Review

Cannabinoid Molecules from *Cannabis Sativa L.* as a Promissing Solution for Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

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Abstract:
Scientists are working to develop new types of antibiotics to combat the growing problem of antibiotic resistance in bacteria. One potential source of these new drugs is the plant *Cannabis sativa* L., which has been used for medical purposes for centuries. The beneficial properties of this plant are mainly due to the presence of compounds called cannabinoids. Researchers are currently exploring the use of cannabinoids to treat various infections, although they are mainly known for their psychoactive effects. Some studies have shown that certain cannabinoids can be effective against harmful bacteria including those that are resistant to common antibiotics. In addition, a combination of different antibiotics has been shown to be more effective than a single antibiotic.

Keywords: *Cannabis sativa L.*; Cannabinoids; Methicillin-resistant *S. aureus* (MRSA); Antibiotics; Bacteria; Biological activity

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1. Introduction

Since Alexander Fleming discovered penicillin in 1928, antibiotics have been a lifesaving treatment for bacterial infections around the world (Zaman et al., 2017; Saleemi et al., 2022). However, the overuse and misuse of these drugs have led to a growing problem of antibiotic resistance, which is a significant threat to global health. The problem is caused by the increasing number of multi-drug resistant organisms (MDRs) that are resistant to most antibiotics, taking place due to the lack of action and insufficient efforts to address the issue of antimicrobial resistance (Zaman et al., 2017; Saleemi et al., 2022). As more and more bacteria become resistant to antibiotics, the options available to treat these infections are becoming increasingly limited. In this regard, researchers are investigating alternative methods for combating these resistant pathogens. One promising area of study is the use of helper molecules, such as resistant breakers or antibiotic potentiators. These molecules work in combination with antibiotics to enhance their effectiveness and make them more efficient against resistant bacteria (Saleemi et al., 2022; Tyers and Wright, 2019). Helper molecules are non-antibiotic compounds that can be used in combination with antibiotics to improve their effectiveness. These molecules work by various mechanisms, such as altering the permeability of bacterial cell membranes, inhibiting enzymes, and blocking the pump that bacteria use to resist antibiotics. These mechanisms can increase the effectiveness of antibiotics against resistant bacteria (Saleemi et al., 2022; Douafer et al., 2019).

The misuse of antibiotics is the leading cause of the emergence of antibiotic-resistant bacteria. The World Health Organization (WHO) has identified this phenomenon as one of the most significant threats to global health. People with weakened immune systems, such as those undergoing chemotherapy, are particularly at risk of becoming infected with these resistant bacteria (Saleemi et al., 2022; World Health Organization, 2017). The emergence of antibiotic-resistant bacteria is a major concern for the development of new medical procedures and treatments. To tackle this problem, it is necessary to create new classes of antimicrobial agents that can effectively fight these organisms. One approach is to use helper molecules in combination with antibiotics, which may reduce the risk of antibiotic resistance. Evaluating these helper molecules is crucial to identify the most effective ones. The WHO has also released a list of the 12 most dangerous families of bacteria that are resistant to antibiotics, highlighting the urgency of finding solutions to this problem (Farha et al., 2020; World Health Organization, 2017).

A major concern is, for example, that certain strains of MRSA have developed resistance to antibiotics commonly used to treat them, such as vancomycin, linezolid, and daptomycin. This limits the treatment options available for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections (Farha et al., 2020; Nannini et al., 2010). Antibiotic resistance in Gram-negative bacteria is a growing concern in the medical field. The World Health Organization notes that many of the most dangerous bacteria are Gram-negative, and new classes of antibiotics to combat these infections have not been discovered in over 30 years. The lack of effective antibiotics and the limited number of new drugs under development highlights the need for alternative treatment options (Farha et al., 2020).

2. Cannabis

Cannabis is a type of plant that belongs to the family Cannabaceae. Since it can adapt to different environmental conditions it can grow in different climates. It is an annual herb that produces male and female inflorescences on different plants. The leaves are arranged in a palm-like shape or in a line, with toothed edges. Usually, the first set of leaves has one leaf, but the number can increase up to thirteen, depending on the specific variety and how it is grown. The way that the plant determines its sex is complex (Tavčar Beković et al., 2019; Pečan et al., 2021; Appendino et al., 2008).

