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Cannabinoids in glaucoma II: The effect of different cannabinoids on intraocular pressure of the rabbit

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ABSTRACT

Thirty-two different cannabinoids were tested for their ability to reduce intraocular pressure (IOP) in the rabbit. These included many of Δ^9- and Δ^8-THC derivatives and metabolites along with other natural and synthetic cannabinoids. In addition, some non-cannabinoid constituents of *Cannabis* were screened using the same model. All compounds were administered intravenously, while only a few were tested topically in mineral oil. Water soluble derivatives of Δ^9- and Δ^8-THC were prepared and tested topically in aqueous solution. The data revealed that certain derivatives of Δ^9- and Δ^8-THC were more active in lowering IOP than the parent cannabinoids. In addition, compounds other than Δ^9- and Δ^8-THC and their derivatives were shown to have activity.

INTRODUCTION

There has been a growing interest in the study of the effects of *Cannabis* and cannabinoids on intraocular pressure (IOP) since Hepler and Frank reported their results in 1971 (1). A significant fall in IOP was observed following marijuana smoking. Various cannabinoids, especially Δ^9-tetrahydrocannabinol (Δ^9-THC), have since been evaluated for their ability to reduce IOP both in humans (2, 3) and in animals (4-8).

In a previous communication (5) we have reported on the use of the rabbit as a primary animal model for the screening of cannabinoids for their IOP effects. While Δ^9-THC and Δ^8-THC significantly lowered IOP by the I.V. route, cannabidiol (CBD) was inactive and cannabinol (CBN) had little activity. Because of the undesirable CNS activity of Δ^9-THC, screening of other cannabinoids and *Cannabis* constituents was initiated with the hope to separate the CNS and IOP effects. More than 400 compounds are known to exist in *Cannabis*, of which there are more than 60 cannabinoids (9).

This investigation was designed to examine the effect of various natural constituents of *Cannabis* on IOP with special emphasis on subclasses of the cannabinoids other than the Δ^9-THC group. In addition, chemical modifications of the structure of Δ^9-THC were carried out and the resulting compounds were tested for IOP lowering properties. All compounds were administered intravenously to the rabbit. Those compounds found to lower IOP by this route were tested by the topical route.

MATERIALS AND METHODS

Adult albino rabbits (2-3 kg) were used in groups of 8 animals per group (5). The animals were placed in restraining wraps and allowed 2 hours of acclimation time before obtaining base line measurements. IOP measurements were carried out by applanation tonography using a calibrated Digilab Pneumotonometer. One drop of topical anesthetic (Ophthaine^R) was applied to each cornea prior to IOP measurement.

The preparation of solutions for dosing, IOP measurement and data analysis was conducted in the same manner as previously reported (5). Light mineral oil of viscosity 80-90° (Saybolt) was used for most compounds tested topically. For water soluble derivatives, aqueous solutions were prepared. A control group (administered the vehicle) was used simultaneously with drug treated groups. The percent change in IOP by a compound at time t was calculated as follows:

$$\% \text{ change in IOP} = \frac{(\Delta IOP_D - \Delta IOP_C) \times 100}{IOP_{(o)D}}$$

where ΔIOP_D is the change in IOP of the drug treated group from time 0 to time t,

ΔIOP_C is the change in IOP of the control group from time 0 to time t, and $IOP_{(o)D}$ is the IOP of the drug treated group at time 0.

Table 1. Effect of Intravenous Administration of Δ^9-THC and Its Derivatives on IOP in Normal Rabbits[1]

