An Indian Perspective on Cannabis for Treatment of Pain

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ABSTRACT

The history related to the use of medicinal Cannabis has been intimately intertwined with India since the beginnings of human civilization. Since its origin in the lower Himalayas, the diverse cultural, medical and religious uses of the Cannabis plant slowly disseminated around the world. After being outlawed as a narcotic drug in the 20th century, Cannabis has been rediscovered as a much needed medicine for chronically ill patients. Since 2000, a number of countries have initialized national programs to cultivate and distribute Cannabis for medical use, and to stimulate research and development to produce modern medicines from this ancient plant. Unfortunately and ironically, India has not benefitted from these developments, despite the countries' claim to fame as a major source of information about the medicinal uses of Cannabis. In India untreated chronic pain is one of the major sources of patient's sufferings and Cannabis medicine can prove to be a welcome alternative to the much more risky opioids derived from the Opium poppy. This review paper explores the origins of Cannabis medicine in India, its historical use as a treatment for chronic pain, and recent scientific developments with Cannabis and its main active constituents, the cannabinoids. Finally, the cannabinoids are compared to opioids for the treatment of pain, in order to make a recommendation for the reintroduction of Cannabis medicine for pain treatment in India today.

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INTRODUCTION

The history of India and the history of Cannabis are intimately intertwined. For at least the last 4600 years, Cannabis has been continuously cultivated and used in Northern India, according to archeological findings[1]. Around 1000 BCE, the medicinal use of Cannabis took definite root in Indian culture. Then, from its origins in the lower Himalayas, the Cannabis plant (*Cannabis sativa* L.) gradually spread over the world. (**Figure 1**).
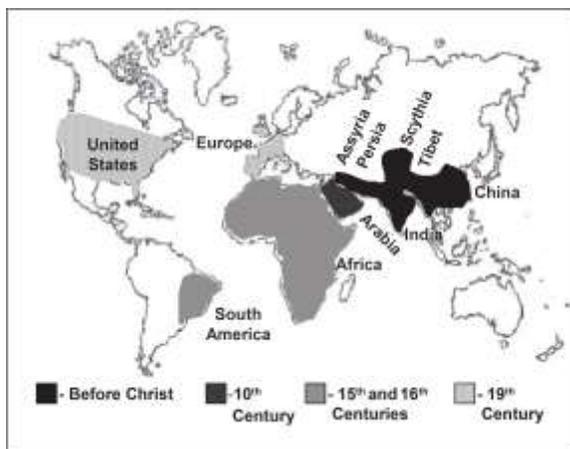

Figure 1 The spreading of medicinal Cannabis use around the world (Taken from Zuardi[13])

Over the millenia, it has been used as a source of fibre, food, (seed) oil and medicine as well as for recreational, religious and spiritual purposes. For example, an ancient mystical *sutra* tells us that Siddhartha (later known as lord *Buddha*) survived for six years, prior to his enlightenment, on a single Cannabis seed per day[2]. Cannabis is believed to be the favorite plant of Hindu god Shiva, and has been an integral part of Hindu practice and culture for ages[3-9]. Also, Muslims regarded it as a holy plant and in Unani Tibbi (the Muslim system of medicine) Cannabis was used for treating numerous diseases[10-12]. However, nowhere do the many applications of the Cannabis plant become more apparent than in the ancient tradition of Ayurvedic medicine. Ayurveda, combining the Sanskrit words for *life* and *knowledge*, is a system of medicine typically based on complex herbal compounds, often mixed with minerals or metal substances. This system has survived for over 3000 years and has been well documented, making it one of the most important sources of traditional knowledge on medicine in the world. These days the medicinal use of Cannabis is rapidly becoming more accepted worldwide, Ayurvedic knowledge on the risks and benefits of this plant is more valuable than ever. By combining traditional and cultural knowledge about Cannabis use with the modern demands of scientific research, medicinal Cannabis may once again move to the forefront of Indian medicine. After all, no other country can boast such a wealth of traditional use of Cannabis, combined with a

well documented history of its risks and benefits.

In fact, India is one of the few places in the world with a true traditional use of medicinal Cannabis; in most other places, the only actual traditional use of Cannabis is in fact its abuse as a narcotic drug. India has the knowledge, tools and means to develop new Cannabis-based medicines that can embrace the best of two worlds *viz*., the traditional preparations and administration forms of the past (perhaps in combination with other herbs and ingredients), and modern-day clinical proof on safety and efficacy. Bringing these sources of knowledge together surely has the potential to develop holistic Cannabis-based medicines, fully supported by clinical trials, but with low abuse potential. The most promising area for the development of such products is chronic neuropathic pain, a medical indication that is severely undertreated in India today. This paper explores the different aspects and implications of this idea.

The long history of Cannabis in India

Cannabis is among the earliest plants cultivated by mankind. The first evidence of its use for medicinal or cultural purpose was found in China, but there the medical use of Cannabis never reached the importance it did in India[10,13]. Nowadays, the strong smelling annual herb is occurring throughout the western Himalayas up to 2400m and is abundantly found throughout the greater part of India.

The earliest written reference to Cannabis in India may occur in the *Atharvaveda*, dating to about 1500 BCE[14,15]. This ancient document hails the 'bhang' plant as one of the five sacred plants and as a source of happiness, donator of joy, and bringer of freedom[16]; "We tell of the five kingdoms of herbs headed by Soma; may it, and kusa grass, and bhang and barley, and the herb saha, release us from anxiety." Grierson[15] suggested this text to be part of an offering, and ingestion or burning would both be typical of ancient practices for this purpose. In the *Sushruta Samhita* (meaning: the verses of Sushruta), dating from around 500 BCE, Cannabis was recommended for phlegm, catarrh and diarrhoea[14,15]. The Sushruta Samhita is among the most important ancient medical treatises, and one of the foundational texts of the medical tradition in India. The *Rajanighantu*, also known as Abhidhana Cudamani, is the famous work of Narahari Pandita, son of Iśvarasuri, who was a resident of Kashmir

around 1300 AD[14,15]. The manuscript mentions Cannabis among various important medicinal plants. It states that "its effects on man are described as excitant, heating, astringent; it destroys phlegm, expels flatulence, induces costiveness, sharpens the memory, excites appetite, etc."

