THE EFFECTS OF GREEN TEA ON SALIVARY PRODUCTION AND VISCOSITY, AND ON QUALITY OF LIFE IN PATIENTS WITH SJÖGREN’S SYNDROME: A PILOT STUDY

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Faculty of Dentistry
University of Toronto

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ABSTRACT

Several beneficial effects of green tea polyphenols (GTPs) have been shown in both in vitro and animal studies. This pilot study tested their effects on relief of dry mouth and quality of life (QoL) in Sjögren’s syndrome (SS) patients. After one month of green tea consumption in 18 SS patients, and three months in 7 patients, there was an improvement in the patients’ oral health and QoL. In addition there was an increase in the unstimulated salivary flow rate and a decrease in the viscosity of stimulated saliva, although not statistically significant. Furthermore, 83% of the patients reported that they would continue to drink green tea. Although the mechanism of action of the GTPs is unknown in this patient population, we have shown that regular green tea consumption by SS patients is a simple yet effective and enjoyable means of dry mouth relief.
ACKNOWLEDGEMENTS

First and foremost, I would like to thank God. You have given me the power to believe in my passion and pursue my dreams. I could never have done this without the faith I have in You, the Almighty.

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All SS patients and non-SS participants for being part of this project, and supporting me until the end. I sincerely hope and pray that there will be a cure for Sjögren’s Syndrome in the near future.

The Ko sisters, Jessica (JuYoung) and Jamie (JuJin) for their friendship and laughter. I am very blessed to have you two as my sisters and friends.

Lastly, and most importantly, I wish to thank my parents, Mi Sook Yoo-Ko and Seok Bin Ko, who continue to be a source of inspiration and love for me. Thank you very much for your prayers all along.

The LORD is my shepherd,
I shall not be in want.
He makes me lie down in green pastures, he leads me beside quiet waters,
he restores my soul.
He guides me in paths of righteousness for his name's sake.
Even though I walk through the valley of the shadow of death,
I will fear no evil, for you are with me; your rod and your staff, they comfort me.
You prepare a table before me in the presence of my enemies.
You anoint my head with oil; my cup overflows.
Surely goodness and love will follow me all the days of my life, and I will dwell in the house of the LORD forever.

A psalm of David, Psalm 23.
TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION..........................................................................................1
  1.1 Sjögren’s Syndrome (SS)..................................................................................2
  1.2 Green Tea..........................................................................................................7
  1.3 Salivary Flow Rate............................................................................................13
  1.4 Salivary Viscosity.............................................................................................17
  1.5 Statement of the Problem and Rationale for the Study.................................20
  1.6 Objectives of the Present Study........................................................................21
  1.7 Hypotheses........................................................................................................21

CHAPTER 2. MATERIALS AND METHODS.................................................................22
  2.1 Study Design.....................................................................................................22
  2.2 Human Subjects................................................................................................22
  2.3 Selection of Green Tea.....................................................................................25
  2.4 Salivary Measures............................................................................................26
    A. Salivary Flow Rate.........................................................................................26
    B. Salivary Viscosity..........................................................................................27
  2.5 Subjective Oral Health Measures.....................................................................30
    A. Oral Health Impact Profile – 14 (OHIP-14)...............................................31
    B. Xerostomia Inventory (XI)..........................................................................32
    C. Quality of Life (QoL) for Dry Mouth Patients.............................................34
    D. Visual Analogue Scale (VAS) for Dry Mouth-related Symptoms..............35
  2.6 Data Analysis....................................................................................................36

CHAPTER 3. RESULTS................................................................................................37
  3.1 Study Progress..................................................................................................37
  3.2 Study Population: Demographics....................................................................38
  3.3 Objective Salivary Outcome Measures............................................................39
    A. Results at Baseline (Time T0).......................................................................39
    B. Results after 1 Month of Green Tea Consumption (Time T1).....................42
    C. Results after 2 Months of Green Tea Consumption (Time T2)...............46
    D. Results after 3 Months of Green Tea Consumption (Time T3)...............48
  3.4 Subjective Oral Health Outcome Measures...................................................51
    A. Results at Baseline (Time T0).......................................................................51
    B. Results after 1 Month of Green Tea Consumption (Time T1).....................55
    C. Results after 2 Months of Green Tea Consumption (Time T2)...............59
    D. Results after 3 Months of Green Tea Consumption (Time T3)...............63
  3.5 Two-way Repeated Measures ANOVA Analysis.............................................65
    A. Objective Salivary Outcome Measures.....................................................66
    B. Subjective Oral Health Outcome Measures............................................71
  3.6 Analysis of Objective Data by Individual SS Patients....................................75
  3.7 Results of an Exit Survey after Green Tea Consumption...............................83
  3.8 Correlation between Study Parameters.......................................................85

CHAPTER 4. DISCUSSION............................................................................................87
  4.1 Baseline Measurements..................................................................................87
  4.2 Salivary Measure Outcomes..........................................................................91
A. Salivary Flow Rate...........................................................................91
B. Salivary Viscosity...........................................................................92

4.3 Subjective Questionnaires...............................................................94
   A. Changes in OHIP-14 and QoL.......................................................94
   B. Changes in Xerostomia Inventory (XI)..........................................97
   C. Changes in the Extent of Dry Mouth as Determined by VAS Scores...........................................................................98

4.4 Correlations between Objective and Subjective Findings................100
4.5 An Exit Survey after Green Tea Consumption.................................101
4.6 Limitations of the Present Study.....................................................102

CHAPTER 5. CONCLUSIONS AND FUTURE DIRECTIONS........................104
CHAPTER 6. SUMMARY........................................................................107
CHAPTER 7. REFERENCES.................................................................108
CHAPTER 8. ABBREVIATIONS............................................................118
CHAPTER 9. APPENDICES.................................................................119
### LIST OF TABLES

Table 1. Revised International Classification Criteria for Sjögren’s Syndrome (SS)  
(European-American Consensus Criteria, 2002) .................................................3
Table 2. Studies of Unstimulated Whole Saliva Flow Rates (ml/min) in Healthy  
Individuals. .............................................................................................................15
Table 3. Studies of Unstimulated Whole Saliva Flow Rates (ml/min) in SS Patients ....16
Table 4. Tea Catechin Analysis in 5 Commercially Available Green Tea ..............25
Table 5. OHIP-14 Individual Items in 7 Dimensions .............................................32
Table 6. Xerostomia Inventory (XI) 11-Items ......................................................33
Table 7. Quality of Life (QoL) 14-Items ...............................................................34
Table 8. Changes in Number of SS Patients through Stages of the Study ..............37
Table 9. Distribution of the Study Population according to Age, Gender, Height,  
Weight, Time since Diagnosis of SS, and Green Tea Drinking Status .................38
Table 10. Differences in the Salivary Parameters between the SS (n=31) and Non-SS  
(n=12) Groups prior to Green Tea Consumption at Baseline Visit ....................39
Table 11. Salivary Outcome Measures in the SS and Non-SS Groups after 1 Month  
of Green Tea Consumption ...............................................................................43
Table 12. Differences in the Salivary Parameters between the SS and Non-SS Groups  
after 1 Month of Green Tea Consumption .........................................................45
Table 13. Salivary Outcome Measures in the SS and Non-SS Groups after 2 Months  
of Green Tea Consumption ...............................................................................47
Table 14. Differences in the Salivary Parameters between the SS and Non-SS Groups  
after 2 Months of Green Tea Consumption .........................................................48
Table 15. Salivary Outcome Measures in the SS and Non-SS Groups after 3 Months  
of Green Tea Consumption ...............................................................................49
Table 16. Differences in the Salivary Parameters between the SS and Non-SS Groups  
after 3 months of Green Tea Consumption ........................................................50
Table 17. Differences in the Subjective Oral Health Measures between the SS (n=31)  
and Non-SS (n=12) Groups prior to Green Tea Consumption at Baseline Visit ......52
Table 18. Differences in the 7 Dimensions of OHIP-14 between the SS (n=31) and  
Non-SS (n=12) Groups prior to Green Tea Consumption ........................................52
Table 19. Differences in Dry Mouth-related Symptoms as Measured by VAS, between  
the SS (n=31) and Non-SS (n=12) Groups prior to Green Tea Consumption ..........54
Table 20. Subjective Oral Health Outcome Measures in the SS (n=18) and Non-SS  
(n=12) Groups after 1 Month of Green Tea Consumption ......................................56
Table 21. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related  
Symptoms in the SS (n=18) and Non-SS (n=12) Groups after 1 Month of  
Green Tea Consumption .......................................................................................58
Table 22. Differences in Dry Mouth-related Symptoms as Measured by VAS,  
between the SS (n=18) and Non-SS (n=12) Groups after 1 Month of  
Green Tea Consumption .......................................................................................59
Table 23. Subjective Oral Health Outcome Measures in the SS (n=7) and Non-SS (n=12)  
Groups after 2 Months of Green Tea Consumption ..............................................60
Table 24. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related Symptoms in the SS (n=7) and Non-SS (n=12) Groups after 2 Months of Green Tea Consumption……………………………………………..61
Table 25. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=7) and Non-SS (n=12) Groups after 2 Months of Green Tea Consumption……………………………………………..62
Table 26. Subjective Oral Health Outcome Measures in the SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption……………………………………………..63
Table 27. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related Symptoms in SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption……………………………………………..64
Table 28. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption……………………………………………..65
Table 29. Characteristics of SS Patients…………………………………………………75
Table 30. Summary of 7 SS Patients’ Salivary Measures at Baseline and after 1, 2, and 3 Months of Green Tea Consumption……………………………………………..78
Table 31. Distribution of Answers by SS Patients Responding to Questions after Daily Green Tea Consumption……………………………………………..84
Table 32. Correlations between Study Parameters at Baseline (T0), 1-Month (T1), 2-Month (T2), and 3-Month (T3) Follow-up Visits……………………………………………..86
LIST OF FIGURES

Figure 1. Principal Differences between Green and Black Tea Processing and the Influence on the Final Polyphenol Content ................................................................. 9
Figure 2. Schematic Model for GTP-mediated Protective Mechanism ........................................ 12
Figure 3. Location of Major Salivary Glands in Humans .......................................................... 14
Figure 4. Outline of Visits Involved in the Green Tea Study .................................................... 24
Figure 5. Cone and Plate Rheometer ....................................................................................... 28
Figure 6. Visual Analogue Scale (VAS) Measuring Oral Dryness at Night or on Awakening in Study Participants ...................................................................................... 35
Figure 7. Unstimulated Salivary Flow Rate at Baseline in the SS (n=21) and Non-SS (n=12) Groups ........................................................................................................... 40
Figure 8. Stimulated Salivary Flow Rate at Baseline in the SS (n=21) and Non-SS (n=12) Groups ................................................................................................................. 40
Figure 9. Viscosity of Unstimulated Saliva at Baseline in the SS (n=10) and Non-SS (n=12) Groups ................................................................................................................. 41
Figure 10. Viscosity of Stimulated Saliva at Baseline in the SS (n=16) and Non-SS (n=12) Groups .................................................................................................................... 41
Figure 11. Changes in Mean Flow Rate for Unstimulated and Stimulated Saliva in the SS and Non-SS Groups (n=12) after 1 Month of Green Tea Consumption ................................................................. 44
Figure 12. Changes in Mean Viscosity for Unstimulated and Stimulated Saliva in the SS and Non-SS Groups (n=12) after 1 Month of Green Tea Consumption ........................................................................ 44
Figure 13. The Mean OHIP-14 Score at Baseline in the SS (n=31) and Non-SS (n=12) Groups .......................................................................................................................... 53
Figure 14. The Mean XI Score at Baseline in the SS (n=31) and Non-SS (n=12) Groups ............................................................................................................................... 53
Figure 15. The Mean VAS Scores in the SS (n=31) and Non-SS (n=12) Groups at Baseline ............................................................................................................................... 55
Figure 16. Changes in Mean Quality of Life (QoL) Score in the SS group (n=18) after 1 Month of Green Tea Consumption .................................................................................. 56
Figure 17. Changes in Mean OHIP-14 Score in the SS group (n=18) after 1 Month of Green Tea Consumption ................................................................................................. 57
Figure 18. The Mean Scores for the 7 Dimensions of OHIP-14 in the SS Group (n=18) after 1 Month of Green Tea Consumption ........................................................................ 57
Figure 19. Changes in Mean Flow Rate of Unstimulated Saliva in the SS (n=6) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption .............. 66
Figure 20. Changes in Mean Flow Rate of Stimulated Saliva in the SS (n=6) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption .............. 67
Figure 21. Changes in Mean Viscosity of Stimulated Saliva in the SS (n=3) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption .............. 68
Figure 22. Changes in Mean Unstimulated Viscosity in the SS (n=2) and Non-SS (n=12) Groups after 1 and 3 Months of Green Tea Consumption .............. 69
Figure 23. Changes in Mean Viscosity of Stimulated Saliva in the SS (n=4) and Non-SS (n=12) Groups after 1 and 3 Months of Green Tea Consumption .............. 70
Figure 24. Changes in Mean OHIP-14 Scores in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption
Figure 25. Changes in Mean XI Scores in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption
Figure 26. Changes in Mean QoL Scores in the SS Group (n=7) after 1, 2, and 3 Months of Green Tea Consumption
Figure 27. Change in Mean VAS of Oral Dryness During Eating in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption
Figure 28. Change in Mean VAS of Difficulty in Swallowing in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption
Figure 29. Changes in Mean VAS for Dry Mouth-related Symptoms in SS group (n=7) after 1, 2, and 3 Months of Green Tea Consumption
Figure 30. Changes in Unstimulated and Stimulated Salivary Flow Rate of 16 SS patients after 1 Month of Green Tea Consumption from Baseline
Figure 31. Changes in Unstimulated and Stimulated Salivary Viscosity of 16 SS patients after 1 Month of Green Tea Consumption from Baseline
Figure 32. Changes in Unstimulated Salivary Flow Rate from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients
Figure 33. Changes in Stimulated Salivary Flow Rate from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients
Figure 34. Changes in Viscosity of Unstimulated Saliva from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients
Figure 35. Change in Viscosity of Stimulated Saliva from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients
LIST OF APPENDICES

Appendix I. Ethics Approval Letter.................................................................120
Appendix II. Inclusion/Exclusion Criteria Worksheet........................................121
Appendix III. Consent Form...............................................................................122
Appendix IV. Green Tea Preparation Instructions.............................................123
Appendix V. Green Tea Compliance Chart..........................................................124
Appendix VI. Oral Health Impact Profile – 14 (OHIP-14) at Baseline..............125
Appendix VII. Xerostomia Inventory (XI) at Baseline......................................126
Appendix VIII. Quality of Life (QoL) for Dry Mouth Patients at Baseline........127
Appendix IX. Extent of Dry Mouth at Baseline..................................................128
Appendix X. Oral Health Impact Profile – 14 (OHIP-14) at Follow-up..............129
Appendix XI. Xerostomia Inventory (XI) at Follow-up.....................................130
Appendix XII. Quality of Life (QoL) for Dry Mouth Patients at Follow-up........131
Appendix XIII. Extent of Dry Mouth at Follow-up..........................................132
Appendix XIV. An Exit Survey........................................................................133
Appendix XV. Testimonials of SS Patients..........................................................134
CHAPTER 1. INTRODUCTION

Saliva is a valuable oral fluid that often is taken for granted. It is critical to the preservation and maintenance of oral health, yet it receives little attention until quantity and/or quality are diminished (Humphrey and Williamson, 2001). There are a number of causes associated with salivary gland dysfunction: therapeutic drugs, particularly when multiple drugs are used (Nederfors et al., 1997); systemic diseases such as Sjögren’s Syndrome (SS); and immunotherapy and/or radiation treatment for head and neck cancer (Turner and Ship, 2007). Inadequate saliva production may lead to oral complications that include dry or burning mouth, yeast infections, difficulty speaking, chewing or swallowing, increased dental decay, sore or cracked tongue, mouth sores, dry cough, altered sense of taste, digestive problems, enlargement of the salivary glands, and difficulty wearing dental appliances (Daniels and Wu, 2000; Hsu and Dickinson, 2006).

Many of the signs and symptoms of SS can be attributed to a loss of normal salivary function. The perception of dry mouth, xerostomia, is an increasingly common finding among SS patients, hence most SS patients carry bottles of water or other fluids with them to aid in speaking, swallowing, and for their overall oral comfort. Many patients report that their quality of life (QoL) has significantly decreased in the advent of oral dryness. However, there is no known cure for SS, nor is there clear knowledge for the prevention or delay of such disease.

A possible link between SS and green tea has been proposed based on the premise that the incidence of SS is more prevalent in the United States than either China or Japan, the two leading green tea-consuming countries (Miyasaka, 1995; Carsons, 2001). Recent studies with a mouse model of SS have suggested that green tea polyphenols (GTPs), which possess anti-inflammatory activities, may provide a new approach to treating SS
and associated diseases (Hsu and Dickinson, 2006). Therefore, a pilot study was designed to investigate the effects of green tea consumption on relief of dry mouth in SS patients and their quality of life.

1.1 Sjögren’s Syndrome (SS)

SS is a chronic autoimmune disease of exocrine glands with associated lymphocytic infiltrates of the affected glands. Most commonly, it is characterized by salivary and lacrimal gland dysfunction that leads to secretory hypofunction and the complaints of dry mouth and dry eyes (von Bültzingslöwen et al., 2007). SS can be manifested alone (primary SS), or in association with other autoimmune rheumatic diseases (secondary SS), usually rheumatoid arthritis (RA), but also including systemic lupus erythematosus (SLE) or other autoimmune connective tissue diseases (Hsu and Dickinson, 2006; Bayetoo and Logan, 2010).

The estimated prevalence of SS in the general population is approximately 0.6% (von Bultzingslowen et al., 2007), which makes SS the second most common systemic autoimmune disease after RA. In Canada, it is estimated that 327,000 people are affected (Bookman, 2007). It is primarily seen in menopausal women in the fourth and fifth decades of life (Tishler et al., 2001; Jonsson et al., 2002) and is more prevalent in women than men, with a ratio of 9:1 (Garcia-Carrasco et al., 2006).

Diagnosis of SS is currently based on various established criteria used throughout the world (Vescovi et al., 2004). Until recently, there were several sets of diagnostic criteria for SS. The discrepancy in diagnostic criteria between American and European groups led to substantial confusion in research publications and clinical-trial reports (Fox, 2005). Since 2002, the most recent classification criteria, the AEC (American European Consensus) Criteria have contributed significantly to define symptoms and
signs indicative of SS (Table 1). These criteria also specify the methods to test for dry eyes and dry mouth complaints, which leads to a more uniform way of defining the syndrome (Parke, 2007). The purpose of creating these criteria was to ensure that research was being conducted on a uniform group of patients. In order to be diagnosed with SS, 4 of 6 categories must be considered to be abnormal, one of which must either be an abnormal minor salivary gland biopsy (IV), or a positive anti-Ro and/or anti-La antibody titre (VI). However, there is still a problem with recognizing the full clinical spectrum of SS since it is enormous, and its coexistence with other diseases such as RA and SLE in the same patient makes it difficult to diagnose when the classification criteria do not include any other associated systemic manifestations.

Table 1. Revised International Classification Criteria for Sjögren’s Syndrome (SS) (European-American Consensus Criteria, 2002) (Adapted from Annals of Rheumatic Diseases, 2002; 61:554)

<table>
<thead>
<tr>
<th></th>
<th>Ocular symptoms: a positive response to at least one of the following questions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?</td>
</tr>
<tr>
<td></td>
<td>2. Do you have a recurrent sensation of sand or gravel in the eyes?</td>
</tr>
<tr>
<td></td>
<td>3. Do you use tear substitutes more than 3 times a day?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Oral symptoms: a positive response to at least one of the following questions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>II.</td>
<td>1. Have you had a daily feeling of dry mouth for more than 3 months?</td>
</tr>
<tr>
<td></td>
<td>2. Have you had recurrently or persistently swollen salivary glands as an adult?</td>
</tr>
<tr>
<td></td>
<td>3. Do you frequently drink liquids to aid in swallowing dry food?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III.</th>
<th>Ocular signs – that is, objective evidence of ocular involvement defined as a positive result for at least one of the following tests:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Schirmer’s I test, performed without anaesthesia (&lt;5 mm in 5 minutes)</td>
</tr>
<tr>
<td></td>
<td>2. Rose Bengal score or other ocular dye score (&gt;4 according to van Bijsterveld’s scoring system)</td>
</tr>
</tbody>
</table>

| IV. | Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert |
histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm$^2$ of glandular tissue.

V. **Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:**

1. Unstimulated whole salivary flow (<1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. **Autoantibodies: presence in the serum of the following autoantibodies:**

Antibodies to Ro (SSA) or La (SSB) antigens, or both

Despite extensive studies of the underlying cause of SS, the pathogenesis remains unclear. In broad terms, the pathogenesis is multifactorial. Environmental factors are thought to trigger inflammation in individuals with a genetic predisposition to the disease (Fox and Stern, 2002; Fox, 2005; Garcia-Carrasco et al., 2006), and could include a viral infection of the glands or any intercurrent infection that stimulates dendritic or glandular cells to activate the human leukocyte antigen (HLA)-independent innate immune system. These changes can lead to release of chemokines and upregulation of adhesive molecules on the high endothelial venules that promote the migration of immune cells into the glands. When lymphocytes enter the gland they interact with dendritic cells and epithelial cells (Jonsson et al., 2002). Within the glands, activation of T and B-lymphocytes occurs by means of HLA-DR-restricted antigen-presenting cells in the presence of co-stimulatory molecules. This acquired immune system maintains immune response with memory lymphocytes and autoantibodies (Sawalha et al., 2003). Production of type 1 interferons (IFNs) by the dendritic cells further perpetuates the process of lymphocyte homing, lymphocyte and metalloproteinase
activation, and apoptosis of glandular cells. These factors might influence the transport of aquaporin in lacrimal and salivary glands, leading to dysfunction of residual glands. In summary, there is thought to be series of 4 events that occurs in SS patients: 1) initiation by an exogenous factors; (2) disruption of salivary gland epithelial cells; (3) T lymphocyte migration and lymphocytic infiltration of exogenous glands; and (4) B lymphocyte hyper-reactivity and production of rheumatoid factor and antibodies to Ro (SS-A) and La (SS-B) (Konttinen and Kasna-Ronkainene, 2002).

SS has been proven to be a progressive disease as patients have shown deteriorating salivary secretions over time as indicated by the rate of dry mouth increasing from 41.5% of patients at initial diagnosis to 84% 10 years after diagnosis (Skopouli et al., 2000). In the early stages of SS, the sensation of dry mouth (xerostomia) is often present predominantly at rest and during the night. Over time, as the disease develops, the dryness is also present during the day and eventually giving rise to difficulties in chewing and swallowing food (Pijpe et al., 2007). Difficulties in speaking, burning sensations in the mouth, a diminished ability to taste foods, and having problems with smell, or having a mucosa that is sensitive to spicy or coarse foods, are frequently mentioned symptoms in SS patients. Enlargement of the salivary glands is often seen in these patients, and in particular, the parotid and submandibular glands, due to the presence of an autoimmune inflammatory process. SS patients with advanced salivary gland hypofunction have obvious signs of mucosal dryness including cracked lips and tongue. Moreover, dryness is not restricted to the eyes and mouth but also occurs at mucosal surfaces in the upper and lower airways, frequently leading to dryness of the nose, throat, and trachea. Patients may also experience dermal dryness, and in female SS patients, desiccation of the vagina and vulva may result in dyspareunia and pruritus (Kassan and Moutsopoulos, 2004).
Since saliva contains protective molecules such as immunoglobulins and lysozymes, patients with reduced salivary output are increasingly susceptible to oral infections such as oral candidiasis, dental caries, and periodontitis (Johansson et al., 1994; Radfar et al., 2003). Lack of saliva at the denture-mucosal interface can produce denture sores and prosthesis retention due to a lack of lubrication (Guggenheimer and Moore, 2003). Apart from the symptoms mentioned earlier, due to long-term effects of a decrease in oral fluids on mucosal hydration and oral function, patients may be restricted in their activities and their participation in society, resulting in reduced health-related QoL and impaired socioeconomic status (Meijer et al., 2009).