Compound	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls) 30 min.	60	120	180	240	300
Δ^9-THC (I)	1.0	+2.5	-16.8*	-15.9*	-21.3*	-24.4*	-19.4*
	1.5[3]	+3.1	-7.5*	-7.6*	-14.5*	-10.3*	-12.7*
Δ^9-THCV (II)	1.5	-7.8*	+8.2*	-3.9	+7.7*	+14.8*	+9.9*
11-OH-Δ^9-THC (III)	1.0	-10.0*	-12.8*	-10.0*	+0.3	-0.3	-8.4*
3'-OH-Δ^9-THC (IV)	0.5	-2.9	-	-12.5*	-7.1	-7.9	-7.5
8α-OH-Δ^9-THC (V)	0.5	+19.3*	+2.5	+6.5	-14.6*	-0.7	-13.5*
8β-OH-Δ^9-THC (VI)	0.5	-4.2	-7.1*	+7.1*	+7.5*	+11.0*	+20.9*
Δ^9-THC Acid A (VII)	1.0	+22.2*	+41.5*	+20.0*	+19.3*	+21.5*	+23.0*
Δ^9-THC Acid B (VIII)	1.0	+14.2*	+1.2	+18.0*	+9.9*	+5.8*	-1.2
9α-OH-HHC (IX)	0.3	-10.6*	-6.3*	-8.8*	-3.1	-3.1	-8.8*
	0.6	-16.4*	-24.7*	-9.4*	-16.7*	-15.0*	-6.6*
	1.0	-20.0*	-7.0*	-7.7*	-14.9*	-13.7*	-8.5*
9β-HHC (X)	1.0	+1.3	+15.1*	+5.0	+10.1*	+15.7*	+17.0*
9α-HHC (XI)	1.0	+1.9	+7.8*	+9.7*	+15.6*	+15.6*	+18.2*
Cannabiripsol (XII) (9α,10β-diOH-HHC)	1.0	+14.8*	+4.5	+2.7	+12.0*	-1.2	-6.5*
Iso-cannabiripsol (XIII) (9β,10α-diOH-HHC)	1.0	+26.5*	+7.9*	+15.1*	+23.3*	+16.0*	+1.2
$\Delta^{9(11)}$-THC (XIV) (with 4.5% Δ^9-THC)[2]	3.0	-8.6*	-5.5*	-7.1*	-5.0	-4.5	+2.4
	14.0	+4.9*	-1.0	-7.2*	-10.6*	-11.2*	-10.7*
10α-OH-$\Delta^{9(11)}$-THC (XV)	0.5	+4.1*	-10.4*	-10.5*	-7.6*	+8.3*	+9.3*
$\Delta^{6\alpha(10\alpha),9}$-DHC-Ac (XVI)	1.0	-0.7	-7.8*	+7.8*	+3.5	0.0	+1.8
9α,10α-Epoxy-HHC (XVII)	0.5	-6.3*	-5.7	-21.3*	-9.6*	-16.2*	-12.9*
	1.0	-12.9*	-17.0*	-43.1*	-31.0*	-21.3*	-22.4*

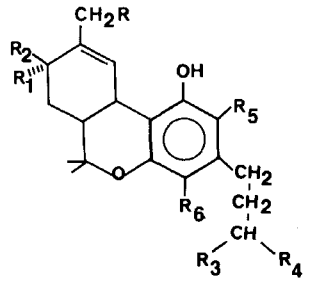
[1]See figure 1 for chemical structures of this group of compounds.
[2]Δ^9-THC is a contaminant in the synthetic $\Delta^{9(11)}$-THC.
[3]Average of 9 runs (see reference 5 for details).
* Denotes significantly different from controls, $p<0.05$.

Most of the compounds used in this study were either isolated from the plant material of *Cannabis sativa* or synthesized in our laboratories following published procedures. Certain cannabinoids were obtained through the National Institute on Drug Abuse (NIDA), particularly Δ^9- and Δ^8-THC and their metabolites.

RESULTS AND DISCUSSION

A total of thirty-three different cannabinoids were screened for IOP lowering properties in the normal rabbit by intravenous injection. Table 1 shows the activity of Δ^9-THC and its related compounds.

Δ^9-THC was active in reducing the IOP in nor-



Δ^9-THC (I); R=R_1=R_2=R_3=R_5=R_6=H, R_4=C_2H_5

Δ^9-THCV (II); R=R_1=R_2=R_3=R_4=R_5=R_6=H

11-OH-Δ^9-THC (III); R=OH, R_1=R_2=R_3=R_5=R_6=H, R_4=C_2H_5

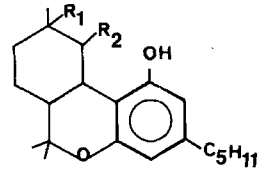
3'-OH-Δ^9-THC (IV); R=R_1=R_2=R_5=R_6=H, R_3=OH, R_4=C_2H_5

