



Original article

# Randomized clinical trial of the effectiveness of complementary therapies for recurrent aphthous stomatitis<sup>☆</sup>

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## ABSTRACT

**Background and objective:** Despite the high prevalence of recurrent aphthous stomatitis (RAS), its aetiology is not yet completely clear and there is no completely remedial treatment available at present. The objective of this study was to evaluate the clinical efficacy and safety of 4 treatments (silver nitrate, propolis, rhubarb and walnut) for RAS.

**Patients and method:** A randomized clinical trial was conducted with 125 patients with minor aphthae, including 25 patients per group: cauterization with silver nitrate, propolis, rhubarb extract, walnut extract and placebo.

**Results and conclusions:** No patient reported adverse effects related to the treatment received. There were significant ( $p < 0.001$ ) differences in the time elapsed until symptom resolution. The fastest treatment was silver nitrate (1.16 days), followed by the 3 alternative treatments (1.60 days with propolis, 1.84 with rhubarb and 2.00 with walnut; with no differences between them), and finally the placebo (4.64 days). The mean healing time of the lesions was statistically higher (8.96 days) for the placebo than for the 4 treatments: silver nitrate (7.32 days), propolis (6.80), rhubarb (7.72) and walnut (8.00).

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## Ensayo clínico aleatorizado sobre la efectividad de tratamientos alternativos en la estomatitis aftosa recurrente

## RESUMEN

## Palabras clave:

Estomatitis aftosa recurrente

Extracto de nogal

Extracto de ruibarbo

Nitrato de plata

Própolis

Tratamientos alternativos

**Fundamento y objetivo:** A pesar de la elevada prevalencia de la estomatitis aftosa recurrente (EAR), su etiología no está del todo aclarada y no existe un tratamiento totalmente curativo. El objetivo de este trabajo fue evaluar la eficacia clínica y la seguridad de 4 tratamientos (nitrato de plata, própolis, ruibarbo y nogal) de la EAR.

**Pacientes y método:** Se realizó un ensayo clínico aleatorizado con 125 pacientes con aftas menores, con 25 pacientes por grupo: cauterización con nitrato de plata, própolis, extracto de ruibarbo, extracto de corteza de nogal y placebo.

**Resultados y conclusiones:** Ningún paciente refirió efectos adversos relacionados con el tratamiento. Hay diferencias significativas ( $p < 0,001$ ) globales en el tiempo hasta la desaparición de los síntomas. El más rápido fue el nitrato de plata (1,16 días), después los 3 tratamientos alternativos (1,60 días con própolis, 1,84 con ruibarbo y 2,00 con nogal, sin diferencias entre ellos), y por último el placebo (4,64 días). En cuanto al tiempo medio de curación de las lesiones, fue estadísticamente mayor (8,96 días) para el placebo que para los 4 tratamientos: nitrato de plata (7,32 días), própolis (6,80), ruibarbo (7,72) y nogal (8,00).

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## Introduction

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of the oral mucosa, affecting approximately 20% of the general population.<sup>1</sup> RAS is characterized by the development of one or more painful ulcers (aphthous ulcers), covered by a white or greyish pseudomembrane and surrounded by a well-defined erythematous halo. The lesions are usually located in the non-keratinized oral mucosa, may persist for days or weeks and present recurrences after very variable remission periods.<sup>2</sup> According to the size of the lesions, three clinical forms of RAS have been described: minor aphthous ulcers, major aphthous ulcers and herpetiform aphthous ulcers.<sup>3</sup>

RAS is a disease of unknown origin, so there is no specific treatment for it. The treatment of RAS is basically aimed at minimizing symptoms and preventing recurrences. The choice of a topical and/or systemic treatment will depend on the severity of the symptoms, the size and number of lesions, as well as the frequency of recurrent episodes.<sup>1</sup>

A wide variety of therapeutic agents are currently used for the treatment of RAS. The topical treatment includes: analgesic-anti-inflammatory drugs (aminosalicylic acid, benzydamine, amlexanox, hyaluronic acid, lactic acid); local anaesthetics (lidocaine, xylocaine); topical antibiotics (tetracyclines); antiseptic agents (chlorhexidine, hexetidine, hydrogen peroxide, povidone iodine); cytoprotectors (sucralfate, carbenoxolone, carboxymethyl cellulose); chemical cauterizers (silver nitrate, sulfuric acid derivatives); antihistamines (diphenhydramine, dexchlorpheniramine); local physical treatments (laser, ultrasound); or the most frequently used, topical corticosteroids (hydrocortisone, triamcinolone, dexamethasone, clobetasol). Systemic treatment is indicated in patients without response to topical therapy, with major aphthous ulcers and with very frequent recurrences. Oral corticosteroids (prednisone), immunosuppressants (cyclosporine, cyclophosphamide, azathioprine, chloroquine) or immunomodulators (colchicine, levamisole, pentoxifylline, thalidomide)<sup>1,4–6</sup> are used.

