J. Pharm. Pharmacol. 1989, 41: 705–709
Received February 27, 1989

The Inhibitory Effects of Cannabinoids, The Active Constituents of *Cannabis sativa* L. on Human and Rabbit Platelet Aggregation

E. A. FORMUKONG, A. T. EVANS AND F. J. EVANS

Department of Pharmacognosy, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK

Abstract—Olivetol, cannabigerol (CBG), cannabidiol (CBD), cannabinol (CBN) and tetrahydrocannabinol (Δ^1-THC) were assessed for their ability to inhibit agonist-induced platelet aggregation and [^{14}C]5-HT release. With the exception of olivetol, (40% maximal effectiveness), none of the compounds inhibited tetradecanoylphorbolacetate (TPA)-induced aggregation of human or rabbit platelets. All of these cannabinoids partially inhibited primary aggregation and totally inhibited secondary aggregation of human platelets when adrenaline was used as the agonist. Inhibition was dose-dependent over the range 10^{-3}–10^{-5} M. Both rabbit and human platelet aggregation induced by adenosine diphosphate was inhibited in a dose-dependent manner and the order of potency was CBG > CBD > olivetol > THC > CBN, the IC50 of CBG being $2{\cdot}7 \times 10^{-4}$ M. PAF-induced aggregation of rabbit platelets was also inhibited by these compounds in a dose-dependent manner over the concentration range 10^{-3} to 10^{-4} M, however [^{14}C]5-HT release was only partially prevented by the cannabinoids in a manner which did not correlate with inhibition of aggregation.

Cannabis sativa L. has been used for the treatment of a number of conditions including asthma and rheumatism (Pars et al 1977). The extract of the plant has both analgesic and anti-inflammatory activities (O'Shaughnessy 1842; Gill et al 1970). The well-known hallucinogenic activity of the plant has led to its legal control and eventual dis-use as a therapeutic agent. A number of investigations using Δ^1-tetrahydrocannabinol (Δ^1-THC), the hallucinogenic component of the herb, have produced conflicting accounts of the effectiveness of that cannabinoid as an anti-inflammatory and analgesic agent (Dewey et al 1972; Chesher et al 1973; Buxbaum et al 1969). However, cannabis contains a number of closely related phenolic compounds apart from Δ^1-THC and these have been shown to possess various biological activities (Pars et al 1977). Recently, several components of cannabis were shown to possess both anti-inflammatory and analgesic activities superior to that of Δ^1-THC (Formukong et al 1988a) while not inducing catalepsy in mice (Formukong et al 1988b). Since catalepsy is proposed as a correlate for the central hallucinogenic action in man (Paton & Pertwee 1973 a, b), they could possibly form interesting molecular templates for the development of drugs for use in the treatment of allergic and inflammatory conditions.

In this communication we report on the ability of chemically related components of cannabis herb to antagonise platelet aggregation in platelet-rich plasma. The agonists chosen were phorbol ester (TPA), adrenaline, ADP and platelet-activating factor (PAF).

Materials and Methods

Materials

Cannabidiol (CBD), cannabinol (CBN) olivetol and Δ^1-THC were obtained from Sigma Chemical Co. (Poole, UK); cannabigerol (CBG) was from Makor Chemicals (Tev. Aviv, Israel). Aggregating agents: PAF, adrenaline, adenosine diphosphate (ADP), tetradecanoglyphorbolacetate (TPA) were from Sigma Chemical Co. (Poole, UK). [^{14}C]5-Hydroxytryptamine (5-HT) 50 m Ci mmol^{-1} was from the Radiochemical Centre (Amersham UK). BN 52021 (Ginkgolide B) was from the Institut Henri Beaufour, Avenue Descartes (France) and kadsurenone (L 652, 731) from Merck, Sharp & Dohme Research Laboratories, Rahway, New Jersey (USA).

Methods

Blood collection. Human blood was collected via venepuncture of the forearm from healthy male donors who had denied receiving any medication within the previous 14 days. Rabbit blood was collected from the marginal ear vein of New Zealand White rabbits. For both human and rabbit blood, nine volumes of blood were mixed with one volume of 3·8% w/v trisodium citrate.

