Clinical trial

Clin Ter 2020; 171 (4):e295-301. doi: 10.7417/CT.2020.2231

The Efficacy of a Dietary Supplement with Carnosine and *Hibiscus Sabdariffa L.* (Aqualief™) in Patients with Xerostomia: a Randomized, Placebo-Controlled, Double-Blind Trial

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Abstract

The purpose of this study was to test the safety and efficacy of Aqualief™ in patients affected by xerostomia. The main ingredients of Aqualief™ are carnosine and dried calyces of *Hibiscus sabdariffa L.* (karkadè) for their buffering effect at pH 7 as well as for their antioxidant, antimicrobial and lenitive properties. In a Randomized, Placebo-Controlled, Double-Blind Trial, sixty patients with xerostomia (RTOG/EORTC grade 1-2) were randomly assigned to receive either placebo, or Aqualief™ tablets (three times/day after meals) for 6 consecutive days. A questionnaire was used to evaluate dry mouth symptoms before and after 6 days of Aqualief™ or placebo application. Unstimulated and stimulated salivary flow rates and pH were measured before and after application. Treatment with Aqualief™ for 6 days induced a significant increase in saliva pH from 6.2 ± 0.5 to 6.4 ± 0.6 ($P < 0.05$) while placebo was ineffective (from 6.2 ± 0.5 to 6.3 ± 0.5). Aqualief™ also induced a significant increase in the pH of stimulated saliva from 6.3 ± 0.5 to 6.6 ± 0.5 ($P < 0.01$). Placebo was ineffective also in this setting (from 6.2 ± 0.5 to 6.3 ± 0.5). Besides an expected normalization of the saliva pH value, Aqualief™ treatment for 6 days greatly increased (56%, $P < 0.0001$) saliva production. Placebo induced a 19% increase ($P < 0.05$), which was likely due to mechanical stimulation. Aqualief™ also increased stimulated saliva production (27% increase with respect to day 0, $P < 0.05$), while placebo was ineffective. Aqualief™ was effective in regulating the saliva pH, in increasing saliva production and improving dry mouth symptoms in xerostomic patients. ***Clin Ter 2020; 171 (4):e295-301. doi: 10.7417/CT.2020.2231***

Key words: *Xerostomia, carnosine, karkadè, saliva pH, stimulated saliva, saliva production, dry mouth symptoms*

Introduction

Xerostomia is defined as the subjective complaint of dry mouth. Symptoms of dry mouth may range from mild oral discomfort to significant oral disease that can compromise patients' health, dietary intake and quality of life. Xerostomia is accompanied by numerous signs and symptoms mainly in the mucous membranes, lips, tongue, salivary glands and teeth (1). Moreover, xerostomia induced by radiotherapy can cause severe depression in head and neck cancer patients (2). Among common causes of xerostomia are medications, mainly anti-cholinergic, sympathomimetic, sedative-hypnotics, opiates, antihistamines and muscle relaxants (3). Other causes of xerostomia are radiation received by patients with cancer in the head and neck area (4) and certain autoimmune diseases, such as Sjögren's syndrome (5).

Although xerostomia is often a manifestation of impaired salivary gland function, it can occur with or without a noticeable decrease in saliva production (hyposalivation) (6). In a population-based sample of aged South Australians, Thomson et al (7) supported the fact that low salivary flow may not be the key factor in the etiology of xerostomia among older people. Several large studies in healthy participants have found that the average unstimulated salivary secretory rate is around 0.3-0.4 mL per minute (8) but the normal range is very broad and includes individuals with very low flow rates who do not complain of dry mouth. Unless saliva is completely absent, patients can be said to have a dry mouth (xerostomia) only on the basis of their subjective symptoms (9). Hypofunction of the salivary gland is defined when the unstimulated whole mouth salivary flow rate is <0.1-0.2 mL/min or stimulated salivary flow rate <0.7 mL/min (10, 11).

Xerostomic patients have also altered salivary characteristics such as resting pH and buffering capacity which can be due to hyposalivation and/or altered saliva composition (12, 13). Such conditions may affect dental health due to the fact that saliva is an essential substance that reduces the incidence and severity of carious lesions and dental erosion by several mechanisms. In particular, saliva neutralizes acids by the presence of HCO_3^- ions and promotes clearance by swallowing. Moreover, saliva plays a role in the formation of the acquired dental pellicle, a perm-selective membrane that prevents the contact of acid with tooth surfaces (14).

