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BASIC RESEARCH:

Cannabis-Based Therapies for Chronic Orofacial Pain: A Systematic Review and Meta-Analysis

Terapias basadas en cannabis para el dolor orofacial crónico: una revisión sistemática y un metaanálisis

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ABSTRACT: To evaluate the effectiveness of cannabis-based therapies in managing chronic pain associated with TMDs, periodontitis, and oral cancer. Chronic orofacial pain, especially in temporomandibular disorders (TMDs), presents a challenge in dental practice. Traditional treatments often have adverse effects and limited efficacy. Cannabis has emerged as a potential alternative due to its analgesic and anti-inflammatory properties. A systematic review and meta-analysis of randomized controlled trials, cohort, and case-control studies was conducted using five databases. Risk of bias was assessed using Cochrane ROB 2.0 and ROBINS-I tools. Six studies were included. Cannabis showed significant pain relief in oral cancer (OR=1.46; 95% CI: 1.24-1.71), while effects in TMDs and periodontitis were inconclusive. Cannabis may benefit oral cancer pain management; further studies are needed for TMDs and periodontitis.

KEYWORDS: Cannabis; Cannabinoids; Chronic pain; Orofacial pain; Temporomandibular joint disorders; Periodontitis; Oral cancer; Analgesics; Dentistry; Systematic review; Meta-analysis.

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RESUMEN: Evaluar la eficacia de las terapias basadas en cannabis en el manejo del dolor crónico asociado con DTM, periodontitis y cáncer oral. El dolor orofacial crónico, especialmente en los trastornos temporomandibulares (DTM), supone un reto en la práctica dental. Los tratamientos tradicionales suelen tener efectos adversos y una eficacia limitada. El cannabis surge como una posible alternativa debido a sus propiedades analgésicas y antiinflamatorias. Se realizó una revisión sistemática y un metaanálisis de ensayos controlados aleatorizados, estudios de cohorte y casos y controles utilizando cinco bases de datos. El riesgo de sesgo se evaluó utilizando las herramientas Cochrane ROB 2.0 y ROBINS-I. Se incluyeron seis estudios. El cannabis mostró un alivio significativo del dolor en el cáncer oral (OR=1,46; IC 95%: 1,24-1,71), mientras que los efectos en las DTM y periodontitis fueron inconclusos. El cannabis puede beneficiar al manejo del dolor por cáncer oral; se necesitan más estudios sobre las DTM y la periodontitis.

PALABRAS CLAVE: Cannabis; Cannabinoides; Dolor crónico; Dolor orofacial; Trastornos temporo mandibulares; Periodontitis; Cáncer oral; Analgésicos; Odontología; Revisión sistemática; Metaanálisis.

INTRODUCTION

Chronic pain represents one of the most significant challenges in the field of public health, and dentistry is no exception. This type of pain, defined as pain that persists for more than three months, considerably affects the quality of life of patients, interfering with basic functions and generating a considerable emotional, social and economic impact (1). Among the most prevalent conditions associated with chronic pain in dental practice are temporomandibular disorders (TMD),(2) a set of disorders that affect the masticatory muscles, the temporomandibular joint (TMJ), and related anatomical structures. TMD commonly manifests with facial pain, limitation in mouth opening, joint noises and jaw dysfunction, affecting daily activities such as chewing, talking, yawning or sleeping (3). The etiology of TMD is multifactorial and includes biomechanical, psychological, neuromuscular, and structural factors. This etiological complexity has made it difficult to develop standardized and effective treatments, leading to a wide variety of therapeutic approaches (4). Periodontitis not only causes structural damage such as bone and tooth loss, but its chronic inflammation releases mediators like interleukins, prostaglandins, and TNF-α that sensitize peripheral nerves, leading to persistent pain. Continuous activation of immune and neural pathways may also contribute to a neuroinflammatory state, establishing a clear link between periodontitis and chronic orofacial pain.

Tumors of the oral and maxillofacial terrain represent a strong economic commitment for patients and society in general, in addition to producing great pain for patients who suffer from it. The main factors that reduce the quality of life of patients with tumors in the facial region are nausea and vomiting after chemotherapy, in addition to cachexia. Researchers face various challenges in the fight against oral and maxillofacial tumors, such as prognosis of the evolution of the disease and intense pain in advanced stages, which requires new therapeutic techniques and pharmacological resources (5).

