Review of Moroccan *Cannabis sativa* L.: Cultivation, phytochemistry, therapeutic uses, and biological activities in *in-vitro*, *in-vivo* and *in-silico* assays

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Review

Abstract

Background: Cannabis sativa's medicinal properties have been known for many cultures. Numerous plant parts have long been utilized in ethnomedicine due to their complexity. This study aimed to compile existing documents on *Cannabis sativa* in Morocco. We reviewed the history, scientific research, extraction procedures, diversity of phytochemicals, traditional uses, and experimental assays.

Methods: To achieve our goal, we utilized proper keywords related to the topics and compiled the bibliography using electronic survey databases and engines, including Scopus, ScienceDirect, PubMed, Public Library of Science, JSTOR, Google Scholar, Web of Science, and the WSU online database (PubChem). The papers were searched for a period from 1912 to 2024 using French, English, and Spanish.

Results: Results showed that 2017 documents have addressed *Cannabis sativa* in Morocco, including scientific articles, theses, conference papers, books, and reports. These documents demonstrated that six varieties, including 'Khardala', 'Critical', 'Amnésia', 'Beldia', 'Gorilla', and 'Pakistana', are cultivated in Morocco, mainly in Northern provinces such as Chefchaouen, Taounate, Larache, Al Hoceima, and Tetouan. Essential oils and extracts of *Cannabis sativa* are rich in chemical compounds; 32 and 24 molecules, respectively. Bioactive molecules, which include polyphenols, flavonoids, terpenes, and cannabinoids, vary depending on the variety, the organs used, the extraction approaches, and the growing areas. They are

mainly extracted by hydrodistillation from aerial parts, while extracts are isolated by maceration, sonification, and decoction from seeds and aerial parts. Further, *in-vivo, in-vitro*, and *in-silico* assays confirmed the biological activities of *Cannabis sativa* L., mainly anti-microbial, anti-parasitic, anti-inflammatory, and anti-cancer effects.

Conclusions: This study is the first to review the topics related to *Cannabis sativa* L. in Morocco and offer new and compiled data in North Africa and the Mediterranean basin.

Keywords: *Cannabis sativa* L., Moroccan varieties, scientific research, extraction of biomolecules, medicinal uses, biological activities.

Background

Plants of the Cannabaceae family belong to the genus Cannabis. More than 700 strains and three distinguished species of cannabis exist, including *Cannabis sativa* L., *C. ruderalis,* and *C. indica* (Osterberger *et al.* 2022). More than 400 bioactive substances have been found in cannabis, with the main ones being terpenes, fatty acids, oils, waxes, flavonoids, polyphenols, and phytocannabinoids (Ashton 2001, Mahlberg and Kim 2004). cannabinol, cannabidiol, Tetrahydrocannabinol, and their carboxylic acid derivatives are the important cannabinoids studied to evaluate their medicinal effects. According to Kogan and Mechoulam (2007), Terpenes and cannabinoids derived from cannabis offer therapeutic potential for treating a variety of ailments, like Parkinson's disease, Alzheimer's disease, tumors, and cancer, and neurological disorders like depression, epilepsy, insomnia, anxiety, and convulsions.

The family Cannabiaceae, which includes *Cannabis sativa* L., is observed in a wide range of environments and elevations, from lowlands to the alpine mountains of the Himalayas, where it may have derived (Russo *et al.* 2008). Since cannabis has been cultivated and used for 5-6 thousand years, the origin of this species is difficult to determine (Piluzza *et al.* 2013). It is also among the earliest plant sources of food and fiber for textiles (Andres *et al.* 2016). Egypt and western Asia are where *Cannabis sativa* L. was first cultivated for textile fiber. Between 1000 and 2000 B.C., it was brought to Europe, and in 1545, it was brought to South America (Chile). Hemp was initially cultivated in North America in 1606, more than 60 years later in Port Royal, Canada (Brenneisen 2007). The United States' current federal regulations forbid the growing of *Cannabis sativa*, including hemp.

The biochemical constituents of *Cannabis sativa* L. have been the subject of investigation since the mid-20th century and remain an area of ongoing research (Turner *et al.* 1980, Hendriks and Bruins 1983, Palmieri *et al.* 2020). The findings of these searches indicated a range of biochemical complexes that vary based on several factors, including the plants sampled, their varieties, growing regions, growth stages, parts used, extraction methods, and environmental conditions (Haney and Kutscheid 1973, Namdar *et al.* 2018, Pavlovic *et al.* 2019, Abdollahi *et al.* 2020, Anderson *et al.* 2021). *Cannabis sativa* L. is recognized for its bioactive constituents, including polyphenols, cannabinoids, flavonoids, and terpenes. The chemicals support the medicinal and environmental applications of the plant.

Morocco is one of the foremost makers of *Cannabis* in the world. Although marijuana has been prohibited in Morocco since the country's independence in 1955 and was outlawed completely in 1974, the drug is nevertheless somewhat tolerated in the nation where it has been grown for centuries. Morocco continues to be one of the world's top producers of Cannabis (Hashish). The production of Cannabis is currently concentrated in the Northern provinces, such as Al Hoceima, Nador, and Taounate. The cultivation of cannabis was initially forbidden throughout Morocco upon its independence; however, it has since grown significantly in the Rif, particularly in areas with good irrigation, first in the Chefchaouen region, at the foot of the Limestone Ridge, and then in the coastal area of the Rif itself. During the Spanish administration, cannabis was authorized for pharmaceutical purposes in small areas in the High Rif Mountain range (Ketama region). Before the 1970s, it was a discreet and family-only use. However, due to the small port of Jebah and the vast portion of the European market it serves, it is now practiced publicly in wide areas and illegally.

In Morocco, *Cannabis sativa* L. is used for medicinal and environmental purposes. In medicine, the plant and its derivatives are traditionally used to manage a wide range of illnesses, including dental pain, anxiety, diabetes, and gastrointestinal diseases, among others. In the laboratory, numerous studies have reported the beneficial effects of extracts and essential oils from Cannabis, including anti-inflammatory, antimicrobial, and antioxidant properties. Equally, the antinociceptive and toxicological impacts of seed oils from Moroccan *Cannabis sativa* L. (Raoui *et al.* 2024). On the other hand, *Cannabis sativa* L. and its by-products are utilized in eco-friendly approaches, such as the replacement of chemicals, the extraction of pollutants, and the management of agronomic pathogens. This plant and its parts (i.e. stems, leaves, roots, etc.)

demonstrated their ability to mitigate the effects of various pollutants, such as colorants, pesticides, and heavy metals, landfill, in the soil, and the water (Mańkowski *et al.* 2020). However, the investigations that addressed chemical compounds and the uses of *Cannabis sativa* L. in Morocco are fragmentary. Therefore, more comprehensive papers are needed to resume all aspects of Cannabis in Morocco.

Materials and Methods

Research method

This study concentrated on Chemical compounds, medicinal uses, pharmacological activities, and environmental benefits of *Cannabis sativa* L. in Morocco. A bibliography of the distributed papers on *Cannabis sativa* L. in Morocco was compiled using electronic databases and search engines, including Scopus, ScienceDirect, PubMed, Public Library of Science, JSTOR, Google Scholar, Web of Science, and the WSU online database (PubChem) (Figure 1). Further, the keywords contained medicinal plants, *Cannabis sativa* L., Cannabis biochemicals, essential oils, extracts, infusions, biological activities, pharmacology, ethnobotany, traditional uses, environmental uses, the consequences of climate change, the impact of geographical location, extraction procedures, altitude, genotypes, were used to collect data. These keywords were used separately and in combinations to achieve the study's objectives. The papers were searched from 1912 to 2024 using French, English, and Spanish. The French language was adopted due to its status as the second language in Morocco. Spain adopted the Spanish language as its official language during the colonial era, from 1912 to 1956. In contrast, English has been considered the principal scientific language in Morocco during the last decades.

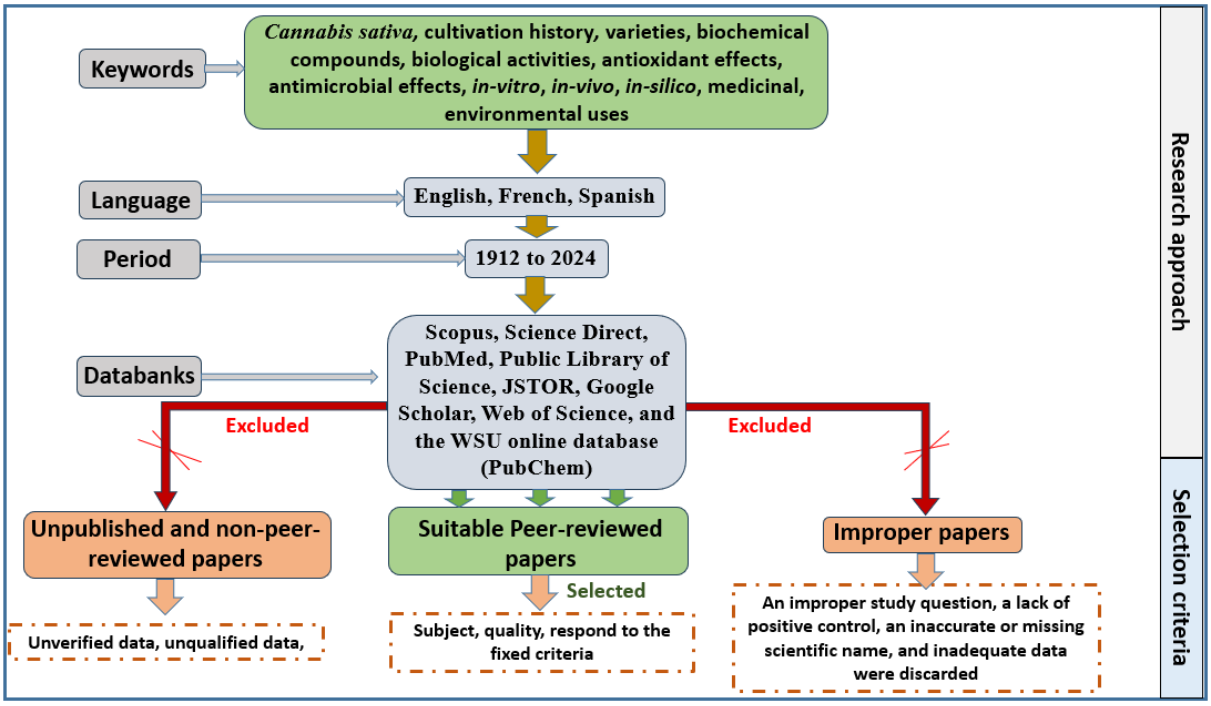


Figure 1. Summary of exploration approach used to collect bibliographic papers on *Cannabis sativa* L. in Morocco

Research Criteria

Research documents were gathered, and research subjects were searched in the sections of the papers involving titles, abstracts, introductions, results, and conclusions. Furthermore, recorded documents were organized depending on various criteria, including the language, publication year, and country. The peer-review process, verified content, source quality, and appropriate content were taken into consideration when choosing the collected papers. On the other hand, publications produced outside of the years 1912-2024 and those lacking adequate content, verification, or peer review were excluded. In total, 278 papers were collected based on the following research approach. Further, 61 documents were eliminated due to their inappropriate contents.

History of Cannabis in Morocco

The first cannabis plants were planted in Morocco in the seventh century when Arab immigrants arrived in the area. During their mystical-ecstatic rites in the 18th century, religious leaders like the Heddawa, led by Sidi Heddi, who settled in the

Eastern Rif and is a famous Moroccan cannabis smoker, drank kif, the local term for cannabis. In certain of the nation's rural areas, cannabis use rose in popularity in the 19th century. About 1890, Hassan ben Mohammed gave the go-ahead for the five hamlets of the Ketama and Bni Khaled tribes to start growing kif. The country's monopoly on tobacco and cannabis was taken over in 1906 by the French-owned Moroccan Kifs and Tobacco Company. A combination of tobacco and hashish was nevertheless permitted for sale in the French protectorate after cannabis growing was outlawed in November 1932 (according to an international convention on drugs). Although the production of cannabis was outlawed totally in 1954 by a new law, it continued to grow. In the 1950s, Ketama developed into a popular vacation spot for young Europeans, much like Kathmandu.

