Research Article

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Treatment with Herbal Mouthwash Mediates Improvement of Symptoms in Xerostomia and Oral Mucositis patients

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Abstract

Oral discomfort and pain are frequent side-effects of many popular prescription medications. Over 500 prescription drugs are known to result in the development of adverse oral conditions. In fact, approximately 40% of patients suffer from xerostomia and oral mucositis, as a result of cancer medications. The number of affected individuals is expected to continue to rise, given that the incidence of major cancers is predicted to grow over the next decade. Regrettably, there are currently lacks of treatments available to effectively improve xerostomia and oral mucositis symptoms. Interestingly, the use of several herbal ingredients (such as chamomile, cinnamon, and peppermint oil) has been reported to effectively improve pain and oral dryness. For this reason, we examined the effectiveness of an herbal mouthwash, Nature's Herbal (a blend of cinnamon oil, chamomile, cranberry, and peppermint extract), to alleviate symptoms of oral pain and dry mouth exhibited by patients diagnosed with oral mucositis and xerostomia. Daily treatment with the mouthwash induced a $53\% \pm 6\%$ and $33.2\% \pm 3.8\%$ improvement in the severity of symptom, for the oral mucositis and xerostomia patients groups, respectively. Overall, the herbal mouthwash induced an improvement in 91% of oral mucositis and 83% of xerostomia patients.

Keywords: Herbal; Xerostomia; Oral mucositis; Mouthwash; Dry mouth; Oral care

Introduction

Over the last decade there has been a surge in the number of individuals worldwide, who rely on prescription drugs to manage disease. However, often overlooked is the fact that the use of medication frequently results in the development of adverse effects for patients. This possesses a significant issue since patients are often unable to discontinue the use of the prescription drugs causing oral discomfort. To date, the uses of a wide variety of prescription medications are known to induce adverse reactions affecting the oral cavity of patients (Table 1) [1]. For instance, regularly prescribed cancer therapeutics such as chemotherapy drugs, radiation

therapy, and checkpoint inhibitors have been observed to cause debilitating oral discomfort for patients [2].

Among the most common medication-induced oral conditions, are xerostomia and oral mucositis. Xerostomia, dryness of the oral cavity, results from insufficient saliva secretion or a complete lack of saliva. Dry mouth, especially when manifested as a chronic condition, can drastically impact the patient's quality of life; producing difficulties in tasting, chewing, swallowing, and speaking. The prevalence of xerostomia in the general population is estimated to be up to 42% [3]. Oral mucositis occurs as a result of the breakdown of the epithelial cell layer lining the oral cavity, leaving the mucosal tissue open to

ulceration and infection. Oral mucositis can bring about severe difficulties; such as pain, nutritional concerns (inability to swallow), and an elevated risk of infection (due to open-sores). It is suggested that nearly 40% of patients, treated with standard chemotherapy drugs, develop mucositis [2] additionally, approximately 80% of patients, receiving radiotherapy and chemotherapy, have been reported to develop oral mucositis [4]. As such, oral mucositis is considered one of the main debilitating complications of cancer treatments, having a significant impact on the patient's quality of life.

Recent projections have suggested that the incidence in the United States of most major cancers will continue to rise significantly over the next decade [5], leading to a growing pool of patients with drug-induced oral complications. Unfortunately, to date there exists an absence of effective therapeutic alternatives to replace the high number of oral discomfort inducing medications, as well as a lack of capable treatments to alleviate oral discomfort. Of note, previous publications have highlighted the effectiveness of herbal ingredients to alleviate pain [6,7]. In this study, we evaluated the effectiveness and safety of an herbal-based mouthwash, Nature's Herbal, to improve symptoms of pain and dry mouth, exhibited by patients diagnosed with oral mucositis and xerostomia. Nature's Herbal mouthwash is composed of a blend of herbal compounds including cinnamon oil, chamomile, cranberry, aloe, and peppermint extract. The results of our study indicated that this herbal formula is safe for daily use and capable of improving the symptoms of oral mucositis and xerostomia.

Results

To determine the efficacy of the herbal ingredients to alleviate oral pain and dryness, the study conducted questionnaires among separate patient groups (xerostomia and oral mucositis). In each group participants, were treated with a dose of herbal mouthwash (10-15 mL) for 20-30 seconds (four times per day), for 7 days. During each day of treatment, patients participating in the study were asked to self-evaluate their degree of oral discomfort (on a scale of 0 to 10). The results of the patient questionnaires revealed that the herbal composition of the mouthwash was effective in relieving symptoms of oral dryness and pain.

Patients corresponding to the oral mucositis group reported an average improvement in the severity of symptoms of 53% ± 6% (Table 1), and 91.6% (11 of 12 patients) indicated an improvement (defined as ≥ 25%

improvement) in oral pain levels following treatment with the herbal mouthwash (Figure 1a). Furthermore, among patients diagnosed with xerostomia, the use of the herbal mouthwash led to an improvement (defined as ≥ 25% improvement of dry mouth symptoms) in 83.3% (10 of 12 participants) of patients (Figure 1b), with an average improvement in the severity of symptoms of 33.2% ± 3.8% (Table 1).

