Title : Screening of P450 Enzyme Inhibitors for Controlling Multiple-Herbicide-Resistant Weeds Using Molecular Docking and Molecular Dynamics Simulation

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ABSTRACT

Cytochrome P450 monooxygenase enzymes, especially those in the CYP81A subfamily, play a crucial role in herbicide detoxification in plants, including rice crop (*Oryza sativa*) and late watergrass weed (*Echinochloa phyllopogon*). Since CYP81As contribute to multiple herbicide resistance in late watergrass, inhibiting their function could enhance herbicide effectiveness, leading to targeted plant mortality after herbicide application in rice cultivation. This research aimed to identify a novel selective inhibitor targeting CYP81As in late watergrass. First, the 3D structures of CYP81A6 from rice, CYP81A12, A21, and A24 from late watergrass were constructed *in silico* from their amino acid sequences due to the absence of experimentally determined structures. A set of 596 compounds was selected from the PubChem database based on 95% similarity to 19 reported substrates with high binding preference for these CYP81As and was then subjected to molecular docking analysis using AutoDock Vina 1.2.3. The top five potent compounds identified through molecular docking results and binding specificity analysis were two derivatives of penoxsulam, along with derivatives of propyrisulfuron, pyraclonil, and pyrazosulfuron-ethyl**.** These top-ranking inhibitors were further analyzed using molecular dynamics simulations to evaluate their binding efficiency and stability. Among them, ethyl 1-[(4,6-dimethoxypyrimidin-2-yl) carbamoyl]-3-sulfamoylpyrazole-4-carboxylate exhibited the most promising interaction with CYP81A12, A21, and A24 of late watergrass while showing minimal interaction with CYP81A6 of rice, suggesting highly selective inhibitory properties. Based on these findings, the identified compound may serve as a potential candidate for future herbicide development. This study highlights the capability of computational screening in targeting CYP81As to overcome herbicide resistance in late watergrass, paving the way for more effective weed management strategies.

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