FOLIA MEDICA CRACOVIENSIA
Vol. LXV, 4, 2025: 101–111
PL ISSN 0015-5616 eISSN 2957-0557
DOI: 10.24425/fmc.2025.156701

Cannabis sativa in the fight against drug-resistant bacteria and fungi

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Abstract: Drug resistance in bacteria and fungi is a global threat to public health. The purpose of this publication is to review the latest scientific achievements, mainly from 2020–2025, concerning the use of hemp compounds from *Cannabis sativa* in combating drug-resistant bacterial and fungal infections. The literature review confirms that *C.sativa*, a plant with a documented centuries-old therapeutic history, is a rich source of cannabinoids and terpenes that combat drug-resistant bacteria: *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and fungi: *Cryptococcus neoformans*, as well as species from the *Candida and Aspergillus*. The potential of hemp compounds is based on their activity in interacting directly with pathogens by disrupting cell membrane integrity, eradicating biofilm, having a bactericidal effect on bacterial spores, acting synergistically, affecting host inflammatory pathways, and the human endocannabinoid system.

Keywords: drug resistance, bacteria, fungi, *Cannabis*, cannabinoids, terpenes.

Submitted: 21-Oct-2025; **Accepted in the final form:** 30-Nov-2025; **Published:** 31-Dec-2025.

Introduction

Antimicrobial Resistance (AMR) in bacteria, viruses and fungi is one of the top 10 most serious global threats to public health. The World Health Organization (WHO) estimates that in 2019, bacterial antimicrobial resistance directly caused 1.27 million deaths globally and indirectly contributed to 4.95 million fatalities [1]. In the face of the incessant spread of multi-drug resistant bacterial strains (e.g., methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*) and the increase in fungal infections (e.g., *Cryptococcus neoformans*, *Candida*) [2], for which available therapies are insufficient, there is an urgent need to discover and develop new classes of compounds capable of combating these pathogens. The healthcare system struggles with a limited number of new approved antibiotics being introduced into clinical practice. This shortage necessitates the intensive search for alternative strategies, including a return to traditional

medicine and the study of natural products. In this context, *Cannabis sativa*, a plant with a documented therapeutic history dating back over 8,000 years, has become the subject of intensive molecular and pharmaceutical research. Hemp can contain as many as 565 different compounds, of which 120 are cannabinoids and 150 are terpenes [3, 4]. The key and best-characterized phytocannabinoids are Δ9-tetrahydrocannabinol (Δ9-THC), known for its psychoactive effects, and cannabidiol (CBD), which is not psychoactive and is the main focus of interest due to its wide range of pharmacological effects, including anti-inflammatory and anticonvulsant properties [3]. Other important cannabinoids with proven antimicrobial activity are cannabigerol (CBG) and cannabichromene (CBC). Terpenes, although often overlooked in studies focusing on CBD and Δ9-THC, constitute a significant part of the therapeutic profile of *C.sativa*. Monoterpenes, such as β-myrcene, α-pinene, limonene, and linalool, and sesquiterpenes, such as β-caryophyllene and α-humulene, show anti-inflammatory and analgesic potential, and also synergistically enhance the antibacterial effect of other compounds [5]. This chemical diversity allows *C.sativa* to be seen as a source of natural medicines that can act multi-targetedly due to their ability to simultaneously affect pathogens directly, host inflammatory pathways, and the human endocannabinoid system [6].

Drug-resistant bacteria

WHO in 2024 included 24 pathogens from 15 families on its priority list of bacterial pathogens that pose a threat due to antibiotic resistance, with those of critical priority including rifampicin-resistant *Mycobacterium tuberculosis*. The high priority group includes carbapenem-resistant *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. *Streptococcus pneumoniae* resistant to macrolides was classified as a medium priority bacterium [7]. Although literature data from recent years are not numerous, they already preliminarily indicate the potential use of cannabinoid and terpene compounds isolated from *C. sativa* against even these life-threatening drug-resistant bacteria.

