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Comparative effectiveness of alternative medication in minor aphtous stomatitis

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Abstract

Minor aphthous stomatitis is the most common oral mucosal disease and affects almost 20% of the population. Currently, there is an increasing interest across the globe in alternative therapies that use natural products versus synthetic agents.

The objectives of the study were represented by the identification of the required time for healing, the pain intensity reduction, the recurrence of affection and the satisfaction of patients with minor aphthous stomatitis treated with Propolis tincture spray, Aloe Vera tincture, and sodium bicarbonate solution. The study was a randomized and double-blinded clinical trial, conducted on 100 patients divided in four groups, which were diagnosed with minor aphthous stomatitis. At the beginning and during the study, patients were daily specifically questioned, examined and monitored to establish the healing stage of aphthous lesions (including erythema), the pain intensity reduction, impress regarding the taste and easiness in application of the used substances, and the apparition/existence of any adverse event. Achieved results were compared.

This study demonstrated that the therapy with Propolis tincture and Aloe Vera tincture is a rapid, low cost and easy-to-apply method, and yielded good results in treating minor AS.

Keywords: minor aphthous stomatitis, Propolis tincture, Aloe Vera tincture, Sodium bicarbonate solution, healing.

Introduction

Common superficial oral lesions include recurrent aphthous stomatitis, candidiasis, recurrent labial herpes, erythema migrants, hairy tongue, and lichen planus [1,2].

The recognition and the classification of oral lesions have a considerable significance in the process of diagnosis. The correct diagnosis is accomplished through the knowledge of the various lesions, a thorough history and a comprehensive clinical oral examination for the precise diagnosis in the process of differentiating between the specific conditions, management, as well as counselling [3-5]. Ulceration due to aphthous stomatitis (AS) represents the most common oral mucosal inflammatory disease, most frequently starts during the second decade of life, affects about 20% of the population and has a female predilection [6,7]. The etiology of AS is varied and is due to the perturbation of the oral ecosystem. The oral environment is unique, and is able to induce reactivity of products from the prosthetic restoration materials. The biological reactivity of dental materials in the oral cavity can induce reactions of the oral tissues against the bacteria's adhesion, reactions to the mechanical irritation, to the direct toxic effect, and to the allergens [8]. Habitually, AS lesions begin with prodromal burning sensation, 2-48 hours before the appearance of an ulceration. AS debut is painful. It has the appearance of a rounded ulceration masked by fibrin, with erythematous margins, located especially on the nonkeratinized oral mucosa [9,10].

The described clinical types of aphthous stomatitis are:

- Minor-type (Mikulicz type) of AS, which represents 80–90% of all aphthous ulcer, usually is solitary, had 2-3 mm diameter, and heals spontaneously in two weeks;
- Major-type (Sutton type) represents about 10% of of AS, usually have 1–3 cm in size, are profound indurated, and lasts between 10 days-6 weeks, or more; about 64% of these ulcers heal with scarring;
- Herpetiform aphthae are grouped, multiple, very small ulcerative lesions (more than 100 ulcer lesions), with 1-2 mm diameter,

extremely painful, and it takes more than 15 days to completely heal; affects the keratinized oral mucosa and more than 30% of lesions heal with scarring [6,9,11].

Medical products which are not considered part of conventional care, represent the alternative medicine [12]. Currently, there is an increasing interest across the globe in alternative therapies that use natural products, as opposed to synthetic agents.

Propolis is a resinous mixture composed of mixing beeswax, saliva, sap flows, and various botanical products in the surrounding area [13-15]. For a long period, it has been used as a remedy for various types of ailments, and is thought to have anti-inflammatory, anti-bacterial, and anti-viral properties, because its very high levels of bioflavonoids and other bioactive compounds, which stimulate, rejuvenate the body and provide powerful support to the immune system [16,17]. Propolis tincture has a complex composition and has analgesic, antifungal, bactericidal, antiviral effects that stimulate regeneration processes [18]. ApiLand® Propolis tincture (Romania) contains 95% purified Propolis and can also be found in spray form [19].

Aloe Vera is the most effective species according to the latest medical research in the field, from about 400 existing species. Aloe Vera contains over 150 bioactive substances, with anti-inflammatory, analgesic, antiseptic and cicatrizing effects [20]. External effects of Aloe Vera Tincture are represented by their anti-inflammatory, analgesic, antiseptic and cicatrisation properties. Aloe tincture provides a special skin care and helps alleviate pain and it can be used on sprains, eczema and wounds. [21-23]. Dacia Plant® Aloe Vera Tincture 50 ml (Romania) is a hydroalcoholic solution, made by cold preparation of fresh Aloe Vera leaves [24].

