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Evolution and Classification of *Cannabis sativa* (Marijuana, Hemp) in Relation to Human Utilization

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Abstract *Cannabis sativa* has been employed for thousands of years, primarily as a source of a stem fiber (both the plant and the fiber termed "hemp") and a resinous intoxicant (the plant and its drug preparations commonly termed "marijuana"). Studies of relationships among various groups of domesticated forms of the species and wild-growing plants have led to conflicting evolutionary interpretations and different classifications, including splitting *C. sativa* into several alleged species. This review examines the evolving ways *Cannabis* has been used from ancient times to the present, and how human selection has altered the morphology, chemistry, distribution and ecology of domesticated forms by comparison with related wild plants. Special attention is given to classification, since this has been extremely contentious, and is a key to understanding, exploiting and controlling the plant. Differences that have been used to recognize cultivated groups within *Cannabis* are the results of disruptive selection for characteristics selected by humans. Wild-growing plants, insofar as has been determined, are either escapes from domesticated forms or the results of thousands of years of widespread genetic exchange with domesticated plants, making it impossible to determine if unaltered primeval or ancestral populations still exist. The conflicting approaches to classifying and naming plants with such interacting domesticated and wild forms are examined. It is recommended that *Cannabis sativa* be recognized as a single species, within which there is a narcotic subspecies with both domesticated and ruderal varieties, and similarly a non-narcotic subspecies with both domesticated and ruderal varieties. An alternative approach consistent with the international code of nomenclature for cultivated plants is proposed, recognizing six groups: two composed of essentially non-narcotic fiber and oilseed cultivars as well as an additional group composed of their hybrids; and two composed of narcotic strains as well as an additional group composed of their hybrids.

Keywords *Cannabis sativa* · Marijuana · Hemp · Taxonomy · Classification · Evolution

Introduction

This review reports on recent agricultural, industrial and medicinal advances concerning *Cannabis sativa*, stressing how, to meet various utilitarian needs, humans

have guided the evolution of the plant into a range of diverse domesticated kinds. These have been recognized as "land races," "cultivars," "strains" and "biotypes," which have been grouped taxonomically as species, subspecies and varieties. Two comprehensive categories of domesticated plants are evident, one kind selected for stem fiber and rarely usable for narcotic purposes and the other kind selected for narcotic content. Within the narcotic category, two sets of plants have been recognized, but the distinction between these has been obscured by extensive hybridization. In parallel, within the non-narcotic category, two sets of plants have been recognized, but the distinction between these has also been obscured by extensive hybridization. Further complicating the overall variation pattern, cultivated plants regularly escape to the wild, abandon the domesticated features that shackled them to servitude in cultivation, and establish colonies throughout the world that often interbreed by long-distance pollination with their domesticated relatives. This review first summarizes the history and ecology of *C. sativa*, then examines phenotypic and physiological aspects of the plant that have been moulded by human selection, and concludes with an examination of how to classify the confusing variation patterns that have been generated.

The subject of this review is how humans have domesticated *Cannabis*, causing it to evolve in divergent ways to supply different products. Virtually all major crops have undergone domestication, although the degree of divergence among the different kinds of cannabis plant is more extreme than in most other plants. "The Classification and Nomenclatural Issues" section provides background for the evolutionary nature of domestication, stressing that so-called "artificial selection" (selection by humans) is by nature quite comparable to natural selection, although classifying domesticated plants requires special considerations. There is an intriguing symbiotic aspect of the evolutionary relationship between *Cannabis* and humans: cultural evolution of cannabis use over millennia (i.e., how people have discovered new uses and created new technologies) is the cause of biological evolution of the plant, so that one can discern with exceptional insight how human preferences have resulted in morphological, anatomical, chemical and physiological transformations of the plant.

Cannabis sativa, best known as the source of marijuana, is probably the world's most recognizable, notorious and controversial plant. Because of its criminal association, almost all research and economic development – both narcotic and non-narcotic aspects – were suppressed for most of the 20th century. Most investigations authorized in Western countries were either forensic studies to aid law enforcement, or medical and social research specifically intended to document and reduce harmful effects. By the last decade of the 20th century, however, several developments contributed to a surge of scientific and technological development of *C. sativa* (reviewed in Small & Marcus, 2002; Small, 2007, 2014b). First, in many countries (with the conspicuous exception of the United States), after a half century of prohibition of cultivation, there was a resurrection of production of the plant for non-narcotic purposes. Second, non-narcotic hemp has acquired a reputation for being phenomenally beneficial for the environment, and has become a leading symbol of sustainable agriculture (Montford & Small, 1999a, b; Small, 2012). Third, there has been a substantial and increasing usage of marijuana prescribed for medical purposes. Fourth, in much of Western society there has been a growing tolerance of the extremely widespread recreational use of marijuana, as reflected by a romantic, idealized image in the media, less enthusiastic law enforcement, and even decriminalization in some jurisdictions. Although this article

mentions recent potential medical applications, the intent is not to assess the physiological harm or benefit of marijuana, and indeed most countries (even those with provisions for usage of medical marijuana) have officially adopted the position that there are no legitimate medical benefits. The current sociological, philosophical, political and legal debates concerning cannabis drugs are also outside the boundaries of this review.

Until recently, the genera *Cannabis* and *Humulus* (best known for *H. lupulus*, the hop plant) were considered to constitute the Cannabaceae (Small, 1978a). Recent phylogenetic studies have considerably expanded the family (Sytsma et al., 2002; Yang et al., 2013), but it is clear that *Cannabis* and *Humulus* are well separated from the eight or so other genera that are now included, and constitute a coherent phylad. Grudzinskaya (1988) added the fossil genus *Humulopsis* and split *Humulus* into two genera (although only *Humulus* is currently accepted). *Humulus* species are vines, and easily distinguished from *Cannabis*. However, the fruits (achenes) are very similar, and could be confused. Older texts commonly use the obsolete orthography Cannabinaceae and Cannabiaceae for the family (Miller, 1970). The Cannabaceae are closely related to the Urticaceae and Moraceae, and have sometimes been put in the latter families. A conclusion of this review is that only one species, *C. sativa* L., merits recognition, and the" Classification and Nomenclatural Issues" section of this contribution is concerned with classification issues and the various taxonomic groups of *Cannabis* that have been recognized to date.

The vernacular word "cannabis" has evolved as a generic abstraction from the genus name *Cannabis*, conventionally italicised. Non-italicised, cannabis is employed as a noun and adjective, and frequently (often loosely) used both for cannabis plants and/or any or all of the intoxicant preparations made from them. *Cannabis sativa* is usually called "hemp" when used as a source of fiber, "hempseed" when used as a source of seed oil, and "marijuana" (more commonly spelled "marihuana" in the past) when used for euphoric inebriants and therapeutic drugs. "Industrial hemp" refers to non-narcotic cultivars of the crop grown for fiber or oil, usually licensed for these purposes. The industrial hemp industry is making great efforts to point out that "hemp is not marijuana." Nevertheless, both names have been applied loosely to all forms of *C. sativa*. Although the term "hemp" mostly indicates *C. sativa*, it has also been applied to dozens of species representing more than 20 genera, often prominent fiber crops. For examples, Manila hemp (abaca) is *Musa textilis*, sisal hemp is *Agave sisalina*, and sunn hemp is *Crotolaria juncea*. Especially confusing is the phrase "Indian hemp," which has been used both for narcotic Asian varieties of *C. sativa* (so-called "*C. indica* Lamarck," a name alluding to the historical narcotic use in India) and *Apocynum cannabinum*, which was used by North American Indians as a fiber plant. Adding further to the confusion, "Indian hemp" is sometimes applied to jute (*Corchorus capsularis*), another fiber plant (Ash, 1948). Law enforcement personnel in the U.S. commonly call ruderal *Cannabis* plants (i.e., those growing as established weeds) "ditch weed" (a reflection of its weedy propensities and adaptation to moist soils as found in drainage channels). There are dozens of species with an epithet like *cannabinus* in the scientific name, indicative of similarity with *C. sativa*, but the resemblance is generally superficial (Small, 1975e).

Cannabis sativa is an annual plant, growing vegetatively in the early part of its life cycle, and induced to flower by photoperiod, the timing of induction being one of many

adaptive features of the plant, discussed in this review (in the "Evolution of Photoperiodism Under Domestication" section). The plants are predominantly dioecious, with pistillate plants bearing only female flowers and staminate plants developing only male flowers (Figs. 1 and 2). Male (staminate) plants die after anthesis while female (pistillate) plants persist until frost. Female plants grown in a greenhouse or in climates lacking a cold winter can remain alive for years, although declining steadily in vigor. This potential longevity has led some to term the plants "annual or perennial depending on climate," but it is clear that the species is normally an annual. Sex expression has been remarkably manipulated in domesticated plants, and this topic is dealt with in the "Evolution of Sex Expression Under Domestication" section. The main stalk is erect, furrowed (especially when large), with a somewhat woody interior, and may be hollow in the internodes. Although the stem is more or less woody, the species is frequently referred to as a herb or forb. Plants vary enormously in height depending on environment and whether selected for fiber (the tallest kind), but are typically 1–5 m (heights of 12 m or more in cultivation have been claimed).

The leaf of *Cannabis* is probably more widely recognized than the foliage of any other plant. The leaves tend to be decussate on the lower stem (with opposite pairs, the succeeding pairs turned 180°), usually alternate near the stem apex, petiolate, palmately compound (except for small unifoliolate leaves at branch apices), with an odd number (3–13) of coarsely serrate, lanceolate leaflets. The foliage and stems of some populations are sometimes anthocyanin-streaked, and frost often causes plants to become suffused with purple; as discussed in the "Evolution of Color Under Domestication" section, this represents one of the kinds of coloration that has been preferentially selected.

Fig. 1 *Cannabis sativa* in flower, pistillate (female) plants at *left*, staminate (male) plants at *right*. (Note: unless otherwise stated, all photos are by the author)

Fig. 2 Painting of *Cannabis sativa* from Köhler (1887). **a** Flowering male branch. **b** Fruiting female branch. **c** Cluster of male flowers. **d** Fruit (achene) surrounded by perigonal bract. **e** View of wide (flat) side of achene. **f** View of narrow side of achene. **g** Pistil, showing ovary and two stigmatic branches. **h** Pistil surrounded by young perigonal bract

Cannabis has been employed for numerous purposes, primarily fiber from the main stalk, narcotic drugs from the flowering parts (used mostly illicitly for recreation and more or less legally as medicinals), and oilseed (employed for human food, livestock feed, nutritional supplements, industrial oils, and occasionally as a biofuel). Historically, the same plants were often used simultaneously for different purposes. However, this review is particularly concerned with how humans have selected kinds of *Cannabis* that are especially productive for just one of the three commodities. The stem is an important source of bast (phloem) fiber, and the extensive modification of the anatomy of strains domesticated for fiber is discussed in detail in the "Evolution of Stem Fiber Production Under Domestication" section. Much of the above-ground parts

of the plant are pubescent with stiff, pointed cystolithic trichomes, which are a mechanical defense against herbivores. By definition, such hairs contain a basal concentration of calcium carbonate, which presumably is unpleasant to chew, so protecting the plants from being eaten. Small, secretory, resin-producing glands are also present on the shoot epidermis. The unique chemicals (cannabinoids) in these glands have undergone considerable evolution under the hand of mankind, and are discussed in detail in the "Evolution of Narcotic Drug Production Under Domestication" section. *Cannabis* is also employed as a source of a multi-purpose fixed (i.e., non-volatile vegetable) oil in the achenes ("seeds"), and this additional dimension of variability caused by human selection will be examined in the "Evolution of Seed Oil Production Under Domestication" section.

Geography, Ecology and Ancient Domestication

Cannabis sativa is widely regarded as indigenous to temperate, western or central Asia. However, no precise area has been identified where the species occurred before it began its association with humans. De Candolle (1885) speculated that the ancestral area was the southern Caspian region, and other authors (e.g., Walter, 1938; Sharma, 1979) have suggested that the plant is native to Siberia, China or the Himalayas. Certainly, the plant is of Old World origin. For at least the last 6000 years, *C. sativa* has been transported widely, providing extensive opportunities for establishment outside of its original range (Abel, 1980; Clarke & Merlin, 2013). Because the species has been spread and modified by humans for millennia, there does not seem to be a reliable means of accurately determining its original geographical range, or even whether a plant collected in nature represents a primeval wild type or has been influenced by domestication (Schultes, 1970). The seeds of some wild-growing populations in India are remarkably small, unlike those collected from any other area of the Old World, but whether this is indicative of an ancient wild form is unclear. As discussed in this review, whatever ecological constraints once limited *C. sativa* to its ancestral home range, over the millennia it has become adapted to grow in much of the world.

Of the well over 100 informal or vulgar names that have been recorded for the marijuana form of *C. sativa*, "weed" is the most frequent, and accurately reflects the nature of the species. *Cannabis* growing outside of cultivation is indeed basically a weed, growing mostly in habitats created or modified by humans (Fig. 3). The extremely wide range of circumstances in which one finds weedy growth includes: the borders of fields, on rubbish heaps near settlements or habitations, in farmyards, waste places, vacant lots, in disturbed areas of pastures, in fallow fields (but not those that are sod-bound), along or beside roadsides, railways, ditches, creeks, fence rows, borders of cultivated fields, bridge embankments, lowland drainage tributaries and open woods (Haney & Bazzaz, 1970; Haney & Kutscheid, 1975). The species seems very poorly adapted to penetrating into established stands of perennial vegetation, and generally invades such areas only after the soil is freshly disturbed. As a colonizer, weedy hemp spreads slowly, except in drainage channels, a habitat to which it is very well adapted.

The circumstances and adaptations of extant wild-growing populations of *C. sativa* provide a basis for judging its ecology before human influence. The species thrives in

Fig. 3 Ruderal (weedy) hemp near Ottawa, Canada. This photo shows several characteristic habitat features of *Cannabis sativa*: (1) The plants are in an open, sunny location. (2) They are growing near a manure shed, in nitrogen-rich soil. (3) A stream is nearby, maintaining a moist substrate. (4) The soil near the stream is alluvial (sandy and well-drained). (5) Competition from other plants is limited

mammalian-manured, continuously moist but well-drained soil, in open areas with limited competition from other plants. This suggests that ancestral *C. sativa* grew on the alluvial soils near streams and other water bodies, and depended on herds of wild, large, mammalian grazers to deposit excrement (Fig. 4).

Cannabis sativa is the most widely cited botanical example of a crop that is postulated to have evolved initially as a "camp follower" (Anderson, 1954; Schultes, 1970). Humans at the hunter-gatherer stage are thought to have been nomadic, often traveling among temporary camps, and creating trails among these. Abandoned camp-sites and paths would tend to be open (unshaded), located frequently near lakes or streams, and the soils would be enriched by deposition of organic materials (excrement and unused remains of harvested animals and plants). Seeds and roots from gathered plants that humans would have selected for their usefulness would also be deposited in these open, fertilized areas. This amounts to selective planting of desirable plants in protected situations where they will receive excellent light and soil – a precursor of cultivation. Inevitably, people would have noticed and eagerly harvested materials from the plants that were growing along their routes and former homesteads, especially in garbage dumps, and such plants would have been among the first that would have been considered for deliberate planting. As described by Anderson (1954), this explanation is variously known as the "rubbish heap" or "dump heap" hypothesis (in archaeology, rubbish heaps are referred to as "kitchen middens"). It is interesting that, in parallel, some monkeys have been shown to create "monkey gardens" – concentrations of preferred food plants in areas where they have discarded seeds (Rindos, 1984). Uncultivated, colonizing plants that grow vigorously in human-cleared areas are known

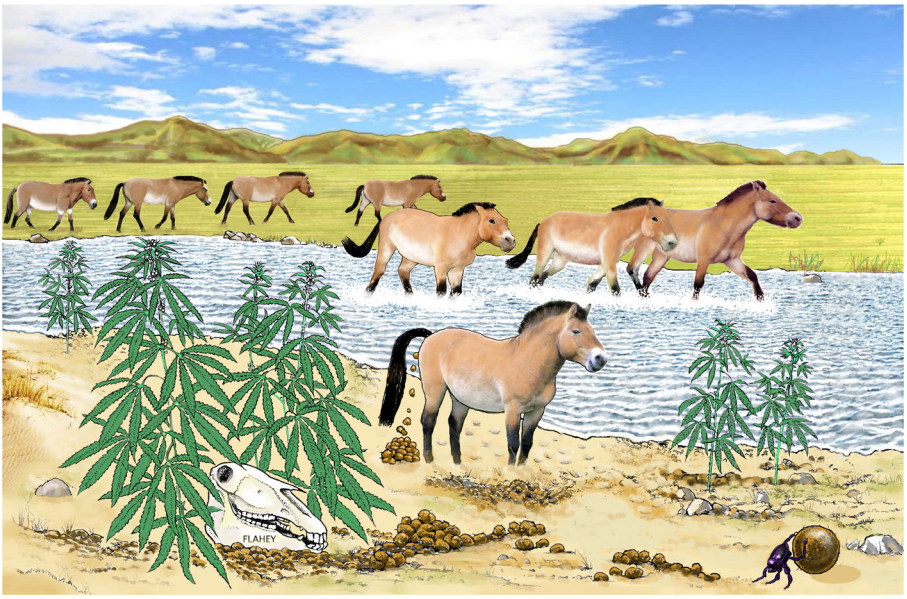


Fig. 4 An interpretation of the pre-human ecology of *Cannabis sativa*. The habitat requirements of modern ruderal hemp (natural adaptation to well manured, moist but well drained soils and open sunny locations, as shown in Fig. 3) suggest that the ancestral plants thrived near streams frequented by mammalian herds. Prepared by B. Flahey

as weeds. It is no accident that many, probably the majority of the world's major domesticated crops are related to, or are known to have originated from such plants. The ability to be weedy clearly pre-adapts plants to being domesticated. *Cannabis sativa* is superbly adapted for the role of camp follower. It is very weedy by nature. It is also a nitrophile, and would have grown exceptionally well in the manured soils around early settlements. Its propagules are thought to be distributed by streams, which as noted above are often near campsites, as well as by people and animals, including domesticates. Because *Cannabis* has products (stem fiber, edible seeds, intoxicating tissues) that could have been easily harvested and utilized by prehistoric peoples, it was almost certainly associated with humans in very early times (Fig. 5). Indeed, hemp may have been harvested by the Chinese 8500 years ago (Schultes & Hofmann, 1980), and has probably been grown for at least 6000 years, making it one of the world's oldest crops. For most of its history, *C. sativa* was most valued as a source of stem fiber, considerably less so as an intoxicant, and only to a very limited extent as an oilseed crop. Hemp is one of the oldest sources of textile fibers, with extant remains of hempen cloth trailing back 6 millennia. Hemp grown for fiber was introduced to western Asia and Egypt, and subsequently to Europe somewhere between 1000 and 2000 BC. Cultivation in Europe became widespread after 500 AD. A superb documentation of historical usage and cultural diffusion of *Cannabis* is provided by Clarke and Merlin (2013).

For most plants, nitrogen is the most critical limiting nutritional element, and most wild plants are adapted to substrates in which nitrogen is in short supply. Most annual domesticated crops, however, have been bred to be nitrophiles, with the capacity to utilize large amounts of nitrogen for productive growth (Emerich & Krishnan, 2009).

Fig. 5 An interpretation of the early domestication of *Cannabis sativa* in accord with the "camp-follower" and "dung-heap" hypotheses of crop origin. The plant would have been collected from the wild as a source of stem fiber, edible seeds, and inebriating resin. Seeds discarded on refuse dumps near temporary camps would have found ideal conditions (manured soil, an open sunny location, probably proximity to a water supply, and limited competition), and consequently would have become desirable companions for mankind. The pipe-smoking shown represents artistic license, as ancient methods of smoke inhalation in the Old World are controversial (Clarke & Merlin, 2013). Prepared by B. Flahey

Modern agriculture in fact is to a considerable degree based on the creation of crops that can utilize nitrogen fertilizers. The "Green Revolution" of the middle of the last century greatly increased agriculture production, especially in the Developing World, by selecting new cultivars that are especially capable and efficient at using nitrogen fertilizers (Borlaug, 2000). Wild *C. sativa* is a natural nitrophile, thriving in well-manured substrates, and stripping soils readily of nitrogen. Notes accompanying herbarium specimen collections of the species commonly mention the presence of nearby manure. Vavilov (1926) observed that wild hemp in Russia thrives in low places and ravines into which wild animal excrement is washed, and on soils manured by grazing cattle. Manure not only supplies nutrients, but the humus is important in retaining moisture that hemp demands (Dewey, 1914). Weedy hemp in the U.S. has been collected on sandy soils very low in nitrogen, but the plants are dwarfed (Haney & Bazzaz, 1970). Cultivars are typically fertilized with nitrogen at a rate of 100 kg/ha/season (Bócsa & Karus, 1998), which is higher than the recommended rates for some modern high-yielding field crops.

Several terms are used to denote plants of different degrees of "wildness" growing outside of cultivation, and it is critical to be aware of their ambiguity in discussing *C. sativa* as a weed. Plants that develop as a result of seeds unintentionally scattered from cultivated plants are said to be "volunteers," a label used in agriculture. For the most part volunteers appear on or very near the field where the maternal plants were grown. The word "spontaneous" is used in floristics to denote plants that appear locally

as a result of human activities, but do not spread. Such plants can be domesticates (e.g., tomatoes growing only on refuse heaps where tomato seeds were discarded; cereals growing only near mills where the seeds were processed), or wild (e.g., seeds of foreign plants transported in ship ballast and appearing only where the ballast has been discarded). The term *ruderal* (applied both to plants and their habitat) means growing in waste places or rubbish, and is descriptive of the habitat of perhaps the majority of weeds. One also encounters "feral" applied to hemp (and other weeds), although mostly the word is used for escaped domesticated animals (such as dogs and horses) that are living outside of human control. Both the words feral and ruderal are ambiguous, since they are applied to a) those escaped domesticates that basically retain all of their domesticated charateristics but nevertheless establish and spread vigorously outside of cultivation, and to b) types of plants that differ dramatically from domesticates, with adaptations specifically suited to wild existence. The term "wild" is also ambiguous. It has been used in a narrow sense to refer to populations of a species that are essentially uninfluenced genetically by domestication, and in a broad sense to include all populations growing outside of cultivation. The distinctions discussed in this paragraph are examined additionally in the "Classification and Nomenclatural Issues" section.

Weedy hemp is particularly widespread in southeast and central Asia, common in many European countries and, less frequent in South America, Australia and Africa (Davidyan, 1972). According to Haney and Kutscheid (1975), *C. sativa* seldom becomes naturalized as a result of escapes from cultivated hemp in subtropical and tropical areas. In North America, the species is best established in the American Midwest and Northeast, and in southern Ontario and southern Quebec, all areas where hemp cultivation was concentrated historically in recent centuries. *Cannabis sativa* has been collected growing outside of cultivation from Canadian provinces from British Columbia to New Brunswick (Small, 1972b; Small et al., 2003). Naturalized hemp is uncommon in the western U.S., rare in the U.S. south of 37° N latitude, and very rare in Mexico (Haney & Kutscheid, 1975). In most of the world, wild-growing *Cannabis* is of limited concern, but there have been long-continued efforts by law-enforcement to eradicate ruderal plants in North America. In contrast to the huge social costs, the deleterious effects of *Cannabis* as a weed in North America are relatively minor. Discovery of extensive growth of ruderal hemp on a farm often invites unwelcome attention, from the legal authorities as well as from delinquents who mistakenly believe that ruderal hemp in North America is as intoxicating as high-quality marijuana. As an agricultural weed, however, ruderal hemp is of limited importance (Small et al., 2003).

Reflective of its extensive geographical distribution, ruderal *C. sativa* occurs in a wide range of climates. Domesticated forms of the plant have narrower tolerances than the wild-growing counterparts (Small et al., 2003). Both domesticated and wild plants of *Cannabis sativa* develop best in full sun, and weedy plants thrive in open areas. However, some wild plants have been observed growing well in shaded habitats in Europe (Janischevsky, 1924) and Canada (Small et al., 2003). Both domesticated and wild plants of *C. sativa* are tolerant of hot, arid conditions provided that the roots are adequately supplied with water, but ruderal plants in Europe have been observed to be much more drought resistant than cultivars (Janischevsky, 1924). In North America, Haney and Bazzaz (1970) noted that wild hemp in sandy soils in Illinois survives dry conditions in deep, loose-textured soils by virtue of the roots growing to gain access to deep water sources. *Cannabis sativa* does not tolerate cold temperatures well, but once

again the weedy forms are more stress-tolerant; in northern areas, the seeds germinate at lower temperatures and the seedlings survive frost better than do cultivars (Haney & Kutscheid, 1975). Compared to most fiber cultivars (which tend to have hollow stems), wild plants are also relatively wind resistant, due to low stature and woodier, flexible stems. Wild plants in the Old World have adapted to various habitats for thousands of years, while those in North America have a history of only a few hundred years. Not surprisingly, in Eurasia the species grows wild over an enormous range of climates and altitudes, much greater than in North America. Vavilov (1926) observed vast stands of wild hemp in Eurasia. In the Himalayas, *C. sativa* occurs at altitudes of thousands of meters.

Humans, animals, water, and insects have been proposed as disseminating agents for wild hemp. Since wild *C. sativa* is dioecious, the most effective dispersal agents should distribute at least a seed of each sex to a given site, although pollen is distributed so widely that even isolated plants may participate in reproduction. Since birds are strongly attracted to the seeds, Haney and Bazzaz (1970) suggested they are likely the most important wild animals distributing them in North America. Virtually no wild hemp seeds fed to upland game birds (quail and doves) survived (Small et al., 2003), but it is possible that some seeds are transmitted by adhesion to claws or bills (Merlin, 1972). Weedy hemp in North America is often found in alluvial sites disturbed by flooding, and flood waters may serve to distribute the seeds (Haney & Bazzaz, 1970). Ruderal hemp clearly depends heavily on human activities for dispersal. Because large wild herds of mammalian grazers probably were important to providing manured habitats for *Cannabis*, and the species characteristically grows in moist areas, the mammals may have distributed seeds caught up in mud on their hooves. In more recent times, domestic livestock may similarly serve as distribution vectors. Seed weight in *C. sativa* varies enormously, from more than 1000 seeds to the gram in some wild Asian plants to less than 15 seeds to the gram for some cultivated plants (Vavilov, 1926; Watson & Clarke, 1997). The ecology of the species may differ considerably according to the size of the seeds, and this remains to be studied.

Both wild and cultivation plants that grow for many generations in a particular location tend to evolve adaptations to their local climates, and these adaptations may make a given biotype quite unsuitable for a foreign location. In the "Evolution of Narcotic Drug Production Under Domestication" and "Classification and Nomenclatural Issues" sections, the narcotic "Group 4" (so-called "indica type") is discussed. This is established in the arid area of Afghanistan and western Turkmenistan, and when strains from this region are grown in high-humidity climates their dense flowering tops retain moisture and succumb to "bud mold" caused by *Botrytis cinerea* and *Trichothecium roseum* (McPartland et al., 2000). In the "Evolution of Photoperiodism Under Domestication" section, photoperiodic adaptation to latitude is discussed, and it is pointed out that when strains adapted to the season of one area are grown in an unsuitable latitude they may fail to develop seeds.

Phenotypic Plasticity: a Key to Success

Phenotypic plasticity is "the ability of individual genotypes to alter their growth and development in response to changes in environmental factors" (Barrett, 1982). It is

flexibility of response, and allows a population to survive in a broad range of environments, especially marginal conditions. It is a key component of the genetic system of weeds (Bradshaw, 1965; Baker, 1974), and is often critical to the ability of species to diversify and adapt in response to natural and human-caused selection (West-Eberhard, 2003). Most of the ecological adaptations of *Cannabis* discussed in the previous section contribute to its exceptional adaptive phenotypic plasticity. Some particular aspects related to this topic are dealt with in the following.

Nature vs. Nurture in the Determination of Characteristics

In the early 20th century, a sort of Lamarckian conception of semi-permanent induction of characteristics by the environment was sometimes applied to explain why *C. sativa* strains suited for fiber production in temperate climates, when transplanted to hot, dry climates, would apparently transform into narcotic cultivars, and vice-versa (for a proponent of this viewpoint, see Bouquet, 1950). As explained in the "Classification and Nomenclatural Issues" section, maintaining the purity of a strain of *Cannabis* requires stabilizing selection and protection from contaminating pollen, and the absence of these probably accounts for observations that *Cannabis* grown in a foreign location seemed to transform remarkably in a few generations. It is clear that although environment does influence the development of the characteristics of *Cannabis*, indeed of all organisms, strains selected for fiber or narcotic characteristics retain their capacities for such production so long as their gene frequencies are maintained. Of course, the ability of *Cannabis* to change genetically as a result of hybridization and selection should not be confused with the concept of phenotypic plasticity.

Surviving Soil Infertility

Like many weeds, *C. sativa* is very plastic in a range of edaphic conditions, responding with dramatically increased growth to a good supply of soil nutrients, but able to produce dwarfed plants in very infertile conditions and still produce a few seeds. Given that the species is a nitrophile, it has a remarkable ability to survive in soils deficient in this element.

Root Flexibility in Relation to Ground Water Level

Cannabis develops a laterally branched taproot. The root system provides another example of flexible response in relation to environmental circumstances. Haney and Bazzaz (1970) noted that wild hemp in sandy soils in Illinois seemed able to tolerate dry conditions because the roots penetrated to deep water sources. In coarse textured, well-drained soils the primary root of wild hemp can extend more than 2 m down, allowing access to a low water table. In medium-textured, moderately water-retentive soils the primary root develops to a depth of about 1 m, with extensive laterals concentrated in two locations: near the surface and at about 1 m, a bet-hedging strategy enabling acquisition of both surface and moderately deep water. If the water table is near the surface (generally undesirable for good growth of *C. sativa*), the root system is shallow.

Resistance to Catastrophic Stem Damage

Cannabis sativa normally has a dominant leader stem which produces a central stalk. As discussed in the following paragraphs, the species has an amazing capacity to recover from catastrophic damage to the main stem.

The European corn borer (*Ostrinia nubilalis*) or ECB (Fig. 6a), is a major Lepidopteran pest of *C. sativa*. Young ECB larvae eat hemp leaves until half-grown, then bore holes into the stems. A typical entrance hole resulting from an attack on the main stem is shown in Fig. 6b. The insect is indigenous to the Old World, where it apparently once reproduced mainly in association with *Cannabis* and its close relative *Humulus* (although also attacking many other plant species). It was not exposed to corn (i.e., maize, *Zea mays*), which is indigenous to the Americas, until post-Columbian times ("European hemp borer" would have been a better choice of name). In a study of ECB infestation of a large experimental field, Small et al. (2007) discovered that ECB damage to *Cannabis increased* the shoot weight of the plant by 20 %, concomitantly enlarging seed production, indicating that *Cannabis* is adapted to the insect. The

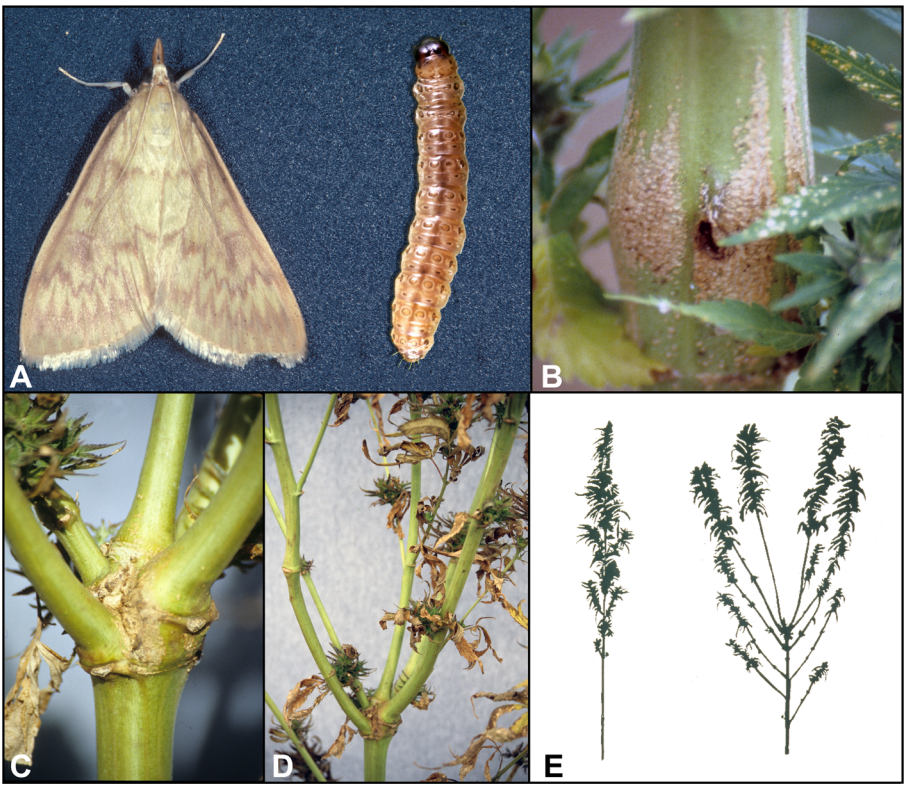


Fig. 6 Response of *Cannabis sativa* to European corn borer (*Ostrinia nubilalis*). **a** *Left*: female adult; photo by Frank Peairs, Colorado State University, Bugwood.org (CC BY 3.0). *Right*: larva; photo (public domain) by Keith Weller, U.S. Agricultural Research Service. **b** Photograph of a European corn borer infestation site on a *Cannabis sativa* stem. Note frass around entrance. **c**, **d** Photographs of site of branch proliferation caused by European corn borer damage. **e** Silhouettes of normal plant (*left*) and plant developed after European corn borer damaged the leader. Figures **b**–**e** based on Small et al. (2007)

expanded productivity observed was due to branch proliferation at the site of the attack (see Fig. 6c and d). Figure 6e shows silhouettes of a normal and an ECB-damaged plant, and it is evident that the increased number of branches resulting from the damage has produced more biomass and more seeds. (The insect preferred larger stems, but was unaffected by THC content.)

There is controversy whether insect damage may, at least in a limited sense, be good for plant productivity. McNaughton's (1983) classic paper in this regard proposed that in some circumstances plants can respond to herbivory by just growing faster ("compensation" or "overcompensation"). Verkaar (1986) surveyed papers purporting to support the hypothesis that grazing can have positive effects on plant growth and fitness, and concluded that "the hypothesis may only be tenable under very particular circumstances." Additional literature on the topic is reviewed in Small et al. (2007).

Horticulturally, it is well known that destroying leader buds to induce proliferation of flowers or fruits in a range of plants can increase productivity, so it is logical that insects that carry out this activity might also be beneficial to crop production. Moreover, humans have engaged in the practice of damaging stems to increase productivity of *Cannabis*. Pate (1998b) noted that when growing hemp for seed, the number of flowers per plant and the number of seeds produced can be increased by "topping" the plants when 30 to 50 cm high. Dewey (1902) observed that hemp grown in North America at the turn of the century was sometimes topped to make it spread and produce more seed. Clandestine growers of narcotic strains also sometimes remove the tops of their plants to produce more of the desired high-THC inflorescences, the "buds" (see the "Evolution of Narcotic Drug Production Under Domestication" section).

Evolution of Sex Expression Under Domestication

Sexual selection is often recognized as a special kind of natural selection (Darwin, 1859). It involves competition within a gender for the opposite sex, and is important in evolution. In nature, males often are especially important in sexual selection. Human selection of the sexual characteristics of domesticated species is also a powerful evolutionary force but, by contrast, the males of domesticates have lost much of their importance. Farmers often favor females of livestock (bulls are much harder to manage than cows, do not produce milk or calves, and only a limited number are needed for reproduction). As discussed in the following paragraphs, male *Cannabis* plants have also suffered significantly under domestication: (a) humans have created many cultivars that are monoecious (the plants bearing both male and female flowers), but a preponderance of female flowers has been favored; (b) cultivars have been created by hybridization that are entirely female; (c) for narcotics production, male plants are usually eliminated; (d) clones maintained for narcotics production are female. A curious aspect of sexual evolution of *Cannabis* under domestication has to do with the fact that humans have turned a normally dioecious species into forms that are monoecious. This constitutes reversing the normal pattern thought to exist in nature – that dioecious species have evolved from monoecious ones (Lewis, 1942).

The wild plants of *C. sativa* are among the small minority (4 % according to Yampolsky and Yampolsky (1922), 6 % according to Renner and Ricklefs (1995), or some undetermined higher figure according to Bawa (1980)), of flowering plants with

male reproductive organs (stamens) and female reproductive organs (carpels) confined to separate plants (i.e., the populations are dioecious, with unisexual flowers, those on a given plant either entirely male or entirely female). Staminate plants, with male flowers only, are routinely called males, and pistillate (carpellate) plants, with female flowers only, are called females, and this standard terminology (albeit technically incorrect, since the sporophytic phase of plants is asexual) is followed here.

Floral primordia are normally initiated in mid-summer, with development proceeding from the base upwards to the top of the inflorescence. The flowers of *Cannabis* are small but very numerous. The staminate inflorescences are large, showy, loose, axillary, cymose panicles (thyrses), while the pistillate ones are small, obscure, congested, axillary, spicate cymes. Male flowers are pedicellate, with five greenish or whitish tepals and five stamens with flaccid filaments opposite the tepals. The male flowers fall away after anthesis. The female flowers consist of a superior, unilocular ovary and a short apical style with two long filiform stigmatic branches. Unlike the male flowers, the female flowers are essentially sessile. A perigonal bract (sometimes called a floral bract) subtends each female flower, and grows to envelop the fruit (this is important in narcotic resin production, and additional detail is given in the "Evolution of Narcotic Drug Production Under Domestication" section). In contrast to the male flowers, the female perianth is not at all recognizable as tepals, consisting of a thin undivided layer adhering to the ovary (this unusual anatomical feature is very important ecologically as discussed in the "Evolution of Propagules Under Domestication" section, and for classification purposes, as discussed in the "Classification and Nomenclatural Issues" section).

The sexes are dimorphic not just with respect to reproductive organs: male plants tend to be 10–15 % taller, although less robust than the female plants, with slimmer stems, less branching, smaller leaves, and a more delicate appearance, and they die after shedding their pollen. Female plants protected from frost can remain alive for years (gradually losing vitality), although the species is normally an annual. However, cloned biotypes of female marijuana plants are often regenerated for many years by repeated cuttings, which does maintain plant vigor. Before sex in plants was widely understood, many 18th century European botanists (males at the time, reflecting their perception of masculine superiority) often referred to the vigorous females as males, and the wimpy males as females (Bouquet, 1950). (However, by that period some European botanists appreciated the true nature of sex in flowering plants (Anonymous, 1933).)

The sole purpose of the males is to produce pollen, and they excel at this task: a single flower can produce about 350,000 pollen grains (Faegri et al., 1989), and there are hundreds of flowers on larger plants. The stigma is densely covered with receptive trichomes to receive pollen. *Cannabis* is wind-pollinated, and the pollen can be blown long distances. It has been claimed that crossing has occurred at a span of over 300 km (Clarke, 1977). Cabezudo et al. (1997) noted that *C. sativa* pollen, apparently from marijuana cultivated in North Africa, was transported by wind currents to southwestern Europe. Hemp pollen is a significant allergen for some people (Lindemayr & Jager, 1980), so its presence is often monitored. Stokes et al. (2000) recorded that in August in the Midwestern United States (where cultivation of hemp is not permitted, but weedy hemp is common) hemp pollen represented up to 36 % of total airborne pollen counts! Because the pollen of *Cannabis* spreads remarkably, an isolation distance of about 5 km is usually recommended for generating pure-bred seed, exceeding the distance for

virtually every other crop (Small & Antle, 2003). Because of widespread clandestine cultivation, the pollen can be found, at least in small concentrations, over most of the planet. While the inverse square law dictates that the probability of pollen distribution decreases rapidly with distance, it is likely that there is frequent genetic interchange among populations.

Although self-fertilization is possible in *C. sativa*, inbreeding depression is pronounced (conversely, so is hybrid vigor). To promote outcrossing, male plants of a given population tend to come into flower 1–3 weeks before female plants have receptive stigmas. Male flowers at anthesis are very attractive to bees, including bumble bees and honey bees, which collect substantial amounts of pollen. Pollen-collecting flies are also often present. However, these insects do not visit the female flowers and so do not play a role in pollination.

Inheritance of sexual expression in *Cannabis* has been studied extensively (Hoffmann, 1970). Sexual differentiation in dioecious strains is based on a pair of sex chromosomes, the male being heterogametic (XY, the Y chromosome allegedly larger (Sakamoto et al., 1998), unlike mammals, but like some other plants), producing an approximately 50:50 sex ratio. However, sex expression appears to be somewhat determined autosomally, with an X/autosome dosage type chromosome system (Ainsworth, 2000). Sex development is labile, modifiable by a wide range of environmental factors and hormonal treatments (Heslop-Harrison & Heslop-Harrison, 1969). The application of auxins or ethylene feminizes *Cannabis* (Heslop-Harrison, 1956; Mohan Ram & Jaiswal, 1970), whereas gibberellins are masculinizing (Atal, 1959; Chailakhan, 1979). The proportion of female plants has been reported to be increased after exposure of seeds to ultraviolet light, and decreased by shorter day-length during the growing season, and higher nitrogen concentrations in the soil (see Haney & Kutscheid, 1975 for references). Such factors can result in sex reversal, and indeed the aberrant production of plants with male, female, and intergradient flowers. In a survey of over 1400 U.S. herbarium specimens, 55 % were male, but only 41 % of the plants collected along streets and highways were male; Haney and Bazzaz (1970) speculated that this could be due to the higher carbon monoxide levels near roadways. This is intriguing as carbon monoxide has been shown to favor the development of female flowers (Heslop-Harrison & Heslop-Harrison, 1957).

There have been numerous studies of male-associated and female-associated DNA markers (e.g., Mandolino et al., 1999, 2002; Sakamoto et al., 2000; Flachowsky et al., 2001; Peil et al., 2003; Shao et al., 2003; Cristiana Moliterni et al., 2004; Rode et al., 2005; Sakamoto et al., 2005).