The World Health Organization estimates that one-third of the world's population does not have regular access to modern basic medicines. In parts of Africa, Asia and Latin America, almost half of the population faces a persistent shortage of these drugs. However, as an alternative, they have traditional medicine, easily accessible and relatively inexpensive. Similarly, the use of both medicinal plants and alternative and complementary medicine is increasing in developed countries.<sup>7</sup>

Alternative therapies have also been proposed for the treatment of RAS, mainly based on the use of different medicinal plants.<sup>5,8,9</sup> Although many of these remedies are considered to be fairly safe and may be valid for the treatment of RAS, consideration should be given to the possibility of interaction with conventional medications.<sup>10,11</sup>

In Morocco, traditional medicine with remedies based on the use of medicinal plants is a cheap and affordable source for a large part of the population, especially the rural population. Thus, in this study, several natural therapeutic agents that are easily accessible for patients in this geographic environment in North Africa are analyzed as an alternative to conventional pharmacological treatments for RAS.<sup>12</sup>

The objective of this study was to evaluate the clinical efficacy and safety of 4 therapeutic options (silver nitrate, propolis, rhubarb extract and walnut extract) against a placebo for the treatment of RAS.

## Patients and methods

A randomized clinical trial was conducted, following the CONSORT guidelines,<sup>13</sup> with 125 patients who came to receive dental

care for canker sores to a dental office in Tetuan (Morocco) in the period between January 2013 and June 2016. *A priori*, patients who came due to a painful lesion in the oral mucosa and, on the same day, after examination by the dentist, proved to be a canker sore; that is, trauma injuries such as burns, self-cuts, etc. were excluded. Inclusion criteria included not being a regular drinker/smoker, patients with known alterations in the blood count and those with systemic diseases related to the development of oral ulcers. The study protocol was approved by the Human Research Ethics Committee of the Faculty of Dentistry of the University of Granada (Ref. FOD-UGR-012/2013). Patients were provided with the necessary information about the purposes of this study in order to obtain their consent.

The calculation of the sample size was performed to compare the quantitative effect variables (days of symptom/lesion remission) with a power of 80%, an alpha error of 5% and to detect a standardized difference of 0.8, substantial according to the Cohen scale.<sup>14</sup> Twenty-five patients would be needed in each group, according to SamplePower 2.0 (SPSS Inc., Chicago, IL, USA).

Of the 173 patients with aphthous ulcers treated sequentially in the clinic during the 3 years of the study, the 125 patients included (who met the inclusion criteria and who agreed to participate in the study) (Fig. 1) were enumerated from 1 to 125 depending on their order of entry into the study. With the help of a computer program, patients were randomly distributed in 5 groups of 25, one for each therapeutic option, including placebo. The treatments were administered by a dental hygienist, except silver nitrate, which was applied by the doctor. All patients were diagnosed and treated on the first day of their lesion development.

The agents used were the following:

- a) Silver nitrate (Argenpal<sup>®</sup>, B. Braun Medical, SA, Barcelona, Spain). It is administered in the form of 50 mg bars for direct application on lesions. The administration of this drug was performed by the doctor in the dental office, in a single session. Five minutes before applying the caustic agent the lesions were anesthetized with a spray containing 10% lidocaine (Xilonibsa<sup>®</sup>, Aerosol 10%, Barcelona, Spain). Immediately prior to the use of silver nitrate, to prevent burns in the healthy tissue surrounding the lesion, the perilesional area was protected with petroleum jelly. After application, the patient was instructed to rinse thoroughly with water.
- b) 18% propolis administered in aerosol form (Oropropolis Spray Buccal<sup>®</sup>, Laboratoire Pharmasoft, Fez, Morocco).
- c) 5% rhubarb extract (*Rheum palmatum*) administered as a solution with an applicator brush (Souakine Soluté<sup>®</sup>, Cosmetique Medicale, Rabat, Morocco).
- d) 5% extract of walnut bark (*Juglans regia*), which is administered as a solution (Pyravex Soluté<sup>®</sup>, Laboratoires Norgine Pharma, Casablanca, Morocco).
- e) Finally, the placebo is composed of flavoured distilled water administered as an aerosol. In the treatments of propolis, rhubarb, walnut, or placebo, the patient was instructed to apply/spray 3 times a day, and was asked to avoid eating or drinking after the administration for as long as possible to optimize its permanence and action on the lesion.