Traditionally, chronic pain management in dentistry has relied on pharmacological therapies such as nonsteroidal analgesics (NSIDs), muscle relaxants, tricyclic antidepressants, and, in severe cases, opioids. While these treatments can offer

symptomatic relief, their prolonged use carries significant adverse effects, such as gastrointestinal disturbances, dependence, tolerance, and, in the case of opioids, a worrying contribution to the public health crisis related to their abuse, (6) in this context, medical cannabis has emerged as a potentially effective and safer therapeutic alternative for the management of chronic pain, including TMD (7).

Cannabis contains phyto cannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which act on the human body's endocannabinoid system. This system regulates multiple physiological functions, including pain perception, inflammation, mood, and stress response (8). The interaction of cannabinoids with CB1 and CB2 receptors (9) has demonstrated analgesic, anti-inflammatory, and anxiolytic effects, which has sparked growing interest in their clinical application (10). Several studies have shown that cannabis can reduce pain intensity, improve sleep quality, and decrease anxiety in patients with chronic pain (11). These properties make it a promising option for those suffering from TMD and other painful conditions in dentistry, such as trigeminal neuralgia, alveolar osteitis, or persistent postoperative pain (12).

CBD has been shown to reduce alveolar bone loss associated with periodontitis, as well as decreased inflammation and inhibition of periodontal bacterial activity. In terms of cancer-related pharmacological effects, CBD has shown antiproliferative and anti-invasive effects, inhibition of angiogenesis, and reduction of pain. In addition, some clinical trials and systematic reviews have reported that cannabinoids may be as effective as opioids in pain management, however with a more favorable safety profile, especially with regard to the risk of dependence and overdose (13). However, the clinical use of cannabis in dentistry still faces significant challenges. These include variability in the concentrations of active compounds in available products, (14) lack of standardization in doses and routes of administration, the scarcity of specific clinical guidelines, and legal restrictions in several countries (15). Added to this is the need for more professional training and the existence of social and cultural prejudices that still surround the use of cannabis for therapeutic purposes (16).

Consequently, it is essential to continue researching the efficacy, safety and applicability of medical cannabis within the dental therapeutic framework (17). Current scientific evidence, although promising, is still limited in terms of high-quality methodological studies specifically focused on TMD (18). Therefore, it is necessary to carry out systematic reviews and meta-analyses that synthesize the available findings, identify gaps in knowledge, and guide future research. (19) Such studies not only contribute to evidence-based clinical decision-making, however may in addition influence the formulation of more inclusive and patient-centered health policies (20). CB1 receptors are primarily located in the central nervous system, while CB2 receptors are found in peripheral tissues, including immune cells. Their activation modulates pain and inflammation.

The present systematic review and meta-analysis aims to evaluate the effectiveness of medical cannabis in the control of chronic pain associated with temporomandibular disorders, periodontal disease, and oral cancer. Through the rigorous analysis of the available scientific literature, it seeks to offer a comprehensive vision of the benefits, limitations and clinical considerations of the use of cannabinoids in this context, thus contributing to the development of safer, more effective and humane therapeutic strategies for pain management in dentistry.

MATERIALS AND METHODS

This systematic review with meta-analysis was carried out in accordance with the guidelines

of the Prisma 2020 declaration (preferred reporting items for systematic reviews and meta-analyses) and was previously registered in the international database Prospero (registration number: crd42024624150). The authors included randomized controlled trials (RCTs), cohort and case-control studies evaluating the therapeutic use of cannabis or cannabinoids (natural or synthetic) in the treatment of chronic pain associated with temporomandibular disorders (TMD), periodontitis and oral cancer. Research on chronic pain control in oral diseases was in addition considered. Studies had to report relevant clinical outcomes on pain intensity, frequency, or duration. The authors excluded preclinical, in vitro, animal studies, narrative reviews, letters to the editor, and studies without primary clinical data. A PICO framework was formulated to define the research question as follows: P (Population): adults with chronic oral diseases experiencing persistent orofacial pain, including periodontitis and oral cancer; I (Intervention): use of cannabis or cannabinoid-based therapies (e.g., CBD, THC, or synthetic cannabinoids); C (Comparison): placebo, standard analgesic treatments (e.g., NSAIDs, opioids), or no treatment; and O (Outcome): reduction in pain intensity, improvement in jaw function, quality of life, and assessment of adverse effects.

