Review Article

Antimicrobial Efficacy of *Cannabis sativa L.* (Bhang): A Comprehensive Review

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ABSTRACT

Therapeutic products derived from plants are gaining popularity since long time and this is primarily due to their ability to overcome the side effects of allopathic forms of medicine. Besides this, multi-drug resistance by pathogens to currently used antibiotics triggered the search for identifying natural antimicrobial products that are effective in combating infections. Considering this, we have focused on the various investigations related to antimicrobial properties of the well-known wildly growing plant i.e., *Cannabis sativa*. *Cannabis sativa* is an annual herbaceous plant belonging to the family Cannabaceae. It is known by various names worldwide as Marijuana, Bhang, Dogga, Hashish, Grifa etc. The plant and its preparations have many medicinal properties including antimicrobial properties, which are thought to be beneficial for human health. From our review study, we have found that the leaves of a plant can act as most prominent source for isolating antimicrobial compounds. Also *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis* and *Candida albicans* were found most susceptible towards the different plant extracts, indicating the greater effectiveness of the plant in diseases caused by these pathogens. Furthermore ethanol, methanol and distilled water can be considered as the best solvents for extracting different plant secondary metabolites. This review is intended to encourage utilization of *Cannabis sativa* in treating diseases related to microbial infections. Moreover, it will also help to provide us with an idea of selecting plant parts, pathogens and solvents for conducting further study.

Keywords: *Cannabis sativa,* antimicrobial properties, multi-drug resistance, secondary metabolites, microbial infections.

INTRODUCTION

Plants are the richest source of many therapeutic agents, which are used for powerful drug discovery in different countries.[1, 2] The therapeutic value of plants is due to the presence of some chemical substances within the plant tissues which produce a definite physiological action on the human body; include alkaloids, flavonoids, glucosides, tannins, gums, resins, essential oils etc.[3] It is estimated that there are 250,000 to 500,000 species of plants on the earth with biologically and chemically diverse groups.[4] Though, plants have been used as traditional medicines for the treatment of various diseases throughout most of human history, but actually they have gained popularity in the late 1990s.[5] However, plants are still an important source of medicines, especially in developing countries where the plant-based therapeutic products are still used to meet the health care needs.[6] The World Health Organization (WHO) estimates that the traditional systems of medicines are accepted by almost 80% of the population throughout the world.[7] Further, the National Health Interview Survey (NHIS) conducted by the Centers for Disease Control and Prevention (CDC) in 2007 indicate that around 40% of adults in the United States used some form of complementary and alternative medicine, indicating that such medical practices are prevalent even in the developed nations.[8] In recent years, there are considerable challenges with the treatment of infections caused by bacterial strains of clinical importance that show multi-drug resistance (MDR) properties, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and the recently emerged extremely drug-resistant *Mycobacterium tuberculosis* XDR-TB. Therefore, due to the potent antimicrobial activity of many plant secondary metabolites[9] and the ability of some of them to modify the resistance associated with MDR strains[10], researchers are increasingly turning their attention towards the development of new effective drugs from natural sources.

Cannabis sativa is an angiosperm belonging to the family Cannabaceae.[11] It is known by various names worldwide as Marijuana in America; Bhang, Ganja and Charas in India; Kif in North Africa; Dogga in South Africa; Krori in Tunisia, Habak in Turkey; Hashish in Middle East; Djomba or Liamba in Central Africa and Brazil; Sodom, Tampl, Gum, Gauge and Stuff in Kinshasa, Swala and Whiskt in Ghana; Grifa in Mexico and Macohna in some parts of South America.[12] The plant grows well at low temperature, and well-adjusted to moderate climates. Today, the plant is commonly known as a powerful psychoactive substance, but for many years it was cultured primarily for its fibers, that were used in the production of rope, clothes and ship sails.[13] *Cannabis sativa* extracts as medicine was described in China and India before the birth of Christ.[14] The plant and its preparations have been used for its sedative, narcotic, antispasmodic, analgesic and many other properties including its use for photo phabia, asthma and piles.[15, 16] *Cannabis* also induces an increase in heart rate, lowers blood pressure due to vasodilatation and stimulates appetite.[17] Its extracts may represent an efficacious and

