A061 COX-2 inhibitory effects of natural and modified fatty acids

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The finding in 1991 of the inducible isoenzyme cyclooxygenase-2 (COX-2) has led to a novel approach for treatment of inflammation. Unlike traditional NSAIDs, COX-2 selective inhibitors are proved to be both anti-inflammatory and non-ulcerogenic, since the biosynthesis of prostaglandins catalysed by the constitutive COX-1 is unaffected (1).

We have evaluated the effect of isolated natural compounds as well as extracts, on the COX-2 catalysed prostaglandin biosynthesis, using a radiochemical enzyme assay (2). Bioassay guided fractionation of the Swedish medicinal plant *Plantago major* L. led to isolation of the fatty acids, linoleic and α-linolenic acid, as active principles (3). The inhibitory effects of other natural, structurally related fatty acids were also investigated. Further, the inhibitory effects of these compounds on COX-2 and COX-1 catalysed prostaglandin biosynthesis were compared with the inhibition of some synthesized analogues of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) with ether or thio-ether functions.

Several of the fatty acids as well as all of the thio-ether containing fatty acids inhibited the enzymatic activity of COX-2. The compounds α-linolenic acid and all-(*Z*)-5-thia-8,11,14,17-eicosatetraenoic acid were found most selective towards COX-2, with COX-2/COX-1 ratios of 0.1 and 0.2, respectively.

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A062 Dereplication of commonly known COX-2 inhibitors of natural origin

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The process of dereplication seeks to avoid repetitive isolation of ubiquitous structures with known biological activity in a specific assay. Fatty acids such as linolenic and linoleic acids and triterpenoids ursolic and oleanolic acid were found to be such compounds, which are needed to be dereplicated (1, 2). In the search of new COX-2 inhibitors, a dereplication protocol was developed to identify unsaturated fatty acids and other known molecules, which are active in the *in vitro* bioassay for the prostaglandin biosynthesis (3). The protocol comprises purification with solid phase extraction followed by HPLC-DAD separation combined with bioassay and LC-MS analysis. This procedure was applied to several plant extracts and a herbal preparation with COX-2 inhibitory activity.

Linolenic and linoleic acids were found in extracts of *Acronychia pedunculata* (leaves: EtOAc, stem bark: CH_2Cl_2), *Gynandropsis gynandra* (whole plant: CH_2Cl_2), *Lannea coromandelica* (stem bark: CH_2Cl_2), *Trichosanthes anguina* (whole plant: CH_2Cl_2), and Khadirarishtaya (herbal preparation: heptane and CH_2Cl_2 extracts). LC/ESI/MS was used to confirm the identity of the fatty acids.

The use of this protocol helps the rapid identification of linolenic and linoleic acids in the active fractions, thereby enabling the isolation of novel compounds.

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