REVIEW

History of Cannabis and Its Preparations in Saga, Science, and Sobriquet

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Cannabis sativa L. is possibly one of the oldest plants cultivated by man, but has remained a source of controversy throughout its history. Whether pariah or panacea, this most versatile botanical has provided a mirror to medicine and has pointed the way in the last two decades toward a host of medical challenges from analgesia to weight loss through the discovery of its myriad biochemical attributes and the endocannabinoid system wherein many of its components operate.

This study surveys the history of cannabis, its genetics and preparations. A review of cannabis usage in Ancient Egypt will serve as an archetype, while examining first mentions from various Old World cultures and their pertinence for contemporary scientific investigation. Cannabis historians of the past have provided promising clues to potential treatments for a wide array of currently puzzling medical syndromes including chronic pain, spasticity, cancer, seizure disorders, nausea, anorexia, and infectious disease that remain challenges for 21st century medicine. Information gleaned from the history of cannabis administration in its various forms may provide useful points of departure for research into novel delivery techniques and standardization of cannabis-based medicines that will allow their prescription for treatment of these intractable medical conditions.

Contents

1. Introduction. – Humans have utilized cannabis products in various forms throughout recorded history. A case for the co-evolution of cannabis with the human species has even been advanced [1]. The plant is remarkable in its morphological variability (*Fig. 1*, seed size), and versatility as a foodstuff and fuel (achenes or 'seeds'), fiber (stalks), and pharmaceutical (unfertilized flowering tops). Its biochemical diversity, while possibly exceeded in sheer numbers by other herbs and common food plants, is likely unrivaled with respect to its extensive complement of bioactive compounds and their potential medical applications.

Fig. 1. *Seed-size variation in cannabis.* Seeds at right are a feral plant in Kashmir (800 seeds/g) and those at left are culinary seeds from China (15 seeds/g) (see text for details; photo *E. B. R.*, from collection of *David Watson*, *HortaPharm BV*, Amsterdam).

Phytocannabinoids [2] are unique to cannabis, and number some 66-odd molecules [3]. Tetrahydrocannabinol (THC) is the predominant psychoactive cannabinoid, and has partial agonist activity at cannabinoid receptors CB_1 and CB_2. Its metabolic breakdown product, cannabinol (CBN), also has modest psychoactive effects, while other representatives have their own unique attributes (reviewed in [4]). Whereas cannabinoid-like structures have been reported from the New Zealand liverwort, *Radula marginata* [5], no actual biochemical activity at cannabinoid receptors has been reported to date. Recently, modulation of tissue necrosis factor alpha (TNF-α) in *Echinacea* spp. extracts was demonstrated to occur *via* CB_2 receptors [6].

This article will examine the cannabis plant, its genetics, preparations, and history in medical usage. While prior historical surveys have appeared from this author in general terms [7], in relation to migraine [8], obstetrics and gynecology [9], psychiatric aspects [10–12], pain management [13], and a treatise on cannabis in India [14], the focus here will be on less frequently reported data and their correlations to modern scientific investigations of therapeutic application of cannabis and cannabinoids.

The reader is also referred to excellent works on cannabis history by other authors [15–23].

2. The Ticklish Matter of Taxonomy. – Cannabis is a unique dioecious annual plant, generally placed in the Cannabaceae family (occasionally rendered, Cannabidaceae) along with hops, *Humulus* spp. However, it has also been assigned at various times to the Moraceae or Urticaceae. Recently, it has been suggested that cannabis should properly belong in the Celtidaceae on the basis of chloroplast restriction site maps [24], and chloroplast *mat* K gene sequences [25]. While the generic nomenclature of cannabis is less controversial, the species classification is quite so. The name *Cannabis sativa,* or 'cultivated cannabis', was probably first employed by *Fuchs* in his herbal of 1542 accompanied by a splendid illustration of European hemp [26], thus pre-dating the monotypic assignation of Linneaus in his *Species Plantarum* [27] by some 211 years. Soon thereafter, *Lamarck* described *Cannabis indica,* a short, psychoactive upstart from the Indian subcontinent, as morphologically distinct [28], and a lasting consensus on the issue has never been regained. Two basic camps remain, favoring single or multiple species. The former group has been championed by *Ernest Small* [29] and others, with more recent support on morphological grounds [30], and from research into short tandem repeat DNA markers of cannabis that failed to clearly differentiate fiber and drug strains [31].

A polytypic treatment of cannabis was advanced by *Schultes et al.* [32] and *Anderson* [33] a generation ago based on morphological attributes. These botanists described three putative species, *Cannabis sativa* L. (tall, branched plants for fiber, seed or psychoactive use), *Cannabis indica* Lam. (short, broad-leafed plants from Afghanistan with equal complements of THC and CBD utilized to produce hashish), and *Cannabis ruderalis* Jan. (short, unbranched 'roadside' plants usually weak in cannabinoids; *Fig. 2*,*a*–*c*, plant examples). The taxonomic debate over the number of cannabis species even led to judicial disputes, as court cases involving cannabis in the USA were occasionally challenged on the basis of imprecise legislative language prohibiting solely *Cannabis sativa.*

The multi-species concept has recently gained credibility based on systematic chemotaxonomic work by *Karl Hillig* with *Paul Mahlberg*. They conducted a genetic analysis of 157 cannabis accessions of known geographic origin. A principal component analysis of allozyme frequencies at 17 gene loci revealed two major groupings [34]. A '*sativa*' gene pool included East European ruderal (roadside) accessions, as well as hemp fiber and seed landraces from Europe and Central Asia. The '*indica*' gene pool included Far Eastern fiber and seed landraces, narrow-leaflet drug strains from Southern Asia, Africa and South America, wide-leaflet drug strains from Afghanistan and Pakistan, and feral populations from Nepal and India. Ruderal accessions (*Cannabis ruderalis*) from Central Asia formed a putative third gene pool. A geographic map based on the results depicted an epicenter of origin for *C. sativa* in current Kazakhstan, and one for *C. indica* in the Western Himalayas. *Hillig* concluded that the number and frequency of allozyme mutations in both gene pools was indicative of an ancient split between *sativa* and *indica* that may pre-date human intervention. Not surprisingly, the greatest evidence for narrowing of the gene pool was observed in drug strains, particularly the narrow-leaflet *indica* strains. This may be partly due to a restriction in the number of pollinators in these strains since staminate plants are often culled during cultivation to maximize THC production (*vide infra*). This process has accelerated notably in the last 30 years with selective breeding pressure.

Fig. 2. *Plant examples. a*) *Sativa* type form, but *indica* genetics (*E. B. R.*, *HortaPharm BV*); *b*) *indica* type, broadleaf (*E. B. R.*, *HortaPharm BV*); *c*) *ruderalis*-type form, Rif Mountains, Morocco.

Hillig and *Mahlberg* conducted a chemotaxonomic study of the same set of accessions examined in the genetic analysis. Cannabinoid content was determined by gas chromatography (GC) and starch-gel electrophoresis [35]. The results supported a two-species concept (*C. sativa* and C. *indica*) and led to other interesting observations. To digress momentarily, phytocannabinoids are produced in cannabis by glandular trichomes (*Fig. 3*, trichomes) as carboxylic acids from geranyl pyrophosphate and olivetol precursors to yield the parent phytocannabinoid compound, cannabigerolic acid (CBGA). This cannabinoid accumulates in a newly discovered plants harboring a metabolic dead-end at this molecule (genotype homozygous for allele B_O) [36]. In drug strains, in contrast, the enzyme tetrahydrocannabinolic acid synthase (recently crystallized by *Shoyama et al.*) [37] catalyzes the conversion of CBGA to THCA (the precursor of THC, which forms by decarboxylation of THCA under heat or storage) with highest yields in plants homozygous for the co-dominant B_T allele. Other strains produce an abundance of cannabidiol (CBD) *via* the B_D allele (also co-dominant), or cannabichromene (CBC) *via* the recessive B_C allele [38]. To further

complicate the picture, certain cannabis strains are capable of utilizing a different precursor than olivetol, namely 4-carboxy-5-propylresorcinol (*Raphael Mechoulam*, personal communication, 2005), to form the propyl phytocannabinoids: cannabigivarin (CBGV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), and cannabichromivarin (CBCV) after decarboxylation. Lest anyone think this fact a bit of biochemical irrelevancy, these previously little studied variants may be of considerable pharmaceutical importance, as THCV was recently demonstrated to be a potent antagonist at cannabinoid receptors CB_1 and CB_2 [39]. The maturation of *Mendelian* genetic techniques has produced a modern revolution in the potential for creative medical cannabis phytochemistry that may be applied to various biochemical targets.

Fig. 3. *Cannabis glandular trichomes* in vivo (photo *E. B. R.*, courtesy of *Bedrocan BV*, Netherlands)

Returning to the observations of *Hillig* and *Mahlberg* [35], the difficulty in reducing THC content in East Asian *C. indica* hemp fiber strains is easily explained by the retention of the B_T allele in these accessions. Furthermore, the highest CBC levels were found in the male staminate flowers of these fiber strains. The origin of the genetic pathway leading to the biosynthesis of the propyl phytocannabinoids seems to reside in *C. indica* drug strains, rather than in *C. sativa*, but these cannabinoid variants were unusual outside of accessions from the western Himalayas and Southern Africa, and Indian feral plants.