Many cultivars, especially those selected for stem fiber production, are monoecious (with both male flowers and female flowers, and often with sexually intergradient flowers, on the same plants), or at least substantially so (i.e., some plants may also be entirely or mostly male, some may also be entirely or mostly female). In monoecious forms, staminate flowers, if present (frequently on the upper part of flower-bearing stems) are produced before the pistillate flowers (frequently on the lower parts of stems); staminate flowers, if present, are also produced before transitional hermaphroditic flowers (some of which are sometimes sterile), which are also often encountered. In some populations, one finds plants that are 100 % male, 100 % female, and a spectrum of plants with intermediate sexuality (a population structure that has been termed “subdioecy”). While male plants almost always die after shedding pollen, the

presence of even a few female flowers on hermaphroditic plants seems to protect them against dying before seed set (personal observation). However, in a plantation setting there is a much reduced need for the prodigious pollen production that is normal in the wild plants, so hermaphroditic plants tend to be bred that are predominantly female.

Recently escaped plants are occasionally monoecious, but monoecy is associated with inbreeding depression, and is therefore very rare in wild *C. sativa*, which is naturally strongly outcrossing (Heslop-Harrison & Heslop-Harrison, 1969). Monoecy is also associated with smaller, less vigorous pollen grains. Migalj (1969) found that the acetolyzed pollen grains of dioecious strains tended to have a diameter averaging about 33 μm, while the grains of monoecious strains were smaller, with a diameter averaging about 27 μm; and the pollen of dioecious plants was also more uniform, while that of monoecious plants were more variable in size and in number of pores. Zhatov (1983) reported that pollen viability in monoecious strains tends to be lower than in dioecious strains.

Some artificial hybrids obtained by pollinating females of dioecious lines with pollen from monoecious plants are predominantly female (so-called "all-female," these generally also produce some hermaphrodites and occasional males). All-female lines are productive for some purposes (e.g., they are very uniform, and with very few males to take up space they can produce considerable grain), but the hybrid seed is expensive to produce. So-called "feminized" seeds are often offered in the marijuana trade, these producing plants with female flowers only (as noted below, only female plants are normally used for narcotics production).

For production of narcotic resin, male plants are eliminated before they can shed pollen to fertilize the females, as unfertilized female inflorescences are highly valued (see the "Evolution of Narcotic Drug Production Under Domestication" section). Female narcotic plants have as much as 20 times the concentration of THC as corresponding males (Clarke & Merlin, 2013). By contrast, male fiber plants, although also less productive than corresponding females, produce a higher quality of fiber, and before the 20th century were often harvested separately by hand, when labor was cheap. Today, males are considered undesirable for fiber, because they senesce earlier and degenerate, thus decreasing the overall quality of fiber harvested. In former, labor-intensive times when the plants were hand-harvested separately, selection pressures were probably more or less equal for the sexes, or perhaps there was some preference for male plants. Monoecious varieties are commonly utilized today for fiber, so that all plants mature simultaneously and their quality is uniform. For production of oilseed, dioecious varieties are frequently employed, although at present there are very few varieties exclusively used for oilseed production. Several "dual-purpose" varieties are grown for simultaneous production of fiber and oilseed, and these may be monoecious or dioecious. Because female plants are more valued for oilseed and narcotics, selection has been much more directed to the females than the males.

Humans propagate many crops vegetatively (e.g., apples, potatoes, strawberries) as clones, a tactic to avoid the variability produced by sexual reproduction, in order to maintain a uniform genotype that is especially desirable. This is the method increasingly being used to propagate (female) strains of narcotic *Cannabis*, particularly the most desirable biotypes (Chandra et al., 2010b). In perhaps an ultimate departure from normal plant sexual reproduction, propagules of narcotic strains, generated by tissue culture, have been encapsulated to form "synthetic" or "artificial" seeds (Chandra et al., 2010a; Lata et al., 2011).

Evolution of Propagules Under Domestication

In nature, plants reproduce mainly by distributing propagules, mostly seeds and fruits (occasionally vegetative tissues), commonly by wind, water, gravity, and cooperating wild animals. Humans have domesticated many wild plants, frequently specifically to harvest the seeds or fruits. Many wild plants cast off their seeds or fruits as soon as they mature, by various mechanisms. This has two undesirable consequences from the human perspective: when a seed or fruit drops away it is more difficult to collect; and when seeds or fruits do not remain attached to the plant at maturity, it necessitates repeated collection of propagules from each plant over the weeks that they sequentially mature. Selecting mutations that inactivate the separation mechanisms (abscission of fruits, dehiscence of fruits to release seeds) so that the mature seeds or fruits remain on the plant greatly facilitates harvest. This is the most important way that humans have domesticated the majority of crops (Harlan, 1995; Fuller & Allaby, 2009). Cereals currently supply more than half of the calories consumed by humans (Small, 2009), and in all of them a "domesticated syndrome" of characteristics is recognizable whereby the edible fruits (caryopses) have lost the features in their wild ancestors that cause the grains to detach and scatter away (see, for example, Sakuma et al., 2011). Although the precise anatomical and morphological changes that keep cereal grains attached differ between domesticated cereals and domesticated *C. sativa*, one can recognize a comparable domesticated syndrome of propagule characteristics in all strains of fiber hemp, oilseed hemp and narcotic hemp.

Cannabis plants domesticated for fiber, oilseed, or narcotics tend to differ from plants adapted to wild (ruderal) existence, most characteristically in the achenes (Small, 1975a). For many crops and their wild progenitors, propagule characters are an excellent index or gauge of the relative state of domestication, and this is the case in *Cannabis* (Small, 1975a). In contrast to the achenes of domesticated forms of *Cannabis*, wild achenes are smaller (generally less than 3.8 mm long), disarticulate more readily (facilitated by an attenuated base), are covered by a tightly adhering camouflagic mottled layer (homologous with the perianth), have relatively thick pericarp walls, are relatively long-lived, and do not all germinate more or less simultaneously (Vavilov, 1926; Small, 1975a). By examining the relative development of these achene features, one can often evaluate whether a *Cannabis* plant is merely recently escaped from cultivation or derived from plants that have lived in the wild for a considerable period and consequently evolved wild characteristics. The morphological differences between the achenes of wild and domesticated *C. sativa* are shown in Fig. 7.

The anatomy, morphology and germination behavior of the achenes is key to the survival of wild hemp. The attenuated base and well-developed abscission zone of the wild achenes facilitate disarticulation as soon as the fruits are ripe, and this minimizes the period that they are available for predation by birds. Additionally, the camouflagic mottled layer covering the achenes of wild plants keeps the fallen ones hidden from mammalian and insect herbivores. Janischevsky (1924), working on the ecology of ruderal Russian hemp, noted that birds are very infrequently seen on the ground in pursuit of fallen seeds. By contrast, the achenes of domesticated plants mostly remain on the plant, and birds perch on the infructescences gorging on the seeds. In contrast to the thin wall of domesticated achenes, the comparatively thick wall of wild achenes provides mechanical protection. Additionally,

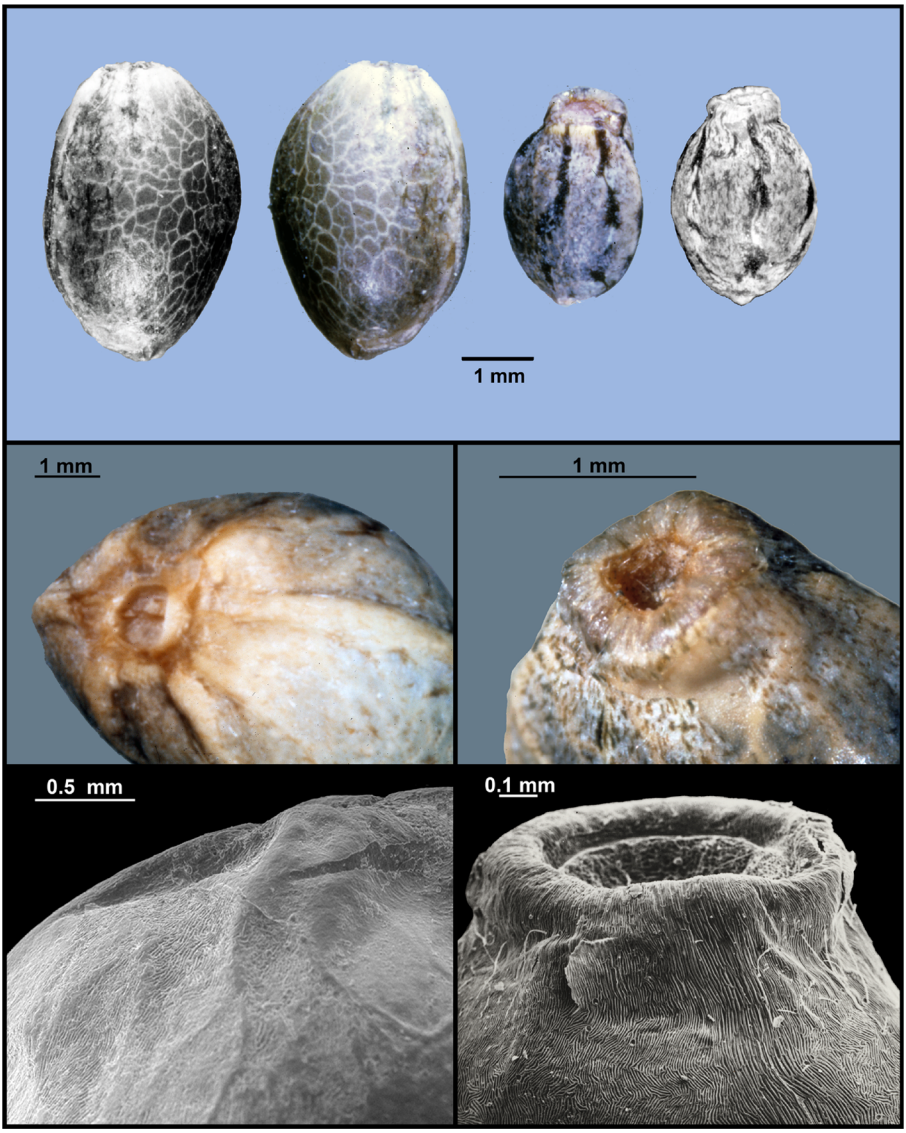


Fig. 7 Achenes ("seeds") of *Cannabis sativa*. *Left side* shows achenes of domesticated plants, *right side* shows achenes of ruderal plants. *Top row* illustrates that domesticated fruits are larger, lack a camouflagic persistent covering layer derived from the perianth, and lack an elongated attachment base that facilitates disarticulation in the wild form. *Center row* compares by light microscope, and *bottom row* compares by scanning microscope the attachment base. In the wild fruits a well-developed abscission area is present, and a basal "neck" bordering this abscission zone, which facilitates disarticulation, is evident

apparently because of the presence of a water-soluble inhibitor (Small et al., 2003), achenes of wild races remain dormant in the soil at least until the spring, and germinate irregularly for several years, providing protection against the entire population being subjected to a catastrophe (Scholz, 1957; Haney & Kutscheid, 1975; Small & Brookes, 2012).

In contrast to the adaptive characters of the achenes of wild *Cannabis*, the features facilitating disarticulation have been greatly weakened in domesticated forms. The achenes tend to remain on the plant for easy harvest, the development of a thick pericarp to protect the seed has been lessened, the camouflagic perianth attached to the pericarp tends to slough off since it is no longer needed, larger seeds have been selected to give the seedlings a better start, and dormancy has been eliminated so that the seeds germinate immediately and produce a dependably uniform crop.

Janischevsky (1924) alleged that he had discovered a symbiotic relationship between wild hemp and the red bug *Pyrrhocoris apterus*. He observed it apparently feeding on the attenuated base (the attachment area) of the achene, and concluded that the base was an elaiosome, i.e., a fleshy edible appendage of the achene serving to attract dispersal vectors, constituting an adaptation for distribution of the seeds. However, the insect is a generalized feeder that has no fidelity to *Cannabis*, and the base of wild achenes do not develop a genuine elaiosome, although the detachment zone is a weak area of the protective pericarp, and might offer some limited nutrition to insects.

Evolution of Photoperiodism Under Domestication

Photoperiodism is a physiological reaction of organisms to length of day or night. In the following discussion the term is used with specific reference to induction of flowering. Tournois (1912) is credited with the first discovery of photoperiodism in plants (see Jarillo et al. (2008) for a review of the subject). Based on studies of hemp and its relative Japanese hop, Tournois observed that flowering was promoted by short daylight (giving rise to the expression short-day plants) and delayed by long days. Today, *Cannabis* has been evaluated to be a quantitative (facultative) short-day plant – that is, flowering is normally induced by a required duration of days with a minimum uninterrupted period of darkness (10–12 h for most cultivars), but at least in some cases flowering may occur regardless of light regime. Some strains of *Cannabis* can produce flower buds under continuous illumination (Borthwick & Scully, 1954; Heslop-Harrison & Heslop-Harrison, 1969); however, before these open, some cultivars require short days, while others will flower in continuous light, but only after a long period of growth (Schaffner, 1926; Borthwick & Scully, 1954; Heslop-Harrison & Heslop-Harrison, 1969). The critical daylength may be longer for male plants than for female plants in a given population, which is consistent with the fact that males normally come into flower faster (Borthwick & Scully, 1954). Flowering is induced in *Cannabis* mainly by shortening daylight hours in late summer, but also to some extent by intrinsic, genetic factors. However, environmental stresses also have some effect on flowering time, especially drought, which is the most important factor in speeding up maturation. As noted below, hybridization may also play a role in inducing flowering.

Latitudinal Photoperiodic Adaptation

A world-wide, north–south pattern of clinal (geographically-graduated and genetically fixed) photoperiodic adaptation correlated with stature has evolved in *Cannabis*. Bergmann's Rule states that within a taxonomic group of animals, individuals are larger in colder environments (an ecogeographic generalization with mixed validity).

For plants, the reverse is often the case: the shorter, colder season at higher latitudes (or altitudes) limits growth and accordingly stature. Annual plants like *Cannabis* are designed to maximize propagule production, achieved in part by growing as large as possible within the limitations of the length of their season and the cultural conditions of their growth sites. It seems clear that the historical migration of *Cannabis* throughout much of the world for purposes of cultivation was accompanied by strong selection for local photoperiodic regime. During domestication, some populations could have been selected for photoperiodic insensitivity (like some cultivars of strawberry and other crops), but this has not been important for *Cannabis*. Wild plants and cultivars are photoperiodically adapted to their local climate; plants adapted to growth in northern areas tend to come into flower readily with shortening days, allowing time for seeds to mature before a killing frost; and conversely plants adapted to areas closer to the equator tend to come into flower slowly with shortening days, in order to grow for a longer period in the milder environment. Russian (U.S.S.R.) agronomists classified hemp into four eco-geographical maturation groups, respectively adapted to a longer season: Northern, Middle-Russian, Southern, and Far Eastern (Serebriakova & Sizov, 1940; Davidyan, 1972), and noted that races of *Cannabis* are available to meet the local photoperiodic requirements of most regions of the country.

When plants adapted to the photoperiod of semi-tropical climates are grown in north-temperate climates, they may mature so late that they succumb to cold weather before they can produce seeds (Heslop-Harrison & Heslop-Harrison, 1969). Such photoperiodic differences are apparent when *Cannabis* populations obtained from different latitudes are grown together in a northern experimental garden. In Ottawa, Canada, where I have grown over 1,000 accessions outdoors, those from the northern-most locations (Siberia) sometimes produced seeds in less than a month after planting, while some from near-equatorial locations (India, Africa) sometimes remained vegetative after 5 months (and were killed by frost). When hemp cultivation was authorized in Canada in 1998 (after more than a half century of prohibition), the only source of cultivars with reliably low THC (a requirement) was the European Union; embarrassingly, most of the cultivars were so late-maturing that they were unsuitable for Canadian locations. (It is possible to harvest vegetative plants of hemp for fiber, but Canadian plants are chiefly grown for oilseed.)

Most drug forms have historically been cultivated in areas south of the north-temperate zone, sometimes close to the equator, where they may be photoperiodically adapted to near-12-h days and an associated long season. (In the "Evolution of Narcotic Drug Production Under Domestication" and "Classification and Nomenclatural Issues" sections, two groups of narcotic plants are discussed; many strains of the less common Group 4 ("indica-type") are able to mature in relatively northern locations. Although Group 4 strains originate from relatively southern areas of the Northern Hemisphere, they seem to mature earlier than Group 3 ("sativa-type") strains because of adaptation to a shorter season due to drought.) By contrast, non-narcotic plants (both wild and legally cultivated) are mostly found in north-temperate climates, and are photoperiodically adapted to mature by the fall season in such locations. When drug strains are grown in north-temperate climates maturation is much-delayed until late autumn, or the plants die from cold weather before they are able to produce seeds. Before illicit marijuana growers became acquainted with the fact that most narcotic strains are very late-maturing, they often found that their clandestine outdoor plants remained

vegetative, not producing the congested flowering tops ("buds") that are most valued. Particularly in California, hybridization and selection produced narcotic strains that are capable of flowering outdoors (Clarke & Merlin, 2013). Of course, photoperiod can easily be controlled indoors by varying light (or dark) period, which is one of the reasons why marijuana is commonly grown in buildings.

In addition to photoperiodic adaptation, climate adaptation determines the success of *Cannabis* crops selected in one part of the world but grown in a quite foreign location. Most hemp cultivars (mostly fiber strains) were developed for relatively cool northern regions, and do not perform well when moved closer to the equator (Watson & Clarke, 1997).

Autoflowering (day-neutral) Strains

So-called "autoflowering" strains are genotypes that are indifferent to length of day, flowering when the plants reach a certain age or size. Some forms of *C. sativa* growing naturally in the extreme north appear programmed to come into flower quite early irrespective of daylength, and since the season is short, such indifference to daylenth is adaptive. At the equator, on the other hand, seasonal photoperiodic cycles are insignificant and indeed the seasons are often longer than required for full development. Some forms of *C. sativa* growing naturally near the equator appear programmed to come into flower only after a lengthy perior of growth, which is also adaptive in maximizing propagule production in a climate that permits large plants to develop. Autoflowering strains have been claimed in the underground marijuana literature to have been generated by hybridization of short-season and long-season plants. It does seem that hybridization can produce odd effects on photoperiodic response; I have observed hybrid-generated seedlings come into flower in less than 2 weeks, at a height of only 5 cm! Autoflowering plants can be grown in continuous light (since dark periods are not necessary for induction of flowering) and so autoflowering strains are becoming more common in the marijuana trade (Potter, 2014).

Evolution of Leaflet Size Under Domestication

The evolution and ecology of leaf size is a complex subject, and is related to the total number of leaves, their turnover rate and their orientation (e.g., Whitman & Aarssen, 2010). Nevertheless, there is a trend, exhibited in numerous annual plants, whereby the leaves of domesticated forms are larger than is the case in related wild species. This is likely due to the greater photosynthetic capacity of larger leaves, the result of selection by humans to be more productive in a given limited area. This pattern seems to be true for the three classes of domesticated *Cannabis* (fiber, narcotic drugs and oilseed) all of which tend to have larger leaves than do wild *Cannabis* plants. In *Cannabis*, the photosynthetic area of individual leaves is often larger in domesticated plants by virtue of (1) having more leaflets *and* (2) having leaflets that are larger, especially wider. This pattern of larger leaves with wider leaflets in domesticates compared to wild relatives is frequently encountered in other crops with compound leaves, for example in carrot (*Daucus carota*; Small, 1978b), and in alfalfa (*Medicago sativa*; Small, 2011). Based on modelling considerations for tomato leaves, Sarlikioti et al. (2011) concluded that

for a given leaf area, bigger but fewer leaflets were better at intercepting light than more but smaller leaflets.

Environment can modify leaf size. The leaves of wild plants growing in the wild are often small simply because of environmental modification – from the more stressful conditions encountered in the wild. In *Cannabis*, however, the leaflets of wild plants are typically relatively small even in excellent growth conditions. When grown closely together as done conventionally, the branching of fiber cultivars is suppressed and they lose most of their lower leaves. The fewer leaves that survive near the top of the plants are larger, partly as a matter of physiological compensation, but also as a genetically controlled tendency to produce larger leaves.

Some kinds of Chinese fiber land races (Group 2, discussed in the "Classification and Nomenclatural Issues" section) and southern Asian narcotic races (Group 4 ("indica type"), discussed in the "Evolution of Narcotic Drug Production Under Domestication" and "Classification and Nomenclatural Issues" sections) are noted for their large leaves with wide leaflets – a clear reflection that they are the products of considerable domestication. As discussed in Clarke and Merlin (2013), these groups are ancient and have undergone long periods of selection.

Larger leaves (and larger leaflets) in domesticated *Cannabis* may be the result of greater photosynthetic demand, but there are also reasons why leaflets should be narrower and smaller in related wild plants. Brown et al. (1991) examined the hypothesis that the feeding efficiency of leaf-eating insects is lowered on leaves that are small, dissected, or needle-like, all patterns that make insects work harder to reach the edible lamina. It seems plausible that the smaller, narrower leaflets in wild plants of *C. sativa* are adaptive in making their foliage less accessible to herbivores, and the reduced need for such protection in domesticated plants has allowed them to develop bigger, wider leaflets. It is also possible that smaller and narrower leaflets are more resistant to wind damage, another advantage in wild plants.

As pointed out in the "Evolution of Narcotic Drug Production Under Domestication" section, the two fundamental classes of narcotic plants differ in leaflet width, Group 3 ("sativa type") plants having narrower leaflets than Group 4 ("indica type") plants. (The underground marijuana literature sometimes also contends that the leaves of Group 4 tend to have fewer leaflets than those of Group 3.) Coincidentally, Group 4 plants have much shorter internodes, resulting in pronounced crowding of the foliage, and darker green foliage. These variables seem to be correlated in the same ways that shade leaves differ from sun leaves. Many plants develop smaller, lighter-green leaves in the sun, and larger, darker-green leaves in the shade (e.g., Nobel, 1976; Givnish, 1988), and the crowded (therefore shaded) leaves of Group 4 seem to reflect this observation.

Evolution of Color Under Domestication

This section examines colors of parts of the plant that appear to have been selected in domesticated *Cannabis* as a result of human preferences.

Propagules that are edible and therefore attractive to various herbivores need to be inconspicuous, and the "Evolution of Propagules Under Domestication" section discussed how a camouflagic mottled layer covering the achenes of wild *C. sativa* serves to hide them from herbivores. Also pointed out in that section is that this

layer tends to be sloughed off in domesticated strains, because it is no longer needed since humans protect the plants against herbivores. Figure 8a contrasts the quite dark achenes of a domesticated narcotic strain (typical of the "seeds" of numerous criminal confiscations I have observed in Canada) and the much lighter achenes of a fiber strain (most European strains have seeds that tend to be lighter shades of brown or gray). In these samples, the camouflagic perianth layer is absent and the color pigmentation resides in the pericarp (achene wall, surrounding the true seed). (It should be noted that achenes exposed to sunlight for long periods may become bleached.) Larger achenes are appropriately planted deeper, and this may be related to their color. Kluyver et al. (2013) proposed that ancient agricultural practices buried seeds quite deeply, leading to an increase in seed size under domestication so that seedlings would have the energy to grow out of the soil. Deeply buried seeds are probably more protected against herbivores, and may therefore be more tolerant of light coloration, which would tend to attract herbivores. However, darkness of the pericarp of domesticated achenes does not seem to be correlated with their size.

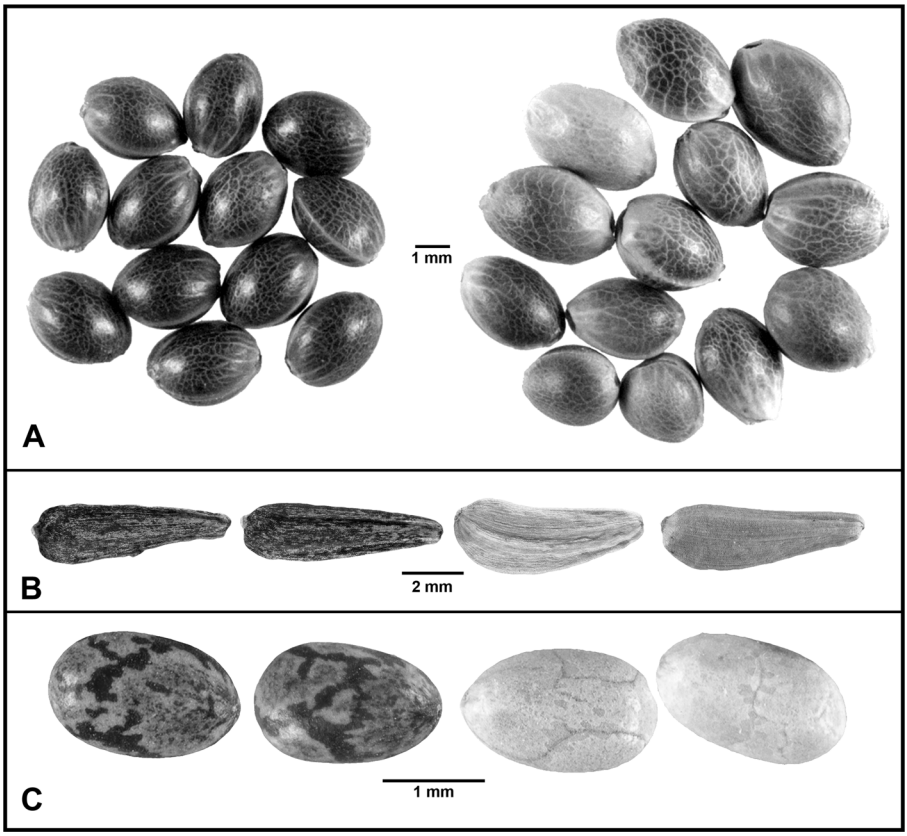


Fig. 8 Selection for whitish achenes ("seeds") under domestication. **a** *Left*: dark domesticated achenes (lacking a perianth layer) of a narcotic selection of *Cannabis sativa*. *Right*: whitish domesticated achenes (also lacking a perianth layer) of a fiber cultivar. **b** *Left*: normal brown achenes of coast tarweed (*Madia sativa*). *Right*: white achenes of a cultivar. **c** *Left*: normal brownish achenes of golden chia (*Salvia columbariae*). *Right*: white achenes of a cultivar. Photos (public domain) for **b** and **c** by Steve Hurst, U.S. Department of Agriculture

Differences in darkness of pericarps among domesticated strains of *C. sativa* may be the result of random fixation, but they may also reflect a frequently observed preference for light-colored achenes, as exemplified in Fig. 8b and c (for additional examples of similar color selection of fruits and seeds, see Heiser (1988) and Small (2013). The presence of lighter-colored *Cannabis* achenes in European fiber hemp cultivars (Group 1, discussed in the "Classification and Nomenclatural Issues" section) has been recorded by Vavilov (1931) and Serebriakova (1940). Lighter-colored achenes also are present in Chinese fiber strains, and indeed Clarke and Merlin (2013) hypothesized that Chinese fiber strains (Group 2, discussed in the "Classification and Nomenclatural Issues" section) imported into Europe in the 19th century contributed genes to European land races, and were responsible for the origin of lighter-colored achenes in European cultivars. However, human preference for lighter-colored propagules seems to be so universal that probably such selection occurred independently in Europe and China. It is possible that lighter-colored achenes arose in *Cannabis* not because of a human preference for lighter color, but because lighter color is associated with some other aspect of the achenes that is of value. Diederichsen and Raney (2006) found that in a large collection of oilseed flax (*Linum usitatissimum*) lighter-colored (yellow) seeds were heavier and had a higher oil content than darker-colored (brown) seeds, and it seems possible that the lighter color of the flax seeds is the result of correlation with selection for larger, more nutritious seeds.

Another example of human preference for light hues is provided by the inflorescences of narcotic cultivars that have been selected by clandestine breeders in the last several decades. The stigmas of the female flowers are whitish, although becoming brown with age. High concentrations of female flowers in the inflorescence of narcotic strains is extremely desirable, since this increases potency (see the "Evolution of Narcotic Drug Production Under Domestication" section). The secretory glands responsible for producing narcotic compounds are present in high density on the perigonal bracts, and these often glisten under strong light, also contributing to a whitish appearance of the female inflorescence. There appears to have been selection for strains developing whitish inflorescences. So-called "white strains" are very popular, as reflected by such names as White Diesel, White Fire, White Gold, White Haze, White Ice, White Label, White Queen, White Rhino, White Russian, White Skunk, White Widow, Early Pearl, Silver Haze and X-Haze.

Humans are fond of mutations of domesticated plants that develop purplish foliage, due to prominence of anthocyanin pigments (e.g., 'Crimson King', a very popular variant of Norway maple; "purple" (red) cabbage). When *C. sativa* is exposed to significant frost, it tends to become quite purple (or less green, since chlorophyll tends to degrade, revealing the anthocyanins), and sometimes the same effect is noticed at high altitudes (perhaps related to high, damaging insolation), demonstrating a propensity for violet coloration. Purple coloration of the inflorescences of narcotic strains became quite attractive to consumers in the second half of the 1970s (Clarke & Merlin, 2013; note Fig. 9), many expressing the belief that such strains are qualitatively superior. Examples of purplish strain names include Purple Bubba Kush, Purple Butter, Purple Cheese, Purple Diesel, Purple Dogg, Purple Erkle, Purple Haze, Purple Kush, Purple Maroc, Purple Monkey Balls, Purple Nepal, Purple Passion, Purple Pine, Purple Pineberry, Purple Power, Purple Pussy, Purple Snow, Purple Urkle, Purple Wreck, Grand Daddy Purple, Blackberry, Blueberry, Grape Ape and Mendocino

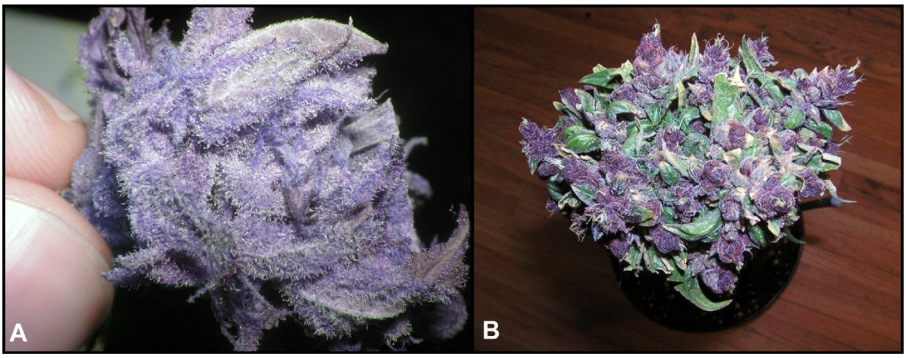


Fig. 9 Narcotic strains of *Cannabis sativa* illustrating selection of purple (anthocyanin) coloration under domestication. **a** Power to the Purple. Photo by Psychonaught, released into the public domain. **b** Purple Haze. Photo by HansRoht (CC BY 3.0)

Purple. [Article 2.2 of the current nomenclatural code for cultivated plants (Brickell et al. 2009) forbids the use of the term "strain" as equivalent to "cultivar" for the purpose of formal recognition. Nevertheless, Snoeijer (2002) treated *Cannabis* strain names as equivalent to cultivar names. Although *Cannabis* strains are conceptually identical to *Cannabis* cultivars, in this review the strain names are not denoted in single quotes, the convention for cultivar names. In fact, very few *Cannabis* strains satisfy the descriptive requirements for cultivar recognition.]

Evolution of Shoot Architecture Under Domestication

This section is concerned with how human selection of *C. sativa* for different purposes (fiber from the stem, drugs from the inflorescence, or oilseeds) has altered the shoot by comparison with that of wild-growing plants. Shoot features that are of particular adaptive importance to *C. sativa* include its main stem ("stalk"), and patterns of branching with respect to the disposition of the foliage and reproductive organs. As noted earlier, male plants are less robust than females, and die after flowering. The comments in this section pertain mostly to female plants.

Wild-growing plants of *C. sativa* normally develop a dominant central stem, from which, under good growth conditions, spreading side branches arise. Figure 10 shows the appearance of well-developed wild plants. As with numerous annual herbaceous plants, ultimate size depends on availability of nutrients, water and light; and crowding from competition tends to suppress lower branching and promote vertical growth. In a given wild population, one may find plants that are less than 30 cm in height, and other that exceed 2 m. The widespread assertion on the internet that there is a unique wild species, "*Cannabis ruderalis*," that is quite short, is rubbish – very short plants growing outside of cultivation have simply developed in a stressful environment, or are photoperiodically adapted to short-seasons and so do not have time to become large. (Janischevsky (1924), the author of *C. ruderalis*, noted that well-manured plants of his alleged species grow to heights of 2 m or more.)

The stature and branching pattern of *C. sativa* have been altered in domesticated plants in ways that maximize production of the desired product (stem fiber, drugs from

Fig. 10 Strong branching patterns typical of well-developed, open-grown, wild (ruderal) female plants of *Cannabis sativa*. *Left*: collected from a weedy site near Ottawa Canada. *Right*: cultivated in southern Ontario from seeds from Georgia (Eurasia)

the inflorescence, or oilseed). These differences have become genetically fixed by selection, but are accentuated by density of planting. The various field configuration patterns that are encountered are shown in Fig. 11, and are discussed in the following paragraphs.

The two top illustrations in Fig. 11 show shoot configurations typical of narcotic *C. sativa*. As discussed in the "Evolution of Narcotic Drug Production Under Domestication" and "Classification and Nomenclatural Issues" sections, there are two basic classes of narcotic plants, Group 3 ("sativa type," taller ones, at top right) and Group 4 ("indica type," shorter ones, at top left). All of these plants are naturally (genetically) very well branched (like wild plants), but the internodes in Group 4 are much shorter than in Group 3. Narcotic forms are planted at relatively low density, leaving room for the branches to develop well and produce abundant flowers. Maximizing branch production is desirable as this maximizes flower production, the perigonal bracts around the female flowers producing most of the narcotic chemicals that are desired. As discussed in the "Evolution of Narcotic Drug Production Under Domestication" section, male narcotic plants are removed to prevent production of seeds, which are not the desired product.

The short internodes of Group 4 result in quite crowded leaves, and this in turn results in several microhabitat and associated physiological features: higher humidity and lower water loss (likely adaptive, as Group 4 occurs in quite arid areas), and intra-crown shading the "Evolution of Leaflet Size Under Domestication" section discusses the resulting development of shade leaves). Moreover, as pointed out by Clarke and Merlin (2013), when allowed to go to seed the infructescences are so crowded that natural seed dispersal

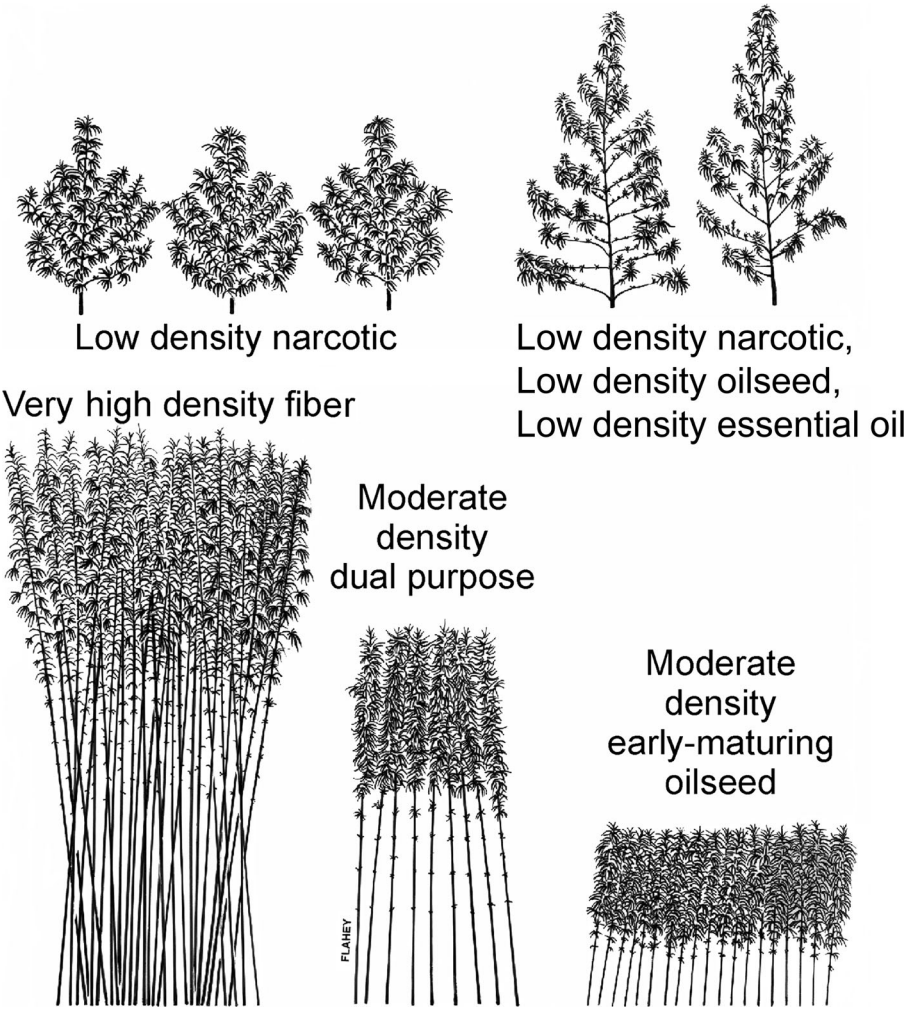


Fig. 11 Common categories of shoot architecture of cultivated *Cannabis sativa* in field configurations maximizing production of the desired harvest product. *Top left*: short, conical, well-branched, female, narcotic plants of Group 4 ("indica type," discussed in the "Evolution of Narcotic Drug Production Under Domestication" and "Classification and Nomenclatural Issues" sections) are grown well-spaced to maximize development of both foliage and flowers containing cannabinoids. *Top right*: Tall, well-branched plants are grown well-spaced to maximize production of flowers (for harvest of either cannabinoids or essential oil) or achenes (for production of seed for planting). *Bottom left*: fiber cultivars are grown at very high density to produce unbranched, tall plants that maximize quantity and quality of stem fiber. *Bottom right*: some modern oilseed cultivars are grown as short, relatively unbranched plants to maximize production of achenes while minimizing production of stem tissues, and to facilitate machine harvesting. *Bottom center*: "dual-purpose" cultivars are grown at moderate density, tend to be somewhat branched and of medium to tall height, a compromise strategy for production of both stem fiber and oilseeds

is very limited (the seeds mostly remain within the infructescence), and consequently Group 4 seems to have very limited capacity to escape to the wild. The short stature of narcotic Group 4 minimizes production of stem tissues (in contrast to fiber strains) while maximizing production of floral tissues, and represents a parallel strategy to advanced oilseed cultivars (discussed in the "Evolution of Seed Oil Production Under Domestication"

section), which similarly have very short stature and very compact inflorescences, also minimizing stem tissues while maximizing desired reproductive tissues.

As pointed out in the "Geography, Ecology and Ancient Domestication" section, *Cannabis* requires fertile soil and good water availability. As discussed in the "Evolution of Stem Fiber Production Under Domestication" section, tall *Cannabis* for fiber has been traditionally produced near rivers, streams or ponds which not only furnish irrigation water but also provide the water in which the stems are immersed to extract (by "retting") the fiber from the stems. By contrast, areas of southern Asia, where narcotic *Cannabis* developed historically, are often arid. Also, soils may be rather infertile. The dwarf nature of narcotic plants of Group 4 appears to suit them to such areas where soil nutrients and water are limited.

As discussed in the "Evolution of Narcotic Drug Production Under Domestication" section, for the last half-century narcotic plants have frequently been grown clandestinely indoors to avoid detection by law enforcement, a situation in which tall plants are frequently too large (once overhead lighting and ventilation are installed in a room). Legitimate, authorized medicinal marijuana growers also often find tall plants to be too awkward to raise in greenhouses and specially fitted secure rooms. It is possible to adjust height by controlling the photoperiod. Alternatively, indoor growers sometimes resort to removing the tops, pinching stem buds to promote branching, trellising, and other techniques to limit the height of plants (Clarke, 1981). However, plants that are naturally shorter are often grown in these circumstances. "Breeders continue to develop early-maturing and high-yielding varieties that are short and compact for indoor grow room use and to avoid detection outdoors" (Clarke & Merlin, 2013).

As discussed in the "Evolution of Narcotic Drug Production Under Domestication" section, in Asia one method of preparing hashish involved using hands or leather to collect (by adherence) sticky resin from the inflorescences at the top of the plants (alternatively and more conventionally today, hashish is prepared by filtering techniques, described in the "Evolution of Narcotic Drug Production Under Domestication" section). Accordingly, strains suitable for hashish collection based on stickiness should not be too tall. As Bouquet (1950) recorded: "The cultivators, dressed in leather, moved about through the plantations. The resin sticks to their clothes, which are scraped from time to time with a blunt curved knife. This method of collection shows clearly that in those regions the plant does not grow to any great height." In a similar vein today, dwarf varieties of tree fruits have been bred to facilitate collection. An added benefit of low stature is greater wind resistance.

As discussed in the "Evolution of Essential Oil Production Under Domestication" section, a very recent market has developed for the production of essential (volatile) oil, a product substantially from the perigonal bracts, exactly the same source for narcotic drugs. Accordingly, plants of the same architecture as narcotic plants (especially as shown at top right, Fig. 11) are often used as sources of essential oil. Indeed, as discussed in the "Evolution of Essential Oil Production Under Domestication" section, narcotic strains are often pleasant-smelling and therefore suitable for harvest of essential oil, although they pose security problems.

As discussed in the "Evolution of Seed Oil Production Under Domestication" section, there has been comparatively limited selection of strains of *C. sativa* in historical times specifically for oilseed production. Since plants that are big and well-branched produce many flowers (such as those shown at top right in Fig. 11), when allowed to produce

seeds they do so very well. Such plants were occasionally used as sources of oilseeds, but more often as sources of seed to reproduce the following season's plants. In more recent times, as discussed in the "Evolution of Seed Oil Production Under Domestication" section, short plants with flowers (and hence seeds) congested on short branches (as shown at bottom right in Fig. 11) have been grown at moderate densities to produce oilseeds, a strategy that reduces the production of stem tissue in a given area while maximizing the production of seeds on a given acreage. Plants with limited (or at least short) branching are naturally superior than irregularly branching plants for the purpose of fully and uniformly occupying a field, and maximally utilizing solar irradiation.

As discussed in the "Evolution of Stem Fiber Production Under Domestication" section, strains of *Cannabis* selected for harvest of stem fiber are tall and have limited branching, both characteristics accentuated by growing the plants at extremely high densities. As detailed in the "Evolution of Stem Fiber Production Under Domestication" section, these traits maximize quantity and quality of fiber. Woody tissues in the stem have been suppressed so that the stems are much hollower than in any other category of *C. sativa*. This makes the stems weaker and less flexible, but the high density of planting protects the plants from being lodged (blown over) by wind. Because of the limited branching, seed production is much more limited than in strains used for oilseed. However, sometimes "dual purpose" cultivars are grown (see bottom center, Fig. 11) with intermediate characteristics between fiber and oilseed strains, so that both products can be harvested, albeit in relatively modest amounts.

