PATIENTS SATISFACTION SURVEY AND TOTAL ANTIOXIDANT CAPACITY IN PATIENTS WITH XEROSTOMIA COMPARED TO A PLACEBO GROUP: AN EVALUATION OF AN ANTIOXIDANT GEL FOR MANAGEMENT OF XEROSTOMIA

A Thesis

by

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ABSTRACT

The aim of this study was to evaluate the clinical performance of an antioxidant (AO) gel used to treat patients suffering from drug-induced xerostomia compared to a placebo gel.

The study was a double-blind, prospective, randomized clinical trial. It included adult subjects with drug-induced xerostomia (n=43). Unstimulated whole salivary flow was measured using the spit technique. A Xerostomia Visual Analog Scale (XVAS) was used to assess symptoms of xerostomia and a patient satisfaction survey (PSS) to measure satisfaction with the gel. XVAS survey evaluations were performed at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks. PSS evaluations were performed at 2 weeks, 4 weeks, 8 weeks, and 10 weeks. There was a crossover and wash out period from 4 to 6 weeks. Saliva was collected at each visit to measure Total Antioxidant Capacity (TAC).

43 patients were randomized into two groups, active or placebo. Symptoms improved in the treatment group (n=21) compared to the control group (n=15) after 10 weeks in the following PSS domains: Ability to eat, $p<.05$ at week 2, and Soothing effect, $p<.05$ at week 4. A significant difference was identified between the groups with the XVAS survey regarding the soothing effect after using the AO dry mouth gel ($P<0.05$). TAC analysis did not show any significant correlation with the use of gel.

The topical application of an antioxidant gel containing phloretin and ferulic acid compared to a placebo improved symptoms of drug-induced xerostomia. However, no significant anti-oxidant effect was found using TAC analysis.

DEDICATION

I dedicate my thesis to my husband and mother, Aly and Nazneen for their unlimited support throughout all of my academic pursuits.

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All work for the thesis was completed by the student, under the advisement of Dr. Rees of the Department of Periodontics.

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1. INTRODUCTION AND LITERATURE REVIEW

Specific Aims

The purpose of this study was to analyze the effect of an active anti-oxidant gel compared to a placebo gel on patients who complained of xerostomia, used by the same patients in a crossover study. Moreover, the analysis evaluated quality of life metrics and the objective metrics of salivary volume and total anti-oxidant capacity (TAC) within the two study populations. The null hypothesis was that the active gel treatment will not provide statistically significant additional alleviation in patient symptoms nor improve measurable saliva when compared to the control group.

Saliva and Its Functions

Whole saliva consists of a mixture of fluids from the major and minor salivary glands. Once excreted in the mouth, it contains crevicular fluid, food, microorganisms, oral epithelial cells, neutrophils, bronco-alveolar and nasal secretions.[1] Major salivary glands include the parotid, sublingual, and submandibular glands while 400 or more minor salivary glands are present in most soft tissues of the oral cavity.[2] The submandibular, sublingual and minor salivary glands primarily produce mucinous saliva while the two parotid glands primarily produce serous (watery) saliva. In most instances, unstimulated whole saliva is predominantly mucinous while stimulated salivary output is primarily serous from the parotid glands. Mucinous saliva is believed to provide the necessary soothing lubrication needed to prevent xerostomia while deficiencies in serous saliva may be more suggestive of salivary gland injury and resulting reduced salivary

flow.[3] Normal production of saliva is between 0.5 to 1.5 liters per day.[4] It is composed of 99% water and some electrolytes such as sodium, potassium, calcium, phosphate, and bicarbonate. Some organic components in saliva include immuno-globulins, proteins, mucins, and enzymes.[5] Since the organic component of protein and mucin aid with lubrication and coating of oral tissues, unstimulated saliva may be more protective in minimizing soft tissue damage in the oral cavity from microbial, chemical, and physical injury.[6]

Saliva plays a crucial role in lubrication of the oral and oro-pharyngeal soft tissues as well as in speech, mastication, taste, swallowing, and digestion. It buffers an otherwise acidic oral environment, contains antibodies and enzymes that contribute to host defense, and helps in tooth remineralization. Consequently, a salivary output sufficient to enable a patient to benefit from its many components is essential for oral health. When salivary function is reduced, patients are at a higher risk for developing caries and periodontal diseases, as well as experiencing denture discomfort, having difficulty in speaking and swallowing, and for developing diseases such as candidiasis when compared to patients who have normal salivary flow rates.[4, 7, 8]

Xerostomia

The term xerostomia describes a clinical state in which an individual perceives that their mouth is dry. The term salivary hypofunction represents actual and significant measurable reductions in salivary flow rate. In an effort to achieve standardization, most researchers now use this term to denote a flow rate of 0.1 ml/min or less.[9] Prevalence of

dry mouth and/or salivary hypofunction is nearly 100% among patients suffering from Sjögrens syndrome or receiving radiation for head and neck cancers.[10]

Symptoms of dry mouth may worsen during nighttime because salivary flow rate reaches its lowest circadian levels while asleep. Moreover, snoring, sleep apnea and mouth breathing may worsen the symptoms.[8] Consequently, performing saliva output collection as nearly as possible to morning waking offers the best opportunity to determine minimal daily salivary flow levels.[10, 11]

Xerostomia is a subjective sensation of mouth dryness and it is typically but not always related to salivary gland hypofunction or lower levels of normal salivary output.[9] Xerostomia has been reported to affect 1 out of every 4 or 5 adults worldwide, while 40-60% of the older adult population between 60-80 years of age complain of xerostomia.

Some individuals may complain of oral dryness despite having what clinically appears to be adequate production of saliva. However, most mouth dryness is due to dysfunction of the salivary glands for reasons ranging from medication-associated reduced salivary gland output to salivary gland destruction caused by radiation therapy, chemotherapy, or various systemic diseases and disorders such as Sjogren's Syndrome, sarcoidosis, scleroderma, rheumatoid arthritis, lupus erythematous, diabetes mellitus, HIV/AIDS, and others. When studying medication associated xerostomia, it is often not clear whether or not oral dryness is caused by a specific disease or by the medication used in treatment of the disease. Social and psychological factors, including but not limited to depression, anxiety, and stress may also induce dry mouth.[7] The prevalence of dry mouth, salivary hypofunction and saliva gland damage is nearly 100% among

patients suffering from Sjögrens syndrome or receiving radiation for head and neck cancers.[10]

Xerostomia in the Elderly

It is well established that patients 65 years of age or older are at higher risk for developing xerostomia and salivary hypofunction, although age itself does not appear to cause the salivary flow reduction.[3] Instead, this reduction of flow appears to be due to the presence of systemic diseases and disorders as well as the use of medications.[12] One study looked closely at the elderly population living in several long-term geriatric facilities in France. The authors examined and queried 769 individuals and found that 287 residents suffered from xerostomia. The incidence and severity of mouth dryness increased as residents aged and the use of anticholinergic medications increased. However, the total number of medications taken, even xerogenic medications, did not result in a statistically significant reduction in salivary flow among xerostomic patients. The amount of medication did not appear to play a significant role. Conversely sialagogue medications which induced sialorrhea successfully protected against the harmful effects of dry mouth.[13] These findings appear to attribute dryness to systemic factors affecting the individuals and suggest that xerogenic drugs do not necessarily cause salivary gland damage.

Medication Induced Xerostomia

To date, over 1800 drugs have been identified as being associated with mouth dryness, while xerostomic adverse effects have been confirmed in studies involving more than 400 medicaments. Most often the causative drugs have been those used for

prevention or treatment of high blood pressure, anxiety, depression or other psychiatric conditions, hypersensitivity reactions, Parkinson's disease, pain, and skeletal muscle spasm.[9, 14]

Medications that have anti-sialagogue effects frequently lead to symptoms of xerostomia. These primarily include anticholinergic agents such as antipsychotics, antidepressants, diuretics, anti-hypertensives, antihistamines, sedatives and anxiolytics, and opioid analgesic agents as well as non-steroidal anti-inflammatory drugs. In the current study, subjects were considered for participation if one or more medications inducing xerostomia were taken for longer than a year. It is believed that medication induced xerostomia is not associated with destructive changes in the salivary glands. Therefore individuals who have a history of previous head or neck radiotherapy, chemotherapy or specific autoimmune diseases such as Sjogren's Syndrome or lupus erythematous were excluded from the study since these conditions are known to be associated with glandular damage. [15]

Saliva production may be significantly reduced due to the synergistic effect of multidrug therapy.[14] However, this does not always seem to occur.[4] As age increases, salivary production may be slightly reduced and is worsened if the elderly individual is afflicted with two or more systemic diseases and taking several types of medications that have been identified as potentially causing xerostomia. Recently it has been confirmed that some sedatives may induce relatively severe salivary hypofunction.[16] Antidepressants may also decrease salivary flow rates when compared to healthy subjects who are not taking antidepressants.

Medication Induced Salivary Gland Dysfunction

Polypharmacy is often described as the simultaneous use of multiple drugs in a single individual often for the same abnormality or condition.[17] It is sometimes defined as the simultaneous use of 4 or more drugs.[18] Polypharmacy is a phenomenon most often seen in elderly individuals and is often the cause of xerostomia. Multidrug use may be the result of multiple prescriptions written by several different physicians for the same patient, but is often medically necessary to control single or multiple systemic disorders. A cross-sectional observational study of 120 elderly (>60 years old) hospitalized patients receiving polypharmacy confirmed an increased at risk of drug-induced xerostomia. The data showed that multidrug therapy may have a synergistic effect on the severity of the xerostomia. It was reported that using alcohol-containing antiseptic mouthwashes for more than two weeks worsened xerostomia in polypharmacy subjects. This finding affirms that oral health management can sometimes unintentionally worsen clinical findings and that the dental care provider must be cautious in avoiding any iatrogenic practices that can further lower the patient's quality of life.[18]

The decrease in unstimulated salivary flow rates induced by some medications and by polypharmacy can be highly variable. Patients with multiple medical disorders requiring treatment with multiple xerostomia-inducing medications are likely to have more significantly reduced salivary output. Patients with salivary gland hypofunction are indeed more susceptible to the adverse side effects and discomfort of dry mouth compared to patients with normal salivary gland function.[18]

In salivary gland hypofunction cases, prescribing medications that stimulate salivary gland output tends to alleviate dry mouth symptoms. Parasympathomimetic agents such as pilocarpine or cevimeline are often used for this purpose. In most individuals, these medications stimulate multiple types of exocrine glands increasing sweat, saliva, and tear production. They have been used to improve salivary output in patients suffering from Sjogren's Syndrome, Parkinson's disease, or other diseases that diminish salivary gland function. Sialagogues may also increase function in salivary glands damaged from head and neck radiotherapy. It is certainly possible that medication-induced salivary output may be more responsive to sialagogue therapy since the salivary glands are likely undamaged. As an example, a recent study evaluated salivary output in a group of patients taking the mild synthetic opioid, tramadol. The drug was shown to reduce salivary flow rates by 64 %. After administration of pilocarpine, salivary flow rates increased by 20% in comparison to baseline after Tramadol intake. Interestingly, maximum salivary flow was increased by 147% compared to baseline.[19]

Despite the immense data available on this topic, there has been no evidence-based list of medications that cause xerostomic symptoms until a systematic review was sponsored by the World Workshop in Oral Medicine in 2015. The objective of the study was to organize a list of medications that induce both salivary gland dysfunction (MISGD) and xerostomia or subjective sialorrhea. The authors developed what they termed the Anatomical, Therapeutic, and Chemical Classification System. This scheme first identified the organ or anatomic body systems, such as the cardiovascular and

musculoskeletal systems, that may require medication therapy. They then identified the types of pharmacological and chemical agents required to treat these systems and finally the specific medications in each treatment system that have been reported to cause xerostomia, salivary hypofunction, or sialorrhea. Finally, they classified the level of evidence supporting each reported drug (See Table 1). This intense and extensive review offers much needed information necessary to identify drugs that may be associated with patient complaints of xerostomia. Those drugs with high or moderate levels of supportive evidence were highlighted in the list. This classification system serves to confirm the effect many medications may have on salivary function. Unfortunately, the influx of new drugs into the medical market potentially adds to the list of offenders, which have the effect but have not yet been identified. Drugs used to treat the following systems were often strongly associated with xerostomia or other adverse salivary effects: Cardiovascular, alimentary and metabolism, genitourinary and sex hormones, anti-infective, anti-neoplastic, and immunomodulation agents, nervous system, musculoskeletal, sensory organs, and respiratory. The author identified 126 specific drugs, 56 of which showed strong evidence in regards to disruption of salivary gland function. These drugs fell into eight of the ten anatomical groups. Thirty-six of the drugs belonged in the nervous system category. Oxybutynin, tolterodine, duloxetine, quetiapine, bupropion, olanzapine, solifenacin, clozapine, fluoxetine, and venlafaxine were the most cited in the literature.[1, 12, 20]

The pathogenesis of medication-induced salivary gland dysfunction can be explained by their effects on the central nervous system. The initiation of salivary

secretion involves secretory cells that are supplied with muscarinic M1 and M3 receptors, alpha-1 and beta-1- adrenergic receptors and peptidergic receptors. Hence, drugs that have antagonistic actions on these autonomic receptors may affect the function of salivary glands and lead to xerostomia. It is known that anti-muscarinic drugs trigger oral dryness by blocking parasympathetic innervation from stimulating the secretory cells. Moreover, it was interesting that the use of the aminobisphosphonate alendronate reduced the unstimulated secretion of saliva.[20]

Table 1 ACT Levels. (Wolff A, Joshi RK, Ekstrom J, et al. A Guide to Medications Inducing Salivary Gland Dysfunction, Xerostomia, and Subjective Sialorrhea: A Systematic Review Sponsored by the World Workshop on Oral Medicine VI. Drugs R D 2016).