2.1 *Biologically active compounds in Cannabis sativa*

Cannabis sativa (*C. sativa*) is a plant that has been extensively studied and more than 420 chemical compounds have been found (Tavčar Beković et al., 2019; Pečan et al., 2021). The most significant ones are present in the trichomes, which are small glands on the surface of the plant. These trichomes are found on both male and female plants but are especially concentrated on certain parts of the female plant. The resin produced by the trichomes contains various ingredients including cannabinoids, terpenes, and flavonoids, which are all secondary metabolism products. Cannabinoids are the most active biological components of cannabis, and over 90 different cannabinoids have been identified so far. They are divided into two categories: endogenous cannabinoids produced by the human body, and exogenous cannabinoids that can be made synthetically or by the *C. sativa* plant. They work by binding to cannabinoid receptors and thus causing specific effects (Pečan et al., 2021; Appendino et al., 2008).

3. Main cannabinoids

3.1 *Δ⁹-Tetrahydrocannabinol (THC)*

Δ⁹-Tetrahydrocannabinol (THC) is a solid substance that can be dissolved in alcohols, hydrocarbons and oils but not in water. It has a boiling point of 165 °C, which is the lowest temperature required for it to be inhaled (Tavčar Beković et al., 2019). As a controlled substance, it is classified as a Schedule II drug and is only allowed for medical and research purposes. THC is an active ingredient approved by the US Food and Drug Administration and the European Medicines Agency and is used in authorized medicines. It works by partially activating the cannabinoid receptors CB1 and CB2, primarily located in the central nervous system and in the immune system. This decreases the concentration of the second messenger molecule *c*AMP and results in psychoactive effects. The discovery of these receptors in the brain also led to the discovery of endocannabinoids such as anandamide and 2-arachidonoyl glyceride (2-AG). THC is a lipophilic molecule that can bind to various entities in the brain and body, such as fat. It also has mild antioxidant properties that can protect neurons against oxidative stress caused by excessive glutamate (Pečan et al., 2021).

3.2 *Cannabidiol (CBD)*

Cannabidiol (CBD) is a compound that was first isolated from cannabis in 1940, its structure was identified in 1963 (Tavčar Beković et al., 2019). It can be obtained through various extraction methods and is also semi-synthetically derived from limonene. At room temperature, it is a solid substance that is colourless and boils at 175 °C (Tavčar Beković et al., 2019). When exposed to certain acids or high temperatures during smoking, it can convert to THC in small amounts. CBD is widely used in dietary supplements and cosmetics. It is a phytocannabinoid that is derived from cannabis and has pain-relieving, anti-inflammatory, anti-tumoral and chemo-preventive properties but it doesn't have psychoactive effects. CBD activates the endoplasmic reticulum stress and suppresses AKT/*m*TOR signalling, promoting autophagy and apoptosis. It also raises the production of reactive oxygen species (ROS) which further enhances apoptosis. CBD also regulates the expression of intercellular adhesion molecule 1 (ICAM-1) and tissue matrix metalloproteinase-1 (TIMP1) inhibitors and reduces the expression of DNA 1 binding inhibitor (ID-1) which in turn inhibits cancer cell invasiveness and metastasis. CBD also activates the transient receptor potential of vanilloid type 2 (TRPV2) which may increase the uptake of various cytotoxic agents in cancer cells. CBD's pain-relieving effect is brought about by its binding to CB1 receptors (Pečan et al., 2021).