safe alternative for treating insomnia, sick headaches, neuralgia, migraine, mania, whooping cough, dysuria, hyperemesis gravidarum and in relieving pain in dysmenorrhoea and menorrhagia.[18-21] *Cannabis* is being used as a shampoo and for other cosmetic purposes.[13] It can be administered to patients suffering from rabies, cholera, rheumatism, epilepsy and tetanus. Also observation is that *Cannabis sativa* have been used for the treatment of specific human ailments such as allergies, burns, cuts and wounds, inflammation, leprosy, leucoderma, scabies, smallpox and sexually transmitted diseases.[22]

Gender identification of *Cannabis* is done on the basis of its flowers. The flowers (and to a lesser extent the leaves, stems, and seeds) of this plant contain psychoactive and physiologically active chemical compounds known as cannabinoids that are consumed for recreational, medicinal, and spiritual purposes.[23] The term "cannabinoids" represents a group of C_{21} terpenophenolic compounds found uniquely in *Cannabis sativa* and includes their analogs and transformation products.[24, 25] The male variety of this plant is known to produce greater amount of cannabinoids. Cannabinoidal yield is also higher in more tropical environment; this is mainly due to reactions, such as alkylation and condensation.[26, 27]The 86 known cannabinoids[28, 29] from *Cannabis* plant can be classified into 11 structural types (figure1): Cannabigerol (CBG), Cannabichromene (CBC), Cannabidiol (CBD), Δ^9-Tetrahydrocannabinol (THC), Δ^8-THC, Cannabicyclol (CBL), Cannabielsoin (CBE), Cannabinol (CBN), Cannabinodiol (CBND), Cannabitriol (CBT) and miscellaneous types. Of which, the most prevalent cannabinoids are Δ^9-Tetrahydrocannabinol (THC), Cannabidiol (CBD), Cannabinol (CBN), Cannabigerol (CBG), Cannabichromene (CBC) and Cannabinodiol (CBND).[30, 29]Δ^9 Tetra-hydrocannabinol (THC) is one of these cannabinoids which is considered the most active element of this plant.[31] Other compounds from this plant have little or no psychoactive effects. Cannabinoids induce their effects by interacting with various neurotransmitters and neuromodulators, such as gamma-aminobutyricacid (GABA), histamine, serotonin, dopamine, glutamate, norepinephrine, prostaglandins and opioid peptides.[32] Basically, there are three sources of cannabinoids; phytocannabinoids occur uniquely in the *Cannabis* plant; endogenous cannabinoids or endocannabinoids are produced in the bodies of humans and animals and synthetic cannabinoids which are similar compounds produced in the laboratory.[33, 34] The main objective of this review is to encourage utilization of *Cannabis sativa* in developing potential therapeutic agents based on their antimicrobial performance.