Given this scenario and the untoward consequences of xerostomia on the quality-of-life of affected patients, it does not come to surprise that many approaches have been pursued in order to prevent and/or treat xerostomia. These approaches can be broadly divided into three main categories (15): i) protection of the salivary glands; ii) stimulation of salivary glands to produce more saliva; iii) reduction of xerostomia symptoms when the remaining salivary glands cannot be stimulated efficiently. Overall, in spite of there

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ISSN 1972-6007

being available a long list of preventive and therapeutic measures for the treatment of xerostomia, most of these are burdened by high costs, unfavorable side effects and/or lack of proven efficacy. For this reason, identification of new preparations for the treatment of xerostomia is still an important medical need.

Interestingly, although pH is significantly altered in xerostomic participants and involved in oral and dental health, it is not an issue addressed in many commercial oral moisturizers that are used by patients suffering from dry mouth. Delgado et al. (14, 16) recently investigated the pH of the most commonly used oral moisturizers and dry mouth treatment products. They found a large variation in pH values, most of which were characterized by an acidic pH due to the presence of citric acid as siologenic ingredient. They also found that there is a strong correlation between the pH values and the erosive potential of these products thus concluding that it is imperative that the moisturizers themselves should not have pH values below the critical pH of enamel or root dentin.

Based on these premises, a novel product, Aqualief™, containing two key ingredients, carnosine and dried calyces of *Hybiscus sabdariffa L.* (karkadé) was designed with the aim of stabilizing the saliva pH at a neutral level and to improve the acid buffering capacity of saliva. Carnosine and karkadè were also selected for their multiple biological effects which can aid in the protection of the oral cavity. Carnosine, in particular, has been reported to possess anti-inflammatory, antioxidant, antiglycation, and chelating activities (17). Also Karkadè has been reported to have several favorable effects (18) i) antioxidant activity due to the presence of ascorbic acid, phenolic acids, anthocyanins and flavonoids; ii) broad spectrum antimicrobial activity due to different components including protocatechuic acid, endowing it with activity against cariogenic bacteria such as *Streptococcus mutans*; iii) anti-inflammatory effects due to the ability of the polyphenol constituents to inhibit cyclooxygenase-2.

In this article, a randomized, double-blind, placebo-controlled clinical study with Aqualief™ is described in xerostomic participants.

Materials and methods

Patient Selection

Sixty patients with xerostomia (grade 1-2 according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC)) from different etiologies (burning mouth syndrome (n= 8), oncological (several conditions)(n=28); human immunodeficiency virus (n=2); hypertension/selective serotonin reuptake inhibitors/other drugs (n=13); lateral cheilitis (n=2); Other (n=7)) were recruited at the Clinica Odontoiatrica dell'Università degli Studi dell'Insubria (Varese, Italy). Exclusion criteria were: a) participants under treatment using drugs to treat hyposalivation (e.g. pilocarpine); b) with xerostomia grade ≥ 3 according to the Late Radiation Morbidity Scoring Schema: Complete dryness of mouth No response on stimulation; c) patients with severe hyposalivation (saliva flow rate at baseline <0.1 ml min^{-1}) because of to their inability to dissolve the tablet formulation.

Written informed consent was received from all patients before study initiation. The study was conducted in accordance with the principles laid out by the Declaration of Helsinki 1964 and its subsequent amendments and with the International Committee on Harmonization Guidelines for Good Clinical Practice and in compliance with local ethical and legal requirements. The study was approved by the ethics committee at the participating site. Clinical trial information: NCT03612414.

Study Design

The study was a prospective, randomized, double-blind, placebo-controlled trial undertaken at the Clinica Odontoiatrica dell'Università degli Studi dell'Insubria (Varese, Italy). Eligible patients who had developed xerostomia RTOG/EORTC grade 1-2 were randomized in a 1:1 ratio, with one group receiving three Aqualief™ tablets (after breakfast, lunch, dinner) daily for 6 days. The second group received a placebo tablet given with the same regimen. Randomization was performed using the website http://www.randomization.com, obtaining a randomization plan, which assigned participants to either the intervention group or the control group. This randomization plan was delivered to a person unrelated to the study in order to prevent both participants and researchers from identifying the product. The primary objective of the study was to assess the safety and efficacy of Aqualief™ in stabilizing the saliva pH at a neutral level compared with placebo. The secondary objective was to determine whether Aqualief™ induced an increase of unstimulated or stimulated saliva and in ameliorating the symptoms related to oral dryness.