Table 1 Medications reported to induce xerostomia, salivary gland hypofunction, or sialorrhea with higher and moderate level of evidence, grouped according to their inclusion in first, second, fourth, and fifth ACT levels

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
Alimentary tract and metabolism	**Drug for functional GI disorder**	**Synthetic anti-cholinergics, quaternary ammonium compounds**	**Propantheline**	**A03AB05**
		Belladonna alkaloids, tertiary amines	**Atropine**	**A03BA01**
			Hyoscyamine	A03BA03
		Belladonna alkaloids, semisynthetic, quaternary ammonium compounds	**Scopolamine/ hyoscine**	**A03BB01**
	Anti-emetics and anti-nauseants	**Other anti-emetics**	**Scopolamine/ hyoscine**	**A04AD01**
	Anti-obesity preparations, excl. diet products	**Centrally acting anti-obesity products**	**Phentermine**	**A08AA01**
			Dexfenfluramine	A08AA04
			Sibutramine	**A08AA10**
		Peripherally acting anti-obesity products	Orlistat	A08AB01
		Serotonin–noradrenaline–dopamine reuptake inhibitor	Tesofensine	ND
Cardiovascular system	Cardiac therapy	Anti-arrhythmics, class Ib	Mexiletine	C01BB02
	Anti-hypertensives	Methyldopa	Methyldopa	C02AB01
		Imidazoline receptor agonists	**Clonidine**	**C02AC01**
	Diuretics	**Thiazides, plain**	**Bendroflumethiazide**	**C03AA01**
		Sulfonamides, plain	Furosemide	C03CA01
		Vasopressin antagonists	Tolvaptan	C03XA01
	Beta-blocking agents	**Beta-blocking agents, non-selective**	**Timolol**	**C07AA06**
		Beta-blocking agents, selective	Metoprolol	C07AB02
			Atenolol	C07AB03
	Calcium channel blockers	Dihydropyridine derivatives	Isradipine	C08CA03
		Phenylalkylamine derivatives	**Verapamil**	**C08DA01**
	Agents acting on the renin-angiotensin system	ACE inhibitors, plain	Enalapril	C09AA02
			Lisinopril	C09AA03
Genitourinary system and sex hormones	**Urologicals**	**Drugs for urinary frequency and incontinence**	**Oxybutynin**	**G04BD04**
			Propiverine	**G04BD06**
			Tolterodine	**G04BD07**
			Solifenacin	**G04BD08**
			Trospium	G04BD09
			Darifenacin	G04BD10
			Fesoterodine	G04BD11
			Imidafenacin	**ND**
		Alpha-adrenoreceptor antagonists	Alfuzosin	G04CA01
			Terazosin	G04CA03
Anti-infectives for systemic use	Anti-virals for systemic use	Protease inhibitors	Saquinavir	J05AE01
		Nucleoside and nucleotide reverse transcriptase inhibitors	Didanosine	J05AF02
			Lamivudine	J05AF05
		Non-nucleoside reverse transcriptase inhibitors	Nevirapine	J05AG01
			Etravirine	J05AG04
		Other anti-virals	Raltegravir	J05AX08
			Maraviroc	J05AX09
Anti-neoplastic and immunomodulating agents	**Anti-neoplastic agents**	**Monoclonal antibodies**	**Bevacizumab**	**L01XC07**

Table 1 ACT Levels Continued.

Guide to Medications Inducing Salivary Gland Dysfunction, Xerostomia and Subjective Sialorrhea

Table 1 continued

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
Musculoskeletal system	**Muscle relaxants**	**Other centrally acting agents**	**Baclofen**	**M03BX01**
			Tizanidine	**M03BX02**
			Cyclobenzaprine	**M03BX08**
	Drugs for treatment of bone diseases	**Bisphosphonates**	**Alendronate**	**M05BA04**
Nervous system	Anesthetics	Opioid anesthetics	Fentanyl	N01AH01
	Analgesics	Natural opium alkaloids	Morphine	N02AA01
			Dihydrocodeine	N02AA08
		Phenylpiperidine derivatives	Fentanyl	N02AB03
		Oripavine derivatives	**Buprenorphine**	**N02AE01**
		Morphinan derivatives	**Butorphanol**	**N02AF01**
		Other opioids	Tramadol	N02AX02
			Tapentadol	N02AX06
		Other anti-migraine preparations	**Clonidine**	**N02CX02**
	Anti-epileptics	Fatty acid derivatives	Sodium valproate/valproic acid	N03AG01
		Other anti-epileptics	**Gabapentin**	**N03AX12**
			Pregabalin	N03AX16
	Anti-Parkinson drugs	**Dopamine agonists**	**Rotigotine**	**N04BC09**
	Psycholeptics	**Phenothiazines with aliphatic side-chain**	**Chlorpromazine**	**N05AA01**
		Phenothiazines with piperazine structure	**Perphenazine**	**N05AB03**
		Butyrophenone derivatives	Haloperidol	N05AD01
		Indole derivatives	Sertindole	N05AE03
			Ziprasidone	**N05AE04**
			Lurasidone	N05AE05
		Diazepines, oxazepines, thiazepines, and oxepines	**Loxapine**	**N05AH01**
			Clozapine	**N05AH02**
			Olanzapine	**N05AH03**
			Quetiapine	**N05AH04**
			Asenapine	N05AH05
		Benzamides	Amisulpride	N05AL05
		Lithium	**Lithium**	**N05AN01**
		Other anti-psychotics	**Risperidone**	**N05AX08**
			Aripiprazole	**N05AX12**
			Paliperidone	**N05AX13**
		Benzodiazepine derivatives (anxiolytics)	Clobazam	N05BA09
		Benzodiazepine-related drugs	**Zolpidem**	**N05CF02**
			Eszopiclone	N05CF04
			Zopiclone	N05CF01
		Other hypnotics and sedatives	**Scopolamine/ hyoscine**	**N05CM05**
			Dexmedetomidine	N05CM18

Table 1 ACT Levels Continued.

First level, anatomical main group	Second level, therapeutic subgroup	Fourth level, chemical subgroup	Fifth level, chemical substance	ATC code
	Psychoanaleptics	**Non-selective monoamine reuptake inhibitors**	Desipramine	N06AA01
			Imipramine	**N06AA02**
			Amitriptyline	**N06AA09**
			Nortriptyline	**N06AA10**
			Doxepin	N06AA12
			Dosulepin	N06AA16
		Selective serotonin reuptake inhibitors	**Fluoxetine**	**N06AB03**
			Citalopram	**N06AB04**
			Paroxetine	**N06AB05**
			Sertraline	**N06AB06**
			Escitalopram	**N06AB10**
		Other anti-depressants	**Bupropion**	**N06AX12**
			Venlafaxine	**N06AX16**
			Reboxetine	**N06AX18**
			Duloxetine	**N06AX21**
			Desvenlafaxine	N06AX23
			Vortioxetine	**N06AX26**
		Centrally acting sympathomimetics	**Methylphenidate**	**N06BA04**
			Dexmethylphenidate	**N06BA11**
			Lisdexamfetamine	**N06BA12**
	Other nervous system drugs	Drugs used in nicotine dependence	Nicotine	N07BA01
		Drugs used in alcohol dependence	Naltrexone	N07BB04
		Drugs used in opioid dependence	**Buprenorphine**	**N07BC01**
	ND	**ND**	**Dimebon**	**ND**
			Tesofensine	ND
Respiratory system	Nasal preparations	Anti-allergic agents, excl. corticosteroids	Azelastine	R01AC03
	Drugs for obstructive airway diseases	**Anti-cholinergics**	**Tiotropium**	**R03BB04**
	Anti-histamines for systemic use	**Aminoalkyl ethers**	**Doxylamine**	**R06AA09**
		Piperazine derivatives	Cetirizine	R06AE07
			Levocetirizine	R06AE09
		Other anti-histamines for systemic use	Ebastine	R06AX22
			Desloratadine	R06AX27
Sensory organs	**Ophthalmologicals**	**Sympathomimetics in glaucoma therapy**	**Brimonidine**	**S01EA05**
		Anti-cholinergics	**Atropine**	**S01FA01**
		Other anti-allergics	Azelastine	S01GX07

ACE angiotensin-converting enzyme, *ATC* Anatomical Therapeutic Chemical, *GI* gastrointestinal, *ND* not determined

[a] Bold type indicates higher level of evidence

Evaluating Oral Dryness

Three metrics involving oral dryness have been used in clinical research. First is self-reported xerostomia. Since this method is primarily based on patient perception without guidelines to measure oral dryness, it is probably of little research value other than to serve as a basis for further scientific research. Secondly, reduced salivary output (hyposalivation) is confirmed through measurement of unstimulated whole saliva flow. The saliva measurement is considered positive when there is a level of unstimulated salivary flow that is below established norms. The median of normal unstimulated salivary output has been determined to be 0.3-0.4 ml. per minute while salivary hypofunction is identified as 0.1 ml or less of unstimulated flow per minute. Variations between 0.1 and 0.3 ml per minute are considered within the standard deviation of normal output although an unstimulated whole salivary flow rate of 0.1-0.2 ml/min is considered very low normal[21]. Thirdly, the oral cavity is clinically assessed for diagnostic signs and symptoms often associated with physical changes and injury occurring in individuals with clinically assessed dry mouth. This method is also problematic since these diagnostic signs and symptoms associated with xerostomia may be the result of some other factor resulting in false positives. Available evidence indicates that measurements of unstimulated or stimulated salivary output or both, constitute the most accurate method now available to assess salivary output.[7]

Dry mouth symptoms can range from mild oral discomfort to severe oral diseases that compromise patients' well-being, food consumption, and quality of life.[9] Only limited

data is available regarding the prevalence of xerostomia in the U.S. population and estimates range widely from 0.9% to 64.8%.[10]

Unstimulated whole saliva often is collected by means of the draining or drooling method, in which a patient's head is tilted forward and pooled saliva is drooled into a sterile container. An unstimulated rate of 0.1ml/minute or less is suggestive of salivary hypofunction. A more recent study defined unstimulated hyposalivation as being less than a range of 0.1-0.2 ml/min.[22] However, use of this range appears confusing and could result in inconsistent study findings. Consequently, we have elected to continue with the definition of hyposalivation as representing an unstimulated salivary flow rate of 0.1 ml. per minute or less.

