PACIFIC INFORMATION SERVICE ON STREET-DRUGS

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: editors

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A Mini-Review of *Cannabis sativa* (Marihuana)

Compilations of the literature on *Cannabis sativa* are available through 1970(1,2) and recent comprehensive reviews on most aspects of *Cannabis sativa* have been published (3-15). The intent of this article is to bring before the readers the current status of the constituents and biological effects in humans of grass.

Although recently the triterpenes friedelin and epifriedelanol, as well an N-(p-hydroxy-β-phenylethyl)-p-hydroxy-*trans*-cinnamamide (16), have been reported isolated from *Cannabis sativa* roots, and some incompletely characterized alkaloids have been reported from this plant (17), the constituents of interest from a pharmacological point-of-view continue to be the cannabinoids. The structures of the cannabinoids isolated to date are presented in Table 1.

The only cannabinoids of the 29 now known to have been shown definitely to have psychotomimetic properties are the Δ^8 and Δ^9-tetrahydrocannabinols. Undoubtedly, the corresponding acids of these compounds are also active, since they are decarboxylated to the respective active parent compounds during the smoking process. Although evidence is lacking, it would be surprising if eventually the methyl and propyl homologues of the tetrahydrocannabinols are not also shown to be active. Evidence to substantiate this would be primarily academic, however, since these homologues are only trace constituents of marihuana.

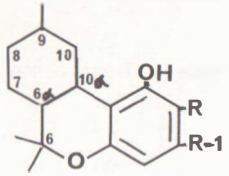
Since most of the 29 known cannabinoids have been isolated in minute amounts, they have never been evaluated for psychotomimetic effects. Indeed, it is presumptuous to presume that those cannabinoids not having the THC skeleton, are devoid of psychotomimetic effects.

It has been demonstrated that the active cannabinoids occur not only in the female, but in the male plants of *C.sativa* as well, and that practically all parts of the plant contain them (10,18,19). The highest concentrations are found in extracts of the bracts.

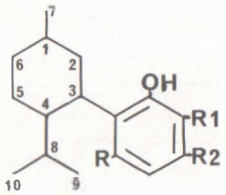
Although it is generally recognized that *Cannabis* is a monotypic genus, i.e. *Cannabis sativa* L.(Syn. *Cannabis indica*), considerable morphological variation exists between plants grown in various parts of the world. No correlations can yet be made with regard to cannabinoid content and geographic distribution, yet it is known that, for example, *C.sativa* plants of American origin are low in the active cannabinoids, whereas plants of Mexican origin are generally high in active cannabinoids. Such data are not available for plants from a large number of geographic areas. Work on this problem is undoubtedly underway and it should not be long before these data are available.

Similarly, because of the obvious morphological variation in *C.sativa* plants that have been examined to date, it would not be surprising if some botanist having access to adequate samples did not reclassify *C.sativa* into a number of varieties or sub-species. It would indeed be unfortunate if such a classification were proposed without due consideration for the obvious phenotypic nature of the chemical variation that also exists in this plant (19).

Table 1 - Structures of Cannabinoids from *Cannabis sativa* L.

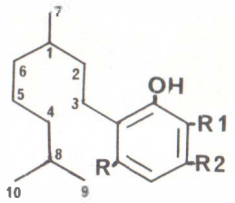


Cannabinoid	R	R-1	Other
Δ^9-Tetrahydrocannabinol	H	C_5H_{11}	$\Delta^{9,10}$
Δ^9-Tetrahydrocannabiorcol	H	CH_3	$\Delta^{9,10}$
Δ^9-Tetrahydrocannabivarin	H	C_3H_7	$\Delta^{9,10}$
Δ^9-Tetrahydrocannabivarinic Acid	COOH	C_3H_7	$\Delta^{9,10}$
Δ^9-Tetrahydrocannabinolic Acid	COOH	C_5H_{11}	$\Delta^{9,10}$
Δ^8-Tetrahydrocannabinol	H	C_5H_{11}	$\Delta^{8,9}$
Cannabinol	H	C_5H_{11}	$\Delta^{6\alpha,7};\Delta^{8,9};\Delta^{10,10\alpha}$
Cannabivarin	H	C_3H_7	$\Delta^{6\alpha 7};\Delta^{8,9};\Delta^{10,10\alpha}$
Cannabiorcol	H	CH_3	$\Delta^{6\alpha,7};\Delta^{8,9};\Delta^{10,10\alpha}$
Cannabinolic Acid	COOH	C_5H_{11}	$\Delta^{6\alpha 7};\Delta^{8,9};\Delta^{10,10\alpha}$

