Marijuana and the Cannabinoids

FORENSIC SCIENCE AND MEDICINE

Steven B. Karch, MD, SERIES EDITOR

HERBAL PRODUCTS: *TOXICOLOGY AND CLINICAL PHARMACOLOGY, SECOND EDITION,* edited by ***Richard L. Kingston and Timothy S. Tracy,*** *2007*

CRIMINAL POISONING: *INVESTIGATIONAL GUIDE FOR LAW ENFORCEMENT, TOXICOLOGISTS, FORENSIC SCIENTISTS, AND ATTORNEYS, SECOND EDITION,* by ***John H. Trestrail, III,*** *2007*

FORENSIC PATHOLOGY OF TRAUMA: *COMMON PROBLEMS FOR THE PATHOLOGIST*, by ***Michael J. Shkrum and David A. Ramsay,*** *2007*

MARIJUANA AND THE CANNABINOIDS, edited by ***Mahmoud A. ElSohly,*** *2006*

SUDDEN DEATHS IN CUSTODY, edited by ***Darrell L. Ross and Theodore C. Chan,*** *2006*

THE FORENSIC LABORATORY HANDBOOK: *PROCEDURES AND PRACTICE*, edited by ***Ashraf Mozayani and Carla Noziglia,*** *2006*

DRUGS OF ABUSE: *BODY FLUID TESTING,* edited by ***Raphael C. Wong and Harley Y. Tse,*** *2005*

A PHYSICIAN'S GUIDE TO CLINICAL FORENSIC MEDICINE: *SECOND EDITION,* edited by ***Margaret M. Stark,*** *2005*

FORENSIC MEDICINE OF THE LOWER EXTREMITY: *HUMAN IDENTIFICATION AND TRAUMA ANALYSIS OF THE THIGH, LEG, AND FOOT,* by ***Jeremy Rich, Dorothy E. Dean, and Robert H. Powers,*** *2005*

FORENSIC AND CLINICAL APPLICATIONS OF SOLID PHASE EXTRACTION, by ***Michael J. Telepchak, Thomas F. August, and Glynn Chaney,*** *2004*

HANDBOOK OF DRUG INTERACTIONS: *A CLINICAL AND FORENSIC GUIDE,* edited by ***Ashraf Mozayani and Lionel P. Raymon,*** *2004*

DIETARY SUPPLEMENTS: *TOXICOLOGY AND CLINICAL PHARMACOLOGY,* edited by ***Melanie Johns Cupp and Timothy S. Tracy,*** *2003*

BUPRENORPHINE THERAPY OF OPIATE ADDICTION, edited by ***Pascal Kintz and Pierre Marquet,*** *2002*

BENZODIAZEPINES AND GHB: *DETECTION AND PHARMACOLOGY*, edited by ***Salvatore J. Salamone,*** *2002*

ON-SITE DRUG TESTING, edited by ***Amanda J. Jenkins and Bruce A. Goldberger,*** *2001*

BRAIN IMAGING IN SUBSTANCE ABUSE: *RESEARCH, CLINICAL, AND FORENSIC APPLICATIONS*, edited by ***Marc J. Kaufman,*** *2001*

TOXICOLOGY AND CLINICAL PHARMACOLOGY OF HERBAL PRODUCTS, edited by ***Melanie Johns Cupp,*** *2000*

CRIMINAL POISONING: *INVESTIGATIONAL GUIDE FOR LAW ENFORCEMENT, TOXICOLOGISTS, FORENSIC SCIENTISTS, AND ATTORNEYS,* by ***John H. Trestrail, III,*** *2000*

Marijuana and the Cannabinoids

Edited by

Mahmoud A. ElSohly, PhD

The School of Pharmacy, The University of Mississippi;
ElSohly Laboratories Inc., Oxford, MS

Humana Press Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

www.humanapress.com

Production Editor: Melissa Caravella

Cover design by Patricia F. Cleary

Cover Illustration: Medical *Cannabis* cultivar (Fig. 1, Chapter 1; *see* complete caption on p. 3).

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: orders@humanapr.com; or visit our Website: www.humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eIBSN 1-59259-947-8

Library of Congress Cataloging-in-Publication Data

Marijuana and the cannabinoids / edited by Mahmoud A. ElSohly.
p. ; cm. -- (Forensic science and medicine)
Includes bibliographical references and index.
ISBN 1-58829-456-0 (alk. paper)
1. Cannabinoids. I. ElSohly, Mahmoud A. II. Series.
[DNLM: 1. Cannabinoids. 2. Cannabis. QV 77.7 M33515 2006]
QP801.C27M355 2006
615'.7827--dc22

2006012285

Preface

Although primarily used today as one of the most prevalent illicit leisure drugs, the use of *Cannabis sativa* L., commonly referred to as marijuana, for medicinal purposes has been reported for more than 5000 years. Marijuana use has been shown to create numerous health problems, and, consequently, the expanding use beyond medical purposes into recreational use (abuse) resulted in control of the drug through international treaties.

Much research has been carried out over the past few decades following the identification of the chemical structure of THC in 1964. The purpose of *Marijuana and the Cannabinoids* is to present in a single volume the comprehensive knowledge and experience of renowned researchers and scientists. Each chapter is written independently by an expert in his/her field of endeavor, ranging from the botany, the constituents, the chemistry and pharmacokinetics, the effects and consequences of illicit use on the human body, to the therapeutic potential of the cannabinoids.

Mahmoud A. ElSohly, PhD

Contents

Contributors

RUDOLF BRENNEISEN, PhD • Department of Clinical Research, Laboratory for Phytopharmacology, Bioanalytics and Pharmacokinetics, University of Bern, Bern, Switzerland

ROBERT C. CLARKE, BA • International Hemp Association, Amsterdam, The Netherlands

HALA N. ELSOHLY, PhD • National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, The School of Pharmacy, The University of Mississippi, Oxford, MS

MAHMOUD A. ELSOHLY, PhD • National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, The School of Pharmacy, The University of Mississippi; ElSohly Laboratories Inc., Oxford, MS

RODGER L. FOLTZ, PhD • Center for Human Toxicology, University of Utah, Salt Lake City, UT

MARILYN A. HUESTIS, PhD • Chemistry and Drug Metabolism, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD

STEVEN B. KARCH, MD • Consultant Pathologist/Toxicologist, Berkeley, CA

JAG H. KHALSA, PhD • Chief, Medical Consequences Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), National Institute on Drug Abuse, Bethesda, MD

BARRY K. LOGAN, PhD • Washington State Toxicologist and Director of Forensic Laboratory Services Bureau, Washington State Patrol, Seattle, WA

BILLY R. MARTIN, PhD • Louis and Ruth Harris Professor and Chair, Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA

TIMOTHY P. MURPHY, BA • ElSohly Laboratories Inc., Oxford, MS

RICHARD E. MUSTY, PhD • Department of Psychology, University of Vermont, Burlington, VT

LIONEL P. RAYMON, PharmD, PhD • Kaplan Medical, Pharmacology Chair and Department of Pathology, Miller School of Medicine, University of Miami, Miami, FL

MICHAEL D. ROTH, MD • Professor of Medicine, Division of Pulmonary and Critical Care, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA

MICHAEL L. SMITH, PhD, DABFT • Division of Forensic Toxicology, Office of the Armed Forces Medical Examiner, Rockville, MD