Preparation of platelet-rich plasma (PRP). PRP was prepared by centrifuging the citrated blood at 250 *g* for 15 min. Platelet-poor plasma (PPP) was obtained by further centrifugation at 1500 *g* for 10 min. The PRP tube was capped, stored at room temperature (20°C) and used between 30 min and 3 h of preparation. The platelet count was adjusted to $1{\cdot}6 \times 10^8$ cells mL^{-1}.

Platelet aggregation. Aggregation was monitored using a Payton Minigator II aggregometer set at zero and 100% light transmission using 500 μL PRP and PPP, respectively. Test drugs (10^{-3}–10^{-5} M) were added to stirred platelets in a cuvette at 37°C, 5 min before the addition of aggregating agent. Controls received only the vehicle and aggregation was monitored for a minimum of 5 min. The final concentration of ethanol as vehicle did not exceed 1% v/v, and was shown to have no effect on agonist-induced aggregation or

Correspondence to: F. J. Evans, Department of Pharmacognosy, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK.

on antagonist-induced inhibition of aggregation. Platelet shape change was detected as an initial decrease in light transmission; this was followed by aggregation in two distinct phases, i.e. primary and secondary aggregation.

Platelet release reaction. Platelets were labelled with [^{14}C]5-HT by incubation of 10 mL PRP with 1·5 μL [^{14}C]5-HT (50 m Ci mmol^{-1}) at 37°C for 30 min. Test drugs were added as above to PRP 5 min before the addition of PAF as release agent. The reaction was terminated after 2 min with ice cold 5% formaldehyde in EDT (100 mM). The mixture was centrifuged in an Eppendorf centrifuge at 1500 *g* for 5 min. The contents were removed and added to 4 mL of scintillant; this was done in triplicate.

Results

Adrenaline-induced aggregation

The cannabinoids inhibited adrenaline ($4{\cdot}0 \times 10^{-6}$ M)-induced aggregation of human platelets in a dose-dependent manner (Table 1). The order of potency was Δ^1-THC > CBN > CBG > olivetol > CBD. However, olivetol was the most effective, producing a maximum inhibition of about 86%. With the exception of CBD, these compounds totally inhibited the second phase of aggregation but only partially inhibited the primary phase, as typically shown for olivetol in Fig. 1A. In contrast, CBD (Fig. 1C) only inhibited second phase aggregation, an effect which was more marked when a submaximal dose of adrenaline ($2{\cdot}0 \times 10^{-6}$ M) was used as the agonist (Fig. 1B). Both CBN and Δ^1-THC exhibited an optimum effect at 5×10^{-4} M thereafter increases in dose led to a diminished response.

Phorbol ester (TPA)-induced aggregation

In the dose range 10^{-3} to 10^{-7} M none of the cannabinoids inhibited TPA ($1{\cdot}6 \times 10^{-5}$ M)-induced aggregation of rabbit platelets ($P < 0{\cdot}05$). TPA is generally more potent in the induction of aggregation of human platelets (Edwards et al 1983) than of rabbit platelets. In the dose range 10^{-3} to 10^{7} M, CBN, CBD, CBG and Δ^1-THC exhibited no significant ($P > 0{\cdot}05$) effect upon TPA ($1{\cdot}6 \times 10^{-5}$ M)-induced aggregation of human platelets. However, olivetol produced a maximal inhibitory effect of about 40% at a dose of $2{\cdot}8 \times 10^{-3}$ M ($P < 0{\cdot}05$) (Fig. 2).

ADP-induced aggregation

All of the compounds used inhibited ADP (10^{-6} M)-induced aggregation of human platelets (Table 1) in a dose-dependent manner. The second phase of aggregation was totally inhibited whilst primary phase aggregation was partially inhibited (Fig. 3A). The order of potency of the compounds was CBG > CBD > olivetol > Δ^1-THC > CBN (Table 1). With ADP (10^{-6} M)-induced rabbit platelet aggregation the cannabinoids produced a partial inhibition of primary aggregation (Fig. 3B). The effect was dose-dependent (Table 1) and the inhibitory potency was CBD > Δ^1THC > olivetol > CBN. Δ^1-THC and CBD were the most effective, producing a maximal inhibition of about 76%.

