CONSTITUENTS OF CANNABIS SATIVA L. INHIBIT LIPOXYGENASE ACTIVITY

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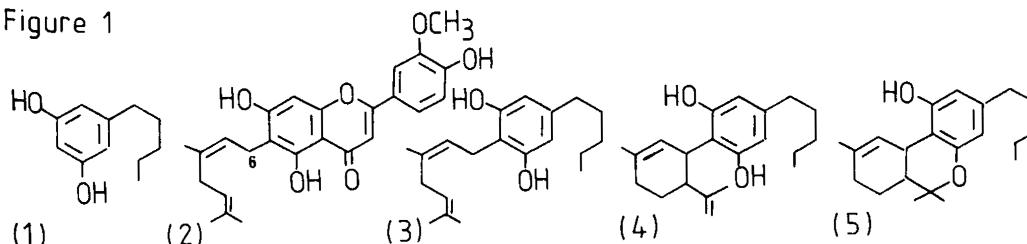
In continuing studies on the basis for the established antiphlogistic activity of cannabis (Gill *et al*, 1970) we have examined the effects of constituents of this herb on arachidonate metabolism. Whereas olivetol (1), cannflanvin-A (2) and CBG (3) are potent inhibitors of prostaglandin (PG)E_2 production, the cannabinoids CBD (4) and THC (5) are inhibitory only at toxic dose levels, and at lower doses actually stimulate PGE_2 secretion (Barrett *et al*, 1984). In contrast we have found that cannabinoids strongly inhibit the activity of soybean lipoxygenase (Tab. 1). This enzyme activity was measured by means of a spectroscopic assay (Magee, 1965) at pH 9.0 and 30°C. Inhibition appeared to be competitive in the presence of substrate, but brief preincubation with the inhibitor abolished this effect. Cannflavin-A (2) was inhibitory at higher concentrations and olivetol (1) was inactive.

Tab. 1. Molar inhibitory concentrations

	Compound	IC_{50} lipoxygenase	IC_{50} PGE_2 secretion
(1)	Olivetol	not active	2.2×10^{-7}
(2)	Cannflavin-A	1.0×10^{-4}	7.1×10^{-8}
(3)	Cannabigerol	2.2×10^{-6}	3.2×10^{-6}
(4)	Cannabidiol	2.9×10^{-6}	stimulation followed by
(5)	Tetrahydrocannabinol	3.2×10^{-6}	inhibition 2.1 to 6.4×10^{-5}

Previous interest in the relationship between the pharmacological actions of cannabinoids and arachidonate metabolism has focussed on modulation of PGE_2 levels through effects on cyclo-oxygenase and phospholipase A_2, primarily because inhibitors of these enzymes are known to antagonise the cataleptic and hypotensive effects of THC (5) in animals (Burstein and Ozman 1982, Fairbairn and Pickens 1981). The results presented here suggest an alternative mechanism. Following lipoxygenase inhibition, stimulation of phospholipase A_2 would result in greater availability of free arachidonate for PG synthesis via cyclo-oxygenase. From the similarity in structures of these constituents (Fig. 1), cyclooxygenase activity appears to reside in the di-hydroxy benzene ring, whilst lipoxygenase activity appears to reside in the substituent at C-6.

Figure 1



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