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Original Research

The therapeutic effect of cannabidiol in oral mucosa lesions: a scoping review of in vivo and clinical studies

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Aim: This study aims to analyze the potential therapeutic effect of cannabidiol use on oral mucosa lesions in clinical and *in vivo* studies. **Methods:** A scoping review was conducted considering the question: "Is there a therapeutic effect of the use of cannabidiol (CBD) on lesions of the oral mucosa?". Four distinct databases were searched (PubMed/MEDLINE, Embase, Web of Science, and Scopus) and gray literature until August 2023. Original clinical and in vivo studies were included, involving human and animal subjects where CBD was applied topically to the oral mucosa or administered systemically for the treatment of lesions or superficial/deep alterations of the oral mucosa. **Results:** A total of 610 records were found in the initial searches. Twelve studies were assessed in full text for eligibility and five studies were excluded. Seven studies were included in this review. Five studies were conducted with *in vivo* design and only two studies had clinical design in humans. Considering results from *in vivo* studies, all of them presented better clinical results for oral mucosa lesion groups treated with CBD-based therapy compared to placebo. Regarding histological features, four studies found statistically significant improvement in CBD-based therapy and only one study did not find a significant improvement. For clinical studies, all studies presented positive clinical results (primarily regarding pain control) in the use of CBD-based therapies. **Conclusion:** CBD appears effective in treating oral mucosa lesions (oral mucositis, ulcers, burning mouth syndrome). CBD-based therapies can reduce inflammation *in vivo* studies and hold promise for pain control and lesion healing in oral mucosa lesions in clinical studies. However, the limited number of clinical trials, heterogeneity in cannabis-based therapies, and a lack of standardized protocols underscore the need for further rigorous, interdisciplinary research to establish consistent dosing and assess the efficacy of various cannabinoids in treating oral mucosa conditions.

Keywords: Cannabis. Cannabidiol. Oral ulcer. Pathology, oral.

Introduction

Cannabis sativa L. is an herbaceous plant from the Cannabaceae family that has been used by humans for many years in many parts of the world[1]. Cannabinoids are found within the active metabolites that they contain[2]. The most well-known cannabinoids are delta-9-tetrahydrocannabinol (THC), with psychotropic effects, and cannabidiol (CBD), without psychotropic effects. The absence of psychotropic effects in CBD is the main reason why it is chosen for medicinal purposes[2,3]. Studies have shown that CBD has anti-inflammatory properties in humans[4,5], antioxidants[6,7], and analgesic effects[8,9].

The human body can synthesize metabolites similar to THC and CBD, such as anandamide, which is why these molecules are referred to as endocannabinoids[10]. Specific receptors for these molecules (cannabinoids) are distributed throughout the body's tissues; thus, forming a true internal communication network that the literature has defined as the endocannabinoid system[11,12]. The large number of endocannabinoid receptors in living organisms results in different therapeutic possibilities and varied forms of administration with therapeutic purposes, which can be delivered systemically through oral consumption in the form of tablets[13], by lung inhalation from cigarettes or vaporizers[14-16], and by topically applied directly to the skin or oral mucosa[17,18].

There is a tendency towards an increase in topical use on the skin, being potentially effective for the treatment of uncommon pathologies, such as granulomatous pyoderma and epidermolysis bullosa[19,20]. The use of Cannabinoids for the treatment of oral mucosa lesions has limited evidence with contradictory results among studies[21,22]. CBD was able to inhibit the production of TNF-α and IL-1β in macrophages present in gingival ulcers in an *in vitro* experiment[23]. A CBD spray has inhibited inflammation, reduced pain, and accelerated the healing of oral ulcers in mice[17]. On the other hand, a systematic review evaluating the effects of cannabis extracts on oral ulcers did not demonstrate a statistical difference between Cannabis sativa and the control group[24]. In addition to its therapeutic properties, it has been demonstrated that plant-based medicines have fewer side effects and therefore present a valid and safe alternative to conventional treatments[22,25,26], justifying their choice.

Despite promising results in the dental field, few pathological entities of the oral mucosa have been evaluated through the use of cannabis for their therapeutic potential[22]. Furthermore, there is no consensus in the literature on what is the optimal dosage to select for each case[22]. Previous studies, such as those focusing on oral mucositis related to chemotherapy and radiotherapy, have indicated CBD's potential for managing oral lesions; however, limited research exists on its application across a broader spectrum of oral mucosal pathologies. This gap highlights the need for a more comprehensive investigation into CBD's effects and dosage efficacy for various oral lesions[27]. Therefore, the objective of this scoping review was to analyze the potential therapeutic effect of cannabidiol use on oral mucosa lesions in clinical and *in vivo* studies.