As a result of the Rif region's increased cannabis production starting at the end of the 1950s, Interior Minister Driss Basri made significant efforts every year during planting season to raise awareness among the local populace and dissuade farmers from cultivating cannabis. In the years 1980-2000, cannabis crop size tripled. There were multiple violent clashes, and things didn't start to improve until Mohammed VI arrived. The United Nations Office on Drugs and Crime reported that Morocco had 134,000 hectares of cannabis fields at the start of the twenty-first century. This area produced 3,080 tons of hashish annually, bringing in $214 million for farmers and $12 billion for traffickers.

In December 2020, Morocco voted in favor of the World Health Organization's recommendations downgrading the international arrangement of therapeutic cannabis, and shortly after, announced plans to reform national public policies to authorize the production of cannabis for medical purposes in certain areas of the country. Further, 75 operators, including cooperatives, agro-industrialists, individuals, and pharmaceutical manufacturing companies, have already been granted marketing, processing, or export permits, and over 400 farmers have already been granted growing permits.

Geographical distribution and cultivated varieties

After their arrival in the 7th century, Arab immigrants who brought Cannabis were installed in the North of Morocco. The first farming of Cannabis appeared in the Eastern Rif Mountains, and the species was named kif (the local name for cannabis). In contrast, the plants were cultivated under the Spanish protectorate.

A new law came into force in 1954 to completely ban cannabis cultivation, but in practice, the crop continued to flourish in the Northern provinces. In the 1950s, Ketama became a destination for Cannabis in Morocco and Northwest Africa. Currently, Cannabis crops are found in the Majority of Northern provinces of Morocco after its current legislation status (Figure 2). It is found in Nador, Taounate (Northeast), Chefchaouen, Al Hoceima, Tetouan (North northwest), and Larache on the Atlantic coasts. In 2004, cannabis cultivation was at 120,500 hectares (ha), with the largest cultivation area found in Chefchaouen (75,195 ha, or 62 % of the total cultivation area), followed by Taounate (14,718 ha, or 12%), Larache (11,892 ha, or 10%), Al Hoceima (10,524 ha, or 9%) and Tetouan (8,225 ha, or 7%). However, currently the cultivated areas have decreased to 47.000 ha in 2018, and 55.000 ha in 2019.

The peasants of the Rif and those of other ancient cannabis growing areas of Morocco (the Sahara Oasis, the High Atlas) have adapted cannabis plants to their environment for hundreds of years, since the introduction of Indian hemp in Morocco in the 14th century. The work and know-how of the peasants, in symbiosis with the climatic conditions and resources, benefiting from exchanges and gifts of seeds between neighbors or travelers, have made it possible to develop local varieties of kif (cannabis herb), specific to the country. In their search for varieties that have a higher yield, farmers have currently tested several seeds. Currently, 5 principal varieties of *Cannabis sativa* L. are reported in Morocco, including ‘Khardala’, ‘Critical’, ‘Amnésia’, ‘Beldia’, and ‘Gorilla’ (Figure 3). These varieties are variable in morphology, ecology, growing areas, and chemical compounds. This shift in Moroccan cannabis culture is best exemplified by a particular imported type known as "Khardala," which experts refer to as the "new cannabis culture." Growers abandoned the hybrid variety "Pakistana" due to its dismal yields, and this is how Khardala progressively supplanted it. But Khardala is also doomed to disappear and will one day be replaced by other varieties (Gaouriya, Critical, Kush, LemonHaze, etc.), with higher yields and higher THC levels. In addition to the health, water, and ecological damage that it causes, the frantic and anarchical dynamic of announcing new varieties of cannabis also portends to destroy the local strain on which the success of the medicinal valorization project started by Morocco could depend.

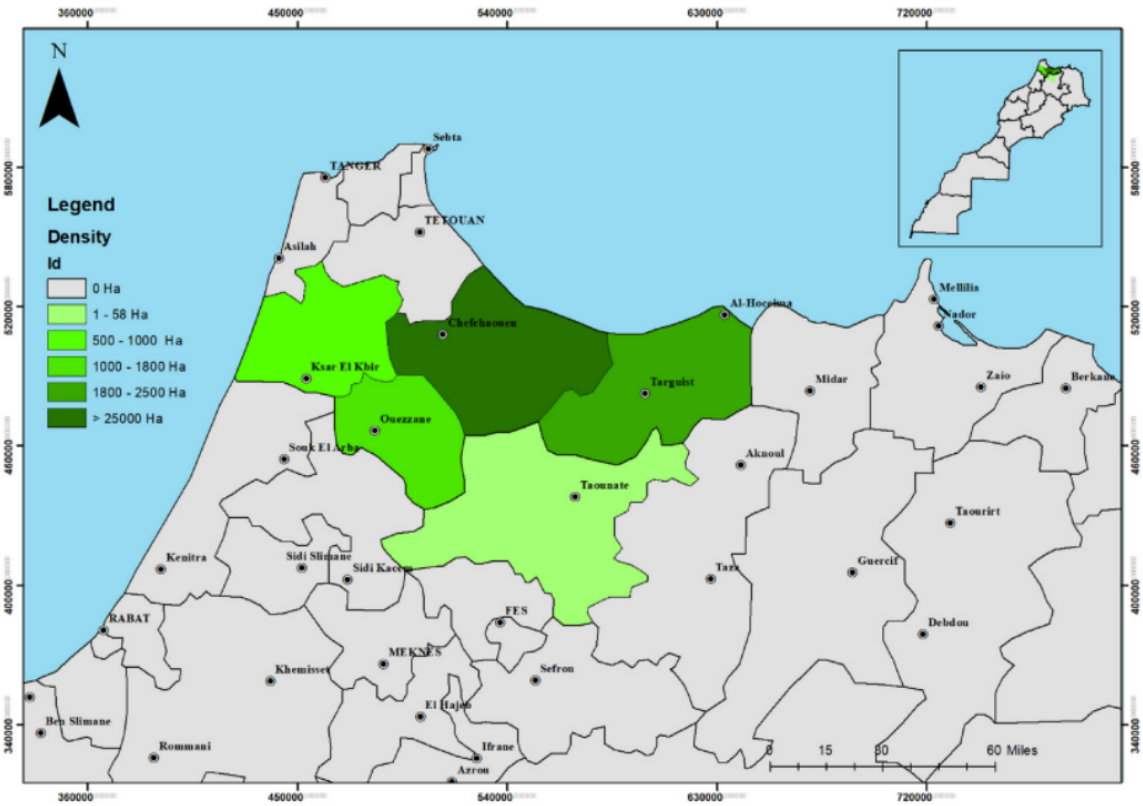


Figure 2. Cultivation of Cannabis in Morocco and Distribution of the total land area (from Dali *et al.* 2023, with kind permission of the authors).

Scientific Research on Cannabis in Morocco

The scientific papers addressed Cannabis in Morocco from the first half of the 19th century. The first papers appeared in 1944 in 'Journal d'agriculture traditionnelle et de botanique' by Chevalier (1944). The first papers were scientific articles and only mentioned the presence and geographical distribution of *Cannabis sativa* L. in the North of the country. The scientific exploration of the plant increased over time, depending on the language and topics.

From 1912 to 2024, 217 papers have addressed the topics related to *Cannabis sativa* L. in Morocco (Figure 4). These papers were dominated by scientific articles (184, 84.79%), followed by theses (10, 4.61%), conference papers (6, 2.76%), reports (4, 1.84%), abstracts (4, 1.84%), books (4, 1.84%), and reports (4, 1.84%). In contrast, only one annex (0.46 %) has addressed the topic of *Cannabis sativa* L.



Figure 3. Varieties of *Cannabis sativa* L. in Morocco (A: 'Beldia'; B: 'Khardala'; C: 'Critical')

The number of documents was significantly higher in the period from 2000 to 2024, with 177 items, followed by 37 items from 1956 to 2000. Further, only 3 papers were recorded between 1912 and 1956. Most papers were published in English and French, while a few papers were published in Spanish. The recorded papers have addressed various topics, including medicinal uses, phytochemicals, biological activities, geographical distribution, environmental benefits, and economic values.

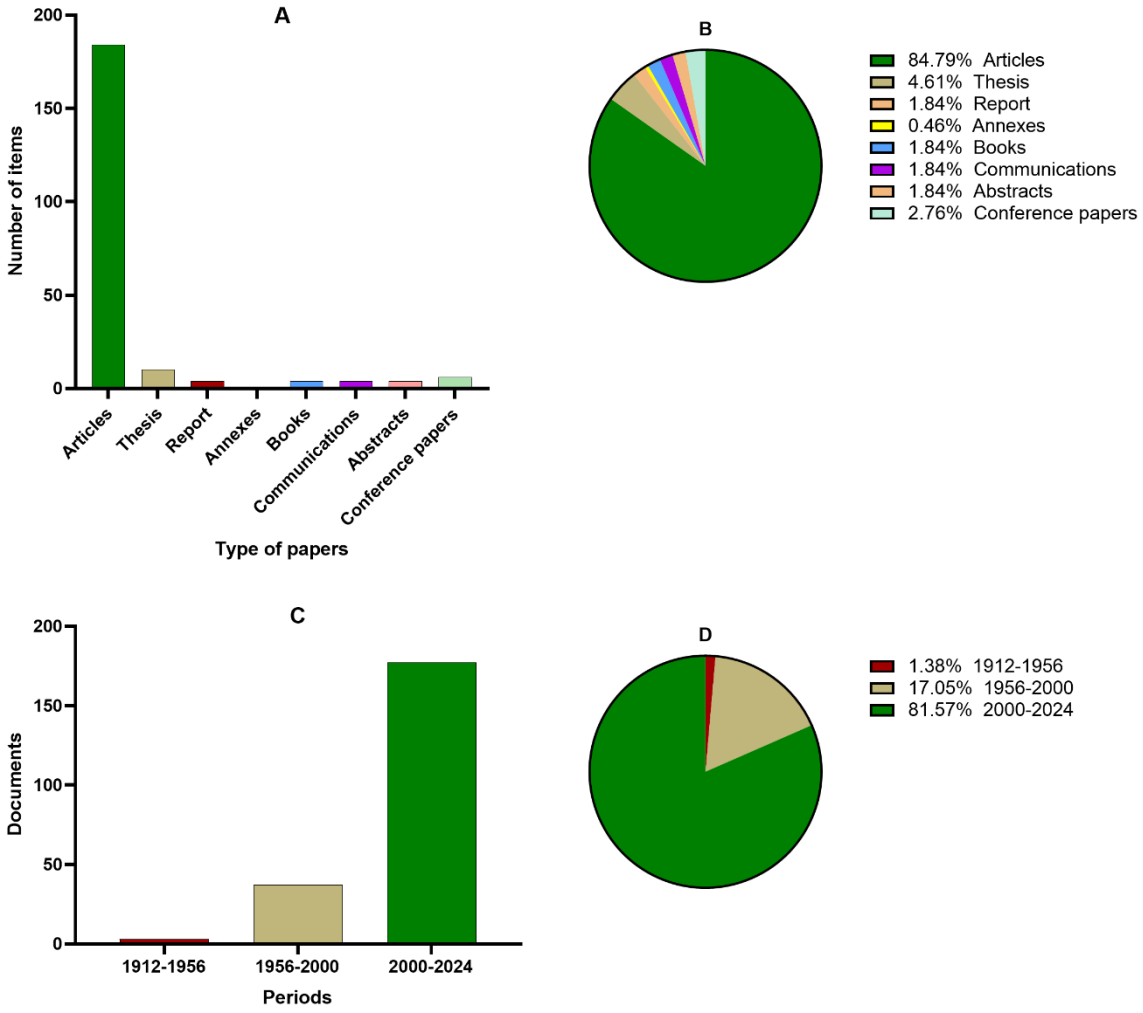


Figure 4: Published papers on *Cannabis sativa* L. in Morocco (A and B) depending on periods (C and D) from 1912 to 2024

Extraction advances

Distinctive methods were employed to extract bioactive molecules from various parts of *Cannabis sativa* L. growing in Morocco (Table 1). Furthermore, essential oils were primarily obtained from the aerial parts of *Cannabis sativa* L., including leaves and dried inflorescences, through hydrodistillation. Moreover, the identification of chemical composites was achieved using Gas Chromatography-Mass Spectrometry (GC-MS). On the other hand, seed oils were extracted using different approaches, including the Soxhlet method, aqueous enzymatic extraction, and cold extraction. In other studies, mixture design extraction was employed using various solvents, including 2-propanol, n-hexane, and ethyl acetate. Active molecules in seed oils were identified using high-performance liquid chromatography with diode-array detection (HPLC-DAD), Gas chromatography-flame ionization detection (GC-FID), and Gas Chromatography-Mass Spectrometry (GC-MS). Moreover, extracts of *Cannabis sativa* L. were obtained from various solvents, including water and organic solvents such as hexane, methanol, ethyl acetate, chloroform, Glycerol, dichloromethane, and ethanol. The extractions were performed using maceration, Soxhlet, sonication, and ultrasonic-assisted extractions from defatted hemp seeds, leaves, flowers, and entire plants of *Cannabis sativa* L. The chemical compounds of *Cannabis sativa* L. organic and aqueous extracts were identified by different methods, including high-performance liquid chromatography with ultra-violet detection (HPLC-UV) and HPLC-UV, GC-MS, high-performance liquid chromatography connected with diode array detection (HPLC-DAD), and electrospray

ionization with mass spectrometry (HPLC-DAD/ESI-MS), phytochemical screening, and high-performance liquid chromatography attached to electrospray ionization tandem mass spectrometry and diode-array detection (HPLC-DAD-MS).