However, symptoms of dry mouth in SS patients are not curable or preventable at present, and whether they can be prevented or delayed is still unknown. The current treatment to relieve dryness-related symptoms is mainly based on stimulation of the residual secretory capacity of the affected salivary glands and, if this is no longer successful, various supportive and palliative treatment options are available (Baudouin et al., 2004; Hsu and Dickinson, 2006).

Masticatory stimulatory techniques are the easiest to implement and have few side effects in patients who have remaining salivary function. Sugar-free gums or mints are often used to relieve oral dryness. Combined gustatory and masticatory stimulatory techniques that employ lozenges, mints, and/or candies, are easy for most patients to implement. Systemic salivary stimulation through the use of the muscarinic agonists pilocarpine and cevimeline has recently been approved for SS patients. Although common and frequent side effects of both medications include sweating, flushing, urinary urgency, and gastrointestinal discomfort, they are rarely considered severe or serious. The duration of action for pilocarpine and cevimeline is 2 to 3 hours and 3 to 4 hours, respectively (Petrone et al., 2002).
In patients who do not respond to the various stimulation techniques mentioned earlier, several symptomatic treatment options have been suggested: use of air moisturizers; frequent sips of water; use of oral rinses, gels, and mouthwashes; use of saliva replacements (saliva substitutes or artificial saliva); and increased humidification (Fox et al., 1998; Jonsson et al., 2002). Water is frequently consumed by SS patients to relieve dry mouth; however, it is not a good long-lasting moisturizer of the oral mucosa since it is not retained in the mouth. Most patients carry water bottles of water with them to aid in speaking and swallowing, and for their overall oral comfort.

Due to the dehydration of the oral cavity and its subsequent deleterious effects, SS patients require more frequent dental visits and must work closely with their dentist and dental hygienist to maintain optimal dental health. An individualized treatment regime is significant to best manage patient’s oral problems and to prevent further oral disease.

1.2 Green Tea

Tea, a product made up from the leaves and buds of the plant *Camellia sinensis*, is the most widely consumed beverage aside from water with a per capita worldwide consumption of approximately 0.12 liters per day (Graham, 1992; McKay and Blumberg, 2002; Cabrera et al., 2006; Sharangi, 2009). The tea plant originated in Southeast Asia and is presently cultivated in over 30 countries (Graham, 1992). The economic and social interest of tea is significant and its consumption is part of many people’s daily routine as an everyday drink and as a therapeutic aid in many illnesses (Cabrera et al., 2006).

Depending on the manufacturing process, teas are classified into 3 major types: ‘non-fermented’ green tea, which is prepared in such a way as to preclude the oxidation
of green leaf polyphenols; ‘semi-fermented’ oolong tea, a partially oxidized product; and ‘fermented’ black tea which is produced when oxidation is promoted (Graham, 1992) (Figure 1). The majority of tea produced and consumed worldwide is in the form of black tea (76-78%), with 20-22% involving green tea, and less than 2% for oolong tea (Kuroda and Hara, 1999; Wu and Wei, 2002). While black tea is consumed mainly in Europe, North America, and North Africa (except Morocco), green tea is widely consumed in China, Korea, Japan, and Morocco; oolong tea is popular in China and Taiwan (Cabrera et al., 2006).
Figure 1. Principal Differences between Green and Black Tea Processing and the Influence on the Final Polyphenol Content (modified from Cabrera et al., 2006).
EGCG: (-)-epigallocatechin gallate; EGC: (-)-epigallocatechin; ECG: (-)-epicatechin gallate; EC: (-)-epicatechin
Although health benefits have been attributed to green tea consumption since the beginning of its history, scientific investigations on this beverage and its constituents have been underway for less than 3 decades (McKay and Blumberg, 2002). In the past few years, green tea has received a great deal of attention especially due to its content of polyphenols, which are strong antioxidants that possess important biological properties (Dufresne and Farnworth, 2001). The polyphenol content in green tea ranges from 30% to 40%, which is much higher in comparison to that of black tea, which varies from 3% to 10%.

The green tea polyphenols (GTPs), also referred to as green tea catechins, are present in the leaves of *Camellia sinensis*, and are primarily responsible for the beneficial properties of green tea. The 4 major types of green tea polyphenols and their abundance are: (-)-epigallocatechin-3-gallate (EGCG; ~59%); (-)-epigallocatechin (EGC; ~19%); (-)-epicatechin-3-gallate (ECG; ~13.6%); and (-)-epicatechin (EC; ~6.4%), with EGCG being the most widely studied (McKay and Blumberg, 2002; Yang *et al.*, 2002; Singh *et al.*, 2010).

There have been numerous *in vitro* and animal studies, and some clinical trials providing strong evidence that these naturally occurring phytochemicals may play a protective role against a range of diseases including several cardiovascular diseases, cancer, and diabetes (Sueoka *et al.*, 2001; Johnson *et al.*, 2010). In addition, green tea intake has a positive impact on bone density (Singh *et al.*, 2010), cognitive function (Kuriyama *et al.*, 2006), dental caries (Awadalla *et al.*, 2009), kidney stones (Curhan *et al.*, 1998), mortality (Suzuki *et al.*, 2009), obesity (Moon *et al.*, 2007; Basu *et al.*, 2010), etc. (McKay and Blumberg, 2002; Wu and Wei, 2002). These consistent findings have demonstrated that GTPs are potent antioxidants that also possess chemo-preventive, anti-apoptotic, and anti-inflammatory activities (Hsu and Dickinson, 2006). The anti-
inflammatory activities and anti-arthritic effects, particularly of EGCG are supported by \textit{in vitro} and \textit{in vivo} data indicating that EGCG itself or EGCG as contained in green tea can regulate the expression of cytokines, chemokines, metallocopperproteinases (MMPs), aggrecanase, reactive oxygen species (ROS), nitric oxide (NO), cyclo-oxygenase 2 (COX-2), and prostaglandin E$_2$ (PGE$_2$) in cell types relevant to the pathogenesis of autoimmune diseases such as RA (Haqqi \textit{et al.}, 1999; Singh \textit{et al.}, 2010; Hsu and Dickinson, 2006).

Although the protective roles of GTPs against the damage incurred by autoimmune diseases have been providing promising results, their roles against SS in particular have not been studied extensively. Recently, studies have been performed (Hsu \textit{et al.}, 2005) investigating whether EGCG affects autoantigen expression in human cells since antibodies against the autoantigens SS-A/Ro and SS-B/La are primary markers for SS. Cultures of an immortalized human salivary acinar cell line incubated with 100 μM EGCG for various time periods have shown that EGCG inhibited the transcription and translation of major autoantigens including SS-B/La, SS-A/Ro, coilin, DNA topoisomerase I, and α-fodrin. Subsequent studies (Hsu \textit{et al.}, 2007) using an accepted mouse model of SS, the non-obese diabetic (NOD) mouse, showed that mice fed with water containing 0.2% GTPs had reduced lymphocytic infiltration of the submandibular gland and reduced serum antoantibody production 3 weeks after the onset of diabetes. Consistent inhibitory effects of EGCG have also been reported (Gillespie \textit{et al.}, 2008).

As shown in Figure 2, there are 3 potential major strategies that have been proposed for ameliorating SS directly involving the acinar cells, which could be selective inhibition of 1) their apoptosis, 2) autoantigen expression, and 3) production of pro-inflammatory cytokines (Yang \textit{et al.}, 1999). Although relative contributions of the antioxidant and modifying properties of GTPs in the mitogen-activated protein kinases
(MAPK) signal pathway in the protection from a given stress have not been fully known, GTPs may delay autoimmune disease onset and/or reduce the severity of the symptoms if appropriately administered (Hsu and Dickinson, 2006).

Figure 2. Schematic Model for GTP-mediated Protective Mechanism (Hsu et al., 2006). Inhibition could be achieved by activation of the p38 MAPK pathway or reduction in reactive oxygen species, which would reduce c-Jun NH2-terminal Kinase (JNK) activation.

In human trials, both the method of delivery of the tea and its bioavailability in the target tissues are important issues, and in particular, the levels of tea catechins in tissue and saliva (Lee et al., 1995; Yang et al., 1999). The results have shown that drinking green tea leads to an increase of secreted salivary GTPs in a concentration range 10 times higher than the serum levels (Yang et al., 1999). The elimination half-life of the salivary catechins was 10-20 min, much shorter than that of the plasma (3-5 hours), and the salivary catechin levels became undetectable after 3 hours of consumption. Moreover, it was suggested that drinking a tea solution delivers much higher
concentrations of tea catechins to the target tissues than using tea capsules especially in the oral cavity (Yang et al., 1999).

Tea consumption in general has not displayed any acute or chronic toxic effects and, in fact, it promotes a generally healthy lifestyle (Schwarz et al., 1994; Singh et al., 2010). Harmful effects of green tea overconsumption could be due to its caffeine content. A daylong consumption of green tea improves the cognitive and psychomotor performance of healthy adults in a manner similar to coffee, but green tea is less likely than coffee to disrupt sleep quality at night (McKay and Blumberg, 2002). With respect to the caffeine content in tea manufactured by different fermentation processes, the order is: black tea > oolong tea > green tea (Lin et al., 2003). In addition, it is known that a cup of green tea contains 40-55 mg caffeine while a cup of coffee has 125-150 mg of caffeine (McKay and Blumberg, 2002). Although green tea caffeine content is low, the negative effects produced by the overconsumption of caffeine may include nervousness, sleep disorders, vomiting, headaches, and tachycardia (Singh et al., 2010).

1.3 Salivary Flow Rate

In healthy humans, the daily production of whole mixed saliva normally ranges from 0.5 to 1.5 L. About 90% of mixed saliva is secreted from 3 pairs of major salivary glands (Figure 3): the parotid glands, which are located opposite the maxillary first molars, and the submandibular and sublingual glands, both of which are found in the floor of the mouth. The remaining 10% is from numerous minor glands that are found in the lower lip, tongue, and buccal and labial mucosa (Humphrey and Wiliamson, 2001; Mese and Matsuo, 2007). The contributions of the different salivary glands during unstimulated flow are: 20% from the parotid glands, 65% from the submandibular glands,
7% to 8% from the sublingual glands, and less than 10% from numerous minor glands (Humphrey and Wiliamson, 2001). Stimulated high flow rates drastically change percentage contributions from each gland, with the parotid contributing more than 50% of total salivary secretions. It is known that the submandibular and sublingual salivary glands, which are the most active glands under resting condition, are among the first glands to be involved in SS, whereas the parotid gland, the most active gland when stimulated, appears to be the last salivary gland to be affected. This explains why many SS patients in the early stages particularly suffer from oral dryness when at rest or during the night, and the effect of stimulants becomes insufficient as the disease proceeds (Van der Reijden et al., 1999).

**Figure 3. Location of Major Salivary Glands in Humans**
(modified from Tucker and Miletich, 2010).

It is very important to distinguish between xerostomia and hyposalivation (Nederfors, 2000). Xerostomia is the subjective sensation of dry mouth, while hyposalivation is the objective finding of a reduced salivary flow rate. In other words, some individuals may complain of oral dryness and clinically appear to have adequate salivary output. Conversely, some with no complaints of oral dryness may appear to have
little salivary output (Baum, 1989). To evaluate such patients more completely, unstimulated whole saliva can be collected to measure its flow rate (Wang et al., 1998) and it is the basis for one of the diagnostic tests for SS (Stuchell et al., 1984; Wang et al., 1998) although recently it has been suggested that the stimulated salivary flow rate is more meaningful (personal communication with Dr. Arthur Bookman, 2011).

Unstimulated whole saliva is a complex mix of fluids secreted to the oral cavity collected by either the drooling or the spitting method (Navazesh and Christensen, 1982). Stimulated saliva is secreted in response to either masticatory or gustatory stimulation and paraffin and citric acid (2-5%) are commonly used to obtain these samples. Generally, an accepted range of normal flow rate for unstimulated whole saliva is anything above 0.1 ml/min and any flow rate below 0.1 ml/min is considered evidence of hyposalivation (Sreebny and Valdini, 1988). As indicated in Table 2, several studies have suggested that the average flow rate of unstimulated whole saliva is about 0.3 – 0.4 ml/min in healthy individuals.

Table 2. Studies of Unstimulated Whole Saliva Flow Rates (ml/min) in Healthy Individuals.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Unstimulated whole salivary flow rate (ml/min) (Mean ± SD)</th>
<th>Sample size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heintze, et al., 1983</td>
<td>0.31 ± 0.22</td>
<td>629</td>
</tr>
<tr>
<td>Nahir, et al., 1987</td>
<td>0.25 ± 0.16</td>
<td>20</td>
</tr>
<tr>
<td>Sreebny and Zhu, 1996</td>
<td>0.41 ± 0.31</td>
<td>52</td>
</tr>
<tr>
<td>Fenoll-palomares, et al., 2004</td>
<td>0.48 ± 0.15</td>
<td>159</td>
</tr>
<tr>
<td>Flink, et al., 2005</td>
<td>0.35 ± 0.18</td>
<td>108</td>
</tr>
</tbody>
</table>

SD: Standard deviation
On the other hand, as shown in Table 3, unstimulated flow rates of SS patients are found to be much lower than those of healthy individuals from various studies.

### Table 3. Studies of Unstimulated Whole Saliva Flow Rates (ml/min) in SS Patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Unstimulated whole salivary flow rate (ml/min) (Mean ± SD)</th>
<th>Sample Size (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spielman, et al., 1982</td>
<td>0.11 ± 0.06</td>
<td>23</td>
</tr>
<tr>
<td>Stuchell, et al., 1984</td>
<td>0.10 ± 0.06</td>
<td>9</td>
</tr>
<tr>
<td>Sreebny and Zhu, 1996</td>
<td>0.01 ± 0.02</td>
<td>13</td>
</tr>
<tr>
<td>Nahir, et al., 1987</td>
<td>0.09 ± 0.10</td>
<td>9</td>
</tr>
<tr>
<td>Wang, et al., 1998</td>
<td>0.07 ± 0.09</td>
<td>30</td>
</tr>
<tr>
<td>Dawson, et al., 2001</td>
<td>0.12 ± 0.17</td>
<td>134</td>
</tr>
<tr>
<td>Pijpe, et al., 2007</td>
<td>0.08 ± N/A</td>
<td>60</td>
</tr>
</tbody>
</table>

N/A: Not available

Unstimulated salivary flow rate reflects the basal activity of the salivary glands. Their secretions play the principal role in protecting and maintaining the integrity of the oral tissues. On the other hand, stimulated flow rate is considered an important indicator of reserve secretory function of the salivary glands (Wang et al., 1992; Van der Reijden, 1999). Widely accepted normal values for stimulated flow rates are 1.0 to 2.0 ml/min in healthy individuals (Sreebny and Zhu, 1996), and values below 0.5 ml/min are considered as hyposalivation in response to the chewing of paraffin wax (Sreebny et al., 1992). Two studies of mean paraffin-stimulated whole salivary flow rates in SS patients have shown following values: 0.46 ± 0.26 ml/min (Dawson et al., 2001) and 0.71 ± 0.72 ml/min (Wang et al., 1998).

One limitation of salivary flow-rate studies is that it is very difficult to establish normal ranges or “cut-off” values to distinguish normal from abnormal salivary function (Wang et al., 1998; Ghezzi et al., 2000). The amount of saliva in the mouth is not constant and varies within a person over time (Dawes, 1972) and between individuals (Dawes, 1987; Ship et al., 1991). Edgar (1990) has suggested that salivary flow is a very
individualized measurement and ideally should be recorded as a base reference after the age of 15. Unfortunately, dentists do not routinely measure the salivary flow rate of their patients, so when a patient complains of experiencing a dry mouth, there is usually no baseline data for comparison.

Although salivary flow rates vary widely from person to person, they are quite stable for an individual when the collection procedure is well standardized (Heintze et al., 1993; Sreebny and Zhu, 1996). Several factors including circadian rhythm (Dawes, 1970; Dawes, 1972), therapeutic drugs (Dodds et al., 2005), and collection methods (Navazesh and Christensen, 1982) are known to affect the flow rate of saliva. Therefore, when saliva is used in research studies, non-standardized methodology has partly contributed to the high variability in the data published for saliva parameters including flow rate, composition, viscosity, and lubrication properties (Schipper et al., 2007).

1.4 Salivary Viscosity

Interestingly, some clinical trials have reported weak to no correlation between subjective mouth dryness and objective sialometric values (Fox et al., 1987; Sreebny and Valdini, 1988). This indicates that lubricating and hydration functions of saliva may not only be dependent on quantity but also on quality (e.g., structure and composition of saliva secretions) of saliva secreted (Christersson et al., 2000). The rheological properties of saliva include viscosity, solubility, elasticity, and adhesiveness, as a result of the unique chemical and structural characteristics of its mucins (Veerman et al., 1989). The lubricating action of saliva is essential for good oral health, facilitating movement of the tongue and lips on swallowing and eating, and being important for clearly articulated
speech. The efficacy of saliva as a lubricant depends on its viscosity and how this changes with shear rate (Waterman et al., 1988).

To date, there have been limited viscosity measurements made on the saliva of healthy individuals. Newtonian fluids are known to follow a simple relationship between shear stress and shear rate as their viscosity is constant. However, whole saliva is classified as a non-Newtonian fluid as its viscosity decreases with increasing shear rate (Waterman et al., 1988; Schwartz, 1987; Van der Reijden et al., 1993; Kusy and Schafer, 1995; Rantonen and Meurman, 1998; Christersson et al., 2000). The main reason for the shear thinning characteristic of whole saliva is due to the presence of large glycoproteins, such as mucins, which contribute the weak gel character (Veerman et al., 1989). Many studies have suggested that the salivary glands are different in the type of secretion they produce, which is based on the ratio of serous to mucous glandular cells. Serous cells, which are mainly found in the parotid glands, produce a watery fluid that is essentially devoid of mucus. Thus, when the parotid gland is stimulated by mechanical means, contributing more than 50% of total salivary secretions, its viscosity becomes more watery than that of unstimulated saliva (Park et al., 1997; Rantonen and Meurman 1998). On the other hand, mucous cells present in the submandibular and sublingual glands predominantly secrete a very mucus-rich fluid, which is viscous and more or less elastic (Stokes and Davies, 2007; Davies et al., 2009). Therefore, the presence of high molecular weight proteins in saliva secreted by the submandibular and/or sublingual glands leads to high elasticity, slowing down the spreading of saliva. This is perceived as ‘thick and mucous-like’ viscoelastic saliva whereas the parotid gland gives the most watery saliva (Mese and Matsuo 2007; Stokes and Davies, 2007; Davies et al, 2009). Furthermore, observations by van der Reijden et al. (1993) have shown that linear
viscoelasticity and viscosity of saliva excreted from different salivary glands decreases in the following order: sublingual > palatal ~ whole saliva ~ submandibular > parotid.

Viscosity is defined as a fluid’s resistance to shear and is measured in centiPoise (cP). The shear rate refers to a gradient in the velocity of a flowing material and is expressed in “reciprocal seconds” (sec⁻¹). The highest shear rates in a fluid, and thus, the highest degree of shear thinning typically occur near a surface in contact with the fluid. Several studies have reported the viscosity of unstimulated whole saliva. Park et al. (2007) have observed the mean viscosity of saliva collected from 20 healthy donors to be 2.5 cP at a shear rate of 90 s⁻¹. Similar findings were observed with a mean viscosity of saliva collected from 7 healthy donors to be 2.57 cP ± 0.4 at a shear rate of 100 s⁻¹ (Van der Reijden, 1993), and from a single donor to be 1.7 cP ± 0.2 at a shear rate of 100 s⁻¹ (Stokes and Davies, 2007). The degree of shear thinning behaviour, as well as the viscosity, reported by different authors varies due to potential differences in measuring methods and conditions, saliva collection and handling, circadian rhythm, and individual variation (Van der Reijden et al., 1993; Rantonen and Meurman, 1998; Schipper et al., 2007). In addition, saliva is intrinsically nonhomogeneous, as the sample can simultaneously consist of liquid, gaseous (bubbles), and gel phases, which can largely affect the reliability of the measurements. Therefore, it was suggested that saliva collection should be standardized along with the many factors including glandular source, circadian rhythm, medications, etc. that influence the composition of saliva (Schipper et al., 2007).

The significance of the viscosity of saliva in general has been the subject of odontology studies (Ericsson and Stjerström, 1951). It has been found that salivary viscosity is greatly influenced by pH and the presence of calcium (Nordbo et al., 1984). Increased salivary viscosity is suggested to promote carious formation by decreasing the
rate of salivary flow and diffusion, and increasing the precipitation of calculus (Ericsson and Stjerstrom, 1951; Beisbrock et al., 1992).

In the oral diagnosis associated with SS, salivary viscosity has not been demonstrated as a clinically relevant variable despite the fact that one of the common complaints from SS patients is having mucous-like viscous and/or ropey saliva. Although knowledge of salivary viscosity and its clinical significance in SS is limited, changes in salivary characteristics and properties are reflected in some way by the functions of saliva within the oral cavity. Therefore, alterations in salivary composition appear to be reflected in its viscosity and in oral complaints (Chimenos-Kustner and Marques-Soares, 2002). In the case of patients with SS, salivary viscosity may be associated with dry mouth-related symptoms since whole saliva collected from the SS patients appear to be foamy and highly viscous (Sreebny and Zhu, 1996). However, no previous studies have measured the viscosity of whole saliva in SS patients.

1.5 Statement of the Problem and Rationale for the Study

SS is considered an under-diagnosed, under-treated, and under-researched disease (Venables, 2004) and many current studies suggest that there is no known cure for SS, nor is there a specific treatment to restore the function of damaged salivary glands. Although recent animal studies have introduced beneficial effects of GTPs against SS, it is not known whether the protective effect of GTPs can be observed only at the doses used in animal studies, which are generally higher than the levels commonly consumed by humans. Furthermore, the bioavailability and tissue distribution of GTPs in humans are largely unknown. Currently, the positive effects of green tea and GTPs have not been investigated in clinical trials with human patients with SS.
There is a strong possibility that the GTPs associated with green tea consumption may provide protection of glandular cells from autoimmune-induced damage or the delay of progression of damage in SS patients. Rather than looking at the direct interaction between salivary glands and green tea components, this pilot study was designed to elucidate whether green tea consumption could cause any changes in salivary flow rate and viscosity in human patients with SS. In addition it was anticipated that this study would determine whether there was a positive impact of green tea consumption on patients’ subjective relief of dry mouth, overall oral health, and their quality of life. For the present pilot study, at the bare minimum, the drinking of green tea should provide external moisture to the oral cavity during the course of the day.

1.6 Objectives of the Present Study

The objectives of the present pilot study were:

1) To investigate the effects of green tea consumption on salivary flow rates and viscosity of both unstimulated and stimulated saliva in SS patients.

2) To evaluate the impact of green tea consumption on SS patients’ quality of life (QoL).

3) To examine the effects of green tea consumption on subjective relief of dry mouth-related symptoms and behaviours in SS patients.

1.7 Hypotheses

Subjectively, there would be a positive effect of green tea consumption on patients’ relief of dry mouth, overall oral health, and their quality of life. Objectively, there would be an increase in salivary flow rate and a decrease in salivary viscosity.
CHAPTER 2. MATERIALS AND METHODS

2.1 Study Design

A prospective pilot study was conducted over the span of 6 months (October, 2010 – March, 2011). All participants were evaluated in terms of salivary measures and subjective oral health measures at various times: prior to the green tea consumption (T0), after 1 month (T1), 2 months (T2), and 3 months (T3) of green tea consumption (Figure 4). Each visit lasted approximately 1 hour and took place in room 316 at the University of Toronto, Faculty of Dentistry at 124 Edward Street, Toronto, Ontario.

The study protocol was granted approval from the Research Ethics Board of the University of Toronto (Reference number: #25418, Appendix I).

2.2 Human Subjects

Study participants were divided into 2 groups: SS patients/experimental group and non-SS/control group. SS patients had been previously identified and recruited through: the Sjögren’s Society of Canada, the Faculty of Dentistry at the University of Toronto, Dr. Laing’s private dental practice and/or the Sjögren’s Syndrome 4th National Patient Conference (March 27, 2010; Mississauga, ON). Healthy control participants (age- and gender-matched participants with no symptoms of dry mouth) were recruited from the Faculty of Dentistry or from recruitment advertisements to the general Toronto population. After a brief description of the study, those who were interested in participating received a telephone call, a letter, or an email message informing them of more details of the study. If they agreed to participate and met the inclusion/exclusion criteria (Appendix II), they were invited to attend our testing centre at the Faculty of
Dentistry. After being given verbal and written explanations of what was involved for the study participation, subjects signed a Consent Form (Appendix III).