In addition to the treatment applied, data were collected on each patient's age, sex, number of lesions per episode, morphology and location, recurrence rate (number of episodes/year), possible treatment adverse effects (bad taste, burning in the application site, allergy to some component, interaction with other drugs, etc.) and the time to remission (in days) of both symptomatology and lesions after starting treatment.

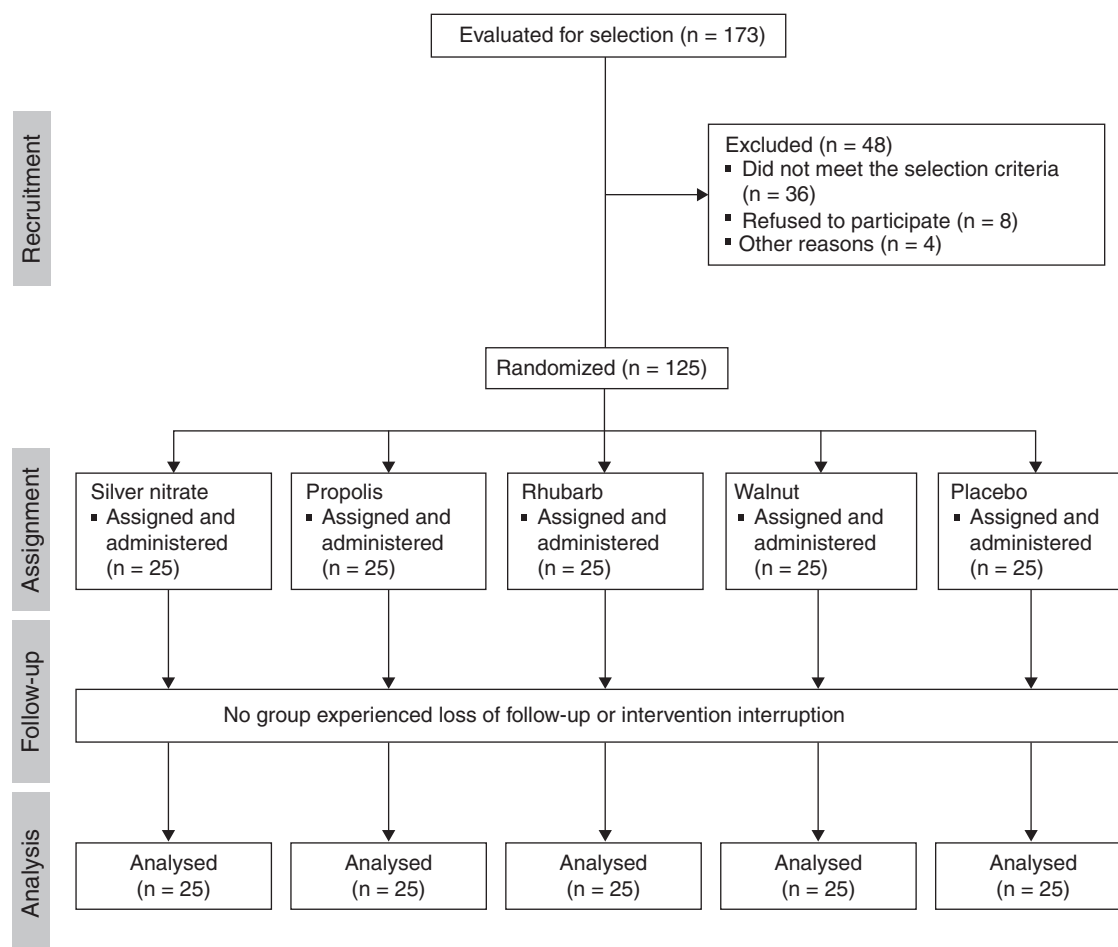


Fig. 1. Flow chart showing phase-progress of the randomized clinical trial.

