



The Medicinal Uses of Cannabis and Cannabinoids

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History of cannabis as a medicine

Ethan Russo

Thousands of years ago in Central or North-East Asia, someone stumbled upon the knowledge of cannabis as medicine. Perhaps it was first ingested because of its sweetly intoxicating aroma or perhaps because an unusual mental change was perceived when hemp was burned. We cannot say with authority, but today cannabis is one of the most versatile medicines available, although only potentially so, due to its prohibited legal status. Here we will review the recorded history of cannabis use as a therapeutic agent. Further details can be found in the historical reviews by Merlin (1972), Abel (1980), Mechoulam (1986), Aldrich (1997) and Russo (2001b, 2002).

It has been claimed that cannabis was used by the Bylony Culture in Central Europe 7000 years ago (Kabelík *et al.*, 1960), but the earliest well-documented evidence of cannabis use is from China, where carbon-14 dating has confirmed it from 4000 BCE (Li, 1974). The first record of therapeutic use is in the *Shen Nong Ben Cao Jing* or *Pên-tsau Ching*, a traditional herbal written in the first or second century, but which was based on the oral traditions passed down from the Emperor Shên-nung in the third millennium BCE. Hemp seed was a common Chinese foodstuff at this time, but its psychoactive effects and hallucinatory potential were also noted, along with an ability to allay senility (Shou-zhong, 1997). Julien documented the legend of Hua-Tho, a second-century emperor who was given a hemp-based anaesthetic during surgery (Julien, 1849). Folk art depicts him as playing chequers during the operation!

In Ancient Egypt, hieroglyphic data, fabric and pollen remains provide evidence of cannabis use as a fumigant, as a salve to treat ophthalmologic conditions and as a suppository to increase vaginal contractions (Mannische, 1989). Similar uses from 29 medical citations and a few obscure ones ('hand of a ghost') attributed to superstitious afflictions were recorded in the Sumerian and Akkadian medical literature of 2000 BCE, which was later collected in the Assyrian Library of the Assyrian king Ashurbanipal (Thompson, 1924, 1949; Russo,

manuscript in preparation). Clear written documentation of *bhang* as one of five sacred herbs to allay anxiety is noted in the *Atharva Veda* (11.6.15) in India in the second millennium BCE. The Ayurvedic tradition of using cannabis extends to at least the early pre-Christian centuries (Chopra and Chopra, 1957; Dwarakanath, 1965), with a strong case for smoked medicine being made by certain authors (Walker, 1968; Oman, 1984), supported by documentation of the Ayurvedic ‘smoke-roll’ and even modern techniques of rolling a hashish cigarette with no pipe or paper (Clarke, 1998). Archaeological smoking paraphernalia with cannabinoid residues has also been found in remains from fourteenth-century Ethiopia, pre-dating the Columbian conquest (van der Merwe, 1975). However, some early cannabis clinical claims remain controversial, as is the reported finding of carbonised cannabis metabolites in a fourth-century tomb in Ancient Judea, said to be from inhaled material used as an aid to childbirth (Zias *et al.*, 1993).

Less debate surrounds the Ancient Greek and Roman sources, where the term ‘cannabis’ was employed explicitly. Herodotus reported that the ritual use of burned cannabis as part of the funeral rites of the Scythian nomads of the Asian plains in the fifth century BCE caused them to dance and sing (Herodotus, 1998, Book 1, Verse 202). Physical proof of this Scythian rite has been unearthed more recently (see Artamonov, 1965; Rudenko, 1970).

Subsequent classical authors also noted the medicinal effects of cannabis. In the first century CE, Dioscorides published his *Materia Medica*, in which cannabis seed was recommended for the treatment of otalgia (Dioscorides, 1968). Pliny (1951) also noted the use of cannabis root to treat cramped joints, gout and burns around the same time. Galen, in the second century CE noted the gastrointestinal effects of cannabis, and that it could be psychoactive when taken in excess (Brunner, 1973). As evidenced in the above citations, cannabis and its various parts were employed orally, topically, via inhalation, by vaginal suppository and by clyster. Certainly, the evidence supports an early empirical knowledge of the versatility and pharmacokinetics of this phyto-medicinal.