As noted above, different densities of planting are used to increase or suppress branching. The different classes of strains have been genetically selected to grown well at either high or low concentrations. Unlike fiber strains that have been selected to grow well at extremely high densities, drug strains tend to be less tolerant of high population densities (de Meijer, 1994).

The different architectures selected by humans are advantageous in production of particular desired products (stem fiber, seeds, or narcotics from the inflorescences), but there are associated susceptibilities to herbivores and pathogens. The long stalks of fiber strains makes them attractive to stalk-boring insects and stalk-canker fungi (McPartland, 1998). Congested inflorescences, as found in many superior narcotic and oilseed strains, makes the plants attractive to budworms and gray mold, *Botrytis cinerea* (McPartland, 1998). Susceptibility to pests and diseases also differs according to density of cultivation. The very dense plantations in which fiber crops are grown raises the humidity around the stalks and increases infections by fungal diseases. On the other hand, the dense canopy may be protective against many insects. By contrast, both drug and many oilseed crops are grown in open rows, and the increased sunlight is attractive to flea beetles and birds (McPartland, 1998).

Evolution of Stem Fiber Production Under Domestication

A Brief History of Fiber Production and Usage

Hemp is one of the oldest sources of textile fiber. It was harvested by the Chinese 8500 years ago (Schultes & Hofmann, 1980), and to this day China remains the world's

chief producer. Hemp cultivation was introduced to western Asia and Egypt, and subsequently to Europe somewhere between 1000 and 2000 B.C. Cultivation in Europe became widespread after 500 A.D. Hemp was first grown in South America in 1545 (in Chile), and in North America in Port Royal, Acadia in 1606 (Small, 1979b). The hemp industry flourished in the U.S., particularly in Kentucky. Hemp was widely grown in North America until the early part of the 20th century, followed by a brief revival during World War II after supplies of tropical fibers were cut off (for the same reason, substantial renewed cultivation also occurred in Germany at the same time). Hemp was one of the leading fiber crops of temperate regions from the 16th through the 18th centuries. It was widely used for rot-resistant, coarse fabrics, such as sailcloth, as well as for paper, and was the world's leading cordage fiber (used for rope and similar purposes) until the beginning of the 19th century. The majority of all twine, rope, ship sails, rigging and nets up to the late 19th century was made from hemp fiber. During the age of sailing ships, *Cannabis* was considered to provide the very best canvas, and indeed this word, as well as the genus name *Cannabis,* are derived from an Arabic word for hemp. Until the middle of the 19th century, hemp rivalled flax (*Linum usitatissimum*) as the chief textile fiber of vegetable origin, and was described as "the king of fiber-bearing plants – the standard by which all other fibers are measured" (Boyce, 1900).

The extraordinarily labor-intensive technology traditionally employed to extract fiber from hemp stems and prepare it for weaving is shown in Fig. 12. After hand-harvesting, fiber was crudely separated by "retting," (discussed in this section), hand-stripping and/or beating, scutching (removal of smaller bits of adhering woody tissues from the phloem fiber, accomplished in the past with mechanical tools), hackling ("hackles" were the steel "brushes" traditionally used to separate the fibers), and perhaps additional combing to remove the remaining pieces of stalks, broken fibers and extraneous material.

Today, several dozen European fiber hemp cultivars make up the bulk of modern registered *Cannabis* cultivars; most of these originate from European land races dating back at least hundreds of years (de Meijer, 1995, 1998), and are described in the "Classification and Nomenclatural Issues" section as constituting "Group 1." Land races and cultivated selections from China are of much older origin, often more variable, and are described in the "Classification and Nomenclatural Issues" section as "Group 2."

Several developments in the late 19th and early 20th centuries, listed in decreasing order of importance in the following, combined to drastically curtail the importance of hemp fiber outside of Asia. (1) Ships once used enormous amounts of hemp for sails, because hemp fabric is very water- and rot-resistant. The "age of sailing ships" is usually defined for Western countries as lasting from the 16th century to the mid-19th century (peaking in importance in the 19th century, the "Golden Age of Sailing"). The development of motorized ships drastically reduced the need for hemp fiber. (2) Sailing ships also used enormous amounts of hemp for rope (a single ship could require 60 tonnes of hemp rope, 30 km for rigging alone; an anchor cable could exceed 60 cm in diameter). Hemp rope tended to hold water in the interior and to prevent internal rotting they were tarred, a laborious process that was made unnecessary when abaca was substituted. (3) The Industrial Revolution (approximately 1760–1840 in Britain) initiated sustained economic

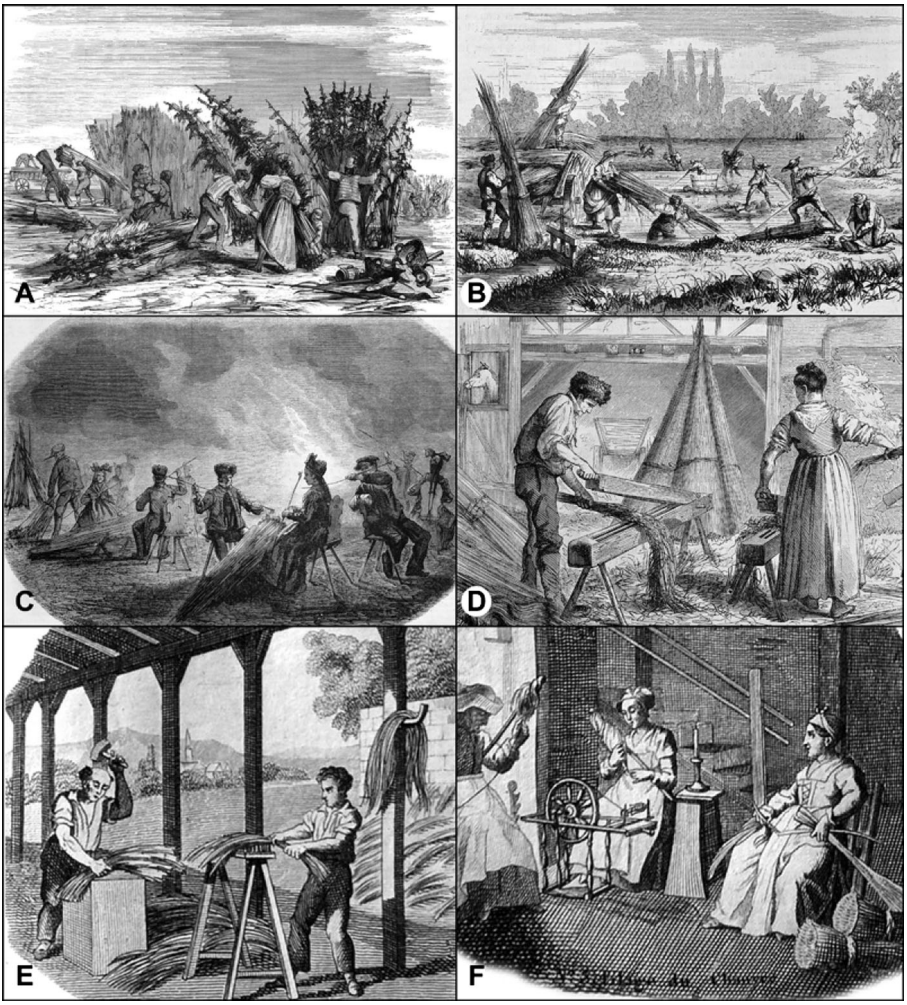


Fig. 12 Traditional 19th century European hemp technology. **a** Cutting down plants at base. **b** "Water retting," the process of immersing stems for a week or more so decay microorganisms loosen attachment of fiber to other tissues. **c** An alternative to retting: hand-stripping the fiber-bearing "bark." **d** Using a "hand break" to crudely separate fiber from retted stems. **e** *Left*: Beating dried hemp stalks with a hand tool to crudely separate fiber from retted stems. *Right*: Hackling (drawing partially cleaned hemp bark fiber through a bed of nails to clean off remaining undesired tissues). **f** Spinning fiber into thread. (**a**–**e** from Lallemand and Levy (1860). **f** and **g** from Anonymous (1822))

growth and living standards in the Western world, but also accentuated differences for the cost of fiber production between rich temperate regions and poor tropical and semi-tropical regions. As a fiber crop, hemp (like flax) is best adapted to temperate regions, in contrast to other leading fiber crops such as cotton (*Gossypium* spp.), jute (*Corchorus capsularis*), and sisal hemp. Outside of Asia, production costs (largely determined by labor) in recent centuries have been much cheaper for tropical and semi-tropical fiber crops, and this contributed to making hemp substantially less competitive. (4) Hemp fiber was once important for

production of coarse but durable clothing fabric. In the 19th century softer fabrics took over this market. As the world has judged, cotton is a remarkably more attractive choice for apparel. The invention of the modern cotton gin by Eli Whitney in 1793 enormously increased the efficiency of cotton production, and has been claimed to have contributed to the demise of hemp fiber, which is relatively difficult to separate cleanly from other parts of the plant. Increasing limitation of cheap labor for traditional production in Europe and the New World led to the creation of some mechanical inventions for preparing hemp fiber, but too late to counter growing interest in competitive crops. (5) Human-made fibers began influencing the marketplace with the development of rayon from wood cellulose in the 1890s. Largely during the 20th century, commercial synthetic fiber technology increasingly became dominant (acetate in 1924, nylon in 1936, acrylic in 1944, polyester in the 1950s), providing competition for all natural fibers, not just hemp. (6) Hemp rag had been much used for paper, but the 19th century introduction of the chemical woodpulping process considerably lowered demand for hemp. (7) A variety of other, minor usages of hemp became obsolete. For example, the use of hemp as packing (oakum), once desirable because of resistance to water and decay, became antiquated. (8) The growing use of the cannabis plant as a source of marijuana drugs in the Western world in the early 20th century gave hemp a very bad image, and led to legislation prohibiting cultivation of hemp. By the end of the Second World War hemp cultivation essentially ceased in North America, most of Western Europe, and most non-Asian countries, but continued at a diminished level in Asia, Eastern Europe, France and the Soviet Union.

The Recent Resurrection of Fiber Usage

A surge of interest in re-establishing the hemp industry began in the 1990s, particularly in Europe and British Commonwealth countries. At the time, governments generally were hostile to growing any form of *Cannabis sativa* for fear that this was a subterfuge for making marijuana more acceptable. Nevertheless, cultivation resumed in the temperate-climate regions of many Western countries. For example, the first crops were established in Australia (Tasmania) in 1990, in England in 1993, in Germany in 1995, and in Canada in 1998. The impetus for growing hemp in the West, despite the hurdle of overcoming governmental reluctance, was economic, motivated by the general need to find new profitable crops. Today, the United States is the only notable Western nation to persist in prohibiting hemp cultivation, at least at the federal level. (Most U.S. states have enacted resolutions or legislation favoring the resumption of hemp cultivation, although federal laws have precedence.) China has always been the predominant producer of hemp, primarily for fiber, but about 3 dozen other countries currently grow significant commercial crops. Security regulations for cultivating hemp in most Western countries are usually stringent, and represent a significant cost. Such requirements may involve the use of approved cultivars obtained from authorized sources, secure fencing and storage facilities, careful maintenance of records, governmental inspections, sampling to ensure material has insignificant levels of THC (the chief intoxicating chemical), and personnel free of recent criminal records. The legislative burden that accompanies hemp puts the crop at a unique disadvantage.

Current Economic Value of Fiber Hemp

Based mostly on fiber products, hemp was once touted, rather unrealistically, as "the new billion dollar crop" (Popular Mechanics, 1938), with the claim that it "can be used to produce more than 25,000 products, ranging from dynamite to Cellophane." Hemp is a natural fiber, and to appreciate its current importance it is desirable to have some background into the nature of fiber and the world market for it. "Fiber" has several meanings, but for purposes of this review it refers to thread-like material, either obtained from natural sources or human-made, and used in various forms (especially woven into fabrics, matted as in paper, or glued together as in fiberboard). Wood fiber provides over three-quarters of all fiber produced, but except for the category man-made cellulosics, this is excluded from the following analysis. "Mineral fibers" (mostly made of glass, steel, asbestos, or carbon) are also excluded from this discussion. There are two basic classes of fiber: natural and synthetic. The world's *natural* fiber market includes fibers extracted directly from plant and animal species. Cotton and wool are the leading natural fibers. By contrast, *synthetic* fibers are prepared from fossil fuels. Examples include polyester, polypropylene and nylon. *Man-made cellulosics* is an intermediate category (sometimes included in synthetics, and sometimes termed "regenerated fibers"); high-cellulose material, primarily salvaged from timber processing and crop residues (especially cotton), are chemically processed and converted to produce manufactured fibers. Rayon and acetate are examples. The world's fiber market today is dominated by synthetic fibers, especially polyester, which is made mostly from ethylene derived from coal. Polyester constitutes three-quarters of all synthetic fibers. The world's *textile* market uses fiber for fabrics generally and clothing in particular. Cotton currently accounts for almost 40 % of the total textile fiber market (and 85 % of the natural fiber textile market), but polyester is more important, accounting for over 50 % of the total textile fiber market. For years, polyester has been gaining market share while cotton has been losing ground. Animal fibers such as wool and silk, which are protein-based, have also been losing popularity.

Today, hemp constitutes only about 0.3 % (on a tonnage basis) of the world's natural fiber production (excluding wood fiber). The economic trend for fiber hemp has been discouraging: global production fell from over 300,000 tonnes in the early 1960s to about 30,000 tonnes in the first decade of the twenty-first century. The total world value of hemp fiber is about 6 % that of flax (the most comparable stem fiber), and about 0.05 % that of cotton, the leading natural annual fiber crop. (Curiously, all three of these crops are also employed as oilseeds.)

At present, there are only small, niche markets for the production of hemp fiber for various purposes. Traditional usage of the fiber for clothing, cordage and paper continues, but these products are very expensive and appeal to a very small clientele. However, the hemp industry has been reinvigorated by new fiber-based products (see Roulac (1997), Bouloc (2006) and Small (2014b) for extensive analyses). Both the outer (bark, phloem) long fibers and the short internal (hurds, wood) fibers are now being employed in specialty pulp products and composites. These usages include fiberboard, insulation, pressed fiber products, masonry products (concrete, stucco, plaster, tiles), carpets, straw-bale construction materials, livestock bedding, and a very wide range of plastics. The automotive industry has particularly pioneered the

development of pressed fiber and moulded plastic components. The considerable rot-resistance of the fiber is being exploited in geotextile products such as landscaping fabric. The usage of hemp for these new fiber applications has been primarily in Europe, and subsidization was important in establishing the new hemp-related industries.

Modern Fiber Hemp Technology

The traditional and still major first step in extracting the most desirable ("long") fibers found in the phloem-associated tissues is to ret ("rot") away the softer parts of the plant. Traditionally this is accomplished either by exposing the harvested stems to microbial decay in the field ("dew retting") or by submerging the stems in water ("water retting"), the latter practiced only in countries which tolerate the associated pollution. The result is to slough off the outermost tissues of the stem and to loosen the inner woody core (the "hurds") from the phloem fibers. Occasionally, hemp is "stand retted" – the standing crop is dehydrated by the application of a desiccant herbicide and retting occurs while the crop is erect (and dead). Rarely, hemp is frost retted – the stems allowed to ret overwinter. A variety of experimental retting techniques have also been attempted, such as retting in plastic bags (Li et al., 2009) and ensilage (Idler et al., 2011).

In traditional hemp processing the long fibers are fractionated from the internal woody hurds in two steps, *breaking* (stalks are crushed, in more recent times using rollers that break the woody core into short pieces) and *scutching* (the remaining hurds, short fibers ("tow") and long fibers ("line fiber," "long-line fiber") are separated). Today, a single, relatively expensive decorticator machine can do these two steps as one.

As with other bast fiber crops, hemp phloem fibers are arranged in bundles parallel to the stem axis, and are embedded in a pectic polysaccharide network. The pectin network cementing the fibers together is the major obstacle to obtaining high-quality fiber. A commonly used technique to improve fiber separation is chemical processing with sodium hydroxide or diluted sulphuric acid. Steam explosion is a potential technology that has been experimentally applied to hemp (Garcia-Jaldon et al., 1998). Decorticated material (i.e., separated at least into crude fiber) is the raw material, and this is subjected to steam under pressure and increased temperature which "explodes" (separates) the fibers so that one has a more refined (thinner) hemp fiber that currently is only available from water retting. Other methods that have been considered to augment or replace traditional retting include ultrasonic techniques, enzymatic retting, and the use of improved decay microorganisms. (Traditional water retting is effective because bacteria that are present secrete pectinolytic enzymes; filamentous fungi producing pectinase are more important in dew retting.) Because ease of retting is important for fiber cultivars, there has been selection against the polysaccharide matrix cementing the fibers together.

Most hemp fiber used in textiles today is water retted in China (Zhang et al., 2008). Relatively crude alternatives may be employed to produce a less pure grade of fiber, mostly for non-textile applications. This involves production of "whole fibers" (i.e., harvesting an amalgamation of both the long fibers from the cortex and the shorter fibers from throughout the stem), and technologies that utilize shortened hemp fibers.

This approach is currently dominant in Western Europe and Canada, and commences with field dew retting (typically 2–3 weeks). A principal limitation is climate – the local environment should be suitably but not excessively moist at the close of the harvest season. Once stalks are retted, dried and baled, they are processed to extract the fiber. In general in the EU and Canada, fibers are not separated into tow and line fibers, but are left as "whole fiber."

Fig. 13 Hemp stem subjected to retting (decomposition of the softer tissues). The fiber in the top portion has been separated from the woody core. Photo by Natrij, released into the public domain

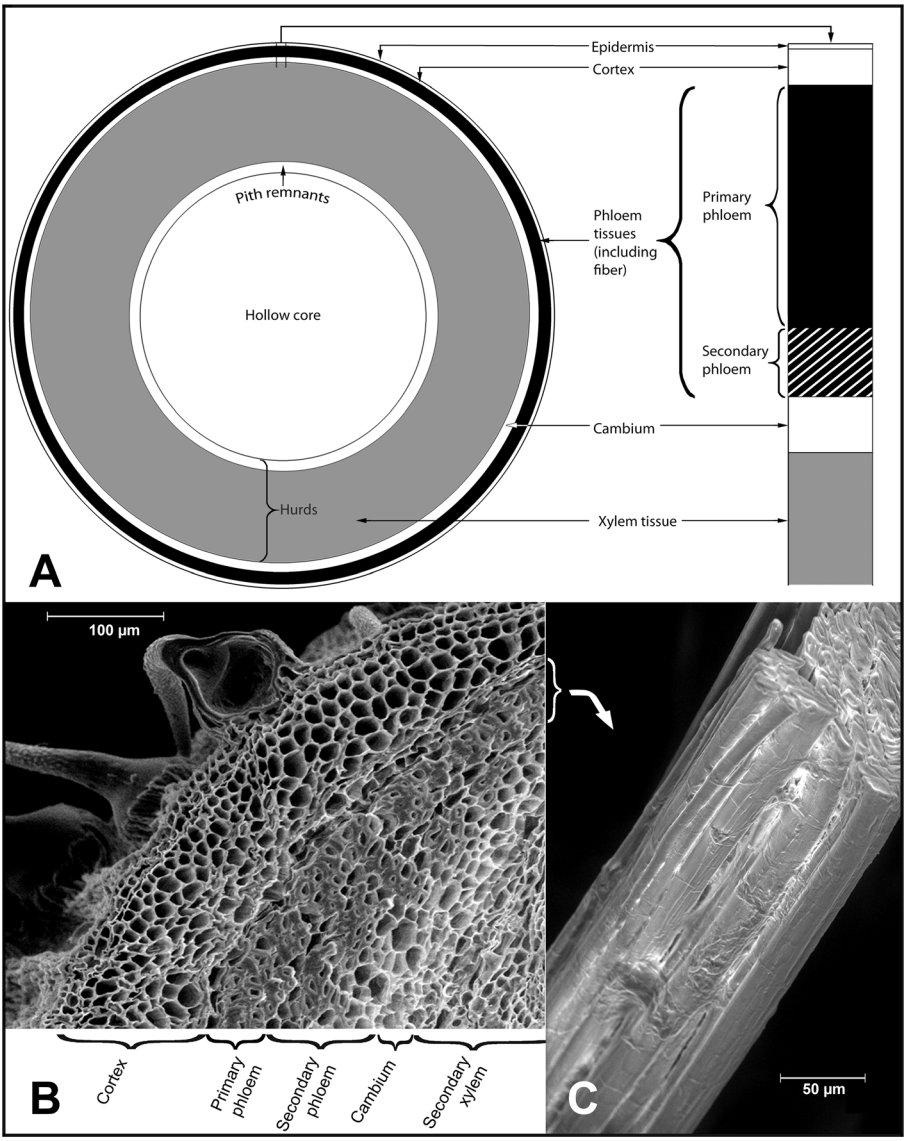


Fig. 14 Structure of a hemp stem with special reference to fiber. **a** Scaled diagram of a cross section of a mature hemp stem, showing detail (*at right*) of the outer portion. The relative proportions of primary and secondary fiber, hurds, and hollow core vary with maturity, position in stem, conditions of cultivation and genetic background. In fiber extraction, the epidermis and cortex are removed, and the valuable phloem fibers are separated at the cambium from the woody central core (hurds). **b** Scanning electron micrograph of a portion of a hemp stem cross section. **c** Scanning electron micrograph of a bundle of primary fibers. (**a** prepared by B. Brookes. **b** and **c** prepared by E. Small and T. Antle)

How Selection has Modified *Cannabis sativa* for Fiber Production

The fiber from bast fiber crops comes particularly from the stem phloem tissues, constituting a ring of fibrous material just under the outer surface of the stem

(Figs. 13 and 14). As in other stem fiber plants, hemp fiber serves to stiffen the stem, producing structural support, but at the same time providing flexibility so that the stem can bend but not break in response to wind and other environmental forces. The long axis of the fibers is parallel to the stem axis (an arrangement that naturally keeps the stem upright and resists stem bending). The fiber cells of hemp are alive initially, but die at maturity as their cells walls become blocked by deposit of lignin. The very valuable primary fibers are initiated in the apical meristem at the tip of the growing main stem, and subsequently elongate (much more so in the internodes than at the nodes). The primary fibers are slightly separated from the epidermis of the stem by several layers of cells (the cortex). Upon completion of internode elongation, a cambium (thin cylinder of meristematic tissue running the length of the stem), located internally to the primary fibers, produces (a) secondary bast fibers towards the outside of the stem (but inside the primary bast fibers) and (b) xylem (woody "hurds" tissue) towards the center of the stem. The term "bark" is often used to indicate all stem tissues external to the cambium, so that "bast fibers" is synonymous with "bark fibers" (de Meijer, 1994). A pith made up of undifferentiated cells initially occupies the center of the very young stems, but is more or less crushed by the developing hurd fibers, and the center of the pith tends to become hollow.

The mature hemp stem consists of several concentric cylinders of tissue (Fig. 14a). A multicellular cortex is found immediately internal to the unicellular epidermis; as with other stem fiber crops, removal of the cortex in "decortication" is a key initial step in fiber extraction (a partly decorticated hemp stem is shown in Fig. 13). Internal to the cortex is the primary phloem fiber tissue, in which the principal fiber of interest is found, and immediately internal to this is the secondary phloem fiber tissue, a less desirable fiber generated by the cambium, the next discernible layer proceeding toward the stem center. As noted above, the cambium produces the hurds towards the center, resulting in the degeneration of the pith that once occupied the center of the stem. Pith tissue is evident in young stems, but is mostly replaced in the growing stem by short-fiber – relatively soft, woody tissue – which constitutes a secondary product of economic value. The center of the pith becomes hollow, but only to a limited extent at the nodes, and less so towards the base of the stalk. The woody tissue and the remnants of the pith constitute the "hurds." [The pith remnants constitute less than 1 % of the hurds, but some authors mistakenly refer to the entire hurds as pith; the phrase "woody core" is often applied to all tissues internal to the cambium, and the phrases "woody fibers" and "wood fibers" pertain to the hurd fibers. "Shives" rather than "hurds" is more often used for flax than for hemp, and "core" is more frequently applied to fiber cultivars of kenaf, *Hibiscus cannabinus*.] Like the trunk of most trees, the stalk becomes thicker (and woodier) towards the base, for support. This progressive thickness towards the base is due mostly to more hurd tissue being formed, but the primary fibers (the highest quality fibers) are progressively supplemented towards the base of the stalk by secondary fibers (of lower quality), and so the upper third of the stem produces higher quality fiber than the lower third. Traditionally, mechanical bending ("breaking") is applied to the decorticated stems to separate the phloem fiber from the hurds.

The primary bast fibers are the most valuable product of the stems, and are 3–55 μm long (van der Werf, 1994); they are amalgamated in fiber bundles which can be 1–5 m

long (Fig. 14c). The fibers in the bundles are cemented together by a complex mixture of pectins, hemicelluloses and lignin. As the stem matures, the cambium produces additional (secondary) bast fibers, which are short (about 2 mm long) and more lignified. The woody core fibers of the hurds are even shorter, 0.5–0.6 mm long, and like hardwood fibers are cemented together with considerable lignin. Male plants, although less productive, produce a higher quality of fiber, in part because of their lower lignin content (van der Werf, 1994).

Fiber hemp plants, by contrast with *Cannabis* plants grown for marijuana or oilseed, and also in contrast with wild plants, have been selected for features maximising fiber production. Selection for fiber has resulted in strains that have much more primary phloem fiber and much less woody core than encountered in narcotic strains, oilseed strains and wild plants. Fiber varieties may have less than half of the stem made up of woody core, while in non-fiber strains of *Cannabis*, more than three quarters of the stem can be woody core. Moreover, in fiber strains more than half of the stem exclusive of the woody core can be fiber, while non-fiber strains rarely have as much as 15 % fiber in the corresponding tissues. Also important is the fact that in fiber strains, most of the fiber can be the particularly desirable long primary fibers (de Meijer, 1994).

Since the stem nodes tend to disrupt the length of the fiber bundles, thereby limiting quality, tall, relatively unbranched plants with long internodes have been selected. Another strategy has been to select stems that are especially hollow at the internodes (Fig. 15, right hand side), with limited hurds, since this maximises production of long phloem fiber (although the decrease in woody tissues makes the stems less resistant to lodging by wind). Similarly, limited seed productivity concentrates the plant's energy into production of fiber, and fiber cultivars often have low genetic propensity for seed output. Selecting monoecious strains overcomes the problem of differential maturation times and quality of male and female plants. Except for being less robust and the troublesome characteristic of dying after anthesis, male traits are favored for fiber

Fig. 15 Cross sections of stems at internodes of a fiber plant (*right*) and of a narcotic plant (*left*). Fiber cultivars have stems that are hollower at the internodes, i.e., with less woody tissues, since this allows more energy to be directed into the production of phloem fiber

production. In former, labor-intensive times, the male plants were harvested earlier than the females, to produce the best fiber. Fiber strains have been selected to grow well at extremely high densities, which increase the length of the internodes (contributing to fiber length) and increase the length of the main stem while limiting branching (contributing to ease of harvesting). The high density of stems also contributes resistance to lodging, desirable because woody supporting hurd tissue has been decreased by selection. The limited branching of fiber cultivars is often compensated for by possession of large leaves with wide leaflets, which obviously increase the photosynthetic ability of the plants.

In summary, humans have modified *Cannabis* for fiber production. Fiber quantity and quality have been improved by selection for plants that are taller, have less vigorous branching, have slimmer, hollower, more easily rettable stems with more and longer primary phloem fiber, less secondary phloem fiber and less wood. Sexual reproduction has been limited so that the plants divert less of their energy into pollen and seed production. Selection was unconscious until recent times, when plant breeders realized that selecting for the traits listed above resulted in more and better harvest of primary fiber. Today, except in China which continues to grow hemp for fabric, fiber hemp is grown not just for primary fiber but also for the less valuable secondary phloem fiber and woody core, since there are many new applications for these. One may expect that future fiber cultivars will be selected that reflect these new uses.

In the Northern Hemisphere, most fiber strains (cultivars or land races) have been grown in relatively northern locations (mostly north of 35° north latitude), while most narcotic strains have been grown (outdoors) in more southern areas. Accordingly, most fiber strains are photoperiodically adapted to flower earlier than most narcotic strains. Since fiber plants have not been selected for narcotic purposes, the level of intoxicating constituents is usually limited.

Evolution of Essential Oil Production Under Domestication

The characteristic odor of *Cannabis* plants is due to its "essential oil" (volatile oil, ethereal oil), an indistinct chemical category of compounds responsible for scent. Commercial preparations of the essential oil, called "*Cannabis* flower essential oil" and "hemp essential oil," have been prepared from the female inflorescences and/or the younger foliage. *Cannabis* essential oil is a mixture of volatile compounds, including monoterpenes, sesquiterpenes and other terpenoid-like compounds that are manufactured in the same epidermal glands in which the cannabinoids of *Cannabis* (discussed in the "Evolution of Narcotic Drug Production Under Domestication" section) are produced (Malingré et al., 1975; Meier & Mediavilla, 1998). The cannabinoids are biosynthesized from some of the terpenoids, but are odorless (Clarke & Watson, 2002). The essential oil is quite different from fixed hempseed oil from the seeds, the topic of "Evolution of Seed Oil Production Under Domestication" section. Many of the terpenes (particularly limonene and alpha-pinene) volatilize readily and will only be available in fresh material, so the composition of extracted essential oil differs from the volatiles released around the fresh plant (Ross & ElSohly, 1996). Accordingly, a pleasant odor of the living plant is not necessarily indicative of a pleasant-smelling essential oil. Yields are very small – about 10 L/ha (Mediavilla &

Steinemann, 1997), so essential oil of *C. sativa* is expensive, and today is simply a novelty. Essential oil of different strains varies considerably in odor, and this may have economic importance in imparting a scent to cosmetics, shampoos, soaps, creams, oils, perfumes and foodstuffs. Switzerland has been a center for the production of essential oil of *C. sativa* for the commercial market. Narcotic strains produce much higher numbers of flowers than fiber strains, the bracts associated with the female flowers providing most of the essential oil, so narcotic strains are naturally adapted to essential oil production. Switzerland has permitted strains with higher narcotic THC content to be grown than is allowed in other Western countries, giving it an advantage with respect to the essential oil market. Nevertheless, essential oil has often been produced from low-THC *Cannabis*. The THC content of essential oil obtained by steam distillation can be quite low, but produces a product satisfying the needs for very low THC levels in food and other commercial goods. The world market for hemp essential oil for simply flavoring products is very limited at present, and probably has weak growth potential. Aromatherapy – the therapeutic use of volatile oils – has become popular, and it is possible that *Cannabis* volatile oils could achieve considerable market penetration. There is no evidence at present that they are as effective as presently utilized aromatherapy oils. Nevertheless, there is a large market for *Cannabis* products of whatever nature merely because *C. sativa* is notorious, and it would not be surprising if its essential oils marketed for aromatherapy achieved market success.

What adaptive significance odor has for wild plants of *C. sativa* is unclear, although the terpenes present are repellent to some insects (Thomas et al., 2000) and are antimicrobial (Novak et al., 2001). Some wild populations produce quite nauseous smells, and the odor of some narcotic strains is also objectionable (note the popular strain Skunk). Perhaps facetiously, it may be pointed out that the odor of marijuana has affected human evolution, since the distinct smell has widely attracted law enforcement officers, resulting in the incarceration of millions, reducing their Darwinian fitness (potential for leaving progeny).

Narcotic strains tend to be more attractive in odor than fiber strains, and many of the marketed marijuana strains have attractive odors. Clarke and Merlin (2013) noted that "Pioneering marijuana breeders continued selecting primarily for strong potency (high Δ^9-THC content), followed by more aesthetic considerations of flavor, aroma, and color. Modifying adjectives such as 'minty,' 'floral,' 'spicy,' 'fruity,' 'sweet,' 'purple,' 'golden,' or 'red' were often associated with selected varieties." Industries that offer products that are consumed by mouth, like marijuana, are very concerned about organoleptic preferences (taste, odor and texture) of their offerings since these are critical criteria by which consumers judge acceptability. Probably odor (which is interconnected with taste) is the only organoleptic factor of interest, although the abrasiveness of the foliage, caused by the presence of cystolith hairs (Fig. 16c), may also be significant since there has been some consumption by mouth. In southern Asia, "bhang" is a low-intoxicant preparation of *Cannabis* leaves, typically combined with milk products (THC is soluble in fat), and sometimes eaten by lower classes. In the illicit drug counterculture/underground trade, hundreds of strains of *Cannabis sativa* are offered, and as often reflected by their names (e.g., Lemon-lime Kush, California Orange Bud and Fruity Juice), some of these differ in olfactory and/or taste qualities, likely mostly because of different profiles of the terpenes that are present. Although the terpenes are volatile, some remain in the secretory glands unless they are crushed. The

odor of fiber strains is quite divorced from the quality and quantity of fiber in the stem (the fiber has no particular smell), but the odor of marijuana harvested from narcotic strains is unavoidable, and so has been more susceptible to selection. It is plausible that in the past narcotic land races with pleasant odors were selected more often than was the case for fiber strains. However, it is also apparent that some strains with a foul smell are appreciated by many. Bouquet (1950) noted "Ganja [marijuana] has a pronounced fetid smell, much appreciated by addicts."

In the "Evolution of Narcotic Drug Production Under Domestication" section, the possibility that the terpenes of *Cannabis* modify its narcotic and medicinal effects is discussed. If so, it is possible that unconscious selection for terpene profile has been significant in the biochemical evolution of *Cannabis* narcotic strains.

Evolution of Seed Oil Production Under Domestication

As noted elsewhere in this review, the achenes of *Cannabis* are usually referred to as seeds. The true "seed" portion is enclosed within the fruit wall (pericarp), which (along with a relatively thin seed coat) forms the protective "hull." Most of the seed is made up of two oil-rich cotyledons, upon which the germinating seedling relies for nourishment. Edible oil is usually obtained by cold-pressing the seed.

A Brief History of Oilseed Production and Usage

Cannabis seeds have been employed for at least 3000 years as food for humans and livestock. Indeed, hempseed was one of the "five grains" of ancient China, along with foxtail millet, broomcorn millet, rice, and barley or wheat (Huang, 2000). In the past, hemp seed has generally been a food of the lower classes, or a famine food. Crushed peanut-butter type preparations have been produced from hemp seed in Europe for centuries, but were rather gritty since technology for removing the hulls was rudimentary. Until about 1800, hemp oil was one of the more popular lighting oils. The cultivation of hemp as an oilseed crop reached a zenith in 19th and early 20th century Russia, when, in addition to the edible uses, the seed oil was employed for making soap, paints and varnishes. However, for most of history the seeds were of very minor economic importance, and by the middle of the 20th century, commercial use was negligible, and selections suitable for dedicated oilseed production were unavailable. For most of the latter part of the last century the seeds were usually employed as wild bird and poultry feed, although occasionally also as human food. World hemp seed production (mostly in China) fell from about 70,000 tonnes in the early 1960s to about 34,000 tonnes at the beginning of the twenty-first century.

The Recent Development of Oilseed Products

At the close of the 20th century, reminiscent of how new hemp fiber applications resurrected the fiber crop mostly in Europe (as discussed in the "Evolution of Stem Fiber Production Under Domestication" section), a similar development of oilseed products, primarily in Canada, witnessed the founding of an expanding hempseed industry. *Cannabis sativa* is now being grown as a major new source of edible and

industrial oilseed products. With the growing recognition of the health benefits of hempseed oil, discussed below, hemp seed production has been increasing. Indeed, the economic prospects for continued development as an oilseed crop are much better than for continued development as a fiber crop. Although China remains the major grower of hemp (both for fiber and oilseed), certified organic production of hemp seed for food purposes can often be done domestically, giving farmers in countries where cultivation is permitted an advantage. At present, oilseed hemp is not competitive with linseed for production of oil for manufacturing, or to sunflower and canola for edible vegetable oil. However, as mentioned in this section, there are remarkable dietary advantages to hempseed oil, which accordingly has good potential for penetrating the salad oil market, and for use in a very wide variety of food products. Additionally as noted later, there is also good potential for hemp oil in cosmetics and skin-care products.

For human consumption of the tasty embryo, the achene is hulled (= dehulled). Hulled hemp seed is a very recent phenomenon, first produced in quantity in Europe. Hemp seed is now often found canned or vacuum-packed. Modern seed hulling using mechanical separation produces a smooth, white, gritless hemp seed meal that needs no additional treatment before it is consumed. This seed meal should be distinguished from the protein-rich, oil-poor seed cake remaining after oil has been expressed, that is used for livestock feed. The seed cake is also referred to as "seed meal," and has proven to be excellent for animals (Mustafa et al., 1999).

Nutritional Aspects of Hempseed Oil

According to an ancient legend (Abel, 1980), Buddha, the founder of Buddhism, survived a 6-year interval of asceticism by eating nothing but one hemp seed daily. This apocryphal story holds a germ of truth – hemp seed is quite nutritional, primarily because of the very high content of unsaturated fatty acids (of the order of 75 %). Good general accounts of dietary aspects of hemp oil are Pate (1998b), Callaway (2002), Leson and Pless (2002) and Oomah et al. (2002).

The quality of an oil or fat is most importantly determined by its fatty acid composition. Hemp is of high nutritional quality because it contains high amounts of unsaturated fatty acids, mostly oleic acid (18:1; 10–16 % content in the achenes, depending on strain), linoleic acid (18:2; 50–60 %), alpha-linolenic acid (18:3; 20–25 %), and gamma-linolenic acid or GLA (18:3; 1–6 %). [The notations C:D are the lipid numbers, with C specifying the number of carbon atoms and D the number of double bonds.] In contrast to shorter-chain and more saturated fatty acids, these essential fatty acids do not serve as energy sources, but as raw materials for cell structure and as precursors for biosynthesis for many of the body's regulatory biochemicals. The essential fatty acids are available in other oils, particularly fish and flaxseed, but these tend to have unpleasant flavors compared to the mellow, slightly nutty flavor of hempseed oil. GLA is a widely consumed supplement known to affect vital metabolic roles in humans, ranging from control of inflammation and vascular tone to initiation of contractions during childbirth. GLA has been found to alleviate psoriasis, atopic eczema and mastalgia, and may also benefit cardiovascular, psychiatric and immunological disorders. Ageing and pathology (diabetes, hypertension, etc.) may impair GLA metabolism, making supplementation desirable. As much as 15 % of the human population may benefit from addition of GLA to their diet. At present, GLA is

available in health food shops and pharmacies primarily as soft gelatin capsules of borage (*Borago officinalis*) or evening primrose (*Oenothera biennis*) oil, but hemp is almost certainly a much more economic source. Although the content of GLA in the seeds is lower, hemp is far easier to cultivate and higher-yielding.

There are other fatty acids in small concentrations in hemp seed that have some dietary significance, including stearidonic acid (Callaway et al., 1996) and eicosenoic acid (Mölleken & Theimer, 1997). Nutritional supplements featuring stearidonic acid are often made from black currant (*Ribes* species) seed, but some hemp cultivars are potential alternative sources. Stearidonic acid is apparently not an important human dietary supplement, but may be required for people with a deficiency of the enzyme delta-6-desaturase (Pate, 1998b). Eicosenoic acid is important in the production of cerebrosides, which are components of nerve membranes and the "white substance" of the brain. Because of the extremely desirable fatty acid constitution of hemp oil, it is now being marketed as a dietary supplement in capsule form.

Linoleic acid and alpha-linolenic acid are the only two fatty acids which must be ingested and are considered essential to human health (Callaway, 2004). While the value of unsaturated fats is generally appreciated, it is much less well known that many dieticians consider the Western diet to be seriously nutritionally unbalanced by an excess of linoleic (an omega-6 fatty acid) over alpha-linonenic acid (an omega-3 fatty acid). A century ago, the typical North American diet ratio of omega-6 to omega-3 fatty acids was about 1–3:1; today it is about 10–14:1. In hempseed, linoleic and alpha-linolenic occur in a ratio of about 3:1, considered optimal in healthy human adipose tissue, and apparently unique among common plant oils (Deferne & Pate, 1996). Omega-3 fatty acids seem to reduce inflammation, prevent heart arrhythmias, dilate bloods vessels and counter clotting. By contrast, omega-6 fatty acids promote an inflammatory response and encourage clotting. When insufficient omega-3 is provided (relative to omega-6), there seems to be an increased incidence of common diseases, including heart disease, Crohn's disease, asthma, Alzheimer's and some kidney diseases.

Tocopherols are major antioxidants in human serum (Mölleken et al., 2001). Alpha-, beta-, gamma- and delta- tocopherol represent the Vitamin E group. These fat-soluble vitamins are essential for human nutrition, especially the alpha-form, which is commonly called vitamin E. About 80 % of the tocopherols of hempseed oil is in the alpha form. The vitamin E content of hempseed is comparatively high. Natural antioxidants in hempseed oil, such as α-tocopherol, are believed to stabilize the highly polyunsaturated oil, tending to keep it from going rancid, at least within the intact seed. Sterols in hemp seeds probably serve the same antioxidant function, and are also desirable from a human health viewpoint. Phytosterols are membrane constituents in all plants. Medically, they are known to reduce blood cholesterol and so are therapeutic for atherosclerosis (Mölleken et al., 2001).

Hempseed protein has recently become very popular as a nutritional supplement, although evidence for its health value is relatively limited. Hemp seeds contain 25–30 % protein, with all eight amino acids essential in the human diet present, and a reasonably complete amino acid spectrum (although lysine is low, as in most vegetable protein). About two thirds of hempseed protein is of the edestin type, which is easily digestible. Although the protein content is smaller than that of soybean, it is much higher than in grains like wheat, rye, maize, oat and barley. The oilcake remaining after oil is expressed from the seeds is employed as a very nutritious feed supplement for livestock, but it also

has potential for production of a high-protein flour. Proteins are potential allergens, but human allergies to hemp protein have rarely been reported (Nayak et al., 2013).

Environmental Control of the Development of Nutritional Components

In the "Evolution of Narcotic Drug Production Under Domestication" section, it is noted that the concentration of THC, the principal intoxicant chemical of *C. sativa*, depends to an extent on the environment in which the plant develops. Environment can also alter the fatty acid chemistry of *Cannabis*. This was demonstrated by Przybylski et al. (1997), who compared oilseed quality of hemp grown in Canada (under colder conditions) with the same varieties grown in Europe (under warmer conditions). The Canadian-grown seed oil was about 15 % higher in unsaturated fatty acids, with about 10 % more of alpha- and gamma- linolenic acids. It appears that in general a cooler climate is preferable for development of the unsaturated fatty acids, but if the growing season is too short, grain productivity is low and the fatty acid profile may be inferior.

