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Cannabis sativa L.: A Comprehensive review on legislation, decriminalization, phytochemistry, antimicrobial activity, and safety

REVIEW ARTICLE

Cannabis sativa L.: A comprehensive review on legislation, decriminalization, phytochemistry, antimicrobial activity, and safety

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Abstract

Throughout history, medicinal and aromatic plants have been used extensively to cure a variety of ailments. This article provides a comprehensive overview of *Cannabis sativa*, specifically focusing on its legislative status, decriminalization, phytochemistry, antimicrobial activity, and safety. The study begins by briefly outlining the plant's history, including its cultivation, harvesting, and storage methods. The review analyzes extensively the antimicrobial properties of *Cannabis sativa* and its derivatives, specifically examining their reported antiviral, antibacterial, antifungal, and antiparasitic capabilities, which have been documented in databases such as Scopus, ScienceDirect, PubMed, and Web of Science. The paper also discusses trends in studies about the plant object of the study, the different bioactive compounds that were identified in the plant (phenolic acids, flavonoids, alkaloids, cannabinoids, and terpenes), and safe consumption in several cannabis-based products including candies, desserts, wine and as food flavoring. Furthermore, this study has reported information about the legalization and decriminalization of cannabis use across the globe with a specific focus on Morocco because it has the largest cultivated area of *C. sativa* plant. However, some substances with potential antimicrobial properties were not investigated in this review due to the lack of data on their activity. The authors hope that their efforts will inspire future studies on the therapeutic uses of *Cannabis sativa* and its derivatives, ultimately leading to improved health outcomes.

Keywords: Antimicrobial activity, *Cannabis sativa*, Decriminalization, Phytochemistry, Safety

1. Introduction

Due to their accessibility and low price, medicinal plants have been employed for primary healthcare in emerging nations generally, and Morocco in particular [1]. *Cannabis sativa* also called hemp is a plant from the Cannabaceae family originating from central and southwest Asia [2]. In fact, this plant was largely used in traditional Chinese medicine, Ayurveda, Europe, and Arab culture for millennia. 5000 years ago, hemp seeds were used in Chinese civilization against fatigue, malaria, and inflammatory diseases. Moreover, it was known for its action to improve mood and reduce pain in Assyrian and Egyptian civilizations [3]. However, in Europe in some parts, it was employed in aristocrats' desserts as a sign of wealth, while in its utilization was condemned by the church because of its use in witchcraft. In the counterpart, it was in the Arab civilization by poor class [3]. Since the publication of the first paper in 1841, a large number of

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papers have reported on the chemical composition of *Cannabis sativa*. The plant is known to contain nonvolatile compounds such as flavonoids, cannabinoids, phenolic acids, fatty acids, alkaloids, and steroids, as well as volatile compounds such as α-humulene limonene, α-terpinolene, β-selinene, and others [4−7]. Furthermore, the nutritional value and safe usage of this plant were also reported in the literature [8]. Recently, Rull et al. (2023) [9] published a review of the history of *C. sativa*, and Schanknecht et al., (2023) [10] presented scientific evidence of the utilization of cannabis in the treatment of melanoma. Other review articles have reported on the impact of cannabinoids on the central nervous system, COVID-19 treatment, and the methodology of detection and quantification of cannabis phytochemicals, as published by Madden et al. (2023), Pérez et al. (2022), and Zhang et al. (2022) [11−13]. Lately, some nations (USA, Canada, Morocco, etc.) have passed new legislation allowing the legalization and decriminalization of cannabis usage in various contexts [14,15].

By summarizing its antimicrobial action, the current study aims to highlight the current directions in *C. sativa* research (Antiviral, antibacterial, antifungal, and antiparasitic properties). Furthermore, it has led to an exploration and summary of the various bioactive chemicals found in hemp plant. The current study also revealed a number of biomolecules that had not been fully explored, as well as information about the legalization and decriminalization of cannabis use. Hence, a thorough review was carried out in order to better guide future research studies for potential use to enhance health conditions.

2. Methodology of research

The methodology of this research follows a comprehensive literature review approach to provide an overview of the history, traditional usage, research trends, phytochemistry, safety, and antimicrobial properties of *C. sativa* and its derivatives. The data for this study were obtained from reputable online databases, including PubMed, Scopus, ScienceDirect, and Web of Science. The search terms used were "*Cannabis sativa*", "phytochemistry", "safety", "traditional use", "antiviral", "antibacterial", "antifungal", and "antiparasitic" to capture all relevant studies on the topic. The data were exhaustively examined, and relevant papers were filtered based on their relevance and quality. The inclusion criteria for this review were research papers published in both French and English until 2022 that reported on the phytochemistry and/or antimicrobial properties of *C. sativa.*

The current paper is a comprehensive literature review that was established to provide an overview of the history, traditional usage, research trends, phytochemistry, safety, and antimicrobial properties of *C. sativa* and its derivates. The cited data was accessible from online databases: PubMed, Scopus, ScienceDirect, and Web of Science. Key terms used were, "*Cannabis sativa*", "phytochemistry", "safety", and "traditional use". For antimicrobial activity, the terms used were "antiviral", "antibacterial", "antifungal", and "antiparasitic". The obtained data were exhaustively examined and filtered. Our investigation comprised of all the research papers on the phytochemistry and/or antimicrobial properties of *C. sativa* published in both French and English until 2022.

3. Research trends on *C. sativa*

C. sativa appeared in literature for 182 years. Since 1841 when the first publication on marihuana has seen the light, significant interest was observed in the last decades in fact by 2000, 74 papers were published while this number increased to 814 papers published by 2022 (Fig. 1A). This quantum leap in the trend of published papers suggests an increasing interest among scientists in the possible health benefits of hemp. Many types of research were conducted across the globe, the USA has ranked number one with 2191 published documents, followed by Italy in the second place with 747 documents and Canada ranked in third place with 461 published documents, while Morocco has only 37 published documents despite its consideration as the largest producers of cannabis resins (Fig. 1B). Research articles had the lion's share with 76% of total published papers followed by reviews with a percentage of 13.4% (Fig. 1C). Furthermore, numerous investigations evaluating *C. sativa* in different domains including medicine (16.7%), agriculture and biological sciences (15.6%), pharmacology, toxicology and pharmaceutics (15.4%), biochemistry, genetics and molecular biology (13.7%), and others provide convincing data regarding the potential of this widely used natural product in clinical care. In order to enhance its pharmacological properties, hemp chemical profiles, agronomical features, and adaptability and safety use have all been described in the literature to have been improved (Fig. 1D).

4. *Cannabis sativa* synonyms

Cannabis americana Pharm. ex Wehmer; *Cannabis chinensis* Delile; *Cannabis erratica* Siev.; *Cannabis foetens* Gilib.; *Cannabis generalis* E.H.L.Krause; *Cannabis gigantea* Crevost; *Cannabis indica* Lam. ; *Cannabis indica* f. afghanica (Vavilov) Vavilov; *Cannabis indica* var. kafiristanica Vavilov; *Cannabis intersita* Soják;

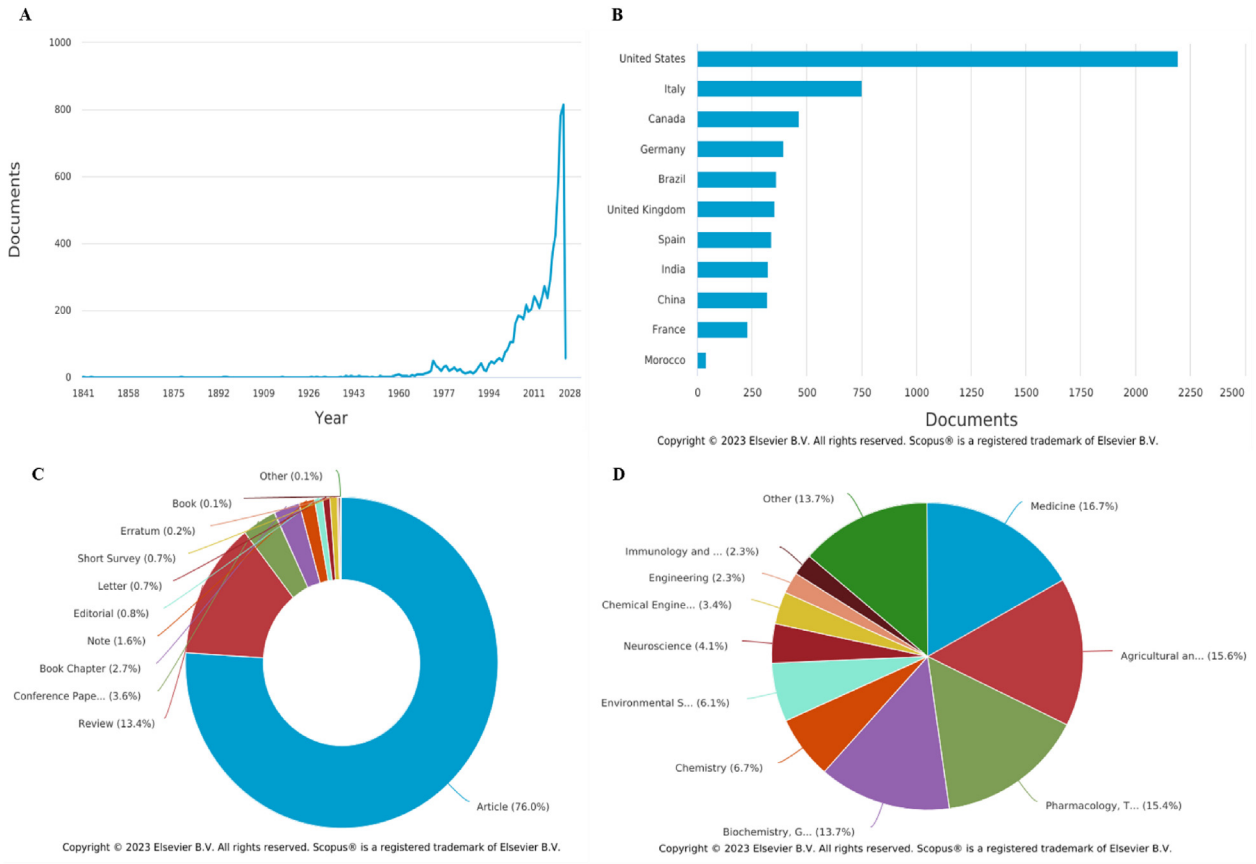

Fig. 1. Research trends in Cannabis sativa. (A): Documents published by year; (B): Top ten countries publishing papers; (C): Types of documents published; (D): Percentage of publications according to different research areas. Data retrieved from Scopus database January 2023.

Cannabis kafiristanica (Vav.) Chrtek; *Cannabis lupulus* (L.) Scop. ; *Cannabis macrosperma* Stokes; *Cannabis ruderalis* Janisch. ; *C. sativa* f. afghanica Vavilov; *C. sativa* f. chinensis (Delile) A.DC. *C. sativa* f. pedemontana A.DC. ; *C. sativa* subsp. indica (Lam.) E.Small & Cronquist; *C. sativa* subsp. intersita (Soják) Soják; *C. sativa* var. gigantea (Delile ex Vilm.) Alef. ; *C. sativa* var. indica (Lam.) E.Small & Cronquist; *C. sativa* var. indica (Lam.) Wehmer; *C. sativa* var. kafiristanica (Vavilov) E.Small & Cronquist; *C. sativa* var. kif A.DC. ; *C. sativa* var. macrosperma (Stokes) Asch. & Graebn. ; *C. sativa* var. monoica Hol. ; *C. sativa* var. praecox Serebr. *C. sativa* var. ruderalis (Janisch.) S.Z.Liou; *C. sativa* var. ruderalis Janisch. *C. sativa* var. sativa; *C. sativa* var. spontanea Vavilov; *C. sativa* var. vulgaris Alef. ; *Cannabis intersita* Soják; *Polygonum viridiflorum* Poir [16].

5. History and traditional usage

Since ancient times and for about 5000 years ago, the Chinese emperor Chen Nung has cited hemp when he draws for the first time the Chinese pharmacopeia. Meanwhile, the seeds were used by Chinese physicians for their oil proteins against fatigue, rheumatism, malaria, eczema, and their use against inflammatory diseases [17]. Additionally, Asian holy texts, in India, Tibet, Hinduism, and Buddhism have referred to its religious use and have considered it in main religious rituals also used its flowers and resins to facilitate meditation and communication with the spirits [17]. Asian civilizations were not the only ones reporting *C. sativa*, in fact, the library of Ashurbanipal in Assyrian civilization, Ebers Papyrus (Egyptian medical papyrus for herbal knowledge) had reported that this plant was used to reduce pain and to improve mood. Besides, cannabis use in medieval Arabic culture was mainly connected to social situations in medieval Arabic society. While, in medieval Europe Italian were the first to start large-scale cultivation and commercialization of *C. sativa.* Also, Aelius Galenus, a roman physician has reported hemp use by Roman aristocrats as cannabis-based dessert. Meantime, American continent was free from *C. sativa* until the arrival of European colonists where its usage was limited for

textile manufacturing. In 1484, Pope Innocent VIII (Giovanni Battista Cybo-Tomasello), has condemned witchcraft use of *C. sativa*. While it was prescribed by some physician in Europe for various effects including euphoria, sedation, stimulation of appetite, hallucinations, and aphrodisiac effect [3].

