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Industrial *Cannabis sativa* (Hemp or fiber type): Antiviral Activities-An updated Review

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Abstract

Cannabis sativa has been used for thousands of years for recreational, medicinal, or religious purposes. Industrial *Cannabis sativa* (Hemp of fiber type) has been cultivated for millennia as a source of fiber, food, medicine and utilization of hemp for essential oils. Cannabinoids have been shown to have activity against herpes viruses, which are DNA-type viruses, as well as the RNA-type viruses, SARS-COV-2 and HIV/SIV. Tribal people in the Indian Himalayan region used cannabis as a home made herbal medicine for many diseases. During, Covid-19, the infusion of cannabis flower with a morning cup of tea has saved the life of many people. Antiviral activities of some of the most abundant cannabinoids have been documented in silico, *in vitro*, and *in vivo*. Studies of the antiviral activities of the more than 100 less abundant cannabinoids are still needed as are carefully designed clinical trials. Based on the established therapeutic efficacy of CBD and Λ 9-THC, these and other cannabinoids are under investigation for additional pharmacological activities, including activity as antiviral agents. However, clinical trials and scientific data supporting antiviral activity of cannabis oil against dengue, Covid-19, Nipah virus (NiV), monkeypox, and lumpy skin viral disease is lacking.

Keywords: *Cannabis sativa*; CBD- Cannabidiol; CBDA- Cannabidiolic acid; CBGA-Cannabigerolic acid; Hemp; Dengue; SARS-COV-2; Monkeypox; Nipah virus; Lumpy skin viral disease

1. Introduction

Cannabis sativa is a flowering plant from the *Cannabaceae* family and genus *Cannabis*. *Cannabis* is a plant notorious for its psychoactive effect, but when used correctly, it provides a plethora of medicinal benefits [1-47]. *Cannabis* has been used for thousands of years for recreational, medicinal, or religious purposes. *Cannabis* is also a wild noxious weed with notorious psychoactive principle, Λ9-tetrahydrocannabinol (THC) found growing in India, China, Bhutan, Nepal, Pakistan, Afghanistan, Iran, and Morocco[1-45]. *Cannabis* has a long history in India, recorded in legends and religion. It was found in various habitats ranging from sea level to the temperate and alpine foothills of the Indian Himalaya Region from where it was probably spread over the last 10,000 years [1-25-45]. Many historians believed that Indian Himalayan Region was the centre of origin of *Cannabis sativa* L. and *Cannabis indica* L. [1-49]. Tribal people in the Himalayan region used *Cannabis* as a home made herbal medicine for many diseases. During, Covid-19, the infusion of *Cannabis* flower with a morning cup of tea has saved the life of many people [1-23]. *Cannabis* oil was used as dengue mosquito repellent for controlling dengue viral fever , bacterial infections and fungal diseases [1-49-87]. However, due to the presence of psychoactive molecules, Λ9-tetrahydrocannabinol (Λ9-THC) and Λ8-tetrahydrocannabinol (Λ8-THC), *Cannabis* cultivation and its use is restricted/regulated in many countries [1-49-82-85].

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Introduced into Western medicine by William O'Shaughnessy in 1838 to treat a variety of conditions, including rheumatic pain and epilepsy, the use of cannabinoids (CBs) in clinical practice entered a period of latency and oblivion due to political barriers and problems in establishing quality control [1-45]. *Cannabis* was (re) introduced into British medical practice in the early 1840's by Irish physician Dr. William O'Shaughnessy, an army surgeon serving in Calcutta, India [1- 45-82-85-87]. In the Victorian period, cannabis was widely used for a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, the convulsions of tetanus, rabies, and epilepsy, and as a sedative [1-45]. *Cannabis sativa* extracts were typically administered orally in the form of an alcoholic tincture and were commonly incorporated in proprietary medicines [1-45]. With the introduction of synthetic drugs, herbal remedies were increasingly viewed as unpredictable and many of them, including cannabis extracts and tinctures, were removed from the British Pharmacopoeia of 1932 but retained in the British Pharmaceutical Codex of 1949 [1-44-82-87].

Industrial *Cannabis sativa* (Hemp of fiber type) has been cultivated for millennia as a source of fiber, food, medicine for cancer, wound healing, antiviral activity, and utilization of hemp for essential oils [1-48]. In addition to fiber and essential oils, the hemp plant produces hundreds of secondary metabolites including flavonoids, diterpenes, triterpenes, and cannabinoids [1-48]. Unlike primary metabolites such as proteins, nucleic acids, lipids, and carbohydrates that are essential for life, secondary metabolites benefit plants in other ways such as deterring predators, attracting pollinators, or preventing infection [1-48].

