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Cannabinoids in Orofacial Pain - A Scoping Review

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ABSTRACT

Background: Safe, effective cannabinoids from Cannabis Sativa L. show promise as complementary therapy for chronic/acute pain, inflammation, anxiety, and sleep disorders. Objective: The aim of this study is to conduct a comprehensive review of the literature on the use of cannabinoids in the management of orofacial pain. Methods: This scoping review investigates the use of cannabinoids to treat orofacial pain. It focused on scientific articles published in indexed journals with no date limit from PubMed/MEDLINE. Researchers defined a guiding question ("treatment with cannabinoids for orofacial pain?") and excluded non-centralized studies, editorials, and non-indexed journals. Reviewers independently selected studies and extracted key data for further analysis. Results: Although 833 articles were considered, only 11 met criteria (mostly recent systematic reviews). These studies originated from various countries with a focus on research from the past few years (2021-2022). Conclusion: Cannabinoids show promise for orofacial pain due to pain relief and inflammation reduction, but more research is needed.

Key-words: Cannabis. Facial Pain. Marihuana Medicinal.

INTRODUCTION

Improving accessibility to medications derived from Cannabis Sativa L. and the effectiveness of this group of drugs in chronic and acute pathologies, whose symptoms may include pain, inflammation, anxiety, depression, and sleep disorders, make phytocannabinoids an option as complementary therapy for those that are not sufficient for complete remission of the painful condition (Li et al., 2021).

In addition to the effectiveness of phytocannabinoids, they are deemed safe for users, as their lethal dose is practically impossible to achieve with the currently indicated dosage. Research involving this class of medications is progressing rapidly, with a large number of clinical studies being conducted by the scientific community worldwide, with much information requiring constant review and updating to tailor cannabinoid components (whether isolated or used in combination) to each individual and their symptomatology. Cannabis contains over 500 components, approximately 100 of which have pharmacological effects. Two of these components are of particular medical interest: δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), with THC exhibiting greater psychoactive and analgesic effectiveness, while CBD has a greater impact on pain by primarily acting as an anti-inflammatory (Grossman, Tan, Gadiwalla, 2021; Mlost, Bryk, Starowicz, 2020).

Patients with orofacial pain of different etiologies frequently report experiencing acute pain (pulpitis, periodontitis, and periapical pathologies), chronic pain (temporomandibular dysfunction, with myalgia and arthralgia or both), neuropathic pain (trigeminal neuralgia, burning mouth syndrome), among others. Considering that many treatments for these and other pains are ineffective or become recurrent with periods of exacerbation due to the progressive and degenerative nature of the pathology, this study aims to provide a comprehensive and updated view of what has been researched and written about cannabinoid prescription in orofacial pain, as well as to aggregate different approaches, theories, and results from previous studies to contribute to filling possible gaps in the study of these valuable compounds.

Given the relatively recent interest and emerging body of research on the use of cannabinoids in managing orofacial pain, a scoping review is deemed the most appropriate method for our study. This approach allows us to comprehensively explore the current status quo regarding cannabinoids and orofacial pain management, providing a valuable overview of existing studies, methodologies, and findings, as well as identifying areas where further research is needed.

The aim of this study is to conduct a comprehensive review of the literature on the use of cannabinoids in the management of orofacial pain.

METHODS

Scoping Review

This is a Scoping Review (ScR) conducted based on the methodological assumptions of the Joanna Briggs Institute (JBI), which includes the following phases: defining the research question; identifying relevant studies; selecting studies; mapping data; and grouping, synthesizing, and reporting results. Additionally, assumptions from the PRISMA-ScR by the Equator network, according to the criteria of Munn et al., 2018.

To construct the guiding question, the Population, Concept, and Context (PCC) strategy was applied: 1. Population: patients with orofacial pain; 2. Concept: treatment;

3. Context: cannabinoids. Therefore, the guiding question defined for the search and selection of studies was: "What is the scientific production regarding the treatment with cannabinoids in patients with orofacial pain?"

Eligibility Criteria

The eligibility criteria were defined as studies published in scientific publications without a publication date limit. This broad scope aims to outline a profile of production over the years regarding treatment with cannabinoids in patients with orofacial pain. Studies that mention treatment with cannabinoids in patients with orofacial pain without addressing it as a central theme were excluded, along with editorials, opinion articles/scientific dissemination texts, and interviews.