Despite the different usage during ancient and medieval times, the 20th century was a turning point, exactly in 1932 was retracted from British pharmacopeia and added to the list of banned substances. In the USA, cultivation and/or possession of *C. sativa* was considered a federal crime by the Marihuana tax act established in 1937 [18]. Nowadays, in Pakistan *C. sativa* leaves were used for wound healing, as anodyne, sedative, tonic, and narcotic effect. In Nepal, marijuana was used for humans and livestock, gastrointestinal disease, pain, and snake bite. The same for Kenya and Uganda where it was used as an ethnoveterinary remedy [3]. On the counterpart, many people think that the use of cannabis is a matter of personal freedom because it heightens senses, improves communication, and fosters original ideas "thinking outside of the box", according to those who claim that it does so [19]. In Morocco, *C. sativa* aerial parts are largely used as narcotic, analgesic, hypnotic, and sedative. Also, it was reported it uses as cicatrizing, antifungal, astringent, against itching, and to treat the abscess and hair loss. Finally, this plant was used also as an emmenagogue, galactagogue, and as an abortifacient agent for pregnant women [20].

6. Vernacular names

English: hemp, cannabis, marijuana; **French:** Chanvre; **German:** Hanf; **Thai:** kancha chin (กัญชาจีน), kancha (กัญชา); **Italian:** Canapa; **Spanish:** Cáñamo; grifa; hachís; mariguana; marijuana; **Chinese:** Xian ma; ye ma; **Japanese:** Mashinin; Indian: Bhang; charas; ganja; **Portuguese:** Canhamo; maconha; **Classic Arabic:** Al-Bhango; Al-Hashish; Al-Qanaap [16]. In Morocco, *C. sativa* has different names, **kîf (كيف)** in High Moulouya and Fez- Boulemane. While in eastern Morocco, Mechraa Bel Ksiri (Northwest); Taounate (Central); Mokristet (North west); Ksar Lakbir (Northwest), in Tata province (South), and in Agadir-Ida-Outanane (Southwest), it's called **l-kîf (الْكِيفْ)**. **Laḥšîš (لَحْشِيشْ)**, was another naming of hemp in eastern Morocco, while **Šîra (شِيرَ)** was the designation used by the majority of Moroccan habitants [20,21].

7. Plant taxonomy

C. sativa is classified taxonomically as follows (WFO, 2023).

Kingdom: Plantae (plants).
Subkingdom: Tracheobionta (vascular plants).
Superdivision: Spermatophyta (seed plants).
Division: Magnoliophyta (flowering plants).
Class: Magnoliopsida (dicotyledons).
Subclass: Hamamelididae.
Order: Urticales.
Family: Cannabaceae.
Genus: Cannabis.
Species: sativa.

8. Botany and ecology

C. sativa is a diecious herbaceous plant that could reach a height of about 6 m. Additionally distinguished by fluted stems (1–4 m). The stipulate leaves are opposite, palmate, and have segments that are unequally long, elongated, and toothed towards the lowest section of the plant. The leaves become alternating, simple, or simply three-segmented near the top of the axis. These plants have hairs that secrete resin and are tectorial, and cystolithic. Compared to female plants, male plants are spindlier and have fewer leaves. The male flowers are grouped in panicles and have been stripped down to 5 free, greenish-yellow sepals and 5 erect-netted stamens in the floral bud. The female flowers are in compact cymes and are interspersed with bracts. A smooth, greyish, ovoid achene measuring 2.5–3.5 mm in length and 2.5–3 mm in diameter, the fruit is commonly referred to as "chenis." Sex identification is only achievable during the final stage of growth, when flower creation starts. Male plants produce tiny pollen sacs that will fertilize female plants with stigmas that are hairy and sticky. An extremely thin-walled calyx with glands that secrete resin is covered by the involucre of the female flowers, which feature two long white, yellow, or pink stigmas. In the leaf axils, the female flowers bloom in pairs. Their calyx, which is about 3–6 mm long, is entirely encircled by a carpel. The calyx of the male flowers has five sepals that are about 5 mm long and are either yellow, white, or green in color. They feature five 5 mm long stamens and a bloom that is angled downward. The sepals' upper surface is coated in glandular trichomes (hairs) (Paczesny, 2014; WFO, 2023).

Regarding the agro-climatic conditions, it was found that scattered rainfall, low humidity and sunny climate increases the rate of psychoactive compounds on one hand. On the other hand, the temperature in association with relative humidity are factors influencing cannabinoids content. Finally, high ultraviolet radiation produces significantly higher amounts of cannabinoids [22].

With regards of soil composition, it has been shown that cannabinoids content is negatively correlated with the potassium (K) content. Also, the interaction of the major elements (N, P, K) and calcium are positively correlated to total cannabinoids content [22]. Moreover, the presence of trace elements such as Mg and Fe are crucial for the production of cannabinoids by the plant, since they intervene in the enzymatic reactions as cofactors [3,23].

9. Cultivation, harvesting and storage

C. sativa could be cultivated in and outdoors under different conditions, cultivation from seeds normally starts in late March and until early April. The obtained healthy seedlings are transplanted directly into the field. In fact, seed germination starts after four to five days by providing a favorable environment for optimum germination (heat, air, …). In order to maintain the quick and normal development of young hemp, the seedling needs to be kept under fluorescent light for a photoperiod of about 18 h during the initial vegetative growth and to be fully exposed to full spectrum for a photoperiod of 18 h. While propagation from vegetative cuttings is performed under three essential types grafting, air-layering, and cuttings [24]. Finding the ideal harvesting stage is a crucial step in the development of marihuana in order to get the desired chemical profile. In fact, daily evaluation of the cannabinoid content in the plant's various sections is mandatory. The peak level of chemicals is observed during the budding period, after which it plateaus for around one to two weeks before declining when senescence sets in. Moreover, the mature buds are usually the first to be harvested in order to give time for other buds to finish their maturation stage. The hue of the stigmas, which shrivel and turn brown as the blooms age, serves as a visual cue of maturity. Either the intact buds or the buds that have been cut into smaller pieces can be dried. Afterward, separation of any residual leaves from the buds if necessary. To separate tiny stems and seeds, the buds are delicately rubbed over variously sized screens. The storage process is also an important part in order to maintain the quality of the harvested product. According to the FDA (Food and Drug administration) recommendations the hemp biomass could be stored in polyethylene bags in a temperature of 18–20 °C for short-term conservation and under −10 °C for long-term storage in dark conditions [24].

In Morocco, hemp cultivation is concentrated mainly in the north, exactly in the provinces of Chefchaouen, Al Hoceima and Larache, which together account for more than 75% of production. The first two are considered traditional cannabis cultivation areas, while the Larache region is an extension area where this culture is more recent [25] Fig. 2. Moroccan marijuana is presumably related to indica marijuana in terms of origin. According to field research conducted in Bab Berred and Kétama in 2004 and 2010, rural workers who have been growing cannabis for years and are actively involved in its trafficking had combined two cannabis strains: a Moroccan variety and a Pakistani variety, which gives the resin a slightly more golden hue [26]. Hemp cultivation in Morocco takes place at the end of winter season (February–March) exactly after ploughing and preparing the ground for seeds that are mainly for the previous year production or bought. The culture is led on plots in Bour or in irrigate according to the climatic conditions (rains, temperature and altitude). Also, numerous practices were established such as weeding process which is important for plant health, and separation which consists in removing the male plants when they have finished their missions of pollination. Generally, cannabis culture cycle takes five to six months while harvesting in mainly during the period July and September when female plants reach maturity. The harvest is followed by a drying in well reserved places, this operation lasts approximately one month. Then the dried plants are transferred to a room for storage [27].

The transformation of the cannabis plant into resin, or hashish, is generally done by the method of shuffling. The bunches are put on a fabric sieve, and covered in transparent plastic. The first step is to beat the plastic-covered bunches to extract the leaves. Then the leaves are put again on the sieve, covered with plastic and all is beaten with two long thin sticks during half an hour. Afterward, the plastic and the sieve are removed to collect the powder of the first beating, this powder is considered of first quality. The operation is repeated 2 or 3 times to obtain other powders of inferior quality. Finally, comes the last step before commercialization, it is the preparation of the paste from the powder using a compression machine that gives the resin a rectangular and flattened shape, a bar weighing 150 or 250 g [28].

10. Legalization decriminalization of *C. sativa*

Despite the wide restriction of *C. sativa* cultivation, production, and usage by laws in different countries this is still used on a large scale. Many people see that the use of cannabis is considered a freedom of choice and helps users to increase their senses,

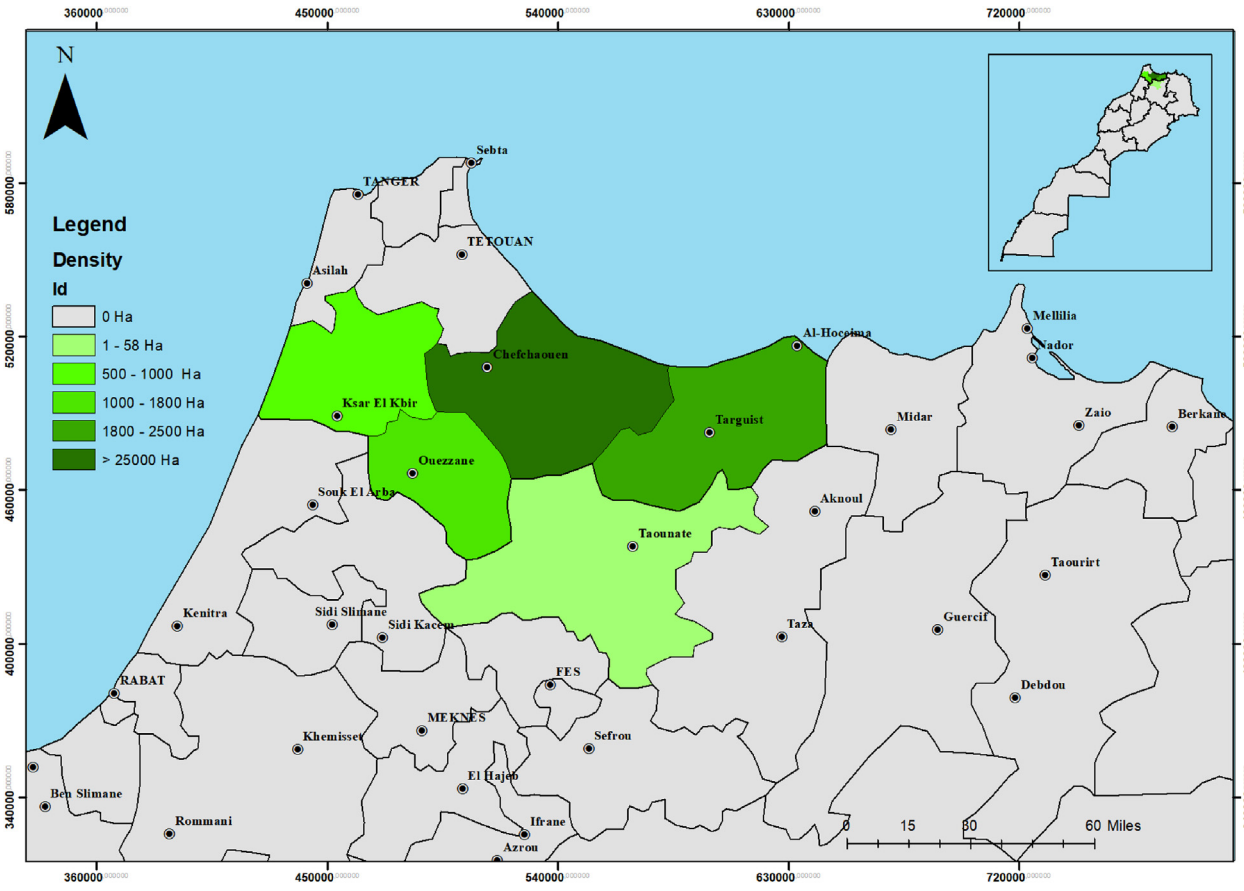

Fig. 2. Cannabis sativa cultivation areas in Morocco.

facilitates communication, and promotes creative thoughts as they claim "thinking outside the box" [19]. Alongside this recent scientific evidence about the medicinal potential of cannabis has set the path for decriminalization and regulation by law of cannabis use in various countries across the globe. In fact, the Dutch government in July 2020 expanded its regulations to allow an experiment in the cultivation and production of cannabis for the supply of coffee shops. While in 2021 Switzerland allowed pilot trails under the Narcotics Law in order to gain scientific knowledge about alternative methods of regulating the non-medical use of cannabis. Legalization of the whole cannabis supply chain in Canada, parts of the United States, and Uruguay, as well as the adoption of policies allowing for-profit businesses to produce and sell cannabis for recreational use [14]. Furthermore, the annual report communicated by the United Nations on Drugs and Crime (UNODC) has put Morocco as the top international producer of cannabis resin in 2020. The same agency has noted a regression of cultivated areas from 2016, where the cultivated area was 47 000,00 ha with a production of 35 652,83 tons and a harvested area of 46 605,00 ha to a cultivation area of 21 048,71 ha and a production of about 596,03 tons in a harvested area of 20 913,21 ha by 2019 [29]. Therefore, on July 14th, 2021, Morocco by a royal decree published in the official bulletin has allowed the cultivation and production, transport, importation, exportation, and marketing of cannabis and their products which will promote thereafter the licit use of *C. sativa* in Morocco [15].