The treatments have different administration vehicles (they are marketed products) and, therefore, the study is not blind to the patient, except for the placebo group, as it was indicated that it was an additional treatment. The time to symptom remission was assessed by the physician through daily telephone follow-up, advising the patient to go to the clinic when the symptoms had ceased, allowing the clinician to verify the resolution of the lesions. The clinician was blind to the treatment received, except in the case of the resolution of lesions through silver nitrate. No patient discontinued treatment.

Data were processed using the statistical software IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA), with the methods specified at the bottom of each table of results. A value of  $p < 0.05$  was considered a minimum level of significance. The expert who performed the analysis was blind to the group assigned to each patient.

## Results

Table 1 shows the description of the patients at baseline. The mean age  $\pm$  standard deviation of the 125 patients was  $33 \pm 12$  years, 46 men and 79 women. The majority (75.2%) had a single lesion, predominating a rounded morphology (54.4%). The most frequent sites were the tongue (28.8%) and the lower labial mucosa (25.6%). On average, there were 3.11 episodes/year. None of these variables showed statistically significant differences according to group. Other baseline data not shown in Table 1 are as follows: when comparing age with some clinical parameters of the study, a higher mean age was observed in patients with

irregular morphology lesions ( $43 \pm 7$  years) compared to those with rounded ( $33 \pm 13$  years) or oval morphology ( $31 \pm 12$  years) ( $p < 0.001$ , with ANOVA). Comparison of age with the rest of the parameters (number of lesions, lesion site, annual recurrence rate, disappearance of symptoms and/or lesions) was not statistically significant.

Table 2 shows time to remission (in days) regarding symptomatology and lesions. Significant differences were observed ( $p < 0.001$ ) over time until the disappearance of symptoms. The fastest was silver nitrate (1.16 days, 95% CI 1.01–1.31) (1.60 days with propolis, 1.84 with rhubarb and 2.00 with walnut, with no differences between them), and finally, placebo (4.64 days). As for the mean time to lesion healing, it was statistically higher (8.96 days) for placebo than for the 4 treatments: silver nitrate (7.32 days), propolis (6.80), rhubarb (7.72) and walnut (8.00). In most patients treated with silver nitrate, the symptoms disappeared after one day; most patients treated with propolis, rhubarb extract or walnut extract, after 2 days; and in most of those treated with placebo, the symptoms disappeared after 5 days. Finally, although not shown in the tables, no adverse effects related to the different treatments applied were observed during follow-up.

## Discussion

### Validity of the study

This study presents some limitations derived from its design, but we believe that they do not compromise its validity. In relation to internal validity, the acceptance rate (only 8 patients declined

