Antibacterial activity of cannabinoids on the bacteria that cause tuberculosis: a systematic review

Atividade antibacteriana dos canabinoides sobre a bactéria causadora da tuberculose: uma revisão sistemática

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Abstract

Objective: Identify any antibacterial activity of cannabinoids against Mycobacterium tuberculosis. Methods: Based on the guiding guestion "Do cannabinoids have antibacterial activity against M. tuberculosis?", we carried out a systematic review to investigate the topic. We searched for experimental, pre-clinical and clinical studies that evaluated the effects of phytocannabinoids or synthetic cannabinoids on M. tuberculosis. Studies that addressed the effects of endocannabinoids were excluded. Two independent reviewers carried out the studies selection, which after inclusion were subjected to a guality assessment. Results: 486 publications were found, of which two were included in this review: a pre-clinical in vitro study and a pre-clinical study with animals. Both studies identified an antibacterial activity of cannabidiol (CBD) against M. tuberculosis at different concentrations. Conclusion: We found preliminary evidence of the antimicrobial action of CBD on M. tuberculosis. Despite the promising results, further investigations on the subject are still warranted to verify a possible therapeutic application and the possible effects of other cannabinoids.

Keywords: Cannabinoids, Cannabidiol, Tuberculosis, Mycobacterium tuberculosis, Antibacterial.

Resumo

Objetivo: Identificar a existência de atividade antibacteriana dos canabinoides sobre Mycobacterium tuberculosis. Métodos: A partir da pergunta norteadora "Os canabinoides têm atividade antibacteriana sobre a Mycobacterium tuberculosis?", realizamos uma revisão sistemática para investigar o tema. Consideraram-se estudos experimentais, pré-clínicos e clínicos que avaliaram os efeitos de fitocanabinoides ou canabinoides sintéticos em M. tuberculosis, tendo sido excluídas investigações com endocanabinoides. A seleção dos estudos foi feita por dois revisores independentes, e os artigos selecionados foram submetidos a uma avaliação de qualidade. Resultados: Foram encontradas 486 publicações, das quais duas foram incluídas nesta revisão: um estudo pré-clínico in vitro e um estudo pré-clínico em animais. Os dois estudos identificaram atividade antibacteriana do canabidiol (CBD) para a M. tuberculosis em diferentes concentrações. Conclusão: Verificamos evidências preliminares de ação antimicrobiana do CBD sobre M. tuberculosis. Apesar dos resultados promissores, ainda são necessárias mais investigações sobre o assunto para se verificar uma possível aplicação terapêutica e os possíveis efeitos de outros canabinoides.

Palavras-chave: Canabinoides, Canabidiol, Tuberculose, Mycobacterium tuberculosis, Antibacteriano.

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INTRODUCTION

Studies of the pharmaceutical potential of Cannabis' active ingredients have increased after the discovery of the endocannabinoid system and the endogenous CB1 and CB2 receptors which, when activated, interfere with various signaling pathways, causing different effects on tissues and organs.⁽¹⁾

Cannabinoids are involved in pathophysiological processes (pain and inflammation) and can act on the gastrointestinal (modifying mobility and secretion, used as antiemetics⁽²⁾), cardiac (reducing atrial contraction and causing hypotension through the activation of cannabinoid receptors⁽³⁾), and pulmonary systems (with anti-inflammatory effect mediated by endocannabinoid metabolic pathways⁽⁴⁾), among others.

Studies show that CB1 and CB2 receptors are present in the lungs and bronchi, responding to endocannabinoids, synthetic cannabinoids, and phytocannabinoids.⁽⁵⁾ Tetrahydrocannabinol (THC), for example, can activate these receptors, while cannabidiol (CBD) and cannabinol (CBN) modulate cellular functions⁽⁴⁾. Exposure of lung tissue to the endocannabinoid anandamide, for example, causes hypoxic pulmonary vasoconstriction⁽⁶⁾, while synthetic cannabinoids induce lung inflammation.⁽⁷⁾

Infection of the lungs by the bacterium *Mycobacterium tuberculosis* is effectively controlled in most individuals due to the immune response of macrophages, dendritic cells, and fibroblasts, forming a granuloma and preventing the progression of the infection to tuberculous disease, called latent infection.⁽⁸⁾ A study showed that granuloma formation and disease containment is dependent on the early migration of alveolar macrophages to the interstitium induced by interleukin 1 (IL-1R), which defines whether the immune response will be Th1 or Th17 (faster or slower, respectively), determining the severity of the disease.⁽⁹⁾ COX-2 metabolites of endocannabinoids regulate the functions of alveolar macrophages that have CB1 and CB2 receptors on their membranes.^(4,10,11)

The impacts of (endo)cannabinoids when activating these receptors in the lung are still unclear. However, one study shows that the activation of cannabinoid receptors on alveolar macrophages selectively inhibits the release of angiogenic and lymphogenic factors, which may assist in vascular remodeling during chronic inflammation.⁽¹⁰⁾ Another study, in turn, showed that the CBD improves lung function and decreases inflammation in a mouse model.⁽¹²⁾

Given the above, this study aimed to identify the existence of the antibacterial activity of cannabinoids against *M. tuberculosis*.

