



Review

Cannabis and epilepsy: An ancient treatment returns to the fore



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ABSTRACT

Cannabis has been associated with the treatment of epilepsy throughout history, and if ancient Assyrian sources referring to “hand of ghost” are considered credible, this relationship may span four millennia. A tradition of usage continued in Arabic medicine and Ayurvedic practice in India, which led, in turn, to early experiments in Europe and North America with “Indian hemp.” Lack of standardization, bioavailability issues, and ultimately prohibition were all factors in cannabis-based medicines failing to maintain mainstream usage in seizure treatment, but investigation was resumed in the 1970s with interesting signals noted in both laboratory and clinical settings. Early case studies showed promise, but lacked sufficient rigor. Resumption of research coupled with mass experimentation by families of epilepsy patients has led to intense interest in cannabis-based medicines for its treatment once more, with greatest focus on cannabidiol, but additional investigation of tetrahydrocannabinol, tetrahydrocannabinolic acid, and other phytocannabinoids.

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1. Introduction

Epilepsy has afflicted mankind from a time before recorded history, and has figured in the earliest writings of ancient peoples, along with their varied interpretations of its meaning, significance, and treatment. While many of the early interventions would seem magical, superstitious, or worse to modern practitioners, these interventions often included elaborate recipes of herbs, some of which would be recognized today as pharmacologically active. Noteworthy among these was cannabis, either as a simple (sole agent) or *theriac* (complex mixture). It was only in the 19th century that more formal observations of cannabis with presumably THC-predominant preparations as an anticonvulsant were undertaken, and only in the last few years that rigorous clinical trials have been initiated with the seemingly more versatile, less controversial cannabidiol (CBD).

1.1. Ancient Asian sources and sorcery

The strongest evidence for use of cannabis comes from Mesopotamia, that area of the Fertile Crescent that lies at the crossroads of history, and has seen countless dominant cultures over time. Its ancient *materia medica* was best preserved in the mound of Kouyunjik in Nineveh, on

the Tigris River near modern Mosul, Iraq. For some five decades, Reginald Campbell Thompson studied Assyrian medical texts from the Royal Library of Ashurbanipal, who ruled 668–626 BCE. Six hundred-odd broken tablets compiled the writings of the much earlier Akkadian and Sumerian cultures dating to the second millennium BCE [1–3].

While it may be impossible to guarantee the identity of medicinal plants in the tablets with assurance, some 30 references to *azallû* in Akkadian (Ancient Assyrian), and *AZALLA* in Sumerian were felt to clearly point to cannabis, as summarized in an examination of its synonyms [4](p. XVIII):

Sami nissati ‘a drug for sorrow’, coupled with the property of spinning and making a cable, makes ‘hemp’, *Cannabis*, the Indian *bhāng*, *binj*, certain, which is 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 assignments have been disputed [5], but as discussed in greater detail in a prior publication [6], many of Thompson’s contemporaries and successors accepted Thompson’s interpretations, and no alternative identities would come close to fitting the descriptions of a plant that suggested

Abbreviations: CBD, cannabidiol; CBDA, cannabidiolic acid; CBN, cannabinol; ED₅₀, effective dose in 50%; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV, tetrahydrocannabinavarin.

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psychoactivity, was a source of fiber, was insecticidal, and could be delivered by fumigation, orally, cutaneously, or per rectum. The plant in question was pounded and filtered as is done with hashish to this day, and its seed, stem, leaf, and flower were all employed. Indications described for this medicinal plant included: amorous aid, erectile dysfunction, neuropathic-type pain, tonic benefits, urinary stones, lung congestion, possible spasticity, anxiety, grief, and depression.

Pertinent to the subject of epilepsy, numerous passages in the Kouyunjik cuneiform refer to treatment of a condition labeled “hand of ghost.” One example is cited twice (K. 2448 + 6836 and K. 2615) [7] (1, 4, 4) and (99, 2, 4), transliterated [8] (p. 524), “AZALLA U.HLA *sindi sa qat etemmi*” and translated [9] (p. 21), “Root of caper which is on a grave, root of acacia, right horn of an ox, left(?) horn of a kid that has been covered, seed of tamarisk, seed of laurel, *Cannabis*; these seven drugs area cataplasm for the hand of a ghost, with which to bind his temples.” A similar account appears elsewhere (K. 7642) [7] (102, 39).

Another passage is noted (K. 6261) [7] (89, 1, 5) translated [9] (p. 22):

—[*Calendula*], *Chrysanthemum segetum*, lupins, asa(dulcis), IR.KULLA-plant, EL.KULLA-plant, —*Crataegus Azarolus*(?), tamarisk, seed of tamarisk, —tragacanth, the plant *Alasara*(?), black [alum], white alum, nitre, AZAG.PAD-salt, roses, *Cannabis*, fir-turpentine, pine-turpentine, *nuhurtu*-asafoetida, root of *nuhurtu*-asafoetida, the plant *kansam*, mustard, shoot of *Conium maculatum*, rue, fennel, mint, Amni, hellebore, asafoetida. Thirty-two drugs for removing sorcery, either in wine or in beer in GIS.LIS of tamarisk he shall drink.

