Allergenic Properties of Naturally Occurring Cannabinoids

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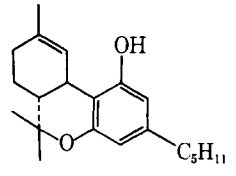
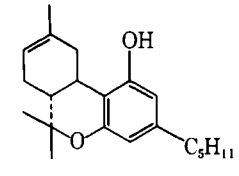
Abstract □ The guinea pig maximization test was used to determine the potential of seven cannabinoids to produce allergic contact dermatitis. Δ^9-Tetrahydrocannabinol and cannabinol were found to be extreme (Grade V) sensitizers. Cannabidiol, Δ^8-tetrahydrocannabinol, and cannabichromene were moderate (Grade III) sensitizers. Cannabigerol and cannabinol methyl ether were not sensitizers. Most of the cannabinoids were found to be allergenically cross-reactive. Additionally, it was shown that the presence of a free 1′-hydroxyl group was required for sensitization, but not to elicit a response in sensitive animals.

Keyphrases □ Cannabinoids—naturally occurring, allergenic properties, determined by the guinea pig maximization test for skin sensitivity □ Allergenicity—of naturally occurring cannabinoids, guinea pig maximization test for skin sensitivity □ Sensitizers, skin—allergenic properties of naturally occurring cannabinoids, guinea pig maximization test

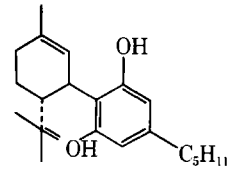
Δ^9-Tetrahydrocannabinol (I) was shown to be a potent skin sensitizer in the guinea pig, and serum from sensitive animals sensitized guinea pig mast cells for degranulation (1). Tetrahydrocannabivarol, a Δ^9-tetrahydrocannabinol homologue, was also found to be a potent skin sensitizer (2). In view of these findings, a systematic study comparing the sensitizing potential of I to six other cannabinoids was conducted utilizing the guinea pig maximization test. The cross-allergenicity of these cannabinoids was also studied.



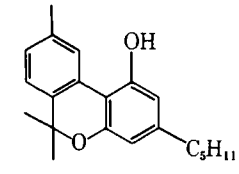
Δ^9-Tetrahydrocannabinol
I



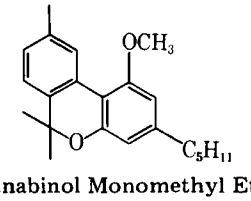
Δ^8-Tetrahydrocannabinol
II



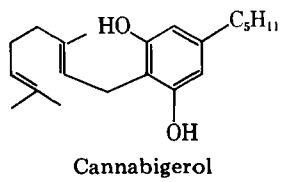
Cannabidiol
III



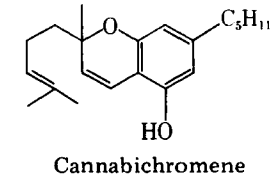
Cannabinol
IV



Cannabinol Monomethyl Ether
V



Cannabigerol
VI



Cannabichromene
VII

EXPERIMENTAL

Female Hartley guinea pigs, weighing 350–400 g, were used[1]. Food[2] and water supplemented with vitamin C were available *ad libitum*. Δ^9-Tetrahydrocannabinol (I), Δ^8-tetrahydrocannabinol (II), cannabidiol (III), and cannabinol (IV) were obtained from the National Institute on Drug Abuse, Rockville, Md. Cannabigerol (VI) was synthesized according to the literature procedure (3); cannabinol monomethyl ether (V) was synthesized from cannabinol as previously reported (4); cannabichromene (VII) was synthesized by the literature procedure (5). The purity of each cannabinoid was shown to be >95% by GC analysis.

Ten guinea pigs were used for maximization testing of cannabigerol and cannabinol methyl ether. Twenty guinea pigs were used for maximization testing of the remaining cannabinoids. The maximization method of Magnusson and Kligman (6) was used to determine the sensitizing capacity of each cannabinoid. A 5% water-in-oil emulsion of each cannabinoid (50 mg/ml of emulsion) was prepared by dissolving the cannabinoid in complete Freund's Adjuvant[3] and emulsifying using adjuvant–sterile water (1:1, v/v). A 5% solution of each cannabinoid was dissolved in sterile paraffin oil. Guinea pigs were sensitized by duplicate 0.1-ml intradermal (id) injections of cannabinoid emulsion, cannabinoid in paraffin oil, and adjuvent alone.

Topical induction sites were prepared by application of 10% sodium lauryl sulfate in petrolatum over the intradermal induction sites, 6 days after intradermal induction. Forty-eight-hour occlusive patches of the cannabinoid in petrolatum (0.03% w/w) were applied directly over the intradermal induction sites on day 7, after removal of the sodium lauryl sulfate. On day 23 the animals and nonsensitive control animals were given topical open epicutaneous skin tests with 100 and 50 μg of each cannabinoid in 10 μl of alcohol. The sites were observed 24, 48, and 72 hr later for erythema and edema. The Draize scoring system (7) was used to rank the intensity of erythema and edema based on a 0 to +4 rating scale. The mean erythema and edema scores from the three test readings were summed to provide an intensity score for each animal. The intensity scores of the 20 animals in each group were averaged to provide an average score. Animals demonstrating sensitivity to homologous sensitizing cannabinoids were skin tested with the other cannabinoids to determine if cross-allergenicity occurred.