Sodium bicarbonate, a white solid crystalline substance, is a salt composed of sodium ions and bicarbonate ions. Sodium bicarbonate can be administered to raise the alkalinity. It has weak disinfectant properties, and can be an effective antifungal [25-27].

The products used in this study are presented in figure 1.

Figure 1. Used products in study: A. Propolis tincture spray (ApiLand®, Romania); B. Aloe Vera Tincture (Dacia Plant®, Romania); C. Sodium bicarbonate

The aim of this study was to evaluate the healing effects of Propolis tincture, Aloe Vera tincture and sodium bicarbonate solution on minor aphthous stomatitis.

Material and methods

The study was performed according to ethical principles and good clinical practice. Subjects were invited to participate in this clinical trial and all participants signed written informed consent prior to the beginning of this study. The study was a randomized and double-blinded clinical trial.

The objectives of the study were represented by the identification of the required time for healing, the pain intensity reduction, the recurrence of affection and the satisfaction of patients with minor recurrent

aphthous stomatitis treated with Propolis tincture spray (ApiLand®, Romania), Aloe Vera tincture (Dacia Plant®, Romania) and sodium bicarbonate solution.

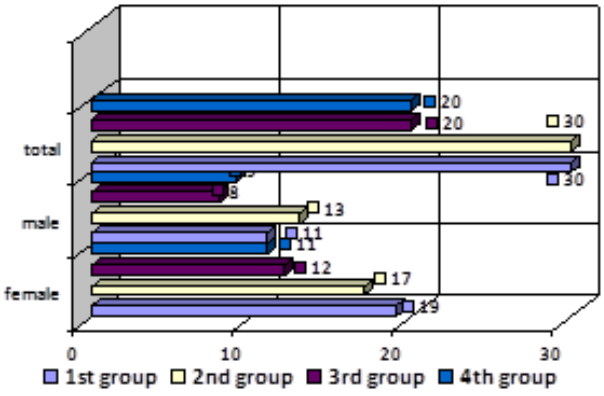
The clinical trial was conducted in 111 patients diagnosed with minor aphthous stomatitis. During the study, 9 subjects withdrew voluntarily and 2 subjects were excluded from the study, for lack of cooperation. The study was conducted during the period of 2015-2018 at the University of Medicine and Pharmacy of Tîrgu Mureş and Titu Maiorescu University of Bucharest Dental clinics. The reason for presenting of patients was the recurrence of aphthous stomatitis. The inclusion criteria of patients were as follows: an age range of 12-29 years; having at the presentation in the dental office one aphthous stomatitis lesion, measuring under 1 cm in diameter, well-demarcated, and in accessible area of the mouth, less than 48 hours' from the ulcer apparition; with at least quarterly or biannual eruptive episodes; without other established acute or chronic diseases; systemic nonsteroidal anti-inflammatory, and immunomodulatory treatments within 1 month prior to the study.

The mean (±SD) of patients' age was 20.5 ± 8.5 years in the included patients in the study.

Eligible patients (100) were randomized in four groups: the group of patients who benefited from Propolis spray tincture therapy (1st group, n=30, 19 female and 11 male), Aloe Vera tincture in solution therapy (2nd group, n=30, 17 female and 13 male), sodium bicarbonate solution therapy (3rd group, n=20, 12 female and 8 male) and the control group with applications in the area of aphthous stomatitis lesion of distilled water (4th group, n=20, 11 female and 9 male).

The distribution of the patients in groups, after gender and the products used, is presented in graph 1.

Graph 1. The distribution of the patients in groups, after gender and the products used



Only the head of Oral Pathology Department of Titu Maiorescu University of Bucharest knew the contents of the vials. The vials were marked only with a single digit code (1, 2, 3, and 4).

Application of substances was performed 4 daily, for 4 days, as following:

- 1st group of patients: ApiLand spray with 95% purified Propolis tincture was applied by spraying 4 times/day, by 2-3 puffs in the affected area;
- 2nd group of patients: Dacia Plant Aloe Vera tincture solution was used 4 times daily by rinsing the oral cavity with one teaspoon of tincture diluted in 100 ml of water;
- 3rd group of patients: Sodium bicarbonate solution, was utilized by rinsing 4 times daily the oral cavity with one teaspoon of powder in 100 ml of waters;
- 4th group of patients: Distilled water, by local application with micro brush applicators.

