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REVIEW PAPER

A recent update on the antibacterial effects of distinct bioactive molecules derived from the *Cannabis* plant

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ABSTRACT

The number of human infections with multidrug-resistant (MDR) bacteria is increasing worldwide and constitutes a serious threat to human health. Given the lack of novel antibiotic compounds worsening this dilemma, alternative antibiotic-independent treatment and prevention strategies of infectious diseases applying natural compounds appear highly appreciable. Given the long-known health-beneficial and disease-alleviating properties of *Cannabis*, we performed a literature search summarizing current knowledge regarding the antibacterial effects of extracts from different parts of the *Cannabis sativa* plant and of defined *Cannabis*-derived molecules and their potential mode of action. The included studies revealed that various extracts and essential oils of *C. sativa* as well as major cannabinoids exerted potent activities against a broad spectrum of Gram-positive bacteria and against some Gram-negative bacterial species including MDR strains. Particularly the disruption of the bacterial cytoplasmic membrane by some cannabinoids resulted in potent antibacterial effects against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*. Furthermore, defined cannabinoids inhibited the formation of and eradicated existing bacterial biofilms. In conclusion, given their antibacterial properties distinct *Cannabis*-derived molecules expand the repertoire of antibiotics-independent treatment options in the combat of bacterial infectious diseases which should be further addressed in future studies including clinical trials.

KEYWORDS

Cannabis, *Cannabis sativa*, cannabinoids, antibacterial effects, novel antibacterial therapies, multidrug-resistant (MDR) pathogens, anti-biofilm effects, antibacterial synergies, natural compounds

INTRODUCTION

Emerging bacterial resistances and need for novel antibacterial treatment strategies

Antimicrobial resistance constitutes a major threat to mankind. In fact, the number of human infections with multidrug-resistant (MDR) bacteria is increasing globally and accounted for approximately 1.27 million worldwide deaths in 2019 [1]. Antibiotic resistance development of bacterial pathogens reduces the efficacy of crucially needed antibiotics for invasive surgery and chemotherapy, but also hampers therapeutic approaches for usually easy-to-treat diseases [2]. Therefore, there is urgent need to develop novel antibacterials and to identify molecules improving the antimicrobial efficacy of common antibiotics [3].

Cannabis sativa as a therapeutic drug

Cultivated for almost 12,000 years, the plant *C. sativa* provided fibers for ropes and nets, as well as seeds for food and oil [4]. Furthermore, psychotropic and medicinal effects of ingredients of *Cannabis* supported its utilization for religious rituals as well as for the topical

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treatment of inflammatory morbidities or as pain reliever throughout thousands of years [4]. The discovery of phytocannabinoids and the identification of their chemical structure characterized by a lipid structure featuring alkylresorcinol and monoterpene moieties [5], led to the exploration of the endocannabinoid system as the main pharmacological target for cannabinoids [4, 5]. Despite ongoing debates about the legal status of *Cannabis,* there is evidence for its useful therapeutic application in modern medicine. *Cannabis* and its derivates show potent relieving effects on chemotherapy-induced nausea [6], pain due to underlying cancer or rheumatic diseases [7, 8], Parkinson's disease and multiple sclerosis related symptoms [9, 10] as well as sleeping disorders [11], for instance.

Research question

Given the rising incidences of infections caused by MDR bacterial pathogens, it is utmost appreciable to identify natural compounds with antibacterial effects in order to reduce the application of common (e.g., synthetic) antibiotics and to combine antibiotics with natural substances to increase their antibacterial potencies. Given their potential as a therapeutic/preventive measure in the combat of infections caused by bacterial pathogens including MDR strains, we performed a literature search summarizing current knowledge regarding the antibacterial effects of extracts and bioactive molecules derived from the *Cannabis* plant.

METHODS

Literature research strategy

The literature research was performed from June 10th to June 14th, 2024 using the online meta database "PubMed" of the NLM and U.S. National Institute of Health, which combines accesses to several databases for medical and biomedical studies. The search terms cannabis "AND" antibacterial "AND" resistance provided a total of 34 results.