Included in the study were those who were over the age of 18, and who were able to understand and communicate in English unless a translator was available. To be included in the SS group, a diagnosis of SS was mandatory.

Exclusion criteria were as follows: anyone with medications that were known to cause oral dryness, those who were allergic to any teas (i.e., green tea, black tea, white tea, red tea, etc.), any pregnant or lactating women, or those who had a present history of cancer, severe infections, or other uncontrolled diseases. Non-SS control patients were age- and gender-matched participants who had no symptoms of dry mouth and who had no diagnosis of any autoimmune diseases.
SS group (experimental group)
- Baseline visit (T0)
- 1-month follow-up (T1)
- 2-month follow-up (T2)
- 3-month follow-up (T3)

Non-SS group (control group)
- Baseline visit (T0)
- 1-month follow-up (T1)
- 2-month follow-up (T2)
- 3-month follow-up (T3)

Figure 4. Outline of Visits Involved in the Green Tea Study.
SS: Sjögren’s Syndrome. During each visit, all participants were evaluated in terms of salivary measures, and subjective oral health measures using questionnaires.
2.3 Selection of Green Tea

Four main green tea catechin compounds from infusions of green tea were analyzed using high-performance liquid chromatography (HPLC) coupled with mass spectrometry (LC/MS/MS). Five commercially available brands, prepared as described below, were quantitatively analyzed as previously described (Mata-Bilbao et al., 2007).

The 4 green tea catechins are (-)-epigallocatechin (EGC), (-)-epigallocatechingallate (EGCG), (-)-epicatechin (EC), and (-)-epicatechingallate (ECG). The total catechin levels were determined by summing each level of the 4 catechins as summarized in Table 4. Michael Leadley from the Analytical Facility for Bioactive Molecules (AFBM) Mass Spectrometry Department at The Hospital for Sick Children performed tea catechin analysis.

Table 4. Tea Catechin Analysis in 5 Commercially Available Green Tea.

<table>
<thead>
<tr>
<th>Catechins (mg/250 ml)</th>
<th>Twinings Green Tea</th>
<th>Twinings White Tea</th>
<th>Fujian Green Tea</th>
<th>PaiMuDan-Majesteas Green Tea</th>
<th>Sencha-Majestas White Tea</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGCG</td>
<td>79.75</td>
<td>54.25</td>
<td>34.00</td>
<td>23.43</td>
<td>33.25</td>
</tr>
<tr>
<td>ECG</td>
<td>26.25</td>
<td>37.00</td>
<td>8.35</td>
<td>8.20</td>
<td>7.98</td>
</tr>
<tr>
<td>EGC</td>
<td>89.00</td>
<td>38.50</td>
<td>34.50</td>
<td>10.95</td>
<td>69.00</td>
</tr>
<tr>
<td>EC</td>
<td>92.75</td>
<td>67.25</td>
<td>28.00</td>
<td>19.85</td>
<td>68.75</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>297.75</strong></td>
<td><strong>197.00</strong></td>
<td><strong>104.85</strong></td>
<td><strong>64.43</strong></td>
<td><strong>178.98</strong></td>
</tr>
</tbody>
</table>

EGCG: (-)-epigallocatechingallate; ECG: (-)-epicatechingallate; EGC: (-)-epigallocatechin; EC: (-)-epicatechin. Green tea infused for 3 minutes.

Twinings Green Tea was selected due to its highest levels of total catechins. Twinings Canada representatives were approached with this information and asked if they would be interested in donating some green tea to our study. They graciously supplied us with sufficient numbers of tea bags for all study participants. Each participant was supplied with 1-, 2-, or 3-month supplies of green tea in bags. In order to standardize
the intake at their private settings, instructions on how to prepare a cup of green tea were explained (Appendix IV):

1) Bring water to a boil, then let it sit for 5 minutes to reach a temperature from 165-175°F (~70°C).

2) Pour water over the tea bag. Use 1 tea bag per cup (8 oz.).

3) Steep the tea bag for 2-5 minutes (recommended brewing time is 2-3 minutes) to suit your taste preferences. Never judge tea strength by its colour.

All participants were required to consume at least 4 cups of green tea on a daily basis at any time of the day. It was recommended that they abstain from drinking other types of tea, but to otherwise continue their usual daily diet throughout the study period. It was advised that they record a daily consumption of tea to determine compliance (Appendix V).

2.4 Salivary Measures

A. Salivary Flow rate

In order to diminish any possible influence of the circadian rhythm on salivary flow rate, the time of day of salivary collection was standardized to be between 09:00 and 11:00 in a quiet room. All subjects were instructed to refrain from eating and/or drinking (except for water) for at least 1 hour prior to saliva collection. The spitting method was used for all saliva collection due to its simplicity. Before the collection, several sips of distilled water were consumed and/or swilled around the mouth for at least 30 seconds to obtain a ‘neutral’ mouth state. Then unstimulated saliva was collected for 10-15 minutes by spitting using the following protocol (Stokes and Davies, 2007):

(a) All subjects were asked to sit in a forward position with the elbows resting on the knees. The tongue, cheeks, and jaw should not be moved.
(b) Then they collected saliva with closed lips, and expectorated once after approximately each 60-second period. When expectorating, they were told only to drool passively and not to spit actively.

(c) Once the unstimulated saliva had been collected, stimulated saliva was collected. Saliva production was stimulated by mechanical means (i.e., chewing on a gum base) to determine the maximum amount of saliva that the individual patient could actually produce, using the following protocol:

(a) Several sips of distilled water were consumed and/or swilled around the mouth for at least 30 seconds to obtain a ‘neutral’ mouth state.

(b) Initial chewing took place for 30 seconds in order to soften the gum base and remove saliva from the mouth by swallowing.

(c) During the subsequent 5 min, stimulated saliva was collected by the spitting method while the patient chewed on the same bolus of gum base. The number of strokes per minute was standardized to 60 strokes per minute. The collected saliva was measured to determine production rate for a total collection time of 5 minutes.

Both unstimulated and stimulated salivary flow rates were measured in volume per minute (ml/min).

**B. Salivary Viscosity**

Salivary viscosity was measured using the AR2000, a cone and plate rheometer housed in the Rheology Laboratory in the Department of Mechanical & Industrial Engineering, which measures the viscosity of fluids. As depicted in Figure 5, the fluid is ideally confined in a small gap between one plate that is stationary and another that is moving at a constant velocity. This tangential movement causes shear flow, imparting a
shear stress and a shear rate to the fluid. Shear stress is the force applied per unit area whereas shear rate is the ratio of velocity of rotating cone to the gap distance between plates. Viscosity is simply defined as a fluid’s resistance to flow under an applied shear stress – the ratio of shear stress and shear rate (Barnes et al., 1989).

![Diagram of Cone and Plate Rheometer](image)

**Figure 5. Cone and Plate Rheometer**

ω: angular velocity; α: cone angle. The top plate moves at a constant velocity while the bottom plate is stationary.

Theoretically, the velocity at any point on the rotating surface (either the cone or the plate) is given by rω, where r is the distance from the centre of rotation and ω is the rotation rate. If the cone angle is small (less than 4°), then the distance between the cone and plate at this point is given by rα, where α is the angle between the cone and plate in radians. Thus the shear rate, \( \dot{\gamma} \), is given by \( r\omega/r\alpha \) or simply \( \omega/\alpha \). Since the quantity is the same everywhere in the liquid, it follows that the shear rate is also the same everywhere. Shear stress, \( \sigma \) is described as \( 3T/2\pi R^3 \), where R is the radius of the plate and T is torque (Barnes, 2002). The viscosity is then given by \( \eta = \sigma/\dot{\gamma} = 3T\alpha/2\pi\omega R^3 \).

The AR2000 rheometer was operated in a shear rate controlled mode. In a shear rate controlled mode, the machine applies a known rotational velocity to produce a measured resistance to rotation, which is measured as torque. It uses the torque value to calculate the shear stress. The viscosity of a fluid is simply shear stress divided by shear rate.
All measurements were carried out at 37°C by using a Peltier plate. Prior to measurements, the instrument was calibrated using a standard calibration liquid (Brookfield viscosity standard, 5 centipoise (cP) at 37°C). Since SS patients are limited in the amount of saliva that they can produce, the measurement geometry chosen was 0.5° for the cone angle, 40 mm for the diameter of the plate, and the minimal amount of saliva required for analysis was 0.15 ml. The range of shear rates was standardized to be 1 to 500 s⁻¹ according to the oral physiological shear rate although an important physiological shear rate for saliva in vivo is in the range of 0 to 300 s⁻¹ (Balmer and Hirsch, 1978). The viscosity of each sample was measured 3 times. The mean viscosity value at a single shear rate of 100 s⁻¹ was used. This was determined based on the human saliva samples and various shear rates. From the preliminary testing at this shear rate, a reliable and reproducible salivary viscosity value was found. Several previous studies of saliva have also used a single shear rate of either 90 or 100 s⁻¹ in repeated viscosity measurements (Rantonen and Meurman, 1998; Stokes and Davies, 2007; Davies et al., 2009).

The handling of saliva sample was standardized: 1) all measurements were performed as soon as samples were collected to minimize the time between collection and measurement; 2) the saliva was placed in the rheometer immediately after collection by pipetting directly from the collection tube, avoiding air bubbles and any particulate matter; 3) the saliva samples were handled on ice to avoid any possible changes of properties in saliva samples over time; and 4) the saliva was not centrifuged or subjected to any other process, which might alter its structure (Veerman et al., 1989).
2.5 Subjective Oral Health Measure

As mentioned earlier, xerostomia is defined as a subjective perception of dry mouth and can therefore be assessed only by directly questioning individuals. Studies that have measured salivary flow rates have suggested that xerostomia may or may not be associated with salivary gland dysfunction and reduced salivary flow since only 50% to 80% of subjects complaining of xerostomia exhibit decreased salivary flow (Spielman et al., 1982; Sreebny 1989). Since dry mouth is an important symptom that can have negative effects on the quality of life (QoL) and oral health in general, all study participants were asked to fill out questionnaires at the start (T0), at each monthly visit (T1 and T2), and at the end of the study period (T3). All questionnaires were distributed by the principal investigator but self-administered by participants.

The first set of questionnaires was administered prior to the green tea treatment (at T0). Demographic questions (i.e., birthdate, gender, height, and weight) were included as well as his/her current status of smoking and green tea consumption (Appendix II). Moreover, 4 additional sets of questionnaires included: Oral Health Impact Profile-14 (OHIP-14), Xerostomia Inventory (XI), Quality of Life (QoL) for Dry Mouth Patients, and Visual Analogue Scale (VAS) for Dry Mouth-related Symptoms (Appendices VI - IX). These were administered during each visit as shown in Figure 4. The QoL questionnaire for Dry Mouth Patients was the only questionnaire set which was not measured in the healthy control group since it was not applicable to them. In addition, at the end of the study, all SS participants filled out an exit survey about their experiences of drinking green tea (Appendix XIV).
Sources of Questionnaire Items

The items included in the questionnaires were adapted from different sources:

1) Oral Health Impact Profile – 14 (OHIP-14)

OHIP-14 is a 14-item questionnaire designed to measure oral health in 7 dimensions: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (Table 5) (Slade, 1997) (Appendix VI). All questions measure the frequency of problems associated with the teeth, mouth or dentures. This questionnaire is derived from an original extended version of 49-items (Slade and Spencer, 1994) based on a theoretic model developed by the World Health Organization (WHO) and adapted for oral health by Locker (1988). The model explains that the consequences of oral disease are hierarchically linked from a biological level (impairment) to a behavioural level (functional limitation, discomfort and disability) and lastly to the social level (handicap). The OHIP-14, in spite of being a short-questionnaire, has been shown to be reliable (Slade, 1997); sensitive to changes (Allen et al., 2001; Locker et al., 2004); and to have adequate cross-cultural consistency (Allison et al., 1999). Using a 5-point Likert scale coded “Never” (score 0), “Hardly ever” (score 1), “Occasionally” (score 2), “Fairly often” (score 3) and “Very often” (score 4), participants rated how frequently they had experienced each item addressed in the 14 questions during the past 3 months at T0 (baseline visit). All 14-item scores were calculated to yield a single summary score with a possible range of 0 to 56 based on combined scores for each of the 7 dimensions. Moreover, the unweighted ratings were calculated to yield subscale scores for each of the 7 dimensions (ranging from 0-8 based on responses to 2 questions in each category). For both measures, higher scores indicated more frequent problems and poorer oral health in general.
Table 5. OHIP-14 Individual Items in 7 Dimensions (Slade and Spencer, 1994).

<table>
<thead>
<tr>
<th>Dimension</th>
<th>OHIP-14 Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional limitation</td>
<td>Because of trouble with your teeth, mouth or dentures:</td>
</tr>
<tr>
<td></td>
<td>1. Have you had trouble pronouncing any words?</td>
</tr>
<tr>
<td></td>
<td>2. Have you felt that your sense of taste has worsened?</td>
</tr>
<tr>
<td>Physical pain</td>
<td>4. Have you had painful aching in your mouth?</td>
</tr>
<tr>
<td></td>
<td>5. Have you found it uncomfortable to eat any foods?</td>
</tr>
<tr>
<td>Psychological discomfort</td>
<td>6. Have you been self-conscious?</td>
</tr>
<tr>
<td></td>
<td>7. Have you felt tense?</td>
</tr>
<tr>
<td>Physical disability</td>
<td>8. Has your diet been unsatisfactory?</td>
</tr>
<tr>
<td></td>
<td>9. Have you had to interrupt meals?</td>
</tr>
<tr>
<td>Psychological disability</td>
<td>9. Have you found it difficult to relax?</td>
</tr>
<tr>
<td></td>
<td>10. Have you been a bit embarrassed?</td>
</tr>
<tr>
<td>Social disability</td>
<td>11. Have you been a bit irritable with other people?</td>
</tr>
<tr>
<td></td>
<td>12. Have you had difficulty doing your usual jobs?</td>
</tr>
<tr>
<td>Handicap</td>
<td>13. Have you felt that life in general was less satisfying?</td>
</tr>
<tr>
<td></td>
<td>14. Have you been totally unable to function?</td>
</tr>
</tbody>
</table>

2) Xerostomia Inventory (XI)

The XI is an 11-item summated rating scale that was developed to enable measurement of the severity of dry mouth symptoms in epidemiologic and clinical studies (Thomson and Williams, 2000). In comparison to a “conventional” single-item approach used to measure xerostomia, a multi-item rating scale approach of XI was used to measure severity of xerostomia. The constituent items cover both experiential and behavioural aspects of the condition (Table 6) (Appendix VII). Thomson (2007) has suggested that XI can be used for discriminative or evaluative purposes. With the former, the aim is to discriminate individuals with mild (or no) symptoms from those with more severe symptoms at a given time; with the latter, the ability to accurately depict change in symptoms is the key consideration, particularly if these measures are to be used as outcome measures in intervention studies (Johnstone et al., 2001; Bots et al., 2005).
Study participants were asked to indicate which 1 of 5 response options best described their symptoms. The response options were “Never” (score 1), “Hardly ever” (score 2), “Occasionally” (score 3), “Fairly often” (score 4), and “Very often” (score 5) (Thomson and Williams, 2000). All 11-item scores are added to yield a single summary score with a possible range of 11 to 55, with higher scores indicating a greater xerostomia.

**Table 6. Xerostomia Inventory (XI) 11-Items** (Thomson, 2007).

<table>
<thead>
<tr>
<th>Xerostomia Inventory (XI) Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My mouth feels dry</td>
</tr>
<tr>
<td>2. I have difficulty in eating dry foods</td>
</tr>
<tr>
<td>3. I get up at night to drink</td>
</tr>
<tr>
<td>4. My mouth feels dry when eating a meal</td>
</tr>
<tr>
<td>5. I sip liquids to aid in swallowing food</td>
</tr>
<tr>
<td>6. I suck sweets or cough drops to relieve dry mouth</td>
</tr>
<tr>
<td>7. I have difficulties swallowing certain foods</td>
</tr>
<tr>
<td>8. The skin of my face feels dry</td>
</tr>
<tr>
<td>9. My eyes feel dry</td>
</tr>
<tr>
<td>10. My lips feel dry</td>
</tr>
<tr>
<td>11. The inside of my nose feels dry</td>
</tr>
</tbody>
</table>
3) Quality of Life (QoL) for Dry Mouth Patients

Despite the considerable psychological and social impact of xerostomia, few studies to date have addressed the extent of its influence on QoL. Previously, a QoL questionnaire was used and validated in a study evaluating the efficacy of saliva substitutes in post-radiotherapy cancer patients with xerostomia (Dirix et al., 2007; Dirix et al., 2008). However, a QoL questionnaire has seldom been incorporated in protocols assessing the efficacy of new treatments for xerostomia in patients with SS. As indicated in Table 7, 14-items were included to measure the effects of dry mouth on QoL in patients with SS (Appendix VIII).

The response options were: “Not at all” (score 1), “A little” (score 2); “Moderately” (score 3), “Quite a lot” (score 4), and “Very much” (score 5). A QoL score was calculated (100 – sum of all 14-item scores) to provide a single score with a possible range of 30 to 86, with the higher scores indicating a better QoL (Dirix et al., 2007).

Table 7. 14-Items in Quality of Life (QoL) (modified from Dirix et al., 2007)

<table>
<thead>
<tr>
<th>Quality of Life (QoL) Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>My dry mouth…</td>
</tr>
<tr>
<td>1. Restricts the amount and type of food I eat</td>
</tr>
<tr>
<td>2. Gives me an uncomfortable feeling in my mouth</td>
</tr>
<tr>
<td>3. Makes me worry</td>
</tr>
<tr>
<td>4. Restricts my social life</td>
</tr>
<tr>
<td>5. Makes it awkward to eat in front of other people</td>
</tr>
<tr>
<td>6. Makes it difficult to speak to other people</td>
</tr>
<tr>
<td>7. Is the cause of considerable tension</td>
</tr>
<tr>
<td>8. Makes me worry about the look of my teeth and mouth</td>
</tr>
<tr>
<td>9. Makes me feel depressed</td>
</tr>
<tr>
<td>10. Restricts me in my daily activities</td>
</tr>
<tr>
<td>11. Troubles my intimate relation</td>
</tr>
<tr>
<td>12. Gives my food less or a different taste</td>
</tr>
<tr>
<td>13. Diminishes my will to live</td>
</tr>
<tr>
<td>14. Invades every aspect of my live</td>
</tr>
</tbody>
</table>
4) Visual Analogue Scale (VAS) for Dry Mouth-related Symptoms

A VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured (Wewers and Lowe, 1990). Operationally a VAS is usually a horizontal line, 10 cm in length, anchored by word descriptors at each end, as illustrated in Figure 6. Study participants are requested to mark on the line the point that they felt represented their perception of their current state. VAS has been widely used in pain research to evaluate the amount of pain that a patient feels since from the patient’s perspective this spectrum appears continuous; pain does not take discrete jumps, as a categorization of none, mild, moderate and severe would suggest (Scott and Huskisson, 1976; Wewers and Lowe, 1990). In the same manner, xerostomia can be evaluated in patients with dry mouth (Dirix et al., 2007; Oh et al., 2008). Here, we measured dry mouth-related symptoms that a participant subjectively perceived using VAS (modified from Oh et al., 2008) (Appendix IX).

Please draw a vertical line cutting the horizontal one to indicate the degree of your dry mouth-related symptom: Oral dryness at night or on awakening.

```
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not dry at all</td>
</tr>
</tbody>
</table>
```

Figure 6. Visual Analogue Scale (VAS) Measuring Oral Dryness at Night or on Awakening in Study Participants
(modified from Oh et al., 2008)

There are 11 items included: 1) oral dryness at night or on awakening; 2) oral dryness at other times of the day; 3) oral dryness during eating; 4) difficulty in swallowing foods; 5) difficulty in eating dry foods; 6) amount of saliva in usual everyday life; 7) dryness of skin; 8) dryness of eyes; 9) dryness of lips; 10) dryness of tongue; and
11) dryness of inside of nose. Each item on this questionnaire was measured in centimeters to give a single score, and evaluated separately.

2.6. Data Analysis

All statistics were performed using the statistical package SPSS (SPSS, IL.) for Windows and/or Mac (versions 19.0). At each testing appointment, comparisons were made at the intra-group and/or inter-group levels with respect to salivary flow rate, salivary viscosity, and subjective oral health measures obtained from the questionnaires of OHIP-14, XI, QoL, and VAS for dry mouth symptoms. The paired samples t-test was used to compare the differences between baseline scores and the scores measured at follow-up visits after green tea consumption with respect to all study parameters at the 5% significance level in the SS and non-SS groups. The independent samples t-test was used to compare the difference between the two groups at the 5% significance level for all study parameters. Repeated Measures ANOVA was used to detect changes over the course of the study between two groups. Associations between various combinations of study parameters including salivary flow rate, salivary viscosity, OHIP-14 scores, XI scores, and QoL scores at each testing visit were evaluated by the Pearson’s correlation test (2-tail) at the 1% or 5% significance level.
CHAPTER 3. RESULTS

3.1 Study Progress

After 57 SS patients and 12 non-SS control participants were recruited, 31 SS patients and 12 non-SS participants consented to participate in the study. Although 12 non-SS participants completed the study by attending monthly follow-up visits, the number of SS patients declined over time as seen in Table 8. While 31 SS patients participated in the subjective measures portion of the project, only 21 SS patients attended our testing room for the baseline salivary measurements. For each of the other 10 SS patients who had difficulty in attending due to medical complications and/or distance required to travel, their baseline questionnaires were collected by mail. Two of these 10 SS patients consumed the green tea for one month but could not attend for a follow-up visit. They did, however, complete their 1-month questionnaires. After 1 month of green tea consumption, 16 of the original 21 SS patients returned for a follow-up visit. The other 5 SS patients had to withdraw from the study due to severe medical complications, or difficulty consuming, and/or dislike of the flavour of green tea. After 2 and 3 months of green tea consumption, 7 SS patients had follow-up visits to complete the study.

Table 8. Changes in Number of SS Patients through Stages of the Study.

<table>
<thead>
<tr>
<th>Group</th>
<th>Measures</th>
<th>Baseline (n)</th>
<th>1 Month (n)</th>
<th>2 Month (n)</th>
<th>3 Month (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>Objective outcome</td>
<td>21</td>
<td>16</td>
<td>6*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Subjective outcome</td>
<td>31</td>
<td>18</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Non-SS</td>
<td>Objective outcome</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Subjective outcome</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

57 SS patients were recruited, 31 agreed to participate, but only 21 could attend our testing centre at time 0, 16 at the 1-month appointment, and 7 at the 2- and 3-month appointments.

*One SS patient was unable to attend at 2-month follow-up visit due to illness but continued to consume green tea and was able to attend the 3-month follow-up visit.
3.2 Study Population: Demographics

All study participants were females. The non-SS control participants ranged from 38 to 58 years (mean 47.8yrs). For the SS group, there were 31 participants at time 0 (T0) whose ages ranged from 47 to 73 years (mean 59.4yrs), 18 patients at 1 month (T1) with ages from 50 to 73 years (mean 63.6 yrs), and 7 patients at 2 and 3 months (T2, T3) with ages from 57 to 73 years (mean 64.5 yrs). The average time since diagnosis of SS at baseline, 1 month, and 2 and 3 months were 10.3 years, 7.7 years, and 16.8 years, respectively. The independent t-test indicated that there were no significant differences ($p < 0.05$) between the SS group and the non-SS group in terms of height, weight, and whether or not they were green tea drinkers previously.

Table 9. Distribution of the Study Population According to Age, Gender, Height, Weight, Time since Diagnosis of SS, and Green Tea Drinking Status.

