Cannabinoids as dental pulp capping agents: a scoping review protocol

Canabinóides como agentes de protección pulpar: um protocolo de revisão de escopo

Cannabinoides como agentes protectores de la pulpa dental: una revisión del alcance

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ABSTRACT
Exposure of the dental pulp and its contamination with bacteria from the oral environment can lead to pulp inflammation, toothache, necrosis and, in immature teeth, interruption of the rhizogenesis process; Therefore, it makes sense to suggest that bioactive materials can lead to the maintenance of pulp viability. Cannabinoids have been investigated in different areas of health and have already been studied in relation to their influence on dental pulp cells and apical papilla stem cells. This work proposes a protocol for the development of a scoping review with the objective of mapping the available literature on the use of cannabinoids as pulp protection agents. This scoping review protocol was prepared following the Peters methodology and the recommendations of the reviewer's manual for scoping reviews of the Joanna Briggs Institute (JBI) and PRISMA-ScR, and was registered in the Open Science Framework (OSF) under the DOI: https://doi.org/10.17605/OSF.IO/HYD28. Searches will be carried out in the Pubmed, Web of Science, Scopus, Cochrane, LILACS and VHL Portal databases, as well as in gray literature repositories. Data analysis will be descriptive and will involve both qualitative and quantitative data, from which a narrative synthesis will be constructed on the use of cannabinoids as protective agents for dental pulp. It is expected that the results obtained in this scoping review will provide support for future debates related to the topic and so that knowledge gaps found during the development of the review can be emphasized.

Keywords: cannabis, cannabinoids, dental pulp capping, endodontics.

RESUMO
A exposição da polpa dentária e sua contaminação com bactérias do meio bucal pode levar à inflamação pulpar, odontalgia, necrose e, em dentes imaturos, à interrupção do processo de rizogênese; dessa forma, faz sentido aventar que materiais bioativos podem levar à manutenção da viabilidade pulpar. Os canabinóides vem sendo investigados em diferentes áreas da saúde e já...
foram estudados em relação à sua influência sobre células da polpa dentária e células tronco da papila apical. Este trabalho propõe um protocolo para o desenvolvimento de uma revisão de escopo com o objetivo de mapear a literatura disponível acerca do uso de canabinóides como agentes de proteção pulpar. O presente protocolo de revisão de escopo foi elaborado seguindo a metodologia de Peters e as recomendações do manual do revisor para revisões de escopo do Joanna Briggs Institute (JBI) e do PRISMA-ScR, e foi registrado no Open Science Framework (OSF) sob o DOI: https://doi.org/10.17605/OSF.IO/HYD28. Serão realizadas buscas nas bases de dados Pubmed, Web of Science, Scopus, Cochrane, LILACS e Portal BVS, bem como em repositórios de literatura cinzenta. A análise dos dados será descritiva e envolverá tanto dados qualitativos como quantitativos, a partir dos quais se construirá uma síntese narrativa sobre o uso de canabinóides como agentes protetores da polpa dentária. Espera-se que os resultados obtidos nesta revisão de escopo fornecem respaldo para futuros debates relacionados ao tema e para que possam ser enfatizadas as lacunas de conhecimento encontradas no decorrer do desenvolvimento da revisão.


RESUMEN
La exposición de la pulpa dental y su contaminación con bacterias del ambiente bucal puede provocar inflamación pulpar, dolor de muelas, necrosis y, en dientes inmaduros, interrupción del proceso de rizogénesis; Por lo tanto, tiene sentido sugerir que los materiales bioactivos podrían conducir al mantenimiento de la viabilidad de la pulpa. Los cannabinoïdes han sido investigados en diferentes áreas de la salud y ya se han estudiado en relación a su influencia sobre las células de la pulpa dental y las células madre de la papila apical. Este trabajo propone un protocolo para el desarrollo de una revisión de alcance con el objetivo de mapear la literatura disponible sobre el uso de cannabinoïdes como agentes protectores de la pulpa. Este protocolo de revisión de alcance fue elaborado siguiendo la metodología Peters y las recomendaciones del manual del revisor para revisiones de alcance del Instituto Joanna Briggs (JBI) y PRISMA-ScR, y fue registrado en el Open Science Framework (OSF) bajo el DOI: https://doi.org/10.17605/OSF.IO/HYD28. Las búsquedas se realizarán en las bases de datos Pubmed, Web of Science, Scopus, Cochrane, LILACS y VHL Portal, así como en repositorios de literatura gris. El análisis de datos será descriptivo e involucrará datos tanto cualitativos como cuantitativos, a partir de los cuales se construirá una síntesis narrativa sobre el uso de cannabinoïdes como agentes protectores de la pulpa dental. Se espera que los resultados obtenidos en esta revisión de alcance brinden apoyo para futuros debates relacionados con el tema y para que se puedan enfatizar las brechas de conocimiento encontradas durante el desarrollo de la revisión.

