Cannabis and Cannabinoids
Pharmacology, Toxicology, and Therapeutic Potential

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Ethan Russo
Editors

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Preface

> I wish to propose for the reader's favourable consideration a doctrine which may, I fear, appear wildly paradoxical and subversive. The doctrine in question is this: that it is undesirable to believe a proposition when there is no ground whatever for supposing it true.
>
> Bertrand Russell
> From "Introduction:
> On the Value of Scepticism"
> *Sceptical Essays,* 1928

Cannabis is still sending *"signals of misunderstanding."*[1-3] The result is an exaggeration of beneficial or deleterious effects as well as occasional intermixture of medical science with other moral categories.

This book deals with health aspects of the cannabis plant and the cannabinoids while mainly factoring out societal aspects. Some authors refer to social topics that require discussion even within the bounds of a narrow handling of medicinal aspects.

Scientists with different views on the therapeutic benefits of cannabis and with different assessments of potential harms get a hearing, so that the book reflects and considers the frictions and controversies surrounding many themes in this area.

The different opinions and judgments, often only reading between the lines, possibly result in a deeper insight into the controversial aspects of this topic than a more homogenous book might allow. At the same time, it was the intention of the editors to offer a clearly structured overview of the subject, as well as an insight into many facets of modern cannabinoid research. Leading experts in their fields have contributed to this volume. Most are members of the International Cannabinoid Research Society, which includes about 200 scientists. Some of them are also members of the International Association for Cannabis as Medicine, which deals particularly with the medical use of cannabis and the cannabinoids.

We would like to cordially thank all authors for their pleasant cooperation in contributing their texts to the project. We were particularly glad to have their many proposals for additional topics and suggested modifications. These completed and significantly improved the manuscript from concept to final realization. For their assistance in translation work and in

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Franjo Grotenhermen
Ethan Russo

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Chapter 1

Botany of Natural *Cannabis* Medicines

Robert C. Clarke
David Paul Watson

INTRODUCTION

Cannabis is among the very oldest of economic plants, providing fiber, edible seed, and drug resin. Human selection for varying uses and natural selection pressures imposed by diverse climates have resulted in a wide variety of growth forms and chemical compositions. Innovative classical breeding techniques have been used to improve drug cannabis, resulting in many cannabinoid-rich cultivars suitable for medical use. The production of cannabinoids is unique to *Cannabis,* and cultivars with specific chemical profiles are being developed for diverse potential pharmaceutical uses.

NATURAL LIFE CYCLE

Cannabis is an annual plant, propagated from seed, and grows vigorously in open sunny environments with light, well-drained soil and ample nutrients and water, and reaches up to five meters (16 feet) in height in a four- to six-month growing season. Feral *Cannabis* populations are frequently found in association with human habitation. Agricultural lands, roadsides, exposed riverbanks, meadows, and disturbed lands are ideal habitats for wild and feral *Cannabis,* as they provide adequate sunlight.

Seeds usually germinate in three to seven days. During the first two to three months of growth juvenile plants respond to increasing day length with more vigorous vegetative growth characterized by an increasing number of leaflets on each leaf. Later in the season (after the summer solstice), shorter days (actually longer nights) induce flowering and complete the life cycle (see Figure 1.1). Cannabis begins to flower when exposed to short day

FIGURE 1.1. Close-Up Photo of a *Cannabis* Inflorescence, with Each Seed Concealed Within a Perigonal Bract Covered with Glandular Trichomes

lengths of 12 to 14 hours or less (long nights of 10 to 12 hours or more) depending on its latitude of origin. However, a single evening of interrupted darkness can disrupt flowering and delay maturation. If an individual plant is not crowded by its neighbors, as is the case for the crops intended for seed or drug production, flower-bearing limbs will grow from small buds located at the base of the leaf petioles originating from nodes along the main stalk. The flowering period is characterized by leaves bearing decreasing numbers of leaflets.[1]

Cannabis is normally a dioecious plant, with male and female flowers developing on separate plants. The sexes of *Cannabis* are anatomically indistinguishable before they begin flowering. However, Mandolino and Ranalli[7] report success using RAPD analysis to identify male-specific DNA markers. The development of male and female plants varies greatly. The male flowers hang in loose clusters along a relatively leafless upright branch, in contrast to crowded clusters of individual female flowers at the base of each leaf along the branch. Male *Cannabis* flowers require air currents to carry pollen grains to the female flowers, which results in fertilization and consequent seed formation. The male plants finish shedding pollen and die before the seeds in the female plants ripen four to eight weeks after being fertilized. Pollen has been frozen and successfully used for seed production up to three years later.

