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MDT

Cannabinoids as Therapeutics

Edited by R. Mechoulam

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Preface

Twenty years ago the endocannabinoid system was unknown. We knew much about the use over millennia of *Cannabis* plant preparations both as a medicine and as "a drug that takes away the mind" (as so-well stated in ancient Assyrian clay tablets). During the early part of the last century considerable progress was made on the chemistry and pharmacology of *Cannabis*, but it was only after the identification in 1964 of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the active constituent of the plant that this field caught the interest of many research groups and hundreds of papers on the chemistry, biochemistry, metabolism and clinical effects of this compound were published. However, its mechanism of action remained unknown for nearly two decades. In the mid-1980s the presence of a cannabinoid receptor in the brain was identified and shortly thereafter it was cloned. This was followed by the isolation of the major endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol, and the clarification of their biosyntheses and degradations. These advances led to an avalanche of publications in a wide variety of fields. We are now in the midst of major advances in biochemistry/physiology associated with the actions of the endocannabinoids.

This short volume tries to present an up-to-date picture in some of the major fields of endocannabinoid research. The first chapter in this book, on the use of *Cannabis* in India, can be viewed as an expression of thanks to the herbal practitioners, who for centuries passed on the medical traditions associated with the drug. The chemistry chapter is a short summary of active plant, synthetic and endogenous cannabinoids being investigated today, many of which are mentioned later in the book. Cannabidiol is an unusual cannabinoid – it does not bind to the known receptors and yet exerts a variety of effects. Hence a chapter is devoted to it. Most of the remaining chapters deal with the endocannabinoid system and the endocannabinoids in a variety of conditions and physiological systems. A chapter describes the research done on Sativex®, a standardized plant extract, shortly to be introduced in Canada as a drug for multiple sclerosis symptoms.

Numerous fields known to be affected by cannabinoids were not reviewed. The vast expanse of emotions is one of them. Most marijuana users smoke the drug in order to 'get high'. But we know very little about the mechanisms through which cannabis affects emotions. Under certain circumstances Δ^9-THC causes aggression, although usually it leads to sedation. Anxiety is another emotional aspect affected by cannabinoids. Although a short chapter is devoted to the calming of anxiety by cannabinoids it does not attempt to present a mechanistic picture. And we know next to nothing on the chemistry link-

ing endocannabinoids with stress, fear, love, satisfaction or despair. Are the endocannabinoids one of nature's tools to shape emotions? This is probably one of the fields which will be explored in the future. But books review the past. Possibly the next edition of this book, in 5 or 10 years time, will report on the progress made in associating endocannabinoids with emotions. Until then we shall have to remain content with more mundane topics such as neuroprotection, reproduction, appetite and effects on cancer.

The multitude of endocannabinoid effects seems like a fertile field for exploration by pharmaceutical firms. We soon expect to see the introduction of a synthetic cannabinoid antagonist in the treatment of obesity and, possibly later, drugs for neuroprotection, pain, multiple sclerosis, rheumatoid arthritis and cancer. Will post-traumatic stress disorder, schizophrenia and Tourette's syndrome come next?

Raphael Mechoulam Jerusalem, January 2005

Cannabinoids as Therapeutics
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Cannabis in India: ancient lore and modern medicine

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Introduction: Ayurvedic medicine

India is a land steeped in faith and mysticism. *Ayurveda*, combining the Sanskrit words for life and knowledge, is a system of medicine intertwined inextricably with these traits. That a core of belief combined with empirical experimentation could produce a viable medical regimen still widely practiced after well over 3000 years is astounding to Western physicians. Cannabis was similarly bound to faith and mysticism in India in the past, in the Hindu and Islamic traditions, as well as in numerous other minority religions [1]. Merlin recently explained it well [2], "with the powerful tools of modern science and human imagination, our understanding of our deep-rooted desire to experience *ecstasy* in the original sense of the word (to break the mind free from the body and communicate with the 'gods' or the ancestors) will become clear with time". This chapter will seek to examine the medical claims for cannabis of the past, and place them in a contemporary light given current pharmacological knowledge.

Ayurveda is based on a conceptual medical system that seeks to balance three functional elements, called *doshas*, that the human body is composed of, and are commonly represented as *Vata* or *Vayu* (ether or air), *Pitta* (fire and water) and *Kapha* (phlegm or water and earth). Nadkarni [3] has rejected these simple relationships in favor of more abstract assignations [3]:

> "…the word *Vayu*, does not imply 'Wind' in Ayurvedic literature, but comprehends all the phenomena which come under the functions of the Central and Sympathetic Nervous Systems; that the word *Pitta* does not essentially mean 'Bile' but signifies the functions of Thermogenesis or heat production and metabolism, comprehending in its scope the process of digestion, coloration of blood and formation of various secretions and excretions and that the word *Kapha* does not mean 'Phlegm' but is used primarily to imply the functions of Thermo-taxis or heat regulation and secondarily formation of the various preservative fluids, e.g., Mucus, Synovia, etc., …"

Good health in Ayurveda is dependent upon attaining an equilibrium state of these factors. Disease is due to an imbalance or disharmony of the Tridosha system as the results of some cause, internal or external. A disease of prolonged extent will overflow its site of origin and spread through the body. Therapy is effected by a combination of religious, magical and prescriptive regimens, herbal therapy being an important element of the latter.

According to Kapoor [4], the *materia medica* of India comprises in excess of 2000 drugs, mostly of vegetal origin, with 700 medicinal plants known even during Buddhist times, *c*.250 BCE. Cannabis remains important among them.