In another chemotaxonomic analysis focusing on the terpenoid essential oil components of cannabis in 162 cannabis samples [40], *Hillig* found support for the demarcation of wide-leaflet strains of *C. indica* based on their content of the rare sesquiterpenoid alcohols, guaiol, bulnesol, and β- and γ-eudesmol. Some 120 terpenoids have been identified in cannabis [3], some of which demonstrate unique biochemical properties that may well synergize with the cannabinoids [4].

An additional analysis of various agronomic traits in 69 cannabis accessions by *Hillig* [41] also favored assignment of Asian hemp and drug strains to *C. indica* apart from *C. sativa.* Further support for this interpretation is provided by a recent study in

cannabis that demarcated hemp from drug strains on the basis of amplified fragment length polymorphisms in a few accessions [42]

Finally, an earlier study of flavonoid variation in 53 cannabis plants from eight countries provides evidence for restricted gene flow between *C. indica* and *sativa* due to the fact that luteolin-*C*-glycuronide was detected in almost all *sativa* samples but only rarely in *indica* [40][43]. Certain flavonoids, such as cannflavin A with notable anti-inflammatory potential [44][45] are unique to cannabis. Some 21 flavonoids have been identified in the genus [3].

3. A Bit of Geography. – The great plant explorers of the 19th and 20th centuries have all placed the geographic origin of cosmopolitan cannabis in Central Asia. *De Bunge* [46] reported the presence of wild cannabis growth in the marshes of the Southern Caspian Sea, in current-day Iran and Azerbaijan. *De Candolle* [47] noted wild strains corresponding to modern areas south of the Caspian, in Siberia, Kazakhstan, the Xinjiang-Uighur Autonomous Region, the deserts of Kirghizstan, beyond Lake Baikal, South Central Russia, and perhaps the area south of the Caucasus. Subsequent authors have often felt that no truly wild cannabis still exists, and that all contemporary strains derive from cultivated forebears whose feral ancestor is now lost. Twentieth-century analysis has placed the center of diversity for cannabis in Central Asia, possibly in the Pamir plain [48] in current day Tajikistan, bordering Afghanistan, Kyrgyzstan, and the Xinjiang Uighur Autonomous Region of Western China. *Bouquet* [49] placed its origin in current day Kazakhstan, Mongolia, Northwest China, and the Russian Far East. *Sharma* [50] felt the origin of cannabis was in the Himalayan foothills, but offered little botanical documentation. Previously, *Hooker* [51] observed wild plant specimens in the southwestern Himalaya Mountains. Similar regions were also supported by *Vavilov* [52] who felt that *Cannabis indica* originated in Central Asia, Northwest India including the Punjab and Kashmir, all of Afghanistan, Tajikistan, Uzbekistan, and the Western Tian Shan mountain range. These field observations of wild-growing cannabis nicely match the chemotaxonomic data of *Hillig* [34] (*vide supra*).

While spontaneously growing cannabis was observed from Eastern Europe to the Altai Mountains, *Vavilov* distinguished truly wild forms [53], and observed of cannabis its tendency to mirror man's peregrinations (p. 229), '*Wild hemp and weed hemp follow the dwelling places of nomads. Owing to its biological peculiarities, hemp followed man naturally, keeping near his dwelling places, settling on rubbish and everywhere where the soil was manured*'. He further observed that the seeds of wild cannabis were quite small and marbled in appearance (*Fig. 1*), again paralleling observations of *Hillig* [41].

4. Cannabis Preparations: *Bhang*, *Ganja*, and *Charas*. – Beyond the array of morphological forms of cannabis, its preparations have similarly varied. Three basic herbal forms predominate, and they are known by the Indian names: *bhang* (a seeded mixture of cannabis flowers, leaves, and stems, known as 'grass' in the USA), *ganja* (seedless unfertilized female flowering tops, termed *sinsemilla*, 'without seed', in North America), and *charas* (more commonly known as *hashish* in Arabic, a collection of cannabis resin *via* hand rubbing or sifting of trichomes from the cannabis flowers) [14] (*Fig. 4*). Interestingly, despite a seeming abundance of native cultivated cannabis in 19th- and 20th-century India, *charas* was preferentially imported from Yarkand

(current Shache in the Xinjiang-Uighur Autonomous Region) due to its reportedly superior potency and improved ability to produce resin [54][55].

Selective breeding in cannabis drug strains has favored more intoxicating strains, especially in the last generation of controlled indoor cultivation. Cannabis fields in certain locales such as Morocco and Afghanistan in generations past would tend to yield equal proportions of THC and CBD in pooled samples of sifted trichomes. In contrast, however, cannabidiol has become virtually absent from North American [56] and European drug strains [57], due to selective breeding for THC content in the last two decades. This enforced absence of CBD in contemporary black market cannabis strains has implications for medical efficacy and tolerability [58][59].

Current figures on cannabis potency provide the following for THC content: 6–8% THC in Europe with 16% in the Netherlands (due to a consumer preference for *ganja*/*sinsemilla*) [57], while, in the USA, herbal cannabis averaged 7% THC, hashish 11.2% [60] (with observed increase in recent years probably attributable to the development of modern extractive techniques on domestic cannabis supplies (*vide infra*)). Overall, cannabis potency has risen slowly in the last four decades due to selective breeding, but stronger strains have always existed, as evidenced by occasional samples up to 14% THC content noted in the USA in the 1970s [61]. Herbal cannabis samples exceeding 18% THC content are distinctly rare from any source [60].

In addition to traditional methods of hashish production discussed above, modern techniques of sifting flowering tops with *Millipore* mechanical filters, or isolation of trichomes with cold-water extraction have emerged [62] (*Fig. 4*,*d*; sifted hashish, and *Fig. 4*,*e*, water hash), and are advertised on the Internet and in counter-culture magazines. *Clarke* has estimated that a theoretical maximum of 54% THC might be produced within the glandular trichomes of high potency strains [63].

Recreational cannabis is most often smoked in contemporary times, which, while producing uniquely rapid onset of psychoactive effects, also presents risks of pulmonary irritation [64]. Smoking is also a relatively inefficient delivery system, with up to 70% destruction of THC *via* pyrolysis [65] and additional losses through sidestream smoke leading to a bioavailability of only 10–27% [66]. Modern vaporizers have become popular, but do not eliminate polyaromatic hydrocarbons [67], and still are relatively inefficient in preservation of available THC due to incomplete decarboxylation of THCA and loss through exhalation, with an overall bioavailability estimated at *ca.* 30% [68].

Oral application of cannabis has ancient roots and is historically the more common mode of medical administration (*vide infra*). Limited bioavailability is an issue, however, with delayed onset of activity after oral ingestion for 1–2 h or more, and the need for a fatty carrier or tincture [69]. Folk usage of cannabis infusions ('*ganja* tea') as a tonic or medicinal has been longstanding in Jamaica [70], but lipophilic THC has a very limited solubility in H_2O. Despite a recommendation by the *Dutch Office of Medicinal Cannabis* to administer the drug in this way [71], in a recent investigation, only *ca.* 5.7% of available THC was recruited from herbal cannabis into the resulting tea [72]. This could be increased with lipid carriers, such as use of *ghee,* clarified butter, in traditional Indian cannabis confections.

Pharmaceutical forms of cannabinoid administration including oromucosal cannabis extracts [58][73] are further considered in other contributions in this journal issue.

Fig. 4. *Cannabis forms. a*) *Bhang,* or unmanicured herbal cannabis, Rif Mountains, Morocco; *b*) *ganja* or *sinsemilla,* (photo *E. B. R.*, Hash, Marihuana and Hemp Museum, Amsterdam); *c*) *charas,* or *hashish,* 'soapbar' from Morocco, as encountered in the UK; *d*) sifted hashish, Amsterdam; *e*) water hash, Amsterdam.

5. History of Medicinal Cannabis. – 5.1. *Egypt.* Egypt is universally recognized as one of the great early civilizations, with an advanced medical system. In prior generations, most authorities have claimed an absence of definitive evidence of

cannabis in Ancient Egypt, but *Nunn* (1996) cited no less than six supporting experts that it was employed medicinally [74–78] (from [78], p. 156):

> '*There is general agreement with the view of* Dawson *that* shemshemet *means cannabis, and the identification was strongly supported by the use of hemp in rope making. As a drug, it has remained in active use ever since pharaonic times. It does not appear very often in the medical papyri, but it was administered by mouth, rectum, vagina, bandaged to the skin, applied to the eyes and by fumigation*'.

This assignation as cannabis derives from the following passage written on stone from the Pyramids Texts from the Egyptian Old Kingdom in Memphis, at the end of the Fifth Dynasty, dated to around 2350 B.C. (Utterance 319, '*The king is identified with the sun-god*') [79] (p. 101): '*The King has tied the cords of the* ŝmŝmt-*plant* [...]'. Of this, *Dawson* wrote [75] (p. 44–45): '*The word* [...] *is spoken of as a plant from which ropes are made, which make the equivalence with hemp*, Cannabis sativa, *much more likely*'. If accurate, this may represent the oldest written description of cannabis. The hieroglyphic ('sacred carving') symbols for *shemshemet* (*Fig. 5*) represent from left to right: a basin or pool (phonogram for ŝ, or 'sh' sound), an owl (phonogram for 'm'), the same two characters repeated, a flat loaf of bread (phonogram for 't'), an unpronounced ideographic determinative symbol for grain (above), and another unpronounced ideographic determinative symbol (to the right) denoting a plant [80].