A systematic search of the electronic databases Pubmed/Medline, Scopus, Embase, web of science, and Cochrane library was conducted from inception to April 2025, with no language or country restrictions. Combinations of mesh terms and free text related to the following were used: "cannabis", "cannabinoids", "chronic pain", "temporomandibular joint disorders", "orofacial pain" “periodontitis”, “cancer oral” y equivalents. "cannabis" [mesh terms] or "cannabinoids"[mesh terms] or cannabis or cannabinoid* or cannabidiol or THC or "medical marijuana") and ("chronic pain"[mesh terms] or "chronic pain" or persistent pain or "long-term pain" or "orofacial pain") and ("temporomandibular joint disorders"[mesh terms] or "temporomandibular disorders" or TMD or TMJ or "jaw pain") title-abs-key(cannabis or cannabinoid* or cannabidiol or THC or "medical marijuana") and title-abs-key("chronic pain" or "persistent pain" or "long-term pain" or "orofacial pain") and title-abs-key("temporomandibular disorders" or TMD or TMJ or "jaw pain") TS=(cannabis or cannabinoid* or cannabidiol or THC or "medical marijuana") and TS=("chronic pain" or "persistent pain" or "long-term pain" or "orofacial pain") and TS=("temporomandibular disorders" or TMD or TMJ or "jaw pain") ; 'cannabis'/exp or 'cannabinoid'/exp or cannabis or cannabinoid* or cannabidiol or THC or 'medical marijuana' and 'chronic pain'/exp or 'persistent pain' or 'orofacial pain' and 'temporomandibular joint disorder'/exp or TMD or TMJ or 'jaw pain' ("cannabis" or "cannabinoids" or "cannabidiol" or "THC" or "medical marijuana") and ("chronic pain" or "persistent pain" or "orofacial pain") and ("temporomandibular disorders" or TMD or TMJ or "jaw pain"); ("cannabis"[mesh] or "cannabinoids"[mesh] or cannabis or cannabinoids or cannabidiol or THC or "medical marijuana") and ("chronic pain"[mesh] or "orofacial pain"[mesh] or "temporomandibular joint disorders"[mesh] or "periodontal diseases"[mesh] or periodontitis or "dental pain"[mesh] or "oral cancer"[mesh] or "oral neoplasms"[mesh] or "oral inflammation") and ("systematic review"[publication type] or "meta-analysis"[publication type] or "randomized controlled trial"[publication type]) title-abs-key(cannabis or cannabinoid* or cannabidiol or THC or "medical marijuana")and title-abs-key("chronic pain" or "persistent pain" or "long-term pain" or "orofacial pain")and title-abs-key("temporomandibular disorders" or TMD or TMJ or "jaw pain" or periodontitis or "oral cancer" or "oral neoplasms") ; TS=(cannabis or cannabinoid* or cannabidiol or THC or "medical marijuana") and TS=("chronic pain" or "persistent pain" or "long-term pain" or "orofacial pain") and TS=("temporomandibular disorders" or TMD or TMJ or "jaw pain" or periodontitis or "oral ; ('cannabis'/exp or 'cannabinoid'/exp or cannabis or cannabinoid* or cannabidiol or

THC or 'medical marijuana') and ('chronic pain'/exp or 'persistent pain' or 'orofacial pain') and ('temporomandibular joint disorder'/exp or TMD or TMJ or 'jaw pain' or 'periodontitis'. Exclusion criteria included studies lacking primary clinical data, animal models, and narrative reviews. Data management was performed using standardized extraction forms. Bias was assessed independently by two reviewers, with discrepancies resolved by consensus or a third reviewer. Sensitivity and specificity measures were evaluated where applicable (21).

ASSESSING RISK OF BIAS

Methodological quality was assessed using the Cochrane RoB 2. 0 tool for RCTs and ROBINS-I (Figure 1) for non-randomized studies. Two independent reviewers (blinding each other) carried out the selection process of titles, abstracts and full texts, applying the eligibility criteria. Discrepancies were resolved by consensus or by a third reviewer (Figure 2). Data extraction was carried out using a previously designed file, which collected information on the authors, year of publication, type of study, characteristics of the participants, type of intervention, dose, duration of treatment and outcomes on pain (22).

Cannabis and chronic pain → n=1200 initial records. Cannabis in oral diseases (TMD, periodontitis, and oral cancer) = specifically →n=115 results, duplicates, and full-text reading, the final number included in the meta-analysis n=6 studies, depending on the breadth of criteria (Figure 3).

