Analisis Penambatan Molekul Senyawa Hibrida dari Vildagliptin dan Analog Kurkumin terhadap DPP-4, DPP-8, dan DPP-9 Menggunakan Autodock dan Autodock Vina = Molecular Docking Analysis of Hybrid Compound of Vildagliptin and Curcumin Analogue to DPP-4, DPP-8, and DPP-9 using AutoDock and AutoDock Vina

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Abstrak

Diabetes melitus (DM) merupakan penyakit kronis serius yang terjadi karena adanya gangguan sekresi dan resistensi insulin. Inhibitor dipeptidil peptidase-4 (DPP-4) merupakan salah satu golongan senyawa antidiabetes yang minim efek samping dibandingkan golongan obat diabetes lainnya. Mekanisme kerja inhibitor DPP-4 adalah memperpanjang dan meningkatkan aktivitas Glucagon Like Peptide-1 (GLP-1). Namun, beberapa inhibitor DPP-4 memiliki efek samping yang tidak diinginkan seperti nyeri sendi dan radang pankreas. Efek samping tersebut diindikasikan berkaitan dengan penghambatan terhadap dipeptidil peptidase-8 (DPP-8) dan dipeptidil peptidase-9 (DPP-9). Kurkumin merupakan senyawa bioaktif yang memiliki berbagai aktivitas seperti antidiabetes, antikanker, dan antihipertensi. Namun, efikasi klinik kurkumin sangat terbatas karena bioavailabilitasnya yang rendah. Pendekatan hibridisasi kurkumin dengan fragmen farmakofor vildagliptin diharapkan dapat memperbaiki keterbatasan kurkumin. Pada penelitian tahap awal ini, dilakukan pengujian in silico yaitu penambatan molekuler senyawa hibrida dari vildagliptin dan analog kurkumin terhadap DPP-4, DPP-8, dan DPP-9 menggunakan program AutoDock dan AutoDock Vina yang divalidasi menggunakan nilai Root Mean Square Deviation (RMSD) Redocking. Hasil penambatan molekuler senyawa hibrida dari vildagliptin dan analog kurkumin terhadap DPP-4, DPP-8, dan DPP-9 menggunakan 10 senyawa didapatkan tiga senyawa yang lebih selektif terhadap DPP-4 yaitu senyawa dengan substituen hidroksil dan metoksi, substituen metil, dan substituen trifluorometil masing-masing memiliki nilai selektivitas sebesar 0,254, 0,8, 0,214 . Nilai energi ikatan bebas ketiga senyawa tersebut masing-masing sebesar -9,42 kkal/mol, -8,95 kkal/mol, dan -8,41 kkal/mol. Dapat disimpulkan bahwa senyawa hibrida dari vildagliptin dan analog kurkumin memiliki potensi sebagai penghambat DPP-4, tetapi hanya terdapat tiga senyawa yang lebih selektif terhadap DPP-4.

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Diabetes mellitus (DM) is a chronic disease that occurs due to impaired secretion and insulin resistance. Dipeptidyl peptidase-4 (DPP-4) inhibitors are one class of antidiabetic compounds having minimal side effects compared to other classes of antidiabetic drugs. The mechanism of action of DPP-4 inhibitors is to extend and increase the activity of Glucagon Like Peptide-1 (GLP-1). However, some of the DPP-4 inhibitors have side effects such as joint pain and pancreatitis. These side effects are thought to have an association with inhibition of dipeptidyl peptidase-8 (DPP-8) and dipeptidyl peptidase-9 (DPP-9). Curcumin is a bioactive compound that has various activities such as antidiabetic, anticancer, and antihypertensive. However, the clinical efficacy of curcumin is very limited due to its poor bioavailability. Curcumin hybridization approach with vildagliptin pharmacophore fragments is expected to improve the limitations of curcumin. In this preliminary study, in silico testing was carried out by molecular docking of

the hybrid compound of vildagliptin and curcumin analogue against DPP-4, DPP-8, and DPP-9 using the AutoDock and AutoDock Vina programs which were validated using the Redocking Root Mean Square Deviation (RMSD) values. The results of molecular docking of the 10 hybrid compounds of vildagliptin and curcumin analogue to DPP-4, DPP-8, and DPP-9 show that three compounds are more selective towards DPP-4. These namely compounds with hydroxyl and methoxy, methyl, and trifluoromethyl substituents, which have selectivity value of 0.254, 0.8, 0.214, respectively. The free binding energy of the three compounds is -9.42 kcal/mol, -8.95 kcal/mol, and -8.41 kcal/mol. It can be concluded that the hybrid compound of vildagliptin and curcumin analogue has the potential to inhibit DPP-4, but there are only three compounds that are more selective towards DPP-4.<i/>