The patients were asked to retain from eating and drinking for 30 min after application of substances. Oral hygiene of each patient was performed twice daily with Colgate Total ™ toothpaste and Colgate 360° toothbrush (made available to patients by researchers), 30 minutes

before the application of used substances in study. No other substances or medications were permitted during the study.

At the beginning and during the study, patients were daily specifically questioned, examined and monitored, to establish the healing stage of aphthous lesions (pain intensity and erythema), impress regarding the taste and easiness in application of the used substances, and the apparition/existence of any adverse event.

All the patients were monitored for 1 year.

First outcome was related with the assessment of efficacy of used substances in study, by evaluating the level of pain and erythema, daily for 6 days and compared to baseline. Patients classified the severity of pain by using visual analogue scale (VAS), on a 10 cm line, marked at one end with "no soreness" and the other end with "worst possible soreness". The level of erythema was evaluated on a four-point scale ranging from 0 to 3 (0 = no erythema; 1 = light red/pink; 2 = red but not dark in color; 4 = dark in color).

The second outcome was in reference with the overall assessment of the used substance on three-point description scale (poor, moderate, and good). The third outcome was to establish the recurrence rate of aphthous stomatitis in a period of 1 year.

At the end of the study, the results were unblinded.

Results and discussions

At base line, no significant differences were founded between the pain and the erythema level in all four groups.

The pain intensity reduction after the determination of VAS score is presented in table 1.

Table 1. Reported pain intensity according to used Visual Analogue Scale (VAS)

Group	VAS	Base line	2nd day	3th day	4th day	5th day	6th day	7th day
ApiLand® Propolis tincture spray (30 patients)	0-1	-	-	3p = 10%	5p = 16.66%	11p = 36.66%	20p = 66.66%	27p = 90%
	2-3	-	6p = 20%	4p = 13.33%	6p = 20%	10p = 33.33%	7p = 23.33%	3p = 10%
	4-5	4p = 13.33%	7p = 23.33%	8p = 26.66%	9p = 30%	9p = 30%	3p = 10%	-
	6-7	11p = 36.66%	8p = 26.66%	9p = 30%	10p = 33.33%	-	-	-
	8-9	10p = 33.33%	7p = 23.33%	6p = 20%	-	-	-	-
	10	5p = 16.66%	2p = 6.66%	-	-	-	-	-
Dacia Plant® Aloe Vera tincture (30 patients	0-1	-	-	1p = 3.33%	3p = 10%	10p = 33.33%	18p = 60%	25p = 83.33%
	2-3	-	4p = 13.33%	3p = 10%	5p = 16.66%	9p = 30%	8p = 26.66%	5p = 16.66%
	4-5	4p = 13.33%	6p = 20%	5p = 16.66%	10p = 33.33%	11p = 36.66%	4p = 13.33%	-
	6-7	11p = 36.66%	7p = 23.33%	13p = 43.33%	12p = 40%	-	-	-
	8-9	11p = 36.66%	10p = 33.33%	8p = 26.66%	-	-	-	-
	10	4p = 13.33%	3p = 10%	-	-	-	-	-
Sodium bicarbonate solution (20 patients)	0-1	-	-	-	1p = 5%	5p = 25%	8p = 40%	12p = 60%
	2-3	-	2p= 10%	3p = 15%	2p = 10%	6p = 30%	6p = 30%	7p = 35%
	4-5	3p = 15%	4p = 20%	3p = 15%	8p = 40%	7p =35%	6p = 30%	1p = 5%
	6-7	7p = 35%	4p = 20%	9p = 45%	9p = 45%	2p = 10%	-	-
	8-9	7p = 35%	8p = 40%	5p = 25%	-	-	-	-
	10	3p = 15%	2p =10%	-	-	-	-	-
Distilled water (20 patients)	0-1	-	-	-	-	2p = 10%	6p = 30%	9p =45%
	2-3	-	1p = 5%	1p = 5%	2p = 10%	6p = 30%	8p = 40%	9p = 45%
	4-5	3p = 15%	4p = 20%	3p = 15%	8p = 40%	11p = 55%	6p = 30%	2p = 10%
	6-7	7p = 35%	5p = 25%	8p = 40%	8p = 40%	1p = 5%	-	-
	8-9	7p = 35%	7p = 35%	7p = 35%	2p = 10%	-	-	-
	10	3p = 15%	3p =15%	1p = 5%	-	-	-	-

The period of the pain reduction started with the first application of products with active substances (groups 1, 2, and 3). We founded group differences at the later visits (day 4, 5, 6, and 7), compared with the base line (at patients presentation) and at comparison between groups. Recorded VAS scores showed that the pain intensity was the lowest in the first group of patients (who were treated with ApiLand® spray with 95% purified Propolis tincture), followed by the second group of patients (treated with Dacia Plant® Aloe Vera

tincture solution) and the third group of patients (treated with Sodium bicarbonate solution). The scores in the fourth group of patients (distilled water) at all 7 sessions showed that painful intensity was the highest of the four groups surveyed. Studying the VAS scores recorded in 7 assessments, we found that there were no significant differences in VAS scores in the first and second patient groups. In the third and fourth group of patients, we found that there were differences in favor of the third group of patients.