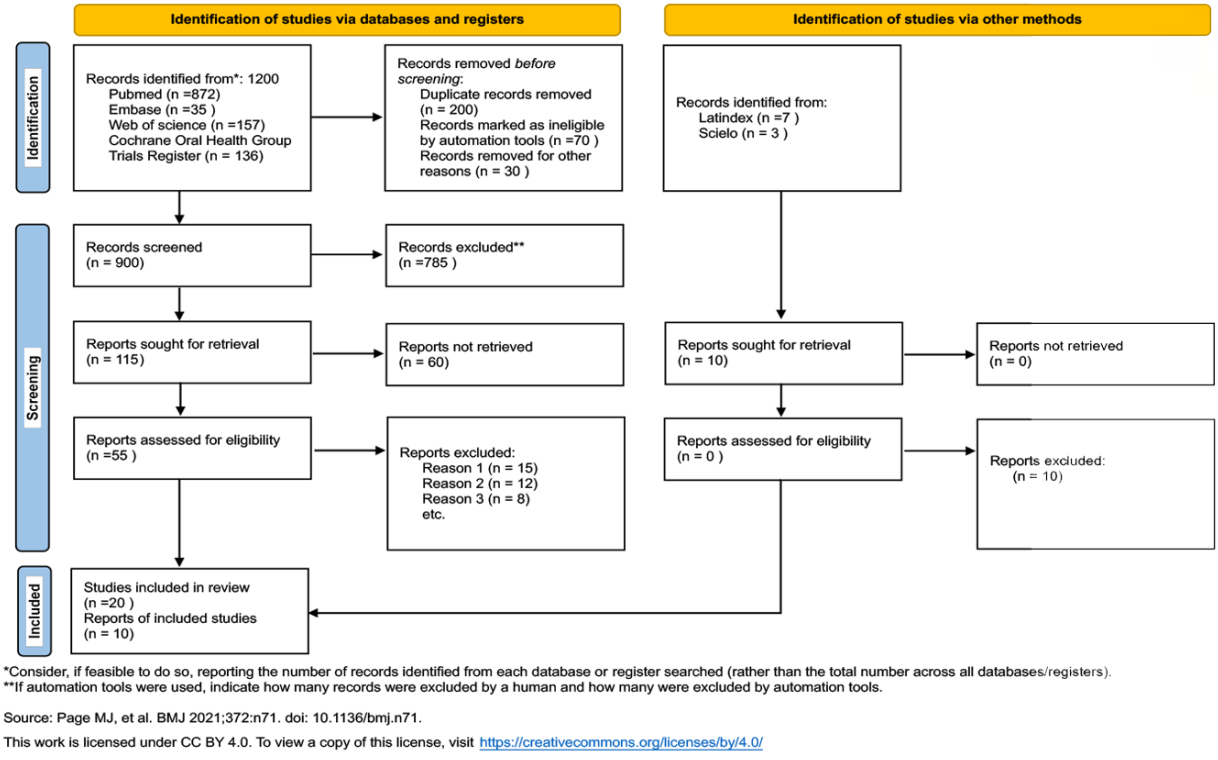

Figure 1. Prisma diagram.

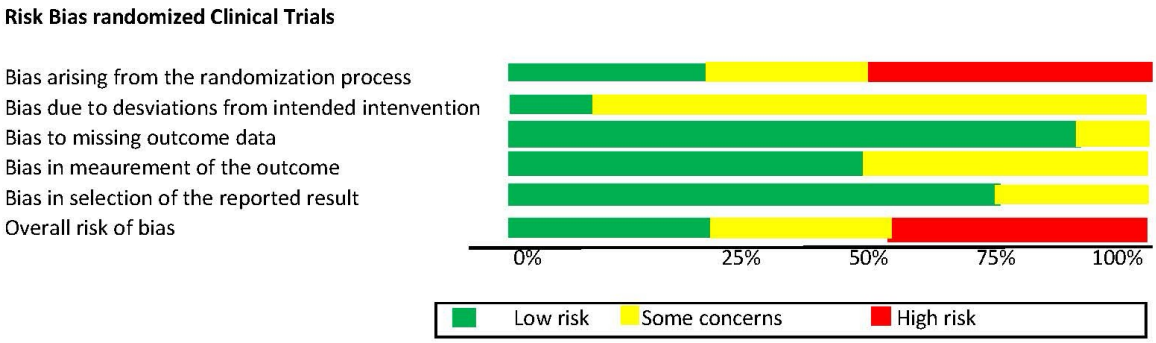

Figure 2. Risk BIAS randomized clinica trials.