Dry Mouth Questionnaire (DMQ)

A modified Thomson's questionnaire (19) was used in order to obtain subjective information about the severity of dry mouth before and after treatment with Aqualief™/placebo (Table 1). Every participant answered an initial DMQ about the symptoms related to oral dryness, and after 6 days of applications, patients answered again the DMQ. The following items were included in the DMQ: (1) Does your mouth feel distinctly dry?; (2) Do you have difficulties in swallowing dry foods?; (3) Does your mouth feel dry when eating a meal?; (3) Does the skin of your face feel dry?; (4) Do your eyes feel dry?; (5) Do your lips feel dry?; (6) Does the inside of your nose feel dry?; DMQ used a 1-to-3 rating scale where 1 = "never", 2= "sometimes" and 3 = "very often".

Measurement of saliva production and saliva pH

Saliva production was determined by the spit method at baseline (t=0) and after 6 days of treatment (t=1). Unstimulated saliva was collected every 30 s for 5 consecutive min in a tube which was then weighed to estimate the flow of resting saliva. After a rest of two minutes and upon chewing paraffin wax, stimulated saliva was measured for 5 min as for

Table 1. Baseline characteristics of the study participants (unpaired t-test)

Parameter	Placebo group (n=30)	Treatment group (n=30)	P-value
Age (mean±SD)	53±20	50±19	n.s.
Gender Male (%) Female (%)	 16 14	 15 15	
pH			
unstimulated	6.2±0.5	6.2±0.5	n.s.
stimulated	6.2±0.5	6.3±0.5	n.s.
Saliva flow (ml min^{-1})			
unstimulated	0.42±0.22	0.36±0.18	n.s
stimulated	0.93±0.66	0.85±0.75	n.s.
Dry mouth questionnaire (DMQ)			
Item 1	2.35±0.12	2.25±0.44	n.s.
Item 2	1.94±0.91	2.21±0.93	n.s.
Item 3	1.39±0.78	1.71±0.81	n.s.
Item 4	1.61±0.84	1.62±0.87	n.s.
Item 5	1.56±0.73	1.37±0.65	n.s.
Item 6	1.96±0.88	2.29±0.69	n.s.

Items: (1) Does your mouth feel distinctly dry?; (2) Do you have difficulties in swallowing dry foods?; (3) Does your mouth feel dry when eating a meal?; (3) Does the skin of your face feel dry?; (4) Do your eyes feel dry?; (5) Do your lips feel dry?; (6) Does the inside of your nose feel dry?

unstimulated saliva (20). The pH of resting and stimulated saliva was measured by a pH-sensitive electrode as already reported (21) (Fig. 1).

Study product

Aqualief™ (Helsinn Healthcare SA, Lugano, Switzerland) is a 400 mg mucoadhesive oral tablet with smooth surfaces. The maximum diameter is 13 mm and the maximum thickness is 4 mm. The dissolution time of the tablet