Antimicrobial activity of *Cannabis sativa*

Antimicrobial studies on the *Cannabis sativa* grown in different parts of the world have been carried out by many researchers (Table 1). Wasim *et al.* (1995)[17] studied the antimicrobial activity of aqueous, ethanolic and petroleum ether extracts of the leaves of *Cannabis sativa* against *Baccilus subtilus, Baccilus pumilus, Staphlococcus aureus, Micrococcus flavus, Proteus vlugaris, Bordetella bronchioseptica, Candida albicans* and *Aspergillus niger* using well diffusion method. Results showed that ethanolic and petroleum ether extract exhibited activity both against Gram-positive and Gram-negative bacteria and also against the fungi, whereas aqueous extract did not show any antimicrobial activity. The antimicrobial activity of seed's oil of *Cannabis sativa* extracted with hexane and methanol solvent was evaluated by Leizer *et al.* (2000)[35] against *Aspergillus niger* (mycelium-forming fungi), *Escherichia coli, Staphylococcus aureus, Saccharomyces cerevisiae* (yeast, single cell fungi) and *Pseudomonas aeruginosa*. Results showed that the oil extracted with methanol exhibited potent activity against *Saccharomyces cerevisiae*, however, it did not displayed antibacterial properties. Appendino *et al.* (2008)[36] extracted all five major cannabinoids from *Cannabis sativa*: Cannabidiol (CBD), Δ9-Tetrahydro cannabinol (THC), Cannabigerol (CBG), Cannabichromene (CBC), and Cannabinol (CBN), and observed their antibacterial activity. They found that all of them showed potent activity against a variety of methicillin-resistant *Staphyloccocus aureus* (MRSA) strains of current clinical relevance. Borchardt *et al.* (2008)[37] studied the antimicrobial activity of aqueous ethanolic extract of *Cannabis sativa* (stem and leaf) against *Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans* using disc diffusion method. The extract was found to have very good antibacterial activity only against *Staphylococcus aureus.*

Radwan *et al.* (2009)[38] isolated and studied antimicrobial property of nine new cannabinoids [(±)-4-acetoxycannabichromene, (±)-3"-hydroxy-Δ(4",5")-cannabichromene, (-)-7-hydroxycannabichromane, (-)-7*R*-cannabicoumarononic acid A, 5-acetyl-4-hydroxycannabigerol, 4-acetoxy-2-geranyl-5-hydroxy-3-*n*-pentylphenol, 8-hydroxycannabinol, 8-hydroxycannabinolic acid A, and 2-geranyl-5-hydroxy-3-*n*-pentyl-1,4-benzoquinone]. Cannabinoids were isolated from the hexane, dichloromethane, ethyl acetate, ethanol, aqueous ethanol and aqueous extracts of whole buds of a high-potency variety of *Cannabis Sativa* through 1D and 2D NMR spectroscopy, GC-MS and HRESIMS. Antimicrobial property of these cannabinoids were studied against *Candida albicans* ATCC 90028, *Candida krusei* ATCC 6258, *Aspergillus fumigates* ATCC 90906, methicillin-resistant *Staphylococcus aureus* ATCC 33591, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853 and *Mycobacterium intracellulare* ATCC 23068. Compound 2, 5, 6, 7 and 8 displayed significant antimicrobial activities compare to other isolated compounds.

The antibacterial activity of freshly extracted essential oils from industrial hemp varieties was evaluated by Nissen *et al.* (2010)[39] against Gram positive bacteria, with regard to food-borne pathogens or gastrointestinal bacteria and

Gram negative bacteria. They characterized essential oils through the gas chromatography and gas chromatography-mass spectrometry. Their results showed that essential oils of industrial hemp can significantly inhibit the microbial growth, depending on variety and sowing time. Antibacterial activity of crude alkaloid extracted from *Cannabis sativa* leaf was investigated by Das and Mishra in 2011[40] against bacterial strains representative of skin, mouth and ear microflora and also against β strain of *E. coli*. This study revealed the effectiveness of the plant against all the tested strains.