The single seed in each female flower ripens in about three to eight weeks and will either be harvested by humans, eaten by birds or rodents, or drop to the ground. A large female plant can produce over one kilogram of seed. This completes the natural four to six month life cycle. If the seeds are not consumed by birds or rodents, they may germinate the following spring. *Cannabis* seeds are a balanced source of essential fatty acids (EFAs), and easily digestible protein and are usable as human food or animal feed (see Chapter 38). EFAs have been shown to have many important physiological roles and hemp seed oil is a valuable nutraceutical.[3]

AGRICULTURAL FIELD PRODUCTION

For hemp crops grown for fiber or seed, both male and female plants are usually left in the field until harvest. The male plants pollinate the females and then die before the seeds ripen. In the early 1970s, a handful of North American marijuana cultivators began to grow *sinsemilla* (Spanish for "without seed") marijuana. The sinsemilla effect is achieved by eliminating staminate plants from the fields, leaving only the unfertilized pistillate plants to mature for later harvest. In lieu of setting seed in the earliest flowers, the pistillate plants continue to produce additional flowers, which are covered by resin glands, thus increasing the percentage of psychoactive and medically valuable Δ^9-tetrahydrocannabinol (THC) or other cannabinoids.

This technique was originally developed in India, but historians are unsure of its history prior to 1800. Since 1975, sinsemilla has been the primary style of North American and European marijuana production.

Throughout the 1980s, the vast majority of domestically produced North American drug cannabis was grown outdoors, but in the 1990s the popularity of growing in greenhouses and indoors under artificial lights rapidly expanded. Crops grown from seed make large plants of both genders that take up a lot of space, and exhibit a range of characteristics. A *Cannabis* breeder relies on this variation as potential to improve varieties. However, a drug cannabis producer wants a profitable and uniform crop, and uses female clones that improve grow room yields, but preclude the possibility of seed production and varietal improvement.

VEGETATIVE CROP PRODUCTION

Much of the *Cannabis* presently used for medical purposes is grown indoors under artificial lights. Metal halide and sodium vapor light systems are most often set up in attics, bedrooms, or basements. Most modern indoor growers produce vegetatively propagated crops. Only female drug *Cannabis* plants are economically valuable, and garden space is limited. It is both difficult and expensive to purchase reliable drug *Cannabis* seed, sales of which are prohibited in many nations. In addition, the legal systems of many nations penalize growers of large quantities of cannabis with harsher penalties. Under artificial growing conditions, crops are reproduced vegetatively by rooting cuttings of only female plants, transplanting and inducing flowering almost immediately. Cuttings taken from one plant are all identical members of a single clone and they will all respond in the same way to environmental inputs. Given that environmental influences are constant, the clone will yield a uniform crop of nearly identical seedless females each time it is grown.

Female "mother" plants are maintained in a constantly vegetative state under 18 hour or longer day lengths. Serial cuttings can be removed, rooted, grown under long day length and used to replace older mother plants, indefinitely. If the cutting material remains free of viruses or other pathogens there is no loss of vigor after multiple rounds of vegetative propagation. Whenever they are required, rooted small cuttings (10 to 30 cm tall) are moved into a flowering room with a day length of 10 to 13 hours, to mature 7 to 14 weeks later.

Cloned plants can mature fully, form flowers from top to bottom and look like a rooted branch from a large plant grown from seed when they are less than one meter tall. The length of time between the induction of flowering under short days and final maturity of the female floral clusters depends largely on the variety being grown and the day length. Some cultivars ma-

ture much more quickly than others. Cannabis plants mature faster when they are given shorter day lengths of 10 hours, but most cultivars have an optimum day length requirement, for maximum production, of around 12 or 13 hours. Under ideal conditions, yields of dried floral clusters can reach 1,200 grams per square meter per year or more, as a result of multiple cropping three or five times per year.