PAF induced aggregation

PAF ($2{\cdot}7 \times 10^{-7}$ M)-induced aggregation of rabbit platelets was inhibited by the cannabinoids in a dose-dependent manner (Table 1). The order of inhibitory potency was CBD > CBG > CBN > Δ^1-THC > olivetol. These compounds did not affect platelet shape change but a complete reversal of the PAF platelet response was achieved following addition of the antagonists (Fig. 4). In the same system, the specific receptor antagonists L 652,731 and BN 52021 inhibited PAF-induced platelet aggregation with IC50's of 3·3 and $6{\cdot}0 \times 10^{-6}$ M, respectively and were about 100 times more potent than the cannabinoids.

Platelet release reaction

All of the cannabinoids inhibited [^{14}C]5-HT release induced by PAF (Table 2) but this effect did not correlate with the inhibition of platelet aggregation.

Discussion

It has been observed clinically (Schaeffer et al 1979) that, generally, there is a decrease in the ability of the blood platelets in users of cannabis to aggregate. This observation was further supported by the work of Levy et al (1976) who demonstrated that Δ^1-THC partially antagonized ADP-induced aggregation of washed human platelets. These observations suggested that in-vitro platelet aggregation might provide a rapid means for the further investigation of the peripheral effects of the constituents of *Cannabis sativa* L.

All of the cannabinoids tested in the present study

Table 1. The effect of cannabinoids on adrenaline (4×10^{-6} M)-, ADP (10^{-6} M)- and PAF ($2{\cdot}9 \times 10^{-7}$ M)-induced aggregation of blood platelets. Maximal effects are expressed as mean ± s.e.m. of controls for at least 4 experiments, each experiment constituting a new sample of blood. Each blood sample was repeated at least four times. * Indicates a significant difference to controls ($P < 0{\cdot}05$) as calculated by Student's *t*-test.

	Adrenaline-induced human platelet aggregation		ADP-induced human platelet aggregation		ADP-induced rabbit platelet aggregation		PAF-induced rabbit platelet aggregation	
Compound	IC50(M)	Max effect (%)	IC50(M)	Max effect (%)	IC50(M)	Max effect (%)	IC50(M)	Max effect (%)
Cannabidiol	$3{\cdot}88 \times 10^{-3}$	ND	$5{\cdot}8 \times 10^{-4}$	79·2 ± 4·0*	$4{\cdot}2 \times 10^{-4}$	75 ± 3·0*	$2{\cdot}8 \times 10^{-4}$	77·1 ± 3·6*
Δ^1-THC	$3{\cdot}98 \times 10^{-5}$	75 ± 1·2*	$11{\cdot}0 \times 10^{-4}$	66·2 ± 3·7*	$4{\cdot}0 \times 10^{-4}$	76 ± 5·1*	$8{\cdot}0 \times 10^{-4}$	60·0 ± 2·0*
Cannabinol	$8{\cdot}91 \times 10^{-5}$	66 ± 3·3*	$12{\cdot}5 \times 10^{-3}$	33·4 ± 1·4*	$2{\cdot}5 \times 10^{-3}$	46·0 ± 2·4*	$5{\cdot}6 \times 10^{-4}$	76·3 ± 4·3*
Cannabigerol	$5{\cdot}0 \times 10^{-4}$	69 ± 1·2*	$2{\cdot}7 \times 10^{-4}$	90 + 4·3*	ND	ND	$5{\cdot}2 \times 10^{-4}$	100*
Olivetol	$3{\cdot}16 \times 10^{-4}$	86 ± 2·5*	$9{\cdot}8 \times 10^{-4}$	70·5 ± 2·4*	$6{\cdot}0 \times 10^{-4}$	67 ± 4·3*	$9{\cdot}4 \times 10^{-4}$	86 ± 2·2