Palabras clave: cannabis, cannabinoïdes, recubrimiento pulpar, endodoncia.
1 INTRODUCTION

Exposure of the dental pulp and its contamination with bacteria from the oral environment can lead to pulp inflammation, toothache, necrosis and, in immature teeth, interruption of the rhizogenesis process; Therefore, it makes sense to suggest that bioactive materials could lead to the maintenance of pulp viability (Rosa et al, 2017).

Research into the presence and influence of the endocannabinoid system on teeth and their supporting tissues has been going on for some years and began with the search for cannabinoid receptors in human odontoblasts; observed that odontoblasts have cannabinoid receptors and, more than that, that they play an important role in the physiology and maintenance of pulp vitality (Que et al, 2017). In 2021, Qi and collaborators, in an in vitro study, evaluated the action of tetrahydrocannabinol (THC) on human dental pulp cells (CPDH) and observed that it stimulated odontogenesis and osteogenesis - important processes in pulp regeneration -, which suggests that the THC should be investigated for use as a pulp protectant (Qi et al, 2021). In the same year, research was carried out evaluating in vitro the hypothesis that CBD influences the odontology and osteogenesis of human pulp cells, reaching the conclusion that CBD had a biphasic influence on the viability of CPDH, promoting significant cell migration and improving collagen synthesis, and mineralized deposits, as well as causing an increase in the expression of angiogenic and odontogenic genes (Qi et al, 2021). Still in 2021 another in vitro research was developed to evaluate whether the stem cells of the apical papilla expressed the components of the Endocannabinoid System (ECS) and the results showed that the stem cells of the apical papilla express the genes of the main components of the SEC and that endocannabinoids can affect the viability, gene expression and mineralization of apical papilla stem cells (Meneses; Pizzatto; Sipert; Diogenes, 2021).

In 2023, research was carried out to evaluate the influence of CBD on the migration and differentiation of pulp stem cells and it was observed that CBD attenuated the production of pro-inflammatory cytokines stimulated by TNF-alpha in pulp stem cells; This information corroborates the hypothesis that CBD is a possible therapeutic agent to treat pulpitis and promote dentin/pulp regeneration in regenerative cell therapy techniques within the field of endodontics, although additional investigations are still needed (Yu et al, 2023). There is even a cannabinoid-
based medicine in the patent process that aims to treat and prevent dental pulp diseases (Stahl, 2023).

A preliminary search was carried out in the Cochrane Database of Systematic Reviews, Joanna Briggs Institute (JBI), Open Science Framework (OSF), The International Prospective Register of Systematic Reviews (PROSPERO) and PubMed/MEDLINE databases searching for scoping or systematic reviews. that addressed the use of cannabinoids as pulp protection agents, and there was no published study or registered protocol on this topic. The justification for this work lies, therefore, in the importance of mapping and summarizing the evidence available in the literature regarding cannabinoids in pulp protection, which could cause changes in clinical practice if research shows positive results for the action in question. The scoping review was chosen as the research method, which is a method that presents a systematic and well-structured search, and is commonly used to map the existing literature in a given field in terms of its nature, characteristics and volume (Peters; Godfrey, 2015).

It is expected that this study will contribute to knowledge about new materials and active principles that can be used in the protection and regeneration of the dentine-pulp complex and to evidence-based clinical practice, in addition to stimulating the development of clinical research that come to fill the scientific gaps in the area. Thus, the objective of this work is to present a protocol for the development of a scoping review on the use of cannabinoids as pulp protection agents.

2 METHODOLOGY

This is a scoping review protocol to guide a review study on the use of cannabinoids as pulp protection agents, following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta Analyses Extension for Scoping Reviews (PRISMA-ScR), Joanna Briggs Institute (JBI) guideline methodology for scoping reviews. This type of review is a method that presents a systematic and well-structured search, and is commonly used to map the existing literature in a given field in terms of its nature, characteristics and volume (Peters; Godfrey, 2015).