DONALD F. STANFORD, MS • National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, Oxford, MS

DONALD P. TASHKIN, MD • Professor of Medicine, Division of Pulmonary and Critical Care, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA

JANE S-C. TSAI, PhD • Director, Research and Development, Roche Diagnostics, Indianapolis, IN

H. CHIP WALLS, BS • Technical Director, Forensic Toxicology Laboratory, Miller School of Medicine, University of Miami, School of Medicine, Homestead, FL

DAVID P. WATSON • CEO, HortaPharm BV, Amsterdam, The Netherlands

Chapter 1

Cannabis *and Natural* Cannabis *Medicines*

Robert C. Clarke and David P. Watson

1. Introduction

Cannabis plants produce many compounds of possible medical importance. This chapter briefly explains the life cycle, origin, early evolution, and domestication of *Cannabis*, plus provides a brief history of drug *Cannabis* breeding and looks into the future of *Cannabis* as a source of medicines. *Cannabis* is among the very oldest of economic plants providing humans with fiber for spinning, weaving cloth, and making paper; seed for human foods and animal feeds; and aromatic resin containing compounds of recreational and medicinal value. Human selection for varying uses and natural selection pressures imposed by diverse introduced climates have resulted in a wide variety of growth forms and chemical compositions. Innovative classical breeding techniques have been used to improve recreational drug forms of *Cannabis*, resulting in many cannabinoid-rich cultivars suitable for medical use. The biosynthesis of cannabinoid compounds is unique to *Cannabis*, and cultivars with specific chemical profiles are being developed for diverse industrial and pharmaceutical uses.

2. Life Cycle and Ecology

Cannabis is an annual crop plant propagated from seed and grows vigorously when provided an open sunny location with light well-drained soil, ample nutrients, and water. *Cannabis* can reach up to 5 m (16 ft.) in height in a 4- to 8-month spring-to-autumn growing season. Feral *Cannabis* populations are frequently found in association with human habitation. Disturbed lands such as active and disused farm fields, roadsides, railways, trails, trash piles, and exposed riverbanks are ideal habitats for

From: *Forensic Science and Medicine: Marijuana and the Cannabinoids*
Edited by: M. A. ElSohly © Humana Press Inc., Totowa, New Jersey

wild and feral *Cannabis* because they provide open niches exposed to adequate sunlight.

Seeds usually germinate in 3–7 days. During the first 2–3 months of growth, juvenile plants respond to increasing day length with a 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. *Cannabis* begins to flower when exposed to short day lengths of 12–14 hours or less (long nights of 10–12 hours or more) depending on its latitude of origin. However, a single evening of interrupted darkness can disrupt flowering and delay maturation. Conversely, a day or two of short day length can induce flowering that may be irreversible in early-maturing varieties. If an individual plant grows with sufficient space, as in seed or resin production, flower-bearing limbs will grow from small growing points 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 and an accompanying change from vegetative growth and biomass accumulation to floral induction, fertilization, seed maturation, and resin production *(1)*.

Cannabis is normally dioecious (male and female flowers developing on separate plants), and the gender of each plant is anatomically indistinguishable before flowering. However, Mandolino and Ranalli *(2)* report success using random amplified polymorphic DNA analysis to identify male-specific DNA markers, and female-associated DNA polymorphisms were also described by Hong et al. *(3)*. The floral development of male and female plants varies greatly. Whereas male flowers with five petals and prominent stamens hang in loose clusters along a relatively leafless upright branch, the inconspicuous female flowers are crowded into dense clusters along with small leaflets at the base of each larger leaf along the branch (*see* Fig. 1). Pollen grains require air currents to carry them to the female flowers, resulting in fertilization and consequent seed set. Viable pollen can be carried by the wind for considerable distance *(4)*; the male plants cease shedding pollen after 2–4 weeks and usually die before the seeds in the female plants ripen. Pollen has been frozen and successfully used for seed production up to 3 years later.

The single seed in each female flower ripens in 3–8 weeks and will either be harvested, be eaten by birds or rodents, or fall to the ground, where they may germinate the following spring. This completes the natural 4- to 6-month life cycle. A large female plant can produce up to half a kilogram of seed. *Cannabis* seeds are a balanced source of essential fatty acids and easily digestible proteins and are suitable for use as whole foods and dietary supplements. Essential fatty acids have been shown to have many important physiological roles, and hemp seed oil is a valuable nutraceutical *(5)*. Recent research has confirmed that topical application of hemp seed oil is effective in treating ear, nose, and throat ailments *(6)*.

3. Field Crop Production

When industrial hemp crops are grown for fiber or seed, both male and female plants are usually left standing in the field until harvest. Most medical *Cannabis* is grown for its psychoactive resin by a different technique. In the early 1970s, a handful

Fig. 1. Medical *Cannabis* cultivars grown in the United Kingdom by GW Pharmaceuticals, which form the basis for GW's development of prescription medicines. The larger inflorescence **(A)** is a cannabidiol (CBD)-rich cultivar containing only traces of Δ^9-tetrahydrocannabinol (THC), and the smaller inflorescence **(B)** is a THC-rich cultivar containing only traces of CBD.

of North American illicit marijuana cultivators began to grow *sinsemilla* (Spanish for "without seed") marijuana that within a few years became the predominant style of North American and European marijuana production. The sinsemilla effect is achieved by eliminating male plants from the fields, leaving only the unfertilized and therefore seedless female plants to mature for later flower and/or resin harvest.* In lieu of setting seed in the earliest flowers, the female plants continue to produce additional flowers covered by resin glands, which increases the percentage of psychoactive and medically valuable Δ^9-tetrahydrocannabinol (THC) or other cannabinoids in these flowers. Yields of terpenoid-rich essential oils produced in the resin glands along with the closely related terpenophenolic cannabinoids are also significantly raised in seedless flowers *(7)*. Throughout the 1980s, the vast majority of domestically produced North American and European drug *Cannabis* was grown from seed in outdoor gardens, but during the 1990s the popularity of growing sinsemilla in greenhouses and indoors under artificial lights grew rapidly.

4. Greenhouse and Grow Room Production

Most *Cannabis* presently used for medical purposes is grown indoors under artificial lights. Modern indoor growers most often grow their own clones under halide and sodium vapor light systems set up in attics, bedrooms, or basements. Crops grown from seed are typically made up of large male and female plants that require a lot of space and exhibit a wide range of physical and biochemical characteristics. A *Cannabis* breeder relies on this variation as genetic potential for improving varieties, whereas a drug *Cannabis* producer wants a profitable and uniform crop and uses female clones to improve grow room yields. Consequently, vegetative production of female clones and the production of seedless flowers preclude the possibility of seed production and variety improvement. Vegetatively propagated crops are preferred because indoor garden space is limited, only female *Cannabis* plants produce resin of medical value, and it is both inconvenient and expensive to purchase reliable drug *Cannabis* seed. In addition, the legal systems of many nations penalize growers of more plants (vegetative, male or female) with harsher penalties. Under artificial growing conditions, crops are reproduced vegetatively by rooting cuttings of only select female plants, transplanting, and inducing flowering almost immediately so that the mature crop is short and compact. Cuttings of one plant are all genetically identical members of a single clone, so they will all respond in the same way to environmental influences and will be very similar in appearance. When environmental influences remain constant, the clone will yield serial crops of nearly identical uniform seedless females each time it is grown.