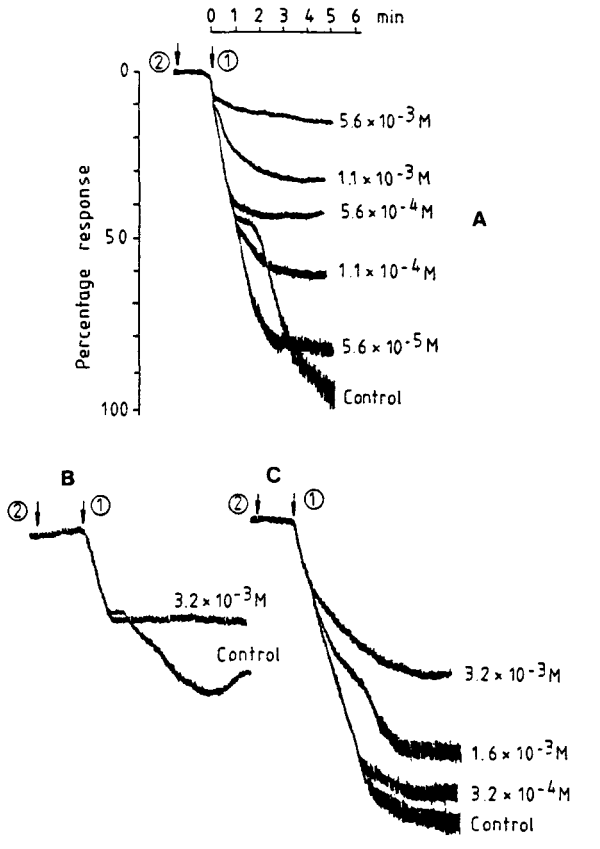

FIG. 1. A. The effect of a typical antagonist (olivetol) on the response of human platelets to adrenaline (4×10^{-6} M)-induced aggregation. olivetol was introduced at arrow 2 in the doses indicated and incubated for 5 min before the addition of adrenaline at arrow 1. Aggregation was monitored for not less than a further 5 min. B. The effect of CBD on the response of adrenaline (2×10^{-6} M)-induced aggregation of human platelets. CBD ($3{\cdot}2 \times 10^{-3}$ M) was introduced at arrow 2, 5 min before the introduction of adrenaline at arrow 1 and the aggregation was further monitored for at least 5 min. C. The effect of CBD on the response of adrenaline ($4{\cdot}0 \times 10^{-6}$ M)-induced aggregation of human platelets. CBD in the doses indicated was introduced at arrow 2, 5 min before the introduction of adrenaline at arrow 1 and the aggregation was further monitored for at least 5 min.

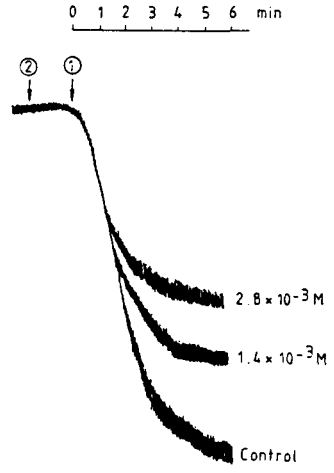

FIG. 2. The effect of olivetol at the doses indicated on TPA ($1{\cdot}6 \times 10^{-5}$ M)-induced aggregation of human platelets. Olivetol was introduced at arrow 2, 5 min later TPA was introduced at arrow 1. Aggregation was monitored for a further 5 min.

inhibited adrenaline-induced platelet aggregation in a dose-dependent manner (Table 1) (Fig. 1A). For these experiments human, rather than rabbit, blood platelets were used since Bygdeman & Johnson (1969) reported complications when using adrenaline as an agonist for platelet aggregation in species other than man. Olivetol, the simplest compound of this series of phenolics and the biosynthetic precursor of the other cannabinoids, was the most effective inhibitor of adrenaline-induced aggregation, producing a maximal inhibition of about 86%. However, Δ^1-THC was the most potent of the series with an IC50 of $3{\cdot}98 \times 10^{-5}$ M. Olivetol is structurally related to eugenol, a known analgesic isolated from clove oil, inhibited *p*-benzoquinone-induced writhing in mice with an IC50 of 0·63 mg kg^{-1} which makes it approximately 30 times more potent than aspirin in that test (Formukong et al 1988a). Prenylated phenolics of the olivetol type may, therefore, provide a series of low molecu-