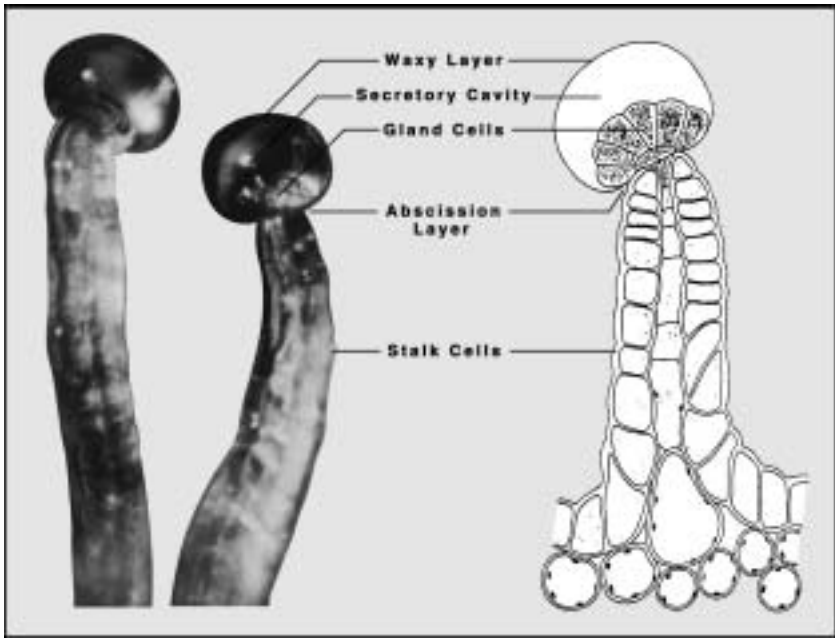
Male plants can also be kept in a vegetative state and induced to flower when pollen is required. However, they are often more difficult to revert from flowering to the vegetative state than females. In vitro techniques would allow long-term storage of wide varieties of living germplasm. Several research groups have reported success[6,7] with reproducing undifferentiated callus tissue and meristems.

RESIN GLAND DEVELOPMENT

When resin gland development commences, the medically important cannabinoids and the associated terpenoids begin to appear (see Figure 1.2). Terpenoids are the primary aromatic principles found in the essential oil of *Cannabis,*[5,10] although cannabinoids are odorless. Most interesting medically, are the cannabinoid-rich terpenoid secretions of the head cells of glandular hairs distributed across the surface of the female inflorescence. (Male plants are usually of no consequence for drug production, as they have few glandular trichomes.) Solitary resin glands most often form at the tips of slender trichome stalks which form as extensions of the plant surface. The cluster of one or two dozen head cells atop each stalk secrete aromatic terpenoid-containing resin with a very high percentage of cannabinoids (≥80 percent) which collect under a thin waxy membrane surrounding the secretory head cells.[2] The secreted resin component is, in large part, segregated from the secretory cells. This isolates the resin from the atmosphere as well as membrane-bound enzyme systems within the secretory cells, possibly protecting the terpenoids and cannabinoids from oxidative degradation and enzymatic change. At the base of each cluster of resin head cells lies an abscission layer allowing the gland and its secreted resin to be easily removed. *Cannabis* resin (hashish or charas) is simply formed from resin glands that have been rubbed or shaken from the plant and compressed into a dense mass.[2]

Resin glands containing cannabinoids and terpenoids may have an adaptive significance for the *Cannabis* plant as defense against environmental challenges, including insect and fungal attack.[9] However, *Cannabis* crops are still subject to infestation by a wide variety of pests, particularly under greenhouse conditions.[8] Certainly, the intoxicating effects of this *Cannabis* resin have increased cannabis predation by humans, as well as encouraged its domestication, thus dramatically widening its distribution.

FIGURE 1.2. Microscope Photograph and Drawing of a Cannabis Resin Gland, with Secretory Head Cells Easily Visible Underneath the Transparent Cannabinoid- and Terpenoid-Rich Resin