For the next thousand years Europe was largely silent about cannabis, with rare exceptions – a recurrent theme in cannabis therapeutics this author has dubbed *cannabis interruptus* (Russo, 2001b). According to archaeological and pollen records, cannabis came to the British Isles during the Roman era (Dark, 2000), becoming an important grain, fibre source and medicinal. Two early herbal citations are noteworthy: the first is from the ninth century in the *Old English*

Herbarium Manuscript V, translated from Anglo-Saxon (Pollington, 2000, p. 301):

(1) For wounds take this plant which one calls ‘chamepithys’ and another name ‘hemp’, pound it and lay it onto the wound; if the wound be very deep then take the sap and wring it into the wound. (2) For pain of the innards take the same plant, give it to drink, it takes away the pain.

Subsequently, although hemp was one of many ingredients in a ‘holy salve’ described as ‘partly Irish’ in the tenth-century medico-religious text the *Lacnunga* (Grattan and Singer, 1952, p. 123), it remained for the dominant Arabic culture of the era to advance cannabis therapeutics (Lozano, 2001). Sabur ibn Sahl in ninth-century Persia described the use of a multi-herbal preparation containing the juice of cannabis tops, which was instilled into the nostrils to treat a variety of pains, including migraine, and to preserve pregnancy (Kahl, 1994; Russo, 2001b, 2002). Many Arabic writers preserved the Greek knowledge but a few, including Avicenna, Al-Biruni and Maimonides, extended the list of indications to include digestive ills, treatment of parasites, dandruff, and obstetrical and gynaecological ailments (Russo, 2002). Little notice was paid to these developments in the West, aside from the attribution of homicidal urges to hashish-crazed assassins by Marco Polo and others, which modern study later proved to be apocryphal (Aldrich, 1970). The first known government sanction on the herb occurred at the behest of King al-Zahir Baybars at the close of the thirteen century (Hamarnah, 1957), but it was singularly ineffective.

A famous treatise on agriculture penned by Abu al-Fadl Radi ad-Din al-Ghazzi al-’Amiri, who lived in Damascus between 1457 and 1529 (Hamarnah, 1957), described cannabis with considerable vitriol yet acknowledged a medical role:

It causes sudden death or madness, hectic fever, consumption, dropsy, dyspnea, trembling, fatigue, pallidity, cirrhosis of the liver and darkens the vision. It depraves the body and defiles religion. Most physicians agree that it is intoxicating, as quoted from Ibn al-Baitar’s *Jami’* and this was confirmed by ash-Shailh Abu Ishaq in his *at-Tadhkira fil-Khilaf*, and an-Nawari in *Sharh al-Muhadhdhab*. They approved small doses for medical treatment.

Meanwhile, in Europe, cannabis therapeutics began to emerge once more, but faced challenges. Hildegard von Bingen, a twelfth-century abbess, musician, visionary and herbalist, described cannabis in her *Physica* (Fankhauser, 2002). But after the Papal Bull of Innocent VIII in 1484, cannabis became associated with witchcraft and its use went

underground (de Pasquale and Costa, 1967). Rabelais resurrected it under a pseudonym in his *Gargantua et Pantagruelion* in the mid-sixteenth century (Rabelais, 1990).

Most European herbalists echoed the Classics when citing the indications for cannabis, but a few English authorities extended them (see review by Crawford, 2002): Gerard in 1597 recommended cannabis for jaundice and colic (Gerard and Johnson, 1975); Langham and Harper (1633, p. 306) observed that when properly prepared as a drink the seed was effective ‘to make thee merry, fierce, hardy to fight, and comely to see’; Culpeper noted the benefits of cannabis for inflammation of the head in 1649 (Culpeper, 1994); Salmon (1710) cited benefits for cramps and contractures; and Short (1751, p. 138) claimed benefit for enuresis or, more prosaically, ‘pissing the bed’. Even Linnaeus acknowledged an analgesic effect in his *Materia Medica* (Linné, 1772).