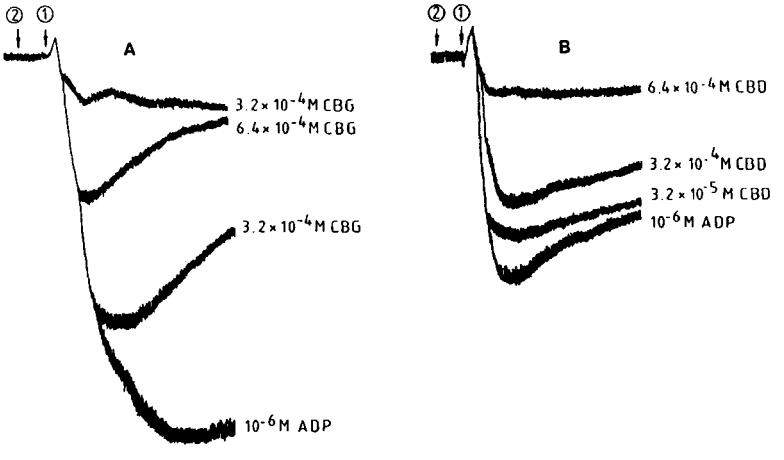

FIG. 3. A. The effect of a typical antagonist (CBG) on the response of human platelets to ADP (10^{-6} M)-induced aggregation. CBG in the doses indicated was introduced at arrow 2 and incubated for 5 min before the addition of ADP at arrow 1. Aggregation was monitored for not less than a further 5 min. B. The effect of a typical antagonist (CBD) on the response of rabbit platelets to ADP (10^{-6} M)-induced aggregation. CBD was introduced at arrow 2 in the doses indicated and incubated for 5 min before the addition of ADP at arrow 1. Aggregation was monitored for not less than a further 5 min.

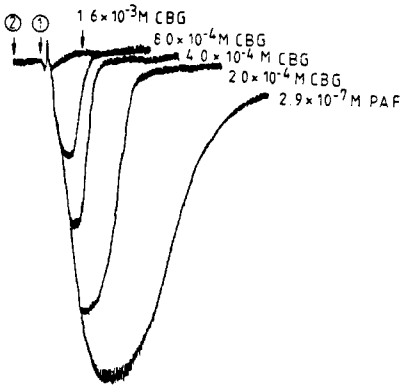

FIG. 4. The effect of a typical antagonist (CGB) on the response of rabbit platelets to PAF ($2{\cdot}9\times10^{-7}$ M)-induced aggregation. CBG was introduced at arrow 2 in the doses indicated and incubated for 5 min before the introduction of PAF at arrow 1. Aggregation was monitored for not less than a further 5 min.

lar compounds with activities similar to aspirin. With the exception of CBD, the cannabinoids only partially inhibited adrenaline-induced primary aggregation, whereas all the substances tested, including CBD, totally inhibited second stage aggregation (Fig. 1C). This effect was more marked when a submaximal dose of adrenaline was used to initiate the aggregation (Fig. 1B). It is unlikely that these compounds were reacting as adrenoceptor antagonists on human platelets. This observation was further supported by the fact that two of the cannabinoids, CBN, and Δ^1-THC, exhibited an optimum effect at 5×10^{-4} M, further increases in dose producing a diminished effect. Similar dose responses have previously been reported for the inhibition of *p*-benzoquinone-induced writhing by cannabis extracts containing these substances (Formukong et al 1988a). A range of phenolic constituents of cannabis, including olivetol, have been shown to be effective inhibitors of phorbol ester-induced inflammation of mouse skin (Formukong et al 1988a). The phorbol ester receptor is believed to be the Ca^{2+} and phospholipid-dependent protein kinase C (Kikkawa et al 1983), subsequent phosphorylation of a number of substrate proteins (Brooks et al 1988) resulting in platelet aggregation. In the present study we found that, with the exception of olivetol, the cannabinoids were incapable of inhibiting either human or rabbit platelet aggregation induced by the phorbol ester TPA. Nevertheless, the inhibition of cyclo-oxygenase by olivetol may, in part, be responsible for the activity of that compound in blood platelets, although Morrice (1987) has shown that olivetol in high doses, will prevent the activation of protein kinase C by TPA.

Table 2. The effect of the cannabinoids on PAF ($2{\cdot}7\times10^{-7}$ M)-induced release of [^{14}C]5-HT. The results are mean ± s.e.m. of four separate experiments.