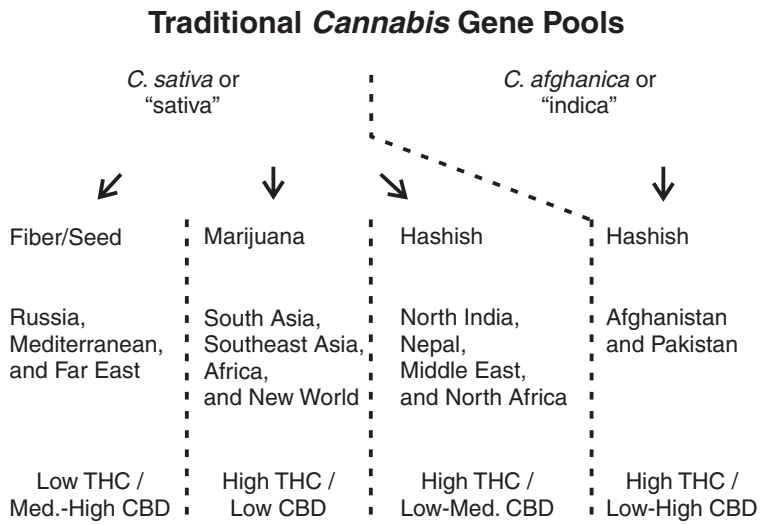


Source: Drawing from RC Clarke. *Hashish!* Los Angeles: Red Eye Press, 1998. Photo courtesy of Joop the Crystal Man.

CANNABIS *ORIGINS*

Cannabis likely originated in Central Asia or near the Altai or the Tian Shan mountains and was first cultivated in China and soon after in India. Different cultures have traditionally used cannabis for a variety of purposes (see Figures 1.3 and 1.4). European and eastern oriental societies most often used cannabis for its strong fibers and nutritious seeds. Races of fiber and seed *Cannabis* are nearly always relatively low in THC, with an approximately twofold cannibidiol (CBD) content averaging about twice as high. THC is the primary psychoactive compound produced by cannabis. Nonpsychoactive CBD is the other most common naturally occurring cannabinoid. African, Middle Eastern, South Asian, and Southeast Asian cultures used cannabis widely for its psychoactive properties and to a lesser extent for fiber and food.

FIGURE 1.3. The Four Major *Cannabis* Gene Pools



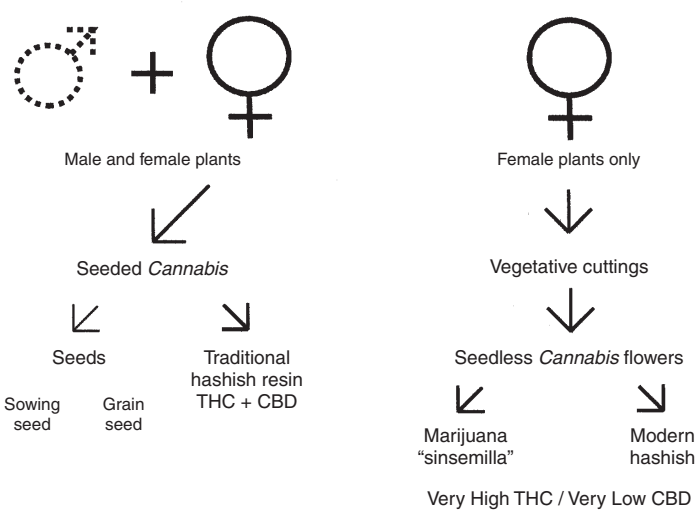
Most modern medical *Cannabis* varieties are a blend of traditional "sativa" marijuana varieties with "indica" hashish varieties.

Source: Adapted from Meijer de EPM. *Cannabis* germplasm resources. In Ranalli P, ed. *Advances in Hemp Research.* Binghamton, NY: The Haworth Press, 1999, pp. 133-151; and from Clarke RC, *Hashish!* Los Angeles: Red Eye Press, 1998.

Note: The traditional *Cannabis* gene pools originate either from *C. sativa,* which comprises the vast majority of naturally occurring hemp and drug land races, or from *C. afghanica* from Afghanistan and Pakistan, which is commonly called "indica" and has become a component in many modern drug *Cannabis* cultivars.

The vast majority of the varieties from these regions are high in psychoactive THC (often 5 to 10 percent) with a widely varying CBD content (usually nil, but often up to 5 percent). The South Asian section of the *Cannabis* gene pool was spread by humans far and wide from Africa to Sumatra by early traders and eventually to the equatorial New World. Cannabis was adopted in many of these locations and improved as a psychoactive drug plant. All modern drug varieties used as medical cannabis are derived from these traditional drug varieties.

