai sumber literatur. Penggunaan sebatian terbitan asid usnic adalah kerana aktiviti antivirus yang luarbiasa. Kajian terbaru menunjukkan bahawa asid usnik juga mempunyai aktiviti larva yang tinggi terhadap Aedes aegypti. Kombinasi model saringan maya berasaskan ligan dan struktur dibina berdasarkan penapisan farmakofor, saringan dok molekul diikuti dengan ramalan farmakokinetik termasuk *drug-likeness* dan penyaringan CYP2D6 untuk memberikan sebatian pelopor untuk setiap sasaran (denggi, Influenza A dan selesema burung A). Pangkalan data sebatian terbitsan asid usnik disaring menggunakan model farmakofor terpilih untuk menghasilkan seratus enam belas sebatian untuk DENV-3 NS5, dua puluh tiga sebatian untuk Influenza A, dan dua puluh satu sebatian untuk perencat Avian Influenza A. Pada tahap penyaringan maya berikutnya, dokumentasi molekul dan analisis interaksi menunjukkan bahawa empat puluh satu sebatian DENV, empat sebatian Influenza, dan lima sebatian selesema Avian yang berkebarangkalian boleh merencat sasaran. Penyaringan selanjutnya oleh ramalan ADME dan ramalan *drug-likeness* menghasilkan tujuh sebatian hit untuk DENV, dua sebatian hit untuk Influenza A dan dua sebatian hit untuk Avian Influenza A. Kesemua sebatian hit yang terhasil di saring menggunakan enzim sitokrom P450 untuk menghasilkan molekul pelopor, yang dinamakan sebagai 362 (denggi), sebatian 4 (Influenza A) dan sebatian 5 (Avian Influenza A). Di samping itu, simulasi dinamik molekul sebatian pelopor 362, 4 dan 5 dilakukan untuk mengesahkan kestabilan kompleks dan postur pengikat yang diperoleh dalam eksperimen dok. Secara keseluruhan, sebatian pelopor 362, 4 dan 5 yang dijumpai untuk DENV, Influenza A dan Avian Influenza A, masing-masing, menunjukkan nilai farmakofor yang tinggi, intraksi yang signifikan, farmakokinetik yang sangat baik, dan ciri-ciri seperti ubat secara umum. Oleh itu, ia membuktikan bahawa model penyaringan maya yang digunakan dalam kajian ini berkesan.

ABSTRACT

Emerging viral infections continue to pose a significant threat to global public health in recent years. Viral diseases such as Dengue, Influenza (H1N1), and Avian Influenza have caused a significant challenge to the healthcare systems, economic growth, and development. Still now, there are no drugs available to combat the DENV and Avian Influenza A viruses. On the other hand, only two drugs have been developed against Influenza A virus based on the neuraminidase enzyme but need to annual updating because these drugs ineffective against the new subtype of Influenza A. Even though new antiviral drugs have been developed and approved annually, the cost and environmental issues remain the main challenges for scientists. The new innovative approaches involving computational technology need to be employed in drug development and discovery. Thus, the studies aimed to discover new potential antiviral lead compounds from usnic acid derivatives in-house database through virtual screening via various in silico approaches such as pharmacophore filtering, molecular docking screening, and pharmacokinetic prediction. There were three main parts covered; Part 1: Discovery of anti-DENV's lead compound, Part 2: Discovery of anti-Influenza A's lead compound and Part 3: Discovery of anti-avian Influenza A's lead compound. Four hundred twenty-eight usnic acid derivatives as in-house database was generated by retrieved from the various literature sources. The use of usnic acid derivatives is due to their incredible antiviral activities. According to current research, usnic acid has strong larvicidal properties toward *Aedes aegypti*. The combination of ligand-based and structure-based virtual screening model was built leading by pharmacophore filtering, molecular docking screening followed by pharmacokinetic predictions including drug-likeness and CYP2D6 filtering to afford the lead compounds for each target (dengue, Influenza A and avian Influenza A). The in-house usnic acid derivatives database was screened using the selected pharmacophore models to afford one hundred sixteen compounds for novel DENV-3 NS5 protease, twenty-three compounds for Influenza A, and twenty-one compounds for Avian Influenza A inhibitors. In the next virtual screening stage, molecular docking and interaction analysis indicated that forty-one DENV compounds, four Influenza compounds, and five Avian Influenza compounds could plausibly be active against the targets. Further filtering by ADME prediction tools and drug-likeness prediction of forty-one, four and five compounds from DENV, Influenza and Avian Influenza, respectively, resulted in seven hit compounds for DENV, two hit compounds for Influenza and two compounds for Avian Influenza virus, respectively. The lead molecule, called compound-362, compound-4, and compound-5, was discovered after screening the hit compounds against DENV, Influenza, and Avian Influenza utilising the cytochrome P450 enzyme. To corroborate the durability of docked complexes and the binding conformation established during docking testing, a molecular dynamic (MD) simulation of lead compounds 362, 4 and 5 was performed. Ultimately, the lead compounds 362, 4 and 5 discovered for DENV, Influenza A and Avian Influenza A, respectively, exhibited a high pharmacophore fit value, string binding affinity, excellent pharmacokinetics, and drug-like characteristics in general. Thus, it proved that the virtual screening model employed in this study was reliable.

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