2. *Cannabis sativa*: Classified into 2 types

Cannabis sativa L., is classified into two types as Industrial *Cannabis sativa*, hemp or fibre type and Medical *Cannabis sativa* L.(drug or marijuana) based on its THC content [1-45]. Medical *Cannabis sativa* (drug or marijuana) contains a very high levels of THC (above 0.3 to 38% of dry weight) [1-45, 82-87]. On the other hand Industrial *Cannabis sativa* L. (Hemp) contains very low levels of THC (0 to 0.3% of dry weight) [1-45]. Industrial *Cannabis sativa* (hemp), as a diverse plant, can be a revolutionary crop for a better future and for upcoming generations [1-48]. It is an eco-friendly and worthwhile crop that complements a sustainable growth system. Industrial hemp farming has the potential to dramatically minimize the amount of carbon impact on the environment and can be cultivated with a little or no usage of chemical pesticides or fertilizers [1-49]. The stalks, seeds, and leaves are converted into various construction materials, textiles, paper, food, furniture, cosmetics, and healthcare products [1-45]. Biochar, bioplastics, biofuels, and biopesticides are some of the innovative applications of the hemp plant, which are subjects of research and debate at present time [1-45, 82-87].

3. Industrial *Cannabis sativa* (Hemp); Secondary metabolites

In addition to fiber and essential oils, the hemp plant produces hundreds of secondary metabolites including flavonoids, diterpenes, triterpenes, and Cannabinoids [1-50]. Unlike primary metabolites such as proteins, nucleic acids, lipids, and carbohydrates that are essential for life, secondary metabolites benefit plants in other ways such as deterring predators, attracting pollinators, or preventing infection [1-49-87].

Several secondary metabolites that are unique to *Cannabis sativa* L. include some Cannflavins (flavonoids), Cannabisins (lignans), and Cannabinoids [1-48]. Hemp produces over 100 Cannabinoids including Cannabidiol (CBD), Cannabidiolic acid (CBDA), the psychotropic Cannabinoid, Λ9- tetrahydrocannabinol (Λ9-THC), Λ9-tetrahydrocannabinolic acid-A (Λ9-THCA-A), Cannabigerol (CBG), Cannabigerolic acid (CBGA), and Λ9-tetrahydrocannabutol [1-50]. Despite legal restrictions, Cannabinoids and other compounds from hemp have a long and extensive history of safe use in humans[1-88]. These products have been administered orally, sublingually, dermally, and by inhalation. As a class of natural products, Cannabinoids have been shown to have suitable oral bioavailability, metabolism, blood–brain barrier permeability, and safety for use as therapeutic agents [1-49-87]. Based on the established therapeutic efficacy of Cannabidiol (CBD) and Λ9-tetrahydrocannabutol (Λ9- THC), these and other cannabinoids are under investigation for additional pharmacological activities, including activity as antiviral agents [1-50]. Among the vast range of compounds, multiple research papers have shown that Cannabinoids, such as Cannabidiol (CBD)and Λ-9-tetrahydrocannabinol (THC) have antiviral effects[1-50]. There is limited evidence that demonstrates the therapeutic effects of Cannabinoids in viral infections [1-50]. Some scientists believed that Λ9-tetrahydrocannabutol (Λ9- THC), may be advantageous in viral illnesses, when the inflammatory response of the host is pathogenic[1-50]. The anti- inflammatory properties of Cannabinoids were found to be associated with the treatment of COVID-19 [1-49-88].

Female *Cannabis* flowers have densely packed glandular structures called trichomes that store the phytocannabinoids, tetrahydrocannabinolic acid (THCA) and Cannabidiolic acid (CBDA) which must be decarboxylated by heat to produce Δ9-tetrahydrocannabinol (THC: intoxicating) and Cannabidiol (CBD: non-intoxicating) [1-45]. The two cannabinoids

the most well known for their therapeutic properties are, Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) [1-50]. THC and CBD are the neutral homologs of tetrahydrocannabinolic acid (THCA) and Cannabidiol acid (CBDA) respectively [1-50]. A conventional classification model of Cannabinoids is due to their chemical contents dividing them to eleven subclasses including Cannabigerol (CBG), Δ9-tetrahydrocannabinol (Δ9-THC), Cannabidiol (CBD), Cannabichromene (CBC), Cannabinol (CBN), (−)-Δ8-transtetrahydrocannabinol (Δ8-THC), Cannabicyclol (CBL), Cannabinodiol (CBND), Cannabielsoin (CBE), Cannabitriol (CBT) and miscellaneous [1-45, 82-88].