Peters and collaborators proposed developing the scoping review in a nine-stage structure, which are 1) definition of the research question and study objectives; 2) Establishment of
inclusion criteria; 3) Description of the project for searching for evidence, selecting studies, extracting data and presenting results; 4) Carry out the search for evidence; 5) Select the evidence; 6) Extract data from selected studies; 7) Analyze the evidence; 8) present the results and, finally, 9) summarize the evidence, present the conclusion and implications of the findings (Peters et al., 2020). This protocol was registered in the OSF- Open Science Framework database under DOI: https://doi.org/10.17605/OSF.IO/HYD28.

First stage: defining the research question and study objectives

In accordance with the guidance of the JBI guideline for scoping reviews, the research question was created based on the PCC mnemonic, where “P” (population) is the scientific studies on the topic, “C” (concept) is the use of cannabinoids and “C” (context) is in pulp protection.

This composition generated the question “What evidence is available in the literature regarding the use of cannabinoids as pulp protection agents?”

Second stage: establishment of inclusion criteria

Review-type works, original articles, theses, dissertations, manuals, government documents and documents from scientific societies that discuss the use or action of cannabinoids as pulp protection agents will be included. The studies included must be available in English, Spanish, Portuguese or French and, if necessary, an external translator will be consulted. Complying with the standard in the JBI scope review manual, there will be no time limit on the search. Conference abstracts, editorials, duplicate articles, books and articles not available free of charge through the CAFe platform will be excluded.

Third stage: project description of evidence search, study selection, data extraction and presentation of results

A search strategy was developed based on the selection of keywords suitable for the research question, defined by DeCS (descriptors in health sciences). No keyword was defined
for the “P” element, which is scientific studies, for two reasons: first, because work from different methodologies will be included; and second, because the return obtained with the search strategy using the keywords linked to the elements concept (use of cannabinoids) and context (pulp protection) did not return an excessive number of studies, making it possible to analyze them all without distinction by type of study. Chart 1 presents the keywords chosen based on the research question.

Subsequently, each keyword was consulted in the MeSH (Medical Subject Headings) metadata system, finding all related input terms, so that they could be included in the search strategy. Chart 2 presents the construction of the strategy.

<table>
<thead>
<tr>
<th>Elements of the mnemonic</th>
<th>Definition</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population/problem</td>
<td>scientific studies</td>
<td>not defined</td>
</tr>
<tr>
<td>Concept</td>
<td>cannabinoids use</td>
<td>“Cannabis”, “Cannabinoids”</td>
</tr>
<tr>
<td>Context</td>
<td>dental pulp protection</td>
<td>“Dental Pulp Capping”, “Endodontics”</td>
</tr>
</tbody>
</table>

Source: Prepared by the authors (2024)

Chart 1. Elements of the PCC mnemonic and its related keywords.

<table>
<thead>
<tr>
<th>Keywords, input terms and use of Boolean operators in the final construction of the search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 “cannabis”</td>
</tr>
<tr>
<td>a Entry Terms: “Cannabis” OR “Cannabi” OR “Hemp Plant” OR “Hemp Plants” OR “Marihuana” OR “Marijuana” OR “Cannabis indica” OR “Cannabis sativa” OR “Hemp” OR “Hemps” OR “Hashish” OR “Hashishs” OR “Bhang” OR “Bhangs” OR “Ganja” OR “Ganjas”</td>
</tr>
<tr>
<td>b</td>
</tr>
<tr>
<td>2 “cannabinoids”</td>
</tr>
<tr>
<td>b Entry Terms: “Cannabinoid” OR “Cannabinoids” OR “Cannabidiol” OR “Cannabinol” OR “Dronabinol”</td>
</tr>
<tr>
<td>3 “Dental pulp capping”</td>
</tr>
<tr>
<td>c Entry Terms: “Dental pulp capping” OR “Pulp Capping” OR “Pulp Cappings” OR “Dental Pulp Cappings”</td>
</tr>
<tr>
<td>4 “Endodontics”</td>
</tr>
</tbody>
</table>
The databases chosen to carry out the research were Pubmed, Web of Science, Scopus, Cochrane, LILACS and Portal BVS. Gray literature was consulted through repositories such as the Catalog of Theses and Dissertations of the Coordination for the Improvement of Higher Education Personnel (CAPES). Filters were not used in any database.

