A019 Tetrahydroamentoflavone from *Semecarpus anacardium* and its effect on COX-1/COX-2 catalysed prostaglandin biosynthesis.

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Semecarpus anacardium L. (Anacardiaceae), nuts have been used in Ayurvedic medicine for the treatment of neuritis, rheumatoid arthritis and helmintic infection (1,2). A chloroform extract of the nuts significantly reduced acute carrageenan-induced paw oedema in rats and was active against the secondary lesions of adjuvant-arthritis (3). The antiarthritic activity of *S. anacardium* extract was also studied through the stabilizing action of the extract on lysosomal membranes (4). The above ethnomedicinal background of *S. anacardium* nuts, for the treatment of arthritis, prompted us to undertake this study. Our main objectives are i) to screen various extracts of *S. anacardium* for COX-1/COX-2 inhibitory activity ii) to isolate the active compounds using bioassay directed fractionation.

The powdered seeds (1.0 Kg) were extracted with n-hexane, chloroform, ethyl acetate (EtOAc) and methanol (MeOH), using Soxhlet apparatus. The EtOAc and MeOH extracts were tested in COX-1/COX-2 catalysed prostaglandin biosynthesis *in vitro* assay. EtOAc and MeOH extracts exhibited 49.2 and 29.8% inhibition respectively. Bioassay directed fractionation of EtOAc extract (14.9 g), resulted in the isolation of active compound, 4',4''',5,5'',7,7''-hexahydroxy-3''',8-biflavanone (tetrahydroamentoflavone, 2.0 g). The structure of the compound is elucidated with the help of UV, IR, ^{1}H- and ^{13}C-NMR and Mass spectroscopy. Tetrahydroamentoflavone (THA) exhibited good inhibitory activity towards COX-1 (IC_{50} = 386 µM) whereas it showed only slight inhibitory activity of 17% in the COX-2 assay. An IC_{50} value of THA in the COX-2 assay could not be determined because of the precipitation of the test compound in higher concentrations in the assay solution. The results show that THA is more selective towards COX-1 than COX-2. Apart from THA, other constituents present in EtOAc extract could be responsible for anti-inflammatory activity. Further studies are required to characterize other compounds responsible for activity.

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A020 Synthesis and antiallergic effect of ardisiaquinone A, a potent 5-lipoxygenase inhibitor

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Arachidonic acid metabolism has been suggested to contribute to the pathogenesis of various types of inflammation. In the arachidonic acid cascade, 5-lipoxygenase is an important enzyme catalyzing the oxygenation of arachidonic acid specially at C-5, the initial step in the biosynthesis of the slow-reacting substances of anaphylaxis, which are known to be leukotrienes C4, D4 and E4. A group of leukotrienes is regarded as one of the chemical mediators of bronchial asthma. Ardisiaquinone A (1), isolated from *Ardisia sieboldii* Miq. (Myrsinaceae), was found to inhibit specifically 5-lipoxygenase. Thus the antiallergic evaluation of **1** prompted us to develop effective synthesis of dimeric benzoquinone. A cross-coupling reaction between **3** and **4** derived from the common intermediate **2** led to the synthesis of **1** in 33% overall yield. With a large quantity of **1** in hand, the antiallergic effects of **1** were examined. Pre-treatment with **1** (0.1-10 µM) significantly inhibited compound 48/80-induced production of cysteinyl-leukotrienes (LTC_4, LTD_4 and LTE_4) in rat peritoneal mast cells, but not histamine release at IC_{50} 5.56 µM. Pre-administration with 1 (0.1-1 mg/kg, s.c.) dose-dependently inhibited rat homologous passive cutaneous anaphylaxis (PCA). Compound **1** (1-5 mg/kg, s.c.) dose-dependently prevented the allergen-induced increase of tracheal pressure in ovalbumin-sensitized guinea pigs, especially during the late phase. These results show that a 5-lipoxygenase inhibitor, ardisiaquinone A, partially attenuates the allergen-induced increases of vascular permeability and tracheal pressure via the inhibition of cyc-LTs produced in mast cells.