The erythema levels in the groups is presented in table 2.

Table 2. Level of erythema in treated and placebo groups

Product	Level of erythema	Level of lesions erythema						
		Base line	2nd day	3th day	4th day	5th day	6th day	7th day
ApiLand® Propolis tincture spray (30 patients)	No erythema	-	-	-	21p=70%	28p=93.33%	30p=100%	30p=100%
	Light red/pink	-	-	8p=26.66%	6p=20%	2p=6.66%	-	-
	Red but not dark	11p=36.663%	11p=36.663%	11p=36.66%	2p=6.66%	-	-	-
	Dark in color	19p=63.33%	19p=63.33%	11p=36.66%	1p=3.33%	-	-	-
Dacia Plant® Aloe Vera tincture (30 patients)	No erythema	-	-	-	19p=63.33%	27p=90%	28p=93.33%	30p=100%
	Light red/pink	-	-	7p=23.33%	7p=23.33%	2p=6.66%	2p=6.66%	-
	Red but not dark	10p=33.33%	10p=33.33%	11p=36.66%	2p=6.66%	1p=3.33%	-	-
	Dark in color	20p=66.66%	20p=66.66%	12p=40%	2p=6.66%	-	-	-
Sodium bicarbonate solution (20 patients)	No erythema	-	-	-	10p=50%	10p=50%	12p=60%	17p=85%
	Light red/pink	-	-	5p=25%	4p=20%	9p=45%	7p=35%	3p=15%
	Red but not dark	7p=35%	7p=35%	7p=35%	4=20%	1p=5%6	1p=5%	-
	Dark in color	13p=65%	13p=65%	8p=40%	2p=10%	-	-	-
Distilled water (20 patients)	No erythema	-	-	-	7p=35%	8p=40%	9p=45%	16p=80%
	Light red/pink	-	-	3p=15%	4p=20%	6p=30%	7p=35%	3p=15%
	Red but not dark	7p=35%	7p=35%	6p=30%	5p=25%	4p=20%	3p=15%	1p=5%
	Dark in color	13p=65%	13p=65%	11p=55%	4p=20%	2p=10%	1p=5%	-

At base line, no significant differences were founded in groups. In all ulterior assessments, the first and second groups of patients (treated with Propolis and Aloe Vera tinctures) presented the lowest level of erythema. There were no significant differences in the level erythema in the first and second patients group. The highest erythema level was in the fourth group of patients (distilled water).

The second outcome was in reference with the overall assessment of the used substance. The distribution of scores in overall assessment of the treatment is presented in table 3. It is visible that in the "good" score, the best percentages were in the first group/Propolis (90%) and second group/Aloe Vera (86.66%), unlike the third group/Sodium Bicarbonate (50%) and fourth group/Distilled water (10%).

AS disease recurrence after 1 year of monitoring was the third outcome of this study. After one year of monitoring of the patients at every three months, is visible that the best results are in first group/Propolis tincture, with a total of 13.33% recurrences, and in second group/Aloe Vera (16.66% recurrences) in comparison with the results of fourth group/Distilled water, where appeared 75% of recurrence of AS (table 4).

Table 3. Distribution of scores in overall assessment of the treatment

Score	Group 1, ApiLand® Propolis tincture spray (30 patients)	Group 2, Dacia Plant® Aloe Vera tincture (30 patients)	Group 3, Sodium bicarbonate solution (20 patients)	Group 4, Distilled water (20 patients)
Good	27p (= 90%)	26p (= 86.66%)	10p (= 50%)	2p (= 10%)
Moderate	3p (= 10%)	3p (= 10%)	7p (= 35%)	8p (= 40%)
Poor	-	1p (= 3.33%)	3p (= 5%)	10p (= 50%)