Inclusion and exclusion criteria

After careful assessment, review articles were excluded which also held true for other papers that were unrelated to the research question. Studies matching the above-mentioned search terms examining the antimicrobial effects of extracts and defined molecules derived from the *Cannabis* plant against human pathogenic bacteria were included. Excluded, however, were studies addressing the impact of *Cannabis* on the gut microbiome, on immune function, on bacterial virulence or on bacterial membrane vesicle release, for instance. Furthermore, studies about other plant species were excluded. Finally, 16 papers were included into our study.

Data extraction

The included search results were divided in two groups: The first group represents studies exploring antibacterial effects of differently extracted substance mixtures from *Cannabis* [12–18], while the second group includes studies examining the antibacterial effects of isolated cannabinoids as single substances [19–27]. Furthermore, the antibacterial effects of *Cannabis* extracts and single defined cannabinoids against different bacterial species were summarized, evaluated, and discussed.

RESULTS

Antibacterial properties of distinct *Cannabis* extracts

Seven of the included studies tested the antibacterial activity of mixtures of substances extracted from *Cannabis*, including *Hemp* seed oil and ethanolic as well as hexanoic extracts derived from the seed's marc [12], *Cannabis* inflorescences resin [13], ethanolic leaf or plant extracts [14, 16, 18], and furthermore, *Hemp* essential oils [15] and acidic hexane extract of dried flowering tops [17]. Fifteen different bacterial species were tested, including six Gram-positive and nine Gram-negative bacteria [12–18] and among those, also several antibiotic-resistant clinical isolates such as methicillin-resistant *Staphylococcus aureus* (MRSA) and MDR *Klebsiella pneumoniae*.

In their study, Chakraborty and colleagues tested the antibacterial effects of ethanolic plant extracts derived from *Cannabis sativa, Thuja orientalis, and Psidium guajava* against both, clinical and non-clinical MRSA isolates applying the disc diffusion method [14]. While *C. sativa* extract caused greater inhibition zones if compared to synthetic antibiotics against which the bacterial strains were resistant, the combination of *C. sativa* and *T. orientalis* extracts led to even greater zones of inhibition than vancomycin [14].

These results were supported by Malikova et al. who assessed the cannabinoid content and antibacterial activity of ethanolic *C. sativa* extracts across the whole plant vegetation cycle [18]. The study revealed that in weeks 1–13 of cultivation all ethanolic extracts exhibited antibacterial activity against all tested *S. aureus* strains including both, methicillin-sensitive *S. aureus* (MSSA) and MRSA isolates with minimum inhibitory concentrations (MICs) of 256 μg mL^{-1} or even below [18]. The lowest MICs of 32–64 μg mL^{-1} were detected in extracts taken from plants in weeks 5–13 of cultivation, while the cannabinoid contents peaked in plants at full maturity in the 11th week [18].

Furthermore, Zengin et al. tested the anti-staphylococcal activity of *Hemp* essential oils in a cell viability assay including four clinical *S. aureus* isolates with different antimicrobial susceptibility patterns [15]. The MIC of the compounds against all *S. aureus* isolates was 8 mg mL^{-1} and the additionally measured minimum bactericidal concentration (MBC) was twice as high [15]. An anti-biofilm assay with *Hemp* essential oils against respective *S. aureus* isolates revealed minimum biofilm eradication concentrations (MBEC) of 16–24 mg mL^{-1} [15]. Notably, the *Hemp* essential oils were further analyzed regarding their molecular

contents by gas chromatography/mass spectrometry and flavonoids, phenols and phenolic acids, but no phyto-cannabinoids could be identified [15].

Two other studies addressed the antibacterial activities of *Hemp* seed oil and ethanolic/hexanoic seed marc extracts as well as hexanoic flower top extracts against both, Gram-positive and Gram-negative bacterial species [12, 17].

When testing *Hemp* seed oil, ethanolic and hexanoic seed marc extracts against Gram-positive bacteria such as *S. aureus* including MRSA, *Staphylococcus epidermidis,* and *Cutibacterium acnes,* MICs ranging from 128 to 2048 μg mL^{-1} could be determined with the best susceptibility of *S. aureus* towards *Hemp* seed oil and of *S. epidermidis* towards the ethanolic marc extract [12]. When tested against Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa,* however, no growth inhibitions were detected even upon exposure to high doses of respective compounds [12].

