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THE POTENTIAL OF *Cannabis* sp. IN PAIN MEDICINE: A PERSPECTIVE

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review paper

Summary

Long before they were even properly named, plants form *Cannabis* genus (*C. indica* L., *C. sativa* L. and *C. ruderalis* L.) had their usefulness in the folk medicine. Recently, it has been scientifically proven that cannabinoids mainly act through two types of endocannabinoid receptors in the central nervous system (CB1) and immune cells (CB2). The usage can be either from recreational usage in glaucoma or in research for acute and chronic pain therapy. Some clinical studies support the use of hemp oil and hemp seed in the pain medicine. However, until today, there is still no evidence to suggest that medical cannabis can be used solely as cure, but the use of hemp seed and oil from hemp seeds or flowers in practice, refers to symptomatic treatment as adjunctive therapy. Treatment consists of an individual dose titration phase (with patient supervision) of delta-9-tetrahidrocannabinol (THC) or cannabidiol (CBD) and a maintenance phase. The main goal of this is study was the overview of therapeutic benefit to the familiar and wildly used hemp plant in acute and chronic pain, mostly because of its cost-effectiveness. Overall, this review paper highlights more possibilities of hemp plant usage in further symptomatic pain treatments.

Keywords: hemp oil, hemp seed, acute pain, chronic pain, humans, THC, CBD

Introduction

There is a growing interest of using plants due to their nutritional value of heling properties (Klir et al., 2019; Moses et al., 2017; Vinković et al. 2018; Grubišić et al., 2019; Singh, 2020; Šain et al., 2020). There is around 80% of the global population that still uses botanical drugs and natural substances as a source of therapeutic drugs against various pharmacological targets including cancer, brain performance, cardiovascular function, microbial infection, inflammation, pain, etc. (Sen et al., 2015; Martin et al., 2017; Tucak et al., 2019). Even with the modern medicine of Western primary health-care services, in rural areas health care often coexist with traditional medicine which include medicinal plants and traditional healers (Vandeborek et al., 2004).

There are three most important species of genus *Cannabis* that have a potential in medicinal use. They are the Indian hemp *Cannabis indica* L. (cannabis), the industrial hemp *Cannabis sativa* L. and *Cannabis ruderalis* L., which is growing wildly in Central and Eastern Europe and Russia. The industrial hemp, *C. sativa* L., is, as its name suggests, mostly used for industrial purposes. Industrial hemp stem was used for decades as a raw material in fiber production, but also by product – hemp hurds slices, which are woody core of the hemp plant is often considered to be waste, even though it can valuable and used in eg. as ecofriendly and innovative material in construction industry, in and paper industry, etc. (Cigasova et al., 2015, 2016; Zelca et al., 2017; Momeni et al., 2021).

There are more than 500 different chemical compounds that have been detected in the hemp plant, about one hundred of them are cannabinoids, compounds not detected in any other plant (Beaulieu, 2006). Beside the cannabinoids hemp plant contain flavonoids, terpenes, fatty acids which among others have potential medicinal use.

Pain is the bodily experience of suffering, the feeling of transmitting sensory nerves through the left brain and to the sensitive area of the brain, where the experience is felt. There are several pain signals and transmissions that give specific message to the brain, which then produces different pain sensations: somatic pain (imagine), visceral pain (tissues or organs become stretched or due injury or disease) and neuropathic pain (nerves themselves sustain injury) (Watson et al., 2000). Looking at the way of life and job requirements in the 21st century it is no surprise that there is an increase in chronic pain problems. Given that all approved medication has some unwanted side-effects and can be costly, it has made our mines turn to the nature's solutions, such as potential use of cannabis in acute and chronic pain treatment. So, the aim of this review is to discuss and overview of potential uses of *Cannabis* sp. in pain therapy.