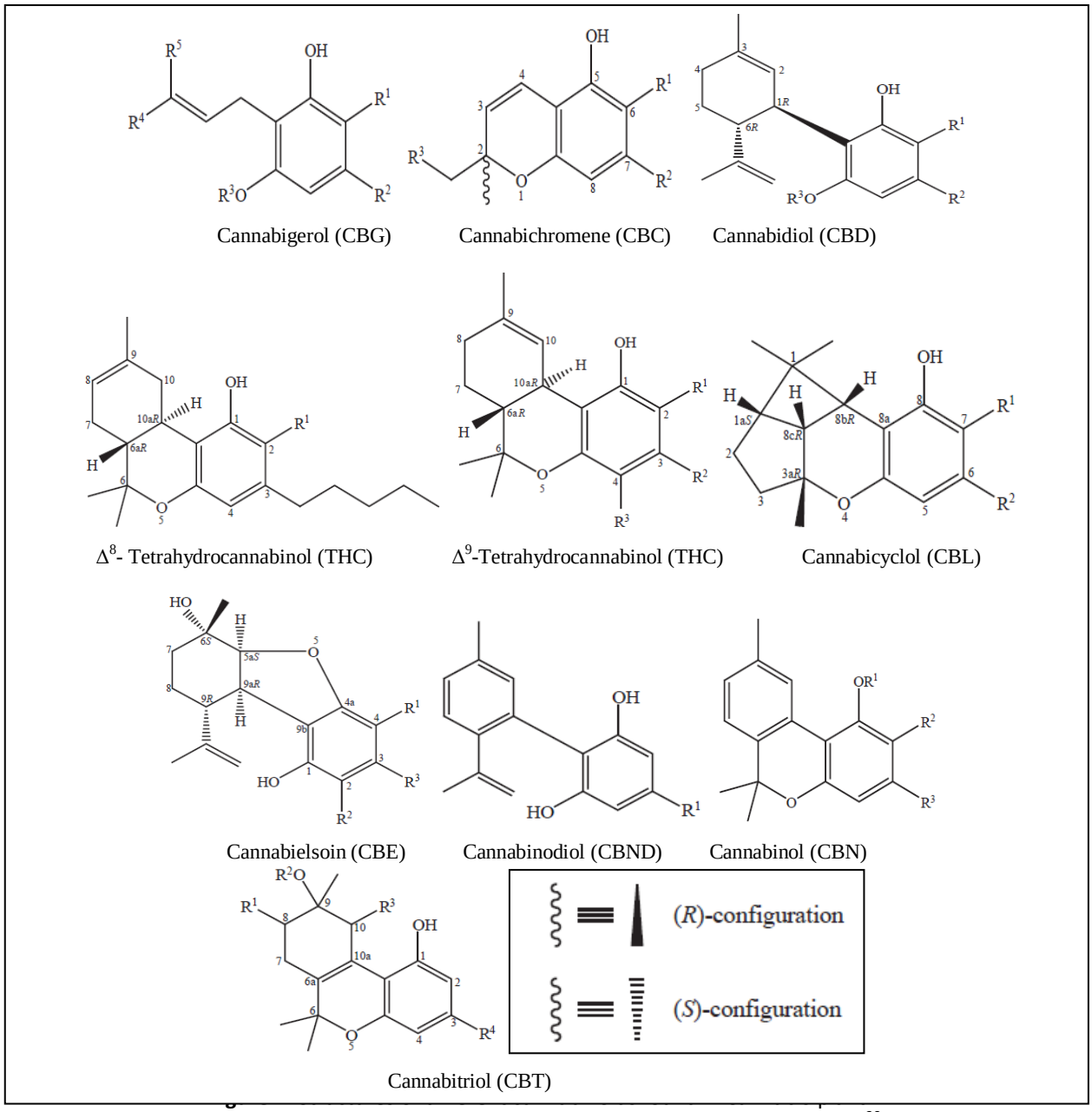

Figure 1: Structures of different cannabinoids found in *Cannabis* plant[29]

Ali *et al.* (2012)[41] investigated the antibacterial activity of the seed's oil, petroleum ether and methanol extracts of the whole plant of *Cannabis sativa* against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* using the cup plate agar diffusion method. Their results showed that oil of the seeds of *Cannabis sativa* exerted pronounced antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*, moderate activity against *Escherichia coli* and high activity against *Pseudomonas aeruginosa*. The petroleum ether extract of the whole plant exhibited pronounced antibacterial activity against both *Bacillus subtilis* and *Staphylococcus aureus* organisms, high activity against *Escherichia coli* and inactive against *Pseudomonas aeruginosa*. The methanol extract of the whole plant also showed pronounced antibacterial activity against *Bacillus subtilis*, low activity against *Staphylococcus aureus* and high activity against both Gram negative organisms. Lone and Lone in 2012[42] evaluated the antimicrobial activity of cannabinoids extracted by aqueous and acetone extraction from *Cannabis sativa* leaf against *Pseudomonas aeruginosa*,