In line, the study by Muscara and colleagues revealed a lack of antimicrobial effects exerted by two hexane extracts of flowering tops (from a new Chinese accession of *C. sativa*) against *E. coli* and *P. aeruginosa* [17]. Furthermore, several clinical MSSA and MRSA isolates were included into the analyses, and the MICs and MBCs of respective compounds determined. While MICs of the extracts against the MSSA isolates were 39.06 μg mL^{-1}, the MBC of the extracts tested against the MSSA and the MRSA bacteria ranged from 39.06 to 78.13 μg mL^{-1} [17].

In a very recent study from 2024, Armassa et al. examined the effects of ethanolic extracts derived from *C. sativa* leaves and stems against several Gram-negative bacteria including MDR isolates [16]. When applying the disc diffusion method, the greatest inhibition zone could be detected when testing the ethanolic extracts against *P. aeruginosa,* followed by *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* [16]. The lowest MICs (namely, of 0.78 mg mL^{-1}), however, were detected in case of stem extracts against *S. maltophilia*, whereas the lowest MBCs were measured for the leaf extracts against *A. baumannii*, MDR *K. pneumoniae*, *S. maltophilia,* and *P. aeruginosa*. In addition, the authors assessed an MBC of 12.5 mg mL^{-1} for the leaf extracts against a clinical *Enterococcus faecalis* strain. Hence, the results revealed distinct antimicrobial effects of the here used ethanolic *C. sativa* extracts even against MDR Gram-negative pathogens [16].

In 2024, Vozza Berardo and colleagues tested another mixture of substances derived from *Cannabis* including resins of female inflorescences against Gram-positive bacteria such as *Bacillus thurigensis* and *Micrococcus luteus* and against Gram-negative species including *Pseudomonas protegens* and *E. coli* [13]. The authors recorded bacterial growth rates in the presence of resin concentrations ranging from 1 to 4 μg mL^{-1} sampled from five different *C. sativa* strains. While *P. protegens* showed no significantly reduced growth rate at any resin concentration, 2 μg mL^{-1} of the resins derived from all five *C. sativa* strains were sufficient to significantly reduce the growth of *E. coli*, whereas the same concentration was determined for four out of five resins against *M. luteus*. The growth rate of *B. thurigensis* could even be significantly reduced by 1 μg mL^{-1} in four out of five samples [13].

Antibacterial activities of defined cannabinoid molecules

To further specify which specific molecules of *C. sativa* show antibacterial properties, nine more search results were included in this literature review, investigating the activity of major cannabinoids and their corresponding acids [19–22, 25, 27] as well as nine less common cannabinoids [24] and nine minor-oxygenated cannabinoids [26]. Furthermore, potential synergies of cannabidiol (CBD) and other cannabinoids with broad-spectrum antibiotics were analyzed [15, 20, 23].

Antibacterial effects of Δ9-THC and cannabidiol. In 1976, van Klingeren and Ten Ham performed a study on the antibacterial effect of Δ9-tetrahydrocannabinol (Δ9-THC) and CBD [19]. The authors determined MICs of both substances against three Gram-negative bacterial species (namely, *E. coli, Proteus vulgaris*, and *Salmonella* Typhi) and four Gram-positive species including *S. aureus, Streptococcus pyogenes, Streptococcus milleri,* and *Streptococcus* (*Enterococcus*) *faecalis*. While no antimicrobial activities were detected against the Gram-negative bacteria (MIC values >100 μg mL^{-1}), MICs of 1–5 μg mL^{-1} for CBD, and of 2–5 μg mL^{-1} for Δ9-THC against the Gram-positive strains were measured. By repeating the measurements on horse blood agar instead of nutrient broth, however, the MICs increased by up to ten-fold, which was further validated by testing the bactericidal activity within four hours and measuring the bacterial growth reduction with and without horse serum added to the samples. Hence, both *Cannabis*-derived molecules can exert bacteriostatic and bactericidal properties, but with poor effects in the presence of blood [19].