**Table 1**  
Baseline description of patients with recurrent aphthous stomatitis (n = 125).

Variable	All (n = 125)	Group					Overall p-value
		Silver nitrate (n = 25)	Propolis (n = 25)	Rhubarb (n = 25)	Walnut (n = 25)	Placebo (n = 25)	
<i>Age (years)</i>							
Range	8–56	8–51	11–56	12–56	13–56	12–54	
$\bar{x} \pm SD$	33 $\pm$ 12	33 $\pm$ 11	31 $\pm$ 14	34 $\pm$ 13	36 $\pm$ 13	30 $\pm$ 11	0.559 <sup>a</sup>
<i>Sex, n (%)</i>							
Male	46 (36.8)	8 (32.0)	8 (32.0)	10 (40.0)	9 (36.0)	11 (44.0)	
Female	79 (63.2)	17 (68.0)	17 (68.0)	15 (60.0)	16 (64.0)	14 (56.0)	0.883 <sup>b</sup>
<i>No. of lesions, n (%)</i>							
1	94 (75.2)	19 (76.0)	17 (68.0)	22 (88.0)	17 (68.0)	19 (76.0)	
2	26 (20.8)	6 (24.0)	6 (24.0)	1 (4.0)	7 (28.0)	6 (24.0)	
3	5 (4.0)	–	2 (8.0)	2 (8.0)	1 (4.0)	–	
$\bar{x} \pm SD$	1.29 $\pm$ 0.54	1.24 $\pm$ 0.44	1.40 $\pm$ 0.65	1.20 $\pm$ 0.58	1.36 $\pm$ 0.57	1.24 $\pm$ 0.44	0.630 <sup>a</sup>
<i>Morphology of lesions, n (%)</i>							
Rounded	68 (54.4)	13 (52.0)	14 (56.0)	15 (60.0)	13 (52.0)	13 (52.0)	
Oval	45 (36.0)	9 (36.0)	9 (36.0)	6 (24.0)	11 (44.0)	10 (40.0)	
Irregular	12 (9.6)	3 (12.0)	2 (8.0)	4 (16.0)	1 (4.0)	2 (8.0)	0.861 <sup>b</sup>
<i>Location of lesions, n (%)</i>							
Tongue	36 (28.8)	8 (32.0)	4 (16.0)	9 (36.0)	8 (32.0)	7 (28.0)	
Lower lip mucosa	32 (25.6)	6 (24.0)	7 (28.0)	6 (24.0)	4 (16.0)	9 (36.0)	
Upper lip mucosa	13 (10.4)	2 (8.0)	3 (12.0)	2 (8.0)	2 (8.0)	4 (16.0)	
Buccal mucosa	9 (7.2)	1 (4.0)	2 (8.0)	4 (16.0)	1 (4.0)	1 (4.0)	
Soft palate	8 (6.4)	2 (8.0)	1 (4.0)	1 (4.0)	3 (12.0)	1 (4.0)	
Several	27 (21.6)	6 (24.0)	8 (32.0)	3 (12.0)	7 (28.0)	3 (12.0)	0.435 <sup>c</sup>
<i>Annual recurrence rate, n (%)</i>							
Once a year	3 (2.4)	1	1 (4.0)	1 (4.0)	–	1 (4.0)	
2 times/year	37 (29.6)	7 (28.0)	6 (24.0)	8 (32.0)	7 (28.0)	9 (36.0)	
3 times/year	49 (39.2)	10 (40.0)	8 (32.0)	10 (40.0)	11 (44.0)	10 (40.0)	
4 times/year	19 (15.2)	4 (16.0)	4 (16.0)	4 (16.0)	4 (16.0)	3 (12.0)	
5 times/year	13 (10.4)	4 (16.0)	5 (20.0)	–	2 (8.0)	2 (8.0)	
6 times/year	4 (3.2)	–	1 (4.0)	2 (8.0)	1 (4.0)	–	
$\bar{x} \pm SD$	3.11 $\pm$ 1.12	3.20 $\pm$ 1.04	3.36 $\pm$ 1.29	3.00 $\pm$ 1.19	3.16 $\pm$ 1.07	2.84 $\pm$ 0.99	0.535 <sup>a</sup>

 $\bar{x} \pm SD$ : media  $\pm$  standard deviation.<sup>a</sup> ANOVA.<sup>b</sup> Chi squared.<sup>c</sup> Chi square after collapsing into 3 categories: tongue, labial mucosa and the rest.**Table 2**  
Time (days) until disappearance of recurrent aphthous stomatitis symptoms and lesions (n = 125).

Until the disappearance of:	Group					Comparison	
	Silver nitrate [A] (n = 25)	Propolis [B] (n = 25)	Rhubarb [C] (n = 25)	Walnut [D] (n = 25)	Placebo [E] (n = 25)	Overall p-value <sup>a</sup>	In pairs <sup>b</sup>
<i>Symptoms, n (%)</i>							
One day	21 (84.0)	10 (40.0)	8 (32.0)	4 (16.0)	–		
2 days	4 (16.0)	15 (60.0)	13 (52.0)	17 (68.0)	–		
3 days	–	–	4 (16.0)	4 (16.0)	–		
4 days	–	–	–	–	10 (40.0)		
5 days	–	–	–	–	14 (56.0)		
6 days	–	–	–	–	1 (4.0)		
$\bar{x} \pm SD$	1.16 $\pm$ 0.37	1.60 $\pm$ 0.50	1.84 $\pm$ 0.69	2.00 $\pm$ 0.58	4.64 $\pm$ 0.57	<0.001	A $\neq$ BCD $\neq$ E
95% CI	1.01–1.31	1.39–1.81	1.56–2.12	1.76–2.24	4.41–4.87		
<i>Lesions, n (%)</i>							
6 days	6 (24.0)	9 (36.0)	2 (8.0)	1 (4.0)	–		
7 days	7 (28.0)	12 (48.0)	9 (36.0)	4 (16.0)	–		
8 days	11 (44.0)	4 (16.0)	11 (44.0)	17 (68.0)	9 (36.0)		
9 days	–	–	–	–	9 (36.0)		
10 days	1 (4.0)	–	3 (12.0)	3 (12.0)	6 (24.0)		
11 days	–	–	–	–	1 (4.0)		
$\bar{x} \pm SD$	7.32 $\pm$ 0.99	6.80 $\pm$ 0.71	7.72 $\pm$ 1.06	8.00 $\pm$ 0.91	8.96 $\pm$ 0.89	<0.001	ABCD $\neq$ E, B $\neq$ CD
95% CI	6.91–7.73	6.51–7.09	7.28–8.16	7.62–8.38	8.59–9.33		