8α-OH-Δ^9-THC (V); R=R_2=R_3=R_5=R_6=H, R_1=OH, R_4=C_2H_5

8β-OH-Δ^9-THC (VI); R=R_1=R_3=R_5=R_6=H, R_2=OH, R_4=C_2H_5

Δ^9-THC-Acid A (VII); R=R_1=R_2=R_3=R_6=H, R_4=C_2H_5, R_5=COOH

Δ^9-THC-Acid B (VIII); R=R_1=R_2=R_3=R_5=H, R_4=C_2H_5, R_6=COOH



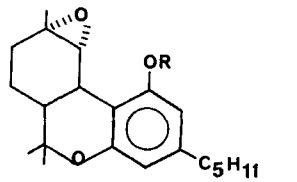
9α-OH-HHC (IX); R_1=α-OH, R_2=H

9β-HHC (X); R_1=β-H, R_2=H

9α-HHC (XI); R_1=α-H, R_2=H

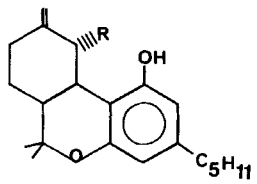
Cannabiripsol (XII); R_1=α-OH, R_2=β-OH

iso-cannabiripsol (XIII); R_1=R_2=β-OH



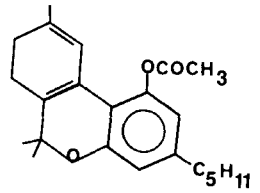
9α,10α-Epoxy-HHC (XVII); R=H

9α,10α-Epoxy-HHC-Ac (XVIII); R=C(=O)-CH_3



$\Delta^{9(11)}$-THC (XIV); R=H

10α-OH-$\Delta^{9(11)}$-THC (XV); R=OH



$\Delta^{6\alpha(10\alpha),9}$-DHC-Ac (XVI)

Figure 1. Chemical structures of Δ^9-THC related compounds.

mal rabbits at both the 1.0 and 1.5 mg/kg given I.V. The activity at the 1 mg/kg dose seemed to be slightly higher than that at 1.5 mg/kg. Other data, not shown in this table, indicate that doses as low as 0.25 mg/kg would reduce IOP in the rabbit by the I.V. route. At higher doses (>2 mg/kg) however, Δ^9-THC loses its ability to reduce IOP. This is consistent with the biphasic nature of the pharmacologic activity of the compound (10).

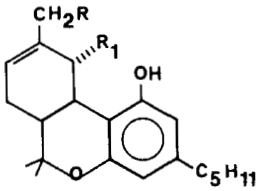
The C_3-homolog of Δ^9-THC, namely Δ^9-THCV, showed no significant activity at 1.5 mg/kg indicating that reducing the length of the side chain lowers the ability of the compound to reduce IOP.

Of the Δ^9-THC metabolites and/or conversion products, 9α, 10α-epoxy-HHC was the most active in reducing IOP (more active than Δ^9-THC). 3'-OH-Δ^9-THC, 11-OH-Δ^9-THC and 10α-OH-$\Delta^{9(11)}$-THC showed variable degrees of lowering of the IOP but neither cannabinoid was as active as the parent compound, Δ^9-THC. The other cannabinoids listed in Table 1 did not show any appreciable decrease in IOP at the doses given. The apparent activity of $\Delta^{9(11)}$-THC was attributed to the presence of 4.5% Δ^9-THC. The results of screening those compounds (Table 1) indicate that: 1) Reduction of the double bond of Δ^9-THC destroys the IOP lowering properties. The resulting 9α- and 9β-HHC were inactive in the IOP screen. 2) Hydroxylation of Δ^9-THC on the side chain or the terpene portion results in lowering or loss of activity. 3) Sub-

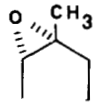
Table 2. Effect of Intravenous Administration of Δ^8-THC and Its Derivatives on IOP in Normal Rabbits[4]