Stimulated whole saliva is collected by challenging the salivary glands to produce maximum output through mastication. An inert material such as paraffin wax is chewed and salivary flow rates are measured. Gustatory stimulation is accomplished by stimulating salivary gland output with a sialagogue such as citric acid. Following salivary gland stimulation, the patient expectorates into a collection tube. Stimulated whole salivary flow rates 0.7 ml/minute or below have been suggested to be consistent with salivary hypofunction. Patients suffering from hyposalivation tend to experience inadequate bicarbonate and urea buffering, tooth erosion, and decreased remineralization, any of which can lead to an increased dental caries rate.[3, 21]

Clinically Assessed Dry Mouth

Patients may suffer from xerostomia with or without hyposalivation, or may experience hyposalivation with or without symptoms of xerostomia. Therefore,

including a clinical assessment of oral dryness is an important component in oral care for these patients. One study suggests that measuring unstimulated salivary flow rates in older adults may or may not confirm salivary gland hypofunction even in those who complain of xerostomia and in those whose oral examination findings are suggestive of dry mouth.[7]

Diagnosis of Xerostomia

Patient Surveys: Several authorities have affirmed that asking only a few questions is beneficial in confirming a clinical diagnosis of xerostomia.[11, 23] Recommended questions to ask the patient include:

Does the amount of saliva in your mouth seem to be too little?[23]

Does your mouth feel distinctly dry?[24]

Does your mouth feel dry when eating a meal? [25]

Do you sip liquids to aid in swallowing dry food?[25]

Do you have difficulty swallowing?[26]

Do you have dry lips?[26]

Do you have difficulty speaking?[26]

Do you have difficulty eating dry foods?[26]

These questions appear to primarily assess the sensation of oral dryness. They may well facilitate the diagnosis of xerostomia, but they are subjective in nature and responses may be influenced by level of understanding and personality of the persons being queried. Others have suggested that a more detailed questionnaire and evaluation system may more accurately measure the degree of hypofunction.[23] It is not yet clear that

these questions are of benefit in assessing treatment outcomes for afflicted patients. A clinical oral examination should be conducted to assess the oral soft tissues for evidence of the physical changes associated with oral dryness to include the presence of periodontal diseases and increased incidence of dental caries.

A thorough head and neck examination should be completed to assess the major salivary glands for enlargement, tenderness, or masses. The healthcare provider should palpate and "milk" the salivary glands while examining the intraoral salivary ducts to determine if they are capable of producing an adequate amount of saliva.[15]

If there is suspicion of an underlying systemic condition associated with mouth dryness, blood studies may be beneficial in establishing the underlying etiology. Referral to a rheumatologist or other medical specialist is indicated if Sjogren's Syndrome, rheumatoid arthritis, or various other autoimmune diseases are suspected, or glandular disfigurement is identified.[27]

A complete blood count may be requested especially if an infectious process is suspected, and hemoglobin A1C or other serum glucose tests may be appropriate for a patient who is believed to be a potentially undiagnosed or inadequately controlled diabetic.[15]

Minor salivary gland biopsy is a useful diagnostic tool for identifying underlying pathological changes associated with salivary gland dysfunction, especially when the clinician is attempting to identify the underlying etiology of salivary dysfunction as it relates to systemic diseases.[9,23,24]

Current Management of Xerostomia

Treatment planning to relieve patients from dry-mouth should be tailored to the individual patient. A multidisciplinary model of care for xerostomia and salivary gland hypofunction should include the following components: (1) patient education—a patient-centered process emphasizing daily oral hygiene, regular dental visits, use of topical fluoride, tobacco-use cessation counseling, avoiding caffeine products, dietary modifications, and other interventions; (2) management of systemic conditions and medications used in consultation with the patient's physician, oncologist, or other health care providers; (3) preventive measures to reduce oral disease and associated complications; (4) pharmacological treatment with salivary stimulants (sialagogues) and substitutes; and (5) for patients who cannot tolerate sialagogues, palliative measures to improve salivary output, such as use of sugar-free salivary stimulants like a chewing gum, mints, lozenges, raw carrots, celery and possibly capsaicin products.[9]

Oxidative Stress in Oral Health

Several research studies have explored the role of normal saliva in maintaining healthy teeth and oral soft tissues. An important aspect of this research is the correlation between inflammation, oxidative stress markers, and the total anti-oxidant capacity (TAC) of saliva. It is now known that inflammation and oxidative stress begins with a proliferation of free radicals including reactive oxygen species (ROS). Free radicals are uncharged molecules that are typically highly reactive and short-lived. They have an unpaired valence electron and so they attempt to "rob" electrons from other molecules. Unchecked, the process of "electron theft" can result in deterioration of cell walls and

ultimately cell or tissue damage. It has been found that in the oral cavity free radicals tend to result from external sources, such as alcohol, nicotine, and hydrogen peroxide, as well as from performance of various dental procedures and placement of a variety of dental materials, including veneers, implants, and crowns. Oral infections due to gingivitis, periodontitis or even root caries also generate free radicals as part of the inflammatory response.[28]

An excess of ROS or free radicals leads to oxidative stress. Prolonged oxidative stress can result in the development of a chronic inflammatory state including systemic inflammatory disease.[29] However, oxidative stress can be reversed when free radicals are neutralized by anti-oxidant (AOs). These large, complex molecules work to stop the damage that free radicals start by "donating" electrons to free radicals. Each type of antioxidant works either by halting the electron theft or by stopping the entire process.

Normal saliva is rich in AOs, including uric acid, albumin, ascorbic acid, glutathione, and specific AO enzymes. When patients experience dry mouth, they are generally producing reduced quantities of saliva leading to low levels of AOs. When AO levels in saliva are too low to neutralize the free radicals, the tissues are prone to oxidative stress. In fact, several studies have implicated high levels of oxidative stress markers[30] and low levels of salivary AOs (measured by total antioxidant capacity) in oral diseases including periodontal disease, aphthous ulcers, dental caries, and oral cancer.[31-35]

Research Supporting the Positive Effects of Anti-oxidants

AOs are important factors in minimizing the effects of free radicals and oxidative stress in the oral cavity. Published literature supports the topical use of polyphenols in the oral cavity to amplify the TAC of saliva and reduce oral oxidative stress.[36] Polyphenols are reactive metabolites found in plant-derived foods, particularly fruits, seeds, and leaves. Polyphenols have a chemical structure enabling them to attach to oral epithelial cells in a manner that results in a "time release" effect in the mouth allowing the polyphenols to work in concert with salivary AOs to significantly reduce oxidative stress in the oral cavity.[36] The polyphenolic AOs, phloretin and ferulic acid, mitigate the adverse effects on oral fibroblasts caused by ROS from nicotine, alcohol, hydrogen peroxide, and other sources[37]. Moreover, carefully controlled mixtures of bioactive AOs have promoted the proliferation and migration of human oral fibroblasts.[28] Epidemiological human studies, animal studies, and in vitro studies have shown evidence that directly and indirectly support the importance of the presence of polyphenols in prevention of oral cancer.[38] It has also been shown that polyphenols inactivate periodontal pathogens and increase AO capacity of oral fluids (saliva and crevicular fluid), thereby suggesting a protective effect against most periodontal diseases.[39] There is also growing evidence to indicate that AOs may benefit individuals with xerostomia or salivary hypofunction.[40, 41]

Xerostomia and Oxidative Stress

Oxidative stress may be associated with some forms of xerostomia and ROS levels may increase as salivary hypofunction worsens. Saliva may be the first line of

defense against reactive oxygen species (ROS). [42] In a state of decreased salivary output, such as found in drug-induced xerostomia, ROS such as peroxidases flourish, which results in a reduction of the protective function of the saliva. Oxygen radicals mediate apoptosis thus causing oxidative damage to membrane lipids and proteins resulting in reduced function. The lack of antioxidants has been implicated in tissue damage leading ultimately to adverse effects associated with oral dryness.[43]

One study concluded that the severe salivary hypofunction found in Sjögren's Syndrome may result from lowered TAC in the salivary glands. [41] The ionizing radiation used in cancer treatment destroys tumors but can also cause changes in the morphology and function of the salivary glands and oral mucosa.[44] Furthermore, an increase in ROS-induced oxidative DNA damage has been implicated as the source of minor idiopathic salivary gland dysfunction found in some xerostomic patients.[39]

AOs have been used in the treatment of xerostomia caused by radiation damage to salivary glands. It has been found that the AO, superoxide dismutase, may protect salivary glands by neutralizing the superoxide ROS. [45] Another study on the polyphenolic AO, resveratrol, concluded that this natural AO can protect salivary glands from damage from direct ionizing radiation similar to that administered in cancer radiotherapy, and it may be effective at lessening the side effects from salivary gland dysfunction caused by irradiation when taken prior to the therapy.[46] Polyphenols are also found in green tea. Epigallocatechin-3-gallate (EGCG) is the most potent green tea polyphenol. This polyphenol in MightTeaFlow™ lozenges was utilized in a study population consisting of patients with xerostomia and SS patients. After 8 weeks of

therapy, the formulation resulted in statistically significant increases in saliva production (unstimulated saliva increased 3.8 fold and stimulated saliva 2.1 fold).[40]

Products for Management of Xerostomia

There are many over-the-counter products touted to be beneficial in managing xerostomia and salivary dysfunction. Although there is little evidence to support the benefits of many of these products, some studies have documented improved effectiveness in salivary output with resultant improvement in xerostomia. A recent study evaluated lycopene-enriched virgin olive oil for treatment of drug-induced xerostomia. The oil contained the antioxidant, coenzyme Q10, which has been reported to increase adenosine triphosphate (ATP) production and stimulate secretory ability, and its use led to an increase in salivary secretion. Lycopene is a carotenoid found in tomatoes. This product, Surat™, was used as a spray three times a day for three-months in 60 patients and then compared with participants using an inert placebo. All subjects were taking medications that can cause hyposalivation. These drugs were classified as xerogenic according to the Anatomical, Therapeutic, and Chemical Classification System. [20, 47] The subject group was also suffering from polypharmacy-induced xerostomia. The authors reported an overall statistically significant increase in unstimulated saliva in both the treatment group and the placebo group, but the difference between the groups was not statistically significant. Symptoms also improved significantly in both groups. The reason for the improvement in both treatment and placebo groups was not determined. Results of this study suggested a significant increase of unstimulated salivary flow rate and improvement in xerostomia symptoms and

complaints.[48] Table 2 is a modified summary of various other topical products that have been evaluated.[22] A similar product has been studied under the name of Xerostom™ which contains olive oil, betaine, and xylitol and is marketed in the form of a toothpaste, mouth rinse, mouth spray, and gel.[49]

The antioxidant gel ProVantage™ consists of ferulic acid, which is found in seeds and leaves of plants. Phloretin is derived from apples and polyphenolic antioxidants[50]. Polyphenolic antioxidants may provide some protection against xerostomia by preventing tumor necrosis factor-alpha induced cytotoxicity. They were mixed with a base of menthol, thymol and essential oils, sage, and clove flower oil. These ingredients have shown to aid in antiseptic activity[51-53]. The gel also included xylitol which supports inhibition of *Streptococcus mutans*.[54]

Table 2 Modified from Navarro-Morante Study-Summary of Trials on Topical Interventions. (Navarro Morante A, Wolff A, Bautista Mendoza GR, Lopez-Jornet P. Natural products for the management of xerostomia: a randomized, double-blinded, placebo-controlled clinical trial. J Oral Pathol Med 2016).

Author	*Type of preparation*	*Vector*	*Sample characteristics*	*Design*	*Duration*	*Sialometry (results)*	*Subjective assessment (results)*	*Oral quality of life (results)*
Alpoz	Xialine placebo	Spray	Sjogren's	Single-blind, crossover study	Two weeks	No	Questionnaire (no superiority vs placebo with regard to burning tongue, diminished taste, and waking up at night to sip water)	No
Alpoz	Buccotherm placebo	Spray	Xerostomia mixed etiology	Single-blind study	Two weeks	Yes (no superiority vs. placebo)	VAS (no superiority vs placebo)	No
DeRossi	Green tea	Lozenges	Medication-induced Xerostomia Sjogren's	Double-blind, placebo-controlled, randomized design	Eight weeks	Yes (Increase unstimulated and stimulated salivary flow rates)	VAS (improvement with no superiority vs. placebo)	No

Table 2 Modified from Navarro-Morante Study-Summary of Trials on Topical Interventions Continued.