11. Phytochemistry of *C. sativa*

11.1. Volatile compounds

Numerous research papers were conducted to elucidate the different bioactive compounds present in *C. sativa* essential oils. A high variety was noticed between the different hemp plants across the globe. Thanks to gas-chromatography coupled to mass spectroscopy (GC−MS) several volatile

compounds have been identified in forbidden fruits and cholocope of hemp among them we cite β-caryophyllene, α-humulene (α-caryophyllene), β-farnesene, Selina-4(15),7(11)-diene, and Selina-3,7(11)-diene. Moreover, vomifoliol and dihydrovomifoliol were among the sesquiterpenes isolated from *C. sativa* [30]. Further investigations have reported the volatile chemicals present in *C. sativa* inflorescences and aerial parts such as β-myrcene, α-pinene, β-pinene, trans-β-ocimene, limonene, α-terpinolene, γ-selinene, guaiol, γ-eudesmol, β-eudesmol, bulnesol, β-caryophyllene oxide, γ-caryophyllene, β-selinene, α-cadinene [4,5,31–37], Fig. 3.

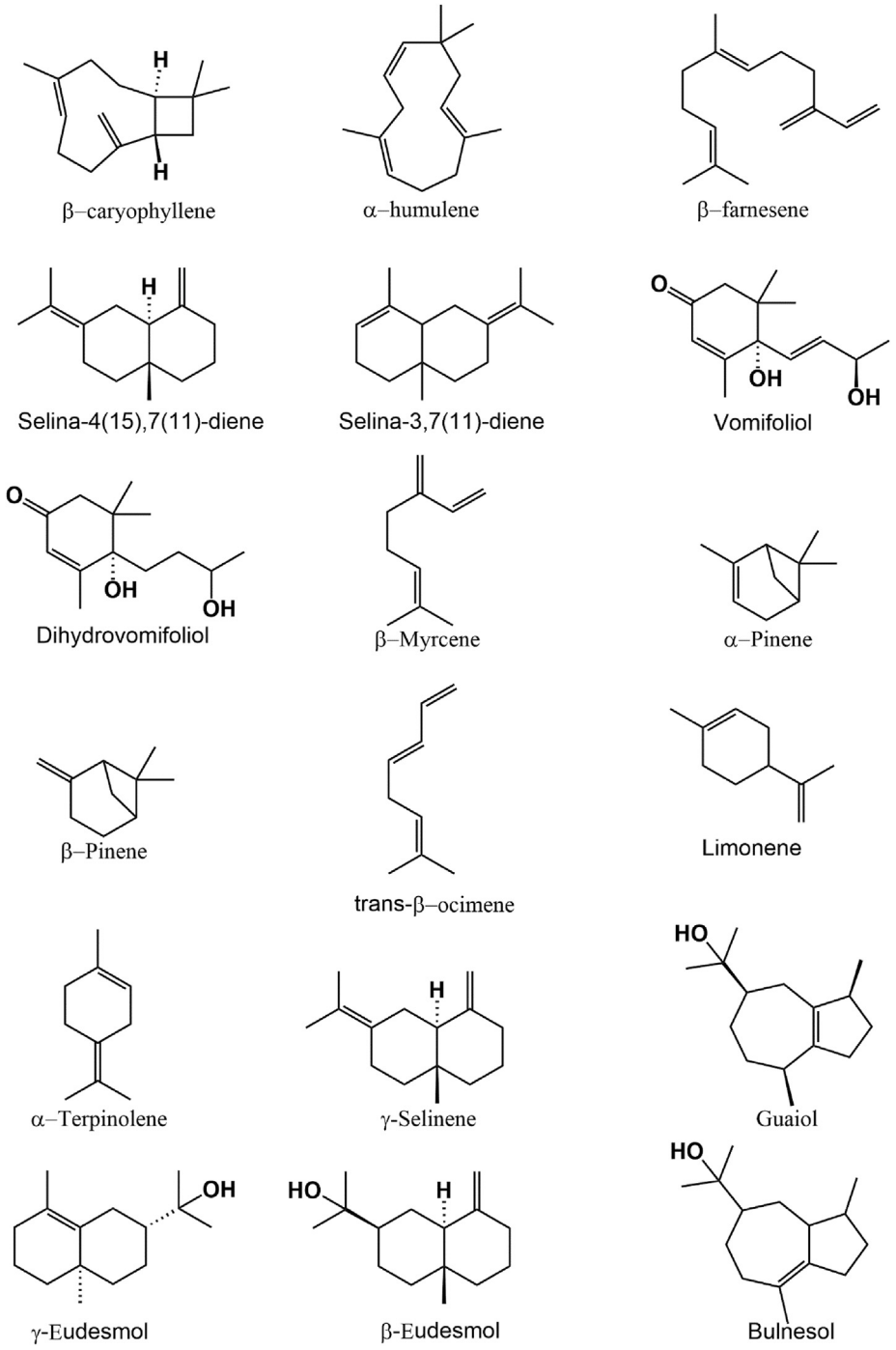

Fig. 3. Major compounds identified in Cannabis sativa essential oils.

11.2. Cannabinoids

C. sativa is a plant of great richness with different cannabinoids. Recently it was reported that its forbidden fruits and cholocope were rich with cannabigerol (CBG), cannabigerolic acid (CBGA), cannabidiol (CBD), cannabidiolic acid (CBDA), cannabichromanon (CBCN), cannabichromene (CBC), tetrahydrocannabivarin (THCV), Δ^9-tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCA-A) [33]. In addition to the compounds mentioned above the HPLC analysis of inflorescences showed the presence cannabidivarinic acid (CBDVA), tetrahydrocannabivarinic acid (THCVA), cannabidivarin (CBV), Cannabicitran, prenylspirodinone [4,6,31,38–42] Fig. 4.

11.3. Phenolic acids and flavonoids

The chemical screening of EtOH and MeOH extract showed the presence of several such as alkaloids, flavonoids, cardiac glycosides, phenols, terpenes, resins, and steroids [43,44]. Among all investigated *C. sativa* extracts several compounds were identified using different techniques. It was declared in several studies the identification of several flavonoids such as, cannflavin A, cannflavin B, luteolin-7-*O*-glucuronide, apigenin-7-*O*-glucuronide, vitexin-4-*O*-glucoside, vitexin-2-*O*-rhamnoside, vitexin, isovitexin, rutin, quercetin, naringenin, genistin, apigenin and diosmetin, homoorientin, orientin, protocatechuic, gentisic, rhamnetin, norisoboldine Fig. 5. Also, *C. sativa* were reported to be

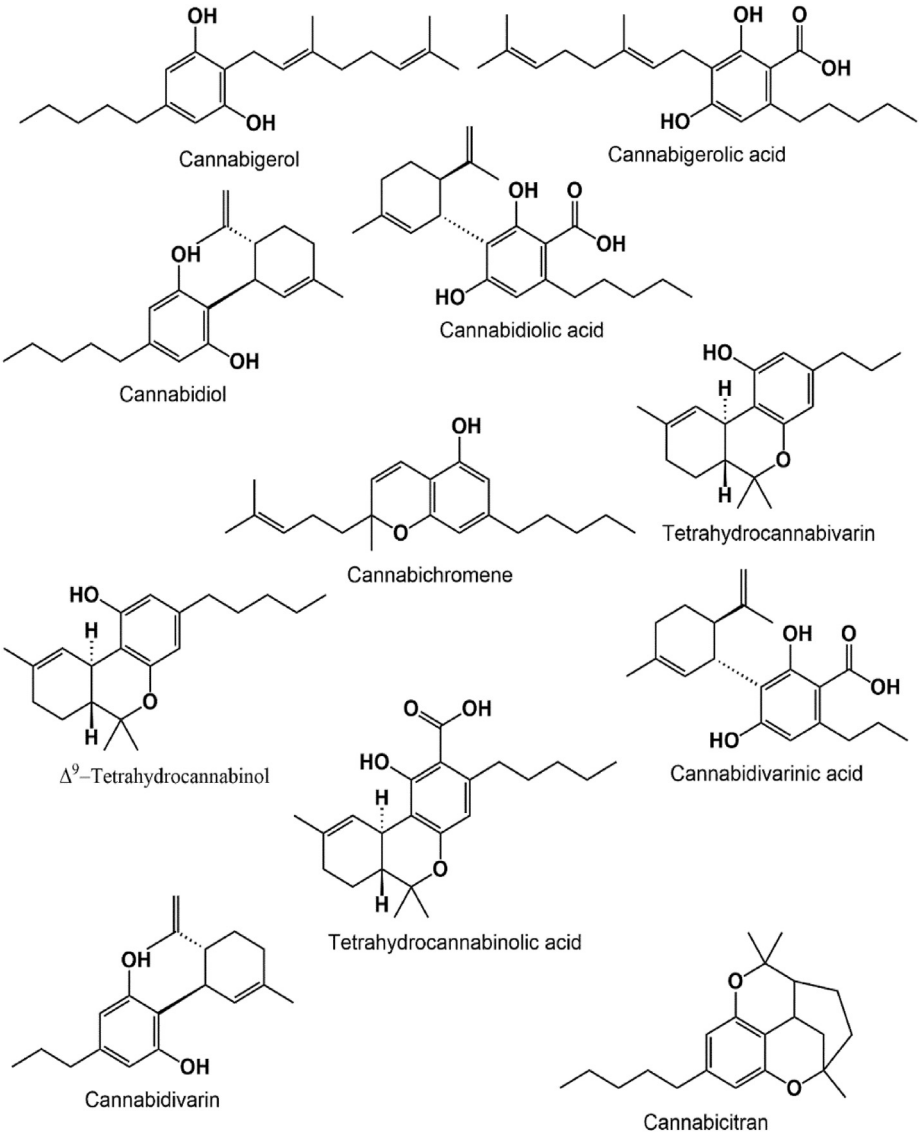

Fig. 4. Major cannabinoids identified in Cannabis sativa L.

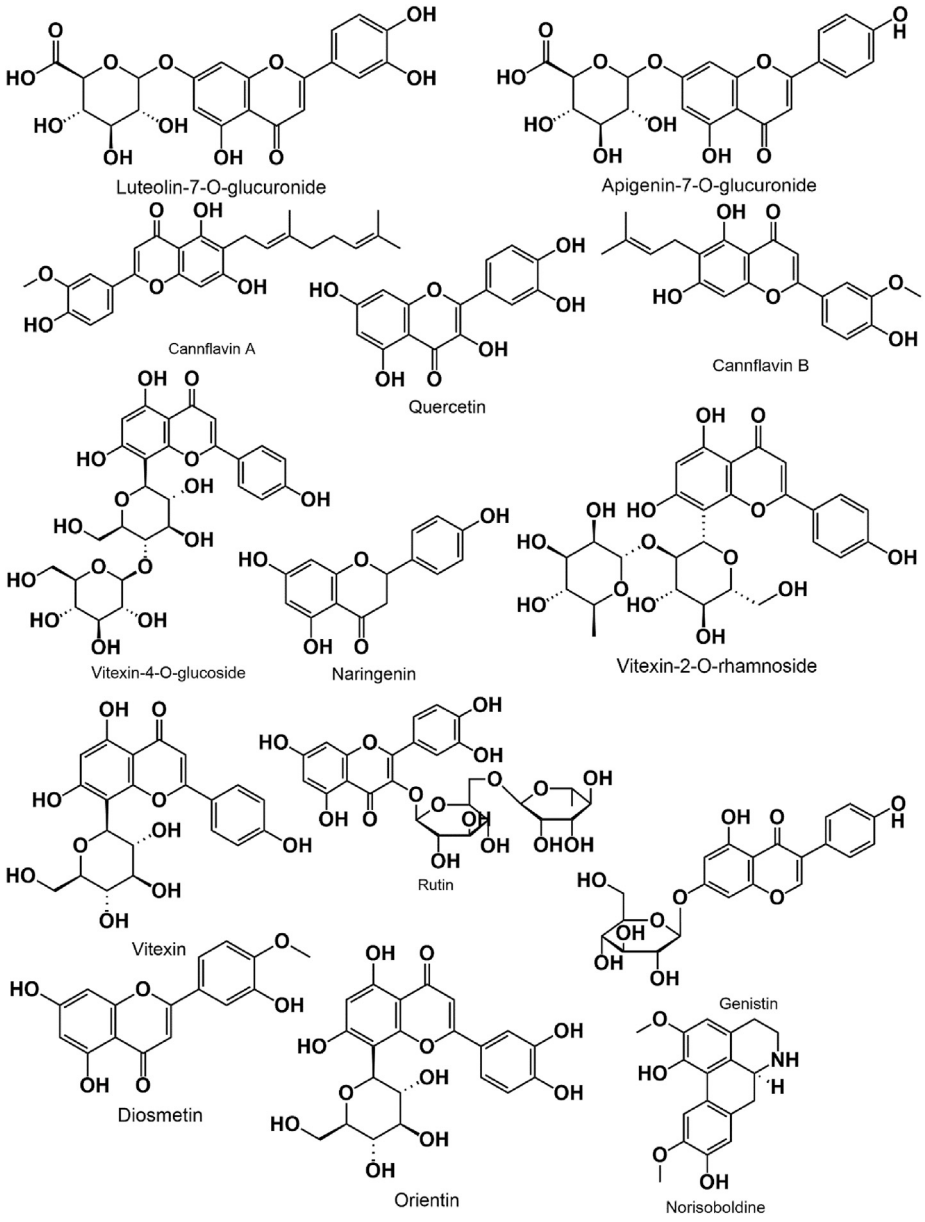

Fig. 5. Flavonoids present in Cannabis sativa.

rich with several phenolic compounds like, catechol, 4-hydroxyacetophenone, caffeic acid, 2,5-dihydroxybenzoic acid, 3,5-dimethoxybenzaldehyde, p-coumaric acid, ferulic acid, dihydroquercetin, polygalic acid, syringic acid, sinapinic acid, and benzoic acid, vanillic acid salicylic acid Fig. 6 [7,45–51]. Furthermore, the seeds were characterized by the presence of hydroxycinnamic acid amides such as N-trans-caffeoyltyramine, N-trans-coumaroyltyramine, N-feruloyltyramine, and Tri-p-coumaroyl spermidine Fig. 7. Meanwhile, lignanamides were among the secondary metabolites found mainly, Cannabisin A, Cannabisin B, Cannabisin C, Cannabisin D [52]. Investigation of roots chemical composition using liquid chromatography coupled to mass spectroscopy was able to identify some molecules named respectively, p-coumaroyltyramine, feruoiltyramine (Fig. 8) [53,54].