95% CI: 95% confidence interval;  $\bar{x} \pm SD$ : mean  $\pm$  standard deviation.The “ $\neq$ ” symbol refers to a statistically significant comparison ( $p < 0.05$ ).<sup>a</sup> ANOVA.<sup>b</sup> With Bonferroni method after performing 10 comparisons in pairs.

to participate) is high. On the other hand, although blinding of the patient was not possible, since treatments were already being marketed and were all different, the study was designed to be observer-blind regarding the variable “disappearance of symptoms”, and partially (not possible with silver nitrate) regarding the variable “disappearance of lesions”. Regarding external

validity, note that these are patients who require care by the dentist on the same day. It could reasonably be argued that these patients are more likely to require dental care or more painful aphthous ulcers. Some data lead us to believe that our patients requiring dental care would be similar to those that do not require dental care. For example, in this study, patients older than 40 years of

age had irregular morphology and localized lesions, especially in the soft palate. These data coincide with those published in other studies,<sup>1,15</sup> which indicate a direct relationship between age and RAS lesions with irregular morphology of the lesions and their preference for the soft palate and tonsillar pillars. Finally, a conservative attitude would lead us to consider that the conclusions of this study, in relation to patients not requiring dental care for their aphthous ulcers, should be taken with caution.

### Therapeutic options

Many therapeutic options have been proposed for the treatment of RAS, although, so far, none have shown to result in complete remission.<sup>1</sup> Many of these treatments are used without research that demonstrate their specific therapeutic usefulness in the treatment of RAS and can have important side effects.<sup>5</sup> For this reason, alternative therapies based on natural products are sought, especially among medicinal herbs, which have fewer adverse effects and are more accessible to the population due to their lower cost.<sup>16</sup>

Below, our findings are compared with those of other authors. The differences between the results published in the different studies regarding the disappearance of symptoms and/or lesions might be determined by the different sample sizes, their sociodemographic characteristics, different forms of drug administration, different concentrations and excipients, diseases treated and symptomatology evaluation subjectivity. Therefore, caution is also required in the interpretation of the findings.

### Disappearance of symptoms

In the present study, the symptoms had disappeared in 84% of the patients treated with silver nitrate one day after the cauterization of the lesions, being the most effective treatment regarding the disappearance of symptoms. Cauterization destroys nerve terminals, reducing pain. Our results coincide with those of Alidaee et al.,<sup>17</sup> who observed a relief of symptoms one day after cauterization in 70% of their patients treated with silver nitrate. Similarly, Soyulu Özler,<sup>18</sup> in a comparative study between silver nitrate and placebo, found a significant reduction of pain on the first day after treatment with silver nitrate. Other caustic agents based on sulfonated phenolics (Debacterol<sup>®</sup>, HybenX<sup>®</sup>) have been used for the treatment of RAS. Porter et al.<sup>19</sup> observed a significant decrease in symptomatology 2 days after treatment. Rhodus and Bereuter<sup>20</sup> found that most of the patients (over 70%) experienced symptom relief slightly later, 3 days after treatment.

Propolis is a resinous compound rich in flavonoids obtained by bees and widely used since ancient times for its anti-inflammatory, antiseptic and fungicidal properties. In the present study, the symptoms were relieved after 2 days in all patients treated with propolis (100%). This data agrees with some published works,<sup>21,22</sup> which coincide in indicating that symptomatology disappeared 2 days after the start of treatment. Bellón Leyva and Calzadilla Mesa<sup>23</sup> observed symptomatology relief within 3 days in most of their patients treated with 5% propolis. In this sense, Vynograd et al.<sup>24</sup> conducted a comparative study of the treatment of ulcerative genital herpes lesions with propolis, acyclovir and a placebo, observing that pain had disappeared 3 days later in 90% of the patients treated with propolis, being this treatment the most effective of the 3 administered.