Mycobacterium tuberculosis

Mycobacterium tuberculosis most often attacks the lungs, but can also occur in the brain, bones, lymph nodes, or the genitourinary system. According to the WHO, in 2023, tuberculosis caused 1.25 million deaths and was the leading cause of death for people infected with *HIV* (161,000 cases) and deaths related to antimicrobial resistance. Multidrug-resistant tuberculosis is caused by bacteria that do not respond to isoniazid and rifampicin, the two most effective first-line drugs [8]. *In vitro* and cell model studies indicate that CBD shows direct anti-tuberculosis activity against *M. tuberculosis* located both outside the cells and inside infected macrophages, and importantly, without toxicity to human cells. The minimum inhibitory concentration (MIC) for *M. tuberculosis* H37Rv strain was 25 μM. A significant reduction in the number of bacteria was noted in macrophage cells infected with tuberculosis bacilli after 24 hours of CBD treatment [9]. However, other studies of the same strain and the same cannabinoid show an MIC >64 μg/ml, although with 70% inhibition at a concentration of 64 μg/ml [10]. Studies evaluating the risk of tuberculosis after cannabis use unfortunately indicate that smoking and sharing water pipes (e.g., bongs) significantly increased the risk of active tuberculosis and contributed to about 12% of cases. However, other forms of consumption did not show a significant effect on the risk of tuberculosis [11]. These few

results come mainly from laboratory and epidemiological studies; clinical evidence for the effectiveness of CBD in the treatment of tuberculosis is still lacking [9].

Pseudomonas aeruginosa

The course of the disease caused by *Pseudomonas aeruginosa* can range from mild wound infections to pneumonia, sepsis, or urinary tract infections, which can lead to multi-organ failure and death, especially in immunocompromised, hospitalized people, or those struggling with chronic diseases such as cystic fibrosis. Results of microbiological analyses using the disc diffusion method indicate the inhibition of growth of this bacterium induced by hemp essential oils (zones ranging from 1 to 8 mm) [12] and by ethanol extract of hemp leaves (10–22 mm) [13].

Staphylococcus aureus

Staphylococcus aureus is responsible for a wide spectrum of infections, from skin infections, pneumonia, rheumatic fever, to sepsis. In 2019, *S. aureus* caused about 1.1 million deaths [5]. Microbiological studies showed that cannabidiol was the most effective compound against a wide range of *S. aureus* strains. The MIC for CBD in combating staphylococcal infections (Methicillin-Sensitive *S. aureus*, MSSA) ranged from 0.65 to 32 mg/l. CBD also showed rapid, concentration-dependent bactericidal activity, observed as early as 2–3 hours at a concentration of 2 mg/l. Similarly, CBDA acid showed rapid bactericidal activity at a concentration of 40 μM (14.3 mg/l) although re-growth of bacteria was observed after eight hours. Particularly promising data concerned drug-resistant strains, where CBD was effective at very low concentrations, i.e., the MIC for CBD against MRSA strains ranged from 0.5 to 4 mg/l [5]. This low, submicromolar efficacy is comparable to some conventional antibiotics and highlights its ability to penetrate and combat β-lactam-resistant strains [14]. In addition, CBD was shown to retain activity against vancomycin-resistant strains *S. aureus* (VRSA), showing an MIC in the range of 1 to 2 mg/l. It was also found that some cannabinoids, such as CBCA, CBGA, cannabidivarin (CBDV), and CBC, showed rapid, concentration-dependent bactericidal activity against MRSA persistent bacteria, even in the stationary phase. However, others, such as CBDA, THCVA, CBDVA, (±)11-nor-9-carboxy-Δ9-THC, (±)11-hydroxy-delta-9-THC, cannabicyclol (CBL), and vancomycin, did not show bactericidal activity against MRSA persistent bacteria [5].

In studies using essential oils extracted from hemp (13 cultivated varieties, 8 breeding lines, 9 wild specimens), their varied activity against *S. aureus* was observed. Inhibition zones for the growth of this bacterium ranged from 2 to 11 mm for oils from wild hemp, which were found to have higher concentrations of CBD, THC, and terpenes (β-caryophyllene, α-humulene, caryophyllene oxide, and humulene epoxide). The above results indicate that cannabinoids and terpenes contained in essential oils from wild hemp may be useful in the treatment of, for example, skin diseases caused by *S. aureus*. Moreover, the results suggest that the role of the full phytochemical profile of the plant may be more important than a single isolated component. In the context of combating drug resistance, this study indicates the possibility of moving away from the analysis of single isolates in favor of standardizing and validating full chemotypes, which is important for future breeding and selection of varieties with desired medicinal activity [12].