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Historical uses of hemp in anesthesia

Although throughout the history there were many attempts in producing a state of general anaesthesia, more specifically in finding a way to undertake a surgical procedure without feeling pain, they remained individual efforts (Mixa et al., 2016; Sicgin et al., 2016). Those can be traced throughout the history in the writings of Sumerians, Babylonians, Assyrians, Egyptians, Greeks, Romans, Indians and Chinese. Most of those writings show use of a particular plant such as poppy or cannabis. One of the most used plants in the history of anaesthesia is cannabis. Its use dates back to ancient times. Ancient physicians in vary parts of the world mixed cannabis to treat pain and other ailments. For example, in ancient China the use of cannabis in medicine was a very early development. It is described in Shennong Bencaojin, the oldest Chinese pharmacopeia (RCOA, 2020). Hua Tuo was the early Chinese surgeon who is credited with the first use of cannabis as an aesthetic. He reduced plant to powder and mixed it with wine for administration prior to conducting surgery. In ancient Egypt there was use of cannabis as suppositories for relieving the pain of haemorrhoids. Furthermore, in ancient India it was a major religious and medicinal component, frequently used to relieve the pain of childbirth. Additionally, Islamic world used properties of *C. sativa* L. extensively for ten centuries, while ancient Greeks did not use cannabis only for humans, but also in veterinary medicine, to dress wounds and sores on their horses (RCOA, 2020).

The usage of *C. indica* L. as a potential analgesic is described in many ancient texts and traditional practices for pain relief. During Middle Ages there was an Islamic Golden Age, in which scientist and scholars made significant progress in science and medicine. But, even though it was rigorously researched in was not until the 19th century that there was a breakthrough in anaesthesia (WFSA, 2020). The two most memorable events together allowed the transition to modern anaesthesia and surgery. The first public demonstration of ether anaesthesia that took place at Massachussetts General Hospital in Boston on 16th October 1846 and the use of nitrous oxide for extraction of teeth by Horace Wells in 1844. It was an official beginning of what is now known as modern anaesthesia and analgesia (RCOA, 2020).

In the 19th century cannabis was introduced to Western medicine. Initially, it was reduced tussle powder and mixed with wine for administration. The drug Marinol was created in 1970s, when THC had been synthetized. The main mode for administrating cannabis is smoking, because it is almost immediately effective (WFSA, 2020).

Legislative and main species of genus *Cannabis*

C. sativa L., the industrial hemp, is mostly produced in Europe, over 70% (Fig. 1), whereas more than 40% of that production is located in France, estimating that Europe cultivates up to 25% of the world's industrial hemp known as "Cannabis Europe", which refers only to European production. Industrial hemp cultivation area in the EU is monitored by the European Industrial Hemp Association (EIHA).

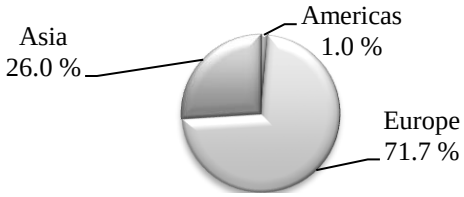

Fig. 1. Production of *Cannabis sativa* L. - industrial hemp seed by region (Average 1994 – 2018) (FAOSTAT, 2020)

The main difference between the *C. sativa* L. and *C. indica* L. plants is that Indian hemp has been overtaken by the phytocannabinoid delta-9-tetrahidrocannabinol (THC), while in industrial hemp THC is present in negligible traces, without psychoactive influence (Jakešević, 2015).

According to European Monitoring Centre for Drugs and Drug Addiction (2017), in most European countries a permitted level of THC for industrial hemp, which is grown for fiber is 0.2% (Italy, Denmark, Belgium, Slovakia), or 0.3 % (Luxemburg), up to 1 % (Switzerland, Czech Republic, Malta). As a consequence, the EIHA is advocating to re-establish this benchmark in Europe to the globally prevalent 0.3% limit.

Asian continent is still to reach its full potential with production of only 26%, this could be due to the fact that usage of *Cannabis sativa* L., is still illegal in most countries (Taiwan, Singapore, Malaysia, People's Republic of China). Moreover, Americas have production of just 1%, which is a great omission on their part considering most countries had legalized THC (Canada, Mexico, Peru, United states of America, Uruguay).

The popularity of the industrial hemp is increasing every day. This is because of their multi-purpose uses. The stem of industrial hemp can be used for fiber, while the seed is used for oil extraction and inflorescence is used for phytocannabinoids extraction. The top 5 hemp products for the EU are clothing, bags or back pack, hemp seed oil, soaps and hemp seed (according to EIHA). Except for humans

use, the seeds, oil, cake and meal can be used for animal fed (Klir et al., 2019).