About two centuries ago the modern age of Cannabis investigation began in India. In 1839, the seminal work of Sir William B. O'Shaughnessy on Cannabis was written[17], and then republished in England a few years later[18]. It was titled '*On the preparations of the Indian Hemp or Gunjah*'. O'Shaughnessy served as a medical doctor in India with the British and made his first contact with Cannabis use there. Unlike the European fiber Cannabis, these Indian varieties did contain a significant amount of bioactive chemicals called cannabinoids (see below), as a result of the hot climate they were growing in, and the genetic types of Cannabis (varieties) present in India. He studied the literature on the plant, described many popular preparations, and evaluated its toxicity in animals. O'Shaughnessy also described various successful human experiments using controlled doses of Cannabis preparations for several common diseases of the time. This work basically constituted the first real clinical trials with Cannabis. In his writings, Cannabis was identified as potential treatment for a wide range of disorders including cholera, rheumatic diseases, rabies, and infantile convulsions. For the first time in history, miraculous recoveries were evidenced in a series of tetanus victims, due to the therapeutic properties of Cannabis[19,20].

In 1877, the Bengal Government appointed a special officer, named Babu Hem Chunder Kerr, to make a full inquiry into the details of cultivation of Cannabis in India. The *Kerr report* submitted an extremely detailed report encompassing history, religious context, cultivation and employment of Cannabis in all its preparations[21]. This would form an important source for the subsequent *Report of the Indian Hemp Drugs Commission*[16] which was subsequently published in 1894 (**Figure 2**).
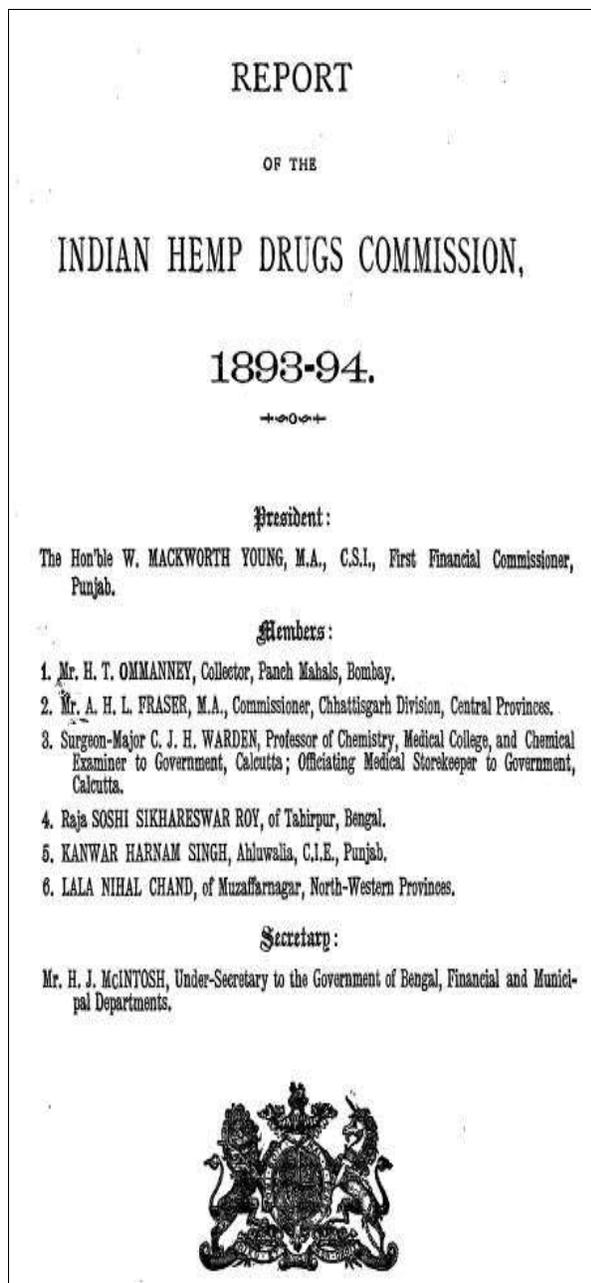
REPORT

OF THE

INDIAN HEMP DRUGS COMMISSION,

1893-94.

President:

The Hon'ble W. MACKWORTH YOUNG, M.A., C.S.I., First Financial Commissioner, Punjab.

Members:

1. Mr. H. T. OMMANNEY, Collector, Panch Mahals, Bombay.
2. Mr. A. H. L. FRASER, M.A., Commissioner, Chhattisgarh Division, Central Provinces.
3. Surgeon-Major C. J. H. WARDEN, Professor of Chemistry, Medical College, and Chemical Examiner to Government, Calcutta; Officiating Medical Storekeeper to Government, Calcutta.
4. Raja SOSHI SIKHARESWAR ROY, of Tahirpur, Bengal.
5. KANWAR HARNAM SINGH, Ahluwalia, C.I.E., Punjab.
6. LALA NIHAL CHAND, of Muzaffarnagar, North-Western Provinces.

Secretary:

Mr. H. J. McINTOSH, Under-Secretary to the Government of Bengal, Financial and Municipal Departments.