Subsequent studies, where an ethanol extract from hemp leaves was used, confirmed the activity of complex hemp extracts against *S. aureus* (growth inhibition zone from 10 to 20 mm).

The obtained plant extracts may therefore constitute a promising and healthy solution in the fight against increasing antibiotic resistance and may be an alternative to synthetic compounds aimed at inhibiting bacterial development [13].

Furthermore, the effect of cannabis compounds on the biofilm produced by *S. aureus* was studied. Bacterial biofilm is a multilayered, complex structure formed by bacteria and other microorganisms that attach to a surface and surround themselves with a special matrix of extracellular polymeric substances (EPS), forming a type of biological membrane. Such a membrane is significantly more resistant to external factors, such as antibiotics and disinfectants. Biofilm produced by microorganisms is a key factor in chronic infections and resistance, and the ability to prevent its formation or break it down is an extremely valuable feature of new antimicrobial substances [15]. The most promising results indicating the degradation of biofilm produced by *S. aureus* and/or MRSA were obtained using CBC, CBCA, CBD, CBG, CBGA, THCV, Δ8-THC, and exo-THC, for which the minimum miofilm eradication concentration (MBEC) ranged from 2 to 8 mg/l, which corresponded to similar MIC values. Summarizing the above results, it was proven that cannabinoids, especially CBD, show potential in the field of anti-biofilm activity [2, 5].

In the context of AMR, an important direction of research is synergism, which is a phenomenon in which two or more factors cooperating with each other exert a stronger effect than the sum of their individual actions. Against MRSA, it was observed that CBD and essential oils from *C.sativa* (containing terpenes, flavonoids, and other phytochemicals) can act synergistically when combined with bacitracin. For example, CBD in combination with bacitracin reduced the MIC against MRSA by 32 to 64 times [5]. However, CBD did not show any synergy when combined with antibiotics such as dicloxacillin, daptomycin, nisin, or tetracycline. Therefore, the use of whole extracts, which include the *entourage effect*, where terpenes such as α-pinene, β-caryophyllene, limonene, and linalool can enhance the action of cannabinoids [3], may be an effective strategy for overcoming drug resistance.

In 2020, Mohammed *et al.* [16] studied THC not as a direct antibiotic, but as an immune response modulator that can reduce mortality and toxicity symptoms caused by bacteria. This is particularly important in the case of *Staphylococcus aureus*, which produces a deadly enterotoxin B causing acute respiratory distress syndrome (ARDS). Administering THC to mice after exposure to *Staphylococcus aureus* enterotoxin B led to 100% survival, reduced lung inflammation, and inhibited the cytokine storm. Single-cell RNA sequencing of lung cells confirmed apoptosis of immune system cells with the participation of the mitochondrial pathway. Transcriptomic analysis of these cells showed an increase in mitochondrial respiratory chain enzymes, and metabolomic analysis of the serum of treated mice revealed elevated concentrations of amino acids, lysine, N-acetylmethionine, carnitine, and propionyl-L-carnitine. Additionally, it was found that THC caused a decrease in miR-185 expression, which correlated with an increase in the number of pro-apoptosis target genes. These results were compared with gene expression in bronchoalveolar lavage fluid from COVID-19 patients and similarities were shown between cytokine and apoptotic genes. In summary, this study suggests that THC can be effectively used to protect the host against the virulence of the *S. aureus* as well as SARS-CoV-2 [16].

Streptococcus pneumoniae and Streptococcus pyogenes

Streptococcus pneumoniae is responsible for the development of respiratory tract infections, sinusitis, otitis media, meningitis (mainly in children), pneumonia, and sepsis. The implementation of

pneumococcal vaccines has led to a decrease in morbidity and mortality, however, due to serotype heterogeneity and antibiotic resistance, WHO still considers diseases caused by *S. pneumoniae* a serious public health problem [17]. The previously described studies using essential oils on *S. aureus* also proved effective against *S. pneumoniae*, for which growth inhibition zones of approximately 3 to 11 mm were observed [12].