Methods

This review was reported following the PRISMA to *scoping reviews*[28]. The study registration was performed in the OSF (10.17605/OSF.IO/CN53D).

Study design

We chose a scoping review approach instead of a systematic review, aligning with guidance that recommends scoping reviews when there is a need to map, report, and discuss various characteristics rather than address a specific research question precisely[29]. Consequently, scoping reviews do not aim to provide a critically appraised and synthesized answer to a particular question[29], providing a general overview of existing content, and establishing future directions for studies and gaps in literature[30-32].

Review question and searches

The present scoping review was conducted considering the question: "Is there a therapeutic effect of the use of cannabidiol on individuals or animals with lesions of the oral mucosa?". The question followed the acronym PCC framework[33]:

Population: Individuals or animals with alteration or pathology in the oral mucosa.

Concept: The healing effect of soft tissue being measured using clinical or histological criteria that follow: **Clinical:** 1) Ulcer size; 2) Presence and severity of Oral Mucositis; 3) Pain (burning mouth syndrome and UAO); 4) Levels of anxiety and depression (burning mouth syndrome); 5) Quality of life; 6) Satisfaction with the intervention. **Histological:** 1) Edema, hyperemia, and presence of inflammatory infiltrate; 2) Hematological cell count (leukocytes, erythrocytes, and platelets); 3)Activity of antioxidant enzymes and oxidative stress; 4) Increase of cytokines, TNF and IL-6; 5) Size of ulcers, cellular positivity and epithelial thickness; 6) Average fluorescence intensity; 7) Cellular viability; 8) Cell apoptosis rate; 9) Expression levels and nuclear translocation of Nrf2; 10) Protein expression levels.

Context: Application of cannabidiol extract.

A structured search was carried out in PubMed/MEDLINE, Embase, Web of Science, and Scopus, until August 2023. Keywords and MeSH terms were used to build the search syntax of each database. Details of all strategies in each database are displayed in Table 1.

Table 1. Search summary used according to the databases

Database	Syntax
Pubmed	(Oral ulcer OR ulcer OR ulceration OR aphthous OR stomatitis OR burning mouth síndrome) AND (cannabis OR cannabidiol)
Embase	((Oral ulcer) OR (ulcer) OR (ulceration) OR (aphthous) OR (stomatitis) OR (burning mouth síndrome)) AND ((cannabis) OR (cannabidiol))
Scopus	ALL("Oral ulcer" OR "ulcer" OR "ulceration" OR "aphthous" OR "stomatitis" OR "burning mouth síndrome") AND ALL("cannabis" OR "cannabidiol")
Web of Science	TS=(Oral ulcer OR ulcer OR ulceration OR aphthous OR stomatitis OR burning mouth síndrome) AND TS=(cannabis OR cannabidiol)

The search approach involved the utilization of pertinent keywords and entry terms associated with MeSH Terms, adapted to the structure of each individual database. The detailed search strategy can be found in Table 1. The gathered records were imported into EndNote™ software (Thomson Reuters, Rochester, New York, NY) to create a virtual library. Duplicate studies were identified and removed. Two independent reviewers (MM and LAC) assessed the titles and abstracts of all papers. Gray literature was manually explored in the 100 first hits of Google Scholar using the following syntax: ((Oral ulcer) AND ((cannabis) OR (cannabidiol)). The same reviewers proceeded to evaluate the full-text articles and resolve any discrepancies through discussion to reach a consensus.

Eligibility criteria

Were included: (1) Original published articles, (2) *In vivo* or clinical studies in humans or animals, (3) studies using CBD in either commercial or experimental extract form, (4) studies applying CBD topically to the oral mucosa or systemically for the treatment of lesions or superficial/deep alterations of the oral mucosa. Were not included: (1) Letters to the editor and reviews, (2) *in vitro* studies, (3) studies where mucosal lesions were treated with therapies other than CBD, (4) studies focusing on skin lesions, (5) studies addressing ulcers in areas of the body other than the oral cavity, (6) studies investigating the use of cannabis for the treatment of pain and other conditions not localized to the oral cavity.