Cannabis: its history in the medicine of India

Cannabis sativa seems to have diffused from a geographic point in Central Asia, according to classical plant explorers [5–8] and more modern authorities [9–11]. Sharma [12] felt its origin was in the Himalayan foothills, but offered little documentation. This botanical sleuthing has been supported by physical evidence of cannabis flowers and seeds associated with *haoma-soma* religious rites in ancient Bactrian sites in excavations by Sarianidi [13, 14] in Margiana (present day Turkmenistan), dating to the second millennium BCE. Philological support derives from the term *bhanga*, also seemingly originating among the Central Asian Arya peoples [15].

The *Zend-Avesta*, the holy book of Zoroastrianism, which survives in fragments, dating from around 600 BCE in Persia, alludes to the use of *Banga* in a medical context, identified as hemp [16]. Of this use, Bouquet stated [10]: "It is solely to its inebriating properties that hemp owes the signal honour of being sung in the *Vedas*, and it was probably the peoples of Northern Iran who discovered those properties, for they were already using the leaves (*Cheng*) and the resin (*Cers*) as inebriants before the Hindus." Mahdihassan [17] has attempted to draw a philological link between the *Ho-Ma* of the Chinese, the *Hao-Ma* of the *Avesta* and the *So-Ma* of Sanskrit, felt cognate to cannabis.

The earliest written reference to cannabis in India may occur in the *Atharvaveda*, dating to about 1500 BCE [18]: "We tell of the five kingdoms of herbs headed by Soma; may it, and *kusa* grass, and bhanga and barley, and the herb *saha*, release us from anxiety." Grierson [18] suggested this to be part of an offering, and ingestion or burning would both be typical of ancient practices for this purpose.

In the *Sushruta Samhita* (meaning the verses of Sushruta), perhaps dating from the third to the eighth centuries BCE, cannabis was recommended for phlegm, catarrh and diarrhea [18]. As noted, an anti-phlegmatic would be interpreted in Ayurvedic medicine as possessing a wide variety of effects. Similarly, Dwarakanath [19] has maintained that cannabis was employed in Indian folk medicine in aphrodisiacs and treatments for pain in the same era [19], while Sanyal observed [20] that "They also used the fumes of burning Indian Hemp (Canabis Indica) [*sic*] as an anaesthetic from ancient times…".

Watt [21] felt that by this early date the sexual dimorphism of cannabis was already evident to its cultivators, as well as the superiority of bhanga (mistakenly assigned as female) for cordage, and *bhang* (mistaken as male) for medical and mystical application. It was also likely about this time that the preparation of *ganja* (labeled *sinsemilla* in contemporary North America) was developed by isolating female cannabis plants to prevent fertilization, and increase resin production.

Aldrich [22] documented the development of tantric cannabis usage around the seventh century as a mingling of Shaivite Hinduism and Tibetan Buddhism. Apparently, the 11th century text, *Mahanirvana Tantra*, is currently still consulted with regard to sexual practices, withholding of male ejaculation and promotion of sexual pleasure in both genders.

An anonymous work, *Anandakanda*, added some 43 Sanskrit cannabis synonyms (Tab. 1) [23], many attesting the remarkable rejuvenating effects of cannabis. Dash [23] described the lengthy methods of cultivation, processing and mixing of cannabis with eight other medicinal plants, that when combined with personal isolation and celibacy for 3 years produce a result in which "it is claimed that the man lives for 300 years free from any disease and signs of old age". He dated this work to the 10th century, while Rao [24] placed it in the range of the 9th to the 12th centuries, and noted some 10 known manuscripts.

There is philological debate among Sanskrit scholars as to whether the identification of bhanga as cannabis can be authenticated before the year 1000 [25, 26]. Wujastyk [26] and Meulenbeld [25] dated the *Anandakanda*, or Root of Bliss, to *c*.1200, also noting its full accounting of cannabis' side effects. Their candidate for the first uncontested source for cannabis is the *Cikitsasarasangraha* of the Bengal author Vangasena, in the late 11th century, who included bhanga as an appetizer and digestive, noting it as "a drug like opium whose mode of action is to pervade the whole body before being absorbed and digested" [26]. It was also suggested in two recipes for a long and happy life. A contemporary work, the *Dhanvantariyanighantu*, observed a narcotic effect [26].

In the 12th–13th centuries from Gujarat, Nagarjuna's *Yogaratnamala* (The Garland of Jewels of Yoga), suggested cannabis smoke as a method by which to produce an impression of spirit possession in one's enemies [26].

The *Rajanighantu* of the 13th century added additional synonyms (Tab. 1), with attributed activities characterized as [18] (1) *katutva* (acridity), (2) *kashayatva* (astringency), (3) *ushnatva* (heat), (4) *tiktatva* (pungency), (5) *vatakaphapahatva* (removing wind and phlegm), (6) *samgrdhitva* (astringency), (7) *vakpradatva* (speech giving), (8) *balyatva* (strength-giving), (9) *medhakaritva* (inspiring of mental power) and (10) *sreshthadipanatva* (the property of a most excellent excitant).

According to interpretation of this source [27], "Its effects on man are described as excitant, heating, astringent; it destroys phlegm, expels flatulence, induces costiveness, sharpens the memory, excites appetite, etc."