Synthetic Λ 9-THC was approved by the United States Food and Drug Administration in 1985 as the drug dronabinol for the treatment of nausea associated with cancer chemotherapy and for anorexia associated with weight loss in AIDS patients [1-50]. The synthetic Λ 9-THC analog nabilone has been approved in the United States for the control of chemotherapy-induced nausea and in Canada as an adjunct therapy for chronic pain management [1-50]. Discovered in 1940, CBD lacks the psychotropic properties of Λ 9-THC but exhibits other activities including some with established therapeu- tic benefit. In 2018, CBD isolated from hemp was approved in the United States as the drug epidiolex for the treatment of epileptic seizures known as Lennox–Gastaut syndrome and Dravet syndrome [1-50].

4. Industrial *Cannabis sativa* (Hemp): Antiviral Activities

During most of the last century, legal restrictions impeded cultivation of hemp, isolation of cannabinoids, and research on the antiviral properties of cannabinoids and other hemp secondary metabolites[1-70, 76-81]. On the basis of literature survey and van Breemen, Simchuk (2023) [48] reported that cannabinoids have been shown to have activity against herpes viruses, which are DNA-type viruses, as well as the RNA-type viruses SARS-COV-2 and HIV/SIV [48-58, 76-81]. The most studied antiviral cannabinoids to date have been CBD and Λ 9-THC, which have been approved as drugs by the FDA for unrelated pharmacological activities[48-75-81]. These two cannabinoids function as antiviral agents through multiple mechanisms of action, some of which overlap such as inhibition of the SARS-CoV-2 main protease 3CL- pro and inhibition of ACE2, which is the human cell receptor for SARS-CoV-2, CBD and Λ 9-THC also have anti-inflammatory activities that can help suppress the pro-inflammatory effects of SARS-CoV-2 and HIV/SI [48-58, 76-83]. Other cannabinoids have recently been shown to have antiviral activities that include some unique mechanisms of action[1-48-58, 76-81]. For example, CBDA and CBGA can prevent cell entry and infection by SARS-CoV-2 [48-58, 76-81]. Research on the antiviral activities of the more than 100 less abundant cannabinoids is just beginning, and there is potential to discover even more potent antiviral agents among these unique chemical structures[1-48-75-85].

Importantly, clinical trials are needed to explore the safety and efficacy of antiviral cannabinoids. Based on the multiplicity of active cannabinoids acting by different mechanisms of action, combinations of cannabinoids should be explored for activity. Combination therapy has become the mainstay of HIV antiretroviral therapy due to the superior activity of drug mixtures that act by complementary mechanisms of action [1-48]. van Breemen, Simchuk (2023) [48] reported that although most antiviral cannabinoids have shown individual activities in the low micromolar range, combinations of cannabinoids acting through complementary mechanisms of action might show synergistic effects that might be efficacious at lower concentrations [48]. Synergy among cannabinoids known as an entourage effect has already been established for pharmacological activities such as pain management [47].

Nipah virus (NiV), an emerging zoonotic bat borne virus that can cause severe respiratory illness and deadly encephalitis in humans [22]. Nipah virus (NiV) outbreak was first reported in 1998 from Malaysia and then recorded in Bangladesh, India, Philippines, Singapore and Thailand[22]. A recent fifth outbreak of Nipah virus (NiV) during August-September 2023 in Kerala State, India brought this emerging-re-emerging virus into the spotlight again[22]. Due to the lack of vaccines and drugs with proven effectiveness against Nipah virus (NiV), treatment of patients is limited to supportive and prophylactic[22], Fruit bats are the main reservoir for this virus, which can cause disease in humans and animals[22]. Nipah virus (NiV) can be transmitted from bats or livestock to humans, typically via contaminated food (fruit or raw date palm sap), and person-to-person through respiratory secretions[22]. Hemp seed oil has gained remarkable popularity due to its perceived therapeutic properties, particularly antiviral properties for potential health benefits[22]. During the recent outbreak of Nipah virus (NiV), the local traditional healers in India used hemp oil as the mouth wash for controlling throat infections, head ache, vomiting and suggested for the consumption of hemp seeds and oil as the functional food[22]. The consumption of hemp seed and oil has drastically reduced the fever. Therefore, there is a growing evidence that hemp oil might inactivate the Nipah virus (NiV). However, clinical trials and scientific data supporting antiviral activity of *Cannabis* oil (CBD oil) against Nipah virus (NiV) is lacking[22]. Therefore, further research should focus on exploring the molecular mechanisms of hemp oil against Nipah virus (NiV) is warranted [22]. Multicenter clinical trials should be performed to validate the efficacy of hemp oil alone or in the form of formulations for the treatment of viral diseases [22].

Hemp plants produced a diversity of chemical constituents with the potential to inhibit viral replication [1-76]. However, clinical trials and scientific data supporting antiviral activity of Cannabis oil against Nipah virus (NiV) is lacking [22]. Therefore, further research should focus on exploring the molecular mechanisms of essential oils particularly hemp oil and their individual chemical compounds against Nipah virus (NiV) is warranted[22].

