Soluble Epoxide Hydrolase Inhibitory Activity of Natural Isothiocyanates

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Background: Soluble epoxide hydrolase (sEH) is a key enzyme involved in metabolizing endogenously derived fatty acid epoxides, such as epoxyeicosatrienoic acids (EETs) to their corresponding diols which lack the biological activities of their precursor EETs. Therefore, sEH is considered an important therapeutic target in a wide range of human cardiovascular diseases.

Objectives: This study was undertaken to investigate the potential inhibitory activity of six Isothiocyanates (ITCs) towards sEH enzyme. Additionally, molecular docking simulation was applied to understand the interaction between the enzymes and the ligands tested.

Methods: Rigid molecular docking was conducted using the human soluble epoxide hydrolase (sEH) crystal structure (3ANS) in Autodock Vina to estimate reversible binding energies of the ITCs. The sEH inhibitory activities of the tested ITCs were tested using a fluorescence-based assay and PHOME as a substrate. The selectivity of the tested sEH inhibitors was tested by measuring the inhibitory effect on microsomal epoxide hydrolase (mEH) and Cytochrome P450 (CYP) enzymes using human liver microsomes.

Results: Docking resulted in binding poses that suggest the ITCs may be acting by irreversible antagonism. Sulforaphane and phenyl isothiocyanate displayed the strongest sEH inhibitory activity with IC50 values < 10 µM. None of the tested ITC exhibited a significant inhibition of mEH enzyme compared to valpromide, a positive control inhibitor. Allyl and benzyl isothiocyanate appeared to significantly inhibit CYP2D6, whereas only allyl isothiocyanate inhibited the other enzymes. The other ITCs also appeared to lower CYP activity, however their difference was not found to be statistically significant compared to no inhibitor controls.

Conclusion: These findings indicate that natural ITCs demonstrate promising sEH inhibitory activities, likely by an irreversible mechanism. However, the selectivity of the smaller ITCs, especially against CYP enzymes, may need to be improved to avoid clinically-significant drug interactions.

Biography

Fawzy A. Elbarbry, is a pharmacist, researcher, and academic expert in pharmacology and pharmaceutical sciences. He is recognized for his work in pharmacokinetics, drug metabolism, and personalized medicine, with numerous peer-reviewed publications. A licensed pharmacist and Board-Certified Pharmacotherapy Specialist, Dr. Elbarbry is committed to evidence-based practices and enhancing therapeutic outcomes. He is also a passionate educator and mentor, fostering critical thinking in pharmacy practice. His contributions have significantly advanced pharmacy education and research worldwide.