INTISARI

Insektisida pyrethroid merupakan golongan senyawa sintetik yang diturunkan dari pyrethrin, insektisida alamiah yang diisolasi dari ekstrak bunga *Chrysanthemum cinerariifolium*. Sejumlah penelitian telah mengindikasikan pyrethroid bersifat toksik, terutama sebagai *Endocrine Disrupting Chemicals* (EDC) dan mengganggu homeostasis hormon. Gangguan pada biosintesis hormon sex steroid melibatkan enzim-enzim gonadal steroidogenik, yang terklasifikasikan dalam kelas cytochrome P450 (P450scc, P450c17, P450arom), kelas hydroxysteroid dehydrogenase (3β-HSD2, 17β-HSD1, 17β-HSD3), dan kelas oxidoreductase lain (5αR2). Penelitian ini bertujuan untuk mempelajari mekanisme aksi pyrethroid pada enzim-enzim gonadal steroidogenik yang bertanggungjawab pada biosintesis hormon sex steroid, melalui konstruksi model *virtual screening tools* untuk sistem enzim-enzim tersebut, yang dibangun menggunakan kombinasi metode komputasional berupa homology modeling, pharmacophore mapping, docking, dan QSAR.

Homology modeling diterapkan untuk memodelkan struktur 3D enzim-enzim 3β-HSD2, 17β-HSD3, dan 5αR2, menghasilkan model-model protein yang representatif dengan kualitas stereokimia baik, sehingga cukup layak untuk digunakan sebagai target protein dalam studi docking. Enzim lainnya (17β-HSD1, P450scc, P45c17, dan P450arom) telah tersedia struktur kristalnya di PDB. Studi docking dilakukan pada substrat dan dataset inhibitor pada masing-masing enzim yang spesifik, menghasilkan orientasi yang rasional, namun memiliki *score* docking yang berkorelasi rendah terhadap aktivitas biologis. Analisis *docking-based QSAR* diterapkan untuk menggantikan *scoring function* docking. Persamaan-persamaan QSAR yang dihasilkan memiliki kualitas statistik sangat baik ($r > 0.9$; $RMSE < 0.5$) dan memiliki *predictive power* yang tinggi ($Q^2 > 0.8$). Hasil prediksi potensi inhibisi terhadap enzim gonadal steroidogenik menunjukkan bahwa pyrethroid cenderung lebih poten terhadap 3β-HSD2, 17β-HSD3, P450c17, dan P450arom. Pyrethroid kurang poten menginhibisi 17β-HSD1 dan P450scc.

Kata kunci: pyrethroid, enzim gonadal steroidogenik, homology modeling, pharmacophore mapping, docking, QSAR.

ABSTRACT

Pyrethroids insecticides are synthetic compounds derived from pyrethrin, a natural insecticide isolated from the extract of *Chrysanthemum cinerariifolium* flower. Pyrethroids have been indicated as toxic agents, particularly as Endocrine Disrupting Chemicals (EDCs) and they can interfere with hormone homeostasis. The alteration of sex steroid hormone biosynthesis involves the gonadal steroidogenic enzymes, that are classified into cytochrome P450 class (P450scc, P45c17, P450arom), hydroxysteroid dehydrogenase class (3β-HSD2, 17β-HSD1, 17β-HSD3), and other oxidoreductases (5αR2). This research aims to investigate the mechanism of action of pyrethroids on the gonadal steroidogenic enzymes that are responsible to sex steroid hormone biosynthesis, through the construction of virtual screening tools models for these enzymes, which are built using a combination of homology modeling, pharmacophore mapping, docking and QSAR approaches.

Homology modeling was applied to model the 3D structure of 3β-HSD2, 17β-HSD3, and 5αR2 enzymes, that produces the representative models with good stereochemical quality, so these are quite feasible to be used as a protein target in docking studies. The crystal structure of other enzymes (17β-HSD1, P450scc, P450c17 and P450arom) have been available in PDB. Docking studies performed on the substrate and inhibitor datasets on each specific enzymes, producing a rational orientation, but have a low correlation between docking score against biological activity. The docking-based QSAR was performed to supersede the docking scoring function. The resulted QSAR equations have an excellent statistical quality ($r > 0.9$; RMSE < 0.5) and have a high predictive power ($Q^2 > 0.8$).The results of predicted inhibition potential to gonadal steroidogenic enzymes shows that pyrethroids tend to be more potent against 3β-HSD2, 17β-HSD3, P450c17, and P450arom. Pyrethroids are less potent inhibits 17β-HSD1 and P450scc.

Keywords: pyrethroid, gonadal steroidogenic enzymes, homology modeling, pharmacophore mapping, docking, QSAR.