Additionally, undergraduate theses, dissertations, and theses were also excluded. Only scientific articles published in indexed journals were included, without language restrictions. Articles published in non-indexed journals and those not addressing treatment with cannabinoids in patients with orofacial pain were excluded.

Source of Information

The searches were conducted in the following database: PubMed/MEDLINE. The following DeCS/MeSH descriptors or keywords were used: Cannabis; Facial Pain; Marihuana Medicinal.

The searches were conducted using the keywords or compound terms across all mentioned databases, such as box 1 below.

Selection of Scientific Evidence

Study selection was conducted in duplicate by three reviewers (DSA, LMG, and CVBA) independently. Any potential discrepancies were resolved through consensus, with the involvement of a third evaluator (DPM). The selected studies were organized into an electronic form built in an Excel spreadsheet, which was also used to extract relevant data. The following information was extracted: author, year of publication, title, study origin, objectives, and results.

Tabulation Process

The articles were initially selected according to the eligibility criteria by reviewers using Rayyan, as previously reported. After reading the full text of the selected articles, data tabulation occurred in separate tables using Excel.

Summary of Results

The results were categorized and analyzed descriptively, utilizing tables to synthesize the data from the studies based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flowchart model. In this instrument, data analysis and review writing will be conducted using a checklist composed of 27 items divided into 7 main topics, following the criteria of Tricco et al., 2018.

RESULTS

Of the 833 articles initially selected, only 11 were included in this study, as described in figure 1. Among these, the majority were systematic reviews (54.5%), with six out of eleven articles falling under this category. Reviews and systematics reviews accounted for 18.2% of the studies, representing two of the selected articles. The

remaining articles included two laboratory experimental studies (18.2%) and one cohort study (9.1%).

The included articles originated from diverse countries, with Ireland contributing the most (27.3%) with three studies. Brazil and Japan each contributed two studies (18.2% each), while England, Australia, Italy, Israel, and the Netherlands each accounted for one study (9.1% each). The publication years of these articles span from 2014 to 2023, with a notable concentration in recent years: four studies were published in 2021 (36.4%), followed by three in 2022 (27.3%), and one each in 2014, 2016, 2020, and 2023 (9.1% each), as described in box 2 and 3.

DISCUSSION

Grossman et al., (2021), demonstrated that the topical application of CBD significantly reduces myofascial pain, offering a promising therapeutic alternative for a condition that severely impacts patients' quality of life. This conclusion is supported by Votrubec et al. (2021), who also reported significant pain reduction and improved muscle function with topical CBD in their study. These findings suggest that topical administration may offer a direct and effective approach to pain management, minimizing systemic side effects often associated with oral administration of cannabinoids. The emphasis on the need for further research into cannabis for orofacial pain by Grossman et al., (2021), aligns with Votrubec et al., (2021) observations of the limited efficacy of synthetic cannabinoids like AZD1940 and GW842166, thereby underscoring the potential of natural cannabinoids, especially in topical form, for managing specific pain conditions.

The comparative analysis by Votrubec et al., (2021), between non-steroidal anti-inflammatory drugs (NSAIDs) and synthetic cannabinoids in postoperative pain management provides valuable insights. NSAIDs were found to be more effective than synthetic cannabinoids for controlling postoperative pain, highlighting the need for better cannabinoid formulations or alternative delivery methods to improve efficacy. These findings are in line with Crescente et al., (2023), who noted the low oral bioavailability of cannabinoids and emphasized the potential benefits of topical applications for chronic nociceptive and neuropathic pain. Both studies suggest that optimizing cannabinoid delivery methods could enhance their analgesic effects and reduce adverse outcomes.

These results are similar to those found in the study of Golanska , (2021) that evaluated the etiology, diagnosis, and treatment of temporomandibular myofascial pain syndrome using a CBD formulation applied to the masseter muscle and reduced its activity, pain intensity and improved its condition suggesting healthy lifestyle patterns such as rest, physical activity and nutrition should also be deliberated upon. Fruit and vegetable eating patterns alleviate pain by maintaining an anti-inflammatory environment and maintaining the highest hydration index due to their macronutrient and electrolyte content. Furthermore, CBD oils can also be used in treatment, as they bring back physical, emotional and cognitive balance, relieving stress and anxiety.