Table 1. Applied methods to extract and identify the chemical compounds of *Cannabis sativa* L. in Morocco

Extract	Solvents	Plant Materials	Extraction method	Identification Approach	References
Essential oils		Dried inflorescences	Hydrodistillation	GC-MS	(El Bakali *et al.* 2022)
		Leaves	Hydrodistillation	GC-MS	(Kabdy *et al.* 2024a)
		Aerial parts	Hydrodistillation	GC-MS	(Rejdali *et al.* 2024, Kabdy *et al.* 2024a)
Seed oils		Seeds	Soxhlet and Aqueous Enzymatic Extraction	HPLC-DAD	(Allay *et al.* 2024)
		Seeds	Soxhlet Extraction	GC-MS	(Raoui *et al.* 2024)
		Seeds	Cold Extraction	GC-FID and HPLC-DAD	(Mokhtari *et al.* 2022)
	n-hexane, ethyl acetate, and 2-propanol	seeds	Mixture design	HPLC-DAD	(Mansouri *et al.* 2023)
Extracts	50% aqueous acetone	Seeds	Soxhlet and sonification extraction	HPLC-DAD/ESI-MS2	(Benkirane *et al.* 2023)
	Hexane extract	Seeds	Maceration	HPLC-UV/GC-MS	(Haddou *et al.* 2023a)
	Ethanol, Chloroform, Ethyl Acetate, Dichlorom ethane, Methanol, Water, and Hexane	Plant residue without resin	Sonication	ND	(Aazza 2021)
	Ethanol, Chloroform, and Hexane	Fresh flowers	Soxhlet method	Phytochemical screening	(Ahidar *et al.* 2024a)
	ethanol, chloroform, and hexane	Leaves	Maceration and Soxhlet extraction		(Ahidar *et al.* 2024b)
	distilled water	Female plants co-products	Maceration, sonication, and decoction		(Balafrej *et al.* 2023)
	Water, Glycerol, and Ethanol	Leaves	Ultrasonic-assisted extraction, optimal mixture-process design (OMPD) mixed with artificial neural networks (ANNs)		(Fadil *et al.* 2024)
	Water, methanol, and acetone	Defatted hempseeds	Sonication and simplex lattice mixture design	HPLC-DAD and MS	(Benkirane *et al.* 2022)

Diversity and variability of Chemical compounds

Essential oils

Currently, Bonini *et al.* (2018) reported the presence of 538 natural composites in *Cannabis sativa* L., proving its biochemical value. Among them, more than 100 are identified as phytocannabinoids. In Morocco, various studies have addressed the biochemical compounds of essential oils unearthed from materials of *Cannabis sativa* L. However, these studies demonstrated that the biochemical mixtures of *Cannabis sativa* L. are significantly variable depending on variety, growing area, altitude, used parts, and extraction procedures (Table 2).

Currently, El Bakali *et al.* (2022) conducted a comparative study of phytochemicals in essential oils extracted from 3 cultivars of *Cannabis sativa* L. raised in Chefchaouen, located in the central zone of North Morocco. In this analysis, the writers used essential oils isolated from dry inflorescences of 'Beldiya', 'Mexicana', and 'Critical Plus' employing hydrodistillation and afterward subjected to chemical examination utilizing GC-MS. The obtained data demonstrated that cultivars differed significantly concerning essential oil output and chemical profile. In contrast, Mexicana demonstrated the lowest production of essential oil (0.33%), while Critical Plus variety showcased the greatest productivity (0.688 %). A medium yield was recorded in 'Beldiya' with 0.345 %. For most of the main chemicals, "Critical Plus" displayed the lowest values, nevertheless. The biochemical constituents were discovered to be a prominent richness of biochemicals, particularly terpenoids. Moreover, β-caryophellene (13.39 to 25.32%), β-myercene (10.03 to 20.09), α-humulene (4.88 to 8.73%), caryophellene oxide (1.46 to 6.07%), decane (1.41 to 4.46%), and α-pinene (1.91 to 3.66%) were the most prevalent components in the essential oil. The superior accounts of these biocompounds were described in 'Beldiya', mainly decane, caryophellene oxide, and β-caryophellene. In 'Mexicana', the most dominant constituents were β-myercene, followed by α-humulene, and lastly α-pinene. In another study, Kabdy *et al.* (2024a) evaluated the biochemical composites of essential oils found in leaves (aerial fragments) of *Cannabis sativa* L. growing in Rif. Moreover, the essential oils were extracted through hydrodistillation and examined by Gas Chromatography-Mass Spectrometry (GC/MS). The obtained findings confirmed the discovery of 32 chemical constituents, accounting for 96.94% of the total compounds. The detected chemical classes were sesquiterpene hydrocarbons with 67.63%, followed by oxygenated sesquiterpenes with 25.91%, and oxygenated monoterpenes with 0.99%. Further, the primary elements of essential oil were (E)-caryophyllene (nearly 41.59%), followed by α-humulene (with nearly 14.93%), and caryophyllene oxide (with only 11.4%).

Rejdali *et al.* (2024) evaluated the constituents of essential oils isolated from *Cannabis sativa* L. growing in Al-Hoceima, located in Northern Morocco. In this study, the authors used the aerial materials of *Cannabis sativa* L. subsp. sativa L. collected from Rif highlands, reaching an altitude of 1250-1450 meters on the Mediterranean coast. Extraction was performed using hydrodistillation, while GC-MS Analysis detected the biochemical constituents. When the essential oil was extracted, the yield was estimated at 0.23 ± 0.02 % (w/w). The EO extract contained a total of 28 biochemical elements or 100% of the overall composition. Further, the main constituents were Caryophyllene (with 31.77%), followed by α-humulene (with 11.21%), and β-myrcene (with 8.76%). A study conducted in Morocco revealed that α-humulene (with 12.8%), caryophyllene oxide (with 10.6%), and (E)-caryophyllene (with 35.0%) dominated the molecules of *Cannabis sativa* L. EO isolated from the aerial materials sampled from the outskirts of Ketama zone in the Rif (Nafis *et al.* 2019). Moreover, El-Mernissi *et al.* (2024b) analyzed the biochemical components of essential oil taken from inflorescences and leaves (air-dried) of *Cannabis sativa* L. Moreover, plant material was collected in the fluorescence phase. The extraction was guided using hydrodistillation in a Clevenger-type apparatus. Moreover, GC-MS examination of the CSEO was achieved by employing a Thermo Scientific GC system (TRACE GC ULTRA) connected with a mass spectrometry sensor and the split injection approach. Attained results displayed that the CSEO yield was estimated at 0.14 ± 0.03 % v/w. The assessment of the volatile constituents of CSEO via GC-MS evaluation uncovered the existence of 24 sesquiterpenes (representing 75.68% of total compounds), followed by 7 monoterpenes (representing 17.08%), while cannabinoids were absent. Nine terpenes were discovered to have concentrations below 1%, whereas 22 of the total detected terpenes had values above 1%. With 31.54% of the composition, β-caryophyllene was the most abundant of the sesquiterpenes. It was followed by α-humulene with 12.62 %, elina-3,7(11)-diene (with 3.36%), aromadendrene (with 2.94%), and caryophyllene oxide (with 2.46%). Bulnesol, on the other hand, was a small chemical that accounted for only 0.54% of the overall makeup. It was also observed that the predominant monoterpenes in the cannabis essential oils were d-limonene (with 3.10%), followed by β-myrcene (with 4.83%), and α-pinene (with 4.69%).

Table 2. Comparison of biomolecules of essential oils from varieties of *Cannabis sativa* L. (a>b significantly different)

N	Compound name	'Critical Plus'	'Mexicana'	'Beldiya'
1	Acetic acid, butyl ester	0.45 ± 0.01^{b}	0.31 ± 0.00^{b}	1.05 ± 0.01^{a}
2	p-Xylene	0.47 ± 0.01^{b}	0.34 ± 0.01^{b}	1.13 ± 0.00^{a}
3	Nonane	0.63 ± 0.01^{b}	0.46 ± 0.00^{b}	1.43 ± 0.01^{a}
4	α-Pinene	4.81 ± 0.00^{a}	7.08 ± 0.01^{b}	4.10 ± 0.01^{a}
5	1-ethyl-3-methyl-Benzene	0.65 ± 0.01^{b}	0.44 ± 0.00^{b}	1.34 ± 0.00^{a}
6	4-methyl- Nonane	0.40 ± 0.01^{b}	0.31 ± 0.01^{b}	1.23 ± 0.01^{a}
7	4-methyl-1-Decene	0.56 ± 0.01^{b}	0.38 ± 0.01^{b}	1.12 ± 0.01^{a}
8	β-Pinene	2.72 ± 0.01^{b}	3.66 ± 0.02^{a}	1.91 ± 0.01^{c}
9	1-ethyl-2-methyl-Benzene	0.50 ± 0.00^{b}	0.36 ± 0.00^{b}	1.14 ± 0.00^{a}
10	β-Myrcene	10.03 ± 0.01^{c}	20.09 ± 0.02^{a}	10.78 ± 0.01^{b}
11	Decane	1.93 ± 0.01^{b}	1.41 ± 0.01^{b}	4.46 ± 0.00^{a}
12	1,2,3-trimethyl-Benzene	0.57 ± 0.00^{b}	0.41 ± 0.00^{b}	1.33 ± 0.01^{a}
13	d-Limonene	7.06 ± 0.01^{a}	3.71 ± 0.02^{b}	2.05 ± 0.01^{c}
14	Eucalyptol	1.19 ± 0.01^{a}	0.42 ± 0.00^{b}	0.65 ± 0.00^{b}
15	α-Ocimene	1.39 ± 0.01^{a}	1.13 ± 0.02^{a}	0.89 ± 0.01^{a}
16	*p*-Mentha-1,4(8)-diene	1.29 ± 0.02^{a}	0.87 ± 0.00^{a}	0.21 ± 0.01^{b}
17	Linalool	1.10 ± 0.01^{a}	0.00 ± 0.00^{a}	0.00 ± 0.00^{a}
18	Undecane	0.00 ± 0.00^{c}	0.62 ± 0.01^{b}	1.23 ± 0.01^{a}
19	β -Caryophyllene	13.39 ± 0.01^{c}	26.17 ± 0.01^{a}	25.32 ± 0.02^{b}
20	*trans*-α-Bergamotene	1.31 ± 0.01^{a}	0.64 ± 0.00^{b}	0.66 ± 0.01^{b}
21	α -Humulene	4.88 ± 0.01^{b}	8.73 ± 0.02^{a}	7.38 ± 0.02^{a}
22	Alloaromadendrene	0.00 ± 0.00^{b}	1.37 ± 0.01^{a}	0.43 ± 0.01^{b}
23	Eudesma-4(14),11-diene	1.20 ± 0.00^{a}	1.27 ± 0.01^{a}	1.24 ± 0.01^{a}
24	Guaia-1(10),11-diene	1.54 ± 0.01^{a}	0.98 ± 0.00^{ab}	0.89 ± 0.00^{b}
25	Guaia-3,9-diene	5.27 ± 0.02^{a}	0.05 ± 0.01^{b}	0.00 ± 0.00^{b}
26	Selina-3,7(11)-diene	7.52 ± 0.01^{a}	0.09 ± 0.01^{b}	0.00 ± 0.00^{b}
27	*cis*-α-Bisabolene	1.24 ± 0.01^{a}	0.53 ± 0.02^{b}	0.38 ± 0.01^{b}
28	Caryophyllene oxide	1.46 ± 0.01^{c}	5.28 ± 0.02^{b}	6.07 ± 0.01^{a}
29	Champacol	1.24 ± 0.01^{a}	0.13 ± 0.01^{b}	0.22 ± 0.00^{b}
30	α-Humulene epoxide II	0.40 ± 0.00^{b}	1.21 ± 0.01^{a}	1.54 ± 0.02^{a}
31	Cubedol	1.42 ± 0.02^{a}	0.23 ± 0.01^{b}	0.29 ± 0.01^{b}

Extracts

The investigations that addressed the biochemical components in the extracts prepared from *Cannabis sativa* L. are less abundant compared to essential oils. However, the compilation of these studies showed that extracts of *Cannabis sativa* L. are rich in biochemical components, including terpenes, flavonoids, and polyphenols (Table 3). Further, these chemicals are significantly variable (qualitatively and quantitatively) depending on the extraction method, solvents, time, used parts, variety, and growing conditions.