4. Effect of cannabinoids on methicillin-resistant *Staphylococcus aureus* (MRSA)

4.1 Methicillin-resistant Staphylococcus aureus (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most prevalent modern pathogens (Otto, 2013). *Staphylococcus aureus* (*S. aureus*) is known to cause a wide range of pyogenic infections, involving several organs, and both hospital-acquired and community-acquired infections are well recognized. In nature, *S. aureus* infections can be fatal. Some strains have developed resistance to several β-lactam antibiotics used in hospitals. MRSA is a significant opportunistic pathogen that causes both nosocomial and community-acquired infections (community-associated MRSA, CA-MRSA) (Chakraborty et al., 2018; Deurenberg et al., 2007). *S. aureus* is a Gram-positive, coagulase-positive coccus of the family of Staphylococcaceae. Since it was first identified in 1961, MRSA has spread throughout the world and become one of the most frequent pathogenic bacteria causing healthcare-associated infections. MRSA can cause various types of life-threatening infections, such as septic shock, endocarditis and severe pneumonia (Chakraborty et al., 2018).

Different MRSA strains have emerged worldwide, and they have become resistant to a variety of antibiotics, including penicillin, tetracycline, methicillin and vancomycin. Recently, in several countries, MRSA has been found to infect livestock and humans exposed to those infected animals. This type of MRSA has been named livestock-associated MRSA (LA-MRSA) (Chakraborty et al., 2018; Nemati et al., 2008). The interactions among these different types of MRSA reservoirs have been reported, including nosocomial infections by CA-MRSA and importation of LA-MRSA in hospitals, leading to hospital-acquired infections (Chakraborty et al., 2018; Moore et al., 2009; Skov and Jensen, 2009). Due to a modification in penicillin-binding protein 2a, MRSA has a decreased affinity to β-lactam.

The *mec*A gene encodes this protein and is located on a mobile SCC*mec* cassette chromosome. This genetic element resists most currently available β-lactam antibiotics. Unfortunately, though several agents and protocols have been proposed, no prophylactic strategies have been yet proven useful. Therefore, new alternative therapies must be developed to kill extended-spectrum β-lactamase (ESBL) strains of MRSA. Herbal medicine can solve this problem, and many plant extracts have been reported to possess inhibitory activity towards *S. aureus* as well as MRSA and ESBL-MRSA (Chakraborty et al., 2018).

4.2 Antimicrobial activity of different cannabinoids from Cannabis sativa on MRSA

The idea that cannabinoids from Cannabis sativa can have antibacterial properties was first reported in the 1950s (Rabinovich et al., 1959). At the time, the bactericidal properties of cannabis were studied before the full chemical makeup of the plant was understood. This means that the antibacterial effects were not attributed to a specific component. In 1976, it was discovered that Δ^9-THC and CBD can be used as bacteriostatic agents and were able to kill a panel of human pathogenic strains (Turner et al.,2019; Klingeren and Ham, 1976).

There has been significant interest in the antibacterial properties of various *C. sativa* plant extracts, such as the oil and extract from the plant. Different methods have been used to isolate these extracts, with cold-pressing and solvent extraction techniques being commonly used to produce products such as cosmetics and food. However, new technologies are being developed to improve the efficiency of these methods, such as pressurized liquid extractions and ultrasonic extractions, which use less solvent and have shorter processing times than traditional methods (Fathordoobady et al., 2019).

According to a study by Farha et al. (2020), cannabinoids present in *C. sativa* have been found to have antibacterial properties against MRSA. Selected known cannabinoid analogues that are active against MRSA USA300 are depicted in **Figure 1.** They can inhibit the formation of biofilms and also eradicate pre-existing ones. Research results indicate that cannabigerol specifically targets the cytoplasmic membrane of Gram-positive bacteria and has been shown to be effective against MRSA in a mouse model *in vivo*. Additionally, cannabinoids have also been found to be effective against certain gram-negative organisms by

targeting their inner membrane. The study also shows that these compounds can be used in combination with polymyxin B against multi-drug resistant gram-negative pathogens, indicating the broad-spectrum therapeutic potential of cannabinoids. The study discovered that of the five major cannabinoids and some of their derivatives, seven molecules are potent antibiotics with minimum inhibitory concentrations of 2 μg/mL. This group includes cannabichromene (CBG), CBD, cannabinol (CBN), cannabichromene acid (CBCA), and THC along with its Δ^8- and exolefin regioisomers. However, it was also found that these compounds lose potency when the benzoic acid moiety is present or when the *n*-pentyl substituent is replaced with *n*-propyl. Additionally, the two most common human metabolites of THC, (±)-11-nor-9-carboxy-Δ^9-THC and (±)-11-hydroxy-Δ^9-THC, as well as cannabicyclol were inactive at the highest concentrations screened (minimum inhibitory concentration (MIC): >32 μg/mL) (Farha et al., 2020).