Epstein	Biotene placebo	Mouthwash	Xerostomia radiation therapy	Double-blind, crossover design	Two weeks	No	VAS (superiority vs placebo)	No
Femiano	Artificial saliva Citric Acid Distilled water	Mouthwash	Xerostomia Medication usage	Double-blind, randomized	4 weeks	Yes (None of the drugs tested affected unstimulated whole saliva flow)	Questionnaire (artificial saliva and citric acid provided immediate relief from oral dryness)	No
Gil-Montoya	Antimicrobial proteins placebo	Mouthwash and oral gel	Elderly institutional medication usage	Rnadomized, doube-blind and crossover	4 weeks	Yes (No effect on stimulated whole saliva flow)	VAS (improvement in terms of the presence of dry mouth, and the need to drink fluids to swallow)	Yes (Improvement in terms of OHIP values)
Gomez-Moreno	Malic acid placebo	Spray	Antidepressant Medication-induced xerostomia	Double-blind, randomized	Two weeks	Yes (Increased unstimulated and stimulated salivary flows rates)	Questionnaire (improvement of dry mouth among 85.7% of treated subjects, in contrast to just 14.2% for	No

Table 2 Modified from Navarro-Morante Study-Summary of Trials on Topical Interventions Continued.

Karim **(Present study)**	Antioxidants	Gel	Medication induced xerostomia	Double-blind, crossover design	10 weeks	Yes (Improvement with superiority vs. placebo)	VAS (Improvement with no superiority vs. placebo)	No
Lopez-Jornet	Toothpaste (triclosan, fluoride, mineral salts, aloe vera) versus Biotene	Toothpaste mouthwash	Xerostomia hyposialia Medication usage Sjogren's syndrome	Double-blind, crossover design	Two weeks	Yes (Unstimulated salivary flow increased)	VAS (the efficacy of the use of a toothpaste and mouthwash based on triclosan, fluoride, gingival revitalizers, and mineral salts, with positive clinical)	No
Navarro-Morante	Lycopene placebo	Spray	Xerostomia Medication usage	Double-blind, randomized	12 weeks	Yes (improvement with no superiority vs. placebo)	VAS (improvement with no superiority vs placebo)	Yes (improvement with no superiority vs. placebo)
Silvestre	Mixt (solution potassium thiocyanate, potassium chloride, sodium,	Spray	Xerostomia and mixed etiology	No randomized No placebo	7 days	Yes (20 patients 54% reported some improvemen	VAS (immediate relief)	No

Validity and Reliability of Surveys

From table 2 it is evident that many studies use Visual Analog Scales (VAS) to determine improvement or worsening of symptoms. Several studies have been conducted to prove their validity and reliability for the clinical diagnosis of xerostomia and salivary gland dysfunction. Visual Analog Scales (VAS) are widely used to measure pain as well. Most pain studies demonstrate the VAS as being valid and reliable to assess between chronic and experimental pain.[55, 56]

There are several advantages of using a scale to represent patients' response to questions asked. Investigators are able to visualize ratio properties of their responses

which is not evident when using ordinal or categorical measurements that are challenging to quantify and translate. Use of a scale is beneficial in analyzing changes in xerostomia over time. The main study that has made use of a VAS within the field of xerostomia included an 8-item VAS for xerostomia. They measured unstimulated and stimulated saliva in 36 healthy subjects who were given an antisialogogue or placebo and found significant reliability for 7 of the 8 VAS items. Difficulty swallowing and lip dryness had a strong significant reliability whereas the amount of saliva in the mouth was not significant. Significant correlations were observed measuring moving averages for VAS and salivary flow rate values. The validity of the VAS questionnaire was decided by comparing baseline VAS values with the baseline salivary measurements. This study showed that nearly all the VAS items were significantly reliable.[57]

In another study evaluating the use of a xerostomia VAS in older people who were residents at community care centers, investigators also found VAS to be highly reliable and valid. This study compared the VAS to oral health-related quality of life measures and found a significant association between subjective and objective dry mouth. It even compared the Fox questionnaire to VAS. The Fox questionnaire is answered using ordinal categories from rare to always. Questions were converted in a manner that they could be answered with a VAS. The validity of subjective dryness when measured with VAS instrument was high. The correlation between the scores in regards to the question "does your mouth feel dry?" was very significant. Over all, this study demonstrated that dry mouth conditions correlate with quality of life in frail elderly people.[25, 58]

Total Antioxidant Capacity

The concept of Total Antioxidant Capacity (TAC) was formulated to identify all the cumulative effects of the antioxidants present in plasma and body fluids. It may be a convenient method for quantification of antioxidant effectiveness in preventing disease.[59] Uric acid is the major antioxidant in saliva accounting for 85% of TAC of both stimulated and unstimulated saliva. Other naturally occurring salivary antioxidants include albumin, ascorbate, and glutathione. It has been claimed that unstimulated saliva contains higher total antioxidant capacity than stimulated samples. Consequently, since saliva carries so many antioxidants, it is difficult, time consuming, expensive, and probably unnecessary to measure AOs in both unstimulated and stimulated saliva independently. Therefore, TAC of unstimulated saliva could be a suitable measure of the antioxidant systems since AOs function together and measurement of any individual antioxidant may be less representative of the whole antioxidant status.[60]

TAC activity in saliva is measured by the 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) radical cation (ABTS+). This method works based on the ability of antioxidant molecules to quench the long-lived ABTS+, blue-green chromophore with characteristic absorption at 734 nm.[31] The reaction is based on the ability of aqueous and lipid antioxidants to inhibit the oxidation of the 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) to ABTS+. ABTS+ is formed by the interaction of ABTS with ferrylmyoglobin radical species, generated by the activation of metmyoglobin with hydrogen peroxide resulting in the blue-green color. The antioxidants in the sample cause suppression of the absorbance of ABTS+.[61] The capacity of the antioxidants to

prevent ABTS oxidation is then compared with that of standard Trolox, a water soluble tocopherol (Vitamin E) analogue via an antioxidant analysis assay kit. It is called the "Trolox equivalent antioxidant capacity" (TEAC) method or 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid assay.[62] There are other methods to measure TAC as well. They include the "ferric reducing-antioxidant power" (FRAP), which is based on reduction of ferric ions to ferrous ions. This is done by the effect of reducing power of the plasma constituents measured spectrophotmetrically at 593 nm. Another TAC method includes the "oxygen radical absorbance capacity" (ORAC). It is based on the ability of plasma to trap peroxyl radicals formed from thermal decomposition of azo initiators and measurement of fluorescence decay of B-phycoerythrin. This study utilized the TEAC method due to its simplicity and reported high analytic quality.[63]

Based on current literature, there appears to be strong indications that free oxygen radicals may play a damaging role in the development of salivary gland hypofunction. However, there is insufficient information about using ProVantage AntiOxidant™ Gel as a means of reducing oxidative stress in medication related xerostomic individuals and whether or not its daily use leads to any differences in salivary volume and TAC in patients with hyposalivation or the sensation of xerostomia compared to controls. There is also evidence that reduced levels of saliva are linked to subtle or obvious inflammation of the oral soft tissues, which may also be adversely influenced by free oxygen radicals. Anecdotal studies indicate that many patients find relief from the discomfort associated with xerostomia when treated with antioxidant therapy. Thus, it is the purpose of this study to evaluate the role of ProVantage AO

Gel™ therapy in management of medication-induced xerostomia. We propose evaluation of the TAC and ROS levels in patients with medication-associated xerostomia before and after use of ProVantage AO Gel™ as well as to assess any patient- perceived improvement in comfort following AO therapy compared to controls.

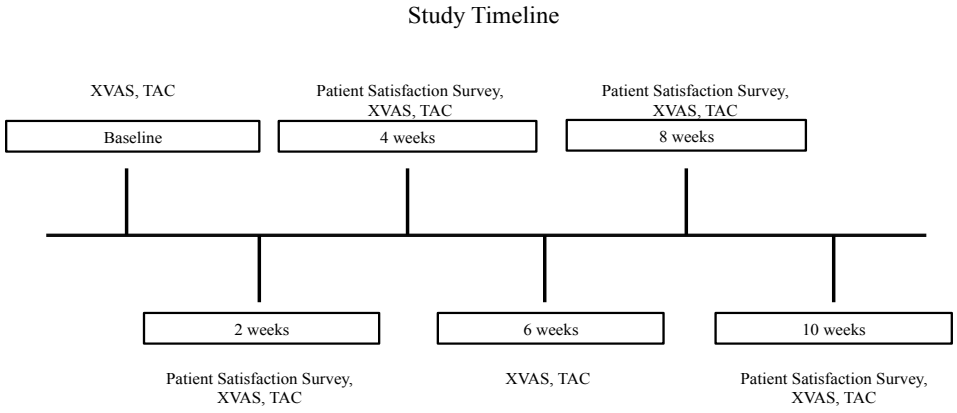
2. METHODS AND MATERIALS

This prospective cohort study was a crossover clinical trial to test the effect of a topically applied active antioxidant gel against a placebo in improving the quality and quantity of saliva as well as reducing clinical symptoms of medication-induced xerostomia. Changes in salivary flow rate and patient-perceived oral health using various quality-of-life criteria were determined at baseline, two weeks, and four weeks prior to crossover period of 2 weeks and again at baseline, two, and four weeks after crossover (Figure 1). Patient satisfaction regarding the treatment modality was also evaluated.

In this study, 45 human patients with medication-induced xerostomia were enrolled. For the purpose of this study, a patient with "medication-induced xerostomia" was defined as a patient who had been using at least one systemic medication for at least a year that had been reported to cause xerostomia as a side effect, and who did not have a history of Sjogren's Syndrome, sarcoidosis, or head and neck radiation therapy. Upon enrollment, each patient completed four Patient Satisfaction Survey (PSS) and six Xerostomia Visual Analog Scale (XVAS) evaluations. Each participant was given a gel to use at home, blinded to which was the active gel or inactive placebo. At the initial visit, informed consent was obtained from each patient, surveys completed, saliva collected, and instructions were given to use the gel three (3) times per day: after their normal oral care regimen in the morning, mid-day after eating, and just before bed.

Patients returned to Texas A&M University College of Dentistry (TAMUCOD) at 2 weeks and 4 weeks after the initial appointment for saliva sampling and completion of the XVAS. After 4 weeks of using the active gel or placebo, all patients stopped using any gel product and continued only with their normal oral care regime for a period of 2 weeks (washout period). At the conclusion of the two-week washout period, patients returned to TAMUCOD to provide salivary samples and to establish a new baseline at week 6. At that office visit, they were given the second gel and instructed to resume the same usage schedule of three (3) times per day. They were asked to return to TAMUCOD at 8 weeks and again at 10 weeks to complete the visual analog scale (XVAS) and provide saliva samples (Figure 1).

Figure 1 Study Timeline



The gel products were arranged in numerical order from 1 to 45 marked as either A or B. and randomized so that neither the patient nor investigator was able to

distinguish between the active gel or placebo, and the investigator did not know how many patients were using the active gel or placebo during the pre- or post-crossover period.

Patients were assigned the number on their product series; for example each patient was given a specific number with an A and B component but the patient was known by his/her initial number, 1, 2 etc. throughout the study to ensure privacy and assure operator blindness. Patients were not allowed to undergo dentist/hygienist dental prophylaxis, debridement, or scaling and root planing during the trial period but were instructed to use their own personal oral care regime. Patients were compensated $15 per visit for participating in the study.

Patient Population

Inclusion criteria for the study participants were adults ranging in age from 18 to 85 years. At the initial visit, the investigators provided informed consents. Once a patient consented to participate in the study, a xerostomia visual analog scale survey and patient satisfaction survey were completed to determine the baseline level of xerostomia per patient. Past medical and dental records were reviewed to determine probable cause of xerostomia. Patients with xerostomia likely due to medication were admitted into the study. During each subsequent visit patients completed the PSS and XVAS, and salivary flow was measured, and saliva samples were collected for total antioxidant capacity assay. The selection criteria included:

Inclusion criteria:

- Age: 18-85
- Both men and women of all ethnicities were included.
- Systemic conditions: generally healthy, ASA I or II.
- Has used at least one systemic medication for one or more years that had been reported to cause xerostomia as a side effect.

Exclusion criteria:

- Current smoker or smoker within the past 10 years
- Pregnancy
- History of head and neck radiation treatment or recent chemotherapy.
- History of salivary impairments such as salivary stones or previous salivary gland surgeries due to neoplasm or sialolithiasis.
- Allergy to any of the following ingredients: phloretin, ferulic acid, thyme, sage oil, clove flower oil, xylitol.
- Presence of primary biliary cirrhosis, sarcoidosis, uncontrolled diabetes, HIV, Sjogren's Syndrome.