<table>
<thead>
<tr>
<th></th>
<th>SS group</th>
<th></th>
<th></th>
<th>Non-SS group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=31)</td>
<td>1 month (n=18)</td>
<td>2,3 months (n=7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs) Mean ± SD (n)</strong></td>
<td>59.4 ± 9.54 (31)</td>
<td>63.6 ± 6.3 (18)</td>
<td>64.5 ± 5.3 (7)</td>
<td>47.8 ± 6.9 (12)</td>
</tr>
<tr>
<td><strong>Gender (%)</strong> Female</td>
<td>31 (100)</td>
<td>18 (100)</td>
<td>7 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Height (cm) Mean ± SD</strong></td>
<td>163.4 ± 19.5</td>
<td>164.2 ± 5.5</td>
<td>164.0 ± 3.5</td>
<td>162.1 ± 5.3</td>
</tr>
<tr>
<td><strong>Weight (lb) Mean ± SD</strong></td>
<td>149.9 ± 24.4</td>
<td>149.1 ± 21.2</td>
<td>144.6 ± 23.6</td>
<td>143.9 ± 35.4</td>
</tr>
<tr>
<td><strong>Time since diagnosis of SS (yrs) Mean ± SD</strong></td>
<td>10.3 ± 9.1</td>
<td>7.7 ± 5.7</td>
<td>16.8 ± 12.7</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Green tea drinking status (%)</strong></td>
<td>5 (21.2)</td>
<td>5 (27.8)</td>
<td>3 (42.9)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (78.8)</td>
<td>13 (72.2)</td>
<td>4 (57.1)</td>
<td>7 (58.3)</td>
</tr>
</tbody>
</table>

N/A: not applicable.
3.3 Objective Salivary Outcome Measures

A. Results at Baseline (Time T0)

Baseline differences between the SS and non-SS groups in terms of baseline salivary flow rate and viscosity of both unstimulated and stimulated saliva are listed in Table 10, significant \( p \)-values are indicated in bold. There were significant differences between the 2 groups in terms of unstimulated salivary flow rate, stimulated salivary flow rate, and the viscosity of both unstimulated and stimulated saliva. In comparison to the SS group, the non-SS group had higher flow rates of both unstimulated and stimulated production of saliva, and higher viscosity of unstimulated saliva (Figures 7, 8, 9, and 10). There were no significant differences in stimulated salivary viscosity between the 2 groups.

Note that of the 21 SS patients who attended the clinic at the baseline appointment, only 10 were able to produce any unstimulated saliva; hence in Figure 9, data from only 10 SS patients are included for viscosity analysis.

Table 10. Differences in the Salivary Parameters between the SS (n=31) and Non-SS (n=12) Groups prior to Green Tea Consumption at Baseline Visit.

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>0.06 ± 0.03</td>
<td>0.42 ± 0.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>0.51 ± 0.12</td>
<td>1.62 ± 0.30</td>
<td>0.000</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>2.23 ± 0.31</td>
<td>4.66 ± 0.92</td>
<td>0.026</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>3.15 ± 0.65</td>
<td>2.66 ± 0.27</td>
<td>0.569</td>
</tr>
</tbody>
</table>

* \( p \)-value obtained from independent-samples \( t \)-test (\( p \leq 0.05 \)). Significant \( p \)-values are indicated in bold. SE: standard error; cP: centipoise.

Since less than the required amount of saliva could be collected from 11 SS patients for unstimulated saliva and from 5 for stimulated saliva, only 10 SS patients (for unstimulated saliva) and 16 SS patients (for stimulated saliva) are included for viscosity analysis. However, all 31 SS patients and 12 non-SS participants are included for salivary flow rate analysis.
Figure 7. Unstimulated Salivary Flow Rate at Baseline in the SS (n=21) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal line indicates medians with the 75th quartiles at the top and the 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers. Outliers and extreme cases are indicated by * and °, respectively, which represent participant number 28 from the SS group and participant number 2 from the non-SS group.

Figure 8. Stimulated Salivary Flow Rate at Baseline in the SS (n=21) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal line indicates medians with the 75th quartiles at the top and the 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers.
Figure 9. Viscosity of Unstimulated Saliva at Baseline in the SS (n=10) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal line indicates medians with the 75th quartiles at the top and the 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers. Outliers and extreme cases are indicated by * and °, respectively, which represent participant numbers 3 and 9 from the non-SS group.

Figure 10. Viscosity of Stimulated Saliva at Baseline in the SS (n=16) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal line indicates medians with 75th quartiles at the top and 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers. Outliers and extreme cases are indicated by * and °, respectively, which represent participant number 26 from the SS group and participant number 3 from the non-SS group.
B. Results after 1 Month of Green Tea Consumption (Time T1)

The overall salivary outcome measures in both the SS and non-SS groups after 1 month of green tea consumption are listed in Table 11. For the SS group, no significant changes in both unstimulated and stimulated salivary flow rates were observed although there was a slight increase in stimulated salivary flow rate after 1 month of green tea consumption (Figure 11). However, for the non-SS group, there was a significant increase in unstimulated salivary flow rate ($p \leq 0.05$).

Among the 16 SS patients who came in to our testing centre for both baseline and 1-month follow-up visits, 10 SS patients gave either 0 ml or less than 0.15 ml of unstimulated saliva while 4 SS patients gave 0 ml of stimulated saliva. These amounts are less than that required for viscosity analysis. Therefore, 6 SS patients for the unstimulated saliva and 12 SS patients for the stimulated saliva were included for viscosity analysis. The results showed that with respect to unstimulated salivary viscosity, no significant differences were observed between baseline (T0) and 1-month follow-up visit (T1) for both the SS and non-SS groups (Figure 12). However, there was a significant decrease in stimulated salivary viscosity in the SS group, indicating less viscosity at T1. For both the SS and non-SS groups, after 1 month of green tea consumption, a decreasing trend in viscosity of both unstimulated and stimulated saliva was observed although no statistical significance was indicated.
Table 11. Salivary Outcome Measures in the SS and Non-SS Groups after 1 Month of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>1 month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>SS</td>
<td>0.06 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>0.00 ± 0.00</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.42 ± 0.08</td>
<td>0.55 ± 0.09</td>
<td>0.13 ± 0.01</td>
<td><strong>0.056</strong></td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>SS</td>
<td>0.48 ± 0.14</td>
<td>0.61 ± 0.16</td>
<td>0.13 ± 0.15</td>
<td>0.364</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.62 ± 0.30</td>
<td>1.50 ± 0.36</td>
<td>-0.12 ± 0.15</td>
<td>0.443</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>SS</td>
<td>2.38 ± 0.18</td>
<td>1.97 ± 0.32</td>
<td>-0.41 ± 0.35</td>
<td>0.300</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.66 ± 0.92</td>
<td>3.49 ± 0.37</td>
<td>-1.17 ± 0.91</td>
<td>0.223</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>SS</td>
<td>3.41 ± 0.83</td>
<td>1.72 ± 0.28</td>
<td>-1.69 ± 0.74</td>
<td><strong>0.044</strong></td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>2.62 ± 0.25</td>
<td>2.15 ± 0.22</td>
<td>-0.47 ± 0.27</td>
<td>0.112</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples t-test (p ≤ 0.05). Significant p-values are indicated in bold. The difference between baseline and 1 month was zero to continue with three significant digits. However, when four significant digits were included, the difference and the p-value would be non-zero. SE: standard error; cP: centipoise. Since less than the required amount of saliva could be collected from 10 SS patients for unstimulated saliva and from 4 SS for stimulated saliva, only 6 SS patients (for unstimulated saliva) and 12 SS patients (for stimulated saliva) are included for viscosity analysis. However, all 16 SS patients and 12 non-SS participants are included for salivary flow rate analysis.
Figure 11. Changes in Mean Flow Rate for Unstimulated and Stimulated Saliva in the SS (n=16) and Non-SS Groups (n=12) after 1 Month of Green Tea Consumption.
The error bar represents the standard error (SE).

Figure 12. Changes in Mean Viscosity for Unstimulated and Stimulated Saliva in the SS and Non-SS Groups (n=12) after 1 Month of Green Tea Consumption.
Since less than the required amount of saliva could be collected from 10 SS patients for unstimulated saliva and from 4 SS for stimulated saliva, only 6 SS patients (for unstimulated saliva) and 12 SS patients (for stimulated saliva) are included for viscosity analysis. The error bar represents the standard error (SE).
Differences in the salivary parameters between the SS group and the non-SS group after 1 month of green tea consumption are listed in Table 12. Data analyzed by independent samples t-test showed a significant difference ($p \leq 0.05$) in terms of unstimulated salivary flow rate between the SS and non-SS groups: while no change in unstimulated salivary flow rate was observed for the SS group, a slight increase in unstimulated salivary flow rate was indicated for the non-SS group. For both groups, there was a decreasing trend with respect to viscosity of both unstimulated and stimulated saliva after 1 month of green tea consumption.

Table 12. Differences in the Salivary Parameters between the SS and Non-SS Groups after 1 Month of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>0.00 ± 0.00</td>
<td>0.14 ± 0.06</td>
<td>0.017</td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>0.13 ± 0.15</td>
<td>-0.12 ± 0.15</td>
<td>0.234</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>-0.41 ± 0.35</td>
<td>-1.17 ± 0.91</td>
<td>0.445</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>-1.69 ± 0.74</td>
<td>-0.47 ± 0.27</td>
<td>0.145</td>
</tr>
</tbody>
</table>

* p-value obtained from independent samples t-test ($p \leq 0.05$). Significant p-value is indicated in bold. 16 SS patients and 12 non-SS control participants are included for the flow rate analysis. Since less than the required amount of saliva could be collected from 10 SS patients for unstimulated saliva and from 4 SS for stimulated saliva, only 6 SS patients (for unstimulated saliva) and 12 SS patients (for stimulated saliva) are included for viscosity analysis. However, all 16 SS patients and 12 non-SS participants are included for salivary flow rate analysis.
B. Results after 2 Months of Green Tea Consumption (Time T2)

All 12 non-SS control participants were included for salivary outcome measures including the flow rate and viscosity of unstimulated and stimulated saliva. However, there was 1 SS patient who could not attend the 2-month follow-up visit due to illness but continued to consume green tea for the 3-month follow-up visit. Salivary outcome measures for the SS group and the non-SS group after 2 months of green tea consumption are listed in Table 13. The results analyzed by paired samples $t$-test showed that there was no significant change ($p > 0.05$) with respect to all salivary parameters for the SS group. However, a slight increase in unstimulated salivary flow rate, $0.04 \pm 0.02$ ml/min, and a slight decrease in stimulated salivary flow rate, $0.06 \pm 0.11$ ml/min were found.

With respect to the mean viscosity for the SS group, a slight increase in unstimulated saliva and a small decrease in stimulated saliva were observed although no statistical significance was identified. Since less than the required amount of saliva could be collected from 4 SS patients for unstimulated saliva and from 3 SS for stimulated saliva, only 2 SS patients (for unstimulated saliva) and 3 SS patients (for stimulated saliva) were included for viscosity analysis.

For the non-SS group, a significant increase ($p \leq 0.05$) in unstimulated salivary flow rate was found although slight decreases in the viscosity of unstimulated saliva and stimulated saliva were observed in comparison to the baseline.
Table 13. Salivary Outcome Measures in the SS and Non-SS Groups after 2 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>2 month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate</td>
<td>SS</td>
<td>0.008 ± 0.01</td>
<td>0.04 ± 0.03</td>
<td>0.04 ± 0.02</td>
<td>0.189</td>
</tr>
<tr>
<td>(ml/min)</td>
<td>Non-SS</td>
<td>0.42 ± 0.08</td>
<td>0.67 ± 0.14</td>
<td>0.25 ± 0.09</td>
<td>0.016</td>
</tr>
<tr>
<td>Stimulated salivary flow rate</td>
<td>SS</td>
<td>0.42 ± 0.25</td>
<td>0.35 ± 0.20</td>
<td>-0.06 ± 0.11</td>
<td>0.586</td>
</tr>
<tr>
<td>(ml/min)</td>
<td>Non-SS</td>
<td>1.62 ± 0.30</td>
<td>1.66 ± 0.34</td>
<td>0.04 ± 0.14</td>
<td>0.794</td>
</tr>
<tr>
<td>Viscosity of Unstimulated saliva</td>
<td>SS</td>
<td>1.98 ± 0.30</td>
<td>3.51 ± 1.16</td>
<td>1.52 ± 0.86</td>
<td>0.327</td>
</tr>
<tr>
<td>(cP)</td>
<td>Non-SS</td>
<td>4.66 ± 0.92</td>
<td>3.64 ± 0.37</td>
<td>-1.01 ± 0.83</td>
<td>0.134</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva</td>
<td>SS</td>
<td>3.15 ± 1.35</td>
<td>2.04 ± 0.18</td>
<td>-1.11 ± 2.02</td>
<td>0.542</td>
</tr>
<tr>
<td>(cP)</td>
<td>Non-SS</td>
<td>2.62 ± 0.25</td>
<td>2.21 ± 0.18</td>
<td>-0.41 ± 0.24</td>
<td>0.119</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples t-test (p ≤ 0.05). Significant p-value is indicated in bold.

One SS patient was not able to attend 2-month follow-up visit due to illness but continued to participate in the study by consuming green tea for 3-month follow-up. Since less than the required amount of saliva could be collected from 4 SS patients for unstimulated saliva and from 3 SS for stimulated saliva, only 2 SS patients (for unstimulated saliva) and 3 SS patients (for stimulated saliva) are included for viscosity analysis. However, all 6 SS patients and 12 non-SS control participants are included for salivary flow rate analysis.
Differences in the salivary parameters between the SS and non-SS groups after 2 months of green tea consumption are presented in Table 14. Independent samples \( t \)-test \((p \leq 0.05)\) showed a significant difference in terms of unstimulated salivary flow rate between the SS and non-SS groups. Moreover, while both the unstimulated and stimulated salivary flow rates increased for the non-SS group, only unstimulated salivary flow rate increased for the SS group.

**Table 14. Differences in the Salivary Parameters between the SS and Non-SS Groups after 2 Months of Green Tea Consumption.**

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>0.04 ± 0.02</td>
<td>0.25 ± 0.09</td>
<td>0.034</td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>-0.06 ± 0.11</td>
<td>0.04 ± 0.14</td>
<td>0.579</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>1.52 ± 0.86</td>
<td>-1.01 ± 0.83</td>
<td>0.086</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>-1.11 ± 1.52</td>
<td>-0.41 ± 0.24</td>
<td>0.416</td>
</tr>
</tbody>
</table>

* \( p \)-values obtained from independent samples \( t \)-test \((p \leq 0.05)\). Significant \( p \)-value is indicated in bold.

**C. Results after 3 Months of Green Tea Consumption (Time T3)**

Salivary outcome measures including unstimulated salivary flow rate, stimulated salivary flow rate, unstimulated salivary viscosity, and stimulated salivary viscosity in the SS group \((n=7)\) and the non-SS group \((n=12)\) after 3 months of green tea consumption are listed in Table 15. Data analyzed by paired samples \( t \)-test indicated that there was no significance change \((p \leq 0.05)\) since the baseline visit in terms of all salivary parameters for the SS group. However, for the SS group, it was observed that the unstimulated salivary flow rate increased from \(0.04 \pm 0.03\) ml/min to \(0.12 \pm 0.07\) ml/min.
For the non-SS group, a significant increase in unstimulated salivary flow rate was found ($p \leq 0.05$) at 3-month follow-up. Moreover, a slight increase in stimulated salivary flow rate was indicated.

In terms of viscosity, for the non-SS group, both the unstimulated and stimulated saliva decreased. However, for the SS group, while the stimulated salivary viscosity slightly decreased, a small increase in unstimulated salivary viscosity was noticed.

### Table 15. Salivary Outcome Measures in the SS and Non-SS Groups after 3 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>3 month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>$p$-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SS</td>
<td>0.04 ± 0.03</td>
<td>0.12 ± 0.07</td>
<td>0.09 ± 0.06</td>
<td>0.171</td>
</tr>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>Non-SS</td>
<td>0.42 ± 0.08</td>
<td>0.72 ± 0.14</td>
<td>0.31 ± 0.10</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td></td>
<td>SS</td>
<td>0.54 ± 0.25</td>
<td>0.53 ± 0.22</td>
<td>-0.01 ± 0.08</td>
<td>0.878</td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>Non-SS</td>
<td>1.62 ± 0.30</td>
<td>2.00 ± 0.38</td>
<td>0.38 ± 0.24</td>
<td>0.140</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>SS</td>
<td>1.89 ± 0.20</td>
<td>2.19 ± 0.43</td>
<td>0.31 ± 0.23</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.66 ± 0.92</td>
<td>2.94 ± 0.24</td>
<td>-1.72 ± 0.92</td>
<td>0.087</td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>SS</td>
<td>2.64 ± 1.08</td>
<td>1.30 ± 0.16</td>
<td>-1.34 ± 0.94</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>2.62 ± 0.25</td>
<td>2.22 ± 0.24</td>
<td>-0.39 ± 0.23</td>
<td>0.117</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples $t$-test ($p \leq 0.05$). Significant $p$-value is indicated in bold.

Since less than the required amount of saliva could be collected from 4 SS patients for unstimulated saliva and from 3 SS for stimulated saliva, only 3 SS patients (for unstimulated saliva) and 4 SS patients (for stimulated saliva) are included for viscosity analysis. However, all 7 SS patients and 12 non-SS control participants are included for salivary flow rate analysis.
Differences in the salivary parameters between the SS and non-SS groups after 3 months of green tea consumption are listed in Table 16. A significant difference ($p \leq 0.05$) in terms of unstimulated salivary viscosity between the groups was found. While an increasing trend of salivary viscosity was observed in the SS group, the opposite trend was observed in the non-SS group. Unstimulated salivary flow rates for both groups showed an increasing trend after 3 months of green tea consumption.

**Table 16. Differences in the Salivary Parameters between the SS and Non-SS Groups after 3 months of Green Tea Consumption.**

<table>
<thead>
<tr>
<th>Salivary Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>$p$-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated salivary flow rate (ml/min)</td>
<td>0.09 ± 0.06</td>
<td>0.31 ± 0.10</td>
<td>0.117</td>
</tr>
<tr>
<td>Stimulated salivary flow rate (ml/min)</td>
<td>-0.01 ± 0.08</td>
<td>0.38 ± 0.24</td>
<td>0.143</td>
</tr>
<tr>
<td>Viscosity of unstimulated saliva (cP)</td>
<td>0.31± 0.23</td>
<td>-1.72 ± 0.92</td>
<td><strong>0.052</strong></td>
</tr>
<tr>
<td>Viscosity of stimulated saliva (cP)</td>
<td>-1.34 ± 0.94</td>
<td>-0.39 ± 0.23</td>
<td>0.163</td>
</tr>
</tbody>
</table>

* $p$-value obtained from independent samples $t$-test ($p \leq 0.05$). Significant $p$-value is indicated in bold.
3.4 Subjective Oral Health Outcome Measures

A. Results at Baseline (Time T0)

Prior to the green tea consumption, the baseline subjective oral health measures including Oral Health Impact Profile-14 (OHIP-14, Slade and Spencer, 1994), Xerostomia Inventory (XI, Thomson et al., 1999), and Quality of Life (QoL, Dirix et al., 2008) were obtained from 31 SS patients and 12 non-SS participants. Their mean scores for the SS and non-SS groups are listed in Table 17. There were significant differences ($p < 0.05$) between the SS and non-SS groups in terms of OHIP-14 and XI (Figures 13 and 14). Results from the SS group indicated higher mean scores in both OHIP-14 and XI questionnaires in comparison to the non-SS group. A QoL questionnaire was only evaluated for the SS group since it was originally designed to examine the QoL in patients with dry mouth.

As presented in Table 18, the 7 dimensions of the OHIP-14 were evaluated for both the SS and non-SS groups prior to green tea consumption. These include: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Data analyzed by independent samples $t$-test showed that for the SS group, the mean scores were significantly higher than for the non-SS group with respect to all 7 dimensions.
Table 17. Differences in the Subjective Oral Health Measures between the SS (n=31) and Non-SS (n=12) Groups prior to Green Tea Consumption at Baseline Visit.

<table>
<thead>
<tr>
<th>Oral Health Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHIP-14</td>
<td>20.24 ± 1.90</td>
<td>7.50 ±1.94</td>
<td>0.000</td>
</tr>
<tr>
<td>XI</td>
<td>51.16 ± 1.16</td>
<td>28.58 ± 2.04</td>
<td>0.000</td>
</tr>
<tr>
<td>QoL</td>
<td>65.74 ± 11.71</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*p-value obtained from independent samples t-test. A QoL was only evaluated in the SS group. Significant p-values are indicated in bold. N/A: not applicable.

Table 18. Differences in the 7 Dimensions of OHIP-14 between the SS (n=31) and Non-SS (n=12) Groups prior to Green Tea Consumption at Baseline Visit.

<table>
<thead>
<tr>
<th>OHIP-14 Dimensions</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Limitation</td>
<td>2.97 ± 0.32</td>
<td>0.25 ± 0.18</td>
<td>0.000</td>
</tr>
<tr>
<td>Physical Pain</td>
<td>3.50 ± 0.36</td>
<td>2.00 ± 0.54</td>
<td>0.030</td>
</tr>
<tr>
<td>Psychological Discomfort</td>
<td>3.55 ± 0.41</td>
<td>1.58 ± 0.42</td>
<td>0.009</td>
</tr>
<tr>
<td>Physical Disability</td>
<td>2.81 ± 0.39</td>
<td>0.83 ± 0.32</td>
<td>0.005</td>
</tr>
<tr>
<td>Psychological Disability</td>
<td>3.23 ± 0.41</td>
<td>1.50 ± 0.47</td>
<td>0.010</td>
</tr>
<tr>
<td>Social Disability</td>
<td>2.06 ± 0.34</td>
<td>0.83 ± 0.24</td>
<td>0.037</td>
</tr>
<tr>
<td>Handicap</td>
<td>2.32 ± 0.35</td>
<td>0.50 ± 0.23</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*p-value obtained from independent samples t-test. Significant p-values are indicated in bold.
Figure 13. The Mean OHIP-14 Score at Baseline in the SS (n=31) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal lines indicate medians with the 75th quartiles at the top and the 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers. Outliers and extreme cases are indicated by °, which represents participant number 26 of the SS group.

Figure 14. The Mean XI Score at Baseline in the SS (n=31) and Non-SS (n=12) Groups.
Data are represented as box plots; horizontal lines indicate medians with the 75th quartiles at the top and the 25th quartiles at the bottom of the boxes. 95% confidence intervals are presented as whiskers.
All study participants were asked to use a visual analogue scale (VAS) to mark the point on a 10-cm long line to indicate their perceived dry mouth-related symptoms. The differences in these symptoms between the SS and non-SS groups are shown in Table 19 and Figure 15. Results showed significant differences between the groups ($p \leq 0.05$). The non-SS group indicated significantly lower VAS scores than the SS group with respect to all categories.

As observed in Figure 15, the order from the most severe to the least oral dryness-related symptoms that the SS patients subjectively perceived are as follows: oral dryness at times of the day other than at night or on awakening, dryness of eyes, dryness of tongue, difficulty in eating dry foods, dryness of lips, difficulty in swallowing foods, oral dryness during eating, and oral dryness at night or on awakening.

### Table 19. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=31) and Non-SS (n=12) Groups prior to Green Tea Consumption.

<table>
<thead>
<tr>
<th>Visual Analogue Scale (VAS)</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>$p$-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or on awakening</td>
<td>7.83 ± 0.43</td>
<td>2.45 ± 0.81</td>
<td>0.00</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>9.43 ± 2.83</td>
<td>1.85 ± 0.53</td>
<td>0.01</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>6.26 ± 0.54</td>
<td>0.87 ± 0.25</td>
<td>0.00</td>
</tr>
<tr>
<td>Difficulty in swallowing foods</td>
<td>5.36 ± 0.55</td>
<td>0.65 ± 0.25</td>
<td>0.00</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>7.21 ± 0.61</td>
<td>1.56 ± 0.47</td>
<td>0.09</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>3.61 ± 0.49</td>
<td>5.18 ± 0.76</td>
<td>0.0005</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>7.12 ± 0.42</td>
<td>4.28 ± 0.77</td>
<td>0.00</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>8.06 ± 0.38</td>
<td>3.57 ± 0.78</td>
<td>0.01</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>7.41 ± 0.51</td>
<td>4.90 ± 0.40</td>
<td>0.00</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>7.05 ± 0.41</td>
<td>1.60 ± 0.48</td>
<td>0.00</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>7.47 ± 0.35</td>
<td>3.06 ± 0.67</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*p-values obtained from independent samples t-test for differences in means ($p \leq 0.05$). Significant $p$-values are indicated in bold.
Figure 15. The Mean VAS Scores in the SS (n=31) and Non-SS (n=12) Groups at Baseline.
VAS: Visual Analogue Scale. The error bar represents the standard error (SE).