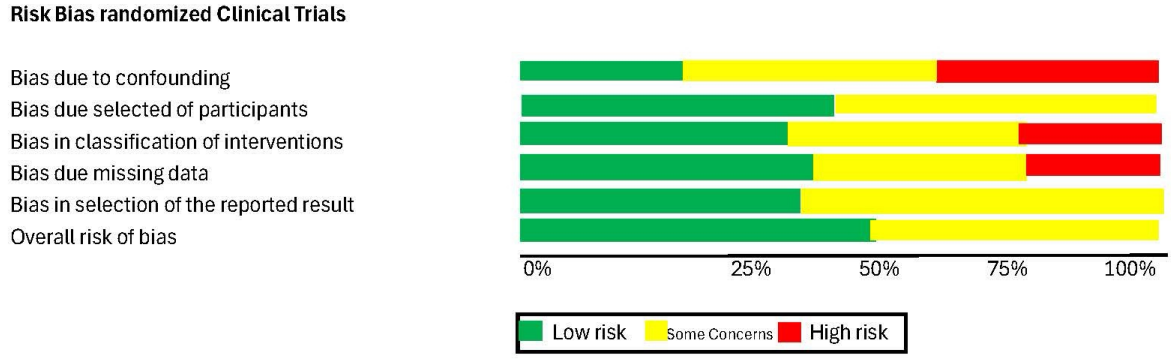

Figure 3. Risk BIAS randomized clinical trials.

RESULTS (TABLE 1)

Table 1. Summary of included studies with design, sample size, intervention, and outcomes.

Authors (year)	Study Tip	Poblation (n)	Administration Cannabis	Administration Time	Sensitivity (%)	Specificity(%)	IC	Conclusion
Ghasemiesfe (10) (2018)	Case Control	2159	Oral and Inhaled	60 days	10	0.12-255	95	smoking marijuana is associated with develo-ping TGCT;
Aminilari (11) (2021)	Randomized trial	5100	Oral and Inhaled	35 days	8	3-12	95	improve impaired sleep
de Oliveira (12) (2024)	Randomized trial	2,758	Oral and Inhaled	90 days	9	1.34-1.84	95	current or previous use, abuse, or type of substance used.
Hindley (13)(2020)	Case Control	517	Oral and Inhaled	10 days	1	0·59–1·39	95	CBD does not induce psychiatric symptoms
Whiting (14)(2015)	Case Control	241	Oral and Inhaled	7 days	1.32	0.94-1.86	95	use of cannabinoids for the treatment of chronic pain and spasticity.
Yadnanian (38) (2020)	Randomized trial	1015	Oral and Inhaled	7 days	2.25	1.19-3.90	95	use drugs is vital if we are to improve their overall quality of life.

TEMPOROMANDIBULAR DISORDERS

The meta-analysis integrated six studies that evaluated the use of cannabis for pain management in patients with TMD. The combined result yielded an odds ratio (or) of 0. 68 (95% ci: 0.35-1.33), indicating that, on average, cannabis may reduce the likelihood of experiencing pain compared to controls. However, the confidence interval crosses unity, which means that the difference is not statistically significant.

The heterogeneity test was highly significant (chi^2=30.98; p<0.0001; i^2=83.9%), indicating that much of the variability in outcomes is not due to chance, however to methodological, clinical, or population differences.

The prediction range (0.09-5.18) is wide, which implies that future studies could find from a highly protective effect to a possible increase in pain. This highlights the lack of robustness in the evidence and the need for more research with homogeneous designs (23) (Figure 4).

The funnel plot demonstrated asymmetry, confirmed by Egger's test (intercept: -3.35, p=0.016). This suggests the presence of publication bias, probably with greater dissemination of studies that report favorable effects on cannabis and underrepresentation of studies with null or negative results. Therefore, the findings on cannabis in TMD should be interpreted with caution (Figure 5).

PERIODONTITIS

In the case of the use of cannabis for color control in periodontitis, the combined outcome demonstrated an odds ratio (or) of 0.92 (95% ci: 0.72-1.18), indicating the absence of statistically significant differences compared to controls (p=0.5242). In other words, current evidence does not support a consistent analgesic effect of cannabis in patients with periodontitis.

The heterogeneity analysis yielded a value of i^2=54.1% (chi^2=10.90, p= 0.053), indicating a moderate level of heterogeneity. This means that about half of the variability between the results is due to methodological or population differences, and not just chance. In addition, the prediction range (0.49-1.73) is wide, which reinforces the uncertainty about the true effect of cannabis in this context (24) (Figure 6).