Table 4. Disease recurrence after 1 year of monitoring

Product	Disease recurrence after 1 year of monitoring/patients				Total
	3 months	6 months	9 months	12 months	
ApiLand® Propolis tincture spray (30 patients)	-	-	2p = 6.66%	2p = 6.66%	4p = 13.33%
Dacia Plant® Aloe Vera tincture (30 patients)	-	1p = 3.33%	2p =6.66%	2p = 10%	5p = 16.66%
Sodium bicarbonate solution (20 patients)	-	2p = 10%	3p = 15%	3p = 15%	8p = 40%
Distilled water (20 patients)	1p = 5%	3p = 150%	5p = 25%	6p = 30%	15p = 75%

In conformity with the followed outcomes of study, Propolis and Aloe Vera tinctures demonstrated good efficiency in the treatment of AS through alternative medication. The efficacy of both alternative medication has been proven. Healing evolution of patients in the group of ApiLand® Propolis tincture spray was better and faster than in other patient groups. In descending order, the other groups were the Aloe Vera, Sodium Bicarbonate and Distilled Water Groups. The lesions recovery of the patients with sodium bicarbonate solution in the third group of patients was slower than in patients treated with tinctures. Delayed recovery was founded in 4th group of patients/Distilled water.

Groups treated with tinctures presented lower recurrence than the other two groups of patients.

No allergic reactions or any other adverse event were detected in any of the studied groups of patients.

The use of both tinctures is an easy and inexpensive alternative therapy that greatly improves cure of the mucosa affected by minor AS.

It is essential to review the patients to assess their progress and response to any treatment instituted, and patients must be aware of the treatment's limitations. The diagnosis and treatment of oral lesions is often challenging, requiring attentive anamnesis, careful clinical examination [2,28].

Propolis tincture has antimicrobial action (bacteriostatic and bactericidal on both Gram positive bacteria and gram negative bacteria), antimycotic (against Candida albicans), antiviral (against Herpes simplex), analgesic, anti-inflammatory, anesthetic, scarring, immunostimulant, antioxidant and mucolytic actions [29]. The mechanisms of Propolis action on diseases is not fully elucidated [17]. The immunomodulatory activity of Propolis is one of the most studied areas in conjunction with its anti-inflammatory property [30-34]. Anti-inflammatory properties and antibacterial activity of Propolis are due to the interaction between their bioactive constituents, through the interplay of flavonoids, esters and aromatic acids, while the bactericidal action results from the presence of cinnamic acid and coumarin [35-37]. Propolis contains various organic acids, minerals, vitamins (B1, B2, B6, C, E), nicotinic acid, pantothenic acid and aminoacids [38]. Propolis contains elements such as iron and zinc, which are important for the synthesis of collagen [39,40]. The antioxidant properties of Propolis have been studied by many researchers, which ascertained that their use had positive effects on oxidative status and can be used for the alleviation of oxidative stress [41-46]. The antioxidative activity deserves special interest because Propolis could be topically applied successfully to prevent and treat damaged skin [47-49].

Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids [50,51]. Aloe vera mechanisms of action are represented by its healing properties, anti-inflammatory action, effects on the immune system, antiviral and antitumor activity, and antiseptic effect [52-55]. After Babaee et al [56], the effects of Aloe Vera gel on minor AS lesions is considered curative as it decreased the healing time.

Different modalities in the management of minor AS can be used [57-59]. Several authors [60,61] consider that systemic interventions are

often reserved for the patients who did not respond to topical treatments of minor AS.

After the research of El-Haddad et al [62], honey was found to be effective and safe in reducing minor aphthous ulcer pain, size, and erythema in a Saudi cohort. Babaee et al [63] constated that myrtle is beneficial in reducing the size of ulcers, the pain intensity and the level of erythema in patients with AS.

There is not enough evidence to support or refute the use of alternative treatments for the therapy of minor AS [64]. Depending upon the response to treatment, the alternative therapies could be trialled [65].

Conclusions

- The therapeutic effect of Propolis Tincture was faster than Aloe Vera tincture.
- Reduction of clinical symptomatology, pain degree and recurrence in minor AS lesions were observed in all patients treated with alternative natural products.
- The use of spray form is easier and more comfortable than the rinse solutions.

Conflict of interest: None to declare.