McDonough et al., (2014), highlighted the effectiveness of Sativex®, a THC and CBD combination, for neuropathic pain, suggesting a synergistic potential that can be further explored in orofacial pain management. This combination's efficacy in allowing dose self-titration to minimize adverse effects demonstrates a promising direction for cannabinoid-based therapies. However, the lack of standardized preparations and the challenge of consistent therapeutic outcomes remain significant barriers. Hossain et al., (2020), and Haviv et al., (2022), provide additional insights into the role of endogenous

cannabinoids, such as 2-Arachidonoylglycerol (2-AG) and Anandamide (AEA), in pain modulation, proposing that targeting endocannabinoid pathways could offer physiological advantages and fewer side effects compared to external cannabinoid use.

Research by Haviv et al., (2022), and Pereira et al., (2021), found that patients with chronic orofacial pain have lower levels of endocannabinoids like 2-AG, suggesting a potential biomarker role for these compounds in diagnosing and treating such pain conditions. Heiliczer et al., (2022), further corroborated this by demonstrating significant correlations between endocannabinoid levels and various patient characteristics, such as sex, Burning Mouth Syndrome (BMI), and sleep quality. These findings imply that personalized treatment approaches based on endocannabinoid profiles could improve pain management outcomes.

Vivanco-Estela et al., (2021), highlighted the efficacy of CBD in reducing orofacial hypersensitivity in experimental parkinsonism, particularly noting the influence of hormonal factors and sex differences on treatment outcomes. This underscores the necessity for personalized approaches in cannabinoid therapy, considering variables like sex and hormonal status to optimize therapeutic effects. These findings advocate for tailored CBD dosing strategies, especially in conditions like Parkinson's disease, where hormonal fluctuations might significantly impact treatment efficacy. Also, Pereira et al., (2022), reviewed the potential of cannabinoids, particularly CBD, for treating BMS, emphasizing the neuroprotective, anti-inflammatory, and antioxidative properties of cannabinoids. This review calls for comprehensive investigations into the cannabinoid system as a therapeutic strategy for BMS, potentially leading to effective treatments that address the condition's multifactorial etiology and complex diagnosis. This aligns with the broader consensus across the studies that more research is needed to fully understand and harness the therapeutic potential of cannabinoids for various pain conditions, particularly in the orofacial region.

CONCLUSION

Natural and synthetic cannabis components, for topical or systemic use, particularly CBD and THC, show significant potential for treating orofacial pain due to their antinociceptive and anti-inflammatory effects. Despite promising results, further research is needed to understand their effects and interactions. Phytocannabinoids, flavonoids, and terpenes offer synergistic benefits, highlighting the need for innovative therapeutic formulations.

List of abbreviations

JBI: Joanna Briggs Institute
OSF: Open Science Framework
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
ScR: Scoping Review
THC: δ-9 tetrahydrocannabinol
CDB: Cannabidiol
NSAIDs: Non-steroidal anti-inflammatory drugs
2-AG: 2-Arachidonoylglycerol
AEA: Anandamide
BMS: Burning Mouth Syndrome

Declarations

Ethics approval and consent to participate

The microdata used in this research were obtained from unrestricted access databases. Therefore, submission to the Research Ethics Committee was not necessary.

Consent for publication

Not applicable.

Competing interests

The author declares they have no competing interests.

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No funding was received for this study.

Authors contributions

CVBA: Contributed to the study concept, design, acquisition and interpretation of data for the research and drafting of the manuscript. LMG: Contributed to the study concept, design, acquisition and interpretation of data for the research and drafting of the manuscript. DPM: Contributed to the study concept, design, acquisition and interpretation of data for the research and drafting of the manuscript. DSA: Contributed to the study concept, design, and critically revised the manuscript. All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of the research by ensuring that questions related to the accuracy or integrity of any part of the research are appropriately investigated and resolved.

