THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA

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A Thesis Submitted in Partial Fulfillment of the Requirements for the
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บทบาทของสารสกัดคอร์ไดเซปินในการดูแลสุขภาพช่องปากของผู้ป่วยสูงอายุเบาหวานประเภท 2 ที่มีภาวะปากแห้ง

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาปรัชญาดุษฎีบัณฑิต
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THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA

Suranaree University of Technology has approved this thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

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ปณิธาน สนพะเนา : บทบาทของสารสกัดคอร์ไดเซปินในการดูแลสุขภาพช่องปากของผู้ป่วยสูงอายุเบาหวานประเภท 2 ที่มีภาวะปากแห้ง (THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA) อาจารย์ที่ปรึกษา : ผู้ช่วยศาสตราจารย์ ทพ.ดร.ไพบูลย์ จิตประเสริฐวงศ์, 239 หน้า.

คำสำคัญ: ภาวะปากแห้ง/คอร์ไดเซปิน/เบาหวาน/ผู้สูงอายุ/ยาสีฟัน/สุขภาพช่องปาก/การสำรวจทันตสุขภาพ

วัตถุประสงค์: เพื่อสำรวจความชุกของสภาวะปากแห้งในกลุ่มผู้ป่วยสูงอายุเบาหวานประเภท 2 และผลกระทบต่อสมรรถนะการทำงานของช่องปาก ค้นหาปัจจัยเสี่ยงหลักที่ก่อให้เกิดภาวะปากแห้ง รวมทั้งการทดลองทางคลินิกเพื่อทดสอบประสิทธิภาพของยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปินจากถั่งเช่าสีทอง ต่อสุขภาพช่องปากในกลุ่มผู้ป่วยสูงอายุเบาหวานประเภท 2 ที่มารับบริการในโรงพยาบาลมหาวิทยาลัยเทคโนโลยีสุรนารี วิธีการวิจัย: (1) เป็นการศึกษาภาคตัดขวางเชิงวิเคราะห์ ในผู้ป่วยสูงอายุเบาหวานประเภท 2 จำนวน 623 ราย ประเมินโดยใช้แบบสอบถามเชิงโครงสร้าง ผู้ป่วยทุกรายถูกสัมภาษณ์โดยผู้วิจัย โดยปัจจัยเสี่ยงต่อการเกิดภาวะปากแห้ง วิเคราะห์โดยใช้สถิติการถดถอยโลจิสติกแบบสองกลุ่มและการวิเคราะห์ถดถอยพหุ (2) จากนั้นเป็นการทดลองวิจัยทางคลินิกแบบสุ่มที่มีกลุ่มควบคุม ศึกษาในผู้ป่วยสูงอายุเบาหวานประเภท 2 ที่มีภาวะปากแห้งจากการประเมินในการศึกษาขั้นแรก จำนวน 101 ราย (กลุ่มควบคุม 50 ราย และกลุ่มรักษา 51 ราย) เพื่อทดสอบประสิทธิภาพของยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปินเทียบกับยาสีฟันผสมฟลูออไรด์ทั่วไป ในประเด็นภาวะปากแห้ง การหลั่งน้ำลายและความชุ่มชื้นของช่องปาก ผลลัพธ์: (1) ในผู้ป่วยสูงอายุเบาหวานประเภท 2 จำนวน 623 ราย พบว่ามีภาวะปากแห้งร้อยละ 38.4 ทั้งนี้สัมพันธ์กับเพศ อายุ ชนิดของยาสีฟันที่ใช้ จำนวนปีที่เป็นเบาหวาน ระดับน้ำตาลสะสมในเลือด โรคร่วมอื่นที่นอกจากเบาหวาน ยาที่รับประทาน การสูบบุหรี่ การดื่มเครื่องดื่มแอลกอฮอล์ และการใส่ฟันปลอม โดยพบว่าผู้ที่ใช้ยาสีฟันที่มีส่วนผสมของสมุนไพรรสเผ็ดมีโอกาสเสี่ยงต่อการเกิดภาวะปากแห้ง 9.32 เท่า ในทางตรงกันข้าม ผู้ที่ใช้ยาสีฟันที่มีส่วนผสมของน้ำตาลเทียมกลับช่วยลดการเกิดภาวะปากแห้งได้ อีกทั้งยังพบว่าการมีภาวะปากแห้งสัมพันธ์กับการเกิดปัญหาด้านสมรรถนะการทำงานของช่องปากตามมาในทุกด้าน ไม่ว่าจะเป็นการพูด การรับรู้รสชาติ การกลืน และการบดเคี้ยว (2) จากการทดสอบเปรียบเทียบประสิทธิภาพของยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปินเทียบกับยาสีฟันผสมฟลูออไรด์ทั่วไป พบว่ากลุ่มที่ใช้ยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปิน สามารถช่วยลดภาวะปากแห้ง รวมทั้งเพิ่มการหลั่งน้ำลายและความชุ่มชื้นของช่องปากได้อย่างมีนัยสำคัญทางสถิติ

ภายในสองสัปดาห์ และมีแนวโน้มที่ดีขึ้นเมื่อใช้ครบสี่สัปดาห์ โดยกลุ่มที่ใช้ยาสีฟันผสมฟลูออไรด์ทั่วไป ไม่พบความแตกต่างเมื่อเปรียบเทียบทั้งภายในกลุ่มและระหว่างกลุ่ม ทั้งนี้ไม่พบรายงานความเสี่ยงหลังจากการใช้งานของยาสีฟันทั้งสองกลุ่ม

สรุปผล: ภาวะปากแห้งสามารถพบได้ทั่วไปในกลุ่มผู้ป่วยสูงอายุเบาหวานประเภท 2 ทั้งนี้ผลการศึกษาชี้ว่ายาสีฟันที่มีส่วนผสมของสมุนไพรรสเผ็ดอาจจะเพิ่มความเสี่ยงการเกิดภาวะปากแห้งที่อาจนำไปสู่ปัญหาของสมรรถนะการทำงานของช่องปาก โดยยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปินสามารถช่วยเพิ่มการหลั่งของน้ำลายและเพิ่มความชุ่มชื้นของช่องปาก นำไปสู่การบรรเทาภาวะปากแห้งได้ ดังนั้น เจ้าหน้าที่ด้านทันตสุขภาพควรมีความตระหนักและติดตามด้านทันตสุขภาพในกลุ่มผู้ป่วยสูงอายุเบาหวานประเภท 2 มากยิ่งขึ้น โดยเน้นด้านภาวะปากแห้งควบคู่ไปกับการดูแลทันตสุขภาพด้านอื่น ๆ และการใช้ยาสีฟันที่มีส่วนผสมของสารสกัดคอร์ไดเซปินถือว่าเป็นผลิตภัณฑ์ใหม่ที่มีประสิทธิภาพและเป็นอีกหนึ่งทางเลือกที่มีความปลอดภัยในการเลือกใช้เพื่อบรรเทาภาวะปากแห้งได้เป็นอย่างดี

สาขาวิชาเวชศาสตร์ปริวรรต
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ลายมือชื่อนักศึกษา_____
ลายมือชื่ออาจารย์ที่ปรึกษา_____
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PANITAN SONPANAO : THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA. THESIS ADVISOR : ASST. PROF. PAIBOON JITPRASERTWONG, DDS, MSc., Ph.D. 239 PP.

Keywords: Xerostomia/ Cordycepin/Diabetes/Elderly/Toothpaste/ Oral health/ Dental health surveys

Aim: To investigate the prevalence of xerostomia in elderly patients with Type 2 diabetes mellitus (T2DM), its impacts on oral function, and to determine potential risk factors for xerostomia, as well as to clinically test a toothpaste containing cordycepin extract for oral health care in elderly with T2DM and xerostomia at Suranaree University of Technology Hospital (SUTH). Methods: (I) An analytical cross-sectional study was conducted on 623 T2DM elderly patients using a valid structural questionnaire. Patients were interviewed and data were recorded. Risk factors for xerostomia were analyzed using bivariate and multiple logistic regression analysis. (II) A randomized clinical trial was conducted on 101 T2DM elderly patients with xerostomia to evaluate over a four-week period the effectiveness of a toothpaste containing cordycepin extract and fluoridated toothpaste on their xerostomia, salivary flow rate, and oral moisture. Results: (I) Among the study participants, 38.4% of the diabetic elderly patients had xerostomia, which was associated with sex, age, type of toothpaste, years of diabetes, hemoglobin A1c level, other systemic diseases, medications, smoking, alcohol consumption, and denture wearing. It was significant that xerostomia was associated with toothpaste containing spicy herbal extracts (OR: 9.32 [3.46 to 15.25]) while toothpaste containing artificial sweeteners tended to lower the risk of xerostomia. In addition, T2DM older adults with xerostomia had greater impaired oral functions which included difficulties in speaking, tasting, swallowing, and chewing. (II) In comparison to the regular fluoridated toothpaste group, cordycepin toothpaste significantly reduced xerostomia, increased salivary flow rate, and improved oral moisture in the second week. The trend remained positive in the fourth week. In the

fluoride toothpaste group, no differences were found with comparisons both within and between groups, and no adverse events were reported.

Conclusions: Xerostomia is prevalent in elderly patients with T2DM. The results suggest that toothpaste containing spicy herbal extracts might increase the risk for xerostomia, resulting in various oral function problems. Additionally, xerostomia sufferers who used cordycepin toothpaste had a tendency to improve saliva production and oral moisture, which could also alleviate the symptoms of xerostomia. Therefore, greater awareness of xerostomia in this group should be raised to monitor dental health and professionals should work in parallel with other aspects of oral health promotion. Also, toothpaste containing cordycepin extract is considered a novel, effective, and secure alternative to xerostomia treatment.

School of Translational Medicine
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Student's Signature _____
Advisor's Signature _____
Co-advisor's Signature _____
Co-advisor's Signature _____

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Panitan Sonpanao

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CHAPTER I

INTRODUCTION

1.1 Thesis title

THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA

1.2 Background and Problems

Oral health is an important part of overall physical health related to the quality of life. Saliva is one of the components needed to support the complete function of the oral organs. The qualitative and quantitative relationship of saliva with oral pathology leading to xerostomia was discussed in a previous study. (Han P et al., 2015).

The prevalence of xerostomia is more common in the elderly people, but it is a high impact condition if occurring in young people. The effects of xerostomia can be discomfort, difficulty in speaking, swallowing, and tasting (Kuthasema P et al., 2010). It can cause oral diseases that affect general health (Thomson WM. et al., 2006). It also affects the quality of dentures, leading to the malnutrition (Narhi TO., 1994).

Dry mouth can cause oral tissue rupture which becomes prone to infection, resulting in the deterioration of oral health. Abnormalities of the salivary glands can occur for many reasons including systemic diseases such as diabetes mellitus, impaired immune diseases such as Sjogren's syndrome, Graft Versus Host Disease, salivary gland infection and inflammation, salivary gland cancer, side effects of radiotherapy and chemotherapy in head and neck cancer, side effects from drug use, and the elderly condition (Ogawa, M. and T. Tsuji, 2015).

Diabetes can directly or indirectly affect the function and structure of the salivary glands, thereby causing insufficient saliva production in the oral cavity.