11.4. Alkaloids

Since 1975 till today, several alkaloids were isolated and identified and isolated from *C. sativa* among them we cite cannabisativine, anhydrocanabisativine, trigonelline, muscarine, hordenine, choline, L-(+)-isoleucine betaine, neurine, hexadecamide, N-(p-

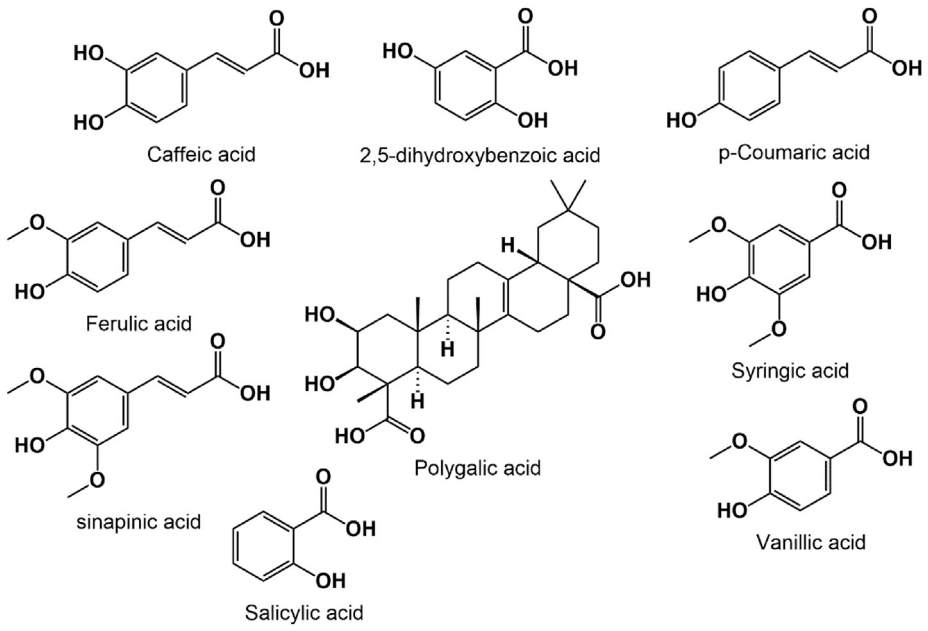

Fig. 6. Phenolic acids present in Cannabis sativa.

hydroxy- p-phenylethyl)-p- hydroxy- (trans)-cinnamide Fig. 9 [55–58].

11.5. Mineral composition

Hemp seeds were found to be an important source of minerals. It was reported a high amount of potassium (K) followed by phosphorus (P), magnesium (Mg), and Calcium. Also, it was noticed the presence of important portions of iron (Fe), Manganese (Mn), zinc (Zn), copper (Cu) and boron (B) [59].

11.6. Fatty acids, tocopherols and phytosterols composition

A study conducted on the chemical composition of *C. sativa* has highlighted the presence of numerous phytosterols such as Δ^5-avenasterol (fucosterol), stigmasterol, β-sitosterol, and campesterol. Also, it was indicated the presence of α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol Fig. 11 (A). Fatty acids determined were palmitic acid, stearic acid, elaidic acid, cis-Vaccenic acid, linoleic acid, γ-

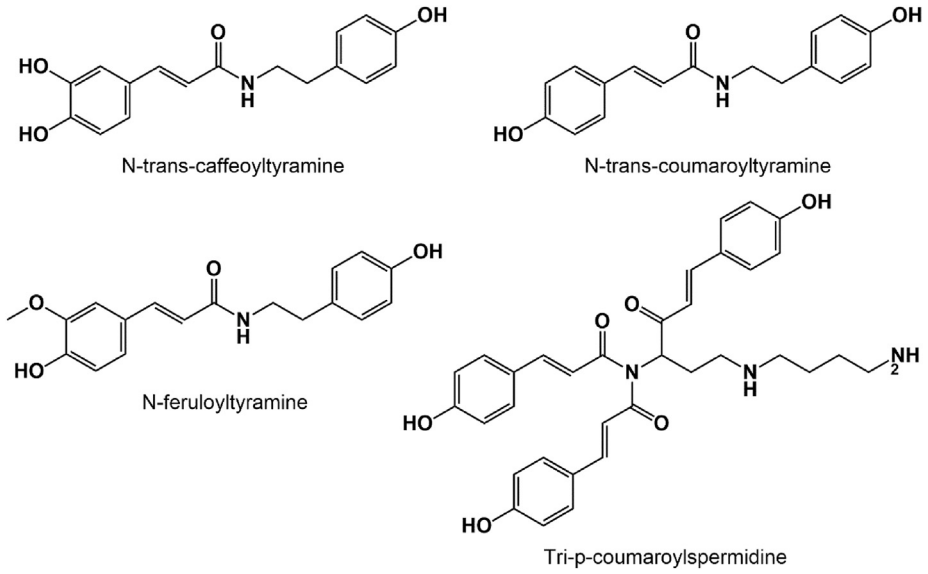

Fig. 7. Hydroxycinnamic acid identified in Cannabis sativa.

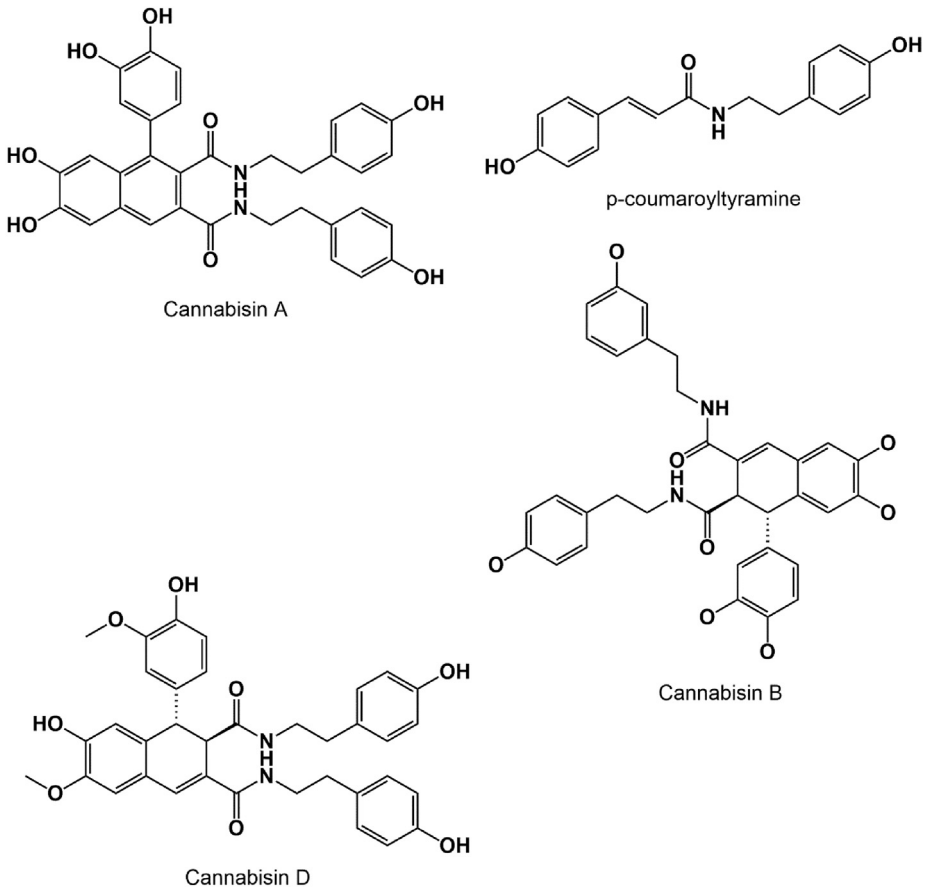

Fig. 8. Lignanamides found in Cannabis sativa L.

linoleic acid, α-linolenic acid, stearidonic acid, arachidic acid Fig. 11 (B) [60,61]. Roots extract analyzed using GC–MS indicated the presence of several esters ethyl palmitate, ethyl linoleate, ethyl elaidate, ethyl stearate, oleamide, stigmastan-3,5,22-trien, stigmasta-3,5-diene, β-amyrone, 4-campestene-3-one, β-amyrin, stigmasta-4,22-dien-3-one, glutinol, stigmast-4-ene-3-one, epifriedelinol, friedelin [62] (Fig. 10).

12. Antimicrobial properties of *C. sativa* and its derivates

12.1. Antiviral activity

In order to evaluate the antiviral activity of *C. sativa* several *in vitro* and *in silico* studies were assessed. Different bioactive compounds named identified in *C. sativa* such as THC, CBD and CBN

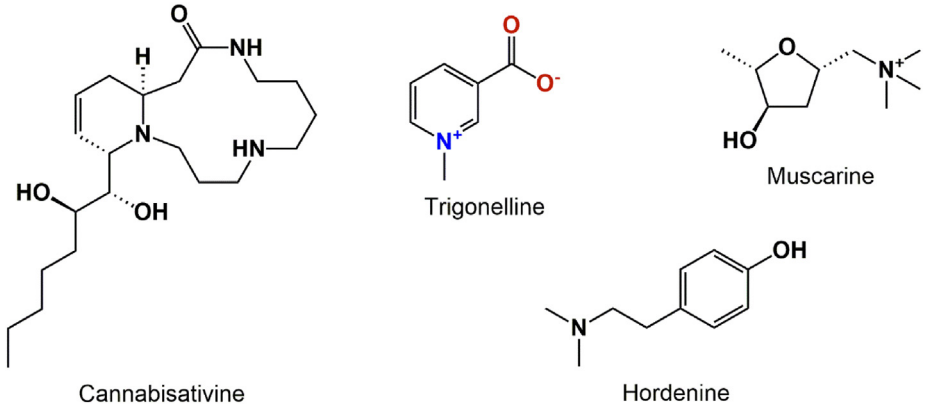

Fig. 9. Main identified alkaloids from Cannabis sativa.

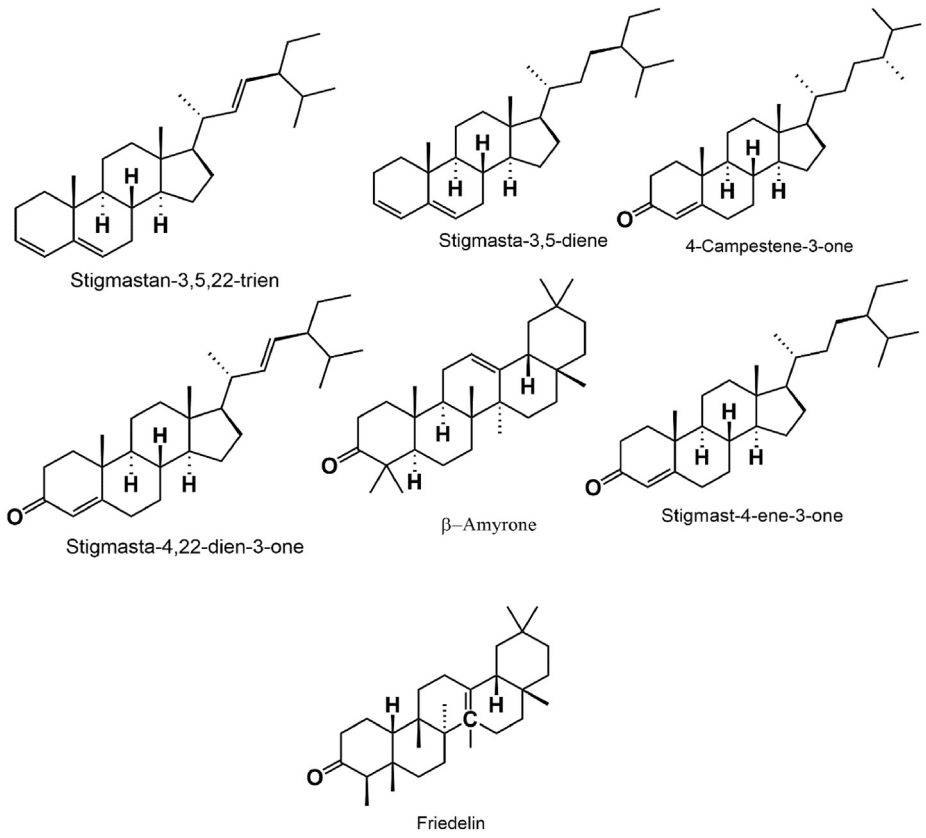

Fig. 10. Different esters identified from Cannabis sativa.

were subject to *in vitro* antiviral activity against SARS-CoV-1 and SARS-CoV-2 main proteases and the angiotensin converting enzyme 2. The obtained results indicated that THC and CBD were efficient inhibitors of SARS-CoV-1 and SARS-CoV-2. The lowest IC_{50} values recorded for THC and CBD for SARS CoV1 were respectively 104.43 μg/mL and 100.78 μg/mL. While, the IC_{50} values for SARS-CoV-2 were 100 μg/mL and 102 μg/mL respectively for THC and CBD. Meanwhile, CBN showed weak antiviral potential when compared to THC and CBD. Furthermore, CBD was recorded to be the most active compound from *C. sativa* with a recorded IC_{50} value of 1.86 μM against SARS-CoV-2 which was four time higher than the GC376 used as positive control. Followed by, THC that was distinguished by an IC_{50} value of 16.23 μM against SARS-CoV-2 proteases. This intense response recorded by CBD against SARS-CoV-2 was explained by the ability of cyclohexene ring B found in CBD chemical structure to rotate. Molecular docking studies revealed that CBD did not fit into the binding pocket of SARS-CoV-2 main protease which is due to the interaction of the aromatic ring with the catalytic residue Cys145. Also, the hydroxy group found in resorcinyl ring A is able to establish hydrogen bonding with His164 [63]. Whereas, exploring antiviral activity of Cannabichromanon, Cannabinolic acid and Cannabinol against three main SARS-Cov-2 enzymes namely, main protease, papain-like protease, Angiotensin Converting enzyme-2 (ACE-2) using a computational approach (*in silico)* indicated that these three bioactive compounds demonstrated their potential ability to inhibit SARS-CoV-2 enzymes which was reflected on their high affinity with the different tested compounds, except for ACE-2 where it was noticed a moderate affinity with *C. sativa* compounds [64] Table 1.