Figure 2 Opening page of the report of the Indian Hemp Drugs Commission[16]

Its findings exceeded 3000 pages after exhaustive investigation and testimony, and may be summarized as follows[22] : (1) Moderate use of Cannabis drugs had no appreciable physical effects on the body. As with all drugs, excessive use could weaken the body and render it more susceptible to diseases. Such circumstances were not peculiar to Cannabis, however. (2) Moderate use of Cannabis drugs had no adverse effect on the brain, except possibly for individuals predisposed to act abnormally. Excessive use, on the other hand, could lead to mental instability and ultimately to insanity in individuals predisposed by heredity to mental disorders. (3) Moderate use of Cannabis drugs had no adverse influence on morality. Excessive usage, however, could result in moral degradation. Although in certain rare cases Cannabis intoxication could result in violence, such cases were few and far between. The commission advocated against governmental suppression of Cannabis drugs. In the report[12], many positive statements accompanied descriptions of their religious associations, and particularly their legion medical usage, both human and veterinary. The report concluded that: "Cannabis indica must be looked upon as one of the most important drugs of Indian Materia Medica."

Despite such nuanced recommendations, the British Government of India finally prohibited consumption of Cannabis resin in India in the 1930's. Since then the cultivation and use of Cannabis has

dwindled[23]. These decisions were closely linked to developments that happened in other parts of the world. At that time, the active principle of Cannabis had not yet been isolated and the drug was used in the form of tinctures or extracts whose power was dependent on different factors, such as origin and age of the plant, and mode of preparation[19]. Unfortunately, no laboratory techniques existed at the time to check the quality of Cannabis products. In addition, various medications appeared in the early 20th century, with known efficacy for the treatment of the same main indications that Cannabis was typically used for. Fore example, vaccines were developed for various infectious diseases, such as tetanus. Meanwhile, effective analgesics such as aspirin appeared, and the recently invented hypodermic needle allowed the injectable use of morphine. As a narcotic and sedative, Cannabis was rivalled by newly developed substances such as chloral hydrate, paraldehyde and barbiturates[19]. As a result, from 1954 onwards the World Health Organization (WHO) started proclaiming that Cannabis and its preparations no longer served any useful medical purpose and were therefore essentially obsolete. In subsequent years, the medicinal use of Cannabis gradually disappeared from all medical pharmacopoeias all over the world.

Despite these challenges, Cannabis use remained common in 20th-century India. As recent as 1957, two authorities in India noted in their review paper '*The use of Cannabis drugs in India*' that[23]; "Cannabis undoubtedly has remarkable therapeutic properties; …the drug has no constipating action, it does not depress the respiratory centre (as opioids do); and there is little or no liability to addiction formation". In 1965, Dwarakanath[24] listed the names of 48 modern Ayurvedic and eight Unani Tibbi formulas containing Cannabis for a wide range of indications in a *Report to the United Nations*. The author felt that a legitimate role for Cannabis products persisted, stating that: "these drugs should be allowed to be used by Ayurvedic and Unani physicians until such time as the benefits of modern medicine are extended to rural areas. Banning their use by the large mass of Ayurvedic and Unani physicians for therapeutic purposes may create a vacuum which may not be easily filled for a long time to come." Unfortunately, the vacuum left by banning Cannabis, particularly for the treatment of severe pain, has still not been filled sufficiently by other medications even today[25,26].

Presently, the plant is popularly known in India mainly as a source of narcotics in various forms and names, such as bhang, charas, ganja, marijuana, hashish, weed, grass etc. It is illegal to produce, manufacture, possess, sell, purchase, transport, use, consume, import or export any narcotic drug or psychotropic substance except for medical or scientific purposes under the Narcotic Drugs and Psychotropic Substances Act in India[27]. Nevertheless, cultural use remains common in various parts of India and in surrounding countries such as Nepal[26]. Efforts for research and cultivation of varieties of Cannabis called industrial hemp are increasingly being undertaken in many countries across the world. Hemp is a type of Cannabis with no abuse potential, but with an excellent quality of fibers and very nutritious seeds. Hemp grows very well in India and is currently being reintroduced as an agricultural crop e.g. for local manufacturing of textiles (e.g. Bombay Hemp Company; www.boheco.org).

Cannabis as a well-known remedy for pain

In recent years, self-medicating patients from around the world have ascribed a long list of therapeutic effects to Cannabis, but many of these claims have not yet undergone rigorous clinical testing in humans. In fact, the limited evidence available today on the risks and benefits of medicinal Cannabis remains a major obstacle for its acceptance by medical professionals[28]. More studies are certainly needed in order to use Cannabis responsibly, but the large number of Cannabis products in use today, combined with the many medical indications that Cannabis could potentially be beneficial for, make it nearly impossible to decide which studies should be funded and executed first. When deciding which medical claims seem to be most reliable, and should therefore be further investigated in modern studies, a look at historical records may help us in the right direction.

Throughout history, one of the most persistent medical uses of Cannabis is the treatment of intense pain. Indeed, the application of this plant as a potent analgesic has been described in many ancient texts and traditional practices. The uses range from drinking milk medicated with Cannabis, to applying an external compress and fumigation for pain relief[29]. Based on its narcotic properties Cannabis seems to have been used as an anaesthetic by the ancient Indian and Chinese surgeons, sometimes in

combination with alcohol[30]. It was used as a household remedy and by Hakims (Unani physicians) and Vaidyas (Ayurvedic physicians) as pain-reliever as well as appetizer, aphrodisiac, antispasmodic, antidiarrheal and diuretic[23]. The 18th century Persian medical text Makhzan-al-Adwiya, written by M. Husain Khan (as described by O'Shaughnessy[18]), was extremely influential in the Unani Tibbi, or Arabic-tradition medicine on the Indian subcontinent. In it, Cannabis was described in its various preparations as an intoxicant, stimulant and sedative, but also as treatment for inflammations and neuralgic pains.