Female "mother" plants used for cutting stock must be maintained in a constantly vegetative state under 18-hour or longer day lengths or they will begin to flower. Serial cuttings can be removed, rooted, grown under long day length, and used to replace older mother plants indefinitely. If the mother plants remain free of viruses or other pathogens, there is no loss of vigor after multiple rounds of vegetative propaga-

*This technique was first encountered by British working in India, but we are unsure of its history prior to 1800.

tion. Serially propagated clones have been maintained for more than 20 years. Whenever flowering plants are required, small rooted cuttings (10–30 cm tall) are moved into a flowering room with a day length of 10–13 hours to mature in 7–14 weeks.*

Vegetatively produced plants can fully mature when they are less than 1 m (3 ft.) tall and form flowers from top to bottom and look like a rooted branch from a large plant grown from seed. The length of time between the induction of flowering and full maturity of the female floral clusters depends largely on the variety being grown and the day length. Some cultivars mature much more quickly than others, and plants tend to be shorter when mature than those of slower-ripening varieties. *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 flower production in the shortest time—around 12–13 hours. Under ideal environmental conditions and expert management, yields of dried flowers commonly reach 400 g/m^2 per crop cycle. As a result of multiple cropping four or five times per year, total annual yields can add up to more than 2 kg of dried flowers per square meter.

In vitro techniques combined with low temperatures would allow long-term storage of wide varieties of living germplasm and could be an important storage technique for germplasm collections and breeders. Several research groups have reported success with vegetatively reproducing and initiating shooting in undifferentiated callus tissue and rooting of branch tips. The induction of rooting in callus and branch tips is straightforward. However, inducing shoots in callus tissue has proven more problematic and needs additional improvement *(2,8)*. Further research and commercial applications of in vitro techniques are expected in the near future.

5. Resin Gland Anatomy and Development

As resin gland development commences, the medically important cannabinoids and the associated terpenes begin to appear. Although the cannabinoids are odorless, terpenes are the primary aromatic principles found in the essential oil of *Cannabis (9,10)*. Most interesting economically and medically are the cannabinoid-rich terpenoid secretions of the head cells of glandular hairs densely distributed across the myriad surfaces of the female flowers. Male plants are of no consequence in medicine production because they develop few glandular trichomes and consequently produce few cannabinoids or terpenes. Solitary resin glands most often form at the tips of slender stalks that form as extensions of the plant surface and glisten in the light. The cluster of one to two dozen glandular head cells atop each stalk secretes aromatic terpene-containing resins with very high percentages of cannabinoids (>80%) that collects in vesicles under a thin membrane surrounding the secretory head cells. The secreted resin component is in large part physically segregated from the secretory cells *(11)*. This isolates the resin from the atmosphere as well as membrane-bound enzyme systems within the secretory cells, possibly protecting the terpenes and cannabinoids from oxidative degradation and enzymatic change. At the base of each cluster of resin head

**Cannabis* breeders maintain male clones in the same way and induce them to flower whenever pollen is required to produce seed. However, males are often more difficult than females to maintain in the vegetative state.

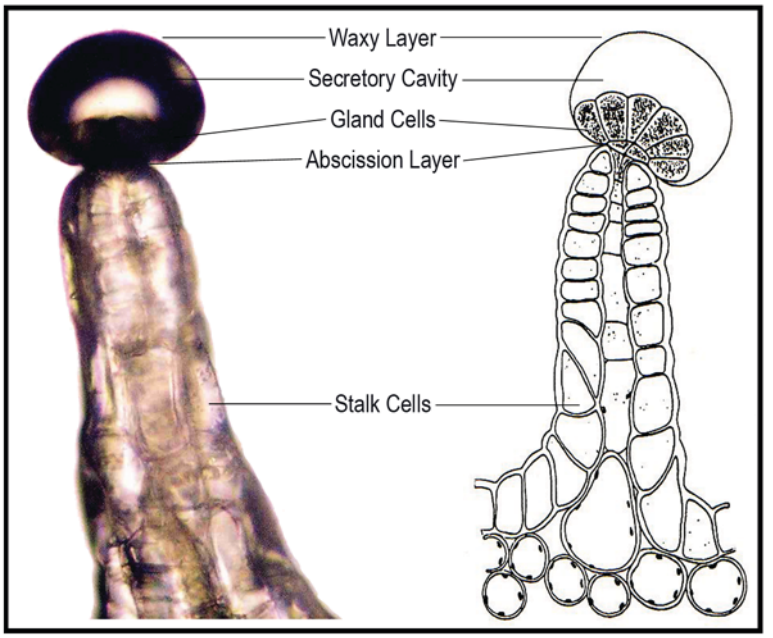


Fig. 2. Microscope photograph and drawing of a *Cannabis* resin gland. The secretory head cells are easily visible within the transparent blister of cannabinoid and terpenoid-rich resin. (Photo courtesy of David Potter, drawing from ref. *14*.)

cells lies an abscission layer allowing the resin gland and secreted resin to be easily removed by mechanical means (*see* Fig. 2). Hashish or charas is simply millions of resin glands that have been rubbed, shaken, or washed from fresh or dry plants and compressed into a dense mass *(11)*.

Resin glands containing cannabinoids and terpenes may have an adaptive significance in reducing insect and fungal attack *(12)*. However, *Cannabis* crops are subject to infestation by a wide variety of pests *(13),* particularly under greenhouse and grow room conditions.

6. Cannabinoid and Terpenoid Biosynthesis

It is not surprising that cannabinoids are produced along with terpenoid compounds. Terpenes comprise a large group of compounds synthesized from C_{10} isoprene subunits. Monoterpenes (C_{10}) and sesquiterpenes (C_{15}) are the classes most commonly found in *Cannabis*. Terpenoids are the primary aromatic constituents of *Cannabis* resin, although they constitute only a small percentage of organic solvent extracts. Cannabinoids are terpenophenolic compounds chemically related to the terpenoid compounds as the ring structure is derived from a geranyl pyrophosphate C_{10} terpenoid subunit. Cannabinoids make up a large portion of the resin and can make up as much as 30% by weight of dried flowering tops. Cannabinoids are not significantly present in extracts prepared by steam distillation *(15)*.

Our basic understanding of the biosynthesis of the major cannabinoids comes largely from the research of Yukihiro Shoyama and colleagues at Kyushu University in Japan *(16,17)*. Cannabinoid biosynthesis begins with the incorporation of geranyl pyrophosphate (a terpenoid compound) with either a C_{10} polyketide for the propyl (C_3 side chain) or a C_{12} polyketide for the pentyl (C_5 side chain) cannabinoid series into either cannabigerovarin (CBGV) or cannabigerol (CBG), respectively. Research by Etienne de Meijer at HortaPharm B.V. in the Netherlands shows that there is a single allele (Pr) controlling the propyl pathway to CBGV and another allele (Pe) controlling the pentyl pathway to CBG. The biosyntheses of THC, cannabidiol (CBD), and cannabichromene (CBC) (or tetrahydrocannabivarin [THCV], cannabidivarin [CBDV], or cannabichromavarin [CBCV]) are controlled by a suite of three enzymes, each controlled by a single allele: T, D, and C, respectively. The three enzymes can likely use either propyl CBGV or pentyl CBG for the propyl and pentyl pathways, depending on which substrate is available. This hypothesis was verified by Flachowsky et al. *(18)*. Continued research by de Meijer et al. *(19)* (*see* Fig. 3) has shown that CBD and THC biosynthesis are controlled by a pair of co-dominant alleles, which code for isoforms of the same synthase, each with a different specificity for converting the common precursor CBG into either CBD or THC. The group also identified by random amplified polymorphic DNA analysis three chemotype-associated DNA markers that show tight linkage to chemotype and co-dominance.