Table 1. Indian names for cannabis in Sanskrit and Hindi

Indian name	Meaning
ajaya	the unconquered, invincible
ananda	the joyful, joyous, laughter moving, bliss
bahuvadini	causing excessive garrulousness
bhang, *bhanga*	hemp, mature cannabis leaves
bhangini	breaks three kinds of misery
bharita	the green one
capala	agile, capricious, mischievous, scatter-brained
capta	light-hearted
chapala	the light-hearted, causer of reeling gait, causer of vacillation
charas	cannabis resin (*hashish*), either hand-rubbed or sifted
cidalhada	gives happiness to mind
divyaka	gives pleasure, lustre, intoxication, beauty
dnayana vardhani	knowledge promoter
ganja	unfertilized female cannabis flowers
ganjakini	the noisy, vibrator
gatra-bhanga	body disintegrator
harshani	joy-giver
harshini	the exciter of sexual desire, the rejoicer, delight-giver, causer of elation
hursini	the exciter of sexual desire
Indrasana	Indra's food
jaya	victorious, the conquering
kalaghni	helps to overcome death
madhudrava	helps excrete nectar
madini	the intoxicator, sex intoxicator
manonmana	accomplishes the objects of the mind
matulani	wife of the datura
matkunari	an enemy of bugs
mohini	fascinating
pasupasavinaini	liberates creatures from earthly bonds
ranjika	causer of excitement
sakrasana	the worthy food of Indra
samvida manjari	flower causes garrulousness
sana	cannabis
sarvarogaghni	which cures all diseases
sawi	green leaved
Shivbooty	Shiva's plant
siddha	which has attained spiritual perfection
sidhamuli	on whose root is *siddha*
siddhapatri	vessel of highest attainment
siddhi	success giver
siddhidi	which endows *siddhi* on others
sidhdi	emancipation, beatitude, fruit of worship
suknidhan	fountain of pleasures
tandrakrit	causer of drowsiness
trailokya vijaya	victorious in the three worlds, conqueror of the three regions of the universe
trilok kamaya	desired in the three worlds
ununda	the laughter mover
urjaya	promoter of success
vijaya	victorious, promoter of success, all-conquering
vijpatta	the strong leaved
virapattra	leaf of heroes
vrijapata	strong nerved

About the same time, in the *Sharangadhara Samhita*, fresh extracts of bhang were employed medicinally [19], and it was linked to opium: "Drugs which act very quickly in the body first by spreading all over and undergoing change later are vyavayi; for example, bhanga, ahiphena" [28]. Additionally, cannabis was cited as an intoxicant and employed as the primary ingredient in a therapeutic mixture of herbs: "This recipe known as *jatiphaladi churna* if taken in doses of one karpa, with honey, relieves quickly grahani (sprue [chronic diarrhea]), kasa (cough), swasa (dyspnoea), aruchi (anorexia), kshaya (consumption) and pratishyaya [nasal congestion] due to vata kapha (rhinitis)" [28]. Inter-relationships of Tantra and Ayurveda in this work were explored by Sharma [29].

The 15th-century *Rajavallabha*, written by Sutradhar Mandan for Rana Kumhha of Mewar, attributed several additional qualities to cannabis [18]:

> "Indra's food (i.e., *ganja*) is acid, produces infatuation, and destroys leprosy. It creates vital energy, the mental powers and internal heat, corrects irregularities of the phlegmatic humour, and is an *elixir vitae.* It was originally produced, like nectar from the ocean by the churning with Mount Mandara, and inasmuch as it gives victory in the three worlds, it, the delight of the king of the gods, is called *vijaya*, the victorious. This desire-fulfilling drug was obtained by men on the earth, through desire for the welfare of all people. To those who regularly use it, it begets joy and destroys every anxiety."

Dymock added [27], "The Rahbulubha alludes to the use of hemp in gonorrhoea."

According to Chopra and Chopra [30], "In *Dhurtasamagama* (A.D. 1500), ganja is described as a soporific which 'corrects derangements of humours and produces a healthy appetite, sharpens the wit and act as an aphrodisiac'." In the *Ayurveda Saukhyam* of Todarananda [31] it was said of cannabis that "It causes unconsciousness, intoxication and talkativeness".

During the Renaissance European awareness of the psychoactivity of cannabis was kindled with the writings of Garcia da Orta, a Spanish Jew, who in the service of Portugal visited India in 1563. In addition to his descriptions of the plant as *bangue*, and a good illustration, he noted important medical properties [32], "The profit from its use is for the man to be beside himself, and to be raised above all cares and anxieties, and it makes some break into a foolish laugh." In another passage, stimulation of energy and appetite was noted: "Those of my servants who took it, unknown to me, said that it made them so as not to feel work, to be very happy, and to have a craving for food."

Soon thereafter, it was observed [30], "In *Bhavaprakash* (A.D. 1600), cannabis is mentioned as 'anti-phlegmatic, pungent, astringent and digestive'. On account of these marked narcotic properties it was probably also used as an anaesthetic, sometimes combined with alcohol, by the ancient Indian and Chinese surgeons."

The 18th century Persian medical text *Makhzan-al-Adwiya*, written by M. Husain Khan, was extremely influential in the *Unani Tibbi*, or Arabic-tradition medicine on the subcontinent. In it, cannabis was described in its various preparations as an intoxicant, stimulant and sedative, but also the following [33]:

> "The leaves make a good snuff for deterging the brain; the juice of the leaves applied to the head as a wash, removes dandriff [sic] and vermin; drops of the juice thrown into the ear allay pain and destroy worms or insects. It checks diarrhea, is useful in gonorrhea, restrains seminal secretions, and is diuretic. The bark has a similar effect.
>
> The powder is recommended as an external application to fresh wounds and sores, and for causing granulations; a poultice of the boiled root and leaves for discussing inflammations, and cure of erysipelas, and for allaying neuralgic pains."