Subsequent cannabis mentions occur in a succession of medical papyri, written in Hieratic script on fibers of the pith of the sedge, *Cyperus papyrus*. Perhaps because writing in Ancient Egypt and Mesopotamia was both labor- and resource-intensive, prescriptions were quite parsimonious in their instructions with respect to preparations, and assumed certain basic background rudimentary knowledge on the part of the physician-herbalist. The oldest example for cannabis is contained in *Papyrus Ramesseum III*, A 26, *ca.* 1700 B.C. [81] (p. 82): '*A treatment for the eyes: celery; hemp; is ground and left in the dew overnight. Both eyes of the patient are to be washed with it early in the morning*'. This suggests a parallel to modern use of cannabis in glaucoma treatment [82][83], or, possibly, for anti-inflammatory effects.

A different passage reads (E 821, *Ebers Papyrus 821*, 1550 B.C.) [77] (p. 209): '*Another (to cool the uterus and eliminate its heat):* ŝmŝm-t; *ground in honey; introduced into her vagina* (*iwf*). *This is a contraction*'. This was felt by *Ghalioungui* to describe an obstetric aid. It has parallels to therapeutic applications of cannabis as a vaginal suppository in the 19th century to treat gynecological disorders and migraine [84].

Cannabis was employed in the same papyrus as a poultice on a toenail (E 618, *Ebers Papyrus 617–618*) [85] (p. 339):

> '*If you find a painful finger or a toe, from water having been around them (serosity), their odor being malignant, whereas they have formed maggots* [worms], *you must say to this patient: "A problem that I can treat". You must prepare for him treatments to kill the vermin* [...]. *Another for the toenail: honey: 1/4; ochre 1/64; cannabis: 1/32;* hedjou *resin: 1/32,* ibou *plant: 1/32. Prepare as for the preceding, and dress with it*' [translation *E. B. R.*].

Fig. 5. *Cannabis in various ancient languages*

The antibacterial effects of honey are well-known, but less attention has been paid of late to the antibiotic effects of cannabis and its components [86], antihelminthic activity prominently described in the later Arabic literature [87], or insecticidal potential [4][14]. These reported vermicidal properties of cannabis thus may have predated *Galen*'s reports [88][89] by 1700 years!

Contemporaneously, about 1550 B.C., the *Hearst Papyrus* also contained a prescription for sore nails, identical in components (H 177) [85] (p. 398): '*This will be pounded. Dress with this*'. [translation *E. B. R.*]. In the 19th and early 20th century, corn plasters composed solely of cannabis resin were popular in Western medicine.

Subsequently, the *Berlin Papyrus* contains two pertinent prescriptions, dated to *ca.* 1300 B.C. The first is contained in a section titled, '*ÂAÂ-Liquid, Actions of Gods, of the Dead*' (Bln 58–59) [85] (p. 416):

> '*Remedy to drive away the* âaâ *deriving from a god, from a goddess, the seed of a dead man or woman, for chasing the flight of the interior*-ib, *the heart-haty and driving away the neglect of the interior*-ib: [...]. *Another* [remedy]: khet-des *tree;*

âpechyt-*insect; bryony grains;* djas *plant, cannabis;* mout-*part of the laundryman beetle. Fumigate the man with this*' [translation *E. B. R.*].

Obviously, this prescription may be too cryptic for adequate analysis of the logic behind the magic, or understanding of any medical intent. However, it is extremely important in context for the fact that the mixture was burned ritually, and there is the possibility that psychoactive or other physiological properties of cannabis were operative. In 1927, *Cyril Bryan* suggested that *âaâ* was due to '*Bilharzia*' (schistosomiasis) or '*Chlorosis Aegyptica*' (ancylostomiasis, hookworm disease) [90], and this might be sensible given previous evidence from the *Ebers Papyrus*, and known anti-parasitic effects of cannabis.

Another prescription from the *Berlin Papyrus* is much more accessible (Bln 80–81) [85] (p. 419): '*Ointment to prepare for driving away the fever:* [...] *Another: extremities of cannabis stems; white oil. Plaster with this*' [translation, *E. B. R.*]. Since a systemic antipyretic effect of this locally applied prescription seems far-fetched, it may be more likely that an antibiotic property was desired from the remedy.

Another spirit cure seems apparent in the *Berlin Papyrus 3027* (H) in '*Book on Protection the Mother and Child*' [85] (p. 477):

'*To repel the substance*-bââ: tepaout-*vesicles of sycamore; fresh dates;* hemou-*part of castor; a vegetable plug (made from filaments) of the* debyt-*plant;* mesta-*liquid. This will be drunk by the woman*' [translation *E. B. R.*].

While this indication also remains obscure, this internal remedy is perhaps an early documentation of the utility of cannabis in obstetrics [9].

The *Chester Beatty VI Papyrus* has been dated to 1300. It contains a complicated set of passages as follows (Bt 11–13b) [85] (p. 457):

'*Another remedy, for the part of the body named* sâq, *the bladder, to drive away the* chenefet-*substances and whatever other anal affliction of a man or woman:* [...]. *If the problem manifests itself in a fashion due to divine action, with abscesses of the bladder, some* setet *of the joints, then he will lose water between his buttocks, then he will have a fever on account of this that he has sustained, his urine will flow, the evacuations will be painful, his anus is heavy, the flow from the abdomen is without end, you must say to this patient, "It is a heaviness of the anus, a problem that I can treat". This remedy you must prepare for him until he is cured: goose fat: 5* ro; *honey: 5* ro; *human milk: 15* ro. *This will be placed in the anus four days following.*

Another remedy, which is prepared after this: water of wheat-mimi: *1; cannabis juice: 1; juice of* qebou-*plant: 1; goose fat: 1; lotus leaves: 1; acacia leaves. This will be prepared in a homogeneous mass and placed in the anus four days following*' [translation *E. B. R.*].

Once more, it is not totally clear what complex illness might be represented, but certainly antipyretic effects of cannabis could have been helpful in this clyster, or, even more likely, a benefit might be noted on urinary incontinence [91], or diarrhea, as in the success in treating cholera with cannabis in 19th-century India [14][92], or modern evidence of the ability of cannabinoids to allay intestinal hypersecretion [93].

Another papyrus passage also describes rectal administration (Bt 24) [85] (p. 459):

'*Another remedy to prepare after this, as a washing, to drive away the burning substances called* kapou *in the anus and to refresh it: cannabis: ¼;* djaret-*plant: 1/32;* mesta-*water: 25* ro. *This will be placed in the anus, four days following*'.

The above suggests analgesic and anti-inflammatory effects, but may have modern parallels in efforts to bypass hepatic first-pass effects of THC through the use of the pro-drug, THC-hemisuccinate, as a rectal suppository [94].

At this juncture, cannabis disappears from the historical record for some time, one of many examples this author has termed *cannabis interruptus* [8], an ungrammatical Latin coinage designed to reflect an herbal disappearing act. This is hardly difficult to understand, in view of the perishable nature of the evidence, and humanity's propensity toward constant warfare, invasion, and cultural conflict. Was cannabis really present in Egypt? Many readers may remain unconvinced at this point that *shemshemet* denotes cannabis, but recent physical evidence of its presence has been excavated [81]. Hemp fibers were found in the tomb of *Amenophis IV* (*Akhenaten*) at El-'Amarna, *ca.* 1350 B.C. and confirmed in two separate scientific analyses [95]. Cannabis pollen has also been identified from mid-third-millennium B.C. soil samples from Nagada [96] and in geological strata of similar vintage in the eastern Nile Delta [97]. More convincing yet is the finding of several pollen grains *inside* the mummy of *Rameses II*, who died *ca.* 1213 B.C. [98]. A photomicrograph (p. 163) seems to confirm this assignation, and not that of hops, *Humulus lupulus,* a European species not identified in Ancient Egypt. Samples containing cannabis pollen from another mummy has also been documented [99], *ca.* 100 B.C., during the *Ptolemaic* era.

In the 1st century B.C., *Diodorus Siculus*, a Greek from Sicily documented that Egyptian women of Thebes employed a 'nepenthic' potion reminiscent of that *Homer*'s *Odyssey,* to cure anger and sorrow [49]. Examination of the passage (I. 97) reveals that the translator renders this term as 'quieting pain', [100] (p. 332–333) and also finds this comparable to *Homer*'s account. Various authors have claimed this to be cannabis, but no definitive proof is possible.

In 1976, an important translation of the *Fayyum Medical Book* was published [101], a document written in Egyptian Demotic script dating to the second half of the 2nd century C.E. This seemed to represent a compilation of knowledge back to the 6th century B.C., and, while the format is reminiscent of the *Ebers Papyrus,* there is very little overlap in content. Strong parallels can be noted to the *materia medica* of *Pliny*, *Galen*, and *Dioscorides* with support for the concept that the flow of medical knowledge of the time was *from* Alexandria *to* Greece and Rome rather than *vice versa*. The treatises of greatest interest here concerns curing of '*ryty*-tumors' consisting of sores, swellings, abscesses, and tumors, as well as those pertaining to fevers and diseases of the ear. The Demotic term for cannabis was *mŝy.*

Under *ryty*-tumors, we see the following [101] (p. 101):

Method 3

Another (prescription) for curing the tumour [...] [to be tritu]*rated finely; fine powder to be made* [...]. *Another (prescription): mecon* [...] *cannabis according to*

that which is above; another: resin of pine, chalcedony, according [...] *ash of* [cadmia] *kite* [?], *cannabis kite; to be bandaged over it.*

Subsequently, we see [101] (p. 103):

Method 4

[...] *to paralyse* [the tu]*mours: extract of herbs, papyrus, sap of the* hur-*tree, lotus leaf, cannabis,* [...], *heated* [...], *sweet clover* [...].