MATERIAL AND METHODS

This is a systematic review of scientific literature registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) under the ID CRD42021253894, following the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta Analyzes (PRISMA).⁽¹³⁾

The guiding question "Do cannabinoids have antibacterial activity against *Mycobacterium tuberculosis*?" was defined using the acronym PEO,⁽¹⁴⁾ in which P (Population) corresponded to *M. tuberculosis*, E (Exposure), to cannabinoids, and O (Outcome) was related to antibacterial activity.

The inclusion criteria were experimental, pre-clinical and clinical studies that evaluated the effects of phytocannabinoids or synthetic cannabinoids on *M tuberculosis*. Articles that addressed the effects of endocannabinoids were excluded, as well as those that assessed the risk of acquiring tuberculosis with the recreational use of cannabinoids. It should be noted that in order to reach a greater number of publications on the topic, no time frame, country/continent or language of publication was established for the bibliographic survey.

For the search expression, free and controlled vocabulary was used, composed of terms indexed in the Health Sciences Descriptors (DeCS), Medical Subject Headings (MeSH) and Embase Subject Headings (Emtree), with their respective synonyms in Portuguese, English and Spanish, combined using the Boolean operators OR and AND (Table 1).

Table 1

Simplified search strategy in English used in databases.

| Acronym | Keyword | Search vocabulary |
|------------|----------------------------|--|
| Population | Mycobacterium tuberculosis | "Mycobacterium Tuberculosis" |
| Exhibition | Canabinoids | (Cannabis OR Bhang OR Bhangs OR Cannabi OR "Cannabis indica" OR "Cannabis indicas" OR "Cannabis sativa" OR "Cannabis sativas" OR Ganja OR Ganjas OR Hashish OR Hashishs OR Hemp OR "Hemp Plant" OR "Hemp Plants" OR Hemps OR "indicas, Cannabis" OR Marihuana OR Marihuanas OR Marijuana OR Marijuanas OR "Plant, Hemp" OR "Plants, Hemp" OR "sativas, Cannabis" OR Cannabinoids OR phytocannabinoids OR Canabidiol OR canabidiol OR Dranabinol OR THC OR Tetra-Hidrocanabinol OR Tetraidrocanabinol OR Canabigerol OR canabicromeno OR canabiciclol OR canabielsoin OR canabinol OR canabinodiol OR canabitriol OR "Medical Marijuana" OR "Marijuana, Medical" OR "Medical Cannabis" OR "Cannabis, Medical" OR "Marijuana Treatment" OR "Treatment, Marijuana" OR "Medical Cannabis" OR "Cannabis, Medical" OR "Marijuana Dispensaries" OR "Dispensaries Marijuana") |
| Outcome | Antibacterial activity | ("Antibacterial Agents" OR "Antimycobacterial Agents" OR "Anti-Bacterial Compounds" OR "Bacteriocidal Agents" OR Bacteriocide OR "Bacteriostatic" OR "antitubercular Agents" OR "Anti-Tuberculosis Agent" OR "Tuberculostatic Agent" OR "Antitubercular Antibiotics") |

Made by the authors

The search was carried out on August 22, 2022 in the databases LILACS, PubMed, EMBASE, Scopus, Web of Science, PsycINFO, BMC's BioMed Central Journals, Cochrane Library, Epistemonikos, Health Systems Evidence and Center for Review Dissemination. At LILACS, the search was carried out in English, Portuguese and Spanish. In the other databases, English was used. Furthermore, gray literature was limited to study protocol registration databases recommended in the Methodological Guidelines of the Ministry of Health,⁽¹⁵⁾ such as Clinical Trials and the gray literature databases Open Grey, Gray Literature Report, Scientific Repository of Open Access of Portugal (RCAAP), Brazilian Digital Bank of Theses and Dissertations (BDTD), and Google Scholar. A manual search was also carried out by checking the references cited in the included articles.

Subsequently, the publications were exported to the Qatar Computing Research Institute's Rayyan QCRI online reference manager⁽¹⁶⁾ for study selection. This selection was made through reading and analysis of titles and abstracts by two independent reviewers, whose disagreements were resolved by a third reviewer.

The selected articles proceeded to the full reading stage and confirmation of eligibility occurred with the articles that presented a description of the antibacterial effects of cannabinoids in tuberculosis. Subsequently, for data extraction and analysis, a synthesis matrix was created with author, year, objective and study design, in addition to the main results, article quality, methodological quality and relevance. The risk of bias assessment was also included, which was carried out using the ROBIS⁽¹⁷⁾ an instrument which evaluates three domains: pre-intervention (confounding, selection of study participants), at the time of the intervention (bias in the classification of the intervention), and post-intervention (deviation from the intended intervention, missing data, measurement of the outcome, selective reporting of results).