Nutritional Cosmetics

Since the 1990s, hemp oil has become very significant as a "cosmeceutical" (cosmetic-nutraceutical), i.e., a body care product that promotes the health of skin and allied parts of the body because of the topical absorption of biochemicals. These products include bubble baths, creams, lip balms, lotions, moisturizers, perfumes, shampoos and soaps. Skin readily absorbs essential fatty acids, so that lotions rich in these substances can replenish cells damaged by sun and dry air (Wirtschafter, 1995). Linoleic acid, alpha linolenic acid and gamma linolenic acid specifically have several functions related to skin care: they influence cell membrane functions including fluidity, transport of electrolytes and activity of hormones, and they stimulate cell immunology; these fatty acids are considered to have potential for treating neurodermatosis and psoriasis (Vogl et al., 2004).

Industrial Fluids

The vegetable oils have been classified by "iodine value" as drying (120–200), semi-drying (100–120), and non-drying (80–100), determined by the degree of saturation of the fatty acids present (Raie et al., 1995). The suitability of coating materials prepared from vegetable oil depends on the nature and number of double bonds present in the fatty acids. Linseed oil, a very good drying oil, has a very high percentage of linolenic acid. Hempseed oil has been classified as a semi-drying oil, like soybean oil, and is therefore more suited to edible than industrial oil purposes. Nevertheless hemp oil has found applications in the past in paints, varnishes, sealants, lubricants for machinery, and printing inks, although petrochemical extracts have made these uses obsolete, and resurrection of such industrial end uses is unlikely because hempseed oil is expensive (de Guzman, 2001). However, larger production volumes and lower prices may be possible, in which case hemp oil may find industrial uses similar to those of linseed (flax), soybean, and sunflower oils, which are presently used in paints, inks, solvents, binders and polymer plastics. Hemp shows a remarkable range of variation in oil constituents, and selection for oilseed cultivars with high content of valued industrial constituents is in progress.

Hemp seed oil has been used experimentally as diesel fuel, but far cheaper vegetable oils are available.

The Narcotic Potential of the Oilseed

Hemp seeds contain virtually no THC, but if improperly processed, THC contamination can result from contact of the seeds with the resin secreted by the epidermal glands on the leaves and floral parts, and also by the failure to sift away all of the perigonal bracts (which have the highest concentration of THC of any parts of the plant) that cover the seeds (Ross et al., 2000). Seed oil prepared from seeds coated with resin may have small levels of THC, and the same is true for foods made with the seeds. It has been suggested that trace amounts of cannabinoids (and also terpenes) could have health benefits (Leizer et al., 2000) but, as noted next, the presence of cannabinoids is currently very disadvantageous from a regulatory point of view.

Although much of the Western hemp-growing world uses 0.3 % THC in the plant as a maximum concentration for authorized cultivation, regulations in various countries allow only a much lower level of THC in human food products manufactured from the seeds. Permitted levels in seeds in various countries range from 10 ppm down to 0.005 ppm. Limits have been set not just because of concerns about possible toxicity, but also because of potential interference with drug tests (Grotenhermen et al., 1998). Cannabinoids are very lipid soluble and accumulate in fatty tissue throughout the body. They are released very slowly and so can remain in the body for more than a month after consumption. The Drug Enforcement Agency and the Office of National Drug Control Policy of the U.S. raised concerns over tests conducted from 1995 to 1997 that showed that consumption of hempseed products available during that period led to interference with drug-testing programs for marijuana use. Federal U.S. programs utilize a THC metabolite level of 50 parts per billion in urine. Leson (2001) found that this level was not exceeded by consuming hemp products, provided that THC levels are maintained below 5 ppm in hemp oil, and below 2 ppm in hulled seeds.

How Selection has Modified Cannabis sativa for Oilseed Production

In the "Evolution of Propagules Under Domestication" section, it was noted that achenes in domesticated plants of *C. sativa* differ in several respects from those of wild plants. This information is not repeated here, but it should be noted that oilseed hemp seed shows all of the features characteristic of seeds of domesticated plants. "The Evolution of Shoot Architecture Under Domestication" section, which discusses the evolution of shoot architecture in the various groups of domesticated plants, supplements the information presented below on oilseed strains.

Today, there are very few cultivars bred specifically for oilseed production, and indeed most hemp seed in Europe is currently obtained from so-called "dual usage" plants (employed for harvest of both fiber and seeds), which are not capable of producing as much seed as oilseed strains. Growing hemp to the stage that mature seeds are present compromises the quality of the fiber, because of lignification in the stem. As well, the woody hurds that are useful as a secondary product become more

difficult to separate. The lower quality fiber, however, is quite utilizable for pulp and non-woven usages. Of the European dual-usage cultivars, 'Uniko B' and 'Fasamo' are particularly suited to being grown as a source of oilseed.

It appears that in the past when seeds were harvested from cultivated *C. sativa*, they came from plants that were grown additionally for other purposes, either for fiber or narcotics. Dewey (1914) noted that a Turkish type of land race called Smyrna, that he thought was a narcotic strain, was commonly used in the early 20th century in the U.S. to produce birdseed, because (like most narcotic types of *Cannabis* and unlike fiber types) it is quite branched, producing many flowers, hence seeds. Until Canada replaced China in 1998 as a source of imported seeds for the U.S., most seeds used for various purposes in the U.S. were imported from China. Small and Marcus (2000) examined the growth of some Chinese hemp land races, which were quite branched, and altogether rather reminiscent of Dewey's description of Smyrna. Although similar in appearance to narcotic strains of *C. sativa*, the Chinese land races examined were low in intoxicating constituents, and it is probable that what Dewey thought was a narcotic strain was not.

"The Evolution of Photoperiodism Under Domestication" section, pointed out that plants of *C. sativa* are locally adapted to increasingly shorter seasons of northern latitudes by becoming smaller, and this pattern would apply to plants grow for oilseed, as well as those cultivated for fiber and narcotics. The "Evolution of Shoot Architecture Under Domestication" section, dealing with shoot architecture, pointed out that plants grown for narcotics are spaced sufficiently apart to provide for branches (hence flowers and THC content) to develop well, and likely at whatever latitude *C. sativa* was grown, farmers learned the appropriate density required to maximize seed production. However, as pointed out in the next paragraph, large, branched plants do not appear to represent the best way to maximize oilseed yield.

Until very recent times, the widespread cultivation of hemp primarily as an oilseed was largely unknown, except in Russia. It is difficult to reconstruct the type of plant that was grown there as an oilseed, because (1) such cultivation has essentially been abandoned; (2) land race germplasm in the Vavilov Research Institute (St. Petersburg) seed bank, the world's largest collection, has been extensively hybridized (Small & Marcus, 2003; Hillig, 2004b) due to inadequate maintenance. A land race certainly was grown in Russia specifically for seeds, and Dewey (1914) gave the following information about it: "The short oil-seed hemp with slender stems, about 30 in. high, bearing compact clusters of seeds and maturing in 60 to 90 days, is of little value for fiber production, but the experimental plants, grown from seed imported from Russia, indicate that it may be valuable as an oil-seed crop to be harvested and threshed in the same manner as oil-seed flax." Some very recently bred oilseed cultivars are indeed short, compact, and ideal for high-density planting. These include 'FINOLA' and 'Anka', which are relatively short, little-branched, mature early in north-temperate regions, and are ideal for high-density planting and harvest with conventional equipment. It appears that modern hempseed breeders have intuitively reconstructed the kind of plant that used to be grown in Russia for oilseed. Low stature is desirable in fiber selections to avoid channelling the plants' energy into stem tissue, in contrast to fiber cultivars for which a very tall main stalk is desired. Compact clustering of seeds also decreases stem tissue, promotes retention of seeds, and facilitates collection.

Although some forms of *C. sativa* have quite large seeds, until recently oilseed forms appear to have been selected mainly for a heavy yield of seeds. In Europe, most cultivars have been selected for fiber yield, and these do not differ much in oilseed potential (Mölleken & Theimer, 1997). By contrast, some drug strains (which have been selected for prodigious production of flowers), when left to go to seed can yield a kilogram of seeds on a single plant (Clarke & Merlin, 2013). Percentage or quality of oil in the seeds does not appear to have been important in the past (techniques for analysing the nutritional chemicals were simply not available until fairly recently), although selection for these traits is now being conducted. As noted in the "Evolution of Propagules Under Domestication" section, domesticated achenes are thinner-walled than wild achenes, and thinness of pericarp is an important criterion for modern hemp oil seed breeders since the pericarp is a waste product. Most significantly, modern selection is occurring with regard to mechanized harvesting, particularly the ability to grow in high density as single-headed stalks with very short branches bearing considerable seed.

Evolution of Narcotic Drug Production Under Domestication

Pharmacological Terminology for Marijuana

The word "narcotic," consistently used in this review to describe the psychological effects associated with marijuana, has been extensively and ambiguously employed in lay, legal and scientific circles. The term is most widely used as an arbitrary juridical category – a narcotic is simply a substance or preparation that is associated with severe penalties because of real or alleged dangerous, addictive properties. "Legally, cannabis has traditionally been classified with the opiate narcotics, and while they may share some euphorogenic and analgesic properties, they are otherwise quite distinct pharmacologically" (Le Dain, 1972). Etymologically, based on "narcosis," a narcotic would be expected to be a substance promoting sleep, and indeed some use the term to characterize any drug which produces stupor or insensibility. As will be seen, at least one compound in *Cannabis* has important sedative properties. The pharmacological classification of cannabis is controversial. It has been characterized as a sedative-hypnotic-general-anesthetic like alcohol and nitrous oxide; a mixed stimulant-depressant; a mild hallucinogen, especially at higher doses; a "psychedelic," like LSD at very high doses; and as a separate category of psychic experience (Le Dain, 1972). The following terms have been used to describe cannabis: psychedelic (mind-manifesting or consciousness-expanding), hallucinogenic (hallucination-producing), psychotomimetic (psychosis-imitating), illusinogenic (illusion-producing), and psychodysleptic (mind-disrupting); as noted in Le Dain (1972, p. 396), these terms are problematical. There is little dispute that cannabis is a "psychotropic" or "psychoactive" drug (one altering sensation, mood, consciousness or other psychological or behavioral functions). Clearly, it is popular (albeit largely illegal), employed primarily as a social inebriant and euphoriant. In this review the terms "narcotic" and "intoxicant" are used to refer to forms of *C. sativa* that are high in THC, and the term "non-narcotic" refers to forms low in THC. Although "narcotic" is often used pejoratively, the intent here is simply to indicate that there are associated drug-induced, intoxicating mental effects.

A Brief History of Narcotic Cannabis Drug Production and Usage

Russo et al. (2008) provide documented evidence for the earliest use of *C. sativa* as a pharmacologically active agent, in a 2700-year-old grave in China. However, over the last millennium cannabis consumption became more firmly entrenched in southern Asia from Afghanistan to India, than anywhere else in the world. Not surprisingly, the most highly domesticated drug strains were selected there. While *Cannabis* has been extensively used as a narcotic for thousands of years in the region and subsequently in the Near East, parts of Africa, and other Old World areas, widespread narcotic use simply did not develop in temperate region countries, where by contrast fiber hemp was raised. The use of *Cannabis* as a recreational inebriant in sophisticated, largely urban settings began substantially in the latter half of the 20th century. Up until then, drug preparations of *Cannabis* were used predominantly as a recreational intoxicant in poor countries and the lower socio-economic classes of developed nations. After World War II, marijuana became associated with the rise of a hedonistic, psychedelic ethos, first in the United States and eventually over much of the world, with the consequent development of a huge international illicit market. Cultivation, commerce, and consumption of drug preparations of *Cannabis* were proscribed in most countries during the 20th century, but narcotic cannabis contributes substantially to the current illicit drug problem of the world. According to the United Nations Office on Drugs and Crime (2014), cannabis is the most widely used illicit substance in the world, consumed by up to 227 million, constituting 4.9 % of those between the ages of 15 and 64. The highest prevalence occurs in Western countries and several nations in Africa. Estimates for the U.S., the leader in usage, range up to 25 %. Marijuana has been claimed to be at least the fourth most valuable crop in America, outranked only by corn, soybeans and hay (Small & Marcus, 2002). Indicative of how widespread is the use of cannabis in the U.S., about 10 % of paper currency has been found to be contaminated with cannabinoid residues (Lavins et al., 2004).

Currently, there is an explosion of interest in narcotic forms of cannabis, in part because of possible medical applications, but also because of increasing tolerance of illegal recreational usage. Nevertheless, governments have long maintained a costly war against the consumption of cannabis. Although narcotics are widely viewed as intrinsically evil, the world's leading controlled narcotic crops have some legitimate, useful applications (Small, 2004; Small & Catling, 2009).

Cannabis drug preparations have been employed medicinally in folk medicine since antiquity in Asia, and were extensively used in Western medicine between the middle of the 19th century and World War II, particularly as a substitute for opiates (Mikuriya (1969); see Russo (2007) for an extensive review). Alcoholic tinctures were particularly popular. Medical use declined with the introduction of synthetic analgesics and sedatives, and until the end of the 20th century there was very limited authorized medical use. So-called "compassion clubs" in Western nations have dispensed marijuana to ill people, often illegally. Several European and Commonwealth countries and many states of the U.S. currently allow medical dispensation of marijuana, while Uruguay and several U.S. states permit the sale by licensed vendors of marijuana for recreational use. In the last several decades there has been a great upsurge of interest in using marijuana for treatment of various ailments, especially for alleviating nausea, vomiting and anorexia following radiation therapy and chemotherapy; as an appetite stimulant for AIDS patients; for relieving the tremors of multiple sclerosis and epilepsy; and as an analgesic for chronic

neuropathic pain. Extracts have been used for specific purposes, notably THC for glaucoma, spasticity from spinal injury or multiple sclerosis, pain, inflammation, insomnia, asthma and other conditions; and CBD (described later) for moderating the effect of THC, and for some psychological problems. The medical efficacy of cannabis drugs has been examined in thousands of research papers and hundreds of reviews (e.g., Grotenhermen & Műller-Vahl, 2012), but is beyond the scope of this review (for an excellent source of information, see Pertwee (2014)). There is not yet a medical consensus that any particular cannabis-based treatment is preferable to other available therapies. Most Western countries are curiously ambivalent about the therapeutic status of cannabis, with limited prescriptions for marijuana, its constituents or chemical analogues, but nevertheless listing it as a Schedule 1 controlled substance, defined as having high potential for abuse and no currently accepted medical use.

Glandular Trichomes

The psychoactive chemicals of *Cannabis* (cannabinoids, notably THC, as presented in the following paragraphs) are produced in specialized tiny secretory epidermal glands. These are termed "trichomes" or "hairs" (the former term is often restricted to plants and the latter to animals). Different kinds of glandular epidermal trichomes occur (Fig. 16), often

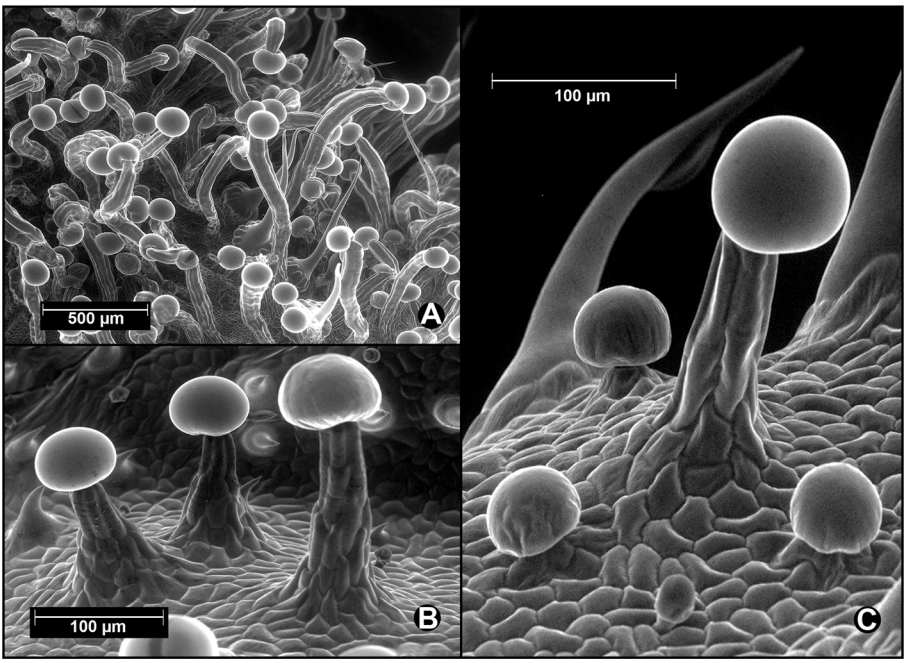


Fig. 16 Scanning electron micrographs of secretory glands of the abaxial epidermis of perigonal bracts (i.e., the single bract covering each pistil) of narcotic forms of *Cannabis sativa*. **a** Dense concentration of long-stalked glands. **b** Three long-stalked glands. **c**. A long-stalked secretory gland (*center*) around which are three short-stalked multicellular glands. Also show is a cystolith hair (a unicellular, claw-like structure with a calcium carbonate concentration embedded in the base). Resin containing cannabinoids is synthesized in the spherical heads. The perigonal bracts are the most intoxicating part of narcotic forms of the plant. Prepared by E. Small and T. Antle

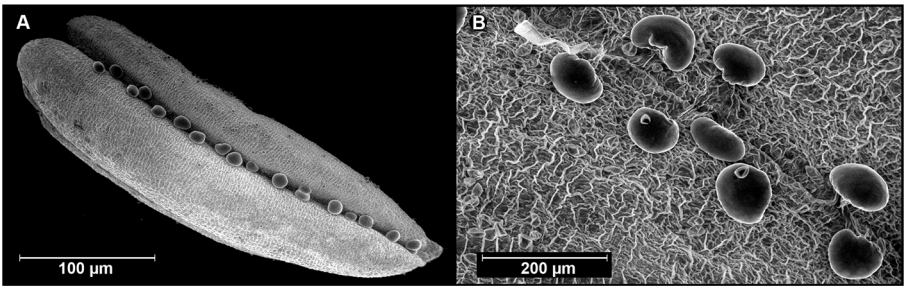


Fig. 17 Scanning electron micrographs of short-stalked secretory glands on an anther of *Cannabis sativa*. **a** A line of glands separating the pollen-containing segments. **b** Close-up of several of the glands. Prepared by E. Small and T. Antle

classified as long-stalked, short-stalked or sessile (essentially lacking a stalk, sessile glands hardly look like trichomes). Rather different glands are present on the anthers (Fig. 17), but since the female plants are the source of drugs, the discussion is confined to their glands. In the female's glandular trichomes, the essential part of the gland is a more or less hemispherical head, sometimes compared in size to the head of a pin. Inside the head at its base there are specialized secretory "disk cells," and above these there is a non-cellular cavity where secreted resin is accumulated, enlarging the covering sheath (a waxy cuticle) of the head into a spherical blister. This may eventually rupture, releasing resin onto the surface of the plant. Hot conditions seem to favor release of the resin, but apparently there has been selection for strains that retain resin within the gland heads so that when fabric sieves are used to prepare hashish (as described later), they will not become clogged with sticky resin. However, strains that produce extruded sticky resin have been favored when hands or leather are used to rub off the resin for hashish preparation (McPartland & Guy, 2004; Clarke, 1998). Clarke and Watson (2002) state that there is an "abscission layer" at the base of the head, although there seems no reason why dropping the heads is adaptive from the plant's perspective. However, it does seem that some strains have been selected for ease of harvesting the heads for making narcotic preparations. The resin is a sticky mixture of cannabinoids and a variety of terpenes. In marijuana varieties the resin is rich in THC, the chief intoxicant of *Cannabis*. The secretory glands differ notably in density on different organs of the plant (high concentrations occur on the lower surface of the young leaves, on young twigs, on the tepals, and especially on the perigonal bracts (Fig. 16), where they are very dense and productive). Given this distribution, the glands would seem to be protective of young and reproductive above-ground exposed tissues (the roots and achenes, which are not exposed, lack glands). Clarke (1998) observed that marijuana varieties differ widely in the size of glands. Selection of narcotic forms appears to have favored greater gland size, greater gland density, or both. Small and Naraine (2015) found that recently selected strains with very high levels of THC have very large gland heads. Mahlberg and Kim (2004) observed that the cannabinoid content of the long-stalked glands that they examined possessed about 20 times the cannabinoid content of sessile glands (which are usually much smaller than the former). The glands of *Cannabis* have been extensively examined by Mahlberg and associates (Hammond & Mahlberg, 1977, 1978; Kim & Mahlberg, 1995, 1997, 2003; Mahlberg & Kim, 1991, 1992, 2004; Mahlberg et al., 1984; Turner et al., 1980, 1981a, b).

It has been established that cannabinoids are synthesized within the secretory glands, not elsewhere and transported to the glands (Sirikantaramas et al., 2005; Stout et al., 2012).

There is some evidence for cannabinoid production outside of the epidermal glands, but only in trace amounts. Laticifers occur in the foliage and stems (Bouquet, 1950). These are of the unbranched, nonarticulated form, made up of an elongated secretory cell producing a kind of latex. Furr and Mahlerg (1981) detected cannabinoids in laticifers of *C. sativa*. Veliky and Genest (1972), Pacifico et al. (2008), and others found no production of THC in tissue cultures, suggesting that non-secretory cells do not produce cannabinoids. However, some experiments demonstrated production of cannabinoids in cell cultures of *Cannabis*, but in extremely limited amounts (Heitrich and Binder (1982); Hartsel et al. (1983); see review of Mandolino and Ranalli (1998)).

Cannabinoids

Cannabis contains a seemingly unique class of terpenophenolic secondary metabolites, the cannabinoids, of which more than 100 have been described (Grotenhermen & Russo, 2002; ElSohly & Slade, 2005; ElSohly, 2007; Radwan et al., 2009; de Meijer, 2014), but only a few are psychoactive (later, a broader conception of "cannabinoids" is presented). There are reports in the literature that cannabinoids occur in other plants (e.g., in the liverwort *Radula variabilis* (Toyota et al., 2002) and in the composite *Helichrysum* (Bohlmann & Hoffmann, 1979), but virtually all specialists on the cannabinoids are of the view that cannabinoids are more characteristic of *Cannabis* than any other plant. Additional chemical investigation is required to establish whether some of the cannabinoids that have been described occur as original metabolic products of the plant or are degenerative products or artifacts. The more important cannabinoids are shown in Fig. 18. These have a basic 21-carbon skeleton (22 in the carboxylated forms). In the living plant the cannabinoids exist predominantly in the form of carboxylic acids, which decarboxylate into their neutral counterparts (as shown in Fig. 18) with time or when heated, as provided when marijuana is smoked or cooked (e.g., in brownies). Delta-9-tetrahydrocannabinol (Δ^9-THC, or simply THC) is the predominant psychoactive component (for other cannabinoid abbreviations, see the legend of Fig. 18). (The designation Δ^9-THC employs formal chemical nomenclature for pyran-type compounds. In an alternative nomenclature system often employed in Europe, based on regarding the cannabinoids as substituted monoterpenoids, this is known as Δ^1-THC.) THC is the world's most popular illicit chemical, and indeed the fourth most popular recreational chemical after caffeine, ethyl alcohol and nicotine, all of which are addictive. Other THC isomers also occur, particularly Δ^8-THC, which is also psychoactive. Δ^8-THC is much less abundant in *C. sativa*, occurring only in trace amounts if at all, and is somewhat less potent than Δ^9-THC. CBN, the principal degeneration or transformation product produced when THC ages, has limited psychoactive potential (Russo, 2007), and the other molecules shown in Fig. 18 are not euphoriant, and if present almost always occur only in small concentrations. Oxygen, high temperatures, light, and high humidity gradually decrease the potency of cannabis drugs, but storage in a dark, cool place with exclusion of air minimizes loss of activity for up to several years.

THC is very potent in humans, causing a "high" at a dose of 10 μg/kg through smoking, 30–50 μg/kg after i.v. injection and 120 μg/kg from ingestion. A THC

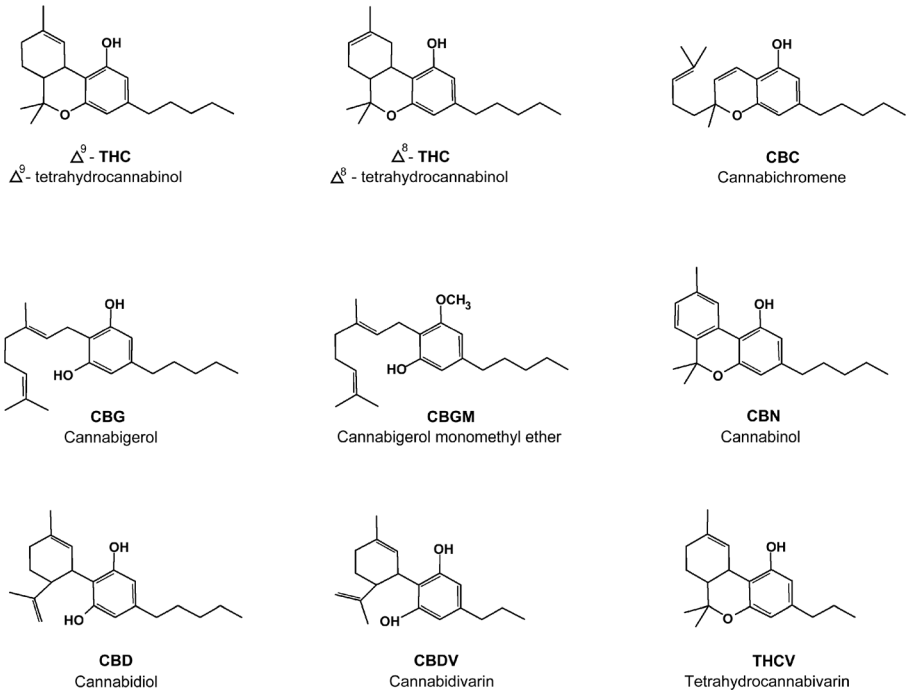


Fig. 18 Chemical diagrams (decarboxylated forms) of several of the well-known cannabinoids. Delta-9 tetrahydrocannabinol (Δ^9-THC) is the chief intoxicant chemical and predominates in narcotic strains, while the isomer delta-8 tetrahydrocanninol (Δ^8-THC), which is somewhat less intoxicating, is usually present in no more than trace amounts. Cannabinol (CBN), which has limited intoxicating ability, is a frequent degradation or oxidation product, usually not appreciably present in the fresh plant. The remaining compounds shown are not intoxicant or at least not appreciably so, and except for CBD are usually present in trace amounts or are absent. CBD (cannabidiol) is the chief nonintoxicant chemical, and predominates in non-intoxicant strains; it has notable sedative effects. Cannabichromene (CBC) is often detected in narcotic strains. Cannabigerol (CBG) is the biosynthetic precursor (in the carboxylated form, as shown in Fig. 19) of THC and CBD. It is more often observed in non-intoxicant strains than in narcotic strains. Cannabigerol monomethy ether (CBGM) has been detected especially in populations from northeastern Asia. Cannabidivarin (CBDV) has been reported in populations from central Asia. Tetrahydrocannabivarin (THCV) is usually present in trace amounts but occasionally in significant quantities, especially in populations from Asia and Africa

concentration in marijuana of approximately 0.9 % has been suggested as a practical minimum level to achieve an intoxicant effect but, as discussed later, CBD (the predominant cannabinoid of fiber and oilseed varieties) antagonizes (i.e., reduces) and potentiates (modifies) the effects of THC. Concentrations of 0.3 to 0.9 % are considered to have "only a small drug potential" (Grotenhermen & Karus, 1998). The state of Colorado, which recently authorized the recreational use of marijuana, set a legal maximum limit for driving an automobile of 5 ng/mL THC of blood (many other states have zero tolerance). Grotenhermen et al. (2005) came to the following conclusions (cf. Armentano, 2013). After smoking "typical medium to strong doses" of 15–20 mg THC, peak THC levels in blood occur 5–10 min after inhalation, and a waiting period of about 3 h after smoking seems sufficient to reduce THC level to below a THC blood level of 5 ng/mL. Typical oral doses in social settings are in the 10–20 mg range, the effects occurring later than do those of smoking, usually peaking 2–3 h after

ingestion, and usually decreasing below the level of 5 ng/mL THC of blood in 4 h. Additional information contrasting smoked and eaten cannabis is provided later.

There is a general inverse relationship in the resin of *Cannabis* between the amount of THC present and the amount of CBD. Whereas most drug strains contain primarily THC and little or no CBD, fiber and oilseed strains primarily contain CBD and very little THC. CBD can be converted to THC by acid catalyzed cyclization, and so could serve as a starting material for manufacturing THC, but the illicit drug trade has access to easier methods of synthesizing THC or its analogues than by first extracting CBD from non-drug hemp strains.

There have been numerous studies of cannabinoid variation, mostly employing the predominance of either THC or CBD respectively as indicators of narcotic kinds and non-narcotic kinds (for examples, Fetterman et al., 1971; Small & Beckstead, 1973a, b; Small et al., 1975; Avico et al., 1985). In the "Classification and Nomenclatural Issues" section, two subspecies are recognized using THC content for separation. *Cannabis sativa* subsp. *sativa* has limited THC and *C. sativa* subsp. *indica* has appreciable THC. A dividing line of 0.3 % (dry weight content in the inflorescence or young infructescence) was established by Small et al. (1976) based on study of variation in several hundred populations, and subsequently was adopted in the European Community, Canada, parts of Australia, and the U.S.S.R. as a criterion between cultivars that can be legally cultivated under licence and forms that are considered to have too high a drug potential (in some countries the allowable level is currently different). For a brief period, the 0.3 % threshold was also accepted as maximum concentration for importing hemp into the U.S. As noted above, a level of about 1 % THC is considered the threshold for marijuana to have intoxicating potential, so the 0.3 % level is conservative, and some jurisdictions (e.g., Switzerland and parts of Australia) have permitted the cultivation of cultivars with higher levels. It is well known in the illicit trade how to screen off the more potent fractions of the plant in order to increase THC levels in resultant drug products. Nevertheless, a level of 0.3 % THC in the flowering parts of the plant is reflective of material that is too low in intoxicant potential to actually be used practically for illicit production of marijuana or other types of narcotic drugs.

CBC is a frequent minor constituent of highly-intoxicating strains of *C. sativa*, especially from Africa, and strains high in CBC have been selected for medicinal experimentation. De Meijer et al. (2009a) provide evidence that CBC is present in substantial amounts in juvenile plants and declines with maturation; these authors found variants in which CBC persisted into maturity, and noticed that this is associated with a reduced presence of perigonal bracts and secretory glands. CBG rarely dominates the resin of *Cannabis* (Fournier et al., 1987). Some geographical races with minor or trace amounts of cannabinoids have been described, notably for CBGM in some northeastern Asian populations, CBDV in some populations from central Asia, and THCV in some collections from Asia and Africa.

Adaptive Purpose of the Cannabinoids

The natural function of the abundant secretory glands, and of the large volume of resin they produce, has not been established. The glands are rich in terpenes, which are very common in higher plants, and are known to be protective against many harmful organisms, but why the plant elaborates some of these chemicals into cannabinoids is

not clear. There is some evidence that drought, high light intensity, and high elevations (and therefore greater UV light) increase the release of exudate on the leaf surfaces, and this has led to the hypothesis that the resin is a protective sunscreen (Bouquet, 1950, stated that the resin is an "insulating protective varnish" against high temperature and moisture loss.) Pate (1983) hypothesized that THC is protective against ultraviolet-B radiation. However, Lydon et al. (1987) concluded that "the contribution of cannabinoids as selective UV-B filters in *C. sativa* is equivocal." The glands and consequently the resin that is secreted are concentrated on the abaxial ("lower") side of the leaves (the same is true for the perigonal bracts in the inflorescence); it hardly makes sense for a sunscreen to be present on the shaded lower side of the foliage rather than the exposed upper side, and employing a resinous sunscreen seems quite speculative in view of the fact that plants commonly use several other strategies for reducing the intensity of solar radiation (see, for example, Small, 2014a). The cannabinoids appear to provide some protection against bacteria and fungi (McPartland et al., 2000). *Cannabis sativa* has minor allelopathic properties (Inam et al., 1989; McPartland, 1997; McPartland et al., 2000), and chemicals leached into the soil may inhibit competing plants, as suggested by Haney and Bazzaz (1970). Insects are by far the principal herbivores of plants, which employ many chemical defences against them. Curiously, insects lack endocannabinoid receptors (discussed later in this section), and so are incapable of responding to the cannabinoids in the same way as most animal groups. Ledbetter and Krikorian (1975) suggested that exuded resin could be a mechanical defence, ensnaring small insects like flypaper. "Touch-sensitive glandular trichomes" rupture when touched by an arthropod, rapidly releasing a sticky exudate which can discourage, even kill herbivorous insects (Krings et al., 2002). In living (but not dried) cannabis glands, the resin head readily ruptures when touched, suggesting that the released resin is indeed anti-herbivorous. Why the cannabinoids have evolved remains open to speculation (indeed, why other species in the Cannabaceae have secretory epidermal cells is equally unclear). Most secondary compounds are likely a) metabolic waste products, b) generalized anti-biotics (against all harmful classes of organisms; see Pate (1994)), or c) evolutionary holdovers from ancestors in which the chemicals were adaptive. The cannabinoids probably fall within one or more of these categories.

Factors Associated with Variation of THC

Cannabinoids levels in the plant generally increase from the seedling stage to the flowering period (Phillips et al., 1970; Latta & Eaton, 1975; Turner et al., 1975; Small, 1979b; Hemphill et al., 1980; Kushima et al., 1980). Seasonal fluctuations in relative proportion of THC and CBD have been observed (Phillips et al., 1970; Latta & Eaton, 1975; Pate, 1998a), with differences in staminate and pistillate plants (Turner et al., 1975). The plants of some populations of cultivars have proven to be rather uniform in THC content, whereas in others considerable variation among plants has been found (Mechtler et al., 2004).

Cannabinoid content differs in different parts of the plant, increasing in the following order: large stems, smaller stems, older and larger leaves, younger and smaller leaves, flowers, perigonal bracts covering the female flowers (and consequently covering the fruits). Epidermal secretory glands are present on all of the preceding structures, explaining the presence of cannabinoids. There are reports of cannabinoids in minute

Fig. 19 Biosynthetic pathway of THC and CBD, the predominant cannabinoids of *Cannabis sativa*. *CBGA* = cannabigerolic acid, *THCA* = tetrahydrocannabinolic acid, *CBDA* = cannabidiolic acid (the carboxylyated forms respectively of CBG, THC, and CBD). Decarboxylation (conversion of THCA to THC and conversion of CBDA to CBD) is not part of the biosynthetic pathway, but occurs spontaneously with aging and/or heat. In the living plant, Δ^9-THC is carboxylated (with a –COOH moiety attached to the benzene ring), and in this form (known as THCA) it is only marginally psychoactive. With mild heat (as applied when smoking or vaporizing marijuana), drying, or short-term aging after harvest, Δ^9-THC-COOH decarboxylates to form Δ^9-THC, which is psychoactive

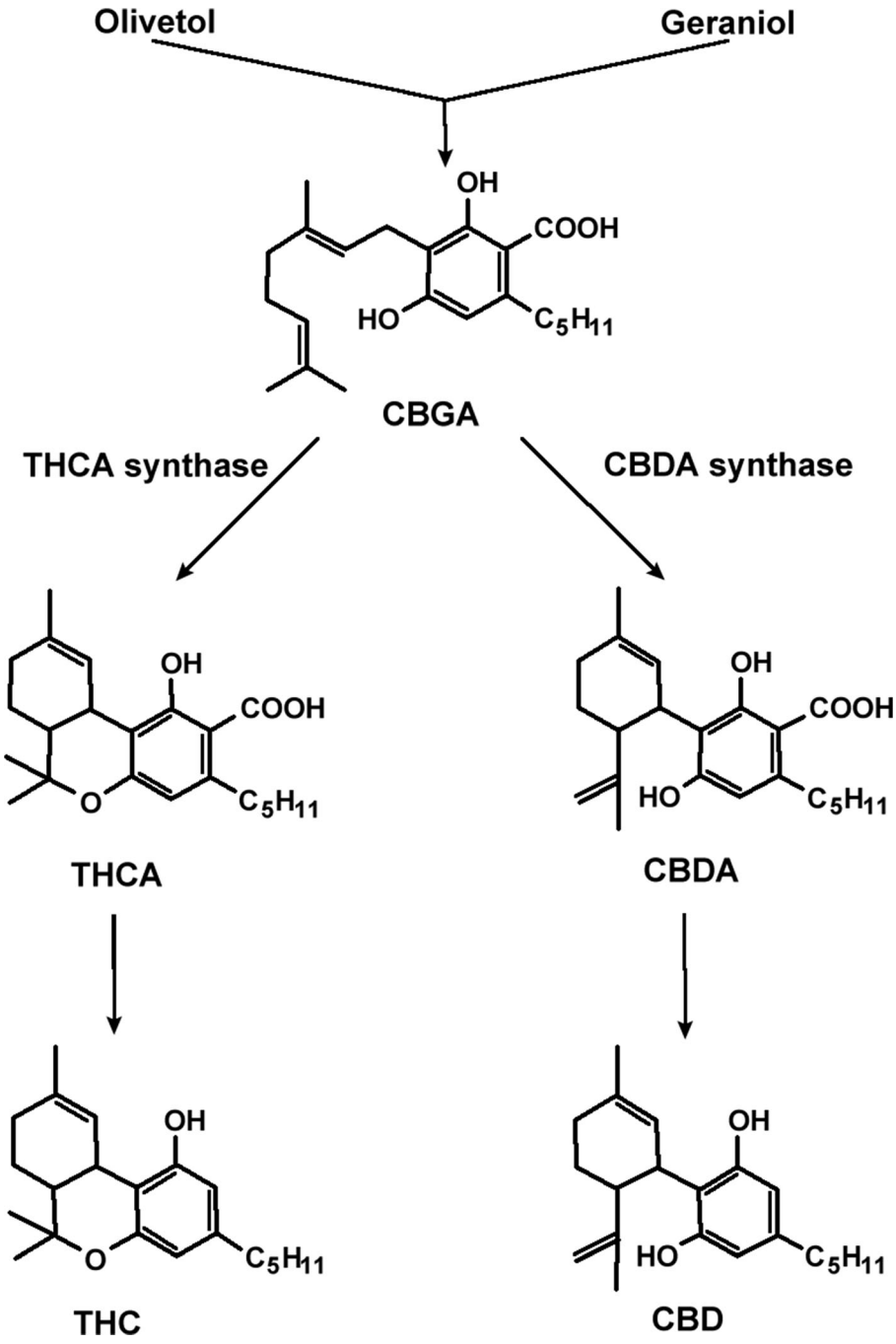
amounts in achenes (excluding bracts) and roots, but this could be due to contamination, as the resin of the plant is easily transferred. THC and other cannabinoids have been reported in the pollen (Paris et al., 1975; Ross et al., 2005), but it may be that this also is the result of contamination from the secretory glands of the anther (note Fig. 17).

Various environmental circumstances can modify, albeit relatively slightly, the cannabinoid content of *Cannabis*. Factors that have been examined include temperature (Bazzaz et al., 1975; Sikora et al., 2011), nutrient availability (Coffman & Gentner, 1975, 1977; Bócsa et al., 1997), light intensity (Potter & Duncombe, 2012), untraviolet light intensity (Lydon et al., 1987; Pate, 1994), light quality (Mahlberg & Hemphill, 1983), and photoperiod (Valle et al., 1978). Haney and Kutscheid (1973) demonstrated that wild hemp populations in Illinois were highest in cannabinoids when stressed, either by nutrient limitations or by drought, although shading did not have any measurable effect. However, stress tends to make the plants drop their lower leaves which are naturally low in THC, and so it is difficult to evaluate the effects of stress on a whole-plant basis. Stress also makes for smaller plants with less biomass, and hence a lower overall production of cannabinoids per unit area of land occupied. The range of THC concentrations developed by low-THC cultivars (those typically with no more than 0.3 % THC) under different circumstances on the whole is limited, for the most part generally not varying more than 0.2 percentage points when grown in a range of circumstances, and usually less.

Biosynthesis and Genetics of the Cannabinoids

The biosynthetic pathways of the major cannabinoids with pentyl side chains (CBC, CBC, CBG, and THC) were established in the 1990s. The first event in the pentyl cannabinoid biosynthesis is the production of cannabigerol (CBG), produced by condensation of a phenol-derived olivetolic acid and a terpene-based geranylpyrophosphate catalysed by the enzyme geranylpyrophosphate:olivetolate geranyltransferase (Fellermeier & Zenk, 1998). From CBG, Δ^9-THC, CBD, and CBC are synthesized, each by a specific synthase enzyme. The enzyme converting CBG to THC was clarified by Taura et al. (1995). The enzyme converting CBG to CBD was studied by Taura et al. (1996) and Taura et al. (1997). An outline of the biosynthesis of the two most important cannabinoids, THC and CBD, is shown in Fig. 19. For more complete analyses of cannabinoid biosynthesis, see Sirikantaramas et al. (2007), Flores-Sanchez and Verpoorte (2008), van Bakel et al. (2011) and Gagne et al. (2012).

As emphasized by Hillig (2002) and de Meijer et al. (2003), it is important to distinguish quantitative and qualitative aspects of cannabinoid inheritance. The



absolute quantity of cannabinoids produced by an individual plant or by a population (on an acreage basis) depends on growth and developmental traits (such as size and

proportion of tissues constituted by secretory glands), which are (a) probably determined polygenically, (b) are unrelated to cannabinoid biosynthetic pathways, and (c) are subject to strong environmental modification. Qualitative aspects, discussed in the next paragraph, relate to the genetic control of genes influencing the relative amounts of the cannabinoids.

F_1 hybrids between high-THC narcotic strains and high-CBD fiber cultivars are usually more or less intermediate between the parents. Small (1979b) found that numerous first generation hybrids were indeed more or less intermediate in THC proportion. Beutler and Der Marderosian (1978) crossed a ruderal low-THC form and a narcotic race with higher THC, and also found that the first generation hybrids were more or less intermediate, although many tended to have lower THC proportions. As expected for an outcrossing species, F_1 hybrids frequently show evidence of heterosis for various characteristics. Various authors have observed cannabinoid segregation ratios in F_2 generation hybrids (see literature citations in de Meijer et al., 2003), and as discussed in the next paragraph, this is due to allelic segregation.