After the introduction of Cannabis from India into Europe in the mid-19th century, a number of medical practitioners both in India and in Great Britain soon noted success in the use of Cannabis for treatment of migraine, as well as neuropathic and other pain conditions[31,32]. As a result, in 1860 the first clinical conference about Cannabis took place in America, organized by the Ohio State Medical Society[33]. In the second half of the 19th century, over 100 scientific articles were published in Europe and the United States about the therapeutic value of Cannabis[34]. However, the climax of the medical use of Cannabis by Western medicine occurred in the late 19th and early

20th century. Many famous laboratories marketed extracts or tinctures containing Cannabis, including Merck in Germany, Burroughs-Wellcome in England, and Bristol-Meyers Squibb, Parke-Davis and Eli Lilly in the United States[19]. Many of those products were focused on treating various types of pain. The scientist Dymock, in Europe around 1890, illustrated such use of Cannabis quite well when he stated[35] : "I have given the [Cannabis] extract in doses of from 1/2 to 1 grain to a large number of hospital patients suffering from chronic rheumatism; it entirely relieved the pains".

In India, treatment of pain conditions with Cannabis products extended well into the 20th century. For example, the use of Cannabis in Unani medicine around the 1950s included treatment of insomnia, migraine, neuralgic pains, asthma, etc.[23]. In a 1962 book about medicinal plants of India[36], the author stated: "Cannabis resin is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, for migraine, anaesthetic in dysmenorrhea, neuralgia, severe pains of various kinds of corns, etc." And in 1965, Dwarakanath[24] maintained that Cannabis was employed in Indian folk medicine in aphrodisiacs and as treatment for pain.

Around the same time, Sanyal[37] observed that: "They also used the fumes of burning Indian Hemp (Cannabis Indica) as an anaesthetic from ancient times…". In 1977, Sharma[11] noted that "even today [Cannabis] is used with restraint and judgment by students of Indian medicine. There are reports claiming the value of Cannabis in the treatment of high blood pressure, migraine headaches, and even cancer." Interestingly, the use of concentrated Cannabis extracts for the treatment, and possibly even curing, of cancer is once again in the spotlights, after recent studies showed a remarkable effect of isolated cannabinoids on a range of cancer cell types *in vitro* and *in vivo*[38].

In 1996 an interesting scientific experiment took place, when Indian native Cannabis was extracted and used to treat cancer pain in a modern clinical trial with 42 human subjects[39]. Although some patients felt no analgesia with doses of 25 mg of extract, the majority of patients experienced more than 50% pain relief with no use of adjunctive medicine. By any modern standards this is an impressive and significant therapeutic effect. Since the mid-1990s, many of the traditional claims made for Cannabis have been investigated in modern studies around the world, and some even have become accepted as a proven treatment. As a result,

fully regisered products such as Marinol® (containing synthetic THC in sesame oil), Nabilone® (a synthetic analogue of THC) and Sativex® (a mixture of THC- and CBD-rich Cannabis extracts) were developed and these are now available on prescription in many countries.

In the neurological realm, the ability of Cannabis to treat severe pain is the subject of a great deal of current research. Results to date are very encouraging, in terms of basic understanding of the biochemical pathways involved[40,41] as well as the benefits seen in clinical trials[42,43]. Cannabis seems to be most efficient in the treatment of neuropathic types of pain, which means that the source of the pain originates from damage of the nervous system itself. In contrast, acute types of pain do not seem to respond as well to cannabinoid treatment[44]. The safety profile of cannabinoids was found to be very acceptable when used in doses appropriately for medical treatment[45-47].

Based on modern pharmacology, it is now understood that the analgesic effects of cannabinoids are caused by their interaction with the endogenous cannabinoid (endocannabinoid) system[48]. In short, plant-derived cannabinoids are able to interact with the body's own endocannabinoids, by

binding to so-called cannabinoid-binding (CB) receptors, of which currently two types are known. CB1 receptors modulate neurotransmitter release in the brain and spinal cord, where they are present in high densities in certain parts of the central nervous system[49]. They are also present in nociceptive and nonnociceptive sensory neurons of the dorsal root ganglion and trigeminal ganglion[50], as well as in defense cells such as macrophages, mast cells, and epidermal keratinocytes[51]. CB2 receptors are expressed at considerable levels in cells of the immune system[52], where they regulate neuroimmune interactions and can interfere with inflammatory hyperalgesia. Other receptors are believed to respond to (endo)cannabinoids a well, including the orphan receptor GPR55, and the vanilloid receptor TRPV1[53]. These receptors have become an important target for the development of a new generation of pain medication[53,54].

Comparing cannabinoids to opioids

Severe pain can have a wide range of sources, including infection, injury, cancer or auto-immune disease. Throughout medical history the various origins of pain have been notoriously difficult to classify and to treat. Because pain cannot be directly measured on an objective scale, it is important to believe the patient when he describes his level of pain. In medical research, pain intensity is therefore scored using a Visual Analogue Scale (VAS) or a Numeric Rating Scale (NRS) where patients indicate their pain on a scale typically ranging from 0 (no pain at all) to 10 (worst pain imaginable)[55]. However, the subjective nature of pain makes it difficult to accurately determine the exact effect of any pain medication on a patient.

The "pain ladder", or analgesic ladder, was created by the World Health Organization (WHO) as a guideline for the use of drugs in the management of pain (**Figure 3**).
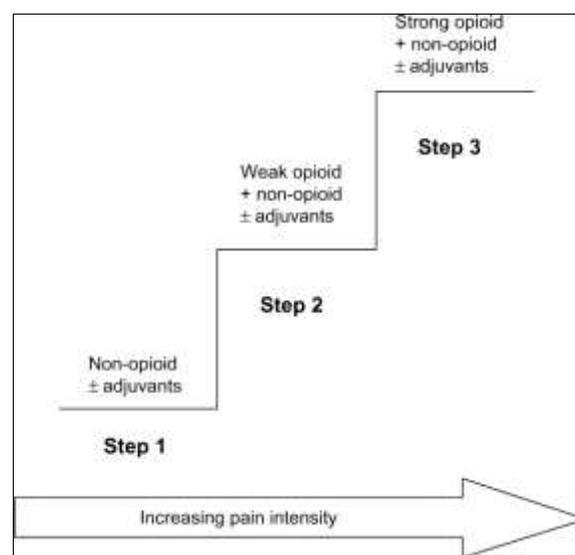