Ali Gorji (personal communication, 2004) has recently consulted this work and added that it was helpful for stomach problems, nausea and uterine inflammation. Campbell [1], translated additional Persian names from this source: "Bhang is the Joy-giver, the Sky-flier, the Heavenly-guide, the Poor Man's Heaven, the Soother of Grief". Dymock and co-authors added a few more synonyms [34]: "the inebriating leaf", "fakir's grass", "the green tent" and "the throne giver". Chopra and Chopra [30] rendered another passage from the *Makhzan* as follows: "It is said that bhang is one of the best of God's gifts, it is a cordial, a bile absorber, and an appetizer, and its moderate use prolongs life. It quickens the fancy, deepens thought and sharpens judgment."

A nexus with Western medicine

The medical use of so-called Indian hemp was reintroduced to the West in the 19th century. In 1813, Ainslie [35] cited the use of *ganjah* and *bangie* as intoxicants, but also to treat diarrhea, and in a local application for hemorrhoids. In 1839, the seminal work of Sir William B. O'Shaughnessy on cannabis was written [36], then republished in England in 1843 [33]. His contribution was a model of modern investigation, involving a review of classical Sanskrit and Unani sources, a description of cannabis preparations including bhang (mature cannabis leaves), ganja (unfertilized female flowers), and *charas* (processed cannabis resin), an examination of contemporary Indian ethnobotanical uses and experiments of cannabis extracts in dogs, finally culminating with a series of human clinical trials with appropriate cautious dose titration. His treatise on the subject demonstrated the apparent clinical utility of cannabis in a wide range of disorders including cholera, rheumatic diseases, delirium tremens and infantile convulsions. For the first time miraculous recoveries were evidenced in a series of tetanus victims due to cannabis. Noting the anti-spasmodic and muscle-relaxant effects, it was tried in rabies, where [33] "the influence of a

narcotic, capable either of cheering or of inducing harmless insensibility, would be fraught with blessing to the wretched patient". Although no cure was forthcoming, the patient was visibly relieved of distress, and able to take some sustenance through his suffering. Its palliative benefit was not lost upon the physician, "the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases". Summing up his experience with cannabis, O'Shaughnessy concluded that "in hemp the profession has gained an anti-convulsive remedy of the greatest value".

A series of other practitioners both in India and in Great Britain soon noted success in extending the use of cannabis to treatment of migraine, and neuropathic and other pain conditions [37, 38]. Few clinical syndromes seemed unassailable: another Western physician in India observed the alleviation not only of an alcohol hangover with accompanying headache, but the patient's cholera as well [39]. Churchill employed cannabis to treat excessive uterine bleeding [40], and Christison applied it to childbirth [41] (reviewed in [42]).

In little more than a decade, a section on cannabis was deemed worthy of inclusion in Johnston's *The Chemistry of Common Life*, wherein the topic was treated at length [43]: "In India it is spoken of as the increaser of pleasure, the exciter of desire, the cementer of friendship, the laughter-mover, and the causer of the reeling gait, – all epithets indicative of its peculiar effects." About the same time, medical usage became common in North America [44].

In 1870, Dutt provided information on certain bhang preparations [45], "Numerous confections of *bhang* such a *Kamesvara modaka*, *Madana modaka*, *Balyasakrasana modaka*…are considered aphrodisiacs and are used in chronic bowel complaints, and nervous debility." A recipe for *Madana modaka* was then supplied, containing numerous herbs, but with "hemp leaves with flowers and seeds fried in clarified butter, equal in weight to all the other ingredients", which was "used in cough, chronic bowels complaints and impotence".

In 1877, Kerr submitted an extremely detailed report from Bengal encompassing history, religious context, cultivation and employment of cannabis in all its preparations [46]. This would form one source for the subsequent *Report of the Indian Hemp Drugs Commission* [47]. Documentation of ganja production, necessitating culling of male plants by the "ganja doctor" to prevent fertilization and increase resin production, was emphasized. Despite some apparent value judgments expressed, the author observed, "I am of opinion, however, that no moral gain whatever will be effected by the total suppression of ganja."

Watt noted that cannabis was [21] "valuable as a remedy for sick headache, and especially in preventing such attacks. It removes the nervous effects of a malady." Watt listed numerous contemporary European physicians on the subcontinent and their successes in treating a large variety of disorders with cannabis preparations. Dymock was one such [34]: "I have given the extract in doses of from ½ to 1 grain to a large number of European hospital patients suf-

fering from chronic rheumatism; it entirely relieved the pains and made them excessively talkative and jolly, complaining that they could not get enough to eat." Dymock also appreciated popular Indian descriptions of the time [34]: "When the *ganja* pipe begins to smoke all cares at once disappear" and "Smoke *ganja* and increase your knowledge".

Cannabis in its various forms remained the focus of intense scrutiny, and continued to harbor critics. Because of concerns of its moral dangers, the British and colonial authorities in India organized a commission to examine all aspects of the issue [47]. Its findings exceeded 3000 pages after exhaustive investigation and testimony, and may be summarized as follows [48]. (1) Moderate use of cannabis drugs had no appreciable physical effects on the body. As with all drugs, excessive use could weaken the body and render it more susceptible to diseases. Such circumstances were not peculiar to cannabis, however. (2) Moderate use of cannabis drugs had no adverse effect on the brain, except possibly for individuals predisposed to act abnormally. Excessive use, on the other hand, could lead to mental instability and ultimately to insanity in individuals predisposed by heredity to mental disorders. (3) Moderate use of cannabis drugs had no adverse influence on morality. Excessive usage, however, could result in moral degradation. Although in certain rare cases cannabis intoxication could result in violence, such cases were few and far between.

The commission advocated against governmental suppression of cannabis drugs. Many positive statements accompanied descriptions of their religious associations, and particularly their legion medical usage, both human and veterinary [1]:

> "It is interesting, however, to note that while the drugs appear now to be frequently used for precisely the same purposes and in the same manner as was recommended centuries ago, many uses of these drugs by native doctors are in accord with their application in modern European therapeutics. *Cannabis indica* must be looked upon as one of the most important drugs of Indian Materia Medica."