12.2. Antibacterial activity

In order to evaluate the antibacterial properties of *C. sativa* several studies have been established on different extracts of this herbaceous plant. In the study conducted by Kumar et al., (2009) *C. sativa* leaves aqueous extract showed inhibitory effect on *Rathyibacter tritici* with a zone inhibition of 14.5 mm and a minimal inhibitory concentration of 1% [65]. In a similar study evaluating the antibacterial activity of Indian *C. sativa* leaf aqueous extract, it was

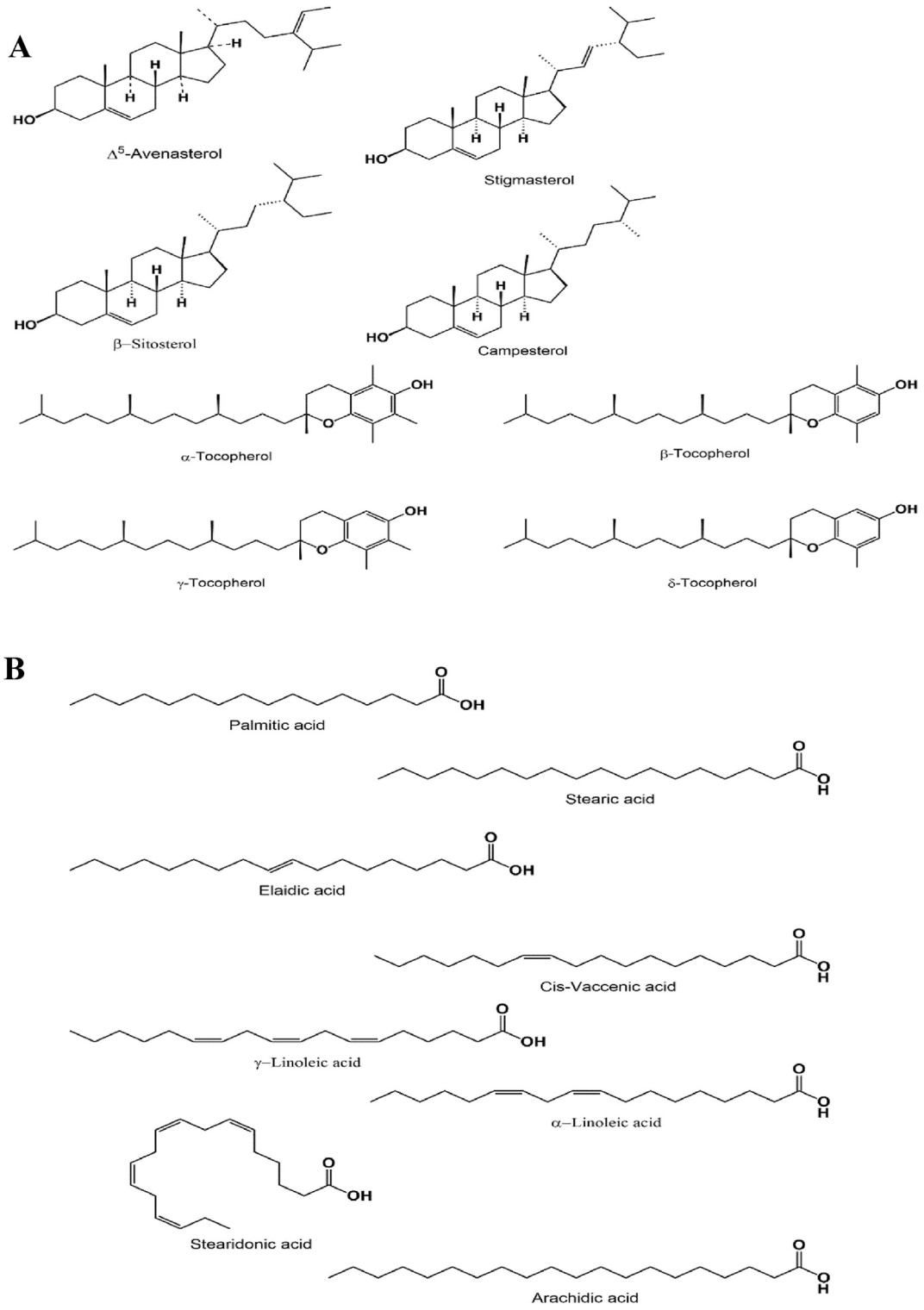

Fig. 11. Example of phytosterols, tocopherols (A), and fatty acids (B) identified from Cannabis sativa.

reported that all investigated bacterial strains derived from burns patients were found to be resistant to this extract while with a zone inhibition range of 11 and 18 mm, EtOH, MeOH, and benzene extracts shown moderate antibacterial activity toward *Staphylococcus aureus*, *Klebsiella* sp, and *Pseudomonas* sp. Furthermore, it was discovered that *Escherichia coli* was resistant to every examined

Table 1. Antiviral activity assessed by Cannabis sativa bioactive compounds.

Compounds	Origin	Method used	Strains	Results	Ref
THC CBD CBN	Germany	*In vitro* *In silico*	SARS-CoV-1 SARS-CoV-2 main protease and ACE2	THC inhibited SARS CoV-1 and SARS-CoV-2 main protease with IC_{50} of 104% and 100%. CBD inhibited SARS-CoV-1 and SARS-CoV-2 main protease with IC_{50} of 100.78% and 102%. THC IC_{50} = 16.23 μM against SARS-CoV-2 protease. CBD IC_{50} = 1.86 μM against SARS-CoV-2 protease.	[63]
CBCN CBDA	Saudi Arabia	*In silico*	SARS-CoV-2 main enzymes: Main protease. Papain-like protease. ACE2	High binding affinity exerted on SARS-CoV-2 main protease and papain-like protease. Moderate activity on Angiotensin Converting Enzyme 2 (ACE-2).	[64]

extract. Regarding, *S. aureus*, *E. coli*, and *Pseudomonas* sp., EtOH extract has recorded the lowest MIC value of 25 mg/mL. Additionally, the MIC value for *S. aureus* derived from benzene extract was comparable to that of EtOH extract. While the lowest MIC value against *Klebsiella* sp. was 50 mg/mL for EtOH, benzene, and MeOH extracts (V. Kumar et al., 2011). In the same context, the study conducted by Kakar et al., (2012), MeOH (70%) and n-hexane extract were able to exhibit antibacterial activity against different gram negative and gram positive bacteria. At 100 mg/mL both extracts were able to exhibit high antibacterial activity with a zone inhibition ranging from 14.2 mm to 19.3 mm for MeOH extract and from 10 to 15 mm for n-hexane extract [66]. Similarly, *C. sativa* leaves exposed at different time lapse to acetone and methanol in order to obtain acetone and MeOH extract were found to exhibit antibacterial activity. The extracts with long extraction time (18 h) were the most effective on bacterial strains. In fact, MeOH and Acetone leaves extracts were able to inhibit *S. aureus* and *P. aeruginosa* growth with a zone inhibition of 20 and 18 mm respectively [67] Table 2.

Interestingly, the published data by Khatak et al., (2014) indicated an antibacterial action of n-hexane and propanol extracts from *C. sativa* leaves against *P. aeruginosa* and *E. coli* with a zone inhibition ranging from 15 to 20 mm. Moreover, propanol extract at 10 mg/mL was able to inhibit both strains with a zone inhibition of 17 and 19 mm respectively for *E. coli* and *P. aeruginosa* [68]. Moreover, several extracts (Acetone, EtOH, MeOH, and H_2O) showed antibacterial activity against several gram negative and gram positive bacteria with the exception of *P. aeruginosa*. Experiments realized confirmed that MeOH extract had the greatest potential for suppressing *B. subtilis* and *S. aureus*, with a MIC value of 1.56 mg/mL. Acetone extract, which had a MIC value of 3.12 mg/mL and was particularly effective against *B. subtilis*, came next. At a MIC of 6.25 mg/mL, the ethanolic extract could only inhibit *S. aureus* and *B. subtilis*. However, the aqueous extract MIC was 25 and 12.5 mg/mL for *S. aureus* and *B. subtilis*, respectively, showing that it had a mild effect on these bacteria which confirms the results reported in previous studies. Additionally, it was reported that *P. aeruginosa* was unaffected by *C. sativa* extracts while *E. coli* showed only weak activity, with a MIC of 50 mg/mL [69]. Conducted research on *C. sativa* aqueous extract, showed that it has the ability to inhibit *S. aureus* and *Klebsiella pneumoniae* with MIC values of 1000 and 500 mg/mL, respectively which was in contradiction with the results reported earlier. Hemp aqueous extract combined with gentamycin had a synergistic effect, too [70].With an IC_{50} ranging between 2.6 and 49.6 μM C. *sativa* n-hexane extract was found to exhibited high antibacterial activity on various bacterial strains Table 2. The chemical analysis of this extract indicated its richness with seven major compounds Prenylspirodinone, Cannabinol, Cannabichromene, Cannabidiol, Δ^1-Trahydro-cannabidivarol, and Δ^9-Tetrahydrocannabinol. Prenylspirodinone, a newly discovered chemical, was only found to be effective on *Bacillus thuringiensis* MTCC 809 with a zone diameter of 49.6 mm. It's also important to note that the seven substances examined had no effect on the strains of *Klebsiella pneumonia* ATCC 75388, *Salmonella Typhimurium* MTCC 98, and *E. coli* ATCC 25922 [42] Table 3. Khan and his collaborators have demonstrated that MeOH from *C. sativa* leaves had no inhibitory effect on *S. aureus*, but it had a zone diameter of 15.3 mm for *S. Typhi* (MIC = 0.025 μg/mL) and 12.6 mm (MIC = 0.050 μg/mL) for *P. aeruginosa*, indicating that it was quite active on those bacteria. *Microsporum luteus* and *B. septica* had inhibition zones of 9.2 mm and 10.8 mm, respectively, and were considered resistant to the MeOH extract of *C. sativa* [71]. In contrast, Chauhan et al., (2017)

study found that the MeOH extract from fresh *C. sativa* leaves was endowed with significant antibacterial activity, particularly against *S. aureus*, which was in contrast to the findings of several previous investigations. The lowest observed MIC value was 0.219 mg/mL against *P. aeruginosa* and *S. aureus*, followed by 0.438 mg/mL for *E. coli* and *B. subtilis*, and finally 0.875 mg/mL against *K. pneumoniae* [72]. With zone diameters ranging between 34 and 37.5 mm and MIC values between 5 and 10 mg/mL, ethanolic extracts of two Italian *C. sativa* samples have demonstrated their moderate antibacterial activity against gram positive bacteria *B. cereus*, *B. amyloliquefaciens*, and *B. huringiensis*. However, when tested on gram negative bacteria no inhibitory action was recorded [73]. Nevertheless, when combining *Thuja orientalis* EtOH extract, the mild activity of *C. sativa* leaf EtOH extract against clinical and non-clinical MRSA strains was potentiated, leading to inhibition of 33.5 mm (non-clinical) and 27.7 mm (clinical). Similarly, when *Psidium guajava* ethanolic extract and *C. sativa* extract were combined, a synergistic effect was also noted; the inhibition zones achieved for non-clinical and clinical MRSA isolates, respectively, were 29.4 mm and 24.4 mm. The authors attributed the discovered antibacterial activity to the plant's abundance in several secondary metabolites [44]. Research conducted to assess antibacterial ability of Pakistanian hemp extracts of roots, stems, and leaves using different solvents with increasing polarities. With inhibition zones ranging from 13.2 mm to 28.4 mm, extracts of leaves, stems, and roots demonstrated the strongest antibacterial potential against different bacterial strains, such as *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, *Microsporum morganii*, and *H. influenzae*. Stems had the most noticeable antibacterial effect among all tested parts [74]. Similarly, leaves MeOH extract of *C. sativa* was able to inhibits 10 isolates of *Streptococcus pyogenes.* Inhibition diameters were ranging from 18.8 to 22.8 mm while the lowest MIC value was about 20 mg/mL while the MBC was 30 mg/mL [43]. As for EtOH extract from hemp seeds, it was mentioned a dose dependent prevention from bacterial growth and biofilm formation. A decrease in OD of bacterial strains that was proportional to the increase of EtOH extract concentration. Also, it is important to highlight that this extract is endowed with selective action when tested on different probiotics *Lactobacillus* sp and *Bifidobacterium* which indicates that *C. sativa* EtOH extract is able to maintain gut microbiota without any side effects. At a concentration of 0.5 and 1 mg/mL a total inhibition of biofilm formation was noticed in *S. aureus* ATCC 35556 with a percentage of 80%. The presence of various bioactive compounds, including caffeinetyramine and cannabisin have highly contributed to the obtained pharmacological effect, also the presence of hydroxyl groups in their chemical structures, is what accounts for this high effectiveness in preventing the growth of bacteria and the formation of biofilms. Additionally, these substances may interact with a number of pathways to block the production of cell walls, proteins, or lipids [75] Table 2.