Indian hemp (or cannabis) have 5 – 20 % THC (Pospišil, 2013). The British government of India prohibited consumption of *C. indica* L. in the 1930's (Bapat et al., 2015). European countries set their own national drug laws, although all of them are parties of the UN Single Convention (Bifulco and Pisanti, 2015). Nowadays, this plant is known as narcotics and it has several names as ganja, marijuana, weed, hasish, etc. In most of the countries the production, manufacture, consume, import or export is illegal.

The use of *C. indica* L. in medicinal purposes is legalized in the Netherlands, Austria, Spain, Portugal, Germany, Finland, Italy, Poland, Sweden, the United Kingdom, Switzerland, Canada, Bangladesh, Israel, Columbia, Uruguay, much of the United States (EIHA; Piper et al., 2017). Most countries legalized medicinal usage, however, recently the recreational purposes have been increasingly popularized.

C. rudealis L. is traditionally used in Russian and Mongolian folk medicine for treating depression. Because of its lowest producing biotypes of THC it is rarely used for recreational purposes. Due to its transition from vegetative to flowering stage with age, as opposed to the light cycle it is bred with *C. sativa* L. and *C.s indica* L. to create "auto-flowering cannabis strains" that exhibit the hardiness of *C. rudealis* L. plant while maintaining the medicinal effects of *C. sativa* L. and *C. indica* L. (EIHA; Piper et al., 2017).

The influence on human

Cannabis is a psychoactive drug from *Cannabis* plant used primarily for medical or recreational purposes. Most common plants are *C. sativa* L., *C. indica* L. and *C. ruderalis* L. (Greydanus et al., 2013).

Beside the THC, the other important cannabinoid is cannabidiol CBD. Unlike THC, CBD does not have psychoactive effect. Both cannabinoids appear in the plant, they work synergistically and chemically they have the same molecular structure: 21 carbon atoms, 30 hydrogen atoms and two oxygen atoms (Fig. 2).

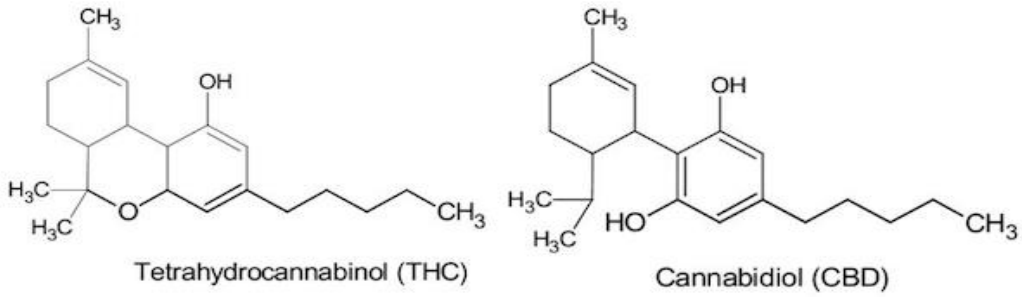

Fig. 2. Molecular structure of THC and CBD (Greydanus et al., 2013)

The difference is in the arrangement of the atoms, which explains different effects on the organism of the consumer. They also are chemically similar to human body endocannabinoids. It allows them to interact with endogenous cannabinoid receptors.

THC is the main psychoactive component of cannabis (Greydanus et al., 2013; Vulfsons et al., 2020). It can be used by smoking, vaporizing, as an extract or within food (Watson et al., 2000). Effects of cannabis are mental and physical. Some of the mental effects are a general change in thought and perception, short-term memory impairment, altered sense of time, impaired body movement, increase in appetite and relaxation (Vulfsons et al., 2020). Additionally, physical effects include increased heart rate, nausea and respiratory problems. The high lipid-solubility results in long persistence in the body. There are two types of cannabinoid receptors, CB1, and CB2, both of which are G protein-coupled receptors. CB1 receptor is primarily found in the brain and some peripheral tissues, while CB2 receptor is primarily found in peripheral tissues, but also in neuroglial cells (Zagožen et al., 2021). THC appears to alter cognition and mood through actions on the CB1 receptors, which inhibit a secondary messenger system, that can be blocked by selective CB1 receptor antagonist rimonabant, that was discontinued due to the dysphoric effect. It is metabolized by the liver cytochrome P450 system (Greydanus et al., 2013; Grichnik and Ferrante, 1991; Altun et al., 2015).