The Active Gel

The active gel, labeled by PerioSciences as AO ProVantage™, contains compounds generally recommended as safe by the FDA, and is currently dispensed in dental offices along with an antioxidant-containing toothpaste and mouthwash. The gel was launched as a cosmetic in 2010 after completion of a six-week safety study with 100 patients. While the gel is extremely well tolerated and many practitioners use the gel

with xerostomia conditions, no medical claims have been made in marketing the AO ProVantage™. Anecdotal evidence provided by dentists, as well as preliminary data from a pilot clinical study indicate that AO ProVantage™ provides symptomatic relief from dry mouth that may be equal to or superior to other marketed non-prescription remedies. The gel is composed of glycerin 10%, water, xylitol, propylene glycol, PEG 12, sorbitol, poloxamer 407, cellulose gum, phloretin, ferulic acid, thyme, sage oil, clove flower oil, potassium sorbate, menthe piperita (peppermint) leaf oil, spilanthes, acmella extract, sodium hyaluronate, caprylic/carpic triglyceride, sodium chloride, sodium citrate and disodium EDTA.

Study Organization

PerioSciences cotracted with TAMUCOD to provide the active gel and placebo gel similar in texture and taste in identical containers. The Thesis Committee conducted regular meetings to monitor progress, solve problems, ensure proper recruitment and retention of patients, ensure proper treatment protocol, address potential adverse events, and review data management.

Patient Recruitment Plan

Patients consented into the study were registered patients of the TAMUCOD Stomotology Center and the dental college. After discussion of the proposal and signing of the informed consent approved by the TAMUCOD Institutional Review Board (IRB), a fully executed copy of the consent document was provided to the participant and the original retained by the principal investigator.

Participating patients attended 6 clinical sessions in this crossover random controlled double blinded study. At the first session, baseline xerostomia assessment and saliva collection was obtained and other data collected as necessary and the active or placebo gel was dispensed to participants. Data was again collected at two weeks intervals for a total of four weeks. This was followed by a two week washout period and the procedure was repeated for another 4 weeks using the opposite of the active or placebo gel previously dispensed.

At each visit the patient was examined, a patient questionnaire completed, and saliva was collected to be quick frozen and subsequently used to determine variations in total antioxidant capacity, and salivary output.

Measurement of TAC

TAC of each saliva sample was measured by antioxidant assay kit from Cayman Chemical. Each assay kit included a 96-well plate in which two blanks, two total activity, two nonspecific binding, two maximum binding, two sets of standards, and 36 duplicate saliva samples were assayed. Saliva was diluted 1:2 with assay buffer before assaying. Trolox standard wells were prepared by adding 10 µl of Trolox standard, 10 µl of Metmyoglobin, and 150 µl of Chromogen per well. Sample wells needed 10 µl of sample, 10 µl Metmyoglobin, and 150 µl of Chromogen to wells. To obtain reproducible results, antioxidant levels of the samples should fall within the standard curve. Reaction was initiated by adding 40 µl of Hydrogen Peroxide Working Solution to all the wells being used. The covered plate was incubated for 5 minutes at room temperature. The

absorbance was read at 750 nm using a plate reader. The data for the standard curve was plotted and compared to the sample results to determine TAC levels between visits.

Measurement of Salivary Flow

Patients were asked to supply two saliva samples during each visit including the initial visit. They were instructed to provide these samples before eating, drinking, brushing, or rinsing after waking. To measure the quantity of saliva, one unstimulated sample was collected without stimulation after a non-alcohol containing, purified water rinse. This was accomplished at the beginning of the visit by having the patient spit into a sterile container over 5 minutes. A second saliva sample was collected at the end of the visit using the same collection protocol to measure Total Antioxidant Capacity (TAC) in the saliva sample. Saliva was quick-frozen and stored and stored for future assessment.

Gel Usage

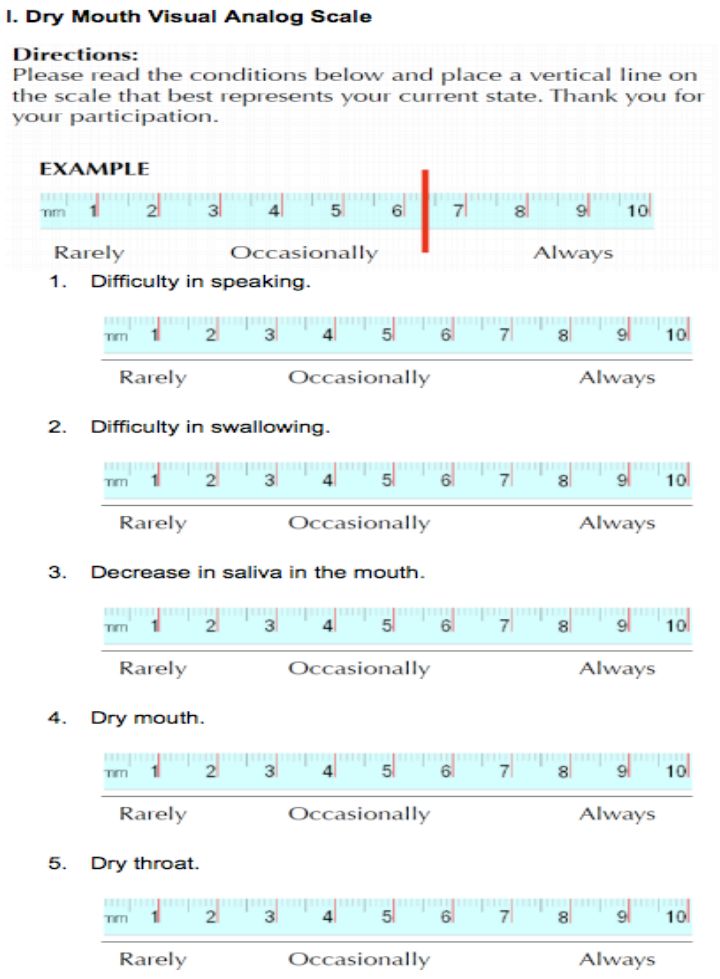
The gel tubes were weighed on a calibrated scale at every visit to monitor the usage of the gels throughout the study on a calibrated scale. These values were recorded to ensure compliance and measure usage amount.

Survey Instruments

To assess the impact on oral health-related quality of life (OHQOL) among xerostomia patients, the study used two different instruments. Xerostomia Visual Analog Scale (XVAS) were based on the work of Thomson and Patient Satisfaction Survey (PSS).[23] The visual analog scale (VAS) evaluated the occurrence of specific symptoms, using a 10-point scale ranging from “Rarely” to “Always.” Subjects were asked to mark a vertical line through a 10cm horizontal ruler to show level of symptoms (0, rarely

experiencing symptoms; 10, always experiencing symptoms). The VAS was used to evaluate symptoms at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks. It consisted of five items: (1) Difficulty in speaking; (2) difficulty in swallowing, (3) decrease in saliva in the mouth, (4) dry mouth, and (5) dry throat.

Figure 2 Xerostomia Visual Analog Scale



PSS measured perceived satisfaction on five aspects of the AO gel product using a simple five-point Likert scale, from “Very Satisfied” to “Very Unsatisfied.” Subjects were asked to evaluate changes to symptoms as they finished using the gel. The satisfaction scale asks participants to best describe how their symptoms are now compared to how they were before applying the gel. The questionnaire was completed at baseline, 2 week, 4 week, 8 week, and 10 week visits. It assessed the following five variables:

1) Time it took to feel relief after using the dry mouth gel.
2) Confidence in breath after using the dry mouth gel.
3) Ability to eat after using the dry mouth gel.
4) The soothing effect in the mouth after using the dry mouth gel
5) The ability to sleep through the night after using the dry mouth gel.

Figure 3 Patient Satisfaction Survey

II. Please make *ONLY ONE* selection that best represents your agreement with the statement.

How Satisfied are you with:	Very Satisfied	Satisfied	Neutral	Unsatisfied	Very Unsatisfied
1. Time it took to feel relief after using the dry mouth gel.					
2. Confidence in breath after using the dry mouth gel.					
3. Ability to eat after using the dry mouth gel.					
4. The soothing effect in the mouth after using the dry mouth gel.					
5. The ability to sleep through the night after using the dry mouth gel.					

Data Collection and Analysis

All survey data was entered and stored at TAMCOD. All saliva specimens were stored frozen in an -80 degrees Celsius freezer at TAMUCOD for TAC analysis. The samples were centrifuged at 1250g for 10 min at 4 degrees Celsius prior to freezing. Forms were organized for each patient visit. Each form had space for the following identifiers: patient number, patient initials, treatment type, and visit number. Treatment/measurement performed was recorded on the form. When a visit was completed, the investigators checked each form for accuracy and completeness. After forms had been reviewed for clinical features and checked for completeness, they were

logged into the database and a forms checklist for each patient updated. After logging the data, forms were entered into a computer, producing primary and secondary data files. The data entry procedure was designed to allow only codes listed on the form and values in the expected format to be entered. Reports were developed to list completion status, exits, and forms for subsequent statistical analysis.

Confidentiality of patient data is always an important consideration. The biostatistician did not receive the patient's name or any identifier such as medical record number or SSN. Copies of data forms were stored in a locked file cabinet in the locked office of the Principal Investigator.

The software platform for the study was Microsoft ® 2000. Programs and data resided on a computer at TAMUCOD. The computer is located in a room with restricted access. In addition to passwords necessary to log into the computer and receive access to the database directory, security limited entry to the database to only specific users via password. The computer was backed up daily to an external hard drive. The study database was backed up to zip disk or CD periodically. The computer is protected with an uninterruptible power supply (ups).

For this study, 45 patients were recruited, and using a within patient standard deviation of 12 ng/mL and a type I error rate of 0.05, a difference between treatments of 24 units was considered significant. As this patient population is considered to be highly motivated, a 20% drop-out rate is assumed, so 45 patients were recruited for the study. Active gel and placebo groups were compared using Mixed Model Analysis. Medians were used to describe characteristics of the patient population.

The primary hypothesis of the study was that the active gel would increase TAC in saliva compared to placebo. A linear mixed model statistical analysis was used to examine the outcome variable TAC. The "between" factor was the two treatment groups (active gel versus placebo), while the "within" factor was the time measurements made (baseline, 2 week, 4 week, 6 week, 8 week, and 10 weeks).

A linear mixed model statistical analysis was used to examine each outcome variable listed below. The "between" factor was the two treatment groups (active gel versus placebo), while the "within" factor was the time measurements made (baseline, 2 week, 4 week, 6 week, 8 week, and 10 weeks). The secondary hypotheses that the active gel provided better treatment outcomes than placebo included: (1) TAC analysis, (2) salivary flow rate, (3) Xerostomia Visual Analog Scale.

Five aspects of the antioxidant gel product were assessed using a simple five-point Likert scale, from "Very Satisfied" to "Very Unsatisfied." Patient responses to the satisfaction survey were combined into a total score. In this analysis the time measurements included baseline, 2 week, 4 week, 6 week, 8 week and 10 weeks.

To analyze data, IBM SPSS V20 was utilized. All tests, unless otherwise noted, were performed using $p < 0.05$.

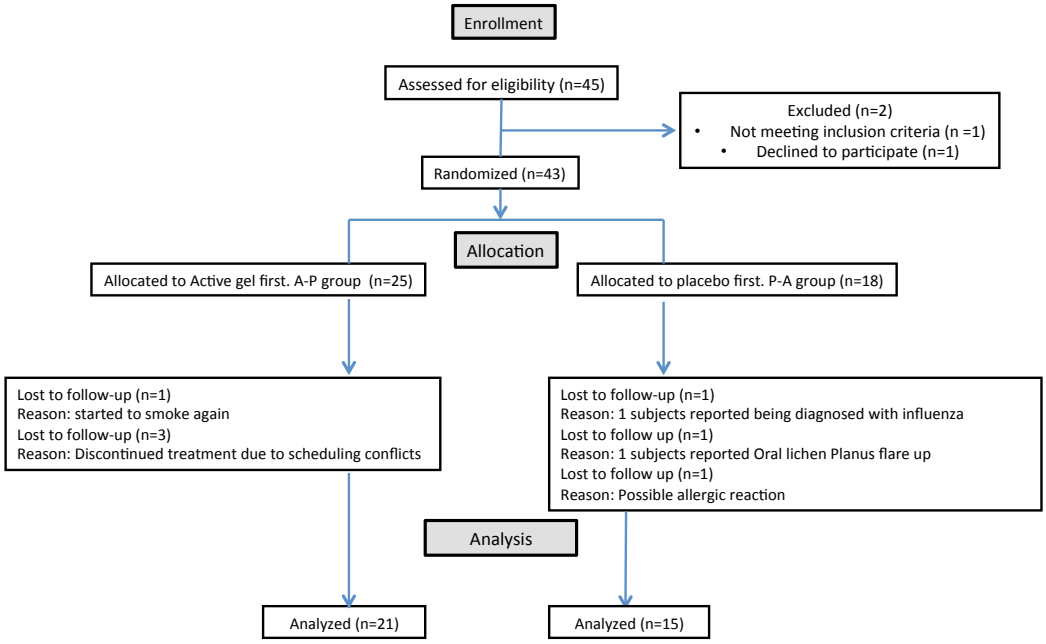
Analysis strategies included performing Mixed Model Analysis. Certain models were used to account for the effects of missing data on the analysis. Missing data, when using a mixed-models approach (as MIXED in SPSS), is not problematic. In a mixed-models approach, the patient is considered randomly chosen from a larger group of subjects. These models have been found to be tolerant of missing data as long as the

missing data are random. Active gel and placebo groups was compared using paired t-test. Medians and semi-interquartile ranges were used to describe characteristics of the patient population when the data was continuous and non-normally distributed.