B. Results after 1 Month of Green Tea Consumption (Time T1)

The subjective oral health outcome measures obtained from OHIP-14, XI, and QoL questionnaires after 1 month of green tea consumption in the SS group (n=18) and the non-SS group (n=12) are listed in Table 20. For the SS group, both OHIP-14 and XI summary scores decreased by 6.00 ± 2.22 scores and 3.22 ± 2.12 scores, respectively. As shown in Figure 17, there was a significant difference between baseline and 1 month for the SS group in terms of OHIP-14 ($p \leq 0.05$). Moreover, after 1 month of green tea consumption, lower scores were observed for all 7 dimensions of OHIP-14 in the SS group (Figure 18). However, for the non-SS group, although slight decreases in both OHIP-14 and XI scores were observed, there was no statistical significance in terms of difference when compared to the baseline.
With respect to QoL score, for the SS group, there was a significant increase in comparison to the baseline (Figure 16). As mentioned earlier, the QoL was not evaluated in the non-SS group.

Table 20. Subjective Oral Health Outcome Measures in the SS (n=18) and Non-SS (n=12) Groups after 1 Month of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Oral Health Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>1 Month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHIP-14</td>
<td>SS</td>
<td>23.06 ±11.95</td>
<td>17.06 ± 11.02</td>
<td>- 6.00 ± 2.22</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>7.5 ± 1.94</td>
<td>5.75 ± 1.99</td>
<td>-1.75 ±1.55</td>
<td>0.282</td>
</tr>
<tr>
<td>XI</td>
<td>SS</td>
<td>52.28 ± 1.81</td>
<td>49.06 ± 2.64</td>
<td>- 3.22 ± 2.12</td>
<td>0.148</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>28.58 ± 2.04</td>
<td>27.25 ± 2.63</td>
<td>-1.33 ± 2.34</td>
<td>0.580</td>
</tr>
<tr>
<td>QoL</td>
<td>SS</td>
<td>62.04 ± 2.68</td>
<td>70.59 ± 2.30</td>
<td>8.55 ± 1.91</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A: not applicable. A QoL was only evaluated in the SS patients group.  
*p-values obtained from paired samples t-test (p ≤ 0.05). Significant p-values are indicated in bold.

Figure 16. Changes in Mean Quality of Life (QoL) Score in the SS group (n=18) after 1 month of Green Tea Consumption.  
*Significant p-value is obtained from paired samples t-test (p ≤ 0.05). The error bar represents the standard error (SE).
Figure 17. Changes in Mean OHIP-14 Score in the SS group (n=18) after 1 month of Green Tea Consumption.
*Significant *p*-value is obtained from paired samples *t*-test (*p* ≤ 0.05). The error bar represents the standard error (SE).

Figure 18. The Mean Scores for the 7 Dimensions of OHIP-14 in the SS Group (n=18) after 1 Month of Green Tea Consumption.
The error bar represents the standard error (SE).
After 1 month of green tea consumption, all study participants were asked to use a visual analogue scale (VAS) to mark the point on a 10 cm-long line to indicate their perceived dry mouth-related symptoms. The differences in these symptoms between baseline (T0) and 1 month-follow up (T1) in the SS and non-SS groups are presented in Table 21. The paired samples t-test indicated a statistical significance only with “dryness of inside of nose” after 1 month of green tea consumption.

**Table 21. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related Symptoms in the SS (n=18) and Non-SS (n=12) Groups after 1 Month of Green Tea Consumption.**

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>1 Month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>SS</td>
<td>8.15 ± 0.52</td>
<td>7.38 ± 0.56</td>
<td>-0.77 ± 0.41</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>2.45 ± 0.81</td>
<td>1.99 ± 0.81</td>
<td>-0.46 ± 0.33</td>
<td>0.190</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>SS</td>
<td>7.29 ± 0.55</td>
<td>6.18 ± 0.65</td>
<td>-1.10 ± 0.60</td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.69 ± 0.53</td>
<td>2.12 ± 0.78</td>
<td>0.43 ± 0.42</td>
<td>0.333</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>SS</td>
<td>6.32 ± 0.73</td>
<td>5.55 ± 0.73</td>
<td>-0.77 ± 0.59</td>
<td>0.211</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.87 ± 0.25</td>
<td>1.53 ± 0.60</td>
<td>0.67 ± 0.46</td>
<td>0.171</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>SS</td>
<td>5.74 ± 0.77</td>
<td>4.47 ± 0.72</td>
<td>-1.27 ± 0.67</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.65 ± 0.25</td>
<td>0.91 ± 0.50</td>
<td>0.26 ± 0.50</td>
<td>0.612</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>SS</td>
<td>7.17 ± 0.77</td>
<td>6.19 ± 0.91</td>
<td>-0.97 ± 0.51</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.56 ± 0.47</td>
<td>1.13 ± 0.48</td>
<td>-0.43 ± 0.55</td>
<td>0.459</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>SS</td>
<td>3.34 ± 0.69</td>
<td>3.09 ± 0.56</td>
<td>-0.25 ± 0.63</td>
<td>0.694</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>5.18 ± 0.76</td>
<td>5.16 ± 0.93</td>
<td>-0.03 ± 0.64</td>
<td>0.970</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>SS</td>
<td>7.14 ± 0.57</td>
<td>7.09 ± 0.54</td>
<td>-0.06 ± 0.56</td>
<td>0.922</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.28 ± 0.77</td>
<td>3.31 ± 0.71</td>
<td>-0.97 ± 0.89</td>
<td>0.289</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>SS</td>
<td>8.35 ± 0.43</td>
<td>7.43 ± 0.67</td>
<td>-0.92 ± 0.53</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.57 ± 0.77</td>
<td>3.26 ± 0.80</td>
<td>-0.31 ± 1.03</td>
<td>0.770</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>SS</td>
<td>7.81 ± 0.56</td>
<td>6.85 ± 0.62</td>
<td>-0.96 ± 0.47</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.90 ± 0.79</td>
<td>4.26 ± 1.06</td>
<td>-0.64 ± 0.90</td>
<td>0.492</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>SS</td>
<td>7.34 ± 0.64</td>
<td>6.55 ± 0.73</td>
<td>-0.79 ± 0.49</td>
<td>0.126</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.60 ± 0.48</td>
<td>2.27 ± 0.82</td>
<td>0.67 ± 0.48</td>
<td>0.191</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>SS</td>
<td>7.29 ± 0.58</td>
<td>5.49 ± 0.90</td>
<td>-1.81 ± 0.71</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.06 ± 0.67</td>
<td>2.74 ± 0.89</td>
<td>-0.32 ± 0.68</td>
<td>0.652</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples t-test (p ≤ 0.05). Significant p-value is indicated in bold.
Table 22. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=18) and Non-SS (n=12) Groups after 1 Month of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>-0.77 ± 0.41</td>
<td>-0.46 ± 0.33</td>
<td>0.557</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>-1.10 ± 0.60</td>
<td>0.43 ± 0.42</td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>-0.77 ± 0.59</td>
<td>0.67 ± 0.46</td>
<td>0.065</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>-1.27 ± 0.67</td>
<td>0.26 ± 0.50</td>
<td>0.105</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>-0.97 ± 0.51</td>
<td>-0.43 ± 0.55</td>
<td>0.474</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>-0.25 ± 0.63</td>
<td>-0.03 ± 0.64</td>
<td>0.804</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>-0.06 ± 0.56</td>
<td>-0.97 ± 0.89</td>
<td>0.388</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>-0.92 ± 0.53</td>
<td>-0.31 ± 1.03</td>
<td>0.606</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>-0.96 ± 0.47</td>
<td>-0.64 ± 0.90</td>
<td>0.762</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>-0.79 ± 0.49</td>
<td>0.67 ± 0.48</td>
<td><strong>0.043</strong></td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>-1.81 ± 0.71</td>
<td>-0.32 ± 0.68</td>
<td>0.141</td>
</tr>
</tbody>
</table>

*p-value obtained from independent samples t-test (p ≤ 0.05). Significant p-values are indicated in bold.

C. Results after 2 Months of Green Tea Consumption (Time T2)

The subjective oral health outcome measures obtained from OHIP-14, XI, and QoL questionnaires for the SS group (n=7) and non-SS group (n=12) after 2 months of green tea consumption are listed in Table 23. The results indicated that there was a significant difference (p ≤ 0.05) between baseline (T0) and 2-month follow-up (T2) with respect to the mean XI score for the SS group. Although no statistical significance was found in terms of the mean OHIP-14 and QoL scores, there was a slight decrease in the OHIP-14 score and an increase in the QoL score for the SS group. Moreover, no
significant change was observed in the non-SS group with respect to OHIP-14 and XI scores although both scores decreased after green tea consumption.

Table 23. Subjective Oral Health Outcome Measures in the SS (n=7) and Non-SS (n=12) Groups After 2 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Oral Health Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>2 Month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHIP-14</td>
<td>SS</td>
<td>19.29 ± 3.85</td>
<td>17.00 ± 4.53</td>
<td>-2.29 ± 1.23</td>
<td>0.278</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>6.50 ± 1.84</td>
<td>5.18 ± 1.87</td>
<td>-1.32 ± 0.84</td>
<td>0.347</td>
</tr>
<tr>
<td>XI</td>
<td>SS</td>
<td>51.43 ± 3.33</td>
<td>46.43 ± 4.59</td>
<td>-5.00 ± 1.63</td>
<td><strong>0.022</strong></td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>28.58 ± 2.04</td>
<td>25.55 ± 2.68</td>
<td>-3.03 ± 2.11</td>
<td>0.175</td>
</tr>
<tr>
<td>QoL</td>
<td>SS</td>
<td>63.29 ± 3.18</td>
<td>70.83 ± 6.45</td>
<td>7.67 ± 3.84</td>
<td>0.102</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples t-test (p ≤ 0.05). Significant p-value indicated in bold.

After 2 months of green tea consumption, all study participants were asked to use a visual analogue scale (VAS) to mark the point on a 10-cm long line to indicate their perceived dry mouth-related symptoms. The VAS scores for the dry mouth-related symptoms in the SS (n=7) and non-SS (n=12) groups after 2 months of green tea consumption are listed in Table 24. For the SS group, a significant decrease in “dryness of lips” (p ≤ 0.05) was observed although there was a decreasing trend in all other symptoms except for patients’ perceived amount of saliva in usual everyday life and dryness of skin. For the non-SS group, although there were no significant changes in any of dry mouth-related symptoms after green tea consumption, there were slight increases in VAS scores with all the symptoms except for dryness of eyes and lips, and difficulty in eating dry foods.

The mean differences in dry mouth-related symptoms as measured by VAS, between the SS and non-SS groups after 2 months of green tea consumption are presented in Table 25. Independent samples t-test indicated that there was no significant difference between 2 groups in terms of the dry mouth-related symptoms.
Table 24. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related Symptoms in the SS (n=7) and Non-SS (n=12) Groups after 2 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>Group</th>
<th>Baseline (Mean ±SE)</th>
<th>2 Month (Mean ±SE)</th>
<th>Difference (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>SS</td>
<td>8.80 ± 0.61</td>
<td>8.57 ± 0.61</td>
<td>-0.23 ± 0.27</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>2.45 ± 2.79</td>
<td>2.64 ± 0.85</td>
<td>0.19 ± 0.52</td>
<td>0.299</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>SS</td>
<td>7.64 ± 0.79</td>
<td>7.36 ± 0.78</td>
<td>-0.29 ± 0.45</td>
<td>0.548</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.69 ± 1.85</td>
<td>2.71 ± 0.79</td>
<td>1.02 ± 0.59</td>
<td>0.153</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>SS</td>
<td>6.16 ± 1.25</td>
<td>5.59 ± 1.01</td>
<td>-0.57 ± 0.55</td>
<td>0.342</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.87 ± 0.25</td>
<td>1.71 ± 0.82</td>
<td>0.84 ± 0.71</td>
<td>0.235</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>SS</td>
<td>4.76 ± 1.29</td>
<td>4.40 ± 1.22</td>
<td>-0.36 ± 0.57</td>
<td>0.556</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.65 ± 0.25</td>
<td>1.01 ± 0.53</td>
<td>0.36 ± 0.55</td>
<td>0.410</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>SS</td>
<td>7.53 ± 1.19</td>
<td>6.74 ± 1.49</td>
<td>-0.79 ± 0.32</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.56 ± 0.47</td>
<td>1.54 ± 0.66</td>
<td>-0.02 ± 0.84</td>
<td>0.992</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>SS</td>
<td>1.70 ± 0.73</td>
<td>1.76 ± 0.68</td>
<td>0.06 ± 0.21</td>
<td>0.798</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>5.18 ± 0.76</td>
<td>4.51 ± 0.96</td>
<td>-0.67 ± 0.84</td>
<td>0.622</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>SS</td>
<td>6.96 ± 0.65</td>
<td>7.04 ± 0.66</td>
<td>0.09 ± 0.90</td>
<td>0.927</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.28 ± 0.77</td>
<td>4.32 ± 0.92</td>
<td>0.04 ± 0.69</td>
<td>0.760</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>SS</td>
<td>8.87 ± 0.44</td>
<td>8.27 ± 0.45</td>
<td>-0.60 ± 0.29</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.56 ± 0.78</td>
<td>2.35 ± 0.77</td>
<td>-1.21 ± 1.31</td>
<td>0.300</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>SS</td>
<td>8.54 ± 0.52</td>
<td>7.66 ± 0.77</td>
<td>-0.89 ± 0.34</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.90 ± 0.79</td>
<td>4.36 ± 1.30</td>
<td>-0.54 ± 1.00</td>
<td>0.772</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>SS</td>
<td>7.73 ± 0.94</td>
<td>6.93 ± 1.22</td>
<td>-0.80 ± 0.72</td>
<td>0.308</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.60 ± 0.48</td>
<td>2.26 ± 0.77</td>
<td>0.66 ± 0.56</td>
<td>0.288</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>SS</td>
<td>8.71 ± 0.33</td>
<td>8.67 ± 0.65</td>
<td>-0.04 ± 0.49</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.06 ± 0.67</td>
<td>3.65 ± 0.95</td>
<td>0.59 ± 0.53</td>
<td>0.433</td>
</tr>
</tbody>
</table>

*p-value obtained from paired samples t-test (p ≤ 0.05). Significant p-value is indicated in bold.
Table 25. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=7) and Non-SS (n=12) Groups after 2 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>-0.23 ± 0.27</td>
<td>0.19 ± 0.52</td>
<td>0.218</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>-0.29 ± 0.45</td>
<td>1.02 ± 0.59</td>
<td>0.174</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>-0.57 ± 0.55</td>
<td>0.84 ± 0.71</td>
<td>0.147</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>-0.36 ± 0.57</td>
<td>0.36 ± 0.55</td>
<td>0.207</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>-0.79 ± 0.32</td>
<td>-0.02 ± 0.84</td>
<td>0.339</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>0.06 ± 0.21</td>
<td>-0.67 ± 0.84</td>
<td>0.699</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>0.09 ± 0.90</td>
<td>0.04 ± 0.69</td>
<td>0.401</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>-0.60 ± 0.29</td>
<td>-1.21 ± 1.31</td>
<td>0.628</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>-0.89 ± 0.34</td>
<td>-0.54 ± 1.00</td>
<td>0.619</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>-0.80 ± 0.72</td>
<td>0.66 ± 0.56</td>
<td>0.143</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>-0.04 ± 0.49</td>
<td>0.59 ± 0.53</td>
<td>0.404</td>
</tr>
</tbody>
</table>

*p-value obtained from independent samples t-test (p ≤ 0.05).
D. Results after 3 Months of Green Tea Consumption (Time T3)

The subjective oral health outcome measures obtained from OHIP-14, XI, and QoL questionnaires for the SS and non-SS groups after 3 months of green tea consumption are listed in Table 26. The results analyzed by paired samples \( t \)-test indicated that for the SS group, there was a significant increase \((p \leq 0.05)\) with respect to the QoL score in comparison to the score measured at baseline (T0). Although no statistical significance was found in terms of changes in OHIP-14 and XI scores, there were slight decreases in these scores for the SS group. For the non-SS group, there were no significant changes in either of the OHIP-14 or XI scores although there was a slight decrease in OHIP-14 score.

Table 26. Subjective Oral Health Outcome Measures in the SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Oral Health Measures</th>
<th>Group</th>
<th>Baseline (Mean ± SE)</th>
<th>3 Month (Mean ± SE)</th>
<th>Difference (Mean ± SE)</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHIP-14</td>
<td>SS</td>
<td>19.29 ± 3.85</td>
<td>16.86 ± 4.3</td>
<td>-2.43 ± 2.42</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>6.50 ± 1.84</td>
<td>4.08 ± 1.45</td>
<td>-2.42 ± 1.55</td>
<td>0.148</td>
</tr>
<tr>
<td>XI</td>
<td>SS</td>
<td>51.43 ± 3.33</td>
<td>49.29 ± 4.59</td>
<td>-2.14 ± 1.70</td>
<td>0.253</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>28.58 ± 2.04</td>
<td>29.00 ± 3.08</td>
<td>0.42 ± 2.53</td>
<td>0.872</td>
</tr>
<tr>
<td>QoL</td>
<td>SS</td>
<td>63.29 ± 3.18</td>
<td>71.29 ± 4.59</td>
<td>8.0 ± 3.75</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\( *p \)-value obtained from paired samples \( t \)-test \((p \leq 0.05)\).

The mean VAS scores for the dry mouth-related symptoms in the SS group \((n=7)\) and in the non-SS group \((n=12)\) after 3 months of green tea consumption are listed in
Table 27. The results showed that for the SS group, there was a decrease in mean VAS score for all related symptoms, except for dryness of skin. Data analyzed by paired samples \( t \)-test indicated that the statistical significance \((p \leq 0.05)\) between baseline and 3-month follow-up scores was observed with oral dryness at times of the day other than at night or on awakening and difficulty in eating dry foods.

Table 27. Results from Visual Analogue Scale (VAS) Analysis for Dry Mouth-related Symptoms in SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>Group</th>
<th>Baseline (Mean ±SE)</th>
<th>3 Month (Mean ± SE)</th>
<th>Difference (Mean ±SE)</th>
<th>(p)-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>SS</td>
<td>8.80 ± 0.61</td>
<td>7.39 ± 1.00</td>
<td>-1.41 ± 0.62</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>2.45 ± 2.79</td>
<td>2.33 ± 0.81</td>
<td>-0.13 ± 0.83</td>
<td>0.884</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>SS</td>
<td>7.64 ± 0.79</td>
<td>6.40 ± 0.85</td>
<td>-1.24 ± 0.56</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.69 ± 1.85</td>
<td>2.61 ± 0.89</td>
<td>0.92 ± 0.65</td>
<td>0.188</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>SS</td>
<td>6.16 ± 1.25</td>
<td>4.46 ± 1.02</td>
<td>-1.70 ± 0.66</td>
<td>0.261</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.87 ± 0.25</td>
<td>2.28 ± 0.77</td>
<td>1.41 ± 0.64</td>
<td><strong>0.049</strong></td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>SS</td>
<td>4.76 ± 1.29</td>
<td>3.47 ± 1.00</td>
<td>-1.29 ± 1.04</td>
<td>0.261</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>0.65 ± 0.25</td>
<td>1.72 ± 0.64</td>
<td>1.07 ± 0.55</td>
<td>0.081</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>SS</td>
<td>7.53 ± 1.19</td>
<td>6.00 ± 1.72</td>
<td>-1.53 ± 0.65</td>
<td><strong>0.058</strong></td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.56 ± 0.47</td>
<td>2.05 ± 0.69</td>
<td>0.49 ± 0.49</td>
<td>0.336</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>SS</td>
<td>1.70 ± 0.73</td>
<td>1.64 ± 0.83</td>
<td>-0.06 ± 0.31</td>
<td>0.859</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>5.18 ± 0.76</td>
<td>5.78 ± 0.56</td>
<td>0.59 ± 0.84</td>
<td>0.497</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>SS</td>
<td>6.96 ± 0.65</td>
<td>8.04 ± 0.54</td>
<td>1.09 ± 1.09</td>
<td>0.357</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.28 ± 0.77</td>
<td>4.09 ± 0.92</td>
<td>-0.18 ± 0.68</td>
<td>0.794</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>SS</td>
<td>8.87 ± 0.44</td>
<td>7.81 ± 0.77</td>
<td>-1.06 ± 0.78</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.56 ± 0.78</td>
<td>2.89 ± 0.88</td>
<td>-0.68 ± 1.11</td>
<td>0.554</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>SS</td>
<td>8.54 ± 0.52</td>
<td>7.49 ± 0.97</td>
<td>-1.06 ± 0.53</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>4.90 ± 0.79</td>
<td>4.09 ± 1.10</td>
<td>-0.81 ± 0.82</td>
<td>0.344</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>SS</td>
<td>7.73 ± 0.94</td>
<td>7.07 ± 1.23</td>
<td>-0.66 ± 0.67</td>
<td>0.367</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>1.60 ± 0.48</td>
<td>2.79 ± 1.06</td>
<td>1.19 ± 0.85</td>
<td>0.190</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>SS</td>
<td>8.71 ± 0.33</td>
<td>8.46 ± 0.66</td>
<td>-0.26 ± 0.44</td>
<td>0.581</td>
</tr>
<tr>
<td></td>
<td>Non-SS</td>
<td>3.06 ± 0.67</td>
<td>3.88 ± 1.07</td>
<td>0.82 ± 0.83</td>
<td>0.348</td>
</tr>
</tbody>
</table>

*\(p\)-value obtained from paired samples \( t \)-test \((p \leq 0.05)\). Significant \(p\)-values are indicated in bold.
Table 28. Differences in Dry Mouth-related Symptoms as Measured by VAS, between the SS (n=7) and Non-SS (n=12) Groups after 3 Months of Green Tea Consumption.

<table>
<thead>
<tr>
<th>Oral Health Measures</th>
<th>SS group (Mean ± SE)</th>
<th>Non-SS group (Mean ± SE)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dryness at night or awakening</td>
<td>-1.41 ± 0.62</td>
<td>-0.13 ± 0.83</td>
<td>0.232</td>
</tr>
<tr>
<td>Oral dryness at other times of the day</td>
<td>-1.24 ± 0.56</td>
<td>0.92 ± 0.65</td>
<td>0.022</td>
</tr>
<tr>
<td>Oral dryness during eating</td>
<td>-1.70 ± 0.66</td>
<td>1.41 ± 0.64</td>
<td>0.004</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>-1.29 ± 1.04</td>
<td>1.07 ± 0.55</td>
<td>0.075</td>
</tr>
<tr>
<td>Difficulty in eating dry foods</td>
<td>-1.53 ± 0.65</td>
<td>0.49 ± 0.49</td>
<td>0.029</td>
</tr>
<tr>
<td>Amount of saliva in usual everyday life</td>
<td>-0.06 ± 0.31</td>
<td>0.59 ± 0.84</td>
<td>0.482</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>1.09 ± 1.09</td>
<td>-0.18 ± 0.68</td>
<td>0.345</td>
</tr>
<tr>
<td>Dryness of eyes</td>
<td>-1.06 ± 0.78</td>
<td>-0.68 ± 1.11</td>
<td>0.781</td>
</tr>
<tr>
<td>Dryness of lips</td>
<td>-1.06 ± 0.53</td>
<td>-0.81 ± 0.82</td>
<td>0.802</td>
</tr>
<tr>
<td>Dryness of tongue</td>
<td>-0.66 ± 0.67</td>
<td>1.19 ± 0.85</td>
<td>0.107</td>
</tr>
<tr>
<td>Dryness of inside of nose</td>
<td>-0.26 ± 0.44</td>
<td>0.82 ± 0.83</td>
<td>0.272</td>
</tr>
</tbody>
</table>

*p-value obtained from independent samples t-test (p ≤ 0.05). Significant p-values are indicated in bold.

