The Medicinal Molecules of Aquilegia:? A Hybrid Experimental and Computational Approach to Discover Painkillers and Neurodegenerative Therapeudics

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Traditionally used Asian and European medicinal plants are often analysed to create western medicines. North American Aquilegia roots show medicinal potential in its historical use as a painkiller, yet chemical analyses of this genus are sparse. Many current painkillers have harmful side effects, such as being addictive or harming the kidney and liver. Aquilegia extracts also inhibit 15-Lipoxygenase (15-LOX), an enzyme which promotes ferroptosis in neurons. Inhibiting 15-LOX has improved prognostics in Parkinson's Disease and Cerebral Ischemia models. In this work, I aimed to identify the molecular basis behind North American Aquilegia roots' analgesic properties and their inhibition of 15-LOX. From LC-MS data of a methanol extraction of four North American Aquilegia species, I identified 22 molecules. Marker compounds of the roots, the potential analgesics, were subsequently identified. In the second part of this project, compounds from Aquilegia were screened with molecular docking and ADME analysis to find drug-like candidate inhibitors. Molecular dynamics simulations were employed to verify stable inhibition of predicted inhibitors that were not experimentally verified. Ultimately, this project 1) provided the first comprehensive profiling of the major metabolites of three North American Aquilegia species, 2) determined three natural products which underlie the analgesic properties of Aquilegia and 3) identified multiple candidates for development of 15-LOX-A inhibiting drugs, including Berberine and Apigenin, two FDA-approved supplements, and a new potential bioavailable inhibitor, Aquiledine. After further experimental in-vivo testing, these new natural products can become future analgesics and Neurodegenerative Therapeutics.

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