Data collection

Data extraction was performed independently by the same reviewers using a predefined electronic spreadsheet. The following data were extracted: author data, year of publication, details of the model used (for *in vivo* studies), description of the type of study (for clinical studies), study groups, evaluated variables, biological context, and main results of analyzed studies, the main active component of the evaluated therapy, the origin of the product (commercial or experimental), delivery vehicle and the concentration/doses applied.

Strategy for data synthesis

The extensive variability in materials and methods, particularly concerning study design and outcome evaluation within the included articles, led to the formation of numerous smaller subcategories of results. This diversity precluded any attempt at quantitative analysis. Consequently, a comprehensive descriptive analysis of the results was conducted, organizing the studies into two main groups: in vivo studies and clinical studies, further categorized based on their specific oral lesions.

Results

A total of 610 records were found in the initial searches and two additional records in gray literature (Figure 1). After the exclusion of duplicates, 508 manuscripts remained for title and abstract screening. Twelve studies were assessed in full text for eligibility, and five studies were excluded. Table 2 presents the reasons for the exclusion of these papers. Seven studies were included in this review.

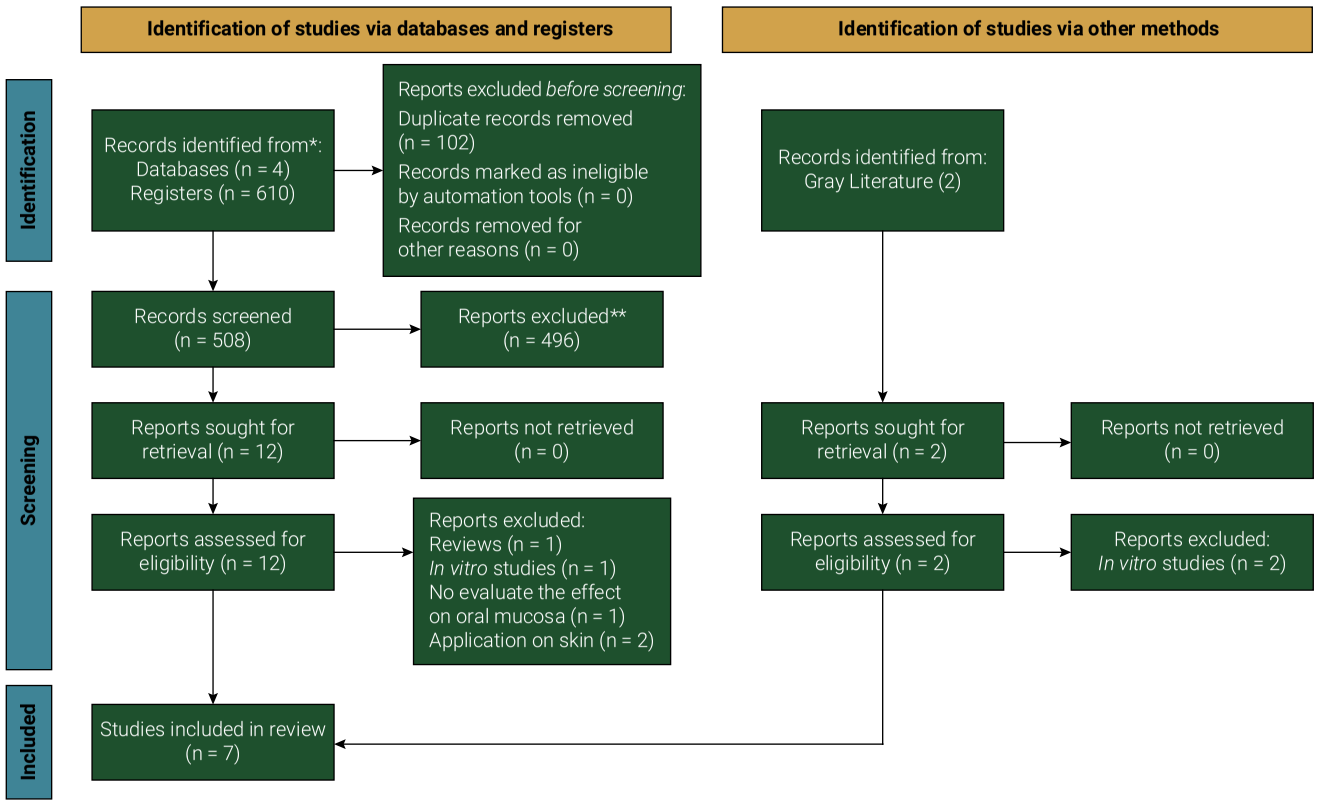

Figure 1. Prisma flow diagram

Table 2. Excluded studies and their reasons

Studies	Exclusion reasons
Cuba et al.[27]	Review
Kongkadee et al.[23]	*in vitro* study
Darling et al.[34]	Not evaluate the effect on oral mucosa
Serpell et al.[35] and Jiménez-Rodríguez et al.[36]	Application on skin