References

1. Gonsalves WC, Chi CA, Neville BW. Common Oral Lesions: Part I. Superficial Mucosal Lesions, Am Fam Physician. 2007 Feb 15;75(4):501-6.
2. Siu A, Ramos DM, Landon K. Differential diagnosis and management of oral ulcers, Frontline Medical Communications, Semin Cutan Med Surg 2015, 34:171-177.
3. Shulman JD, Beach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in U.S. adults: data from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Dent Assoc. 2004;135:1279–86.
4. Santosh AB, Boyd D, Laxminarayana KK. Proposed Clinico -Pathological Classification for Oral Exophytic Lesions, J Clin Diagn Res. 2015; 9(9):ZE01-8.
5. Patil S, Rao RS, Majumdar B, Jafer M, Maralingannavar M, Sukumaran A. Oral Lesions in Neonates. Int J Clin Pediatr Dent 2016;9(2):131-8.
6. Liang MW, Neoh CY. Oral aphthosis: management gaps and recent advances. Ann Acad Med Singapore. 2012; 41(10):463-70.
7. Edgar NR, Saleh D, Miller RA. Recurrent Aphthous Stomatitis: A Review. The Journal of Clinical and Aesthetic Dermatology. 2017;10(3):26-36.
8. Alnazzawi AA. Oral diseases associated with fixed prosthodontic restorations. Saudi Medical Journal. 2017;38(3):322-4.
9. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic Features of Common Oral Ulcerative Lesions: An Updated Decision Tree. International Journal of Dentistry. 2016;2016:7278925.
10. Lodi G, Varoni E, Robledo-Sierra J, Villa A, Jontell M. (2017) Oral Ulcerative Lesions. In: Farah C., Balasubramaniam R., McCullough M. (eds) Contemporary Oral Medicine. Springer, Cham, https://link.springer.com/referenceworkentry/10.1007%2 F978-3-319-28100-1_12-1#citeas
11. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc2003;134:200–7.
12. http://www.europarl.europa.eu/cmsdata/135562/ENVI%202017-10%20WS%20CAM%20%20PE%20614.180%20(Publication).pdf
13. https://en.wikipedia.org/wiki/Propolis
14. https://draxe.com/bee-propolis/
15. https://www.honeycolony.com/article/top-10-health-benefits-of-propolis/
16. Wagh VD. Propolis: A Wonder Bees Product and Its Pharmacological Potentials. Advances in Pharmacological Sciences. 2013;2013:308249 doi:10.1155/2013/308249.
17. Pasupuleti VR, Sammugam L, Ramesh N, Gan SH. Honey, Propolis, and Royal Jelly: A Comprehensive Review of Their Biological Actions and Health Benefits. Oxidative Medicine and Cellular Longevity. 2017;2017:1259510.
18. Mot D, Tirziu E, Nichita E. Study of Bactericidal Properties of Propolis, Animal Science and Biotechnologies, 2014;47(1):256-9.
19. https://www.apiland.ro/propolis/tinctura-de-propolis-purificat-95-spray.html
20. Di Scala K, Vega-Gálvez A, Ah-Hen K, Nuñez-Mancilla Y, Tabilo-Munizaga G, Pérez-Won M, Giovagnoli G. Chemical and physical properties of aloe vera (Aloe barbadensis Miller) gel stored after high hydrostatic pressure processing, Food Sci. Technol, Campinas.2013;33(1): 52-9.
21. Egesie UG, Chima KE, Galam NZ. Anti-inflammatory and Analgesic Effects of Aqueous Extract of Aloe Vera (Aloe barbadensis) in Rats, Afr. J. Biomed. Res. 2011;209 -12.
22. Hajhashemi V, Ghannadi A, Heidari AH. Anti-inflammatory and wound healing activities of Aloe littoralis in rats. Research in Pharmaceutical Sciences. 2012;7(2):73-8.
23. https://www.nutritiv.ro/aloe-vera/tinctura-de-aloe-laxativ-natural-si-antiinflamator-pentru-uz-intern-sau-extern-50-ml-dacia-plant.html