MRSA's ability to form biofilms on necrotic tissues and medical devices is considered a major factor in its ability to persist in both the environment and host organism, as stated by Otto (2013). These biofilms, which are highly structured communities of MRSA on surfaces, are known to be resistant to many antimicrobial compounds and are less susceptible to host immune responses. Studies have shown that certain cannabinoids such as CBG have the ability to inhibit MRSA biofilm formation. The research used static solid surface abiotic assays to test the effects of increasing concentrations of cannabinoids on MRSA biofilm formation under conditions that favour biofilm growth.

The results showed that the effectiveness of the cannabinoids in inhibiting biofilm formation correlated with their antibacterial activity against MRSA. The five major cannabinoids tested were found to be effective in repressing MRSA biofilm formation, with CBG having the most potent antibiofilm activity. In fact, just 0.5 μg/mL (1/4 MIC) of CBG was able to inhibit biofilm formation by about 50%. Overall, this experiment highlights the potent ability of cannabinoids to inhibit MRSA biofilm formation (Farha et al., 2020).

Martinenghi et al. (2020) found that purified CBDA and CBD extracted from *C. sativa* L. had exhibited potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA USA300) when compared to four conventional antibiotics clindamycin, ofloxacin, meropenem, and tobramycin. CBD was found to be particularly effective against Gram-positive bacteria with a minimal inhibitory concentration between 1 and 2 μg/mL, while CBDA had two-fold lower activity.

Blaskovich et al. (2021) also reported that CBD was effective against MRSA biofilms with a minimum biofilm eradication concentration (MBEC) of 1-2 or 2-4 μg/mL, similar to its minimum inhibitory concentration (MIC). These MBEC values were found to be much better than daptomycin and clindamycin against MRSA. Confocal microscopy showed that CBD was able to penetrate the biofilm and kill the bacteria.

Overall, CBD is reported to have useful antimicrobial activity against a broad spectrum of more than 20 species of Gram-positive bacteria, including several strains of MRSA, with potential clinical utility for nasal decolonization due to its consistent MIC of 1-4 μg/mL (Blaskovich et al., 2021).

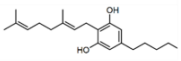
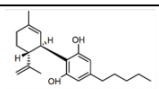
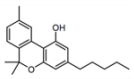
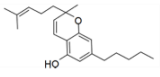
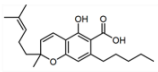
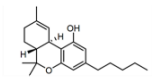
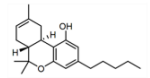
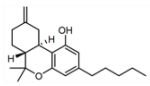
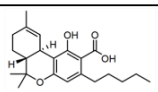
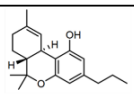
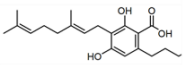
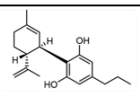
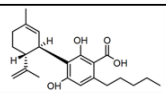
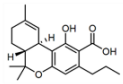
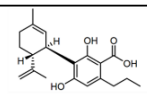
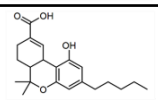
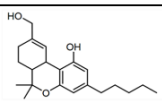
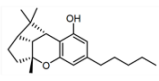
Entry	Name	(Abbreviation)	Structure	MIC (μg/mL)
(1)	Cannabigerol	(CBG)		2
(2)	Cannabidiol	(CBD)		2
(3)	Cannabinol	(CBN)		2
(4)	Cannabichromene	(CBC)		8
(5)	Cannabichromenic acid	(CBCA)		2
(6)	(-)Δ⁹-Tetrahydrocannabinol	(THC)		2
(7)	(-)Δ⁸-Tetrahydrocannabinol	(Δ⁸-THC)		2
(8)	*exo*-Tetrahydrocannabinol	(*exo*-THC)		2
(9)	Δ⁹-Tetrahydrocannabinolic acid A	(THCAA)		4
(10)	Δ⁹-Tetrahydrocannabivarin	(THCV)		4
(11)	Cannabigerolic acid	(CBGA)		4
(12)	Cannabidivarin	(CBDV)		8
(13)	Cannabidiolic acid	(CBDA)		16
(14)	Tetrahydrocannabivarinic acid	(THCVA)		16
(15)	Cannabidivarinic acid	(CBDVA)		32
(16)	(±) 11-Nor-9-carboxy-Δ⁹-THC			>32
(17)	(±) 11-Hydroxy-Δ⁹-THC			>32
(18)	Cannabicyclol	(CBL)		>32

