EFFICACY OF CANNABIDIOL (CBD) FOR THE TREATMENT OF RECURRENT APHTHOUS ULCERS

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A Thesis Submitted in Partial Fulfillment of the Requirements
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ประสิทธิภาพของแคนนาบิไดออล (ซีบีดี) ต่อการรักษาแผลร้อนในภายในช่องปาก

น.ส.ฉพภิญโญ อุ้มปรีชา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	EFFICACY OF CANNABIDIOL (CBD) FOR THE TREATMENT OF RECURRENT APHTHOUS ULCERS
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Field of Study	Oral Medicine
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ฉพภิญโญ อุ้มปรีชา : ประสิทธิภาพของแคนนาบิไดออล (ซีบีดี) ต่อการรักษาแผลร้อนในภายในช่องปาก. (EFFICACY OF CANNABIDIOL (CBD) FOR THE TREATMENT OF RECURRENT APHTHOUS ULCERS) อ.ที่ปรึกษาหลัก : ผศ. ทญ. ดร.กนกพร พะลัง

วัตถุประสงค์ของงานวิจัยนี้คือ 1) เพื่อศึกษาผลของแคนนาบิไดออลต่อการแพ้เมื่อใช้บนผิวหนังมนุษย์ 2) เพื่อประเมินผลข้างเคียงเฉพาะที่และทางระบบของแคนนาบิไดออลเมื่อทาบนเยื่อเมือกช่องปากปกติ 3) เพื่อเปรียบเทียบประสิทธิภาพของแคนนาบิไดออลร้อยละ 0.1 ไตรแอมซิโนโลน อะเซโตไนด์ร้อยละ 0.1 และยาหลอก (ขี้ผึ้งป้ายปากบริสุทธิ์) ในการรักษาแผลร้อนใน การศึกษานี้ประกอบไปด้วย 3 ขั้นตอน ขั้นตอนที่ 1 เป็นการทดสอบการแพ้ต่อแคนนาบิไดออลบนผิวหนังมนุษย์ในอาสาสมัครสุขภาพดีจำนวน 100 คน ขั้นตอนที่ 2 อาสาสมัครสุขภาพดีจำนวน 50 คน ได้รับการตรวจช่องปาก วัดสัญญาณชีพ และตรวจเลือดก่อนและหลังการทาแคนนาบิไดออลบนเยื่อเมือกช่องปากปกติวันละ 3 ครั้ง เป็นเวลา 7 วัน ผลพบว่าไม่มีอาสาสมัครคนใดมีอาการแพ้หรือมีผลข้างเคียงต่อแคนนาบิไดออล สัญญาณชีพและผลเลือดก่อนและหลังการใช้แคนนาบิไดออลไม่แตกต่างกัน ขั้นตอนที่ 3 ศึกษาผู้ป่วยแผลร้อนในที่เข้ารับการรักษา ณ คลินิกบัณฑิตศึกษาเวชศาสตร์ช่องปาก คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัยจำนวน 69 คนได้รับการสุ่มให้เข้าอยู่ในกลุ่มการรักษาหนึ่งในสามกลุ่ม ได้แก่ แคนนาบิไดออล ไตรแอมซิโนโลน อะเซโตไนด์ หรือยาหลอก ให้อาสาสมัครทายาที่แผลวันละ 3 ครั้ง เป็นเวลา 7 วัน วัดขนาดแผลและขอบเขตสีแดงรอบแผลก่อนรักษา วันที่ 2, 5, และ 7 อาสาสมัครประเมินความเจ็บปวดแผลทุกวัน ให้คะแนนความพึงพอใจในตัวยาในวันสุดท้าย และทำแบบสอบถามคุณภาพชีวิต (แบบประเมินผลกระทบของสุขภาพช่องปาก-14) ในวันแรกและวันสุดท้าย ผลพบว่าแคนนาบิไดออลและไตรแอมซิโนโลน อะเซโตไนด์ลดขนาดแผลมากกว่ายาหลอกอย่างมีนัยสำคัญทางสถิติในทุกวันประเมินผล อย่างไรก็ตาม การลดขนาดขอบเขตสีแดงรอบแผลของแคนนาบิไดออลมากกว่ายาหลอกอย่างมีนัยสำคัญทางสถิติในวันที่ 2 ในขณะที่ไตรแอมซิโนโลน อะเซโตไนด์ลดขนาดขอบเขตสีแดงมากกว่ายาหลอกอย่างมีนัยสำคัญทางสถิติในทุกวันประเมินผล ความเจ็บปวดแผลในกลุ่มที่ได้แคนนาบิไดออลน้อยกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติในวันที่ 5 แต่ไตรแอมซิโนโลน อะเซโตไนด์ลดความเจ็บปวดมากกว่ายาหลอกอย่างมีนัยสำคัญทางสถิติในวันที่ 4, 5, และ 7 อาสาสมัครที่ได้แคนนาบิไดออลมีความพึงพอใจในตัวยาสูงกว่ากลุ่มที่ได้ยาหลอกแต่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ คะแนนแบบประเมินผลกระทบของสุขภาพช่องปาก-14 ระหว่างอาสาสมัครที่ได้รับยาทั้ง 3 กลุ่มไม่แตกต่างกัน แคนนาบิไดออลลดขนาดแผลร้อนในและช่วยส่งเสริมการหายของแผลโดยไม่ก่อให้เกิดผลข้างเคียง มีคุณสมบัติลดการอักเสบในระยะแรกและบรรเทาอาการปวดในระยะท้ายของแผลร้อนใน

สาขาวิชา เวชศาสตร์ช่องปาก ลายมือชื่อนิสิต .....

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KEYWORD: cannabidiol, CBD, cannabis, recurrent aphthous ulcer, RAU, recurrent aphthous stomatitis, RAS

Chalapinyo Umpreecha : EFFICACY OF CANNABIDIOL (CBD) FOR THE TREATMENT OF RECURRENT APHTHOUS ULCERS. Advisor: Asst. Prof. Kanokporn Bhalang, D.D.S., M.S., Ph.D.

The objectives of this research were 1) To investigate the allergic reactions to cannabidiol (CBD) when used on human skin. 2) To assess local and systemic side effects of CBD when used on normal oral mucosa. 3) To compare the efficacy among 0.1% CBD, 0.1% triamcinolone acetonide (TA), and placebo (pure oral paste) in recurrent aphthous ulcer (RAU) treatment. This project was composed of 3 phases. Phase 1, a skin patch test was performed on 100 healthy subjects. Phase 2, CBD was applied to normal oral mucosa of 50 healthy subjects 3 times/day for 7 days. Oral examination, vital signs, and blood tests were performed before and after CBD application. No subject had an allergic reaction or side effects to CBD. The vital signs and blood tests were similar before and after CBD administration. Phase 3, 69 RAU patients at the Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University randomly received one of three treatments: CBD, TA, or placebo. The medications were applied to the ulcers 3 times/day for 7 days. The pseudomembranous ulcer and erythematous border size were measured before treatment and on day 2, 5, and 7. Pain ratings were recorded daily. The subjects rated their satisfaction at the last visit and completed a quality of life questionnaire (OHIP-14) at the first and last visit. CBD and TA significantly reduced the pseudomembranous ulcer size more than placebo at all evaluated time points. However, the erythematous border size reduction was significantly higher in the CBD group compared with the placebo group only on day 2, while TA significantly reduced the erythematous border size at all evaluated time points. Pain scores in the CBD group were significantly lower than the placebo group on day 5, whereas TA significantly reduced the pain level more than placebo on day 4, 5, and 7. The subjects receiving CBD reported higher satisfaction compared with placebo, however, the differences were not significant. The OHIP-14 scores among the patients using the three medications were similar. CBD reduces ulcer size and accelerates ulcer healing without side effects. It exerts an anti-inflammatory effect at the early stage and an analgesic effect at the late stage of RAU.

Field of Study: Oral Medicine Student's Signature .....

Academic Year: 2021 Advisor's Signature .....

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Chalapinyo Umpreecha

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CHAPTER 1

Introduction

1.1 Background and rationale

A recurrent aphthous ulcer (RAU) is the most common painful oral lesion (1) and affects patient quality of life (QoL) (2). RAU is self-limiting ulceration (3). It is more common in females (4), children, and adolescents (2). Prevalence decreases in elders (5). Despite having a high prevalence (~20% of the population) (2), the precise etiology remains unclear (6). However, there are evident supporting associations between RAU and immunological disorders (7). A combination of several predisposing factors leads to the development of ulcers including trauma, nutritional deficiencies, food allergies, genetics, endocrine disorders, stress, microbial factors, anxiety, and hormonal defects (1, 2).

Clinically, RAU presents as an ovoid or round well-defined ulcer, with a pseudomembranous yellowish gray center, and an erythematous circumscribed border (8). RAU has been divided into three groups related to the number, size of ulcers, and healing pattern: minor aphthous ulcer, major aphthous ulcer, and herpetiform ulcer. Minor aphthous ulcer is the most common type (~80% of the RAU patients). It typically presents as less than 1 cm in diameter (1) and spontaneously heals in 4–14 days without scarring (9).

Currently, there is no curative RAU treatment. The treatment aims are primarily pain relief, reducing inflammation, and promoting wound healing to reduce the number, duration, and size of the ulcer. The first-line medication for RAU is topical steroids (10). Antiseptics, anti-inflammatory agents, analgesics, antibiotics, natural substances, and laser therapy have also been used to treat RAU (11).

Although topical steroids are an effective first-line medication for RAU, they also have numerous side effects, especially suppressing the immune response that can lead to developing oral candidiasis from long-term steroid use (12). Therefore, herbal medicines have been supported as an alternative treatment.

Several natural substances have been investigated for pain relief, anti-inflammation, and promotion of wound healing. In recent years, there is a significant public interest in the medical use of cannabis. One of the major medicinal components of cannabis is cannabinoids (13). They are synthesized in the human body called endocannabinoids and produced by the cannabis plant called phytocannabinoids. The two active medical components of the cannabis plant are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (14). THC has several medicinal effects including being psychoactive. In comparison, CBD is non-psychoactive and has meaningful analgesic, anti-inflammatory, anti-convulsant, anti-spasmodic, and anxiolytic effects (15). Furthermore, CBD suppresses pro-inflammatory cytokine expression (16, 17). Wound healing is a complex and dynamic process (18). Inflammation plays a crucial role in the wound healing process. However, excessive inflammation can delay healing (19, 20). Reducing pro-inflammatory cytokine expression optimizes healing time and reduces pain intensity (20). Thus, CBD may promote wound healing due to its anti-inflammatory effects.

The safety of CBD has been shown in animal and human studies, and it has low adverse events, despite prolonged use (21). Therefore, CBD extracted from cannabis may be an alternative treatment for RAU due to its medical effects, i.e., reducing pain and inflammation and promoting wound healing (22). In the dental area, we found a study using CBD in oral traumatic ulcerative lesions in rats, which

concluded that it reduces inflammation in the early stage of the wound healing process in microscopic findings although it did not promote clinical improvement adequately (23). Other studies found that CBD may be an alternative treatment for periodontitis (24). Cannabinoid compounds demonstrate efficacy in the treatment of symptoms associated with neuropathic orofacial pain because of their analgesic properties (25). A literature review concluded that CBD might be a promising candidate for the management of chemo- and radio-induced oral mucositis (26). Recently, a study demonstrated that topical application of CBD on trauma- and acid-induced ulcers on mice tongues can relieve pain, reduce inflammation, and promote wound healing (22). However, the effect of CBD when applied to human skin, the local and systemic side effects of CBD on the normal oral mucosa, and the efficacy of CBD in treating RAU have not been reported.

The aims of this study were to investigate the potential allergic reactions to 0.1% CBD when used on human skin, to assess the local and systemic side effects of 0.1% CBD when used on normal oral mucosa, and to compare the efficacy among 0.1% CBD, 0.1% triamcinolone acetonide (TA), and placebo (pure oral paste) in treating RAU.

1.2 Research questions

1.2.1 Is 0.1% CBD safe when used on human skin?

1.2.2 Is 0.1% CBD safe when used on normal oral mucosa?

1.2.3 Is there a different efficacy among 0.1% CBD, 0.1% TA, and placebo in the treatment of RAU?

1.3 Research objectives

1.3.1 To investigate the potential allergic reactions to 0.1% CBD when used on human skin.

1.3.2 To assess local and systemic side effects of 0.1% CBD when used on the normal oral mucosa.

1.3.3 To compare the efficacy among 0.1% CBD, 0.1% TA, and placebo in the treatment of RAU.

1.4 Research hypothesis

1.4.1 Hypothesis A

H_0: There is no subject had positive allergic reactions to 0.1% CBD when used on human skin.

H_a: There are some subjects had positive allergic reactions to 0.1% CBD when used on human skin.

1.4.2 Hypothesis B

H_0: There are no significant differences in any of the evaluated vital signs and blood parameters before and after the 7-day 0.1% CBD application.

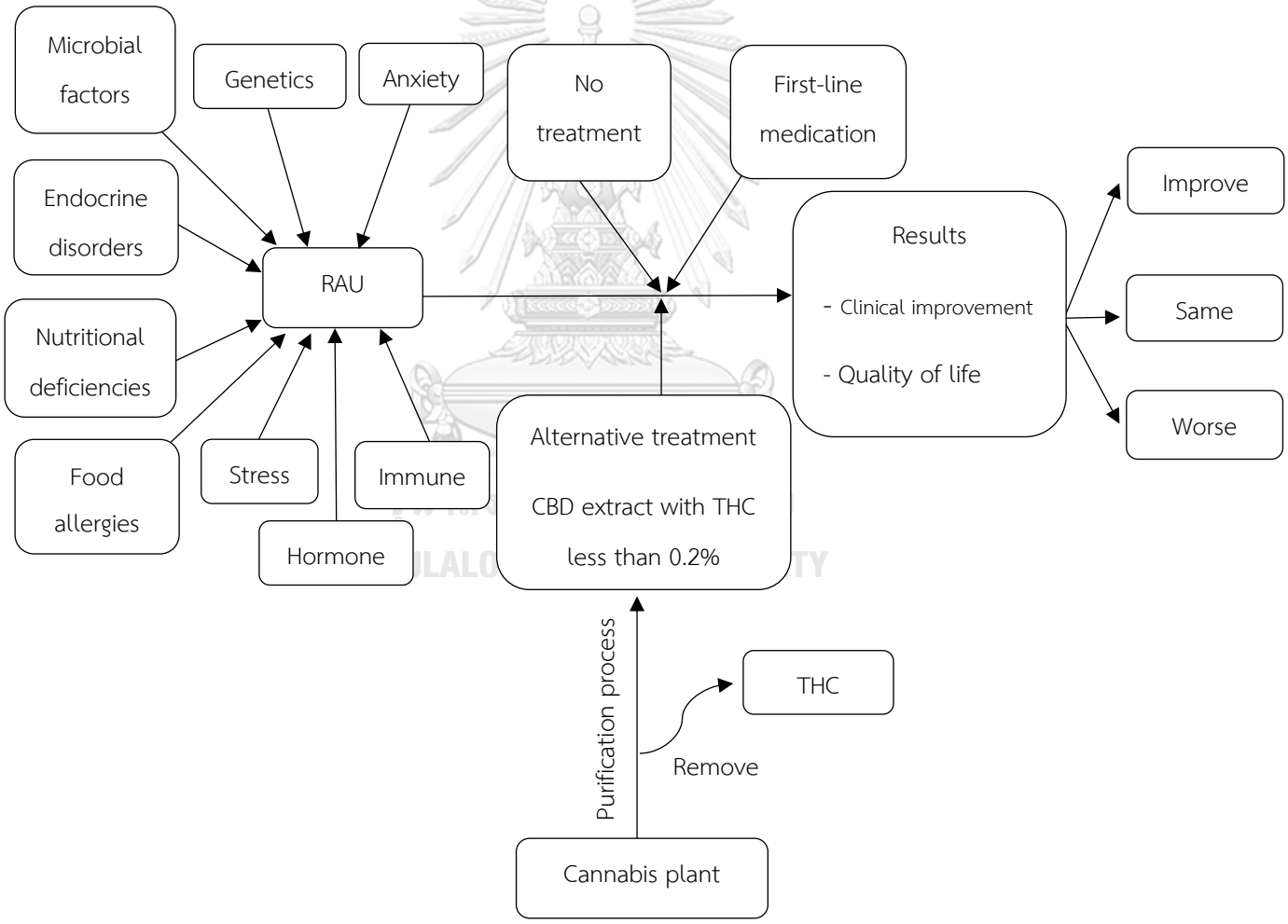
H_a: There are significant differences in the evaluated vital signs and blood parameters before and after the 7-day 0.1% CBD application.

