

An introduction to the ethnopharmacology of Cannabis.

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Abstract.

With the recent passing of Federal legislation and subsequent release of the Narcotic Drugs Amendment Act (2016) in Australia, the re-introduction of cannabis back into the therapeutic armamentarium of medical practitioners is underway. Whilst touted as a new therapy in most academic and medical arenas, cannabis has been utilised as a medicine by numerous cultures for millennia, and a journey through historical records confirms the modern science behind the history of use for many clinical indications of this plant. This review seeks to provide a broad overview of this ethnopharmacological record to demonstrate that cannabis is not a new drug therapy discovered by science, but rather is experiencing a renaissance after 80 years of prohibition. Whilst not the panacea many advocates and the media express it to be, mounting scientific evidence supports the adoption of this plant based medicine across a growing number of clinical indications.

“If you would understand anything, observe its beginning and its development”.

– Aristotle (384-322BCE).

Introduction

The Cannabis family (Cannabaceae) comprises 10 genera and approximately 180 species and is extent throughout tropical and temperate environments worldwide. (1) Of these genera, it is the Cannabis genus (mainly *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*) that has been firmly intertwined with human evolution throughout the Ages. The dried inflorescences (i.e. florets), leaves, seeds, bast fibre and glandular trichomes (i.e. hashish) harvested off the inflorescences of the Cannabis plant have been a valuable commodity and medicine to our hominid ancestors for over 10,000 years. (2, 3)

Believed to have originated in central Asia, (3, 4) many scholars place the centre of *Cannabis* genus diversity possibly occurring in a region extending from the Pamir plain of Tajikistan, which borders Afghanistan, Kyrgyzstan and the Xinjiang region of Western China. (5) However, more recent ethnobotanic modelling is indicative cannabis may have originated in the Himalayan mountains from Kashmir through to Nepal and even into Bhutan and Burma, (3, 6, 7) and likely spread from there through human usage and trade. Specific psychoactive chemovars rich in Δ^9 -tetrahydrocannabinol (THC) likely originated in these Himalayan regions whereby it spread through China, India, the Middle East and regions of Northern Africa via established trade routes. The seeds of such plants, and others, would have been highly valued for their medicinal qualities and allowed for the spread and cultivation of this plant, and its own hybridisation and evolution, to occur across the ancient world. (3)

Determining the exact time that our hominid ancestors began using *Cannabis* sp. is challenging to quantitate due to the fact its cultivation, use and consumption very likely predated currently accepted archaeological timelines for the appearance of writing in human evolution. (4) Some of the earliest evidence of human usage of *Cannabis* sp is as a fibre in net making by the Gravettians, an Upper Palaeolithic industrial culture ranging from Spain to Russia. (8) Primarily hunters and gatherers, evidence shows that hunting nets made from cannabis fibre were used by these people and have been dated from between 24,980 to 22,870 BCE. (9) Ethnobotanical evidence from Taiwan posits that cannabis was used as a fibre some 10,000 years ago (10) and suggests that various *Cannabis* sp. have been used since the late Neolithic period (4000-2000 BCE) throughout Asia as a medicine, fibre crop, food and also as an entheogen. (11, 12)

Ethnopharmacological use (Before the Common Era)

Whilst still contested, recent archaeological evidence is suggestive that human civilisation is ostensibly much older than currently believed, and that the human ancestral story is potentially incomplete. Monolithic stone temple structures with ornate carvings have been uncovered in Turkey at a site called Gobekli Tepe, which have been carbon dated to 9130BCE. (13) If proven accurate, this would be one of the oldest examples of ancient civilisation, which would predate most of what is extent in Egypt by some 5000 years, and predate Stonehenge by 6,000 years. (14) During a period where humanity was largely believed to be nomadic hunter-gatherers, it could be posited that such civilisations may have used plants such as cannabis much earlier than previously documented. Archaeological investigation of the site is ongoing and at this time, no samples of plant material or pottery having been found.