	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls)					
		30 min.	60	120	180	240	300
Δ^8-THC (XIX)	1.5	-7.7*	-3.6	-13.4*	-8.3*	-16.5*	-6.1*
	3.0	+1.2	-7.0*	-6.5*	-5.6*	-19.1*	-9.9*
11-OH-Δ^8-THC (XX)	0.5	-6.2*	+3.7	-27.1*	-9.7*	-23.1*	-3.4
	1.5	-18.6*	+0.3	-23.8*	-19.8*	-21.6*	+1.5
10α-OH-Δ^8-THC (XXI)	0.1	-11.1*	-25.1*	-21.1*	-15.2*	-3.5	+11.7*
	0.2	-4.1	-21.8*	-20.0*	-11.8*	-1.8	+14.1*
	0.3	-6.5*	-21.9*	-14.8*	-18.3*	-11.2*	+1.2
8α,9α-Epoxy-HHC (XXII)	1.0	-14.4*	-8.2*	-3.9	-11.3*	-7.8*	-1.9
	1.0	-12.1*	-16.5*	-16.2*	+1.3	-7.4*	-12.8*
8β,9β-Epoxy-HHC (XXIII)	1.0	+2.6	+4.3	+0.4	-10.4*	-12.2*	+7.8*
	5.0	-13.1*	-0.7	-20.1*	-6.6*	-15.1*	-17.0*

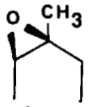
[4] See figure 2 for chemical structures.
*Denotes significantly different from controls, $p<0.05$.



Δ^8-THC (XIX); R=R_1=H
11-OH-Δ^8-THC (XX); R=OH, R_1=H
10α-OH-Δ^8-THC (XXI); R=H, R_1=OH



8α,9α-Epoxy-HHC
(XXII)



8β,9β-Epoxy-HHC
(XXIII)

Figure 2. Chemical structures of Δ^8-THC related compounds. Partial structures XXII and XXIII only show the portion of the molecule with structural change.

stitution on the aromatic ring of Δ^9-THC results in loss of activity. 4) Migration of the double bond to the exocyclic position results in loss of activity.

Δ^8-THC group

All Δ^8-THC related compounds shown in Table 2 were active in reducing IOP with 10α-OH-Δ^8-THC being the most active and the 8β, 9β-epoxy-HHC the least active. The activity of Δ^8-THC was slightly less than that of Δ^9-THC. However, 11-OH-Δ^8-THC was found to be more active than either of Δ^8- or Δ^9-THC. The 8α, 9α-epoxide was more active than the 8β, 9β-epoxide and about as active as the par-compound (Δ^8-THC). The significance of this finding is that the 8α, 9α-epoxide, which was found to have the least CNS activity among Δ^8-THC metabolites (11), appears to lower IOP more than either the 8β, 9β-isomer or Δ^8-THC itself. This suggests possible separation of the CNS activity from the IOP lowering properties. Work is in progress to ascertain if this relationship would hold true in other animal models.

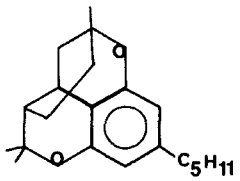
Cannabichromene (CBC) and related compounds

The testing of these compounds at doses higher than those used for Δ^8- and Δ^9-THC was possible since all compounds shown in Table 3 lack CNS activity. CBC, cannabicitran (CBT) and Bis-cannabichromene (Bis-CBC) were tested at 1 and 10 mg/kg I.V. while cannabicyclol was tested at 1 mg/kg only. All compounds were found to exhibit IOP

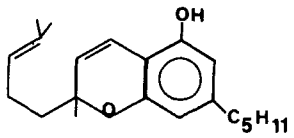
Table 3. Effect of Intravenous Administration of CBC and Its Derivatives on IOP in Normal Rabbits[5]

Compound	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls) 30 min.	60	120	180	240	300
CBC (XXIV)	1.0	-11.1*	-10.8*	+6.9*	-9.8*	-11.1*	+2.3
	10.0	-6.4*	-8.6*	+1.0	-10.5*	-13.4*	-21.3*
CBT (XXV)	1.0	-19.3*	-16.6*	-18.3*	+4.8*	-4.3*	+13.1*
	10.0	-5.6*	-23.3*	-7.2*	-5.8*	-1.6	+6.1*
CBL (XXVI)	1.0	+7.3*	+7.3*	-4.6	-17.2*	-10.3*	-13.9*
Bis-CBC (XXVII)	10.1	-3.2	-6.4*	-2.5	-10.5*	-8.3*	-3.8
	1.0	-2.0	-10.0*	-3.3	-5.0	+1.3	-4.7

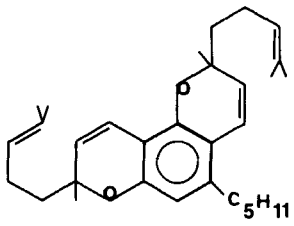
[5] See figure 3 for chemical structures.
*Denotes significantly different from controls, $p<0.05$.