[...]

Another (prescription): heated cannabis, sulphate of copper, ammoniac salt, to be triturated finely with (extract of) waterparsnip; to cause them to appear [...].

The latter passage is particularly interesting in its specification for heated cannabis, suggesting that decarboxylation of phytocannabinoid precursors might have been operative. Interestingly, centuries later, *Marcandier* published his *Traité du chanvre* [102], claiming benefit of cannabis on tumors (p. 38): '*The seed and the green leaves, crushed and applied in the form of cataplasm, to painful tumors, appear to be strongly resolutive and intoxicating*' [translation *E. B. R.*]. It has been well-established that all the phytocannabinoids are active cytotoxics in a variety of cancer cell lines [103][104]. *Marcandier* echoed earlier claims of the herbalist *Parkinson* that cannabis roots were effective for tumors and other inflammation in 1640 in the *Theatrum Botanicum, The Theater of Plants* [105] (p. 598):

[...] '*the same decoction of the rootes, easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter*'.

Cannabis roots have proven to harbor terpenoids, sterols [106], and alkaloids [107], but no cannabinoids. Cannabis roots have received little research attention in recent decades.

Returning to the *Fayyum Medical Book*, for ear trouble, we see [101] (p. 105):

Another (prescription) for recovering from acute [pain in the] *ear* [...].

Another (prescription): wild water cucumber, thorn acacia, cannabis undivided; to be triturated finely; [to one] ear of them [...].

For treatment of fever, we see [101] (p. 123):

Fever of any kind of disease: acacia (measure) 1/2, cannabis [mul]*berry 1/4; to be triturated finely; to lift his mouth on* [...].

Comparison of these above passages on cannabis with those from the Classical herbalists *Dioscorides*, *Galen*, and *Pliny* for similar indications [7][8][13][88] shows strong concordance in symptomatic relief claimed.

Unfortunately, at this juncture, the Egyptian cannabis lexicon seems to suffer another lull. Although a Coptic word for cannabis is noted by *Manniche* [81],

approximating the Greek characters: ερβισι (*erbisi*), the subsequent medical papyri are more magical than herbal or pharmacological in their content. Thus, cannabis is not seen in the early 3rd century C.E. *Leyden Papyrus* [108], nor in the 9th and 10th century C.E. *Chassinat Papyrus* [109], although the latter is incomplete and missing substantial opening portions.

Rather, by this time, Egyptian medicine had become Islamic medicine. A certain ambivalence reigned concerning cannabis, better known as *hashish,* or *shadanaj,* '*the Royal grain*' (*Fig. 5*): while many derided its psychoactive effects on the basis of a ban on intoxicants in Muslim *sharia* law, a begrudging acknowledgement was frequently made of its abundant medical attributes. A full account is beyond the scope of this article, but the interested reader is referred to excellent reviews by *Lozano* for medical issues [87][110], or *Rosenthal* [111] for legal-political aspects. A few highlights may be illustrative, however.

In the 9th century C.E., *Ibn al-Baytar* (*al-Dimashqi*), a native of Moorish Spain who migrated to Egypt, noted the vermicidal and vermifugal properties of cannabis [87], quite in keeping with local traditions of centuries earlier. The same author took note of the ability of cannabis to soothe neuropathic pain, an indication that has seen modern proof in clinical trials [112][113]. In the 10th century, the Egyptian-born physician *Ishaq ibn Sulayman*, also known as *Itzhaq ben Shlomoh Israeli* in Hebrew and *Isaac Judaeus* in the West [114][115], again remarked on the ability of cannabis to treat otalgia or moisture in the ear [87]. In the 12th century, the Jewish philosopher *Mussa bin Maimun* (*Moshe ben Maimon* or *Moses Maimonides*) traveled from his native Spain to become a physician to the Egyptian royal court. He, too, included cannabis in his *materia medica* [116] as *qinnab*, with mention of it as an oil seed, but without discussion of its psychoactive attributes.

As noted by *Rosenthal* [111], there is no documentation of smoking of cannabis in Islamic medicine, and this delivery technique may not have been adopted until after the introduction of tobacco in the 16th century.

At the end of the 16th century, *Prosper Alpinus* (*Prospero Alpini*), a Venetian, reported on the psychoactive properties of Egyptian cannabis [117][118]. Little impact was evident in Europe, however, until the *Napoleonic* invasion of Egypt. A prohibition on cannabis usage was attempted subsequently by the French, but was seemingly no more effective than that imposed by King *al-Zahir Baybars* in the 13th century [119]. Effort was made to advance scientific investigation as *Napoleon* was accompanied by 300 scientists and scholars [120], and, in 1809, *Rouyer* reported on 81 medicinal plants in use in that country, noting the intoxicating effects of electuaries and smoked forms of Egyptian cannabis in contrast to the effects of European hemp strains [121].

The first in-depth Western analysis of the medical benefits of cannabis in Egypt was not undertaken until the 1830s, when, after self-experimentation, *Aubert-Roche* hypothesized that its neurotropic effects might be of benefit in treatment of plague, now known to be an infection due to *Yersinia pestis.* In his hands, hashish treatment yielded resolution of 5/8 buboes and survival of 7/11 patients during an epidemic in Alexandria. Of the latter, he felt cannabis responsible for 5/7 cures. Symptomatic relief seemed apparent for symptoms including prostration, fever, agitation, pain, bronchitis, and sleep disturbance associated with the disease [122]. This publication spurred on new medical applications of cannabis extracts and tinctures in Europe in an analogous

manner to that engendered by *O'Shaughnessy* in India [14][92]. While medical usage in Europe and North America became widespread, it was rarely smoked except as cannabis cigarettes for asthma. Problems with lack of standardization, quality control, and ability to accurately titrate clinical dosing hampered wider acceptance of cannabis medicines, and, subsequently, legal barriers developed by the mid-twentieth century. While opiate alkaloids were isolated early in the 19th century, the identification, isolation, and synthesis of THC was not achieved until 1964 [123]. It was only after this juncture, and the discovery of the cannabinoids receptors in 1988 [124], and anandamide in 1992 [125] that the scientific foundation was uncovered to allow for the re-emergence of cannabis as a modern medicine.

5.2. *Cannabis-Historical Notes from Other Cultures.* Less attention has been paid to what may be extensive early documentation of clinical cannabis from Mesopotamia, that crossroad of history known by many names over the millennia: Sumer, Akkad, Babylonia, Assyria, and now modern Iraq. The recent looting of the Iraq Museum in Baghdad highlights the importance of documenting this ancient heritage properly before it may be irretrievably lost.

The bulk of our knowledge of cannabis and other *material medica* in Mesopotamia derives from the mound of Kouyunjik in ancient Nineveh, across the Tigris River from the modern Iraqi city of Mosul. A great contributor to this literature was *Reginald Campbell Thompson*, who devoted some 50 years of his career to deciphering Assyrian medical texts in cuneiform (*wedge form*), now housed in the British Museum in London (*Fig. 6*). Within the Kouyunjik complex lay the Royal Library of Ashurbanipal, a patron of science and education, who ruled 668–626 B.C. By 1929, a total of 19,000 whole baked clay tablets or pieces thereof had been excavated. Some 660 of these tablets were medical in orientation. These represented the sum of collected knowledge of the preceding Akkadian and Sumerian cultures in the second millennium B.C. The city was ruined by invading Scythians in 612 B.C, after which the site and city of Nineveh were largely ignored for more than 2000 years.

The identity of various ancient drugs is subject to discussion, but *Thompson*'s methods were impeccable in their performance [126–128], over the course of many years joining fragments of cuneiform tablets and deciphering their contents. Each of 660 medical tablets was surveyed, and the relative incidence of each herb was noted. These were scrutinized in light of the plant synonym and equivalent lists from Sumerian and Akkadian (Assyrian) that the ancients provided for their own education [129]. These were then analyzed in view of other ancient and modern Middle Eastern botanical sources, while comparing philological constructs in related languages. *Thompson* lived and worked in the Middle East for decades, expending much effort in increasing his knowledge of indigenous flora [126].

In *Thompson*'s analysis [127], cannabis was known as *azallû* in Akkadian or Ancient Assryian, and *A.ZAL.LA* in Sumerian (*Fig. 5*), and was the 48th most commonly mentioned herb, with *ca.* 30 citations in the Kouyunjik tablets. Some of *Thompson*'s thoughts concerning this identification of cannabis were summarized [130] (p. XVIII):

> Sami nissati *'a drug for sorrow', coupled with the property of spinning and making a cable, makes 'hemp',* Cannabis, *the Indian* bhang, binj, *certain, which is*