7. Medical Values of Terpenes

The terpenoid compounds found in *Cannabis* resin are numerous, vary widely among varieties, and produce aromas that are often characteristic of the plant's geographic origin. Although more than 100 different named terpenes have been identified from *Cannabis*, no more than 40 known terpenes have been identified in a single plant sample, and many more remain unnamed *(11)*. Terpenes are produced via multibranched biosynthetic pathways controlled by genetically determined enzyme systems. This situation presents plant breeders with a wide range of possible combinations for developing medical *Cannabis* varieties with varying terpenoid profiles and specifically targeted medical uses. Preliminary breeding experiments confirm that the terpenoid profiles of widely differing parents are frequently reflected in the hybrid progeny.

Only recently have *Cannabis* essential oils become economically important as flavorings and fragrances *(17)*. Early *Cannabis* medicines were formulated from alcoholic whole flower or resin extracts and contained terpenes, although they were not recognized to be of medical importance. Several of the monoterpenes and sesquiterpenes found in *Cannabis* and derived from other botanical and synthetic sources are used in commercial medicines. Other as-yet-unidentified terpenes may be unique to *Cannabis*. The highly variable array of terpenoid side-chain substitutions results in a range of human physiological responses. Certain terpenes stimulate the membranes of the pulmonary system, soothe the pulmonary passages, and facilitate the absorption of other compounds *(15)*. Terpenoid compounds are incorporated into pulmonary medical products such as bronchial inhalers and cough suppressants. Casual studies indicate that when pure THC is smoked, it produces subjectively different effects than it does when combined with trace amounts of mixed *Cannabis* terpenes. Clinical trials

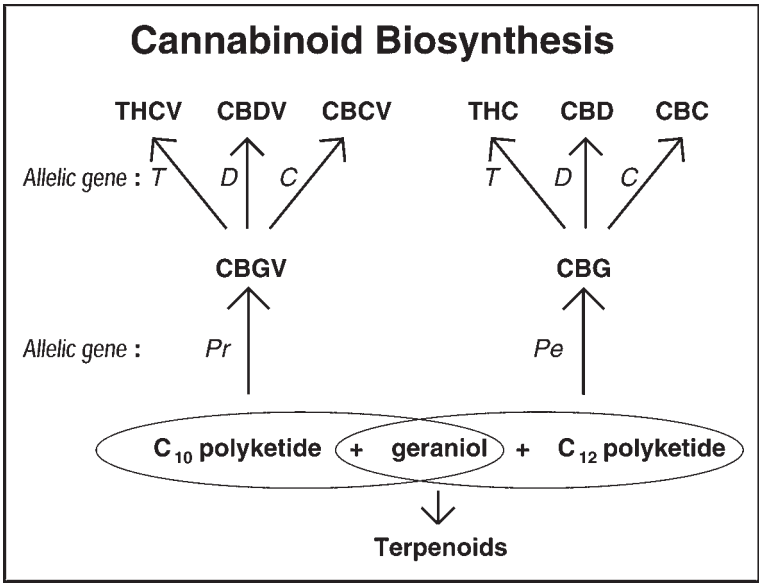


Fig. 3. Cannabinoid biosynthesis is mediated by enzymes controlled by individual genes *(16–18)*. Terpenoid biosynthesis also begins along the same general pathway by utilizing geraniol molecules directly. THCV, Δ^9-tetrahydrocannabivarin; CBVD, cannabidivarin; CBCV, cannabichromavarin; THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol; CBC, cannabichromene; CBGV, cannabigerovarin; CBG, cannabigerol. (Adapted from ref. *19*.)

using whole plant extracts of known cannabinoid content and varying terpenoid profiles will determine whether terpenoid compounds have an effect on the pharmacokinetics of the cannabinoids.

8. Cannabis's Origin, Domestication, and Dispersal

Cannabis originated either in the riverine valleys of Central Asia or in northern South Asia along the foothills of the Himalayas and was first cultivated in China on a large scale for fiber and seed production and soon after in India for resin production. Various cultures have traditionally used *Cannabis* for different purposes. European and East Asian societies most often used *Cannabis* for its strong fibers and nutritious seeds. Species of *Cannabis* from these regions are usually relatively low in THC (average <1% dry weight), with a CBD content averaging about twice as high.* 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. The vast majority of races from these regions are high in psychoactive THC (often 5–10%) with widely varying CBD content (0–5%). Early on, traders spread the South Asian section of the *Cannabis* gene pool far and wide from eastern Africa to Sumatra and eventually to the

*THC is the primary psychoactive compound produced by *Cannabis*, and nonpsychoactive CBD is the other most common naturally occurring cannabinoid.

semi-tropical New World. Central Asian hashish varieties, popularly called "indicas," were introduced to the West much more recently. Drug *Cannabis* use was adopted by indigenous cultures in many of these locations, and highly psychoactive races evolved. All modern drug varieties used as medical *Cannabis* are derived from these two traditional drug variety gene pools.

Certainly, the enchanting psychological and effective medical effects realized from smoking or eating *Cannabis* resins, along with its value as a food and fiber plant, have increased predation by humans, encouraged its early domestication as a crop plant, and hastened its dispersal worldwide first into natural and, more recently, into artificial environments.

9. *The* Cannabis *Species Debate*

Twentieth-century taxonomists have variously characterized *Cannabis*. Although all taxonomists recognize the species *Cannabis sativa*, Small and Cronquist *(20)* subdivided *C. sativa* into two subspecies, each with two varieties based largely on cannabinoid content and traditional usage. Schultes et al. *(21)* divided *Cannabis* into three separate species: *C. sativa*, *C. indica*, and *C. ruderalis*. Several other researchers do not preserve *C. ruderalis*, but recognize both *C. sativa* and *C. indica (22,23)*. We consider *C. sativa* to include all wild, hemp, and drug *Cannabis* races, with the possible exception of those traditionally used for hashish production in Central Asia. These morphologically and chemically distinct Central Asian races deserve the separate specific name of *C. afghanica* following the variety name for *C. indica* determined by Vavilov and Bukinich *(23)*. Some Chinese races may also deserve taxonomic distinction separate from either *C. sativa* or *C. indica (24)*. Validation of these theories awaits further chemotaxonomic and genetic research.

In all of these taxonomic interpretations, *C. sativa* represents the largest and most diverse taxon and is commonly referred to by marijuana breeders and growers, as well as medical *Cannabis* users, as "sativa." *C. afghanica* is commonly known as "indica" (*see* Fig. 4). Individual plants of these hashish varieties have their own distinctive acrid organic aromas and are often rich in CBD as well as THC. The wide variety of morphological, physiological, and chemical traits encountered in *Cannabis* has proven very attractive to plant breeders for years.