The antibiotic effects of CBD were further tested against an extended spectrum of Gram-positive and Gram-negative bacteria by Blaskovich et al. [20]. Therefore, the authors tested several *S. aureus* strains, including MRSA and even vancomycin-resistant *S. aureus* isolates and determined MICs of 1–2 μg mL^{-1} upon CBD exposure. Moreover, more than 20 Gram-positive bacterial strains, including MDR *Streptococcus pneumoniae,* vancomycin-resistant *Enterococcus* species (VRE) and *Clostridioides difficile* showed MIC values of 1–4 μg mL^{-1}, whereas higher MICs (i.e., of 4–8 μg mL^{-1}) were obtained when testing CBD against *S. epidermidis* [20]. The reduced efficacy of CBD in the presence of blood was also underscored in this study, given MIC values of >256 μg mL^{-1} against MRSA after adding 50% human serum, for instance. Meanwhile, rather discouraging results were obtained when testing CBD against Gram-negative bacterial species as indicated by MIC values of >64 μg mL^{-1} against most of the included strains such as MDR *K. pneumoniae, A. baumannii* and *Salmonella* Typhimurium. However, the growth of at least four out of 15 Gram-negative species including *Moraxella catarrhalis, Legionella pneumophilia, Neisseria meningitidis,* and

Neisseria gonorrhea could be inhibited by CBD with MIC values of 0.25–1.0 μg mL^{-1} [20].

Rather conflicting results were obtained in a study by Gildea et al. [21] addressing the antibacterial efficacy of CBD against *Salmonella* species. The authors measured CBD MICs of 0.0125 μg mL^{-1} and 0.125 μg mL^{-1} against *S.* Typhimurium and *Salmonella* Newington, respectively, and hence, obtained much lower MIC values if compared to the results from the study by Blaskovich et al. (i.e., CBD MIC of >64 μg mL^{-1} when tested against *S.* Typhimurium) [20]. Of note, Gildea et al. also described a gain of resistance in both, *S.* Typhimurium and *S.* Newington against repeated exposure to low CBD concentrations as early as 12 h [21], whereas Blaskovich et al. did not find such CBD resistance development in *Salmonella* [20].

Martinenghi and colleagues also performed MIC measurements of CBD against two Gram-positive and Gram-negative species each [22]. When testing CBD against *S. aureus* and *S. epidermidis* MIC values between 1 and 4 μg mL^{-1} were obtained, while *P. aeruginosa* and *E. coli* were not affected by the presence of CBD as indicated by MICs >64 μg mL^{-1} [22].

Antibacterial activity of other cannabinoids. In addition to Δ9-THC and CBD, Appendino et al. [25] and Farha et al. [27] also screened cannabichromene (CBC), cannabinol (CBN), cannabigerol (CBG), and further cannabinoids and derivates regarding their antimicrobial activity against *S. aureus* including MSSA and MRSA strains. The analyses revealed MIC values for CBC ranging from 1 to 2 μg mL^{-1} [25] to 8 μg mL^{-1} [27], whereas for both, CBN and CBG MICs between 1 μg mL^{-1} and 2 μg mL^{-1} were measured [25, 27]. Other derivatives such as cannabidivarin and Δ9-tetrahydrocannabidivarin [27], chemically modified derivates of respective major cannabinoids [25], as well as newly extracted cannabinoids [24] and minor oxygenated cannabinoids [26], presented much higher MICs than the five major cannabinoids indicative for negligible or even absent antibacterial activity. In additional tests, Farha et al. [27] showed that out of the five major cannabinoid molecules, CBG appeared to be the most effective antibiotic substance given the lowest concentration needed in order to inhibit biofilm formation and notably, due to its highest potency against non-growing, dormant "persister" subpopulations of MRSA bacteria [27]. Additionally, no spontaneous resistant mutants or development of resistance to CBG were detected in MRSA, neither at lethal dosages of 2xMIC to 16xMIC nor by below-MIC exposition over 15 days [27].