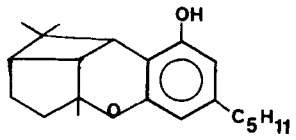
CBT (XXV)



CBC (XXIV)



Bis-CBC (XXVII)



CBL (XXVI)

Figure 3. Chemical structures of CBC and related compounds.

lowering properties at the doses tested. However, fluctuation in the activity of this group of compounds does exist. Because of the lack of CNS activity and other undesirable side effects and because of the reported anti-inflammatory properties of CBC (12,13) further testing of these compounds both in the monkey and in humans becomes worthwhile.

Other cannabinoids

Cannabinol (CBN), cannabigerol (CBG), cannabielsoin (CBE), cannabidiol (CBD), cannabidiol monomethylether (CBD-MME) were tested at different doses and their activities are shown in Table 4. While CBD, CBG and CBD-MME were inactive, CBN and CBE showed slight activity at 10.0 and 5.0 mg/kg respectively.

Table 4. Effect of Intravenous Administration of Different Cannabinoids on IOP in Normal Rabbits [6]

Compound	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls) 30 min.	60	120	180	240	300
CBN (XXVIII)	1.5	+5.5*	+3.3	-7.5*	+1.7	+10.0*	+8.6*
	10.0	+7.9*	-2.3	-9.3*	-7.9*	-5.8*	+3.3
CBG (XXIX)	1.0	0.00	+24.0*	+12.4*	+13.1*	+18.3*	+17.0*
CBE (XXX)	3.0	-	-2.6	+5.0*	+2.6	-12.7*	+3.5
	5.0	-	-13.7*	-15.4*	-4.7*	-11.1*	-1.7
CBD (XXXI)	1.0	-3.5	-2.9	+0.7	-2.8	-1.2	-5.4
	10.0	+11.9	-1.4	-3.1	+0.7	+1.1	+0.2
CBD-MME (XXXII)	1 mg/kg	-4.4	-8.2*	-0.9	+4.6	-3.8	-10.7*
	2 mg/kg	-0.1	+9.0*	-0.6	+3.2	-0.5	+2.1
	5 mg/kg	+7.5*	+2.8	-4.7	+2.0	-7.1*	-8.3*

[6] See figure 4 for chemical structures.
* Denotes significantly different from controls, $p<0.05$.

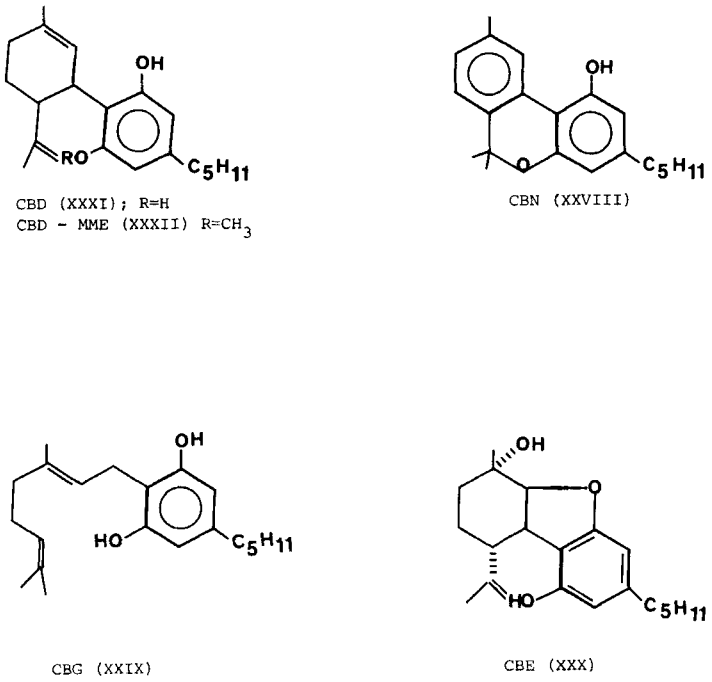


Figure 4. Chemical structures of other cannabinoids tested.