Currently, Haddou *et al.* (2023a) evaluated the phytochemicals of diverse *Cannabis sativa* L. seed extracts in samples gathered from Morocco using HPLC-UV/GC-MS. The seeds were collected in the northern areas, in the Rif, Ketama. The maceration procedure was used to get the extracts. Four solvents were used: hexane (EHx), aqueous (EAq), ethanolic (EEt), and dichloromethane extract (EDm). The yield was variable depending on the extract solvent. The maximum yield was recorded in the hexane extract with 11.76%, followed by the dichloromethane extract with 4 %, while the lowest values were recorded in the ethanolic and aqueous extracts with 2.4 and 2 %, respectively. In terms of diversity, 6 chemicals were identified in seed extracts with dominance of Linoleic acid (42.92%), 7-Octadecenoic (22.91%), and Palmitic acid (15.97%). Moreover, 12 chemicals were detected in the dichloromethane extract, with dominance of catechin acid di-hydrate (52.42 %), 6-hydroxyflavon (6.32%), and 8-methoxyflavon (3.37%). Furthermore, 20 chemicals were detected in the ethanolic extract, with the dominance of Naringin (41.92%), Rutin (10.08%), and Hesperidin acid (7.62%). In the aqueous extract, 14 phytochemicals were detected with the dominance of Catechin acid di-hydrate (23.04%), O. dianisidine (4.02%), p-Coumaric

acid (2.25%), and Cinnamic acid (2.22%). Oil of Cannabis seed contained unsaturated fatty acids, corresponding to a search conducted by the Royal Gendarmerie's Laboratory of Research and Technical and Scientific Analyses in Rabat. The study focused on the biomolecules of the seed oil from Al Hoceima: linoleic acid (with 51.3 %) as the predominant constituent, followed by 20.3% for oleic acid, α-linolenic acid (with 15.7%), palmitic acid (with 7.9%), stearic acid (with 2.7%), arachidic acid (with 0.8%), arachidonic acid (with 0.4%), and palmitoleic acid (with 0.2%) (Stambouli *et al.* 2006).

In another research, Haddou *et al.* (2023b) investigated the chemical compounds in seed Extracts from Moroccan *Cannabis sativa* L. collected from the zones of Chefchaouen and Ketama (Northern Morocco). Four solvents were used: ethanolic (EEt), dichloromethane (EDm), hexane (EHx), and aqueous (EAq), and identification of bioactive molecules was done by High-performance liquid chromatography. Results discovered 18 chemical constituents in seed extracts. Further, Quercetin 3-O-β-D-glucoside and Vanillin were the most predominant in the dichloromethane extract (60.15% and 58.60%, respectively). Naringin was the most abundant in the ethanol extract (741.02), while Vanillin was the most abundant in the aqueous extract (652.38). HPLC-ESI-FULL-MS evaluation recorded the existence of significant bioactive compounds in seven extracts of *Cannabis sativa* L. seeds distilled in methanol, acetone, ethanol, water, chloroform, ethyl ether, and hexane (Metouekel *et al.* 2024). In total, 13 chemical molecules were detected in the extracts. The identification of inactive cannabinoids such as CBDA and Dihydrocannabinol is consistent with their established precursory functions in the production of active cannabinoids. Additionally, some polyphenols, including Cannabisin A, B, and C, were identified in the ethanol extract. Other compounds, such as isomers, like Cannabisin B [isomer 1], phosphatidylinositol, and tetrasaccharides hydrate, were also identified in the extracts.

Regarding the quantity, Haddou *et al.* (2023b) evaluated the quantity of polyphenols in different *Cannabis sativa* L. seed extracts from Morocco. Further, seeds were collected in the north, and the extracts were obtained by a maceration procedure. Four solvents were used: ethanol (EEt), dichloromethane (EDm), hexane (EHx), and aqueous extract (EAq). Findings showed that the highest polyphenols were recorded in the aqueous and ethanol extracts (with 29.98±0.56 (for aqueous) and 130±0.08 (for ethanol) mg GAE/g), related to the other solvents: dichloromethane extract (32.03 mg GAE/g), aqueous extract (28 mg GAE/g), and hexane (5.41 mg GAE/g). Haddou *et al.* (2023b) investigated the quantity of flavonoid compounds in seed extracts of *Cannabis sativa* L. from the zones of Ketama and Chefchaouen. Four solvents (extracts) were used: dichloromethane (EDm), hexane (EHx), ethanol (EEt), and aqueous solvent (EAq). The highest flavonoid concentration was obtained by the ethanolic extract (12.82 mg/100g), followed by the dichloromethane (6.47 mg/100g) and the aqueous solvent (5.61 mg/100g). However, the hexane extract had the lowest flavonoid content (4.22 mg/100g). In another study, Aazza (2021) applied the multivariate optimization approach for phenolic biomolecules in extracts from the waste of Moroccan *Cannabis sativa* L. Total phenolic contents were quantified by spectrophotometry. The results demonstrated that the type of extraction solvent had a substantial and strong impact ($p < 0.05$) on the antioxidant function and phenolic components of *Cannabis sativa* L. extracts. Total phenolic content estimates in various extracts made with various solvents varied between 1.90 (min) and 19.07 (max) mg GAE/g DP. The largest phenolic constituents were acquired in the ethanol extract, which was followed by the methanol extract. In contrast, dichloromethane was the least effective solvent for extracting TPC from waste of *Cannabis sativa* L., whereas hexane, water, and while ranked third and fourth, respectively. The simplex centroid design showed that the binary interface between ethanol and water, about the fraction of ethanol (70%) and water (30%), produces the highest TPC yield values. In another paper, total polyphenols and flavonoids in extracts from *Cannabis sativa* L. flowers were sampled in the Ketama region (Ahidar *et al.* 2024b). The extracts were prepared using the Soxhlet procedure using three solvents: ethanol, chloroform, and hexane. Ethanol had the highest yield (29.83%) from the Soxhlet extraction of flower powder from *Cannabis sativa* L. utilizing three different solvents. Chloroform followed by hexane yielded about 26.23% and 14.10 %, respectively. Findings demonstrated that the total polyphenols and flavonoids were significantly variable in extracts depending on the type of solvent. The lowest TPC values were recorded in chloroform (1.802±0.01 mg EAG/g extract), followed by ethanol (1.938±0.01 mg EAG/g extract), while the highest value was recorded in hexane (2.225±0.01 mg EAG/g extract). The lowest value of flavonoids was recorded in chloroform (0.242±0.02 mg EQ/g extract), followed by ethanol (0.267±0.01 mg EQ/g extract), whereas the maximum quantity was recorded in chloroform (0.442±0.01 mg EQ/g extract). Metouekel *et al.* (2024) conducted a chemical screening to evaluate the chemicals from the extracts of *Cannabis sativa* L. seed. Five distinct areas in Morocco's northern province of Al-Hoceima were used to gather the plant. A 24-hour dynamic maceration using seven distinct organic solvents, distilled water, methanol, ethanol, acetone, chloroform, ethyl ether, and hexane in descending order of polarity was part of the extraction process. All extracts underwent a qualitative biochemical screening using HPLC-ESI-FULL-MS. Between 72.470 ± 1.74 and 395.390 ± 104.88 mg EQ/g, the TPC value fluctuated. 395.390 mg EGA/g of ethanol produced a great TPC concentration. Between 14.753 ± 5.81 to 69.809 ± 3.60 mg EQ/g, the TFC value fluctuated. Methanol (69.247 ± 2.32 mg EQ/g) and chloroform (69.809 ± 3.60 mg EQ/g) had the highest values.

Table 3. Quantitative difference of biochemical compounds in the extracts of Moroccan *Cannabis sativa* L.

N	Chemicals (mg/100 g)	Retention time (min)	Aqueous extract (mg/100 g)	Ethanol extract (mg/100 g)	Dichloromethane extract (mg/100 g)
1	Gallic acid	2.4	0.4	0.91	0.61
2	Hesperidin acid	4.07	26.66	0.45	0.45
3	4-Hydroxybenzoic acid	5.89	494.15	421.8	6.22
4	Caffeic acid	6.4	0.21	0.16	0.821
5	Syringic acid	6.72	1.6	2.2	1.29
6	Vanillic acid	6.91	300.24	3.84	4.1
7	Vanillin	7.11	652.38	57.65	60.15
8	p-Coumaric acid	8.15	0.92	0.44	0.24
9	Sinapic acid	8.41	0.41	52.66	18.61
10	Ferulic acid	8.46	0.29	14.22	0.09
11	Naringin	9.39	46.08	741.02	3.02
12	Quercetin 3-O-β-D-glucoside	9.6	0.12	3.45	58.6
13	Rutin	9.64	36.53	0.24	0.29
14	Salicylic acid	11.3	0.1	9.33	0.108
15	Quercetin	12.21	0.13	0.16	0.36
16	Cinnamic acid	12.4	31.59	88.86	0.12
17	Kaempferol	13.72	51.84	1.09	1.11
18	Chalcone	17.39	4.35	4.43	4.5

Traditional uses of *Cannabis sativa* L. by Moroccan populations

Therapeutic uses

Due to its chemical compounds, the Moroccan population adopted *Cannabis sativa* L. in their traditional medicine (BENNIS *et al.* 2023, Elachouri *et al.* 2023). Currently, the therapeutic uses of the plant and its derivatives have been recorded in various ethnobotanical surveys, mainly in Northern areas (Bouarfa *et al.* 2020, Drioua *et al.* 2023). However, traditional uses differ depending on the population, used segments, treated diseases, and administration methods (Figure 5).

Bouarfa *et al.* (2020) conducted an ethnobotany survey to explore the traditional utilizations of *Cannabis sativa* L. in the Taounate region (Northern Morocco). 120 respondents were questioned regarding cannabis use in three locations for this survey: Khlalfa in the north, Tafrant in the southwest, and Oudka in the northwest. A well-structured questionnaire was used to conduct this study in April 2016. The questions included information on cannabis types, their medicinal applications, and use methods. Farmers, users, and herbalists make up most of the respondents. They range in age from seventeen to sixty. They make up 1.67% of women and 98.33% of men, and the distribution of their educational attainment is as follows: 3.33% are academics, 32.50 % are college, 25 % are secondary, 4.17 % are illiterate, and 35 % are primary. The availability of cannabis, its lower cost, and their occasionally diminished trust in modern medicine were the reasons given by 50% of survey participants who said they preferred herbal cannabis treatments over medical care. The other 50% said they preferred medical care. According to the poll, cannabis is used to treat several illnesses, including anxiety, blood sugar, scarring injuries, asthma, dental discomfort, entero-gastric disorders, and stomach irritation. Cannabis resin can be applied straight as a powder, crushed, or heated just a little bit. Cannabis can be consumed as a joint or Sebsi, or inhaled by burning a tiny bit of hashish. This latter is made from a combination of Nicotiana tabacum "Taba Beldia" and cannabis. According to the survey's findings, 52% of participants said cannabis helps with pain, while 48% said it helps with sleeplessness.