Compound	Dose (M)	PAF-induced [^{14}C]5-HT-release % inhibition ± s.e.m.
Cannabidiol	$1{\cdot}6\times10^{-4}$	7·3 ± 2·8
	$2{\cdot}6\times10^{-4}$	13·5 ± 2·1
	$7{\cdot}9\times10^{-4}$	48·3 ± 1·3
Olivetol	$5{\cdot}6\times10^{-4}$	21·2 ± 2·3
	$1{\cdot}6\times10^{-3}$	41·5 ± 2·7
	$2{\cdot}8\times10^{-3}$	16·4 ± 4·2
Cannabigerol	$4{\cdot}0\times10^{-4}$	39·7 ± 2·7
	$7{\cdot}9\times10^{-4}$	53·2 ± 1·2
	$1{\cdot}6\times10^{-3}$	17·0 ± 2·3
Δ^1-THC	$1{\cdot}6\times10^{-4}$	35·3 ± 5·6
	$3{\cdot}2\times10^{-4}$	31·1 ± 1·3
	$1{\cdot}6\times10^{-3}$	38·2 ± 4·4
Cannabinol	$1{\cdot}6\times10^{-4}$	25·0 ± 5·8
	$8{\cdot}0\times10^{-4}$	51·5 ± 1·0
	$1{\cdot}6\times10^{-3}$	37·6 ± 6·2

The cannabinoids were effective inhibitors of PAF-induced aggregation of rabbit platelets. PAF is known to be involved in several disease conditions including inflammation, allergic reactions and asthma (Vargaftig & Braquet 1987). Inhibitors of PAF-induced biological responses are, accordingly, potential drug templates. PAF-induced aggregation was inhibited in a dose-dependent manner, the order of potency being CBD > CBG > CBN > Δ^1-THC > olivetol. Although the cannabinoids were able to induce a complete inhibition of PAF-induced aggregation of rabbit platelets they were approximately 100 times less potent than the specific receptor antagonists L 652731 and BN 52021. Inhibition of [^{14}C]5-HT release was not dose related and did not correlate with inhibition of platelet aggregation (Table 2).

The constituents of cannabis inhibited ADP-induced aggregation in both human and rabbit platelets (Table 1). Second stage aggregation was completely inhibited and primary aggregation was partially inhibited (Fig. 3). CBD and THC were the most effective antagonists producing a maximal inhibition of aggregation of about 76%. Levy et al (1976) have demonstrated that Δ^1-THC antagonises ADP-induced aggregation of washed human platelets and in that system Δ^1-THC was more potent than in platelet-rich plasma used by us. The effect of Δ^1-THC on ADP-induced aggregation could, in part, be explained by the observation of Bloom & Hillard (1985) that Δ^1-THC affects adenylate cyclase activity and hence modulates cellular cAMP levels. However, the activity of Δ^1-THC has been linked to prostaglandin production (Howes & Osgood 1976). Several constituents of cannabis have been shown to both stimulate (White & Tansik 1980; Burnstein & Hunter 1978) and inhibit prostaglandin levels in-vitro (Burnstein & Raz 1972; Barrett et al 1985). The compounds used are known to inhibit the activity of several enzymes of the arachidonate cascade including cyclo-oxygenase and lipoxygenase (Evans et al 1987a) and to both stimulate and inhibit phospholipase A_2 activity (Evans et al 1987b). The actions of the cannabinoids on membrane associated enzymes are complex and dose-dependent. Although these actions are possibly associated with the ability of the cannabinoids to act as anti-oxidants, specific structural alterations may be critical in determining enzyme targets.

Acknowledgements

We are grateful to the M.R.C. and the government of Cameroon for financial support.

References

Barrett, M. L., Gordon, D., Evans, F. J. (1985) Isolation from *Cannabis sativa* L of Cannflavin, a novel inhibitor of prostaglandin production. Biochem. Pharmacol. 34: 21019-2024

Bloom, A. S., Hillard, C. J. (1985) Cannabinoids,, neurotransmitter receptors and brain membranes. In: Marihuana '84. (ed). Harvey, D. J. IRL Press, Oxford

Brooks, S. F., Evans, F. J., Aitken, A. (1988) Platelet protein phosphorylation induced by phorbol esters with different biological activity and the effect of Ca^{2+} ionophore. Eur. J. Biochem. In press

Burstein, S., Raz, A. (1972) Inhibition of PGE2 biosynthesis. Prostaglandins 2: 369

Burstein, S., Hunter, S. A. (1978) Prostaglandins and Cannabis VI. Release of arachidonic acid from HeLa cells by delta-1-tetrahydrocannabinol and other cannabinoids. Biochem. Pharmacol. 27: 1275–1280

Buxbaum, D., Sanders-Bush, E., Efron, D. H. (1969) Analgesic activity of tetrahydrocannabinol in the rat and mouse. Fed. Proc. 28: 735