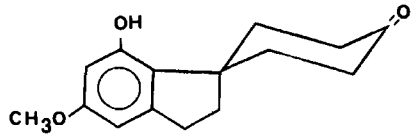
Non-cannabinoid phenols

Certain non-cannabinoid phenols were tested for possible activity in lowering IOP. These included two spiroindans (cannabispiran and dehydrocannabispiran), one dihydrostilbene (canniprene) and the cannabinoid precursor olivetol. The data shown in Table 5 indicate that the only promising compound in this group is canniprene which showed appreciable reduction in IOP at 1.0 mg/kg. Thus, canniprene and its related compounds represent a separate lead from marijuana to new antiglaucoma agents.

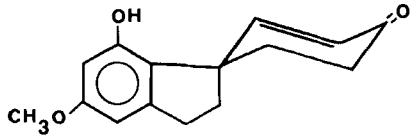
Table 5. Effect of Intravenous Administration of Certain Non-Cannabinoid Constituents of Cannabis on IOP in Normal Rabbits[7]

Compound	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls) 30 min.	60	120	180	240	300
Cannabispiran (XXXIII)	1.0	+5.4	-3.3	+5.0	-22.3*	+2.5	-2.9
Dehydrocannabispiran (XXXIV)	1.0	+2.3	-11.9*	+3.7	-12.4*	+4.6	+23.9*
Canniprene (XXXV)	1.0	-16.1*	-30.8*	-21.9*	-24.7*	-23.3*	-21.2*
	1.0	+6.6*	-12.2*	-12.2*	-7.0	+13.1*	-1.4
Olivetol (XXXVI)	1.0	+0.4	+2.3	+3.0	-0.8	-6.1	+6.8*

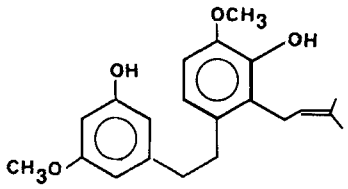
[7] See figure 5 for chemical structures.
* Denotes significantly different from controls, $p<0.05$.



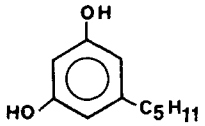
Cannabispiran (XXXIII)



Dehydrocannabispiran (XXXIV)



Canniprene (XXXV)



Olivetol (XXXVI)

Figure 5. Chemical structures of certain non-cannabinoid constituents of *Cannabis*.

Effect of topical administration of selected compounds on IOP in the rabbit

Δ^9-THC, Δ^8-THC, 9α,10α-epoxy-HHC and 9α-OH-HHC which showed significant activity by the I.V. route, were tested for their IOP lowering effects by topical application as a 1% solution in mineral oil. Table 6 shows that the 9,10-epoxide of Δ^9-THC has the most consistent ability to lower IOP followed by 9α-OH-HHC, then the epoxide acetate. Δ^9-THC and Δ^8-THC showed erratic responses and no significant activity.

It is to be noted that both the 9α,10α-epoxy-HHC and 9α-OH-HHC are much more polar than Δ^9-THC and Δ^8-THC. This property might play an important role in the partitioning of these compounds into the eye. Acetylation of the phenolic group of 9α, 10α-EHHC significantly reduces its topical activity probably as a result of the formation of

Table 6. Effect of Topical Administration of Different Cannabinoids on IOP in Normal Rabbits[8]

Compounds	Dose of 1% Sol. in Mineral Oil	% Change in IOP at Different Times (Corrected for Controls) 30min.	60	120	180	240	300
9α,10α-Epoxy-HHC (XVII)	60λ	-19.2*	-8.7*	-36.3*	-14.2*	-19.5*	-9.0*
	60λ	-1.3	-8.2*	-13.1*	-15.0*	-24.6*	-26.8*
	60λ	-11.0*	-12.9*	-19.0*	-34.0*	-26.0*	-12.9*
	60λ	-6.0*	-17.7*	-18.7*	-7.7*	-7.7*	-8.3*
Δ^9-THC (I)	60λ	-2.6	-2.3	-5.6*	+12.5*	-5.2	+4.6
Δ^8-THC (XIX)	60λ	-3.2	-9.6*	-11.7*	+7.4*	+13.1*	+1.8
9α,10α-Epoxy-HHC-Ac (XVIII)	60λ	-2.0	-1.3	-11.1*	-0.6	-16.8*	-7.3*
9α-OH-HHC (X)	60λ	+3.4	-1.1	-6.7*	-16.9*	-14.3*	-10.7*
	60λ	+14.9*	+4.1*	-2.8	-6.6*	-11.6*	-11.6*

[8]See figure 1 for chemical structures.
* Denotes significantly different from controls, $p<0.05$.