Inheritance of the key cannabinoids THC and CBD has been shown to be determined by the allelic status at a single locus (referred to as B) (de Meijer et al., 2003; Mandolino et al., 2003; Pacifico et al., 2006). De Meijer et al. (2003; cf. Mandolino & Ranalli, 2002, Mandolino et al., 2003; Mandolino, 2004) found evidence that THC development in *C. sativa* is under the partial genetic control of codominant alleles. Allele B_D is postulated to encode CBD synthase while allele B_T encodes THC synthase. This model holds that plants in which CBD is predominant have a B_D/B_D genotype at the B locus, plants in which THC is predominant have a B_T/B_T genotype, and plants with substantial amounts of both THC and CBD are heterozygous (B_D/B_T genotype). De Meijer and Hammond (2005) found that plants accumulating CBG have a mutation of B_D (which they term B_0) in the homozygous state that encodes for a poorly functional CBD synthase; and de Meijer et al. (2009b) selected a variant of this that almost completely prevents the conversion of CBG into CBD.

Shoyama et al. (2001) transferred the THC-synthase gene from *Cannabis* to tobacco (*Nicotiana tabacum*), inducing it to convert CBG to THC. This raises the prospect that transgenic tobacco (or indeed any other plant) could be smoked as a marijuana substitute!

Breeding for High and Low Levels of Cannabinoids

Clandestine marijuana breeders, for several decades, have produced "improved" types of drug plants, and hundreds of selections have been named and offered in the illicit trade; Snoeijer (2002), Danko (2010), Rosenthal (2001, 2004, 2007, 2010), Grisswell and Young (2011), and Oner (2011a, b, 2012) list many named selections. Because of legal constraints, very few of these appear to possess protected status as accorded by national and international agreements governing registered cultivated varieties and intellectual property. In the Netherlands, some firms are (or were) authorized to distribute drug selections, and there have been some claims for property rights for these. In 1998, a pharmaceutical drug cultivar called 'Medisins' was registered in the Netherlands by HortaPharm, one of the earliest officially recognized drug cultivars, followed by 'Grace' registered by GW Pharmaeuticals in 2004, both awarded plant breeders rights (Clarke & Merlin, 2013). Pharmaceutical varieties developed in the

Netherlands by HortaPharm BV were transferred to GW Pharmaceuticals, centered in the United Kingdom, which has plant breeder's rights to at least 30 to 40 selections (Anonymous, 2006). GW Pharmaceuticals, the world's leading pharmacological firm dedicated to cannabis-based drugs, is developing strains that predominantly produce one of the four major cannabinoid compounds (THC, CBD, CBC, CBG), as well as varieties with mixed cannabinoid or terpene profiles (Clarke & Merlin, 2013) Some of these selections produce single cannabinoids reportedly at high levels "over 10 %" without significant amounts of any other cannabinoids. Other private firms, especially in the Netherlands, have also selected "medicinal" lines with particular cannabinoid profiles as well as other attributes.

Breeding for low-THC cultivars in Europe has been reviewed by Bócsa (1998), Bócsa and Karus (1998) and Virovets (1996). Pacifico et al. (2006) were unable to detect cannabinoids in some plants of European fiber cultivars ('USO-31' and 'Santhica 23'). However, at present no commercial cultivar seems to be 100 % free of THC. THC content has proven to be more easily reduced in monoecious varieties, which are inbred, than in dioecious varieties, which are outbred.

A simple way of making plants THC-free is to eliminate the capacity to produce any kind of cannabinoid. De Meijer et al. (2009b) noted that there are two ways of accomplishing this: (1) disrupt the morphogenesis of the glandular trichomes, and (2) block one or more biochemical pathways crucial for the formulation of the cannabinoids. Gorshkova et al. (1988) reported on plants that lacked glandular trichomes and plants with odd glandular trichomes (with white heads), both types lacking cannabinoids, but a cultivar or selection in which all plants lack glandular trichomes has not been described. De Meijer et al. (2009b), based on selections from a fiber hemp cultivar ('USO-31'), discovered a genetic factor (termed a "knockout gene") that completely blocks cannabinoid biosynthesis in *C. sativa*, apparently functioning by preventing the conversion of the phenolic precursors of the cannabinoids into the cannabinoids.

Traditional hashish prepared in Asia is typically rich in both the intoxicant THC and the sedative CBD, and land races have been selected for making hashish. By contrast, most narcotic cultivars have been selected just for THC, and indeed most have limited or no CBD. An explanation for the presence of CBD in traditional hashish land races was offered by Clarke and Watson (2007): "Hashish cultivars are usually selected for resin quantity rather than potency, so the farmer chooses plants and saves seed by observing which one produces the most resin, unaware of whether it contains predominantly THC or CBD."

Endocannabinoids

The term "cannabinoids" has been expanded from its original meaning referring to a unique class of compounds synthesized by *Cannabis*. Some researchers also include in the term cannabinoids a) chemically synthesized analogues ("synthetic cannabimimetics" Ashton (2012)), and b) chemicals of quite different structure called "endocannabinoids" (endogenous cannabinoids), found in animals including humans, which trigger the cannabinoid receptors, particularly those that function in neurochemistry, as noted below.

In the early 1970s, opiate receptors were discovered in the brain that bind to morphine and other opiates (chemically, molecules that bind to cellular receptors are

called *ligands*; pharmacologically, chemicals contacting and activating receptors are *agonists*, those that attach to a receptor but do not activate it or displace an agonist, preventing activation, are *antagonists*). Analogous to the discovery of opiate receptors, in the 1990s it was found that the brain and some other organs have specific G-protein coupled receptors that recognize THC and other cannabinoids, and trigger responses (Fig. 20). This discovery is key to understanding the molecular basis of cannabinoid pharmacological activity, and to exploring and developing cannabis-based therapies. While the receptors fortuitously respond to the cannabinoids from *C. sativa*, they appear to routinely function mainly in response to molecules produced by the body's

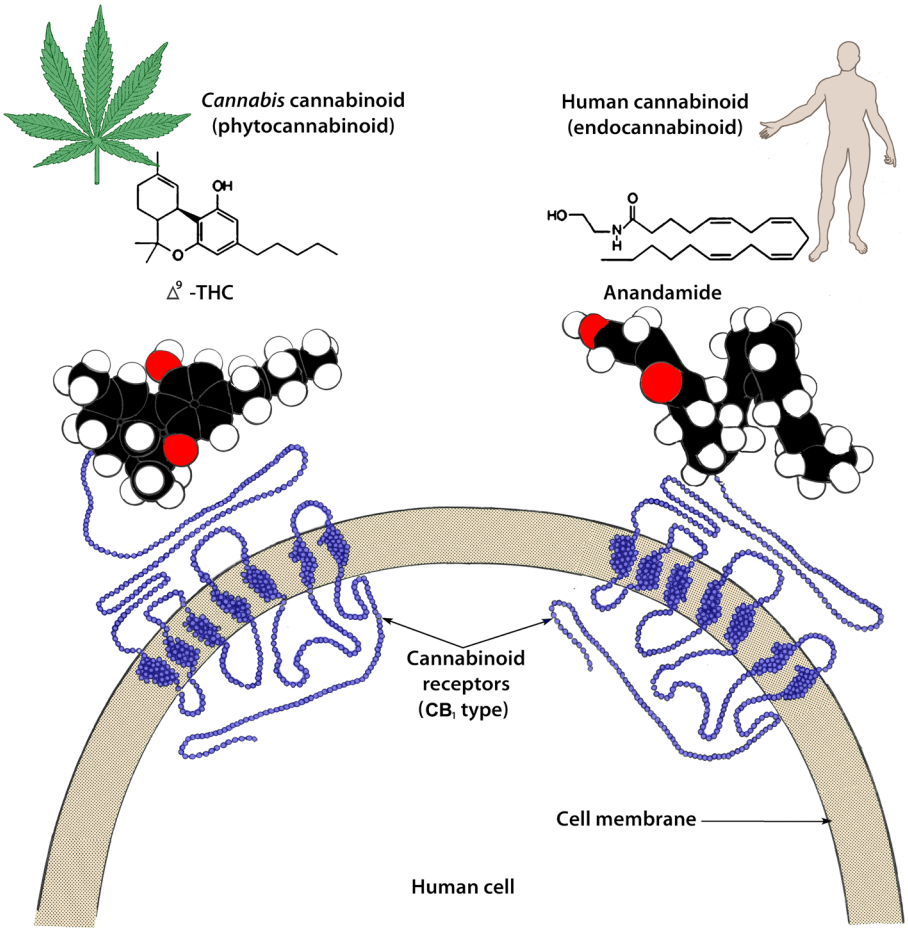


Fig. 20 A simplified interpretation of the similar actions of *Cannabis*-based and human-based cannabinoids. *Left*: a molecule of Δ^9-THC, the chief natural cannabinoid of *Cannabis sativa*, contacts and affects a type CB_1 receptor embedded in the human cell membrane at bottom (note the characteristic structure of this polypeptide chain – a portion outside the membrane, winding through the membrane seven times, and a portion inside the membrane). *Right*: a molecule of anandamide, one of the chief natural endocannabinoids of the human's body's internal cannabinoid system, similarly contacts and affects a type CB_1 receptor. The discovery that the cannabinoids of *Cannabis sativa* affect (either positively or negatively) the human brain and other organs of the body through the internal endocannabinoid control system of the human body provides indisputable evidence that marijuana has medicinal properties (but not necessarily warranting medical usage)

metabolism (Grotenhermen, 2003, 2004a, b; Onaivi et al., 2005). These molecules, which, have a variety of metabolic functions, are called endocannabinoids, and are derivatives of fatty acids (they are thus quite distingushable chemically from the cannabinoids of *C. sativa*). Cannabinoid receptors have been located in nerve terminals in the central nervous system, as well as in peripheral tissues, including sympathetic ganglia, dorsal root ganglia, adrenal glands, heart, lung, urinary bladder, reproductive tissues, gastrointestinal tissues and immune cells. *Cannabis* drugs and extracts exert their biological functions through the receptors. Many of the potential therapeutic uses for cannabis drugs appear to be related to the ways the drugs act on the cannabinoid receptors and how this influences human physiology (Joy et al., 1999; Onaivi et al., 2005).

There are at least two types of receptors, CB_1 receptors with an apparent neuromodulatory role, and CB_2 receptors which appear to be immunomodulatory. The two kinds have substantially different distributions, but collectively they are in virtually all organs and body tissues. Within the brain, the distribution of CB_1 receptors is consistent with the known effects of cannabinoids on cognition, memory and motor function. The distribution of CB_1 receptors on pain pathways in the brain, spinal cord, and on terminals of peripheral nervous system primary afferent neurons is also consistent with cannabinoid-induced analgesia. In the central nervous system, the CB_1 receptors are responsible for such effects of marijuana as catalespy, depression of motor activity, analgesia, and feelings of well-being. In peripheral neurons, activation of the CB_1 receptors suppresses neurotransmitter release to the heart, bladder, intestines and vas deferens. The distribution of CB_2 receptors primarily on peripheral and central immune cells has been hypothesized to modulate immune effects of THC, through release of cytokines.

Phytocannabinoids from Plants other than Cannabis

The endocannabinoid system described above (or variations of it) is extremely widespread in most groups of organisms, reflecting its importance to life. The molecules produced within a given species that regulate (activate or deactivate) its own endocannabinoid system are in many cases capable of influencing the endocannabinoid system of quite unrelated species. Higher plants do not have endocannabinoid systems. (Oddly, insects also lack functional endocannabinoid systems, as discussed by McPartland et al., 2001; facetiously, insects cannot get high from smoking marijuana). However, a considerable number of chemicals produced by higher plants has been discovered to influence the CB receptors of humans (Gertsch et al., 2010). The term "phytocannabinoids" was once restricted to the cannabinoids of *Cannabis*, but has been enlarged by Gertsch et al. (2010) as follows: "any plant-derived natural product capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids or both." Very curiously, β-caryophyllene, a major compound of the essential oil of *C. sativa* (and many other plants), directly activates the CB_2 receptors, and thus *C. sativa* produces two quite distinctive classes of phytocannabinoids. N-alkyamide in echinacea (*Echinacea* species) has also been shown to directly stimulate the CB_2 receptor system. Anandamide (N-arachidonoylethanolamine), the first-discovered endocannabinoid in humans (Devane et al., 1992), critically affects brain functioning, and THC exerts its effects by substituting for it (Fig. 20). Anandamide's tone (functionality) is affected by N-linoleoylethanolamide and N-oleoylethanolamide,

which are found in a number of plants, most interestingly in cacao (*Theobroma cacao* L.) the source of chocolate, supporting the intuitive belief of many that the euphoric experiences from consuming chocolate and marijuana have some similarities (these chemicals do not directly affect the CB receptors, but exemplify indirect effects). Gertsch et al. (2010) provide other examples of plant constituents that directly or indirectly affect CB receptors. These authors point out that THC is the most potent phytocannabinoid activator of the CB_1 receptor yet discovered. They also note that dietary contact with phytocannabinoids during mammalian evolution may have played a beneficial role in adapting species for survival (McPartland and Guy (2004) extensively examine adaptive and co-evolutionary hypotheses between humans and plant constituents that affect the human endocannabinoid system.)

The Two Domesticated Kinds of Narcotic Plants Differing in Cannabinoid Balance

Two discernibly different groups of narcotic *Cannabis* were selected in Asia. The classification of these is explored in the "Classification and Nomenclatural Issues" section, where they are termed Group 3 ("sativa type") and Group 4 ("indica type") (the latter probably arose from the former). Here, some differences are examined. In Asia, strains of both kinds were often used to prepare hashish, but in most Western nations they are almost always employed to prepare marijuana. Table 1 summarizes differences that have been alleged to distinguish the two kinds (no adequate statistically based study of differences has been published).

Group 3 is referred to as the "sativa type" in the narcotics trade. Strains of this group tend to resemble European fiber cultivars, often being almost as tall although usually much more branched, and tending to have relatively narrow leaflets. These strains characteristically have very high THC level in the cannabinoids, and no or small amounts of CBD. As pointed out in the "Classification and Nomenclatural Issues" section, usage of the term *sativa* to indicate extremely intoxicating (high-THC) plants is quite inconsistent with the tradition of employing the epithet taxonomically for non-intoxicant plants. Group 3 is extremely widespread in the illicit trade of Western nations.

Group 4 is referred to as the "indica type" in the narcotics trade. (The terms indica and sativa are widely employed, in the senses explained in this and the previous paragraph, in innumerable books and websites providing instructions on how to (usually illegally) cultivate marijuana.) Indica strains tend to be short (about a meter in height) and compact under the conditions they are usually grown; they are often also highly branched, with large leaves and wide leaflets. The appearance is reminiscent of a short, conical Christmas tree. Strains of this group characteristically have moderate levels of both THC and CBD in the cannabinoid profile. Like the sativa type, the indica type has historically been employed to produce hashish in southern Asia, particularly in Afghanistan and neighboring countries. Hashish is prepared by pooling collections from many plants, so individual plants may vary in proportions of cannabinoids (i.e., not all plants necessarily have moderate levels of both THC and CBD). Clarke (1998) and McPartland and Guy (2004) interpreted Group 4 as having evolved in the cold, arid regions of Afghanistan and western Turkmenistan, and explained its short height as an adaptation to the relatively short

Table 1 Alleged differences between the two basic kinds of domesticated narcotic *Cannabis*. (Most of these differences are discussed in Clarke (1998) and Clarke and Merlin (2013))

Feature	Group 3	Group 4
Narcotic trade terminology (see Table 2A for additional names)	"Sativa type"	"Indica type"
Early distribution area (see Fig. 25)	Widespread (southern Asia)	Restricted (Afghanistan, Pakistan, northwestern India)
Seasonal adaptation	Relatively long (late-maturing), often in semi-tropical regions	Relatively short (early-maturing), adapted to relatively cool, arid regions
Height (under optimal growth conditions)	Relatively tall (2–4 m)	Relative short (1–2 m)
Habit	Diffusely branched (longer internodes); less dense, more elongated "buds"	Bushy (short internodes), often conical; very dense, more compact "buds"
Leaflet width	Leaflets narrow	Leaflets broad
Intensity of leaf colour	Leaves lighter green	Leaves dark green
Aroma (i.e., odour + "taste")	Relatively pleasant aroma (often described as "sweet")	Relatively poorer aroma (sometimes described as "sour" and "acrid")
Ease of detachment of heads from secretory glands (McPartland & Guy, 2004)	Variable	Easily detached
Presence of CBD	Little or no CBD	Substantial CBD
Psychological effects	Relative euphoric: a "cerebral high" promoting energy and creative thought (occasionally panic attacks in inexperienced users, or a drained feeling); recommended for daytime use	Relatively sedative: physically relaxing, producing lethargy ("couchlock"); recommended as a "nightcap"

growing season. The early-flowering nature of Goup 4 is also an adapation to a relatively short growing season.

Group 3 strains are very potent, hence more popular, although harder to grow indoors because of their tallness. Hybrids between the two groups have proven to be well adapted to indoor cultivation and are widely cultivated (Clarke & Watson, 2007). Increasingly, strains with alleged percentages of "sativa" and "indica" are being sold. There are varying descriptions in the literature about their contrasting psychological effects (see, for example, Hazekamp and Fischedick (2012) and Smith (2012); also see Table 1). These descriptions generally credit the high-THC sativa type with producing a more euphoric "high," and the lower-THC type with substantial CBD with producing a more attenuated experience, consistent with how CBD in marijuana substantially alters the effects of THC, as explained in the following subsection.

"The Evolution of Shoot Architecture under Domestication" section provided information on the evolution of stem architecture in the two groups of narcotic plants, and the "Evolution of Propagules under Domestication" section provided information on how the achenes of domesticated plants (including these narcotic groups) have been modified by comparison with wild plants. This information is not repeated here.

Medicinal Importance of Combining THC and CBD

Although widely said to be non-psychoactive, it has long been appreciated that CBD has sleep-inducing or sedative properties (Carlini & Cunha, 1981). It is apparent that CBD antagonizes (reduces) and interactively modifies (potentiates) the effects of THC. CBD ameliorates (in a therapeutic sense) the effects of THC, blocking anxiety provoked by THC, reducing psychotic experiences associated with high-THC marijuana, and attenuating memory-impairment effects of THC (Russo & Guy, 2006; Zuardi et al., 2006; Zuardi et al., 2012; Mechoulam, 2012). The combination of THC (a euphoric) and CBD (which reduces the high of THC but seems to prolong the duration) is now appreciated to have medicinal advantages. Reducing the intensity of the THC experience is considered especially beneficial for inexperienced users, who may be subject to panic and other disturbing symptoms on exposure to a high level of THC. Sativex® (Fig. 23a and b), a cannabinoid-based analgesic marketed by The United Kingdom firm GW Pharmaceuticals, exploits the advantages of combining equivalent amounts of THC and CBD. This buccal ("oromucosal") spray is applied under the tongue or inside the cheeks (never into the nose).

Herbal Mixtures vs. Pure Chemicals

In the prestigious report *Marijuana and medicine: assessing the science base* (Joy et al., 1999), the following statement is presented: "Defined substances, such as purified cannabinoid compounds, are preferable to plant products, which are of variable and uncertain composition. Use of defined cannabinoids permits a more precise evaluation of their effects, whether in combination or alone." Modern medicine has been said to prefer single-component "silver bullets" rather than multi-component "herbal shotguns" (Spelman, 2009). However, the issue is not as simple as it may appear.

Western-based medicine has become reliant on single-molecule pharmaceuticals, and indeed even with the resurgence of alternative (especially herbal-based) modalities,

there is widespread disrespect (in the West) for traditional plant-based medicines because they are not precisely defined mixtures. However, the perspective that herbal (crude drug) preparations are inherently inferior is short-sighted. Many herbal products in Europe are standardized and have been clinically demonstrated to be efficacious in double-blind placebo-controlled trials.

Defenders of herbal medicine often point out that there may be synergistic (increasing potency or other desirable effects) or mitigative (decreasing toxicity), therapeutic interactions among the constituents of crude drugs, and that over time humans have learned by trial and error the circumstances when these crude drugs are efficacious (Lewis & Elvin-Lewis, 2003). Of course, research is required to examine the comparative merits of crude drugs, extracts and synthetic analogues, and this is particularly true for *C. sativa*. Crude drugs (marijuana, hashish) are currently the main options exercised for medical use of *C. sativa*, and indeed they are often chosen in preference to extracts and synthetic analogues by patients. It is very well known that extracted cannabinoids produce somewhat different effects from crude marijuana (Fairbairn & Pickens, 1981; Johnson et al., 1984; Pickens, 1981; Ryan et al., 2006; Segelman et al., 1974; Whalley et al., 2004; Wilkinson et al., 2003), and often do not satisfy patients as well as crude drugs, and this suggests that interactions of natural constituents are very important therapeutically (McPartland 2001; McPartland & Russo, 2001; Russo & McPartland, 2003).

The non-cannabinoid components in marijuana may also contribute significantly to potential therapeutic effects, and so any consideration of medicinal marijuana and of THC delivery systems needs to take this into consideration. Potentiating interactions of the cannabinoids and various terpenes, as well as the 20 or so flavonoids that are present, have been hypothesized to modify synergistically the psychological and physiological effects of cannabis drugs (Clarke, 1998; McPartland, 2001; McPartland & Mediavilla, 2002; Russo, 2011).

A number of psychoactive analogues of THC have been synthesized and tested experimentally (Russo 2003). The following two have been especially marketed commercially. Dronabinol is the synthetically manufactured (-)-trans-isomer of Δ^9-THC. Marinol® is a dronabinol preparation, dissolved in sesame oil, provided as capsules. It is a registered trademark of Unimed Pharmaceuticals, Inc., and is available in North America and some European countries. Nabilone is a synthetic derivative of Δ^9-THC with a slightly modified molecular structure. It is marketed under the name Cesamet®, a registered trademark of ICN Canada Ltd., and is available in Canada, in the U.S. (through Valeant Pharmaceuticals International) and some European countries. These synthetic preparations of THC are expensive and are often considered to be less effective than simply smoking preparations of marijuana.

Evolving Technologies for Preparing and Consuming Narcotic Cannabis

Marijuana (Fig. 21a), composed of inflorescences and the smallest leaves of intoxicant varieties, and prepared by forcing herbal material through a screen to break it up, has become the most widely used illegal drug in the world. Hashish (Fig. 21d and e) is a relatively pure preparation of the resinous secretions of intoxicant varieties of the plant. Marijuana is sometimes referred to as "herbal-type" cannabis, in contrast to hashish, a "resin-type" form of cannabis. Hashish oil ("hash oil") is a solvent extract (often of tar-

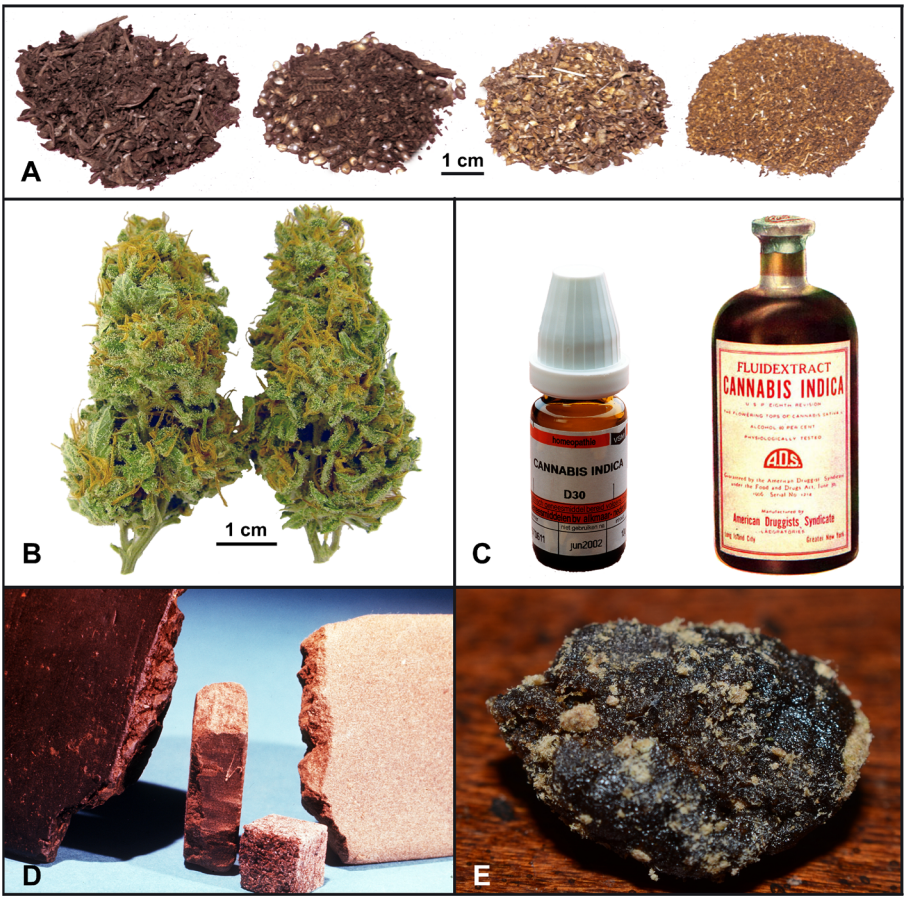


Fig. 21 Marketed forms of narcotic *Cannabis sativa*. **a** Grades of marijuana made with substantial amounts of foliage (increasing quality, i.e., lesser content of twigs and seeds, which contain little or no THC, towards the right) commonly encountered in the 1960s through the 1980s. THC content rarely exceeded 5 % dry weight. **b** "Buds" (unfertilized, congested, female inflorescences, with large numbers of perigonal bracts rich in secretory glands), increasingly popular since the 1980s. THC content typically ranges between 10 and 20 %. Achenes ("seeds"), which do not contain cannabinoids, are not present. Sometimes the small unifoliate leaflets present are trimmed away with scissors to additionally increase THC content. Photo provided by James Burton, Stichting Institute of Medical Marijuana. **c** Medicinal alcoholic extracts (illegal in most jurisdictions). Photo at right is in the public domain. **d** Confiscated bricks and cubes of hashish. Such preparations are primarily an Asian product and are often made from narcotic races with more or less equal amounts of THC and CBD. THC contents generally range from 5 to 15 %, dry weight). **e** "Bubble hash," a very potent form of hashish (THC content has been claimed to sometimes exceed 50 %) produced by modern technology. The expression "bubble hash" arose because it was noticed that such preparations tend to "bubble" when burned for consumption. Photo by J. Adams (CC BY 2.0)

like consistency). Up until the last 2 decades, in the Western world marijuana often included a substantial content of foliage. The bracts of the flowers are much richer in THC, and the market for marijuana has evolved towards the use of the inflorescences (so-called "bud," or much less frequently "cola," Fig. 21b). Indeed, races with female marijuana plants have been selected to produce flowering heads with abundant flowers in tight heads. Female plants are grown in the absence of male plants, so the females are

protected against receiving pollen, and do not develop seeds (the expression "sinsemilla," based on Spanish for "without seeds," is used to characterize the product). Marijuana in current illicit markets typically has a THC content of 5 to 10 % (levels as high as 25 % have been reported), while medicinal marijuana currently marketed under license by authorized sources typically contains 10–20 % THC. Hashish in illicit markets typically has a THC content of 5 to 25 % (levels as high as 45 % have been reported), and hashish oil a content of 20–50 % (levels exceeding 60 % are occasionally reported).

"Hashish" as traditionally made in Asia is prepared by a variety of methods (see Clarke (1998) and Hamayun and Shinwari (2004)), but is always a mixture of resinous herbal material collected from the female inflorescences of *C. sativa*. It is predominantly prepared by filtering cannabis material through very fine fabric screens (such as silk) or sieves, and mechanically agitating the material to collect a resinous or powdery material with a higher concentration of the plant's secretory glands than in conventional marijuana. Additional treatments vary depending on region, but the result is normally a solidified, sticky mass of material, mostly pressed or rolled to form hardened resinous cakes. Hashish in the illicit trade may be prepared in part by the use of solvents, and may therefore contain toxic residues. Hashish oil is prepared by solvent extraction, and given the lack of quality oversight in illegal operations may be particularly dangerous.

An alternative method of preparing hashish in Asia (now largely abandoned because it is so labor-intensive) is to rub the female inflorescences by hand so that the sticky resin glands and secretions stick to the hands, and are scraped off. Similarly in the past, people dressed in leather brushed against the sticky inflorescences until resin accumulated on their garments, subsequently scraping off the resin (Bouquet, 1950). Stickiness of the secretory glands is due to terpene secretions over the outer surface of the glands. In very windy, dry or cold environments, secretions tend to volatilize more readily, decreasing stickiness; by contrast, in hot, still environments (whether outdoors or under intense grow-lights) secretions appear to accumulate more readily, and the gland surfaces can become very sticky. It is unclear whether narcotic land races were selected that were particularly suitable because they tended to secrete resin readily rather than retaining it within the gland heads, but this seems plausible.

New, Western-country technologies have been created to produce preparations rich in the THC-containing resin glands. The Asian tradition of using filters is employed, but the millipore screens now commonly used have much smaller openings (50–150 microns in diameter), and the techniques utilized produce a material that is very much richer in presence of secretory glands, very much lower in presence of other herbal material, and is (usually) higher in THC, by comparison with conventional Asian hashish. Clarke (1998) refers to the preparations so produced as "high-tech hash." In the illicit drug trade, the usually powdery preparations first produced (very inappropriate called "pollen;" more aptly termed "resin powder") are often compressed so that they have a superficial similarity to conventional but much cruder Asian hashish. Some technologically sophisticated, commercially available devices for production of high-grade hashish are shown in Fig. 22. Preparations can be produced that consist mostly of resin glands and have over 30 % THC (even over 50 %). These advanced techniques are very wasteful of material (although the low-THC residue can be salvaged for other uses), and so high-tech hashish is sold at premium prices, and

Fig. 22 Recent commercially available extraction systems for preparation of purified, high-THC concentrates of secretory glands starting with herbal material (leaves and flowers). **a** The "Pollinator©" is a dry sifting machine. Herbal material is placed in the revolving drum, which is perforated with 150 micron holes. Resin glands are expelled through the holes and collect in the box containing the drum. **b** The "Bubbleator©" is constructed like a small washing machine. Frozen herbal material is placed, along with ice-water, in a series of bags that are perforated with holes of decreasing size that permit the resin glands to be expelled. These in turn are placed in the device, which agitates the bags for a period, and then the separated resin glands are purified by additional sieving, and dried. This device takes advantage of the insolubility of the resin in water, and the brittleness of the glands when frozen. **c** The "Ice-O-Lator©" at right is a similar but simpler apparatus, in which an agitating device is placed on top of a bucket. Detailed operating instructions are available at various websites. These devices may be considered to be illegal drug paraphernalia in some countries. Photographs courtesy of Mila and Chimed Jansen of the Pollinator Company (note Jansen & Teris, 2002)

consumers employ efficient smoking or vaporization methods. "Dry" technique involves simply agitating material on a motorized flat screen or in a drum-like screen. An example of this kind of apparatus is shown in Fig. 22a. Sometimes the material is frozen just prior to sieving, as the stalked glands become much more easily detached. Ultrasonic vibrators have been employed as an alternative to the use of motor-driven shakers. "Wet technologies" exploit the fact that mature secretory glands are heavier than water (as well as the property of the resin of being basically insoluble in water), while most plant parts are lighter than water. When mixed with water, the glands can thus be substantially separated. Freezing can also be employed to make the secretory glands more separable. Examples of this class of apparatus are shown in Fig. 22b and c.

Safer Drug Delivery Systems

The extremely serious health hazards of smoking tobacco are well known: bronchitis, emphysema, lung cancer, heart disease and numerous other disorders. As a system for delivering the target chemical (nicotine in the case of tobacco), smoking of any herbal is likely to also deliver hundreds of toxins, and this unhealthy consequence is certain when marijuana is smoked. Many of the ingredients common to marijuana and tobacco smoke (including hydrocyanic acid, oxides of nitrogen, acrolein, reactive aldehydes and several known carcinogens) are known to be toxic to respiratory tissue. Accordingly, in the interests of harm reduction, it is preferable to utilize efficient systems that increase the proportion of cannabinoids taken up while decreasing exposure to numerous other volatilized substances. Smoking cannabis preparations with an increased proportion of THC is the most common way of achieving this. The

widespread criticism that, because cannabis products in the illicit trade have increased in potency (THC content) during the past 20 years (Cascini et al., 2012), they are more dangerous, tends not to be taken seriously by informed pharmacologists. This is not only because higher potency material means less material needs to be smoked, but also because cannabis dosage is titrated by experienced users. Similarly when consuming alcoholic beverages, whether beer, wine, or liqueurs, experienced users tend to self-dose up to a particular level of intoxication, and the different concentrations of alcohol present is of relatively limited importance. (However, King et al. (2005) stated that "how far this parallel hold for cannabis is unknown.")

Regardless of smoking technique, because of incomplete decarboxylation of THCA, loss through exhalation, and destruction by pyrolysis, a maximum of about 30 % of the THC in cannabis preparations is absorbed (Russo, 2007).

Properly prepared hashish contains much higher levels of the cannabinoids than does marijuana (this is often not true in the illegal trade), and therefore a smaller quantity needs to be consumed in comparison to marijuana. Accordingly, less toxins are absorbed in smoking, and at least in this limited sense hashish is safer than marijuana.

Water pipes (devices to draw smoke through water; small contraptions are commonly called bongs, larger ones are hookahs) are widely employed to smoke cannabis in order to filter out toxins created by combustion and reduce pulmonary irritation. Water filters like these do remove gas-phase smoke toxins, such as ammonia, acetaldehyde, benzene, carbon monoxide, hydrogen cyanide, and nitrosamines, but are mostly ineffective against tars (polycyclic hydrocarbons).

A technique now extensively used in the consumption of cannabis drugs is vaporization, i.e., heating to produce steam or vapor without burning. Devices that heat marijuana to 180 to 190 °C vaporize THC without burning plant materials, thus not producing "smoke." Inhaling the resulting steam is a way of reducing (but not eliminating all of) the toxic materials produced during burning. Modern vaporizers have become popular, but do not eliminate polyaromatic hydrocarbons (Russo, 2007)

Medicinal Marijuana Preparations

Medicinal marijuana is currently being dispensed in many jurisdictions. A variety of forms are available, as shown in Fig. 23, including edible preparations. Oral consumption in the form of foods or tinctures is a way of avoiding all lung problems, and during the 19th century oral use was common both for medical and recreational use. However, becoming "high" from oral consumption is notoriously slow and comparatively unreliable. Some degradation of THC by acids in the stomach and gut may occur. Because THC is lipophilic, orally consumed cannabis is absorbed better by the intestinal mucosa if some fat is ingested simultaneously (this is usually accomplished by adding a fatty liquid, such as cream to cannabis tea, or considerable butter when baked in brownies; animal lard and vegetable oils are also used). Smoking produces effects within seconds to minutes, with a maximum after about 30 min, and a duration of 2 or 3 h. The rapid action of smoking is due to THC being transported quickly to the brain. By contrast, eating does not produce effects for 30 min to 2 h, and the effects are relatively prolonged, lasting 5 to 8 h or even longer. (Eating raw cannabis material that has not been heated to decarboxylate the acidic form of THC will produce only a minimal effect.) The slow action of

Fig. 23 Medicinal forms of marijuana products. **a**, **b** Sativex®, cannabinoid spray, an alcoholic extract with about equal amounts of THC and CBD, sprayed under the tongue. Photos provided by GW Pharmaceuticals. **c** Foods made with fats (usually butter) enriched with THC from marijuana. Such products are distributed in medicinal marijuana dispensaries. Photo released into the public domain. **d**, **e** Marijuana "buds" distributed in California compassion clubs. Photos released into the public domain. Although allowed or at least tolerated in some jurisdictions, the materials illustrated here are illicit in some circumstances or regions

orally ingested THC is due to its being transported from the stomach to the liver where it is converted to 11-hydroxy-THC, a more potent and longer lasting cannabinoid than THC. Smoking and eating modes of metabolizing THC are contrasted in Fig. 24.

Cannabinoids can be absorbed through skin (hence concern has been expressed about the possible presence of THC in hemp oil used in cosmetics), and so patches are sometimes employed. Cannabinoids can also be readily absorbed through mucosal tissues, and vaginal sprays and rectal suppositories are occasionally used as a form of THC absorption. Rectal absorption is lower than oral absorption, but is more constant. Sativex (described above), taken by mouth, represents mucosal application.

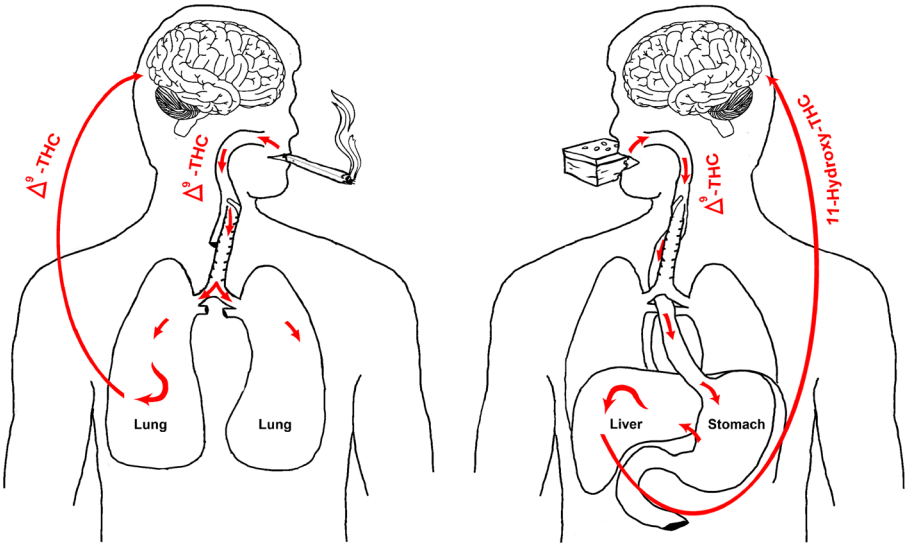


Fig. 24 A contrast of the metabolism of inhaled and eaten marijuana. *Left*: Vaporized THC from smoking is carried to the lungs where it is transported by blood vessels to the brain, exerting its psychoactive effects quickly (usually within 10 min). *Right*: Most orally ingested THC is transferred by blood vessels from the stomach to the liver, where it is converted to 11-hydroxy-THC, a more potent, longer-lasting metabolite, resulting in delayed (usually an hour or more) onset of psychoactive effects which may last up to 24 h and be stronger, less predictable, and less pleasant. Figure prepared by B. Brookes

Summary of Recent Evolutionary Changes in Narcotic Strains

As detailed above, narcotic forms of *Cannabis* were initially selected many centuries ago, and during these early times fairly primitive techniques were employed to make intoxicant preparations. Particularly in recent decades, a considerable understanding of the biochemistry and genetic control of cannabinoid metabolism has been achieved, and strains are now being generated rich in particular cannabinoids for potential medicinal applications. Sophisticated techniques for breeding strains have been developed, including the generation of all-female lines. Technologies have been created to collect and concentrate the THC-rich heads of the glandular trichomes, and this development seems to have resulted in the selection of strains in which the THC-rich heads abscise readily. Strains have been selected differing in architecture, cannabinoid profile (geographical biotypes have been found with one or more rare cannabinoids in unusually high presence), terpene profiles (a variety of different essential oil profiles seem to have been selected), concentration and distribution of the secretory glands (very large densities of the glands and larger glands are present on the floral bracts of some strains), and inflorescence color (white and purple are popular in recent times). In response to demand for very high levels of THC, there has been selection for congested female inflorescences (production of numerous, well-formed “buds” being a recent quality criterion). The two basic kinds of narcotic plants (Group 3, characterized by very high THC levels, and Group 4 characterized by moderate amounts of THC supplemented by sedative CBD) have become foundational breeding material for generating by hybridization a wide range of strains.

Classification and Nomenclatural Issues

Several botanists have contributed to clarification of the taxonomy of *Cannabis* in recent decades (especially note Small and Cronquist (1976); Small (1979a, b); Hillig (2004a, b, 2005); Hillig and Mahlberg (2004); McPartland and Guy (2004), Clarke and Merlin (2013)). Based on these studies collectively, the following groups of domesticated plants have been recognized as warranting particular taxonomic attention (compare the postulated ancient Eurasian distribution ranges shown by the same numbers in Fig. 25, and the key information given in Table 2A):

(1) Non-narcotic plants domesticated for stem fiber (and to a minor extent for oilseed) in western Asia and Europe; cannabinoids low in THC and high in CBD (part of Small's *C. sativa* subsp. *sativa* var. *sativa*; Hillig's *C. sativa* "hemp biotype").
(2) Non-narcotic plants domesticated for stem fiber (and to a minor extent for oilseed) in East Asia, especially China; cannabinoids low to moderate in THC and high in CBD (part of Small's *C. sativa* subsp. *sativa* var. *sativa*; Hillig's *C. indica* "hemp biotype;" Clarke and Merlin's *C. indica* subsp. *chinensis*).
(3) Narcotic plants domesticated in a wide area of south-central Asia for very high THC content; cannabinoids mostly or almost completely THC (part of Small's *C. sativa* subsp. *indica* var. *indica*; Hillig's *C. indica* "narrow-leaflet drug biotype;" the narcotic trade's "sativa type").