Streptococcus pyogenes causes pharyngitis, scarlet fever, impetigo, erysipelas, lymphadenitis, lymphangitis, and otitis media. In 2019, *S. pyogenes* caused 0.2 million deaths worldwide [5]. Although *S. pyogenes* is not on the WHO priority list of bacteria, research on this bacterium may be useful in relation to the related drug-resistant *S. pneumoniae*. With respect to *S. pyogenes*, antibacterial activities of CBD, CBG, and Δ-THC were also demonstrated, achieving MIC in the range of 0.65–50, 0.59, and 5–50 mg/l, respectively. These values are comparable to recognized antibacterial drugs such as fusidic acid (1–>16 mg/l), mupirocin (0.06–6.25 mg/l), retapamulin (0.016–0.25 mg/l), ozenoxacin (≤0.004–2~ mg/l), amoxicillin (≤0.063–>2 mg/l), benzylpenicillin (0.023–256 mg/l), erythromycin (≤0.063–>256 mg/l), levofloxacin (0.38–1024 mg/l), penicillin (0.004–0.25 mg/l), rifampicin (64–>1024 mg/l), tetracycline (1–≤16 mg/l), and trimethoprim (8–>512 mg/l) [5].

Bioavailability of Cannabinoids

Due to the low oral bioavailability of CBD, various formulations, excipients (e.g., oil-based), routes of administration, and postprandial use can increase the clinical utility of this cannabinoid. It is suggested to test CBD with existing antibiotics to prolong their effectiveness through the use of antibiotic adjuvants. Cannabinoids may be suitable for treating bacterial skin and wound infections due to their antibacterial, wound-healing, and skin-moisturizing properties. Additional therapeutic properties, such as anti-pruritic and anti-inflammatory effects, may further enhance their effectiveness in these cases. These findings highlight the significant potential of cannabinoids in antimicrobial treatment, opening up possibilities for synergistic approaches, biofilm eradication, and effective action against persistent bacteria [5].

Research methodology

The studies cited above used very diverse hemp material, including methanol extract (from seeds and whole plants or from leaves and branches), hydro-alcoholic extract, 80% ethanol extract from seeds, 0.1% extract (in acetic acid and hexane) from dried, flowering tops of plants, and the cannabinoids themselves. As can be seen, very disparate MIC values were obtained, which was caused by the use of different materials and methods, including the difference in the size of the inoculum used, and even the type of 96-well plates used. It turned out that polystyrene was the most suitable for testing CBD and its derivatives. However, the most important influence was the culture medium used. Changing from Mueller-Hinton broth (CAMHB), in which the content of calcium (Ca++) and magnesium (Mg++) ions is precisely adjusted, to Mueller-Hinton agar (MH-F) increased the MIC values for CBD sixteen-fold in the case of *S. aureus*. Furthermore, changing from nutrient broth to horse blood agar increased the MIC values for CBD and THC tenfold in the case of *S. aureus*. These differences may have resulted from the high binding of CBD to proteins, which affected tests conducted against *S. pyogenes*, where blood is required in the culture medium. Therefore, it is important to comply with the established guidelines of the European Committee

on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI), which will allow for the standardization of experimental parameters, such as inoculum size, incubation conditions, and culture medium, as well as a better understanding of the full antibacterial potential of cannabinoids [5].

