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, ¹H- and ¹³C-NMR and Mass spectroscopy. Tetrahydroamentoflavone (THA) exhibited good inhibitory activity towards COX-1 (IC₅₀ = 386 µM) whereas it showed only slight inhibitory activity of 17% in the COX-2 assay. An IC₅₀ value of THA in the COX-2 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.

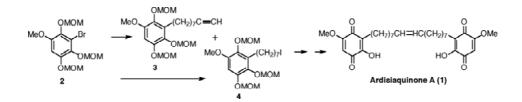
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A020 Synthesis and antiallergic effect of ardisiaquinone A, a potent 5-lipoxygenase inhibitor

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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 μ M) significantly inhibited compound 48/80-induced production of cysteinyl-leukotrienes (LTC4, LTD4 and LTE4) in rat peritoneal mast cells, but not histamine release at IC₅₀ 5.56 μ M. 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.



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