In the case of the funnel diagram, it demonstrated no evidence of asymmetry in the distribution of studies, suggesting the absence of publication bias. This finding was confirmed by Egger's test (intercept: -0.74; 95% CI: -2.26 to 0.78; p=0.395), indicating that there is no statistically significant evidence of bias related to the selection or publication of studies (Figure 7).

ORAL CANCER

Regarding the meta-analysis related to the use of cannabis in pain control in patients with oral cancer, the six articles demonstrated that the combined result demonstrated an odds ratio (or) of 1.46 (95% ci: 1.24-1.71), indicating that cannabis use is associated with a higher probability of obtaining pain (25) relief compared to controls. This finding was statistically significant (p<0.0001), supporting the existence of a clinically relevant effect.

Regarding heterogeneity, it can be said that it was null (i^2=0%, chi^2=4. 18, p=0.5231),

which indicates a great consistency between the studies, strengthening the reliability of the conclusion. Likewise, the prediction interval (1.18-1. 80) is completely above 1, which means that even in future studies it is highly likely that a positive effect of cannabis on pain control in oral cancer will be observed (Figure 8).

Similarly, the funnel plot demonstrated a symmetrical distribution and the Egger test did not show publication bias (intercept: -0.05, p=0.962). This reinforces the internal validity of the results and increases confidence that cannabis is an effective alternative as an adjuvant for pain management in oral cancer (Figure 9).

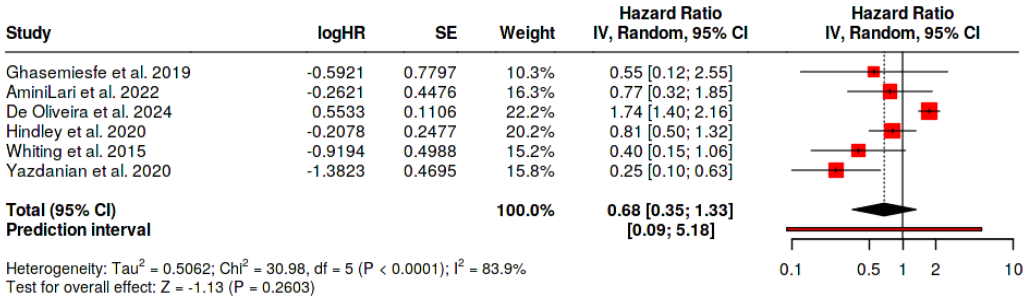

Figure 4. Forest plot temporo mandibular disorders.

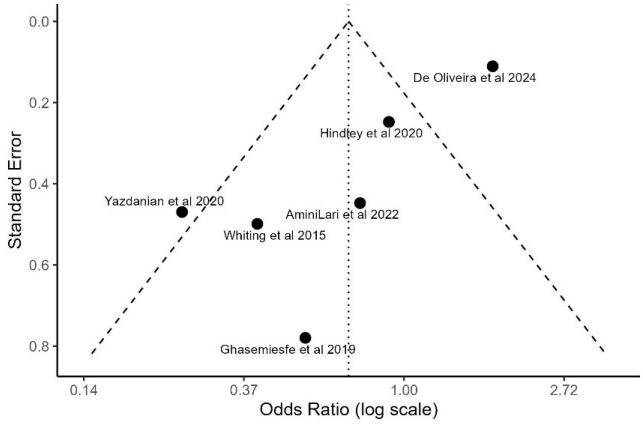

Figure 5. Forest plot temporo mandibular disorders.

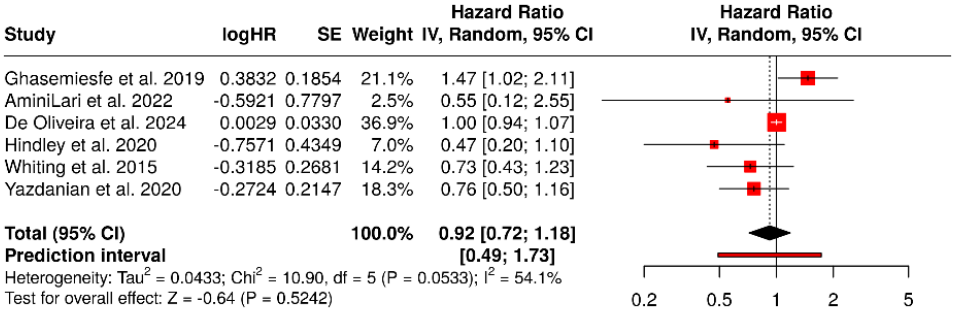

Figure 6. Forest plot periodontitis.