Mzali *et al.* (2023) conducted an ethnobotanical survey to explore the medicinal uses of *Cannabis sativa* L., mainly the Beldiya variety in Al Hoceima and Taounate. Over four months, 85 surveys were prepared and given to herbalists, peasants, traditional consultants, and plant consumers. Topics including the sections of the plant utilized, the methods of management, the symptoms, the dose, the rate of use, and the negative outcomes of *Cannabis sativa* L. were covered by the open-ended and closed-ended questions on the questionnaires. All age groups polled reported using cannabis, although the 30-44 (36.5%) and 45-59 (32.9%) age groups had the greatest consumption rates. A noteworthy rate of 16.5% was also found by

the youngest group (15-29). The lowest percentage, 14.1%, was seen in the oldest group (60 years and older), which may be due to cultural, historical, and health-related reasons. According to the findings, cannabis use is common in Morocco across a range of occupational groups. Half of the entire use comes from farmers, with workers coming in second (18.8%) and herbalists in third (8.2%). Furthermore, the left 18% was split uniformly between jobless people and housewives. With 57.6 % of the overall consumption, the flowers and flowering tops were the most commonly used plant components. The second most popular component, which accounted for 29.4% of usage, was their sin, which contains the active chemicals. Less frequently, seeds, leaves, roots, and entire plants were utilized. According to this survey, fumigation was the most popular method of cannabis consumption in both regions, with 57.6 % of participants choosing to breathe in the fume created from torching cannabis. Traditionally, people would wrap it with tobacco or smoke it in a pipe or joint. Oral administration was preferred by 29.4% of respondents to prevent the short-term and long-term influences of cannabis inhalation on the gastric and respiratory systems. In most cases, doses were administered as a measurable tablespoon (11.8%), quantifiable pinch (56.5%), and standardized handful (58.82%). In addition, the cannabis leaves may be applied to treat abdominal worms in kids, relieve combined pain, interrupt diarrhea, inhibit migraines, or lessen prolonged cancer pain by lowering inflammation when taken orally as a tea. Hashish had numerous medicinal benefits and was typically smoked. It is used to improve rest and alertness by delaying the beginning of sleep and extending its duration.

Based on a recent survey conducted in the province of Taounate, cannabis is reportedly utilized to cure eleven distinct illnesses (Balafrej *et al.* 2024). Most of these remedies were suggested by friends, relatives, herbalists, or the patients themselves. 156 responders (50.8%) indicated using cannabis to cure inhalation disorders, according to the results. Children between the ages of 6 and 12 months are susceptible to this poorly understood illness, which is typified by symptoms like head enlargement, diarrhea, and unceasing screaming.

According to the applicants, this illness is usually triggered by convincing magic or smell. Further, 11.1% of participants stated its use for diabetes, followed by injuries (8.1%), pain (7.8%), anxiety (6.8%), for insomnia (5.5%), for cancer (2.9%), for head pains (2.9%), for stomach illnesses (2%), for faintness (1.6%), and for glaucoma (0.7%). The most used plant portions were flowers and leaves with 46.4 %, followed by seeds with a lower percentage. Of the plant components that were used by the informants, 86.5% were dry and 13.5% were fresh. The most popular preparation technique was smoking (83.1%), followed by vegetable oil (with 13.9%) and powder (with only 3.1%). For instance, smoking *Cannabis sativa* L. flowers and/or leaves was recommended as a therapy for inhalation disorders. Inhalation was the most popular method of delivery (83.1 %), followed by topical application of oil (13.9 %) and oral (with only 3.1 %).

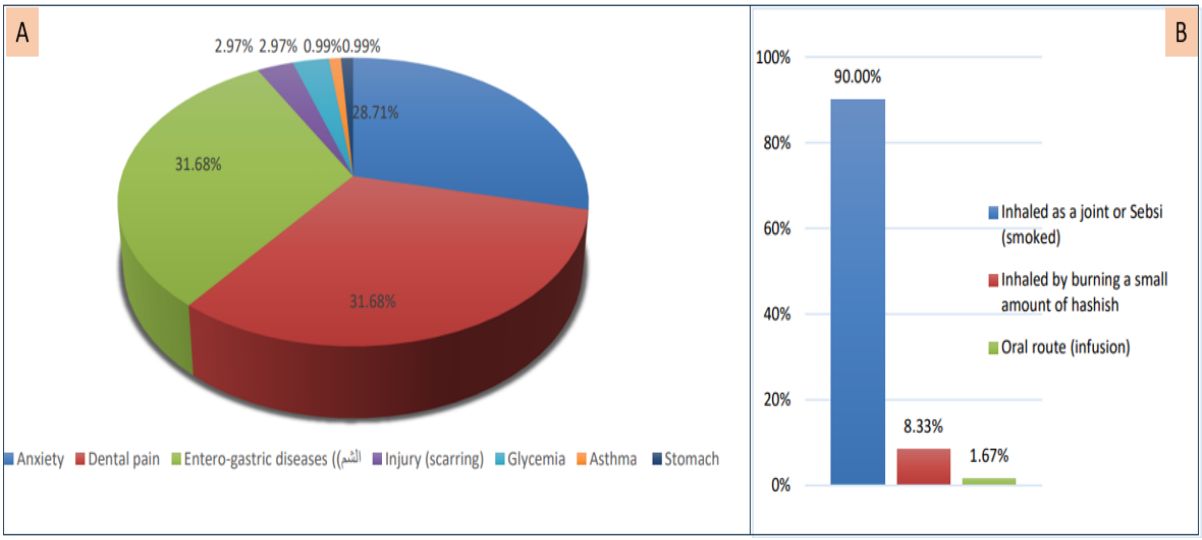


Figure 5. Therapeutic uses of *Cannabis sativa* L. among Moroccan populations

This subsection has discussed a wide range of studies related to the medicinal uses of the plant. However, no study has combined therapeutic efficiency and the biomolecules of the plant. Therefore, future research should address the effect of the quality and quantity of biomolecules on each therapeutic application of the Cannabis derivatives.

Cosmetic use of cannabis

Medicinal plants are widely used in the cosmetic field due to their richness in chemical compounds (Bourgou *et al.* 2021, Desam and Al-Rajab 2021, Sun *et al.* 2022). Similarly, *Cannabis sativa* L. is currently reported among the medicinal plants reported in the Moroccan cosmetic arsenal (Taaifi *et al.* 2021, El-Mernissi *et al.* 2024b). Seeds of *Cannabis sativa* L. are extensively used for the care of hair and skin by women in Al Hoceima and Taounate, where they have an elongated record of conventional usage (Mzali *et al.* 2023). To create herbal treatments with a variety of skin and hair advantages, the seeds are combined with henna paste or olive oil. These advantages include correcting skin color, moisturizing the skin, feeding hair follicles, avoiding hair loss, and promoting hair growth. Oil of Cannabis, which is made from the cold pressing of seeds, has been shown in scientific research to be beneficial for skin and hair health. Fundamental fatty acids, particularly vitamins (carotenoids and tocopherols), alpha-linolenic acid, and antioxidants (phenolic composites and content of flavonoids) are all abundant in Cannabis oil. In this subsection, all detailed studies neglected the cosmetic importance of bioactive molecules recorded in the extracts and their comparison.

Biological activities

In vitro assays

Antioxidant effects

Metouekel *et al.* (2024) estimated the antioxidant potential of extracts from seeds of Moroccan *Cannabis sativa* L. For the various Cannabis extracts from seeds and the controls (quercetin, ascorbic acid, and butylated hydroxytoluene (BHT)), the antioxidant potential was measured using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) (the value was represented as IC_{50} values), ferric-reducing capacity (FRAP) of plasma (estimated as values of EC_{50}), and total antioxidant capability (TAC) (expressed as µg EAA/mg values) assays (Table 4). The results demonstrated that every solvent had intriguing antioxidant power, especially the methanolic and ethanolic solvents, which had IC_{50} values for free radical scavenging activity (DPPH) of 20.28 ± 3.25 and 31.63 ± 0.53 µg/mL, correspondingly. Acetone presented good antioxidant property with values of EC_{50} estimated at 159.5 µg/mL±13.44, followed by chloroform with 165.99 µg/mL±14.69, diethyl ether with 236.63 µg/mL±5.13, and ethanol extracts with 300.61 µg/mL±14.69. The ethanolic extract performed better in the total antioxidant capability (TAC) test with a value estimated at 300.694 µg EAA/mg± 92.68. However, these actions were nearly identical to those observed for quercetin, ascorbic acid, and the artificial antioxidant BHT (Table 4). The presence of newly identified chemicals such as 2,4-DBAL and benzenepropanoic acid in the volatile portion and Cannabisin A, B, and C in the non-volatile portion of the examined seeds may be the main cause of our extracts' antioxidant efficacy. In another paper, the antioxidant actions of *Cannabis sativa* L. extracts from seeds were assessed utilizing DPPH (in vitro assays) and β-carotene (Haddou *et al.* 2023b). According to the results, the ethanol (0.36 mg/mL) and aqueous (0.78 mg/mL) extracts both reduced DPPH by 50%. The ethanolic and hexane extracts of β-carotene showed 36±0.12 and 33±0.14 % antioxidant action, respectively. The dichloromethane came in second with a percentage of 3.52±0.19. Lastly, the lowest activity was displayed by the aqueous extract (1.73% ±0.20). With a proportion of 1.73% ±0.20, the aqueous extract had the lowest activity. Aazza (2021) assessed the in vitro antioxidant qualities of Moroccan *Cannabis sativa* L. waste extracts using multivariate optimization. The antioxidant properties were measured by the DPPH) radical scavenging capacity, and ferric-reducing antioxidant power (FRAP). Four solvents and their combinations were used: ethanol, water, methanol, and hexane. Outcomes showed that DPPH radical scavenging activity varied between 25.03 ± 0.21 and 51.90 ± 0.10%. The highest value was obtained in 50% ethanol and 50% hexane.

Ahidar *et al.* (2024b) evaluated the antioxidant action of flowers of *Cannabis sativa* L. (from Ketama region). The antioxidant activity was measured in three solvents (ethanol, chloroform, and) using DPPH° free radicals. Results showed that *Cannabis sativa* L. repressed the DPPH radical in a dose-dependent manner. Compared to hexane and chloroform extracts, the ethanolic extract exhibited more activity. The most notable is the ethanolic extract, which has an IC_{50} value of 231.39 µg/mL. Hexane and chloroform extracts have IC_{50} values estimated at 376.40 and 769.60 µg/mL, respectively.

Benkirane *et al.* (2022) evaluated the antioxidant activity of seeds from non-industrial hemp varieties harvested from four dissimilar Moroccan regions. Two varieties, Beldia and Critical, collected from Jebha, Tamorot, Ratba, and Galaz (North Morocco), were used to extract seed oils. The antioxidant potential was evaluated by the total antioxidant capacity assay (TAC). Radical scavenging ability was measured utilizing DPPH and ABTS free radicals. Cupric-reducing antioxidant capability (CUPRAC) and FRAP analyses were employed to measure the reducing power. Results showed that antioxidant properties (IC_{50} and EC_{50}) were significantly variable depending on origin and test. TAC varied between 2.62±0.13 and 4.14±0.08 (Ratba) for the Critical variety and between 1.83±0.05 and 3.59±0.05 mg mL-1 (Ratba). DPPH-IC_{50} varied between 1.83±0.05 and 4.28±0.31 mg mL-1 (Ratba) for Beldia and between 1.64±0.00 and 4.37±0.18 mg mL-1 (Ratba) for Critical variety. ABTS varied between 2.45±0.06 and 5.62±0.22 mg mL-1 (Ratba) for Beldia and between 2.45±0.03 and 6.02±0.13 mg mL-1 (Ratba) for

Critical variety. CUPRAC varied between 1.83±0.05 and 7.64±0.27 mg mL-1 (Ratba) for Beldia and between 2.79±0.12 and 9.29±0.25 mg mL-1 (Ratba) for Critical variety. FRAP varied between 2.38±0.02 and 4.37±0.11 mg mL-1 (Ratba) for Beldia and between 2.79±0.12 and 9.29±0.25 mg mL-1 (Ratba) for Critical variety.

Oils of *Cannabis sativa* L. showed significant antioxidant effects in in vitro assays. (Kabdy *et al.* 2024b) evaluated the antioxidant potential of essential oils prepared from samples of *Cannabis sativa* L. in Morocco. In vitro assessments of antioxidant potential were done by the DPPH, the iron reduction, and the β-carotene methods. Results showed that the antioxidant activity was important due to its ability to reduce iron potency with an IC_{50} of 1.49 mg/mL± 0.46, scavenge DPPH with an IC_{50} of 1.16 mg/mL± 0.08, and β-carotene/linoleic acid with an IC_{50} estimated at 1.8 mg/mL± 0.2. (Raoui *et al.* 2024) evaluated the antioxidant potential of seed oil from Moroccan *Cannabis sativa* L. Antioxidant potential was evaluated in vitro using DPPH radical scavenging and FRAP methods. The results exhibited the capacity of seed oils to reduce DPPH radical scavenging and FRAP. El-Mernissi *et al.* (2024b) evaluated the antioxidant potential of *Cannabis sativa* L. EO. The antioxidant potential of volatile composites was tested using DPPH, FRAP, and TAC. The obtained results showed that the essential oil presented high antioxidant aptitude with EC_{50} = 1.74 ± 0.05 for FRAP, IC_{50} = 0.981 ± 0.059 mg/mL for DPPH, and 0.101 ± 0.001 mg AAE/g for TAC. In another paper, Rejdali *et al.* (2024) evaluated the antioxidant properties of the EO of *Cannabis sativa* L. subsp. *sativa* sampled in Al-Hoceima. Cannabis aerial portions were gathered, and extraction was completed by hydrodistillation. The antioxidant potential of EO was estimated by the DPPH technique. According to the data, the observed inhibition percentages range from 33% to 51%, which is considered moderate. Our essential oils' IC_{50} values (4.45 mg/mL) were much greater than that of ascorbic acid (0.16 mg/mL).