Local traditional healers in the rural part of India used Cannabis oil as the dengue mosquito, *Aedes aegypti* repellent [19, 63-75]. Cannabis oil was used as dengue mosquito repellent for controlling dengue viral fever, bacterial infections and fungal diseases [19, 63-75]. Tribal people in the Indian Himalayan region used Cannabis as a home made herbal medicine for many diseases[1-22-75]. During, Covid-19, the infusion of Cannabis flower with a morning cup of tea has saved the life of many people [1-49]. In India during the recent outbreak of Monkeypox, Cannabis oil was used for the external body applications as a preventive measures to control the monkeypox viral disease [59-60]. But the no of monkeypox cases in India were very low and preventive measures were adopted by the local traditional healers [59-60]. Hemp oil was also used for controlling the monkeypox disease [59-60]. In addition to this, hemp oil was also used to control lumpy skin viral disease of cattle in India [53]. However, the clinical trials and scientific evidence is lacking.

Antiviral activities of some of the most abundant cannabinoids have been documented in silico, in vitro, and in vivo [1-48-58, 76-81-83]. Studies of the antiviral activities of the more than 100 less abundant cannabinoids are still needed as are carefully designed clinical trials[1-48-58]. Based on the preclinical evidence of antiviral activity as well as oral bioavailability and long history of safe human use of cannabinoids individually or as mixtures, multiple clinical studies of antiviral cannabinoid safety a efficacy are in progress worldwide using CBD [48] and Λ -THC [48-59, 76-81]. There is very limited in vivo investigation of the antiviral effect of these compounds[48-59]. Despite the therapeutic effect, cannabis is an illicit drug that can be consumed in a harmful and abusive manner. Thus, preclinical and clinical trials in humans are very restricted due to the legalization of cannabis compounds in a few countries [1-75]. Studies on the effects of the compound containing both CBD and THC are also limited. Besides, there is still a gap in revealing the exact mechanism of how cannabinoids and terpenes help in reducing replication of various viruses [48-75]. Moreover, due to the wide range of activities of Cannabinoids and terpenes, further in vivo and clinical studies are essential to determine the effective dose of the cannabis compounds to maximize their therapeutic benefits in viral infections [1-75-81]. In short, we are still very far from the level of evidence required to consider cannabis compounds as a regimen for viral illnesses [1-75].

5. Conclusion

Industrial hemp, as a diverse plant, can be a revolutionary crop for a better future and for upcoming generations. It is an eco-friendly and worthwhile crop that complements a sustainable growth system. Industrial hemp farming has the potential to dramatically minimize the amount of carbon impact on the environment and can be cultivated with a little or no usage of chemical pesticides or fertilizers. The stalks, seeds, and leaves are converted into various construction materials, textiles, paper, food, furniture, cosmetics, and healthcare products. Biochar, bioplastics, biofuels, and biopesticides are some of the innovative applications of the hemp plant, which are subjects of research and debate at present time. However, due to the presence of psychoactive molecules, Λ9-tetrahydrocannabinol (Λ9-THC) and Λ8-tetrahydrocannabinol (Λ8-THC), cannabis cultivation and its use is restricted/regulated in many countries.

Several secondary metabolites that are unique to *Cannabis sativa* L. include some cannflavins (flavonoids), cannabisins (lignans), and cannabinoids[1-49]. Hemp produces over 100 cannabinoids including cannabidiol (CBD), cannabidiolic acid (CBDA), the psychotropic cannabinoid 9-tetrahydrocannabinol (Λ9-THC), Λ 9-tetrahydrocannabinolic acid-A (Λ 9-THCA-A), cannabigerol, cannabigerolic acid (CBGA), and Λ 9-tetrahydrocannabutol. Despite legal restrictions, cannabinoids and other compounds from hemp have a long and extensive history of safe use in humans. These products have been administered orally, sublingually, dermally, and by inhalation. As a class of natural products, cannabinoids have been shown to have suitable oral bioavailability, metabolism, blood–brain barrier permeability, and safety for use as therapeutic agents [1-49]. Based on the established therapeutic efficacy of CBD and Λ 9-THC, these and other cannabinoids are under investigation for additional pharmacological activities, including activity as antiviral agents.

During the recent outbreak of Nipah virus (NiV), the local traditional healers in India used hemp oil as the mouth wash for controlling throat infections, head ache, vomiting and suggested all the patients for the consumption of hemp seeds and oil as the functional food. The consumption of hemp seed and oil has drastically reduced the fever. Therefore, there is a growing evidence that hemp oil might inactivate the Nipah virus (NiV). Hemp plants produced a diversity of chemical constituents with the potential to inhibit viral replication. However, clinical trials and scientific data supporting antiviral activity of cannabis oil against dengue, Nipah virus (NiV), monkeypox, and lumpy skin viral disease is lacking.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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