Figure 1. Selected known cannabinoid analogues that are active against MRSA USA300. MIC: minimum inhibitory concentration. From Farha et al (2020).

5. Current challenges and future perspectives

As Vickers (2017) notes, the complexity of cannabis-related laws is a major barrier to the development of effective cannabinoid research. The difficulty of complying with legal requirements for cannabis research can prevent researchers and funding agencies from exploring new and innovative products. However, as CBD becomes more accepted in the U.S. and other countries, research into new methods of CBD administration is expected to increase. One such method being explored is the use of transdermal and topical delivery systems. Recognizing this potential, the National Center for Complementary and Integrative Health in the United States has expressed interest in funding CBD research. In the coming years, pharmaceutical companies or other research institutions are also likely to focus on the evaluation and development of topical or transdermal delivery systems for CBD, as this approach offers many advantages, as noted by Kamel (2015).

As antibiotic resistance becomes more prevalent, researchers are exploring new ways to treat bacterial infections. One area of interest is the use of plant compounds, such as those found in *C. sativa*, as potential antibacterial agents. Although preliminary research in this area has yielded mixed results, the potential benefits of using Cannabis extracts as antibiotics are still being studied. Factors such as the specific extracts examined and the methods used to test their activity may contribute to these varying results. Additionally, studies have shown that cannabis extracts and in particular purified cannabinoids, show promise in their ability to combat multi-drug resistant organisms, especially those Gram-positive. Furthermore, cannabinoids have been found to have antimicrobial properties against a range of bacteria, including those harmful to humans. They also have the potential to enhance the effectiveness of traditional antibiotics by acting as a natural antimicrobial agent. As a result, cannabinoids may be considered promising candidates for the development of new combination therapies to combat antibiotic-resistant bacteria (Karas et al., 2020).

The way cannabinoids impact the development and management of infections in animal models is not yet fully understood. Some studies have suggested that certain cannabinoids, such as Δ^9-THC, may suppress the immune system and make it less effective against intracellular pathogens (Schofs et al., 2021). However, other research suggests that cannabinoids may also be beneficial in protecting against bacterial infections caused by extracellular attacks and excessive immune responses. Despite the advancements made in identifying bacterial targets and developing new antimicrobial methods, more research is needed to understand the role of cannabinoids in treating various infections. Safety and toxicity concerns surrounding cannabis extract products have been alleviated using non-psychotropic cannabinoids, which have been found to possess in vitro properties that can fight against bacterial infections (Saleemi et al., 2022). Overall, the available data suggests that cannabinoids and other cannabis compounds have promising in vitro antibacterial properties that warrant further exploration as potential antimicrobial agents against clinically significant bacteria.

6. Conclusion

In summary, cannabinoids, particularly those found in *Cannabis sativa*, show promise as a potential treatment for MRSA and other antibiotic-resistant bacterial infections. Studies have shown that cannabis extracts and purified cannabinoids possess antimicrobial properties against a range of Gram-positive bacteria, including MRSA. In addition, cannabinoids have been found to have the potential to enhance the effectiveness of conventional antibiotics by acting as natural antimicrobial agents. This makes cannabinoids attractive candidates for the development of new combination therapies to combat antibiotic-resistant bacteria. While more research is needed to fully understand the mechanisms of action and potential side effects of cannabinoids in the treatment of MRSA, the available data suggest that they are a promising drug for the treatment of this and other antibiotic-resistant infections, so more efforts should be invested in this field of research.

Conflicts of Interest: The authors declare no conflict of interest.

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