Table 4. Antioxidant properties of *Cannabis sativa* L. extracts and oils from Morocco

	Extracts	DPPH	β-carotene	IC_{50} Reduction power	References
Seed	Aqueous extract	0.78 mg/mL	1.73% ± 0.20		(Haddou *et al.* 2023b)
	Ethanol extract	0.36 mg/mL	36% ± 0.12		
	Dichloromethane extract		3.52% ± 0.19		
	Hexane extract	1.5-2 mg/mL	33% ± 0.14		
Flowers	Ethanolic extract			231.39 µg/mL	(Ahidar *et al.* 2024a)
	Hexane extract			376.40 µg/mL	
	Chloroform extract			L	
Leaves	Chloroform extract			741.6-826.33 µg/mL	(Ahidar *et al.* 2024b)
	Ethanolic extract			222.96-256.21 µg/mL	
	Hexane extract			353.67-455.28 µg/mL	
Leaves	Essential oils	1.16 ± 0.08 mg/mL	1.8 ± 0.21 mg/mL	1.49 ± 0.46 mg/mL	(Kabdy *et al.* 2024a)

Antimicrobial effects

Many essays have studied the inhibitory properties of essential oils and extracts of Moroccan *Cannabis sativa* L. and recorded different results (Table 5). For example, Haddou *et al.* (2023b) tested the antimicrobial activity of Moroccan *Cannabis sativa* L. seed extracts. The assessed strains were one Gram-positive *Staphylococcus aureus* (ATCC 6538), one Gram-negative *Escherichia coli* (ATCC 1051.4.2.36), and three fungal strains, *Candida Albicans, Penicillium* sp., and *Aspergillus niger*. Further, the agar well diffusion method (80 µL of the plant extract) was used in the in vitro assay, and the evaluation was done by the inhibition zone. Further, the microdilution approach was used to evaluate minimum bactericidal concentration (MBC), fungicidal concentration (MFC), and inhibitory concentration (MIC). With inhibition zone sizes ranging from 12 to 23 mm, the evaluated plant extracts showed antibacterial qualities against every bacterial and fungal strain that was studied. The hexane extract produced the shortest inhibition diameter (Inhibition zone IZ of only 07 mm) against *Listeria monocytogenes*, whereas the ethanol produced the maximum inhibition diameter (IZ = 23 mm) counter Penicillium sp. With MIC fluctuating from 0.03 (min) to 1.25 (max) mg/mL, the data indicated that all four extracts demonstrated an inhibitory activity against the investigated species of bacteria and fungi. Additionally, the findings showed that the *Cannabis sativa* L. seed extracts exhibited fungicidal and bactericidal capacities, with values extending from 0.03 to 1.25 for MBC and MFC, respectively. The fungus Penicillium sp. was the most resistant strain, but the Gram-positive bacterium Staphylococcus aureus was the greatest

vulnerable strain to all the examined seed extracts. Further, the antimicrobial property of the tested extracts augmented in order: Ethanol (EET)> Dichloromethane (EDm)> Hexane (EHx)> Aqueous (EAq).

El-Mernissi *et al.* (2024b) evaluated the antimicrobial activity of *Cannabis sativa* L. essential oil (CSEO). Aerial parts were collected from the Tafrant (Taounate, Morocco). Hydro-distillation was used to remove the plant's air-dried inflorescences and leaves. Four microbial strains (*Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli)* and four fungal species (*Aspergillus flavus, Fusarium proliferatum, Aspergillus niger,* and *Candida albicans*) were used to test the antimicrobial effectiveness of CSEO. The disk diffusion procedure was utilized to evaluate the antibacterial potential. The microdilution method was employed to verify the minimum inhibitory concentration (MIC). The essential oil presented high antibacterial potential against *E. coli* (11.33 mm), followed by *K. pneumonia* (9 mm), and *P. aeruginosa* (9.34 mm). further, with MICs fluctuating from 0.0052 to 0.0208 mg/CSEO proved antifungal property against *C. albicans* and *F. proliferatum*, with 18.66 mm± 0.88, 41.89% ± 3.60, and MICs of 0.39 and 0.013 mg/mL, correspondingly. In another study, Metouekel *et al.* (2024) measured the antibacterial and antifungal action of seven extracts from seeds of Moroccan *Cannabis sativa* L. ("*Cannabis sativa*, subsp. indica" and "*Cannabis sativa* subsp. sativa"). To filter and choose only the active extracts, the disc diffusion approach was utilized to qualitatively assess the antibacterial activity of seven solvents. All used samples were tested at various concentrations, fluctuating from 5 (min) to 100 (max) mg/mL against *Pseudomonas aeruginosa, Listeria monocytogenes, Bacillus cereus, Staphylococcus aureus, Escherichia coli,* and *Enterococcus faecalis*. A spectrophotometer (BioTek, Epoch™ 2 Microplate Spectrophotometer, Santa Clara, CA, USA) was then used to follow the extracts' activity kinetics and conduct a quantitative analysis utilizing microdilutions on a 96-well microplate. Unfortunately, the examined bacterial and fungal strains were not inhibited by any of the seven Cannabis extracts from seeds. It was surprising to discover that these extracts had a stimulatory effect on bacterial growth in the 24-hour spectrophotometer monitoring period. This surprising finding raises the possibility that the chemicals in the cannabis seed extracts encourage rather than prevent bacterial development. To comprehend the processes underlying this stimulatory impact and to investigate the possible ramifications, more research is required. Only one study has examined the antiviral properties of seven different *Cannabis sativa* L. extracts. The findings of the in vitro test against SARS-CoV-2 demonstrated that none of the *Cannabis sativa* L. extracts had any discernible antiviral properties.

Anti-inflammatory effects

Haddou *et al.* (2023b) evaluated the anti-inflammatory influences of *Cannabis sativa* L. seed extracts. The anti-inflammatory influence of four extracts was investigated and calculated by applying the in vitro process of stabilizing the RBC membrane, whose lysis was caused by either hypotonicity or heat. The various extracts of *Cannabis sativa* L. seeds grown in Morocco demonstrated a significant dose-dependent inhibitory impact versus erythrocyte hemolysis brought on by hypotonicity and heat, which is likely due to the extracts' capacity to successfully shield rat red blood cell membranes. Bioactive compounds like naringin and hesperidin, which had the maximum affinity estimates for the two proteins under study, BSA and LXO, respectively, are responsible for this action. This activity is directly related to the chemical compounds contained in the extracts of the plant. Therefore, new studies are required to explore the anti-inflammatory effect of each compound or their synergetic interactions.

Toxicity evaluation

Only one study has addressed the toxicity of Moroccan *Cannabis sativa* L. Metouekel *et al.* (2024) evaluated the cytotoxicity of Moroccan *Cannabis sativa* L. seed extracts. Cytotoxicity was tested on Monkey kidney cells (Vero). Further, to conduct bioassays, kidney cells were planted in 96-well plates at a 3 × 105 concentration of viable cells/mL (3 × 104 cells/well). Additionally, extract dilutions fluctuating between 1.5 to 200 µg/mL were employed. Toxicity against cells was assessed by microscopic analysis of their morphology during a 72-hour incubation period. The 50 % cytotoxic concentration (CC_{50}) was defined as the dose at which the sum of cells was lowered to 50 % of the controls. The data obtained indicate that the seed extracts under investigation do not cause Vero cells to become cytotoxic. The majority of solvents (acetone, diethyl ether, ethanol, chloroform, hexane, and methanol) showed minimal cytotoxicity, with cytotoxic effects mostly occurring at doses of 200 µg/mL or above. Although the aqueous extract's CC_{50} concentration is lower at 25 µg/mL, it still exhibits notable cytotoxicity. However, particular emphasis should be paid to the aqueous extract, which calls for more research on its toxicity and safety, particularly if it is going to be used in formulations for nutrition and cosmetics. The studies addressing the toxicity of Cannabis are very limited in Morocco; therefore, this avenue is very prominent for researchers.

Table 5. Anti-microbial and antifungal activity (inhibition zone expressed in mm) of EO and extracts of *Cannabis sativa* L. growing in Morocco with the agar well diffusion method.

Plant material	Type of extract	Solvents	Bacteria									References
			E. coli	***P. aeruginosa***	***S. aureus***	***L. monocytogenes***	***M. luteus***	***B. subtilis***	***K. pneumoniae***			
		Aqueous extract	12±0.01	10±0.02	12±0.02	08±0.01						(Haddou *et al.* 2023b)
Seeds	Extracts	Dichloromethane extract	14±0.01	10.50±0.01	16±0.01	08±0.02						
		Ethanolic extract	15±0.02	09.2±0.02	18±0.02	7.90±0.02						
		Hexane extract	12.50±0.01	11±0.02	12.50±0.01	07±0.02						
Aerial parts		Essential oils	11.1 ± 0.3	12.6 ± 0.2	13.0 ± 0.2		11.4 ± 0.1	13.0 ± 0.3	8.5 ± 0.2			(Nafis *et al.* 2019)
air-dried inflorescences and leaves		Essential oils	0	15 ± 0.00a	28 ± 0.00				0			(El-Mernissi *et al.* 2024b)
			Fungi (mm)									
			C. albicans	***C. glabrata***	***C. krusei***	***C. parapsilosis***	***A. niger***	***A. flavus***	***F. proliferatum***	***Penicilliu m sp***	***Rhodotorul a sp***	(Nafis *et al.* 2019)
			12.0 ± 0.7	13.0 ± 0.2	12.5 ± 0.2	15.0 ± 0.3	47.67 ± 1.59%	43.67 ± 1.53%	59.17 ± 0.76%			(El-Mernissi *et al.* 2024b)
			41.33 ± 1.1									
Seeds	Extracts	Aqueous extract	13±0.01				13.00±0.01			12±0.02	7±0.01	(Haddou *et al.* 2023b)
		Dichloromethane extract	16±0.02				14.00±0.01			13±0.01	7±0.02	
		Ethanolic extract	16±0.02				18.50±0.01			23±0.02	9.50±0.01	
		Hexane extract	12.50±0.01				14.20±0.02			10±0.01	9.50±0.02	

In vivo assays

Antioxidant effects

In Morocco, only one paper has addressed the in vivo antioxidant potentials of *Cannabis sativa* L. Currently, Kabdy *et al.* (2024b) evaluated the in vivo antioxidant capacities of Moroccan *Cannabis sativa* essential oil to impulsive chronic mild stress in Mice. The aerial fragments of *Cannabis sativa* were harvested in the Rif zone (Morocco), and essential oils were obtained from the leaves via hydrodistillation based on the Clevenger apparatus. Antioxidant properties were estimated by lipid peroxidation, superoxide dismutase activity (SOD), reduced glutathione (GSH), and catalase activity (CAT). Adult male Swiss albino mice weighing 24-28 g were used in the studies reported in this article. In addition to a positive control test with UCMS treated with 10 mg/kg of fluoxetine, the tested animals were arbitrarily allotted to six groups and administered essential oils at successive doses of 2.5, 5, and 10 mg/kg. When comparing stressed and unstressed mice, the quantity of MDA in brain homogenates indicated a substantial increase in peroxidation of brain lipids ($p < 0.001$). The substantial drop in TBARS values demonstrated that EO treatment at various dosages successfully decreased oxidative stress. Furthermore, the findings imply that fluoxetine and the maximum dosage of EO (10 mg/kg) were equally effective. In the brains of harassed mice, treatment with *Cannabis sativa* L. EO at different doses successfully reversed the alterations in antioxidant markers, leading to higher levels of diminished glutathione and refurbishment of catalase and SOD activity. Remarkably, the maximum dosage of *Cannabis sativa* L. EO (10 mg/kg) restored antioxidant resistance in the brain of stressed mice with comparable effectiveness to fluoxetine. Despite the discussed data, further studies are needed to explore the antioxidant potential of chemical compounds recorded in the extracts of Cannabis.