The dehulling process effect on antibacterial activity was also investigated, eight cultivars of whole and dehulled *C. sativa* seeds from different geographical location were tested against six gram negative and gram positive bacterial strains. Hydromethanolic extract of the different cultivars has exhibited high antibacterial activity against bacterial strains. As mentioned in the same study, the lowest MIC and MBC values were 0.01 and 0.018 mg/mL and it was recorded against *B.cereus* by whole seeds of "Tiborszallasi" cultivars. While the highest MIC and MBC value recorded by whole hemp seeds were 0.9 and 1.2 mg/mL respectively against *E. coli and S. Typhi* by "Fedora 17" cultivars. Concerning the dehulled hemp seeds, the high antibacterial activity was exhibited by "Fedora 17" cultivars against *B. cereus* with a MIC and MBC values of 0.01/0.018 mg/mL, followed by "Tiborszallasi" cultivars with a MIC/MBC values of 0.037/0.075 mg/mL. Moreover, It was noticed in this study that the antibacterial activity of dehulled seeds increased in comparison with the whole seeds hemp which was explained by the involvement of lipophilic compounds which was obvious on MIC and MBC values recorded that were in some cases lower that the MIC and MBC values recorded by streptomycin and ampicillin used as positive controls [50]. Aiemsaard and his colleagues (2022) have mentionned the ability of Thailand *C. sativa* EtOH extract to inhibit significantly the growth of 23 *Staphylococcus pseudintermedius* with a MIC_{50} value equals to 0,00625 mg/mL and an MBC_{50} value of 0.025 mg/mL. Time kill kinetics assay has also indicated that the antibacterial activity of *C. sativa* ethanolic extract was time dependent and not concentration dependent, the results of the same study revealed that the exposure to the EtOH extract for 3 h caused a 99% death of bacterial cell. While bacterial exposer for about 24 h to EtOH extract induce the death of 99.99% of *S. pseudintermedius* ATCC 4905 [76]. A study performed by Skala et al., (2022) on *C. sativa* extracts (ethanolic, buthanolic and dimethyl ether extracts) obtained from forbidden fruits and cholocope. The findings of this study

Table 2. Antibacterial activity of Cannabis sativa volatile and organic extracts.

Extracts	Origin	Yield	Method used	Strains	Results	Ref
Extracts						
Aqueous extract (Leaves)	India	ND	Agar diffusion method Agar dilution method	*Rathyibacter tritici*	Zone inhibition of 14.5 mm MIC = 1%	[65]
MeOH extract (leaves)	Pakistan	ND	Agar diffusion method Microdilution technique	*S. aureus* *B. septica* *M. luteus* *P. aeruginosa* *S. Typhi*	*S. Typhi* MIC = 25 mg/mL; Inhibition zone: 15.3 mm *P. aeruginosa* MIC = 50 μg/mL; Inhibition zone: 12.6 mm Low diameter for the other bacteria.	[71]
MeOH extract (leaves)	Himachal Pradesh, India	ND	Well diffusion technique	*S. aureus* *E. coli* *P. aeruginosa* *K. pneumoniae*	MIC = was 0.219 mg/mL against *P. aeruginosa* and *S. aureus*. MIC = 0.438 mg/mL against *E. coli* and *B. subtilis*. MIC = 0.875 mg/mL against *K.pneumoniae*.	[72]
Leaves (Acetone, EtOH, MeOH, H_2O)	India	ND	Agar well diffusion method	*S. aureus* *E. coli* *P. aeruginosa* *K. pneumoniae*	MeOH extract MIC = 1.56 mg/mL against *B. subtilis* and *S. aureus*. Acetone extract MIC = 3.12 mg/mL against *B. subtilis*. EtOH extract MIC = 6.25 mg/mL against *S. aureus* and *B. subtilis*. Aqueous extract MIC = 25 and 12.5 mg/mL for *S. aureus* and *B. subtilis*. Aqueous extract MIC = 50 mg/mL.	[69]
Aqueous extract (leaves)	India	ND	Agar diffusion method	*Staphylococcus aureus* *Klebsiella pneumoniae*	MIC = 1000 mg/mL against *S. aureus* MIC = 500 mg/mL against *K. pneumoniae* Aqueous extract + gentamycin = Synergy	[70]
n-hexane propanol extracts (leaves)	India	ND	Agar well diffusion method	*E. coli* *P. aeruginosa*	Inhibition zone ranging between 15 and 20 mm.	[68]
EtOH extract (Flowers)	Italy	ND	Agar well diffusion method	*B. cereus* *B. thuringiensis* *B. amyloliquefaciens* *Pseudomonas orientalis* *Stenotrophomonas maltophilia*	Inhibition zone ranging between 34 and 37.5 mm MIC values between 5 and 10 g/mL.	[73]
Roots; stems; leaves	Pakistan	ND	Agar diffusion method	*E. coli, S. aureus,* *P. aeruginosa,* *K. pneumoniae,* *A. baumannii,* *M. morganii,* *H. influenzae*	Inhibition zone ranging between 13.2 mm and 28.4 mm. Resistance to n-hexane extract. Weak to moderate activity by water extract.	[74]

(*continued on next page*)

Table 2. (continued)

Extracts	Origin	Yield	Method used	Strains	Results	Ref
EtOH extract (seeds)	Turin, Italy	ND	Microdilution technique Antibiofilm assay	*S. aureus* *Lactobacillus* sp. *Bifidobacterium*	↑ [EtOH] extract ↔ ↓ *S. aureus* OD. 80% inhibition of biofilm with 0.5 and 1 mg/mL Inactive on *Lactobacillus* sp. and *Bifidobacterium*	[75]
MeOH extract (Leaves)	Owerri, Nigeria	ND	Agar diffusion method Macrodilution technique	*Streptococcus pyogenes*	Inhibition zone ranging between 18.8 mm and 22.8 mm MIC = 20 mg/mL MBC = 30 mg/mL	[43]
Whole and dehulled seeds (Eight cultivars)	Teruel, Spain	ND	Microdilution technique	*B. cereus; S. aureus; L. monocytogenes; E. faecalis; E. coli; S. Typhimurium*	**Whole seeds** Lowest MIC = 0.01 mg/mL and MBC = 0.018 mg/mL against *B. cereus by* "Tiborszallasi" cultivars. -Highest MIC = 0.9 mg/mL and MBC = 1.2 mg/mL recorded by *E. coli* and *S. Typhi* by "Fedora 17" cultivars. **Dehulled seeds** Lowest MIC = 0.01 mg/mL and MBC = 0.018 mg/mL by "Fedora 17" against *B. cereus*. "Tiborszallasi" cultivars MIC/MBC values of 0.037/0.075 mg/mL against *B. cereus*.	[50]
Whole plant (EtOH)	Thailand	ND	Broth dilution technique Time-kill kinetics	*Staphylococcus pseudintermedius* (23 strains)	MIC_{50} = 6.25 μg/mL. MBC_{50} = 25 μg/mL. 3 h exposer to MIC caused 90% death. 24 h exposer to MIC caused 99.99% death.	[76]
Inflorescences	Croatia	Ranging between 0.75 and 8.83%	Broth dilution technique	*S. aureus; E. coli; P. aeruginosa; B. subtilis*	MIC value ranging from 10.42 μg/mL to 66.03 μg/mL.	[31]
EtOH, ButOH, Dimethylether extracts from Cholocope and forbidden fruits	Czech	4%	Broth dilution technique	*S. aureus; S. epidermidis; S. saprophyticus; S. lugdunensis; S. epidermidis; Streptococcus pyogenes;*	MIC ranging from 4 to 128 μg/mL for bacteria on *S. aureus.*	[77]

Essential oils

Essential oil	Origin	Yield	Method used	Strains	Results	Ref
Eos from Dry inflorescences (Steam distillation)	Italy	Ranging between 0.13% and 1.01%.	Microdilution technique	*S. aureus* *L. monocytogenes* *P. fluorescens* *B. thermosphacta* *S. Enteritidis* *S. Typhimurium;* *E. faecium*	Lowest MIC and MBC (0.08 μL/mL) by "Gran Sasso Kush" on *L. monocytogene*. Moderate activity by "Carmagnola Lemon"; MIC = 1.25 μL/mL and MBC >20 μL/mL. "Futura" MIC ranging between 0.625 μL/mL and μL/mL.	[82]

Eo (inflorescences)	Italy (Abruzzo territory)	0.20%	Microdilution technique	*P. fluorescens* *B. thermosphacta* *S. Enteritidis* *E. faecium* *L. monocytogenes* *S. aureus*	Lowest recorded MIC/MBC value was of 1.25 μL/mL against *S. aureus*. MIC = 2.5 μL/mL against *L. monocytogenes.* Bacteriostatic effect on *P. fluorescens*, *S. Enteritidis*, *S. Typhimurium*, *B. thermosphacta*, and *E. faecium* with a MIC = 5 μL/mL	[35]
Eo (hydrodistillation)	Morocco	2.7% (v/w)	Microdilution technique. Checkerboard assay method	*M. luteus* *S. aureus* *B. subtilis* *E. coli* *P. aeruginosa* *K. pneumoniae*	Inhibition zone ranging between (8.5−15 mm). Lowest MIC = 1.2 mg/mL against *B. subtilis, E. coli,* and *P. aeruginosa.* MIC = 4.7 mg/mL against *B. luteus, S. aureus*. Highest MIC = 37.8 mg/mL against *K. pneumoniae.* Eo + ciprofloxacine: Synergy action.	[36]
17 Eos from different cultivars (steam distillation)	France	ND	Agar diffusion method Microdilution technique	*S. aureus* *S. epidermidis* *L. monocytogenes* *E. faecalis* *Bacillus* sp.	Lowest MIC = 0.5 μg/mL Highest MIC = 32 μg/mL	[37]
Eo "Futura 75" (Fresh aerial parts)	Italy	0.28%	Microdilution technique Planktonic Susceptibility Assay	*S. aureus* (sensitive) *MRSA* *H. pylori*	MIC and MBC against *S. aureus* and MRSA was 8 and 16 μg/mL. *H.pylori* MIC = 64 μg/mL 24 μg/mL for biofilm eradication	[5]
Eos (Futura, Fibranova, carmagnola)	Italy; France	0.25% to 0.31%	Microdilution technique	*Clostridium sporogens* *Enterococcus faecium* *Streptococcus salivarius* *Pectobacterium carotovorum* *Pseudomonas savastanoi* *Clostridium bifermentas*	Futura MIC ranging between 1.40% and 1.78% (v/v) Fibranova MIC ranging between 1.57% and >2% (v/v) Carmagnola MIC ranging between 1.54% and >2% (v/v) Futura lowest MBC = 2.19% and 3.12% (v/v) against *Streptococcus salivarius* and *Pectobacterium carotovotrum*.	[79]
EOs (different cultivars)	Austria	ND	Agar diffusion method	21 bacterial strains	"SwissMix" zone inhibition of 15 mm against *Acinetobacter calcoaceticus* "Fedrina 74 Zone inhibition of 16 mm against *Brevibacterium linens.*	[78]

indicated that *S. aureus* is the most sensitive strain to all tested extracts with lower MIC values for the different extracts with a MIC value ranging between 0.004 and 0.008 mg/mL. On the other hand, it was observed resistance by *S.pyogenes* towards *C. sativa* extracts that was reflected on high MIC values (0.064–0.128 mg/mL). This resistance was explained by high affinity between the bioactive compounds present in the different extracts and blood proteins that are normally found in the bacteria medium (Skala et al., 2022) Table 2.