**Fourth stage: carrying out the search for evidence**

The search in the databases will be carried out by two researchers independently, in order to guarantee methodological rigor. All studies retrieved through the search strategy will be imported into the Rayyan software, where they will be managed.

**Fifth stage: selection of evidence**

According to the JBI scoping review guideline, a pilot test will be carried out with reviewers to assess their affinity with the selection based on the inclusion criteria. 25 random studies will be selected for reviewers to analyze the title and abstract and determine whether they meet the defined inclusion criteria; agreement between reviewers must be greater than 75% for collection to be carried out independently (Peters et al, 2020).

The pre-selection follows, considering the evaluation of the titles in relation to the inclusion criteria. Subsequently, the pre-selected articles will be evaluated in full to determine
the final composition of the review sample in question. In addition to the research, the references of the retrieved studies will be searched for more sources that can be included and were not retrieved by the databases. Any differences of opinion between the reviewers will be clarified by the opinion of a third reviewer. All the reasons that led to the exclusion of studies will be described and the research results will be presented in the form of a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for scoping review) flowchart (Tricco et al, 2018).

Sixth stage: data extraction

The extraction of data from the included articles will be carried out independently by the reviewers, using an extraction tool developed by the researchers themselves, with its variables presented in chart 3. Each study will have its data extracted by two researchers calibrated through a pilot test carried out with five articles, comparing agreement between researchers and convergence towards the objectives of the work. This tool may undergo changes during the research, if necessary; such modifications will all be documented in the final draft of the review.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Name of study authors</td>
</tr>
<tr>
<td>Title</td>
<td>Full title of the study</td>
</tr>
<tr>
<td>Year</td>
<td>Year of publication of the study</td>
</tr>
<tr>
<td>Local</td>
<td>Location where the study was carried out</td>
</tr>
<tr>
<td>Language</td>
<td>Publication language</td>
</tr>
<tr>
<td>Goal</td>
<td>Describe the objective of the study</td>
</tr>
<tr>
<td>Methodology</td>
<td>Type of study, detailing the methodology</td>
</tr>
<tr>
<td>Results</td>
<td>Study results, according to objectives</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Describe the conclusions</td>
</tr>
<tr>
<td>Problems and limitations</td>
<td>Detail problems in the methodology or execution of the work, as well as its limitations</td>
</tr>
</tbody>
</table>

Source: Prepared by the authors (2024)
Seventh stage: analysis of evidence

The product review of this protocol will cover the quantitative and qualitative analysis of the evidence found, and a narrative synthesis of the information found regarding the use of cannabinoids in pulp protection will be presented. Statistical analysis will be performed using SPSS software (version 24.0, IBM Corp). An analysis will also be presented regarding the characteristics of the available literature on the subject of cannabinoids in pulp protection.

Eighth stage: presentation of results

This scoping review will present its results through a PRISMA-ScR flowchart. The data obtained may be presented descriptively or in tables, charts, illustrations, graphs or flowcharts, in a way that facilitates the dissemination of knowledge on the topic.

Ninth stage: synthesis of evidence, conclusions and implications of results

The results of this scoping review will provide a basis for future debates and research on the use of cannabis in endodontics, especially in pulp protection. Scientific gaps will become evident, providing direction for further investigations.

3 RESULTS AND DISCUSSION

This research protocol was developed by professors and students in the area of endodontics, following all the methodological criteria proposed by the Joanna Briggs Institute manual (JBI, 2020) and PRISMA-ScR (Tricco et al, 2018). The construction of a protocol is essential to guarantee quality in the development of a scope review work, clearly delimiting the objectives of the review, the characteristics of the work and the methodology for extracting and analyzing the information obtained (JBI, 2020). According to Peters and collaborators, the definition of rigorously detailed procedures in the protocol prevents the occurrence of biases in the execution of the review (Peters et al, 2020). If there is a mapping of the available evidence
regarding the use of cannabinoids in pulp protection, it will be possible to identify the gaps in knowledge that need to be filled by new research.

4 FINAL CONSIDERATIONS

This scoping review protocol clearly determines the methodological steps necessary to map the studies available in the literature on the use of cannabinoids as pulp protection agents. The scope review is intended to provide a comprehensive view of the literature on the use of cannabinoids in endodontics, in the area of pulp protection, offering a scientific basis for the development of new studies and products, optimizing the endodontist's possibilities.
REFERENCES