Mechanisms of antibacterial action

The mechanisms of antimicrobial action of cannabinoids are intensively studied, but many aspects are still not fully understood. It is generally accepted that their key target is Gram-positive bacteria, due to structural differences in the cell wall compared to Gram-negative bacteria. The main proposed mechanism is the disruption of the integrity of the bacterial cell membrane, leading to its depolarization and ultimate lysis [18]. This activity is closely related to the physicochemical properties of the compounds. Structure-activity relationships (SAR) studies have revealed that the antibacterial potential is strongly determined by chemical features such as the monoterpene region, the aromatic alkyl side chain, and the presence of free, phenolic carboxyl groups. The monoterpene region affects the potency of cannabinoids, as cyclic forms, such as CBD, are more effective than acyclic forms, such as CBGA. The length of the aromatic alkyl side chain and the decarboxylation of aromatic COOH groups enhance antibacterial properties, indicating that maintaining the lipophilic prenyl groups and phenolic hydroxyl groups is essential for antibacterial action against Gram-positive bacteria. Despite strong lipophilicity, which would suggest non-specific membrane damage, activity is sensitive to subtle chemical modifications. For example, methylation and acetylation of phenolic hydroxyl groups or esterification of carboxyl groups significantly reduced antibacterial activity. This sensitivity suggests that the mechanism of action extends beyond simple hydrophobic damage. Specific interaction with membrane components or other intracellular targets is therefore required, suggesting a specific, although still not fully understood, mechanism of activity [18].

In summary, microbiological studies consistently show that *C. sativa* contains compounds with strong, but selective antimicrobial activity, directed mainly against Gram-positive bacteria that have developed resistance to the main classes of antibiotics available on the market [2]. Cannabinoids such as CBD, CBG, and Δ-THC are a promising individual alternative or can be used as an adjunct to traditional antibiotics, especially in the treatment of *S. aureus*, MRSA, and *S. pyogenes*. Their favorable safety profile places them as potential candidates for antibacterial therapies, although rigorous clinical trials, standardized tests, and long-term safety studies are essential to fully exploit their potential in the fight against drug-resistant bacteria. Despite these promising results, research on cannabinoids is still at an early stage. In the future, the additive and synergistic potential of cannabinoids with conventional antibiotics and other antimicrobial agents should be investigated, their structure-activity relationships optimized, and cannabinoid formulations and delivery systems refined to fully utilize their therapeutic potential in clinical settings [5].

Fungi

Fungal infections pose an increasingly serious public health problem, killing over 3.8 million people and affecting over a billion annually worldwide [19]. In 2022, the WHO published its first list of 19 priority pathogenic fungi that pose the greatest threat to human health. Pathogenic fungi were divided into categories based on their impact on public health and the risk of resistance to

antifungals. The critical priority group included: *Cryptococcus neoformans*, *Candida auris*, *C. albicans*, *Aspergillus fumigatus*. Fungi in the high priority group are, for example, *Candida glabrata*, *C. tropicalis*, *C. parapsilosis*. Fungi in the medium priority group include, for example, *C. krusei* and *Cryptococcus gattii* [20].

Cryptococcus neoformans

This fungus causes cryptococcosis, which can lead to pneumonia, meningitis, and encephalitis, especially in patients with *HIV* and AIDS, solid organ transplant recipients, cancer patients, people using intravenous drugs, and people with diseases requiring immunosuppressive drug therapy. Currently available antifungal drugs (azoles and allylamines, which affect the ergosterol biosynthesis pathway; polyenes, which directly affect ergosterol; echinocandins, which inhibit the synthesis of β-glucan cell wall, and pyrimidine analogs, which block protein synthesis or inhibit DNA replication) are unfortunately strongly nephrotoxic, can cause myelosuppression and gastrointestinal disorders [19]. Therefore, new antifungal drugs are still being sought, including from *C. sativa*. The latest research results by Hue Dinh *et al.* from 2025 [19] using CBD and CBDV indicated that both cannabinoids acted fungicidally against *C. neoformans* (MFC (minimum fungicidal concentration) 25 μg/ml and 50 μg/ml, respectively) already 30 minutes after application. Their action was significantly faster than in the amphotericin B control, where killing action was observed after 4 hours. Interestingly, the MIC values of phytocannabinoids were tested depending on different culture conditions and it was found that they changed depending on pH and medium choice, namely both RPMI1640 (pH = 4.0) and YNB (pH = 4.5) increased the MIC values for CBD and CBDV 2–4 times compared to RPMI (pH = 7.4) [19]. The above results show how important the standardization of experimental parameters is, similarly to the case of bacterial cultures described above in this article.

It was also found that within the *Cryptococcus*, CBDV was active against all nine tested strains, covering six species, for which the MIC was most often 12.5 μg/ml. Although CBD was active against only one of the nine *Cryptococcus* strains (*C. deneoformans*), its MIC was lower at 3.13 μg/ml [19].