Antibacterial modes of action of cannabinoids

Martinenghi and colleagues also determined the MICs of cannabidiolic acid (CBDA), the carboxylated form of CBD, against distinct Gram-positive bacteria and collectively found MICs that were twice as high as those of CBD [22]. In addition, radiolabeled macromolecular synthesis assays revealed that at near-MIC concentrations of CBD almost all signaling pathways except that for lipid synthesis were shut down in MRSA, but not *E. coli* [20], which was accompanied by a CBD dose-dependent membrane depolarization in the former but not the latter. Based upon these observations, Martinenghi et al. and Blaskovich et al. hypothesized that CBD was able to permeabilize the cytoplasmic membrane of Gram-positive bacteria resulting in cell death [20, 22]. This hypothesis was further supported by results obtained from bacterial cytological profiling experiment, in which a usually not cell-penetrable marker was taken up by the MRSA bacteria in a dose- and time-dependent manner, as detected by fluorescence microscopy [20].

Appendino et al. investigated the anti-staphylococcal effects of an extended panel of cannabinoids and their carboxylated forms and the underlying modes of action [25]. Therefore, six strains of *S. aureus* including MRSA as well as clinical isolates expressing an efflux pump were screened regarding the MICs in presence of five cannabinoids and their derivates. Concerning CBD and CBDA, previously described results of two-fold higher MICs for the acidic derivate could be confirmed. Δ9-THC, CBN, CBG, and CBC showed antibacterial efficacies against the tested strains that were comparable to CBD (MIC values of 1–2 μg mL^{-1}), while Δ9-THC-acid presented even four- to eight-fold higher MICs than its decarboxylated derivate. Moreover, adding further polarized groups to CBG resulted in decreased membrane permeability, or an increased membrane solubility causing lower intracellular concentrations and hence, less antibacterial activity resulting both in increased MICs. Collectively, the authors hypothesized that the bacterial cytoplasmic membrane may be considered as a specific, but yet elusive, target structure for cannabinoids [25].

When performing gene-knockout tests with *Bacillus subtilis*, no suppressors for supra-lethal CBG concentrations were found in a study by Farha and colleagues [27]. The authors identified, however, more than 40 transposon mutants that were sensitive to sub-lethal concentrations of CBG, and were enriched for genes encoding for membrane-related proteins. Hence, the obtained results further support the hypothesis that CBG and possibly other cannabinoids may act on the cytoplasmic membrane of bacteria [27].

Synergies between cannabinoids and common synthetic antibiotics

Farha et al. investigated the antibacterial effects of the five major cannabinoids, and could also confirm their antibiotic activity against Gram-positive bacteria including MRSA [27]. Conversely, Δ9-THC, CBD, CBN, CBG, and CBC failed to affect Gram-negative bacterial strains including *E. coli* due to the outer membrane of the bacteria serving as a permeability barrier and preventing the substances to interact with the cytoplasmic membrane. When co-incubating *E. coli* with the cannabinoids plus polymyxin B in sub-lethal doses known to permeabilize exclusively the outer membrane, however, the cannabinoids could get access to the cytoplasmic membrane of the *E. coli* bacteria and exert their antimicrobial effects [27].

Gildea et al. further addressed potential synergies between CBD and common synthetic antibiotics on *S.* Typhimurium [23]. The results revealed that CBD could improve the antimicrobial effects of ampicillin and polymyxin B, but not of kanamycin when given in combination. Additionally, the risk for the development of resistances were reduced by co-treatment if compared to mono-treatment with respective substances [23]. The evidence for potential synergies between distinct antibiotics and CBD against Gram-negative bacteria was further supported by Blaskovich et al. showing that sub-MIC dosages of polymyxin B or colistin could reduce the CBD MIC when tested against *A. baumannii* from >64 μg mL^{-1} upon CBD mono-treatment to 4–8 μg mL^{-1} [20].

Anti-biofilm efficacy of cannabinoids

Farha et al. demonstrated that the five major cannabinoids could effectively suppress biofilm formation in *S. aureus* including MRSA isolates and that this effect correlated with the bacterial growth inhibiting effects of respective molecules [27]. The most potent anti-biofilm activity was observed for CBG with a concentration as low as 0.5 μg mL^{-1} that was needed to inhibit biofilm formation. Moreover, the MBEC of CBG was detected at 4 μg mL^{-1} [27].