Study characteristics

The majority (n=5, 71.4%) of included studies were carried out with *in vivo* designs[17,18,37-39] and only two studies had clinical designs[13,40]. The studies were published between 2018 and 2023 and the study authors were from China, Brazil, Italy, and Thailand. The oral mucosal pathologies analyzed included oral ulcers, oral mucositis, and burning mouth syndrome. CBD was the most commonly used active component, only one study evaluated the application of CBD together with THC[13]. Details of study characteristics and their respective clinical and histological results are displayed in Table 3 and discussed in the next subtopics.

The forms of application reported in studies were systemic, through intraperitoneal and intravenous injection or oral consumption of an extract. Additionally, topical application was reported, using an oral spray by dripping directly onto the oral mucosa. The variables evaluated were mostly at the histological level, such as inflammation degree, hematological cell count, cellular activity, oxidative activity, and rate of cellular apoptosis. At a clinical level, the dimensions of the lesion, pain, and level of anxiety and depression were evaluated. Most of the studies (n=6; 85.7%) used experimental cannabis-based therapies (Table 4) and only one used a commercial medication: Bediol®.

Table 3. Study characteristics of the included studies.

Author, year, and country	Study design	Details of the model used	Experimental group	Control group	Variables evaluated	Biological context	Main results
Klein et al.[37], 2018 (Brazil)	*In vivo*	Rat tongue ulcers were created mechanically. 60 individuals divided into 3 groups (n=20) in a randomized manner.	CBD	2% polyoxyethylensorbitan monooleate (Tween 80) in saline solution.	**Clinic:** Ulcer size every 3 to 7 days **Histology:** degree of inflammation at 3 and 7 days.	Scarring of oral wounds.	**Clinical**: in the center area, dimensional differences in the area of the ulcer treated with CBD compared to the control group. **Histological:** After 3 days, the groups treated with CBD showed a lower degree of inflammation compared to the control group. **No differences were** found between groups after 7 days.
Cuba et al.[38], 2020 (Brasil)	*In vivo*	Mice with chemotherapy-induced oral mucositis. 90 individuals divided into 5 groups (n=18) in a randomized manner.	CBD	Positive: FU + mechanical trauma + placebo. Negative: FU + placebo. Placebo: Tween 80 in saline (0.2 ml).	**Clinic:** Ulcer size every 4 to 7 days **Histology:** degree of inflammation, blood cell count, and oxidative enzymes over 4 and 7 days.	Scarring of oral wounds.	**Clinical:** The size of the ulcer in the groups treated with CBD was smaller compared to the control group at days 4 and 7. **Histological:** in the center area, differences in inflammation levels were observed between the groups. Greater numbers of erythrocytes and leukocytes were found in the groups treated with CBD after 4 days, with no differences observed after 7 days. Oxidative activity was lower in the groups treated with CBD after 7 days.
Qi et al.[17], 2021 (China)	*In vivo*	Ulcers on the tongue of hardened rats created by acid etching. Individuals are divided into 3 groups. It does not specify quantity or randomization method.	CBD	N/E	**Clinic:** Ulcer size every 2 and 4 days. **Histology:** degree of inflammation and expression of cytokines.	Scarring of oral wounds.	**Clinic:** The application of CBD reduced the size of ulcers in a dose-dependent manner. **Histological:** Mucosa treated with CBD showed a decrease in inflammatory activity and in the expression of NLRP3, IL-1β, IL-18, and TNF-α proteins.
Li et al.[39], 2022 (China)	*In vitro and In vivo*	Mice with chemotherapy-induced oral mucositis. 60 individuals divided into 5 groups (n=6) in a randomized manner.	5- fluorouracil o 5-fluorouracil + CBD	Tween 80 at 2% + DMSO* at 3% + saline solution at 95%.	**Clinic:** size tongue ulcers. **Histology:** cytological report, expression of cytokines, antioxidant enzymes and epithelial thickness, cell proliferation, and apoptosis after 4, 7, and 10 days.	Scarring of oral wounds.	**Clinic:** The application of CBD reduced the size of ulcers in a dose-dependent manner, compared to the control group. **Histological:** Compared to the control, there were decreased levels of pro-inflammatory cytokeratins, increased expression of antioxidant enzymes, and increased epithelial thickness. An increase in cell proliferation and a decrease in cellular apoptosis were also observed.