Numerous studies have been conducted on *C. sativa* volatile compounds, starting with that assessed by Novak et al., in 2001 that has reported the antibacterial activity of various *C. sativa* cultivars from Austria against 21 bacterial strains. "SwissMix" was observed to be active against *Acinetobacter calcoaceticus* with a zone inhibition of 15 mm, while "Fedrina 74" cultivar was noted to be very active on *Brevibacterium linens*, as indicated by an inhibition diameter of 16 mm. With a 14 mm diameter, "Felina 34" displayed modest action on *S. aureus*. Regarding other cultivars, a moderate activity toward bacterial strains was identified [78]. Similarly, in 2010 Nissen and his colleagues have demonstrated the ability of various *C. sativa* Eos from various cultivars (Futura, Carmagnola, Fibranova) to inhibit various gram negative and gram positive bacteria. In fact, Futura Eo cultivar was the only effective on *Clostridium sporogens*. Also, the lowest MBC value for this variety was 2.19% (v/v) against *Streptococcus salivarius* and 3.12% (v/v) against *Pectobacterium carotovotrum.* α-humulene failed to exhibit antibacterial action against both gram negative and gram positive strains, however α-pinene demonstrated a strong ability to suppress bacterial growth with a registered MBC value against gram positive bacteria that ranges from 1.39 to 1.67% (v/v) and between 1.35 and 1.66% (v/v) against gram negative bacteria [79]. Mexican-origin volatile compounds from the n-hexane extract of *C. sativa* shown a strong inhibitory effect on sensitive and MDR bacterial strains. According to reports, the moderate activity IC_{50} of fraction C derived from volatile compounds was 10.45 mg/mL for *S. aureus* and 15.93 mg/mL for MRSA, respectively [80]. Finally, the antibacterial activity of *C. sativa* inflorescences extracted using SCCO2 under various extraction conditions also showed that the various extracted showed significant antibacterial activity that was more potent in gram positive bacteria than gram negative bacteria. *B. subtilis*, *S. aureus*, and *E. coli* had the lowest MIC values, 10.42 g/mL, whereas *P. aeruginosa* had the highest, 13.79 mg/mL [31] Table 2.

Regarding *C. sativa* Eo from aerial parts of "Futura 75" cultivars, was able to inhibit both sensitive and multidrug-resistant *S. aureus* with MIC and MBC values of 8 and 16 mg/mL. In addition, a minimum dosage of almost three times the MIC value (24 mg/mL) was required to eradicate the biofilm. The authors also pointed out that naringenin a major component in *C. sativa* Eo was able to inhibit resistant *S. aureus* with a MIC value of 0.512 mg/mL and a minimum concentration eradicating biofilm of 2048 mg/mL. Futura 75 Eo and naringenin's capacity to inhibit *H. pylori* was demonstrated by their strong antibacterial activity when tested using the microdilution method, with MIC values of 0.64 mg/mL for Eo and 0.32 mg/mL for Naringenin, respectively. The findings of using Eo and naringenin in contrast to conventional antibiotics showed that *C. sativa* and its derivatives have 2 to 16 times active than commonly used antibiotics (metronidazole and clarithromycin) [5]. Additionally, bactericidal effect of Eo, α-pinene and β-myrcene extracted from *C. sativa* aerial parts was registered when tested on *Listeria monocytogenes.* Both Eo and β-myrcene gave an MBC of 2048 mg/mL. While an MBC of 1024 mg/mL made α-pinene more potent *L. monocytogenes*. Additionally, it was shown that *L. monocytogenes* aggregated at a concentration of 0.256 mg/mL, and a loss of motility was seen. This was supported by RT-PCR, which showed downregulation of the regulatory gene PrfA and flagellar motility genes. In addition, *L. monocytogene*'s ability to produce biofilms was reduced by 29–69% after being exposed to sublethal concentrations of 0.256 mg/mL and 0.128 mg/mL. Also, the exposer to 0.265 mg/mL attenuated the virulence of *L. monocytogenes* and induced an increase in survival rate in *Galleria mellonella* infected larvae [81] Tables 2 and 3.

Moroccan *C. sativa* Eo was modestly active on the strains it examined, with an inhibitory zone between (8.5–15 mm). MIC values recorded were between 1.2 and 37.8 mg/mL indicating that *B. subtilis, P. aeruginosa,* and *E. coli* were very sensitive to *C. sativa* Eo while *K. pneumoniae* a gram negative bacterium was found to be resistant to Eo action. It was also found that ciprofloxacin plus the essential oil of *C. sativa* had a complete synergistic effect against *S. aureus*, *E. coli*, *K. pneumoniae*, and *B. subtilis*. While, on *M. luteus* and *P. aeruginosa*, a partial synergy was observed when Eo and ciprofloxacin were combined. These synergistic interactions between the volatile compounds in *C. sativa* and conventional antibiotics may be crucial for slowing the development of antibiotic resistance [36]. In addition to that, 17 Eos hemp varieties were examined for their antibacterial potential. None of them, according to these findings, have the ability to suppress gram negative bacteria. Even though they were able to

Table 3. Antibacterial activity of Cannabis sativa bioactive compounds.

Compounds	Yield	Method used	Strains	Results	Ref
Cannabidiol (Extration by $SCCO_2$)	ND	Plate Assays for Antibacterial Screening Time Kill kinetics DAPI staining SEM analysis	*Salmonella Newington* *Salmonella Typhimurium*	MIC = 0.0125 μg/mL against *S. Newington.* MIC = 0.125 μg/mL against *S. Typhimurium.* Membrane destabilization 24 h exposer to CBD showed increase of resistance by *S. Newington* and *S. Typhi.* Exposer to 1.25 μg/mL inhibit biofilm formation.	[84]
CBD and CBDV	ND	Microdilution technique	*S. aureus* ATCC 6538 *E.coli* ATCC 13762	-IC_{50} = 29.1 and 35.4 μM for CBD and CBDV against *E. coli* after 72 h of exposition. - IC_{50} = 30.8 μM and 1.84 μM for CBDV and CBD against *S. aureus* after 72 h of exposition.	[41]
CBD and CBDA	ND	Microdilution technique Time kill kinetics	*S. aureus* ATCC25923 *S. epidermis* MRSA	CBD MIC = 1−2 μg/mL. CBDA MIC = 2 and 4 μg/mL. Additive effect between CBD and ATB 1.03 < FICI < 1.50 22 h exposer to CBD induce a bactericidal effect. -No toxicity on HaCaT.	[83]
CBD	ND	Agar diffusion method	*E. coli* VCS257 *S. aureus*	MIC = 1 μM ↓Membrane vesicles release Loss of protein from membrane vesicles	[93]
Naringenin	ND	Microdilution technique Planktonic Susceptibility Assay	*S. aureus* (sensitive) MRSA *H. pylori*	MRSA MIC = 512 μg/mL *H.pylori* MIC = 32 μg/mL 2048 μg/ml for biofilm eradication	[5]
CBD THC	ND	Agar well diffusion method	*B. cereus* *B. thuringiensis* *B. amyloliquefaciens* *Pseudomonas orientalis* *Stenotrophomonas maltophilia*	CMI > 60 μg/mL	[73]
α-pinene β-myrcene	ND	Microdilution technique Motility assay SEM RT-PCR Biofilm formation assay *Galleria mellonella* Survival Assays	*L. monocytogenes*	β-myrcene MBC = 2048 μg/mL. α-pinene MBC = 1024 μg/mL. At 256 μg/mL: Aggregation Loss of motility ↓ downregulation pf PrfA ↓ Biofilm formation by 29%−69%. ↓ of virulence in *Galleria mellonella* infected larvae	[81]

(*continued on next page*)

Table 3. (continued)

Compounds	Yield	Method used	Strains	Results	Ref
Prenylspirodinone[1]	1–4.2 mg	ND	*S. aureus* ATCC 29213	IC_{50} ranging between 2.6 and 49.6 μM.	[42]
Cannabinol[2]	2–15 mg		*E. coli* ATCC 25922	Prenylspirodinone active on *Bacillus thuringiensis* with	
Cannabichromene[3]	3–27 mg		*B. cereus*	inhibition zone of 49.6 mm.	
Cannabidiol[4],	4–42 mg		*L. lactis*	No effect on *Klebsiella pneumonia*, *Salmonella*	
Δ^1-Trahydro-cannabidivarol[5]	5–30 mg		*S. Typhimurium*	*Typhimurium*, and *Escherichia coli*	
Δ^9-Tetrahydrocannabinol[6]	6–48 mg		*K. pneumonia* ATCC 75388		
			Shigella boydii		
			Bacillus thuringiensis		
			MRSA,		
			Pseudomonas fluorescens		
			Xanthobacter flavus		
			Staphylococcus warneri		
α-humulene		Microdilution method	*Clostridium sporogens*	α-humulene lowest MIC 1.39% (v/v) against *Clostridium*	[79]
			Enterococcus faecium	*bifermentas*	
			Streptococcus salivarius	MBC value against gram + bacteria ranges from 1.39 to	
			Pectobacterium	1.67% and between 1.35 and 1.66% (v/v) against	
			carotovorum	gram- bacteria	
			Pseudomonas savastanoi		
			Clostridium bifermentas		

fight gram positive bacteria. Using agar diffusion method, the cultivars Antal, Carmagnola, Futura 75, Kc Zuzana, Tygra, and Zenith demonstrated promising antibacterial activity against isolates of *Staphylococcus*, *Enterococcus*, and *Bacillus*. In the same setting, several Eos demonstrated strong antibacterial activity with MIC values that were lower than those of the positive controls, ampicillin and ciprofloxacin. Several compounds were identified in the different Eos such as α-pinene, β-pinene, β-myrcene, CBD, α-terpineol, β-caryophyllene, when examined independently, as reported in earlier investigations, were declared to have effective antibacterial activity, particularly against strains of *Listeria* and *Enterococcus* [37] Tables 2 and 3. In the same context, *C. sativa* Eos extracted from Italian cultivars in different time laps were reported to be very active of all bacterial strains. Eo obtained after 4 h of extraction from "Gran Sasso Kush" cultivars were highly active on *L. monocytogenes* with the lowest MIC and MBC (0.08 μL/mL). Additionally, Eo collected after four hours extraction from "Kompolti" cultivars showed inhibition of *P. fluorescens* with a MIC and MBC value of 0.31 μL/mL. As for Eo of "Carmagnola Lemon" cultivars, it was registered a moderate antibacterial activity with MIC and MBC values ranging from 1.25 to >20 μL/mL. Last but not least, the "Futura" cultivars showed high to moderate activity against the various tested bacteria, with MIC values ranging from 0.625 μL/mL to >20 μL/mL against *Enterococcus faecium* ATCC 19434, which was consistent with earlier investigations [82]. Similarly, Pellegrini et al., (2021) have showed that "Futura 75" Eo from *C. sativa* inflorescences from Abruzzo territory in Italy exhibited antibacterial properties. The Eo were very active on different pathogenic and food spoilage bacterial strains. The lowest recorded MIC/MBC value was of 1.25 μL/mL against *S. aureus,* followed by a MIC of 2.5 μL/mL against *L. monocytogenes* (ATCC 19114 and LM 4) and *S. aureus*. Furthermore, it was recorded that the *C. sativa* Eos were able to inhibit the growth of *S. aureus* STA 32 and *L. monocytogenes* ATCC 7644 with a MIC and MBC value of 5 μL/mL. However, this tested Eo has exhibited only a bacteriostatic effect on *Pseudomonas fluorescens*, *S. Enteritidis*, *S. Typhimurium*, *B. thermosphacta*, and *E. faecium* with a MIC value higher than 20 μL/mL [35] Table 2.

As mentioned in phytochemistry section several molecules were identified in *C. sativa* such as THC that has demonstrated weak activity, while CBD has showed moderate bactericidal activity. THC/CBD combo tests revealed moderate activity [73]. Futhermore, CBD and cannabinolic acid (CBDA) two molecules isolated from marijuana MeOH

extract were mentioned to be endowed with antibacterial activity on gram positive bacteria while, no activity was observed on gram negative bacteria. CBD was able to inhibit *S. aureus* ATCC25923, *S. epidermis* and MRSA at very low concentrations of 0.001–0.002 mg/mL. Moreover, CBDA showed high antibacterial activity with MIC values of 0.002 and 0.004 mg/mL against the same strains. Meantime, it was demonstrated that the fractional inhibitory index (FICI) used for synergy test evaluation yielded values ranging from 1.03 to 1.50, indicating that there is no synergistic effect between CBD and the commercialized antibiotics. However, it is important to note that CBD and previously used antibiotics do have an additive effect. Through the use of a time kill kinetics experiment, it was shown that CBD had a significant inhibitory effect on MRSA bacterial culture by causing a drop in optical density. After 22 h of direct contact, it was demonstrated that CBD has bactericidal potential. When tested on Keratinocyte cells (HaCaT), the CBD was discovered to be less hazardous at a concentration seven times greater than the MIC value. Additionally, it has been shown that CBD and CBDA did not exhibit hemolytic activity, supporting the safety of their use [83]. Investigations on CBD and Cannabidivarin (CBDV), indicated high effectiveness on two gram negative and gram positive strains. Also, it was observed that CBD and CBDV were able to inhibit *E. coli* growth with an IC_{50} values of 29.1 and 35.4 μM after 72 h of exposition to the two molecules. While, *S. aureus* was more sensitive to the CBD with a decreasing IC_{50} after 24 h, 48 h, that reached 1.84 μM at 72 h of exposition. Besides, CBDV was less active compared to CBD with an IC_{50} of 30.8 μM after 72 h of exposition [41] Table 3.