Anti-inflammatory effects

Haddou *et al.* (2023b) evaluated the anti-inflammatory effects of *Cannabis sativa* L. seed extracts. Four extracts were tested using the denaturation assay of Bovine Serum Albumin (BSA). The findings revealed that the different extracts of *Cannabis sativa* L., including the dichloromethane extract equal to IC_{50}=93.09 and 107.73 mg/mL in ethanolic and aqueous extract, with IC_{50} equal to 139.93 mg/mL, showed dose-dependent inhibitory action against the BSA proteins denaturation. However, these extracts were relatively low when compared to the reference anti-inflammatory medicine (IC_{50} =62.19 µg/mL). Several *Cannabis sativa* L. seed extracts under investigation have shown a strong ability to prevent erythrocyte hemolysis brought on by heat or hypotonicity. The outcomes demonstrate that the different extracts suppress the hemolysis of the produced red blood cells in a dose-dependent manner. In contrast to ibuprofen (IC_{50} =59.50), the different dichloromethane, ethanolic, and aqueous extracts reduced heat-induced hemolysis with IC_{50}s of 75.55, 80.81, and 89.30µg/mL, correspondingly. In contrast to Ibuprofen (IC_{50} =55.75), the various dichloromethane, ethanolic, and aqueous extracts reduced the erythrocyte hemolysis caused by hypotonicity, with IC_{50} values of 73.54, 66.26, and 107.32 µg/mL, correspondingly. Kabdy *et al.* (2024b) evaluated the anti-inflammatory capacities of *Cannabis sativa* L. essential oil in a mammal model. Three well-known tests for inducing inflammation were employed in the study: carrageenan-induced paw inflammation, xylene-induced ear swelling, and Freund's complete adjuvant (CFA)-induced paw inflammation. While carrageenan caused acute inflammatory reactions in the paw through edema and immune-cell recruitment, xylene caused acute inflammation in the ear. In the xylene-induced ear-swelling test, the results showed that treatment with *Cannabis sativa* L. EO dramatically decreased ear weight, suggesting possible suppression of neutrophil formation. EO decreased paw volume in the carrageenan-induced paw inflammation test, indicating disruption of leukocyte migration and edema production. CSEO restored body weight, decreased C-reactive protein levels, and decreased contralateral paw volume in the CFA-induced paw inflammation test.

Toxicity

When doing in-depth research on possible pharmaceutical compounds, toxicity analysis is essential. It determines the maximum dosages for treatments with no negative side effects, in addition to assessing the drug's safety. Due to its large use among Moroccan populations, many authors have addressed the toxicity and cytotoxicity of *Cannabis sativa* L. For example, El-Mernissi *et al.* (2024) investigated the acute toxicity of Moroccan *Cannabis sativa* L. essential oil. Using the OECD 423 criteria, the acute toxicity was investigated in mice. The main reason oral delivery was used was that there was no established inhalation protocol made especially for mice. No deaths or toxicity symptoms (diarrhea, sedation, urination, skin change, altered food and water consumption, or altered locomotor activity) were seen when EO was administered orally at a dosage of 2 g/kg. Thus, it may be concluded that when administered acutely, CSEO is essentially non-toxic. This result suggests that the lethal dose 50 (LD_{50}) may exceed 2 g/kg. In another study, Kabdy *et al.* (2024b) evaluated the toxicology profile of Moroccan *Cannabis sativa* L. essential oil. The toxicity assessment of EO was conducted by the guidelines outlined by the Organization for Economic Cooperation and Development (OECD) for chemical testing. In this experiment, six mice for a total of 30 mice were assigned to each group and were administered intraperitoneal injections of increasing doses of CSEO (15, 30, 60, 120 mg/kg, i.p.), which were diluted in 0.3 mL of a vehicle solution. Blood samples were collected on day 14 to study possible changes in Aspartate aminotransferase (AST) and Alanine transaminase (ALT). Findings showed that all

the surviving animals were sacrificed, and their livers, kidneys, and spleens, the organs affected by acute toxicity, were examined for any microscopic alterations. The obtained results exhibited that the 60 and 120 mg/kg dosages of CSEO administered intraperitoneally caused neurobehavioral toxicities such as piloerection, abdominal constriction, locomotor disturbances, hypersalivation, lethargy, and eyelid closure. Furthermore, only high doses caused death, which occurred within 8-10 hours;; the calculated lethal dose 50 for CSEO was found to be 42.46 mg/kg. The management of CSEO at doses of 15 and 30 mg/kg did not result in substantial changes in the concentration of biochemical markers. However, at higher doses of CSEO (60 and 120 mg/kg), a substantial improvement in the levels of all researched parameters was observed, suggesting a possible impairment of hepatocyte or renal function. Histopathological assessment of the liver and kidneys showed no significant changes at the lower doses of CSEO but revealed significant damage at the higher doses. The organs removed (liver, spleen, and kidneys) from the 15 and 30 mg/kg groups showed no histological damage. In contrast, at 60 and 120 mg/kg, CSEO caused minor liver damage, such as mild vascular congestion.

Balafrej *et al.* (2023) evaluated the toxicology profile of *Cannabis sativa* L. co-products in mice. In this research, the preparation of extracts was done by three methods: Maceration, Sonication, and Decoction. A single dosage of each extract was used in the acute toxicity test to ascertain the fatal dose (LD*50*), the type of any immediate effects, and the cause-and-effect connection. The Organization for Economic Cooperation and Development's chemical testing criteria, which were revised on June 30, 2022, after being established on October 3, 2008, served as the foundation for our protocol (OECD, 2022). According to these standards, a dose of 2.000 mg kg-1 of the extract is recommended for the acute toxicity assessment. In treated groups, the highest dose of 2.000 mg kg-1 of *Cannabis sativa* L. extracts given by gavage resulted in specific clinical indicators of toxicity. It should be mentioned that all symptoms appeared during the first four hours after the extract was administered and for the duration of the 14-day experiment. They were assessed in both treated and untreated groups. Both males and females showed some clinical toxicity indications during the first two hours after the extract was administered. Except for male mice given maceration extract, we observed a reduction in spontaneous movement, isolation, and somnolence in nearly all treated mice. After being given maceration extract, mice of both sexes developed bradycardia. Furthermore, several mice treated with sonication and decoction extracts showed tremors and tachycardia. During the first three days after the decoction extract was administered, diarrhea, polyuria, and a change in the color of the stools were seen; however, these symptoms vanished after that. Males and females treated with the three extracts under investigation did not die throughout the experiment, indicating that the LD_{50} might be higher than 2.000 mg kg-1 body weight. Additionally, there were no appreciable abnormalities between the liver and kidneys of mice treated with the three *Cannabis sativa* L. extracts and animals that were not treated when viewed under a microscope. All groups' livers and kidneys displayed no obvious abnormalities to the unaided eye. Currently, Raoui *et al.* (2024) assessed the toxicological effects of Moroccan *Cannabis sativa* L. seed oil. Three different animal models were used to study acute toxicity: the hot plate test, the formalin test, and the writhing test. The findings showed that in both formalin test phases, there was a significant increase in heat stimulus latency, a decrease in the number of writhes brought on by acetic acid, and a decrease in licking duration.

Other biological activities

Mahou *et al.* (2023) evaluated the vasorelaxant property of Moroccan *Cannabis sativa* L. threshing residues. Further, *Cannabis sativa* L. was gathered in Tafrante, then the inflorescences and leaves of dried flailing residues were serially extracted employing a Soxhlet extractor with 300 mL of water, dichloromethane, ethanol, hexane, and ethyl acetate. Vascular relaxant effect was tested on Wistar rats (250-350 g). Nitric oxide vascular announcement was restrained by electron paramagnetic resonance (EPR) utilizing a spin trap in rings of aortic rat, and vasodilation effects in phenylephrine precontracted secluded rat mesenteric arterial beds were examined in the presence of indomethacin (inhibitor of cyclooxygenase), L-NAME (inhibitor of nitric oxide synthase), potassium channel blockers (specifically tetraetylamonium, barium chloride, and glibenclamide), and atropine. Findings showed that all extracts of *Cannabis sativa* L. prompted dose-dependent vasorelaxation on the mesenteric vascular bed. The decrease in perfusion pressure brought on by EFCS was lessened when the preparations were incubated with L-NAME, potassium channel blockers, or ODQ (a soluble guanylyl cyclase inhibitor). The vasorelaxant effect of the EFCS was eliminated by endothelial denudation or atropine, indicating the participation of endothelium relaxing factors and muscarinic receptors. Similar to acetylcholine, the extract caused nitric oxide to be released in aortic rings, indicating that EFCS affects the conductance arteries and the muscarinic receptor. Raoui *et al.* (2024) confirmed antinociceptive effects in Moroccan *Cannabis sativa* L. seed oil. Three different animal models, the writhing test, the formalin test, and the hot plate test, were used to investigate antinociceptive activity.

In-silico

Anti-microbial activities

As part of the virtual screening of huge datasets, molecular docking techniques are currently a popular strategy for choosing potent compounds. Metouekel *et al.* (2024) used molecular docking to evaluate the anti-microbial potential of seven extracts from Moroccan *Cannabis sativa* L. seeds. The discovered biochemicals from the volatile part of Cannabis seeds were subjected to docking analyses against predetermined targets in this work. The scores of dockings were employed to assess the phytochemicals' binding affinities for the proteins. With glide scores of -5.928 and -5.886 kcal/mol, respectively, 2,4-dimethylbenzaldehyde, followed by 2,4-di-tert-butylphenol, showed the greatest attractions for the NADPH oxidase active sites in terms of their antioxidant activity. Additionally, beta-ketoacyl-[acyl carrier protein] synthase from *Staphylococcus aureus* and active sites of nucleoside diphosphate kinase from *Escherichia coli* demonstrated considerable antibacterial effectiveness against 2,4-dimethylbenzaldehyde, with a glide score of -5.747 and -6.684 kcal/mol, respectively. With glide scores of -9.709, -9.681, and -9.083 kcal/mol, respectively, the non-volatile portion of *Cannabis sativa* L. seeds demonstrated significant action of Cannabisin A, B, and C against NADPH oxidase, demonstrating a substantial repressive effect. These results imply that these molecules function as strong NADPH inhibitors, suggesting that they have the potential to be strong antioxidants. Cannabisin A showed the best activity against S. aureus in antibacterial tests, while Cannabielsoic acid A showed powerful inhibition versus E. coli with a glide score of -7.241 kcal/mol. Additionally, Cannabisin B and Cannabinolic acid showed notable efficacy in antifungal assessments versus *Candida albicans* and *Aspergillus niger*, with glide scores of −4.809 and −8.66 kcal/mol, respectively. Moreover, 2,4-dimethylbenzaldehyde formed two hydrogen bonds with residues THR 300 and THR 302 in the active site of *E. coli's* beta-ketoacyl-[acyl carrier protein] synthase and one hydrogen bond with residue ALA 300 in the active site of NADPH oxidase. Furthermore, the ASN 112 residue in the S aureus nucleoside diphosphate kinase active site formed a hydrogen bond with. Similarly, in the active sites of *Candida albicans'* sterol 14-alpha demethylase (CYP51), 2,4-di-tert-butylphenol formed a Pi-Pi stacking bond with residue TYR118 and a lone hydrogen bond with residue SER 378. Five hydrogen bonds were formed with residues LYS 134, THR 112, GLU 163, and PHE 425, as well as a single Pi-Pi stacking bond with TYR 159, according to the 2D and 3D visual depictions of the interaction between Cannabisin B and the NADPH oxidase active site. Cannabielsoic acid. In the beta-ketoacyl-[acyl carrier protein] synthase active site of E. coli, A showed dual hydrogen bonding with residues VAL 304 and HIE 333. Additionally, five hydrogen bonds were formed with residues LYS 55, GLU 95, GLU 51, ASN 92, and GLY 116, as well as one Pi-Pi stacking bond with HIE 52 and a Pi-cation bond with LYS 55 during the interaction between Cannabisin A and the *Staphylococcus aureus* nucleoside diphosphate kinase active site. Furthermore, in the active site of sterol 14-alpha demethylase (CYP51) from C. albicans, cannabinolic acid formed two Pi-Pi stacking bonds with residues TYR 118 and PHE 228 and two hydrogen bonds with residues SER 378 and MET 508. Finally, four hydrogen bonds were formed with residues GLU 160, SER 233, GLY 234, and GLU 267 because of the interaction between tetrasaccharide hydrate and the active site of A. niger's beta-1,4-endoglucanase. In conclusion, the antimicrobial activity of Cannabis extracts is the most studied, and the experiments addressed the majority of existing aspects from the species to the molecular levels.