Continue

Continuation

Liu et al.[18], 2022 (China)	*In vitro and In vivo*	Mice with chemotherapy-induced oral mucositis. 18 individuals divided into 2 groups (n=9) in a randomized manner	Nano-micelles with fucoidan-deoxycholic (FD) + CBD	Nano-micelles with FD.	**Clinical:** size of tongue ulcers. **Histology:** expression of P-selectin and cytokeratins, degree of inflammation, after 2,4 and 6 days.	Scarring of oral wounds.	**Clinical:** The size of the ulcer in the groups treated with CBD was smaller than in the control group. **Histology:** Groups treated with CBD demonstrated lower expression of inflammatory factors and anti-inflammatory infiltration.
Gambino et al.[13], 2021 (Italia)	Clinic	Population-based study, patients with burning mouth syndrome. 17 individuals were selected based on inclusion criteria in a prospective study.	Extract: 8% CBD and 6.3% THC diluted in olive oil (proportion 1/10 g).	-	**Clinical:** Assessment of pain, anxiety, and depression on day 0, 4-12-24 weeks	Pain control.	**Clinical:** A decrease in oral symptoms was reported, along with a decrease in anxiety levels.
Umpreecha et al.[40], 2023 (Thailandia)	Clinic	Random, parallel, double-blind controlled test. 72 patients with RAU were randomly divided into 3 groups (CBD, TA, placebo).	0.1% CBD ointment.	0.1% triamcinolone acetonide or placebo.	**Clinical:** Ulcer size, pain, intervention satisfaction, and quality of life.	Healing of oral wounds and pain control.	**Clinical:** Groups treated with CBD showed a greater reduction in ulcer size, decreased pain, higher satisfaction, and improved quality of life compared to placebo. No differences were observed between the groups treated with CBD and TA

N/E: Does not specify. DMSO: Dimethyl sulfoxide. RAU: Recurrent aphthous ulcer. TA: Triamcinolone acetonide.

Table 4. Information about cannabis-based therapies used in analyzed studies.

Author, year	Active component	Commercial or experimental	Vehicle
Klein et al.[37], 2018	Synthetic CBD (≥99) Purity (THC Pharm GmbH, Frankfurt, Germany)	Commercial	2% polyoxyethylensorbitan monooleate (Tween 80) in saline solution.
Cuba et al.[38], 2020	Synthetic CBD (≥99) Purity (THC Pharm GmbH, Frankfurt, Germany)	Commercial	2% polyoxyethylensorbitan monooleate (Tween 80) in saline solution
Qi et al.[17], 2021	CBD	Experimental	N/E
Li et al.[39], 2022	CBD	Experimental	Tween 80 at 2% + DMSO* at 3% + saline solution at 95%.
Liu et al.[18], 2022	CBD	Experimental	Micella with FD**
Gambino et al.[13], 2021	CBD y THC	Commercial (Bediol®)	N/E
Umpreecha et al.[40], 2023	CBD	Experimental	N/E

N/E: Does not specify. CBD: cannabidiol; THC: delta-9-tetrahydrocannabinol; DMSO*: Dimethyl sulfoxide. FD**: fucoidan-deoxycholic.

In vivo studies

Five studies utilized an *in vivo* design[17,18,37-39], and all of them presented better clinical results for oral mucosa lesion groups treated with CBD-based therapy compared to placebo. Regarding histological features, four studies[17,18,37,39] found statistically significant improvement in CBD-based therapy and only one study[38] did not find a significant improvement.

Three studies investigated oral mucositis and observed a positive effect of CBD compared with control groups[18,38,39]. These studies clinically and histologically evaluated chemotherapy-induced oral mucositis in mice. The therapy was administered intraperitoneally in amounts of 3, 10, and 30 mg/kg of animal weight, using Tween 80 in saline solution as the vehicle. One study used an intravenous dose (0.2ml of CBD) and a topical application, through direct application to the lesion of 30 µl of CBD in the form of fucoidan-deoxycholic nano micelles. In all three studies, CBD was used as an experimentally derived active component.