Particular attention remained focused on possible mental health sequelae of cannabis despite the lack of such findings from the Commission. In the conclusions of Mills [49]:

> "Indians used hemp narcotics for a variety of reasons and it is entirely possible that its use at certain times disagreed with certain individuals to the extent that they became muddled or even murderous. Yet the few of those that did become muddled or murderous and that were snared in the net of the colonial state came to be taken as representative of all those in India that used cannabis preparations. From this, colonial government developed an image of all Indian users of hemp narcotics as dangerous, lunatic and potentially violent."

Occasionally, colonial officials were enlightened enough to free themselves from ethnocentric chauvinism. One Captain R. Huddleston, a Deputy Commissioner in the Akola District, wrote in 1872 [50], "Therefore I should not condemn these compounds [cannabis preparations] as being directly connected with crime; that is to say, they are no more the cause of offence than is the bazar liquor with which the Banjara is so often primed when he does highway robbery, or the beer and gin guzzled by the British rough before he beats his wife and assaults a policeman." Modern epidemiological investigation refutes the etiological relationship of cannabis to violence and insanity [51], but the debate continues.

In 1897, cannabis retained a key indication [52], "The treatment of Tetanus by smoking gunjah…promises to supercede all other in India." Waring [52] went on to describe its effective application at the onset of spasms, and titration to patient requirements so long as was needed. In a previous source [53], smoking every few hours was recommended for the duration of need, which in four subjects ranged from 7 days to 1½ months. Lucas [54] introduced the concept of smoking cannabis for tetanus to the British medical press in 1880.

Meanwhile, cannabis spread to other British colonies with the Indian diaspora. Emigrants brought the herb along with them as a work accessory or medicine. In South Africa they adopted the local name *dagga* [55], whereas in Jamaica the Indian name, ganja, has been pre-eminent since the 19th century [56, 57], and its tonic effects are part of national medical lore today [57].

Politics and cannabis collide

At the dawn of the 20th century, cannabis suffered further downturns. In 1914 it was dropped from the pharmacopoeia of Ceylon (now Sri Lanka), over the vociferous objections of its adherents, such as Ratnam [58], whose points of debate included passionate defenses of its medical benefits and poignant political arguments comparing its benign nature to the relative dangers of other popular recreational agents, alcohol in particular. The status of cannabis was compounded by increasingly severe quality-control problems with material exported from India to the UK [59]. These two factors, political and pharmacological, were paramount in the decline of cannabis medicines in the West.

Cannabis use remained common in 20th-century India, however. It was noted [60]:

> "Labourers who have to do hard physical work use hemp drugs in small quantities to alleviate the sense of fatigue, depression and sometimes hunger. … This produces a sense of well-being, relieves fatigue, stimulates the appetite, and induces a feeling of mild stimulation which enables the worker to bear the strain and perhaps the monotony of this daily routine of life more cheerfully."

Similarly, by 1954, cannabis remained integral in Indian faith, as one Brahmin explained to a Western writer [61], "'It gives good *bhakti*', …the sort of devotional act which consists in emptying the mind of all worldly distractions and thinking only of God."

As late as 1957, two authorities in India noted [30], "Cannabis undoubtedly has remarkable therapeutic properties. …the drug has no constipating action, it does not depress the respiratory centre; and there is little or no liability to addiction formation." They went on to describe the usage in veterinary medicine for diarrhea in livestock, treating parasites, "footsore disease, increasing milk-flow in cows, and pacifying them, but also it is often administered to bullocks as a tonic, to relieve fatigue and to impart additional staying power." As a human household remedy, "A mild beverage made from bhang leaves is believed to sharpen the appetite and help the digestion." Religious mendicants were said to employ it for gastrointestinal and rheumatic afflictions during their peregrinations. Continued attestations were claimed for dysmenorrhea, gonorrhea, dysuria, asthma and spasmodic conditions. A fresh leaf poultice was said to reduce eye pain and conjunctivitis, swollen joints and local inflammations, while a piece of charas placed in dental caries was said to alleviate toothache. They noted, "Much of the sanctity attached to bhang is put down to its supposed properties 'clearing the head and stimulating the brain to think'." Finally, contributions to sexual performance were still claimed, as cannabis preparations "are frequently used by both young and middle-aged individuals for stimulating sexual desire and prolonging the sexual act".

Usage in Unani medicine at this time included treatment of insomnia, migraine, neuralgic pains, asthma, spasmodic conditions and previously noted gynecological conditions [30]. A continued contribution to Islamic mysticism was also noted as cannabis use "frees them from worldly bonds, and induces communion with the divine spirit".

In another book about medicinal plants of India [62], the author stated:

> "Charas…is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, migraine, acute mania, whooping cough, cough of phthisis, asthma, anaemia of brain, nervous vomiting, tetanus, convulsion, insanity, delirium, dysuria, and nervous exhaustion; it is also used as an anaesthetic in dysmenorrhea, as an appetizer and aphrodisiac, as an anodyne in itching of eczema, neuralgia, severe pains of various kinds of corns, etc."

Indian charas of good quality is said to have a resin content of about 35–45% [63], which according to the calculations of Clarke [64], might yield a theoretical tetrahydrocannabinol (THC) content of up to 30%. Higher concentrations have been achieved with modern techniques.

Nadkarni [3] observed of cannabis, "All parts of the plant are intoxicating (narcotic), stomachic, antispasmodic, analgesic (anodyne), stimulating, aphrodisiac and sedative."