Figure 3 The 'pain ladder', as developed by the World Health Organization

Originally published in 1986 for cancer pain, it is now widely used by medical

professionals for the management of all types of pain[56]. The three-step approach is inexpensive, in terms of cost of medicine, and 70–90% effective when used properly. The general principle is to start with drugs described for the initial step, and then to climb the ladder if pain remains present. The medications range from common, over-the-counter drugs such as aspirin at the lowest step (level 1) to powerful opioids including methadone, morphine and oxycodone at the highest (level 3). For severe pain conditions only strong opioids are currently available to achieve relief of suffering, short of moving on to more invasive techniques such as surgery or temporary degeneration of the affected nerves (e.g. neurolysis)[56]. To help calm fears and anxiety, adjuvant drugs may be added at any step of the ladder.

It must be noted that there is no standardized dosage in the treatment of pain; every patient will respond differently. The correct dosage is one that will allow adequate relief of pain, resulting in acceptable quality of life for the patient. The dosing regimen should therefore be adapted to achieve the best balance between the analgesic effect and the side effects. That means analgesics should be prescribed with a constant concern for detail. But when pain medication needs to be taken daily, at regular intervals, patients must be able to use such drugs in a home setting. Unfortunately, many policymakers and medical professionals consider opioids too risky to be used or prescribed in such a liberal manner.

In India, an estimated one million people with cancer, plus an unknown number of people with other incurable and disabling diseases, need opioids for pain relief. But despite the fact that India is one of the world's largest producers of medicinal opioids, only a tiny proportion of the population in need have access to them, mainly in the form of morphine[26]. Important barriers that prevent access include cumbersome regulatory and licensing procedures for physicians and hospitals that want to prescribe opioids, combined with harsh punishments in case the regulations are not correctly followed. Through decades of strict regulation, medical professionals developed an increasing fear of morphine; they would not use it and taught their medical students to avoid it. Also, over decades, scientific advances in medicine have resulted in an overemphasis on ''cure'' and a downturn in the practice of symptom control or palliative care, including pain relief[25]. This climate has made the medical community in India shy away from the use of opioid drugs to treat their patients, even

in the absense of proper alternatives for treating severe pain[26]. As a result, the vast majority of patients suffering from severe pain in India remain undertreated today[57].

The basis of this behavior is a widespread fear of the effects of opioid use. The general public, including government officials, associates morphine with inevitable addiction and are reluctant to accept the drug for medical needs. Such fears have been fueled to a large extent by the rapid increase in the use of medical opioids such as Percocet, Vicodin and OxyContin in the United States. As a result of overprescribing of opioids by physicians and pharmacists, overdose deaths in the US have currently reached record levels, also known as the 'opioid epidemic'[58]. Hence, the suggestion by WHO to prescribe and use as much painkillers as needed to effectively treat the pain, may be at odds with a realistic worry about drug abuse and overdose morbidity and mortality.

Cannabis may provide a solution to this difficult medical and ethical dilemma. The main active constituents of the Cannabis plant, the cannabinoids THC and CBD, have already shown to be effective in a wide range of pain models and in clinical trials[42,43,59]. While these cannabinoids exert some of the same potent analgesic effects as the opioids, they are vastly more acceptable in their potential side effects. Most importantly, opioids may lead to respiratory depression which is a major cause of death from opioid overdosing[60]. In contrast, cannabinoids do not have lethal potential even at very high concentrations, due to a lack of cannabinoid receptors in brain areas that control critical physiological functions such as heartbeat and breathing[61,62]. Moreover, the addictive potential of Cannabis is directly related to its content of the psychotropic component THC. Other cannabinoids, such as CBD and THCV, do not show any such potential and have been found safe and well-tolerated even at very high dose[63,64]. Interestingly, cannabinoids and opioids work very well together in the treatment of pain; clear synergistic effects between the two have been observed, and the combined use makes it safer, because it allows the opioid dose to be significantly reduced[65]. This means that an increase of pain patients using Cannabis or cannabinoids may directly result in a lowered need for the more risky opioids, as has been witnessed in several US states that have legalized the medicinal use of Cannabis[48]. In fact, the addictive potential of Cannabis is believed to be so much lower compared to opioids, that cannabinoids are

considered a target treatment for combatting opioid addiction and withdrawal[66].

While the drawbacks of opioids are becoming increasingly more clear, the more mild effects of Cannabis and its therapeutically active cannabinoids are becoming more attractive. Medicinal Cannabis, for example in the form of a standardized oral tablet or extract, may fulfill many of the roles currently played by opioids, and would fit very well in step 2 or 3 of the WHO pain ladder mentioned above. Based on the latest meta-analyses of clinical evidence, it has been been concluded that there is conclusive or substantial evidence that Cannabis is effective for the treatment of chronic pain in adults[48,59]. Meanwhile, the side effects caused by medicinal Cannabis use are believed to be generally mild and manageable, the most commonly observed side effects being dizziness, dry mouth, euphoria, disorientation, and drowsiness[67]. Although these data are encourraging for further exploration of Cannabis as an analgesic, it is important to also highlight the need for more research to better understand the efficacy, dose-response effects, routes of administration, and side effect profiles for the many different Cannabis products that are commonly used today[28,48]. Because the exact balance

between long-term risks and benefits of Cannabis use is still unclear, its medicinal application should be recommended only for treatment-resistant patients, who do not sufficiently respond to conventional drugs and treatments.