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Search	Terms
#1	(Cannabis[MeSH Terms]) OR (Bangue[Other Term])) OR (Cannabi[Other Term])) OR (Cannabis chinensis[Other Term])) OR (Cannabis indica[Other Term])) OR (Cannabis sativa[Other Term])) OR (Cannabis sativa indica[Other Term])) OR (Cânabe[Other Term])) OR (Cânabis[Other Term])) OR (Cânave[Other Term])) OR (Cânhamo[Other Term])) OR (Cânhamo-da-Índia[Other Term])) OR (Ganja[Other Term])) OR (Haxixe[Other Term])) OR (Linho-Cânhamo[Other Term])) OR (Maconha[Other Term])) AND (Endocanabinoides[MeSH Terms])) OR (Endocannabinoids[MeSH Terms])) AND (Dronabinol[MeSH Terms])) OR (THC[Other Term])) OR (Tetra-Hidrocanabinol[Other Term])) OR (Tetraidrocanabinol[Other Term])) OR (delta (9)-THC[Other Term])) AND (Maconha Medicinal[MeSH Terms])) OR (Medical Marijuana[MeSH Terms])) OR (Cannabis, Medical[Other Term])) OR (Cannabis, Medicinal[Other Term])) OR (Dispensaries, Marijuana[Other Term])) OR (Marijuana Dispensaries[Other Term])) OR (Marijuana Treatment[Other Term])) OR (Marijuana, Medical[Other Term])) OR (Marijuana, Medicinal[Other Term])) OR (Medical Cannabis[Other Term])) OR (Medicinal Cannabis[Other Term])) OR (Medicinal Marijuana[Other Term])) OR (Treatment, Marijuana[Other Term])
#2	(Dor Facial[MeSH Terms]) OR (Dor Craniofacial[Other Term])) OR (Dor Miofacial[Other Term])) OR (Dor Orofacial[Other Term])) AND (Facial Pain[MeSH Terms])) OR (Craniofacial Pain[Other Term])) OR (Face Pain[Other Term])) OR (Facial Pain, Neuralgic[Other Term])) OR (Myofacial Pain[Other Term])) OR (Neuralgic Facial Pain[Other Term])) OR (Orofacial Pain[Other Term])) OR (Pain, Craniofacial[Other Term])) OR (Pain, Face[Other Term])) OR (Pain, Facial[Other Term])) OR (Pain, Myofacial[Other Term])) OR (Pain, Neuralgic Facial[Other Term])) OR (Pain, Orofacial[Other Term])
#3	#1 AND #2

Box 1. Literature Search

Authors	Year	Title	Periodic	Country	Type
Grossman et al.	2021	Cannabis and orofacial pain: a systematic review	British Journal of Oral & Maxillofacial Surgery	England	Systematic Review
Votrubec et al.	2021	Cannabinoid therapeutics in orofacial pain management: a systematic review	Australian Dental Journal	Australia	Systematic Review
Crescente et al.	2023	Cannabis Bioactive Compound-Based Formulations: New Perspectives for the Management of Orofacial Pain	Molecules Journal	Italy	Review
McDonough et al.	2014	Neuropathic orofacial pain: cannabinoids as a therapeutic avenue	Int J Cell Biol	Ireland	Systematic Review
Hossain et al.	2020	Targeting Peripherally Restricted Cannabinoid Receptor 1, Cannabinoid Receptor 2, and Endocannabinoid-Degrading Enzymes for the Treatment of Neuropathic Pain Including Neuropathic Orofacial Pain	Int. J. Mol. Science	Japan	Review
Haviv et al.	2022	Reduced Endocannabinoid Tone in Saliva of Chronic Orofacial Pain Patients	Europe Journal of neuroscience	Ireland	Systematic Review
Heiliczer et al.	2022	Salivary Endocannabinoid Profiles in Chronic Orofacial Pain and Headache Disorders: An Observational Study Using a Novel Tool for Diagnosis and Management	Int J of Mollecular Sciences	Israel	Coorte

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Vivanco-Estela et al.	2021	Cannabidiol has therapeutic potential for myofascial pain in female and male parkinsonian rats	Neuropharmacology	Brazil	Laboratory Experimental
Almeida et al.	2016	Endocannabinoid mechanism for orofacial antinociception induced by electroacupuncture in acupoint St36 in rats	Pharmacological Reports	Netherlands	Laboratory Experimental
Pereira et al.	2021	Limonene, a citrus monoterpene, non-complexed and complexed with hydroxypropyl-β-cyclodextrin attenuates acute and chronic orofacial nociception in rodents: Evidence for involvement of the PKA and PKC pathway	Phytomedicine	Brazil	Laboratory Experimental
Pereira et al.	2022	Recent advances in the understanding of the aetiology and therapeutic strategies in burning mouth syndrome: Focus on the actions of cannabinoids	The European journal of neuroscience	Ireland	Systematic Review