1.4.3 Hypothesis C

H_0: There is no significantly different efficacy among the three medications (0.1% CBD, 0.1% TA, and placebo) in the treatment of RAU.

H_a: There is significantly different efficacy among the three medications (0.1% CBD, 0.1% TA, and placebo) in the treatment of RAU.

1.5 Conceptual framework



1.6 Study area

The Oral Medicine Clinic, Faculty of Dentistry, Chulalongkorn University

CHAPTER 2

Review literature

2.1 Recurrent aphthous ulcer (RAU)

A recurrent aphthous ulcer (RAU) is the most common painful oral lesion (1) and affects patient quality of life (QoL) including nutrition, speech, and oral hygiene (2). RAU is self-limiting ulceration (3). The ulcers typically present as an ovoid or round well-defined ulcer, with a pseudomembranous yellowish gray center, and an erythematous circumscribed border (8). The lesions occur most commonly on the non-keratinized oral mucosa. During the prodromal period, patients may have tingling or burning sensations in the area where the ulceration develops approximately 2-48 hours before the ulceration (2).

2.1.1 Prevalence

An average prevalence of RAU is around 20% of the general population. RAU is defined as having a history of spontaneous aphthous ulcer at least 2 times per year (2). It is more common in females (4), white, non-smokers, and higher social classes (5, 27). RAU occurs more commonly in children and adolescents (2). Prevalence decreases in elders (5).

2.1.2 Etiology

The precise etiology remains unclear (6). However, there are evident supporting associations between RAU and immunological disorders. RAU results from the damage of oral epithelium caused by T cell-mediated immune response. RAU formation depends on the activation of the Th1-type immune response (7). A combination of several predisposing factors leads to the development of the ulcers

such as trauma, nutritional deficiencies, food allergies, genetics, endocrine disorders, stress, microbial factors, anxiety, and hormonal defects. An aphthous ulcer may be a clinical manifestation of systemic diseases including Crohn’s disease, ulcerative colitis, coeliac disease, Behçet’s disease, Sweet syndrome, Reiter's syndrome, PFAPA syndrome, anemia, hematinic deficiencies (vitamin B12, folic acid, and iron), and Acquired Immune Deficiency Syndrome (AIDS) (1, 2, 28).

2.1.3 Classification of RAU

RAU is divided into three groups related to number, size of ulcers, and the healing pattern as classified by Stanley in 1972 (29).

2.1.3.1 Minor aphthous ulcer

Minor aphthous ulcer (Miculiz's aphthae) is the most common type (approximately 80% of RAU patients). It typically presents as less than 1 cm in diameter. The most common sites are the nonkeratinized mucosal surfaces like buccal mucosa, labial mucosa, and floor of the mouth. Ulcers resolve spontaneously within 4–14 days without scarring (9).

2.1.3.2 Major aphthous ulcer

It is also known as Sutton's disease, affecting around 15% of RAU patients. Ulcers typically surpass 1 cm in diameter and are deeply indurated. It is most commonly seen in soft palate, lips, and fauces. Gingiva and dorsum of tongue may be infrequently affected. The ulcers prolong from 10 days up to 6 weeks and heal with scarring.

2.1.3.3 Herpetiform ulcer

It is 2-3 mm in diameter, multiple ulcers may be up to 100 in numbers. They account for around 5% of RAU. Ulcers may fuse together and form large, irregularly shaped ulcers. They persist for approximately 10–14 days and resolve without scarring. These ulcers do not contain virally infected cells and they are not preceded by vesicles like herpetic ulcers.

2.1.4 Management and treatment of RAU

Currently, there is no curative RAU treatment. The treatment aims are primarily pain relief, allowing patients to talk, eat, drink, and perform regular oral hygiene, reduction of inflammation, and promotion of wound healing to reduce the number, duration, and size of the ulcer. Treatment should match the disease severity, medical history, and outbreak frequency. Appropriate treatment requires clinical history and some laboratory investigations to find and discard the risk factors of other diseases. Treatments for RAU can be classified into three groups depending on different approaches to management (11, 30).

2.1.4.1 Non-pharmacological treatments

It is advisable to request laboratory investigations, such as complete blood count (CBC), iron, ferritin, transferrin, folic acid, vitamin B12, and abnormality of gastrointestinal disease to rule out possible underlying systemic causes (gastrointestinal disease, nutritional & immune deficiencies, and Behcet's disease) (1, 31, 32). Because of the associations between RAU

and vitamin deficiencies, there is the evidence that treatment with vitamin B12 proves effective in the treatment of RAU (33).

Other predisposing factors should be identified and controlled such as using a soft toothbrush, avoiding local trauma, and practicing good oral hygiene. It is generally recommended to avoid acidic, hard, and salty foods, as well as alcoholic beverages and soft drinks. Using SLS-free toothpaste significantly decreased pain intensity and healing period of RAU (34).

In addition, studies advised that low-level laser therapy is an appropriate treatment for RAU. Four types of lasers (i.e., CO_2, Nd: YAG, diode, and GaAlAs) have been used to treat RAU. Even though all of them have achieved in providing prompt pain relief to patients, CO_2 lasers require an extremely short exposure time about 5–10 seconds. In order to ascertain their efficacy, more clinical trials are needed to compare the efficacy of these lasers with the presently available treatments (35).

2.1.4.2 Local pharmacological treatments

Treatment generally starts with topical medications as first-line therapy due to the lower risk of systemic side effects. If the patients have the prodromic symptoms like burning or tingling in the area where the ulcer will develop, anti-inflammatory agents (5% amlexanox) or topical corticosteroids (0.1% triamcinolone acetonide) are used to prevent the formation of ulcers. In the case that the ulcer is already formed, the drugs in Table 1 can be used to reduce inflammation. Combination with analgesics (diclofenac), antiseptics (chlorhexidine mouthwash and triclosan gel), antibiotics (doxycycline gel),

hyaluronic acid, and natural products (myrtle or quercetin) can be used for pain relief and promotion of ulcer healing (11).

Table 1. Local pharmacological treatments

Local pharmacological treatments
1. Topical corticosteroids (triamcinolone acetonide 0.05-0.5% 3-10 times/day, fluocinolone acetonide 0.025-0.05% 5-10 times/day, clobetasol propionate 0.025%)
2. Analgesics, anti-inflammatory agents, and antiseptics (topical diclofenac 3%, amlexanox ointment 5% 2-4 times/day, chlorhexidine mouthwash or gel 0.2% 3 times/day, and triclosan gel 3 times/day)
3. Antibiotics (doxycycline gel at low doses)
4. Hyaluronic acid (0.2% gel 2 times/day for two weeks)
5. Topical anesthetics (lidocaine 2% spray or gel)
6. Others: natural products (myrtle, quercetin, rosa damascene)

The most extensively used medications in RAU are topical corticosteroids. The indicated drugs are triamcinolone acetonide, fluocinolone acetonide, and clobetasol propionate based on the severity of the lesions. Triamcinolone acetonide is particularly used in small ulcers, the most effective concentration is 0.1%. Although topical steroids are an effective first-line medication for RAU (11), they also have numerous side effects, especially suppressing the immune response that can lead to developing oral candidiasis from long-term steroid use (12).

In severe case of RAU with large lesions affecting the quality of life, intra-lesional injections of steroids can be considered (36). Recently, botulinum toxin has been demonstrated as an effective treatment for RAU (37).

2.1.4.3 Systemic pharmacological treatments

RAU is normally healed with topical medications. In some cases, local pharmacological treatments are not enough for treating RAU due to the severity of ulcers or unknown causes. The second-line therapy with systemic pharmacological treatments is used as in Table 2 ahead when local pharmacological treatments are unable to relieve the pain. Studies show that systemic antibiotics (penicillin G potassium) decrease the ulcer size and relieve the pain (38). Several drugs can control the symptoms including dapsone, colchicine, clofazimine, and pentoxifylline. Although systemic corticosteroids (prednisone) and immune modulators (thalidomide) are used as the first option of systemic pharmacological treatment and can afford complete or almost complete healing of the ulcers, the possible adverse effects of systemic corticosteroids must be concerned (11). Zinc sulfate is an essential cofactor that affects healing and wound reepithelization and can be a possible treatment for RAU (39). Other systemic pharmacological treatments have been studied such as homeopathic medicines, mercurius solubilis, phosphorus, natrum muriaticum, sulfuric acid, nitric acid, nux vomica, arsenicum album, and lycopodium, they can decrease the size of the ulcers and the pain intensity. However, there are no sufficient evidences to support the use of homeopathic medicines as the treatment of RAU (40).

Table 2. Systemic pharmacological treatments

Systemic pharmacological treatments
1. Systemic corticosteroids (initial dose of oral prednisone 25 mg/day and stepwise dose reduction for 2 months)
2. Antibiotics (penicillin G potassium, 50 mg pills 4 times/day 4 days)
3. Colchicine (0.5 mg/day 7 days, 1 mg/day 7 days, and a maintenance dose of 1.5 mg/day)
4. Dapsone (25 mg/day 3 days, 50 mg/day 3 days, 75 mg/day 3 days, and a maintenance dose of 100 mg/day)
5. Clofazimine (100 mg daily for 6 months)
6. Pentoxifylline (400 mg 3 times/day for 1 month)
7. Zinc sulphate (150 mg/day)
8. Immune modulators (thalidomide 50-100 mg/day, levamisole 150 mg 3 times a week for 6 months)
9. Homeopathic substances (natrum muriaticum, mercurius solubilis, sulfuric acid, phosphorus, nitric acid 100 ml of water orally every 12 hours for 6 days)

2.1.5 Quality of life (QoL) in RAU patients

RAU is a painful ulcerative oral lesion (41) that deeply affects patient QoL including pain (during eating, drinking, talking, and swallowing), discomfort (impairment in food and liquid intake), interpersonal relationship problems, and self-confidence (42). RAU causes all of these symptoms with significant negative impacts on oral health-related quality of life (OHRQoL) of patients indicating significantly high scores (43). Evaluations of QoL in RAU patients are important. Several tools assessing OHRQoL in RAU patients are below.

2.1.5.1 Oral Health Impact Profile-49 (OHIP-49)

The extensively used measure in OHRQoL assessment is the Oral Health Impact Profile-49 (OHIP-49). The underlying theoretical framework for OHIP-49 is dependent on Locker's adaptation from the World Health Organization (WHO) classification of disabilities, impairments, and handicaps for oral health measurement. OHIP-49 has a 49-item measurement divided into 7 theoretical domains: functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Responses were scored on a 5-point Likert scale of 0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = very often. The frequency of impacts was calculated by summing the responses across the 49 statements. A shortened version of OHIP-49 has been developed for reducing its number of items and making it more sensitive to specific oral health states using various statistical analysis (44).

2.1.5.2 Oral Health Impact Profile–14 (OHIP-14)

Oral Health Impact Profile-14 (OHIP-14) questionnaire, a shortened form of OHIP-49 (45), was applied to evaluate OHRQoL (46). OHIP-14 consists of 14 items with 7 theoretical domains similar to OHIP-49 and it is scored in a similar manner (44). For each of the OHIP-14 questions, patients were asked the frequency of problems in the previous month. A Likert response format (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = very often) was used to score the frequency of problems encountered because of oral illness. OHIP-14 scores were calculated by summing up the frequency of problems with a possible range from 0 (no impact) to 56 (highest impact) (46). Higher scores correspond to poorer oral QoL. The OHRQoL of patients as measured by OHIP-14 to evaluate therapeutic regimens for RAU demonstrated a significant improvement after treatment (46, 47). OHIP-14 is the most frequently used patient reported outcome measures (PROMs) for the assessment of QoL in RAU literature (48). OHIP-14 is a valid and reliable tool for assessing oral health impacts. It is sensitive and reliable for detecting the impacts in RAU patients (49). The reliability of the Thai OHIP-14 was excellent (α = 0.88) and the validity of the questionnaires showed acceptable properties (50). Lists of questions on OHIP-14 are in Table 3 (51).

Table 3. Oral Health Impact Profile-14 (OHIP-14) questionnaire

Questions	Never	Almost never	Sometimes	Often	Very often
1. Have you had trouble pronouncing any words because of problems with your teeth or mouth?					
2. Have you felt that your sense of taste has worsened because of problems with your teeth or mouth?					
3. Have you had painful aching in your mouth?					
4. Have you found it uncomfortable to eat any foods because of problems with your teeth or mouth?					
5. Have you been self-conscious because of your teeth or mouth?					
6. Have you felt tense because of problems with your teeth or mouth?					
7. Has your diet been unsatisfactory because of problems with your teeth or mouth?					
8. Have you had to interrupt meals because of problems with your teeth or mouth?					
9. Have you found it difficult to relax because of problems with your teeth or mouth?					
10. Have you been a bit embarrassed because of problems with your teeth or mouth?					
11. Have you been a bit irritable with other people because of problems with your teeth or mouth?					
12. Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?					
13. Have you felt that life in general was less satisfying because of problems with your teeth or mouth?					
14. Have you been totally unable to function because of problems with your teeth or mouth?					

2.1.5.3 Chronic Oral Mucosal Disease Questionnaire (COMDQ)

The chronic oral mucosal disease questionnaire (COMDQ) is a tool for evaluating the patient QoL with a chronic oral mucosal disease that consists of 26 items divided into 4 sections: pain and functional limitation (9 items), medication and treatment (6 items), social and emotional (7 items), and patient support (4 items). There is a 5-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = very often) for every item. All scores were calculated by summing up ranging from 0 to 104. Higher scores correspond to lower oral QoL (52). There is a study about the effects of omega-3 oral supplements in RAU patients and the improvement of OHRQoL by using COMDQ. They conclude that using omega-3 oral supplements reduced the severity of RAU and improved OHRQoL. The mean scores of the COMDQ significantly improved by three months and six months in the omega-3 oral supplements receiving group (53).