In 2021, Thailand had 6.1 million people with diabetes, making it the fourth most diabetic country after China, Indonesia, and Japan. In 2021, the International Diabetes Federation (IDF) Western Pacific region estimated that 206 million people (1 in 8 adults) aged 20-79 have diabetes. Adults with diabetes are estimated to number 238 million by 2030, rising to 260 million by 2045. Over 1 in 2 adults living with diabetes are undiagnosed. This is considered the highest number of all IDF Regions, with 2.3 million deaths caused by diabetes in 2021. It is also reported that nearly 541 million adults between the ages of 20 and 79 have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes.

According to the estimation by the IDF, the number of adults with diabetes has increased by 74 million compared to 2019 data (IDF DIABETES ATLAS 9th edition 2019), and 537 million adults (20-79 years old) worldwide have diabetes- 1 in 10. This number is predicted to rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045 based on a 2021 survey. The global prevalence of diabetes is 10.5%, with 44.7% of them undiagnosed of adults (for the Western Pacific region 52.8%). Type II diabetes accounts for about 90% of all people with diabetes. Over 3 in 4 adults with diabetes live in low- and middle-income countries and diabetes was found to be responsible for 6.7 million deaths in 2021 - 1 every 5 seconds. (IDF DIABETES ATLAS 10th edition 2021).

Therefore, diabetes is a major public health problem worldwide, especially in the elderly population. The prevalence of diabetes in all age groups around the world increased from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004). By 2025, two-thirds of people with diabetes are expected to join the elderly population (Rizvi, 2007). The prevalence of diabetes in the Thai population is also high based on the IDF 2021 survey which found that Thai people with diabetes, in 1,000s about 6,066.6 cases by the prevalence of diabetes 11.6% in adults 20–79 years (95% confidence interval 11.5 to 19.5) and the number of Thai adults with undiagnosed diabetes in 1,000s about 39.7% or 2,411.2 cases (95% confidence interval 2,388.5 to

4,043.1) Noticeably, In this diabetic elderly group, xerostomia often follows, which is a major problem that should be overcome.

Nowadays, artificial saliva or chemical drugs are prescribed for relieving xerostomia. However, restoring the function of salivary glands is still challenging. The use of natural herbs as an adjunctive product for tissue regeneration including salivary glands is a fascinating possibility. Chong cao (*Cordyceps militaris*) is one of the most widely known Chinese herbal medicines. It is a fungus belonging to the genus *Cordyceps* and its main biologically active substance is cordycepin (Tuli et al., 2013). Several studies have reported a variety of biological properties of cordycepin including anti-cancer, anti-aging, anti-inflammatory, and anti-oxidant effects (Li XT et al., 2010). In addition, cordycepin may be able to stimulate the function of the salivary glands in the elderly people with xerostomia.

Based on the benefits of *Cordyceps militaris* extracts, Lion Corporation (Thailand) Limited previously collaborated with Suranaree University of Technology conducting research to investigate the effects of *Cordyceps militaris* extract on human salivary gland cells. The study showed the protective effect of cordycepin extracts on these cells by partially decreasing ROS generation. It also restored the expression of salivary proteins, α-amylase (AMY) and aquaporin 5 (AQP5) through its anti-oxidant and anti-apoptotic activities. In addition, the amount of amylase secreted from cordycepin-treated salivary gland cells increased (Jaiboonma, A. et al., 2020). Lion Corporation (Thailand) Limited and Suranaree University of Technology have further expanded their research into producing a toothpaste containing cordycepin extract which is planned for use in diabetic elderly patients with xerostomia to increase the salivation rate.

A previous study on the prevalence of xerostomia among the elderly people in Japan reported that 27.3% complained of xerostomia (Yuki Ohara et al., 2022). Another study in Spain discovered 30.7% complained of xerostomia (Pérez-González et al., 2021). Nevertheless, there are few studies on reducing the prevalence of dry mouth in Thailand. In particular, there have never been any clinical trial conducted in the Nakhon Ratchasima Thai population. Therefore, various conditions relating to xerostomia in Nakhon Ratchasima were investigated including sociodemographic and

health behavior information, oral function, and saliva flow measurement. Moreover, the relationship among the variables that affect xerostomia in the diabetic elderly group were analyzed. Lastly, to carry out a clinical test of oral health care in the diabetic elderly people with xerostomia at the Suranaree University of Technology Hospital, the effect of the toothpaste containing cordycepin extract was determined. The results of our studies will provide useful information to improve the quality of life of the diabetic elderly people suffering from xerostomia.

1.3 Research gap

Although artificial saliva or medication are currently used to treat xerostomic patients, rescuing the salivary gland function is still limited due to glandular damage. The use of cordycepin extracts for improving the function of the salivary gland is promising but still rare. This herbal extract may increase the amount of saliva secretion in the elderly people with xerostomia and is used as an adjunctive therapeutic approach. Moreover, there is no relevant study in the Nakhon Ratchasima Thai population involving xerostomia and its related factors. The clinical tests on toothpaste containing cordycepin extract have also been not conducted on diabetic elderly patients with xerostomia.

1.4 Research questions

1. What is the prevalence of xerostomia in diabetic elderly patients and its related factors?

2. Can cordycepin extract containing toothpaste increase salivation in diabetic elderly patients with xerostomia?

1.5 Research objectives

The primary objectives of this study were:

1. To investigate the prevalence of xerostomia and its impacts on oral functions, as well as determine potential risk factors for xerostomia in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital.

2. To clinically test the effects of toothpaste containing cordycepin extract on increasing salivation in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital.

1.6 Research hypotheses

The hypotheses of this study follow two objectives:

1. Sociodemographic and health behavior, oral function in diabetic elderly patients will be associated with xerostomia.

2. Diabetic elderly patients with xerostomia who receive the toothpaste containing cordycepin extract will have a statistically significant increase in salivation compared to the control group (diabetic elderly patients with xerostomia who receive the regular fluoridated toothpaste).

1.7 Scope and limitations of the study

In this study, the surveyed population group is diabetic elderly patients who come to receive service in the non-communicable diseases (NCDs) clinic at the Suranaree University of Technology Hospital in 4 successive months (December 2021-March 2022).

104 people will be selected and then will be divided into a treatment group and a control group. Each group will have 52 people; the treatment group receiving standard treatment with toothpaste containing cordycepin extract; the control group receiving standard treatment with normal fluoridated toothpaste).

To compare the results at different periods, saliva secretion will be measured at 3 time points; before the clinical test (baseline), at 2 weeks, and at 4 weeks.

For the survey study:

Inclusion criteria

1. Type II diabetic elderly patients (50 years and older) who come to receive service at the Suranaree University of Technology Hospital from December 2021 to March 2022

2. Patients who were in-patients diagnosed with type II diabetes mellitus by a medical doctor and have an appointment with a doctor

Exclusion criteria

1. Patients who were diagnosed with a mental disorder by a medical doctor

2. Patients who refuse to fill out the consent form

For the clinical test study:

Inclusion criteria

1. Type II diabetic elderly patients (from the first part: Survey population) that have given informed consent

2. The lack of other systemic diseases or oral diseases related to infection

3. Patients who were classified as xerostomia by assessment questionnaire on xerostomia

4. No use of antibiotics or any other mouthwash for 2 weeks before the clinical test

5. No history of drug allergies, nor allergy to *Cordyceps,* nor allergy to any herbal extracts

6. No use of artificial saliva

7. No history of ever receiving radiation therapy for the head or neck

Exclusion criteria

1. Patients who need to receive antibiotics during experimental treatment

2. Pregnant women

3. Smoking

1.8 Expected results

Toothpaste containing cordycepin extract can relieve xerostomia. After the experiment with toothpaste, the saliva secretion rate of the treatment group was higher than before the experiment, it increased more than that of the control group, and there were no adverse events in the treatment group.

CHAPTER II

LITERATURE REVIEWS

The literature reviews of this study are relevant to the research topic. I divided them into various topics, including: 2.1) salivary glands, 2.2) Xerostomia, 2.3) Oral health problems in Thailand, 2.4) Diabetes mellitus, 2.5) The prevalence of diabetes in Thai adults, 2.6) Cordycepin, 2.7) Related research, 2.8) Summary, 2.9) Conceptual framework, and 2.10 Study flowchart.

2.1 Salivary glands

Salivary glands are a type of exocrine gland. Usually, they are found in various organs of the digestive tract, especially in the oral cavity. They can also be found in various organs with mucous membranes, such as the genitals, respiratory organs. The salivary glands found outside the mouth will be found very rarely. Therefore, salivary glands usually refer only to oral salivary glands.

In the oral cavity, the salivary glands are responsible for the production of saliva, which is digestive juice for starchy foods and contain a type of enzyme called Amylase as well as mucus for lubrication. Salivary glands consists of 2 groups: Major salivary glands and Minor salivary glands. Major salivary glands are found outside the oral cavity and are responsible for secreting the most saliva, accounting for about 80% of the total saliva. They consist of 3 pairs of glands: the parotid glands that produce and secrete serous saliva, the submaxillary or submandibular glands under the chin, which produce and secrete both serous and mucous saliva, and finally, the sublingual glands which produce and secrete both serous and mucous saliva, but produce predominantly the mucous type (Thaihealthlife, 2018).

Each salivary gland has different acinar cells that produce saliva. The saliva of each gland is different. For example, serous acini cells secrete serous saliva while

mucous acini cells produce mucous saliva. Minor salivary glands are glands that produce and secrete a lesser amount of saliva by secreting saliva only when resting to keep the mouth moist. This type of salivary gland is small and can be found inside the oral cavity. These include the palate, cheeks, under the tongue, and lips.

Major salivary glands have 3 pairs on the left and right sides, consisting of:

1. Parotid glands are the largest salivary glands, measuring 4 x 4 cm. They produce about 20% to 25% of total saliva in the salivary glands and are found on the face in front of both ears. There are open salivary ducts called the Parotid ducts in the buccal bulge at the level of the second molar. The glandular structure has a thick collagenous capsule into which connective tissue septa are inserted and divided into lobes and lobules. The secretory unit contains only serous cells. A large number of intercalated ducts are mixed with the larger striated ducts. In addition, adipose tissue has been found to be mixed with the glands. These glands are the most common of all the salivary glands, in conditions such as mumps, to become swollen.

2. Submandibular glands are glands located below the jawbone, approximately 3x1-2 cm. in size. They produce about 70–75% of the total saliva and produce both mucous saliva and serous saliva, but the most serous saliva. With the salivary ducts open to the oral cavity in the sublingual region, the glandular structure has a thick coat of colloidal capsule. From each gland, there is a main duct that extends forward and medially, passing through the opening in the sublingual papillae on two sides of the frenulum. The tongue area has a secretory unit made up of mostly serous cells and a small number of mucous cells. They have a striated duct that is longer than the intercalated duct, and the intercalated duct smaller than the parotid glands.

3. Sublingual glands are smaller in size than the parotid and submandibular glands. They produce mucous saliva and serous saliva, but mucous saliva is the most abundant. These are classified as mixed seromucous glands, and are in the middle of the face, located on the sublingual floor of the mouth, in which the two jawbones meet. The size is variable, and they produce approximately 5% of the total amount of saliva. They have many small ducts opening into the submandibular duct and

some ducts opening into the floor of the mouth. The glandular structure is a secretory unit that consists mainly of mucous cells and some parts are pure mucous. While the structure does not have capsules, there is a loose connective tissue that forms the glandular tissue into lobes and lobules. They have a short intralobular duct and a small number of striated ducts.