We proposed using multivariate analysis of variance, wherever feasible, rather than individual analysis of covariance adjusting for Type I error rates.

3. RESULTS

Figure 4 Study overview



From the 45 patients screened, two were excluded. One did not meet inclusion criteria because she had Sjogren's Syndrome. The second subject declined to participate. Forty-three subjects were included in the study and randomized into two groups. Twenty-five participants received the active gel first then the placebo. This group was called the Active-Placebo (A-P). The group consisted of 7 males and 14 females with an average age of 61.61 ± 10.52 years. The second group of 18 subjects was called Placebo-

Active (P-A) group because they were given placebo gel first. The P-A group consisted of 4 males and 11 females with an average age of 57 ± 19.01 years. During the course of the study, a total of seven subjects dropped out. Four were from the A-P group. One subject was lost to follow-up because he started to smoke again. Three subjects discontinued due to scheduling conflicts. In the P-A group, 3 subjects also dropped out. One subject was lost to follow-up because she was diagnosed with influenza. One subject reported a flare-up of oral lichen planus while one subject reported a possible allergic reaction from the placebo gel. After subtracting the drop-outs, a total of 21 subjects in the A-P group completed the study and 15 in the P-A group (Figure 2).

Patient Satisfaction Survey Analysis

Figure 5 shows patient satisfaction survey results for both groups at baseline, 2 weeks, 4 weeks, 8 weeks, and 10 weeks. The survey consisted of 5 questions. Subjects that used the active gel first were very satisfied with the soothing effect of the gel. This effect carried through use of the placebo as well. Subjects that used the placebo gel first were unsatisfied with the soothing effect of the gel. However, subjects reported highly satisfactory soothing effects of the active gel after the crossover at week 6. A statistically significant difference ($p < 0.05$) was found in the subjective measure of soothing effect at week 4. The paired t-test showed a statistically significant difference at week 4.

Figure 5 Mean of the Soothing Effect in the Mouth After Using the Dry Mouth Gel

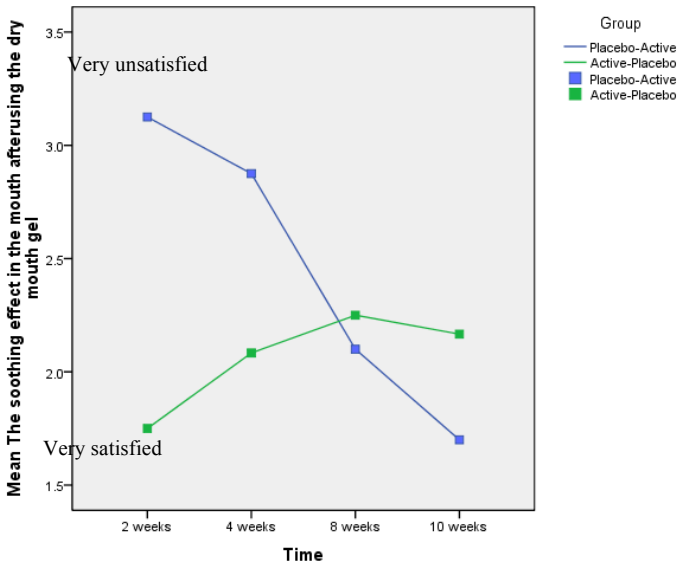


Figure 6 indicates that during use of the active gel, both groups showed less time required to feel relief compared to their response when using the placebo. Placebo group was more unsatisfied before crossover at week 4.

Figure 6 Mean Time It Took To Feel Relief After Using The Dry Mouth Gel

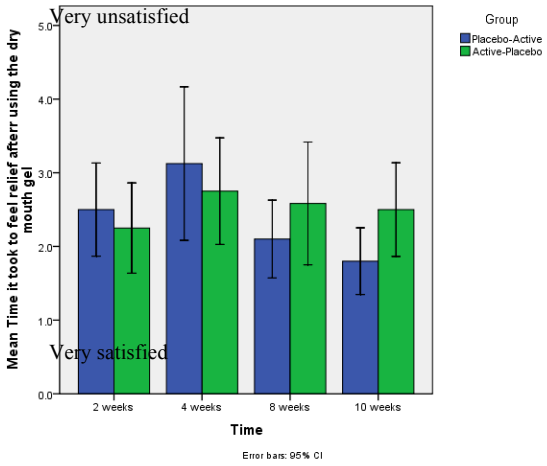


Figure 7 indicates the A-P group voiced greater satisfaction with confidence in breath after use of the active gel first. The two A-P group were more satisfied than the two P-A groups but there was no statistically significant difference between the groups.

Figure 7 Mean Confidence In Breathe After Using the Dry Mouth Gel

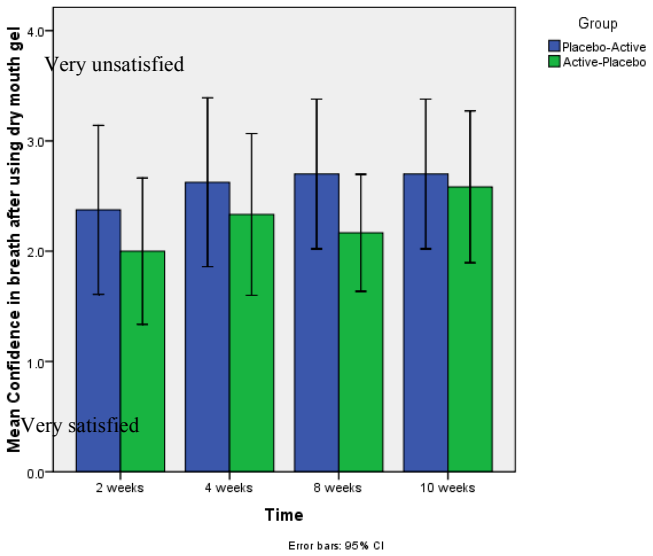


Figure 8 does not indicate a trend in the data for this variable. However, paired t-test shows that the ability to eat at week 2 was significantly different amongst data sets of both the active and placebo groups.

Figure 8 Mean Ability to Eat Using the Dry Mouth Gel

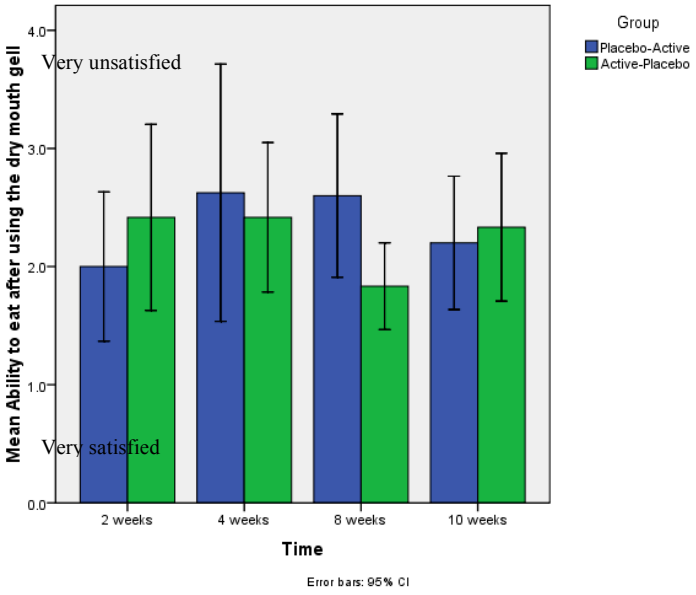
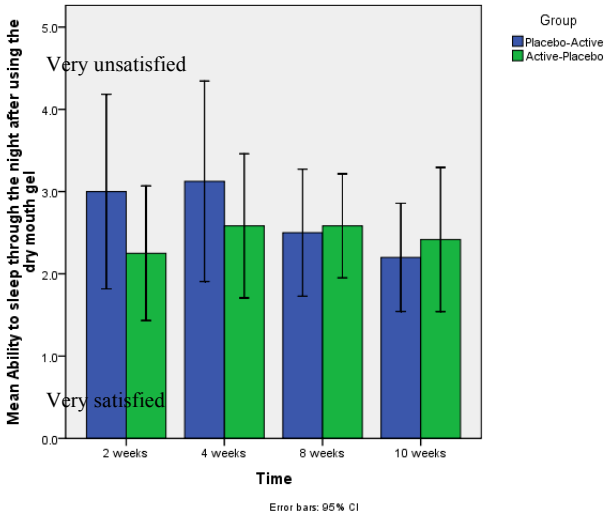


Figure 9 shows subjects report greater satisfaction with the ability to sleep through the night with the active gel in both groups.

Figure 9 Mean Ability to Sleep Through the Night After Using the Dry Mouth Gel



Xerostomia Visual Analog Scale Analysis

The following are the XVAS findings (validated questionnaire to evaluate five questions related to xerostomia) for both groups at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks. The VAS consisted of five items.

In figure 10 there is a trend showing that subjects that used the active gel first had less difficulty speaking over time compared to subjects that began with the placebo gel. Furthermore, once group P-A switched to the active gel, there was a trend towards less difficulty speaking over time.

Figure 10 Mean Difficulty in Speaking

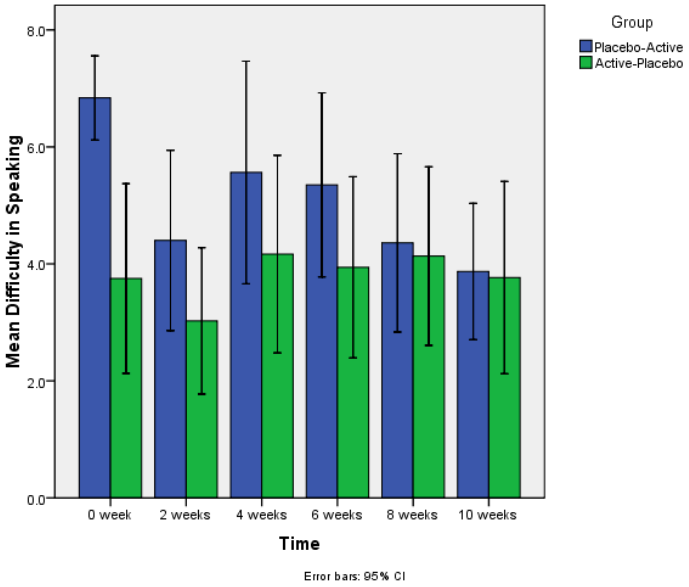
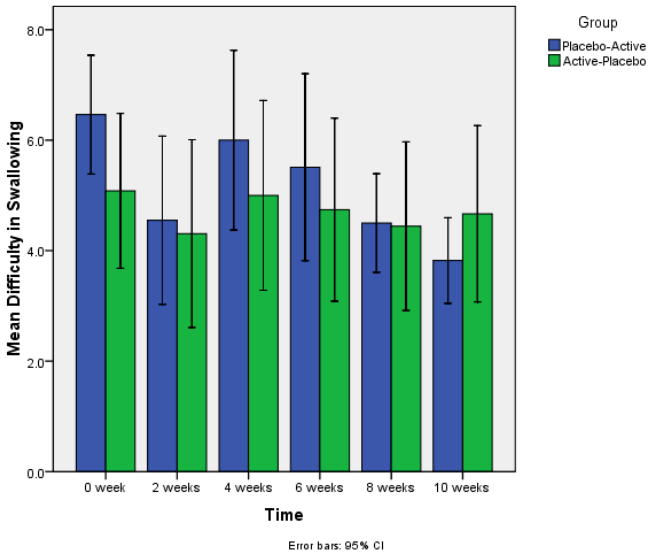