Figure 1: Data collected from (A) oral mucositis and (B) xerostomia patient groups. Patient responses are denoted as those with a ≥ 25% improvement following treatment with herbal mouthwash (black bars) or with < 25% improvement (grey bars).

Table 1: Prescription drugs known to cause oral discomfort.

Drug Type
• Antibiotics
• Anti-cancer medication
• An1i-depressants
• An1idiarrheal drugs
• Anti-hypertensive drugs
• Anti-histamines
• Anti-psychotic drugs
• Bronchodilators
• Diuretics
• Pain medication

Discussion

The results obtained following treatment with the

herbal mouthwash are in agreement with previous reports, describing the capability of several active herbal ingredients, to reduce the sensation of pain, and increase saliva secretion. For instance, in a randomized study of elderly patients, chamomile was shown to provide relief from xerostomia symptoms, such as the sensation of oral dryness, a burning tongue, and difficulty swallowing [8]. Further, cinnamon and chamomile have been shown to reduce the severity and duration of menstruation pain [6,7]. Peppermint oil has also been reported to alleviate abdominal pain symptoms [9]. Although the molecular mechanism, responsible for the ability of these herbal ingredients to improve pain and oral dryness, remains largely unclear, it is probable that the observed effects are mediated through trigeminal sensory neurons and taste cell activation, given that several of these herbal ingredients are known to elicit taste cell responses via the activation of various membrane proteins. Cinnamon, for example, is capable of activating ion channels (transient receptor potential ankyrin 1) located on trigeminal ganglion neurons and oral epithelium, and these ion channels are known to act as sensors of environmental pain, mechanical stimulation, and temperature [10]. In addition, peppermint is able to stimulate ion channels (transient receptor potential melastatin 8) expressed on trigeminal ganglion neurons and taste cells, and similarly known to function as sensors for temperature and pain. Further studies will serve to elucidate the precise molecular mechanism, and to further evaluate the effectiveness of the herbal mouthwash in potentially treating additional patient populations.

Methods

Study design

The study employed a Simon two-stage phase II study design[11], to evaluate the efficacy of the Nature’s Herbal mouthwash to treat oral mucositis (pain) and xerostomia (oral dryness). The studies for oral mucositis and

xerostomia were conducted separately, and the studies were conducted in accordance with IRB regulations and approval. All participants signed informed consent forms in order to be enrolled in the study.

For the oral mucositis study, the population considered for enrollment consisted of patients receiving systemic anti-cancer therapy with anthracyclines, topoisomerase II inhibitors, taxanes, 5-fluorouracil, MTOR inhibitors, bevacizumab, or a combination regimen (containing one or more of these agents).

For the xerostomia study, the population considered for enrollment consisted of patients with a history of xerostomia, or those at high risk for xerostomia.

The study was performed in 2 cohorts (6 patients per cohort). For the benefit of the participants, if only one (1) or more of the first six (6) patients treated develop a significant adverse event as described, the second cohort of the study was allowed to proceed, however, if 2 or more significant adverse effects were noted the study would not proceed. As there were no significant side effects, a total of twelve patients were treated in the study for the evaluation of a clinical response.

The duration of the study was 7 days; with the first treatment starting on Day 1. From Days 1-7, study participants used the mouthwash (at a dose of 10-15 mL) by rinsing for 20-30 seconds, four times a day. Participants were asked to complete a questionnaire (see supplementary figure S1 and S2), once daily on Days 1-7, to self-evaluate symptoms. Participant’s responses were evaluated after seven days of treatment.

Materials

Nature’s Herbal mouthwash, a cGMP-grade formulation of herbal ingredients (cinnamon, peppermint, cranberry, aloe, chamomile, and hydrogen peroxide, in filtered

Table 2: Self-reported patient improvement following 7-day treatment with herbal mouthwash.

Oral Mucositis Patient No.	1	2	3	4	5	6	7	8	9	10	11	12
Responses (%)	50%	31%	18%	70%	83%	50%	43%	50%	50%	78%	80%	33%
Avg. Patient Response	53%											
Std.Error	6%											
Xerostomia Patient No	1	2	3	4	5	6	7	8	9	10	11	12
Responses (%)	33%	13%	43%	29%	29%	29%	50%	22%	29%	33%	25%	63%
Ave.Patient Response	33%											
Std.Error	3.8%											

water, pH 5), was manufactured (USA) and provided for the study by Kiromic, Inc. Hydrogen peroxide content is below 3%, and is therefore not expected to be a significant contributor to the results obtained in this study [12]. Similarly, the pH of the solution is close to dental physiological pH and is not expected to have a significant effect [13,14].

Statistics

The study utilized a Simon 2-stage design with a null hypothesis of 5% IE ($p_0 = 0.05$) and an alternative hypothesis of 25% IE ($p_1 = 0.25$), with a desired significance level (α) and a desired power ($1-\beta$) of 0.05 and 0.9, respectively. For analysis of responses, a positive response was defined as $\geq 25\%$ improvement in severity of symptoms on day 8.

Conflict of Interest

M.C.I. is the Chief Executive Officer and Founder of Kiromic, Inc. The remaining authors are employed by Kiromic, Inc.

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