Considering the clinical outcomes, ulcers treated with CBD showed a greater reduction in size compared to placebo[18,38,39]. Regarding the histological outcomes, two studies[18,39] observed better histological findings in the groups treated with CBD while Cuba et al.[38] did not observe statistical differences in histological evaluation between the group treated with CBD and the placebo. Groups treated with CBD showed reduced expression of inflammatory factors and anti-inflammatory infiltrate[18], decreased levels of proinflammatory cytokeratins, and increased levels of expression of antioxidant enzymes[39].

Ulcers on the tongue were investigated in two studies[17,37]. The ulcers were created (mechanically or with acid) on the tongue of mice[17,37]. One of them administered 5

and 10 mg/kg of weight of CBD intraperitoneally using Tween 80 in saline solution as a vehicle, the other study administered 1 and 10 mg/kg directly to the lesion (topical) without specifying the vehicle used. In both studies, experimentally isolated CBD was used as an active component. The observed clinical and histological results were positive[17,37]. Regarding clinical outcomes, ulcers treated with CBD were smaller in size than those in the placebo group. Histologically, a lower degree of inflammation was observed concerning the control group in the first 3 days (no difference was observed after 7 days)[37] and a decrease in inflammatory activity, and in the expression of the proteins NLRP3, IL-1β, IL-18, TNF-α[17].

Clinical studies

Two clinical studies were found and both studies[13,40] presented positive clinical results (primarily regarding pain control) in the use of CBD-based therapies.

The first of them investigated the effect of cannabidiol extract on humans. It was a prospective single-arm study evaluating burning mouth syndrome. Seventeen patients were evaluated, 14 of whom were female, with an average age was 71 years. The treatment applied was a commercial extract in the form of drops with a concentration of 8% CBD and 6.3% THC (Bediol®), prepared with an olive oil-based vehicle. The dosage ranged from 10 to 40 drops daily, divided into two doses each day. The treatment duration ranged from 5 to 13 days. The main variable evaluated was pain, measured using the visual analog scale (VAS). Additionally, the level of anxiety and depression was assessed using the Hospital Anxiety and Depression Scale (HADS) and the Geriatric Depression Scale (GDS). Based on statistical analyses, the results suggest a significant reduction in pain at 4, 12, and 24 weeks compared to the baseline. For anxiety and depression levels, a significant decrease was reported only after 24 weeks compared to baseline. The authors reported that 3 individuals reported dizziness the first week, 2 reported headaches (on the 5th and 15th day) and 1 individual reported constipation after 24 days of treatment. Despite this, none of the participants had to abandon the study.

The second clinical study analyzed the effect of cannabidiol on recurrent aphthous ulcers (RAU). The study was a randomized, double-blind, controlled clinical trial involving 72 patients with RAU, with ages ranging from 18 to 65 years. Participants were randomly divided into three groups: 0.1% CBD, 0.1% triamcinolone acetonide (TA), and placebo. All therapies were applied topically, directly to the lesions. Ointments with corresponding active components were experimentally prepared, without detailing the vehicles used. The ointments were applied with a calibrated applicator (no quantities in weight or volume are specified), three times a day for seven days, before eating. The variables evaluated were the size of the ulcer in millimeters at baseline, 2, 5, and 7 days. Pain was assessed daily using the VAS scale. Satisfaction with the therapy used and quality of life during the treatment were also evaluated, along with any allergic reactions or side effects. The results suggest that the groups treated with CBD showed greater reduction in the size of ulcers, less pain, higher satisfaction, and improved quality of life compared to the placebo group at all times evaluated. No differences were found between the groups treated with CBD and TA. No side effects were reported.

Discussion

This study was the first to map the available evidence on the use of cannabidiol in lesions of the oral mucosa. Based on the potential properties of CBD reported in the literature, and the results obtained in the analyzed studies, we can consider that (1) the use of CBD appears to be effective in investigated lesions of the oral mucosa (oral mucositis, oral ulcers, and burning mouth syndrome) when using different CBD-based therapies, thus presenting preliminarily positive *in vivo* results when compared to placebo. Complementary histological analyses in most reports demonstrated that CBD-based therapies appear to reduce the inflammatory response in the oral lesions evaluated[17,18,37,39]; and (2) CBD-based therapies seem to be a promising strategy for pain control in oral mucosa lesions[13,40]. The different concentrations used have demonstrated similar results, with no significant differences observed between the dosages reported. However, additional studies are needed to confirm these preliminary findings and their interpretations should be carried out with caution.

