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Multiscale biophysical investigation of flavonoid modulation of phospholipase-driven inflammatory pathways in hepatic damage

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Phospholipase-mediated lipid remodelling is a critical process underlying inflammatory signalling, membrane destabilisation, and cellular dysfunction associated with hepatic injury. It is evident that enzymes, including secretory phospholipase A_2 ($sPLA_2$) and cytosolic phospholipase A_2 ($cPLA_2$), are pivotal in the processes of phospholipid hydrolysis and arachidonic acid release. These enzymes have been shown to be crucial in the initiation of downstream eicosanoid-mediated inflammatory cascades. It is imperative to comprehend the way small bioactive molecules interact with these pathways, to facilitate the development of innovative therapeutic strategies that target inflammation-associated membrane damage. In this study, we examined the molecular and biophysical consequences of the flavonoids morin and kaempferol and compared their behaviour with that of classical non-steroidal anti-inflammatory drugs (NSAIDs). A multiscale strategy integrating computational chemistry, structural biophysics, enzymology, and in vivo inflammatory models was employed to explore the modulation of phospholipase-related pathways. The present study employed a combination of molecular docking and molecular dynamics simulations, in conjunction with binding free-energy calculations, to evaluate the interactions of ligands with key enzymes implicated in inflammatory lipid metabolism, including $sPLA_2$, $cPLA_2$, COX-2, LPCAT3, ACSM, and PRDX6. A range of complementary analyses were performed,

including those of an enzymatic and spectroscopic nature. The purpose of these analyses was to assess protein–ligand interactions, catalytic modulation, and structural perturbations induced by flavonoid binding. In vivo studies using murine inflammatory models induced by secretory phospholipase A_2 revealed significant alterations in hepatic biochemical markers and lipid profiles. The findings from both computational and experimental data sets have repeatedly demonstrated the stability of flavonoid interactions with phospholipase-associated targets. This observation suggests a potential modulation of lipid remodelling pathways, which have been associated with inflammatory membrane damage. It is noteworthy that flavonoids exhibited protective modulatory effects, which were associated with a reduction in inflammatory and oxidative responses. Collectively, these findings illustrate the potential of integrated computational and experimental biophysics approaches to elucidate mechanistic insights into drug–membrane interactions and phospholipase-mediated inflammatory processes. The study also highlights the therapeutic potential of natural flavonoids as modulators of lipid-driven inflammatory pathways relevant to hepatic injury and membrane-associated diseases.

Short Bio

Airam Roggero is a PhD student in Sustainable Chemistry at the Faculty of Sciences of the University of Porto, Portugal, and a recipient of a PhD fellowship funded by the FCT, Portugal. She graduated in Biomedicine from Centro Universitário Lusíada (Brazil) and obtained an MSc from the Institute of Biosciences at UNESP, Brazil. Her research combines biochemical, computational chemistry, ecotoxicological, histological, and experimental approaches to investigate the effects of natural and synthetic NSAIDs on membrane fluidity, lipid remodelling, oxidative stress, inflammation, and enzyme modulation, with emphasis on phospholipases, acetylcholinesterase, and membrane-associated pathways. She has contributed to publications in computational biochemistry, toxicology, ferroptosis, neuroinflammation, and drug repositioning involving NSAIDs and natural compounds, including studies with Lands Cycle. Airam also develops collaborative projects in ethnobotany focused on medicinal plants, bioactive compounds, biofilms, and sustainable applications in health and environmental sciences.

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