2.1.5.4 Oral Health-related Quality of Life-United Kingdom (OHQoL-UK)

The OHQoL-UK development was based on the UK population in awareness of how oral health affects QoL (48). The OHQoL-UK evaluates the negative and positive perspectives of individuals' oral health awareness. It is a valid, reliable, and sensitive tool to assess OHRQoL (49). It consists of 16 items covering 3 sections: physical, social, and psychological effects. The patients are asked to rate "What effect, if any, does the condition of your teeth, gums, mouth, and/or denture have on your (1 of 16 key areas)?": very bad (score 1), bad (score 2), none (score 3), good (score 4), or very good (score 5); and asked to score "How would you rate the impact of this effect on your overall QoL?": none (score 0), little (score 1), moderate (score 2),

great (score 3), or extreme (score 4). The scores were summed up from the individual questions and can produce overall OHQoL-UK scores ranging from 16 (all bad effects of extreme impact) to 144 (all good effects of extreme impact) (44).

2.1.5.5 Oral Impacts on Daily Performance (OIDP)

The Oral Impacts on Daily Performance (OIDP) was an alternative socio-dental indicator that focused on evaluating the serious oral health impacts. The underlying theoretical frameworks resembled OHIP-49 but focused on the handicap and disabling impacts of the oral lesions. Items were selected from different socio-medical and socio-dental indicators of the disabled index. The 8 items consist of eating and enjoyment of food, speaking and pronouncing clearly, cleaning teeth, sleeping and relaxing, smiling (laughing and showing teeth without embarrassment), maintaining the usual emotional state without being irritable, carrying out major work or social roles, and enjoying contact with people. The items are scored depending on the frequency and severity. Frequency scores are grouped according to the frequency is “regular” (score 0=never affected in the past 6 months, score 1=less than once a month, score 2=once or twice a month, score 3=once or twice a week, score 4=3–4 times a week, score 5=every or nearly every day). The frequency of effects can also be sorted by “spell” patterns that are associated with the duration of experienced impacts (score 0 for the length of time was for 0 days, score 1 for up to 5 days in total, score 2 for up to 15 days in total, score 3 for up to 30 days, score 4 for up to 3 months, score 5 for over 3 months in total). The impact severity is scored from 0 (representing none) to 5 (representing very severe). The OIDP scores were calculated by multiplying the frequency of the impact scores with the severity scores. It can

be divided by the maximum possible score (200 points) to provide proportional scores. The tool has been shown to have satisfactory psychometric properties for oral health service research though the reported prevalence of oral health effects is relatively low when compared with other OHRQoL measurements since the extreme impacts are infrequent in most study populations (44). It is suggested that the better method for OIDP is by interview instead of a questionnaire based. The OHIP-14 is reported to provide better results than the OIDP when compared in various settings (54).

2.2 Cannabidiol (CBD)

Cannabis (also known as marijuana) has been planted for a long time in different parts of the world for recreational, spiritual, and medical purposes. In recent years, there is a significant public interest in the medical use of cannabis. Medical cannabis is defined as using cannabis as a medical therapy for treating diseases or alleviating symptoms. The three major medical components of cannabis are cannabinoids, terpenoids, and flavonoids (13). Cannabinoids can be created by the cannabis plant called phytocannabinoids, they interact with the body's receptors to produce several therapeutic and psychotropic effects. Terpenoids contribute to cannabis's flavor and aroma and help cannabinoids for producing desired effects. Flavonoids are like terpenoids in that they are responsible for the flavors and aroma of the cannabis but might have their own extraordinary therapeutic effects.

There are two isotypes of cannabinoid receptors, CB1 and CB2 that can be found in the human body in various organs and tissues (55). CB1 receptors are found particularly in the central nervous system (CNS) where they modulate excitatory and inhibitory neurotransmission. CB1 receptors are predominantly concentrated in the

brain regions associated with memory, executive function, cognition, pain perception, mood, and movement. CB2 receptors are originally expressed on immune cells as an immunomodulator and can be predominantly found in tonsils, thymus gland, spleen, skin, bones, and the blood including macrophage, monocyte, B-cell, and T-cell (14).

2.2.1 Cannabis strains

The cannabis plant has two main subspecies *Cannabis sativa* and *Cannabis indica*. *Cannabis sativa* is typically taller and has thin leaves with pale green color and higher Δ^9-tetrahydrocannabinol (THC) content. It is the long flowering season and is suitable for warmer climates. *Cannabis indica* is generally short, broad leaves with dark green color and has a greater cannabidiol (CBD) content. It is a shorter flowering season and better suited for colder climates (56).

2.2.2 Cannabinoid groups

There are three groups of cannabinoids (14).

2.2.2.1 Endocannabinoids

Endocannabinoids are natural cannabinoids synthesized in the human body and affect a regulatory function. The two most studied endocannabinoids in the human body are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) which interact with the natural cannabinoid receptors (CB1 and CB2 receptor) found in the human body (14). Multiple studies revealed that endocannabinoids play an important role in mood, memory, drug addictions, brain reward systems, and metabolic processes (glucose metabolism, lipolysis, and energy balance) (14, 57).

2.2.2.2 Phytocannabinoids

Cannabinoids are produced by the cannabis plant called phytocannabinoids. There are 100 various cannabinoids separated from the cannabis plant (58). The two active medical components from the cannabis plant are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

The main psychotropic component is THC, which is produced mainly in the leaves and flowers of the cannabis plant. It has several pharmacological actions including psychotropic, anti-inflammatory, analgesic, anti-emetic, appetite stimulant, anti-oxidant, anti-pruritic, bronchodilatory, muscle-relaxant, and anti-spasmodic effects (59, 60). THC acts as a partial agonist at the cannabinoid receptors (CB1 and CB2) (61) with a high binding affinity to the CB1 receptor. It exerts psychotropic effects like memory processing, mood changing, and motor control. THC has some medical properties including reduction of pain, nausea, vomiting, and muscle spasms as well as an appetite stimulant (14). The numerous side effects of THC have been reported such as impaired memory, immunosuppression (58, 60, 62), psychoactive side effects (anxiety, euphoria, and paranoia), and other CNS-related unpleasing effects (depression of motor activity, cognitive impairment, and addiction) (63).

In contrast, CBD is non-psychoactive and has meaningful anti-convulsant, anti-inflammatory, analgesic, anti-spasmodic, and anxiolytic effects (15). CBD can be useful in the treatment of pain and seizures, and may have antipsychotic and anxiolytic properties (14). The binding affinity of CBD for either CB1 or CB2 receptors is little but

it can be antagonizing them in the presence of THC (64). It has a partial agonist for modulating opioid receptors and serotonin 5-HT1A receptors (65, 66). Table 4 depicts the comparison of the properties between THC and CBD (67).

Table 4. Comparison of the properties between THC and CBD

Properties/function	THC	CBD
CB1 receptor	Partial agonist with high binding affinity	Noncompetitive negative allosteric modulator
CB2 receptor	Partial agonist	Receptor modulator
TRPV1, TRPA1 receptors	–	Receptor modulator
Metabolism	Hepatic cytochrome P450 (CYP450) isoenzymes, especially 3A4 and 2C9	Hepatic cytochrome P450 (CYP450) isoenzymes
Psychoactive	Yes	No
Analgesic	Yes	Yes
Anxiolytic	–	Yes
Anticonvulsant	–	Yes
Anti-inflammatory	Yes	Yes
Anti-emetic	Yes	-
Appetite stimulant	Yes	-
Anti-spasmodic	Yes	Yes
Neuroprotective	-	Yes

2.2.2.3 Synthetic cannabinoids

Nabilone is the synthetic cannabinoids created in the laboratory. It can be used to treat anorexia and wasting in HIV patients. Synthetic cannabinoids not only act as a full agonist at both CB1 and CB2 receptors but also have 50-200 times increased affinity for the CB1 receptor compared with endocannabinoids. It enhances the side effects of these cannabinoids and increases the harm (14).

2.2.3 Entourage effect

The entourage effect of cannabis was the basic idea that cannabinoids within the cannabis plant work together with synergistic effects and affect the body like the endocannabinoid system. It was first described by Mechoulam and Ben-Shabat (68). The concept of botanical synergy was supported by other cannabinoids, terpenoids, and flavonoids, to succeed with the highest pharmacological effects. Whole plant cannabis extractions have a better therapeutic effect than individual cannabis extractions (69).

CBD exhibits the entourage effect and can improve the safety and tolerability of THC by decreasing psychotropic properties and antagonizing side effects of THC (anxiety, tachycardia, and sedation) (62).

2.2.4 Pharmacokinetic

Absorption, distribution, and metabolism define the onset and duration of individual dosage forms. Absorption has the most variability depending on bioavailability, lipophilicity, and inherent tissue differences. The properties of cannabinoids are highly lipophilic molecules and also have low water solubility (2–10

μg/mL) (70), susceptible to degradation, especially in solutions which accelerated by temperature, light, and auto-oxidation (71, 72). For oral and topical routes, they are better absorbed in oils, fat, or polar solvents (ethanol). Appropriate product formulation plays an important role in enhancing the stability and solubility of the medications. Salt formation by pH adjustment, micellization (cremophor ELP, polysorbate 80), cosolvency (propylene glycol, ethanol, and PEG400), nano-micro-emulsification, encapsulation in lipid-based formulations (liposomes), complexation (cyclodextrins), and nanoparticles are commonly used methods in marketed products (73-75). The new technology including omega fats in a carrier oil or nano- or ionized particles can increase the absorption or for topical use. Using the ingredients to gently disrupt the skin barriers may allow the higher absorption of active ingredients. Many factors including depth of inhalation, recent meals, duration of breath holding, and temperature of the vaporizer can affect the absorption of cannabis, which can vary from up to 10–60% for inhalation, 20–30% for oral route (76).

2.2.5 Modes of administration

Cannabis products are majorly used by inhaling with smoking/vaporization or taking orally. The topical-transdermal, oromucosal, and rectal routes are minor. The bioavailability of smoking is about 31%. The half-life of CBD after oromucosal spray is approximately 1.4-10.9 hours, 2 and 5 days after chronic oral administration, and 31 hours after smoking. A maximum plasma concentration of CBD is between 0 and 4 hours (77). However, in oral form, CBD is metabolized by the liver and gut enzymes with first-pass hepatic metabolism, it has low bioavailability and poor gastrointestinal permeability from first-pass metabolism and can cause irritation. Alternative routes in addition to systemic delivery are sublingual, transdermal, vaporization, inhalation,

rectal administration, and oral transmucosal delivery formulations. These routes can uptake medications directly into the blood to avoid first-pass hepatic metabolism (78).

2.2.6 Therapeutic uses

Cannabis can treat several complex diseases or rare conditions that conventional treatments are not effective, or where the adverse effects burden of treatment outweighs the benefit. Medical cannabis should not be the first-line medication for any indications. Levels of evidence for medical cannabis in different conditions are summarized below (79).

2.2.6.1 Conclusive evidence of efficacy

2.2.6.1.1 Chemotherapy-induced nausea and vomiting (80, 81)

2.2.6.1.2 Intractable epilepsy (Dravet and Lennox-Gastaut syndromes) (82)

2.2.6.1.3 Multiple sclerosis spasticity symptoms (83)

2.2.6.1.4 Neuropathic pain (84)

2.2.6.2 Moderate evidence of efficacy

2.2.6.2.1 Improving outcomes in sleep disturbances associated with chronic pain, multiple sclerosis, fibromyalgia, obstructive sleep apnea syndrome

2.2.6.2.2 Decreasing intraocular pressure in glaucoma

2.2.6.3 Limited evidence of efficacy

2.2.6.3.1 Dementia

2.2.6.3.2 Parkinson disease

2.2.6.3.3 Positive and negative symptoms of schizophrenia

2.2.6.3.4 Post-traumatic stress disorder

2.2.6.3.5 Appetite and wasting in HIV/AIDS patients

2.2.6.3.6 Traumatic brain injury/intracranial hemorrhage associated disability, mortality, and other outcomes

2.2.6.3.7 Anxiety in social anxiety disorders

2.2.6.3.8 Tourette syndrome

2.2.6.3.9 Palliative care

2.2.6.3.10 Alzheimer's disease

2.2.6.3.11 End-state cancer

2.2.6.3.12 Other demyelinating diseases such as neuromyelitis optica and autoimmune encephalitis

Previous studies show that CBD suppresses pro-inflammatory cytokine expression including tumor necrosis factor alpha (TNF-α) (16), growth factors, interleukin-1 beta (IL-1β) (17), and chemokines and may inhibit proliferation, activation, maturation, migration, and antigen presentation of immune cell (85).

Wound healing is a complex and dynamic process, occurring in overlapping phases of hemostasis, inflammation, proliferation, and tissue remodeling (18).

Inflammation plays a key role in the wound healing process. However, excessive inflammation can delay healing (19, 20). Reducing pro-inflammatory cytokine expression optimizes healing time and reduces pain intensity (20). Thus, CBD may promote wound healing due to its anti-inflammatory effects.

The cannabinoid analgesic effect includes reduction of the neurotransmitter release from presynaptic nerve endings, activation of the descending inhibitory pain pathways, modulation of the postsynaptic neuron excitability, and reduction of neural inflammation (13). The midbrain periaqueductal grey (PAG) acts as a central function in the analgesic and anti-nociceptive effects of cannabinoids. It is exerted by inhibiting a descending pain pathway (86). PAG is an important area of analgesic action for cannabinoids (87), and levels of both AEA and 2-AG are increased in the brain region of chronic pain animal models (88). A summary of cannabinoid signaling systems and potential cellular targets in neuropathic orofacial pain disorders (25) is demonstrated in Figure 1.

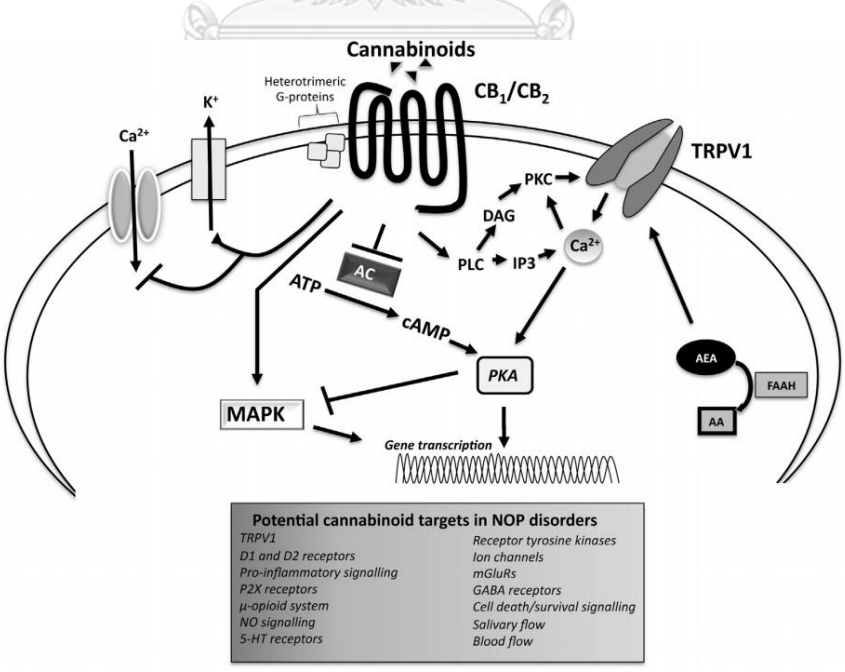


Figure 1. Cannabinoid signaling systems and potential cellular targets in neuropathic orofacial pain disorders

Chronic neuropathic orofacial pain frequently can't be treated with conventional analgesic treatment. Therefore, alternative treatments are sought. The analgesic effect of cannabinoids contributes to neuropathic orofacial pain disorders. Sativex® is a cannabinoid product that can be an alternative option for chronic neuropathic orofacial pain patients (25).