Table 7. Effect of Topical Administration of Water Soluble Derivatives of Δ^8- and Δ^9-THC on IOP[9]

Compound	Dose (mg/kg)	% Change in IOP at Different Times (Corrected for Controls) 30 min.	60	120	180	240	300
Δ^9-THC-Succ. NMG (XXXVII)	60λ (1%)	+16.5*	-8.5	-18.6*	-10.2*	-20.8*	-19.9*
	50λ (2%)	+6.9*	-9.8*	-13.3*	-15.5*	-8.4*	-8.0*
Δ^9-THC-Al-HCl (XXXVIII)	60λ (1%)	-14.7*	-26.0*	-25.3*	-23.4*	-24.5*	-38.9*
	60λ (1%)	+27.2*	-7.1*	-11.9*	-12.3*	-21.6*	-26.9*
Δ^8-THC-Succ. NMG (XXXIX)	50λ (2%)	+10.7*	-16.4*	-11.9*	-1.6	-5.8*	-14.7*
Δ^8-THC-Al-HCl (XXXX)	60λ (1%)	+44.4*	+0.8	+6.9*	-4.4	-15.3*	-23.8*

[9]See figure 6 for chemical structures.
*Denotes significantly different from controls, $p<0.05$.

the less polar acetate.

Preparation of water soluble derivatives of both Δ^9-THC and Δ^8-THC was carried out and the resulting products were tested topically for IOP lowering activity in aqueous solutions. Table 7 shows the effect of topical application of the N-methylglucamine salts of the hemisuccinate esters of Δ^9-THC and Δ^8-THC and the hydrochloride salts of the alaninate esters of both cannabinoids. Significant reduction in IOP was observed with all solutions with the Δ^9-THC derivatives being more active than the corresponding Δ^8-THC derivatives. However, in all cases an increase in IOP was observed 30 minutes after dosing. In addition, conjunctivitis was observed during the first 30-60 minutes. Work is in progress to ascertain if the initial rise in IOP and conjunctivitis could be avoided by the use of less concentrated solutions through the development of a new formulation.

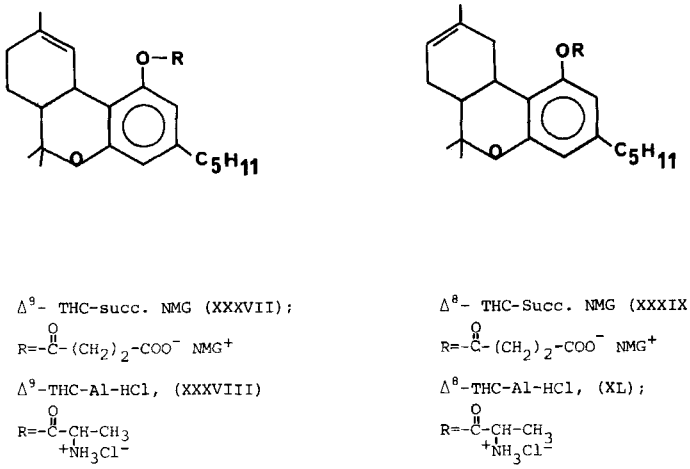


Figure 6. Chemical structure of water soluble derivatives of Δ^9- and Δ^8-THC. (NMG = N-methyl glucamine).

CONCLUSIONS

1. Δ^9- and Δ^8-THC and some of their metabolites reduce IOP by the I.V. route.

2. Among the most active cannabinoids in reducing IOP by I.V. injection are 9α, 10α-EHHC, 9α-OH-HHC, 10α-OH-Δ^8-THC and 8α, 9α-EHHC.

3. Topical application of Δ^9-THC and Δ^8-THC in mineral oil gives erratic results; however, solutions of 9α, 10α-EHHC and 9α-OH-HHC showed significant activity.

4. Water soluble derivatives of both Δ^9-THC and Δ^8-THC produce lowering of IOP but might have inherent irritant activity.

5. CBC and related compounds (CBL, CBT and Bis-CBC) showed moderate activity.

6. Canniprene (a dihydrostilbene constituent of *Cannabis*) was found to reduce IOP at 1 mg/kg. It provides a new lead for development of novel anti-glaucoma agents.