10. *Drug* Cannabis *Breeding*

During the early 1960s, marijuana cultivation came to North America. At first, *Cannabis* seeds found in illicit shipments of marijuana were simply casually sown by curious smokers. Early marijuana cultivators tried any available seed in their efforts to grow potent plants outdoors that would consistently mature before killing frosts. Because most imported marijuana contained seeds, many possibilities were available. Early-maturing northern Mexican varieties proved to be the most favored, as they consistently matured at northern latitudes. The legendary domestic *Cannabis* varieties of the early and mid-1970s (such as Polly and Haze) resulted from crosses between early-maturing Mexican or Jamaican races and more potent, but later-maturing, Panamanian, Colombian, and Thai races.

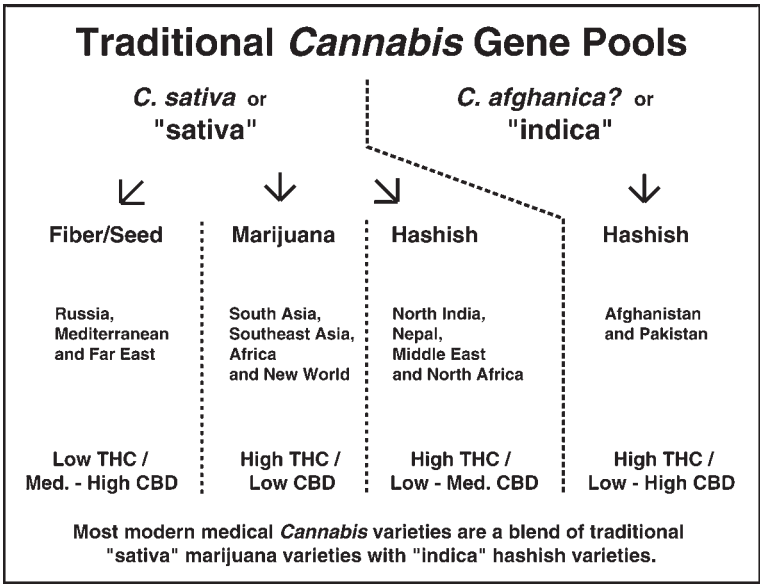


Fig. 4. The four major *Cannabis* gene pools originate either from *C. sativa,* which comprises the vast majority of naturally occurring hemp and drug landraces (adapted from ref. *25*) or from *C. afghanica* from Central Asia, which has become a component in many modern drug *Cannabis* cultivars *(11)*. THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol.

Initially, the new *Cannabis* varieties were aimed at outdoor growing. Soon others were specially developed for greenhouse or artificial light growing, where the plants are sheltered from autumn cold and the growing season can be extended by manipulating day length, allowing later-maturing varieties to finish. Once varieties that would mature under differing conditions were available, pioneering marijuana breeders continued selections for potency (high THC content with low CBD content) followed by the aesthetic considerations of flavor, aroma, and color. Continued inbreeding of the original favorable crosses resulted in some of the "super-sativas" of the 1970s, such as Original Haze, Purple Haze, Pollyanna, Eden Gold, Three Way, Maui Wowie, Kona Gold, and Big Sur Holy Weed.

11. The Introduction of Indica

Indica plants are characterized as short and bushy with broad, dark green leaves, which make them somewhat harder to see from afar. They nearly always mature quite early outdoors, from late August to early October, often stand only 1–2 m (3–6 ft.) tall at maturity, and produce copious resin-covered flowers and leaflets. At least several dozen introductions of indica were made during the middle to late 1970s. Afghani No.1 and Hindu Kush were among the early indica introductions that gained notoriety and are still available today. Following the Soviet invasion of Afghanistan in 1979, many additional introductions were made from Afghanistan and northwestern Pakistan.

Marijuana breeders intentionally crossed varieties of early-maturing indica with their later-maturing sativa varieties to produce early-maturing hybrid crosses (matings of parents from different gene pools), and soon the majority of cultivators began to grow the newly popular indica × sativa hybrids. Many of the indica × sativa hybrids were vigorous growers, matured earlier, yielded well, and were very potent. Skunk No. 1 is a good example of a hybrid expressing predominantly sativa traits, and Northern Lights is a good example of a hybrid expressing predominantly indica traits. By the early 1980s, the vast majority of all domestic sinsemilla in North America had likely received some portion of its germplasm from the indica gene pool, and it had become difficult to find the preindica, pure sativa varieties that had been so popular only a few years earlier.

However, the negative characteristics of reduced potency (lower THC content); slow, flat, sedative, dreary effect (high CBD content); skunky, acrid aroma; and harsh taste quickly became associated with many indica × sativa hybrids. To consumers, who often prefer sativas, indica has not proven itself to be as popular as it is with growers. Also, the dense, tightly packed floral clusters of indica tend to hold moisture and to develop gray mold (*Botrytis*), for which the plants have little natural resistance. Mold causes significant losses, especially in outdoor and glasshouse crops, and was rarely a problem when only pure *C. sativa* varieties were grown. In addition, fungal contamination of medical *Cannabis* could prove a serious threat to pulmonary or immunocompromised patients. Although consumers and commercial cultivators of the late 1970s initially accepted indica enthusiastically, serious breeders of the late 1980s began to view indica with more skepticism. Although indica may currently appear to be a growing bane for *Cannabis* connoisseurs, it has certainly been a big boon for the average consumer, bringing more potent and medically effective *Cannabis* to a wider audience. Indica × sativa hybrids have proven to be well adapted to indoor cultivation where mold is rarely a problem. Indica × sativa varieties mature quickly (60–80 days of flowering), allowing four to five harvests per year, and can yield up to 100 g of dry flowers on plants only 1 m (3 ft.) tall. *C. sativa* varieties are too gangly and tall and take too long to mature to make them desirable for the indoor grower. On the other hand, sativas have unique cannabinoid and terpenoid profiles producing effects considered superior by many medical *Cannabis* users.

Political pressure on marijuana cultivators across North America forced many drug *Cannabis* breeders to relocate to the Netherlands, where the political climate was less threatening. During the 1980s, several marijuana seed companies appeared in the Netherlands, where cultivation of *Cannabis* for seed production and the sale of seeds were tolerated. To North American and European cultivators, this meant increased availability of exotic high-quality drug *Cannabis* seeds and presented yet more possibilities to find varieties that were the most medically effective for individual indications and patients. *Cannabis* seed sales continue in the Netherlands today.

12. *Advances in Medical* Cannabis *Research*

Cannabis available to the medical user comes in two commonly available types. Marijuana (domestically produced or imported *Cannabis* flowers) is nearly always grown from high-THC varieties (up to 30% dry weight in trimmed female flowers)

and contains very little CBD. Very high THC with negligible CBD profiles of modern sinsemilla varieties result from marijuana growers sampling single plants and making seed selections from vigorous individuals with high levels of psychoactivity. Unique individuals may also be vegetatively propagated, thereby fixing the high-THC genotype in the clonal offspring.

Commercially available imported hashish or charas (compressed *Cannabis* resin) is collected from varieties that are predominantly THC (up to 10%) but that often contain up to 5% CBD as well. Imported hashish is produced by bulk processing large numbers of plants. Growers rarely make seed selections from individual, particularly potent plants, and therefore without human intervention the CBD content tends to be closer to that of THC. Hashish cultivars are usually selected for resin quantity rather than potency, so the farmer chooses plants and saves seeds by observing which ones produce the most resin, unaware of whether it contains predominantly THC or CBD. Populations grown from imported indica seeds contain approx 25% plants that are rich in CBD with little THC, 50% that contain moderate amounts of both CBD and THC, and 25% that contain little CBD and are rich in THC.* Marijuana breeders utilized only the high-THC indica individuals in crosses, thereby promoting high THC synthesis and suppressing CBD.