Garcia da Orta was perhaps the first European to explicitly describe the psychoactivity of Indian hemp in 1563 (da Orta, 1913), and eventually this knowledge spread to cognoscenti such as Robert Burton, who in 1621 acknowledged *bange* as an ecstatic agent benefiting depression (Burton, 1907). British explorers soon recognised the plant taxonomically as cannabis, but noted the distinctiveness of Indian hemp and the variability of its effects upon its users. Thomas Bowery and his sailing companions noted its ingestion and smoking in India in the late seventeenth century (Bowrey and Temple, 1905, p. 79):

And it Operates according to the thoughts of fancy of the Partie that drinketh thereof, in Such manner that if he be merry at that instant, he Shall Continue Soe with Exceedinge great laughter for the before mentioned Space of time, rather overmerry then Otherways, laughinge heartilie at Every thinge they discerne; and, on the Contrary, if it is taken in a fearfull or Melancholy posture, he Shall keep great lamentation and Seem to be in great anguish of Spirit, takeinge away all manly gestures or thought from him.

After the Napoleonic invasion of Egypt, another round of prohibition was attempted, and was again unsuccessful. French scientists took notice, but it was not until O’Shaughnessy, a physician in India who carried out work between 1838 and 1840, that Indian hemp truly came into its own in Western medicine (O’Shaughnessy, 1838–1840). O’Shaughnessy used an ethanolic extract of cannabis as the active pharmaceutical ingredient (API) and clinical trials carried out recently have reverted to the use of extracts, albeit prepared with different solvents. O’Shaughnessy listened to local lore, then effected animal studies and human trials to demonstrate the efficacy of cannabis extracts in the

frequently fatal diseases of tetanus and cholera, and in providing a more peaceful passage to inevitable demise in rabies. Soon *Cannabis indica* and extracts were exported to Great Britain and an enthusiastic bout of experimentation extended to Europe and America. This led to a rediscovery of cannabis indications, such as for migraine in England (Clendinning, 1843), neuropathic and musculoskeletal pain in Ireland (Donovan, 1845), mental illness in France (Moreau, 1845), and as an aid to parturition (Churchill, 1849), as first noted in the Ancient Middle East. This model of pragmatic research with plant medicines fell out of favour during the pharmaceutical revolution of the twentieth century, but has been revisited recently.

The existence of the historic use of a botanical in medicine provides a presumption of sufficient safety and efficacy to justify the investigation of the botanical drug. A safe and effective dose can be determined using the appropriate research methodology of the day. Investigation of active principles, a research model that fits in with modern pharmacological research and development practice, can then follow after confirmation of activity in clinical studies. This is not an absolute requirement before clinical investigation.

In nineteenth-century Europe, the *literati* seized upon the ‘new’ substance, and it is known that it contributed to the writings of Gautier, Baudelaire and Dumas, of Le Club des Hachichins in Paris. In America, Fitz Hugh Ludlow (*The Hasheesh Eater*, 1857) and Louisa May Alcott (*Passionate Play*, 1869) also exercised their literary imaginations with cannabis.

At the same time, cannabis became more firmly established in American medicine for a large variety of indications after an extensive report in Ohio (McMeens, 1860). Subsequently, the great physicians of the age supported its medicinal use. Sir John Russell Reynolds described the use of cannabis extract for more than a generation (Reynolds, 1868) for treating medical conditions ranging from insomnia to the dysmenorrhoea that affected his most famous patient, Queen Victoria. Other celebrities employing cannabis therapeutically included Silas Weir Mitchell (1874), Sydney Ringer (1886) and Sir William Gowers (1888). Many useful lessons emerged, among them the unique ability of cannabis to treat neuropathic pain, its anti-anorectic benefits, the requirement for individual dose titration, a rather disturbing difficulty with quality control and an ‘opiate-sparing’ effect.