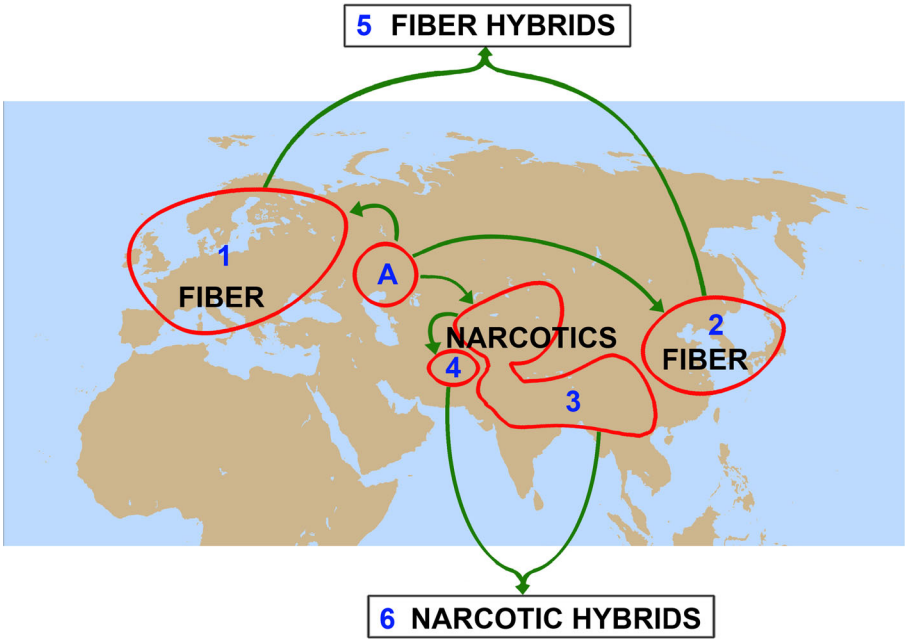


Fig. 25 Approximate postulated geographical locations of ancestral, pre-domesticated *Cannabis sativa* (A) and the four principal groups (1–4) domesticated more than a millennium ago, and subsequently transported to other parts of the world. Table 2A provides summary information on the four domesticated groups. Hybridization, mostly during the last century, has obscured differences between the two fiber groups, 1 and 2 (generating hybrid group 5) and between the two narcotic groups, 3 and 4 (generating hybrid group 6)

Table 2 A comparison of taxonomic concepts and terminology for *Cannabis* groupings of the Old World

A. Domesticated groupings (excluding hybrid groups)

Small and Cronquist (1976)	Hillig (2004a, 2005)	McPartland and Guy (2004)	Clarke and Merlin (2013)	Narcotic trade terms	THC content	CBD content	Principal early Eurasian cultivation area (see Fig. 25)	Use of land races, cultivars or strains
C. sativa subsp. *sativa* var. *sativa*	*C. sativa* "hemp biotype"	*C. sativa* subsp. *sativa*	*C. sativa* subsp. *sativa* ("narrow leaf hemp")	—	Low	High	1	Fiber and oilseed
	C. indica "hemp biotype"	*C. indica* subsp. *chinensis*	*C. indica* subsp. *chinensis* ("broad leaf hemp")	—	Low to moderate	High	2	Fiber and oilseed
C. sativa subsp. *indica* var. *indica*	*C. indica* "narrow-leaflet drug biotype"	*C. indica* subsp. *indica*	*C. indica* subsp. *indica* ("narrow leaf drug")	"Sativa type"	High	Low or absent	3	Narcotics
	C. indica "wide-leaflet drug biotype"	*C. indica* subsp. *afghanica*	*C. indica* subsp. *afghanica* ("broad leaf drug")	"Indica type"	Moderate to high	Moderate to high	4	Narcotics

B. Uncultivated groupings (ruderal, possibly including some truly wild populations)

Small and Cronquist (1976)	Hillig (2004a, 2005)	McParland and Guy (2004)	Clarke and Merlin (2013)	THC content	CBD content	Principal early Eurasian area
C. sativa subsp. *sativa* var. *spontanea*	*C. sativa* "feral biotype"	*C. sativa* subsp. *spontanea* + *C. ruderalis*	*C. sativa* subsp. *spontanea* ("narrow leaf hemp ancestor")	Low (occasionally moderate)	High	Europe; western to north-central Asia (Small & Cronquist include ruderal low-THC plants of eastern Asia)
C. sativa subsp. *indica* var. *kafiristanica*	*C. ruderalis* + *C. indica* "feral biotype"	*C. indica* subsp. *kafiristanica*	*C. indica* subsp. *kafiristanica* ("narrow leaf drug ancestor")	Low to moderate	Low to moderate (occasionally absent)	Asia

(4) Narcotic plants domesticated in southern Asia, particularly in Afghanistan and neighboring countries, for substantial amounts of both THC and CBD (part of Small's *C. sativa* subsp. *indica* var. *indica*; Hillig's *C. indica* "wide-leaflet drug biotype;" the narcotic trade's "indica type").

In addition, two hybrid classes of cultivated plants have been widely generated: (5) between the two fiber groups (1 and 2); and (6) between the two narcotic groups (3 and 4). It should be understood that the hybrid cultivars or strains are not simply first generation hybrids, but represent various degrees of stabilized intermediacy, essentially representing all degrees of variation between the parental groups, so that there is continuous variation among fiber races, and similarly continuous variation among narcotic races.

Beginning with the rise of marijuana as the leading illicit counterculture drug in the 1960s and persisting to the present day with marijuana strains being marketed in the quasi-legal and legal medicinal markets, there has been a fundamental confusion in much of the popular literature over what the terms "sativa" and "indica" designate (note Table 2). Taxonomists have utilized the epithets *sativa* and *indica* to distinguish two taxa, the term sativa traditionally designating non-narcotic plants in contrast to the term indica which has been used to designate narcotic plants. The narcotics trade, however, uses both "sativa" and "indica" as labels for different classes of narcotic plants, and (contradictory to taxonomic tradition) uses the term sativa to designate plants with *more* narcotic potential (i.e., very high THC content, low or no CBD content) and the term indica to designate plants with *less* but still substantial narcotic potential (i.e., moderate THC content and moderate CBD content). Without appreciation of these contradictory usages, it is often impossible for botanists familiar with taxonomic terminology to understand the information in popular literature about marijuana strains that uses the terms indica and sativa.

The domesticated groups of *Cannabis* mentioned above are of Eurasian origin but, especially in the last several hundred years, have been transported to and cultivated in much of the world. In many regions they have escaped, re-evolved characteristics suited to wild existence, and established as self-perpetuating populations outside of cultivation. Because both domesticated and wild *Cannabis* populations are extremely widespread, interbreed spontaneously over vast distances (Small & Antle, 2003), with a common diploid chromosome number ($2n=20$) and no biological barriers to interbreeding (Small, 1972a), wild-growing and domesticated plants exchange genes easily and extensively. In nature, one finds a complete spectrum of intermediate forms, demonstrating continuity of variation between wild and domesticated forms (Small, 1975a). Because domesticated selections are highly susceptible to gene influx from other domesticated selections and from wild-growing forms, to maintain their characteristics they must be protected from "genetic contamination." Moreover, as with many other crops (and domesticated animals), the mutations selected by humans are usually advantageous to humans but disadvantageous to the plants, and unless stabilizing selection is practiced, natural selection can result in degeneration or reversion (sometimes termed atavism) of the genome, with wild characteristics appearing in cultivated plants. Patterns of gene change from various factors are summarized in Fig. 26. The extensive intergradation that has resulted from interbreeding is the chief cause of classification difficulties. This section is concerned primarily with the arrangement of the domesticated groups and wild populations into a classification and naming system. The following relatively extensive presentation of classification theory and practice is

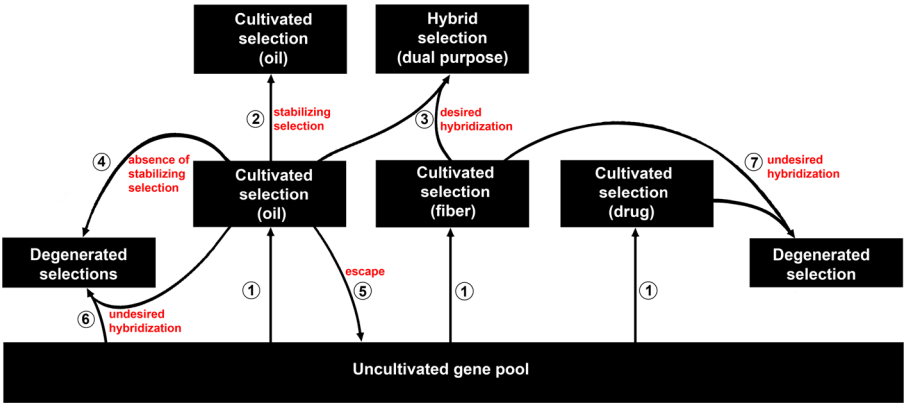


Fig. 26 Patterns of gene flow, genetic stabilization, and genetic destabilization among wild and domesticated races of *Cannabis sativa*. (1) Humans cultivate selections, principally for stem fiber, oilseed, and narcotic floral resin. (2) Such selections retain their desirable characteristics only if maintained by stabilizing selection (shown here for simplicity only for the oilseed form). (3) In recent times, deliberate hybridization among oilseed and fiber kinds has generated valuable new selections. (4) In the absence of stabilizing selection, cultivated plants are likely to undergo populational genetic changes over several generations, that are undesirable agriculturally (degenerative) since the highly selected characters of interest to humans are usually deleterious to the plants (for simplicity, such degeneration is shown only for the oilseed form). (5) Genes from cultivated plants may be released to the uncultivated gene pool. Selections may escape directly from cultivation and re-establish populations outside of cultivation, or pollen from cultivated selections may fertilize wild plants (for simplicity, such gene escape is shown only for the oilseed form). (6) Pollen from uncultivated plants may fertilize a cultivated selection, reducing the desired characteristics of the latter (for simplicity, this is shown only for the oilseed form). (7) Pollen from cultivated plants with undesirable characteristics (e.g., from clandestine marijuana plants) may pollinate a cultivated selection (e.g., grown for fiber or oilseed), reducing the desired characteristics of the latter

required because, with the exception of how the human species *Homo sapiens* should be classified, no other species has generated so much misunderstanding, argument and contradictory literature.

Biological classification is based on scientific evaluation of characters of organisms in order to assess their similarities or evolutionary relationships. Classification of organisms is often controversial because nature presents an extraordinary range of variation patterns, so that a "one size fits all" or "cookie-cutter" approach is unwarranted. Also contributing to disagreement, there are several dogmatic schools of thought regarding assessment procedures and usage of various kinds of genetic information as bases for taxonomic systems. Harlan and de Wet (1971) remarked "The inconsistencies and lack of agreement among taxonomists dealing with the same materials are remarkable, to say the least, and are even more striking when the treatment of different crops are compared."

Ambiguity of Scientific Names

American literary figure James Whitcomb Riley (1849–1916) famously wrote "When I see a bird that walks like a duck and swims like a duck and quacks like a duck, I call that bird a duck." However, defining (and consequently recognizing) a duck, or indeed most groups of living creatures that seem to merit a unique name, is frequently not as obvious as it seemed to Riley. Had Riley been an ornithological specialist on waterfowl, he would have learned that the swimming behaviors of birds called ducks differ greatly

among species, some ducks do not walk like ducks (even if extant ducks do have webbed feet), and most ducks do not quack. Among many duck specialists the inclusiveness of the word duck depends on recent evaluations of avian phylogenetic relationships (e.g., Johnson & Sorenson, 1999). For example, whistling ducks (tree ducks; subfamily, *Dendrocygninae* of the duck, goose and swan family of birds, *Anatidae*) are often considered to belong to tribe *Dendrocygnini* of the goose subfamily *Anserinae*.

It may seem disturbing that one person's duck may be another person's goose or swan, but as long as what is meant by the user of a word or phrase is understood, the terminology is useful for purposes of communicating information. Conversely, an ambiguous word or phrase hinders understanding when it is not clear what meaning is meant. The public and indeed most scientists have little appreciation of how ambiguous "scientific names" can be. As discussed in the following, the subject of the classification of *Cannabis* has been plagued with ambiguity.

Taxonomic Splitting and Rank Inflation

Even when they agree that a set of organisms is distinctive by virtue of shared traits, taxonomists often differ with respect to (1) whether formal nomenclatural recognition is even appropriate and (2) if appropriate, the rank that should be assigned (e.g., species or subspecies). Historically and to this day some taxonomists (facetiously referred to as "splitters") have a "liberal" approach, formally recognizing more groupings than would be accepted by most of their professional peers; and conversely some "lumpers" have a "conservative" approach, recognizing fewer groupings than most taxonomists consider appropriate. Taxonomic splitting is one cause of "taxonomic inflation," the generation of more scientific names than justified. Splitting is often accompanied by rank inflation – the elevation of taxa to a higher rank (especially to the species level) than justified. Taxonomic splitting and rank elevation are attractive to some scientists because these practices amplify the quantity and ranking of taxonomic groups for which they receive credit. However, over-recognition of some groups has resulted in distortion of studies of biodiversity, ecology and conservation (Chaitra et al., 2004; Padial & de la Riva, 2006).

Isaac et al. (2004) noted that populations assigned species rather than a lower rank are often regarded as more important, and that "This encourages elevation to species rank of populations that need protection, regardless of whether there is scientific support for this status.… Such inflation will be biased towards charismatic, large-bodied, rare and endangered forms… that attract high public, scientific and conservation interest." Consistent with this motivation and the fact that *Cannabis* is one of the most charismatic of plants, Hillig (2004b) argued that formal recognition of Chinese hemp (Group 2) as a separate taxon "may foster genetic conservation of this agronomically important group."

The Semantic "Legal Species" Issue

In the 1970s, a curious forensic debate was founded on splitting what had been widely understood up to that time as the species *C. sativa* into three species (*C. sativa* in a narrower sense, *C. ruderalis* Janischevsky and *C. indica* Lamarck). In many Western countries, legislation governing illicit cannabis preparations defines the material as

originating from "*Cannabis sativa* L." Court cases prior to 1970 witnessed some defenses of individuals accused of marijuana offences on the argument that the material in question came from one or more "legal species" of *Cannabis* (i.e., species in addition to *C. sativa*). This claim failed until 1971 because of the prevailing opinion (at least in the Western world) that there is only one species of *Cannabis*, *C. sativa*. However, in 1971 a court challenge was successful, based on the testimony of several botanists that there is more than one species of *Cannabis*. Subsequently for a decade the legal issue was raised in hundreds of courtrooms, especially in the United States and Canada. The ploy was successful because talented lawyers represented taxonomy as simply a factual assessment of existential groups called species (hence expert witnesses were sufficient), whereas in fact one taxonomist's species is another's subspecies. The issue eventually became moot as judges came to realize that recognition of more than one species of *Cannabis* is based merely on splitting of *C. sativa* into several species, and that taxonomic opinion on whether splitting is scientifically correct is irrelevant because the *intent* of legislation using the name "*Cannabis sativa* L." was clearly to designate all forms of *Cannabis* (and certainly the narcotic forms, which many lawyers had speciously argued were exempt from prosecution because they belonged to the "legal species" *C. indica*). The history of the legal-taxonomic debate is detailed in Small (1974, 1975b, c, d, 1976, 1977, 1979a, b).

Domestication Complicates Classification

As noted above, prior to 1970 there was essential unanimity that only one species of *Cannabis* merited recognition. Since then, virtually without exception, those who have espoused the recognition of more than one species of *Cannabis* have done so without addressing the theory and practices of classification of domesticates and their closely related wild populations. Without this background, it is not possible to understand clearly the merits of competing systems of classification of *Cannabis*.

Charles Darwin (1809–1882), the father of evolution, coined the phrase "artificial selection" in the first edition of his work *On the Origin of Species* (Darwin, 1959). He concluded that starting from a wild species human selection could produce divergent breeds so spectacularly different that they mimicked related species produced by natural selection (compare Darwin's analysis of wild birds of different species (Fig. 27) and his analysis of domesticated birds of a single species (Fig. 28)). Darwin (1859) wrote: "There are hardly any domestic races, either amongst animals or plants, which have not been ranked by some competent judges as… distinct species." Although he more clearly appreciated than anyone previously that classifications of domesticated and wild organisms are debatably comparable, Darwin did not explore the issue of appropriate cataloguing of organisms originated by humans. As detailed in the following discussion, the so-called "species" of *Cannabis* that have been recognized are in fact domesticates (i.e., selections made by humans) or their related escapes, and accordingly their recognition as conventional species, while permissible, is misleading.

In common language, "domestication" often refers to taming of wild animals, i.e., habituating them to humans so that they are relatively manageable. In biology, domestication is the process of choosing individuals of a species that have characteristics making them useful to people, the selection usually occurring over generations, so that

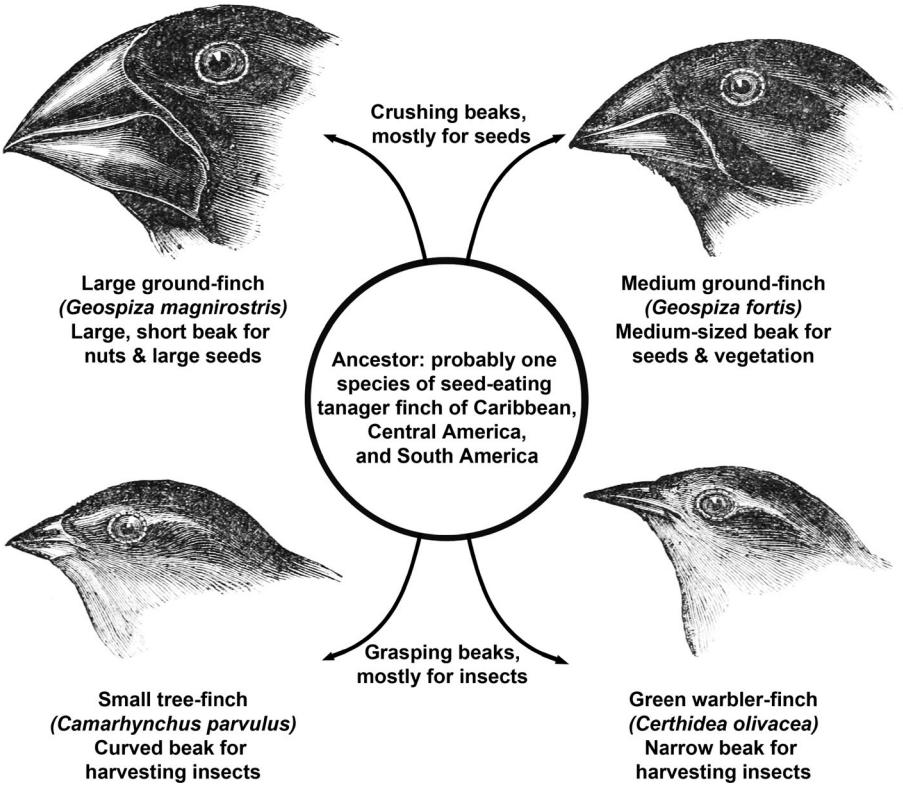


Fig. 27 Four of the 14 "Darwin finches," exemplifying the natural evolution of species. The endemic Galapagos Island species studied by Charles Darwin are now appreciated to belong to four genera of tanagers (family Thraupidae), not the true finch family (Fringillidae). Feeding behavior, adapting the birds to different food resources, and reflected particularly by beak characteristics, was critical to their adaptive radiation into the different species. Bird drawings from Darwin (1845)

the desired traits become genetically fixed. Almost all important species currently employed in agriculture are domesticated. Although the phrase "cultivated plant" is widespread and often used to refer to domesticated plants, many cultivated plants are simply wild plants that are cultivated, and the different concepts should not be confused. The term "cultigen" has been used to refer to domesticates in a broad sense, but has been employed in such different ways (Spencer, 1999; Spencer & Cross, 2007a, b) that its use can be confusing.

Whether domestication is in some fundamental way different from natural selection has been the subject of debate (reviewed in Ross-Ibara et al. (2007)). Domestication is usually conceived of as a form of "artificial" selection, which is true if one defines artificial selection as the result of human activity. However, some (e.g., Darwin, 1859; Darlington, 1973) have argued that unconscious, i.e., non-deliberate selective breeding by humans is as "natural" as the selection that occurs in nature. (Most domestication has been unconscious, occurring over millennia (Zohary, 2004); deliberate breeding for desired characteristics has become important mainly during the last 100 years.) Domestication is, in fact, a form of evolution (which can be simply defined as the alteration of gene frequencies over time). Rindos (1984) stated "Domestication clearly

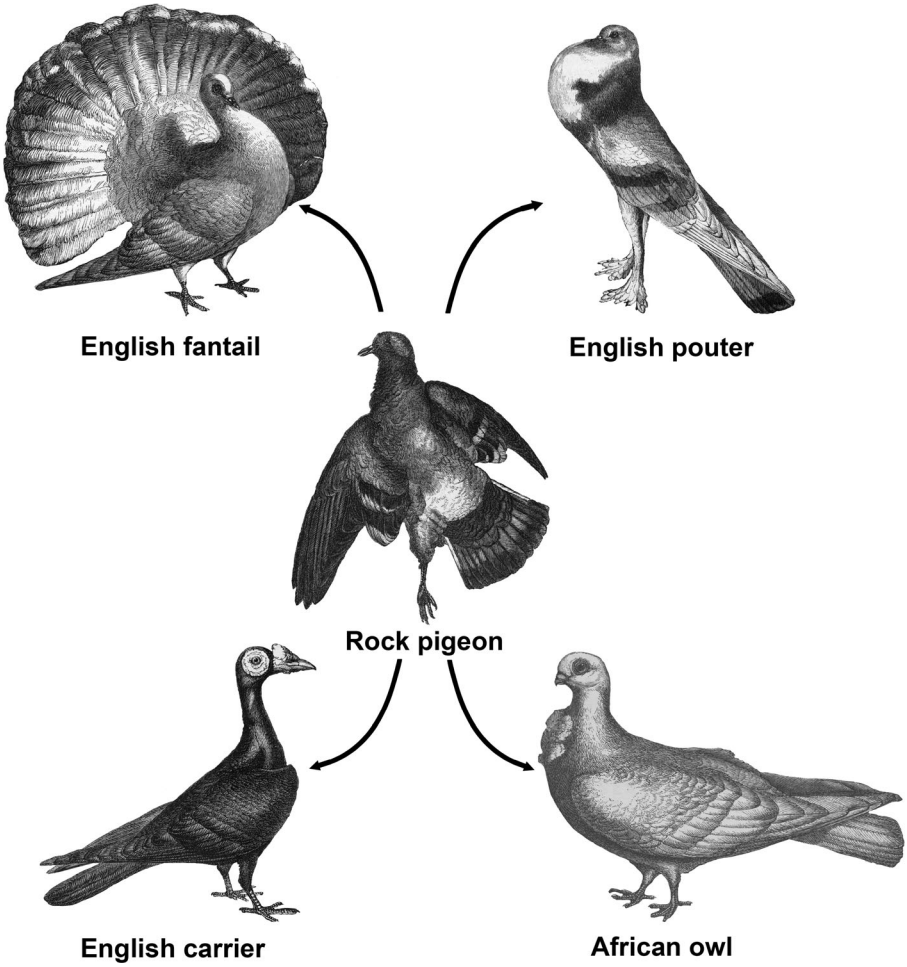


Fig. 28 Four of "Darwin's pigeons," exemplifying the artificial selection of variations desired by humans. The breeds shown here are descended from the wild rock dove (*Columba livia*), the ancestor of all fancy and racing pigeons. Bird drawings from Darwin (1868)

cannot be held to be an exclusively human-mediated phenomenon." This is because man is not the only animal that has usurped the freedom of other species, caring for them but at the same time altering their genome so that they can be more efficiently exploited as a source of food. For example, wood wasps and over 40 species of ambrosia beetles cultivate fungi as food sources, inoculating wood with a fungus which they consume. Some ants and termites also cultivated fungi (see Rindos (1984) and Schultz et al. (2005) for references and additional examples), and there are also ant species that herd, protect, and breed mutualistic aphids and other homopterans (Hölldolber & Wilson, 1990; Schultz & McGlynn, 2000). In emphasizing that the contrast of "artificial selection" and "natural selection" is in fact an artificial distinction, McNeill (1998) stated "It is not good evolutionary thinking to suppose that man is not inescapably a part of the ecosystem."

All domesticated plants arose ultimately from wild ancestors, which may no longer be extant. Plants growing outside of cultivation are commonly said to be "wild," but the term is ambiguous. Basically, a species is "indigenous" (or "native") to a given geographical area if it reproduces there, and is present in that location as the result of natural processes, without the influence of humans. (For rigorous analyses of the concept of indigenous status, see Ratcliffe (1977) and Peterken (1981).) Contrarily, if a species has been transported (deliberately or not) to a location because of human activity and reproduces there without the assistance of humans, it is "introduced" (or "naturalized"). A non-indigenous species that occurs with some frequency in an area because it is often released or escapes, but does not persist indefinitely because of a lack of adaptation to that area, is said to be "spontaneous," "adventive," or "casual." The chief difficulty with determining whether a species is indigenous or introduced is the time dimension. Of course, because of geological and climate changes during the billions of years of Earth's history, most species migrated extensively. In many circumstances, indigenous status should be assessed starting with the end of the last ice age. However, determining the pre-recorded-history location of some plants is very difficult and uncertain with respect to the possible influence of humans.

Plants closely related to domesticated plants and growing outside of cultivation may be: (1) ancestors of the domesticates; (2) escapes from cultivation, either identical to the domesticates or altered by generations of selection for existence in nature; (3) hybrids or introgressants between a wild relative and the domesticate. Often a domesticate arises from a weedy wild species and, conversely, often a weed arises from domesticated plants. When one can distinguish three phases: (a) domesticated crop(s), (b) ancestral or at least closely related (at least somewhat interfertile) wild plants which still have natural distribution ranges, and (c) weedy or ruderal relatives of the crop that interbreed with it, the assemblage is referred to as a "wild-weed-crop complex." When only (a) and (c) can be distinguished, it is simply a "crop-weed complex." Many crops like *Cannabis* exist in crop-weed complexes (Andersson & de Vicente, 2010), with domesticated forms in cultivation, and related ruderal (weedy) forms growing outside of cultivation. The issue of whether all *Cannabis* plants growing outside of cultivation are derived from escapes from cultivation, or whether some of these are free of genes altered by humans, is contentious, and is examined later. Some botanists have recognized wild-growing *Cannabis* as taxonomic groups at different ranks (the most widely used nomenclatural epithets for these are *kafiristanica*, *ruderalis*, and *spontanea*), which is also contentious and examined in the following discussion.

Hybridization especially complicates classification of crop-weed complexes. The entertaining quotation "if my grandmother had wheels she'd be a bus" is not accurate: she would be a hybrid, but not of a kind that is an exact intermediate between a bus and a grandmother. In biological taxonomy, the term "hybrid" often covers more than simply entities that combine two entire genomes (F_1 hybrids). The term is also frequently applied to a range of backcrosses and segregants. In addition, introgression (gene flow from one population to another), a special form of hybridization, often occurs. Frequent hybridization and introgression between the cultivated and ruderal phases of crop-weed complexes, and sometimes also between these and related wild species, often makes classification so difficult that the exercise becomes pointless or arbitrary.

Alternatives for Taxonomic and Nomenclatural Treatment

The professional taxonomic treatment of plants (indeed of all living things) is largely a standardized activity, involving three phases. The first phase is grouping (recognition of assemblages). The second phase is ordering of these assemblages, conventionally in a hierarchical system (like a series of smaller boxes within progressively larger boxes), involving fixed ranks (e.g., subspecies, species, genus, family), although as noted later there are other kinds of arrangements. The third and final phase is naming: the provision of appropriate nomenclature in an unambiguous manner that reflects the nature of the classification system. The possibilities differ somewhat according to the rules of current nomenclatural codes (for general information on nomenclatural codes for the principal kinds of organisms, see David et al. (2012)). In the case of *Cannabis*, two botanical nomenclatural codes are particularly relevant, as well as non-codified classification systems, as discussed in the following.

Treatment of Cannabis Assemblages as Conventional Taxa

Beginning with a code governing botanical nomenclature prepared in 1867, improved internationally accepted versions have been published periodically. The latest is *The International Code of Nomenclature for Algae, Fungi, and Plants* (ICNAFP; McNeill et al., 2012). This is the most respected and universally applied way of determining plant names (the third phase of taxonomic procedures mentioned in the above paragraph). There is no impediment to treating groups that are completely or partly domesticated under this code. All groups that are recognized are assigned a particular rank, and the Latin name for a group (if not newly coined) is determined by examining all eligible names previously applied to members of that group, and by reference to the rules of the code to determine the single, correct name. The code specifies the conventions that must be followed for naming taxa (taxonomic groups), but different taxonomists can disagree about which individuals fall within given groups (i.e., the circumscription of groups) and about the hierarchical organization (i.e., ranks assigned to groups), and these disagreements can mean that a given plant may be identified "correctly" but differently by different taxonomists, and that a given plant name can be interpreted differently by different taxonomists. When a name has been used in different senses so extensively that it is a source of confusion, Article 57 of the ICNAFP provides for stabilizing usage of, or simply abandoning that name. Certainly there has been extensive confusion over how to use some of the species names associated with *Cannabis*, but no one has yet suggested that Article 57 be applied.

Some traditional taxonomists (especially in Europe in the 20th century) subcategorized important crop plants in very extensive, multi-level hierarchies, either formally (i.e., in strict conformity with the botanical code) or quasi-formally. Sometimes hundreds of groups were recognized. Examples of categories that have been used are presented in Jirásek (1961); examples and a critique of excessively complex treatments are presented in Spooner et al. (2003). The eccentricity and unworkability of this approach led to efforts to find a standardized, simple way of classifying the variation within cultivated plants in relation to their wild relatives.

A particular issue that has troubled plant taxonomists is how to categorize groups in which there are both wild and domesticated kinds using traditional formal categories. There have been many proposals. For example, Harlan and de wet (1971) suggested that where both ruderal and domesticated races exist within one species, all of the ruderal races should be recognized as a collective subspecies, and similarly all of the domesticated forms should be placed in a collective cultivated subspecies. Similarly Nesom (2011) treated apparent wild progenitors and their domesticated derivatives in the family Cucurbitaceae as separate subspecies of a given species. However, there is no agreed way of taxonomically separating domesticated plants and their close wild relatives, and indeed limited prospects for the adoption of a universal solution to this issue.

Treatment of Cannabis Cultivar Assemblages as "Groups" Under the Cultivated Plant Code

Carl Linnaeus (1707–1778), the father of modern taxonomy, was aware that some species include domesticated forms differing from those found in nature. He was disinterested, indeed hostile to the expansion of his method of designating species by binomial names to domesticated plants (Hetterscheid et al., 1996). Notably, Linnaeus used Latin phrases (mostly with more than the two terms he standardly employed in binary species names) to describe 12 kinds of *Brassica oleracea* (Linnaeus, 1753), which includes wild plants, and distinctive domesticated crops known as coles, cabbages, and kohlrabis (Oost, 1989). (Today, Linnaeus' cabbage-type groups have been assigned to the formal category *varietas* (a rank translated as variety (var.), although widely confused with the vernacular non-formal term variety as applied to cultivars.) As noted above, plant taxonomists have not reached a consensus on how to classify plants in which there are both domesticated and wild representatives. Nevertheless, confronted by a growing body of plant names that have been applied to cultivated plants, taxonomists created a special code using non-Latin or "fancy" names (Stearn, 1952). Since the middle of the 20th century, domesticated selections of plants satisfying certain descriptive and publication requirements and termed "cultivars" have been the subject of a special, at least partly non-Latinized code of nomenclature (International Code of Nomenclature for Cultivated Plants; ICNCP; latest edition: Brickell et al., 2009). The ICNCP provides the following definition: "A cultivar is an assemblage of plants that (a) has been selected for a particular character or combination of characters, (b) is distinct, uniform, and stable in these characters, and (c) when propagated by appropriate means, retains those characters. Article 9.1, Note 1 restricts the meaning of cultivar as follows: "No assemblage of plants can be regarded as a cultivar…until its category, name, and circumscription has [sic] been published." (Webster's Third New International Dictionary (Gove, 1981) provides a more general definition of a cultivar: "an organism of a kind (as a variety, strain, or race) that has originated and persisted under cultivation.") Cultivars as defined by the ICNCP can be of quite different nature (e.g., they may be hybrids, clones, grafts (i.e., combinations of species), chimeras (with genetically different tissues), and even plants that are distinct simply because they are infected by a microorganism), but frequently many of the cultivars within a given species differ very little genetically. There are a hundred or more recognized cultivars of non-narcotic forms of *Cannabis*, grown for fiber and/or oilseed. Only a handful of

forms bred for authorized medicinal usage currently are regarded as cultivars under the ICNCP (there are also numerous breeding lines). There are also as many as a thousand illicit or quasi-licit narcotic "strains" that are currently circulated in the black, gray and medicinal marijuana trade (as noted earlier, *Cannabis* strains are biologically equivalent to cultivars, although not nomenclaturally). Many cultivated plants of *Cannabis* are "land races" – populations domesticated in a locale, typically selected over long periods by unconscious (non-planned, undeliberate) selection by traditional farmers, usually adapted to local stresses, and often much more variable than modern cultivars. (In numerous crops, land races have provided the raw materials from which cultivars have been selected.) The ICNCP does not adequately address nomenclature for land races (unless they have been recognized as cultivars, which is quite infrequent), but does provide a context for classifying and naming cultivars. There is no provision under the cultivated plant code for special recognition of uncultivated, wild (ruderal) plants, but it is understood that nomenclature for the wild phases of a species normally falls under the comprehensive plant code (ICNAFP). As noted later, the ICNCP is mainly concerned with names of plant groups that differ mostly in minor ways (terms such as "biotype" or "strain" are usually applicable). Except for the "group" category discussed next, the ICNCP has not served to address the issue of names for major divisions of domesticated plants within species or species groups, nor how to distinguish such major divisions from related wild plants.

The cultivated plant code (ICNCP) has been the subject of debate, particularly as it relates to the plant code applying to all plants (ICNAFP). There have been attempts to introduce a parallel term, "culton," for the term "taxon" (see McNeill (1998) for a critique). Mostly in the past, cultivars were sometimes grouped in "convarieties," a troublesome category because it has been used to indicate rank according to the comprehensive nomenclatural code for plants. A peculiarity of the ICNCP, pointed out by McNeill (2004), is that it does "not presume that desirable groupings are necessarily non-overlapping" (i.e., according to Article 3.4, a given cultivar can belong to more than one group).

A key feature of the ICNCP provides for recognition of "groups" of cultivars, allowing considerable flexibility in their formation ("Criteria for forming and maintaining a Group vary according to the required purposes of particular users"), but insisting that "All members of a Group must share the character(s) by which that Group is defined." (A special group category, "grex," within which groups may be recognized, applies only to horticultural hybrids of orchids.) The group concept is flexible in choice of characters serving to define membership (of course, there may be disagreements among specialists about which characters should be the basis for group recognition). Because the group concept of the cultivated plant code has only a single rank (really no rank), it does not provide for using taxonomic rankings as an indication of phylogenetic history.

The group concept provides a simple, sound, alternative way of labelling variation of domesticated forms in the genus *Cannabis*. It eliminates the need to consider rank; what various authors may have treated as species, subspecies, or varieties can be reduced to the same level. The four domesticated assemblages noted in Table 2 can simply be recognized as groups. There is considerable hybridization in *Cannabis*, which often makes identification problematical, but the same is true of most important domesticated plants. Groups that are hybrids between other groups can simply be recognized as separate groups.

The following classification under the cultivated plant code is proposed, with synonymous terminology shown in parenthesis (the designation of groups by number is consistent in this paper; cf. Fig. 25 and Table 2):

1) *Cannabis* Group European Fiber and Oilseed: Plants tracing to European and western Asian fiber and oilseed races, cannabinoids low in THC and high in CBD (part of Small and Cronquist's *C. sativa* subsp. *sativa* var. *sativa*; Hillig's *C. sativa* "hemp biotype").
2) *Cannabis* Group East Asian Fiber and Oilseed: Plants tracing to East Asian fiber and oilseed races; cannabinoids low to moderate in THC and high in CBD (part of Small and Cronquist's *C. sativa* subsp. *sativa* var. *sativa*; Hillig's *C. indica* "hemp biotype;" Clarke and Merlin's *C. indica* subsp. *chinensis*).
3) *Cannabis* Group Narcotic, THC Predominant: Narcotic strains in which THC is the sole or preodominantcannabinoid (part of Small and Cronquist's *C. sativa* subsp. *indica* var. *indica*; Hillig's *C. indica* "narrow-leaflet drug biotype;" the narcotic trade's "sativa type").
4) *Cannabis* Group Narcotic, THC/CBD Balanced: Narcotic strains in which populations have substantial amounts of both THC and CBD (part of Small and Cronquist's *C. sativa* subsp. *indica* var. *indica*; Hillig's *C. indica* "wide-leaflet drug biotype;" the narcotic trade's "indica type;" *C. indica* of Schultes et al. (1974)).
5) *Cannabis* Group European × East Asian Fiber and Oilseed: A group of hybrids between groups 1 and 2.
6) *Cannabis* Group Narcotic Hybrids: A group of hybrids between groups 5 and 6.

Treatment of Crop-Wild Assemblages as Non-formal Groups

"Formal" taxonomic treatment refers to the strict use of the categories and nomenclatural conventions for designating groups of organisms specified in at least one of the codes of nomenclature governing plants. "Informal" classification refers to organizational and naming systems that do not conform to one of the codes.

A number of theorists of plant classification have espoused the view that classification of crop-wild complexes, in which there is at least some interbreeding, is preferably carried out informally (also note the discussion of natural and artificial classification, later). There are endless definitions of "species," no universally accepted criterion or criteria for this fundamental grouping, and considerable heterogeneity in the nature of groups that are called species. Nevertheless, the ability to interbreed and the actual degree to which interbreeding occurs are critical considerations in recognizing species, because gene exchange among populations tends to eliminate the differences that are employed to define species. The so-called "biological species concept" defines species on the basis of actual or potential breeding separateness (and clearly on this basis there is only one species of *Cannabis*). Above the biological species level, evolution is largely bifurcating (although there is debate about the degree to which hybridization or gene transfer among groups at the genus level and above has occurred), a pattern which is compatible with the hierarchical structure of conventional plant taxonomy. However, some systematists (e.g., Minelli, 2003; Pickersgill et al., 2003) have concluded that

variants below the biological species level (often classified as subspecies and varieties) are usually not generated in a hierarchical fashion, either in nature or in cultivation, and so using more than one infraspecific rank for crop-weed complexes, as has been commonly done in an attempt to reflect evolutionary patterns, is usually unjustified.

Harlan and de Wet (1971), frustrated with the inconsistent treatment of crops and their closely related wild relatives, proposed a non-formal system of classification, which is in fact an elaboration of the biological species concept (Spooner et al., 2003). Their so-called "gene pool classification" recognizes: (a) a "primary genepool," based on the crop and wild populations (whether or not recognized as different species) that interbreed readily with it (Harlan and de Wet characterized their primary gene pool as equivalent to the traditional biological species concept); (b) a "secondary genepool," made up of populations that can interbreed with the crop but only with some difficulty; and (c) a "tertiary genepool," made up of populations that can interbreed with the crop but only with considerable difficulty (this group is the equivalent of a "coenospecies" in the terminology of Clausen (Clausen et al., 1948)). Harlan and de Wet further proposed a scheme of hierarchical subpartitioning using non-formal categories (i.e., independent of the codes of nomenclature). No one has succeeded in hybridizing *C. sativa* with any other species in the Cannabaceae, and all plants of *Cannabis* interbreed freely, so classification of *Cannabis* according to Harlan and de Wet's concept is simple: all plants belong to the primary genepool of the one biological species, *C. sativa*.

Jeffrey (1968), consistent with his view that "cultivated plants differ from one another so greatly in their variation patterns that a formal system applicable to all is not only impossible but undesirable," recommended a non-formal system of classification with a maximum of two hierarchical categories to classify cultivars and a new term ("subspecioid") to separate the domesticated from the related wild-growing plants. Other schemes have been proposed to treat crop classification in ways that are distinctive from the way that wild plants are conventionally classified (for examples, see Styles (1986); for reviews, see Hetterscheid et al. (1996) and Hammer and Morimoto (2012)). A comprehensive non-formal classification system for *Cannabis* has not yet been proposed.

Occam's Razor in Relation to the Evolution and Classification of Cannabis

Conventional biological classifications are, at least to some degree, scientific hypotheses theorizing that certain individuals deserve to be grouped together based on consideration of all or some their characteristics. In scientific theory, Occam's razor is a recommendation that explanations be as simple as possible, limiting unproven assumptions (Einstein's razor, variously phrased, holds that scientific explanations should be as simple as consistent with facts). Stephen Hawking in his classic *A Brief History of Time* wrote "It seems better to employ the principle known as Occam's razor and cut out all the features of the theory that cannot be observed." The following are chief, unnecessary presumptions or assumptions that have contributed to confusion concerning the evolution and classification of *Cannabis*.

(1) Assertion: There are wild plants growing outside of cultivation that coincide with pre-domestication populations, and so these can be recognized as conventional taxa (species, subspecies, or varieties).

Observations: There might be genuinely wild *Cannabis* plants that are completely or substantially unaffected by domestication, but no one has demonstrated their existence. It is commonplace for crops that have been domesticated for very long periods to lack any evidence of genuinely wild (not merely escaped-ruderal) ancestral populations. Given the long history, extensive distribution of *Cannabis* by humans, and the ease of genetic exchange between cultivated and uncultivated populations, it is unlikely that unaltered wild forms still exist.

(2) Assertion: The four basic domesticated groups of *Cannabis* were generated over past millennia from different genuinely wild ancestral populations.

Observations: This viewpoint is adopted extensively by Clarke and Merlin (2013), who assign formal scientific names to seven putatively wild ancestors (including the putative ancestor of all forms of *Cannabis*) of the four domesticated groups recognized in this review, while conceding that these are "either extant and unrecognized or extinct." The far simpler and more likely explanation is that humans generated the domesticated groups from a single original wild species, as indeed is the case for innumerable domesticated plants.

Classification Difficulties Due to Obliteration of Populational Differences in Cannabis by Humans

People often distribute crops to areas where they previously did not exist, providing opportunities for genetic exchange with related species, and creating habitats (generally weedy) where hybrids will survive. On occasion, the result is the obliteration of the genetic distinctions between once distinct groups and their natural distribution ranges. For example, this has happened to alfalfa, a complex species in which the two major parents were once the distinct species *Medicago sativa* and *Medicago falcata*. Over the last six millennia, both in cultivation and in nature, these parental lineages have hybridized so extensively that most plants everywhere are of hybrid origin, one can no longer identify the majority of plants as belonging to the original species, and so it is preferable to reduce the original rank of the parents to subspecies of one species (Small, 2011). The carrot species (*Daucus carota*) also illustrates how once distinct classes of domesticated plants can be homogenized. More than a century ago there was a major class of domesticated carrot with purplish roots (dominated by anthocyanins) centered in Afghanistan; however, hybridization and preference for the European orange carrot (the root pigments dominated by carotenes) have virtually eliminated the pure form of purple carrot, except in genebanks (Small, 1978b). Cultivated assemblages are especially prone to losing their distinctness or simply becoming extinct (Jeffrey, 1968), as their human masters' needs and tastes change. In *Cannabis*, hybridization between the most distinctive variations has largely obliterated populational differences, especially between the two kinds of non-narcotic (fiber) forms and between the two kinds of narcotic forms. As discussed above, the two kinds of fiber plant that have been recognized taxonomically have been widely hybridized, by legal breeders, because of the resulting heterosis (hybrid vigor); and the two kinds of narcotic plant that have been recognized have been widely hybridized (mostly illicitly) to provide for the different psychological states that many have come to appreciate, and also to generate plants with desired photoperiodic and size characteristics to meet local needs. Indeed,

according to Clarke and Merlin (2013), "hybrids have become the predominant form of drug *Cannabis* grown throughout Europe and the New World." Hillig (2004b) concluded that most *Cannabis* accessions in the Vavilov Research Institute (St. Petersburg) germplasm bank (most of these are fiber land races), by far the world's largest such collection, are of hybrid origin. Taxonomy is a practical activity, and given the fact that the fiber (low-THC) populations of the world are being homogenized by hybridization, and the narcotic (moderate- to high-THC) populations of the world are similarly being homogenized by hybridization, it makes sense to recognize these two classes of plants as separate, collective, taxonomic groups.