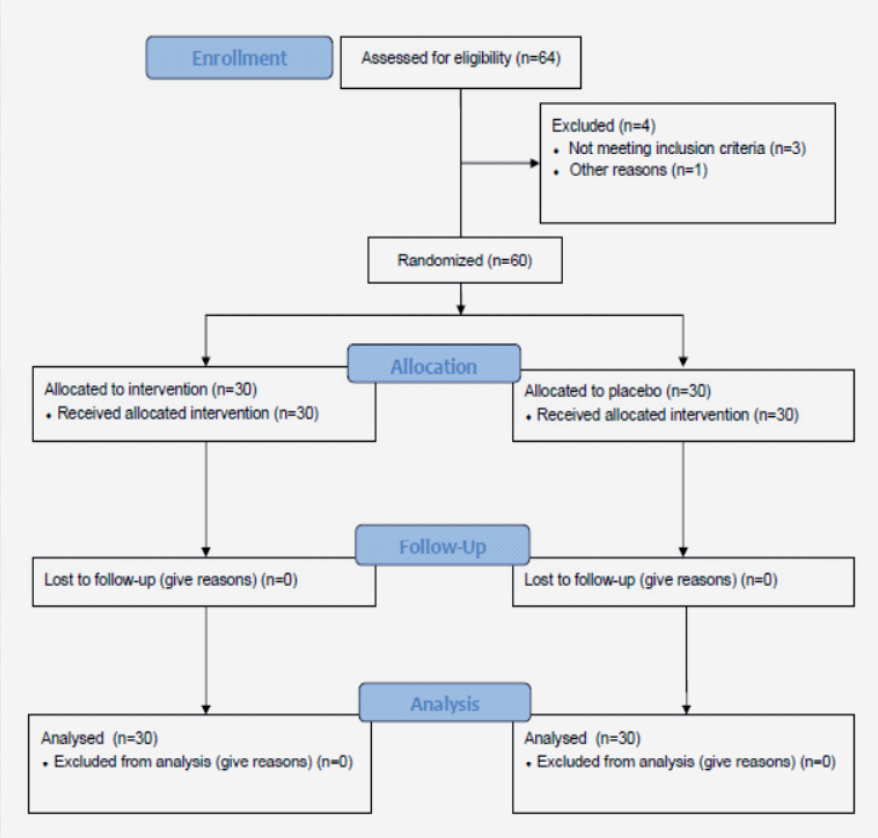

Fig.1. Study-flow diagram

is around 2 h in normal salivation conditions. Aqualief™ contains two ingredients mixed in a specific proportion: carnosine and dried calyces of *Hibiscus sabdariffa L.* (karkadè). Placebo tablets were the same as Aqualief™ without the two ingredients.

Aqualief™ is a food supplement according to EU Dir. no 2002/46/EC, notified to Italian Ministry of Health with ID number 83383. At recommended doses, the intake quantities of the substances meet requirements and limitations set by the Italian Ministry of Health. Due to the presence of flavonoids in *Hibiscus Sabdariffa L.* a medical advice is suggested when used during pregnancy.

Statistical analyses

Sample size estimation

Sample size estimates were based on unpublished data from a previous study, in which differences in unstimulated saliva volume, collected after one week of treatment with Aqualief™ (T7-T0) were 0.47 ml (standard deviation (SD) =0.3 ml) and 0.25 (SD = 0.3) for the Aqualief™ and placebo group, respectively. Assuming a similar study of the same magnitude, 60 xerostomic patients (grade 1-2 according RTOG/EORTC scale, 30 treated with Aqualief™, 30 with placebo) were considered sufficient in order to observe a statistically significant difference between treatment groups (power 80%, significance 5%, α 0.05).

Statistical analysis

Data were analyzed by descriptive statistics. Differences between DMQ scores before and after treatment (intragroup) were analyzed by the Wilcoxon signed-rank test. Mann-Whitney *U*-test for two independent samples was used to identify significant differences between groups at baseline. Following treatment, effect sizes were calculated as follows: Effect size= (mean score before–mean score after)/ standard deviation of score before. Student's *t*-test (paired for intragroup and un-paired for intergroup) was used to analyze both stimulated and unstimulated salivary flow rates and pH values. A p value <0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 6.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com.

Results

Characteristics of the Study Sample

Of the sixty-four patients with xerostomia screened at the Clinica Odontoiatrica dell'Università degli Studi dell'Insubria (Varese, Italy), sixty were enrolled, randomized and addressed to treatments, according to the design reported in Figure 1. Thirty-two percent of the patients reported in the DMQ that they felt dry mouth "very often"; the remaining patients just "sometimes". Mean saliva pH of the patients was 6.2 (range 5.0 – 7.0), a value that was significantly different compared to pH 6.7 ($p<0.0001$, *t*-test). Twenty-five percent showed a pH ≤ 5.5 and 60% ≤ 6.7. The mean saliva flow rate at baseline was 0.43 ± 0.22 ml min^{-1} (range 0.18 - 1.036 ml min^{-1}).

The patients were randomly assigned to receive Aqualief™ tablets or placebo tablets, three times/day after meals, for 6 consecutive days. Patients were assessed on days 0 (baseline) and 6 for safety and saliva production. Baseline characteristics of the patients were generally well balanced among the two groups and no statistical differences were observed for the parameters that were considered (Table 2). The average ages of the patients were 53 ± 20 and 50 ± 20, in the Aqualief™ and placebo groups, respectively.

Study groups did not differ significantly with respect to concomitant medication use. Most patients received at least one concomitant medication.