An additional example is (K. 8127 + 8438) [7] (90, r.20), translated [9] (p. 25), surmising this to be a “neuralgia” [7]:

—that “stoppage of Life” [which besets(?)] that man should not draw nigh his body — hellebore, seed of *Cannabis*, mint, the *azallu*-plant, seed of *Solanum*, seed of daisy, together three grains each in honey of the mountains, oil and *kurunnu*-beer thou shalt mix, let it stand under the stars, in the morning before the sun he shall drink, stand on bitumen, look on lapis, cinnabar (carnelian, gold, silver, and he shall be freed.)

“Hand of a ghost” also appears in the prescription (K. 2477) [7] (94, 2, ii, 12), translated [10] (p. 804), “—and talks much—the hand of a ghost,—*Cannabis*, styrax, oak, *Ricinus*, *Oenanthe*, linseed, kelp (?), myrrh, wax of honey, *lidrusa*-plant, sweet oil, together thou shalt mix, anoint him therewith in oil.”

In an article on diseases of the ears (K. 3486) [11] (97, 6), this account is found, “Lupins, *Calendula*, *Chrysanthemum segetum*, mustard, hellebore, seed of [tamarisk(?)], —*Cannabis*, *Asa foetida* (*nuhurtu*), *Asa foetida* (*tiatu*), mint, twelve drugs for [the hand of a ghost(?)].”

“Hand of ghost” was apparently also treated internally by cannabis [3] (p. 221) [7] (K. 4609.8) (76, 1, 21), and [8] (p. 524), “AZALLA —*ina sikari* NAG.MES-*ma ina'es* he drinks in beer [cannabis] (among 12 herbs for the ‘hand of a ghost.’)” Such administration would certainly increase the likelihood of actual true pharmacological effects in epilepsy for seizures.

Finally, fumigation was also employed for this affliction [7] (K. 8867) (99, 3, r.4), supporting the concept of a parenteral administration of the drug for an acute benefit on seizures.

Thompson never identified the diagnostic entity “hand of ghost” definitively, but later work by an Assyriologist/neurologist team seems to have settled the issue [12], as this syndrome clearly was one associated with epilepsy. Their treatise, based on translation of Neo-Assyrian tablets dating from 718 to 612 BCE, unmistakably describes the various attributes of seizure disorders (auras, tonic extension, absence, complex partial and even gelastic spells) in striking variety (p. 187):

We may say a few words about the “ghosts”— without perhaps straying too far down the dark alleyways of strange arguments. Ghosts roam at night, or may do so, and it is directly clear from the text itself that *sibit etemmi*, “seizure by a ghost”, and *qat etemmi*,

“hand of a ghost” were (or, more accurately, could be) the ancient terms for nocturnal epilepsy.

Also noted [12] (p. 187):

Similarly, the observation of TDP 34, 13: “If his forehead is ‘seized’ and pains him without appeasement from sunrise to sunset, it is ‘hand of ghost’”, will suitably refer to nocturnal (or, specifically, early morning) epilepsy, with severe headache, as commonly, continuing thereafter throughout the day.

The treatise also included prognostic features associated with epileptic variants. Then, as now, the outcome was sometimes fatal [12] (pp. 189):

9–10. [if an] epilepsy demon falls again and again upon him, his eyes are suffused with blood—R: and he blinks his eyes;—if his lower (*var.*: his upper) cheek areas twitch and his hands and feet are extended; if when the exorcist comes to see him *hope is perishing* that he will ever regain consciousness, —hand of the ghost of a murderer. (He will die).

An additional citation adds more detail [12] (p. 190):

16. If at the end of his fit when his limbs become relaxed again his bowels are sometimes seized and has a motion, it is “hand of ghost” (nocturnal epilepsy).

17–18. If at the end of his fit his limbs become paralysed, he is dazed (or dizzy), his abdomen is “wasted” (*sc.*, as of one in need of food) and he returns everything which put into his mouth—, —hand of a ghost who has died in a mass killing, He will die.

Another detailed passage indicates [12] (p. 191):

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27. If his seizure (or Possession) always takes place in the evening, it is the seizure of a ghost (nocturnal epilepsy).

a) Two symptom entries

28. If ditto, he has a feeling of distention in his epigastrium and “his legs are lifted up” (*i.e.*, he sits motionless(?)), —seizure by a ghost.

29. If ditto, he has a feeling of distention in his abdomen and is restless until the middle of the night (*sc.*, when “relieved” by hi fit), seizure by a ghost.

30. If ditto, his eyes become cloudy and his ears hiss, seizure by a ghost.

b) One symptom entries

31. If ditto, and his ears hiss, —seizure by a ghost.

32. If ditto, and his ears (or, hearing) become “paralysed”, —seizure by a ghost.

33. If ditto, and his forehead aches, seizure by a ghost.

34. If ditto, and at the time of his possession he is hot and from the evening watch until the middle watch he remains awake, (waiting) for him, —seizure by a ghost.

46. If his possessing demon begins to possess him in the late afternoon, and that the time of his possession he has —, his forehead and his eyes oppress him and he has internal (or, stomach) pains, —hand of ghost.

Cannabis has an ancient history in ethnobotanical usage in India, as well [13]. Cannabis was one of the primary agents employed for rejuvenation and as a synergist in combination with other herbs [14], to promote health, and to prevent disease. Its primary indications were ordered as follows: sprue syndrome, sterility, impotency, diarrhea, indigestion, epilepsy, insanity, and colic pain.

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