RESULTS AND DISCUSSION

All of the cannabinoids subjected to maximization testing were sensitizers except cannabinol methyl ether and cannabigerol. Δ^9-Tetrahydrocannabinol and cannabinol were rated as extreme sensitizers (Table I), while cannabidiol, Δ^8-tetrahydrocannabinol, and cannabichromene were found to be moderate sensitizers. The allergenic potency of the cannabinoids (in descending order) was I = IV > III > VII > II > VI = V.

The cross-allergenicity of some cannabinoids and eugenol are shown in Table II. The extreme sensitizers, I and IV, provided the greater number of cross-reactions to the other cannabinoids. All cannabinoids tested were cross-reactive with other cannabinoids. However, the moderate sensitizers produced fewer cross-reactions than did the extreme

[1] Kentucky Cavies, Fern Creek, Ky.
[2] Purina guinea pig chow, Ralston-Purina, St. Louis, Mo.
[3] Complete Freund's Adjuvant, Difco Laboratories, Detroit, Mich.

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Table I—Maximization Grading of Cannabinoids

Cannabinoid	Sensitization Rate	Grade	Average Draize Score
I	100	V, Extreme	3.75
IV	100	V, Extreme	3.29
III	60	III, Moderate	1.69
VII	40	III, Moderate	0.38
II	30	III, Moderate	0.70
VI	0	Inactive	0
V	0	Inactive	0

sensitizers. Eugenol did not elicit cross-reactions in any animals. Since cannabinol methyl ether failed to sensitize, but did produce reactions in animals sensitized with cannabinol and cannabidiol, it appeared that a free hydroxyl group in position one was required for sensitization, but not to elicit a reaction in animals already sensitized. The failure of cannabinol methyl ether to elicit reactions in Δ^9-tetrahydrocannabinol-sensitized animals is not understood.

Although many of the biological effects of Δ^9-tetrahydrocannabinol are shared by all naturally occurring cannabinoids, the psychoactive effects are not. Desoize *et al.* (8) found that six natural cannabinoids (I, II, III, IV, VII, and cannabicyclol) suppressed phytohemagglutinin-induced DNA synthesis in normal human peripheral-blood lymphocytes, an *in vitro* model for cell-mediated immune function. In addition, the inhibitory effects of five of these six natural cannabinoids on the passive cutaneous anaphylaxis reaction in rats has been reported (9). Compound I, however, was a more potent inhibitor of passive cutaneous anaphylaxis than the other cannabinoids, and III was least active. Zimmerman *et al.* (10) reported that cannabidiol and cannabinol did not reduce hemagglutination titers to sheep red blood cells in mice at doses of 25 mg/kg, while Δ^9-tetrahydrocannabinol did.

The olivetol moiety of the molecule appeared, in the above studies, to be the portion of the molecule required for the shared activities. Olivetol was found by Desoize *et al.* (8) to inhibit phytohemagglutinin-induced lymphocyte transformation.

In this study, most cannabinoids containing the olivetol moiety were found to be skin sensitizers. Cannabinol methyl ether, which has its hydroxyl function blocked with a methyl ether, was not a sensitizer. The cross-allergenicity of these compounds is likely to be directly related to the presence of the olivetol component.

Table II—Immunological Cross-Reactivity of Cannabinoids

Sensitizing Substance	Skin Test Substance[a] I	IV	III	II	VII	VI	V	Eugenol
I	9/9	4/9	1/9	3/9	3/9	0/7	0/7	0/9
IV	2/9	9/9	0/9	3/9	1/9	4/9	4/9	0/10
III	0/6	0/6	6/10	0/6	0/10	2/6	2/6	0/6
II	0/3	0/3	0/3	3/10	0/3	NT	NT	NT

[a] Expressed as the number of animals with positive reactions to the skin test substance over the number tested.

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Absolute and Relative Bioavailability of Oral Acetaminophen Preparations

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Abstract □ Eighteen healthy volunteers received single 650-mg doses of acetaminophen by 5-min intravenous infusion, in tablet form by mouth in the fasting state, and in elixir form orally in the fasting state in a three-way crossover study. An additional eight subjects received two 325-mg tablets from two commercial vendors in a randomized crossover fashion. Concentrations of acetaminophen in multiple plasma samples collected during the 12-hr period after each dose were determined by high-performance liquid chromatography. Following a lag time averaging 3–4 min, absorption of oral acetaminophen was first order, with apparent absorption half-life values averaging 8.4 (elixir) and 11.4 (tablet) min. The mean time-to-peak concentration was significantly longer after tablet (0.75 hr) than after elixir (0.48 hr) administration. Peak plasma concentrations and elimination half-lives were similar following both preparations. Absolute systemic availability of the elixir (87%) was significantly greater than for the tablets (79%). Two commercially available tablet formulations did not differ significantly in peak plasma concentrations, time-to-peak, or total area under the plasma concentration curve and therefore were judged to be bioequivalent.

Keyphrases □ Bioavailability—absolute and relative, oral acetaminophen preparations, determined by high-performance liquid chromatography □ Acetaminophen—absolute and relative bioavailability of oral preparations, determination by high-performance liquid chromatography □ High-performance liquid chromatography—oral acetaminophen preparations, determination of absolute and relative bioavailability

Acetaminophen (paracetamol) is used extensively as a nonprescription analgesic and antipyretic agent (1). Over 40 oral acetaminophen preparations are available commercially (2). The present study evaluated the absolute bioavailability of orally administered acetaminophen in elixir and tablet forms. Also assessed was the relative

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