Effect of Aqualief™ on the pH of saliva

Aqualief™ treatment for 6 days induced a significant increase ($P < 0.05$) in saliva pH from 6.2 ± 0.5 at baseline to 6.4 ± 0.6 (Fig. 2). Of note, at baseline, four patients had a cariogenic pH (pH ≤ 5.5), while none of these had a cariogenic pH after treatment with Aqualief™. The pH at baseline for the placebo group was 6.2 ± 0.5 and did not significantly increase after 6 days of treatment with placebo tablets (6.3 ± 0.5) (Fig. 2).

Aqualief™ also induced a significant increase in the pH of stimulated saliva from a baseline of 6.3 ± 0.5 to 6.6 ± 0.5 after 6 days ($P < 0.01$), while placebo was ineffective (6.2 ± 0.5 at baseline and 6.3 ± 0.5 after 6 days). Of the participants

Table 2. Change in participants' assessment of dry mouth, as determined by the DMQ between baseline and final value.

Items	Placebo				Treatment			
	T=0	T=6 days	Wilcoxon test	Effect size	T=0	T=6 days	Wilcoxon test	Effect size
1	2.3±0.2	2.1±0.2	n.s.	1	2.2±0.4	1.9±0.3	P<0.05	0.7
2	1.9±0.9	1.9±0.9	n.s.	0	2.2±0.9	1.9±0.6	P<0.05	0.3
3	1.4±0.8	1.3±0.6	n.s.	0.1	1.7±0.8	1. 7±0.8	n.s.	0
4	1.6±0.8	1.6±0.8	n.s.	0	1.6±0.9	1.5±0. 8	n.s.	0.1
5	1. 6±0.7	1.5±0.4	n.s.	0.1	1.4±0.6	1.3±0.6	n.s.	0.3
6	2.0±0.9	2.0±0. 7	n.s.	0	2.3±0.7	2.0±0. 6	P<0.05	0.4

Items: (1) Does your mouth feel distinctly dry?; (2) Do you have difficulties in swallowing dry foods?; (3) Does your mouth feel dry when eating a meal?; (3) Does the skin of your face feel dry?; (4) Do your eyes feel dry?; (5) Do your lips feel dry?; (6) Does the inside of your nose feel dry?

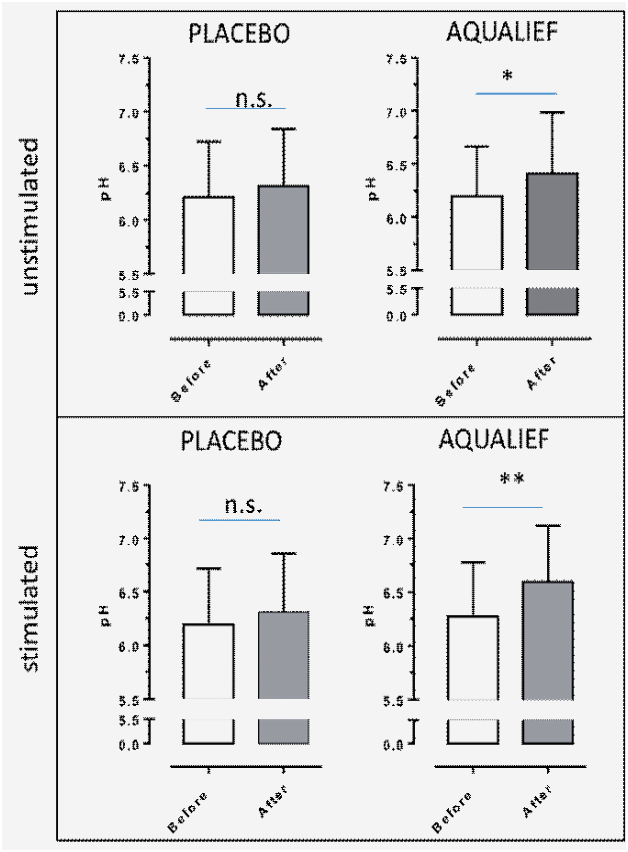

Fig. 2. Effect of Aqualief™ on the pH of unstimulated (A) or stimulated (B) saliva. Saliva pH was measured with a pH-sensitive electrode at time 0 (t =0, baseline) and after 6 days of treatment with AqualiefTM or placebo (t=1). *P < 0.05, paired t-test. N.s., not significant.