A salivary duct opens into the oral cavity under the tongue in a position close to the submandibular glands with multiple salivary ducts. Minor salivary glands are salivary glands that have no name. They are very small, about 1-2 mm. Short ducts that open directly into the oral cavity are widely distributed in the oral cavity, which may have up to about 800-1,000 glands. They are widely distributed in the submucosa and produce the remainder of the total saliva, accounting for approximately 2-5%.

Location of the salivary glands is shown in Figure 2.1

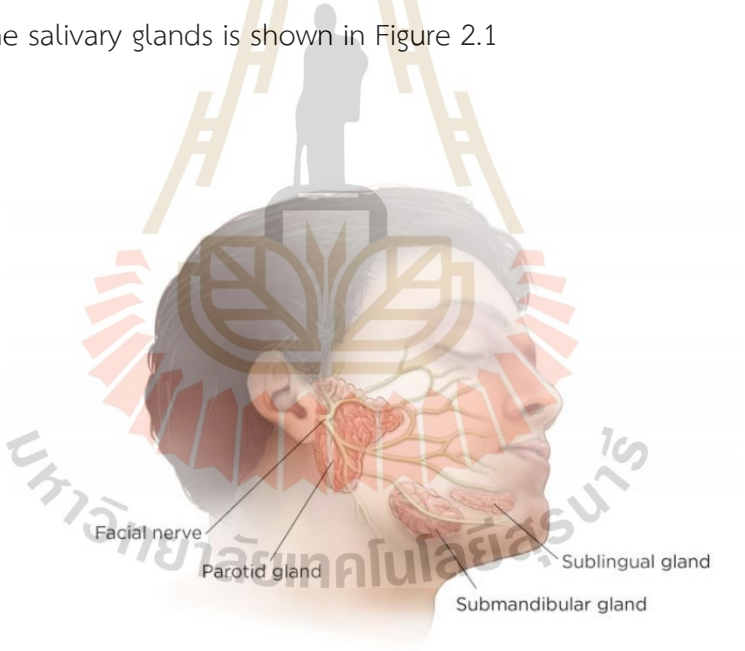


Figure 2.1 Location of the salivary glands**.**

(Memorial Sloan Kettering Cancer Center., 2020)

Characteristics of the salivary glands

Salivary glands are covered with connective tissue structures called interlobular connective tissue septa, and there are connective tissue inserts that divide the glandular tissue into segments called lobes and are inserted into smaller segments called lobules. This connective tissue has the direct function of sustaining the gland and serves as a passage for the glandular ducts that extend into the oral cavity, as well as a home for the blood vessels and nerves that nourish the cells of the salivary glands. The main structure of the salivary glands is divided into two parts: the secretory unit and the duct system.

1. Secretory Unit

The structure of the salivary glands is primarily responsible for the production and secretion of saliva. The tubular part of the gland structure and the alveolar part, but mainly alveoli (alveolar), which are divided into serous alveoli and mucous alveoli.

Serous alveoli

The cells in the serous alveoli are pyramid-shaped, with wide basal cells and narrow terminal cells. The top of the cells usually has a tiny lumen, which can be used as a means to transport the secretions of serous cells. Serous alveoli have basal cells on the basal lamina. The cell edges are clear. There is a nucleus towards the cell base, a cytoplasm at the base, and around the nucleus are colored basic dyes. When viewed with a microscope, you will see the rough endoplasmic reticulum nested and mitochondria are inserted. The apex contains some zymogen granules. These zymogen granules can be stained by the PAS technique. This indicates that the granules are acidic.

Between the basal surface in the serous cells and the basal lamina, there are myoepithelial cells that surround the processes. In alveoli processes, they stick together like baskets called "basket cells." If they are contracted, it will help to expel secretions from the alveoli and pass them on to other ducts further along.

Mixed salivary glands have serous cells, arranged like a crescent. Covered at the end of the mucous alveolus, which are characteristic of mixed salivary glands, by

secretions released from serous cells, they pass through the small ducts between the mucous cells and enter the ducts of the mucous alveoli.

2. Duct System

The structure of the salivary glands is where the salivary ducts are located and can deliver saliva into the oral cavity. This structure exists both inside the glands and outside the glands. Salivary ducts in the glands near the secretory unit, which are the first ducts from the glands, are called intercalated ducts. The saliva from these ducts the passes into larger ducts called the striated ducts. Both the intercalated ducts and the striated ducts are classified as inner gland ducts, called intralobular ducts, that are inserted into the lobules. The saliva then passes into the larger ducts. The outer glandular ducts, called interlobular ducts, are inserted into the lobes and pass saliva into the main duct, which is the largest in the oral cavity. The striated duct is the first duct that carries saliva from the simple cuboidal epithelium ducts.

- Intercalated ducts that follow the striated duct are covered with a simple cuboidal epithelium. There is a nucleus in the middle of the cell. The cytoplasm can stick to dark colors in general. The inside of the cytoplasm has a striped insert called basal striation, with a concave basal membrane inserted into the cytoplasm and mitochondria inserted into it.

- Interlobular ducts are larger ducts that are covered with simple columnar epithelium membranes and will transition to pseudostratified epithelium.

- Main ducts are ducts lined with stratified columnar epithelium membranes, and near the opening into the oral cavity, they become stratified squamous epithelium. Diseases of the salivary glands often occur with parotid glands, with very rare diseases of other glands, especially minor salivary glands. The most common disease of the salivary glands is mumps. In addition, some bacterial salivary gland inflammation, salivary gland stones, tumors, and salivary gland cancer can also be found.

Saliva is a solution secreted in the oral cavity by the salivary glands. It performs important functions, such as: helping lubricate the oral mucosa and esophagus, containing bicarbonate and phosphate to act as pH buffer, helping

cleanse the mouth through the presence of macromolecule proteins and mucin that bind to the oral cavity bacteria, thereby preventing the formation of plaque on the tooth surface. Saliva also contains calcium, phosphate, and protein, acting together as a control substance for demineralization and remineralization help maintain the structure of the teeth. In addition, saliva also contains immunoglobulins, antimicrobial bacterial peptides, and enzymes which help prevent the growth of bacteria. Saliva also contributes to taste and digestion. (Miranda-Rius J et al., 2015).

Abnormal salivary glands can be found for many reasons, including systemic diseases, such as diabetes mellitus, impaired or abnormal immune diseases such as Sjogren's syndrome, Graft Versus Host Disease, infections, inflammation of the salivary glands, salivary gland cancer, side effects from radiation therapy and chemotherapy in the treatment of cancers of the head and neck, side effects from drug use, and elderly conditions (M. Ogawa, T., 2015).

When the salivary glands are damaged, dysfunction will lead to insufficient saliva secretion and xerostomia, or dry mouth. The condition can cause complications such as dental caries, gum disease, and periodontitis; oral yeast infection; discomfort in the mouth due to oral ulcers; inflammation of the mouth tissue; taste changes; difficulty chewing, swallowing, and speaking. This can reduce the quality of life of the patient. (S. D. Tran et al., 2006).

In general, the flow rate of stimulated saliva is an average of 1.5-2.0 ml/min while unstimulated saliva averages 0.3-0.4 ml/min (Villa A et al., 2014) with high individual differences (Mese H, Matsuo R.2007). Furthermore, there is no set standard for how much saliva is required for each individual. Xerostomia is diagnosed only when the flow rate of stimulated saliva is less than or equal to 0.7 ml/min and the flow rate of unstimulated saliva is less than or equal to 0.1 ml/min. (Farsi NM., 2007).

Circadian rhythms in human salivary flow rate

Circadian rhythms are natural 24-hour oscillations that are self-sustaining and regulated by internal components referred to as "clock" transcription factors. They control a variety of physiological and metabolic processes. Saliva bathes the mouth cavity, and both its volume and composition change on a daily basis (Zheng L et al., 2012). The circadian clocks found in mammals regulate a number of physiological processes, including body temperature, sleep-wake cycles, and liver metabolism. The suprachiasmatic nuclei (SCN), which function as the system's core clock, coordinate the activities of peripheral clocks found in numerous peripheral organs. Circadian rhythms are known to be influenced by this system as well as biological processes, including the immune system and metabolism (Nakao, A., 2014).

The rhythm of human preference for timing sleep and wakefulness in relation to the 24 hour solar day determines whether a person is a morning or evening person-or their chronotype (Roenneberg, T. et al., 2003). Saliva flow, salivary protein concentration, and electrolytes have a circadian pattern and are essential in maintaining and protecting oral health (González-González, J.M., 2018). Saliva flow is weak in the morning, increases in the afternoon, and then decreases (Nishide, S. et al., 2019). The circadian rhythm of the salivary glands plays a vital role in controlling food intake and the immune system because it affects the flow of saliva and the ionic composition (Feng, G et al., 2022). Changes in saliva flow and composition can affect oral health, as saliva helps to neutralize acids produced by oral bacteria, remineralize tooth enamel, and lubricate the mouth (Buzalaf, M.A.R. et al., 2012).

2.2 Xerostomia

Saliva is a secretion produced by the salivary glands. Then it enters the oral cavity through the exposed area of the salivary ducts. Salivary gland cells are very sensitive to the condition of the oral cavity and teeth. They play an important role in helping digestion, lubricating the oral organs, preventing dry mouth, helping with the movement of the tongue, helping to speak clearly and having a good buffering ability. keep the oral cavity and tooth surface in balanceThey also have an oral antimicrobial role and help with the digestive system. (Kobkan, 2009).

Xerostomia occurs for several reasons that cause the flow of saliva to decrease: the pathology of the salivary glands, loss of water and minerals in the body, dehydration, elderly patients, smoking, radiation exposure, or cancer of the head and face causing the salivary glands to lose their function. This is because the salivary glands are usually located in radiation-exposed areas, and the cells of the salivary glands are very sensitive to radiation. Chemotherapy in the treatment of cancer and various systemic diseases, especially Sjogren's syndrome, has the effect of making the salivary glands less active. Dry mouth can also be caused as a side effect of drugs that the patient is receiving in the treatment of other systemic diseases. (Kobkan, 2009).

Xerostomia is one of the major risk factors for developing oral disease conditions, and it affects a person's lifestyle significantly. (MS Hopcraft, C Tan, 2010). This is a disease that can occur at any age (Thomson WM et al., 2006) It can cause many cases of taste disorder or loss of taste through factors such as reduced salivary gland activity, underlying diseases, side effects of oral medications, and exposure to radiation from head and neck cancer, etc. (Han P et al., 2015). The average prevalence of dry mouth in the general population is between 10% and 46%. Women have a higher prevalence rate than men, and the prevalence rate is higher in the aging population. (MS Hopcraft, C Tan, 2010).

Patients with diabetes, the elderly, and those undergoing radiation therapy for head and neck cancers should be particularly concerned about xerostomia. Diabetic rats had considerably lower SMG weight, which decreased salivary secretion (Bhattarai, K. R. et al., 2017).

The symptoms of xerostomia can be permanent or transient (Hay DK, Morton RP., 2006). Medicines are the main cause of transient xerostomia (Thomson WM et al., 2006). Permanent xerostomia is usually caused by radiation treatment for head and neck cancers (Bruce S.D., 2004). Symptoms are often found at night. This is because the saliva flow is low and it is found together with sleep and mouth breathing. (Gupta A et al., 2006). They may also be associated with dryness of the lips, throat, eyes, and nose (Villa A, Abati S., 2014).