In 1977, Sharma observed [65] that "even today [cannabis] is used with restraint and judgment by students of Indian medicine. There are reports claiming the value of cannabis in the treatment of high blood pressure, migraine headaches, and even cancer."

In a modern review of Indian uses of cannabis, it was observed [66] that "Cannabis was used medicinally for almost all the ills flesh is heir to". Cannabis remained a key ingredient in two aphrodisiacal preparations, *Madana modaka* and *Kamesvara modaka* [67].

In a treatise entitled *Indigenous Drugs of India* [68] the authors noted the requirement of dose titration due to increasingly inconsistent cannabis preparations. This drawback was addressed in a prior study [69] in which the authors extracted local ganja to produce a 17% THC yield, which at intraperitoneal doses of 75 mg/kg in rats resulted in a potentiation of sub-analgesic doses of morphine.

In 1988 [70] cannabis was still mentioned as a remedy for malaria and blood poisoning, among many other indications. In neighboring Nepal, cannabis retains ethnobotanical applications among some 15 ethnic groups [71], for diarrhea, dysentery, local wound treatment and in veterinary medicine. In discussing the native use of cannabis and opium products by village doctors in India, who provided 80% of the population with their medical care in a report to the United Nations, the author felt that a legitimate role for them persisted [19]:

> "These drugs should be allowed to be used by Ayurvedic and Unani physicians until such time as the benefits of modern medicine are extended to rural areas. Banning their use by the large mass of Ayurvedic and Unani physicians for therapeutic purposes may create a vacuum which may not be easily filled for a long time to come."

Cannabis in contemporary Ayurvedic medicine

According to Chopra and Chopra [30], the modern Ayurvedic properties of cannabis are: *paphahari*, promoting loosening, separation and the elimination of phlegm; *grahini*, promoting retention and binding the bowels; *pachani*, promoting digestion; *ushna*, promoting heat; *pitala*, exciting the flow of bile; *mada-vardhani*, promoting talkativeness or releasing the volitional restraint of speech; *moda-vardhani*, promoting happiness; *vag-vardhani*, stimulating the digestive fire; *dipani*, stimulating appetite; *ruchya*, promoting taste; *nidraprada*, hypnotic. Kapoor [4] described its Ayurvedic attributes as follows [4]: its *rasa* (taste) is *tikta* (bitter); its *guna* (physical properties) are *laghu* (light, easy to digest), *teeshan* (acute, pungent) and *rooksha* (ununctuous); its *veerya*

(energy modality or potency) is *ushana* (heating, digestive); and its *vipaka* (transformation reactions after digestion) are *katu* (constipative, semen increasing). Among its properties and uses, it is conceived of as: *madakari* (causing intoxication), *nidrajanan* (sleep-inducing), *dipan* (affecting appetite), *grahi* (absorbable) and *pachan* (affecting digestion). Dwarakanath's [19] assignations were quite similar to these, but added Muslim descriptions such as constipative, stomachic, appetizer, causing elation, aphrodisiac, retentive, devitalizing, anodyne, hypnotic, anti-convulsant, causing delirium and intoxicating. The same author listed the names of 48 modern Ayurvedic and eight Unani Tibbi formulas containing cannabis for a wide range of indications.

A recent survey of bhang use in the holy city of Varanasi (formerly Benares) found it quite prevalent across socioeconomic strata, especially the working class, businessmen and among the more educated [72]. Most users in the third or fourth decades of life employed it for anxiety or mood disorders for the resulting pleasure, while older people cited benefits on gastrointestinal disorders with improvement in appetite and bowel habits, or for alleviating insomnia. Among the 100 subjects, 90% reported improvement in sleep without daytime fatigue. Improvement in "marital adjustment" was also claimed. All employed bhang orally, generally 1.5 g/day, for gastrointestinal indications, but 56% employed 4–10 g/day, without evidence of associated toxic adverse events.

In 1996, native cannabis was again extracted to a yield of 17% THC, which was then used to treat cancer pain in 42 human subjects [73]. In 11.9% there was no analgesia with doses of 25 mg, but 64.3% had up to 50% pain reduction, and 9.5% had greater than 75% pain relief with no use of adjunctive medicine.

Dash [23] identified cannabis as one of the primary herbs of rejuvenation and a synergist with other agents, promoting health, preventing disease and offering "side benefits". In order of therapeutic priority, its uses were listed as: sprue syndrome, sterility, impotency, diarrhea, indigestion, epilepsy, insanity and colic pain. In addition to the many indications above, the following were also noted: gastritis, anorexia, anal fistula, throat obstruction, jaundice, bronchitis, tuberculosis, torticollis, splenic disorder, delirium, obstinate urinary disorders, sinus problems, anemia, rhinitis, elephantiasis, edema, puerperal sepsis, gout and constipation.

The scientific basis of Indian cannabis claims

This chapter has enumerated the lore of Indian medicine with respect to therapeutic benefits of clinical cannabis, but what is its scientific rationale? The issues will be addressed systemically (Tab. 2).