Box 2. Main Characteristics of Selected Studies

Authors	Aim	Results	Conclusions
Grossman et al.	Evaluate the topical effects of natural and synthetic cannabis components compared to non-cannabinoids on orofacial pain of different etiologies.	Topical cannabidiol reduced myofascial pain, whereas oral AZD1940 and GW842166 were ineffective for post-third molar extraction pain. Studies on cannabis for orofacial pain are needed.	The use of cannabis in healthcare is controversial and socially stigmatized. Evidence supports its use for chronic pain, but research on orofacial manifestations is lacking. Professionals should keep abreast of new evidence and legislation.
Votrubec et al.	Assess the effects of synthetic and natural cannabinoids on postoperative pain and orofacial pain.	NSAIDs were more effective than synthetic cannabinoids for postoperative pain, with topical CBD showing promise and intravenous THC proving ineffective. Adverse events ranged from mild to moderate.	CBD and THC possess antinociceptive and anti-inflammatory properties but come with side effects. They are promising for orofacial pain, yet their use is controversial and under-researched. More studies on dosages and interactions are necessary.
Crescente et al.	Analyze the possible mechanisms of action of cannabinoids.	Cannabinoids have low oral bioavailability but are effective for chronic nociceptive and neuropathic pain via topical application. Topical CBD and eucalyptol demonstrated efficacy in myofascial and orofacial pain.	Phytocannabinoids, flavonoids, and terpenes may synergistically relieve pain and reduce inflammation. Future studies should explore these mechanisms and new formulations for treating orofacial pain. Further research is required.
McDonough et al.	Investigate the potential use of cannabinoids in treating symptoms associated with Orofacial Neuropathic Pain.	Sativex® is effective for neuropathic pain, allowing dose self-titration. Both natural and synthetic cannabinoids have shown efficacy despite adverse effects.	Lack of standardization delays cannabinoid therapies. The pathophysiology of some conditions is uncertain, resulting in varied treatments with limited efficacy and side effects. Cannabinoids are promising for analgesia, with demonstrated efficacy in persistent idiopathic facial pain.
Hossain et al.	Discuss the aforementioned alternative approaches that show potential for treating neuropathic pain, including Peripheral Neuropathic Pain.	Endocannabinoids 2-AG and AEA show potential for neuropathic pain with fewer side effects. 2-AG is more potent than AEA, both acting on CB1 and CB2 receptors.	Preclinical studies suggest targeting CB2 receptors, peripheral CB1 receptors, and endocannabinoid-degrading enzymes can alleviate neuropathic pain with minimal side effects. More research is needed to confirm these strategies for orofacial neuropathic pain.

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Haviv et al.	Evaluate the association between salivary endocannabinoid levels and Chronic Orofacial Pain.	Patients with chronic orofacial pain have lower levels of OEA and 2-AG. Neurovascular pain shows lower levels of AEA and OEA, while neuropathic pain presents lower levels of 2-AG.	Patients with Chronic Orofacial Pain exhibit lower salivary endocannabinoid levels, particularly with neurovascular/migraine and neuropathic pain. This finding may influence future diagnoses and treatments for Chronic Orofacial Pain.
Heiliczer et al.	Investigate salivary endocannabinoid compounds in Chronic Orofacial Pain disorders to assess their efficacy as biomarkers and the influence of clinical parameters on their levels.	Salivary endocannabinoid levels correlated with sex, quality of life, BMI, pain duration, and sleep awakenings in patients with various orofacial pain conditions.	Endocannabinoid profiles in salivary samples correspond to Chronic Orofacial Pain disorders, enabling the use of salivary biomarkers for more accurate diagnosis and management of these patients.
Vivanco-Estela et al.	Test the effect of CBD on myofascial pain related to Parkinson's Disease.	CBD therapy is effective for parkinsonism-induced orofacial nociception.	CBD applied to the masseter muscle showed analgesic potential for orofacial hypersensitivity in experimental parkinsonism. Nociceptive responses vary according to sex and estrous cycle, indicating hormonal influence on CBD efficacy.
Almeida et al.	Evaluate whether electroacupuncture at the St36 point could produce antinociception through the activation of an endocannabinoid mechanism.	Electroacupuncture produced prolonged antinociception for 180 minutes, enhanced by anandamide-metabolizing enzyme inhibitors and reuptake inhibitors, and antagonized by a CB1 antagonist.	This study demonstrated for the first time that the CB1 cannabinoid receptor participates in the antinociceptive effect induced by electroacupuncture.
Pereira et al.	Assess the antinociceptive and anti-inflammatory effects of d-limonene, both isolated and complexed with hydroxypropyl-β-cyclodextrin, in preclinical animal models.	No significant differences were found between the musculoskeletal pain group and controls. Higher pain intensity was accompanied by lower AA levels in the neuropathic group.	Patients with Chronic Orofacial Pain exhibit lower salivary endocannabinoid levels, particularly with neurovascular/migraine and neuropathic pain. This may influence diagnoses and treatments, offering a new dimension in understanding orofacial pain mechanisms.
Pereira et al.	Evaluate the cannabinoid system and the potential of cannabis-based therapeutics in treating patients with BMS.	Given that pure CBD is not associated with psychoactive properties, Epidiolex is a particularly attractive therapeutic option.	BMS is challenging due to multifactorial etiology and complex diagnosis. Cannabinoids, with their neuroprotective and anti-inflammatory properties, may be a promising therapeutic strategy, warranting further research.