Our findings indicate that the main effect of CBD-based therapies is the potential to improve the healing process and provide significant pain reduction. Indeed, CBD can act through several mechanisms to reduce painful and inflammatory symptoms[4]. First, CBD can bind to the CB1 and CB2 cannabinoid receptors in the nervous and immune systems, respectively, which can reduce the perception of pain and modulate the inflammatory response[41]. Furthermore, CBD can also inhibit the production of pro-inflammatory cytokines, which are signaling molecules that contribute to inflammation. Finally, CBD can interact with other receptors in the body, such as the vanilloid TRPV1 receptor, which is involved in pain transmission, and the PPAR-gamma receptor, which can help regulate the inflammatory response[41]. These combined mechanisms may explain the capacity of CBD to reduce painful symptoms and inflammation of lesions of the oral mucosa observed in the present review.

Although some studies have used systemic application of CBD[13], there is a consensus that the preferred treatment approach is through topical application of medications[42]. This is because the goal is to achieve a localized and specific treatment of the lesion. In certain situations, such as when considering the severity and intensity of the injury, high recurrence, or lesions that do not heal, or in patients with specific systemic conditions, it is possible to implement systemic therapy[43-45]. However, the long-term administration of some medications has unwanted effects on patients[46].

Despite this, according to the results of this work, we can observe that the majority of investigated CBD-based therapies for the treatment of lesions in the oral mucosa have been administered through systemic action[13,18,37-39], and only in three studies was the treatment of the lesion was carried out through topical application[17,18,40]. This could be attributed to the fact that the majority of studies were carried out *in vivo*. In these cases, cannabis was administered intravenously and intraperitoneally for the treatment of oral ulcers and mucositis induced in animal models[18,37-39]. In the analyzed clinical studies, systemic therapy (oral drops) was used in patients with burning mouth syndrome, while in the other study, a topical application of CBD was used for recurrent aphthous ulcers.

From *in vivo* studies that administered CBD to oral mucosal lesions[17,18], oral mucositis and ulcers were evaluated. In one study, a dose of 30 µl of an experimental CBD preparation (1 mg/ml) in the form of nanomicelles was applied, and in the second study, 1 and 10 mg/ml of experimental CBD in the form of a spray was used. For the treatment of mucositis, a decrease in Ly6G, a marker of inflammation, was observed[18]. CBD reduced the expression of cytidine monophosphate/uridine kinase 2 (CMPK2), which is responsible for inhibiting the generation of oxidized mitochondrial DNA and suppressing the activation of inflammation[17]. Furthermore, CBD was able to improve the healing capacity of ulcerative lesions, demonstrating a greater reduction in size and faster healing compared to the control group[17,18].

At a clinical level, patients with burning mouth syndrome receive a dose of 5 to 20 drops daily, with treatments varying between 5 and 13 days. In this case, a commercial preparation in the form of oil (Bediol®) was used, containing 8% CBD and 6.3% THC, diluted in olive oil at a proportion of 1/10 g. The results demonstrated a significant reduction in pain at 4, 12, and 24 weeks compared to baseline[13]. When an experimental preparation with 0.1% CBD was applied topically to recurrent aphthous ulcers, a decrease was observed in the perception of pain, improvements in healing times, and in the quality of life reported by patients compared to the placebo group. No significative differences were found in comparison with the control group (0.1% Triamcinolone)[40]. A case report suggested the effectiveness of oral cannabis administration for pain in rare skin lesions[47]. Due to its potential benefits, there is great interest in the use of cannabis for treating different skin conditions, such as psoriasis, pruritus, acne, lupus erythematosus, allergic contact dermatitis, some types of cancer, etc.[48-50].