CBD is suspected of having modifying physiological and psychological 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 recreational and medical *Cannabis* varieties in the Netherlands *(26)* and 47 samples in California *(27)* show that nearly every sample contained predominantly THC with little if any CBD or other cannabinoids. Higher levels of THC (and other medically effective cannabinoid and terpenoid compounds) in medical *Cannabis* are healthier for patients using smoked *Cannabis* because they can smoke less to achieve the same dosage and effect. Recently developed mechanical resin-collecting techniques combined with high-potency Western cultivars are used to make very potent and pure hashish of more than 50% THC and almost no CBD (*see* Fig. 5).

Proponents of medical *Cannabis*, especially traditional hashish users, claim that the additional benefits of herbal preparations are a result, at least in part, of the presence of other cannabinoids such as CBD. Because THC (with traces of CBD) is the prominent cannabinoid found in most domestically produced North American and European marijuana and hashish, how will medical users gain legitimate legal access to other potentially effective cannabinoids?

13. The Future of Medical Cannabis

Cannabis breeders are continually searching for new sources of exotic germplasm and will develop new varieties that will prove particularly effective as medicines.

*The ratio of THC to CBD usually approached 1:1 in populations unselected for cannabinoid content, and the amounts of cannabinoids are rather low. Industrial hemp varieties have been selected for unnaturally low levels of THC (European Union regulations stipulate <0.3% dry weight) and much higher levels of CBD, whereas sinsemilla varieties have been selected for unnaturally high levels of THC (>20% dry weight) at the expense of CBD.

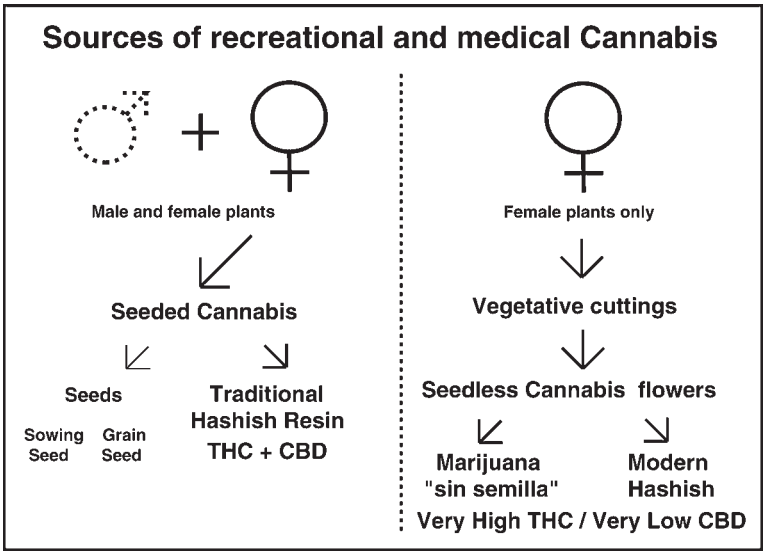


Fig. 5. Both recreational and medical *Cannabis* typically originate from either seeded plants used primarily for traditional hashish production or seedless plants grown primarily for "sinsemilla" marijuana and occasionally for modern hashish production. THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol.

Pure indica varieties are still highly prized breeding stock, and new indica introductions from Central Asia are occasionally received. Sativa varieties from Mexico, South Africa, and Korea are gaining favor with breeders because they mature early but do not suffer from the drawbacks of many indicas. Recently, *Cannabis* breeders have become more interested in variations in subjective effects between different clones and are developing varieties with enhanced medical efficacy based on feedback from medical *Cannabis* users.

Genetic modification has also reached *Cannabis*. Researchers in Scotland have successfully transferred genes for gray mold resistance to an industrial hemp variety *(28)*. Because *Botrytis* is one of the leading pests of *Cannabis*, causing crop loss and contaminating medical supplies, the transfer of resistance into medical varieties would be of great value. In addition, other agronomically valuable traits may also be transferred to *Cannabis*, such as additional pest resistance, increased yields of medically valuable compounds, tolerance of environmental extremes, and sexual sterility. However, so far the acceptance of genetically modified (GM) organisms has been timid. The European Union, for example, has installed strict regulations to prevent the accidental release of GM crop plants, and production of GM *Cannabis* in the European Union may be impractical. *Cannabis* presents a particularly high risk for transmitting genetically modified genes to industrial hemp crops and weedy *Cannabis* because it is wind-pollinated. If sterile female GM clones could be developed and used for production, then gene transfer would be blocked. Genes coding for cannabinoid biosynthesis might also be transferred from *Cannabis* to less politically sensitive organisms.

GW Pharmaceuticals Ltd. in the United Kingdom is engaged in the development of prescription medicines derived from *Cannabis* and, as part of its research program

to develop novel cannabinoid medicines, supports an ongoing breeding project to develop high-yielding *Cannabis* cultivars of known cannabinoid profile. The aims of this research are to create varieties that produce only one of the four major cannabinoid compounds (e.g., THC, CBD, CBC, CBG, or their propyl homologs) as well as selected varieties with consistently uniform mixed cannabinoid and terpenoid profiles. These uniform profiles allow for the formulation of nonsmoked medicinal products, which can meet the strict quality standards of international regulatory authorities. A sublingual spray application of plant-derived THC and CBD began clinical trials for relief of multiple sclerosis-associated symptomology in 1999. These clinical trials have gone on to include patients with neuropathic pain and cancer pain.

14. Conclusion

Cannabis has had a long association with humans, and anecdotal evidence for its medical efficacy is plentiful. Since the 1970s, modern North American and European drug *Cannabis* varieties have resulted largely from crosses made by clandestine breeders between South Asian sativa marijuana varieties that spread early throughout South and Southeast Asia, Africa, and the New World and Central Asian indica hashish varieties. These hybrid varieties are now commonly used in Western societies for medical *Cannabis*.

Largely as a response to increased law enforcement and the limited commercial availability of high-quality medical grade *Cannabis*, patients growing their own plants and self-medicating is a trend rapidly spreading across North America, Europe, and around the globe. The political climate surrounding medical *Cannabis* legislation has become more informed, compassionate, and lenient. *Cannabis* cultivation for personal medical use will eventually be legalized or tolerated in many jurisdictions, if not by the public openly favoring legalization, then by increasing governmental awareness of the inefficiency inherent in attempted prohibition of a popular and effective medicine.

Pharmaceutical research companies are developing new natural cannabinoid formulations and delivery systems that will meet government regulatory requirements. As clinical trials prove successful and the understanding of *Cannabis*'s efficacy and safety as a modern medicine spreads, patients can look forward to a steady flow of new *Cannabis* medicines providing effective relief from a growing number of indications.

References

1. Clarke, R. C. (1981) *Marijuana Botany*, Berkeley: Ronin Publishing.
2. Mandolino, G. and Ranalli, P. (1999) Advances in biotechnological approaches for hemp breeding and industry, in *Advances in Hemp Research*. (Ranalli, P. ,ed.), Haworth Press, New York, pp. 185–211.
3. Hong, S., Song, S-J., and Clarke, R. C. (2003) Female-associated DNA polymorphisms of hemp (*Cannabis sativa* L.) *J. Indust. Hemp* **1,** 5–9.
4. Small, E. and Antle, T. (2003) A preliminary study of pollen dispersal in Cannabis sativa in relation to wind direction. *J. Indust. Hemp* **8,** 37–50.
5. Deferne, J-L. and Pate, D. W. (1996) Hemp seed oil: a source of valuable essential fatty acids. *J. Int.Hemp Assoc.* **3,** 1, 4–7.