By the end of the century, cannabis was in widespread use as a prescription medicine, and appeared in the form of solid extracts, tinctures, cigarettes for asthma, corn plasters and as an ingredient in a large array

of patent medicines (Fankhauser, 2002). It is fascinating to consider that cannabis was often combined with opium and capsicum extracts; it has been argued that this empirical experimentation and manipulation of the endogenous cannabinoid, opioid (endorphin) and vanilloid (capsaicin) systems in the nineteenth century provided better outpatient analgesia than we have at our disposal today. In each instance, these plants (*Cannabis sativa*, *Papaver somniferum*, *Capsicum annuum*) were required to elucidate the nature of analgesia and our endogenous neurotransmitter functions. Thus cannabis informed our discovery of endocannabinoids, the poppy our knowledge of endorphins and enkephalins, and the chile pepper our awareness of the endovanilloid system.

Despite its continued recommendation by physicians (Osler and McCrae, 1915; Fishbein, 1942) and scientists (Dixon, 1923), cannabis faced an onslaught of prohibitive legislation in the early twentieth century, leading to its elimination from pharmacies across the globe despite the endorsement of various commissions (see Figure 1.1). In the UK, cannabis continued to be available clinically until 1971 when it was reclassified as a Class B drug and banned under the Misuse of Drugs Act. Cannabis use became a social issue, whose 800-year-old controversy dogged it everywhere, leading to increasingly stringent international controls. Medical utility and research endeavours unfortunately thus fell by the wayside, while the focus remained solely on its abuse potential, which had rarely been a serious issue over the previous century of therapeutic application.

In 1964, tetrahydrocannabinol, or THC, the main psychoactive component of cannabis, was isolated and synthesised in Israel by Raphael Mechoulam's team (Gaoni and Mechoulam, 1964). In 1972, the National Institute on Drug Abuse (NIDA, USA) began funding studies on cannabis with the intent of demonstrating its deleterious effects. Due to this, however, many adverse event allegations were advanced, including its effects on gynaecomastia, chromosome damage, addiction and cognitive deterioration (Zimmer and Morgan, 1997; Russo *et al.*, 2002). Chronic use studies in Costa Rica, Jamaica and Greece, which were funded by the NIDA, refuted the claims, and were largely ignored (Rubin and Comitas, 1975; Stefanis *et al.*, 1977; Carter, 1980). This crisis led to opportunity, however, as important pathophysiological benefits were soon noted for cannabis as a musculoskeletal and neuropathic analgesic, as an anti-inflammatory, an immunomodulatory, an antiemetic and as an appetite stimulant for patients with AIDS (British Medical Association, 1997). Cannabis was vigorously touted for use by patients with a diverse list of intractable clinical conditions