Vibro cholera, Cryptococcus neoforms, Aspergillus niger and *Candida albicans* using disc diffusion method. Their study revealed that the acetone extract exhibited higher antimicrobial activity against *Pseudomonas aeruginosa*, *Vibro cholera, Cryptococcus neoforms* and *Candida albicans.* Antimicrobial activity of *Cannabis sativa* leaf was evaluated by Mkpenie *et al.* (2012)[43] against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus niger* following disc diffusion method. The plant was extracted for 2, 8 and 18 h with absolute acetone, methanol and their 50% aqueous solutions. Results of their study showed that extracts obtained at 18 h exhibited the strongest inhibitory properties against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* compared to extracts recovered after 2 and 8 h. All the tested extracts were inactive against the growth of *Aspergillus niger*. Nasrullah *et al.* (2012)[44] evaluated the antibacterial activity of methanol and n-hexane extracts of *Cannabis sativa* leaves against *Bacillus cereus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi* using agar well diffusion method. In their study methanol extract exhibited good antibacterial activity than the n-hexane extract. The antimicrobial activity of aqueous and ethanolic extracts of *Cannabis sativa* leaves was evaluated by Mathur *et al.* (2013)[45] against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans* following agar well diffusion assay. Their results revealed that both the extracts were active against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, while inactive against *Escherichia coli* and *Candida albicans.*

Table 1: Antimicrobial activity of *Cannabis sativa* (summary of review)

S.No.	Plant parts	Solvents	Test organisms	References
1	Leaf	Aqueous, ethanolic and petroleum ether	*Baccilus subtilus, Baccilus pumilus, Staphlococcus aureus, Micrococcus flavus, Proteus vlugaris, Bordetella bronchioseptica, Candida albicans* and *Aspergillus niger*	Wasim *et al.,* 1995
2	Seed's oil	Hexane and methanol	*Aspergillus niger (mycelium-forming fungi), Escherichia coli, Staphylococcus aureus, Saccharomyces cerevisiae (yeast, single cell fungi) and Pseudomonas aeruginosa.*	Leizer *et al.,* 2000
3	Whole plant	Acetone	Methicillin-resistant *Staphyloccocus aureus* (MRSA)	Appendino *et al.,* 2008
4	Stem and leaf	Aqueous ethanolic	*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*	Borchardt *et al.,* 2008
5	Whole bud	Hexane, dichloromethane, ethyl acetate, ethanol, aqueous ethanol and aqueous	*Candida albicans* ATCC 90028, *Candida krusei*ATCC 6258, *Aspergillus fumigatus* ATCC 90906, methicillin-resistant *Staphylococcus aureus* ATCC 33591, *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853 and *Mycobacterium intracellulare*ATCC23068	Radwan *et al.,* 2009
6	Leaf	-	Bacterial strains representative of skin, mouth and ear microflora and β strain of *E. coli*	Das and Mishra, 2011
7	Whole plant	Petroleum ether and methanol	*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*	Ali *et al.,* 2012
8	Leaf	Aqueous and acetone	*Pseudomonas aeruginosa*, *Vibro cholera, Cryptococcus neoforms, Aspergillus niger* and *Candida albicans*	Lone and Lone, 2012
9	Leaf	Acetone and methanol	*Staphylococcus aureus*, *Pseudomonas aersuginosa*, *Candida albicans* and *Aspergillus niger*	Mkpenie *et al.,* 2012
10	Leaf	Methanol and n-hexane	*Bacillus cereus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*	Nasrullah *et al.,* 2012
11	Leaf	Aqueous and ethanol	*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Candida albicans*	Mathur *et al.,* 2013
12	Leaf	Methanol, ethanol, acetone and aqueous	*Escherichia coli, Staphylococcus aureus*, *Streptococcus pneumoniae* and *Salmonella typhii*	Monika *et al.,* 2014
13	Leaf	Ethanol and aqueous	*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Salmonella typhi* and *Klebsiella pneumonia*	Naveed *et al.,* 2014
14	Whole plant	Hydro-alcoholic	*E. coli 25922, E. coli ESBL+, S. aureus 25923, MRSA, Pseudomona aeroginosa ESBL+, Pseudomonas, Klebsiella pneumonia* and *Acinetobacter baumannii*	Sarmadyan *et al.,* 2014
15	Leaf	Ethanol, methanol, acetone and aqueous	*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Saccharomyces cerevisiae*	Kaur*et al.,* 2015