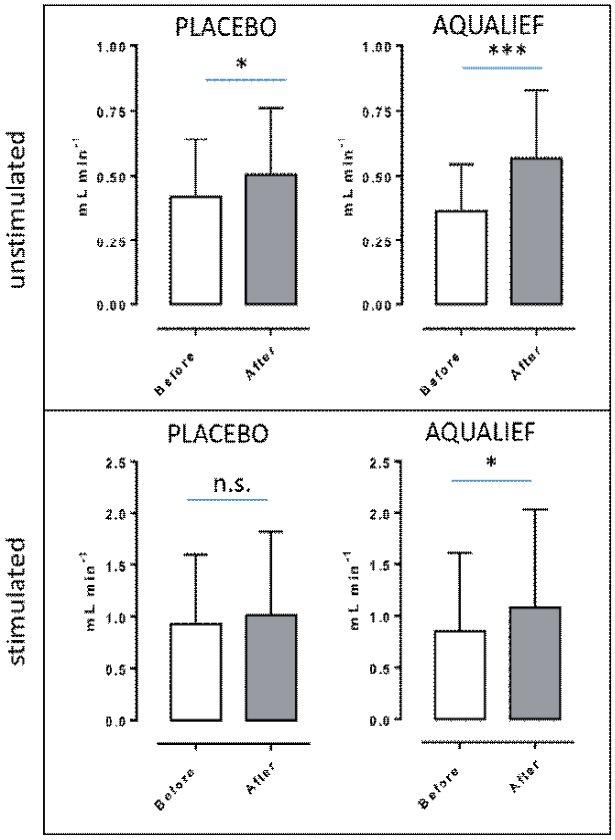

Fig. 3. Effect of Aqualief™ and Placebo on unstimulated (upper panel) or stimulated (lower panel) saliva production. Saliva production was measured as described under saliva production at time 0 (t =0, baseline) and after 6 days of treatment with Aqualief™ or placebo (t=1). *P < 0.05, ****P < 0.0001. N.s., not significant.

that had a cariogenic pH at baseline, none had such a pH after treatment with Aqualief™.

Effect of Aqualief™ on salivation

The effect on salivation of the treatment for 6 days of Aqualief™ or placebo is reported in Fig. 3. The data in the upper panel show the unstimulated (resting) saliva production at baseline (t=0) and after 6 days of treatment (t=1). Placebo induced a significant increase of saliva production (+19%), which is likely due to mechanical stimulation ($P < 0.05$). The effect of Aqualief™, however, was three-fold higher than placebo, with an increase of 56% ($P < 0.0001$). Aqualief™ also promoted an increase in stimulated saliva production from 0.85 ± 0.75 to 1.08 ± 0.95 ml, with an increase of 27% (Fig. 3, lower panel). Placebo, on the other hand, was ineffective in increasing stimulated saliva production (Fig. 3).

Effect of Aqualief™ on dry mouth symptoms

Table 3 shows the effect of placebo or Aqualief™ treatment on dry mouth symptoms as determined by the DMQ. Statistically significant differences were found only in the Aqualief™ group between the start and the end of the treatment for the following items: (1) Does your mouth feel distinctly dry?; (2) Do you have difficulties in swallowing dry foods?; (5) Does the inside of your nose feel dry?

3.5 Safety of Aqualief™

None of the 60 patients (30 treated with Aqualief™, 30 treated with placebo) enrolled in the study reported any treatment-related adverse events during or after the completion of the trial.

This result underline two fundamental safety aspects related either to the ingredients and to pharmaceutical formulation of Aqualief™, in particular: a) Aqualief™ ingredients are safety and well tolerated by patients, and b) the tablet "*per se*" (data from placebo) is well designed and comfortable for an effective use of Aqualief™ over time since Xerostomia is a chronical condition.

Discussion

This article reports the findings of an efficacy study of Aqualief™ in xerostomia patients. Aqualief™ contains two key ingredients, carnosine and karkadé, which were selected and appropriately mixed to achieve the normalization of saliva pH to a neutral value and to increase the saliva buffering activity. Both these two parameters are impaired

Table 3. Dry mouth questionnaire (DMQ)

Items	Placebo			Treatment		
	T=0	T=6 days	Wilcoxon test	T=0	T=6 days	Wilcoxon test
1	2.35±0.12	2.09±0.23	n.s.	2.25±0.44	1.92±0.31	P<0.05
2	1.94±0.91	1.90±0.87	n.s.	2.21±0.93	1.92±0.63	P<0.05
3	1.39±0.78	1.30±0.65	n.s.	1.71±0.81	1.67±0.76	n.s.
4	1.61±0.84	1.65±0.79	n.s.	1.62±0.87	1.46±0.78	n.s.
5	1.56±0.73	1.52±0.45	n.s.	1.37±0.65	1.33±0.58	n.s.
6	1.96±0.88	1.96±0.67	n.s.	2.29±0.69	1.96±0.56	P<0.05