FIGURE 1.4. Recreational and Medical *Cannabis* Sources



Note: Both recreational and medical *Cannabis* typically available to users either originate from seeded field-grown plants used primarily for hashish production or seedless plants grown primarily for "sinsemilla" and occasionally for modern "high-tech" hashish.

CANNABIS *TAXONOMY*

Modern taxonomists have variously characterized *Cannabis.* All taxonomists recognize the species *Cannabis sativa*. Small and Cronquist[13] subdivide *C. sativa* into two subspecies each with two varieties. Schultes et al.[11] divide *Cannabis* into three species; *C. sativa, C. indica,* and *C. ruderalis*. Several other researchers do not preserve *C. ruderalis,* but recognize both *C. sativa* and *C. indica*.[12,14,15] The present authors consider *C. sativa* to circumscribe all wild, hemp, and drug *Cannabis* races with the possible exception of the races used for hashish production in Afghanistan and Pakistan. These morphologically and chemically distinct races may deserve the separate specific name of *C. afghanica* following the variety name for *C. indica* determined by Vavilov.[14] Validation of this theory awaits further chemotaxonomic and genetic research.

In all of these systems, *C. sativa* represents the largest and most diverse taxon. *C. afghanica* is commonly referred to by marijuana breeders and

growers, as well as medical cannabis users, as "indica." Chemovars of this variety have their own distinctive acrid organic aromas and are often rich in CBD as well as THC. The great variety of chemical, physiological, and morphological traits encountered in *Cannabis* has proven very attractive to plant breeders for years.

MEDICAL CANNABIS *TODAY*

Drug *Cannabis* available to the medical user can be assigned to one of two categories. Marijuana (domestically produced and imported cannabis flowers) is nearly always grown from high-THC varieties (up to 20 to 25 percent dry weight in trimmed female flowers) containing very little CBD. Hashish or charas (compressed cannabis resin) is made from varieties that are predominantly THC (up to 10 percent), but they often contain up to 5 percent CBD. Clean high-THC profiles result from marijuana growers making seed selections from individual favorable plants with high THC levels. Hashish is produced by bulk processing large numbers of plants, and, therefore, growers are unable to make seed selections from individual particularly potent plants so the CBD level tends to remain at more natural limits. Hashish cultivars are bred for resin quantity rather than potency, so the farmer selects plants and saves seeds by observing which ones produce the most resin, rather than if it contains THC or CBD. Afghan populations contain approximately 25 percent plants that are rich in CBD with little THC, 50 percent that contain both CBD and THC, and 25 percent that contain little CBD and are rich in THC. CBD is suspected of having effects on the primary psychoactive compound THC and in a medical setting it may also have useful modulating effects on THC or valuable effects of its own. However, analytical surveys of 80 *Cannabis* varieties in the Netherlands (D.W. Pate, personal communication, 1999) and 47 samples in California[4] show that nearly every sample contained predominantly THC usually with less than 5 percent of the other combined cannabinoids. Higher levels of THC and other medically effective cannabinoids and terpenoids are healthier for patients using smoked cannabis as they can smoke less to achieve the same dosage and effect.

MEDICAL CANNABIS *TOMORROW*

Cannabis breeders are continually searching for new sources of exotic germplasm and will develop new varieties that prove particularly effective as medicines. Pure "indica" varieties are still highly prized breeding stock and new "indica" introductions from Central Asia are occasionally re-

ceived. *C. sativa* varieties from South Africa have recently gained favor with breeders, as they mature early.

HortaPharm BV in the Netherlands has an ongoing breeding project to develop high-yielding *Cannabis* cultivars of known cannabinoid profile. The aim of the project is to create varieties that produce only a single one of the four major cannabinoid compounds (e.g., THC, CBD, CBC, CBG, or their propyl homologues) as well as selected varieties with predictable mixed cannabinoid profiles. Some of these single cannabinoid varieties are being commercially exploited by GW Pharmaceuticals Ltd. in England, which began clinical trials in 1999 with whole cannabis extracts.

CONCLUSION

Largely as a response to political pressure and the limited availability of high quality commercial cannabis, the home growing of this crop, whether for medical or recreational use, is a trend rapidly spreading across North America and Europe. Cannabis smoking and cultivation for personal medical use will eventually be legalized or tolerated in many places, if not by the public openly favoring marijuana legalization, then by increasing awareness of the advantages of this potentially useful medicine.

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