6. Grigoriev, O. V. (2002) Application of hempseed (*Cannabis sativa* L.) oil in treatment of ear, nose and throat (ENT) disorders. *J. Indust. Hemp* **7,** 5–15.
7. Meier, C. and Mediavilla, V. (1998) Factors influencing the yield and the quality of hemp (*Cannabis sativa* L.) essential oil. *J. Int. Hemp Assoc.* **5,** 16–20.
8. Liu, Y. and Tang, X. (1984) Green seedling of hemp acquired by tissue culture. *China's Fibre Crops* **2,** 19, 29 [in Chinese].
9. Hendriks, H., Malingre, T. M., Batterman, S., and Bos, R. (1978) The essential oil of *Cannabis sativa* L. *Pharm. Weekbl.* **113,** 413–424.
10. Ross, R. A. and ElSohly, M. A. (1996) The volatile oil composition of fresh and air-dried buds of *Cannabis sativa L. J. Nat. Prod.* **59,** 49–51.
11. Clarke, R. C. (1998) *Hashish!*, Red Eye Press, Los Angeles.
12. Pate, D. W. (1994) Chemical ecology of *Cannabis. J. Int. Hemp Assoc.* **1,** 29, 32–37.
13. McPartland, J., Clarke, R. C., and Watson, D. P. (2000) *Hemp Diseases and Pests,* CAB International, Wallingford, UK.
14. Briosi, G. and Tognini, F. (1894) Intorno alla anatomia della canapa (*Cannabis sativa* L.) parte prima—organi sessual, *Atti dell' Instituto Botanico di Pavia*, Serie I, Vol. 3.
15. McPartland, J. and Mediavilla, V. (2002) *Cannabis and Cannabinoids: Pharmacology and Therapeutic Potential (*Grotenhermen, F. and Russo, E., eds.), Haworth Integrative Healing Press, New York, pp. 401–409.
16. Taura, F., Morimoto, S., Shoyama, Y., and Mechoulam, R. (1995) First direct evidence for the mechanism of delta-1-tetrahydrocannabinol acid biosynthesis. *J. Am. Chem. Soc.* **117,** 9766–9767.
17. Taura, F., Morimoto, S., and Shoyama, Y. (1996) Purification and characterization of cannabidiolic-acid synthase from *Cannabis sativa* L. Biochemical analysis of a novel enzyme that catalyzes the oxidocyclization of cannabigerolic acid to cannabidiolic acid. *J. Biol. Chem.* **271,** 17411–17416.
18. Flachowsky, H., Schumann, E., Weber, W. E., and Peil, A. (2000) AFLP-marker for male plants of hemp (Cannabis sativa L.) Poster presented at the 3rd Bioresource Hemp Symposium, Wolfsburg, Germany, September 13–16.
19. de Meijer, E. P. M., Bagatta, M., Carboni, A., et al. (2003) The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics* **163,** 335–346.
20. Small, E. and Cronquist, A. (1976) A practical and natural taxonomy for *Cannabis. Taxon* **25,** 405–435.
21. Schultes, R. E., Klein, W. M., Plowman, T., and Lockwood, T. E. (1974) *Cannabis*: an example of taxonomic neglect. *Botanical Museum Leaflets, Harvard University* **23,** 337–364.
22. Serebriakova, T. I. (1940) Fiber plants, in *Flora of Cultivated Plants*. Vol.4, Part1 (Wulff, E. V., ed.), State Printing Office, Moscow and Leningrad [in Russian].
23. Vavilov, N. and Bukinich, D. D. (1929) Agricultural Afghanistan. *Bull. Appl. Bot. Genet. Plant Breed.*Supp. **33,** 378–382, 474, 480, 584–585, 604.
24. Hillig, K. W. and Mahlberg, P. G. (2004) Genetic evidence for speciation in *Cannabis* (Cannabaceae). *Genet. Resources Crop Evol.* **52,** 161–180.
25. de Meijer, E. P. M. (1999) *Cannabis* germplasm resources, in *Advances in Hemp Research* (Ranalli, P., ed.), Haworth Press, New York, pp. 133–151.
26. HortaPharm, personal communication (1998) HortaPharm BV develops industrial Cannabis cultivars and provided the starting materials GW Pharmaceuticals breeding project in the United Kingdom.
27. Gierenger, D. (1999) Medical *Cannabis* potency testing. *Bull. Multidisc. Assoc. Psychedel. Stud.* **9,** 20–22.
28. MacKinnon, L. (2003) Genetic transformation of *Cannabis sativa* Linn: a multi purpose fibre crop, doctoral thesis, University of Dundee, Scotland.

Chapter 2

Chemistry and Analysis of Phytocannabinoids and Other Cannabis *Constituents*

Rudolf Brenneisen

1. The Chemistry of Phytocannabinoids and Noncannabinoid-Type Constituents

1.1. Phytocannabinoids

1.1.1. Introduction

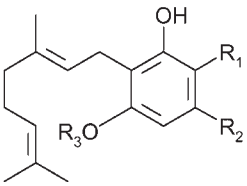
The *Cannabis* plant and its products consist of an enormous variety of chemicals. Some of the 483 compounds identified are unique to *Cannabis*, for example, the more than 60 cannabinoids, whereas the terpenes, with about 140 members forming the most abundant class, are widespread in the plant kingdom. The term "cannabinoids" represents a group of C_{21} terpenophenolic compounds found until now uniquely in *Cannabis sativa* L. *(1)*. As a consequence of the development of synthetic cannabinoids (e.g., nabilone *[2]*, HU-211 [dexanabinol; ref. *{3}*, or ajulemic acid [CT-3; ref. *4*]) and the discovery of the chemically different endogenous cannabinoid receptor ligands ("endocannabinoids," e.g., anandamide, 2-arachidonoylglycerol) *(5,6)*, the term "phytocannabinoids" was proposed for these particular *Cannabis* constituents *(7)*.

1.1.2. Chemistry and Classification

So far, 66 cannabinoids have been identified. They are divided into 10 subclasses *(8–10)* (*see* Table 1).