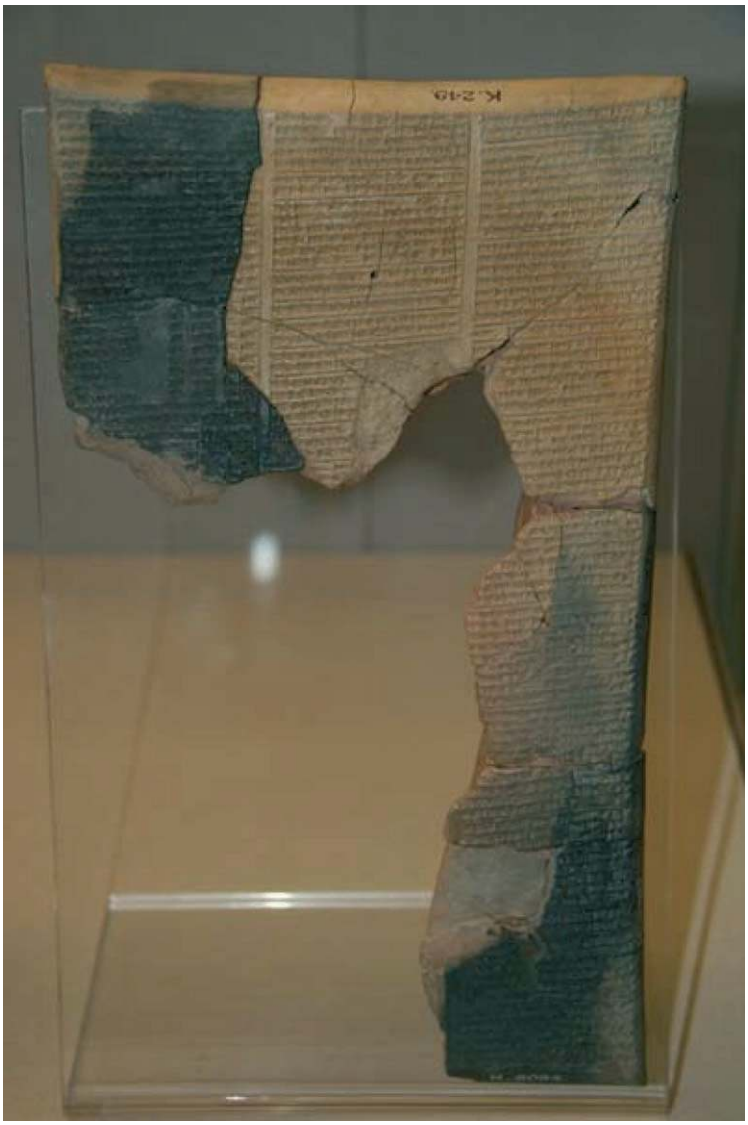


Fig. 6. *Cuneiform clay tablet from the library of Ashurbanipal, Ancient Assyria* (photograph *E. B. R.*, British Museum)

further borne out by the Persian gargarinj, Cannabis sativa, L. *(the* − nj *is a frequent termination)*. GAN.ZI.GUN.NU *is one of the most interesting words in cuneiform; we have already seen that* GAN.ZI.SAR *is* kanasu, *a narcotic "like mandragora", presumably opium;* GUN.NU *is the equivalent of some form of* burrumu, *originally apparently 'to twist, weave' as well as 'to be two-coloured'. Consequently the word* = GAN.ZI + *'weave', i.e.,* the weaving narcotic, and there is great philological similarity between this and the Hindustani *ganjha (cannabis)*, [...].

These views are disputed. In a review, *Farber* [131] pointed out that there is no unequivocal proof of cannabis being the identity of *azallû.* Other dictionaries have conservatively labeled it as '*a medicinal plant*' [132][133], but, many of the great Assyriologists of the age accepted *Thompson*'s assignation, and it is certain that no other known plant in nature aside from cannabis remotely conforms to *Thompson*'s description of its attributes. Although many references to cannabis utilization remain cryptic, descriptions suggest that it could be psychoactive, was used in fabric, was administered as a fumigant, insecticide, orally, cutaneously, and as an enema. It was pounded and strained (as hashish), and its seed, stem, leaf, and flower were all utilized. Recognizable indications included: love potion, impotence, neuralgia, tonic, renal calculi, pulmonary congestion, possible spasticity, depression, and anxiety. The recent identification of '*hand of ghost*' as nocturnal epilepsy [134] is intriguing, as cannabis has anticonvulsant effects mediated by cannabidiol [135], tetrahydrocannabinol [136], and other cannabis components [137] (possibly linalool?). The ability of an insufflated cannabis preparation to treat seizures was also observed by *al-Mayusi* in the 10th and 11th centuries [87].

Another recent finding is intriguing. A '*join*' noted in a previous lacune in an Assyrian clay tablet listing *A.ZAL.LA/azallû* synonyms, was translated to indicate it was '*for or against panic*' (*Irving Finkel*, British Museum, 2003, personal communication), suggesting the duality of cannabinoid activity and its biphasic effects on many symptoms. It could be an early insight into current investigations of emotional modulation by the endocannabinoid system, such as that which demonstrates that aversive memories are under endocannabinoid control [138].

To compare these putative Assyrian indications to the Egyptian prescriptions, cannabis was employed as an anti-inflammatory for skin swelling and bruising, as an enema, fumigant, and for menstrual symptoms. While coincidence is certainly possible, the temporal and symptomatic concordance of the prescriptions is certainly striking, at least, and an alternative identification beyond cannabis strains credulity. Nevertheless, additional examination of the use of cannabis by other ancient peoples may be instructive.

A transition to a new term for cannabis, *kunubu* or *qunnupu,* appeared in Assyria in the 7th century B.C. A document taken from the Royal Correspondence at Kouyounjik, Letter 368 [139] (p. 381) pertains to performance of religious observances undertaken in the court of King *Esarhaddon* (reign 680–669 B.C.) [140] (p. 257), translated as, "*What is used in the sacred rites?' the main items* [...] *for the rites are fine oil, water (?), honey, odorous plants, myrrh (and) hemp*'.

Translating '*Letters and Contracts*, No. 162' [141], *qu-un-na-pu* is noted among a list of spices [142] (p. 13), '*(qunnapu): oil of hemp; hashish*' (translation *E. B. R.*). *Qunnabu* was also noted [143] (p. 306), as an ingredient in a perfume recipe and as a female personal name and 'hypocoristic', or term of endearment! In contrast to *azallû* and *A.ZAL.LA*, there is general agreement on the identification of *qunnabu* as cannabis [143].

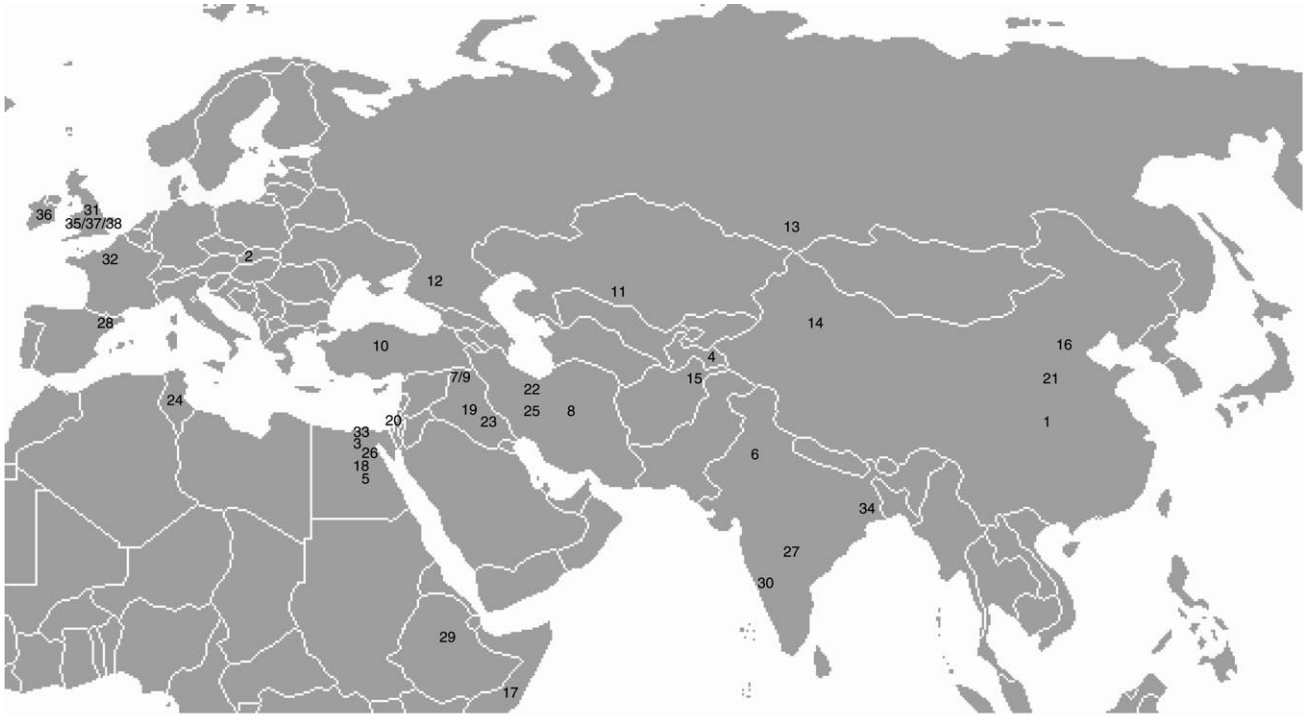
The primary question to submit is whether there is any true support for the contention that cannabis was employed medicinally in the Ancient Middle East. Beyond his prescriptions for cannabis mentioned by name, in the 1st century, *Pliny the Elder* wrote in his *Natural History* [144] (Book XXIV, C. 164), '*The gelotophyllis*

['leaves of laughter'] *grows in Bactria and along the Borysthenes. If this be taken in myrrh and wine all kinds of phantoms beset the mind, causing laughter which persists until the kernels of pine-nuts are taken with pepper and honey in palm wine*'. In subsequent notes (p. 510), the translators identify gelotophyllis as 'Indian hemp, *Cannabis sativa*'. The Borysthenes River of *Pliny*'s narrative is identified as the Dnieper, probably in the present day Ukraine, which was part of the empire and territory of the cannabis-using Scythian tribes, considered subsequently (*Fig. 7*).