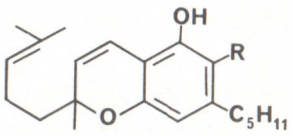


Cannabinoid	R	R-1	R-2	Other
Cannabidiol	OH	H	C_5H_{11}	$\Delta^{1,2};\Delta^{8,9}$
Cannabigerol	OH	H	C_5H_{11}	$\Delta^{1,2};\Delta^{8,9}$
Cannabidiolic acid	OH	COOH	C_5H_{11}	$\Delta^{1,2};\Delta^{8,9}$

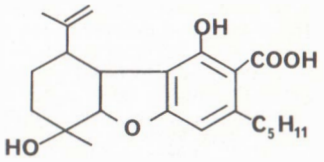
Cannabinoid (cont.)	R	R-1	R-2	Other
Cannabidiol monomethyl ether	OCH_3	H	C_5H_{11}	$\Delta^{1,2};\Delta^{8,9}$
Cannabidiolic Acid monomethyl ether	OCH_3	COOH	C_5H_{11}	$\Delta^{1,2};\Delta^{8,9}$
Cannabidivarin	OH	H	C_3H_7	$\Delta^{1,2};\Delta^{8,9}$
Cannabidivarinic Acid	CH_3	COOH	C_3H_7	$\Delta^{1,2};\Delta^{8,9}$
Cannabidiorcol	OH	H	CH_3	$\Delta^{1,2};\Delta^{8,9}$



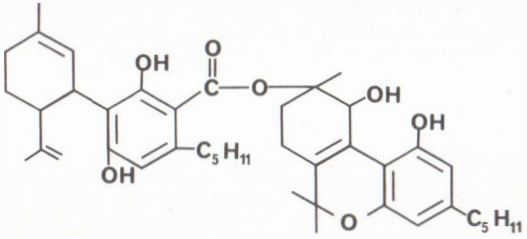
Cannabinoid	R	R-1	R-2	Other
Cannabigerol monomethyl ether	OCH_3	H	C_5H_{11}	$\Delta^{1,2};\Delta^{4,8}$
Cannabigerolic Acid	OH	COOH	C_5H_{11}	$\Delta^{1,2};\Delta^{4,8}$
Cannabigerolic Acid monomethyl ether	OCH_3	COOH	C_5H_{11}	$\Delta^{1,2};\Delta^{4,8}$



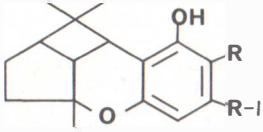
Cannabinoid	R
Cannabichromene	H
Cannabichromenic Acid	COOH



Cannabielsoic Acid



Cannabidiolic Acid Tetrahydrocannabitriol Ester



Cannabinoid	R	R-1
Cannabicyclol (Cannabipinol)	H	C_5H_{11}
Cannabicyclolic Acid	COOH	C_5H_{11}

Marihuana is an aphrodisiac, it produces organic brain damage, facilitates creative thinking, induces respiratory disorders, is toxic to the liver, euphoric, distorts the senses, dilates the pupil with reddening of the conjunctival sac, increases heart rate, swells the uvula, disturbs motor control, sensitizes skin to acne, precipitates paranoia, etc. These are some of the terms used in the claims and counterclaims of today's emotional drug maelstrom, fomented by almost daily articles in lay and pseudoscientific publications. As should have been learned from experiences with earlier "miracle drugs" (penicillin, krebiozen, DMSO) subjective opinions can only confound, not resolve, controversy. Relatively few well-designed animal and especially clinical experiments have been performed with marihuana or hashish. Unfortunately, lay impatience, spurred on by overly-zealous journalism and TV, has not provided enough time in which to perform the definitive objective experiments needed so badly. This does not mean that conclusions cannot now be drawn but, in many cases, such conclusions are, at best, only tentative, pending the results of more and better designed experiments.