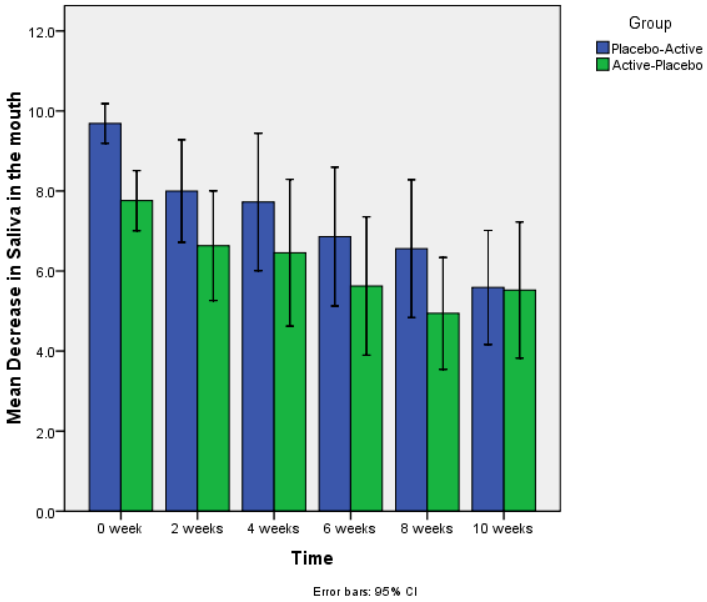
Figure 11 shows there is a trend that difficulty swallowing decreased in group P-A after switching to the active gel. Otherwise, the two groups remained relatively similar for this category.

Figure 11 Mean Difficulty in Swallowing



In figure 12 both groups reported less of a decrease in saliva in the mouth after using the gels. The decrease over time is significant in both groups. However, there is not a statistically significant difference between the groups over time.

Figure 12 Mean Decrease in Saliva in the Mouth



In figure 13 both groups reported a decrease in dry mouth over time.

Figure 13 Mean Dry Mouth

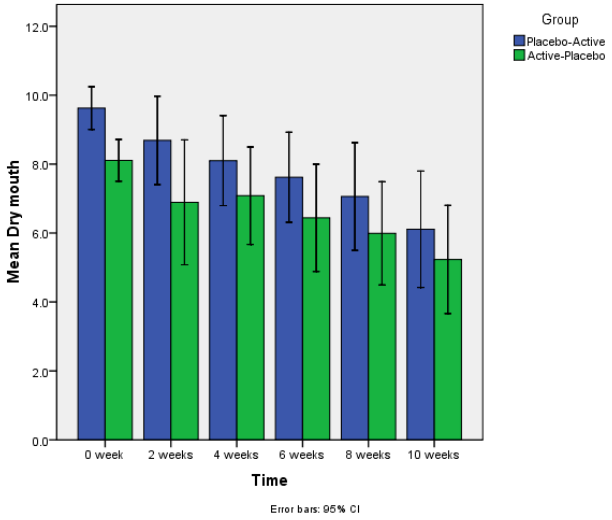
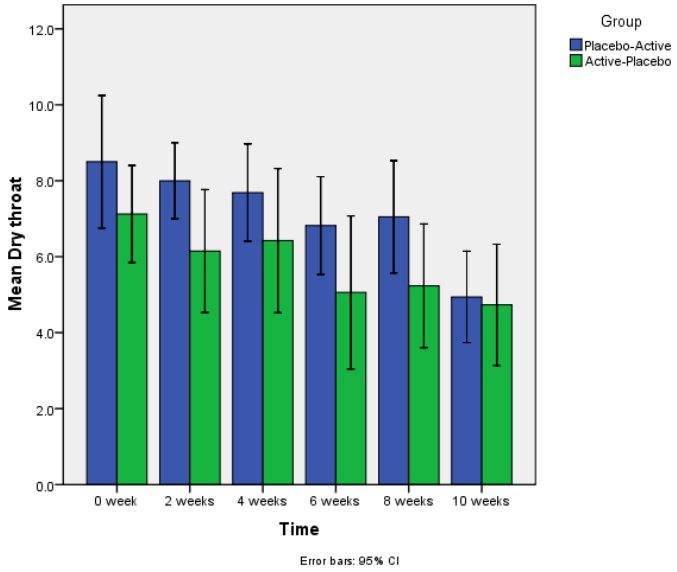


Figure 14 shows there was a non-significant decrease in dry throat reported by both groups throughout the entire study. Placebo group reported higher levels of dry throat at initial baseline (0 week) compared to the active group. Once the placebo group changed to active group after the crossover at week 4 they remained reporting at dry throat at higher levels compared to other group.

Figure 14 Mean Dry Throat



Medication Consumption Analysis

All subjects were taking drugs with potential to cause dry mouth. Figure 15 shows patients that produced salivary flow of <0.2 ml/min and the medications they were taking. For these patients, 25 were prescribed analgesic medications and 19 anti-hypertensive medications.

Figure 15 Medication In Patients With Salivary Flow Rate Levels Of <0.2ml/Min

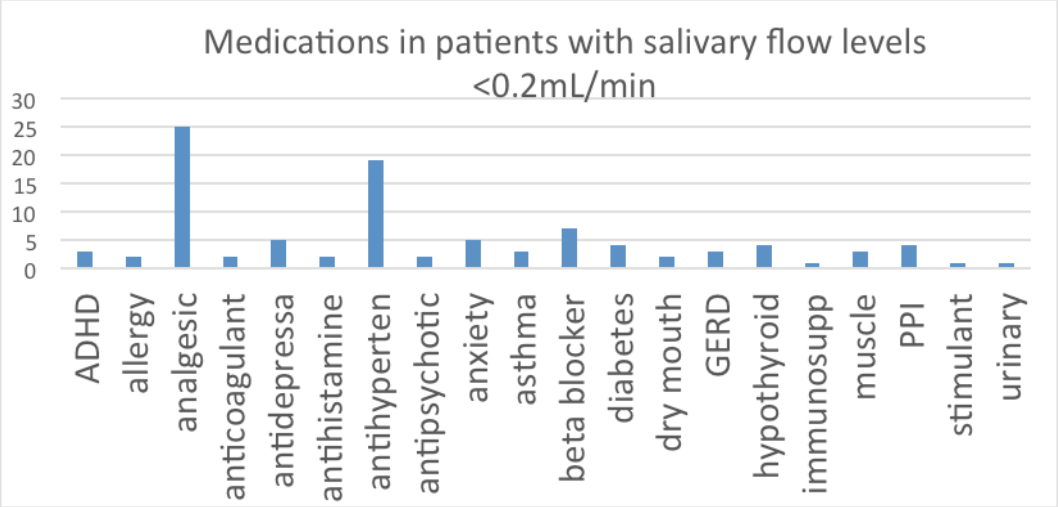
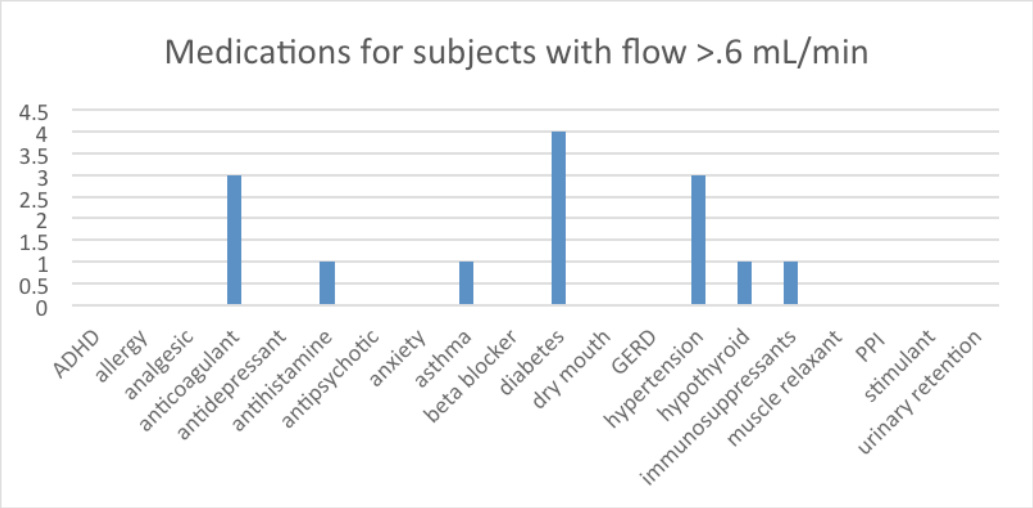


Figure 16 shows patients that produced salivary flow of >0.6 ml/min and the medications they (n=20) were taking. This figure shows that subjects that were able to produce increased saliva were not prescribed any analgesics or anti-hypertensive medications.

Figure 16 Medications For Subjects With Flow >0.6 Ml/Min.



TAC Analysis

All the figures for TAC analysis were done for patients with salivary flow of <0.2 ml/min. Figure 17 shows that the TAC averages during the Active phase increased then decreased slightly by week 4 and the decrease persisted during the placebo phase, but no major change was found from beginning to end. Placebo-Active also increased initially during the active phase then decreased and no major difference was found from the active phase beginning point to the end. Raw values of all subjects' (n=36) TAC are presented in Table 3.

Figure 17 Averages Of TAC Comapring P-A To A-P

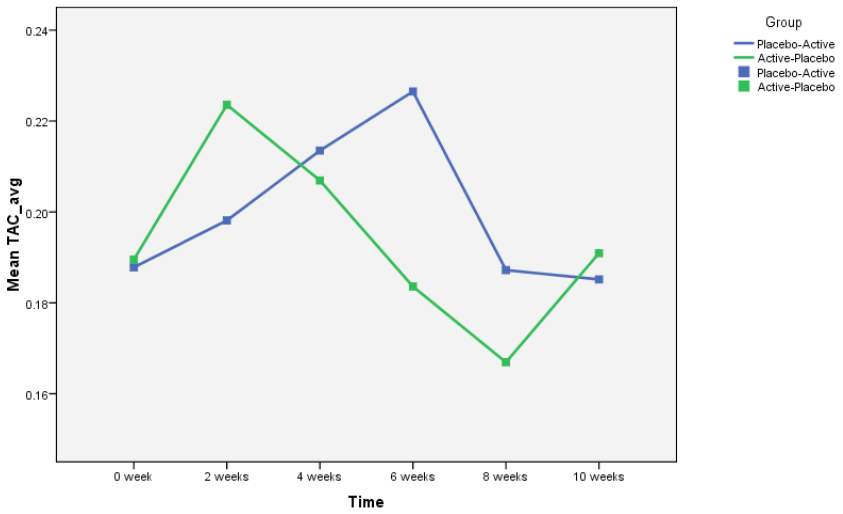


Table 3 TAC Averages For All Subjects In The Study

TAC	P-A (15)	A-P (21)
avg W0	0.165933333	0.174928571
avg W2	0.175833333	0.192904762
avg W4	0.176766667	0.1875
avg W6	0.189833333	0.17574153
avg W8	0.167233333	0.155595238
avg W10	0.165066667	0.154714286

In figure 18 TAC average increased prior to an increase in salivary flow. TAC peaked at week 2 and salivary flow peaked 2 weeks after TAC seemed to increase as the salivary flow increased. No significant relationship was found regarding the activity of the gel.