The oldest cannabis claims are psychiatric from the *Atharvaveda*, citing its usage for anxiety. Current research is supportive, particularly for cannabidiol (CBD) as an anti-anxiety agent as well as an anti-psychotic (reviewed in [74]). Similar benefit may accrue in calming dementia, as THC proved beneficial in Alzheimer's disease patients [75]. Recently, cannabichromene (CBC)

Table 2. Indications for cannabis in India

Cannabis indication	Physiological basis	Reference
Psychiatric		
Anxiety	CBD reduces anxiety in humans	[74]
Extinction of aversive memories	EC control in hippocampus	[77]
Insomnia	Increased sleep in pain/multiple sclerosis patients	[79, 80]
Addiction treatment	Decreased usage of cocaine/alcohol	[84, 86]
Neurological		
Neuropathic pain	EC modulation of CNS pathways Clinical pain reduction	[87, 88] [79, 80]
Muscle relaxation	Spinal interneuron effects?	[79, 89]
Neuroprotection	THC/CBD antioxidant/NMDA antagonism	[91]
Migraine	Effects on periaqueductal grey, 5-HT, inflammation, etc.	[88, 92, 93]
Seizures	CBD anticonvulsant THC anticonvulsant, EC modulation of seizure threshold	[95] [96, 97]
Dermatological		
Anti-psoriatic?	TNF-α antagonism	[99]
Anti-pruritic	Peripheral anti-nociception	[100]
Rheumatic		
Benefit in rheumatoid arthritis	TNF-α antagonism	[99]
Endocrinological		
Appetite stimulation	Hypothalamic effect?	[101]
Oncological		
Anti-nausea	5-HT_3 antagonism or other?	[102, 103]
Tumor reduction	Promotes apoptosis Reduces angiogenesis Anti-prolactin effect Blocks pulmonary carcinogenesis	[104, 105] [104] [106] [107]
Pulmonary		
Asthma	Bronchodilation	[108, 110]
Gastroenterological		
Intestinal spasm	Smooth muscle relaxation	[88, 112]
Secretory diarrhea	EC modulation of secretion	[112]
Gastritis	Anti-inflammatory/gastric cytoprotection	[114, 115]
Jaundice	? immunomodulatory	[116]

(Continued on next page)

Table 2. (Continued)

Cannabis indication	Physiological basis	Reference
Gynecological		
Dysmenorrhea	Smooth muscle relaxation	Reviewed in [42]
Uterine bleeding	EC modulation in uterus	Reviewed in [42]
Lower-urinary-tract symptoms	Increased bladder capacity, decreased incontinence	[118]
Sexual		
Impotence	Pain reduction/spinal effects?	[119]
Premature ejaculation	EC modulation	[120]
Infectious		
Antibiotic	Effects of cannabinoids/terpenoids	[111, 121]
Anti-malarial	Caryophyllene, α-terpineol	[121, 123]
Insecticidal/pediculicidal	Octopamine/GABA	[126–128]

CBD, cannabidiol; CNS, central nervous system; EC, endocannabinoid; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; 5-HT_3, serotonin type-3 receptor; NMDA, *N*-methyl-D-aspartate; TNF-α, tumor necrosis factor-α.

has also demonstrated anti-depressant effects in an animal model [76]. Additional support for benefits of cannabis on mood is evident from work demonstrating the regulation of extinction of aversive memories by the endocannabinoid system [77].

Insomnia treatment is another ancient claim that finds documentation in modern phase II–III clinical-trial results in multiple sclerosis patients and those with chronic neuropathic pain [78–81]. The 19th-century observation of benefit on addiction is echoed in modern studies of alcoholics [82] and cocaine users [83], with experimental support for decreased use rates in clinical experiments for each [84–86].

In the neurological realm, the ability of cannabis to treat pain, particularly of neuropathic origin, is the subject of a great deal of current research. Results to date are very encouraging, in terms of both basic science support (reviewed in [87, 88]) and the benefits in clinical trials [78–80].

Although tetanus is rarely observed in the modern age of immunization, the observed benefits on muscle relaxation underlie current application to treatment of spasms and spasticity in multiple sclerosis and spinal cord trauma [79, 89], where cannabis extracts have proven as effective as any currently available agent [90]. Although rabies remains invariably fatal, the neuroprotective effects of cannabis [91] may warrant new trials of cannabis extracts in its treatment, and that of slow virus (prion) diseases. Indian medical literature on migraine treatment is also supportive, as is a tremendous amount of pathophysiological data [88, 92, 93]. As for clinical trials, however, the words of Dr Mechoulam still ring true [94]: “no modern work exists”.

Another long-held claim pertains to cannabis in epilepsy. Previous experimental work showed some support for CBD [95], but this has been greatly bolstered by current experiments by Wallace et al. [96, 97], demonstrating the anti-convulsant properties of THC, and the modulation of seizure thresholds by anandamide.

Examining additional ectodermal tissue, both eczema and itch were cited in Indian literature as benefiting from cannabis treatment. Recent work demonstrating the value of tumor necrosis factor-α (TNF-α) antagonists in psoriasis [98] may justify the use of cannabis, particularly CBD-rich extracts, in the treatment of related diseases, as CBD shares this mechanism of action [99]. Similarly, the benefits of THC on peripheral pain and itch are becoming increasingly evident [88, 100].

Rheumatic diseases cited by O'Shaughnessy [36] and other authors remain an issue, but experiments underline the benefits of CBD in experimental rodent models of rheumatoid arthritis [99]. Phase II clinical trials are pending. Modern investigation demonstrates that cannabinoid treatments definitely have a clinical role to play in issues of appetite, with benefit seen in HIV/AIDS subjects [101], and in multiple sclerosis/neuropathic pain patients [79].

The role of cannabis in oncology may now extend far beyond its demonstrated ability to allay nausea in chemotherapy [102, 103], but include promotion of apoptosis, and suppression of angiogenesis in a wide variety of tissue types (reviewed in [104, 105]). Additionally, THC has anti-prolactin activity in breast carcinomas [106], and introduces a metabolic block in pulmonary carcinogenesis [107].

The role of cannabis in asthma has been much debated, but it is clear that THC is a bronchodilator [108], as is its terpenoid component, α-pinene [109], and that smooth muscle contraction in the lungs is mediated by endocannabinoids [110]. Given these facts, plus the prominent anti-inflammatory benefits of THC, CBD and terpenoids [111], it is apparent that additional investigation with vaporizer or other non-smoked inhalant technology with cannabis extracts is warranted.