Controversy exists as to whether marihuana is a "true" aphrodisiac (i.e. induces increased libido) or whether it exhibits a sedative or anti-anxiety ("disinhibitory") effect, more similar to that of alcohol. However, little argument can be made with the claim that marihuana enhances sexual pleasure in a manner more satisfying than alcohol, amphetamines or cocaine - usually considered the more sexually stimulating of drugs (2,20-23). The enhancement appears to be due in part to a "disinhibitory" effect, similar to moderate sedative doses of alcohol. In addition, marihuana appears to provide increased sensory awareness: color, sound and texture as well as other modalities appear to be enhanced with the use of marihuana. Feelings of general body warmth, brotherhood, empathy and oneness with others (also common responses to alcohol use) are sensations reported as contributing to more pleasurable sexual relationships. However, the general and genital anesthesia reported with alcohol, resulting in reduced performance, is not nearly as frequent an occurrence with marihuana, providing individual level of intoxication is titrated by the number of inhalations or "tokes" in a manner analogous to drinks of alcohol. The disinhibitory effect seems to produce a degree of brief euphoria and certainly relief from anxiety (22).

One of the more significant findings has been the number of chronic marihuana smokers who have developed tolerance to marihuana, as evidenced by requiring 100 or more grams of marihuana per month (24). This is in agreement with earlier reports of tolerance developing in mice, rats, pigeons, chicks and monkeys (25). Physical withdrawal syndromes to injected THC have been reported for pigeons and monkeys but, to date, not in man. This question may be answered soon if the current European trend to use the five to ten times more potent hashish occurs in the U.S. as expected (24).

Often times, the drug user miscontrues the psychic responses (i.e. hallucinations, sensual alterness, judgements, etc.) as being caused by mechanisms entirely different from those precipitating physical responses. Psychic and physical responses to drugs are the result of drug-induced alterations in physico-biochemical body reactions. To assume otherwise is contrary to long established physiologic and pharmacologic knowledge and fosters within the user a false sense of security that a drug-induced psychic response is not as serious as a drug-induced change, say in heart rate or blood pressure. One of the major differences between psychic and physical drug responses is

our lack of definitive knowledge of how altered physico-biochemical reactions affect motivations and emotions and vice-versa: particularly when, in contrast, knowledge of the biochemical mechanisms regulating, say cardiac function, is progressing reasonably well.

In spite of dramatic claims to the contrary (23,26,27), no well-designed experimental data exist showing that marihuana (or THC) produces organic brain damage, although considerable evidence is accumulating that marihuana may produce more psychic and physical depressions than users acknowledge (20,28-30). Attention span is reduced, brief loss of memory may occur, as well as possibly a decreased rate of learning. The user has an inflated opinion of his mental and physical capabilities, which in combination with poorer critical judgements plus modest hallucinations, particularly with lights and sounds, and some reduced motor performance, makes for a potentially hazardous car driver: a problem of major concern and many mixed opinions (3,20,21). Most opinions seem to support the view that marihuana induced impaired driver performance may be a contributing factor in automobile accidents, although the exact nature and degree of marihuana effect is still the subject of much controverisal experimentation involving questionable simulated methodology short of actual street driving tests. Resolution of this controversy should be forthcoming, since much pressure is being applied to political, legislative and health officials.

It is interesting to note that all of the psychic responses to marihuana listed in Table 2 can be explained on the basis of a disinhibitory (or sedative) activity. Many investigators regard the mild hallucinations as being more a state of brief euphoria resulting from removal of inhibitions and anxiety feelings, and therefore more similar to alcohol depression, than LSD hallucinations. Increased sensual awareness may be the consequence of removal of competitive central nervous activity (i.e. decreased cerebral thought processes and peripheral motor activity) thereby permitting greater numbers of external sensory stimuli to be received and responded to centrally.

Another psychic consequence of chronic marihuana usage is a tendency to decrease long-range planning and "live for today". As a consequence, educational and occupational goals become of secondary importance with a corresponding increase in school and work inefficiency and absenteeism, and eventually rejection by their peer groups (3,21,26). These drop-outs must then find new ways for receiving social acceptance and personal identification. Thus they seek out a new peer group with similar problems and frequently involving drugs as part of the solution to their daily problems. Here then is the central point of this controversy. Society calls such a marihuana peer group (drug culture) as being non-productive for society in spite of the peer group's claim to greater intellectual creativity. The marihuana peer group states that because of the lowered tensions, increased sensual awareness and stimulated intellectual creativity, each person now becomes more productive individually and thus can now contribute to that particular drug culture. Resolution of this intellectual dichotomy will be helped more by philosophical and political facts than by pharmacological data.