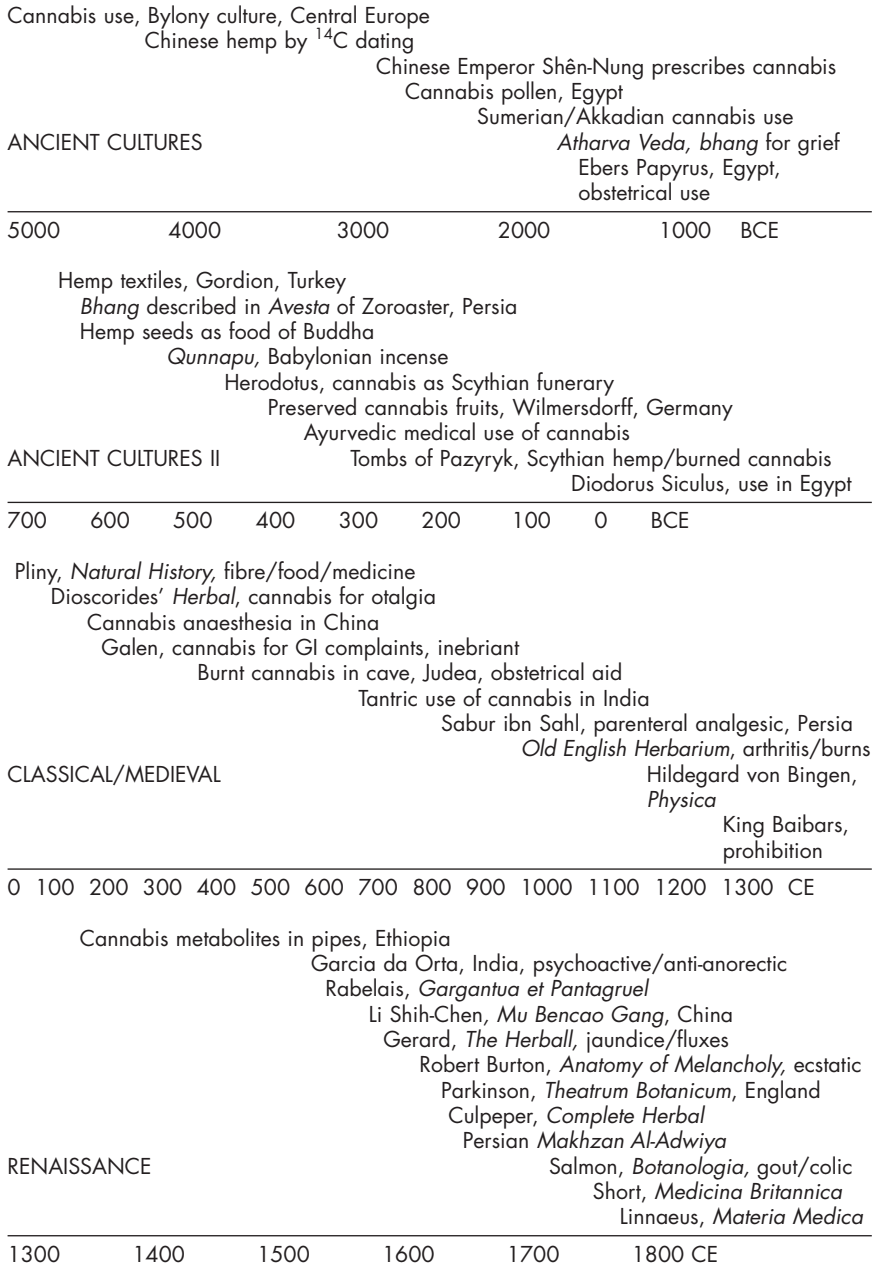


Figure 1.1 Cannabis time line by Ethan Russo, MD. Continued over page.