Clinical characteristics

A decrease in the amount of saliva in the oral cavity causes the oral cavity to dry, which may result in the patient having only a dry mouth, or there may be other symptoms such as dry eyes or other dry tissues, loss of oral protection from the buffering system, oral tissues being more easily infected, and difficulty speaking, eating, and swallowing. There may be ulcers and pain in the oral cavity, malfunctioning taste buds or loss of taste. Dental caries are easy to occur, especially in the cervical area. This figure shows complications in the oral cavity of a patient with xerostomia, as shown in Figures 2.2 and 2.3 below.

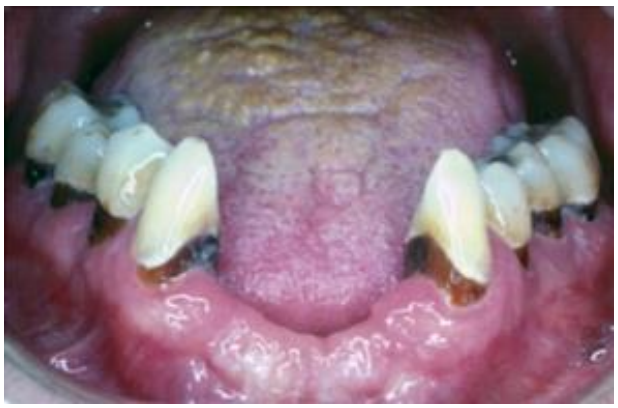


Figure 2.2 Cervical caries in patients with xerostomia after radiotherapy.
(Neville, B. W et al., 2016).

Figure 2.3 Fungal infection in patients with xerostomia.
(Glick, M., 2015).

Symptoms of xerostomia

Symptoms of xerostomia are common in daily life. It is usually caused by dehydration or anxiety, but the symptoms of xerostomia continue to occur. It can be a sign of some diseases and illnesses. There may be other symptoms that occur as well and are common, such as

-Thirst

-Dry, sticky mouth

-Having mouth ulcers

-Sores or cracks in the corners of the mouth, chapped lips.

-Dry, rough, or red tongue

-A stinging or tingling sensation in the mouth, especially on the tongue

-Sore throat

-Hoarse voice

-Bad breath

-Dry nose

-Problems with speech or taste perception

-Problems with chewing and swallowing

-Trouble wearing dentures

If these symptoms persist or do not improve, consult a dentist.

Causes of xerostomia

- Dehydration can be caused by factors or illness with conditions such as not drinking enough water, loss of sweat, vomiting, diarrhea, blood loss, fever, or burns.

- Drug-related side effects: Medicines that commonly cause this condition include drugs for depression and anxiety disorders, as well as medicines for high blood pressure, antihistamines, muscle relaxants, painkillers, and mucus-reducing drugs (Health Education Division, 2019). A variety of drugs can cause xerostomia, including tricyclic antidepressants, beta blockers, diuretics, antipsychotics, and anticonvulsants (Ian N Olver., 2006). I can categorize xerogenic medications into different groups, as shown in Table 2.1

Table 2.1 Xerogenic medications, classified by categories.

Category	Name of the Drugs	References
Anticholinergics	Atropine, scopolamine	Shetty, S. R.,et al (2012) Vinayak, V., et al (2013)
Antidepressants	Amitriptyline	Shetty, S. R.,et al (2012) Vinayak, V., et al (2013)
Antihistamines	Diphenhydramine, chlorpheniramine	Shetty, S. R.,et al (2012)
Antihypertensive	Reserpine, methyldopa, chlorothiazide, furosemide, metoprolol, calcium channel blockers	Shetty, S. R.,et al (2012) Vinayak, V., et al (2013)
Antipsychotics	Haloperidol, phenothiazine derivatives	Shetty, S. R.,et al (2012) Vinayak, V., et al (2013)
Decongestants	Pseudoephedrine	Shetty, S. R.,et al (2012)
Diabetic medications	Metformin	Punit H.,et al (2002) John F Burd.,et al (2018) Kathleen Fenn., et al (2020) M.S. Abdallah., et al (2020)
	Insulin	Bai KY., et al (1995) Vinayak, V., et al. (2013)
	Sulfonylurea	Villa, A., et al. (2014)
	Thiazolidinedione	Saroka, Rachel M., et al. (2015)
	Alpha-glucosidase inhibitor	Garg, A., et al. (2018)

- Side effects from the underlying disease: Such as cerebrovascular disease, high blood pressure, Parkinson's disease, anemia, diabetes, rheumatoid arthritis, cystic fibrosis, oral infection, Alzheimer's disease. This issue includes immune system diseases, such as HIV infection and Sjogren's syndrome.

- Cancer treatment: Chemotherapy can affect saliva production, but it may only happen during treatment. As for radiation therapy, if the patient has been irradiated around the head and neck, which may damage the salivary glands and may be permanent or transient. It depends on the radiation dose and the area to be treated.

- Nerve damage: Surgery or injury to the head and neck can result in nerve damage that can cause dry mouth.

- Drug abuse: If you smoke or drink alcohol, including drugs, this can severely dry your mouth and damage your teeth, such as methamphetamine or cannabis.

- Weather

- Age-related changes: Elderly people have a tendency to have dry mouth due to drug use, body changes, underlying disease, and insufficient intake of nutrients. (Health Education Division, 2019).

There are ways to take care of yourself when your mouth is dry, including:

- Drink more water. You should sip cold water or sip unsweetened drinks.

- Suck on candy or chew sugar-free gum to help stimulate the salivary glands to produce more saliva.

- Suck on ice cubes, because the ice will slowly melt in the mouth and add moisture to the mouth.

- If your lips are dry and cracked, as well, you should nourish the lips with products that contain moisture.

- Avoid beverages containing alcohol and caffeine and don't smoke, because it will make the symptoms of dry mouth worse.

-The drugs used to treat xerostomia depend on the cause.

- Change drugs used to treat diseases. If the doctor determines that the drug the patient is taking is causing xerostomia, the doctor may adjust the dose or change to another drug.

- Use prescription and over-the-counter products to moisturize the mouth, such as artificial saliva, mouthwash, or oral moisturizers, including sprays, lozenges, and gels.

- Use drugs to stimulate saliva production. The doctor may have prescribed pilocarpine, which stimulates saliva production. It is often used in patients with dry mouth from radiation therapy or patients with Sjögren syndrome, but this drug can cause side effects such as headaches or sweating, so patients should always use the drug under the supervision of a physician.

In addition, xerostomia increases the risk of dental caries. The doctor may give the patient protection against dental caries with fluoride. Alternatively, a chlorhexidine mouthwash may be recommended.

Complications of xerostomia

Xerostomia can lead to complications such as dental plaque, dental caries, gingivitis, mouth sores, fungal stomatitis, ulcers, or cracks in the corners of the mouth, chapped lips, difficulty wearing dentures, and a lack of good nutrition because there are problems with chewing and swallowing, etc.

Treatment and management of xerostomia

Treatment for xerostomia requires trying to identify and eliminate the cause. For patients receiving multiple drug treatments, it may be necessary to consult a doctor to modify the drugs or reduce the dosages to try to control their oral health and prevent dental caries and oral yeast infections. Patients should avoid factors that can cause dry mouth, such as too hot and dry environments, smoking, solid foods, alcohol consumption, oral breathing, and should drink water frequently or use artificial saliva, or eat sour foods to stimulate saliva flow. (Kobkan, 2009)

From this study, I defined "standard treatment" as "the standard of treatment for normal type 2 diabetic patients who received the same treatment for all cases, equally and according to their suitability as an individual, which consists of having been examined and evaluated for diabetes treatment, assessment, and control of risk factors to prevent or reduce the occurrence of long-term conditions or complications." Complications are detected in the early stages, before showing symptoms, in order to provide appropriate treatment. When complications occur,

they are referred to specialists for treatment according to the stage of the disease. Type 2 diabetic patients need to see a health educator, a nurse, and/or a dietitian to review the understanding of cooperation and participation in treatment, for motivating and empowering for self-care properly and consistently. Patients should have diabetes awareness, maintenance methods, treatment cooperation, as well as being able to practice self-care properly and continuously. They should have a diabetic patient's handbook with knowledge about diabetes and patient self-care along with recordings of the patient's health data such as weight, waist circumference, blood sugar levels, blood lipid levels, blood pressure, medications, etc. This includes explaining to patients the importance and benefits of having a diabetic patient's handbook. In terms of dental health, dentists or dental public health officers conduct oral health assessments on patients with xerostomia at least every 6 months and must receive dental hygiene education to practice alleviating symptoms of xerostomia or to receive xerostomia medications as recommended by the dentist on a case-by-case basis.

2.3 Oral health problems in Thailand

The rapid changes in Thailand's population structure in the past 3-4 decades resulted in the country becoming an aging society. From about 2000 to 2001, approximately 10% of the total population was 60 or older people. In addition to the increase in the proportion of the elderly people, there is another indicator that shows a step towards an aging society, the aging index. This is a comparison of the substitution structures of the elderly population (aged 60 years and older) with the childhood population (under 15 years). If the aging index is lower than 100, then the elderly population is less than the number of children, but if the aging index is greater than 100, then the elderly population is greater than the child population. (Office of the Permanent Secretary for Social Development and Human Security., 2014).

According to the World Health Organization's survey in 1998, it was discovered that over 390 million people were over the age of 65, with the number predicted to double by 2025. (Petersen, P.E., 2003).

The proportion of elderly people in Thailand is increasing and already accounts for more than 10% of the population. They estimate that by 2025, there will be around 14.9 million senior Thais, with practically every family having at least one person aged 60 and older.

The situation of the elderly people in Thailand

According to a survey conducted by the Department of Older Persons in Thailand in 2016–2021, it was found that the number of elderly people (60 years old and above) was increasing every year (Department of Older Persons, 2016–2021). Details in Table 2.2

Table 2.2 Number of the elderly people (60 years and older) in Thailand, Year 2016-2021.

Year	Population	Number of elderly people (60 years and older)			Percentage
		Male	Female	Total	
2016	65,931,550	4,479,138	5,455,171	9,934,309	15.07
2017	66,188,503	1,252,099	1,691,531	10,225,322	15.45
2018	66,413,979	4,715,598	5,951,205	10,666,803	16.06
2019	66,558,935	4,920,297	6,215,762	11,136,059	16.73
2020	66,186,727	5,130,363	6,496,767	11,627,130	17.57
2021	66,171,439	5,352,987	6,773,029	12,126,016	18.32

However, if the number of elderly people (60 years and older) is classified into various regions in Thailand, it was found that from 2016–2021, the regions with the highest number of elderly people are the Northeast, Central, North, South, and Eastern regions, respectively. (Department of Older Persons, 2016-2021). Details in Table 2.3

Table 2.3 Number of elderly people (60 years and older) in Thailand, 2016-2021, classified by region.

Region/Year	Number of elderly people (60 years and older)s						Order
	2016	2017	2018	2019	2020	2021	
North	2,000,301	2,093,071	2,188,417	2,287,470	2,389,870	2,484,708	3
Central	2,887,109	2,943,630	3,074,743	3,215,275	3,357,878	3,122,898	2
Northeast	3,117,763	3,250,975	3,386,357	3,532,115	3,684,395	3,827,823	1
South	1,238,476	1,280,914	1,330,498	1,382,155	1,440,608	1,495,301	4
Eastern	690,660	656,732	686,788	719,044	754,379	789,878	5

Considering the number of elderly people (60 years and older) in 2016-2021 divided by Regional Health 9, which consists of four provinces, which are Nakhon Ratchasima, Chaiyaphum, Buriram, and Surin, it was found that the provinces with the highest number of elderly people were Nakhon Ratchasima, Buriram, Surin, and Chaiyaphum, respectively. See Table 2.4 for details.