Scattered throughout the literature are numerous suggestions that smoking marihuana produces, in addition to many behavioral and psychological effects, certain physical effects-perhaps the most notable being respiratory

Table 2 - Human Responses to Smoked Marihuana

Parameter	Response
Habituation	Yes
Tolerance	Maybe
Psychic dependence	Yes
Physical dependence	No*
Psychic:	
Hallucinations	Mild
Euphoria	Brief
Toxic psychoses	No*
Sensual Awareness	Increased
Learning rate	Decreased
Memory	Brief loss
Attention span	Shortened
Judgement	Poor
Long-range planning	Decreased
Self-opinions	Inflated
Flashbacks	No*
Physical:	
EEG activity	Slowed
Sedation	Yes
Analgesia	Maybe*
Blood pressure	Increased
Heart rate	Increased
Respiratory rate	Normal
Respiratory depth	Irregular
Rales	Yes
Uvula	Swollen
Mouth	Dry
Nausea, anorexia	Yes
Body weight	Loss
Emesis	Maybe*
Gastrointestinal motility	Increased
Diarrhea	Yes
Pupillary size	Increased
Conjunctival vessels	Dilated
Body temperature	Reduced
Motor activity	Reduced
Motor performance	Poor
Blood glucose levels	Normal
Hepatotoxicity	No

NOTE: * = controversial

disorders such as bronchitis, asthma and oropharyngitis (3,21,24). Bronchial complaints are chiefly bronchitis with dyspnea, productive cough, rales and wheezing. Chest X-rays and sputum cultures are essentially normal. The patients are frequently disabled to the point of being unable to work and may occasionally require hospitalization. Antibiotic therapy does not help. Only a decrease in marihuana consumption has appreciably improved their respiratory symptoms (24).

X-rays reveal sinus congestion in hearly all cases, although pain is minimal. Antibiotics with nasal decongestants usually resolve the rhinopharyngitis, although continued smoking brought reoccurrence as does renewed smoking in marihuana-induced bronchitis and asthmatic attacks. Uvular edema, a common concurrence with marihuana-induced bronchitis and/or rhinopharyngitis, can be a useful diagnostic sign, more reliable than cardiac or conjunctival signs of a marihuana smoker (24).

Many young chronic marihuana smokers develop acne and seborrheic dermatitis, but it is difficult to relate these entities specifically to marihuana, as poor personal hygiene in drug users may be as responsible as THC (32).

Diarrhea, abdominal cramps and emesis have been observed in laboratory animals as well as in humans smoking or receiving intravenous marihuana products. Weight loss usually accompanies the above noted gastrointestinal complaints (24).

Marihuana smoking, particularly by subjects without previous experience, causes an increased heart rate and an increase in peripheral blood flow through arms and legs due to dilatation of the blood vessels. The vasodilatation results in sufficient blood flow through the skin to result in a drop in body temperature through skin heat loss--a definite hazard to scuba divers, skiers or any person who spends time outdoors in a cool or cold environment. Still another similarity between marihuana and ethanol activities. The currently accepted mechanism for this cardiovascular response necessitates considerable caution in the concurrent administration of vasoactive drugs such as amyl nitrite or anesthetics like ethers and alcohol to those persons who may have been smoking marihuana (20,33-38). The field of drug interactions with marihuana is just beginning to be explored, but the potential list of interactions is every bit as large as the known drug interactions with alcohol. Herein lies perhaps the greatest potential hazard of marihuana today: interactions with other drugs-a hazard aggrevated by the lack of much experimental activity at this time.

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News & Comment

Recently the Bureau of Narcotics and Dangerous Drugs (BNDD) have published* the results of analysis of 49,000 "Street-Drug" samples. The results, as reported, are similar to those reported by the various street-drug monitoring programs. Psilocybin usually LSD, THC non-existant (83% were PCP), cocaine mixed with local anesthetics, LSD the most frequently encountered drug.

> "LSD is the drug most often identified in substances alleged or suspected of being something else..... In the number of different kinds of drugs falsely represented, both LSD and PCP tie in first place, heroin is second, and methamphetamine is third."

*Johnson, D. W. and J. W. Gunn. 1972. Dangerous Drugs: Adulterants, Diluents, and Deception in Street Samples. J. Foren. Sci., 17(4): 629-639.

Seventeen samples of alleged THC have been submitted to our laboratory -- results -- 14 PCP, 1 Librium, 2 no drug detected. Two samples alleged to be "Super Weed" were identified as Parsley treated with PCP. Angel's Dust was potent PCP.

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