The reference to Bactria is key, as actual physical remnants of cannabis flowers and seeds, along with opium poppies and ephedra, dating to the late third or early second millennium B.C. have been excavated in Margiana (in present-day Turkmenistan), one component of what has been labeled the *Bactria-Margiana Archaeological Complex* (*BMAC*). Excavation has yielded artifacts supporting usage of these plants ritually as *haoma-soma* hallucinogens [145][146]. This apparent mixture was one of the key sacraments of the developing Zoroastrian religion of Persia, as noted in the use of *banga* in the *Zend-Avesta* [147], dated to the 7th–10th centuries B.C., or earlier. Again, controversy has dogged the discovery. *Bakels* examined residual seed impressions in gypsum and suggested these as too small to be cannabis, rather suggesting broomcorn millet as having been present [148]. The original description of a higher layer, however, referred to cannabis flowers and seeds [149], and, as noted by *Sarianidi*, *Bakels*' examination took place after several years of exposure of the material to the elements [150]. Additionally, examination of contemporary feral cannabis seeds from Kashmir (*Fig. 1*) indicates that these average 2.2 mm in length (dime is 18 mm, and Chinese culinary seeds are 7.2 mm), while broomcorn millet, *Panicum miliaceum,* seems to average 2.8 mm in diameter.

The use of cannabis in Ancient India was claimed in the *Atharva Veda* (passage 11,6,15) *ca.* 1600 B.C., wherein cannabis or *bhanga,* is one of five herbs employed to '*release us from anxiety*'. [151] (Appendix 3, p. 286) [14]. The latter word is frequently translated as 'grief', nicely echoing the Assyrian citations. Cannabis was said to be well established in Ayurvedic medicine by 300–400 B.C. [55], and subsequent cannabis indications in that discipline and Unani (Arabic medicine) parallel almost all the putative coherent Assyrian claims. Cannabis has over 50 synonyms in India, and has been discussed in detail [14], along with its attendant controversy. Some authorities have questioned whether *bhang* was a psychoactive at all [152], and others have questioned whether references to cannabis in Indian literature are reliable prior to the 11th century C.E. [153][154]. Other authorities have argued linguistic links between the *bhang* of the Arya peoples and those of India from ancient times [155], and linguistic relationships to other cannabis root words *sana, cana, etc*. linking Saka and Harappan/Indus Valley cultures [156]. *Nyberg* [157] noted that the word *bang,* while still signifying cannabis in contemporary Iran, has also been applied to other plants throughout history. Ultimately, he opined that (p. 387), '*We have to conclude that hemp is certainly not identical with* soma/haoma, *although it might have been an ingredient in some preparation derived from the use of the original* soma/haoma'. This is consistent with *Sarianidi*'s claims.

Longstanding debate has also been associated with the issue of cannabis use in the Bible. In 1903, one author surmised it had a role in *Samson*'s strength and the madness



1. Hemp, China, 10,000 BCE
2. Cannabis use, Bylony Culture, Central Europe, 5000 BCE
3. Pyramid Texts, Memphis, 2350 BCE
4. Margiana, 2000 BCE
5. Egyptian Papyri, Thebes, 1700-1300 BCE
6. Atharva Veda, India, 1600 BCE
7. Sumerian/Akkadian cuneiform, Nineveh, circa 1500 BCE
8. Zend Avesta, Persia, 750 BCE
9. kunubu in holy rites, Kouyounjik, 680 BCE
10. Hemp fabric, Gordion, 650 BCE
11. Herodotus, Massagetae, 450 BCE
12. Herodotus, Scythians, 450 BCE
13. Frozen Tombs, Pazyryk, 400 BCE
14. Yanghai Tombs, Turpan, 400 BCE
15. Pliny, Bactria, 1st century CE
16. Shen Nung Pen Tshao Ching, China, 150 BCE
17. Cannabis pollen, Africa, year 0
18. Fayyum Medical Book, Fayyum, 160 CE
19. Babylonian Talmud, 200 CE
20. Burnt cannabis, Beit Shemesh, 350 CE
21. Taoist mystical usage, China, 570 CE
22. *Sabur ibn Sahl*, Persia, 850 CE
23. *al-Kindi*, Iraq, 875 CE
24. *Ishak al-Israeli*, Kairouan, 950 CE
25. *al-Razi*, Persia, 950 CE
26. *Maimonides*, Egypt 1150 CE
27. Anandakanda, Southern India, 1200 CE
28. *Sheshet Benveniste*, Barcelona, 1350 CE
29. Ethiopian pipes, 1350 CE
30. *Garcia da Orta*, Goa, India, 1563
31. *Parkinson*, England, 1640
32. *Marcandier*, France, 1758
33. *Aubert-Roche*, Alexandria, 1836
34. *O'Shaughnessy*, Calcutta, 1839
35. *Clendinning*, London, 1843
36. *Donovan*, Dublin, 1845
37. *Gowers*, London, 1888
38. *Reynolds*, London, 1890 (and before)

Fig. 7. *Pictorial map of cannabis history*

of *Saul*, but the concept was based solely on indirect evidence and hypothesis [158], and has not been accepted with credence. However, subsequently *Benetowa* proposed a similar theory on a stronger philological basis in a Polish publication with a French abstract [159]. Her writings were re-presented a few decades later in English [160]. The reader should note that standard Hebrew calligraphy uses no expressed vowels, and pronunciation is known or assumed from the context (p. 40):

> '*Both in the original Hebrew text of the Old Testament and in the Aramaic translation, the word* kaneh *or* keneh *is used either alone or linked to the adjective* bosm *in Hebrew and* busma *in Aramaic, meaning aromatic. It is* cana *in Sanskrit,* qunnabu *in Assyrian,* kenab *in Persian,* kannab *in Arabic and* kanbun *in Chaldean*. In Exodus 30:23, God directs Moses to make a holy oil composed of 'myrrh, sweet cinnamon, kaneh bosm and kassia'. In many ancient languages, including Hebrew, the root *kan* has a double meaning – both hemp and reed'.

The Biblical passage in question has recently been rendered by *Alter* as follows in a recent new literal translation of the Hebrew Masoretic Text [161] (Exodus 30:22–25, pp. 487–488):

> '*And the Lord spoke to Moses, saying, 'And you, take you choice spices five hundred weight wild myrrh, and aromatic cinnamon, half of that, two hundred fifty weight, and aromatic cane, two hundred fifty weight. And cassia, five hundred weight by the shekel of the sanctuary, and olive oil, a* hin. *And you shall make of it oil for sacred anointing, a perfumer's compound, perfumer's work, sacred anointing oil it shall be*'.

The aromatic cane, *kaneh bosem* (קוח בשם; *Fig. 5*) could also be rendered, 'fragrance stalk'. (*Robert Alter*, personal communication, 2005).

Besides its role in anointing, the holy oil of the Hebrews was burned as incense, its use reserved to the priestly Levite class. Additional citations of *kaneh* (קוח) occur in *Isaiah 43:24*, *Jeremiah 6:20*, *Ezekiel 27:19*, and *Song of Songs 4:14*, but the aromatic adjective *bosem* (בשם) is not included in the Hebrew text. Alternative versions of *Exodus* and other *Dead Sea Scroll* writings reveal no additional mention of *kaneh bosem,* as such (*Eugene Ulrich*, University of Notre Dame, personal communication, 2006). Current estimates posit the writing of *Exodus* to the 8th and 9th centuries B.C. [161], while referring to much earlier events. The Talmudic and modern Hebrew word for hemp, *kanabos* (קנבוס), is tantalizingly similar.

While accepting the possibility of *kaneh bosem* as cannabis, *Mechoulam* favored another item of foreign commerce, *pannagh,* mentioned in *Ezekiel 27:17*, as cognate to the Sanskrit, *bhang* [19]. However, there is likewise debate as to that identification with competing candidates mentioned as diverse as millet (*Panicum*), and even ginseng (*Panax*)!

Additional evidence of biblical cannabis use and parallels to ancient Assyrian rites have been examined in two provocative books [162][163].

Although the issue of its use in the Bible has been hotly debated, physical evidence of medicinal cannabis use in Israel/Palestine was recently discovered [164]. In a burial

tomb in Beit Shemesh (midway between Jerusalem and Tel Aviv), the skeleton of a 14-year-old girl was found along with 4th century C.E. bronze coins. Contained in her pelvic area was the skeleton of a term fetus, of a size to that would disallow a successful vaginal delivery. In her abdominal area, gray carbonized material was noted and analyzed, yielding TLC and NMR spectroscopy evidence of Δ^8-THC, a more stable trace component of cannabis. It was surmised that the cannabis had been burned at an unsuccessful attempt at delivery of the fetus, perhaps paralleling the ancient Egyptian usage.

Additional physical evidence of early use of cannabis was discovered in the form of hempen textiles in grave mounds at Gordion in Turkey, woven by Phrygian people sometime before the 7th century B.C. [165].

Cannabis is mentioned twice in *The Syriac Book of Medicines* [166], once as hemp fabric used to treat anal fissures, and once as *bungh* for excessive spittle.