Both THC and CBD are metabolized by the liver cytochrome P450 (CYP-450) system and often the potential of drug-drug interaction of cannabinoids and other drugs or herbs is not recognised for the patients (Vulfons et al., 2020; Mikolašević et al., 2013).

Potential of medicinal use of cannabis

Medicinal cannabis is used not to treat but to alleviate the symptoms of the diseases. Scientific community is very much interested for *Cannabis* sp. pharmacological power, eg. for nausea, food intake, gastro protection, cancer patients, Chron's disease, multiple sclerosis, etc. (Waseem and Seymour, 2016). In recent years a number of nations put the specific laws and programmes to allow patients to use cannabis for relieve the symptoms of e.g. chronic pain, muscular cramps and spasticity in patients with multiple sclerosis or spinal cord damage, as well as for patients affected by neurogenic pain caused by nerve damage and other causes (Bifulco and Pisanti, 2015). It is also used in the treatments of patients with terminal cancer and AIDS, who use the cannabis to alleviate nausea and vomiting, and to stimulate appetite and weight increase of AIDS symptoms, glaucoma, neuropathy, nausea and relapse during chemotherapy in treatment malignant diseases, than pain gains structural psycho-physiological diseases (e.g. in the speech-hearing area), muscle spasticity and pain in the extremities (multiple sclerosis or spinal cord injury), symptoms of motion sickness as in Parkinson's disease, Huntington's disease (movement disorders and dementia), Tourette's syndrome (motor and vocal tics), stimulates appetite and migraine headache (Duraković, 2016; Markus Klarić et al., 2020).

The Ministry of Health of the Republic of Croatia (EMCDDA, 2017) has approved the use of medical hemp for: (i) symptomatic relief of spasticity in patients with multiple sclerosis which spasticity is not adequately controlled by conventional therapy; (ii) in patients with advanced / terminal malignancy and chronic measure to moderately severe pain; (iii) alleviation of nausea and return in patients with malignant diseases receiving emetogenic therapy (antitumor drugs, radiation); (iv) in the treatment of cachexia/anorexia in HV/AIDS patients; (v) in the treatment of Dravet's syndrome (childhood epileptic syndrome) - "cannabidiol Principle".

However, there is no unique list of pathologies that can be treated with cannabis-based drugs, since it is not a cure, but rather a palliative treatment.

The flowers and top leaves of the plant contains a number of chemical compounds which are most important. So, in recent years there is an increased interest of growing industrial hemp because of their flower and seed which can be used for oil production and oil with CBD content (Rozyczko and Brett, 2021). Scientists began to discover what all this interesting herb in its composition was back in 1895 (Shahbazi et al., 2020), when the first cannabinoid was discovered. Cannabidiol (abbreviated CBD), the third isolated cannabinoid compound, was discovered in 1940 (Shahbazi et al., 2020), some 20 years before the most famous THC. Cannabidiol accounts for 40% of industrial hemp extract, its main cannabinoid and is not psychotropic (Russo and Guy, 2006).

In the early 1990s, scientists were quite surprised to find that the human body produces its own cannabinoids (Shahbazi et al., 2020). One is anandamide, or colloquially, the "happiness molecule". This endocannabinoid name was derived from the Sanskrit word *Ananda* meaning happiness and bliss.

Harmful effect of cannabis

The harmful effects of THC in the human body are detrimental, in a sense abuses, hallucinations, feelings of euphoria, disorders in auditory, visual and spatial perception, dehydration, impaired motor skills, drowsiness and redness of the eyes (Markus Klarić et al., 2020). Moreover, influence is to the lungs such that it causes changes similar to those in the lung's chronic tobacco smoker - larynx inflammation, bronchitis, chronic cough. There is also a negative influence of the cannabis on humans. The authors from Croatia reported about two cases of Cannabis induces acute pancreatitis (Mikolašević et al., 2013). Also, there can be a several other like anxieties and loss of appetite (Russo et al., 2006).