The treatment of digestive issues with cannabis has figured prominently in India to the current day. Whether it be through reduction of intestinal spasms, constipation or inhibition of secretory diarrhea processes in cholera, cannabis components offer neuromodulatory amelioration (reviewed in [88, 112]). Given the combination of these factors mediated by THC, the TNF-α antagonism of CBD and the observed up-regulation of endogenous cannabinoids in human inflammatory bowel disease [113], there is every reason to believe that benefits will be forthcoming in clinical trials of cannabis extracts in Crohn's disease and ulcerative colitis. The gastritis claim finds support in studies documenting the benefit of cannabis in ulcer treatment [114], and the gastric cytoprotective effect of the cannabis essential-oil component, caryophyllene [115]. Even claims for treatment of jaundice may find support in recent claimed benefits seen in hepatitis C patients who use cannabis [116].

Hemorrhoids continue to plague mankind, and anecdotal evidence for the benefits of cannabis from rural Kentucky echo the Indian claims [117]. Myriad anti-inflammatory and anti-pruritic mechanisms may underlie the basis of such treatment. The benefits of cannabis in dysmenorrhea and excessive uterine bleeding are plausible given the expression of endocannabinoids in the uterus (reviewed in [42]). The benefits of cannabis in symptoms of the lower urinary tract have been strongly supported by increases in mean maximum cystometric capacity, decreased mean daytime frequency of urination, decreased frequency of nocturia and mean daily episodes of incontinence in multiple sclerosis patients treated with cannabis-based medicine extracts [118].

The persistence of claims of cannabis increasing sexual pleasure and performance is compelling, but not particularly amenable to simple experimental verification. Does cannabis treat impotence? There are frequent claims of such, including a successful pregnancy induced by one man who was previously impotent due to spinal damage, treated successfully with oromucosal cannabis-based medicine [119]. Additionally, recent data demonstrate that a cannabinoid agonist delayed ejaculatory responses in rats [120]. Thus, a convincing case may be made for human clinical trials [88].

Claims of the benefits of cannabis in infectious diseases have received little investigation since studies on bacteria in 1960 [121], wherein the authors demonstrated that an isolated resin from cannabis inhibited growth of *Mycobacterium tuberculosis* down to a dilution of 1:150000. Studies on human herpes simplex virus in 1980 revealed the inhibition of viral growth by THC even at low dosages [122]. A variety of cannabis components are anti-infective (reviewed in [111]), supporting such applications, as well as the use of cannabis in the treatment of malaria, where the essential oil components caryophyllene and α-terpineol demonstrate anti-protozoal activity [123]. Cannabis may yet prove useful in the treatment of dandruff, as suggested in Indian sources. Cannabichromene demonstrated anti-fungal activity [124], and ρ-cymene showed anti-candidal effects [125]. Cannabis effects on the causative yeast in dandruff, *Malassezia ovalis*, could be easily tested.

Clear benefits also seem likely in the treatment of lice, as this ancient indication has been supported by pediculicidal efficacy of cannabis terpenoid components [126], the activity of terpenoids on insect octopaminergic receptors [127], and their allosteric modulation of insect homo-oligomeric γ-aminobutyric acid (GABA) receptors [128]. A whole range of new applications of cannabis as an insecticide are possible [129]. Mechoulam decried the lack of investigation of cannabis effects on intestinal parasites [94], and this remains an area of deficiency in our cannabis knowledge.

Cannabis in India in context

As we have seen, the vast majority of claims for cannabis from India are fully corroborated by modern scientific and clinical investigation. In closing, a pas-

sage from Campbell [1] written for the *Report of the Indian Hemp Drugs Commission* more than a century ago offers a plaintive plea for this venerable herb:

> "By the help of bhang ascetics pass days without food or drink. The supporting power of bhang has brought many a Hindu family safe through the miseries of famine. To forbid or even seriously to restrict the use of so holy and gracious a herb as the hemp would cause widespread suffering and annoyance and to the large bands of worshipped ascetics deep-seated anger. It would rob the people of a solace in discomfort, of a cure in sickness, of a guardian whose gracious protection saves them from the attacks of evil influences, and whose mighty power makes the devotee of the Victorious, overcoming the demons of hunger and thirst, of panic fear, of the glamour of Maya or matter, and of madness, able in rest to brood on the Eternal, till the Eternal, possessing him body and soul, frees him from the having of self and receives him into the ocean of Being. These beliefs the Musalman devotee shares to the full. Like his Hindu brother the Musalman fakir reveres bhang as the lengthener of life, the freer from the bonds of self. Bhang brings union with the Divine Spirit. 'We drank bhang and the mystery I am He grew plain. So grand a result, so tiny a sin.'"

It is appropriate that modern-day cannabinoid researchers have acknowledged the integral role that Indian culture has played in our understanding of the biochemistry of cannabis. Thus, the first endocannabinoid, arachidonylethanolamide, was dubbed anandamide (*ananda* is Sanskrit for bliss; Tab. 1) [130]. In like manner, the most recently identified endocannabinoid, the cannabinoid antagonist *O*-arachidonylethanolamine, which is arachidonic acid and ethanolamine joined by an ester linkage, has been nicknamed virodhamine (*virodha* is Sanskrit for opposition) [131].

It is fascinating to note that our own endogenous cannabinoid physiology encompasses these positive and negative influences, in a manner analogous to THC and CBD effects from cannabis, the Indian phytopharmaceutical that leads us to this knowledge: nature and neurophysiology in symmetry and balance.

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