Besides, Cannabidiol (CBD) showed high inhibition of *Salmonella Newington* growth and *S. Typhymirium* in a dose dependent manner. The same study indicated that *S. Newington* was more sensitive to CBD than *S. Typhi*. Meanwhile, CBD inhibited the two bacterial strains at 6 h using concentrations ranging from 1.25e-7 mg/mL to 0.00125 mg/mL while, studying time kill kinetics, it was found that *S. Newington* was very vulnerable to CBD action when using the lowest concentration While the *S. Typhi* showed a resistance to the same concentration (0.0000125 mg/mL). The MIC value recorded was 0.000125 mg/mL for *S. Typhi*. The membrane integrity was evaluated using DAPI (4′,6-diamidino-2-phénylindole) staining which is a product for which the membrane is impermeable and which binds to AT-rich DNA. Using this technique, it was very easy to confirmed that CBD is able to cause a destabilization of the membrane integrity of the two strains in a dose dependent manner after 5–30 min of exposer. While after 24 h of exposer the two strains started developing resistance toward CBD. In comparison of the obtained results with those obtained by ampicillin it was noted a great similarity between the activity of CBD and Ampicillin. In the same context, treatment of *S. Typhi* with a concentration of 0.00125 mg/mL inhibited the formation of the biofilm by the bacteria. Finally, the scanning electron microscope results showed a reduction in bacterial cells which indicates their death [84] Table 3.

12.3. Antifungal activity

Numerous studies have evaluated the antifungal activity of *C. sativa* and its derivates on different fungal strains. In fact, Butanolic and dimethyl ether extracts of *C. sativa* were found to be more effective on fungal strains especially on *Trichophyton rubrum* and *Microsporum canis* (MIC = 64 μg/mL). While EtOH extract was less effective on the same strains MIC 128 μg/mL. The different extracts were not effective on *Arthroderma insingulare* (Skala et al., 2022). Antello et al. (2022), study have investigated the antimycotic effect of *C. sativa* Eos extracted from two cultivars "Kompolti and Tisza". The acquired results showed that the two Eos were quite efficient against a number of dermatophytes, and in some cases, their activity was even lower than that of the positive control, griseofulvin. In the same investigation, "Tisza" Eo was found to have the lowest MIC value (0.312 μg/mL) against *Arthroderma quadrifidum*, *A. gypseum*, and *A. crocatum* and the highest MIC value (3.97 μg/mL) when tested against *T. rubrum* and *A. insingulare*. In terms of activity, Eo from the "Kompolti" origin was more active on *A. quadrifidium* and *A. crocatum*. While *T. rubrum* and *A. insingulare* had MIC values of 7.49 μg/mL, which were considered to be high [32]. Regarding the antifungal effect of whole hemp seeds on fungi, it was discovered that "Santhica 27" and "KC Dora" recorded the lowest MIC/MBC values, which were 75/150 μg/mL against *A. ochraceus*, *Penicillium ochrochloron*, and *Penicillium funiculosum*, while "Carmagnola" recorded the highest values, which were 1200/1800 μg/mL against *A. fumigatus* and *A. niger*. Conversely, dehulled hemp seeds displayed less antifungal activity than whole hemp seeds, while "Fedora 17"'s measurement of the lowest MIC/MFC against *A. ochraceus* was 200/300 μg/mL. Additionally, it was found that the hydromethanolic extract of hemp seeds' antifungal capabilities were adversely affected by the dehulling procedure when

compared to the hydromethanolic extract of whole seeds [50] Table 4.

12.4. Antiparasitic activity

A study assessed on antileishmanial activity of numerous fractions (A-G) obtained from *C. sativa* volatile compounds using Vacuum Liquid Chromatography. The obtained data revealed an inhibitory potential on *Leishmania donovani* with an IC_{50} of 34.3 μg/mL by fraction A. While fraction B was inactive of the same strain. However, fraction C stopped *L. donovani* growth with an IC_{50} of 22.43 μg/mL. Among all the identified compounds only a-humulene was active on *L. donovani* with an IC_{50} of 9.76 μg/mL [80]. However, De Sousa et al. (2021), had demonstrated that THC and CBD from *C. sativa* have exhibited an important inhibition of β-hematin with an IC_{50} values of 11.3 and 51.1 μM respectively, which was lower in the case of THC than the commercialized drug Chloroquine that has an IC_{50} value of 16.8 μM. The *in vitro* activity against the parasites THC showed an IC_{50} value of 0.79 μM and 0.72 μM for sensitive and resistant strains to Chloroquine, while CBD showed mild activity against sensitive strains with IC_{50} of 4.1 μM. It was also noted that the increase of THC concentration doesn't affect the concentration of free haem inside the parasite which implies that THC mechanism of action is not via hemozoin inhibition [85]. Furthermore, *in silico* anti-malarial activity of more than 125 compounds from *C. sativa* against *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase (*Pf* DHFR-TS) which is an enzyme responsible for the production of folates and thymidylate needed in DNA synthesis and which is a real target of antifolate drugs. The results indicated that 16 compounds showed better binding energy with the selected enzyme where compounds named 7-oxo-9a-Hydroxyhexahydrocannabinol, and 10-oxo-Delta6a,10a-tetrahydrocannabinol were the top hit compounds with the highest binding energy (−9.40 and −9.20) compared to Cycloguanil and WR99210 with a binding energy of −8.50 and −9.10 respectively. In order for the inhibition to occur the interaction between the tested compounds and the tested enzyme need to happen on specific key amino acids such as Ile14, Asp54 and Ileu164 which are found on the active site of *Pf* DHFR-TS. Thus, more than five compounds including 10-oxo-Delta6a,10a-tetrahydrocannabinol didn't form bonds with the amino acids of the active sites which suggests that these ligands are not specific for *Pf* DHFR-TS. On the other hand, Cannabielsoic acid A showed important binding energy of −8.50 with different amino acids especially Ile164 present in *Pf* DHFR-TS active site. However, toxicity prediction test showed that Cannabielsoic acid A is of high toxicity risk. Finally, 7-oxo-9a-Hydroxyhexahydrocannabinol was taken as top hit compound with low toxicity, and high binding energy with Ser 111 and Ile164 present on *P. falciparum* enzyme active site [86] Table 4.

13. Food usage and safety

Legalization impact was immediate, numerous products cannabis-based have been put on sale such as hard candies, desserts, wine. Also, used as flavoring in yogurt, flour, bake, milk, sauce, energy protein bars, chocolate, juice and salads. Moreover, cannabis seeds are largely used for their richness with proteins, lipids insoluble fibers and omega-6, omega-3, and carbohydrates [8]. Recent statistics published by the WHO, 2.5% of the world population consume cannabis which the equivalent of 147 million people across the globe. It was also indicated in the same report that cannabis is not totally safe for use as mentioned it has acute health effect such as impairment of cognitive development especially when used simultaneously during learning period. However, it could highly induce psychomotor impairment which could highly contribute into increasing accident prevalence when been under cannabis effect. Indeed, the WHO has also included some chronic side effect of *C. sativa* such as dependence syndrome that is characterized by low self-control, schizophrenia, respiratory disorders like epithelial injury, inflammation of respiratory tract, and bronchitis. Consumption of cannabis during pregnancy is strongly linked with fetal damages mainly weight loss, and it may increase the risk of developing uncommon cancers after birth [87]. In December 2018, the Agriculture Improvement Act of 2018, also known as the Farm Bill, made a substantial change to the way hemp is regulated in the United States. Hemp is considered as a type of cannabis with low THC level (<0.3% THC/dry weight) that was taken from the list of controlled substances in the USA (CSA) [88]. This legal change performed by the FDA has facilitated the road to conduct studies on CBD and other cannabis derived products. Hence, this legalization by the FDA might enhance the creation of novel hemp-based medications. However, it is important to note that under section 301(ll) of the FD&C Act, the FDA forbids the inclusion of CBD and THC to food products [88]. According to this clause, it is unlawful to introduce

Table 4. Antifungal and antiparasitic activity of C. sativa and its derivates.

Extracts/compounds	Country	Method used	Strains	Results	Ref
ButOH; Dimethyl ether (Forbiden fruits and cholocope)	Czechia	*in vitro*	*Nannizzia fulva* *Trichophyton rubrum* *Arthroderma insingulare* *Trichophyton tonsurans* *Nannizzia gypsea,* *Epidermophyton floccosum* *Microsporum canis* Trichophyton interdigitale	Lowest MIC = 64 μg/mL. EtOH extract lowest MIC = 128 μg/mL	(Skala et al., 2022)
Eo (Tisza; Kompolti cultivars)	Italy	*in vitro*	*Arthroderma quadrifidum* *A. gypseum* *A. crocatum* *T. rubrum* *A. insingulare*	**Tisza** Lowest MIC 0.312 μg/mL Highest MIC 3.97 μg/mL. **Kompolti** Lowest MIC 0.312 μg/mL Highest MIC 7.49 μg/mL	[32]
Whole and dehulled (different cultivars) seeds	Spain	*in vitro*	*A. ochraceus,* *P. ochrochloron,* and *P. funiculosum*	**Whole seeds** lowest value MIC 75 μg/mL MBC 150 mg/mL **Dehulled seeds** Less antifungal activity Lowest MIC/MFC against *A. ochraceus* was 200/300 μg/mL	[50]
Eo (fractions)	USA	*in vitro*	*L. donovani*	Fraction A IC_{50} of 34.3 μg/mL Fraction B inactive Fraction C IC_{50} of 22.43 μg/mL α-humulene was active on *L. donovani* with an IC_{50} of 9.76 μg/mL	[80]
THC CBD	South Africa	*in vitro*	*Plasmodium falciparum* (β-hematin inhibition)	**β-hematin inhibition:** IC_{50} values of 11.3 and 51.1 μM respectively Lower IC_{50} by THC than Chloroquine IC_{50} (16.8 μM) ***Plasmodium falciparum*:** THC IC_{50} = 0.79 μM and 0.72 μM for sensitive and resistant strains to Chloroquine CBD showed mild activity against sensitive strains with IC_{50} of 4.1 μM	[85]
125 compounds from *C. sativa*	Vietnam	*in silico*	*Plasmodium falciparum* (*Pf* DHFR-TS)	16 compounds showed better binding energy Cannabielsoic acid A showed important binding energy of −8.50 with different amino acids especially Ile164 present in *Pf* DHFR-TS active site	[86]

or transmit any food, including animal food or feed, into interstate commerce if it contains an element that is also present in drug products. The legalization of cannabis and the certification of its safe use face numerous obstacles, according to the same agency. These difficulties include the need for more information demonstrating the safety of using *C. sativa*, the requirement to support rigorous scientific research into the therapeutic uses of cannabis products, and rapidly altering legal frameworks at the federal, state, and local levels [88]. In addition, the market is changing and offers a wide range of cannabis products which implies more work in order to promote public health. For better controlling of the plant's safe use, in November 2022 the FDA issued warnings to numerous companies involved in the unauthorized selling of CBD products. The distinction between traditional foods or drinks and CBD-based products was being blurred in the marketing of these products, which may have confused customers. Such misunderstandings can encourage inadvertent or excessive CBD usage. It is crucial to remember that long-term CBD use has been linked to a number of potentially harmful consequences on the male reproductive system, including testicular atrophy, liver damage, and interactions with specific drugs. These dangers emphasize the need for precise regulations and stringent control to guarantee the proper and safe use of CBD products [89]. In January 2023, the FDA responded to the petitions calling for the publication of a regulation that would allow cannabidiol (CBD)-based products to be marketed as dietary supplements made by the Consumer Healthcare Products Association (CHPA), the Council for Responsible Nutrition (CRN), and the Natural Products Association (NPA). However, these petitions were rejected by the FDA because of the restriction the marketing of specific prescription components as dietary supplements. This rebuttal by the FDA was explained by the absence of solid scientific evidence which does not provide a clear understanding of how CBD products could meet the required safety standards for dietary supplements [90]. To date, the U.S. Food and Drug Administration (FDA) has not granted approval for the use of cannabis itself in the treatment of medical conditions. However, the FDA has authorized certain cannabis-derived or synthetic products for specific medical purposes such as Epidiolex, Marinol, Syndros, and Cesamet. Finally, the agency warns against using cannabis that has not been approved by the organization because doing so could have dangerous safety risks as well as unpredictable and unintended consequences [91].

According to United Nations on Drugs and Crimes (UNODC) the aspirations about cannabis legalization is allowing the nonmedical use of this plant by adults. Also, taking care of criminal justice reactions is necessary since treating cannabis possession for personal use as a crime had resulted in many people being detained and getting a criminal record. Moreover, preventing organized crime groups from making money off the illegal cannabis trade. In the same context, it will significantly lower the expense of law enforcement, particularly the cost of policing cannabis uses for personal use, to free up resources for more serious offences. Finally, a huge profit will be collected on both short and long-term from the cultivation, manufacturing, and selling of cannabis, denying cash to organized crime groups and allocating a portion of the proceeds to the treatment and prevention of drug use problems, thereby safeguarding the public's health and safety [92].

14. Conclusion

Research on the phytochemicals present in *C. sativa* has been ongoing since 1841. The present comprehensive review has collected almost all the articles available on the chemical composition of hemp and its antimicrobial activity from various databases. Following the recent legalization and decriminalization of cannabis, research has begun to shift towards exploring the antiviral properties of the plant and its derivatives. However, it is important to note that all studies conducted thus far have been limited to *in vitro* and *in silico* experiments. To better understand and extrapolate results to humans, further studies at pre-clinical and clinical stages are necessary. Such studies can be instrumental in tackling the emergence of multidrug resistance, which poses a real threat to millions of living beings across the globe. This contribution to the One World, One Health strategy aims to reduce the high risks of infectious diseases. The authors' main objective is to provide a guide for future research and the development of therapeutic medicines to help alleviate health issues, which could greatly benefit from the potential of *C. sativa* and its derivatives.

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Conflicts of interest

The authors declare the absence of any known conflicts of interest.

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