Table 2.4 Number of elderly people (60 years and older) in Thailand, 2016-2021, classified by regional health 9.

Regional Health 9	Number of elderly people (60 years and older)						Order
	2016	2017	2018	2019	2020	2021	
Nakhon Ratchasima	400,496	417,303	435,347	453,388	473,457	494,173	1
Chaiyaphum	181,589	188,874	195,784	203,237	211,820	220,041	4
Buriram	223,999	233,177	242,102	251,206	261,571	271,556	2
Surin	201,558	208,995	216,188	224,364	233,657	242,780	3

According to the findings of Thailand's 8th National Oral Health Survey in 2017, they discovered that adults aged 60-74 and 80-85 made up 56.1 percent of the 60–74 year-old age group, with at least 20 permanent teeth, an average of 18.6 teeth per person, and at least four pairs of posterior teeth, accounting for 40.2 percent. Only 22.4 percent of people aged 80–85 have at least 20 permanent and active teeth, with 10 teeth per person on average and 4 pairs of occlusions accounting for 12.1 percent. This results in a significant decrease in chewing efficiency. Although the early elderly group more than half, they have 20 active permanent teeth, but the remaining permanent teeth still have problems, lesions, and abnormalities in the oral cavity that need proper care, to prevent the spread leading to pain and loss of teeth, What are the important problems of tooth loss, especially tooth loss that occurs in the mouth.

This proportion is 8.7 percent among the elderly aged 60–74, but rises to 31.0 percent among the elderly aged 80–85, affecting quality of life. In addition, 52.6 percent were found to have untreated cavities. In older people, the prevalence of root caries associated with gingival recession was 16.5 percent. Periodontitis destroys the tissue that supports the root canal by destroying 36.3 percent of the bone. Severe periodontitis affects 12.2% of the population. (The periodontal groove starts at 6 mm). In addition to the risk of inflammation, discomfort, swelling, infection, and tooth loss, it is also linked to the severity of diabetes. The aforementioned issues can be avoided by leading to suitable and healthy behavior. In terms of oral cavity

cleansing, they both discovered that the elderly people brush their teeth without eating anything before going to bed, and 53.7 percent of them are used to tooth brushing accessories. These include dental floss and interdental brushes, which accounted for only 4.1 percent and 1.9 percent of those who received dental treatments in the previous year, respectively, and 38.6 percent of those who received dental treatments in the previous year. 12.3 percent of those seeking this service do so due to tooth discomfort or hypersensitivity.

Dental preservation is complicated. Many steps that prevent older people from continuing to receive services may eventually lead to tooth extractions. Hence, these issues should be focused on in the elderly group, besides communicating knowledge to understand and be aware of correct self-care for oral hygiene. The main channels through which the elderly group access and receive the most information are communication through public health personnel (54.7%) and television media (36.2%), including support to attend an annual oral health examination, which is 8.4% in this survey. And they received treatment from the first stage. The purpose was to reduce the risk of tooth loss through partial dentures and complete dentures to replace the lost permanent teeth (Report of the 8th National Oral Health Survey in Thailand., 2017).

Oral health care for the elderly people to prevent such problems is very important. The oral problems of the elderly group include teeth that have been used for a long time or older teeth, gingival recession in the cervical area, resulting in gaps between the teeth, and food residues that are easy to adhere to. This includes having less saliva or xerostomia. Risk factors for dental caries and periodontal disease in the elderly people include several factors, such as a removable partial denture, nutritional status associated with a high intake of starchy and sugary foods, and limitations in accessing dental services due to travel inconveniences, physical condition, and cost. The lack of coverage by the dental care facility, lack of transportation, and poor oral hygiene due to changes in the body and muscle strength make it impossible to take care of your oral health by yourself. This can be seen from the significant decrease in brushing efficiency. Cleaning the oral cavity for the elderly people are an important, simple, and effective oral hygiene measure that

can prevent both dental caries and periodontal disease and is included with conditions like hyposalivation and xerostomia, or dry mouth. (Thomson, W., 2015).

According to a survey of dry saliva conditions in the age group 60-74 years old in Thailand, eating dry food and having to drink water immediately was 21.50 percent, 8.6 percent had dried tongue attached to the palate frequently, 16.5 percent had oral feeling dry, and 4.8 percent had mouth Mirror Stuck. (Report of the 8th National Oral Health Survey in Thailand., 2017).

2.4 Diabetes Mellitus

Diabetes mellitus is a condition in which blood sugar levels are higher than usual (hyperglycemia) for extended periods of time, either by pancreatic failure to produce enough insulin hormones or by cells in the body failing to respond to the hormone insulin (insulin tolerance) (Bascones et al., 2011). Insulin is a hormone involved in the regulation of blood sugar balance, (especially glucose). Insulin is introduced into the cells in order for sugar to be used as an energy source, for metabolic processes, and to lower blood sugar levels to normal levels (Landsberg L, 1985 and Newsholme EA, 2001). Diabetes is a chronic disease related to metabolic disorders and is still a major public health problem in Thailand (Chatchalit, 2014).

Diabetes causes numerous noticeable symptoms initially, including thirst, polyuria, impaired eyesight, and weight loss. Diabetes-related hyperglycemia affects many different bodily systems and is a primary cause of several serious disorders, such as strokes and heart block. Eye issues are another risk factor for blindness. Diabetes can lead to renal failure owing to damage to the capillaries in the kidneys, easy wound formation, slow blood clotting, and the patient may develop joint infections which may necessitate amputation to preserve the patient's life. The breakdown of nerves reduces the awareness of many organs. (Brod M et al., 2011).

Type of diabetes

Diabetes can be in numerous forms, and the diagnosis is based on blood sugar levels. Diabetes can be classified into the following types:

Type I diabetes is caused by the pancreas' failure to generate the hormone insulin. This occurs when the body's immune system destroys a group of cells known as beta-cells in the pancreas in an autoimmune reaction. This is the most frequent type of diabetes from infancy to early adulthood. It is hypothesized that the mechanisms for type I diabetes are genetically linked to the immune system. (Chiang JL et al., 2014). Regular intravenous insulin injections are used to treat this group of individuals. This replaces the hormone insulin no longer being produced by the pancreas and restores normal blood sugar levels.

Diabetes mellitus type II is a condition in which cells in the body do not respond to the hormone insulin. This means that the pancreas still produces insulin,

but the cells in the body do not respond to that insulin. As a result, blood sugar levels are still high and persistent. It is different from the characteristics of type I diabetes and is found to account for about 90% of all diabetic patients. This is most common in people over the age of 40, but nowadays, patients with type II diabetes appear more in childhood and adolescence. Diabetes mellitus type II has been found to be linked to obesity (Sanchai T, 2011).

There is also diabetes mellitus in women who are pregnant, known as gestational diabetes mellitus, which is found in women who are pregnant without a history of having diabetes symptoms. However, after pregnancy, people's long-term high blood sugar levels continue to develop and may progress to type II diabetes. (Metzger BE, 1998). Diabetes is also a risk factor for pregnant women over the age of 40. Diabetes is currently seen in around 1 in every 6 pregnant women. Diabetes in pregnant women is caused by insulin resistance (Peter JD, David MH., 2010).

Gestational diabetes mellitus affects both the mother and the child. High blood sugar levels can cause issues like high blood pressure during birth, macrosomia, and there is a potential for congenital defects to affect the baby's brain development. Both mothers and babies are at risk of developing type II diabetes in the future. (Group HSCR et al., 2008).

Another type of diabetes may be called covert diabetes mellitus type I (latent autoimmune diabetes in adults). Patients in this group showed symptoms of type I and type II diabetes. This group of patients accounts for about 10% of the total number of patients with type II diabetes syndrome. (Spijkerman AM et al., 2003). The pre-diabetes stage is the stage in which a doctor determines that a person may be at risk of developing diabetes because their blood sugar levels are higher than normal, which may be called a well-balanced state (blood sugar levels in the range of 110-126 milligrams per deciliter as measured during the fasting period) (Spijkerman AM et al., 2003). Doctors typically offer activity measures, including exercise and nutrition, to those who have been diagnosed with pre-diabetes to prevent or reduce the chance of acquiring diabetes in the future.

Diabetes diagnosis

The criteria for diagnosing diabetes are now different from the original criteria used by the World Health Organization; WHO in 1985. (World Health Organization, 1985). Currently, there are two methods: Method 1: assessing blood sugar levels while fasting, with patients fasting for 8–12 hours before the blood glucose test. Normal people have a blood sugar level of fewer than 110 milligrams per deciliter. (Normal levels vary from 70 to 110 milligrams per deciliter.) Pre-diabetes patients in a well-balanced condition have glucose levels ranging from 110 to 126 milligrams per deciliter. Diabetes is diagnosed when the blood sugar level surpasses 126 milligrams per deciliter. The test, however, must be repeated to validate the outcome. The second technique is to validate diabetic outcomes. (World Health Organization, 1999).

Method 2: Oral glucose tolerance test (OGTT): The OGTT is administered by drinking a glucose solution with a dry glucose weight of 75 g. This procedure is known as "oral glucose loading," and the blood glucose level is evaluated before and 2 hours after drinking the glucose solution (2-hour post-load glucose).

In children, 1.75 grams of glucose are used per kilogram of body weight. If the glucose level is greater than 200 mg/dL 2 hours post-load, the OGTT is considered positive. (Conn JW., 1958). The blood sugar level is used as the basis for diagnosing diabetes as shown in Table 2.5

Table 2.5 Diagnose the blood glucose level of diabetes by measuring the blood glucose level under fasting state and oral glucose tolerance test; OGTT.

Level of blood sugar in the fasting state (Milligrams per deciliter)	**Oral glucose tolerance test (Milligrams per deciliter)**	**Interpretation**
More than 126	More than 200	Diabetes*
Between 110-126	Between 140-200	Well-balanced state
Less than 110	Less than 140	Normal

Remarks * However, repeated diagnostic tests should be performed, and it may be necessary to evaluate both to assess diabetes.

The HbA1c test is another tool for assisting in the diagnosis of diabetes. The mean cumulative glucose test, or HbA1c, is a Hb A test in which HbA1c (glycated hemoglobin) which is accumulated in the blood from glucose reacting with hemoglobin over time is measured. As a result, the cumulative glucose level can be determined before HbA1c dissolves after 120 days of red blood cell age. This represents glucose management during the last several months, and rising HbA1c values indicate a higher risk of chronic problems. (Mekvanich N., 2014).

Hemoglobin is a protein that is found in red blood cells. Hemoglobin (responsible for carrying oxygen and transferring it to other tissues) comes in a variety of forms. Hemoglobin A (HbA) makes up majority of the hemoglobin in red blood cells, typically 97-98 percent, and it is further subdivided into HbA1, HbA2, and so on. HbA1c, also may be subdivided into HbA1a, HbA1b, and HbA1c based on their properties. (The most significant component is HbA1c, which represents approximately 80% of HbA1 and 5% of total HbA.)

Adults also have hemoglobin A1 and A2, as well as HbA1c, a derivative of HbA1 generated by Hb glycosylation. HbA1c is slowly produced inside RBCs by a reaction between hemoglobin and glucose-6-phosphate, which results in a ketoamine (amino-l-desoxifructose) on the N-terminal end of the Hb subunits. HbA1c can make up to 3.5% of the total hemoglobin in the blood. High levels of HbA1c are observed in diabetic patients with poorly controlled diabetes.