Blaskovich et al. provided further evidence on the anti-biofilm effects of CBD in both, MSSA and MRSA [20]. While the MBECs were ranging between 2 and 4 μg mL^{-1}, 32 μg mL^{-1} of CBD were needed to kill >90% of the cells. Yet, by fluorescence dying of released nuclear chromatin, CBD was shown to penetrate and even kill the biofilm [20]. Furthermore, a study by Gildea et al. revealed that also biofilms of *Salmonella* spp. could be eradicated upon CBD upon application at the MIC [21].

Topical and systemic application studies

Given the promising antibacterial properties of CBD and CBG in particular, further efficacy tests were performed. In their study, Blaskovich et al. examined the antibacterial effect of topical CBD application in an *ex vivo* porcine *S. aureus* skin infection model to evaluate its potential for treating clinical morbidities such as atopic dermatitis or acne in humans [20]. Therefore, different formulations with varying CBD concentrations between 5% and 20% were used. Overall, the outcome of topical CBD treatment appeared to be formulation dependent, but some formulations could significantly reduce the bacterial loads. One particularly effective formulation was subsequently tested in an *in vivo* murine skin infection model using immunocompromised mice presenting with a disrupted skin. Results revealed that also in this model topical CBD application could significant reduce the *S. aureus* burdens [20]. When testing the systemic effectiveness of CBD in immunocompromised mice suffering from MRSA thigh infection, neither subcutaneous, nor oral, nor intraperitoneal application resulted in a significant reduction of the MRSA bacteria, however [20].

In contrast, CBG was shown to exert systemic effects. Farha and colleagues infected mice with MRSA via the intraperitoneal route and detected a reduction of bacterial loads by 2.8 orders of magnitude after intraperitoneal CBG treatment which was comparable to vancomycin treated control mice [27].

DISCUSSION

Main findings of this literature review

All studies that were included into this review (including the applied *Cannabis* compounds, bacterial strains, and obtained results) are summarized in the Supplementary Table.

Distinct cannabis extracts. Collectively, various extracts, oils and essential oils of different *Cannabis* plant parts were shown to exhibit pronounced antibacterial effects [12–18]. While most of the samples were found to be active against Gram-positive bacteria, such as *S. aureus* including MRSA [12, 14, 15, 17, 18], contrasting results were obtained when testing the compounds against Gram-negative bacteria such as *E. coli and P. aeruginosa*. While *Hemp* seed oil and marc extracts as well as flowering tops extract did neither inhibit growth of *E. coli* nor of *P. aeruginosa*, resins of *C. sativa* significantly reduced growth rates of the former, for instance [12, 13, 17]. *P. aeruginosa* meanwhile was inhibited by ethanolic leaf extract of *C. sativa* which was also true for other MDR Gram-negative pathogens such as *K. pneumoniae, A. baumannii*, and *S. maltophilia* [16]. Although some included studies provided information on chemical profiles of the utilized *C. sativa* compounds [12, 13, 15, 18], the content of different molecules was very variable as shown for phyto-cannabinoids which could not be detected in *Hemp* essential oils at all [15], while high contents were measured in *C. sativa* resins, for instance [13]. Taking this into consideration and additionally the heterogeneity of the included bacterial species, the results are poorly comparable which each other and evidence concerning which distinct molecules within the extracts were responsible for the antibacterial activities as well as how they interacted with each other awaits further exploration.

Defined cannabinoid molecules. When focusing on defined cannabinoids, especially the five major ones including Δ9-THC, CBD, CBN, CBG, and CBC, displayed pronounced antimicrobial effects against Gram-positive bacteria [20, 22, 27], but were only partly effective when tested against Gram-negative bacterial species [20, 21, 24, 27]. The antibacterial effectiveness, particularly against the latter, could be enhanced, however, when applied in combination with common antibiotics including polymyxin B known as inhibitor of the outer membrane in Gram-negative bacteria [20, 23, 27]. In addition, the major cannabinoids, especially CBD and CBG, displayed potent anti-biofilm forming and even biofilm eradicating effects [20, 27]. One potential mechanism underlying their antimicrobial effects might be the permeabilization of the bacterial cytoplasmic membranes upon cannabinoid exposure resulting in bacterial cell

death [20, 22, 27]. Notably, the antimicrobial activity of cannabinoids such as Δ9-THC and CBD was decreased in the presence of blood given increased MIC values when tested against MRSA upon adding human serum to the nutrient broth [19, 20]. Consistently, CBD showed no systemic antibacterial effect in murine MRSA infection models but was effective upon topical application [20], whereas CBG treatment of mice suffering from systemic MRSA infection resulted in reduced pathogen burdens [27].