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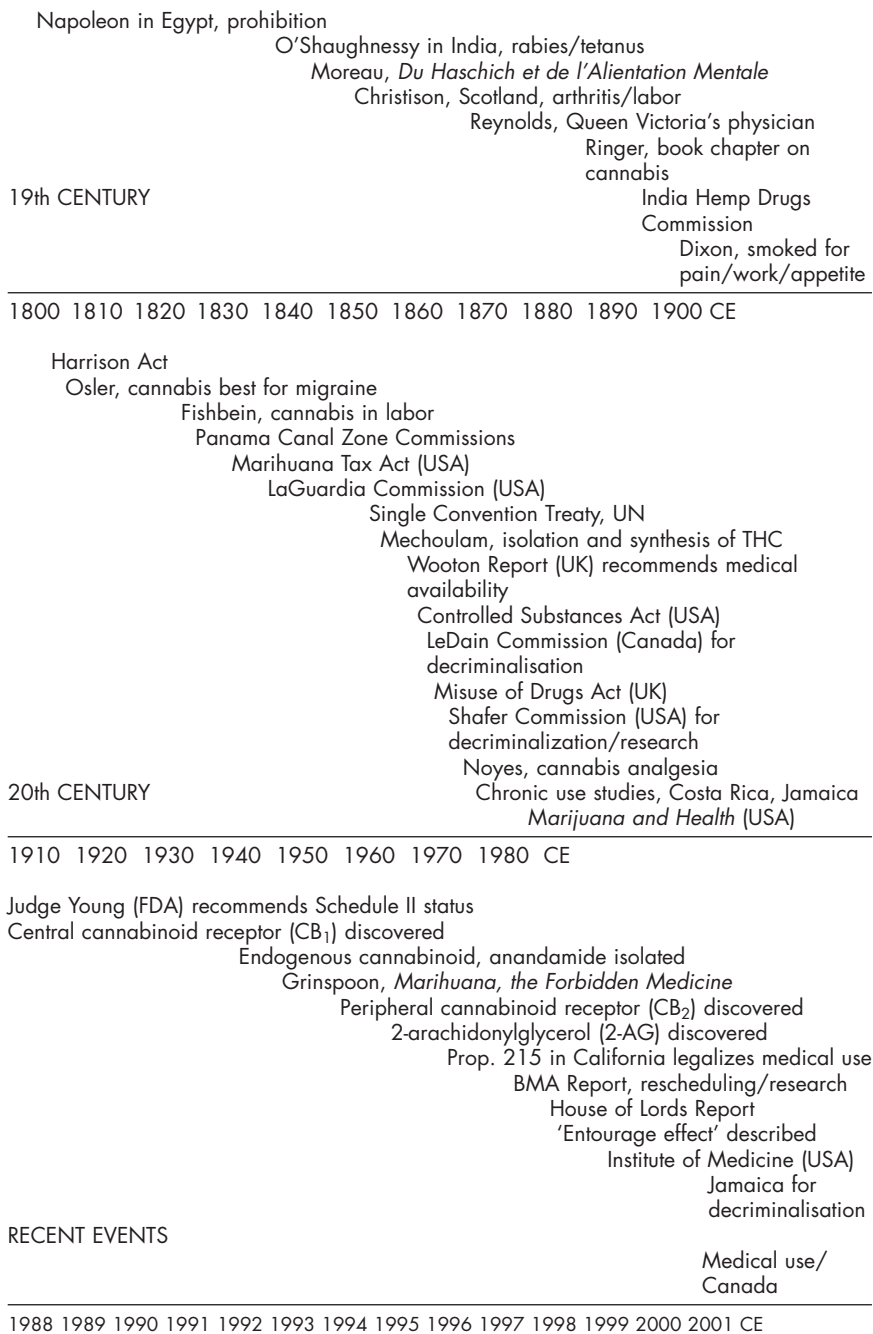


Figure 1.1 *Continued.* Cannabis time line by Ethan Russo, MD.

that were unresponsive to conventional pharmacotherapy (Grinspoon and Bakalar, 1997). At this point, however, even medical users remained subject to arrest in most societies.

In 1988, a cannabinoid receptor (CB₁) was found in the brain (Howlett *et al.*, 1988), and in 1992, anandamide (from *ananda*, Sanskrit for 'bliss'), the first central endogenous cannabinoid, was characterised (Devane *et al.*, 1992). Subsequently, a peripheral receptor (CB₂) was discovered on immune cells (Munro *et al.*, 1993), and, after 5000 years of medical usage, the biochemical basis of cannabis therapeutics became understandable at last.

Cannabis, the plant

Debate continues as to the number of cannabis species in existence. Some authorities identify three: *Cannabis sativa*, *C. indica* and *C. ruderalis* (Schultes *et al.*, 1974), while others recognise only *sativa* (Small and Cronquist, 1976) (Plate 1). The issue has recently been exhaustively revisited with support for a single heterogeneous species based on taxonomic, morphological and genetic parameters (Merzouki, 2001). For further information, see Chapter 4, where an account of the taxonomy and history of cannabis from an evolutionary perspective is given.