Conversely, conclusive scientifically verified archaeological evidence of cannabis use was first observed in China, attributed to the Chinese Emperor

Shen Nung (ca. 2700BCE), (4, 15, 16) based on the *Shen-Nung Pen-tSao Ching* (Divine Husbandman's *Materia Medica*). In this publication, cannabis was utilised for senility, appetite stimulation, rheumatic pain, constipation and disorders of the female reproductive system. (17-20)

Following a descending timeline, it is purported that the Pyramid texts (ca 2350BCE) mention Cannabis as the *Shemshemet* plant which translators cite as a plant from "which ropes are made from". (21, 22) This correlates with reports in other cultures where *Azallu*, the name ascribed to cannabis from the Assyrian culture (ca 1800BCE) possesses the "property of spinning and making cable". (23) The Assyrians utilised cannabis medicinally for grief, epilepsy (medical anthropologists believe this condition was described as the "Hand of the Ghost"), fumigant and insecticide. (5, 20, 24, 25) Thompson further translates that it was a "Drug for Sorrow", (23) possibly being the first recorded mention of cannabis use for depression. Less sophisticated use for cannabis was reported 100 years later in Egypt in the *Papyrus Ramesseum III* (1700BCE) where it was reportedly used for non-specific eye disorders. (5)

Ayurvedic medicine from India also has early documentation recording cannabis use medicinally. In the *Atharvaveda* (1600BCE), cannabis is named *Bhanga* and was revered as one of five herbs that Grierson (26) states were used to relieve anxiety. (5, 27, 28) In 1550BCE, cannabis was reported in the *Ebers Papyrus* of Egypt as being useful as a poultice for infection and was even used vaginally for gynaecological disorders. (5, 22, 29) Cannabis use in infection may well have made use of the terpenes and terpenoids contained within the plant, many which have noted scientifically validated antimicrobial activities. (30) This potential use of cannabis for infection was mirrored in the *Hearst Papyrus* of 1550BCE where it was recorded being useful as a poultice for maladies of the extremities, with further support from the *Berlin Papyrus* of 1300BCE, discovered at the ancient Egyptian site of Saqqara, where it was alleged to have been useful as an ointment for driving away fever (due to infection) and was also suggested that burning the vapours as a fumigant was of medicinal benefit. (5, 20)

500 years later, the *Sushruta Samhita* from India, a text compiled between 800-300BCE, recommended the use of cannabis for diarrhoea, catarrh and phlegm producing conditions of the chest. The *Sushruta* was an epic medical text of the age, cataloging some 1120 illnesses with over 700 medicinal plants within 184 chapters that focused on subject matter pertinent to anatomy, prognosis, pharmacology and toxicology. (28, 31)

During this same time period (ca 750BCE), Russo posits that cannabis was described as *Kaneh Bosem* (translated as "fragrant stalk" or "aromatic cane") and was part of the holy anointing oil of the Hebrew nation. It was mentioned in the Books of Exodus, Ezekiel, Jeremiah and Song of Songs. (5) Similar

evidence of cannabis use in China was discovered dating to 700BCE, when in 2008, researchers found the remains of a Caucasoid shaman in the Yanghai tombs near Xinjiang province. (32) The remains included archery equipment, a harp, bridles and a wooden bowl filled with 700g of cannabis of a high THC chemovar type, showing that local inhabitants revered this plant and the shaman was likely of high social status. (32)

Some 6000 kilometers away in Persia, the Zoroastrian text known as the *Zend Avesta* was written and has been dated to 600BCE. (33) Within this text cannabis (*Banghem*) was listed as one of four herbs that were prohibited as they could cause abortion; the psychoactive effects of the herb also likely being associated with evil or dark magic. A very different view of cannabis was recorded in 215BCE in China within the *Erh-Ya*, one of the oldest surviving encyclopaedias in the world. (20) Cannabis is stated as being a dioecious plant (separate male and female plants), with the unknown author stating that the male plants were better used as a fibre and the female plants making superior medicines (34)...a finding that is still utilised in cannabis cultivation to the present day. (5)

Ethnopharmacological use (Common Era)