7. Among the inactive cannabinoids are CBD, CBG, $\Delta^{9(11)}$-THC, Δ^9-THC-Acid A, Δ^9-THC-Acid B, CBD-monoemethylether, 8α- and 8β-OH-Δ^9-THC, cannabiripsol and iso-cannabiripsol.

8. While hydroxylated metabolites of Δ^9-THC were found to be less active than the parent compound, those of Δ^8-THC were more active.

9. Data presented in this report confirm those findings by Green *et al.* (14) relative to Δ^9-THC, Δ^8-THC, 11-OH-Δ^8-THC, CBD, CBN, 3`-OH-Δ^9-THC, CBG and olivetol. On the other hand, while Green *et al.* (14) found 8α-OH-Δ^9-THC to be slightly active and 8β-OH-Δ^9-THC to be more active than Δ^9-THC, both hydroxylated derivatives were found inactive in this report.

10. Compounds shown to be active in lowering the IOP of the rabbit need to be tested in another animal model (e.g. the monkey) to confirm their activity.

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REFERENCES

1. Hepler, R.S. and Frank, I.M. (1971). Marihuana

smoking and intraocular pressure. *J.A.M.A.*, *217*, 1392.
2. Perez-Reyes, M., Wagner, D., Wall, M.E. and Davis, K.H. (1976). Intravenous administration of cannabinoids and intraocular pressure. In "*The Pharmacology of Marihuana*", (Eds. Braude, M.C. and Szara, S.). Pp 829-832. Raven Press, New York.
3. Purnell, W.D. and Gregg, J.M. (1975). Delta (9)-tetrahydrocannabinol, euphoria and intraocular pressure in man. *Ann. Ophthalmol.*, *7*, 921-923.
4. Green, K. and Bowman, K. (1976). Effect of marihuana derivatives on intraocular pressure in the rabbit. In "*The Pharmacology of Marihuana*", (Eds. Braude, M.C. and Szara, S.). Pp 803-813. Raven Press, New York.
5. ElSohly, M.A., Harland, E.C., Murphy, J.C., Wirth, P.W. and Waller, C.W. (1981). Cannabinoids in glaucoma: a primary screening procedure. *J. Clin. Pharmacol.*, *21*, 472S-478S.
6. Green, K. (1979). Current status of basic and clinical marihuana research in ophthalmology. In "*Symposium on Ocular Therapy*", *11*, 37-49. New York:Wiley.
7. Waller, C.W., Benigni, D.A., Harland, E.C., Bedford, J.A., Murphy, J.C. and ElSohly, M.A. (1984). Cannabinoids in Glaucoma II: The effect of different cannabinoids on intraocular pressure in the monkey. In "*The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects*", (Eds. Agurell, S., Dewey, W.L. and Willette, R.E.). Pp 869-878. Academic Press, New York.
8. West, M.E., Lockhart, A.B. (1978). The treatment of glaucoma using a non-psychoactive preparation of *Cannabis sativa*. *W.I. Med J.*, *27*, 16-25.
9. Turner, C.E., ElSohly, M.A. and Boeren, E.G. (1980). Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. *J. Nat. Prod.*, *43*, 169-234.
10. Bhattacharyya, A.K., Aulakh, C.S., Pradhan, S., Ghosh, P. and Pradham, S.N. (1980). Behavioral and neurochemical effects of Δ^9-tetrahydrocannabinol in rats. *Neuropharmacology*, *19*(1), 87-95.
11. Yamamoto, I., Narimatsu, S., Watanabe, K. and Yoshimura, H. (1981). Pharmacological activity of 8α,9α- and 8β,9β-epoxyhexanhydrocannabinol in mice. *Research Communications in Substances of Abuse*, *2*(4), 409-417.
12. Wirth, P.W., Watson, E.S., ElSohly, M.A., Turner, C.E. and Murphy, J.C. (1980). Anti-inflammatory properties of cannabichromene. *Life Sci.*, *26*, 1991-1995.
13. Wirth, P.W., Watson, E.S., ElSohly, M.A., Seidel, R., Murphy, J.C. and Turner, C.E. (1980). Anti-inflammatory activity of cannabichromene homologs. *J. Pharm. Sci.*, *69*(11), 1359-1360.
14. Green, K., Symonds, C.M., Oliver, N.W. and Elijah, R.D. (1982/1983). Intraocular pressure following systemic administration of cannabinoids. *Current Eye Research*, *2*(4), 247-253.