According to the cycle, each red blood cell is gradually generated from the bone marrow and circulates in the blood vessels for a 3 months. In other words, when each red blood cell ages, it is seized and destroyed by the spleen. Each cell has a life expectancy of roughly 100-120 days based on the usual ratio of red blood cells. As a result, the combination of sugar and red blood cells is determined by the quantity of glucose in the circulation. It is a particular level if the blood sugar is not really high. You might catch more if your blood sugar is quite high. How much glucose is collected in each red blood cell? It is determined by the food you have consumed and how much and how frequently you have consumed it in the past. Counting the days since the blood was tested back 100-120 days will result in what percentage of hemoglobin was glycosylated and became HbA1c. The number of HbA1c, which is more or less a percentage of HbA1c, will be an indicator of the average blood sugar over the past 3 months.

As follows: Synonyms of the HbA1c test

- HbA1C
- A1C
- Hemoglobin A1c
- Hemoglobin A1C
- GHb
- GHB
- Glycohemoglobin
- Glycosylated Hemoglobin
- Glycated Hemoglobin
- Glycated Hb
- Glycated Protein
- Diabetic Control Index
- Hemoglobin-glycosylated

The frequency with which the HbA1c test is performed

HbA1c testing in diabetics. It is advised that you check at least once a year, or as directed by your doctor.

Diabetes patients are subjected to HbA1c testing. It is advised that at least two checks be performed every 3-4 months (HbA1c <7% if the sugar level can be regulated to maintain a satisfactory standard) or more inspections be performed every 3-4 months, depending on the age of the red blood cells.

Interpretation of HbA1c results

The typical HbA1c value is based on the value indicated in the blood test report (if any), but if not, the general value is shown in Table 2.6

Table 2.6 Comparison of the HbA1c range (%) and interpretation of diabetes.

HbA1c (%)	Interpretation
≥ 6.5	Diabetes
Between 5.7 - 6.4	Pre-diabetes
Less than 5.7	Normal

Abnormality of the HbA1c value

1. A lower HbA1c value may result in:

1.1 Hemolytic anemia. Even if there is too much sugar in the blood, you are unable to count the red blood cells bound to the sugar that should be counted because they have been destroyed.

1.2 Renal failure. The kidneys, which produce erythropoietin are generally responsible for encouraging bone marrow to produce red blood cells. As a result of this ongoing impact, the number of red blood cells generated is lower than usual, and HbA1c is also lower.

1.3 It can result from both detectable and undetected blood loss. Because red blood cells must be eliminated from the body first, their creation time is shorter than 120 days. As a result, the captured proportion of HbA1c (even when higher than normal sugars) may be lower than the actual percentage.

2. Higher than normal levels of HbA1c may be caused by:

2.1 You may have had diabetes for at least the past 120 days.

2.2 This may show the result of having diabetes and poor control of the disease. The reasons for not being able to control or change behavior and

exercise, not taking medication or not using the correct medication as prescribed by the doctor, or the absence of a doctor's appointment, such as every 3 months or 6 months to change the treatment to suit.

2.3 High blood sugar without diabetes, such as in people who are under severe stress

2.4 This occurs in the case of a person who has had their spleen removed. As a result, even though many red blood cells have survived for more than 120 days, they cannot be eliminated and continue to circulate in the vascular system. As a result, this impact persisted, coating the HbA1c count with an excessively high percentage.

Treatment and care for people with diabetes

Diabetes is a chronic disease that remains a global public health concern. Patients with diabetes need lifelong care. Because it is a disease that is at risk of serious complications and high treatment costs, such as stroke and heart disease, kidney failure, blindness, and the risk of incisions on the wound, etc. Guidelines for the treatment of patients with type I diabetes use a method of injecting the hormone insulin to replace what cannot be created by the pancreas and lower blood sugar levels to normal.

Diabetes mellitus type II treatment begins with providing advice on healthcare, such as diet and exercise, to keep blood sugar levels normal with the body's mechanisms, but in most cases patients find that they are not very successful due to a busy lifestyle, lack care and health care, do not exercise properly and regularly, and do not pay attention to diet.

For the treatment of type II diabetes, combined chemotherapy is used to make diabetes treatment efficacious. Medicines used to treat type II diabetes are drugs that help regulate the production of the hormone insulin, such as sulfonylureas and meglitinides (Bellamy L et al., 2009 and Blickle JF, 2006), combined with drugs that reduce insulin resistance (such as biguanides), which can enhance the response to intracellular insulin (Collier CA et al., 2006). A class of alpha-glucosidase inhibitors (such as acarbose, voglibose, and miglitol) reduce insulin insufficiency and improve the introduction of sugar into the cells (Kawamori R et al., 2009), etc.

The use of these medications in diabetic patients must be strictly supervised by a doctor. This is a concern because taking diabetic drugs has a considerable risk of negative effects. Caregivers must make diabetic patients aware of the issues that might arise from higher-than-normal blood sugar levels and must be aware of and comprehend the difficulties produced by diabetes. Strict obedience to the doctor's orders In terms of diet and frequent exercise is recommended. Individuals taking chemotherapy must be under the supervision of a physician. It is critical for diabetic patients to encourage family members and those close to them since this allows diabetic patients to live properly and happily in society.

2.5 The prevalence of diabetes in Thai adults

Diabetes is a chronic illness with significant public health implications. The incidence of noncommunicable diseases (NCDs) is growing as people's lifestyles and consumption habits change. Diabetes affects people of various ages and socioeconomic backgrounds. Type I diabetes affects more than 1.1 million children and adolescents under the age of 20, and three out of every four diabetics (352 million) are of working age (20-64 years). Diabetes affects one out of every five people over the age of 65. The increased incidence increases the pressure on countries to maintain regular access to important medicines and suitable channels of treatment, making diabetes management challenging for many people. As a result, substantial health concerns exist (International Diabetes Federation., 2019).

Diabetes is a non-communicable disease that threatens people all over the world. This is caused by improper health behaviors, including eating unhealthy foods, engaging in improper physical activity, smoking, and drinking alcohol. Non-communicable diseases are the number one cause of death in the world and in Thailand. There are more than 40 million deaths worldwide each year, accounting for 71% of all deaths. Most of them are in developing countries. Thailand has an estimated 400,000 deaths due to non-communicable diseases each year, accounting for 76% of all deaths, and half of all deaths are premature. This is at a cost of 2.2 percent of GDP per year (Hfocus, 2019).

People with diabetes are at risk of significant consequences and mortality, such as heart attack, stroke, renal failure, blindness, and partial suspension, if the diabetes is not identified or proper assistance is not available. This lowers one's quality of life and raises the expense of healthcare.

However, diabetes is more common in the elderly group than in other age groups. It is complex in many areas, such as physical, psychological, social, and economic (Rizvi., 2007), and people are at risk of getting geriatric syndrome. (Vischer et al., 2009). Moreover, elderly people with uncontrolled diabetes and two or more complications of diabetes often must receive insulin injections, with a high risk of disability and reduced quality of life (Morewitz., 2006).

According to the 2019 International Diabetes Federation survey, compared with the data released in 2017, it is estimated that the number of adults with diabetes has increased by 38 million. Currently, 463 million adults worldwide suffer from diabetes. The global prevalence of diabetes is 9.3%, and more than half (50.1%) of those who are adults have not yet been diagnosed. Type II diabetes accounts for about 90% of all people with diabetes.

The number of people with type II diabetes is increasing due to the complex influence of social, economic, demographic, environmental, and genetic factors, with the main contributing factors being urbanization, an aging population, reduced physical activity, and being overweight or obese. At the same time, the number of people with type I diabetes is on the rise for unknown reasons. Based on the evidence for preventing type II diabetes, early detection and access to appropriate care for all types of diabetes can avoid or delay complications in people with diabetes. Other important study findings from the 9th edition of the IDF Diabetes Atlas report include:

- The overall number of diabetes patients is expected to reach 578 million by 2030 and 700 million by 2045.

- As a result of their reduced sugar tolerance, 374 million people are at increased risk of acquiring type II diabetes.

- Diabetes is the leading cause of total health-care expenditures. In 2019, these costs totaled approximately US$7.6 billion.

- Diabetes is one of the top ten causes of death worldwide, accounting for more than half of all deaths in people under the age of 60.

- One out of every six babies develops hyperglycemia in the womb.

According to a survey, 4.8 million people in Thailand today suffer from diabetes. Complications often accompany aging. The cause of the disease comes from a sedentary lifestyle, obesity, and aging. Only 35.6 percent, or 2.6 million, of these were diagnosed and treated. In Thailand, the death rate caused by diabetes is as high as 200 per day. Diabetes is estimated to affect 5.3 million people by 2040, with insufficient care leading to complications such as kidney failure and amputations. (Hfocus, 2019).

From 2016 to 2019 surveys, the number and rate of inpatient diabetes cases per 100,000 people (including all diagnoses) increased. classified by province, health service area, and country or region (including Bangkok). Discover the overall situation of the country in 2019. Compared with 2016, 2017, and 2018, the number of cases has increased in 2019 (in 2016, 2017, 2018, and 2019, the number of patients with diabetes was 840,489 cases, 876,970 cases, 941,226 cases, and 1,002,310 cases, respectively).

In the Regional Health 9 region, which includes four provinces: Nakhon Ratchasima, Chaiyaphum, Buriram, and Surin, the number of people with diabetes in 2019 was 110,123, with 1,626.72 cases per 100,000 people.

The provinces in the Regional Health 9 with the highest number and rate of inpatients with diabetes per 100,000 people were Nakhon Ratchasima (42,633 cases, a patient rate of 1,612.93 people), Buriram Province (26,751 cases, a patient rate of 1,678.83 people), Surin Province (22,304 cases, a patient rate of 1,597.71 people), and Chaiyaphum Province (a total of 18,435 cases, a patient rate of 1,621.36 people). (Division of Non-Communicable Diseases, 2019).

Treatment for diabetes aims to maintain blood sugar levels within a normal range by combining exercise, nutrition, and medication to prevent or postpone the development of complications. (Sigal, Kenny, Wasserman, & CastanedeSceppa, 2004). Therefore, attention should be focused on keeping blood glucose levels close to normal, but at the same time, some elderly people may not benefit from strict blood glucose control, or if the control is too strict, it may increase the risk of hypoglycemia. This may have more negative effects than positive ones.

Generally, adults (18–65 years) with diabetes have HbA1c levels below 7%. In the case of strict control, the HbA1c level should be less than 6.5%. In less stringent circumstances, the HbA1c level should be between 7 and 8%. For the elderly people over 65, if they are healthy and can help themselves without serious joint diseases, it is recommended that the control level of HbA1C is less than or close to 7.0%. If the body is unhealthy and fragile, there is a chance of falling or suffering a serious illness, or in patients with dementia who are at a higher risk of severe hypoglycemia, a HbA1c of up to 8.5% may be allowed.

Self-care of diabetic patients is very important because, in the long run, the successful control of blood sugar levels and the prevention of diabetes complications depends on the self-care activities of the patient. This requires self-controlled practice activities and constant self-care. It can be interpolated in a self-care manner, which is part of a lifestyle that leads to an improved quality of life. The Thai Health Promotion Foundation supports activities to promote health and modify the health behaviors of people of all ages by developing and managing knowledge and supporting the organization of a legal and social environment, such as advocating for policies that promote healthy behaviors to reduce risk factors for tobacco and alcohol use.