How Many Species of Cannabis Merit Recognition?

In much of the literature debating the issue of how many species of *Cannabis* deserve recognition, the viewpoint that there are several species has been termed the "polytypic species" concept, and the view that there is just one has been called the "monotypic" view. This is a misinterpretation of the term polytypic, which in taxonomy simply means composed of several elements (taxa or races). A polytypic genus has more than one species; a polytypic species has more than one infraspecific taxon, or is simply variable, containing more than one kind. A genus with more than one species is correctly described as polyspecific; a genus with just one species is monospecific.

Much of the preceding discussion explains that the contention that there are several species of *Cannabis* is simply a semantic preference, not dictated simply by scientific considerations, and that taxonomists are familiar with such competing taxonomic interpretations. However, most taxonomists are suspicious of alleged species that are 100 % interfertile, as are the putative species of *Cannabis*. More critically, when no one has provided a reliable means of morphologically distinguishing the proposed species, few taxonomists would accept their recognition. There is no supreme organization that judges the comparative merit of given taxonomic treatments. However, competing taxonomies are judged by users, the most knowledgeable of which are those who prepare guides to the flora of regions. Today, virtually all authoritative floras recognize only one species of *Cannabis*, *C. sativa* (see for example Qaiser (1973), Tutin and Edmonson (1993), Small (1997) and Wu et al. (2003)) indicating that the designation of more than one species is inappropriate by contemporary standards. As summarized by de Meijer (2014): "A monospecific concept… has implicity been adopted in virtually all, nontaxonomic, publications on *Cannabis*… The current pattern of *Cannabis* diversity is primarily due to intentional actions of humans and reflects a long, intense, and divergent process of domestication which has blurred any natural evolutionary pattern of diversity. It is even questionable if truly wild *Cannabis* still exists."

As discussed above, the recognition of more than one species of *Cannabis* is typical of the overclassification of domesticated crops. Harlan and de Wet (1971) wrote about this problem: "Man has been very active in manipulating the gene pools through repeated introductions or migrations, followed by natural or artificial hybridization. The germ plasm of domesticated plants has been repeatedly and periodically stirred. The environment provided has been artificial, unstable and often very extensive geographically. Selection pressures have been very strong, but biologically capricious and often in diverse directions. The end result is an enormous amount of conspicuous variation among very closely related forms. Faced with this situation, the traditional

taxonomist tends to overclasssify. He finds conspicuous either-or characters, often without intermediates, and frequently bases "species" on them. The characters may be controlled by one or a few genes and have little biological significance. Too many species and too many genera are named."

Based on multivariate statistical similarities of allozyme frequency, Hillig (2005) separated European and west Asian fiber strains (group 1) from the three more easterly domesticated groups: the two narcotic groups (3 and 4) and the east Asian fiber group 2. Additional but less clear support for this separation was found by examination of terpene chemistry (Hillig, 2004a) and cannabinoid chemistry (Hillig & Mahlberg, 2004), and the evidence was clearer for cultivated accessions than for ruderal ones. In these studies Hillig assigned the western Group 1 to "*C. sativa*," and the three eastern groups to "*C. indica*," noting that this had the unexpected effect of combining within *C. indica* two narcotic groups (3 and 4) and the fiber group 2. Hillig's data are valuable in indicating that there was probably in ancient times a genetic differentiation trend between the plants of western Eurasia (and consequently Europe) and those of eastern Eurasia. However, by evolutionary standards this trend seems very minor, since not a single reliable character has been found to distinguish the western and eastern kinds collectively, nor has a combination of characters been suggested that could serve to separate them reliably, as is necessary in conventional plant taxonomic identification keys. The situation is perhaps analogous to human blood group geography, thought to have resulted from a combination of random drift and selection for disease resistance (Anstee, 2010), and certainly not warranting formal taxonomic recognition.

A Rationale for Emphasizing the Principal Selected Character Complexes in the Classification of Cannabis

Aside from groups resulting from hybrid origin or lateral gene transfer, it is usually assumed that organisms sharing a unique set of characteristics arose from a single ancestor. Indeed the cladistics school of classification insists that recognized taxonomic groups must have a single origin, and uses a phyletic pattern of bifurcating groups as the theoretical justification for hierarchical classification. However, adaptive gene complexes within taxonomic groups frequently appear to have arisen recurrently, i.e., repeatedly, independently, and in parallel (e.g., Arendt & Reznick, 2007; Levin, 2001). Many crops appear to have arisen repeatedly and independently within the same species (Diamond, 2002). In the long course of history, fiber strains of *Cannabis* were probably selected independently in different geographic regions, and the same is likely true for narcotic strains, a phyletic pattern that is not hierarchical in organization, and reflects the difficulty of classifying variation within many species. In arguing against the application of hierarchical classification below the species level, Jeffrey (1968) pointed out: "Similar selection pressures, operating on genetically similar but distinct lines, may evoke similar responses in those line, giving rise to parallel variation, the homologous series of Vavilov, a phenomenon by no means confined to cultivated plants, but often exhibited by them to a marked degree." This consideration complicates classification of crop complexes, because it means that critical aspects of the genome may be arrayed in complex ways within a group, and taxonomic recognition of this partitioning may be a debatable issue.

In biological taxonomy, "natural classifications" (sometimes termed general classifications) are based on overall genetic similarities and/or phylogeny, while so-called "artificial" or "special-purpose" classifications are based on selected similarities of particular (practical) interest to people. Artificial classification is unrelated to the concept of artificial selection, and is a phrase, sometimes used pejoratively, to indicate that the merit of such classifications is limited. It is often claimed that restricting the character base to only certain economic considerations means that the resulting classification is not based on evolution, and so not an acceptable basis for biological taxonomy. However, characteristics of domesticated organisms *are* the result of evolution, and when they are produced by strong selective pressures they may merit special taxonomic consideration. This is important for classifying domesticated plants, particularly for *Cannabis*, because biological taxonomy is, above all, intended to convey information, and for useful plants like crops the most useful information often resides in a particular aspect of the genome, not necessarily the entire genome. Characters or character complexes that are selected by humans are adaptive for domesticated plants, at least in the context of cultivation, and using such characters in recognizing taxa does constitute evolutionary classification. For *Cannabis*, my own classification summarized below is based on the recurrent selective pressures (and associated gene selection) for stem fiber or narcotic content (between groups of domesticated plants) and for achene retention or shattering (between wild and cultivated plants). These principal selective evolutionary pressures on *Cannabis* are responsible for the generation of the most obvious and important variation within the genus, and are accordingly appropriate bases for taxonomic delimitation.

A Practical and Natural Taxonomy for Cannabis

The following four-group taxonomic subdivision of *Cannabis* under the ICNAFP code (based on Small and Cronquist (1976)) is an alternative to the six-group classification under the ICNCP code presented in the preceding. The key presented first divides the one species recognized into two groups on the basis of THC and CBD content. As noted in the "Evolution of Narcotic Drug Production Under Domestication" section, the genetic determination of these compounds is probably under the partial genetic control of codominant alleles, and this may provoke the criticism that the division on the basis of predominant cannabinoid is essentially a "one-character taxonomy" (a rather pejorative phrase in classification science). Keys are, by their nature, simplifications of available knowledge, and necessarily limit characters used for identification. As discussed in this review, there are in fact numerous trends that differ between plants of the fiber class and those of the narcotic class.

As shown in Fig. 29, divergent selection for high THC content and high stem fiber content represents a principal dimension of disruptive evolutionary forces in *Cannabis*. All plants domesticated for fiber tend to share a common set of selected characters (e.g., primary fiber constitutes a large percentage of the stem, CBD makes up a large percentage of the cannabinoids, THC rarely is present in large amounts, and the plants are photoperiodically adapted to flower in relatively high latitudes of the Northern Hemisphere), and all plants domesticated for narcotic effects tend to share a different set of contrasting characters (e.g., secondary, not primary fiber constitutes a large

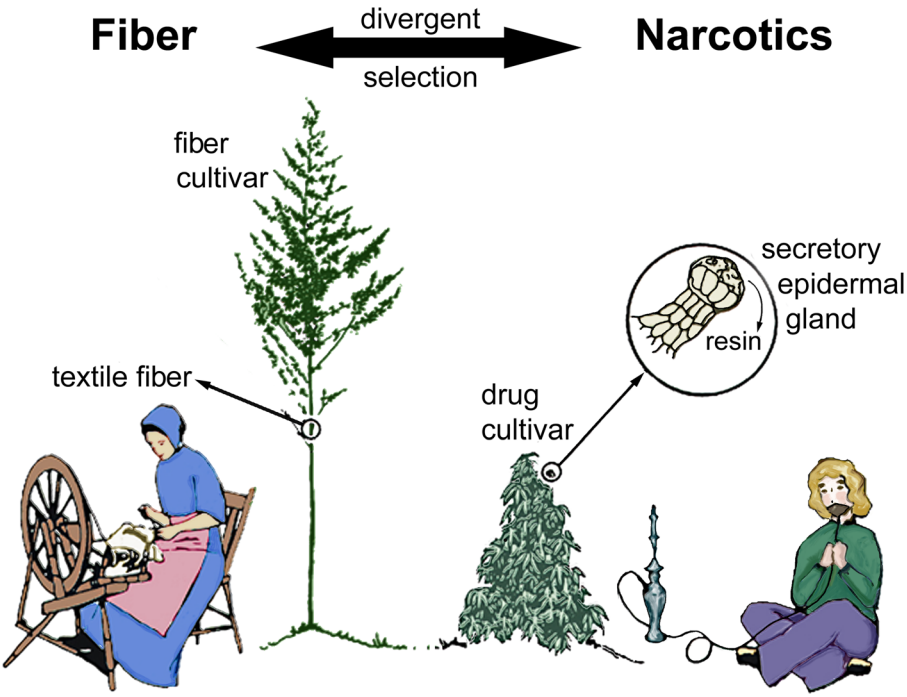


Fig. 29 Divergent selection for fiber and narcotic drug content

percentage of the stem, THC makes up a large percentage of the cannabinoids, and photoperiodic adaptation is usually for relatively lower latitudes of the Northern Hemisphere).

As shown in Fig. 30, divergent selection for achene shattering in ruderal plants and achene retention in domesticated plants is a second principal dimension of disruptive

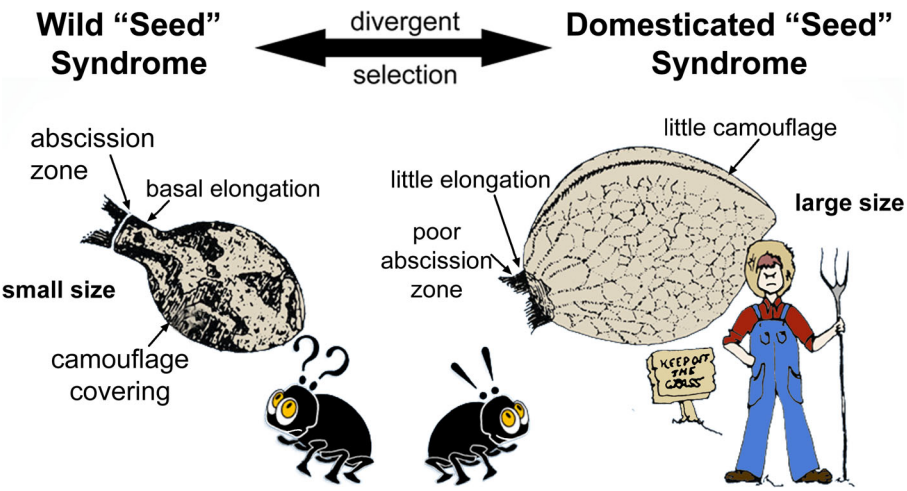


Fig. 30 Divergent selection for adaptive achene ("seed") characteristics between domesticated and wild plants

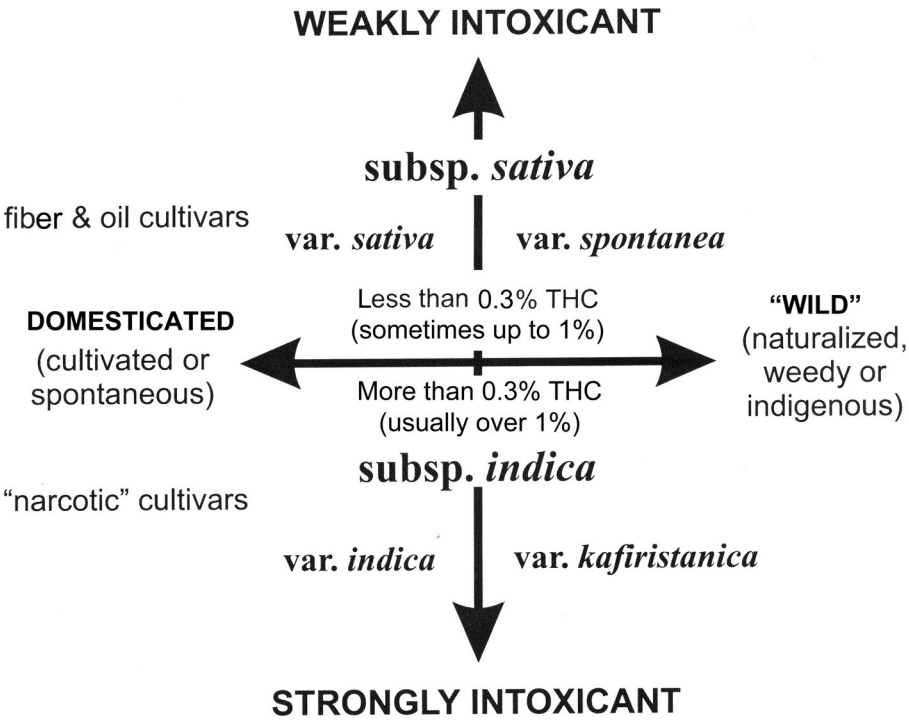


Fig. 31 Classification of *Cannabis sativa* by Small and Cronquist (1976), illustrating conceptual bases of delimitation

selection in *Cannabis* (reflective of a more general disruptive selection for existence in cultivation or existence in nature). The two kinds of disruptive selection are combined in the classification shown in Fig. 31.

Regarding THC concentration, diagnostic for subspecies: as discussed in the "Evolution of Narcotic Drug Production Under Domestication" section, THC concentration is known to vary somewhat with environment, maturity, and other factors, and often there are differences among plants of a population. A minimum level of 1 % is indicative of plants that can be used to prepare marijuana, and frequently it is known whether material available is used for this purpose, and is therefore assignable to subsp. *indica*. Most fiber and oilseed cultivars (with the exception of some East Asian cultivars), by contrast, have less than 1 % and are assignable to subsp. *sativa*.

Regarding achenes ("seeds"), diagnostic for varieties: Only substantially mature achenes exhibit the identification characteristics clearly. In the North Temperate region of the world, geography alone frequently serves to distinguish the cultivated from the wild varieties of a given subspecies: in North America, plants growing in uncultivated situations north of 30° latitude are almost always var. *spontanea*, and in Eurasia, the same is true for plants growing in uncultivated situations north of 35° latitude. Wild-growing plants in southern Asia and northern Africa are frequently var. *kafiristanica*. In many other areas of the world, wild populations are derived from escapes either from cultivated high-THC or low-THC strains, and an analysis of THC levels is required for identification.

Since there is extensive intergradation among the taxa, the classification is necessarily inexact (some plants or populations will be found to be intermediate and not

easily assigned to one of the groups, but this is a well known limitation of classifying groups within a species.

Key to Subspecies and Varieties of Cannabis Sativa *L.*

1. Plants of limited intoxicant ability, delta-9 THC usually comprising less than 0.3 % (dry weight) of upper third of flowering plants, (sometimes up to 1 %), and usually less than half of cannabinoids of resin. Plants cultivated for fiber or oil or growing wild in regions where such cultivation has occurred ..... *C. sativa* subsp. *sativa*

2. Mature achenes relatively large, seldom less than 3.8 mm long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off ..... *C. sativa* subsp. *sativa* var. *sativa*

2. Mature achenes relatively small, commonly less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone toward the base, tending to be mottled or marbled in appearance because of irregular pigmented areas of the largely persistent and adnate perianth ..... *C. sativa* subsp. *sativa* var. *spontanea* Vavilov

1. Plants of considerable intoxicant ability, delta-9 THC usually comprising more than 1 % (dry weight) of upper third of flowering plants, and frequently more than half of cannabinoids of resin. Plants cultivated for intoxicant properties or growing wild in regions where such cultivation has occurred ..... *C. sativa* subsp. *indica* (Lam.) E. Small & Cronquist

3. Mature achenes relatively large, seldom less than 3.8 mm long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off ..... *C. sativa* subsp. *indica* var. *indica* (Lam.) Wehmer

3. Mature achenes relatively small, usually less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone toward the base, tending to be mottled or marbled in appearance because of irregular pigmented areas of the largely persistent and adnate perianth ..... *C. sativa* subsp. *indica* var. *kafiristanica* (Vavilov) E. Small & Cronquist

POSTSCRIPT

William Shakespeare (in *Julius Caesar* Act 4, scene 3) wrote:

There is a tide in the affairs of men
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.
On such a full sea are we now afloat,
And we must take the current when it serves,
Or lose our ventures.

Science is a search for truth, and provides indispensable guidance to society for the creation and adoption of new technologies. Scientific research on *Cannabis* has been

suppressed for most of the last century, a victim of the sometimes observed tendency to avoid examination of sensitive or sinister subjects. Ignorance, however, generally exacerbates problems, and has likely contributed to worsening the substantial harm that has become associated with *Cannabis*. Nevertheless, much of the world is now insisting on a reappraisal of both the industrial and narcotic aspects of *Cannabis*, and indeed there are promising new applications that deserve to be assessed. Because *Cannabis* is first and foremost a plant, evaluation of its potential for harm and benefit needs to take account of its botanical nature, about which much remains to be explored.

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Literature Cited

Abel, E. L. 1980. Marihuana: the first twelve thousand years. Plenum Press, New York.

Ainsworth, C. 2000. Boys and girls come out to play: the molecular biology of dioecious plants. Annals of Botany 86: 211–221.

Anderson, E. 1954. Plants, life, and man. Melrose, London.

Andersson, M. S. & M. C. de Vicente. 2010. Gene flow between crops and their wild relatives. Johns Hopkins University Press, Baltimore.

Anonymous. 1822. Galerie industrielle. Eymery, Paris.

———. 1933. Discovery of sexuality in plants. Nature 131: 392–392.

———. 2006. Medical marijuana: reefer madness, marijuana is medically useful, whether politicians like it or not. The Economist 379(8475): 83–84.

Anstee, D. J. 2010. The relationship between blood groups and disease. Blood 115: 4635–4643.

Arendt, J. & D. Reznick. 2007. Convergence and parallelism reconsidered: what have we learned about the genetics of adaptation. Trends in Ecology and Evolution 23: 26–32.

Armentano, P. 2013. Should per se limits be imposed for cannabis? Equating cannabinoid blood concentrations with actual driver impairment: practical limitations and concerns. Humboldt Journal of Social Relations 35: 45–55.

Ash, A. L. 1948. Hemp: production and utilization. Economic Botany 2: 158–169.

Ashton, J. C. 2012. Synthetic cannabinoids as drugs of abuse. Current Drug Abuse Reviews 5: 158–168.

Atal, C. K. 1959. Sex reversal in hemp by application of gibberellin. Current Science 28: 408–409.

Avico, U., R. Pacifici & P. Zuccaro. 1985. Variations of tetrahydrocannabiol content in cannabis plants to distinguish the fibre-type from drug-type plants. Bulletin on Narcotics 37(4): 61–65.

Baker, H. G. 1974. The evolution of weeds. Annual Review of Ecology and Systematics 5: 1–34.

Barrett, S. C. H. 1982. Genetic variation in weeds. Pp 73–98. *In:* R. Charudattan & H. Walker (eds). Biological control of weeds with plant pathogens. Wiley, New York.

Bawa, K. S. 1980. Evolution of dioecy in flowering plants. Annual Review of Ecology and Systematics 11: 15–39.

Bazzaz, F. A., D. Dusek, D. S. Seigler & A. W. Haney. 1975. Photosynthesis and cannabinoid content of temperate and tropical populations of *Cannabis sativa*. Biochemical Systematics and Ecology 3: 15–18.

Beutler, J. A. & A. H. Der Marderosian. 1978. Chemotaxonomy of *Cannabis* I. Crossbreeding between *Cannabis sativa* and *C. ruderalis*, with analysis of cannabinoid content. Economic Botany 32: 387–394.

Bócsa, I. 1998. Genetic improvement: conventional approaches. Pp 153–184. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), London.

——— **& M. Karus.** 1998. The cultivation of hemp: botany, varieties, cultivation and harvesting. Hemptech, Sebastopol.

———, **M. Máthé & L. Hangyel.** 1997. Effect of nitrogen on tetrahydrocannabinol (THC) content in hemp (*Cannabis sativa* L.) leaves at different positions. Journal of the International Hemp Association 4(2): 80–81.

Bohlmann, F. & E. Hoffmann. 1979. Cannabigerol-ähnliche Verbindungen aus *Helichrysum umbraculigerum*. Phytochemistry 18: 1371–1374.

Borlaug, N. E. 2000. The green revolution revisited and the road ahead. Norwegian Nobel Institute, Oslo. http://www.nufs.sjsu.edu/clariebh/borlaug-lecture.pdf. (Accessed July 10, 2015.)

Borthwick, H. A. & N. J. Scully. 1954. Photoperiodic responses in hemp. Botanical Gazette 116: 14–29.

Bouloc, P. (ed). 2006. Le chanvre industriel: production et utilisations. Groupe France Agricole, Paris.

Bouquet, R. J. 1950. Cannabis. Bulletin on Narcotics 2(4): 14–30.

Boyce, S. S. 1900. Hemp (*Cannabis sativa*). A practical treatise on the culture of hemp for seed and fiber with a sketch of the history and nature of the hemp plant. Orange Judd, New York.

Bradshaw, A. D. 1965. Evolutionary significance of phenotypic plasticity in plants. Advances in Genetics 13: 115–156.

Brickell, C. D., C. Alexander, J. C. David, W. L. A. Hetterscheid, A. C. Leslie, V. Malecot, X. Jin & J. J. Cubey. 2009. International code of nomenclature for cultivated plants. International Society for Horticultural Science, Leuven.

Brown, V. K., J. H. Lawton & P. J. Grubb. 1991. Herbivory and the evolution of leaf size and shape. Philosophical Transactions of the Royal Society, B, Biological Sciences 333: 265–272.

Cabezudo, B., M. Recio, J. M. Sánchez-Laulhé, M. Del Mar Trigo, F. J. Toro & F. Polvorinos. 1997. Atmospheric transportation of marihuana pollen from North Africa to the southwest of Europe. Atmospheric Environment 31: 3323–3328.

Callaway, J. C. 2002. Hemp as food at high latitudes. Journal of Industrial Hemp 7(1): 105–117.

——— 2004. Hempseed as a nutritional resource: an overview. Euphytica 140: 65–72.

———, **T. Tennilä & D. W. Pate.** 1996. Occurrence of "omega-3" stearidonic acid (cis-6,9,12,15-octadecatetraenoic acid) in hemp (*Cannabis sativa* L.) seed. Journal of the International Hemp Association 3(2): 61–63.

Carlini, E. A. & J. M. Cunha. 1981. Hypnotic and antiepileptic effects of cannabidiol. The Journal of Clinical Pharmacology 21: 417–427.

Cascini, F., C. Aiello & G. Di Tanna. 2012. Increasing delta-9-tetrahydrocannabinol (Δ^9-THC) content in herbal cannabis over time: systematic review and meta-analysis. Current Drug Abuse Reviews 5: 32–40.

Chailakhan, M. K. 1979. Genetic and hormonal regulation of growth, flowering and sex expression in plants. American Journal of Botany 66: 717–736.

Chaitra, M. S., K. Vasudevan & K. Shanker. 2004. The biodiversity bandwagon: the splitters have it. Current Science 86: 897–899.

Chandra, S., H. Lata, Z. Mehmedic, I. A. Khan & M. A. ElSohly. 2010a. Assessment of cannabinoids content in micropropagated plants of *Cannabis sativa* and their comparison with conventionally propagated plants and mother plant during developmental stages of growth. Planta Medica 76: 743–750.

———, ———, ———, ——— **&** ———**.** 2010b. Propagation of elite *Cannabis sativa* L. for the production of Δ^9-tetrahydrocannabinol (THC) using biotechnological tools. Pp 98–114. *In:* R. Arora (ed). Medicinal Plant Biotechnology. CAB International, Wallingford.

Clarke, R. C. 1977. The botany and ecology of *Cannabis*. Pods, Ben Lomond.

——— 1981. Marijuana botany: An advanced study: the propagation and breeding of distinctive *Cannabis*. And/Or Press, Berkeley.

——— 1998. Hashish! Red Eye Press, Los Angeles.

——— **& M. D. Merlin.** 2013. *Cannabis*: Evolution and ethnobotany. University of California Press, Los Angeles.

——— **& D. P. Watson.** 2002. Botany of natural *Cannabis* medicines. Pp 1–14. *In:* F. Grotenhermen & E. Russo (eds). *Cannabis* and cannabinoids: pharmacology, toxicology, and therapeutic potential. Haworth Integrative Healing Press, New York.

——— **&** ———**.** 2007. *Cannabis* and natural *Cannabis* medicines. Pp 1–17. *In:* M. A. ElSohly (ed). Marijuana and the cannabinoids. Humana Press, Totowa.

Clausen, J., D. Keck & W. Hiesey. 1948. Experimental studies on the nature of species. 3. Environmental responses of climatic races of *Achillea*. Carnegie Institute of Washington, Stanford.

Coffman, C. B. & W. A. Gentner. 1975. Cannabinoid profile and elemental uptake of *Cannabis sativa* L. as influenced by soil characteristics. Agronomy Journal 67: 491–497.

——— **&** ———**.** 1977. Responses of greenhouse-grown *Cannabis sativa* L. to nitrogen, phosphorus, and potassium. Agronomy Journal 69: 832–836.

Cristiana Moliterni, V. M., L. Cattivelli, P. Ranalli & G. Mandolino. 2004. The sexual differentiation of *Cannabis sativa* L.: a morphological and molecular study. Euphytica 140: 95–106.

Danko, D. 2010. The official High Times field guide to marijuana strains. High Times Corporation, New York.

Darlington, C. D. 1973. Chromosome botany and the origins of cultivated plants, ed. 3rd. Allen & Unwin, London.

Darwin, C. 1845. Journal of researches into the natural history and geology of the countries visited during the voyage of H.M.S. Beagle round the world, under the command of Capt. Fitz Roy, R.N, ed. 2nd. John Murray, London.

——— 1859. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. John Murray, London, U.K.

——— 1868. The variation of animals and plants under domestication, Vol. 1. John Murray, London.

David, J., G. M. Garrity, W. Greuter, D. L. Hawksworth, R. Jahn, P. M. Kirk, J. McNeill, E. Michel, S. Knapp, D. J. Patterson, B. J. Tindall, J. A. Todd, J. van Tol & N. J. Turland. 2012. Biological nomenclature terms for facilitating communication in the naming of organisms. ZooKeys 192: 67–72.

Davidyan, G. G. 1972. Hemp: biology and initial material for breeding. Trudy po Prikladnoi Botanike, Genetikei Selektsii. Bulletin of Applied Botany, of Genetics, and Plant-breeding 48: 1–160. (**In Russian**).

De Candolle, A. 1885. Origin of cultivated plants. D. Appleton & Co., New York.

De Guzman, D. 2001. Hemp oil shows huge gains in food and personal care. Chemical Market Reporter 259(10): 7.

De Meijer, E. P. M. 1994. Diversity in *Cannabis*. Wageningen Agricultural University, Wageningen. (Published doctoral thesis.)

——— 1995. Fibre hemp cultivars: a survey of origin, ancestry, availability and brief agronomic characteristics. Journal of the International Hemp Association 2(2): 66–73.

——— 1998. *Cannabis* germplasm resources. Pp 133–151. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), New York.

——— 2014. Pp 89–110. *In:* R. G. Pertwee (ed). Handbook of cannabis. Oxford University Press, Oxford.

——— **& K. M. Hammond.** 2005. The inheritance of chemical phenotype in *Cannabis sativa* L. (II): canabigerol predominant plants. Euphytica 145: 189–198.

———, ——— **& M. Micheler.** 2009a. The inheritance of chemical phenotype in *Cannabis sativa* L. (III): variation in cannabichrome proportion. Euphytica 165: 293–311.

———, ——— **& A. Sutton.** 2009b. The inheritance of chemical phenotype in *Cannabis sativa* L. (IV): cannabinoid-free plants. Euphytica 168: 95–112.

———, **M. Bagatta, A. Carboni, P. Crucitti, V. M. Moliterni, P. Ranalli & G. Mandolino.** 2003. The inheritance of chemical phenotype in *Cannabis sativa* L. Genetics 163: 335–346.

Deferne, J.-L. & D. W. Pate. 1996. Hemp seed oil: a source of valuable essential fatty acids. Journal of the International Hemp Association 3(1): 4–7.

Devane, W. A., L. Hanus, A. Breuer, R. G. Pertwee, L. A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger & R. Mechoulam. 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258: 1946–1949.

Dewey L H. 1902. Hemp. Pp. 250–251. *In*: U.S. Department of Agriculture (corporate ed.), 1901 Yearbook of the United States Department of Agriculture. Government Printing Office, Washington, D.C.

——— 1914. Hemp. Pp. 283–146. *In*: U.S. Department of Agriculture (corporate ed.), Yearbook of the United States Department of Agriculture 1913. U.S. Department of Agriculture, Washington, D.C.

Diamond, J. 2002. Evolution, consequences and future of plant and animal domestication. Nature 418: 700–707.

Diederichsen, A. & J. P. Raney. 2006. Seed colour, seed weight and seed oil content in *Linum usitatissimum* accessions held by Plant Gene Resources of Canada. Plant Breeding 125: 372–377.

ElSohly, M. A. (ed). 2007. Marijuana and the cannabinoids. Humana Press, Totowa.

——— **& D. Slade.** 2005. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sciences 78: 539–548.

Emerich, D. W. & H. B. Krishnan. 2009. Nitrogen fixation in crop production. American Society of Agronomy, Madison.

Faegri, K., J. Iverson, P. E. Kaland & K. Krzywinski. 1989. Textbook of pollen analysis, ed. 4th. Wiley, New York.

Fairbairn, J. W. & J. T. Pickens. 1981. Activity of cannabis in relation to its Δ^1-trans-tetrahydrocannabinol content. British Journal of Pharmacology 72: 401–409.

Fellermeier, M. & M. H. Zenk. 1998. Prenylation of olvetolate by a hemp transferase yields cannabigerolic acid, the precursor of tetrahydrocannabinol. FEBS Letters 427: 283–285.

Fetterman, P. S., E. S. Keith, C. W. Waller, O. Guerrero, N. J. Doorenbos & M. W. Quimby. 1971. Mississippi-grown *Cannabis sativa* L. Preliminary observation on chemical definition of phenotype and variations in tetrahydrocannabinol content versus age, sex, and plant part. Journal of Pharmaceutical Sciences 60: 1246–1477.

Flachowsky, H., E. Schumann, W. E. Weber & A. Peil. 2001. Application of AFLP for the detection of sex-specific markers in hemp. Plant Breeding 120: 305–309.

Flores-Sanchez, I. J. & R. Verpoorte. 2008. Secondary metabolism in cannabis. Phytochemistry Reviews 7: 615–639.

Fournier, G., C. Richez-Dumanois, J. Duvezin, J.-P. Mathieu & M. Paris. 1987. Identification of a new chemotype in *Cannabis sativa*: cannabigerol-dominant plants, biogenetic and agronomic prospects. Planta Medica 53: 277–280.

Fuller, D. Q. & R. Allaby. 2009. Seed dispersal and crop domestication: shattering, germination and seasonality in evolution under cultivation. Annual Plant Reviews 38: 238–295.

Furr, M. & P. G. Mahlerg. 1981. Histochemcial analyses of laticifers and glandular trichomes in *Cannabis sativa*. Journal of Natural Products 44: 153–159.

Gagne, S. J., J. M. Stout, E. Liu, Z. Boubakir, S. M. Clark & J. E. Page. 2012. Identification of olivetolic acic cyclase from *Cannabis sativa* reveals a unique catalytic route to plant polyketides. PNAS 109: 12811–12816.

Garcia-Jaldon, v., D. Dupreyre & M. R. Vignon. 1998. Fibres from semi-retted hemp bundles by steam explosion treatment. Biomass Energy 14: 251–260.

Gertsch, J., R. G. Pertwee & V. Di Marzo. 2010. Phytocannabinoids beyond the *Cannabis* plant – do they exist? British Journal of Pharmacology 160: 523–529.

Givnish, T. J. 1988. Adaptation to sun and shade: a whole-plant perspective. Australian Journal of Plant Physiology 15: 63–92.

Gorshkova, L. M., G. I. Senchenko & V. G. Virovets. 1988. Method of evaluating hemp plants for content of cannabinoid compounds. Referativnyi Zhurnal 12.65.322. (Abstract, in Russian.)

Gove, P. B. (ed). 1981. Webster's third new international dictionary of the English language unabridged. Merriam-Webster Inc., Springfield.

Grisswell, J. & V. Young. 2011. Professor Grow's book of strains. The 50 *Cannabis* strains most commonly found at dispensaries. Professor Grow, LLC, Firestone.

Grotenhermen, F. 2003. Clinical pharmacodynamics of cannabinoids. Journal of Cannabis Therapeutics 4: 29–78.

——— 2004a. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics 4: 327–360.

——— 2004b. The cannabinoid system – a brief review. Journal of Industrial Hemp 9(2): 87–92.

——— **& M. Karus.** 1998. Industrial hemp is not marijuana: comments on the drug potential of fiber *Cannabis*. Journal of the International Hemp Association 5(2): 96–101.

——— **& K. Műller-Vahl.** 2012. The therapeutic potential of *Cannabis* and cannabinoids. Deutsches Ärzteblatt International 109: 495–501.

——— **& E. Russo.** 2002. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. Haworth Integrative Healing Press (of Haworth Press), New York.

———**, M. Karus & D. Lohmeyer.** 1998. THC limits for food: A scientific study. Journal of the International Hemp Association 5(2): 101–105.

_____, G. Leson, G. Berghaus, O. H. Drummer, H.-P. Krüger, M. Longo, H. Moskowitz, B. Perrine, J. Ramaekers, A. Smiley & R. Tunbridge. 2005. Developing science-based per se limits for driving under the influence of cannabis: findings and recommendations by an expert panel. Nova Institute, Hürth. www.canorml.org/healthfacts/DUICreport.2005.pdf. (Accessed July 10, 2015.)

Grudzinskaya, I. A. 1988. The taxonomy of the family Cannabaceae. Botanicheskiy Zhurnal (Leningrad) 73: 589–593. **In Russian**.

Hamayun, M. & Z. K. S. Shinwari. 2004. Folk methodology of charas (hashish) production and its marketing at Afridi Tirah, Federally Administered Tribal Areas (FATA), Pakistan. Journal of Industrial Hemp 9(2): 41–50.

Hammer, K & Y. Morimoto. 2012. Chapter 7: Classifications of infraspecific variation in crop plants. *In*: L. Guarino & V. Ramanatha Rao (eds.), Collecting plant genetic diversity: Technical guidelines. 2011 update. http://biodiversity-l.iisd.org/news/cgiar-releases-updated-guidelines-for-collecting-plant-genetic-diversity/. (Accessed July 10, 2015.)

Hammond, C. T. & P. G. Mahlberg. 1977. Morphogenesis of capitate glandular hairs of *Cannabis sativa* (Cannabaceae). American Journal of Botany 64: 1023–1031.

——— **&** ———**.** 1978. Ultrastructural development of capitate glandular hairs of *Cannabis sativa* L. (Cannabaceae). American Journal of Botany 65: 140–151.

Haney, A. & F. A. Bazzaz. 1970. Some ecological implications of the distribution of hemp (*Cannabis sativa* L.) in the United States of America. Pp 39–48. *In:* C. R. B. Joyce & S. H. Curry (eds). The botany and chemistry of *Cannabis*. J. & A. Churchill, London.

——— **& B. B. Kutscheid**. 1973. Quantitative variation in the chemical constituents o marijuana from stands of naturalized *Cannabis sativa* L. in east-central Illinois. Economic Botany 27: 193–203.

——— **&** ———**.** 1975. An ecological study of naturalized hemp (*Cannabis sativa* L.) in east-central Illinois. American Midland Naturalist 93: 1–24.

Harlan, J. R. 1995. The living fields, our agricultural heritage. Cambridge University Press, Cambridge.

——— **& J. M. J. de Wet.** 1971. Toward a rational classification of cultivated plants. Taxon 20: 509–517.

Hartsel, S. C., W. H. Y. Loh & L. W. Robertson. 1983. Biotransformation of cannabidiol to cannabielsoin by suspension cultures of *Cannabis sativa* L. and *Saccharum officinalis* L. Plant Medica 48: 17–19.

Hazekamp, A. & J. T. Fischedick. 2012. *Cannabis* – from cultivar to chemovar. Drug Testing and Analysis 4: 660–667.

Heiser, C. B. 1988. Aspects of unconscious selection and the evolution of domesticated plants. Euphytica 37: 77–81.

Heitrich, A. & M. Binder. 1982. Identification of (3R,4R)-Δ1(6)-tetrahydrocannabinol as an isolation artifact of cannabinoid acids formed by callus cultures. Experientia 38: 898–899.

Hemphill, J., J. Turner & P. Mahlberg. 1980. Cannabinoid content of individual plant organs from different geographical strains of *Cannabis sativa* L. Journal of Natural Products 43: 112–122.

Heslop-Harrison, J. 1956. Auxin and sexuality in *Cannabis sativa*. Physiologia Plantarum 4: 588–597.

——— **& Y. Heslop-Harrison.** 1957. Studies on flowering-plant growth and organogenesis. II. The modification of sex expression in *Cannabis sativa* by carbon monoxide. Proceedings of the Royal Society of Edinburgh. Section B. Biology 66: 424–434.

——— **&** ———**.** 1969. *Cannabis sativa* L. Pp 205–226. *In:* L. T. Evans (ed). The induction of flowering. Some case histories. Cornell University Press, Ithaca.

Hetterscheid, W. L. A., R. G. van Den Berg & W. A. Brandeburg. 1996. An annotated history of the principles of cultivated plant classification. Acta Botanica Neerlandica 45: 123–134.

Hillig, K. W. 2002. Letter to the editor. Journal of Industrial Hemp 7(1): 5–6.

——— 2004a. A chemotaxonomic analysis of terpenoid variation in *Cannabis*. Biochemical Systematics and Ecology 32: 875–891.

——— 2004b. A multivariate analysis of allozyme variation in 93 *Cannabis* accessions from the VIR germplasm collection. Journal of Industrial Hemp 9(2): 5–22.

——— 2005. Genetic evidence for speciation in *Cannabis* (Cannabaceae). Genetic Research and Crop Evolution 52(2): 161–180.

——— **& P. G. Mahlberg.** 2004. A systematic analysis of cannabinoid variation in *Cannabis* (Cannabaceae). American Journal of Botany 91: 966–975.

Hoffmann, W. 1970. Hemp (*Cannabis sativa* L.). Pp 415–430. *In:* W. Hoffmann, A. Mudra, & W. Plarre (eds). Textbook of breeding agricultural cultivated plants, Vol. 2. P. Parey, Berlin. (**In German**).

Hölldolber, B. & E. O. Wilson. 1990. The ants. Belknap, Cambridge.

Huang, H. T. 2000. Science and civilization in China, Vol. 6: biology and biological technology, Part V: fermentations and food science. Cambridge University, Cambridge.

Idler, C., R. Pecenka, C. Fürll & H.-J. Gusovius. 2011. Wet processing of hemp: an overview. Journal of Natural Fibers 8: 59–90.

Inam, B., F. Hussain & F. Bano. 1989. *Cannabis sativa* L. is allelopathic. Pakistan Journal of Scientific and Industrial Research 32: 617–620.

Isaac, N. J. B., J. Mallet & G. M. Mace. 2004. Taxonomic inflation: its influence on macroecology and conservation. Trends in Ecology and Evolution 19: 464–469.

Janischevsky, D. E. 1924. A form of hemp in wild areas of southeastern Russia. Učenye zapiski Saratovskogo Gosudarstvennogo imeni N.G. Černyševskogo Universiteta 2(2): 3–17. (**In Russian**).

Jansen, M. & R. Teris. 2002. One woman's work in the use of hashish in a medical context. Journal of Cannabis Therapeutics 2(3/4): 133–141.

Jarillo, J. A., I. del Olmo, A. Gómez-Zambrano, A. Lázaro, L. López-González, E. Miguel, L. Narro-Diego, D. Sáez & M. Piñeiro. 2008. Review. Photoperiodic control of flowering time. Spanish Journal of Agricultural Research 6(Special issue): 221–244.

Jeffrey, C. 1968. Systematic categories for cultivated plants. Taxon 17: 109–114.

Jirásek, V. 1961. Evolution of the proposals of taxonomical categories for the classification of cultivated plants. Taxon 10(2): 34–45.

Johnson, K. P. & M. D. Sorenson. 1999. Phylogeny and biogeography of the dabbling ducks (Genus: *Anas*): A comparison of molecular and morphological evidence. The Auk 116: 792–805.

Johnson, J. M., L. Lemberger, M. Novotny, R. B. Forney, W. S. Dalton & M. P. Maskarinec. 1984. Pharmacological activity of the basic fraction of marihuana whole smoke condensate alone and in combination with delta-9-tetrahydrocannabinol in mice. Toxicology and Applied Pharmacology 72: 440–448.

Joy, J. E., J. Stanley, S. J. Watson Jr. & J. A., Benson Jr. (eds). 1999. Marijuana and medicine: assessing the science base. National Academy Press, Washington, D.C.