2.2.7 Contraindications

Contraindications of cannabis are pregnancy, lactation (89), psychosis (except CBD predominant products) (90), and severe liver or renal diseases (14). Cannabis should be utilized with caution in unstable cardiac conditions because of tachycardia and possible hypotension (due to THC). Patients under 25 years old should not use medical cannabis products with THC due to the potential side effects on brain development, dependency, and addiction (14). Smoking should be avoided in chronic obstructive pulmonary disease (COPD) and asthma patients (79).

Contraindications of CBD are allergy to CBD or sesame oil (14). The signs of an allergy are cutaneous irritation up to anaphylactic reaction. The patients should discontinue using CBD if these symptoms arise. CBD side effects are dose-dependent. Allergy to CBD is rare at a low dose. Adverse symptoms mostly came from the use of high dose CBD (91). Skin reactions found after topical CBD use are from mild irritation. However, we have found no evidence to suggest any irritant or allergic reactions (92). Contraindications of CBD use are the history of alcohol and drug addiction. Although CBD does not consist of the part of cannabis that makes users "high", it may have addictive effects. Another contraindication is the patients with depression, suicidal thoughts, and mood disorders. When prescribing CBD to these patients, physicians should weigh the risks and benefits (93).

2.2.8 Adverse events

Cannabis side effects are dose-dependent. Most adverse effects of cannabis can be relieved by using a “start low and go slow” dosing strategy. Adverse events associated with cannabis-based medicines are listed in Table 5 (79).

Table 5. Adverse events associated with cannabis-based medicines

Adverse events	Most common	Common	Rare
Dry mouth Nausea Drowsiness/fatigue Dizziness Cough, phlegm, bronchitis (smoking only) Anxiety Cognitive effects	✓		
Headache Blurred vision Euphoria		✓	
Cannabis hyperemesis Orthostatic hypotension Diarrhea Depression Ataxia/dyscoordination Tachycardia Psychosis/paranoia			✓

The adverse effect of CBD is liver damage. Using CBD with other drugs including mipomersen, leflunomide, teriflunomide, lomitapide, valproate, and pexidartinib can increase the risk of damage to the liver. It is important to monitor liver function before, during, and after CBD treatment (94). If patients have signs of liver dysfunction such as nausea, vomiting, jaundice, right upper quadrant pain, or dark urine, total bilirubin and transaminase levels should be tested instantly.

Using CBD for 14 days did not affect vital signs, glucose, hematocrit, pH, pCO_2, pO_2, sodium, and potassium levels in a study with rodents (95). Effects of a CBD-containing hemp oil extract on hepato-renal function (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), total protein, total bilirubin, albumin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and creatinine) remained within normal clinical limits (96). A recent large study of cannabis in Canada showed that CBD has low side effects, despite chronic administration, no serious adverse effects are observed. The safety of CBD has been shown in animal and human studies (21), no harm to pulmonary function, cognitive function, and biochemistry (CBC and liver function test) (97), confirming results seen in cannabis decade usage in the USA (98). CBD use may be associated with increased suicidal thoughts (93). Therefore, the doctor should observe any unusual behaviors.

2.2.9 Drug interactions

There are reports about sedation and somnolence with CBD use. Physicians should concern about prescribing CBD with other sedative drugs like opioids and benzodiazepines. A combination of CBD and other sedative medications can cause severe respiratory depression (99). THC and CBD are metabolized by hepatic cytochrome P450. THC is metabolized by CYP2C9, CYP2C19, and CYP3A4. CBD is

metabolized by CYP2C19 and CYP3A4. Hence, serum levels may increase with enzyme inhibitors such as fluoxetine, or decrease with enzyme inducers such as rifampicin and carbamazepine (79). THC and CBD are also enzyme inducers and enzyme inhibitors. THC inhibits CYP2C9, CYP2D6, and CYP3A4 which may affect drugs metabolized by these CYP and increase drug levels. For example, warfarin is metabolized by CYP2C9, so it increases the international normalized ratio (INR) and risk of bleeding. CBD inhibits CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C19, CYP3A4, and CYP2C9 strongly, so using CBD with other drugs that are metabolized by these CYP such as warfarin, clobazam (metabolized by CYP3A4 and CYP2C19), fluoroquinolones (metabolized by CYP1A2), and dihydropyridines (metabolized by CYP3A4) will increase drug levels and may have side effects (100, 101).

2.2.10 Approved drugs

2.2.10.1 Epidiolex® (Phytocannabinoids)

An example of the cannabis-based product via the oral route is Epidiolex®, containing CBD 100 mg/ml, prepared as a liquid solution of a CBD solution for oral intake. It has recently been approved by the U.S. Food and Drug Administration (FDA) in 2018 as an adjuvant treatment for rare and severe forms of epilepsy, Dravet and Lennox-Gastaut syndromes in 2 years of age patients and severe myoclonic epilepsy in infancy (82, 102, 103).

2.2.10.2 Nabiximols (Sativex®) (Phytocannabinoids)

A non-invasive method of administration is the transmucosal dosage form. It has proven to be a better oral dosage for pain relief (104). Sativex® is the current cannabis-based medicines for treating pain via a transmucosal form that received marketing authorization in EU countries (105). Each 100

microliters spray contains 2.7 mg THC and 2.5 mg CBD. Sativex® is an oromucosal cannabinoid sublingual spray for adjunctive treatment to reduce spasticity in multiple sclerosis adult patients who have failed to respond adequately to conventional therapies (106). It is used as an adjunctive treatment for moderate to severe pain in advanced cancer adult patients (107).

2.2.10.3 Cesamet® (Synthetic cannabinoids)

The Cesamet capsule contains 1 mg (2.7 µmol) nabilone. It has been approved by U.S. FDA in 1985. Cesamet is indicated for treating nausea and vomiting associated with cancer chemotherapy in patients who have not responded to conventional antiemetic drugs (108).

2.2.10.4 Marinol® (Synthetic cannabinoids)

Marinol contains 2.5 mg, 5 mg, and 10 mg dronabinol in capsules and was approved by U.S. FDA in 1985. It is indicated for treating anorexia associated with weight loss in AIDS patients and nausea and vomiting associated with cancer chemotherapy in patients who have not responded sufficiently to conventional antiemetic drugs (109).

2.2.11 Previous studies

European Medicinal Cannabis Association (EUMCA) regulates that products from extracts of cannabis must have CBD as the main component in high purity and limit no more than 0.2% by weight of THC to reduce and prevent misuse of cannabis extracts and be considered for medicinal purposes (110).

The regulatory authorities in the Czech Republic have approved the cannabis products from producers that they license in March 2016. Medicinal cannabis products are defined as dried female flowers of the plant *Cannabis sativa* or *Cannabis indica* whose concentration levels range from 0.3% to 21% for THC and from 0.1% to 19% for CBD (111, 112). Most adverse effects of cannabis can be mitigated by using a "start low and go slow" dosing strategy. It is necessary to identify the cannabis concentration to determine the legality of hemp product possession. Analysis of CBD and THC in 50 CBD oil/hemp oil commercial products revealed that most of the products contained <0.1% CBD and <0.01% THC (113).

Axim Biotech has developed controlled-release chewing gums with a combination of THC and CBD (1:1) in oromucosal dosage form. These products are currently in clinical trials for treating several diseases such as multiple sclerosis-associated spasticity, pain, dementia, post-herpetic neuralgia, and Parkinson's disease. Moreover, Axim Biotech has recently produced controlled-release chewing gums in microencapsulated cannabinoids during mastication (114).

According to Giacoppo *et al*., in 2015, a study revealed that topical 1% CBD cream can protect against inflammation, neuronal cell death, and oxidative injury. Studying the experimental model of autoimmune encephalomyelitis (EAE), topical CBD qualifies for the symptomatic treatment of multiple sclerosis. CBD ointment is a safe and effective non-invasive alternative treatment for alleviating neuroinflammation and neurodegeneration (115) and improving the quality of life in inflammatory skin disorders patients (92).

CBD can suppress the release of inflammatory mediators that are related to inflammatory and wound healing processes occurring in the skin. The mode of action involves the NF-κB pathway impairment because CBD could inhibit the TNFα-induced NF-κB-driven transcription. However, the downregulation of genes in skin inflammation and wound healing was not exactly related to the presence of CBD (116).

In 2018, Klein M *et al*., studied the effects of CBD on traumatic ulcerative lesions in rodents. The study revealed that CBD exerts an anti-inflammatory property in the early stage of the wound healing process in microscopic findings although it did not promote clinical improvement adequately (23).

Recently, a study in 2022 by Qi X demonstrated that the effects of CBD oral spray on trauma- or acid-induced oral ulcers on mice tongues can reduce pain, inhibit inflammation, and promote wound healing. Mouse facial grooming behaviors are the signs of orofacial pain. CBD topical spray significantly reduced the severe orofacial pain induced by oral ulcers. CBD accelerates the wound healing process by inhibiting cytidine/uridine monophosphate kinase 2 (CMPK2)-mediated the NOD, LRR, and NLRP3 pyrin domain–containing protein 3 (NLRP3) inflammasome activation and pyroptosis, which are mediated mostly by peroxisome proliferator-activated receptor γ (PPARγ) in the nucleus and partially by CB1 in the plasma membrane (22).

CHAPTER 3

Materials and methods

3.1 CBD Preparation

Cannabis was acquired from local herbal suppliers in Bangkok, Thailand. CBD with THC less than 0.2% was obtained by supercritical carbon dioxide (CO_2) extraction using ethanol as the co-solvent and separated by centrifugal partition chromatography (117). Purification was performed using medium pressure liquid chromatography (118). The cannabinoid composition (CBD and THC contents) of the obtained extracts was determined by High Performance Liquid Chromatography analysis (119). CBD oral pastes were prepared by the Faculty of Pharmaceutical Sciences, Chulalongkorn University (Bangkok, Thailand), and passed cellular and animal safety screening. The stability of cannabis is about 2 years if stored in the dark at room temperature (about 20°C) (71). The shelf life of CBD oral paste used in this study lasted about 2 years.

3.2 Population and sample

3.2.1 Phase 1: CBD effect on human skin

3.2.1.1 Sample population

Healthy volunteers who met the inclusion and exclusion criteria.

3.2.1.2 Sample size

Sample size according to data from Bhalang K *et al*., 2013 (120), we recruited a total sample size of 100 subjects (50 males and 50 females).

3.2.2 Phase 2: CBD effect on normal oral mucosa

3.2.2.1 Sample population

Healthy volunteers who met the inclusion and exclusion criteria.

3.2.2.2 Sample size

Sample size according to data from Bhalang K *et al*., 2013 (120), we recruited a total sample size of 50 subjects (25 males and 25 females).

3.2.3 Phase 3: CBD effect on RAU

3.2.3.1 Sample population

RAU patients from the Oral Medicine Clinic at Faculty of Dentistry, Chulalongkorn University, who met the inclusion and exclusion criteria.

3.2.3.2 Sample size calculation

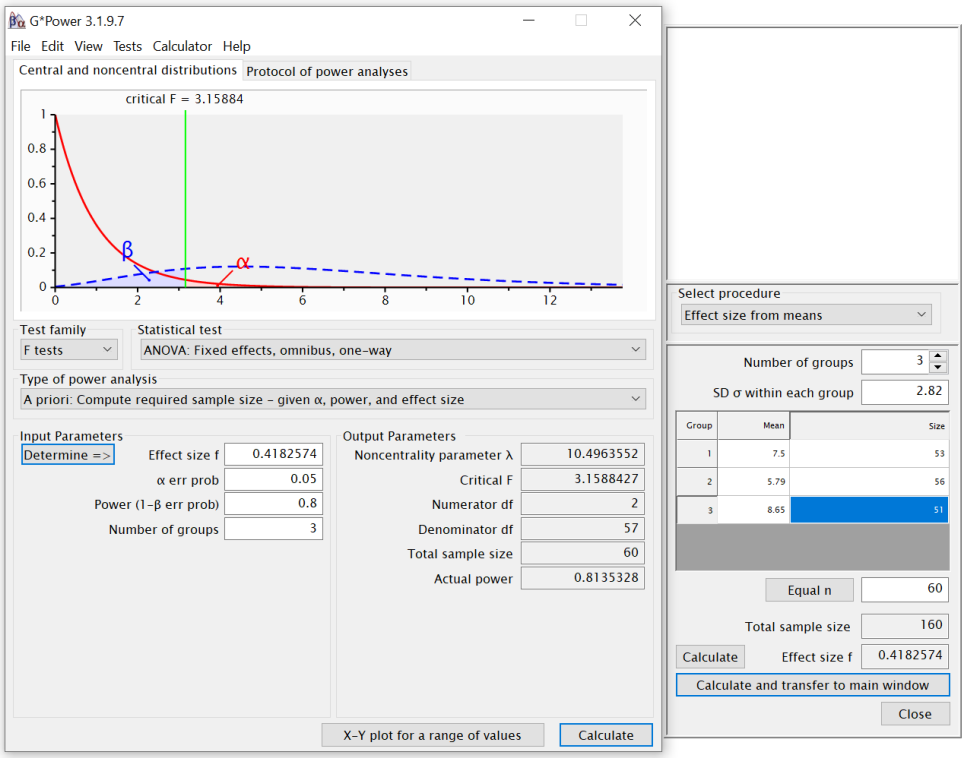
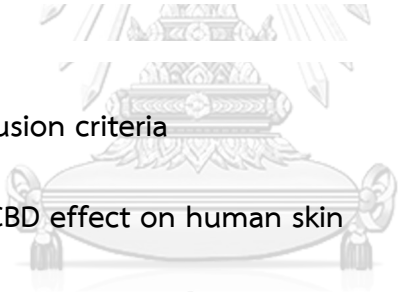


Figure 2. Sample size calculation from the G*Power program

The sample size was calculated by using the G*Power program version 3.1.9.7 with 80% power and 95% confidence interval level according to data from Ofluoglu D *et al*., 2017 (121). The estimated total sample size was 60. To compensate for error or loss of participants during follow up commonly add 10% to the sample size, we recruited a total sample size of 69 patients.

This study was performed with informed consent following protocols approved by the Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University (approval number HREC-DCU 2021-048). The study population composed of 150 healthy volunteers and 69 RAU subjects that agreed to participate after inclusion and exclusion criteria were met.



3.3 Inclusion and exclusion criteria

3.3.1 Phase 1: CBD effect on human skin

Inclusion criteria

1. Age between 18–65 years old.
2. Willing to participate and provide informed consent.
3. Healthy volunteers without systemic diseases (e.g., hypertension, diabetes mellitus, allergy).

Exclusion criteria

1. Pregnancy/lactation.
2. Concurrent bacterial/viral/fungal infections.

3.3.2 Phase 2: CBD effect on normal oral mucosa

Inclusion criteria

1. Age between 18–65 years old.
2. Willing to participate and provide informed consent.
3. Healthy volunteers without systemic diseases (e.g., hypertension, diabetes mellitus, allergy).

Exclusion criteria

1. History of allergies to CBD oral paste used in the study.
2. Pregnancy/lactation.
3. Concurrent oral bacterial/viral/fungal infections.