Figure 18 TAC Active-Placebo Averages Comapred To Salivary Flow Rate

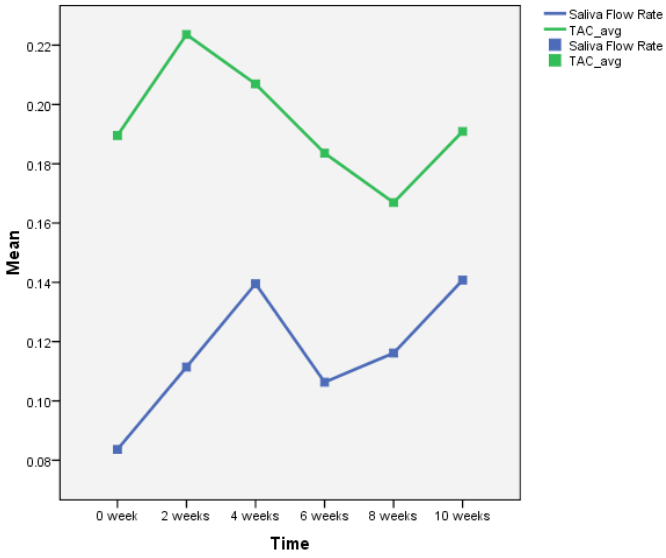
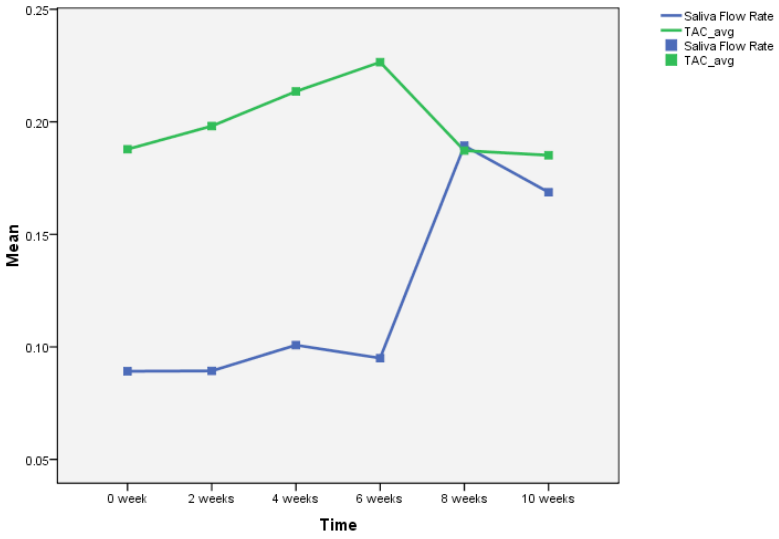


Figure 19 shows Placebo-Active TAC averages increased during the placebo phase and decreased during active phase. Salivary flow peaked during active phase but TAC levels did not change significantly from beginning to end.

Figure 19 Placebo-Active TAC Averages Compared To Salivary Flow.



4. DISCUSSION

The goal of treating xerostomia is to alleviate symptoms and stimulate saliva.[9, 40] In this study population that was affected by drug induced xerostomia, topical application of antioxidant gel was effective in treating some symptoms. The gel improved salivary flow rate and patient satisfaction regarding the soothing effect of the gel. The descriptive results of TAC showed that there was an increase or decrease in TAC as the salivary flow increased or decreased. Observation of the trends associated with dry mouth did not reveal a relationship between VAS or PSS. The results obtained regarding xerogenic effects of medication, showed that anti-hypertensive and analgesic medications were the two dominant classes of drugs taken by patients that produced low salivary flow of <0.2 ml/min.

Topical agents are abundantly available over the counter, and many xerostomic patients find relief of their symptoms with their use. However, a Cochrane review on topical therapy found no strong evidence for alleviating symptoms of dry mouth, indicating that most treatments are palliative and transient.[64] There are several forms of palliative treatment. Salivary substitutes are more viscous in nature such as gels, oils, and mouthwashes. Salivary stimulants entails chewing gums, toothpastes, or lozenges.[9] To date, there is no gold standard available to treat xerostomia with topical agents. Cholinergic stimulants such as pilocarpine will improve salivary flow but have mixed results when it comes to improving patients' assessment of symptoms or quality of life measures.[65] These drugs come with a price of side effects and some patients are unable

to take them due their adverse drug interactions and contraindications with systemic diseases.[66] Side effects include hypersalivation, nausea, emesis, diarrhea, hiccups, hyperhidrosis, cutaneous vasodilatation, bronchoconstriction, bradycardia, hypotension, and difficulty in visual accommodation. They are contraindicated in acute asthma attack, narrow-angle glaucoma, and iritis.[12]

Many agents aid with short-term relief of dry mouth as was described in a study by Gil-Montoya et al. They evaluated the efficacy of mouthwash and oral gel consisting of antimicrobial proteins lactoferrin, lactoperioxidase, and lysozyme in 20 elderly patients during a 4-week period. The study concluded that few symptoms actually improved. Moreover, they found a substantial placebo effect. They also found VAS measurements improved in both active and placebo groups.[67] Femiano et al. evaluated 54 patients reporting drug-induced xerostomia. Subjects were randomly divided into three groups and were dispensed either artificial saliva, 3% citric acid, or distilled water as mouthwash 4 times a day for 30 days. They collected unstimulated whole saliva before and after therapy and answered survey questions. The study concluded that saliva and citric acid produced immediate stimulation ($p < 0.0001$ after 15 min period) but it only persisted for an hour longer in the citric acid group. Moreover, the overall salivary flow rate did not show significant increase in any of the subject groups.[68] On the contrary, Epstein et al. reported that Biotene™ was more effective than placebo.[66]

An antioxidant gel appears to provide a longer lasting soothing effect. In this study, the soothing effect carried through the placebo intervention. Subjects who used the placebo gel first found the gel less satisfying until they transferred to the active

group. The initial improvement in the placebo group could be due to the well-known placebo effect. Once the subjects in the initial active group felt benefit and relief from the active gel intervention they started to associate the placebo gel with a benefit as well.[69, 70] There was not a dramatic beneficial change in the A-P group compared to P-A group when comparing starting point and end point. In other words, both groups found considerably more satisfaction when using the active gel. Epstein evaluated Biotene™ toothpaste and rinse against Biotene Oral Balance™ gel and found the gel to be more soothing to patients than the other Biotene™ products although all products yielded positive responses from patients despite not resulting in any improvement in salivary output. On the other hand, the long-term 6 week improvement in soothing effect and salivary output in the A-P group could indicate a lingering effect of the product. Adherence of polyphenols to mucosal surfaces and persisting for longer time periods may allow the gel to function as a slow-releasing device.[36] Starting a sustained redox cascade event that leads to an increased salivary flow. It is also possible that the placebo gel itself alone had some inherent antioxidant properties. Ferulic acid and phloretin were not utilized in the placebo, but secondary ingredients including: menthol, thyme, sage oil, clove flower oil, and xylitol were used. Several studies have shown that these ingredients carry antioxidant functions as well. [71-74] It was not possible to provide the placebo gel with out these ingredients since it would change the gel consistency, taste, and smell. Despite the similarities of the secondary ingredients, it is evident that the active gel increased satisfaction of patients compared to the placebo. Therefore, it can be

assumed that any differences are attributed to the active components, mainly phloretin and ferulic acid.

Even though no statistically significant differences was found apart from the soothing effect in the mixed model analysis, the patient survey results showed a decrease of symptoms overall. These findings correlate with other studies from Table 2. From general observation, patients who presented with severe dry mouth did not experience alleviation of symptoms, but subjects who had low salivary flow were more content with use of the gel.

A weakness of this study was the methodology used for saliva collection. Collecting only unstimulated whole saliva through the spit method could have led to some salivary output discrepancies. Other methods of collecting saliva include draining, swab, and suction. The spit method obtains saliva that is accumulating in the floor of the mouth while the mouth is closed. The saliva is primarily produced by the submental and submandibular glands producing the bulk of salivary mucins allowing for lubrication in the oral cavity, the protective saliva coating of oral soft tissues, and the formation of dental pellicle. When subjects feel the urge to swallow the saliva, they are urged to spit into a test tube. The method is problematic in that it may cause a stimulatory effect on saliva secretion and may not reflect the most reliable values. In the draining method unstimulated whole salivary flow is collected when the patient is in an upright position. The patient is then instructed to swallow and tilt their head in a forward position to move saliva to the front of the mouth. The patient then lets saliva drain continuously from the lower lip through a funnel, which directs fluid into a graduated cylinder for 15 min. The

remaining saliva is spat out at the end. The draining method has a higher degree of evaporation of saliva compared to the spitting method. This makes the spit technique a more applicable method in patients suffering from severely reduced salivary flow rates. Consensus of saliva experts appears to be that ideally both stimulated and unstimulated saliva should be collected especially if salivary gland injury is suspected as in Sjogren's Syndrome.[20]

Looking at the effect of anti-hypertensive drugs in patients with/without type 2 diabetes mellitus (DM), Djukic et al. found that drug combinations and metoprolol exhibit xerogenic effects. The subject population consisted of 447 (378 hypertensive and 60 healthy) individuals. Patients diagnosed with type 2 DM had more noticeable xerogenic effect of anti-hypertensive drugs.[75] This finding could have played a role in salivary output of several individuals in this patient population who had DM and also took antihypertensive medications. Although not all studies concur, the literature suggests that polydrug therapy may increase the severity of xerostomia.[20, 76] Bardow et al. showed that the total amount of medications taken daily and the number of xerogenic medications had a significant association with xerostomia.[77] Another study showed that subjects taking more than three medications per day had higher risk of developing xerostomia compared to subjects taking only one medication daily.[78] A systematic review by Villa et al. concluded that as the number of medications increases, the severity of xerostomia worsens. This may be due to the fact that taking additional xerogenic drugs potentiates the xerogenic effect of the original medication.[1]

In the present study, one subject reported a possible allergic reaction to the gel. She was given the placebo gel first, from which she developed contact dermatitis of the lips. Crusting, erythema, and eczema-like dryness appeared on the vermilion margin around the mouth. The participant was offered the opportunity to be allergy tested in order to identify any allergen found in the placebo gel. However, she decided not to be tested but to terminate involvement in the study as a safety precaution.

Another patient reported flare-up of oral lichen planus. This patient was type 2 diabetic and studies have shown that diabetic patients are more prone to developing several stomatological manifestations including oral lichen planus and xerostomia.[79-81] It has been reported that most diabetic patients who appear to have oral lichen planus, in fact are experiencing a lichenoid drug reaction to one or more of the medications prescribed for DM.[82]

Fruits and vegetable are known to provide increased amounts of antioxidants. Xerostomia patients also often use over-the-counter dry mouth products that may contain antioxidants components in addition to lubricants. Another weakness of the study is that subjects' dietary habits and gel usage of over-the-counter dry mouth products were not investigated and controlled, respectively, which may have affected the results as confounding factors.[36]

TAC of blood plasma has also been correlated to age, with the 40 -60 year olds showing lower TAC values when compared to 18-24 and 25-39 year old populations.[83] Most of our patients were from the 40-60 year old age group. Many potential factors may have led to the overall inconsistent TAC levels in the study including diet and the

presence of oral inflammatory diseases or conditions. Even though an increase in TAC was observed when using the active gel, overall there was no significant difference.

5. CONCLUSION

The present study demonstrated that drug-induced xerostomia did not lead to a significant alteration of salivary TAC, although all active product participants experienced a significant surge in TAC at two weeks followed by a reduced but still elevated TAC at completion of the active phase. Of interest, individuals in the first active product group continued to have an elevated but not significant TAC level 6 weeks later at the final completion of the 10-week study. An interesting observation was that TAC levels increased prior to peak salivary flow rates suggesting that the antioxidants may trigger a reaction resulting in increased salivary flow. This observation cannot currently be explained on a molecular basis.

Patients receiving the active AO gel had improvement in the carefully selected and evaluated XVAS questionnaires and the Patient Satisfaction Survey. Overall, the VAS testing between the active and placebo groups were not statistically significant except for soothing effect of the gel, with paired T-test showing improved ability to eat at week 2 and in subjective measurement of soothing effect at week 4. Other VAS survey questions also indicated an improvement of symptoms with use of the active AO gel, and suggest that ongoing evaluation of validity testing of VAS changes in salivary output should continue.

Although the study identified large variability in the data, the antioxidant gel formula resulted in an increase of unstimulated whole salivary flow over the 10-week study period. Survey results also indicated an improvement of symptoms using the AO

gel. Although there were insufficient numbers to confirm significance there were strong indications that a surprisingly large percentage of individuals taking xerogenic medications experienced very low normal salivary levels or salivary hypofunction. Additionally those individuals with low salivary output tended to responds much more favorably to AO application.

This antioxidant gel formula showed strong potential to provide a beneficial outcome for patients suffering from drug-induced xerostomia. Further research should include large-scale clinical trials, with or without use of additional sources of AO, to investigate the efficacy of antioxidants in achieving and sustaining oral health.

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