Bygdeman, S., Johnson, O. (1969) Studies on the effect of adrenergic blocking drugs on catecholamine-induced platelet aggregation and uptake of noradrenaline and 5-HT. Acta Physiol. Scand. 75: 129–138

Chesher, G. B., Dahl, C. J., Everingham, M., Jackson, D. M., Marchant-Williams, H., Starmer, G. A. (1973) The effects of cannabinoids on intestinal motility and their antinociceptive effect in mice. Br. J. Pharmacol. 49: 588–594

Dewey, W. L., Harris, L. S., Kennedy, J. S. (1972) Some pharmacological and toxicological effects of 1-trans^{8} and 1-trans ^{9}-THC in laboratory rodents. Arch. Int. Pharmacodyn. 196: 133–145

Edwards, M. C., Taylor, S. E., Williamson, E. M., Evans, F. J. (1983) New phorbol and deoxyphorbol esters: isolation and relative potencies in inducing platelet aggregation and erythema of skin. Acta Pharmacol. Toxicol. 53: 177–187

Evans, A. T., Formukong, E. A., Evans, F. J. (1987a) Actions of cannabis constituents on enzymes of arachidonate metabolism. Antiinflammatory potential. Biochem. Pharmacol. 36: 2037–2040

Evans, A. T., Formukong, E. A., Evans, F. J. (1987b) Activation of phospholipase A_2 by cannabinoids: lack of correlation with CNS effects. FEB. Lett. 211: 119–122

Formukong, E. A., Evans, A. T., Evans, F. J. (1988a) Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. Inflammation 12: 361–371

Formukong, E. A., Evans, A. T., Evans, F. J. (1988b) Inhibition of the cataleptic effect of tetrahydrocannabinol by other constituents of *Cannabis sativa* L. J. Pharm. Pharmacol. 40: 132–134

Gill, E. W., Paton, W. D. M., Pertwee, R. G. (1970) Preliminary experiments on the chemistry and pharmacology of cannabis. Nature 228: 134–136

Howes, J. F., Osgood, P. F. (1976) Cannabinoids and the inhibition of prostaglandin synthesis. In: Marihuana, chemistry, biochemistry and cellular effects. Ed. Nahas, G. G. pp. 313–328. Springer-Verlag, New York pp. 313–328

Kikkawa, U., Takai, Y., Tanaka, Y., Miyake, R., Nishizuka, Y. (1983) Protein kinase C as a possible receptor protein of tumour promoting phorbol esters. J. Biol. Chem. 11442–11445

Levy, R., Schurr, A., Nathan, I., Dvilanski, A., Livne, A. (1976) Impairment of ADP-induced platelet aggregation by hashish components. Thromb. Haemost. (Stuttg.) 36: 634

Morrice, N. A. (1987) Activators and inhibitors of protein kinases. Thesis. University of London

O'Shaughnessy, W. B. (1842) On the preparation of the Indian Hemp of Gunjah. Trans. Med. Phys. Soc. Bengal 8: 421–461

Pars, H. G., Razdan, R. J., Howes, J. F. (1977) Potential therapeutic agents derived from cannabinoid nucleus. In: Advances in Drug Research, vol. 11, ed. Harper and Simmons.

Paton, W. D. M., Pertwee, R. G. (1973a) The pharmacology of cannabis in animals. In: Marihuana, Chemistry, Pharmacology, Metabolism and Clinical Effect. Ed. Mechoulam, R. Academic Press, New York p. 191

Paton, W. D. M., Pertwee, R. G. (1973b) The actions of cannabis in man. In: Marihuana. chemistry, pharmacology, metabolism and Clinical Effect. Ed. Mechoulam, R. Academic Press, New York p. 287

Schaeffer, C. F., Brackett, D. J., Gunn, C. G., Dubowski, K. M. (1979) Decreased platelet aggregation following marijuana smoking in man. J. Okla. State Med. Assoc. 72: 435–436

Vargaftig, B. B., Braquet, P. (1987) PAF-acether today: Relevance for acute experimental anaphylaxis. Br. Med. Bull. 43: 312–335

White, H. L., Tansik, R. L. (1980) Effects of Δ^{9}-THC and CBD on phospholipase and other enzymes regulating arachidonate metabolism. Prostaglandins & Medicine 4: 409–411