Results from not included but related studies

Other studies that did not explicitly match the inclusion criteria for our survey but addressed topics that were related to the focus of our study such as bacterial virulence, membrane vesicles, and immune-modulating properties are briefly commented in the following. Marine et al. demonstrated that in the presence of *Hemp* essential oils, genes encoding for motility and cell invasion were down-regulated in *Listeria monocytogenes,* Caco-2 cells were less distinctly invaded by the Gram-positive enteropathogen, and more *L. monocytogenes* infected *Galleria mellonella* larvae survived [28].

Furthermore, Kosgodage et al. reported, that CBD strongly inhibited the release of membrane vesicles from *S. aureus* and *E. coli* and may contribute to reduce the development of bacterial resistance to antibiotics [29].

In a very recent study from 2024, Balenović and colleagues supplemented broiler feed with *C. sativa* and found increased $CD4^+$ and $CD8^+$ lymphocyte subsets in peripheral blood samples from broilers contributing to enhanced immune function and host resistance to infectious diseases [30].

Limitations of this review

Due to time constraints, this literature review was performed in a limited time frame. Furthermore, "PubMed" was the only utilized data base for this literature survey and the results that were accessed using the previously described search terms were not extended by further varying search terms or other search strategies (e.g. "snowballing system"). Hence, it cannot be ruled out that not all studies matching the research question and including/excluding criteria were acquired. Since the search strategy was carried out by a single researcher, errors in the search cannot be excluded, even though the survey was done as carefully as possible. Given differences in experimental setups including used parts of the plants, extractions methods, and bacterial strains, for instance, direct comparisons of results obtained from different studies are rather challenging.

Conclusion and perspectives

Especially major cannabinoids such as Δ9-THC, CBD, CBN, CBG, and CBC revealed potent activities against a broad spectrum of Gram-positive bacteria and against some Gram-negative species, while the spectrum could be extended by taking advantage of synergies with common antibiotics. Yet, a systemic antibiotic therapy with most cannabinoids seems unrealistic due to poor antibiotic properties in the presence of blood. Since CBG, however, showed systemic effects in murine infection models, more evidence on its effectiveness in the presence of blood and potential interaction with other pharmacological targets in mammal organisms is required. Local applications of CBD or *Cannabis* extracts are meanwhile conceivable. Other studies that had not been included into our survey [28–30] provide evidence for immunostimulatory, bacterial virulence-decreasing, and bacterial membrane vesicle release-dampening effects of cannabinoids. Collectively, results from the here reviewed studies open future perspectives for cannabis-derived molecules as alternative antibiotic-independent treatment and prevention strategies in the combat of bacterial infectious diseases which should be further addressed in future studies including clinical trials.

Ethics statement: Not applicable (literature survey).

Conflict of interests: SB and MMH are members of the Editorial Board of the journal, therefore they did not take part in the review process in any capacity and the submission was handled by a different member of the editorial board. The submission was subject to the same process as any other manuscript and editorial board membership had no influence on editorial consideration and the final decision.

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Authors' contributions: MW conceived and designed the survey, wrote the paper. SB provided critical advice in design of the survey, edited paper. MMH supervised the survey, co-wrote the paper.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1556/1886.2024.00098.

LIST OF ABBREVIATIONS:

CBC	cannabichromene
CBD	cannabidiol
CBDA	cannabidiolic acid
CBG	cannabigerol
CBN	cannabinol
MBC	minimum bactericidal concentration
MBEC	minimum biofilm eradication concentration
MDR	multi-drug resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
Δ9-THC	Δ9-tetrahydrocannabinol

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