Potential of uses cannabis in analgesia

While anaesthesia is defined as a state of controlled, temporary loss of awareness and sensation induced for medical purposes, analgesia is relief from or prevention of pain (ASA, 2020; Vučković et al., 2018). Today we differ an acute and chronic pain and approach to it (Grichnik and Ferrante, 1991). Acute pain is provoked by a specific injury or disease, it is associated with skeletal muscle spasm and sympathetic nervous system activation, it is self-limited and serves a useful biological purpose. Chronic pain, in contrast, may be considered a disease state. It outlasts a normal time of healing, it may arise from psychological state, and has no recognizable end-point. Acute pain treatment is aimed at underlying cause and interrupting the nociceptive signals, while treatment for chronic pain is a multidisciplinary approach and often involve more than one therapeutic modality. In a trial of 40 women undergoing abdominal hysterectomy and receiving a single dose of either a 5 mg of THC in capsule form or placebo no analgesic effect was observed in either group. Additionally, in an experimental trial of 18 healthy

volunteers, oral cannabis extract or placebo were administered after sunburn, no pain reduction was found. It appears that cannabis is not effective analgesic agent in the acute pain setting. However, in meta-analysis of cannabis-based treatments for neuropathic and multiple sclerosis related pain, an overall reduction in pain was found (Iskedjian et al., 2007). Furthermore, the evidence suggest cannabis may be effective for managing arthritis pain, back pain, and truma-related pain, although the quality of the evidence is poor (Niv and Devor, 2004).

In the study of 984 participants which are legal members of medicinal cannabis use in north-eastern US (Pipper et al., 2017), classified their pain as abdominal, back/neck, cancer, chronic pain following surgery, neuropathic, or trauma/injury (Tečić Vuger et al., 2016; Lončarić-Katušin et al., 2019). The participants used medicinal cannabis as joint, pipe, vaporizer, edibles or tincture.

Since chronic patients carry a high prevalence of accompanying symptoms such as depression, sleep disturbance, cognitive dysfunction, and more, a study was completed for cannabis treatment. There were mild improvements found in pain symptoms and severity. Secondly, it had mild beneficial effects for neuropathic pain (Cepeda et al., 2003). Another study was concluded on adults with chronic pain and benefits of cannabis use where it was shown that the benefits of cannabis night be outweighed by their potential harms. Lastly, a study between man and women showed that in men cannabis decreased pain sensitivity when immersing hand in cold water, while in women there was no decrease in pain sensitivity. These results indicate that in cannabis smokers, men exhibit greater cannabis induces analgesia relative to women, as such. sex-dependent differences in cannabis analgesic effects are an important consideration in potential therapeutic effects (Cooper and Haney, 2016). Also, cannabinoids combined with opioids produce synergistic introspective effect, decreasing the lowest effective opioid dose in laboratory animals. Even though, pain patients reported a greater analgesia when cannabis was used with opioids (Cepeda et al., 2003; Buggy et al., 2003; Niv and Devor, 2004), no study showed direct effects of opioids combined with cannabis in humans. In another randomized study it was shown that postoperatively, cannabis users required significantly more opioid rescue analgesia.

Table 1. Dosage in patients with malignant diseases pain relief in patients at the highest tolerable dose of opiates (Ministry of health of Republic of Croatia, 2020)

<table>
<tr><td>First dose</td><td>3 x 2.5 mg
(THC/CBD)</td><td>If patient well tolerate, this dose should be repeated over the next 2 days, followed by a 3 x 2.5 mg/day increase to 3 x 5.0 mg/day.

If there are problems with this initial dose that are not too pronounced, the dose should be repeated over the next 4-5 days because there is a possibility that the problems will subside.
If the problems are too pronounced - treatment is given up.</td></tr>
<tr><td rowspan="3">Further doses</td><td>3 x 5.0 mg
(THC/CBD)</td><td rowspan="3">If well tolerated, the dose should be repeated over the next 2 days, followed by a 3 x 2.5 mg/day dose increase.

If there are problems with this dose that are not too pronounced, the dose should be repeated over the next 4-5 days because there is a possibility that the problems will subside.
If the problems are too pronounced - give up treatment, or take one step.