The Babylonian Talmud, written over the first several centuries C.E., also mentions cannabis in relation to laws related to cultivation of like crops in the fields. A continuity of cannabis in Jewish medicine is apparent in the works of *Maimonides* [116], *Ishak* [87] (*vide supra*), and *Sheshet Benveniste ha-Nasi*, a 12th-century C.E. scholar and physician who published in Barcelona an herbal formula whose efficacy was reportedly confirmed in clinical experiments [167] (p. 198–199):

> '*Take nard, mastic, saffron, cassia, a very hard canella wood, sweet costus, hemp* [קנבוס], *cardamom seed, the fruit of nutmeg, male ginger, galangal, black and long pepper, pure frankincense, aloe wood, tamarisk, nutmeg peel of dry citron, dry cydonias, peeled* trianguli *and peel of pistachio.* [...] *they will eat the amount of a big nut* [...]. *It provides many benefits, such as strengthening sexual desire, curing sterility, repairing all the ailments of the womb, of the stomach and the head, and it is called the head shield*'.

The classical Greek literature also documented knowledge of the inebriating actions of cannabis. *Herodotus*, *ca.* 450 B.C., described how a Central Asian tribe beyond the Araxes River, the Massagetae, an Iranian people, sought an altered state of consciousness as a group experience [168] (p. 89) (Book 1, Verse 202):

> '*They have also discovered a kind of plant whose fruit they use when they meet in groups. They light a bonfire, sit around it, throw this fruit on the fire, and sniff the smoke rising from the burning fruit they have thrown onto the fire. The fruit is the equivalent there to wine in Greece: they get intoxicated from the smoke, and then they throw more fruit on to the fire and get even more intoxicated, until they eventually stand up and dance, and burst into song*'.

This passage would strongly hint at cannabis usage, while the next passage is explicit in use of that word, (*κάνναβις*; *Fig. 5*), in clarifying Scythian ritual [168] (p. 259) (Book 4, Verses 73–75):

> '*After burying their dead, Scythians purify themselves. First they anoint and rinse their hair, then for their bodies, they lean three poles against one another, cover the*

poles with felted woolen blankets, making sure that they fit together as tightly as possible, and then put red-hot stones from the fire on to a dish which has been placed in the middle of the pole-and-blanket structure.

Now, there is a plant growing in their country called cannabis, which closely resembles flax, except that cannabis is thicker-stemmed and taller. In Scythia, in fact, it is far taller. It grows wild, but is also cultivated, and the Thracians use it, as well as flax, for making clothes [...].

Anyway, the Scythians take cannabis seeds, crawl in under the felt blankets, and throw the seeds on to the glowing stones. The seeds then emit dense smoke and fumes, much more than any vapour-bath in Greece. The Scythians shriek with delight at the fumes.

These same Scythians were notable horsemen who traveled and traded widely between China, the Middle East, and Eastern Europe. Physical evidence of their use of cannabis has been unearthed [169][170]. The 'Frozen Tombs' of Pazyryk, dated to the 5th–3rd centuries B.C., were excavated earlier the 20th century in the Altai Mountains of Siberia. *Artamonov* (1965) recovered a small tent and a copper censer containing burned hemp seeds, felt to be utilized much as in the ritual *Herodotus* described. *Rudenko* (1970) also described a leather flask containing hemp seeds, and asserted that smoking of cannabis occurred in everyday life, and not merely as a funerary rite. These seeds (*Fig. 8*) are quite tiny and marbled, consistent with observations by *Vavilov* for wild cannabis strains [53], and recent agronomic analysis [41].

Fig. 8. *Seeds of Scythian cannabis from Pazyryk, Siberia, Russia* (photo *E. B. R.*, with permission from the collection of *David Watson*, *HortaPharm BV*, Amsterdam)

Further unequivocal physical evidence of ancient cannabis usage has been reported from the Yanghai Tombs in the Turpan District of the Xinghian-Uighur Autonomous Region in China [171]. A large amount of cannabis radiocarbon dated to 2500 years ago was found in the tomb of a Caucasoid male, dressed as a shaman. This material was unusually well preserved in the dry and cold environment such that gross and scanning electron microscopic features including glandular trichomes have been preserved. This site and contents resemble those of other 'mummies' of the Tarim Basin associated with hemp artifacts [172]. These nomads may have been speakers of Tocharian, an Indo-European language, and, as the Yuezhi-Kushan people [173], may have provided cultural linkage and possible passage of cannabis knowledge to and from China and India.

The history of cannabis in China is an extensive topic. Physical evidence of hemp fiber usage dates back perhaps 12,000 years [17][21][174], and cannabis seed was one of the staple grains in the region from ancient times, as well. The pictographic representation of cannabis or *ma* (*Fig. 5*) is easily recognizable as stalks of hemp hanging inverted in a shed to dry. The dioecious nature of cannabis, the superiority of male plants for fiber, and female for intoxication were established at very early dates with advanced descriptions of various preparations in the 3rd century B.C. lexicon *Erh-ya* [175]. While oral tradition dictates that the Emperor *Shen-Nung* prescribed cannabis in the 28th century B.C., this was not transcribed until the 2nd century C.E. in the *Shen Nung Pen Tshao Ching* wherein a neuroprotective effect was suggested [176] (p. 148) that, '*Protracted taking may make one fat, strong, and never senile*'. Jumping ahead a few millennia, the well-documented Indian treatise, *Anandakanda*, *ca.* 1200 C.E., suggested strong neuroprotective effects of cannabis as part of a rigorous medical, religious, and ritualistic regimen of celibacy [14], as translated by *Dash* [177] (p. 246), '*it is claimed that the man lives 300 years free from any disease and sign of old age*'. A more recent claim was noted later in the West, when Sir *John Russell Reynolds* wrote of his experience with *Cannabis indica* in treating dementia [178]:

> *In senile insomnia, with wandering; where an elderly person probably with brain-softening, in the 'delirium form' (Durand–Fardel) is fidgety at night, goes to bed, gets up again, and fusses over his clothes and his drawers; thinks that he has some appointment to keep, and must dress himself and go out to keep it; but may be quite rational during the day, with its stimuli and real occupations. In this class of case I have found nothing comparable in utility to a moderate dose of Indian hemp-viz., one-quarter to one-third of a grain of the extract, given at bedtime. It has been absolutely successful for months, and indeed years, without an increase of the dose.*

Here, we have a classic description of 'sun-downing' in incipient *Alzheimer*'s disease, possibly never better portrayed. We also have documentation of a decided tonic effect in keeping the disease at bay for some interval. Modern research has indicated the benefit of THC in agitation of senile dementia [179], but there is every reason to believe that better results would accrue both in terms of clinical benefit and neuroprotection with the additional activity of CBD [180]. Subsequent research has provided more compelling evidence of cannabinoid benefit in preventing microglial activation [181], amyloid deposition [182], and possible benefits on memory due to anticholinesterase effects [183].

In the 2nd century in China, cannabis was reported as a surgical anesthetic when mixed with wine [184].

In an interesting parallel to Middle Eastern and Indian cultures, *Souberain* indicates that crushed cannabis seeds were also utilized in China as an anti-helminthic [185].

Cannabis was also integrated into shamanic and religious rites, and *Needham* reports that cannabis was added to incense burners before 570 C.E. as reported in the Taoist *Wu Shang Pi Yao*, *Essentials of the Matchless Books* [186]. Subsequent ritual religious usage in China is difficult to document, however.

The history of medicinal cannabis in Europe is too extensive to cover here, but has been addressed nicely in other publications. *Kabelik et al.* claimed use by the Bylony Culture in Central Europe from 5000 B.C. [86]. Diligence is required to recognize that most Renaissance herbalists employed native hemp strains of *Cannabis sativa* that were highly CBD-predominant with little or no THC content, while, after 1840, Asian *Cannabis indica* strains containing THC were more often utilized (*vide infra*).

Cannabis has been present in sub-Saharan Africa for at least 2000 years, based on pollen samples [17], and was found incorporated into medical practice of many cultures throughout the continent. An extensive multi-ethnic survey of cannabis (*dagga*) usage has been undertaken in South Africa by *Du Toit* [187]. Various citations attest to medical applications, including a pain-killing tea for headache among the Zulu, and cannabis treatment of headache other traditional cultures, the East Indian and Caucasian minorities, and extensive usage in obstetrical practice. Archeological evidence of cannabis residue in pipes from 14th century Ethiopia has been reported [188].

Cannabis came to the New World in Brazil early in the 15th century concomitant with the slave trade from Africa [189]. It was incorporated into the folk medicine of that country for indications such as rheumatism and toothache [190], and spread rapidly throughout the hemisphere. There is no established documentation of native cannabis in the Western Hemisphere before this time.

6. Miscellaneous Cannabis Oddities and First Mentions. – In this section, various unusual prescriptions and preparations of cannabis will be introduced, that deserve further attention and possible investigation utilizing modern research techniques.

The 9th-century was a rich time for cannabis medicine, and saw the merging of Egyptian and Greek teachings with new experimentation on the herb in the Middle East. The Nestorian-Persian physician *Sabur ibn Sahl* cited use of cannabis various times in his dispensatorium, *Al-Aqrabadhin Al-Saghir*, the earliest known compendium of pharmacology in Arabic [191]. Dr. *Indalecio Lozano* has translated the text (personal communication, 2000), pointing out that *ibn Sahl* described a compound mixture of herbs, including juice extracted from cannabis flowers and seeds utilized to treat migraine, aching pains including uterine, and prevent miscarriage. This preparation was administered *via* instillation into the nostril of the afflicted patient, and likely represents a first mention of cannabis for migraine [8], and a sensible parenteral form of administration. It also highlights the biphasic nature of cannabinoid effects, such that early over-exposure may prevent pregnancy [192], while later cannabinoid effects may preserve it [9].