24. https://comenzi.farmaciatei.ro/farmacie/afectiuni_digestive/constipatie/tinctura_de_aloe_50_ml_dacia_plant-p10029693
25. Malik Y, Goyal S. Virucidal efficacy of sodium bicarbonate on a food contact surface against feline calicivirus, a norovirus surrogate. International Journal of Food Microbiology. 2006, 109 (1–2): 160-3.
26. Rutala WA, Barbee SL, Aguiar NC, Sobsey MD, Weber DJ. Antimicrobial Activity of Home Disinfectants and Natural Products Against Potential Human Pathogens. Infection Control and Hospital Epidemiology. The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America. 2000;21(1):33–8.
27. Zamani M, Sharifi Tehrani A, Ali Abadi AA. Evaluation of antifungal activity of carbonate and bicarbonate salts alone or in combination with biocontrol agents in control of citrus green mold. Communications in agricultural and applied biological sciences. 2007;72(4):773–7.
28. Minic I, Pejcic A, Kostic M, Krunic N, Mirkovic D, Igic M. Prevalence of Oral Lesions in Elderly, West Indian Med J. 2016;65(2):375-8.
29. https://www.apiland.ro/propolis/tinctura-de-propolis-purificat-95-spray.html
30. Tanaka M, Okamoto Y, Fukui T, Masuzawa T. Suppression of interleukin 17 production by Brazilian propolis in mice with collagen-induced arthritis. Inflammopharmacology 2012;20(1)19-26.
31. Bachiega TF, Orsatti CL, Pagliarone AC, Sforcin JM. The Effects of Propolis and its Isolated Compounds on Cytokine Production by Murine Macrophages. Phytotherapy Research 2012; doi: 10.1002/ptr.3731.
32. Okamoto Y, Tanaka M, Fukui T, Masuzawa T. Brazilian propolis inhibits the differentiation of Th17 cells by inhibition of interleukin-6-induced phosphorylation of signal Propolis: Alternative Medicine for the Treatment of Oral Microbial Diseases transducer and activator of transcription 3. Immunopharmacology and Immunotoxicology 2012; Feb 9. [Epub ahead of print] PMID: 22316079.
33. Dimov V, Ivanovska N, Bankova V, Popov S. Immunomodulatory action of propolis: IV. Prophylactic activity against Gram-negative infections and adjuvant effect of the water-soluble derivate. Vaccine 1992;10(12) 817-23.
34. Nunes A, Faccioli LH, Sforcin JM. Propolis: lymphocyte proliferation and IFN-g production. Journal of Ethnopharmacology 2003;87(1) 93-7.
35. Chang H, Yuan W, Haizhu W, Yin X, Xuan H. Bioactive components and mechanisms of Chinese poplar propolis alleviates oxidized low-density lipoprotein-induced endothelial cells injury, BMC Complementary and Alternative Medicine. 2018;18:142.
36. Santos VR. Alternative Medicine for the Treatment of Oral Microbial Diseases, Chapter 7, cdn.intechopen.com/.../InTech-Propolis_alternative_medicin.
37. Saeed F, Ahmad RS, Umair Arshad M, Niaz B, Batool R, Naz R, Rasul Suleria HA. Propolis to Curb Lifestyle Related Disorders: An Overview, International Journal of Food Properties, 2015;19(2):420-437.
38. Ahn MR, Kunimasa K, Ohta T, Kumazawa S, Kamihira M, Kaji K, Uto Y, Hori H, Nagasawa H, Nakayama T. Suppression of tumor-induced angiogenesis by brazilian propolis: major component artepilin C inhibits in vitro tube formation and endothelial cell proliferation. Cancer Letters 2007;252(2):235-43.
39. Lustosa SR, Galindo AB, Nunes LCC, Randau KP, Rolim Neto PJ., Própolis: atualizações sobre a química e a farmacologia. Brazilian Journal of Pharmacognosy 2008;18:447-54.
40. Borrelli F, Maffia P, Pinto L, Ianaro A, Russo A, Capasso F, Ialenti A. Phytochemical compounds involved in the antiinflamatory effect of propolis extract. Fitoterapia 2002;73(suppl. 1):S53-S63.
41. Kocot J, Kiełczykowska M, Luchowska-Kocot D, Kurzepa J, Musik I. Antioxidant Potential of Propolis, Bee Pollen, and Royal Jelly: Possible Medical Application, Oxidative Medicine and Cellular Longevity, vol. 2018;(3):1-29.
42. Mujica V, Orrego R, Pérez J, Romero P, Ovalle P, Zúñiga-Hernández J, Arredondo M, Leiva E. The role of propolis in oxidative stress and lipid metabolism: a randomized controlled trial, Evidence-based Complementary and Alternative Medicine, 2017, Article ID 4272940, 11 pages, https://doi.org/10.1155/2017/4272940.
43. Li S, Tan H-Y, Wang N, Zang Z-J, Lao L, Wong C-W, Fenf Y. The Role of Oxidative Stress and Antioxidants in Liver Diseases, Piva T. ed., International Journal of Molecular Sciences. 2015;16(11):26087-124.
44. Raoa PV, Krishnana KT, Sallehb N, Gan SH. Biological and therapeutic effects of honey produced by honey bees and stingless bees: a comparative review, Brasilian Journal of Pharmacognosy, 2016;26(5):657-64.
45. Maciejewicz W. Isolation of flavonoid aglycones from propolis by a column chromatography method and their identification by GC-MC and TLC methods, Journal of Liquid Chromatography & Related Technologies, 2006;24(8)(8):1171-9.
46. Kuropatnicki AK, Szliszka E, Krol W. Historical Aspects of Propolis Research in Modern Times. Evidence-based Complementary and Alternative Medicine: eCAM. 2013;2013:9641-9.