Kim, E. S. & P. G. Mahlberg. 1995. Glandular cuticle formation in *Cannabis* (Cannabaceae). American Journal of Botany 82: 1207–1214.

——— **&** ———**.** 1997. Immunochemical localization of tetrahydrocannabinol (THC) in cryofixed glandular trichomes of *Cannabis* (Cannabaceae). American Journal of Botany 84: 336–342.

——— **&** ———**.** 2003. Secretory vesicle formation in the secretory cavity of glandular trichomes of *Cannabis sativa* L. (Cannabaceae). Molecules & Cells 15: 387–395.

King, L. A., C. Carpentier & P. Griffiths. 2005. Cannabis potency in Europe. Addiction 100: 884–886.

Kluyver, T. A., M. Charles, G. Jones, M. Rees & C. P. Osborne. 2013. Did greater burial depth increase the seed size of domesticated legumes? Journal of Experimental Botany 64: 4101–4108.

Köhler, F. E. 1887. Medizinal-Pflanzen. Gera-Untermhaus, Berlin.

Krings, M., T. N. Taylor & D. W. Kellogg. 2002. Touch-sensitive glandular trichomes: a mode of defence against herbivorous arthropods in the Carboniferous. Evolutionary Ecology Research 4: 779–786.

Kushima, H., Y. Shoyama & I. Nishioka. 1980. *Cannabis*. XII. Variations of cannabinoid contents in several strains of *Cannabis sativa* L. with leaf-age, season and sex. Chemical and Pharmaceutical Bulletin 28: 594–598.

Lallemand, M. G. & M. Levy. 1860. L'illustration Journal Universel 926. (Weekly newspaper, Nov. 24, Paris, France; accompanying an article by M. Leon Loiseau.)

Lata, H., S. Chandra, N. Techen, I. A. Khan & M. A. ElSohly. 2011. Molecular analysis of genetic fidelity in *Cannabis sativa* L. plants grown from synthetic (encapsulated) seeds following in vitro storage. Biotechnology Letters 33: 2503–2508.

Latta, R. & B. Eaton. 1975. Seasonal fluctuations in cannabinoid content of Kansas marijuana. Economic Botany 29: 153–163.

Lavins, E. S., B. D. Lavins & A. J. Jenkins. 2004. *Cannabis* (marijuana) contamination of United States and foreign paper currency. Journal of Analytical Toxicology 28: 439–442.

Le Dain, G. (chair). 1972. Cannabis. A report of the commission of inquiry into the non-medical use of drugs. Information Canada, Ottawa.

Ledbetter, M. C. & A. D. Krikorian. 1975. Trichomes of *Cannabis sativa* as viewed with scanning electron microscope. Phytomorphology 25: 166–176.

Leizer, C., D. Ribnicky, A. Poulev, S. Dushenkov & I. Raskin. 2000. The composition of hemp seed oil and its potential as an important source of nutrition. Journal of Nutraceuticals Functional and Medical Foods 2: 35–53.

Leson, G. 2001. Evaluating interference of THC in hemp food produces with employee drug testing. Irregularly paginated. *In*: Nova Institute (corporate ed.), Bioresource hemp & other fibre crops: proceedings of the symposium, Wolfsburg, Germany, Sept. 13–16, 2000. Nova Institute, Hürth.

——— **& P. Pless.** 2002. Hemp seed and hemp oil. Pp 411–425. *In:* F. Grotenhermen & E. Russo (eds). Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Haworth Integrative Healing Press, Binghamton.

Levin, D. A. 2001. The recurrent origin of plant races and species. Systematic Botany 26: 197–204.

Lewis, D. 1942. The evolution of sex in flowering plants. Biological Reviews 17: 46–67.

Lewis, W. H. & M. P. F. Elvin-Lewis. 2003. Medical botany: plants affecting human health, ed. 2nd. Wiley, Hoboken.

Li, Y., K. L. Pickering & R. L. Farrell. 2009. Analysis of green hemp fibre reinforced composites using bag retting and white rot fungal treatments. Industrial Crops and Products 29: 420–426.

Lindemayr, H. & S. Jager. 1980. Occupational immediate type allergy to hemp pollen and hashish. Dermatosen in Beruf und Umwelt 28(1): 17–19. (**In German**).

Linnaeus, C. 1753. Species plantarum, Vol. 2 vols. Laurentius Salvius, Stockholm.

Lydon, J., A. H. Teramura & C. B. Coffman. 1987. UV-B radiation effects on photosynthesis, growth and cannabinoid production of two *Cannabis sativa* chemotypes. Photochemistry and Photobiology 46: 201–206.

Mahlberg, P. G. & J. K. Hemphill. 1983. Effect of light quality on cannabinoid content of *Cannabis sativa* L. (Cannabaceae). Botanical Gazette 144: 43–48.

——— **& E. S. Kim.** 1991. Cuticle development on glandular trichomes of *Cannabis sativa* (Cannabaceae). American Journal of Botany 78: 1113–1122.

——— **&** ———**.** 1992. Secretory vesicle formation in glandular trichomes of *Cannabis sativa* (Cannabaceae). American Journal of Botany 79: 166–173.

——— **&** ———**.** 2004. Accumulation of cannabinoids in glandular trichomes of *Cannabis* (Cannabaceae). Journal of Industrial Hemp 9(1): 15–36.

———**, C. T. Hammond, J. C. Turner & J. K. Hemphill.** 1984. Structure, development and composition of glandular trichomes of *Cannabis sativa* L. Pp 23–51. *In:* E. Rodriguez, P. L. Healey, & I. Mehta (eds). Biology and chemistry of plant trichomes. Plenum Press, New York.

Malingré, T., H. Hendricks, S. Batterman, R. Bos & J. Visser. 1975. The essential oil of *Cannabis sativa*. Planta Medica 28: 56–61.

Mandolino, G. 2004. Again on the nature of inheritance of chemotype. Letter to the editor. Journal of Industrial Hemp 9(1): 5–7.

——— **& P. Ranalli.** 1998. Advances in biotechnological approaches for hemp breeding and industry. Pp 185–212. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), New York.

——— **&** ——— 2002. The applications of molecular markers in genetics and breeding o hemp. Journal of Industrial Hemp 7(1): 7–23.

———**, A. Carboni, S. Forapani, V. Faeti & P. Ranalli.** 1999. Identification of DNA markers linked to the male sex in dioecious hemp (*Cannabis sativa* L.). Theoretical and Applied Genetics 98: 86–92.

———, ———**, M. Bagatta, V. M. Cristiana Moliterni & P. Ranalli.** 2002. Occurrence and frequency of putatively Y chromosome linked DNA markers in *Cannabis sativa* L. Euphytica 126: 211–218.

———**, M. Bagatta, A. Carboni, P. Ranalli & E. P. M. de Meijer.** 2003. Qualitative and quantitative aspects of the inheritance of chemical phenotype in *Cannabis*. Journal of Industrial Hemp 8(2): 52–72.

McNaughton, S. J. 1983. Compensatory plant growth as a response to defoliation by gypsy moth larvae. Oikos 49: 329–336.

McNeill, J. 1998. Culton: a useful term, questionably argued. Hortax News 1(4): 15–22.

——— 2004. Nomenclature of cultivated plants: a historical botanical standpoint. Pp 29–36. *In:* C. G. Davidson & P. Trehane (eds). Fourth international symposium on taxonomy of cultivated plants. International Society for Horticultural Science, Leuven.

———**, F. R. Barrie, W. R. Buck, V. Demoulin, W. Greuger, D. L. Hawksworth, P. S. Herendeen, S. Knapp, K. Marhold, J. Prado, W. F. Prud'homme van Reine, G. F. Smith, J. H. Wiersema & N. J. Turland**. (eds.). 2012. International code of nomenclature for algae, fungi, and plants (Melbourne Code). Koenigstein, Germany: Koelz Scientific Books. (Regnum Vegetabile 154.) http://www.iapt-taxon.org/nomen/main.php?page=title. (Accessed July 10, 2015.)

McPartland, J. M. 1997. *Cannabis* as repellent and pesticide. Journal of the International Hemp Asociation 4(2): 87–92.

——— 1998. A survey of hemp diseases and pests. Pp 109–131. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), London.

——— 2001. Advantages of polypharmaceutical herbal *Cannabis* compared to single ingredient, synthetic tetrahydrocannabinoid. Irregularly paginated. *In*: Nova Institute (corporate ed.), Bioresource hemp & other fibre crops: proceedings of the symposium, Wolfsburg, Germany, Sept. 13–16, 2000. Nova Institute, Hürth.

——— **& G. W. Guy.** 2004. The evolution of *Cannabis* and coevolution with the cannabinoid receptor – a hypothesis. Pp 71–101. *In:* G. W. Guy, B. A. Whittle, & P. J. Robson (eds). The medicinal uses of *Cannabis* and cannabinoids. Pharmaceutical Press, London.

——— **& V. Mediavilla.** 2002. Noncannabinoid components. Pp 401–409. *In:* F. Grotenhermen & E. Russo (eds). Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Haworth Integrative Healing Press, Binghamton.

——— **& E. B. Russo.** 2001. *Cannabis* and cannabis extracts: greater than the sum of their parts? Journal of Cannabis Therapeutics 1: 103–132.

———**, R. C. Clarke & D. P. Watson.** 2000. Hemp diseases and pests: management and biological control. CABI, Wallingford.

———**, V. Di Marzo, L. De Petrocellis, A. Mercer & M. Glass.** 2001. Cannabinoid receptors are absent in insects. Journal of Comparative Neurology 436: 423–429.

Mechoulam, R. 2012. Cannabis – a valuable drug that deserves better treatment. Mayo Clinic Proceedings 87(2): 107–109.

Mechtler, K., J. Bailer & K. de Hueber. 2004. Variations of Δ^9-THC content in single plants of hemp varieties. Industrial Crops and Products 19: 19–24.

Mediavilla, V. & S. Steinemann. 1997. Essential oil of *Cannabis sativa* L. strains. Journal of the International Hemp Association 4(2): 80–82.

Meier, C. & V. Mediavilla. 1998. Factors influencing the yield and the quality of hemp (*Cannabis sativa* L.) essential oil. Journal of the International Hemp Association 5(1): 16–20.

Merlin, M. D. 1972. Man and marijuana: Some aspects of their ancient relationship. Associated University Presses, Cranbury.

Migalj, N. D. 1969. Morphology of hemp (*Cannabis* L.) pollen. Botanicheskiy Zhurnal (Leningrad) 54: 274–276. (**In Russian**).

Mikuriya, T. H. 1969. Marijuana in medicine: past, present and future. California Medicine 110(1): 34–40.

Miller, N. G. 1970. The genera of the Cannabaceae in the Southeastern United States. Journal of the Arnold Arboretum 51: 185–203.

Minelli, A. 2003. Biological systematics: the state of the art. Springer, New York.

Mohan Ram, H. Y. & V. S. Jaiswal. 1970. Induction of female flowers on male plants of *Cannabis sativa* by 2-chlorothane phosphonic acid. Experimentia 26: 214–216.

Mölleken, H. & R. R. Theimer. 1997. Survey of minor fatty acids in *Cannabis sativa* L. fruits of various origins Pp. 500–504. *In*: Nova Institute (corporate ed.), Proceedings of the bioresource hemp symposium, Frankfurt am Main, Germany, Feb. 27–March 2, 1997. Nova Institute, Hürth. (**In German**.)

———, **R. Mothes & S Dudek.** 2001. Quality of hemp fruits and hemp oil in relation to the maturity of the fruits. Irregularly paginated. *In*: Nova Institute (corporate ed.), Bioresource hemp & other fibre crops: proceedings of the symposium, Wolfsburg, Germany, Sept. 13–16, 2000. Nova Institute, Hürth.

Montford, S. & E. Small. 1999a. Measuring harm and benefit: the biodiversity friendliness of *Cannabis sativa*. Global Biodiversity 8(4): 2–13.

——— **&** ———**.** 1999b. A comparison of the biodiversity friendliness of crops with special reference to hemp (*Cannabis sativa*). Journal of the International Hemp Association 6(2): 53–63.

Mustafa, A. F., J. J. McKinnon & D. A. Christensen. 1999. The nutritive value of hemp meal for ruminants. Canadian Journal of Animal Science 79: 91–95.

Nayak, A. P., B. J. Green, G. Sussman, N. Berlin, H. Lata, S. Chandra, M. A. ElSohly, J. M. Hettick & D. H. Beezhold. 2013. Characterization of *Cannabis sativa* allergens. Annals of Allergy, Asthma & Immunology 111: 32–37.

Nesom, G. L. 2011. Toward consistency of taxonomic rank in wild/domesticated Cucurbitaceae. Phytoneuron 13: 1–33.

Nobel, P. S. 1976. Photosynthetic rates of sun versus shade leaves of *Hyptis emoryi* Torr. Plant Physiology 58: 218–223.

Novak, J., K. Zitterl-Eglseer, S. G. Deans & C. M. Franz. 2001. Essential oils of different cultivars of *Cannabis sativa* L. and their antimicrobial activity. Flavour and Fragrance Journal 16: 259–262.

Onaivi, E. S., T. Sugiura & V. di Marzo (eds). 2005. Endocannabinoids: the brain and body's marijuana and beyond. CRC Press, Boca Raton.

Oner, S. T. 2011a. *Cannabis indica*: the essential guide to the world's finest marijuana strains, Vol. 1. Green Candy Press, San Francisco.

——— 2011b. *Cannabis indica*: the essential guide to the world's finest marijuana strains, Vol. 2. Green Candy Press, San Francisco.

——— 2012. *Cannabis sativa*: the essential guide to the world's finest marijuana strains. Green Candy Press, San Francisco.

Oomah, B. D., M. Busson, D. V. Godfrey & J. C. G. Drover. 2002. Characteristics of hemp (*Cannabis sativa* L.) seed oil. Food Chemistry 76: 33–43.

Oost, E. H. 1989. Typification of *Brassica oleracea* L. (Cruciferae) and its Linnaean varieties. Botanical Journal of the Linnean Society 101: 329–345.

Pacifico, D., F. Miselli, M. Micheler, A. Carboni, P. Ranalli & G. Mandolino. 2006. Genetics and marker-assisted selection of the chemotype in *Cannabis sativa* L. Molecular Breeding 17: 257–268.

———, ———, **A. Carboni, A. Moschella & G. Mandolino.** 2008. Time course of cannabinoid accumulation and chemotype development during the growth of *Cannabis sativa* L. Euphytica 160: 231–240.

Padial, J. M. & I. de la Riva. 2006. Taxonomic inflation and the stability of species lists: the perils of ostrich's behavior. Systematic Biology 55: 859–867.

Paris, M., F. Boucher & L. Cosson. 1975. The constituents of *Cannabis sativa* pollen. Economic Botany 29: 245–253.

Pate, D. W. 1983. Possible role of ultraviolet radiation in evolution of *Cannabis* chemotypes. Economic Botany 37: 396–405.

——— 1994. Chemical ecology of *Cannabis*. Journal of the International Hemp Association 1(2): 29. **32–37**.

——— 1998a. The phytochemistry of *Cannabis*: its ecological and evolutionary implications. Pp 21–42. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), London.

——— 1998b. Hemp seed: a valuable food source. Pp 243–255. *In:* P. Ranalli (ed). Advances in hemp research. Food Products Press (of Haworth Press), London.

Peil, A., H. Flachowsky, E. Schumann & W. E. Weber. 2003. Sex-linked AFLP markers indicate a pseudoautosomal region in hemp (*Cannabis sativa* L.). Theoretical and Applied Genetics 107: 102–109.

Pertwee, R. G. (ed). 2014. Handbook of cannabis. Oxford University Press, Oxford.

Peterken, G. F. 1981. Woodland conservation and management. Chapman and Hall, London.

Phillips, R., R. Turk, J. Manno, D. Crim & R. Forney. 1970. Seasonal variation in cannabinolic content of Indiana marihuana. Journal of Forensic Sciences 15: 191–200.

Pickens, J. T. 1981. Sedative activity of cannabis in relation to its Δ^1-trans-tetrahydrocannabinol and cannabidiol content. British Journal of Pharmacology 72: 649–656.

Pickersgill, B., M. I. Chacón Sánchez & D. G. Debouck. 2003. Multiple domestications and their taxonomic consequences: the example of *Phaseolus vulgaris*. Schriften zu Genetischen Ressourcen 22: 71–83.

Popular Mechanics. 1938. New billion-dollar crop. Popular Mechanics 144A: 238–239.

Potter, D. J. 2014. Cannabis horticulture. Pp 65–88. *In:* R. G. Pertwee (ed). Handbook of cannabis. Oxford University Press, Oxford.

——— **& P. Duncombe.** 2012. The effect of electrical lighting power and irradiance on indoor-grown *Cannabis* potency and yield. Journal of Forensic Sciences 57: 618–622.

Przybylski, R., J. Moes & A. Sturko. 1997. Effect of growing conditions on composition of hemp oils. Pp. 505–514. *In*: Nova Institute (corporate ed.), Bioresource hemp: proceedings of the symposium, Frankfurt am Main, Germany, Feb. 27–March 2, 1997. Nova Institute, Hürth.

Qaiser, M. 1973. Cannabaceae. Pp 1–3. *In:* E. Nasir & S. I. Ali (eds). Flora of West Pakistan, issue 44. University of Karachi, Karachi.

Radwan, M. M., M. A. ElSohly, D. Slade, S. A. Ahmed, I. A. Khan & S. A. Ross. 2009. Biologically active cannabinoids from high-potency *Cannabis sativa*. Journal of Natural Products 72: 906–911.

Raie, M. Y., A. Ahmad, M. Ashraf & S. Hussain. 1995. Studies of *Cannabis sativa* and *Sorghum bicolor* oils. Fat Science Technology 97: 428–429.

Ratcliffe, D. A. (ed). 1977. A nature conservation review, Vol. 2. Cambridge University Press, Cambridge.

Renner, S. S. & R. E. Ricklefs. 1995. Dioecy and its correlates in the flowering plants. American Journal of Botany 82: 596–606.

Rindos, D. 1984. The origins of agriculture: An evolutionary perspective. Academic, New York.

Rode, J., K. In-Chol, B. Saal, H. Flachowsky, U. Kriese & W. E. Weber. 2005. Sex-linked SSR markers in hemp. Plant Breeding 124: 167–170.

Rosenthal, E. 2001. The big book of buds. Marijuana varieties from the world's great seed breeders. Quick American Archives, Oakland.

——— 2004. The big book of buds: 2. More marijuana varieties from the world's great seed breeders. Quick American Archives, Oakland.

——— 2007. The big book of buds: 3. More marijuana varieties from the world's great seed breeders. Quick American, Oakland.

——— 2010. The big book of buds: 4. Marijuana varieties from the world's great seed breeders. Quick American Publishing, Oakland.

Ross, S. A. & M. A. ElSohly. 1996. The volatile oil composition of fresh and air-dried buds of *Cannabis sativa*. Journal of Natural Products 59: 49–51.

———, **Z. Mehmedic, T. P. Murphy & M. A. ElSohly.** 2000. GC-MS analysis of the total Δ^9-THC content of both drug- and fiber-type *Cannabis* seeds. Journal of Analytical Toxicology 24: 715–717.

———, **M. A. ElSohly, Z. Mehmedic, T. P. Murphy, M. A. ElSohly, M. A. ElSohly, G. N. N. Sultana, Z. Mehmedic, C. F. Hossain & S. Chandra.** 2005. Flavonoid glycosides and cannabinoids from the pollen of *Cannabis sativa* L. Phytochemical Analysis 16: 45–48.

Ross-Ibara, J., P. L. Morrell & B. S. Gaut. 2007. Plant domestifcation, a unique opportunity to identify the genetic basis of adaptation. Pp 205–224. *In:* J. C. Avise & F. J. Ayala (eds). In the light of evolution. Volume 1: adaptation and complex design. National Academies Press, Washington, D.C.

Roulac, J. W. 1997. Hemp horizons: the comeback of the world's most promising plant. Chelsea Green Publishing, White River Junction.

Russo, E.B. 2003. Introduction: cannabis from pariah to prescription. Journal of Cannabis Therapeutics 3: 1–29.

——— 2007. History of cannabis and its preparations in saga, science, and sobriquet. Chemistry & Biodiversity 4: 1614–1648.

——— 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology 163: 1344–1364.

——— **& G. W. Guy.** 2006. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses 66: 234–246.

——— **& J. M. McPartland.** 2003. Cannabis is more than simply Δ^9-tetrahydrocannabinol. Psychopharmacology 165: 431–432.

———**, H. E. Jiang, X. Li, A. Sutton, A. Carboni, F. del Bianco, G. Mandolino, D. J. Potter, Y.-X. Zhao, S. Bera, Y.-B. Zhang, E.-G. Lü, D. K. Ferguson, F. Hueber, L.-C. Zhao, C.-J. Liu, Y.-F. Wang & C.-S. Li.** 2008. Phytochemical and genetic analyses of ancient cannabis from Central Asia. Journal of Experimental Botany 59: 4171–4182.

Ryan, D., A. J. Drysdale, R. G. Pertwee & B. Platt. 2006. Differential effects of cannabis extracts and pure plant cannabinoids on hippocampal neurones and glia. Neuroscience Letters 408: 236–241.

Sakamoto, K., Y. Akiyama, K. Fukui, H. Kamada & S. Satoh. 1998. Characterization: genome size and morphology of sex chromosomes in hemp (*Cannabis sativa* L.). Cytologia 3: 459–464.

———**, N. Ohmido, K. Fukui, H. Kamada & S. Satoh.** 2000. Site-specific accumalation of a LINE-like retrotransposon in a sex chromosome of the dioecious plant *Cannabis sativa*. Plant Molecular Biology 44: 723–732.

———**, T. Abe, T. Matsuyama, S. Yoshida, N. Ohmido, K. Fukui & S. Satoh.** 2005. RAPD markers encoding retrotransposable elements are linked to the male sex in *Cannabis sativa* L. Genome 48: 931–936.

Sakuma, S., B. Salomon & T. Komatsuda. 2011. The domestication syndrome genes responsible for the major changes in plant form in the Triticeae crops. Plant & Cell Physiology 52: 738–749.

Sarlikioti, V., P. H. B. de Visser, G. H. Buck-Sorlin & L. F. M. Marcelis. 2011. How plant architecture affects light absorption and photosynthesis in tomato: towards an ideotype for plant architecture using a functional-structural plant model. Annals of Botany 108: 1065–1073.

Schaffner, J. H. 1926. The change of opposite to alternate phyllotaxis and repeated rejuvenations in hemp by means of changed photoperiodicity. Ecology 7: 315–325.

Scholz, H. 1957. Wild hemp as a ruderal plant of Central Europe. Verhandlungen des Botanischen Vereins der Provinz Brandenburgund der angrenzenden Länder 83(97): 61–64. (**In German**).

Schultes, R. E. 1970. Random thoughts and queries on the botany of *Cannabis*. Pp 11–38. *In:* R. B. Joyce & S. H. Curry (eds). The botany and chemistry of Cannabis. J. & A. Churchill, London.

——— **& A. Hofmann.** 1980. The botany and chemistry of hallucinogens, ed. 2d. Thomas, Springfield.

———**, W. M. Klein, T. Plowman & T. E. Lockwood.** 1974. *Cannabis*: an example of taxonomic neglect. Botanical Museum Leaflets, Harvard University 23: 337–367.

Schultz, T. R. & T. P. McGlynn. 2000. The interactions of ants with other organisms. Pp 35–44. *In:* D. Agosti, J. Majer, L. Alonso, & T. R. Schultz (eds). Ants: standard methods for measuring and monitoring biodiversity. Smithsonian Institution Press, Washington, D.C.

———**, U. G. Mueller, C. R. Currie & S. A. Rehner.** 2005. Reciprocal illumination: a comparison of agriculture in humans and in fungus-growing ants. Pp 149–190. *In:* F. E. Vega & M. Blackwell (eds). Insect–fungal associations: ecology and evolution. Oxford University Press, New York.

Segelman, A. B., R. D. Sofia, F. P. Segelman, J. J. Harakal & L. C. Knobloch. 1974. *Cannabis sativa* L. (marijuana) V: pharmacological evaluation of marijuana aqueous extract and volatile oil. Journal of Pharmaceutical Sciences 26: 962–964.

Serebriakova, T. Y. 1940. Fiber plants, Volume 5, Part 1. *In:* E. V. Wulff (ed). Flora of cultivated plants. State Printing Office, Moscow. (**In Russian**).

——— **& I. A. Sizov.** 1940. Cannabinaceae Lindl. Pp 1–53. *In:* N. I. Vavilov (ed). Kulturnaja Flora SSSR Vol. 5. Kolos, Moscow. (**In Russian**).

Shao, H., S.-J. Song & R. C. Clarke. 2003. Female-associated DNA polymorphisms of hemp (*Cannabis sativa* L.). Journal of Industrial Hemp 8(1): 5–9.

Sharma, G. K. 1979. Significance of eco-chemical studies of *Cannabis*. Science Culture 45: 303–307.

Shoyama, Y., F. Taura & S. Morimoto. 2001. Expression of tentrahydrocannabinoilic acid synthase in tobacco. 9. *In*: Proceedings, 2001 symposium on the cannabinoids. International Cannabinoid Research Society, Burlington.

Sikora, V., J. Berenji & D. Latković. 2011. Influence of agroclimatic conditions on content of main cannabinoids in industrial hemp (*Cannabis sativa* L.). Genetika 43: 449–456.

Sirikantaramas, S., F. Taura, Y. Tanaka, Y. Ishikawa, S. Morimoto & Y. Shoyama. 2005. Tetrahydrocannabinolic acid synthase, the enzyme controlling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. Plant Cell Physiology 46: 1578–1582.

———, ———, **S. Morimoto & Y. Shoyama.** 2007. Recent advances in *Cannabis sativa* research: biosynthetic studies and its potential in biotechnology. Current Pharmaceutical Biotechnology 8: 237–243.

Small, E. 1972a. Interfertility and chromosomal uniformity in *Cannabis*. Canadian Journal of Botany 50: 1947–1949.

——— 1972b. The hemp problem in Canada. Greenhouse Garden Grass 11(3): 46–52.

——— 1974. American law and the species problem in *Cannabis*. Microgram 7: 131–132.

——— 1975a. Morphological variation of achenes of *Cannabis*. Canadian Journal of Botany 53: 978–987.

——— 1975b. American law and the species problem in *Cannabis*: science and semantics. Bulletin on Narcotics 27(3): 1–20.

——— 1975c. Essential considerations of the taxonomic debate in *Cannabis*. Journal of Forensic Sciences 20: 739–741.

——— 1975d. On toadstool soup and legal species of *Cannabis*. Plant Science Bulletin 21: 34–39.

——— 1975e. The case of the curious "*Cannabis*,". Economic Botany 29: 254.

——— 1976. The forensic taxonomic debate on *Cannabis*: semantic hokum. Journal of Forensic Sciences 21: 239–251.

——— 1977. Nomenclatural nonsense and legal marijuana plants. Bulletin of the Pacific Tropical Botanical Garden 7(1): 1–6.

——— 1978a. A numerical and nomenclatural analysis of morpho-geographic taxa of *Humulus*. Systematic Botany 3: 37–76.

——— 1978b. A numerical taxonomic analysis of the *Daucus carota* complex. Canadian Journal of Botany 56: 248–276.

——— 1979a. The species problem in *Cannabis*: science and semantics. Volume 1, Science. Corpus, Toronto.

——— 1979b. The species problem in *Cannabis*: science and semantics. Volume 2, Semantics. Corpus, Toronto.

——— 1997. Cannabaceae. Pp 381–387. *In:* Flora North America Editorial Committee (ed). Flora of North America, north of Mexico, Vol. 3. Oxford University Press, New York.

——— 2004. Narcotic plants as sources of medicinals, nutraceuticals, and functional foods. Pp. 11–67. *In*: F.-F. Hou, H.-S. Lin, M.-H. Chou & T.-W. Chang (eds.), Proceedings of the international symposium on the development of medicinal plants, 24–25 Aug. 2004, Hualien. Hualien District Agricultural Research and Extension Station, Hualien.

——— 2007. *Cannabis* as a source of medicinals, nutraceuticals, and functional foods. Pp 1–39. *In:* S. N. Acharya & J. E. Thomas (eds). Advances in Medicinal Plant Research. Trivandrum, Research Signpost / Transworld Research Network, Kerala.

——— 2009. Top 100 food plants: the world's most important culinary crops. National Research Council Press, Ottawa.

——— 2011. Alfalfa and relatives: evolution and classification of *Medicago*. NRC Research Press, Ottawa, and CABI, Wallingford.

——— 2012. Hemp. Pp 220–222. *In:* S. Fredericks, L. Shen, S. Thompson, & D. Vasey (eds). The Berkshire Encyclopedia of Sustainability: Vol. 4. Natural Resources and Sustainability. Berkshire Publishing, Great Barrington.

——— 2013. North American cornucopia: top 100 indigenous food plants. CRC Press, Boca Raton.

——— 2014a. Blossoming treasures of biodiversity. 44. Saguaro – threatened monarch of the desert. Biodiversity 15(1): 39–53.

——— 2014b. Hemp fiber and composites for the 21st century. Pp 29–64. *In:* V. K. T. Thakur & J. Njuguna (eds). Natural fibers and composites. Studium Press, Houston.

——— **& T. Antle.** 2003. A preliminary study of pollen dispersal in *Cannabis sativa*. Journal of Industrial Hemp 8(2): 37–50.

——— **&** ———**.** 2007. A study of cotyledon asymmetry in *Cannabis sativa*. Journal of Industrial Hemp 12(1): 3–14.

——— **& H. D. Beckstead.** 1973a. Common cannabinoid phenotypes in 350 stocks of *Cannabis*. Lloydia 35: 144–165.

——— **&** ———**.** 1973b. Cannabinoid phenotypes in *Cannabis*. Nature 245: 147–148.

——— **& B. Brookes.** 2012. Temperature and moisture content for storage maintenance of germination capacity of seeds of industrial hemp, marijuana, and ditchweed forms of *Cannabis sativa*. Journal of Natural Fibers 9(4): 240–255.

——— **& P. M. Catling.** 2009. Blossoming treasures of biodiversity. 27. *Cannabis* – Dr. Jekyll and Mr. Hyde. Biodiversity 10(1): 31–38.

——— **& A. Cronquist.** 1976. A practical and natural taxonomy for *Cannabis*. Taxon 25: 405–435.

_____ **& D. Marcus.** 2000. Hemp germplasm trials in Canada. Irregularly paginated. *In*: Nova Institute (corporate ed.), Proceedings third international symposium bioresource hemp. Nova Corporation, Hürth.

——— **& ———.** 2002. Hemp – a new crop with new uses for North America. Pp 284–326. *In:* J. Janick & A. Whipkey (eds). Trends in new crops and new uses. ASHS Press, Alexandria.

——— **& ———.** 2003. Tetrahydrocannabinol levels in hemp (*Cannabis sativa*) germplasm resources. Economic Botany 57: 545–558.

——— **& S. G. U. Naraine.** 2015. Size matters: evolution of large drug-secreting resin glands in elite pharmaceutical strains of *Cannabis sativa* (marijuana). Genetic Resources and Crop Evolution. doi:10.1007/s10722-015-0254-2.

———**, H. D. Beckstead & A. Chan.** 1975. The evolution of cannabinoid phenotypes in *Cannabis*. Economic Botany 29: 219–232.

———**, P. Jui & L. P. Lefkovitch.** 1976. A numerical taxonomic analysis of *Cannabis* with special reference to species delimitation. Systematic Botany 1: 67–84.

———**, T. Pocock & P. B. Cavers.** 2003. The biology of Canadian weeds. 119. *Cannabis sativa* L. Canadian Journal of Plant Sciences 83: 217–237.

———**, D. Marcus, A. McElroy & G. Butler.** 2007. Apparent increase in biomass and seed productivity in hemp (*Cannabis sativa*) resulting from branch proliferation caused by the European corn borer (*Ostrinia nubilalis*). Journal of Industrial Hemp 12(1): 15–26.

Smith, M. H. 2012. Heart of dankness. Underground botanists, outlaw farmers, & the race for the Cannabis Cup. McClelland & Stewart, Toronto.

Snoeijer, W. 2002. A checklist of some Cannabaceae cultivars. Part a: *Cannabis*. Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden.

Spelman, K. 2009. "Silver bullet" drugs vs. traditional herbal remedies: perspectives on malaria. HerbalGram 84: 44–55.

Spencer, R. D. 1999. Cultivated plants and the codes of nomenclature – towards the resolution of a demarcation dispute. Pp 171–181. *In:* S. Andrews, A. C. Leslie, & C. Alexander (eds). Taxonomy of cultivated plants: third international symposium. Royal Bontanic Gardens, Kew.

——— **& R. G. Cross.** 2007a. The international code of botanical nomenclature (ICBN), the international code of nomenclature for cultivated plants (ICNCP), and the cultigen. Taxon 56: 938–940.

——— **& ———.** 2007b. The cultigen. Pp. 163–167. *In*: R. G. van den Berg, N. Groendijk-Wilders, C. Alexander & W. L. A. Hetterscheid (eds.), Proceedings of the fifth international symposium on the taxonomy of cultivated plants. International Society for Horticultural Science, Leuven.

Spooner, D. M., R. G. van den Berg, W. L. A. Hetterscheid & W. A. Brandenburg. 2003. Plant nomenclature and taxonomy. An horticultural and agronomic perspective. Horticultural Reviews 28: 1–59.

Stearn, W. T. 1952. Proposed international code of nomenclature for cultivated plants. Historical introduction. Journal of the Royal Horticultural Society 77: 157–173.

Stokes, J. R., R. Hartel, L. B. Ford & T. B. Casale. 2000. *Cannabis* (hemp) positive skin tests and respiratory symptoms. Annals of Allergy, Asthma and Immunology 85: 238–240.

Stout, J. M., Z. Boubakir, S. J. Ambrose, R. W. Purves & J. E. Page. 2012. The hexanoyl-CoA precursor for cannabinoid biosynthesis is formed by an acyl-activating enzyme in *Cannabis sativa* trichomes. The Plant Journal 71: 353–365.

Styles, B. T. (ed). 1986. Infraspecific classification of wild and cultivated plants. Clarendon, Oxford.

Sytsma, K. J., J. Morawetz, J. C. Pires, M. Nepokroeff, E. Conti, M. Zjhra, J. C. Hall & M. W. Chase. 2002. Urticalean rosids: circumscription, rosid ancestry, and phylogenetics based on rbcL, trnL-trnF, and ndhF sequences. American Journal of Botany 89: 1531–1546.

Taura, F., S. Morimoto, Y. Shoyama & R. Mechoulam. 1995. First direct evidence for the mechanism of delta-1-tetrahydrocannabinoloic acid biosynthesis. Journal of the American Chemical Society 38: 9766–9767.

———, ——— **& ———.** 1996. Purification and characterization of cannabidiolic-acid synthase from *Cannabis sativa* L. The Journal of Biological Chemistry 271: 17411–17416.

———**, S. Sirikantaramas, Y. Shoyama, K. Yoshikai, Y. Shoyama & S. Morimoto.** 1997. Cannabidiolic-acid synthase, the chemotype-determining enzyme in the fiber-type *Cannabis sativa*. FEBS Letters 581: 2929–2934.

Thomas, T. G., S. K. Sharma, A. Prakash & B. R. Sharma. 2000. Insecticidal properties of esential oil of *Cannabis sativa* Linn. against mosquito lavae. Entomon 25: 21–24.

Tournois, J. 1912. Influence de la lumière sur la floraison du houblon japonais et du chanvre déterminées par des semis haitifs. Comptes Rendus Hebdomadaires des Séances de l'Academie des Sciences, Paris 155: 297–300.

Toyota, M., T. Shimamura, H. Ishii, M. Renner, J. Braggins & Y. Asakawa. 2002. New bibenzyl cannabinoid from the New Zealand liverwort *Radula marginata*. Chemical and Pharmaceutical Bulletin (Tokyo) 50: 1390–1392.

Turner, C., P. Fetterman, K. Hadley & J. Urbanek. 1975. Constituents of *Cannabis sativa* L. X. Cannabinoid profile of a Mexican variant and its possible correlation to pharmacological activity. Acta Pharmaceutica Jugoslavica 25: 7–15.

Turner, J. C., J. K. Hemphill & P. G. Mahlberg. 1980. Trichomes and cannabinoid content of developing leaves and bracts of *Cannabis sativa* L. (Cannabaceae). American Journal of Botany 67: 1397–1406.

———, ——— & ———. 1981a. Interrelationships of glandular trichomes and cannabinoid content. I. Developing pistillate bracts of *Cannabis sativa* L. (Cannabaceae). Bulletin on Narcotics 33(2): 59–69.

———, ——— & ———. 1981b. Interrelationships of glandular trichomes and cannabinoid content. II. Developing vegetative leaves of *Cannabis sativa* L. (Cannabaceae). Bulletin on Narcotics 33(3): 63–71.

Tutin, T. G. & J. R. Edmonson. 1993. Cannabaceae. Pp 78. *In:* T. G. Tutin & J. R. Edmonson (eds). Flora Europaea, Volume 1, ed. 2nd. University of Cambridge, Cambridge.

United Nations Office on Drugs and Crime. 2014. World drug report 2014. http://www.unodc.org/wdr/en/cannabis.html. (Accessed July 10, 2015.)

Valle, J. R., J. E. V. Vieira, J. G. Aucélio & I. F. M. Valio. 1978. Influence of photoperiodism on cannabinoid content of *Cannabis sativa* L. Bulletin on Narcotics 30(1): 67–68.

Van Bakel, H., J. M. Stout, A. G. Cote, C. M. Tallon, A. G. Sharpe, T. R. Hughes & J. E. Page. 2011. The draft genome and transcriptome of *Cannabis sativa*. Genome Biology. doi:10.1186/gb-2011-12-10-r102 http://genomebiology.com/content/pdf/gb-2011-12-10-r102.pdf. (Accessed July 10, 2015.)

Van der Werf, H. M. G. 1994. Crop physiology of fibre hemp (*Cannabis sativa* L.). Wageningen Agricultural University, Wageningen. (Published Doctoral thesis.)

Vavilov, N. I. 1926. The origin of the cultivation of "primary" crops, in particular of cultivated hemp. Trudy po Prikladnoj Botanike i Selekcii 16(2): 221–233.

——— 1931. The role of Central Asia in the origin of cultivated plants. Bulletin of Applied Botany, Genetics, and Plant Breeding 26(3): 3–44. (**In Russian and English**).

Veliky, I. A. & K. Genest. 1972. Growth and metabolites of *Cannabis sativa* cell suspension cultures. Lloydia 35: 450–456.

Verkaar, H. J. 1986. When does grazing benefit plants? Trends in Ecology and Evolution 1: 168–169.

Virovets, V. G. 1996. Selection for non-psychoactive hemp varieties (*Cannabis sativa* L.) in the CIS (former USSR). Journal of the International Hemp Association 3(1): 13–15.

Vogl, C. R., H. Mölleken, G. Lissek-Wolf, A. Surböck & J. Kobert. 2004. Hemp (*Cannabis sativa* L.) as a resource for green cosmetics: yield of seed and fatty acid composition of 20 varieties under the growing conditions of organic farming in Austria. Journal of Industrial Hemp 9(1): 51–68.

Walter, H. 1938. Cannabis. Pp 875–909. *In:* O. V. Kirchner, E. Loew, C. Schröter, & W. Wangerin (eds). Lebengeschichte der Blütenpflanzen Mitteleuropas, Vol. 2. Eugen Ulment, Stuttgart. (**In German**).

Watson, D. P. & R. C. Clarke. 1997. The genetic future of hemp. Pp. 122–127. *In*: Nova Institute (corporate ed.), Proceedings of the bioresource hemp symposium, Frankfurt am Main, Germany, Feb. 27–March 2, 1997. Nova Institute, Hürth.

West-Eberhard, M. J. 2003. Developmental plasticity and evolution. Oxford University Press, New York.

Whalley, B. J., J. D. Wilkinson, E. M. Williamson & A. Constanti. 2004. A novel component of cannabis extracts potentiates excitatory synaptic transmission in rat olfactory cortex in vitro. Neuroscience Letters 365: 58–63.

Whitman, T. & L. W. Aarssen. 2010. The leaf size/number trade-off in herbaceous angiosperms. Journal of Plant Ecology 3: 49–58.

Wilkinson, J. D., B. J. Whalley, D. Baker, G. Pryce, A. Constanti, S. Gibbons & E. M. Williamson. 2003. Medicinal cannabis: is Δ^9-tetrahydrocannabinol necessary for all its effects? Journal of Pharmacy and Pharmacology 55: 1687–1694.

Wirtshafter, D. 1995. Nutrition of hemp seeds and hemp seed oil. Pp. 546–555. *In*: Nova Institute (corporate ed.), Bioresource hemp – proceedings of the symposium, Frankfurt am Main, Germany, March 2–5, 1995. 2nd edition. Hemptech, Ojai.

Wu, Z., Z.-K. Zhou & B. Bartholomew. 2003. Cannabaceae Endlicher. Pp 74–75. *In:* W. Zheng-yi & P. H. Raven (eds). Flora of China, Vol. 5. Missouri Botanical Garden Press, St. Louis.

Yampolsky, C. & H. Yampolsky. 1922. Distribution of sex forms in the phanerogamic flora. Gebruder Borntraeger, Leipzig.

Yang, M.-Q., R. van Velzen, F. T. Bakker, A. Sattarian, D.-Z. Li & T.-S. Yi. 2013. Molecular phylogenetics and character evolution of Cannabaceae. Taxon 62: 473–485.

Zhang, L. L., R. Y. Zhu, J. Y. Chen, J. M. Chen & X. X. Feng. 2008. Seawater-retting treatment of hemp and characterization of bacterial strains involved in the retting process. Process Biochemistry 43: 1195–1201.

Zhatov, A. I. 1983. Variability of pollen grains of polyploid hemp. Tsitologiya i Genetika 17: 47–51. (**In Russian**).

Zohary, D. 2004. Unconscious selection and the evolution of domesticated plants. Economic Botany 58: 5–10.

Zuardi, A. W., J. A. S. Crippa, J. E. C. Hallak, F. A. Moreira & F. S. Guimarães. 2006. Cannabidiol, a *Cannabis sativa* constituent, as an antipsychotic drug. Brazilian Journal of Medical and Biological Research 39: 421–429.

———, **J. E. C. Hallak & J. A. S. Crippa.** 2012. Interaction between cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC): influence of administration interval and dose ratio between the cannabinoids. Psychopharmacology 219: 247–249.