Inhibition of Cyclooxygenase by Blocking the Reducing Cosubstrate at the peroxidase site: Discovery of Galangin as a Novel Cyclooxygenase Inhibitor

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Abstract

Earlier we have shown that certain flavonoids (e.g., quercetin and myricetin) are high-affinity reducing cosubstrates for cyclooxygenase 1 and 2 (COX-1 and COX-2). These compounds can bind inside the peroxidase active site of COX-1 and COX-2 and donate an electron from one of their B-ring hydroxyl groups to hematin. Based on these earlier findings, it is speculated that some of the natural flavonoids that are structural analogs of quercetin but lack the proper B-ring hydroxyl groups might function as novel inhibitors of COX enzymes by blocking the effect of the reducing cosubstrates. This idea is tested in the present study. Computational docking analysis together with quantum chemistry calculation shows that galangin, which shares the same overall structure as quercetin but does not have any hydroxyl group in its B-ring, can bind inside the peroxidase active sites of COX-1 and COX-2 in a similar manner as quercetin, but it has little ability to effectively donate its electrons, thereby blocking the effect of the reducing cosubstrates like quercetin. Further experimental studies confirm that galangin can inhibit, both in vitro and in vivo, quercetin-mediated activation of the peroxidase activity of COX-1 and COX-2. The results of this study demonstrate that galangin is a novel naturally-occurring inhibitor of COX-1 and COX-2, acting by blocking the function of the reducing cosubstrates at the peroxidase sites.

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