To date there are several facts regarding cannabis use that are clear. Cannabis originated in Central to Eastern Asia and with hops (*Humulus lupulus*) and it is a member of the Cannabaceae (or Cannabidaceae, in older taxonomic classifications) family. All strains (or 'species') cross-breed indiscriminately, which is of critical import in its husbandry, as windborne pollination from hemp strains will render a medicinal crop all but useless. Maximal potency in cannabinoid production results only when the female flowering tops remain unfertilised. This cultivation technique has been known in India for more than 2000 years, and is used to produce the product *ganja*, known in North America as *sin-semilla*, which is Spanish for 'without seed'.

Cannabis vegetative growth is optimised in bright light and long day-length, while flowering and fruiting requires a cycle of 12 hours or less exposure (Clarke, 1981) (see Chapter 2 for discussion of cannabis propagation). Medical chemovars (varieties distinguished by content of useful metabolites, rather than morphological characteristics) are produced from genetically select seeds, or preferably by clonal propagation with adequate legroom. Ultraviolet exposure and perhaps altitude favour THC production (Pate, 1994). Selective breeding provides the

capability to cultivate clones favouring production of single specific cannabinoids, whether they are THC, cannabidiol (CBD) or tetrahydrocannabivarin (THCV) (Whittle *et al.*, 2001). These C21 or C22 compounds, including carboxylic acid precursors, are unique to the species and bind to endocannabinoid receptors much as the endogenous compound anandamide (Pertwee and Ross, 2002).

Cannabinoid concentration is not uniform throughout the plant biomass; cannabinoids are present in the leaves but are most abundant in the unfertilised flower head, the bracts and, to a lesser extent, in glandular trichomes on the leaves that store resin. The head of the glandular trichome is a cellulose envelope containing resin; when harvested and compacted this constitutes 'hash'. Fibre strains of hemp are best cultivated in dense stands, favouring them over weeds, and allowing development of long strands of cellulose. In both cannabis fibre and seed strains, THC production is low to negligible, while CBD production is maximised. Hemp as a textile was extremely popular in previous ages until the era of synthetics and is currently staging a comeback. So, too, is the hemp seed industry, on account of its product's yield of high protein and essential fatty acids (EFAs), linoleic (LA), linolenic (LNA) and the pharmaceutically important gamma-linolenic acid (GLA) (Wirtshafter, 1997; Pate, 1999).

The terpenophenolic cannabinoids have been assigned a variety of numbering systems, thus THC may appear in the literature as Δ^1 -THC (the monoterpene system, favoured in Europe), or Δ^9 -THC (the dibenzopyran system, preferred in North America). These systems have arisen due to the fact that the open ring in the cannabinol series gives rise to different numbers for substituents than the dibenzopyran system (see Chapter 8, Figure 8.1). Medically important effects of cannabis are also attributable to its terpenoid essential oil content with possible contributions from its flavonoid and phytosterol components (McPartland and Russo, 2001). This raises a critical issue: there is increasing evidence that the biological effects of cannabis are not produced by THC alone, but rather, that the herbal synergy of the whole cannabis extract yields pharmacological results greater than the sum of its parts. This barrage of phytocannabinoids is directly analogous to the orchestrated effects of the various endocannabinoids and their 'inactive' precursors in endogenous systems, dubbed the 'entourage effect' (Mechoulam and Ben-Shabat, 1999). Seemingly, humans and cannabis have coevolved for thousands of years and the neurochemical and psychopharmacological interactions that have developed provide fascinating possibilities for further investigation.

Cannabis research has been confounded by various scientific and political challenges. Vernacular cannabis in the USA is THC rich, but virtually lacking in CBD (Gieringer, 1999). The cannabis produced by the NIDA, the sole legal research supplier in the USA, is not assayed for CBD (Russo *et al.*, 2002), and this low potency product does not represent the pinnacle of therapeutic possibilities for phytotherapy. In Europe, in contrast, a reliance on North African and Middle Eastern strains (referred to collectively as ‘Moroccan’ cannabis) provides chemovars that are richer in CBD, yielding heterogeneous medicinal effects. CBD modulates the ‘high’ of THC, inhibits its hepatic metabolism to the more psychoactive 11-OH-THC, and provides its own anti-inflammatory, antianxiety, antipsychotic and anticonvulsant benefits (McPartland and Russo, 2001). New possibilities attend investigation of South African and South-East Asian cannabis strains with their rich endowment in THCV. These strains are purported to produce analgesic effects with a shorter half-life and have less hangover effects than THC. The weight of the current evidence supports the concept that cannabis will meet its full therapeutic potential as a botanical product rather than as a single new chemical entity (NCE).