3.3.3 Phase 3: CBD effect on RAU

Inclusion criteria

1. Age between 18–65 years old.
2. Willing to participate and provide informed consent.
3. Having a history of RAU (at least 2 times/year) on the nonkeratinized oral mucosa.
4. Presenting with 1–3 aphthous ulcers that were 2–10 mm in diameter and ≤48 hours duration.
5. Ulcer sites were easily accessible for treatment and evaluation (e.g., buccal mucosa, labial mucosa, floor of mouth).

Exclusion criteria

1. History of allergies to CBD or oral paste used in the study.
2. Pregnancy/lactation.
3. Concurrent oral bacterial/viral/fungal infections.
4. Ulcers as a manifestation of systemic diseases such as Behcet's disease, Crohn's disease, ulcerative colitis, or anemia.
5. Ulcers from trauma.
6. Diabetes mellitus patients.
7. Treatment with systemic steroids, immunomodulatory agents, or oral retinoids within 1 week.
8. Treatment with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or other oral topical medications within 48 hours or during study participation.
9. History of dental surgery within 2 weeks of participating in the study.
10. Orthodontic braces or retainers that might come in contact with the ulcers.

3.4 Interventions

Participants were placed into three groups: 0.1% CBD oral paste, 0.1% triamcinolone acetonide (TA), or placebo (pure oral paste). A total of 69 patients (23 subjects in the CBD group, 22 subjects in the TA group, and 24 subjects in the placebo group) was enrolled in this study. When subjects developed aphthous ulcer more than one time (at least 2 weeks apart), they could reenter the project and received a different medication.

3.5 Design

3.5.1 Phase 1: CBD effect on human skin

To investigate whether CBD caused an allergic reaction when used on human skin, 100 healthy subjects (50 males and 50 females) were recruited to participate in the study. 0.1% CBD was loaded in four Finn chambers (Epitest, Tuusula, Finland) and placebo was loaded in the four other chambers. The chambers were applied to the subjects' upper backs. After 48 hours, the chambers were removed and 15 minutes later, any reaction was scored according to the International Contact Dermatitis Research Group (ICDRG) standard (122). Scoring was conducted again 24 hours later. The subjects and researcher were blinded to which chambers contained CBD. The spectrum of patch test reactions according to the ICDRG depicts in Figure 3. Notation of patch test results according to the ICDRG (123) is summarized in Table 6.

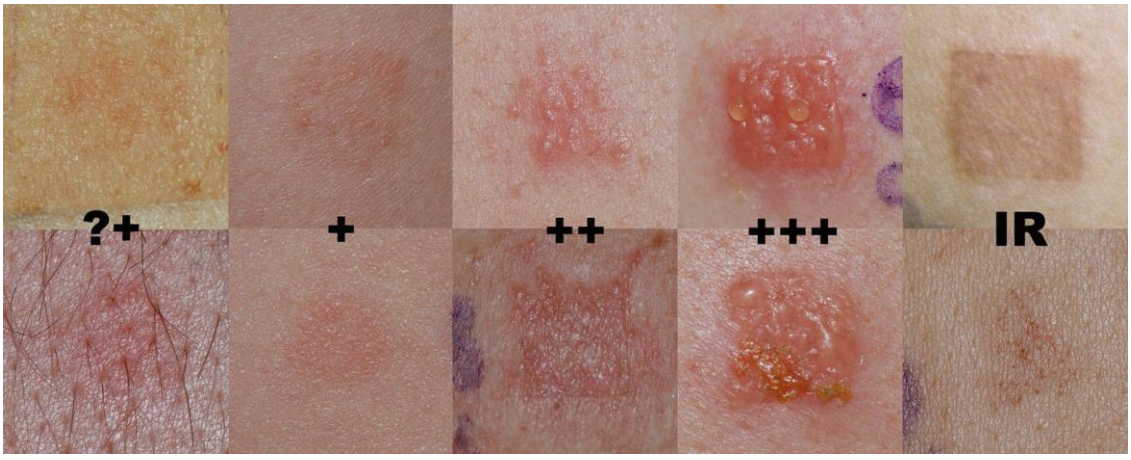


Figure 3. The spectrum of patch test reactions according to the ICDRG

Table 6. Notation of patch test results according to the ICDRG

Symbol	Morphology	Interpretation
-	No visible reaction in any test area	Negative
?+	Faint, non-palpable erythema	Doubtful reaction
+	Palpable erythema—moderate oedema or infiltrate, papules not present or scarce, vesicles not present	Weak positive reaction
++	Strong infiltrate, numerous papules, vesicles present	Strong positive reaction
+++	Coalescing vesicles, pseudo-bullae, or ulceration	Extreme positive reaction
IR	Limited to the exposed area, lack of infiltrating (oedema may be present), 'common reaction' with homogeneous erythema without infiltration, 'poral reaction' with punctate erythema, sometimes slightly papular or hemorrhagic, 'pustular reaction' with one or numerous pustules, possibly efflorescences other than papules and vesicles	Irritant reaction

3.5.2 Phase 2: CBD effect on normal oral mucosa

To assess the local and systemic side effects of CBD when used on normal oral mucosa, 50 healthy subjects (25 males and 25 females) were recruited to participate in the study. The subjects were instructed to apply CBD with a calibrated spoon in a diameter of 1 cm 3 times/day after meals for 7 days on their lower labial mucosa. Oral examination, vital signs, and blood tests were performed before and after 7 days of drug administration. The blood parameters evaluated were glucose, hematocrit, sodium, potassium, chloride, total CO_2, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), total protein, total bilirubin, albumin, blood urea nitrogen (BUN), and creatinine (95, 96).

3.5.3 Phase 3: CBD effect on RAU

To measure the efficacy of CBD for treating RAU, 69 subjects with RAUs randomly received one of three treatments: 0.1% CBD, 0.1% TA, or placebo. This phase of the study was a randomized double blind controlled trial. A research assistant was the only one who knows about the randomized information. The subjects and researcher were both blinded to the treatment type. The medications were applied with a calibrated spoon to the ulcers 3 times/day after meals for 7 days.

The ulcer size was measured on day 0 (before treatment), 2, 5, and 7. Two ulcer size parameters consisting of the pseudomembranous ulcer size and erythematous circumscribed border were measured. The ulcer diameters were measured using a calibrated dental probe with millimeter markings, and the ulcer sizes were calculated using formulas for the surface area of a circle or ellipse. The ulcers were photographed alongside a visual reference of known size as shown in

Figure 4, then a researcher drew the boundary of pseudomembranous and erythematous border size on the captured image. The images were analyzed using computer software (Image-Pro Plus version 4.5 for Windows, Media Cybernetics, Rockville, MD, USA). The Ulcer Severity Score (USS) is indicative of the disease severity. It incorporates six ulcer characteristics: number, size, duration, ulcer-free period, site, and pain (124). It was used at the first visit as a baseline. The ulcers were assessed by an oral medicine specialist. Pain ratings using a visual analog scale (VAS) consisting of a 100-mm horizontal line between the endings marked “no pain” and “unbearable pain” were recorded daily.

If there were more than one ulcer, the easiest access ulcer was chosen for investigation. The subjects and researcher were both blinded to the treatment type. When subjects developed aphthous ulcer more than one time (at least 2 weeks apart), they could reenter the study and received a different medication.

On the last day, the subjects rated their satisfaction with the medication used on a scale of 0 (not satisfactory) to 10 (the most satisfactory). Each subject was interviewed at each visit by the same investigator regarding the emergence of any adverse reactions. The subjects who used all three medications selected their preference among the medications used. The subjects also completed a QoL questionnaire using the Thai Oral Health Impact Profile–14 (OHIP-14) at the first and last visit.

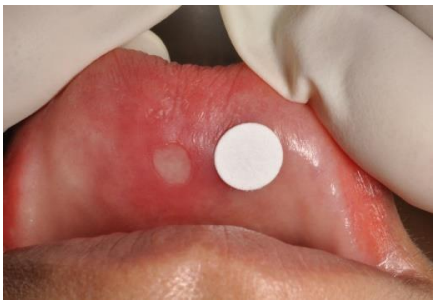


Figure 4. An aphthous ulcer with a visual reference of known size

3.6 Measurements

3.6.1 Ulcer size

The ulcer size was measured on day 0, 2, 5, and 7. Two ulcer size parameters consisting of the pseudomembranous ulcer size and erythematous circumscribed border were measured. The ulcer diameters were measured using a calibrated dental probe with millimeter markings, and the ulcer sizes were calculated using formulas for the surface area of a circle or ellipse. In case of a circle area, we measured a diameter. If ulcers were an ellipse, we measured the longest and the shortest diameters, then calculated the area of the ulcer with these formulas:

- Area of a circle in mm^2 (A) = πr^2

  π = 22/7

  r = radius of circle or diameter/2 (mm)

- Area of an ellipse in mm^2 (A) = πab

  π = 22/7

  a = the longest radius of ellipse or the longest diameter/2 (mm)

  b = the shortest radius of ellipse or the shortest diameter/2 (mm)

The ulcers were photographed alongside a visual reference of known size, then a researcher drew the boundary of pseudomembranous and erythematous border size on the captured image. The images were analyzed using computer software (Image-Pro Plus version 4.5 for Windows, Media Cybernetics, Rockville, MD, USA).

3.6.2 Ulcer Severity Score (USS)

The Ulcer Severity Score (USS) is indicative of the disease severity in aphthous ulcers. It is developed for assessing the efficacy of treatment. The changing scores reflect the change in ulcer severity due to the treatment response (124). The score calculation is as follows:

3.6.2.1 Number: The score defines as the average number of ulcers per crop that patients have been having in the last 3 months. The maximum score for this parameter is 20.

3.6.2.2 Size: The score defines as the average diameter of the ulcers in millimeters. The diagram of different diameter circles is indicated to patients. The maximum score for this parameter is 20.

3.6.2.3 Duration: The score defines as the average ulcer duration calculated in ½ week units. The ulcer lasting 10 days (1½ weeks) will score 3 and the ulcer persisting more than 5 weeks will score a maximum of 10.

3.6.2.4 Ulcer-free period: The score is calculated by 10 minus the average ulcer-free period in weeks, a patient who is never free from ulcers will score the maximum of 10, but a patient who is ulcer free for 8 weeks at a time will score 2.

3.6.2.5 Site: The areas that are always affected by the ulcers are calculated. A score of 1 is for each site of the nonkeratinized surfaces such as buccal mucosa, labial mucosa, buccal sulcus, ventral surface and lateral border of the tongue, soft palate, and floor of the mouth. A score of 2 is for each site of the keratinized and specialized mucosal surfaces such as attached gingiva, alveolar ridge, hard palate, dorsum of the tongue, tonsils, pillars of fauces, uvula, and oropharynx). The combined scores of all the non-keratinized and keratinized surfaces are calculated as the site scores. The maximum score for this parameter is 10.

3.6.2.6 Pain: The pain of ulcers is scored by the patients on a scale of 0 (no pain) to 10 (excruciating ulcer, interfering with talking, eating, and sleeping).

The USS form was used in Table 7. The total score was the summation of the six parameter scores. It was recorded at the first visit as a baseline.

Table 7. The Ulcer Severity Score (USS) form

	Ulcer characteristics	Score	Description of USS
Average number of ulcers			Score = average number of ulcers in a crop Maximum score = 20
Average size of ulcers (in mm)			Score = average diameter of ulcers in mm Maximum score = 20
Average duration of ulcers (in weeks)			Score = number of ½ weeks i.e., half a week (3 days) scores 1, one and a half week (10 days) scores 3. Maximum score = 10
Ulcer-free period (in weeks)			Score = 10 minus the average ulcer-free period in weeks Maximum score = 10 (never free from ulcers)
Pain as perceived by the patient (on a scale of 0–10)			1 for slight discomfort when ulcers are present, 10 for excruciating ulcers interfering with eating and talking Maximum score = 10
Mucosal site	**Group 1** buccal mucosa, labial mucosa, buccal sulcus, ventral of tongue, soft palate, floor of mouth **Group 2** attached gingiva, alveolar ridge, dorsum of tongue, hard palate, tonsils, pillars of fauces, uvula, oropharynx		Score = total of sites affected 1 for each site in group 1 (non-keratinized mucosa), 2 for each site in group 2 (keratinized and specialized mucosa) Maximum score = 10

Evidence of scarring ☐ Yes ☐ No **Total USS: _____/80**

3.6.3 Visual Analog Scale (VAS)

Pain ratings using a visual analog scale (VAS) consisting of a 100-mm horizontal line between the endings marked “no pain” and “unbearable pain” as shown in Figure 5 were recorded daily (before treatment, after applying a medication after dinner for 30 minutes on day 1 to 7).

No pain Unbearable pain

Figure 5. Visual Analog Scale (VAS)

3.6.4 Subject satisfaction

On the last day, the subjects rated their satisfaction with the medication used on a scale of 0 (not satisfactory) to 10 (the most satisfactory). The subjects who used all three medications selected their preference among the medications used.

3.6.5 Quality of life (QoL)

The Oral Health Impact Profile-14 (OHIP-14) questionnaire, a shortened version of OHIP-49 (45), was applied to evaluate oral QoL (46). The reliability of the Thai OHIP-14 was excellent (α = 0.88) and the construct validity of the questionnaires showed acceptable properties (50). The questionnaire consists of 14 items divided into 7 different domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (125) that explore different aspects of oral function and QoL by choosing one of the most offered answers: 0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = very often. Higher scores correspond to poorer oral QoL. The subjects completed a QoL questionnaire using the Thai OHIP-14 at the first and last visit.

3.7 Data collection

The background, demographics, and RAU histories including sex, age, medical histories, current medications, drug and food allergies, location and duration of RAU, history of RAU per year, previous treatments for RAU, and intraoral examination were collected. Outcome assessments were done at the designated time points by the one trained researcher on day 0, 2, 5, and 7.

3.8 Statistical analysis

The background and demographic data were summarized using descriptive statistics. In phase 2, the normal distributions of all variables were determined using the Shapiro-Wilk test. Matched paired differences of vital signs and blood tests before and after drug use were analyzed using the paired-samples t-test (normally distributed variables) or the Wilcoxon signed-rank test (not normally distributed variables). In phase 3, the normal distributions of all variables were determined by the Kolmogorov-Smirnov test. Group differences among the three medications were compared using one-way ANOVA followed by the Bonferroni post hoc test (normally distributed variables) or Kruskal-Wallis test/Median test followed by the Bonferroni correction for multiple tests (not normally distributed variables) for pseudomembranous ulcer size, erythematous border size, pain level, satisfaction, and OHIP-14 score at each monitoring point. The normal distributions of OHIP-14 scores at the first and last visit in each group were determined using the Shapiro-Wilk test. Matched paired differences of OHIP-14 scores at the first and last visit in each group were compared using the paired-samples t-test (normally distributed variables) or the Wilcoxon signed-rank test (not normally distributed variables). The data were analyzed using the SPSS software (SPSS 28 for Windows; SPSS, Chicago, IL, USA). A *p*-value of ≤0.05 was considered significant.