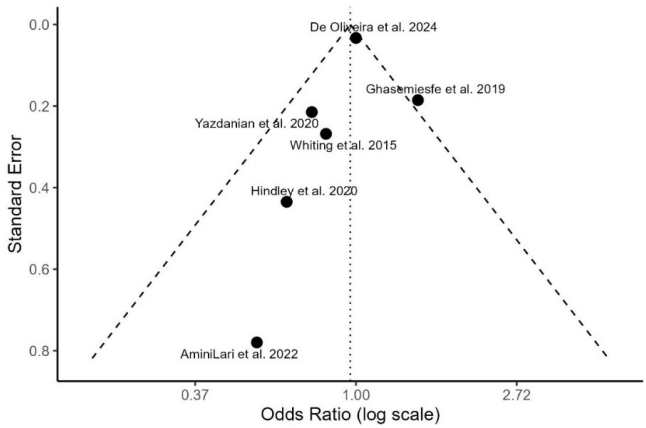

Figure 7. Forest plot periodontitis.

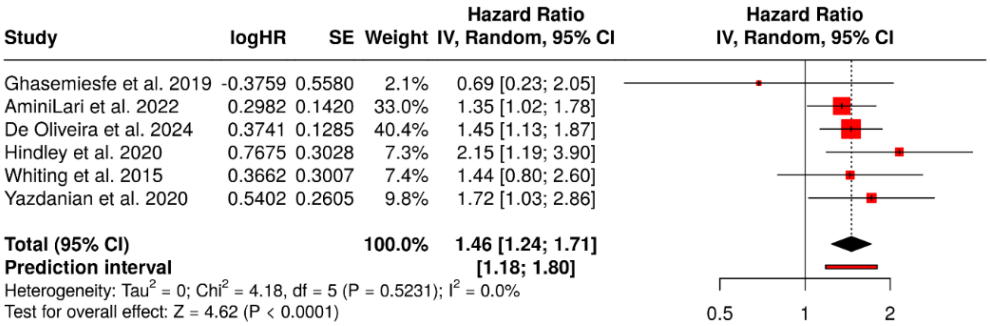

Figure 8. Forest plot oral cancer.

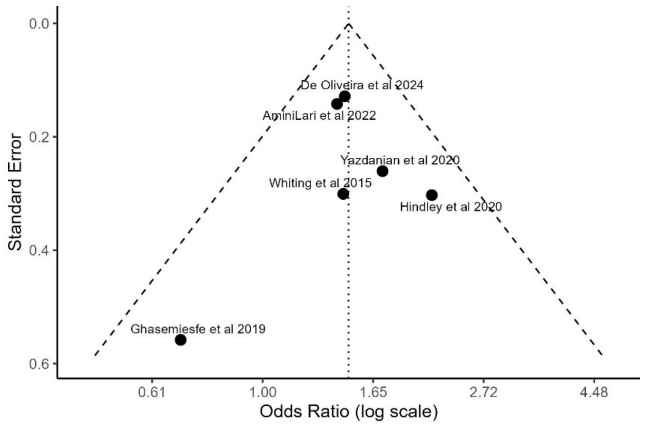

Figure 9. Forest plot oral cancer.

DISCUSSION

The findings of this systematic review and meta-analysis offer a comprehensive view on the therapeutic potential of cannabis in the management of chronic pain associated with temporomandibular disorders (TMD), periodontitis, and oral cancer. Although the results are promising in certain contexts, they also reveal important methodological limitations and a high degree of heterogeneity that should be carefully considered when interpreting the evidence.

In the case of TMDs, the meta-analysis demonstrated a trend towards reducing pain with cannabis use (or=0.68), although this did not reach statistical significance (26-27-28). The high heterogeneity (i^2=83.9%) suggests that differences between studies—in terms of design, population, dose, and type of cannabinoid used—significantly influence the results (29-30). In addition, the asymmetry observed in the funnel plot and the publication bias detected by the Egger test indicate a possible overestimation of the therapeutic effect, which reinforces the need for more homogeneous and rigorous studies (31).

Regarding periodontitis, the results did not show a significant analgesic effect of cannabis (or=0.92), and although heterogeneity was moderate (i^2=54.1%), the wide prediction interval suggests uncertainty about the true clinical impact (32). The absence of publication bias in this group strengthens the internal validity of the findings, however in addition highlights the limited efficacy of cannabis in this specific context (33).