We can reduce the incidence of non-communicable diseases by supporting healthy food factors for well-being, increasing physical activity, and using marketing communications to campaign to change cultural values. expand the concept of health literacy to suit the age groups of children, youth, working-age adults, and the elderly people, as well as the specific population groups such as people with disabilities and individual status groups, to drive people to have health literacy, change to a well-being society, and continuously drive work into target areas, such as establishments, schools, communities, and families, including supporting the work of the network under various mechanisms to reduce the occurrence of non-communicable diseases. These data indicate that the number of diabetic patients in the world and Thailand is high, and this problem should be addressed seriously. In many published studies, it has been found that diabetic patients are significantly associated with xerostomia. Due to reduced saliva flow, 43% of patients reported dry mouth, of which 82% were women. (Sreebny, L. M. et al., 1992). From the study of Siribang-on et al. (2009), they found that there is a prevalence of xerostomia of 62% in patients with type 2 DM compared with 36% in the non-diabetic control group (p = 0.001). The prevalence of hyposalivation (defined as MST values < 25 mm at 3 min) was 46% in the patient group, whereas only 28% of the control group had hyposalivation (p = 0.03). Patients with hyposalivation had significantly higher numbers of Mutans streptococci, Lactobacillus spp., and Candida spp. in their saliva compared with those without hyposalivation. Similarly, López-Pintor, R. M. et al.

(2016) discovered that the prevalence of xerostomia and salivary flow rates were lower in the DM population compared to the non-DM patients. Most studies found a higher prevalence of xerostomia and lower salivary flow rates in DM with respect to the control group. They found only one study about hyposalivation that showed a higher prevalence in DM patients than in non-DM patients. The study, titled "Salivary flow and xerostomia in older patients with type 2 diabetes mellitus in older patients" by Lima DLF. et al. (2017), assessed 120 older patients with diabetes (60 insulin-dependent and 60 non-insulin-dependent) aged 65–91 years, with a mean age of 72.26 ± 6.53 years. Of these, 111 (92.5%) presented a decrease in salivary flow, while 59 (49.2%) reported moderate to severe xerostomia (dry mouth) and hyposalivation, which may be related to the many risk factors for reduction in salivary flow found in the group analyzed, particularly advanced age, type 2 diabetes mellitus, and tooth loss.

2.6 Cordycepin

Chong Cao's scientific name is *Ophiocordyceps sinensis*, and it is classified as a Chinese herb. It is also known as grass worm, or winter worm, and summer grass. It can be found in Tibet, Qinghai, Sichuan, Yunnan, Gansu, the Himalayas in India, Bhutan, and Nepal. The scientific name is *Hepialus armilicanus Oberthiir*. There are some fungi on the worm, and the scientific name is *Cordyceps (Berk.). Saec.*

Chongcao is a fungus that grows in winter and is a parasite that lives with worm larvae. When it's summer, the worm dies, then the fungus grows out of the worm and comes out in a line around the head of the worm (Medthai., 2013).

This plant is known as "winter is a worm Summer is a grass", meaning that, throughout the winter, a worm is buried in the snow. When the weather changes, the ice starts to melt. There is another fungus that releases spores for reproduction, which will be blown to the ground. Then, the worms that were once buried in the snow fall out of hibernation and come up for food. Then they will eat the spores. Over time, the spores begin to grow through the uptake of nutrients and minerals from the worms. The fungus then begins to grow out of the worm because, because these mushrooms need sunlight, they sprout up into the ground from the worm's mouth. Worms will gradually become weaker, so the *cordyceps* used to make medicine is a mixture of worms and dried fungi.

Cordycepin or 3′-Deoxyadenosine (9- (3-deoxy-β-D-ribofuranosyl adenine), is a derivative of the Adenosine nucleoside. The empirical formula (Hill Notation) is $C_{10}H_{13}N_5O_3$. Molecular Weight: 251.24 g / mol, Abbreviation: COR.

This chemical is alkaline with a melting point of 228–231 degrees Celsius and has the highest absorbance at a wavelength of 259 nm. The cordycepin infrastructure is composed of adenine nucleosides made by making an a-N9-glycosidic bond bound with ribofuranose sugars. The chemical synthesis of cordycepin was due to the replacement of the OH group at position 3' of ribofuranose sugars with hydrogen atoms (Tuli et al., 2013). The figure shows the chemical structure of cordycepin, as shown in Figure 2.4 below.

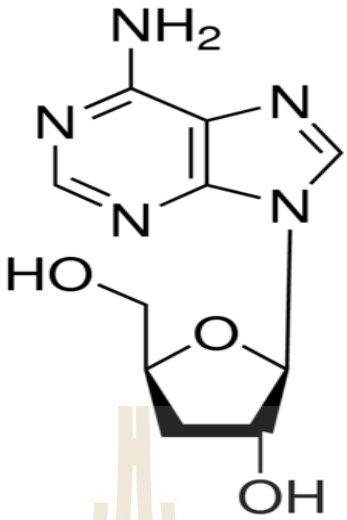


Figure 2.4 Chemical structure of cordycepin**.**
(National Center for Biotechnology Information., 2019)

Cordycepin is a purine nucleoside antimetabolite and antibiotic isolated from the fungus *Cordyceps militaris* with potential antineoplastic, antioxidant, and anti-inflammatory activities. Cordycepin is an inhibitor of polyadenylation, activates AMP-activated protein kinase (AMPK), and reduces mammalian target of rapamycin (MTOR) signal transduction, which may lead to the induction of tumor cell apoptosis and the reduction of tumor cell proliferation. mTOR, a serine/threonine kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related kinase (PIKK) family, plays an important role in the PI3K/AKT/mTOR signaling pathway that regulates cell growth and proliferation, and its expression or activity is often dysregulated in human cancers. (National Center for Biotechnology Information, 2019)

According to research reports, cordycepin is effective in mammalian cells, depending on the concentration of cordycepin. If the concentration is low, it interferes with mRNA and protein synthesis by inhibiting polyadenylation, resulting in cell proliferation and a reduction in proliferation, while a high concentration of cordycepin will stimulate the work of the AMP-activated kinase pathway to help cells maintain cell homeostasis (De Silva et al., 2012).

Due to the anti-UVB stimulation, the effect of cordycepin has been studied in the fields of anti-cancer activity, tumor cells, and the efficacy of cordycepin as an

anti-aging active ingredient. It was found that cordycepin inhibits the production of the enzymes metalloproteinases 1 and 3, which are enzymes that break down fibrous collagen and extracellular matrix, help strengthen the skin. In dermal fibroblast skin cells, it can prevent dermal degeneration (Lee, Y.R. et al., 2009).

In addition, cordycepin is also used as an *in vitro* antioxidant, with DPPH (1,1-diphenyl-2-picryl-hydrazyl) radical scavenging assays. It was found to be able to destroy up to 50% of free radicals, similar to vitamin C, which is used as a reference antioxidant (He, Y.T., 2013).

Therefore, cordycepin has the potential to act as an active ingredient in anti-aging cosmetics, with the benefits of bioactive compounds, especially cordycepin from *Cordyceps militaris*. This causes *Cordyceps militaris* to be widely cultivated for medicinal and functional food purposes and for use in the synthesis and extraction of bioactive compounds for drug and nutritional supplement applications.

Both species of *Cordyceps* have been found to have such uses: *Cordyceps sinensis* and *Cordyceps militaris*. Although *Cordyceps sinensis* is known and more expensive in the herbal and traditional markets due to its rarity in nature, studies comparing the amount of cordycepin and adenosine synthesis between the two species have been scarce. Both species were reported to have considerably different amounts of adenosine synthesis, and the concentration of cordycepin and adenosine in the fruiting bodies of *C. militaris* was higher than that in natural *C. sinensis* (Huang, L. et al., 2009).

According to proximate analysis, the relative concentrations of moisture, total ash, crude protein, crude fat, crude fiber, and carbohydrates are, respectively, 7.18%, 7.48%, 21.46%, 1.80%, 6.40%, and 55.68% for several *Cordyceps* species. Various studies have also reported proximate studies of the mycelial biomass and fruiting bodies of *Cordyceps.* According to analyses, the protein, moisture, ash, fat, and carbohydrate contents of *Cordyceps* fruiting bodies are 59.8%, 5.7%, 5.1%, 8.8%, and 29.1%, respectively, whereas mycelial biomass comprises 39.5%, 13.1%, 5.7%, 2.2%, and 39.6% of each. Contrastingly, the corpus and fruiting bodies of *Cordyceps militaris* (*C. militaris*) were found to contain 14.03 mg/g and 69.32 mg/g of amino acids, respectively. Additional amino acid analysis reveals that proline, lysine,

threonine, and glutamic acid are present in high concentrations in the fruiting bodies. Furthermore, the fatty acid profile shows that roughly 70% of the overall fat proportion is composed of unsaturated fatty acids. Importantly, 0.97 and 0.36 percent and 0.18 and 0.06%, respectively, of cordycepin and adenosine were found in the corpus and fruit bodies (Syed Amir Ashraf et al., 2020).

Studies and research of pharmacological activity, *in vitro* and in animal experiments, found that *cordyceps* can help with homeostasis, stimulate the immune system, have antioxidant activity, have an anti-cancer effect, help lower blood sugar levels, be anti-inflammatory, stimulate sexual performance, etc.

Cautions for Using *Cordyceps*

1. *Cordyceps* has a hypoglycemic effect, so use with caution in diabetics. It will synergize with blood sugar-lowering drugs.

2. *Cordyceps* has an anti-platelet aggregation effect, so please pay more attention to patients receiving anti-platelet aggregation drugs.

3. *Cordyceps* stimulates the immune system, so caution should be exercised in patients receiving immunosuppressive drugs other than *Cordyceps sinensis.*

In addition, the daily recommended consumption for adults (18 years of age and older) is about 3 to 9 grams, and hot water can be used to brew or cook the herb in food. Excessive consumption may have a negative effect when used in pregnant women, lactating women, and children. There is currently insufficient evidence of safety in these groups, and it's not recommended for people who are allergic to *Cordyceps*, have chronic bronchitis, or have an irregular heartbeat. Therefore, be careful when using it. For the safety and benefit of consumers, further research should be conducted to support the therapeutic use of *Cordyceps.* (Shashidhar MG et al., 2013).

Toxicology and dosage of *Cordyceps*

Cordyceps is a plant used in traditional Chinese medicine (TCM) that has many positive pharmacological effects and is considered safe. Some reports have been published on patients who suffer from autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and it is generally suggested to avoid its use in those diseases. Reports are still lacking on

pregnant and lactating women, but some animal studies in mice have revealed that *Cordyceps* has effects on plasma testosterone levels (Wong KL. et al., 2007). Aside from a few negative published studies, *Cordyceps* is widely regarded as a non-toxic medicinal mushroom. In patients with long-term renal failure, a dose of up to 3-6 grams per day was demonstrated to be safe (Zhu et al., 1998). However, no human toxicity report was found, and even animal models failed to determine the median lethal dose. *Cordyceps* dosage up to 80 g/kg body weight/day for 7 days was injected intraperitoneally in mice, and even then it did not cause any fatalities. (Li et al., 2006). In another study, rabbits fed through the mouth for 3 months at a dose of 10 g/kg/day did not show any deviance in blood reports or in kidney or liver functioning (Huang et al., 1987). Even a water extract of *Cordyceps sinensis* was found to be non-toxic to the proliferation of the macrophage cell line RAW264.7 (Mizuha et al. 2007). There are reports of lead poisoning in patients taking *Cordyceps* herbal medicine for treatment. The lead content in the *Cordyceps* powder in these cases was significantly high (20,000 ppm) (Wu et al. 1996). However, the blood lead levels returned to normal upon termination of the product's consumption (Tuli, H. S. et al., 2014). In general, They demonstrated that 3–4.5 g of *cordyceps per* day is sufficient and safe in humans, except in patients suffering from severe liver disease (Mizuno., 1999).