CHAPTER 4

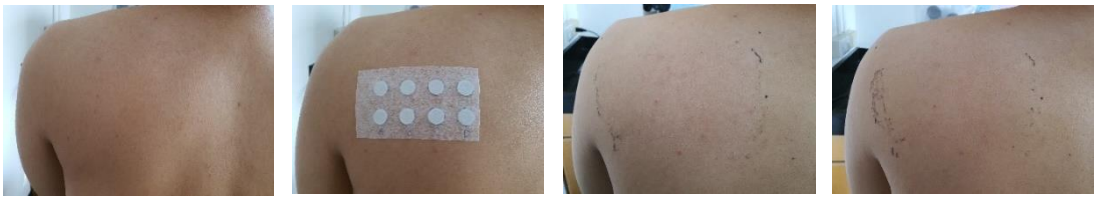
Results

4.1 Phase 1: CBD effect on human skin

The background and demographic data are summarized in Table 8. The age of participants ranged between 18-65 years and the mean age was 38.22±13.79 (standard deviation) years. Investigating the reaction to CBD when used on human skin revealed that no subject had positive allergic reactions on any treated areas. A skin patch test is shown in Figure 6.

Table 8. The background and demographic data in phase 1

	Frequencies, *n (%)*
Sex	
Male	50 (50)
Female	50 (50)
Age range (years)	
18-20	15 (15)
21-30	22 (22)
31-40	20 (20)
41-50	20 (20)
51-60	15 (15)
61-65	8 (8)



(A) (B) (C) (D)

Figure 6. Before skin patch test (A), a skin patch test (B), skin reaction assay results after 48 hours (C), and 72 hours (D)

4.2 Phase 2: CBD effect on normal oral mucosa

A summary of the background and demographic data is presented in Table 9. The age of participants ranged between 18-65 years and the mean age was 39.78±14.33 (standard deviation) years. The normal distributions of all variables determined by the Shapiro-Wilk test are summarized in Table 10. Table 11 depicts the mean and standard deviation (SD) of vital signs and blood tests before and after 7 days of CBD application. The results of assessing the local and systemic side effects of CBD when used on normal oral mucosa indicated that no subject experienced an adverse reaction and there were no significant differences in any of the evaluated vital signs or blood parameters ($p>0.05$) before and after the 7-day CBD application.

Table 9. The background and demographic data in phase 2

	Frequencies, *n (%)*
Sex	
Male	25 (50)
Female	25 (50)
Age range (years)	
18-20	6 (12)
21-30	11 (22)
31-40	11 (22)
41-50	7 (14)
51-60	10 (20)
61-65	5 (10)

Table 10. Normality tests of vital signs and blood parameters determined by the Shapiro-Wilk test

	p
Systolic blood pressure	0.958
Diastolic blood pressure	0.105
Heart rate	0.007
Glucose	0.203
Hematocrit	0.039
Sodium	0.002
Potassium	0.008
Chloride	0.036
Total CO_2	0.038
SGOT	0.002
SGPT	<0.001
ALP	0.147
Total protein	0.388
Total bilirubin	0.515
Albumin	0.038
BUN	0.752
Creatinine	0.501

Table 11. Vital signs and blood parameters before and after the 7-day CBD application

	Before, mean (SD)	**After, mean (SD)**	***p***
Systolic blood pressure (mmHg)	121.04 (14.13)	119.12 (14.09)	0.153[a]
Diastolic blood pressure (mmHg)	69.94 (9.32)	68.28 (10.08)	0.185[a]
Heart rate (BPM)	82.66 (11.74)	82.72 (10.82)	0.480[b]
Glucose (mg/dL)	80.30 (6.82)	80.60 (6.64)	0.527[a]
Hematocrit (%)	41.54 (4.15)	41.54 (4.41)	0.920[b]
Sodium (mEq/L)	140.90 (1.46)	140.42 (1.66)	0.110[b]
Potassium (mEq/L)	4.08 (0.29)	4.08 (0.25)	0.977[b]
Chloride (mEq/L)	101.44 (1.84)	101.72 (1.92)	0.197[b]
Total CO_2 (mEq/L)	24.00 (1.95)	24.26 (1.70)	0.425[b]
SGOT (U/L)	18.96 (4.76)	19.02 (5.64)	0.777[b]
SGPT (U/L)	17.54 (8.66)	17.40 (9.81)	0.188[b]
ALP (U/L)	61.98 (13.84)	62.82 (15.66)	0.323[a]
Total protein (g/dL)	7.47 (0.36)	7.46 (0.37)	0.759[a]
Total bilirubin (mg/dL)	0.67 (0.24)	0.67 (0.24)	0.970[a]
Albumin (g/dL)	4.34 (0.24)	4.33 (0.26)	0.791[b]
BUN (mg/dL)	11.52 (2.58)	11.24 (2.59)	0.335[a]
Creatinine (mg/dL)	0.76 (0.15)	0.76 (0.13)	0.385[a]

[a]*p*-Values from paired-samples t-test.

[b]*p*-Values from Wilcoxon signed-rank test.

4.3 Phase 3: CBD effect on RAU

The normal distributions of background, demographics, and ulcer histories determined by the Kolmogorov-Smirnov test are shown in Table 12. The background, demographics, and ulcer histories are summarized in Table 13. The age of participants ranged between 18-65 years and the mean age was 35.17±10.58 (standard deviation) years. Sixty-nine patients (23 subjects in the CBD group, 22 subjects in the TA group, and 24 subjects in the placebo group) were enrolled in this study. There were no significant differences between the three groups regarding their demographics and ulcer histories (Table 13), except for the ulcer duration, however, after adjusting the results with the Bonferroni correction for multiple tests, the difference was not significant (Table 14).

The normal distributions of all parameters in the USS determined by the Kolmogorov-Smirnov test are shown in Table 15. There were no significant differences between the three groups regarding their USS parameters (Table 16), except for the average number of ulcers, however, after adjusting the results with the Bonferroni correction for multiple tests, the difference was not significant (Table 17).

Table 12. Normality tests of background, demographics, and ulcer histories determined by the Kolmogorov-Smirnov test

	p
Age	<0.001
Duration of the ulcer	<0.001
Ulcer size on day 0 from photograph	0.006
VAS on day 0	0.200
USS	0.200
OHIP-14 scores at the first visit	0.200

Table 13. The background, demographics, and ulcer histories

	CBD (*n*=23)	**TA (*n*=22)**	**Placebo (*n*=24)**	***p***
Sex				
Male, *n (%)*	2 (2.90)	4 (5.80)	7 (10.14)	0.199[a]
Female, *n (%)*	21 (30.43)	18 (26.09)	17 (24.64)	
Age (years), mean (SD)	36.74 (11.32)	35.91 (10.38)	33.00 (10.11)	0.410[b]
Duration of the ulcer (hours), mean (SD)	42.78 (10.51)	35.05 (13.59)	34.67 (12.96)	0.039[b,c]
Ulcer size on day 0 from photograph (mm^2), mean (SD)	5.96 (3.85)	7.16 (4.94)	6.51 (4.97)	0.755[b]
VAS on day 0 (mm), mean (SD)	53.74 (19.57)	50.23 (23.68)	53.21 (25.70)	0.861[d]
USS (scores), mean (SD)	16.26 (4.32)	17.55 (4.61)	19.25 (4.06)	0.066[d]
OHIP-14 scores at the first visit (scores), mean (SD)	25.13 (9.40)	24.68 (9.78)	30.54 (11.88)	0.110[d]

[a]*p*-Values from Pearson's chi-square test.

[b]*p*-Values from Kruskal-Wallis test.

[c]After adjusting the results with the Bonferroni correction for multiple tests, the difference was not significant.

[d]*p*-Values from one-way ANOVA.

Table 14. Pairwise comparisons of the duration of the ulcer among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
Adj. Sig.[a]	1.000	0.070	0.099

[a]*p*-Values from Kruskal-Wallis test after adjusting significant values by the Bonferroni correction for multiple tests.

Table 15. Normality tests of all parameters in the USS determined by the Kolmogorov-Smirnov test

	p
Average number of ulcers	<0.001
Average size of ulcers	<0.001
Average duration of ulcers	<0.001
Ulcer-free period	<0.001
Pain as perceived by the patient	<0.001
Mucosal site	<0.001

Table 16. Comparison of all parameters in the USS among the three medications

USS parameters	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)	*p*[a]
Average number of ulcers (in a crop), mean (SD)	1.00 (0.00)	1.14 (0.35)	1.00 (0.00)	0.037[b]
Average size of ulcers (in mm), mean (SD)	3.91 (1.04)	4.00 (0.93)	4.13 (0.85)	0.742
Average duration of ulcers (in weeks, score=number of ½ weeks), mean (SD)	2.52 (0.73)	2.50 (0.74)	2.58 (0.78)	0.969
Ulcer-free period (in weeks, score=10 minus the average ulcer-free period in weeks), mean (SD)	1.91 (2.30)	2.95 (3.00)	3.58 (2.81)	0.112
Pain as perceived by the patient (on a scale of 0–10), mean (SD)	5.52 (1.73)	5.64 (2.19)	6.58 (1.84)	0.108
Mucosal site (score=total of sites affected, 1 for each site in group 1 non-keratinized mucosa, 2 for each site in group 2 keratinized and specialized mucosa), mean (SD)	1.39 (0.58)	1.32 (0.48)	1.38 (0.65)	0.943

[a]*p*-Values from Kruskal-Wallis test.

[b]After adjusting the results with the Bonferroni correction for multiple tests, the difference was not significant.

Table 17. Pairwise comparisons of the average number of ulcers among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
Adj. Sig.[a]	0.074	1.000	0.078

[a]*p*-Values from Kruskal-Wallis test after adjusting significant values by the Bonferroni correction for multiple tests.

Ulcer sites and pain scores

The most common site of the ulcer was labial mucosa. A summary of the ulcer sites among the three medications is presented in Table 18. The ulcers on the ventral of tongue had the highest average pain levels before treatment, whereas the lowest average pain scores were the ulcers on the alveolar mucosa. A comparison of the ulcer sites and pain scores is demonstrated in Table 19.

Table 18. The ulcer sites among the three medications

The ulcer sites	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)
Labial mucosa, *n* (%)	11 (47.82)	10 (45.45)	13 (54.16)
Buccal mucosa, *n* (%)	5 (21.74)	3 (13.64)	3 (12.50)
Alveolar mucosa, *n* (%)	1 (4.35)	1 (4.55)	2 (8.33)
Attached gingiva, *n* (%)	1 (4.35)	2 (9.09)	1 (4.17)
Mucobuccal fold, *n* (%)	0 (0.00)	2 (9.09)	1 (4.17)
Ventral of tongue, *n* (%)	2 (8.70)	0 (0.00)	2 (8.33)
Dorsal of tongue, *n* (%)	3 (13.04)	3 (13.64)	1 (4.17)
Floor of mouth, *n* (%)	0 (0.00)	1 (4.55)	1 (4.17)

Table 19. Comparison of the ulcer sites and pain scores

The ulcer sites	VAS on day 0				
	n	Mean	SD	Minimum	Maximum
Labial mucosa	34	50.21	24.05	9	90
Buccal mucosa	11	57.18	23.82	24	89
Alveolar mucosa	4	38.75	33.45	13	87
Attached gingiva	4	53.00	16.06	34	73
Mucobuccal fold	3	53.33	30.07	19	75
Ventral of tongue	4	66.00	9.52	56	76
Dorsal of tongue	7	55.43	9.11	42	70
Floor of mouth	2	51.50	45.96	19	84

Ulcer size measurement from dental probe

Although the ulcer diameters measured using a dental probe were calculated using formulas for the surface area of a circle or ellipse, the exact ulcer size is quite difficult to calculate due to the imperfect round or ovoid shape ulcers as shown in Figure 7 and could have resulted in inaccurate ulcer sizes. We compared the ulcer size between the measurements obtained using a dental probe and photograph as shown in Table 20. The normal distributions of pseudomembranous ulcer size between the measurements obtained using a dental probe and photograph determined by the Kolmogorov-Smirnov test are shown in Table 21. The results revealed that they were significantly different on day 5 and day 7 (Table 22). We decided to exclude the ulcer size data measured with a dental probe.

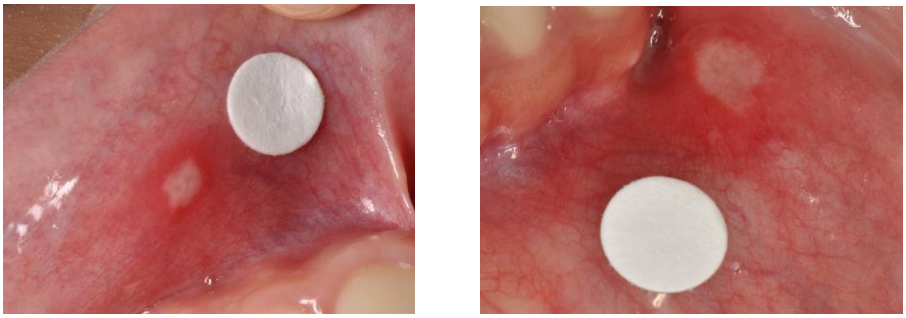


Figure 7. The imperfect round or ovoid shape ulcers

Table 20. Comparison of pseudomembranous ulcer size between the measurements obtained using a dental probe and photograph

	Dental probe (*n*=69)	Photograph (*n*=69)
Day 0 (mm^2), mean (SD)	6.48 (4.45)	6.53 (4.58)
Day 2 (mm^2), mean (SD)	7.15 (6.30)	7.47 (6.14)
Day 5 (mm^2), mean (SD)	5.60 (8.76)	6.16 (8.54)
Day 7 (mm^2), mean (SD)	4.00 (9.21)	4.31 (8.82)

Table 21. Normality tests of pseudomembranous ulcer size between the measurements obtained using a dental probe and photograph determined by the Kolmogorov-Smirnov test

	p
Day 0	0.062
Day 2	0.011
Day 5	<0.001
Day 7	<0.001

Table 22. Differences of pseudomembranous ulcer size in each day between the measurements obtained using a dental probe and photograph

	p
Day 0	0.752[a]
Day 2	0.069[b]
Day 5	0.007[b]
Day 7	0.020[b]

[a]*p*-Values from paired-samples t-test.

[b]*p*-Values from Wilcoxon signed-rank test.

Ulcer size reduction

The normal distributions of adjusted percentage ulcer size in each day determined by the Kolmogorov-Smirnov test are summarized in Table 23. The ulcer size was adjusted to a percentage compared with baseline (100%) as shown in Table 24. The ulcer size reduction analysis among the three medications indicated that the pseudomembranous ulcer size was almost 100% smaller in the CBD group on day 5 as shown in Figure 8 and the erythematous border size was 40% smaller in the CBD group on day 2 as demonstrated in Figure 9 compared with the placebo group. The average ulcer size in the placebo group increased approximately 175% and 135%, respectively, compared with baseline.

CBD and TA reduced the pseudomembranous ulcer and erythematous border size from day 2 onwards. In contrast, the placebo markedly increased the pseudomembranous ulcer and erythematous border size on day 2 and day 5,

however, these sizes were decreased on day 7. Statistical analysis revealed that CBD and TA significantly reduced the pseudomembranous ulcer size more than placebo at all monitoring points (p<0.05). CBD significantly reduced the erythematous border size greater than placebo only on day 2 (p=0.042). In contrast, the erythematous border reduction in the TA group was greater than the placebo group at all monitoring points (p<0.05). Although CBD reduced the pseudomembranous ulcer and erythematous border size less than TA, the differences were not significant. Multiple comparisons of adjusted percentage ulcer size among the three medications are presented in Table 25.

A summary of pseudomembranous ulcer size progression and erythematous border size progression between day 0 and day 7 among the three medications is demonstrated in Table 26 and Table 27 respectively.