Items: (1) Does your mouth feel distinctly dry?; (2) Do you have difficulties in swallowing dry foods?; (3) Does your mouth feel dry when eating a meal?; (3) Does the skin of your face feel dry?; (4) Do your eyes feel dry?; (5) Do your lips feel dry?; (6) Does the inside of your nose feel dry?

in xerostomic patients, leading to acid-induced enamel and dental erosion as well as the creation of an inhospitable environment for protective oral bacteria due to the low salivary pH which promotes the growth of aciduric bacteria.

In xerostomic patients, Aqualief™ was found to normalize saliva pH to a neutral value and to significantly increase the saliva flow rate. Xerostomic patients had an acid saliva in both resting and stimulated conditions (6.2 and 6.3, respectively). These values significantly increased toward a neutral value after 6 days of treatment (6.4 and 6.6). This study has also demonstrated a significant increase of saliva flow rate induced by Aqualief™ compared to placebo which, by itself, showed a slight but significant effect. In fact, placebo increased resting salivation by 19% but was ineffective on stimulated saliva. Such an effect can be explained by considering the placebo tablet as a foreign object and this would also explain its ineffectiveness in the stimulated salivation test where a paraffin wax is used as a foreign object, thereby cancelling the placebo effect. The presence of carnosine and karkadè in the tablet further increased salivation by almost 60% compared to the basal value, an increase of more than three-fold compared to the placebo. Of note, the increase in salivation was also observed in the salivation test.

The effect of Aqualief™ in normalizing saliva pH could be attributed, in principle, to the presence of carnosine and a direct regulation of the pH (22) . However, it should be noted that saliva was collected after the application and dissolution of the tablet so that the residual carnosine in the collected saliva was likely present in negligible amounts, not able to exert a direct effect on the pH. Hence, other mechanisms explaining the increase in pH of the collected saliva should be considered, in particular a boosted salivation (see below) and an increased content of saliva HCO_3^- (data under evaluation) due to the effect of carnosine in stimulating the carbonic anhydrase activity (manuscript in preparation). Eventually, also a change in composition of the oral microbiota following Aqualief™ treatment should be considered. In particular the pH control and buffering activity of Aqualief™ could lead to a reduced growth of acidogenic and aciduric oral microbiota with a consequent reduction in acid production.

As to the salivation-promoting effect of Aqualief™, this is most likely due to a multifactorial action following the balancing effect of Aqualief™ on pH. However, a direct effect of carnosine and/or karkadè components on salivation should not be excluded and merits further investigations.

Moreover, Aqualief™ but not placebo was found to significantly improve dry mouth symptoms, an activity which can be due to several causes such as the increased salivation and/or the normalization of saliva pH which can be considered markers of improved saliva composition.

The main limit of the present study is that xerostomic patients affected by hyposalivation could not recruited to test the salivation effect of Aqualief™ because in preliminary studies we have found that a resting saliva flow > 0.2 ml min^{-1} is required to dissolve the tablet. However, a new water-based formulation of Aqualief™ has been already designed to be used in xerostomic participants affected by hyposalivation and it will be tested in the near future in order to evaluate whether its effect also occurs in case of reduced secretory function of the glands.

Another limitation of the study is that the duration of the effects after discontinuation of treatment has not yet been investigated.

In conclusion, we have shown that the treatment of xerostomia patients with Aqualief™, three times/day for 6 days leads to a significant increase of their saliva production and pH. These properties make Aqualief™ one of the very first commercial products effective in the treatment of xerostomia and does not act by modulating muscarinic or adrenergic receptors for which scientific evidence from a clinical study is now available (23). Overall, Aqualief™ may become a valuable product for the treatment of patients affected by xerostomia and for the prevention of its complications. The efficacy of Aqualief™ in significantly increasing both saliva production and saliva pH makes it suitable not only for the therapy of xerostomia, but also for the prevention of some of its untoward consequences such as, for example, caries.

Acknowledgments

Medical writing was performed by Dr. Fabrizio Marcucci; this assistance was funded by Helsinn.

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