Effects of legislation on research

Cannabis has been regulated by a variety of national and international treaties and laws including the Marihuana Tax Act (USA, 1937), the Single Convention Treaty (United Nations, 1961), the Misuse of Drugs Act (UK, 1971) and the Controlled Substances Act (USA, 1970). These have inhibited cannabis research and therapeutics (Abrams, 1998; Russo *et al.*, 2002), and are in striking contradistinction to the recommendations of various commissions studying the issue (see Figure 1.1). In essence, cannabis is identified internationally as an addictive and dangerous drug with no therapeutic utility. The way that legislation has extensively shaped attitudes to the use of cannabis in modern medicine, and the generation of evidence that would allow a reappraisal of utility, are dealt with in Chapter 13. Legislation trumps science, *pro tem*, but research that scientifically supports the use of therapeutic cannabis-derived medicines may change the law eventually.

In the USA in particular, the NIDA has conducted research solely designed to demonstrate the deleterious effects of cannabis, while barely allowing the study of potential benefits. Thus, natural THC in cannabis

is a Schedule I substance provoking incarceration, while the identical compound, synthetically manufactured and placed in a sesame oil capsule licensed as Marinol ('dronabinol'), can be prescribed legally and was downgraded to Schedule III in 1999.

Fortunately for the therapeutic potential of medicines derived from cannabis, both for treating diseases where current treatments are not satisfactory and for diseases with unmet clinical needs, challenges are being raised to these concepts and are beginning to appear in Europe. Encouraged by progress by the British Medical Association (1997) and the House of Lords Select Committee on Science and Technology (2001) and with support from Home Office licensing and the Medical Control Agency, clinical studies of cannabis by the Royal Pharmaceutical Society and GW Pharmaceuticals have been initiated (Whittle *et al.*, 2001). These studies will investigate with modern methods the considerable anecdotal evidence supporting the popular usage of clinical cannabis (Grinspoon and Bakalar, 1997; Gieringer, 2001).

Once more, contrasts are evident. In the UK, thanks largely to the indefatigable Clare Hodges, who has campaigned for and highlighted the need for cannabis to be medically available for patients with multiple sclerosis, the treatment of pain and spasm in multiple sclerosis is the lead indication for clinical cannabis investigation. In the USA, in contrast, interest in AIDS (Russo, 2001a) and cancer chemotherapy (Musty and Rossi, 2001) are paramount.

What seems evident is that cannabis is addressing the unmet clinical aims for many patients with intractable clinical problems, whether neuropathic, musculoskeletal and cancer-associated pain, arthritis, head injury, stroke, migraine, asthma, nausea, epilepsy, glaucoma or long-neglected areas of obstetrics and gynaecology (Russo, 2002). The knowledge that cannabinoid effects are integral to our human physiology and are tonically active in the nervous system makes further clinical research essential, and it would be short-sighted to ignore the essence of our own being. The disadvantages must coexist with the advantages. Acute THC intoxication may impair short-term memory, but forgetting is as essential to mental function as remembering (Hampson and Deadwyler, 2000) in order to avoid the chaos of a mind lost in tumultuous disorder. This medical research is not the attack of 'legalisers' or 'cannabis carpetbaggers', but is motivated by the highest ideals of medicine: those of providing relief and longer life to those in pain and suffering. This becomes increasingly possible with cannabis, which is a source of food, fibre, fuel and pharmaceuticals, and could be said to be Nature's most versatile botanical treasure.

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