Table 23. Normality tests of adjusted percentage ulcer size in each day determined by the Kolmogorov-Smirnov test

	p
Pseudomembranous ulcer size	
Day 2	0.200
Day 5	<0.001
Day 7	<0.001
Erythematous border size	
Day 2	0.200
Day 5	0.003
Day 7	<0.001

Table 24. Comparison of adjusted percentage ulcer size in each day when compared with baseline (100%)

	CBD (*n*=23), mean (SD)	TA (*n*=22), mean (SD)	Placebo (*n*=24), mean (SD)	*p*
Pseudomembranous ulcer size				
Day 0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)	
Day 2	89.69 (61.57)	83.90 (65.85)	168.28 (88.37)	<0.001[a]
Day 5	78.44 (135.24)	36.21 (58.16)	177.61 (156.65)	<0.001[b]
Day 7	48.54 (149.59)	10.41 (32.48)	142.76 (157.65)	0.001[b]
Erythematous border size				
Day 0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)	
Day 2	97.73 (42.47)	86.98 (57.92)	137.81 (56.83)	0.005[a]
Day 5	91.56 (80.75)	47.88 (55.14)	137.75 (86.52)	<0.001[b]
Day 7	60.03 (81.36)	25.67 (45.02)	115.52 (105.12)	0.001[b]

[a]*p*-Values from one-way ANOVA.

[b]*p*-Values from Kruskal-Wallis test.

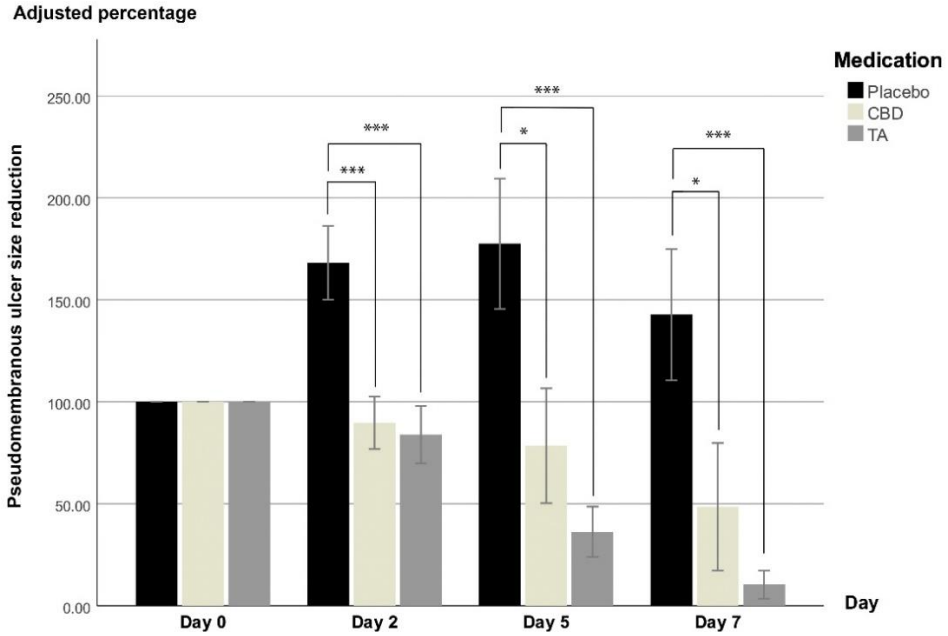


Figure 8. Pseudomembranous ulcer size reduction. Numbers represent percentages. The error bars indicate the standard error (SE) of the mean. Significance is portrayed as * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

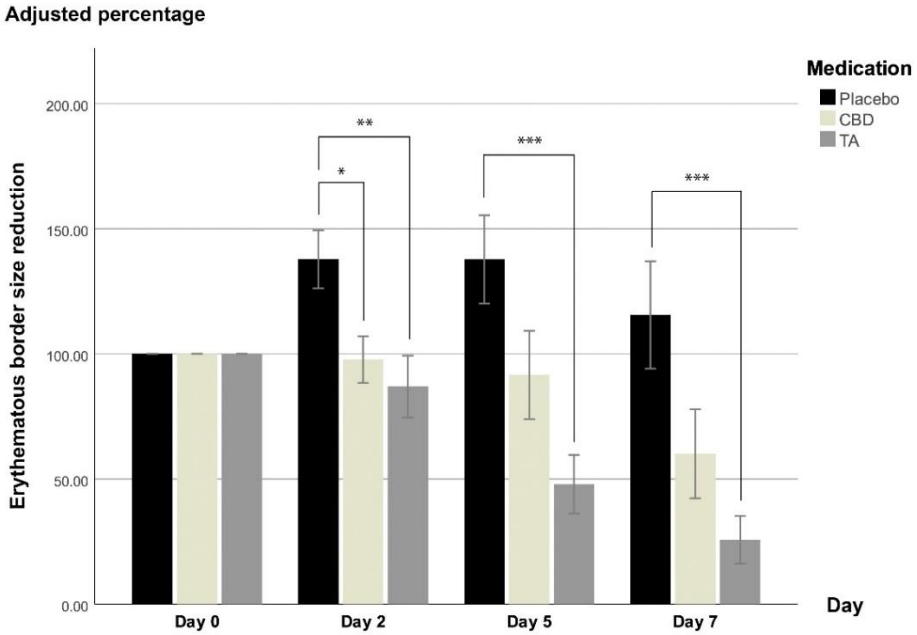


Figure 9. Erythematous border size reduction. Numbers represent percentages. The error bars indicate the standard error (SE) of the mean. Significance is portrayed as * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Table 25. Multiple comparisons of adjusted percentage ulcer size in each day among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
Pseudomembranous ulcer size			
Day 2	<0.001[a]	0.001[a]	1.000[a]
Day 5	0.001[b]	0.033[b]	0.768[b]
Day 7	0.001[b]	0.023[b]	1.000[b]
Erythematous border size			
Day 2	0.006[a]	0.042[a]	1.000[a]
Day 5	0.001[b]	0.244[b]	0.159[b]
Day 7	0.001[b]	0.174[b]	0.298[b]

[a]*p*-Values from one-way ANOVA followed by the Bonferroni post hoc test.

[b]*p*-Values from Kruskal-Wallis test after adjusting significant values by the Bonferroni correction for multiple tests.

Table 26. The pseudomembranous ulcer size progression between day 0 and day 7 among the three medications

	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)
Worse, *n* (%)	2 (8.69)	1 (4.55)	12 (50.00)
Same, *n* (%)	0 (0.00)	0 (0.00)	1 (4.17)
Partial remission, *n* (%)	6 (26.09)	4 (18.18)	2 (8.33)
Complete remission, *n* (%)	15 (65.22)	17 (77.27)	9 (37.50)

Table 27. The erythematous border size progression between day 0 and day 7 among the three medications

	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)
Worse, *n* (%)	2 (8.70)	2 (9.09)	12 (50.00)
Same, *n* (%)	2 (8.70)	0 (0.00)	0 (0.00)
Partial remission, *n* (%)	12 (52.17)	6 (27.27)	6 (25.00)
Complete remission, *n* (%)	7 (30.43)	14 (63.64)	6 (25.00)

Daily pain ratings

The normal distributions of adjusted percentage pain scores determined by the Kolmogorov-Smirnov test are summarized in Table 28. The ulcer pain scores (VAS) were adjusted to a percentage compared with baseline (100%) as shown in Table 29. Comparing the daily pain ratings between the three groups, CBD and TA decreased the pain level from day 1 onwards, while the placebo markedly increased the pain level on day 1–2 and then gradually decreased the pain level from day 3 onwards as demonstrated in Figure 10. Statistical analysis revealed that TA significantly reduced the pain levels on day 4 (p=0.009), day 5 (p=0.023), and day 7 (p=0.008) greater than placebo, whereas the pain levels in the CBD group were significantly lower than the placebo group only on day 5 (p=0.039). However, there were no significant differences in pain reduction between the CBD and TA groups. A summary of multiple comparisons of adjusted percentage VAS in each day among the three medications is presented in Table 30.

Table 28. Normality tests of adjusted percentage pain scores in each day determined by the Kolmogorov-Smirnov test

	p
Day 1	<0.001
Day 2	<0.001
Day 3	<0.001
Day 4	<0.001
Day 5	<0.001
Day 6	<0.001
Day 7	<0.001

Table 29. Comparison of adjusted percentage VAS in each day when compared with baseline (100%)

	CBD (*n*=23), mean (SD)	TA (*n*=22), mean (SD)	Placebo (*n*=24), mean (SD)	*p*[a]
Day 0	100.00 (0.00)	100.00 (0.00)	100.00 (0.00)	
Day 1	86.98 (23.37)	88.96 (23.97)	113.21 (64.69)	0.762
Day 2	68.44 (31.16)	63.46 (27.24)	112.06 (84.14)	0.109
Day 3	47.53 (31.56)	32.21 (28.93)	94.95 (98.99)	0.205
Day 4	29.67 (31.02)	13.05 (23.68)	81.84 (110.40)	0.005
Day 5	13.99 (29.52)	9.79 (22.08)	60.56 (101.06)	0.022
Day 6	9.61 (26.74)	6.01 (13.18)	47.18 (99.65)	0.067
Day 7	5.81 (21.53)	1.53 (5.26)	28.67 (90.62)	0.006

[a]*p*-Values from Median test.

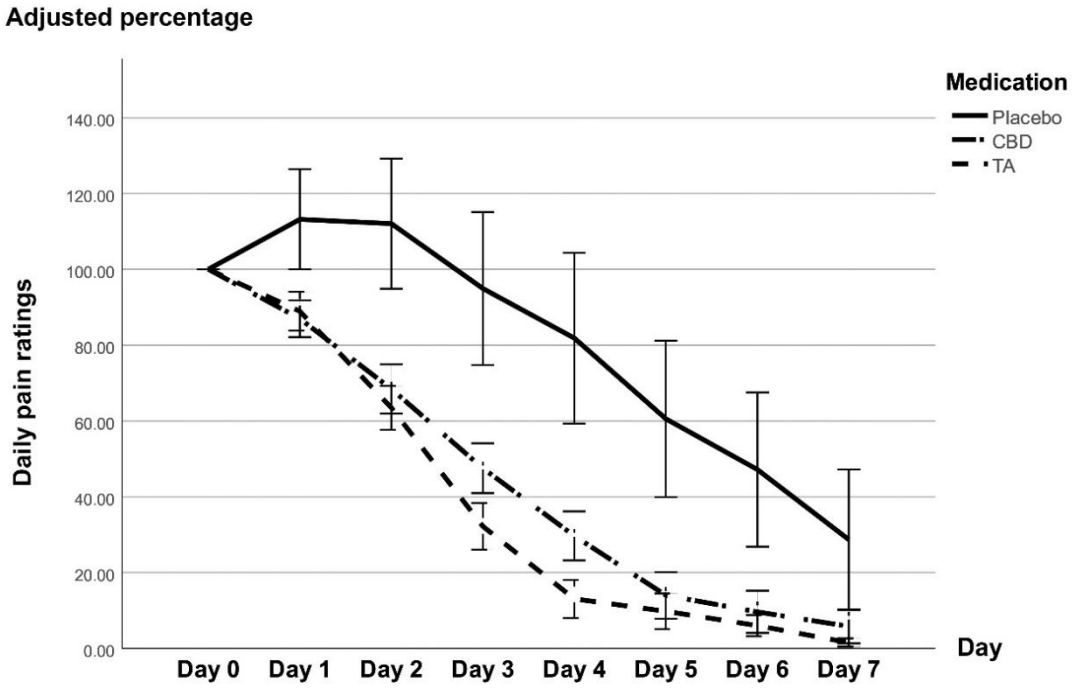


Figure 10. Daily pain ratings. Numbers represent percentages. The error bars indicate the standard error (SE) of the mean.

Table 30. Multiple comparisons of adjusted percentage VAS in each day among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
Day 1	-	-	-
Day 2	-	-	-
Day 3	-	-	-
Day 4	0.009[a]	0.172[a]	0.075[a]
Day 5	0.023[a]	0.039[a]	1.000[a]
Day 6	-	-	-
Day 7	0.008[a]	0.132[a]	0.726[a]

-Multiple comparisons are not performed because the overall test does not show significant differences across samples.

[a]*p*-Values from Median test after adjusting significant values by the Bonferroni correction for multiple tests.

Subject satisfaction

The CBD efficacy in RAU treatment assay results demonstrated that the subjects who received TA were mostly satisfied with the medication with an average satisfaction score of 8.32, followed by CBD with an average score of 7.48, and placebo with an average score of 6.17 as shown in Table 31. Analysis by the Kruskal-Wallis test due to not normally distributed variables ($p<0.001$) indicated that the subjects were significantly more satisfied with TA than placebo ($p=0.025$). The differences in satisfaction scores between subjects receiving CBD and TA were not significant. Although the subjects receiving CBD reported higher satisfaction scores compared with placebo, the difference did not reach statistical significance (Table 32).

Four subjects were treated with all three medications. When these subjects were asked to rank the medications in order of preference, three subjects (75%) selected TA as the most preferred medication followed by CBD, and placebo was the least preferred. One subject (25%) picked CBD as the most preferred medication followed by TA and placebo.

Table 31. Comparison of satisfaction scores among the three medications

	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)	*p*[a]
Satisfaction scores, mean (SD)	7.48 (1.95)	8.32 (1.39)	6.17 (3.03)	0.031

[a]*p*-Values from Kruskal-Wallis test.

Table 32. Multiple comparisons of satisfaction scores among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
Adj. Sig.[a]	0.025	0.537	0.586

[a]*p*-Values from Kruskal-Wallis test after adjusting significant values by the Bonferroni correction for multiple tests.

QoL improvement

The normal distributions of the OHIP-14 score delta in each group determined by the Shapiro-Wilk test are summarized in Table 33. Statistical analysis of the OHIP-14 score reduction in each group revealed that all medications significantly reduced the OHIP-14 scores between the first and last visit (p<0.001) as shown in Table 34. Higher scores correspond to a poorer oral QoL. The QoL improvement results among three groups analyzed by one-way ANOVA due to normally distributed variables (p=0.173) demonstrated that the subjects who received CBD reported the greatest reduction in OHIP-14 scores with an average delta score of 19.83, followed by TA with an average delta score of 19.59, and placebo with an average delta score of 17.71. However, the delta in the OHIP-14 scores at the first and last visit among the three medications was relatively similar (p=0.831) as shown in Table 35. Multiple comparisons of the OHIP-14 score delta among the three medications are shown in Table 36.

Table 33. Normality tests of OHIP-14 score delta between first and last visit in each group determined by the Shapiro-Wilk test

	CBD (n=23)	TA (n=22)	Placebo (n=24)
p	0.549	0.640	0.586

Table 34. Comparison of OHIP-14 score differences between first and last visit in each group

	CBD (n=23)	TA (n=22)	Placebo (n=24)
p^a	<0.001	<0.001	<0.001

[a]p-Values from paired-samples t-test.

Table 35. Comparison of OHIP-14 score delta between first and last visit among the three medications

	CBD (*n*=23)	TA (*n*=22)	Placebo (*n*=24)	*p*[a]
OHIP-14 score delta, mean (SD)	19.83 (11.70)	19.59 (10.61)	17.71 (16.00)	0.831

[a]*p*-Values from one-way ANOVA.