3.5 Two-way Repeated Measures ANOVA Analysis

The 2-way Repeated Measures ANOVA analysis operated by SPSS software only includes the study participants who attended all testing visits (T0, T1, T2, and T3). Therefore, 7 SS patients and 12 non-SS participants were included for the analysis of subjective oral health measures of OHIP-14, XI, and QoL questionnaires (Figures 21 – 27). One SS patient (number 13) was excluded for the analysis of objective salivary measures of salivary flow rate and viscosity (Figures 19 – 20) because she was unable to be present for the appointment at T2 due to illness.
A. Objective Salivary Outcome Measures

There was no time-by-group interaction in terms of unstimulated salivary flow rate as determined by 2-way Repeated Measures ANOVA, indicating that the change over time did not differ between the groups. However, regardless of the group which study participants belonged to, there was a significant change in unstimulated salivary flow rate over the course of green tea consumption ($p < 0.05$). As indicated in Figure 19, for the SS and non-SS groups, an increasing trend of unstimulated salivary flow rate over time was found.

![Figure 19. Changes in Mean Flow Rate of Unstimulated Saliva in the SS (n=6) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption.](image)

One SS patient who was unable to be present for the appointment at T2 due to illness is excluded for the analysis of objective salivary measures of salivary flow rate and viscosity. The error bar represents the standard error (SE).
In terms of stimulated salivary flow rate, as indicated in Figure 20, there was no significant change over time and no time-by-group interaction for either the SS or non-SS groups. There was, however, a slight increase in stimulated salivary flow rate occurring between T1 and T3 for the non-SS group.

**Figure 20.** Changes in Mean Flow Rate of Stimulated Saliva in the SS (n=6) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption. One SS patient who was unable to be present for the appointment at T2 due to illness is excluded for the analysis of objective salivary measures of salivary flow rate and viscosity. The error bar represents the standard error (SE).
The change over time with respect to viscosity of unstimulated saliva could not be analyzed as previously mentioned due to patient unavailability or to their inability to produce enough saliva for testing samples. With respect to stimulated salivary viscosity, there was no time-by-group interaction that reached statistical significance at $p < 0.05$ although there was a trend toward a decrease over time in the SS group (Figure 21). In addition, among 6 SS patients who were included for the 2-way Repeated Measures ANOVA analysis, similar to the collection of unstimulated saliva, there were 3 SS patients who could not produce sufficient quantities to be tested.

![Figure 21. Changes in Mean Viscosity of Stimulated Saliva in the SS (n=3) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption.](image)

The stimulated salivary viscosity was not analyzed in 3 SS patients due to inability to produce enough saliva to be tested. One SS patient who was unable to be present for the appointment at T2 due to illness was excluded for the analysis of objective salivary measures of salivary flow rate and viscosity. The error bar represents the standard error (SE).
Data from study participants who attended at baseline, 1-month, and 3-month follow-up visits (T0, T1, and T3) were analyzed with respect to the change in viscosity of unstimulated saliva over time (Figure 22). Since 5 SS patients showed inability to produce enough unstimulated saliva to be tested, only 2 SS patients were included for viscosity analysis. There was no significant time-by-group interaction for the SS or non-SS groups. No considerable change was found for the SS group while a decreasing trend was observed for the non-SS group.

Figure 22. Changes in Mean Unstimulated Viscosity in the SS (n=2) and Non-SS (n=12) Groups after 1 and 3 Months of Green Tea Consumption. The viscosity of unstimulated saliva was not analyzed in 5 SS patients due to inability to produce enough saliva to be tested. The error bar represents the standard error (SE).
In terms of stimulated salivary viscosity, as indicated in Figure 23, there was no significant no time-by-group interaction for the groups. There was, however, a decrease in the viscosity of stimulated saliva for the SS group while there was no change for the non-SS group between 1- and 3-month follow up visits (T1 and T3). Among 7 SS patients who were included for the 2-way Repeated Measures ANOVA analysis, similar to the collection of unstimulated saliva, there were 3 SS patients who could not produce sufficient quantities to be tested.

**Figure 23. Changes in Mean Viscosity of Stimulated Saliva in the SS (n=4) and Non-SS (n=12) Groups after 1 and 3 Months of Green Tea Consumption.**
The viscosity of unstimulated saliva was not analyzed in 3 SS patients due to inability to produce enough saliva to be tested. The error bar represents the standard error (SE).
B. Subjective Oral Health Outcome Measures

There were no significant changes over time and no time-by-group interaction for the SS and non-SS group as determined by 2-way Repeated Measures ANOVA (Figure 24). There was, however, a decreasing trend in mean OHIP-14 score over time.

![Figure 24. Changes in Mean OHIP-14 Scores in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption. The error bar represents the standard error (SE).](image)
As shown in Figure 25, there were no significant changes over time and no time-by-group interaction for either the SS or the non-SS groups. However, the mean XI score decreased after 2 months of green tea consumption when compared to its baseline score.

Figure 25. Changes in Mean XI Scores in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption.
The error bar represents the standard error (SE).

As shown in Figure 26, there was a significant positive change over time in terms of the mean QoL for the SS group ($p < 0.05$) after 3 months of green tea consumption.

Figure 26. Changes in Mean QoL Scores in the SS Group (n=7) after 1, 2, and 3 Months of Green Tea Consumption.
The error bar represents the standard error (SE).
Data from the VAS questionnaire for various dry-mouth related symptoms analyzed by 2-way Repeated Measures ANOVA showed that there was a significant time-by-group interaction for “oral dryness during eating” and “difficulty in swallowing” as shown in Figures 27 and 28. For both symptoms, a decreasing trend was observed for the SS group while an increasing trend was observed for the non-SS group.

Figure 27. Change in Mean VAS of Oral Dryness During Eating in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption.

Figure 28. Change in Mean VAS of Difficulty in Swallowing in the SS (n=7) and Non-SS (n=12) Groups after 1, 2, and 3 Months of Green Tea Consumption.
For the SS group, there was a decreasing trend with respect to all the symptoms except amount of saliva in usual everyday life and dryness of skin (Figure 29). SS patients’ subjective perceptions of various dry mouth-related symptoms slightly decreased since the green tea consumption began.

**Figure 29. Changes in Mean VAS for Dry Mouth-related Symptoms in SS group (n=7) after 1, 2, and 3 Months of Green Tea Consumption.**
The error bar represents the standard error.
3.6 Analysis of Objective Data by Individual SS Patients

The SS patients who had at least 1 follow-up appointment after consumption of green tea are presented individually in Table 29 in terms of their age, the length of time since being diagnosed with SS, presence of other autoimmune disease(s), and whether or not they had previously been green tea drinkers. Each patient was coded with numbers from 13 to 30.

While 16 SS patients returned for both objective salivary measures and subjective oral health measures, there were 2 patients (numbers 29 and 30) who had difficulty in attending any visits due to medical complications unrelated to green tea consumption and/or distance. They did, however, consume the green tea for 1 month and complete their 1-month questionnaires. There were only 7 SS patients (numbers 13 – 19) who were able to return for the 3-month follow-up visit after the green tea consumption.

Table 29. Characteristics of SS Patients

<table>
<thead>
<tr>
<th>Patients Number</th>
<th>Age</th>
<th>Duration of SS (years)</th>
<th>Presence of other autoimmune disease</th>
<th>Regular green tea drinker</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>59</td>
<td>41</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>2</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>64</td>
<td>21</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>57</td>
<td>13</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>66</td>
<td>22</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>18</td>
<td>66</td>
<td>8</td>
<td>Y</td>
<td>Y</td>
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<td>19</td>
<td>73</td>
<td>11</td>
<td>N</td>
<td>Y</td>
</tr>
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<td>20</td>
<td>63</td>
<td>4</td>
<td>N</td>
<td>N</td>
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<td>21</td>
<td>65</td>
<td>12</td>
<td>N</td>
<td>N</td>
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<td>22</td>
<td>64</td>
<td>2</td>
<td>N</td>
<td>N</td>
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<td>23</td>
<td>60</td>
<td>2</td>
<td>N</td>
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<td>61</td>
<td>6</td>
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<td>N</td>
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<td>25</td>
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<td>5</td>
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<td>N</td>
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<td>26</td>
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<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>27</td>
<td>50</td>
<td>12</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>28</td>
<td>71</td>
<td>5</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>29</td>
<td>72</td>
<td>5</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>30</td>
<td>54</td>
<td>11</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Y = yes, N = no
The flow rate changes of both unstimulated and stimulated saliva from baseline for all 16 SS patients are summarized in Figure 30. At the 1-month follow-up appointment, 3 SS patients (numbers 13, 20, and 23) had an increase in unstimulated salivary flow rate, 3 SS patients (numbers 14, 24 and 28) had a decrease, and the other 10 SS patients (numbers 15 - 19, 21, 22, 25, 26, and 27) had no change in unstimulated salivary flow rate. For the stimulated salivary flow rate, there were 7 SS patients (numbers 16, 17, 20, 21, 23, 25, and 26) who had an increase, 3 SS patients (numbers 14, 24 and 28) had a decrease, and the other 6 SS patients (numbers 13, 15, 18, 19, 22, and 27) had no change in stimulated salivary flow rate. As previously noted, the samples of unstimulated and stimulated saliva were not obtained from 2 SS patients (numbers 29 and 30).

Figure 30. Changes in Unstimulated and Stimulated Salivary Flow Rate of 16 SS patients after 1 month of Green Tea Consumption from Baseline. Saliva samples from patients 29 and 30 were not available for measurements because they had difficulty in attending due to medical complication and/or distance.
Viscosity changes of both unstimulated and stimulated saliva from baseline to 1 month of green tea consumption for all 16 SS patients are presented in Figure 31. After 1 month of green tea consumption, 5 SS patients (numbers 17, 20, 23, 24, and 28) showed a decreased unstimulated salivary viscosity while 1 SS patient (number 13) showed an increased viscosity. Since less than the required amount of saliva was collected from 10 SS patients (numbers 14 – 16, 18, 19, 21, 22, and 25 – 27) for unstimulated saliva, only 6 SS patients were included for the viscosity analysis.

With respect to stimulated salivary viscosity, there was a decrease in 8 SS patients (numbers 16, 17, and 23 – 28) and a slight increase in 4 SS patients (numbers 13, 14, 20, and 21). Less than the required amount of saliva was collected from 4 SS patients (numbers 15, 18, 19, and 22) for stimulated saliva. Therefore, only 12 SS patients were included for the viscosity analysis.

![Figure 31. Changes in Unstimulated and Stimulated Salivary Viscosity of 16 SS patients after 1 month of Green Tea Consumption from Baseline.](image)

Saliva samples from patients 29 and 30 were not available for measurements because they had difficulty in attending due to medical complication and/or distance.
The results showed that there were 7 SS patients who returned for follow-up visits after 2 and 3 months of green tea consumption. Summary of these patients’ salivary measures are presented in Table 30. When less than the required amount of saliva sample was collected from the SS patient, the viscosity analysis was not made.

**Table 30. Summary of 7 SS Patients’ Salivary Measures at Baseline and after 1, 2, and 3 Months of Green Tea Consumption.**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Month After Intake</th>
<th>Unstimulated Flow Rate (ml/min)</th>
<th>Stimulated Flow Rate (ml/min)</th>
<th>Unstimulated Viscosity (cP)</th>
<th>Stimulated Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0</td>
<td>0.03</td>
<td>0.50</td>
<td>2.289</td>
<td>2.689</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.06</td>
<td>0.50</td>
<td>3.220</td>
<td>2.870</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.16</td>
<td>0.80</td>
<td>4.672</td>
<td>2.020</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.06</td>
<td>0.70</td>
<td>3.060</td>
<td>1.200</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0.02</td>
<td>1.60</td>
<td>1.680</td>
<td>1.077</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.01</td>
<td>1.13</td>
<td>n/a</td>
<td>1.220</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.10</td>
<td>1.10</td>
<td>2.343</td>
<td>2.355</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.40</td>
<td>1.13</td>
<td>1.800</td>
<td>1.310</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
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</tr>
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<td>0.40</td>
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</tr>
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</tr>
<tr>
<td>17a</td>
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<td>0.20</td>
<td>1.31</td>
<td>1.687</td>
<td>1.130</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.20</td>
<td>1.74</td>
<td>1.400</td>
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</tr>
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<td></td>
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<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.40</td>
<td>1.46</td>
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</tr>
<tr>
<td>18</td>
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<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
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<td>0</td>
<td>n/a</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>0</td>
<td>n/a</td>
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<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a = not available. 17a: Patient number 17 missed the 2-month follow-up visit to give the samples of both unstimulated and stimulated saliva due to illness.
Changes in unstimulated salivary flow rate from baseline for 7 SS patients after 1, 2, and 3 months of green tea consumption are presented in Figure 32. After 3 months of green tea consumption, the unstimulated salivary flow rate increased in 3 SS patients (numbers 13, 14, and 17). However, no changes were observed over time in the other 4 SS patients (numbers 15, 16, 18, and 19) who were unable to produce any unstimulated saliva.

Figure 32. Changes in Unstimulated Salivary Flow Rate from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients.
Changes in stimulated salivary flow rate from baseline for 7 SS patients after 1, 2, and 3 months of green tea consumption are presented in Figure 33. After 3 months of green tea consumption, 3 SS patients (numbers 13, 16, and 17) showed increased flow rates while 1 SS patient (number 14) had a slightly decreased flow rate.

Figure 33. Changes in Stimulated Salivary Flow Rate from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients.
Viscosity changes of unstimulated and stimulated saliva for 7 SS patients are presented in Figure 34. After 3 months of green tea consumption, 3 SS patients (numbers 13, 14, and 17) had slightly increased viscosities: 0.77 cP for patient 13, 0.12 cP for patient 14, and 0.03 cP for patient number 17. No viscosity measurements were made for 4 patients (numbers 15, 16, 18, and 19) because they were unable to produce any unstimulated saliva.

Figure 34. Changes in Viscosity of Unstimulated Saliva from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients.
In terms of stimulated salivary viscosity, as indicated in Figure 35, there was a slight increase in 1 SS patient (number 14) while there was a slight decrease in 3 SS patient (numbers 13, 16, and 17). No viscosity measurements were made for 3 patients (numbers 15, 18, and 19) because they were unable to produce any stimulated saliva.

Figure 35. Change in Viscosity of Stimulated Saliva from Baseline after 1, 2, and 3 Months of Green Tea Consumption in 7 SS Patients.
3.7 Results of an Exit Survey after Green Tea Consumption

All SS patients were asked to fill out an exit survey after participating in the present study for either 1 month or 3 months. As presented in Table 31, 11 of the 18 SS patients reported that drinking green tea was somewhat effective in relieving dry mouths. In particular, 15 felt a pleasant feeling in their mouths after drinking green tea; 16 felt pleasant about the taste of green tea; 13 reported that they did not notice any changes in the taste of other foods after drinking green tea; and 7 reported weight loss after daily green tea consumption. The majority of the SS patients, 17, 13, and 16, respectively indicated that they did not have any nausea, indigestion, and/or stomach pain due to green tea consumption. But most encouraging from this study was the finding that 15 stated that they would definitely continue to drink green tea on a regular basis while the other of 3 reported “maybe” to the same question.
Table 31. Distribution of Answers by SS Patients Responding to Questions after Daily Green Tea Consumption
(n=18)

<table>
<thead>
<tr>
<th>Questions</th>
<th>Not at all</th>
<th>Little bit</th>
<th>Fair</th>
<th>Much</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>“How effective was having green tea at relieving your dry mouth?”</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>“How effective was having green tea at relieving your dry eyes?”</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>“How pleasant was the taste of the green tea?”</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>“How pleasant did your mouth feel after having green tea?”</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>“Did you notice any changes in taste of other foods due to having green tea?”</td>
<td>13</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“Did you experience weight loss?”</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>“Did you experience nausea?”</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“Did you experience indigestion?”</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“Did you experience stomach pain?”</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>“How likely are you to drink green tea again?”</td>
<td>Never</td>
<td>Maybe</td>
<td>Definitely will</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>3</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.8 Correlation Between Study Parameters

The results of Pearson correlation analyses between various study parameters measured at baseline (T0), 1-month (T1), 2-month (T2), and 3-month (T3) follow-up visits are presented in Table 32. Total numbers of study participants involved for the correlation analysis at each visit were: 43 participants for T0, 30 participants for T1, and 19 participants for both T2 and T3. Significant correlations (indicated in bold) were seen between XI and several study parameters: OHIP-14, QoL, and the salivary flow rate of both unstimulated and stimulated saliva. There was a strong positive correlation between XI and OHIP-14 scores. With a statistical significance ($p < 0.001$), there was also a significant correlation between XI and QoL at all follow-up visits. The flow rates of both unstimulated and stimulated saliva were also negatively correlated with XI at all times tested. It was found that QoL scores were significantly correlated with several parameters including XI, OHIP-14, and flow rates of both unstimulated and stimulated saliva. Correlations were significant between QoL and OHIP-14 at all times tested. QoL was positively correlated with salivary flow rate of both unstimulated and stimulated saliva.

Throughout the study, significant correlations were observed between OHIP-14 scores and all study parameters except the unstimulated salivary viscosity. Both unstimulated and stimulated salivary flow rates were negatively and significantly correlated with OHIP-14. Significant correlations between OHIP-14 and stimulated salivary viscosity were seen only at baseline and 3-month follow-up visit. Moreover, further Spearman correlation analyses between objective salivary measures showed that while unstimulated salivary flow rate was significantly correlated with stimulated salivary flow rate at all visits (except at T2), unstimulated salivary viscosity was significantly correlated with stimulated salivary viscosity only at T0 and T1.
Table 32. Correlations between Study Parameters at Baseline (T0), 1-Month (T1), 2-Month (T2), and 3-Month (T3) Follow-up Visits.

<table>
<thead>
<tr>
<th>Testing Visit</th>
<th>QoL</th>
<th>XI</th>
<th>USFR</th>
<th>SSFR</th>
<th>USV</th>
<th>SSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>OHIP-14</td>
<td>T0</td>
<td>-0.707**</td>
<td>0.629**</td>
<td>-0.608**</td>
<td>-0.670**</td>
<td>-0.283</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>-0.554*</td>
<td>0.659**</td>
<td>-0.482**</td>
<td>-0.408**</td>
<td>-0.269</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>-0.728</td>
<td>0.839**</td>
<td>-0.521*</td>
<td>-0.599*</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>-0.862**</td>
<td>0.750**</td>
<td>-0.692**</td>
<td>-0.686**</td>
<td>0.063</td>
</tr>
<tr>
<td>QoL</td>
<td>T0</td>
<td>-0.302</td>
<td>0.380</td>
<td>0.577**</td>
<td>0.702*</td>
<td>0.300</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>-0.848**</td>
<td>0.555*</td>
<td>0.358</td>
<td>-0.314</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>-0.941**</td>
<td>0.921*</td>
<td>0.923*</td>
<td>1.000**</td>
<td>0.817</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>-0.897**</td>
<td>0.652</td>
<td>0.685</td>
<td>0.682</td>
<td>-0.841</td>
</tr>
<tr>
<td>XI</td>
<td>T0</td>
<td>-0.704**</td>
<td>-0.754**</td>
<td>0.184</td>
<td>0.311</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>-0.619**</td>
<td>-0.502**</td>
<td>-0.231</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>-0.652**</td>
<td>-0.703**</td>
<td>0.198</td>
<td>-0.299</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>-0.722**</td>
<td>-0.625**</td>
<td>-0.388</td>
<td>0.368</td>
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<tr>
<td>USFR</td>
<td>T0</td>
<td>0.762**</td>
<td>0.049</td>
<td>-0.263</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>0.703**</td>
<td>0.322</td>
<td>0.145</td>
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</tr>
<tr>
<td></td>
<td>T2</td>
<td>0.733**</td>
<td>-0.362</td>
<td>0.351</td>
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<td></td>
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<tr>
<td></td>
<td>T3</td>
<td>0.724**</td>
<td>0.035</td>
<td>-0.266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSFR</td>
<td>T0</td>
<td>0.048</td>
<td>-0.410*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>0.406</td>
<td>-0.050</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>T2</td>
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<td></td>
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<tr>
<td></td>
<td>T3</td>
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<td>-0.272</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USV</td>
<td>T0</td>
<td></td>
<td>0.803**</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td></td>
<td>0.851**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td></td>
<td>0.508</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td></td>
<td>0.451</td>
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<td></td>
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</tbody>
</table>

**p < 0.001; *p < 0.05. Significant p-values are indicated in bold.

Total number of study participants involved at each visit for the correlation analysis: 43 participants for T0, 30 participants for T1, and 19 participants for both T2 and T3.

USFR: unstimulated salivary flow rate; SSFR: stimulated salivary flow rate;
USV: unstimulated salivary viscosity; SSV: stimulated salivary viscosity
CHAPTER 4. DISCUSSION

Although an increasing number of studies have been reported in the literature with respect to beneficial effects of green tea against various forms of disease in humans (Sueoka et al., 2001; Kuriyama et al., 2006; Moon et al., 2007; Awadalla et al., 2009; Basu, et al., 2010; Johnson et al., 2010), few studies have thoroughly investigated the effects of green tea in patients suffering from SS (Hsu et al., 2005; Hsu et al., 2007; Gillespie et al., 2008) and, to date, no clinical trials associated with green tea intake in SS patients have been reported.

4.1 Baseline Measurements of SS and Non-SS Participants

Through the use of the objective salivary measures in combination with subjective questionnaires, 31 SS patients and 12 non-SS control participants were compared by means of the study parameters involving salivary flow rate and viscosity, as well as for such questionnaires as OHIP-14, XI, QoL, and VAS scores for dry mouth-related symptoms. As expected due to their having been diagnosed with SS, both mean unstimulated and stimulated salivary flow rates in SS patients were significantly below the means of those for non-SS control participants (Table 10). In agreement with findings from previous reports (Sreebny, 2000; Dawes, 2004), the means of both unstimulated and stimulated salivary flow rates in SS patients were below 0.1 ml/min and 0.5 ml/min respectively, indicating the evidence of salivary hypofunction (Sreebny and Valdini, 1988).

The results of viscosity measurements from the non-SS group showed lower viscosity in stimulated saliva than the unstimulated saliva, which is in accordance with previous observations (Rantonen and Meurman 1998; Park et al., 2007). It is the parotid gland that is most active during mechanical stimulation, contributing more than 50% of
total salivary output through production of watery secretions (Humphrey and Wiliamson, 2001). However, there was an unanticipated finding in the SS group such that the stimulated saliva was more viscous than the unstimulated saliva. When individually analyzed, there were 6 SS patients who were not able to produce saliva under unstimulated conditions but were able to under stimulated conditions. Interestingly, the viscosity of stimulated saliva in 4 of these 6 SS patients was found to be even more viscous (ranged from 4.6 cP to 9.9 cP) than those SS patients who were able to produce saliva under both unstimulated and stimulated conditions.

When comparisons were made between the SS group and the non-SS group with respect to the viscosity of stimulated saliva, there was no significant difference. However, the viscosity of unstimulated saliva in the non-SS group was found to be significantly more viscous than the SS group. Many patients in the early stages of SS are known to suffer from oral dryness particularly when being at rest or during the night even more so than their healthy counterparts due to diminished function of these submandibular and sublingual glands (Atkinson et al., 1990; Vissink et al., 1993). It is anticipated that the submandibular and sublingual glands, which are known to secrete a very mucus-rich and viscous fluid, may be affected in SS patients, resulting in saliva with a similar viscosity to its stimulated saliva.

As correlations between objective salivary measures and subjective measures were noted in Table 32, objective findings of decreased salivary flow rates were significantly associated with poorer oral health as indicated with the OHIP-14 summary score. A high OHIP-14 score indicates a poor oral health. Previously reported OHIP-14 summary scores for the general population have ranged from 5.7 to 8.5 (Wong et al., 2002; Robinson et al., 2003; Fernandes et al., 2006). In agreement with these findings, were our results for the non-SS group who had a mean of 7.50 whereas the SS patients in
our study had a mean of 20.24, indicating significantly poor oral health (Table 17). Of the 7 dimensions of the OHIP-14, SS patients were most affected by psychological discomfort and physical pain (Table 18).

The XI questionnaire is based on discrete scales and consists of questions concerning the frequency of oral dryness, and dry mouth-related symptoms and behaviours. A high XI score indicates a greater severity of xerostomia or perception of dry mouth. Previously reported mean XI summary scores for 42 normal individuals (the mean age: 76.2 yrs) ranged from 12.71 to 28.19 (Thomson, 2007). The results of the present study agreed with the upper levels, the mean of 28.58 ± 2.04 for the non-SS group, which was much below the mean of 51.16 ± 1.16 for the SS group. It is not surprising to find out that the severity of the xerostomia and its related complications were much higher in the SS group than in the non-SS group (Figure 14).