Separating recreational from medicinal use of Cannabis

It goes without saying that Cannabis is not just a benign medicinal herb. Just like the Opium poppy (*Papaver somniferum* L.), Cannabis can be used as a source of narcotics as well as medicine. In fact, Cannabis is the world's most widely abused narcotic drug[68], and may cause various undesired effects when used without restraints. Long term effects may include impaired cognition, dependence, or the development of psychosis in genetically vulnerable individuals[28]. But unlike e.g. opioids, using a high dose of Cannabis will not kill or permanently harm the user. Based on its lack of acute life-threating effects[69], Cannabis has been called a 'soft drug' in some jurisdictions such as The Netherlands[70]. Because of these, and other, reasons, several countries have decriminalized the use of Cannabis for recreational use in recent years[71].

According to the report 'The Use ofCannabis Drugs in India'[23] the uses of Cannabis drugs in the Indian sub-continent can be described under the following categories: 1) medical and quasi-medical use (therapeutic use); 2) use in connection with religious and social customs (cultural use); and 3) euphoric purposes (recreational use). Unfortunately, it is the use or abuse for euphoric purposes which causes public commotion, fear and indignation in the minds of many, often obscuring the medicinal and religious significance of Cannabis in India. Interestingly, historical documents and traditional Indian scriptures may be of help in formulating a balanced message about the appropriate use of Cannabis as a medicine to the public. For example, Hindu scriptures have not encouraged recreational use, intoxication from, or abuse of Cannabis. In fact, the scriptures warn against the over-use of alcohol and other intoxicants such as Cannabis, and they teach against using any substances for intoxication[72].

While a cultural understanding of Cannabis may aid in its appropriate use, the main key for applying Cannabis responsibly as a modern medicine lies in a proper understanding of its main active ingredients. The sticky resin produced by the flowers and top leaves of the plant contains a number of substances called cannabinoids of which delta-9-tetrahydrocannabinol (THC) is the most important. THC is the only psychoactive compound present in Cannabis; all others may have therapeutic effects but do not have any significant potential of making the user feeling 'high'. Pharmacological studies have identified specific receptors for cannabinoids as part of a so-called endocannabinoid system in the human body and these receptors have shown to be present in various tissues and organs, including the brain and immune system[73], as described above. Indian charas (Cannabis resin) of good quality is said to have a THC content of up to 30%[74,75], and even higher concentrations can be achieved with modern techniques of processing Cannabis flowers. Among the many claimed therapeutic indications of THC, its anti-emetic, appetite stimulant, and analgesic effects, as well as relief of symptoms of multiple sclerosis, are the most well established[59,76]. Various other cannabinoids are also under investigation, including cannabidiol (CBD), which has increasing evidence for therapeutic effects particularly in epilepsy, insomnia, anxiety, inflammation, brain damage (as a neuroprotector), psychosis, and others[59,77].

Historically, the intoxicating effects of Cannabis were well-known in India, which is reflected in the three major types of preparation. The weakest type, *Bhang*, consists of dry leaves from which flowers are carefully removed. A stronger type, *Ganja*, is prepared with the flowers of female plants only. The strongest of them all is *Charas*, made exclusively of the resin that covers female flowers[10]. These forms of preparation guarantee the presence of active cannabinoids such as THC and CBD, which explains the intoxicating as well as medicinal effects it has to the user. Indian traditional manuscripts on medicinal plants often have a strong focus on safety and toxicity. Therefore, it is no surprise that Ayurveda has long recognized the intoxicating effects of Cannabis, and has labelled it as a 'toxic' herb.

In Ayurveda, toxic drugs are used for therapeutic purposes only after a treatment called '*Shodhan'*, which is a decontamination procedure to reduce their undesired effects[29]. In one particular study[78] the scientific basis of various Shodhan treatments was evaluated, by looking at their effect on the chemical composition of Cannabis leaves. Treatments included washing the herbal material in cold water, frying in ghee, soaking in milk, and boiling

in the decoction of a specific tree bark. The study clearly indicated the utility of Shodhan techniques in reducing narcotic content of Cannabis, as a considerable reduction of THC content (up to 85%) was observed. A modern understanding of the chemistry of Cannabis explains these reductions by the washing away of trichomes where cannabinoids are produced (washing in cold water), the partial extraction of active compounds with lipophilic solvents (milk, ghee) or evaporation of active compounds by heat (frying).

Despite treatments to reduce their potency, many traditional administration forms of Cannabis have considerable abuse potential, because they are consumed in the form of tasty foods or drinks that may stimulate the consumer to use too much. Examples are the mixing of Cannabis with honey, milk, butter and/or spices[14]. Moreover, because of a lack of quality control and potency testing, the consumer never knows the strength of a product he is consuming. Already in 1982, in a treatise entitled *Indigenous Drugs of India*[79] the authors noted the requirement of proper dose titration due to increasingly inconsistent Cannabis preparations. Although performing Shodhan procedures to remove THC and other cannabinoids reduces the narcotic strength of Cannabis

preparations, it simultaneously destroys the majority of the medicinally active ingredients. Clearly, a proper balance should be found between reducing abuse potential, versus maximizing therapeutic strength of Cannabis products.

A solution to this dilemma may be the development and application of modern dosing techniques and administration forms, to control or limit the intake of pharmacologically active cannabinoids. For example, a Cannabis extract with limited poteny can be made available on prescription through pharmacies only. Or Cannabis medicine can be offered in metered-dose inhaler systems that monitor the total daily intake[80]. Another idea is that the traditional preparation of the typically Indian *Bhang* could be modernized to develop a standardized and quality-controlled, but low potency product that physicians can legally prescribe.