Because of established trade routes throughout Asia and the Middle East, the medicinal knowledge attributed to cannabis spread throughout the Mediterranean region with the Greek historian Herodotus (ca. 484–425 BCE) writing of cannabis use by the Scythians in the 5th century BCE. (10) The classic Greek herbalists Dioscorides, Galen and Pliny (35) wrote of the medicinal virtues of this plant in detail, with Dioscorides (40-90CE) describing the plant in his *magnum opus De Materia Medica*, which was used throughout the world as a foundational medicinal text for almost 1500 years. Dioscorides attributed anti-inflammatory and anti-oedematous activity to cannabis, suggesting it could be of use in arthritis and also wrote of the green fresh juice being useful in otalgia. (5, 36) Interestingly, Dioscorides did not write of its analgesic and psychotropic activity. (36)

Pliny the Elder (23-79CE), author of *Naturalis Historia*, described cannabis having medicinal virtue in clinical indications such as gout, arthritis and diarrhoea and referred specifically to cannabis as *gelatophyllis* (i.e. Leaves of Laughter) from Bactria (Central Asia), (5, 20) denoting the psychoactivity of plants from that region which we now know were likely high in THC. Similarly, the noted physician Galen (ca. 129-216CE) described cannabis as being a narcotic and in his book, *On the Properties of Foods*, described it being cooked into desserts and used for its mild relaxant and narcotic effects. (5, 20, 37)



Figure 1: A hand painted illustration of Cannabis taken from an Arabic copy of *De Materia Medica* circa 15th Century.

The use of cannabis in the management of pain was also appearing in other cultures at this time. In China, the noted physician Hua-Tuo (ca140-208CE) of the Han Dynasty published on the topic of anaesthesia. He used cannabis powder as an infusion in wine as an analgesic for surgery and other painful ailments. (19, 20) Evidence of cannabis being used in labour pain has also been found in Israel, where the remains of a 14-year-old girl were found in a cave who died in childbirth. Analysis of material found at the sight determined it contained phytocannabinoid metabolites and Zias (38) believes it was burnt in a vessel to ease the pain and suffering via an inhaled route. (20, 39)

This knowledge naturally disseminated into the Middle East, with numerous Arabic physicians writing about *Cannabis sp.* in managing various pathologies, including *Ibn al-Baytar*, *Ishaq ibn Sulayman* (5) and the famous Avicenna (*ibn Sina*), who wrote of it in the *Canon of Medicine* (ca. 1025AD). *Jabir ibn Hayyan* (721-815CE), known as Geber in the West, was a polymath who

wrote extensively across many subjects including pharmacy, astrology, philosophy and medicine. He wrote purposely of the medicinal effects of cannabis as an analgesic, which *Ali ibn Abbas Al-Majusi* (ca 900-1000CE) agreed with, also including muscular spasm and extolling the virtues of the plant for epilepsy. (20, 40, 41) Avicenna (980-1037CE), one of the greatest writers and polymaths of the Islamic Golden Age, praised the cannabis plant for other indications, including fever, tumours and otalgia.(40)

Whilst deemed an inebriant and forbidden under Islamic law recreationally, it was nonetheless still revered as a medicine. With the Moorish conquest of the Iberian peninsula (i.e. Spain and Portugal) in the 8th Century, and later parts of North Africa, *Cannabis sp.* were likely brought and spread to places like Northern Morocco, (42) where it still currently inhabits large regions through areas such as the Rif Mountains. This has been posited as a potential route of dispersal through Western Europe.

Hildegard von Bingen (1098-1179CE), a German Benedictine nun and author of *Physica*, documented the use of cannabis for headache and wound management. This sentiment was largely reflected in the *Codex Vindobonensis 93* (ca. 1300CE) housed in the Austrian National Library which also outlined the use of the plant topically in balms and ointments for mastalgia, pain and swelling. (20, 43)

By the 16th Century, cannabis was enjoying continued use as a medicine in India with Da Orta recording clinical observations of the time including allaying anxiety, engendering laughter, increasing appetite and improving work. (44) Continuing the theme of Indian medicine, the Unani system of medicine (i.e. a form of ancient Greek medicine that evolved within Arabic medicine and was practiced in India), described cannabis as an intoxicant and sedative. During this same time in China, *Li Shizhen* (1518-1593CE) wrote the *Compendium of Materia Medica*, which took 27 years to complete. He advocated the use of cannabis for menstrual disorders and associated pain, along with post-partum haemorrhage. (20, 43)