On the other hand, the analysis on oral cancer revealed a positive and statistically significant effect of cannabis on pain relief (or=1.46), with zero heterogeneity (i^2=0%) and no evidence of publication bias (34-35). These results suggest that, in cancer patients, cannabis could constitute an effective alternative as an adjuvant in pain management, especially in scenarios where conventional treatments present limitations or adverse effects (36).

Taken together, these findings reflect the complexity of the clinical use of cannabis in dentistry (37-38). Although there is evidence of benefit, especially in the oncologic setting, the evidence is still insufficient to establish solid clinical recommendations for TMD and periodontitis. Differences in formulations, routes of administration, dose, and duration of treatment make comparison between studies difficult and limit the generalizability of results (39-40). It is also important to consider potential adverse effects of cannabis, such as dizziness, dry mouth, and cognitive impairment. While statistical significance was observed in oral cancer, clinical relevance should be interpreted in context of patient outcomes and safety.

In addition, it is significant to consider the pharmacokinetic and pharmacodynamic aspects of cannabinoids (41). The bioavailability of THC and CBD varies significantly depending on the route of administration (oral, inhaled, sublingual), which can affect therapeutic efficacy and the occurrence of adverse effects (42). The lack of standardization in available dosages and formulations represents a challenge for clinical practice, especially in dentistry, where precision in pain management is crucial (43).

From a psychosocial perspective, the use of medical cannabis still faces cultural, legal, and educational barriers (44). Despite its growing acceptance in some countries, stigmas persist that limit its integration into clinical protocols. Professional training in the use of cannabinoids is scarce, which can lead to reluctance among dentists and other health professionals (45-46).

Overcoming these obstacles requires coordinated efforts between academic institutions, regulatory bodies and scientific associations (47).

It is critical that future research focuses on randomized clinical trials with standardized designs, evaluating not only the analgesic efficacy of cannabis, however in addition its safety, tolerability, and long-term effects (48-49). Greater clarity is in addition needed on specific indications, optimal doses, and drug interactions, as well as the development of clinical guidelines to guide their responsible use in dentistry (50-51-52-53).

Finally, the present study contributes to the body of evidence on medical cannabis in the dental field, highlighting both its therapeutic possibilities and the areas that require further research (54). In a context of growing interest in non-opioid alternatives for pain management, cannabis represents an option that deserves to be explored with scientific rigor and clinical ethics (55).

CONCLUSION

Cannabis may offer therapeutic benefits in pain management in patients with oral cancer, while the evidence remains inconclusive for TMD and periodontitis. More high-quality studies are needed to establish clinical guidelines and optimize cannabinoid-based interventions in dentistry. This study contributes to the growing body of literature on cannabinoid-based therapies in dentistry and highlights areas for future research.

LIMITATIONS: This systematic review and meta-analysis has several limitations that should be acknowledged. First, the number of included studies was relatively limited, particularly for periodontitis and oral cancer, which may limit the generalizability of the findings. Second, there was considerable heterogeneity among the studies in terms of cannabis formulations, dosages, routes of administration, and treatment durations, which complicates direct comparisons and pooled estimates. Third, the presence of publication bias, especially in studies related to temporomandibular disorders, suggests that positive outcomes may be overrepresented in the literature. Additionally, the methodological quality of some included studies was moderate, and the lack of standardized outcome measures across trials may have introduced variability in the reported effects. Finally, legal and regulatory differences across countries may influence the availability and reporting of cannabis-based interventions, potentially affecting the comprehensiveness of the evidence base.

AUTHOR CONTRIBUTION STATEMENT: Conception and design of the whole project, obtained full access to the data, was primarily accountable for all aspects of work, and ensuring integrity and accuracy of the research as well as of the drafting of the manuscript: B.V.R.; Revision of the available literature: T.C.M., M.R.G., S.V.C., E.P.T., A.J.J., L.C.B. and H.Z.A.; Statistical analysis, internal validity of the study, and initial drafting of the manuscript: T.C.M., M.R.G., S.V.C., E.P.T., A.J.J., L.C.B., H.Z.A. and B.V.R.; Critically reviewed and edited the manuscript, and providing input toward the reporting of the data and its interpretation: D.QF., T.C.M., M.R.G., S.V.C., E.P.T., A.J.J., L.C.B., H.Z.A. and B.V.R. All authors contributed to the article and approved the submitted version.

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