Also in the 9th century, *al-Kindi* was a great scientist and physician, whose work has been commemorated on a modern Syrian postage stamp (*Fig. 9*). His passage on

cannabis may be the first report of its muscle relaxant properties as he expands and expounds on previous reports [193] (p. 196):

> **197.** *Galen says that hasheesh, which is called 'the trembling', eases the muscles of the limbs and what flows, and he says, 'It also produces senseless talk'.*

Subsequently, *O'Shaughnessy* noted efficacy of cannabis extracts to produce survival in tetanus in India in 1839 [92], from whence its utilization as a muscle relaxant and antispasmodic in Britain and North America spread rapidly.

Spasticity in multiple sclerosis and other diseases remains a difficult treatment challenge. It was recently demonstrated that spasticity in affected animals is under tonic control of the endocannabinoid system: CB_1 agonists including THC ameliorate

Fig. 9. *Syrian postage stamp commemorating* al-Kindi, *employer of cannabis as a muscle relaxant*

spasticity, while antagonists such as SR141716A (Rimonabant) exacerbate it [194]. Cannabinoid (CB_1) receptors are densely represented in cortical and basal ganglia areas subserving motor control and their corresponding cerebellar counterparts [195]. Endocannabinoid functions are also prominent in interneurons of the spinal cord [196] and neocortex [197] that may relate to pathophysiological mechanisms of spasticity. Clinical work to date has shown considerable benefit of cannabinoid treatment of this disorder [198–200]

Another great Persian physician, *al-Razi*, was probably the first to report in the early 10th century that topical treatment with cannabis leaves would stimulate hair growth [87]. In a fascinating parallel, a similar claim of cannabis benefiting alopecia has been advanced by the Chinese [201] (p. 91), '*The leaves are considered to be poisonous, and the freshly expressed juice is used as an antihelmintic, in scorpion stings, to stop the hair from falling out and to prevent it from turning grey*'. This phenomenon of similar medical claims appearing in separate cultures as support of biological activity is a hallmark of ethnobotany, and strongly supports the need for further investigation of cannabis for proof of pertinent operative mechanisms. Possibilities to explain effects allaying baldness could include anti-inflammatory or anti-oxidant effects of phytocannabinoids or terpenoids, or 5-α-reductase activity of its β-sitosterol component [4].

In 1563, *Garcia da Orta*, a Spanish Jew in service to the Portuguese crown, published the first account of Indian hemp in a modern European language from Goa, India. He noted [202] (p. 56), '*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*'. These observations were supported by observations of work capacity in 20th-century Jamaica [203], while benefit of cannabis preparations in spurring appetite that has been exploited in treatment of HIV/AIDS [204] and cancer chemotherapy [205]. Unknown to him at the time was that this plant also harbored cannabinoids with anorectic effects, such as THCV, that one day might be utilized clinically to allay hunger in obese patients [39][206].

A watershed moment in the history of cannabis as medicine was ushered in by the experiments of *William Brooke O'Shaughnessy* in India in the late 1830s [92]. His incorporation of folk knowledge and application of the scientific method quickly led to the adoption of cannabis extracts and tinctures in Europe and North America. He brought a large supply of cannabis herbal material with him to England from Calcutta, and generously provided this to physicians throughout the British Isles in the form of Squire's Extract, a tincture of Indian hemp. In 1984, a stored sample of this preparation was analyzed *via* gas chromatography and mass spectrometry [207], yielding traces of THC, a greater amount of cannabinol (CBN, breakdown product of THC), various new substances of oxidative origin, but also a generous amount of cannabichromene (CBC). Cannabis plants containing THC with significant complements of CBC are actually quite rare in the annals of cannabinoid analysis. Another such specimen from Durgapur in Western Bengal was analyzed in 1979 [208] to yield 4.43% THC and 0.32% CBC. Could CBC have contributed, in some unique manner, to the benefits attributed to Squire's Extract? This possibility should be considered, as CBC, a known anti-inflammatory analgesic, is also a strong anti-fungal (reviewed in [4]), cytotoxic agent for malignant cells [104], and recently has been reported to demonstrate anti-depressant effects in a rodent model [209].

One of the physicians to utilize Squire's tincture in his practice was *John Clendinning* in London in 1843 [8][210], wherein he became the first Westerner to successfully treat migraine with the material, apparently on himself and several patients. *Michael Donovan* in Dublin [211] enjoyed similar success in migraine, and extended indications to a variety of neuropathic pain syndromes in 1851 [212], presaging clinical trials in the 21st century [213]. *Donovan* was also the first Westerner to note success in treating including trigeminal neuralgia, a claim echoed by Sir *John Russell Reynolds*, *Queen Victoria*'s personal physician, in 1890 [178].

A rather extensive report on the medical value of cannabis extracts and tinctures appeared in the USA in 1860 [214], and included the case of a man with 'hysterical insanity', who displayed episodes of high energy during which he thought himself to be a great inventor, succeeded by times of despair and utter inertia that were likely due to bipolar disease. A tincture of Indian hemp evened the patient's mood, similarly to modern anecdotal reports [215]. A recent review examined the likely benefits of THC and CBD in bipolarity [216], with a recommendation for clinical trials.

It is well-established that THC is anti-emetic, probably based on activity on 5-HT_3 receptors [217], and recently reported brainstem CB_2 receptors modulating anti-emesis [218]. Such mechanisms may be operative in the dangerous syndromes of *hyperemesis gravidarum*, a near fatal case of which was successfully treated with *Cannabis indica* by *Wright* in Ohio in 1862 [219]. Anecdotal and survey reports of efficacy in *hyperemesis gravidarum* continue to the present time [9][220][221], but have not been accompanied by any clinical trial investigation. Given the pathophysiological mystery, and high morbidity and mortality of this affliction, it remains a possible candidate for research.

Prior consideration has been given to neuroprotection *via* cannabinoids. Another empirical example may be apparent in 19th century treatment of *Parkinson* disease. The great neurologist Sir *William Gowers* described its various treatments in 1888 [222] (p. 1012): '*Many of them, especially morphia, conium (Berger), hyoscyamin (Charcot and Oulmont), and Indian hemp, quiet the tremor for a time*'. More intriguing, however, is his description of long-term benefit after prolonged administration (p. 1013):

> '*In one case tremor had commenced in the right arm and leg an hour after a railway accident, and extended, three months later into the left arm. Two years subsequently there was constant lateral movement at the wrist joints, but no tremor of the fingers. A great improvement occurred on Indian hemp, and a year later the tremor had almost ceased, being occasional only*'.

Modern clinical experience with cannabinoids in tremor of multiple sclerosis has yielded mixed results [198][223], with isolated benefit in certain subjects. However, anecdotal information suggests that tremor, bradykinesia, dyskinesia, and other symptoms of *Parkinson* disease may improve with prolonged administration, as was evidenced in a carefully prepared survey study in the Czech Republic in which oral cannabis administration produced sustained benefits only after some several weeks of usage [224]. Given the strong representation of the endocannabinoid system in the basal ganglia underlying *Parkinson* disease mechanisms [225][226], there seems to be a

strong basis for extended clinical trials to capitalize on any neuroprotective or neuromodulatory mechanisms that might be operative with cannabinoid treatment.

Another disorder that has remained problematic to treat is chronic daily headache, an evolutive subset of migraine, often associated with analgesic abuse of aspirin, acetaminophen, or opiates [227]. The first description of this syndrome may well have been that of *Stephen Mackenzie* in 1887 (p. 97) [228], '*The headache to which I wish to draw attention is of a dull, continuous or subcontinuous character, attended sometimes with paroxysmal exacerbations*'. In his hands, he stated of tincture of Indian hemp (p. 97): '*In the majority of cases, it cures the complaint*'. This benefit was obtained after some weeks to months of administration, but persisted after tapering of treatment. Equivalent results with any treatment in the 21st century would be considered unattainable, as the syndrome remains recalcitrant to treatment, and extremely prone to relapse after initial perceived benefits of a given intervention [227]. Further study is warranted [8][229].

Mackenzie's success with cannabis was echoed by *C. R. Marshall* in 1905 [230], who, while noting the decline in contemporary indications for the drug, observed (p. 451): '*It appears, however, to be useful in headache of a dull continuous character*'. Some years earlier, during attempts to isolate from cannabis its active ingredient, *Marshall* experimented with a highly concentrated ethereal extract of cannabis dubbed 'cannabinol' that he placed in his mouth with a glass rod [231]. He noted a local anesthetic effect on tissues of the mouth, followed in 45 minutes by psychoactive effects, with offset in 2½ hours, and disappearance in three. Given that effects of oral cannabis are often slower than this, we may have here the first example of oromucosal administration of cannabis extract, an approach currently utilized for *Sativex* in clinical practice [232][233], but with accompanying modulatory benefits of cannabidiol [59].

7. Conclusions. – This survey has attempted to present a historical background to cannabis and cannabis preparations as medicine, and place these materials in a contemporary scientific context. It is the author's opinion that, while technology of modern humanity has surely advanced over the centuries, it is unlikely that our cerebral evolution has been so rapid that we can claim compelling evidence of superiority of intellect and powers of observation over our immediate ancestors. Thus, their discoveries and experiments demonstrate important insights that may well retain valid lessons that modern science should utilize as points of departure for further research. It remains necessary and proper that the ancient clinical claims be scrutinized with randomized controlled clinical trials that represent the standard for regulatory approval of all medicines, including cannabinoid-based medicines, to ensure their safety and efficacy [58]. We should most assuredly continue to 'mine the past' [234] and 'prospect' for clues and promising leads in clinical research from the experiences of those who have previously trod similar ground with cannabis, the chemical chameleon and most promising medicinal plant.

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