47. Guo X, Chen B, Luo L, Zhang X, Dai X, Gong S. Chemical compositions and antioxidant activities of water extracts of Chinese propolis. Journal of Agricultural Food Chemistry 2011;59(23):12610-6.
48. Messerli SM, Ahn MR, Kunimasa K, Yanagihara M, Tatefuji T, Hashimoto K, Mautner V, Uto Y, Hori H, Kumazawa S, Kaji K, Ohta T, Maruta H. Artepillin C (ARC) in Brazilian green propolis selectively blocks oncogenic PAK1 signaling and suppresses the growth of NF tumors in mice. Phytotherapy Research 2009;23(3):423-7.
49. Sudina GF, Mirzoeva OK, Pushkareva MA, Korshunova GA, Sumbatyan NV, Varfolomeev SD. Caffeic acid phenethyl ester as a lipoxygenase inhibitor with antioxidant properties. FEBS 1993; 329(1-2):21-4.
50. Leech J. What are the benefits of aloe vera?. Medical News Today. MediLexicon, Intl., 1 Aug. 2017. Web. 19 May. 2018. https://www.medicalnewstoday.com/articles/318591.php
51. Surjushe A, Vasani R, Saple DG. Aloe Vera: A short review. Indian Journal of Dermatology. 2008;53(4):163-6.
52. Zawahry ME, Hegazy MR, Helal M. Use of aloe in treating leg ulcers and dermatoses. Int J Dermatol. 1973;12(1):68-73.
53. Fulton JE Jr. The stimulation of postdermabrasion wound healing with stabilized aloe vera gel-polyethylene oxide dressing. J Dermatol Surg Oncol. 1990;16(5):460-7.
54. Schmidt JM, Greenspoon JS. Aloe vera dermal wound gel is associated with a delay in wound healing. Obstet Gynecol. 1991;78(1):115-7.
55. Garnick JJ, Singh B, Winkley G. Effectiveness of a medicament containing silicon dioxide, aloe, and allantoin on aphthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(5):550-6.
56. Babaee N, Zabihi E, Mohseni S, Moghadamnia AA. Evaluation of the therapeutic effects of Aloe vera gel on minor recurrent aphthous stomatitis. Dental Research Journal. 2012;9(4):381-5.
57. Subiksha PS. Various Remedies for Recurrent Aphthous Ulcer: A Review, /J. Pharm. Sci. & Res. 2014;6(6):251-3.
58. Bardellini E, Amadori F, Conti G, Majorana A. Clinical efficacy of a solution composed by sodium bicarbonate and alginate, aloe vera, propoli, chamomile, calendula and honey, in the treatment of minor recurrent aphthous stomatitis in children, Minerva Pediatr. 2016;68(6):507-9.
59. Sabbagh AH, Felemban MF. Therapeutic Management of Recurrent Aphthous Stomatitis: A Review of the Growing, Annals of International Medical and Dental Research, 2014;2(6):1-9.
60. Spivakovsky S. Inconclusive evidence on systemic treatments for recurrent aphthous stomatitis. Evid Based Dent. 2012;13(4):120.
61. Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, Taylor J, Walsh T, Riley P, Yates JM. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database Syst Rev. 2012 Sep 12; (9):CD005411, doi: 10.1002/14651858.CD005411.pub2.
62. El-Haddad SA, Asiri FY, Al-Qahtani HH, Al-Ghmlas AS. Efficacy of honey in comparison to topical corticosteroid for treatment of recurrent minor aphthous ulceration: a randomized, blind, controlled, parallel, double-center clinical trial. Quintessence Int. 2014 Sep;45(8):691-701.
63. Babaee N, Mansourian A, Momen-Heravi F, Moghadamnia AA, Momen-Beitollahi J. The efficacy of a paste containing Myrtus communis (Myrtle) in the management of recurrent aphthous stomatitis: A randomized controlled trial. Clinical Oral Investigations, 2010, 14(1):65-70.
64. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. Journal of Clinical and Experimental Dentistry. 2014;6(2):e168-e174. doi:10.4317/jced.51401.
65. Talacko AA, Gordon AK, Aldred MJ. The patient with recurrent oral ulceration, Australian Dental Journal 2010;55:(1 Suppl): 14–22.

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