Antibacterial and phytochemical investigations of methanol, ethanol, acetone and aqueous extracts of *Cannabis sativa* leaves was done by Monika *et al.* (2014)[46] against *Escherichia coli, Staphylococcus aureus*, *Streptococcus pneumoniae* and *Salmonella typhii* using agar well diffusion method. Their results revealed that all the extracts exhibited antibacterial activity against all the tested strains. Phytochemical screening showed the presence of saponins, tanins, quinones, alkaloids in the plant extracts. The antibacterial activity of ethanolic and hot water extract of *Cannabis sativa* leaf was investigated by Naveed *et al.* (2014)[47] against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Salmonella typhi* and *Klebsiella* following well diffusion method. Their results showed that the plant extracts exerted pronounced activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, while no activity against *Salmonella typhi* and *Klebsiella*. Sarmadyan *et al.*(2014)[48] investigated the antibacterial effect of hydro-alcoholic extract of *Cannabis sativa* against *E. coli 25922, E. coli ESBL+, S. aureus 25923, MRSA, Pseudomonas aeroginosa ESBL+, Pseudomonas, Klebsiella pneumonia* and *Acinetobacter baumannii* following disc diffusion method. They also determined the minimum inhibitory concentrations (MIC) of the active extracts. Their results revealed that the extract was active against *S. aureus 25923, MRSA, E. coli 25922, E. coli ESBL+* and *Klebsiella pneumonia*, while inactive against *Pseudomona aeroginosa ESBL+, Pseudomonas* and *Acinetobacter baumannii*. In MIC determination assay, the lowest value was observed for *S. aureus*. Kaur *et al.* (2015)[49] studied the antimicrobial potency of ethanol, methanol, acetone and aqueous leaf extracts of *Cannabis sativa* against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Saccharomyces cerevisiae* following agar well diffusion method. Results of their study showed that all the extracts were effective against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*, while ineffective against *Pseudomonas aeruginosa*, *Candida albicans* and *Saccharomyces cerevisiae.* Among all the extracts, methanolic extract was found most effective against the tested strains.

CONCLUSION

From the above review, we can conclude that *Cannabis sativa* can be exploited to prepare potent broad-spectrum antimicrobial drugs, because of its remarkable inhibitory activity against a wide range of organisms. More importantly, it can be included in the list of herbal medicines in appropriate concentrations due to its lesser side effects. This study also reveals that the leaves of a plant can be considered as a potential source for isolating antimicrobial compounds. In most of the studies, *Escherichia coli, Pseudomonas aeruginosa, Staphyloccocus aureus* and *Candida albicans* were found significantly inhibited by different plant extracts, suggesting the effectiveness of plant in diseases caused by these pathogens. Solvents used in the extraction methods have great influence on both; the amount of active compounds that can be extracted and the result of the antimicrobial performance of a plant. Considering this, our review also suggests that ethanol, methanol and distilled water can act as potent solvents for extracting different secondary metabolites. To further confirm the therapeutic applicability of *Cannabis sativa,* studies on mechanism(s) of action, in-vivo and toxicological effects of its compounds are required

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Authors' Contributions:

This review study was carried out in collaboration between both the authors. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. Both the authors have read and approved the final version of the manuscript.

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