The impact of xerostomia on QoL in SS patients was evident. The emotional strain of living with xerostomia seemed quite significant; the results showed that a large proportion of patients felt worried (93.5%), tense (71%), or even depressed (64.5%) because of their dry mouth. Furthermore, patients were severely limited in their social activities: the majority found it difficult to speak to (77.4%) or eat with (80.6%) other people. It was clearly shown that the QoL in SS patients is substantially diminished and the poor oral health associated with xerostomia has a significant effect on patients’ perceptions of well-being beyond any effects attributable to other symptoms or damage associated with SS.

The use of questionnaires regarding dry mouth-related symptoms and behaviours is a generally accepted method that may confirm salivary gland hypofunction; however, these studies have used questions based primarily on dichotomous or discrete scales (Suh et al., 2007). In addition for the present pilot study, the continuous scales of VAS
scores were used to examine the extent of dry mouth-related symptoms and behaviours based on the continuous scales. Results indicated that all dry mouth-related symptoms and behaviours were severely affected in the SS patients. Significant differences between the SS group and the non-SS group were found in terms of VAS scores for all categories: oral dryness at night or on awakening, oral dryness at other times of the day, oral dryness during eating, difficulty in swallowing foods, difficulty in eating dry foods, amount of saliva as usual in everyday life, dryness of skin, dryness of eyes, dryness of lips, dryness of tongue, and dryness of inside of nose (Table 19). As shown in Figure 14, the SS group reported that oral dryness at times other than at night or on awakening was the most severe symptom followed by dryness of eyes and oral dryness at night or on awakening. This particular order of symptoms may be due to the fact that secretions from the salivary glands are diminished at night time (Akinson et al., 1990; Vissink et al., 1993). Oral dryness during eating is not considered as severe because when eating or being subject to any other gustatory or mechanical stimulation, the contribution of (serous) parotid saliva to whole saliva increases, resulting only a transient reduction of a dry mouth sensation in these patients (Vissink et al., 1993). Symptoms of difficulty in eating dry foods and swallowing foods were observed in the SS group suggesting a strong evidence of salivary gland hypofunction (Fox et al., 1987). The subjective assessment of the quantity of saliva using scores from VAS indicated that the SS patients perceived significantly less saliva than the non-SS group. Moreover, dryness of skin, eyes, lips, tongue, and inside of nose was significantly affected in the SS group.
4.2 Salivary Measure Outcomes

A. Salivary Flow Rates

i) Unstimulated Saliva

For the SS group, the mean flow rate of unstimulated saliva did not change after 1 month of green tea consumption although 3 of 16 SS patients showed a slight increase. There were 10 SS patients who could not produce any saliva at rest due to their severe dry mouth. After 3 months of green tea consumption, the mean flow rate increased from 0.04 ml/min (baseline level) to 0.12 ml/min for the SS group although the difference was not statistically significant. When the data was monitored on an individual basis, 3 of 7 SS patients who were able to produce any unstimulated saliva had an increased flow rate in comparison to their baseline levels. Even a slight increase in mean unstimulated salivary flow rate seemed to be a monumental finding for the SS patients since most of them had little, if any, salivary secretions to begin with.

For the non-SS group, the mean flow rate of unstimulated saliva increased significantly after 1, 2, and 3 months of green tea consumption in comparison to the baseline level. These findings indicate that the non-SS group had produced more unstimulated saliva for 3-month study period. Overall, there was a trend toward an increase in unstimulated salivary flow rate over time in both SS and non-SS groups (Figure 18).

ii) Stimulated Saliva

For the SS group, there was a slight increase from 0.48 ml/min to 0.61 ml/min after 1 month of green tea consumption although the difference was not statistically significant. Of the 16 SS patients who attended a follow-up after 1 month of green tea
consumption, 7 SS patients produced more stimulated saliva than their baseline levels while 5 SS patients had no change. It must be emphasized that although not statistically significant, the fact that the stimulated salivary flow rate increased at all is significant clinically and emotionally to the patients. After 3 months of green tea consumption, the mean flow rate did not change significantly in the SS group which consisted of 7 SS patients who attended the follow-up appointment. However, when individually monitored, 3 of these patients produced more stimulated saliva than their baseline levels while 1 SS patient produced slightly less stimulated saliva. There were 3 SS patients who were unable to produce any stimulated saliva at all appointments. It appears that their salivary glands have been so severely affected by the manifestations of SS that the effect of stimulants became insufficient (Vissink et al., 1993).

For the non-SS group, although the change in the stimulated salivary flow rate was not statistically significant, there was an increasing trend in the mean flow rate after 3 months of green tea consumption.

**B. Salivary Viscosity**

i) Unstimulated Saliva

For the SS group, there was a slight decrease of the viscosity from 2.3 cP to 1.9 cP after 1 month of green tea consumption although the difference was not statistically significant. Among 16 SS patients who attended the 1-month follow-up visit, there were 6 patients who could produce sufficient quantities to be tested. Five of these 6 patients showed a decreased viscosity of their unstimulated saliva since the green tea consumption began. Interestingly, the mean viscosity for the SS group slightly increased from 1.8 cP to 2.1 cP after 3 months of green tea consumption. Among those 7 SS patients who attended the 3-month follow-up visit, only 3 patients were able to produce
any unstimulated saliva at rest. These 3 patients showed a slight increase in their viscosities in comparison to their baseline levels (Table 30).

Data analyzed by the 2-way Repeated Measures ANOVA showed that there was no significant change over time with respect to unstimulated salivary viscosity in the SS group while there was a consistent decreasing trend in the non-SS group (Figure 22). This may be, in part, due to the limited number of the patients at the 3-month time period (n=3) who were actually able to produce required amount of unstimulated saliva at all to be tested for viscosity analysis, in comparison to the 12 non-SS participants who could consistently produce enough of both unstimulated and stimulated saliva.

Whether the viscosity is due to a ratio of liquid to solid phases or is due to the presence of various mucin-related compounds is unknown. It is possible that since SS patients in general have a higher tooth decay rate than healthy individuals, there is a greater bacterial population whose presence in saliva could increase the viscosity. However this is speculative.

Recent findings at a SS patient conference called Multidisciplinary Sjögren’s Clinic Retreat (June 24th, 2011) indicated that data on stimulated saliva is more meaningful in this patient population than on the unstimulated saliva, since physiologically, there would be no reason to have a change in the viscosity of unstimulated saliva. In light of this, perhaps it is more appropriate to focus on stimulated saliva production.

ii) Stimulated Saliva

For the SS group, a significant decrease in the mean viscosity of stimulated saliva was observed after 1 month of green tea consumption by as much as 50%. This consistent decreasing trend was shown after 2 and 3 months of green tea consumption. When the baseline data from the 16 SS patients were analyzed individually in terms of
stimulated salivary viscosity, there were 4 SS patients (numbers 16, 25, 26, and 27), who had 4.0 cP greater viscosities than the other patients. At the 1-month follow-up visit, these 4 SS patients had drastically decreased viscosities of stimulated saliva than the rest of the SS patients, as shown in Figure 31. After 3 months of green tea consumption, there were only 4 of the 7 SS patients who were able to produce any stimulated saliva (Table 30); 3 of these (numbers 13, 16, and 17) showed decreases in viscosity. The change in viscosity could be due to either an increase in the aqueous portion of saliva and/or a decrease in its mucin content. This would be an area worthy of future investigation. For the non-SS group, the viscosity of stimulated saliva showed almost no change over time since it only decreased by 0.4 cP from 2.6 cP to 2.2 cP after 3 months of green tea consumption.

4.3 Subjective Questionnaires

A. Changes in OHIP-14 and QoL

The results for the changes in subjectively perceived oral health outcome measures using the OHIP-14, XI, and QoL questionnaires showed that there were beneficial effects of green tea consumption in SS patients. Note that the lower the OHIP-14 scores are, the better is the oral health while the higher the QoL scores are, the better is the life quality. For the SS group, after 1 month of green tea consumption, a summary score of OHIP-14 has significantly decreased by 6.00 ± 2.22, indicating less frequent oral health-related problems associated with all 7 dimensions of the OHIP-14: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap (Figure 17). In particular, among SS patients, the impact of oral health-related problems such as physical pain and psychological
disability significantly decreased, implying that the SS group experienced considerably less frequent pain in the mouth, felt less uncomfortable to eat any foods, found it less difficult to relax, and felt less embarrassed since the green tea consumption began. The OHIP-14 scores consistently decreased after 2 months and 3 months of green tea consumption for both the SS and non-SS groups; these findings suggest that the impact of problems with teeth, mouth, and/or dentures has been reduced. It can be concluded that the green tea consumption had a positive impact on overall oral health.

Correlations between the OHIP-14 and QoL questionnaires were noted in the Pearson correlation analysis (Table 32). The OHIP-14 summary score was negatively correlated with the QoL summary score, indicating that the better the oral health is in general, the better is life quality. This is consistent with the findings that after 1 month of green tea consumption, the mean QoL score in the SS group increased significantly in comparison to baseline. In particular, a large proportion of patients felt considerably less worried, tense, or depressed in comparison to the levels observed at baseline. Furthermore, SS patients reported that their social life, intimate relations, and/or daily activities had improved after 1 month of daily green tea consumption. Of the 18 SS patients who returned for the 1-month follow-up, 16 SS patients showed increases in QoL scores. With respect to the SS patients who were available for the 3-month follow-up appointment, the mean QoL score for the SS group also indicated a statistically significant increase. These findings indicate that daily green tea consumption over a 3-month period improved the life quality in the SS group.

Despite limitations of the study, it is conceivable to speculate several factors that may have led to changes in patients’ perception of overall oral health and related life quality after green tea consumption as follows:
1) It has been shown that oral diseases including dental caries, periodontal disease, and tooth loss may significantly impact a person’s overall oral health (Kandelman et al., 2008). It has also been shown that there are beneficial effects with green tea consumption on overall oral health (Cabrera et al., 2006). Several studies (Otake et al., 1991; Dufresne and Farnworth, 2001; Hamilton-Miller, 2001) have reported that frequent intake of green tea can significantly decrease caries formation even in the presence of sugars in the diet; that the presence of GTPs in green tea inhibits the adherence and the growth of bacteria at the tooth surface, and in particular both the glucan synthesis by streptococci and Porphyromonas gingivalis, a bacteria responsible for periodontal disease, respectively. Cross-sectional data from Koyama et al. (2010) have shown that green tea consumption of at least 1 cup/day is significantly associated with decreased odds for tooth loss. It is entirely possible that some or all of these effects of green tea intake may have had a positive influence on the SS patients’ overall oral health and related life quality although the exact mechanisms are unknown.

2) In addition to the cardinal symptoms of oral dryness, SS patients in the present study reported that they also commonly experienced fatigue, pain, and cognitive symptoms. It is evident that psychological distress is frequent in SS patients as they are known to have an increased propensity for depressed mood, and suffer from reduced well-being and impaired vitality (Valtísdóttir et al., 2000; Segal et al., 2011). It has long been said that green tea induces a pleasurable mental feeling. Reports from experimental studies of mood have produced consistent results indicating an association between tea consumption and increased psychological well-being and mood. Furthermore, recent studies have suggested that its positive psychological effects may be caused by the presence of the novel amino acid-glutamic acid analogue theanine (L-theanine) commonly found in green tea: it has been suggested that L-theanine increases alpha
brainwave activity that is associated with increased creativity, increased performance under stress, and improved learning and concentration, as well as decreased anxiety (Ito et al., 1998; Juneja et al., 1999). In another study, after consumption of green tea, regardless of the quantity of green tea consumed, 70.6% of males and 82% of females felt drinking green tea relaxed the mind (Shimbo et al., 2005).

**B. Changes in Xerostomia Inventory (XI)**

A single continuous scale score obtained from the XI questionnaire represented the severity of chronic xerostomia and related symptoms. It should be noted that the higher the XI score is, the greater is the severity of xerostomia perceived by study participants. After 1 month of green tea consumption, the mean XI score for the SS group decreased by 3.22 points from 52.28 to 49.06 points. Although there were minimal changes for most XI items, there was a 50% of decrease in numbers SS patients reporting either ‘fairly often’ or ‘very often’ for their mouth feeling dry, indicating less severe xerostomia in the SS group in comparison to the baseline. When SS patients were analyzed individually, among those who returned for the 1-month follow-up visit, 3 SS patients (16.7%) reported that they experienced less severe dry mouth-related symptoms after green tea consumption as reflected in their XI summary scores changing by 6 points or more. After 2 months of green tea consumption, data analyzed by the paired t-test showed a significant decrease in mean XI score by 5.20 points for the SS group in comparison to baseline, indicating significant improvement in xerostomia and related symptoms. There was an overall decreasing trend over time in terms of mean XI summary score although there was a slight increase by 2.14 points between 2- and 3-month follow-up visits (Figure 24).

For the non-SS group, there were no significant changes over time with respect to mean XI summary score. There were, however, decreases of 1.33 points and 3.09 points
from baseline observed after 1 month and 2 months of green tea consumption, respectively, yet a negligible increase of 0.42 points was observed after 3 months. As previously discussed, these changes, while not significant when compared on an intra-group basis they are significant on an inter-group basis. Therefore, as assessed by mean XI summary scores, it is conceivable to suggest that green tea consumption has a somewhat positive impact on alleviating dry mouth-related symptoms and behaviours for both SS and non-SS groups since there was an overall decreasing trend.

C. Changes in the Extent of Dry Mouth as Determined by VAS Scores

For the SS group, slight decreases in all categories were noticed, suggesting that 1 month of daily green tea consumption somewhat relieved subjectively perceived dry mouth and related symptoms. Both after 2 and 3 months of green tea consumption, this decreasing trend was consistent for all symptoms observed, yet their subjectively perceived quantity of saliva in everyday life was not changed over time and dryness of skin was slightly increased possibly due to a seasonal effect (Table 27). Despite the small sample size, when the SS group was evaluated at the 3-month follow-up visit, among the dry mouth-related symptoms, significant decreases were observed in oral dryness during day-time and when eating dry foods.

For the non-SS group, there were no significant changes found after 1 month of green tea consumption with respect to dry mouth and related symptoms. There was even a slight increasing trend of several symptoms over time: oral dryness at times other than at night and upon wakening, oral dryness during eating, difficulty in swallowing, and difficulty in eating dry foods. As shown in Figures 26 and 27, there was a significant time-by-group interaction for both the oral dryness during eating and difficulty in swallowing observed after 3 months of green tea consumption, indicating that the changes over time with respect to the extent of dry mouth after green tea consumption
over time differs between the 2 groups. Moreover, when individually analyzed, 5 of 12 control participants showed either decreases or no change in oral dryness during eating and in difficulty in swallowing. It is tempting to speculate that for some non-SS control participants, the sensation of astringency of the green tea may have been perceived significantly as a negative attribute involving dryness of the oral surface and puckering sensations of the mucosa and muscles around the mouth, particularly when brewed longer than the recommended time (Lee and Lawless, 1991; Lesschaeve and Noble, 2005; Rossetti et al., 2009). Following on, of interest is the discrepancy between the results from the extent of dry mouth as determined by VAS and salivary flow rates in the non-SS group. Although an increasing trend of salivary flow rates from unstimulated and stimulated conditions was observed, several non-SS control participants perceived oral dryness and dryness-related symptoms after green tea consumption based on VAS. The mechanism associating subjective dry mouth sensation and salivary flow rate has not been fully elucidated in healthy individuals. The lack of an association for healthy individuals could indicate that dry mouth sensation is dependent upon more complex physiological events than simple salivary flow rate. The sensation could be related to mucosal hydration, and since saliva does not necessarily humidify the entire oral mucosa uniformly, it may be possible that even in the presence of sufficient (normal) salivary flow, some localized dry areas exist, thereby triggering the sensation of dry mouth (Dawes, 1987). Moreover, changes in salivary composition have been regarded as factors that influence the perception of dry mouth as well. In fact a negative correlation between mucosal wetness and the protein concentration of residual saliva in normosalivators has been reported (Won et al., 2001). Therefore, the subjective feeling of dry mouth could be related to the oral sensory perception of mucosal wetness, rather than salivary gland output changes (Wolff and Kleinberg, 1998; Lee et al., 2002).
4.4 Correlations between Objective and Subjective Findings

In the current study, using the Pearson correlation analysis, significant correlations between various study parameters were noted at baseline, 1-month, 2-month, and 3-month follow-up visits as shown in Table 32. There was a strong positive correlation with a statistical significance ($p < 0.001$) between the XI and OHIP-14 questionnaires such that the more severe oral dryness that the study participants perceived, the poorer oral health they had in general. Moreover, a significant correlation between the XI and QoL questionnaires was seen at all follow-up visits. A strong negative correlation between these parameters indicates that life quality in SS patients improves as the severity of xerostomia decreases.

Subjective OHIP-14, XI, and QoL questionnaires were all significantly correlated with both unstimulated and stimulated salivary flow rates. A negative correlation between OHIP-14 and flow rates indicates that as the salivary output is reduced, the overall oral health worsens, which is in agreement with a previous report (Stewart et al., 2008). Moreover, a decrease in flow rate is strongly related to greater severity of xerostomia based on the significant correlation with XI. It was also observed that there was a positive correlation between salivary flow rates and QoL in the SS patients, indicating that the stimulatory effect that green tea consumption had on salivary flow rate had an additional beneficial effect on the QoL of the SS patients.

Throughout the study period, there were no consistent significant correlations seen between salivary viscosity and subjective oral health measures, although this is likely due to the small size of the SS patient population at the 2- and 3-month follow-up visits. Further investigations into associations between salivary viscosity and subjective oral health measures are necessary to clarify the current findings.
4.5 An Exit Survey after Green Tea Consumption

There were serendipitous findings reported by 7 SS patients such as weight loss after beginning daily green tea consumption. This is consistent with several reports that the catechins in green tea have anti-obesity effects on body weight and fat in humans (Auvichayapat et al., 2008; Rains et al., 2011). In the current study, these 7 SS patients mentioned that having weight loss was favourable to them because it helped to elevate their body image in a positive way. In addition they felt that the consumption of green tea on a regular basis made them feel more physically energetic, and improved other health-related problems such as heartburn (see the testimonial; Appendix XV). Moreover, 11 of the 18 SS patients who drank green tea for at least 1 month reported that they felt that having green tea on a daily basis was somewhat effective in relieving their dry mouths. More than 80% (15) of these 18 SS had a somewhat pleasant after having green tea in their mouths. Therefore, the fact that daily green tea consumption provided some comfort in their mouths and helped them feel more positive about themselves through weight loss or other means was meaningful for the SS patients, although it may not have relieved the perception of dry mouth directly through the mechanisms of greater saliva production. After participating in the present study, 15 of the 18 SS patients said that they would definitely continue to drink green tea on their own, and the remaining 3 SS patients said that they might continue to drink green tea. Many expressed the appreciation of having an opportunity to be introduced to green tea at all.
4.6 Limitations of the Present Study

The nature of a pilot study is to perform various tasks on a preliminary basis, making note of the pitfalls encountered during testing, which had not been anticipated during the initial design of the study. A number of limitations were identified in the course of the present study including the following:

1) The sample size at the 2- and 3-month follow-up visits was too small. Among SS patients, there were unanticipated numbers of withdrawals from the study. Patients reported several reasons for their withdrawals including severe medical complications unrelated to green tea consumption and fragility in association with having SS, feelings of being a burden on family members, in their requirement for transportation, and/or a dislike of the green tea flavour, the latter, likely being related to over-steeping.

2) Attempts were made to closely match ages of the SS patients and non-SS participants. Although the ages of pair of participants were not identical, our results showed that age had no effect on any study parameters including salivary flow rates, viscosity, and the subjective questionnaires in the current study. It is generally accepted that aging per se has no significant clinical impact on salivary flow rates, yet the prevalence of xerostomia appears to increase with age, mainly affecting the middle-aged and elderly populations. Many times, reduced flow in the older population is linked to side effects of prescription medications and polypharmacy (Hopcraft and Tan, 2010). Therefore, in the present study, any subjects who took prescription medications that were known to cause dry mouth were excluded as indicated in our inclusion/exclusion criteria.
3) Since there are diurnal variables that may affect levels of saliva production in any given individual, it might be prudent to collect baseline salivary samples on more than one occasion. This would provide the patient with greater familiarity of the actual testing procedures although it was verbally explained and demonstrated beforehand.

4) As stated previously, only 4 of the 7 SS patients who were able to attend the 2- and 3-month follow-up visits, could produce a sufficient quantity of stimulated saliva required to test the viscosity. Therefore, conclusions are based on data from these 4 patients. More reliable are the results from the 1-month visit, which included 12 patients for the viscosity analysis.

5) There may have been placebo effects of daily green tea consumption in alleviating the dry mouth and dry mouth-related symptoms in SS patients. It is entirely possible that daily hot water consumption, without the tea, could have had the same effect. However, the numbers of SS patients who were physically able to participate in this study were small enough that this was prohibitive in this pilot study.
CHAPTER 5. CONCLUSIONS AND FUTURE DIRECTIONS

In the present study, it was evident that the SS group experienced severe xerostomia, which negatively affected their overall oral health (Stuchell et al., 1984; Wang et al., 1998; Dawson et al., 2001; Pijpe et al., 2006). The impact of xerostomia on life quality in SS patients was evident as a large proportion of patients felt worried (93.5%), tense (71%), or even depressed (64.5%). Furthermore, the SS group reported that oral dryness at night or/and awakening, oral dryness during eating, and difficulty in eating dry foods were the most severely experienced symptoms.

After 1 month of green tea consumption, the SS group showed that the stimulated salivary flow rate increased although no statistical significance was observed. It must be emphasized that although not statistically significant, the fact that the salivary flow rate increased at all is significant clinically and emotionally to the SS patients. Furthermore, the stimulated saliva was found to be significantly less viscous in the SS group since the green tea consumption began, possibly inducing less dry mouth perception. It was also observed that the SS group perceived improved life quality and better overall oral health after 1 month of green tea consumption. A large portion of SS patients reported that their social life and daily activities had improved, and they felt considerably more relaxed.

The results obtained from the questionnaires of XI and the extent of dry mouth indicated that the dry mouth, and related symptoms/behaviours were slightly reduced for the SS group in comparison to the baseline levels although no statistical significance was shown.

For the 3-month study period, there was a trend toward an increase in unstimulated salivary flow rate and a decrease in stimulated salivary viscosity for the SS group. Despite the small sample size, the fact that the salivary flow rate of unstimulated
saliva increased at all after 3 months of green tea consumption is an encouraging finding for the SS patients. Moreover, the SS group reported that their perceived life quality had enhanced considerably with green tea consumption. Since most SS patients commonly experience fatigue, impaired social interaction, and psychological distress (Segal et al., 2011) as a result of the detrimental impact of dry mouth and other related symptoms on their life, the fact that daily green tea consumption somewhat improved the quality of life for the patients is significant. The symptoms of oral dryness at times of the day other than at night and/or awakening and difficulty in eating dry foods, as assessed by VAS scores, were significantly relieved for the SS group.

Interestingly, several non-SS control participants reported complaints of oral dryness due to green tea consumption but also showed a trend of increased unstimulated saliva flow rate with statistical significance throughout the 3-month study period. This is consistent with situations that have been reported where normal salivary output has been shown by objective testing yet there was a subjective complaint of dry mouth in non-SS individuals (Baum, 1989; Wolff and Kleinberg, 1998). Therefore, the perception of dry mouth is not always associated with a reduction in whole salivary output. In the current study, the complaint by some non-SS participants that dry mouth increased with green tea consumption may be, in part, due to an over-steeping of the green tea performed by some of the study participants. The sensation of astringency from drinking green tea has been regarded as a potential factor that may influence the perception of dry mouth for some individuals (DiSabato-Mordarski and Kleinberg, 1996; Wolff and Kleinberg, 1998; Rossetti et al., 2009) even though the production of saliva had not diminished.