Indeed, only one of the clinical studies included administered drops of CBD orally to patients diagnosed with burning mouth syndrome. The authors reported that approximately a third of the participants experienced some adverse effects, such as flushing, headache, and constipation. Despite this, none of the participants had to abandon the study, considering the mild and temporary nature of these effects[13]. For topical applications on the skin, not all studies detail adverse effects. In several clinical studies where cannabis was used for skin lesions topically, no adverse reactions were reported[19]. In another study, when a single patient was administered cannabis orally, she reported an increase in appetite[47]. In an observational study conducted on 9 patients with multiple sclerosis, the appearance of white lesions in the oral mucosa was described, which the authors attributed to the alcohol used as a vehicle in the commercial preparation, as it was administered orally[51]. Despite this, several authors agree that its use is safe[19,51]. Finally, there is a possibility that the patient may be allergic to both the cannabinoids administered and the additives used in the products, which is why an allergy test is suggested before starting any treatment[52].

Recently, a group of experts with training and experience in cannabis medicine generated a consensus regarding the most appropriate doses of cannabis administered orally for pain control in various systemic conditions (e.g., neuropathic pain, cancer, multiple sclerosis, osteoporosis, fibromyalgia), suggesting that therapies should always start with doses of pure CBD at 5 mg/kg, and can be gradually increased to a maximum of 40 mg/kg[53]. It was reported that, if necessary, a combined CBD and THC

therapy can be managed by the professional, adding to the previously indicated CBD dose 2.5 mg/kg of THC, up to a maximum of 40 mg/kg[53]. In addition to the possible benefits of this type of therapy, it is important to note that many CBD-based products available on the market also contain small quantities of other cannabinoids[49]. This information is relevant for professionals and for the design of research methodologies, as often the specific product compositions are not disclosed, which could affect the results obtained and generate unwanted effects due to a lack of information regarding the quality of the products used[49].

Some authors mention that the application of topical medication for oral lesions presents an extra challenge compared to the skin, due to the presence of saliva and other exudates that produce a washing effect or contamination from the environment[54-56]. For this reason, various methods have been suggested for the transport and delivery of medicines to mucous membranes, such as the use of patches, hydrogels, micelles, or granules with nanotechnology, which can increase contact time with tissues and concentrations absorbed by them[57-60]. Other factors that can also influence the formulations include concentrations of active components, diluents, and vehicles used in products[61,62]. These attributes were not evaluated in the current review. Cannabis extracts have been evaluated *in vitro* skin/mucosa models, demonstrating different penetration capacities depending on the concentration of the active component and the vehicle used[13,61,62].

We are aware that this study has limitations. These include the number of published studies available at the time and the heterogeneity in cannabis-based therapies applied. Furthermore, few conditions of the oral mucosa have been evaluated. More clinical studies need to be conducted, with complete details provided regarding the source of cannabis, the cannabinoids used, concentration, excipients, vehicles, and dosages. A standardized control and follow-up protocol must be rigorously established in clinical studies to ensure the safety of the therapies used. A consensus must be established regarding the dosages, both topical and systemic; for this reason, other cannabinoids and combined "full spectrum" therapies should be analyzed. Finally, due to the significant development of commercial products and studies using cannabis as medicine, it is recommended to establish interdisciplinary research lines to obtain a comprehensive view of conditions, therapies, and evaluated outcomes. Another limitation of the present study is the inclusion of only clinical studies with human participants, which limits our ability to extrapolate the findings. Additionally, different animals were evaluated in *in vivo* studies, making direct comparisons between results challenging. Future studies may also enhance search specificity by incorporating additional oral conditions, such as oral mucositis, into the search strategy to ensure broader and more targeted coverage of relevant pathologies.

Conclusions

We found that CBD appears effective in treating oral mucosa lesions (oral mucositis, ulcers, burning mouth syndrome) using different CBD-based therapies, showing promising *in vivo* results compared to placebo. Histological analyses indicate that CBD-based therapies can reduce inflammation in these lesions. Moreover, we observed

that CBD-based therapies hold promise for pain control and healing lesions in oral mucosa lesions in clinical studies. Different CBD concentrations yielded similar outcomes, highlighting the need for further studies to validate these preliminary results.

Fundings

The authors have no funding related to the present review.

Conflict of Interest

The authors of this work declare that there is no potential conflict of interest.

Data availability

Datasets related to this article will be available to the corresponding author upon request.

Author Contribution

Matias Mederos: confirms the contribution to the study performing conceptualization, methodology, investigation, data curation, and performing the writing of the text. **Luana Carla Salvi:** confirms the contribution of the study-performing reviewer of the text. **Luiz Alexandre Chisini:** confirms the contribution of the study performing conceptualization, methodology, investigation, data curation, and reviewer of the text. All authors actively revised and approved the final version of the manuscript.

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