Another approach focusses on the composition of the Cannabis plants that are allowed to be used in the preparation of medicinal products. It is possible to develop Cannabis varieties with a reduced inherent potential for intoxication, for example types that contain a higher proportion of CBD to counteract the psychotropic effects of THC present in the same plant[81,82]. Also, the content of THC in Cannabis plants may be limited to a certain maximum percentage. Such an approach has already been discussed in Canada, where a maximum THC content of 9% was suggested for medicinal use, based on available clinical study data[83]. As an added benefit, limiting the THC content helps to make sure that the balance between the various components in the Cannabis plant (cannabinoids, terpenes, etc.) remains more comparable to natural Cannabis plants grown in India in historical times. Cannabis plants grown indoors under completely artificial conditions may easily turn into 'supercrops' with cannabinoid contents that are far removed from the traditional medicines that India got used to over millenia of use.

Cannabis according to the TKDL and the CCARS

Looking for descriptions of Cannabis medicine in ancient handbooks written in nearly forgotten languages may be a tedious and nearly impossible job for any scientist. Luckily, such endeavours are not needed any longer. The Traditional Knowledge Digital Library (TKDL) is a unique Indian digital database of traditional knowledge, established in 2001 as a collaboration between the Council of Scientific and

Industrial Research (CSIR) and the Ministry of AYUSH. The objective of the library is to protect the ancient and traditional knowledge of the country from exploitation through biopiracy and unethical patents, and is especially focused on medicinal plants and formulations used in Indian systems of medicine. As of 2010, it had transcribed 148 books on Ayurveda, Unani, Siddha and Yoga, into 34 million pages of information. Data on 80,000 formulations in Ayurveda, 1,000,000 in Unani and 12,000 in Siddha has already been collected in the TKDL[84].

The TKDL describes Cannabis as an important drug of various Indian systems of medicine. The resource contains many formulations with Cannabis mentioned as the principle component (e.g Bhang) or being used as a polyherbal formulation (e.g. Tiryaaq afiyun). The indications mentioned in the TKDL that Cannabis can resolve, or beneficial effects it can have, are: gout, catarrh, coryza, mastitis, analgesic, mania, diphtheria, poisoning, iatrogenic agent, rheumatism, cholera, malaria, pyrexia, spermatorrhea, aphrodisiac, inspissant, atony of bladder, bleeding piles, nausea, vomiting, anorexia, indigestion, dyspepsia, cough/bronchitis, hyperacidity, Incurable, sprue/malabsorption syndrome, curable disease of severe nature, acute diarrhoea, dyspnoea, anaemia/hyperbilirubinemia, intellect promoting, semen promoting, immuno potentiators, anti-oxidant, anti-ageing and strength promoting.

According to a recent review paper by the Central Councel for Research in Ayurvedic Sciences (CCRAS), different pharmacopoeia of Ayurveda report about 191 formulations of 13 different dosage form having Cannabis (*Vijayā*) as an ingredient[85]. Cannabis has been attributed with different pharmacological properties i.e *Tikṭa Rasa*, *Laghu Tĩkṣṇa Guna*, *Uṣṇa Vĩrya* and *Kaṭu Vipāka*. It pacifies *Kapha* and *Vāta Doṣas*, increases *Pitta Doṣa* and has *Dĩpana*, *Pācana*, *Rocana*, *Madakārĩ* and *Vyavāyĩ* action. According to the review paper, Cannabis may be useful to combat more than 29 disease conditions including intestinal disorders, fever, diarrhoea, dyspepsia, urinary disorder etc. According to the authors, Cannabis fulfils the criteria of a good and effective drug, as recommended in the classical texts of Ayurveda. The main part of Cannabis used, for medicinal purpose, is its leaf in processed form (Shodhan, see above) in a typical dose of 125-250 mg.

Usually, texts related to medicinal plants systematically record the part used, pharmacological properties, shodhana

(processing) procedures, actions, medical indications and contraindications of the plant drug. In Ayurveda, different traditionally used names, known as *Paryāya* (synonyms) are often attributed to a single plant to define its morphological description, habitat, and pharmacological characters. For Cannabis, there are about 40 synonyms attributed to describe its morphological and pharmacological characters in various classical texts written over time (**Table 1**)[85]. Many synonyms are of mythological origin, indicating its frequent uses and close relation with various aspects of society during the ancient period. Clearly, this may complicate the search for preparations containing Cannabis in older manuscripts, because we must be very careful in assuring that Cannabis is indeed the plant mentioned.

A complicating factor in the use of traditional sources of information is that diseases and their cures may be described and classified very differently compared to modern medicine. Therefore, a major challenge lies in translating between the two, so that we may learn e.g. how neuropathic pain is defined in Ayurveda and other systems, and how that relates to the way medical science classifies and treats neuropathic pain today.

Table 1 Indian names used to describe Cannabis in Sanskrit and Hindi (taken from Russo[14])

Indian name	Meaning
ajaya	the unconquered, invincible
ananda	the joyful, joyous, laughter moving, bliss
bahuvadini	causing excessive garrulousness
bhang, bhanga	hemp, mature Cannabis leaves
bhangini	breaks three kinds of misery
bharita	the green one
capala	agile, capricious, mischievous, scatter-brained
capta	light-hearted
chapala	the light-hearted, causer of reeling gait, causer of vacillation
charas	Cannabis resin (hashish), either hand-rubbed or sifted
cidalhada	gives happiness to mind
divyaka	gives pleasure, lustre, intoxication, beauty
dnayana vardhani	knowledge promoter
ganja	unfertilized female Cannabis flowers
ganjakini	the noisy, vibrator
gatra-bhanga	body disintegrator
harshani	joy-giver
harshini	the exciter of sexual desire, the rejoicer, delight-giver, causer of elation
hursini	the exciter of sexual desire
Indrasana	Indra's food
jaya	victorious, the conquering
kalaghni	helps to overcome death
madhudrava	helps excrete nectar
madini	the intoxicator, sex intoxicator
manonmana	accomplishes the objects of the mind
matulani	wife of the datura
matkunari	an enemy of bugs
mohini	fascinating
pasupasavinaini	liberates creatures from earthly bonds
ranjika	causer of excitement
sakrasana	the worthy food of Indra
samvida manjari	flower causes garrulousness
sana	Cannabis
sarvarogaghni	which cures all diseases
sawi	green leaved
Shivbooty	Shiva's plant
siddha	which has attained spiritual