RESULTS

486 publications were found, of which 379 were identified in databases, 104 in gray literature and 3 through manual search. Among these, 15 publications were excluded due to duplication and 471 were considered for reading the title and abstract, with 11 studies being selected for reading in full. Of these 11, 5 were excluded because they were secondary studies, 3 because they did not address the use of cannabinoids (Hops, Polygonatum officinale and rimonabant), and 1 for not answering the guiding question. Therefore, 2 articles were considered eligible for our review. Figure 1 demonstrates the selection and inclusion and exclusion process of articles.



Figure 1

Flowchart of articles included in this systematic review, 2022

Modified from Page et al. (2020)⁽¹³⁾

In the present review, a pre-clinical *in vitro* study⁽¹⁸⁾ and a pre-clinical study carried out with animals were included.⁽¹⁹⁾ The antibacterial activity of CBD was identified in both studies, although this was less evident in the study due to Blaskovich et al. (2021).⁽¹⁹⁾ The results in more detail are presented in Table 2.

When the quality of the articles was verified, Abichabki et al. $(2021)^{(18)}$ were evaluated with a final grade of 58.7%,

as they did not mention the purity and solubility of the test, the cell passage number, the measures taken to avoid contamination by mycoplasma, bacteria, fungi and viruses, the cell density, statistical methods, software used, funding sources and conflict of interests. The article by Blaskovich et al. (2021)⁽¹⁹⁾ received a final grade of 91.9%, as they did not mention the test's solubility and metabolic competence.

Table 2

| Summary of the results of the articles included in this systematic review |
|---|
|---|

| Author and year | Objective | Design | Main results | Article quality | Method quality | Relevance |
|--|--|----------|--|-----------------|----------------|-------------------|
| Abichabki et al., 2021 ⁽¹⁸⁾ | To evaluate the antibacterial activity of ultrapure cannabidiol (CBD) against a wide diversity of Gram-negative (GN) and Gram-positive (GP) bacteria (44 different species, 95 strains), comprising standard strains and clinical isolates, and to investigate the antibacterial activity of the CBD + PB combination against GN bacteria, including chromosomal and plasmid- acquired PB-resistant and intrinsically PB-resistant GNB. | In vitro | CBD exhibited antibacterial activity against different species of bacteria, including Mycobacterium tuberculosis, which causes TB, at a minimum inhibitory concentration of CBB for Mycobacterium tuberculosis H37Rv (MIC = $9.37 \pm 1.88 \mu g / mL$) 117 and MDR M. tuberculosis CF86 (MIC = $18.78 \pm 5.95 \mu g / mL$), which should be included in clinical trials with promising efficacy. | 58,7 | 100 | Directly relevant |
| Blaskovich et al., 2021 ⁽¹⁹⁾ | Verify the antimicrobial activity of CBD in different Gram-positive/negative bacteria | In vivo | CBD showed discrete activity against M. tuberculosis H37Rv (MIC>64 µg mL -1, although with 70% inhibition at 64 µg mL) | 91,9 | 100 | Directly relevant |

DISCUSSION

Despite the extensive search carried out in the literature, only two studies were identified that addressed the effect of cannabinoids as an antimicrobial agent for Mycobacterium tuberculosis, the causative agent of tuberculosis. In view of this finding, it is worth highlighting the need for more clinical and pre-clinical studies that investigate this effect, especially considering that one of the aforementioned articles⁽¹⁸⁾ presented a low percentage of approval in relation to its quality.

Regarding the results of the two studies, there was a difference in the minimum inhibitory concentration (MIC) of CBD to observe the antimicrobial effect for the Mycobacterium tuberculosis H37Rv strain, with the study Abichabki et al. $(2021)^{(18)}$ smaller than Blaskovich et al. $(2021)^{(19)}$ (9.37 µg/mL and <64 µg/mL, respectively). This difference may be related to the study method, since the first was *in vitro* and the second involved infection of pig tissue and subsequent treatment with CBD.

Furthermore, there was a difference between the incubation time and addition of other components: in the study by Blaskovich et al. (2021),⁽¹⁹⁾ 0.02% resazurin and Tween-80 were added to each well with incubation for 5

days; in the study by Abichabki et al. (2021),⁽¹⁸⁾ there was no addition of resazurin, and the incubation was 7 days. The effect of CBD in relation to the multidrug-resistant Mycobacterium tuberculosis strain CF86 was also analyzed in the study by Abichabki et al. (2021)⁽¹⁸⁾ and presented an MIC of 18.78 μ g/mL.

The main limitation of this review is the low number of articles found. There are only two of them, the results of our search demonstrate that very little is still known about the possible therapeutic effects of CBD for the treatment of tuberculosis and highlights the need for further investigations in the area.

CONCLUSION

From the preliminary results reported, there appears to be a possible therapeutic effect of CBD for the treatment of tuberculosis. Despite this, it is not known whether other cannabinoids have this potential or which one is supposed to be more effective. Therefore, this review is limited by the available evidence and makes clear the need for other studies involving the use of cannabinoids and their effects on M. tuberculosis.

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