Wrapping up the 18th century was the botanical characterisation and description of *Cannabis sativa* in 1753 (45) by the famous Swedish zoologist, botanist and natural philosopher Carl Linnaeus (1707-1778CE). *Cannabis indica* was later characterised by French biologist Jean Lamarck some 32 years later in 1785. (20)

Ethnopharmacological use (19th century - present day)

Credited with bringing cannabis into Western medicine, the Irish physician William Brooke O'Shaughnessy (1809-1889) was an assistant surgeon contracted to the East India Company. He became fascinated with the therapeutic benefits of the *Cannabis* genus whilst in India, identifying



antiemetic, appetite stimulant, analgesic, muscle relaxant and anticonvulsant actions. (4) He brought this information back to London and was elected into the Royal Society as a Fellow for his contributions to Science.

In his publication, *On the Preparations of the Indian Hemp or Gunjah* published in the Provincial Medical Journal, O'Shaughnessy (Pictured left) listed uses for cannabis including tetanus, cramps, delirium tremens and rheumatism and is quoted as stating after his experience in India that his travels had "led him to believe that in Hemp the profession has gained an anticonvulsant remedy of greatest

value". (20, 46)

Physicians started showing great interest in the plant and with it, a growing body of evidence was being collected. Later in 1843, Clendinning (47) wrote of the benefits of cannabis for the treatment of coughs, rheumatic joint pain and migraine, with opiate withdrawal (20, 47, 48) also being mentioned as a clinically useful application for the plant...a finding that recent scientific studies out of the USA in states that have medicinal cannabis programs have strongly supported when it comes to statistics on reduction in pharmaceutical opioid overdose mortality rates. (49, 50)

By 1848, Cannabis was increasingly being utilised clinically, with physicians reporting its benefit in neuralgia, (51) uterine haemorrhage, (52) enhancing uterine contraction, (53) hyperemesis gravidarum (43) and assisting in restoring natural sleep cycles, the latter being tested by Fronmueller (54) on 1000 patients and reported in 1860. (20) Such support saw cannabis officially included in the United States Pharmacopoeia of 1851, where it was utilised for dysmenorrhoea, shingles, migraine, endometritis, opium withdrawal, nervous headache, infantile convulsions, dementia, sciatica, chronic cystitis, gastric ulcers and chronic alcoholism.

Interest and application of cannabis continued in successive decades, and between 1870 – 1890, it was reported as clinically useful for melancholia, obsession and anxiety (55) with the British Medical Journal reporting benefit in mental depression with insomnia. (56) Migraine prophylaxis, dysmenorrhoea, (57), tremor of Parkinson's Disease, (58) senility and childhood convulsions

also reported benefit from cannabis between the years 1886 – 1890; the latter indication being reported in the Lancet. (59) Another now famous academic institution, the Journal of the American Medical Association, celebrated the impact of cannabis in chronic daily headache. (60) Furthermore, support for cannabis having advantages over opiates for pain management was published by Hare in 1887. (61)

Medical evidence for cannabis continued to be collected between 1900 and 1940, but had largely reached its pinnacle. Having two world wars within this time frame drastically impacted importing and growing of high quality cannabis for medical use. Fankhauser ascribes the main reasons for the decline of cannabis during this period as being the rise of pharmaceutical development, plant based instability of active constituents, economic aspects driving price up and newly imposed legal restrictions in the mid 1930's. (46)

At the birth of the 20th Century, medicine and pharmaceutical sciences now started focusing on single isolated active constituents as medicines, and cannabis came up against barbiturates and other drugs for pain relieving activity. The pharmaceutical industry as we know it today was in its genesis, and also started having more influence over politics and regulations. Science and medicine was now after the active constituents, the silver bullet if you will, and was moving away from plant based medicines that utilised a broad spectrum of active ingredients. Considering that scientists had still not isolated the active principles in cannabis at this time (which would not actually happen until Gaoni and Mechoulam identified THC in 1964), (62) this did not bode well. Cannabis was also being transported from all over the world and was not stored in favorable conditions, greatly impacting quality assurance, which also put many doctors off prescribing it as they wanted reproducible results.

Regulations and Restrictions

This lack of standardisation, quality assurance and therefore an inability to accurately titrate dose hampered cannabis use in a growing scientific evidence-based medical profession in the early to mid-20th century. (5) Yet this was just the beginning of the plant's fall from grace...