From: *Forensic Science and Medicine: Marijuana and the Cannabinoids*
Edited by: M. A. ElSohly © Humana Press Inc., Totowa, New Jersey

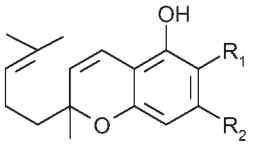
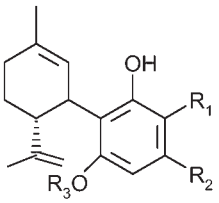
Table 1
Cannabinoids

Compound	Structure	Main pharmacological characteristics
Cannabigerol class		
Cannabigerolic acid (CBGA)	 R_1 = COOH, R_2 = C_5H_{11}, R_3 = H	Antibiotic
Cannabigerolic acid monomethylether (CBGAM)	R_1 = COOH, R_2 = C_5H_{11}, R_3 = CH_3	
Cannabigerol (CBG)	R_1 = H, R_2 = C_5H_{11}, R_3 = H	Antibiotic Antifungal Anti-inflammatory Analgesic
Cannabigerol monomethylether (CBGM)	R_1 = H, R_2 = C_5H_{11}, R_3 = CH_3	
Cannabigerovarinic acid (CBGVA)	R_1 = COOH, R_2 = C_3H_7, R_3 = H	
Cannabigerovarin (CBGV)	R_1 = H, R_2 = C_3H_7, R_3 = H	

(continued)

1. Cannabigerol (CBG) type: CBG was the first cannabinoid identified *(11)*, and its precursor cannabigerolic acid (CBGA) was shown to be the first biogenic cannabinoid formed in the plant *(12)*. Propyl side-chain analogs and a monomethyl ether derivative are other cannabinoids of this group.
2. Cannabichromene (CBC) type: Five CBC-type cannabinoids, mainly present as C5-analogs, have been identified.
3. Cannabidiol (CBD) type: CBD was isolated in 1940 *(13)*, but its correct structure was first elucidated in 1963 by Mechoulam and Shvo *(14)*. Seven CBD-type cannabinoids with C1 to C5 side chains have been described. CBD and its corresponding acid CBDA

Table 1 ***(continued)***

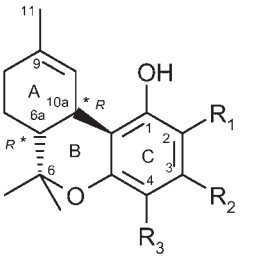
Compound	Structure	Main pharmacological characteristics
Cannabichromene class		
Cannabichromenic acid (CBCA)	 R_1 = COOH, R_2 = C_5H_{11}	
Cannabichromene (CBC)	R_1 = H, R_2 = C_5H_{11}	Anti-inflammatory Antibiotic Antifungal Analgesic
Cannabichromevarinic acid (CBCVA)	R_1 = COOH, R_2 = C_3H_7	
Cannabichromevarin (CBCV)	R_1 = H, R_2 = C_3H_7	
Cannabidiol class		
Cannabidiolic acid (CBDA)	 R_1 = COOH, R_2 = C_5H_{11}, R_3 = H	Antibiotic
Cannabidiol (CBD)	R_1 = H, R_2 = C_5H_{11}, R_3 = H	Anxiolytic Antipsychotic Analgesic Anti-inflammatory Antioxydant Antispasmodic

(continued)

are the most abundant cannabinoids in fiber-type *Cannabis* (industrial hemp). Isolated in 1955, CBDA was the first discovered cannabinoid acid.

4. Δ^9-Tetrahydrocannabinol (THC) type: Nine THC-type cannabinoids with C1 to C5 side chains are known. The major biogenic precursor is the THC acid A, whereas

Table 1 ***(continued)***

Compound	Structure	Main pharmacological characteristics
Cannabidiol monomethylether (CBDM)	R_1 = H, R_2 = C_5H_{11}, R_3 = CH_3	
Cannabidiol-C_4 (CBD-C_4)	R_1 = H, R_2 = C_4H_9, R_3 = H	
Cannabidivarinic acid (CBDVA)	R_1 = COOH, R_2 = C_3H_7, R_3 = H	
Cannabidivarin (CBDV)	R_1 = H, R_2 = C_3H_7, R_3 = H	
Cannabidiorcol (CBD-C_1)	R_1 = H, R_2 = CH_3, R_3 = H	
Delta-9-tetrahydrocannabinol class		
Delta-9-tetrahydrocannabinolic acid A (THCA-A)	 R_1 = COOH, R_2 = C_5H_{11}, R_3 = H	
Delta-9-tetrahydrocannabinolic acid B (THCA-B)	R_1 = H, R_2 = C_5H_{11}, R_3 = COOH	

(continued)

THC acid B is present to a much lesser extent. THC is the main psychotropic principle; the acids are not psychoactive. THC (6a,10a-*trans*-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol) was first isolated in 1942 *(15)*, but the correct structure assignment by Gaoni and Mechoulam took place in 1964 *(16)*.

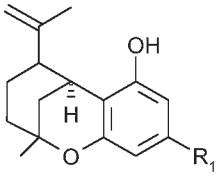
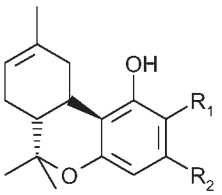
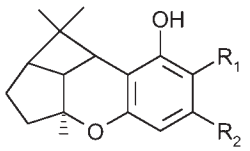
Table 1 ***(continued)***

Compound	Structure	Main pharmacological characteristics
Delta-9-tetrahydrocannabinol (THC)	R_1 = H, R_2 = C_5H_{11}, R_3 = H	Euphoriant Analgesic Anti-inflammatory Antioxidant Antiemetic
Delta-9-tetrahydrocannabinolic acid-C_4 (THCA-C_4)	R_1 = COOH, R_2 = C_4H_9, R_3 = H or R_1 = H, R_2 = C_4H_9, R_3 = COOH	
Delta-9-tetrahydrocannabinol-C_4 (THC-C_4)	R_1 = H, R_2 = C_4H_9, R_3 = H	
Delta-9-tetrahydrocannabivarinic acid (THCVA)	R_1 = COOH, R_2 = C_3H_7, R_3 = H	
Delta-9-tetrahydrocannabivarin (THCV)	R_1 = H, R_2 = C_3H_7, R_3 = H	Analgesic Euphoriant
Delta-9-tetrahydrocannabiorcolic acid (THCA-C_1)	R_1 = COOH, R_2 = CH_3, R_3 = H or R_1 = H, R_2 = CH_3, R_3 = COOH	
Delta-9-tetrahydrocannabiorcol (THC-C_1)	R_1 = H, R_2 = CH_3, R_3 = H	

(continued)

5. Δ^8-THC type: Δ^8-THC and its acid precursor are considered as THC and THC acid artifacts, respectively. The 8,9 double-bond position is thermodynamically more stable than the 9,10 position. Δ^8-THC is approx 20% less active than THC.

Table 1 ***(continued)***

Compound	Structure	Main pharmacological characteristics
Delta-7-*cis*-iso-tetrahydrocannabivarin	 $R_1 = C_3H_7$	
Delta-8-tetrahydrocannabinol class		
Delta-8-tetrahydrocannabinolic acid (Δ^8-THCA)	 $R_1 = COOH$, $R_2 = C_5H_{11}$	
Delta-8-tetrahydrocannabinol (Δ^8-THC)	$R_1 = H$, $R_2 = C_5H_{11}$	Similar to THC (less potent)
Cannabicyclol class		
Cannabicyclolic acid (CBLA)	 $R_1 = COOH$, $R_2 = C_5H_{11}$	
Cannabicyclol (CBL)	$R_1 = H$, $R_2 = C_5H_{11}$	
Cannabicyclovarin (CBLV)	$R_1 = H$, $R_2 = C_3H_7$	

(continued)

6. Cannabicyclol (CBL) type: Three cannabinoids characterized by a five-atom ring and C_1-bridge instead of the typical ring A are known: CBL, its acid precursor, and the C_3 side-chain analog. CBL is known to be a heat-generated artifact from CBC.
7. Cannabielsoin (CBE) type: Among the five CBE-type cannabinoids, which are artifacts formed from CBD, are CBE and its acid precursors A and B.