Anti-inflammatory activity

Haddou *et al.* (2023b) investigated the anti-inflammatory effects of Moroccan *Cannabis sativa* L. seed extracts. Bioinformatics outlines were used to evaluate the extracts' anti-inflammatory activity outcomes, which helped to clarify their atomistic action processes. Molecular tagging against receptors that have been well documented in the literature, such as lipooxygenase (LXO) (Pdbid. 3V03, 4nre, and Bovine Serum Albumin (BSA) have been employed for this purpose. Compounds Hesperidin (5) (PCID: 10621), Naringin (8) (PCID: 442428), and Rutin (15) (PCID: 5280805) demonstrated the highest affinities towards the active sites of BSA and LXO, surpassing the co-crystallized ligands used in this study by -3.3 and -5 Kcal/mol, respectively, according to the results of molecular docking of phytochemicals against these two compounds. For Hesperidin, Naringin, and Rutin, the predicted binding energies with the BSA active site were -9.1 Kcal/mol, -9.5 Kcal/mol, and -8.7 Kcal/mol, respectively. Hesperidin, Naringin, and Rutin were shown to have binding energies of -10.4 Kcal/mol, -9.6 Kcal/mol, and -9.3 Kcal/mol for LXO, respectively. Typically, the main interactions that formed the molecule-protein complexes were alkyl bonds, carbon-hydrogen bonds, and ordinary hydrogen bonds. Using solid interactions primarily of the conventional hydrogen bond type (LEU112, ARG144, LEU115, ARG185, and LEU189), carbon hydrogen bonds (HIS145), LYS114, Pi-Akyl (VAL188 and PRO110), and PiSigma (ILE141), Naringin revealed the highest inhibition power towards the BSA's active site. The amino acids that interact with naringin, including LEU115, LEU112, ARG144, LEU189, ARG185, HIS145, LYS114, and PRO110, are roughly recruited by the two substances hesperidin and rutin. Hespiridin, however, demonstrated the strongest affinity for the LXO active site, resulting in interactions of the Conventional Hydrogen Bonds type (GLU141, TRP109, ARG145, His394, ASN173, and ARG407), Alkyl (Val117), and one unfavorable donor with GLN137. The same amino acids that interact with the co-crystallized ligand, such as ASN173, His394, and Arg407, have been roughly recruited by hespiridin. Further,

His394, ASN173, Arg145, and ARG407 are common amino acids that are recruited with Hespiridin by Rutin and Narinjin, which demonstrated affinity values of -9.3 and -9.6 kcal/mol, respectively.

Phytochemical substances isolated from *Cannabis sativa* L. seeds have been molecularly linked to two proteins that have been extensively reported in scientific literature: lipooxygenase and Bovine Serum Albumin (BSA). The findings unequivocally demonstrate the existence of bioactive substances with strong inhibitory effects on the cressing proteins' active regions. Among all the phytochemical substances examined, rutin, hesperidin, and naringin exhibited the most significant inhibitory actions, with their values of the most failed liaison energies significantly surpassing those of co-crystallized ligands. The primary interactions that were reported in the formation of Ligand-Protein complexes with these three phytocomposed substances were hydrogen, hydrophobic, and electrostatic bonds. Comparing the trained complexes to the Co-Crystallized Ligands references may help to explain their high stability. These findings allow us to conclude the consistency of the anti-inflammatory activity studies' in vitro and in silico outcomes. Additionally, they show the presence of chemicals from natural sources that are promoters and can effectively block BSA and LXO.

Anti-parasitic effects

The anti-parasitic activity of *Cannabis sativa* L. was tested against dermal Leishmaniasis triggered by *Leishmania major*, *L. infantum*, and *L. tropica* (Assouab *et al.* 2022). This study's goal was to use molecular docking to evaluate the phytochemical components of *Cannabis sativa* L. (terpenoids and cannabinoids) against the enzymes Leishmania and human arginase. Delta-9-tetrahydrocannabinol (delta-9-THC), caryophyllene oxide, cannabidiol (CBD), α-pinene, beta-caryophyllene, myrcene, α-humulene, and limonene were the primary constituents of *Cannabis sativa* L. that were utilized in this investigation. Since Glucantime is the first-line treatment for cutaneous leishmaniasis in Morocco, it was chosen as our reference medication. human arginase (h-Arg) (assent ID: 3kv2) and *Leishmania mexicana* arginase (LmArg) (assent ID: 4ITY) crystal structures were obtained from the RCSB Protein Data Bank in PDB format (https://www.rcsb.org, accessed on 13 August 2022). The conformations of the major phytochemical compounds were analyzed through a molecular docking study using Auto Dock tools (ADT) (version 1.5.7). Among the tested ligands, the best binding scores were −6.02, −5.79, −5.88, and −5.55 kcal/mol, respectively, when interacting with LmAr. Although limonene had a score of −4.49 kcal/mol, the last ligand-protein affinity was in fact attributed to Glucantime at −4.30 kcal/mol. These results related to inhibition constants ranging from 38.63 µM for delta-9-THC to 702.95 µM for Glucantime.

Molecular-Interaction Analysis for *Cannabis sativa* L. components and human arginase: The docking results also showed that delta-9-THC, through a pi-cation interaction with HIS 141, a pi-pi stacked interaction with HIS 126, and van der Waals forces with 16 other amino acids, fit in the human arginase active site with a binding energy of −6.35 kcal/mol and an inhibition constant (Ki) of 21.97 µM. Cannabidiol's (CBD) docked structure showed an inhibition constant of 78.86 µM and a negative binding energy of −5.60 kcal/mol. The compiled data demonstrated the capacity of Cannabis extracts to inhibit the parasitic agents. However, no study has addressed the use of active molecules in single and synergistic forms against parasitic agents. Equally, further research is needed to explore the action mechanisms of the plant derivatives against larvae and adults of parasites.

Environmental benefits

Currently, few papers have addressed the environmental uses of Moroccan *Cannabis sativa* L. and its derivatives. The most important uses were phytoremediation and insulation of temperature. El Mansouri *et al.* (2022) evaluated the efficiency of activated Carbon of Waste *Cannabis sativa* L. (WHAC grown in Northern Morocco to remove Eriochrome Black T Dye. Batch experiments were used to investigate the impact of key adsorption parameters (pH, dosage, contact time, and initial concentration) on the adsorption of EBT onto WHAC; new mathematical models were used to optimize some of these parameters. Several isotherm models (Temkin, Freundlich, Langmuir, and Dubinin-Radushkevich) were applied to equilibrium data to assess the adsorption behavior of EBT on the surfaces of WHAC. The results indicated that at pH = 7, an adsorbent dose of 10-70 mg, a contact time of 3 h, and an initial dye concentration of 10 mg L−1, the maximum removal of EBT by WHAC was 44-62.08%. The maximum adsorption capacities were 14.025 mg. g−1 determined using the Langmuir model, and the maximum removal efficiency was at 70 mg, which is equivalent to 62.08% for the WHAC. In a different study, composite materials based on cannabis demonstrated a noteworthy ability to eliminate 33 different kinds of micropollutants from wastewater (ElAbbadi *et al.* 2024). The composite materials based on cannabis were found to be effective in eliminating all suspended particles. For heavy metals, powdered activated carbon achieved a high removal percentage of 90%, although for most other substances, it ranged between 60% and 80%. Moreover, Zine *et al.* (2023) examined the potential for using Moroccan hemp shiv and epoxy to create novel local bio-composites by valorizing hemp leftovers. To achieve this, several samples were made for two sizes and densities of hemp shiv: fibered shiv (FS) and crushed shiv (CS). The findings showed

that as density increased, thermal conductivity increased, and thermal diffusivity decreased. For the most researched samples, the composites' thermal conductivity is still less than 0.1 W/mK. The samples' acoustic absorption coefficients range from 0.2 to 0.59 for crushed shiv composites (CSC) at frequencies between 578 and 1396 Hz and from 0.2 to 0.73 for fibered shiv composites (FSC) at frequencies between 662 and 1396 Hz. The sound absorption coefficient is significantly influenced by density. The acoustic absorption curve moves toward the low frequencies as density increases. Additionally, sound absorption in the middle frequency range (300-600 Hz) is improved by lowering the particle size. To produce these novel composites that can be employed as acoustic and thermal insulators, the results obtained are good. Additionally, it provided the greatest way to manage hemp waste. Similarly, Charai *et al.* (2021) assessed the non-industrial Moroccan *Cannabis sativa* L. fibres' capacity to insulate against heat in green plaster-based construction materials. To assess the impact of fiber content on the thermal insulation quality of plaster and the variation of the thermal capacity of developed bio-composites, one hundred local fibro-plasterboards were created by incorporating Moroccan Hemp Fibers (MHFs) into local plaster at various weight replacement ratios: 0, 2, 4, and 6%. The results of the experiments show how Moroccan hemp stems can enhance plaster's heat transport characteristics and increase its thermal efficiency. When compared to plaster without fibres, the addition of 6% of MHFs by weight to the plaster matrix significantly decreased density, improved thermal insulation, and slowed the rate of heat transfer by 24.5%, 31.3%, and 8.5%, respectively. The greatest results in terms of thermal heat capacity were obtained when MHFs were added at a weight of 2%. Lastly, annual simulations using Energy Plus for a residential building situated in two distinct semi-arid climates of Morocco were conducted to assess the energy performance of produced plasterboards at the building scale. According to the findings, structures with 40 mm Moroccan hemp plasterboard (MHP) have a significant chance of lowering building energy consumption and offering passive thermal comfort to residents, particularly in the summer. Consequently, non-industrial hemp is a promising option for creating regional lightweight, low-impact (LLL) building materials that enhance building energy efficiency. In this section, available data are limited to a few pollutants. This doesn't reflect the environmental potential of the plant. Therefore, new experiments are recommended to discover other features, such as the use of Cannabis extracts and bioactive molecules in the manufacture of biopesticides that could replace the chemical and toxic matters of synthetic pesticides.

Conclusion

In this study, data and documents related to *Cannabis sativa* L. in Morocco were compiled. This review addresses the history, scientific research, geographical distribution, extraction procedures, diversity of phytochemicals, traditional uses, and experimental assays (*in-vivo*, *in-vitro*, and *in-silico* experiences) of *Cannabis sativa* L. in Morocco. The papers were searched for a period from 1912 to 2024 using French, English, and Spanish.

In total, 217 documents were recorded. These papers were dominated by articles, theses, and reports, compared to books, conference papers, and abstracts. The documents were mainly in English and French. The number of documents was significantly higher in the period from 2000 to 2024, followed by 1956 to 2000, compared to 1912-1956. These documents demonstrated that six varieties, including 'Khardala', 'Critical', 'Amnésia', 'Beldia', 'Gorilla', and 'Pakistana', are cultivated in Morocco, mainly in Northern provinces such as Chefchaouen, Taounate, Larache, Al Hoceima, and Tetouan.

The phytochemicals of Moroccan *Cannabis sativa* L. were diverse in quantity and quality. In total, 32 and 24 molecules belonging to polyphenols, flavonoids, terpenes, and cannabinoids were identified in essential oils and extracts, respectively. The essential oils are mainly extracted by hydrodistillation from aerial parts, while extracts were isolated by maceration, sonification, and decoction from seeds and aerial parts. Bioactive molecules belong to and are variable depending on varieties, used organs, extraction approaches, and growing areas. Due to their biochemicals, varieties of species are used by Northern populations to manage a wide range of diseases and cosmetic purposes, including anxiety, dental pain, enterogastric diseases, blood sugar, scarring injury, asthma, and stomach irritation. Further, *in-vivo*, *in-vitro*, and *in-silico* assays confirmed the biological activities of *Cannabis sativa* L., mainly anti-microbial, anti-parasitic, anti-inflammatory, and anti-cancer effects.

This study is the first to review the topics related to *Cannabis sativa* L. in Morocco and offer new and compiled data in North Africa and the Mediterranean basin. However, more investigations are needed to explore sustainable approaches for the cultivation of *Cannabis sativa* L., which is suggested to help in the mitigation of climate change impacts and drought. However, it is crucial to explore how abiotic and biotic stress impacts the quality and quantity of phytochemicals and the biological activities of *Cannabis sativa* L.

Declarations

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Author's contribution: M.E.O., M.A., A.F.L. and M.O. designed the paper and conceived the idea. M.E.O., M.O, Y.M., S.G., A.F.L. and L.B.A was responsible for writing and editing the manuscript, and M.E.O., L.B.A., M.A. and A.F.L provided technical support. All authors discussed and revised the manuscript.
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