Box 3. Objectives, Results, and Conclusions of the Research

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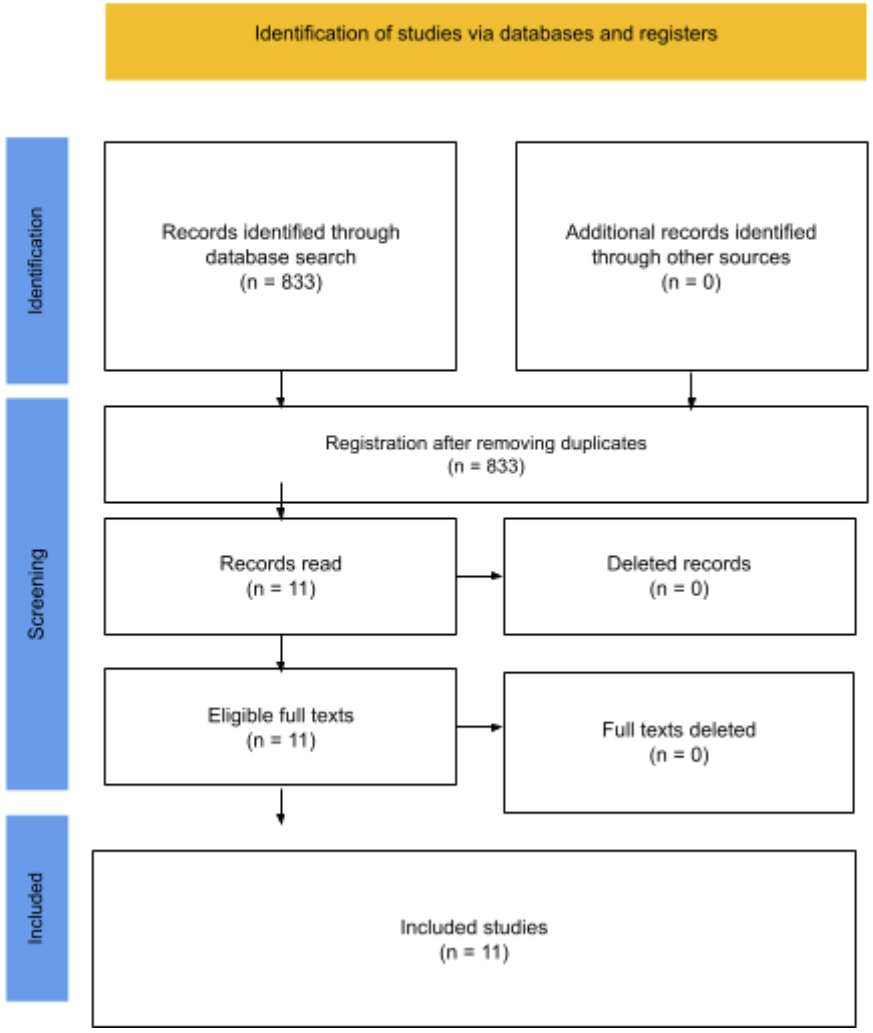

Figure 1. Flowchart.