Rhubarb extract is one of the oldest and best known medicinal herbs of traditional Chinese medicine. It is used for the treatment of constipation, gastrointestinal bleeding and ulcers that appear on mucous membranes, including the oral mucosa.<sup>25</sup> In this study, symptoms had ceased in 84% of the patients treated with rhubarb extract 2 days later. However, the results found by other studies differ from ours. Khademi et al.<sup>26</sup> observed an average duration

of symptomatology of  $6.10 \pm 0.29$  days in patients treated with rhubarb extract. Saller et al.<sup>27</sup> conducted a study in 145 patients with recurrent herpes labialis who were treated with a placebo, rhubarb extract and acyclovir, finding that the rhubarb extract was the one that had the best behaviour in the remission of pain, 2 days after treatment.

Walnut bark extract has traditionally been used for the treatment of ulcers, burns and warts.<sup>28</sup> In our study, in 84% of the patients treated with walnut extract the symptoms had returned within 2 days. Paulo Filho et al.<sup>29</sup> compared the treatment with *Eupatorium laevigatum*, which shares many its components with *J. regia* extract, such as juglones or flavonoids, to the treatment with 0.1% triamcinolone acetonide in Orabase in patients with RAS. 2 days after the start of treatment, they found remission of the symptomatology in 70% of patients treated with the paste and in 33.3% of those treated with triamcinolone acetonide.

### Disappearance of lesions

In the present study, in 52% of the patients treated with silver nitrate, the lesions had been resolved after 7 days and practically all of them (96%) after 8 days. The results observed by other authors who also used chemical cauterization for the treatment of RAS differ somewhat from ours. Alidaee et al.<sup>17</sup> observed that in 83% of their patients treated with silver nitrate the lesions healed after 7 days. Soyulu Özler<sup>18</sup> found that 60% of patients treated with silver nitrate had their lesions resolved after 7 days. Porter et al.<sup>19</sup> found that the lesions had disappeared after 8 days in 50% of patients treated with HybenX<sup>®</sup> caustic agent. The best result is that of the Rhodus and Bereuter study,<sup>20</sup> with 80% of patients in whom the lesions healed after 6 days.

In the present study, among patients treated with propolis, the lesions healed after 6 days in 36% of the cases and after 7 days in 84%. Compared to our results, Quintana Díaz<sup>22</sup> found 56% of patients in whom the lesions healed 7 days after the application of propolis. Also, Lotufo et al.,<sup>16</sup> in a study of 40 patients with minor aphthous ulcers treated with a hydroalcoholic solution of 10% propolis and other treatments, showed a decrease in the duration of the episodes to 7 or fewer days in 38% of their cases treated with propolis, a figure lower than 48% of the present study. These patients also had better results in terms of the duration of the episodes, the number of lesions and the annual recurrence rate. Other studies have demonstrated the efficacy of propolis in reducing recurrences.<sup>30</sup> Vynograd et al.,<sup>24</sup> in a comparative study of 3 treatments, observed that, at 7 days, lesions healed in 33.3% of the subjects treated with propolis, with this therapy being the one with which the lesions healed quicker.

In this study, the percentage of patients treated with rhubarb extract whose lesions had disappeared after 7 days was 44%. The mean healing time of the lesions of patients treated with rhubarb extract was  $7.72 \pm 1.06$  days. Khademi et al.<sup>26</sup> found a lower mean healing time for RAS lesions treated with rhubarb extract ( $6.80 \pm 0.27$  days).

In our study, the lesions had healed after 7 days only in 20% of the patients treated with walnut extract, and in 12% of the cases the lesions disappeared within 10 days. In Brazil, Paulo Filho et al.<sup>29</sup> treated their RAS patients with *E. laevigatum*, a plant that shares many of its components with *J. regia*, finding that disappearance of lesions after 5 days of treatment occurred in 40% of patients, a figure much higher than the one observed by us.

### Adverse effects

None of the patients included in this study had adverse effects related to any of the 5 treatments applied, a fact that coincides with that published in the medical literature.<sup>5,8–12,16</sup>

In conclusion, therapies for RAS, conventional or silver nitrate, and alternatives or propolis, rhubarb and walnut, were effective (compared to placebo) for the treatment of aphthous ulcers. As for the disappearance of symptoms, silver nitrate was superior, but has a similar efficacy in terms of disappearance of lesions. Finally, no patient reported adverse effects related to the different treatments.

### Conflict of interests

The authors declare no conflict of interest.

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