Additionally, it was observed that both cannabinoids prevented biofilm formation in *C. neoformans* by reducing capsule size (at concentrations of 1.56 and 0.78 μg/ml, respectively) and disrupting mature biofilm (3.13 μg/ml for CBDV). The potential for anti-biofilm action is important because fungal infections involving biofilm are considered a significant clinical problem related to the colonization of the central nervous system, contamination of implanted medical prostheses, and drug resistance in many fungal species [19].

The ability of CBD to locally treat *C. neoformans* fungal infection was then tested *in vivo*, using a burn wound model with the insect *Galleria mellonella*, and a significant improvement in the survival of CBD-treated larvae was observed. This is evidence that CBD can be easily adapted to treat topical fungal infections in clinical settings [19].

Additional proteomic analysis showed that the antifungal action of CBD and CBDV was linked to cell membrane destabilization, changes in ergosterol biosynthesis, disruption of metabolic pathways, and selective involvement of mitochondria-related proteins [19].

Other very promising results were obtained from a drug pairing test, which showed no synergistic or antagonistic effects between phytocannabinoids and standard antifungal drugs, including amphotericin B and fluconazole, meaning that phytocannabinoids do not appear to interact with existing antifungal drugs. These results indicate that phytocannabinoids may be promising

potential drugs not only in the treatment of immunocompromised patients caused by *C. neoformans*, but also in community-acquired cases caused by other *Cryptococcus* strains, such as *C. gattii*, which mainly occurs in healthy patients [19].

Candida

C. auris is a new species of yeast that has recently spread, causing candidiasis. *C. albicans*, which is part of the human physiological flora (including the respiratory tract), does not cause problems in healthy people, but can cause disease when immunity is lowered. Of the 12 clinical strains of 10 *Candida* species tested (including those on the WHO list) CBDV was active against only three of them, including C. *albicans*, *C. dubliniensis* (MIC = 12.5 μg/ml) and *C. guilliermondii* (MIC = 25 μg/ml), while CBD was not active against the remaining strains (including those on the WHO list: *C. auris*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. krusei*) up to the highest tested concentration (25 μg/ml) [19]. In the case of *C. albicans*, the hydroxylated derivative CBNA also showed good antifungal activity (IC50 = 4.6 M) [21]. In the study by Zheljazkov *et al.* [12] from 2020, the activity of cannabis essential oil (with CBD, THC and terpenes) against *C. albicans*, *C. krusei* and *C. tropicalis* was confirmed (growth inhibition zones of approximately 1.5 to 9 mm were observed) [12]. *Candida albicans* was also sensitive to an ethanol extract from hemp leaves, which inhibited yeast growth by 20–37 mm [13]. Summarizing the above observations, it can be stated that phytocannabinoids are broadly active against *Candida* spp., and especially against *C. albicans*, and may be suitable as broad-spectrum antifungal drugs.

Aspergillus and other molds

Aspergillus fumigatus causes aspergillosis. Hue Dinh *et al.* [19] tested 5 *Aspergillus* species (including *A. fumigatus*) from various sources (veterinary, clinical, and environmental) and showed no activity of CBD and CBDV on their growth. In the case of other molds, CBD was active against the clinical strain *M. circinelloides* (MIC = 6.25 μg/ml), but not against *R. oryzae* and *F. oxysporum cpx*, while CBDV was active against *R. oryzae* (MIC = 12.5 μg/ml). The activity observed for at least one phytocannabinoid in the case of *M. circinelloides* and *R. oryzae* is important because both can cause human fungal infections with high mortality, especially in immunocompromised patients, and treatment is often difficult. For example, *Mucor spp*. are intrinsically resistant to almost all current antifungal treatments, and *Rhizopus* can easily acquire resistance [19]. Additionally, it was shown that an ethanol extract from hemp leaves was active against *A. niger* (growth inhibition zone 3–10 mm) [13].