In this way, a gradual increase of 3 x 2.5 mg/day or a possible decrease if the disturbances are too pronounced, the highest dose is reached which is still tolerated without major difficulties.

When a dose is reached during titration within the maximum recommended daily dose, which is well tolerated and with a decrease in NRS score, treatment is continued with that dose.</td></tr>
<tr><td>3 x 7.5 mg
(THC/CBD)</td></tr>
<tr><td>3 x 10.0 mg
(THC/CBD)</td></tr>
<tr><td>Further treatment</td><td colspan="2">During treatment, the NRS score should be repeated every 1-2 weeks.

If the reduction in score from pre-treatment is <25%, an attempt should be made to increase the dose, as in the titration phase, by one step. If this is not possible (exceeding the maximum daily recommended dose), or if even increased doses (up to the maximum recommended) do not reduce the NRS score ≥25%, ie. it is <25% compared to the initial condition - treatment should be discontinued.</td></tr>
<tr><td>Maximum daily dose</td><td>3 x 12.5 mg</td><td>The maximum daily dose should not exceed 37.5 mg THC/37.5 mg CBD per day (3 x 12.5 mg/day).
Treatment should be discontinued if any maximum (≤37.5 mg/day) dose tolerated during the first 2 weeks does not result in a ≥25% reduction in NRS.</td></tr>
</table>

*NRS=numeric rating scale used pain scales in medicine

This agrees with retrospective study of postoperative period in patients undergoing major surgery, where cannabinoid use was associated with higher pain scores, and poorer quality of sleep (Holdcroft et al., 2006; Andre et al., 2016; Liu et al., 2019).

In Republic of Croatia the dosage for patients with malignant diseases pain relief is regulated with the law (Ministry of health of the Republic of Croatia, 2020). The treatment consists of a dose titration phase and a maintenance phase. Before starting treatment, it is necessary to assess the state of symptoms using NRS. The recommendation only applies to a situation where patients receive standard analgesic therapy that includes opiates, and despite the highest tolerable dose of opiates still suffer moderate to severe pain (NRS≥4, on a scale of 0-10), and THC/CBD preparation is added as an "add-on" therapy. Because of specificity of the indication, the titration phase should not last longer than 10-14 days and each dose increase is 3 x 2.5 mg/day.

There are several synthetic cannabinoids. One of them is Nabilon, which is an oral cannabinoid synthetic tetrahydrocannabinol analogue, which decreases morphine consumption, pain scores, nausea and vomiting following major surgery. For example, in two studies (Vulfsons et al., 2020; Wedman-St. Louis, 2019) did not find significant differences between groups of patients, undergoing major surgery, who were given 1 mg, 2 mg of nabilone, 50 mg ketoprofen or placebo, so they concluded that, with respect to episodes of nausea and vomiting, quality of sleep, sedation, euphoria, pruritus, no serious adverse event was recorded.

Ministry of health of Republic of Croatia published the highest dose of opiates for palliative and oncological patients (Table 1). We can see that the pain scales are used as indicators of effectiveness of given therapy, where numeric rating scale of THC/CBD doses are indicators for further increment, reduction or parity in pain treatment.

Conclusion

The scientific community has highlighted the risks that the acceptance of *C. indica* L. for medicinal purposes could have on the population, specifically on adolescents, due to frequency of the cannabis abuse and misuse in that age group. So, for that reasons, there will always be efforts to find the line between illegal or legal applications, due to its profitable nature. We should doubtlessly continue the research, but it should include scientific and empirical multidisciplinary approach, with utmost understanding for the patients and the causes for cannabis use. *C. sativa* L. is legal to grow and to use as the source of CBD, so the interest it has reached in the recent years is understandable. The range of use is vast and ever growing. From recreational usage in glaucoma to more recently researched use in acute and chronic pain therapy. Furthermore, forms of consumptions of cannabis are large, from vaporization to smoking and oil consuming, so it is available to huge number of consumers. To conclude, there is a lot more to be done with the hemp, cannabis and cannabinoid, and we have yet to discover all of its benefits and means of usage, but we should not be discouraged because finding the right way or right dose could help a majority of patients dealing with overpowering, everyday pain. And the pain is the most common disease of the 21st century.

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