	perfection
sidhamuli	on whose root is siddha
siddhapatri	vessel of highest attainment
siddhi	success giver
siddhidi	which endows siddhi on others
sidhdi	emancipation, beatitude, fruit of worship
suknidhan	fountain of pleasures
tandrakrit	causer of drowsiness
trailokya vijaya	victorious in the three worlds, conqueror of the three regions of the universe
trilok kamaya	desired in the three worlds
ununda	the laughter mover
urjaya	promoter of success
vijaya	victorious, promoter of success, all-conquering
vijpatta	the strong leaved
virapattra	leaf of heroes
vrijapata	strong nerved

Modernizing an old medicine - the Indian way

Ayurvedic medicine has recognized the importance of Cannabis for millennia, but modern science is only now proving its wisdom. In fact, many ideas now commonly accepted for the production or the use of medicinal Cannabis have originated in India. For example, the most potent forms of Cannabis available today are derived from Cannabis varieties known to botanists as *Cannabis indica,* or Indian hemp. And ancient Indian documentation on Cannabis production emphasizes the necessity of removing male plants by the "ganja doctor" to prevent fertilization of the female plants[16]. This treatment significantly increases the production of the medicinal resin. Contemporary growers know this method as '*sinsemilla*' (from the Spanish: 'without seeds') and virtually all medicinal (as well as most recreational) Cannabis in the world is currently produced in this manner.

Also in the research field of the endocannabinoid system, Indian influences are visible. The discovery of the human endocannabinoid system[73] and the rapidly unfolding therapeutic potential of the cannabinoids - ranging from inflammation and epilepsy to chronic pain and even cancer - are quickly opening up a whole new field of medicine. As a result, the number of scientific papers published on the medicinal properties and applications of Cannabis and its cannabinoids has been growing at an exponential rate since the early 1990's (**Figure 4**).
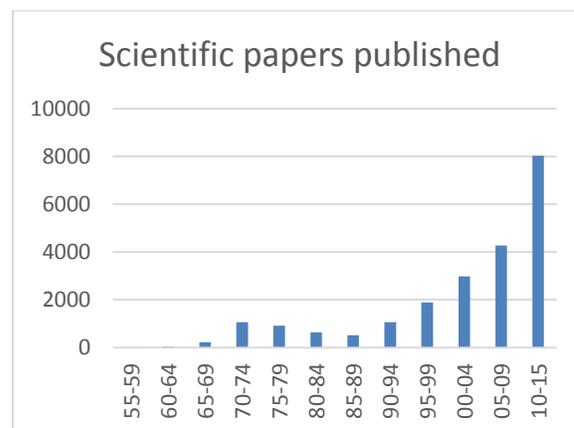

Figure 4 Number of scientific papers published on Cannabis (in PubMed, per 5 year interval)

Many of these cannabinoid researchers to some degree have acknowledged the integral role that Indian culture has played in our understanding of Cannabis. Thus, the first endocannabinoid ever discovered (chemical name: arachidonyl-ethanolamide) was dubbed anandamide (*ananda* is Sanskrit for 'bliss')[86]. In a likewise manner, one of the identified endocannabinoids, chemically known as O-arachidonylethanolamine and acting as a cannabinoid receptor antagonist, has been nicknamed virodhamine (*virodha* is Sanskrit for 'opposition')[87].

Naturally, there are concerns that Cannabis use is not all benign, and that there are negative health and social consequences from its use for some consumers. Clearly, just the fact that the Cannabis plant once was a valuable part of traditional medicine is not reason enough for its re-inclusion into modern medicine. Scientific drug development is a rigorous process and regulatory bodies have stringent requirements to be fulfilled before drugs are approved for marketing[28]. But with the growth of scientific interest for Cannabis, its therapeutic effects as well as its risks are now studied with increasingly accurate scientific methods. Recent experiences in various countries such as Israel, Canada, The Netherlands and several US states with legalization of Cannabis for therapeutic or recreational purposes indicate that it does not pose an unacceptable threat to public health and safety[88-101], even though much remains to be learned[102]. Interestingly, even after more than a century, such conclusions are closely in line with the 1894 Hemp Drugs Commission in India. In their extensive report[16], already discussed above, the commission did not oppose the moderate use of Cannabis for social and medicinal practices in the Indian sub-continent, even though excessive consumption was regarded as injurious.

As a result of these new insights, various countries have been revamping their national policies for supporting use of Cannabis for therapeutic purposes. Those countries already include Canada, The Netherlands, Israel, Australia, Germany, Italy, many US States, as well as various South-American countries. Cannabis-based medicine is already approved for the treatment of pain and spasticity caused by multiple sclerosis in many places[103], and its potential role in the treatment of e.g. epilepsy[104], rheumatoid arthritis[105], and cancer[106] is actively being explored. Based on these developments around the world, Indian regulators would not be out of line when encouraging and facilitating scientists

to explore the potential of their versatile native plant while the world already benefits from it. For too long, there have been no clear guidelines and jurisdiction for obtaining a license for medical or scientific research. This has made research extremely difficult in most states of India.

It is true that the existent safety and efficacy data for cannabinoids is still incomplete[28]. However, the treatment of chronic neuropathic pain in India represents an excellent case for further expanding our knowledge in this field, for a population much in need of new treatment options. The essence of this development would be to copy the useful aspects of traditional Cannabis use but remove its more risky aspects by applying principles of modern medicine. In short: be traditional when we can, and modern when we must. This approach fits very well within the principles of the phytopharmaceutical drug regulations that have already ushered various Indian traditional medicines into the modern world.

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