The above latest, although scarce and preliminary reports, indicate the antifungal effect of hemp compounds on clinically significant and diverse pathogens, although further research, especially in the field of chemical modification of phytocannabinoids, would be advisable to expand their activity and reduce the effective dose [19]. Developing new antifungal drugs is a challenge because fungi are eukaryotes, which makes it difficult to achieve selective toxicity that would not be harmful to host cells. The latest research focuses on identifying precise molecular targets in the fungal cell. *In silico* and *in vitro* studies are being conducted to screen cannabinoids and other compounds from *C. sativa* (e.g., stilbenoids) against key, specific fungal proteins whose inhibition could disrupt their metabolism (enolase, synthase, guanosine monophosphate synthetase, GMP) or cell wall synthesis (glycosylphosphatidylinositol, GPI) [19, 22]. Targeting specific metabolic

pathways represents an evolution in research into cannabis-derived antifungal drugs. This means moving away from the search for non-specific membrane toxins towards developing more selective, new classes of drugs, which is crucial for minimizing systemic toxicity [19].

Clinical application

Despite impressive *in vitro* results in combating drug-resistant bacteria and fungi, the introduction of cannabinoids into routine clinical practice is associated with serious pharmacological and toxicological challenges. Cannabinoids, being highly lipophilic compounds, create difficulties in optimizing bioavailability and stability in drug delivery systems. For effective systemic use, advanced formulations, such as nanoparticles or liposomes, are required to improve their solubility and clearance [23]. In terms of safety, CBD (e.g., in the approved preparation Epidiolex) is generally considered to have a more favorable profile than Δ9-THC. The most commonly reported mild side effects are fatigue, diarrhea, and changes in appetite or body weight [24]. Nevertheless, in some clinical trials and use cases, the possibility of more serious effects, such as liver damage, has been reported, requiring close monitoring of patients, especially at high doses [25].

The biggest barrier to the systemic use of cannabinoids as antibiotics is their strong interaction with cytochrome P450 (CYP) enzymes, which are responsible for the metabolism of most drugs [26]. CBD and Δ9-THC are known inhibitors, and CBD additionally exhibits time-dependent inhibition of several key isoenzymes, i.e., CYP2C19, CYP2C9, and CYP3A4, the most important drug-metabolizing enzyme in the body [27, 28]. Clinical pharmacokinetic studies have shown dramatic consequences of this inhibition. Administration of a CBD-dominant extract together with a mixture of test drugs showed a significant increase in the area under the curve (AUC) of the co-administered drugs. This indicates an increase in the amount of drug absorbed into the body, e.g., the AUC of omeprazole (CYP2C19 substrate) increased by 207%, losartan (CYP2C9 substrate) by 77%, and midazolam (CYP3A substrate) by 56% [28]. Inhibition of CYP3A4 is particularly critical in the context of antimicrobial therapy, as this enzyme metabolizes numerous antifungal drugs (e.g., azoles, such as ketoconazole) and antibiotics (e.g., macrolides). Simultaneous administration of CBD with these drugs can lead to a dangerous increase in their plasma concentration, increasing the risk of toxicity. On the other hand, CYP3A4 inducers, such as rifampicin, can lower CBD plasma concentrations by 50% to 60%, leading to the ineffectiveness of cannabinoid therapy [27]. Therefore, it is essential to design and synthesize new cannabinoid analogs with high antimicrobial activity while minimizing the potential for CYP450 enzyme inhibition. Additionally, in order to bypass hepatic metabolism, local administration of cannabinoids is recommended, e.g., in the form of ointments for the treatment of skin infections and in the form of an aerosol (as currently the only registered drug in Poland, Sativex) for respiratory diseases [23].

Summary

Drug resistance in bacteria and fungi is a global health threat, prompting the search for alternative therapies. Compounds from *Cannabis sativa*, such as cannabinoids and terpenes, show potential in combating drug-resistant pathogens, including *Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis*, and fungi like *Candida* and *Cryptococcus*. Their mechanism of action involves

disrupting cell membranes, eradicating biofilm, and acting synergistically with antibiotics. Despite promising results, clinical challenges like low bioavailability and drug interactions necessitate further research into new delivery methods and cannabinoid analogs.

Funding

From SUM agreements BNW-2-067/N/5/I.

Conflict of interest

None declared.

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