The International Opium Commission held a conference in 1909 in Shanghai due to international concerns over the opium trade that included countries such as the USA, China, France, UK, Japan, Persia, Russia and Portugal. (63) This later led to the International Opium Convention, which was the first international drug control treaty in world history, and was signed at the Hague in January 1912. (63) This convention stated that the signatories would to everything within their power to control all persons manufacturing, importing, selling and distributing morphine, cocaine and their respective salts. (63) Whilst this has little to do with cannabis at this point, a subcommittee

recommended that a prohibition on hashish, that is cannabis, be added to the convention as it was not at present being utilised primarily for medical purposes and had potential to cause harm. (63) The Egyptian delegate mentioned it was at least as harmful as opium and was the principle cause of cases of insanity in Egypt. (63) Whilst it was not signed into the initial treaty, it was outlined that international shipments of cannabis could only be conducted for medical or scientific purposes

But it wasn't until 1937 that US authorities, under Harry Anslinger, condemned the use of cannabis after the lifting of alcohol prohibition and passed the *Marijuana Tax Act*, which effectively made it illegal by tying it up in regulation and being cost prohibitive. This was opposed by the then President of the American Medical Association, Dr. W.C. Woodward. Anslinger referred to the previous International Opium Convention reports that suggested cannabis was not a medicine, but rather a drug, and combined this with an effective propaganda campaign that saw it passed into law that same year. Cannabis was then officially removed from the United States Pharmacopoeia in 1942.

The rest of the world quickly caught up to this new prohibition with the passing of the United Nations *Single Convention on Narcotic Drugs* in 1961 which classified cannabis as a Schedule 1 (less restrictive) and Schedule 4 (most restrictive) substance, being able to be used only for medical or scientific purposes. (63) As the medical profession had largely abandoned cannabis by the 1960's, this effectively stifled use. A decade later, the United Nations released the *Convention on Psychotropic Substances* in 1971, incorporating many of the hallucinogenic drugs that were popular during the counter-culture movement. It also reclassified the scheduling process with Schedule 1 being the most restrictive and Schedule 4 being more lenient. (63) Interestingly, it also rescheduled dronabinol (Synthetically derived THC) as a less restrictive schedule 2 substance but classified plant derived cannabis in Schedule 1 (i.e. no perceived medical benefit). (63) This eventually led to *Cannabis sp* being classified as a Schedule 1 drug of addiction in accordance with the Controlled Substances Act (USA) under President Nixon, and international laws prohibited its trade and use soon after. The War on Drugs had now been officially declared and such classification stifled research into the medical benefits of the cannabis plant for decades after.

Conclusion

It is only now, in certain international jurisdictions and after isolating many of the key phytochemicals within the various *Cannabis* species, that this plant medicine is being reintroduced to the medical armamentarium and gaining acceptance once more. Advances in cultivation, phytochemical analysis and understanding environmental input requirements of cannabis allows for a product that can now be grown to high quality assurance standards in line

with Good Manufacturing Practice, and meeting limits for standardisation of active constituents. Clinical trial evidence is growing, and interestingly, much of it is confirming the reports of the ethnopharmacological usage of ancient cultures and more recent medical use of the plant in the 19th century.

Cannabis is experiencing a renaissance, with many countries around the world adopting it back into accepted usage, with Australia formally doing so with the Narcotic Drugs Amendment Act in 2016. Australia had until recently classified cannabis as a Schedule 9 substance (Drug of Dependence) in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), but has recently down-scheduled cannabidiol (CBD) to Schedule 4 and THC to Schedule 8. Interestingly, the World Health Organizations' Expert Committee on Drug Dependence stated that CBD should not really be scheduled at all due to its safety profile. (64)

Whilst still notoriously difficult to procure due to regulatory red tape, (65) some 519 patients have been approved to use cannabis medicinally in Australia for certain authorised clinical indications as of March 18, 2018. As medical practitioners around the world educate themselves about the therapeutic benefit of the *Cannabis* genus, and the Endocannabinoid System (an entire neuromodulatory system responsible for homeostatic regulation which we would know nothing about if it was not for research into cannabis) upon which the plant interacts, it is hoped this number grows far higher, both at home and abroad.

Authors note:

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