Although the beneficial effects of green tea and GTPs associated with SS were previously reported from in vitro and animal studies (Hsu and Dickinson, 2006; Hsu et al., 2007; Gillespie et al., 2008), their effects in clinical trials involving human SS
patients have never been assessed. This study was unique in that no previous studies have examined the effects of daily green tea consumption on salivary flow rate, salivary viscosity, patient perception of dry mouth, and quality of life in patients diagnosed with SS. From the current study, despite the small sample size, daily green tea consumption was observed to have somewhat positive effects on the quality of life in SS patients, alleviating their emotional strains such as anxiety and stress caused by dry mouth. In conversations with several SS participants, they stated that because they have to live with having dry mouth, they often feel discouraged, worried, saddened, and a burden to their family members particularly due to the increasing medical complications associated with the disease. Since patients’ lives have been affected negatively as a result of having dry mouth, an improved quality of life after daily green tea consumption was an important result in the current study. There were very minimal negative side effects experienced by the SS patients, such as nausea, stomach pain, and/or indigestion. Some SS patients even reported a positive result of weight loss after the consumption of green tea on a regular basis.

In the future, a greater sample size is required to clarify the trend and to overcome the limitations associated with the current project. It is hoped that the results in this study will be continued on a larger scale to help clarify the effects of green tea consumption and GTPs on relief of dry mouth and life quality in SS patients. In future studies, different means to deliver GTPs through the use of green tea gum, green tea extracts, and etc. or different tea types (decaffeinated, black, white, oolong, etc.) may be employed to investigate whether they have similar effects in SS patients as the consumption of green tea had in our current study.
CHAPTER 6. SUMMARY

The major findings of the present pilot study were:

1) The present study has documented novel findings that for SS patients who had consumed green tea over a period of 1 month, had a significant decrease in the viscosity of their stimulated saliva. Although only a limited number of patients continued with the green tea consumption for 3 months, an increasing trend in their unstimulated salivary flow rate and a decreasing trend in viscosity of their stimulated saliva were observed.

2) The SS patients’ perceived quality of life (QoL) had significantly improved since the green tea consumption began.

3) The SS patients’ symptoms of oral dryness were considerably relieved since the green tea consumption began, particularly during day-time and when eating dry foods.

In this study we have shown that the use of green tea in patients with SS is a simple yet effective and enjoyable means of dry mouth relief.
CHAPTER 7. REFERENCES


Konttinen YT, Kasna-Ronkainene L. Sjögren’s syndrome: viewpoint on pathogenesis on pathogenesis. One of the reasons I was never asked to write a textbook chapter on it. Scand J Rheumatol Suppl 2002; 15-22.


Thomson WM. Measuring change in dry-mouth symptoms over time using the Xerostomia Inventory. Gerodontology 2007; 24(1): 30-5.


Turner MD, Ship JA. Dry mouth and its effects on the oral heath of elderly people. JADA 2007; 138(suppl 9): 15S-20S.


CHAPTER 8. ABBREVIATIONS

AEC: American European Consensus
ANOVA: Analysis of Variance
COX-2: Cyclo-oxygenase 2
°C: Celcius
cP: centiPoise
EC: Epicatechin
ECG: Epicatechin gallate
EGCG: Epigallocatechin gallate
EGC: Epigallocatechin
°F: Fahrenheit
GTPs: Green Tea Polyphenols
HLA: Human Leukocyte Antigen
HPLC: High Performance Liquid Chromatography
IFNs: Interferons
JNK: c-Jun NH₂-terminal Kinase
MAPK: Mitogen-activated Protein Kinases
MMPs: Metametalloproteinases
NO: Nitric Oxide
NOD: Non-obese Diabetic
OHIP-14: Oral Health Impact Profile-14
PGE₂: Prostaglandin E₂
QoL: Quality of Life
ROS: Reactive Oxygen Species
RA: Rheumatoid Arthritis
Sec⁻¹: Reciprocal Seconds
SLE: Systemic Lupus Erythematosus
SS: Sjögren’s Syndrome
SSFR: Stimulated Salivary Flow Rate
SSV: Stimulated Salivary Viscosity
USFR: Unstimulated Salivary Flow Rate
USV: Unstimulated Salivary Viscosity
VAS: Visual Analogue Scale
XI: Xerostomia Inventory
CHAPTER 9. APPENDICES
Dear Dr. Gibbard and Ms. Ko:

Re: Your research protocol entitled "The effects of green tea on salivary production and viscosity in patients with Sjögren's Syndrome" by Dr. L. L. Gibbard (supervisor), Ms. J. H. Ko (Master's student)

We are writing to advise you that a member of the Health Sciences Research Ethics Board has granted approval to an amendment (received Oct. 21, 2010, response received Nov. 17, 2010) to the above referenced research study under the REB's delegated review process. This amendment will allow for changes as described in detail in the Amendment application received Oct. 21, 2010.

All your most recently submitted documents have been approved for use in this study.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible.

Best wishes for the successful completion of your project.

Yours sincerely,

Marianna Richardson
Research Ethics Coordinator
Appendix II. Inclusion/Exclusion Worksheet
GREEN TEA PROJECT
Inclusion/Exclusion Criteria for Selection of SS Patients

Name: _____________________                                           Today’s Date: ____________________
Code Number: ______________                                           Height/Weight: ____________________
Gender: M  F                                                       Birth date: ____________________
Smoker: Yes (___ times/week)/ No
Regular green tea drinker: Yes (___ times/week)/ No

Inclusion criteria:                                      Yes      No

Over the age of 18        □ □

Diagnosis of Sjögren’s Syndrome          □ □
  When: __________________________
  Diagnosis of other autoimmune disorders
  If so, name them ______________

Exclusion criteria:                                      Yes      No

Use of any of the following medications (Please circle which one(s)): □ □

List any other medications currently being used:
__________________________________________________________________

Allergies to any teas listed below; if so, please circle which one(s): □ □
  Black, Green, White, Rooibos, Oolong, Tulsi

Pregnant or lactating women □ □

Present history of cancer, severe infections, or other uncontrolled diseases □ □

Meets selection criteria for project: Yes      No
GREEN TEA PROJECT

Inclusion/Exclusion Criteria for Selection of Non-SS Participants

Name: _____________________  Today’s Date: _____________________
Code Number: ______________  Height/Weight: _____________________
Gender: M  F  Birth date: _____________________
Smoker: Yes (___ times/week)/ No
Regular tea drinker: Yes (___times/week)/ No

Inclusion criteria:

Over the age of 18  ☐  ☐

Exclusion criteria:

Diagnosis of autoimmune disorders  ☐  ☐
Which one(s): _____________________

Evidence of dry mouth  ☐  ☐

Use of any of the following medications (Please circle which one(s)):  ☐  ☐

Prozac, Xanax, Halcion, Elavil, Tofranil, Amitriptyline, Paxil, Trazodone, Desyrel,
Lithium, Stelazine, Lopressor, Cardizem, Hydropres, Procardia, Tenex, Capoten, Zestril,
DynaCirc, Dyazide, Minipress, Seldane, Atrohist, Benadryl, Chlorpheniramine,
Tefenadine.

List any other medications currently being used:

__________________________________________

Allergies to any teas listed below; if so, please circle which one(s):  ☐  ☐
Black, Green, White, Roobois, Oolong, Tulsi

Pregnant or lactating women  ☐  ☐

Present history of cancer, severe infections, or other uncontrolled diseases  ☐  ☐

Meets selection criteria for project:  Yes  No
Appendix III. Consent Form
GREEN TEA PROJECT

CONSENT FORM

INTRODUCTION

We invite you to take part in a research study at the Faculty of Dentistry, University of Toronto. It is important that you read and understand several principles that apply to all who take part in our studies:

1. Taking part in a study is entirely voluntary;

2. Personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others;

3. You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled;

4. Your participation is confidential. When results of this study are reported in scientific journals or at meetings, the identification of those taking part is withheld. Medical records are maintained according to current legal requirements, and are made available for reviews, as required by the University Human Subjects Ethics Committee or other authorized users, only under the guidelines established by the Federal Privacy Act.

The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the principal investigator, Dr. Leslie Laing Gibbard, or Ju Hee Ko who will explain it to you.
OBJECTIVE OF THE STUDY

We would like to invite you to participate in a study designed to find out the effects of green tea consumption on salivation and on relief of xerostomia in patients with Sjögren’s Syndrome. The protocol for the study is explained below.

YOUR PARTICIPATION

You will be required to consume four cups of green tea on a daily basis for three months (please refer to Instruction for brewing). The study involves four testing visits (at least one visit per month) to see if the changes in salivation occur in terms of salivary flow rate and viscosity since green tea consumption starts. Each visit will take approximately 30 minutes. The testing will take place in room 316 at the Faculty of Dentistry, University of Toronto, 124 Edward Street. During each visit, you will be asked to fill out some questionnaires pertaining to your dry mouth and its effect on quality of life that will take approximately 15 minutes to complete. Before coming in for testing visits, we ask that you refrain from eating or drinking (except water) for at least 1 hour prior to saliva collection.

The testing will take place between 9:00 and 11:00 AM. During each appointment, we will ask you to complete the questionnaires, and then we will collect 2 saliva samples: 1 will be at rest, called resting saliva; the other will be stimulated by mechanical means (chewing on some wax) as described in more detail below.

Saliva stimulation and collection:
Before saliva collection, we will ask you to consume several sips of distilled water and/or swill around the mouth for at least 30 seconds to obtain a ‘neutral’ mouth state. Then whole unstimulated (resting) saliva will be collected for 10-15 minutes by spitting using the following protocol:
(1) You will be asked to sit in a forward position with the elbows resting on the knees. The tongue, cheeks, and jaw should not be moved.
(2) Then you will collect saliva with closed lips, and expectorate once after approximately each 60-second period. When expectorating, you will be told only to drool passively and not to spit actively. Once the resting saliva has been collected, stimulated saliva will be collected.

Saliva production will be stimulated by the following protocol by mechanical means:
(1) Several sips of distilled water will be consumed and/or swilled around the mouth for at least 30 seconds to obtain a ‘neutral’ mouth state.
(2) Initial chewing will take place for 30 seconds in order to soften the paraffin and remove saliva from the mouth by swallowing.
(3) During the subsequent 5 min, stimulated saliva is collected while you are chewing on the same bolus of paraffin by spitting method. The collected saliva will be measured to determine production rate for a total collection time of 5 minutes.

It is recommended that you are abstained from other types of tea, but to otherwise continue your usual daily diet throughout the study period.
HARMS AND BENEFITS
There are no known complications or invasiveness to the procedures. We will provide the bags of green tea for you to use during the study. You may not benefit directly from the results of the study, but the information will provide us with valuable insight into the characteristics of the Sjögren’s Syndrome as related to dry mouth, and on their quality of life. We hope to be able in the future to identify the oral complications and continuously improve the care offered to patients.

We encourage you to discuss any questions you may have about the study before you agree to participate. You may also call Dr. Leslie Laing Gibbard for information at:

Department of Prosthodontics,
Faculty of Dentistry, University of Toronto,
124 Edward Street, Room 356A
Toronto, Ontario, M5G 1G6
Telephone: (416) 979-4930 extension 4611.

If you have questions about your rights as research participants, please contact the Office of Research Ethics at ethics.review@utoronto.ca, 416-946-3273.
PATIENT'S CONSENT

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to voluntarily take part in this study and accept the risks, which are inherent to the research study. I may withdraw from the study at any time without penalty or loss of any benefits to which I am otherwise entitled.

I have completed the medical and dental questionnaires and I shall inform the researchers who are responsible of this study of any change in my medical or dental status, which may arise during my participation.

A copy of this consent form is available upon request.

Name of participant:

Signature of participant: Date:

Name of investigator:

Signature of investigator: Date:
Appendix IV. Green Tea Preparation Instructions
GREEN TEA PROJECT

INSTRUCTIONS ON HOW TO PREPARE A CUP OF GREEN TEA

We would like to start off by welcoming you to our research study at the Faculty of Dentistry, University of Toronto. Please take the time to read the following instructions carefully. If you have any questions or concerns regarding these instructions or any other issues please forward them to the principal investigator, Dr. Leslie Laing, or assistant Juhee Ko.

Please follow these steps to prepare a cup of green tea at your private settings:

1) Bring water to a boil, then let it sit for 5 minutes to reach about 165-175 F (70°C).
2) Pour over the tea bag. Use 1 tea bag per cup (8 oz).
3) Steep the tea for 2-5 minutes (recommended brewing time is 2-3 minutes) to suit your taste preferences. Never judge tea strength by its color.

Use Step 1-3 to make a cup of green tea. You are required to drink at least 4 cups of green tea on a daily basis at any time of your day. It is recommended that you abstain from drinking other types of tea, but to otherwise continue your usual daily diet throughout the study period.

Once again, we would like to thank you for participating in this study and urge and question, comments or concerns to be forwarded to Dr.Leslie Laing or Ju Hee Ko.

Dr.Leslie P. Laing, BSc, Bed, MSc, PhD (Microbiology & Immunology), DDS, MSc (Prosthodontics), FRCD©
Principal Investigator
Leslie.lainggibbard@dentistry.utoronto.ca
Phone: 416-979-4930 ext 4611
Fax: 416-979-4936

JuHee Ko, BSc
MSc Student
Juhee.ko@utoronto.ca
Phone: 647-982-0205
Appendix V. Green Tea Compliance Chart
## Green Tea (GT) Compliance Chart

<table>
<thead>
<tr>
<th>Date</th>
<th># of GT cups/day</th>
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Appendix VI. Oral Health Impact Profile – 14 (OHIP-14) at Baseline
Oral Health Impact Profile -14 at Baseline
(Slade and Spencer, 1994)

PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION

For the last 3 months,

1. Have you had trouble pronouncing any words because of problems with your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

3. Have you had painful aching in your mouth?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

5. Have you been self conscious because of your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

6. Have you felt tense because of problems with your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

7. Has your diet been unsatisfactory because of problems with your teeth, mouth, and/or dentures?
   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN
8. Have you had to interrupt meals because of problems with your teeth, mouth and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

9. Have you found it difficult to relax because of problems with your teeth, mouth, and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

10. Have you been a bit embarrassed because of problems with your teeth, mouth and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

11. Have you been a bit irritable with other people because of problems with your teeth, mouth, and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

12. Have you had difficulty doing your usual job because of problems with your teeth, mouth, and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth, and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN

14. Have you been totally unable to function because of problems with your teeth, mouth, and/or dentures?

NEVER        HARDLY EVER        OCCASIONALLY        FAIRLY OFTEN        VERY OFTEN
Appendix VII. Xerostomia Inventory (XI) at Baseline
# Xerostomia Inventory (XI) at Baseline
(Modified from Thomson, et al., 1999)

**PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION**

1. I sip liquids to aid in swallowing food
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

2. My mouth feels dry when eating a meal
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

3. I get up at night to drink
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

4. My mouth feels dry
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

5. I have difficulty in eating dry foods
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

6. I suck sweets or cough drops to relieve dry mouth
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

7. I chew gum to relieve dry mouth
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

8. I have difficulties swallowing certain foods
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

9. I have difficulties wearing my denture(s): *(Answer if Applicable only)*
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN
10. The skin of my face feels dry

<table>
<thead>
<tr>
<th>Option</th>
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<tr>
<td>never</td>
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<td>hardly ever</td>
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11. My eyes feel dry

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12. My lips feel dry

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13. My tongue feels dry

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14. The inside of my nose feels dry

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<td>never</td>
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Any comments you would like to add:
Appendix VIII. Quality of Life (QoL) for Dry Mouth Patients at Baseline
Quality of Life (QoL) for Dry Mouth Patients at Baseline
(Dirix et al., 2007)

PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION

My dry mouth ...

1. Restricts the amount and type of food I eat

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

2. Gives me an uncomfortable feeling in my mouth

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

3. Makes me worry

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

4. Restricts my social life

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

5. Makes it awkward to eat in front of other people

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

6. Makes it difficult to speak to other people

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

7. Is the cause of considerable tension

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN

8. Makes me worry about the look of my teeth and mouth

NEVER  HARDLY EVER  OCCASIONALLY  FAIRLY OFTEN  VERY OFTEN
9. Makes me feel depressed

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10. Restricts me in my daily activities

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11. Troubles my intimate relations

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12. Gives my food less or a different taste

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13. Diminishes my will to live

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14. Invades every aspect of my life

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*Please feel free to add any comments you would like:*
Appendix IX. The Extent of Dry Mouth at Baseline
Extent of Dry Mouth at Baseline
(Modified from Oh, et al., 2008)

Please draw a vertical line cutting the horizontal one to indicate the degree of your dry mouth-related symptoms.

a) Oral dryness at night or on awakening

|__________________________|

Not dry at all                      Very dry

b) Oral dryness at other times of the day

|__________________________|

Not dry at all                      Very dry

c) Oral dryness during eating

|__________________________|

Not dry at all                      Very dry

d) Difficulty in swallowing foods

|__________________________|

Not difficult at all                 Very difficult

e) Difficulty in eating dry foods

|__________________________|

Not difficult at all                 Very difficult
f) Amount of saliva as usual in everyday life

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<td>None</td>
<td>Very much</td>
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g) Dryness of skin

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<td>Not dry at all</td>
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h) Dryness of eyes

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<td>Not dry at all</td>
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i) Dryness of lips

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<td>Not dry at all</td>
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j) Dryness of tongue

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<td>Very dry</td>
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k) Dryness of inside of nose

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<td>Not dry at all</td>
<td>Very dry</td>
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Appendix X. Oral Health Impact Profile – 14 (OHIP-14) at Follow-up
Oral Health Impact Profile -14
(Slade and Spencer, 1994)

Please circle one of the answers for each question.

Since the last visit,

1. Have you had trouble pronouncing any words because of problems with your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

3. Have you had painful aching in your mouth?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

5. Have you been self conscious because of your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

6. Have you felt tense because of problems with your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often

7. Has your diet been unsatisfactory because of problems with your teeth, mouth, and/or dentures?
   - Never
   - Hardly ever
   - Occasionally
   - Fairly often
   - Very often
8. Have you had to interrupt meals because of problems with your teeth, mouth and/or dentures?
   NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

9. Have you found it difficult to relax because of problems with your teeth, mouth, and/or dentures?
   NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

10. Have you been a bit embarrassed because of problems with your teeth, mouth and/or dentures?
    NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

11. Have you been a bit irritable with other people because of problems with your teeth, mouth, and/or dentures?
    NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

12. Have you had difficulty doing your usual job because of problems with your teeth, mouth, and/or dentures?
    NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth, and/or dentures?
    NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN

14. Have you been totally unable to function because of problems with your teeth, mouth, and/or dentures?
    NEVER     HARDLY EVER     OCCASIONALLY     FAIRLY OFTEN     VERY OFTEN
Appendix XI. Xerostomia Inventory (XI) at Follow-up
Xerostomia Inventory (XI) Questionnaire
(Modified from Thomson et al., 1999)

PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION

Since the last visit,

1. I have sipped liquids to aid in swallowing food

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

2. My mouth has felt dry when eating a meal

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

3. I have gotten up at night to drink

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

4. My mouth has felt dry

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

5. I have had difficulty in eating dry foods

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

6. I have sucked sweets or cough drops to relieve dry mouth

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

7. I have chewed gum to relieve dry mouth

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

8. I have had difficulties swallowing certain foods

   NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN
9. I have had difficulties wearing my denture(s): (Answer if Applicable only)

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

10. The skin of my face has felt dry

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

11. My eyes have felt dry

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

12. My lips have felt dry

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

13. My tongue has felt dry

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

14. The inside of my nose has felt dry

NEVER    HARDLY EVER    OCCASIONALLY    FAIRLY OFTEN    VERY OFTEN

Any comments you would like to add:
Appendix XII. Quality of Life (QoL) for Dry Mouth Patients at Follow-up
Quality of Life (QoL) for Dry Mouth Patients

(Dirix et al., 2007)

*PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION*

Since the last visit, my dry mouth has...

1. Restricted the amount and type of food I eat
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

2. Given me an uncomfortable feeling in my mouth
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

3. Made me worry
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

4. Restricted my social life
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

5. Made it awkward to eat in front of other people
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

6. Made it difficult to speak to other people
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN

7. Was the cause of considerable tension
   - NEVER
   - HARDLY EVER
   - OCCASIONALLY
   - FAIRLY OFTEN
   - VERY OFTEN
8. Made me worry about the look of my teeth and mouth

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

9. Made me feel depressed

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

10. Restricted me in my daily activities

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

11. Troubled my intimate relations

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

12. Given my food less or a different taste

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

13. Diminished my will to live

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

14. Invaded every aspect of my live

NEVER          HARDLY EVER          OCCASIONALLY          FAIRLY OFTEN          VERY OFTEN

Please feel free to add any comments you would like:
Appendix XIII. The Extent of Dry Mouth at Follow-up
Extent of Dry Mouth at Follow-up
(Modified from Oh et al., 2008)

Please **draw a vertical line** cutting the horizontal one to indicate the degree of your dry mouth-related symptoms.

a) Oral dryness at night or on awakening

<table>
<thead>
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<tbody>
<tr>
<td>Not dry at all</td>
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b) Oral dryness at other times of the day

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<tbody>
<tr>
<td>Not dry at all</td>
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</table>

c) Oral dryness during eating

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</thead>
<tbody>
<tr>
<td>Not dry at all</td>
</tr>
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</table>

d) Difficulty in swallowing foods

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<tbody>
<tr>
<td>Not difficult at all</td>
</tr>
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</table>

e) Difficulty in eating dry foods

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</thead>
<tbody>
<tr>
<td>Not difficult at all</td>
</tr>
</tbody>
</table>
f) Amount of saliva in usual everyday life

| None          | Very much |

g) Dryness of skin

| Not dry at all | Very dry |

h) Dryness of eyes

| Not dry at all | Very dry |

i) Dryness of lips

| Not dry at all | Very dry |

j) Dryness of tongue

| Not dry at all | Very dry |

k) Dryness of inside of nose

| Not dry at all | Very dry |
Appendix XIV. An Exit Survey
An Exit Survey

PLEASE CIRCLE ONE OF THE ANSWERS FOR EACH QUESTION

1. How effective was having green tea at relieving your dry mouth in general?
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

2. How effective was having green tea at relieving your dry eyes in general?
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

3. How pleasant was the taste of the green tea?
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

4. How pleasant did your mouth feel after having green tea?
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

5. Did you notice any changes in taste of other foods due to having green tea?
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

6. How likely are you to drink green tea again?
   NEVER  MAYBE  DEFINITELY WILL

Please circle if any of side effects exhibited throughout the study:

A) WEIGHT LOSS:
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

B) NAUSEA
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

C) INDIGESTION
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

D) STOMACH PAIN
   NOT AT ALL  LITTLE BIT  FAIR  MUCH  VERY MUCH

E) OTHER: ____________________
Please feel free to leave any comments or concerns

** Please take a minute to review the survey and ensure that all of the questions are answered. Thank you! **
Appendix XV. Testimonials of SS Patients
Testimonials of SS Patients

1) From participant number 25

After drinking the green tea for this past month, I have been pleasantly surprised, when I am at home, at the following:

- My use of gum to relieve my dry mouth has decreased.
- The amount of water I feel I need to drink has decreased.
- The amount of saliva in my mouth has increased which makes my mouth feel more comfortable
- My use of lip balm has decreased.

When I am away from home, & usually talking more, I have my water & gum handy at all times.

My biggest surprise:

- While drinking the green tea (& this happened within the first day), my heartburn nearly disappeared! This was amazing to me! This has remained stable for the whole month! For this last reason alone, I will continue to drink the green tea.

Thankyou, Juhee, for the opportunity to participate in this study. Green tea has had a positive effect & opened my mind to experiment with a new product. When we travel to London next time, I am going to a tea shop to learn about different types of green tea which contain high levels of EGCG (& hope they understand). I would like to find a kind which tastes more pleasant. Until then, I will continue with the Twinnings.

2) From participant number 24

Please feel free to leave any comments or concerns

My being in Anime will affect my results and it will therefore affect the survey. The dryness of my mouth has been as minimal that it has not adversely affected our time here. It did last year! Thank you for this opportunity. It has impacted my life. I will be drinking green tea from now on.

** Please take a minute to review the survey and ensure that all of the questions are answered.

Thank you! **

3) From participant number 22

Please feel free to leave any comments or concerns

Green tea didn't make a difference, but I did lose 5 lbs. After I drank it, my mouth was very dry, but weight loss in any way is good plus I know it's good for my health. I will keep trying it.

** Please take a minute to review the survey and ensure that all of the questions are answered.

Thank you! **