Table 36. Multiple comparisons of OHIP-14 score delta between first and last visit among the three medications

	TA-Placebo	CBD-Placebo	TA-CBD
p[a]	1.000	1.000	1.000

[a]*p*-Values from one-way ANOVA followed by the Bonferroni post hoc test.

CHAPTER 5

Discussion

A recurrent aphthous ulcer is the most common painful oral lesion (1) and affects patient quality of life (2). Despite having a high prevalence, the precise etiology remains unclear (6). Although topical steroids are an effective first-line medication for RAU (10, 11), they also have numerous side effects, especially suppressing the immune response that can lead to developing oral candidiasis from long-term steroid use (12). CBD extracted from cannabis may be an alternative treatment for RAU due to its medical effects, i.e., reducing pain and inflammation and promoting wound healing (22).

The present study evaluated the use of CBD, the main non-psychotropic component extracted from cannabis, as a topical treatment for RAU. No subject experienced a positive allergic reaction to CBD either on their skin or oral mucosa. Applying CBD to normal oral mucosa for 7 days did not affect blood pressure, heart rate, glucose, hematocrit, sodium, potassium, chloride, total CO_2, SGOT, SGPT, ALP, total protein, total bilirubin, albumin, BUN, and creatinine. Therefore, we concluded that CBD is safe to be used on human skin and oral mucosa.

The most common site for RAU observed in this study was labial mucosa, while the floor of mouth was the least common site. The ulcers on ventral of tongue had the highest average pain levels because the tongue is sensitive to pain and the pain may be worse if the tongue ulcers come into contact with an object, such as a toothbrush. The tongue is a muscular organ that helps the functions of speech, chewing, taste, and swallowing (126). Due to the ulcers on the tongue, most of the person feels discomfort in eating and drinking, some foods can also aggravate the

tongue ulcer, especially those that are spicy or acidic. The lowest average pain scores were the ulcers on alveolar mucosa. Alveolar mucosa is the soft, thin mucous membrane that lines above the attached gingiva, it has a rich blood supply and numerous elastic fibers (127). The ulcers on alveolar mucosa beyond the mucogingival junction are seldom irritated by physical and chemical stimuli.

Ulcer size, erythematous border size, pain level, satisfaction, and OHIP-14 scores were evaluated in this study. These are the main issues when selecting a medication for treating RAU. The findings from the present randomized, controlled double-blind clinical trial study indicate that CBD treatment reduced pseudomembranous ulcer and erythematous border size and alleviated pain during the 7-day application. The pseudomembranous ulcer size was significantly reduced due to the wound healing promotion and anti-inflammatory effects of CBD (22, 23). The erythematous circumscribed border represents the level of inflammation (128). CBD significantly reduced the erythematous border size greater than placebo on day 2, similar to a study that used CBD in oral traumatic ulcerative lesions in rats, which concluded that CBD exerts an anti-inflammatory property in the early stage of wound healing process (23). Although almost all subjects receiving CBD and TA had complete remission of the pseudomembranous ulcers at the end of the study, the erythematous border and persistent residual inflammation remained around the complete ulcer healing.

The pain scores of the three groups decreased with time (121) because RAU is a self-limiting ulcer (3). Thus, some subjects who received the placebo might have felt better on day 3 onwards due to the reduced ulcer size. At the end of the study, some subjects who received placebo still had large ulcers, however, the average daily pain score on day 3–7 from this group were lower than baseline. The pain relief

effect of the placebo may stem from the paste layer that protects the ulcer from physical and chemical stimuli. Interviewing the two groups of subjects that received oral paste revealed that it produced a lingering cool effect on the ulcer. Moreover, the subjects were blinded to the treatment type, and the placebo may produce some psychologic effects (121). The pain levels in the CBD group were significantly lower than the placebo group due to analgesic effect of CBD (15). Similar to the study that assessed CBD effect on trauma- and acid-induced oral ulcers on mice tongues, it was found that severe pain induced by oral ulcers was significantly reduced after CBD topical application. Their results demonstrated that CBD inhibits inflammation, relieves pain, and promotes wound healing by inhibiting CMPK2-mediated NLRP3 inflammasome activation and pyroptosis, which are mediated mostly by PPARγ in the nucleus and partially by CB1 in the plasma membrane (22).

A study revealed that RAU affects patient QoL due to pain (during talking, eating, drinking, and swallowing), discomfort (impairment in food and liquid intake), interpersonal relationship problems, and self-confidence (42). The higher OHIP-14 scores at the first visit found in our study confirmed that RAU influences an individual's QoL. Although the QoL scores measured by the Thai OHIP-14 between the first and last visit in each group were significantly reduced, the difference in the reduced OHIP-14 scores among three groups was not significant because RAU resolves over time and the placebo may produce some psychologic effects (121).

Previous study (121) has suggested the use of a dental probe for measuring ulcer size. In the present study, we measured the ulcer size with a calibrated dental probe and captured image with a visual reference. Although the ulcer diameters measured using a dental probe were calculated using formulas for the surface area of a circle or ellipse, the exact ulcer size is quite difficult to calculate due to the

imperfect round or ovoid shape ulcers and could have resulted in inaccurate ulcer sizes. We compared the ulcer size between the measurements obtained using a dental probe and photograph, the results revealed that they were significantly different. We, thus, decided to exclude the ulcer size data measured with a dental probe. A minor error for the measuring method using image analysis could stem from the difference in pulling forces used to retract the oral mucosa. To minimize this inaccuracy, we always asked the subjects to retract their oral mucosa with similar pulling forces. Photos were also taken at the same position at every monitoring point.

One of the limitations of this study was the two dimensional measurement of the ulcer. Because ulcer size reduction and pain relief are not the only signs of improvement in healing ulcers, decreases in ulcer depth should also be measured. If the ulcer depth can be incorporated into the measurement, the results may be more comprehensive. Although USS was used at baseline, some parts of the USS overlapped with other measurements. Ulcer size and pain score were recorded at each monitoring point. The number and ulcer sites were collected regarding the ulcer histories at baseline. We, therefore, omitted the use of USS in our analysis to compare the results of different treatments. However, a comprehensive score that includes QoL for assessing an improvement in ulcer treatment would be ideal.

To the best of our knowledge, this is the first clinical trial investigating the effects of CBD for treating RAU. The efficacy of CBD for treating RAU observed in this study was based on the reduction of the pseudomembranous ulcer size and pain relief. Because 0.1% CBD demonstrated promising results for treating RAU, future studies should investigate the use of a higher concentration of CBD for treating RAU and other oral lesions.

CHAPTER 6

Conclusions

The present study demonstrated that CBD reduces ulcer size and accelerates ulcer healing without any local or systemic side effects. CBD exerts an anti-inflammatory effect by reducing the erythematous border size in the early stage and decreases pain intensity in the late stage of RAU. Therefore, CBD may be suitable for RAU patients who desire to avoid the use of steroid medications.

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APPENDIX

APPENDIX A

ใบยืนยันข้อมูลส่วนบุคคลในการเข้าร่วมการวิจัย

ID ..... เพศ ☐ ชาย ☐ หญิง อายุ .....ปี

โรคประจำตัว.....

แพ้ยา.....

แพ้อาหารหรืออื่นๆ.....

ยาหรืออาหารเสริมที่รับประทานในปัจจุบัน.....

กำลังตั้งครรภ์หรือให้นมบุตร ☐ ใช่ ☐ ไม่ใช่

กำลังติดเชื้อแบคทีเรีย ไวรัส หรือรา ☐ ใช่ ☐ ไม่ใช่

APPENDIX B

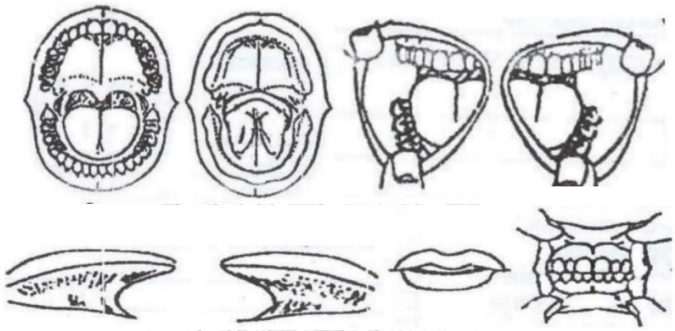
Demographic record form

วันที่..... ID..... เพศ ☐ ชาย ☐ หญิง อายุ .....ปี

โรคประจำตัว .....แพ้ยา อาหารหรืออื่นๆ.....

ยาหรืออาหารเสริมที่รับประทานในปัจจุบัน .....

จำนวนแผลร้อนใน ..... ตำแหน่งที่เป็นแผลร้อนใน.....



ระยะเวลาตั้งแต่เริ่มมีแผล .....วัน .....ชั่วโมง การรักษาแผลร้อนในที่เคยได้รับ.....

- มีประวัติเป็นแผลร้อนในอย่างน้อย 2 ครั้งต่อปี ☐ ใช่ ☐ ไม่ใช่
- ไม่มีประวัติแพ้ CBD หรือยาทาที่ใช้ในงานวิจัยนี้ ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้กำลังตั้งครรภ์หรือให้นมบุตร ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้กำลังติดเชื้อแบคทีเรีย ไวรัส หรือราในช่องปาก ☐ ใช่ ☐ ไม่ใช่
- ไม่มีอาการ/อาการแสดงของโรคระบบทางเดินอาหาร ภาวะโลหิตจาง หรือขาดสารอาหาร ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้เป็นแผลที่เกิดมาจากการกัดโดน กระแทกโดน แปรงฟันโดน หรือฟันปลอมกดทับ ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้ใช้ยากดภูมิคุ้มกันทางระบบ ยาปรับระบบภูมิคุ้มกัน หรือยารักษาสิวชนิดรับประทาน ภายในระยะเวลา 1 อาทิตย์ที่ผ่านมา ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้ใช้ยาแก้ปวดพาราเซตามอล ยาบรรเทาอาการอักเสบที่ไม่ใช่สเตียรอยด์ หรือยาทาเฉพาะที่ในช่องปาก ภายใน 48 ชั่วโมงที่ผ่านมาหรือระหว่างเข้าร่วมการวิจัย ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้ทำศัลยกรรมผ่าตัดในช่องปาก ภายในระยะเวลา 2 อาทิตย์ที่ผ่านมา ☐ ใช่ ☐ ไม่ใช่
- ไม่ได้ใส่อุปกรณ์จัดฟันหรืออุปกรณ์คงสภาพฟันที่อาจเกี่ยวข้องกับแผลในช่องปาก ☐ ใช่ ☐ ไม่ใช่

APPENDIX C

มาตรวัดความปวดด้วยสายตา (Visual Analog Scale: VAS)

ID ..... เพศ ☐ ชาย ☐ หญิง อายุ .....ปี

<u>คำชี้แจง</u> โปรดทำเครื่องหมายกากบาท (×) ลงในตำแหน่งบนเส้นที่ตรงกับความปวดในแต่ละวันของท่านมากที่สุด บันทึกข้อมูลหลังจากทายาหลังอาหารเย็นเป็นเวลา 30 นาที วันที่ 1-7

ก่อนใช้ยา: วันที่.....

วันที่ 1 (วันถัดจากวันที่มาตรวจครั้งแรก): วันที่.....

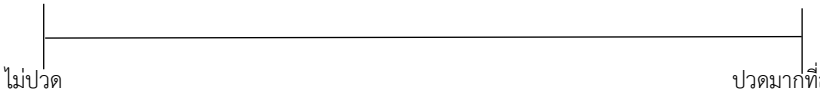
วันที่ 2: วันที่.....

วันที่ 3: วันที่.....

วันที่ 4: วันที่.....

วันที่ 5: วันที่.....

วันที่ 6: วันที่.....



วันที่ 7: วันที่.....

ระดับความพึงพอใจในตัวยา (วงกลม): 0 1 2 3 4 5 6 7 8 9 10

APPENDIX D

แบบประเมินผลกระทบของสุขภาพช่องปาก-14 ฉบับภาษาไทย

Thai Oral Health Impact Profile-14 (OHIP-14)

ID ..... เพศ ☐ ชาย ☐ หญิง อายุ .....ปี วันที่ ..... ☐ ก่อนรักษา ☐ หลังรักษา

คำชี้แจง โปรดทำเครื่องหมาย ✓ลงในช่องที่ตรงกับความคิดเห็นของท่านมากที่สุด ในช่วงที่มีแผลร้อนในภายในช่องปาก ก่อนรักษาหรือหลังรักษา

คำถาม	ไม่เคยเลย	น้อยครั้ง	บางครั้ง	บ่อย	บ่อยมาก
1. คุณมีปัญหาในการออกเสียงคำพูดเนื่องมาจากแผลร้อนในใช่หรือไม่					
2. คุณรู้สึกว่าการรับรสชาติอาหารของคุณแย่ลงเนื่องมาจากแผลร้อนในใช่หรือไม่					
3. คุณมีอาการเจ็บปวดแผลร้อนในใช่หรือไม่					
4. คุณรู้สึกไม่สบายใจเวลารับประทานอาหารเนื่องมาจากแผลร้อนในใช่หรือไม่					
5. คุณรู้สึกรำคาญแผลร้อนในใช่หรือไม่					
6. คุณรู้สึกอึดอัดจากแผลร้อนในใช่หรือไม่					
7. คุณรู้สึกไม่พอใจในการรับประทานอาหารเนื่องมาจากแผลร้อนในใช่หรือไม่					
8. คุณต้องหยุดชั่วขณะระหว่างรับประทานอาหารเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
9. คุณพบว่ามันยากที่จะผ่อนคลายเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
10. คุณรู้สึกอายเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
11. คุณรู้สึกหงุดหงิดง่ายกับผู้อื่นเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
12. คุณมีความยุ่งยากขณะทำงานเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
13. คุณรู้สึกไม่พอใจในการดำรงชีวิตประจำวันเนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					
14. คุณไม่สามารถบดเคี้ยวอาหารได้เนื่องมาจากปัญหาแผลร้อนในใช่หรือไม่					

APPENDIX E

คำแนะนำวิธีการใช้ยา

1. บ้วนปากด้วยน้ำเปล่าก่อนการทาแผลแต่ละครั้ง
2. ตักยาด้วยช้อนขนาดเล็กที่ให้ไป โดยปาดยาส่วนเกินกับขอบตลับยา ให้ยาพอดีกับช้อน
3. ใช้นิ้วป้ายยาทั้งหมดจากช้อนนำมาทาให้ทั่วบริเวณแผลร้อนใน ทาเป็นวงกลม เส้นผ่านศูนย์กลางประมาณ 1 เซนติเมตร
4. ทายาวันละ 3 ครั้ง หลังอาหารเช้า กลางวัน เย็น หรือก่อนนอน เป็นเวลา 7 วันติดต่อกัน
5. หลังทายาห้ามดื่มน้ำ รับประทานอาหาร บ้วนปากและแปรงฟันเป็นเวลาครึ่งชั่วโมง
6. บันทึกมาตรวัดความปวดด้วยสายตา (Visual Analog Scale: VAS) ทุกวัน หลังจากทายาหลังอาหารเย็นเป็นเวลา 30 นาที
7. หากเกิดการเปลี่ยนแปลงที่ผิดปกติ ไม่พึงประสงค์บริเวณที่ทายา ให้อาสาสมัครหยุดใช้ยาทันที
8. เมื่อสิ้นสุดการใช้ยา ให้อาสาสมัครนำตลับยาและช้อนมาคืน

VITA

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