Cordycepin Drug Interaction with Diabetes

There are reports suggesting that patients should be cautious while taking *cordyceps* if they are being treated with antiviral or diabetes medications, as *cordyceps* contains hypoglycemic and antiviral agents. This may affect the additional dose of these drugs. (Holliday and Cleaver 2008). Some research reports that *Cordyceps militaris* extract can significantly lower blood sugar levels. It is based on increased glucose metabolism and prevention of diabetic nephropathy (Dong, Y et al., 2014).

The mechanism of cordycepin's antidiabetic action is not fully understood. But there are some studies describing a possible pathway. They found that cordycepin prevents the production of NO and pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 in LPS stimulated by macrophages. By inhibiting the protein

expression of pro-inflammatory mediators, the expression of type 2 diabetes regulatory genes (11β-HSD1 and PPARλ) is reduced. Cordycepin concentration decreased the expression of co-stimulatory molecules such as ICAM-1 and B7-1/-2 (Shin, S. et al., 2009).

In addition, cordycepin was found to inhibit the expression of genes that regulate diabetes through inhibition of an NF-Kb-dependent inflammatory response (Patel, K.J et al., 2013). In another study, the antidiabetic activity of cordycepin was reported in an alloxan-induced diabetic mouse model. The results indicated a significant improvement in the effectiveness of the glucose tolerance test after cordycepin administration (Ma, L. et al. , 2015). In addition, the effect of cordycepin on diabetic nephropathy by inhibiting apoptosis, renal fibrosis, and rescuing cell autophagy was studied in a rat model of diabetic nephropathy (Cao, T et al., 2019).

Several studies indicate that cordycepin has a high potential for use as a safe anti-diabetic pharmacological medication. For example, in the study of Dong, Y et al. (2014) titled "Studies on the antidiabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic Sprague-Dawley rats," they found that the inhibitory effects on blood urea nitrogen, creatinine, uric acid, and protein revealed the protection of *Cordyceps militaris* extracts against diabetic nephropathy, which was confirmed by pathological morphology reversion. Collectively, *Cordyceps militaris* extract, a safe pharmaceutical agent, presents excellent antidiabetic and antinephropathic activities and thus has great potential as a new source for diabetes treatment. In addition, in the study of Shin, S. et al.(2009) titled "Cordycepin Suppresses Expression of Diabetes Regulating Genes by Inhibition of Lipopolysaccharide-induced Inflammation in Macrophages," they found that cordycepin suppressed T2D regulating genes through the inactivation of NF-KB dependent inflammatory responses and suggested that cordycepin will provide potential use as an immunomodulatory agent for treating immunological diseases and for the toxic effect of cordycepin they tested its effect on the viability of RAW 264.7 by MTT assay. The exposure of cells to cordycepin at 5-40 μg/ml for 24 hr showed no significant adverse effect on the cell viability versus the untreated control.

In a study of Yun, Y.H. et al **(**2003**)** titled “Anti-diabetic Effects of CCCA, CMESS, and Cordycepin from *Cordyceps militaris* and the Immune Responses in Streptozotocin-induced Diabetic Mice”. They investigated the anti-diabetic effect of various fractions of *Cordyceps militaris* (CM), CCCA (crude cordycepin containing adenosine), CMESS (ethanol soluble supernatant), and cordycepin in streptozotocin (STZ) induced diabetic mice, and found that CMESS (ethanol soluble supernatant), and cordycepin may be useful tools in the control of blood glucose levels in diabetes and may be promising new anti-hyperglycemic agents without defects of immune responses and other side effects.

From the results of the research report above it can be concluded that cordycepin extract is considered pharmacologically safe for human consumption and use (Syed Amir Ashraf et al., 2020), and is regarded as relatively safe and non-toxic for human consumption (Tuli, H. S., et al., 2014).

2.7 Related research

Related research on cordycepin

A research study in 2008, Title: Anticancer effects of genistein, green tea catechins, and cordycepin on oral squamous cell carcinoma found that Genistein is a compound extracted from soybean. Its anti-cancer effect on breast cancer is well established now and it was investigated whether it has similar effect on OSCC. It inhibited the growth and invasive-ness of OSCC cells *in vitro*, but these effects did not work in living animals *in vivo*. Catechin is a compound from green tea and its anti-cancer effect on OSCC is known better than other agents. Catechin showed its anti-cancer effect *in vitro* via induction of apoptosis, cell cycle arrest, inhibition of growth, and down-regulation of invasion/metastasis. These effects were confirmed *in vivo* with a mouse model. Cordycepin is one of major pharmacologically important components in *Cordyceps militaris* and may exert its anti-cancer effect as an adenosine receptor agonist. In a recent study, it inhibited the proliferation of OSCC cells via A3 adenosine receptor. But because there is very scarce evidence on this effect, more research is needed on this theme. (Sung-Jin Park. et al., 2008)

A research study in 2018, Title: Cordycepin induces apoptotic cell death of human brain cancer through the modulation of autophagy. Found that cordycepin inhibited cell growth, and induced apoptosis in a dose-dependent manner in both SH-SY5Y and U-251 cell lines. The expression of pro-apoptotic genes, including P53, BAX, Caspase-3, and Caspase-9, were upregulated, whereas the expression of anti-apoptotic gene, BCL-2, was suppressed. Besides, cordycepin induced the generation of reactive oxygen species (ROS) along with the suppression of antioxidant genes, including GPX, SOD, and Catalase. Crucially, the increase in autophagy provided proof that cordycepin was engaged in this process of LC3I/II. The combination of cordycepin with chloroquine, an autophagy inhibitor, further inhibited the growth, and enhanced the death of brain cancer cells. Altogether, this finding suggests that cordycepin induces apoptosis of human brain cancer cells through a mitochondrial-mediated intrinsic pathway and the modulation of autophagy. Therefore, cordycepin could be a promising candidate for the development of anticancer drugs targeting human brain cancers. (Chaicharoenaudomrung, N et al., 2018.)

A research study in 2018, Title: Effects of cordycepin on spontaneous alternation behavior and adenosine receptors expression in hippocampus. Found that Cordycepin, an adenosine analogue, has been reported to improve cognitive function. Important roles in learning and memory of adenosine and its receptors, such as adenosine A1 and A2A receptors (A1R and A2AR), also have been shown. Therefore, they assume that the improvement of learning and memory induced by cordycepin is likely related to hippocampal adenosine content and adenosine receptor density. The effects of cordycepin on the short-term spatial memory by using a spontaneous alternation behavior (SAB) test in Y-maze, and then examined hippocampal adenosine content and A1R and A2AR densities. They found that orally administrated cordycepin (at dosages of 5 and 10 mg/kg twice daily for three weeks) significantly increased the percent of relative alternation of mice in SAB but did not alter body weight, hippocampus weight and hippocampal adenosine content. Furthermore, cordycepin decreased A2AR density in hippocampal subareas; however, cordycepin only reduced the A1R density in DG but not CA1 or CA3 region. The results suggest that cordycepin exerts a nootropic role possibly through modulating A2AR density of hippocampus, which further support the concept that it is mostly A2AR rather than A1R that control the adaptive processes of memory performance. These findings would be helpful to provide a new window into the pharmacological properties of cordycepin for cognitive promotion. (Zhi-Ping Cao et al., 2018).

A research study in 2018, Title: The Anticancer Properties of Cordycepin and Their Underlying Mechanisms. Found that the treatment of various cancer cells with cordycepin effectively induces cell death and retards their cancerous properties. However, the underlying mechanism is not fully understood. Recent evidence has shed light on the molecular pathways involving cysteine-aspartic proteases (caspases), mitogen-activated protein kinases (MAPKs), and glycogen synthase kinase 3 beta (GSK-3β). Furthermore, the pathways are mediated by putative receptors, such as adenosine receptors (ADORAs), death receptors (DRs), and the epidermal growth factor receptor (EGFR). This review provides the molecular mechanisms by which cordycepin functions as a singular or combinational anticancer therapeutic agent. (Yoon SY et al., 2018).

A research study in 2019, Title: Enrichment of cordycepin for cosmeceutical applications: culture systems and strategies. Found that *Cordyceps spp.* is a herbal medication initially used in China and has been reported as the unique resource of cordycepin. Cordycepin exhibits many health benefits, including anti-photoaging and anti-pigmentation; therefore, it potentially is a bioactive ingredient of cosmetic products. In order to enrich cordycepin content in *Cordyceps,* two artificial cultivation procedures, which are solid-state fermentation and liquid culture, were developed and optimized. The aim of this review was to illustrate cordycepin biosynthesis pathway in *Cordyceps*, and its bioactivity for cosmeceutical applications, as well as comparing the two different cultivation procedures. The basic model of artificial cultivation of *Cordyceps* was introduced; meanwhile, the potential application of modern biotechnology to artificial cultivation is also discussed. This review should be of interest to the readers for the development of cordycepin bioproduction in order to be applied in cosmeceutical industry and some other uses. (Kunhorm, P et al., 2019).

A research study in 2019, Title: Cordycepin, isolated from medicinal fungus *Cordyceps sinensis*, enhances radiosensitivity of oral cancer associated with modulation of DNA damage repair. Found that DNA histogram analysis showed that cordycepin combined with RT prolonged the RT-induced G2/M phase arrest. It protracted the duration of DNA double strand breaks, which was detected by immunofluorescent staining of phosphorylated histone H2AX (γ-H2AX). The underlying molecular mechanism might involve the downregulation of protein expression related to DNA damage repair, including phosphorylated ataxia-telangiectasia mutated (p-ATM) and phosphorylated checkpoint kinase 2. Reciprocal upregulation of phosphorylated checkpoint kinase 1 (Chk1) expression was noted, and the radiosensitizing effect of cordycepin could be further augmented by Chk1 mRNA knockdown, indicating a compensatory DNA repair machinery involving phosphorylation of Chk1. *In vivo*, the combination of cordycepin and RT exhibited greater growth inhibition on xenografts and stronger apoptosis induction than RT alone, without exacerbating major toxicities. In conclusion, cordycepin increased the

radiosensitivity of OSCC cells, which is associated with the modulation of RT-induced DNA damage repair machinery. (Nai-Wen Su et al., 2019).

A research study in 2019, Title: Cordycepin Enhances Radiosensitivity in Oral Squamous Carcinoma Cells by Inducing Autophagy and Apoptosis Through Cell Cycle Arrest. Found that cordycepin induced S-phase arrest and prolonged G2/M arrest in the cells that received the combination treatment compared with those that received irradiation alone. Combined treatment induced the upregulation of ATG5 and p21 in an autophagy cascade-dependent manner, arrested the cell cycle in the G2/M phase, and repressed cell proliferation. Thus, they conclude that the combination of cordycepin and IR treatment could be a potential therapeutic strategy for OSCC. (Ho S-Y et al., 2019).

A research study in 2019, Title: Neuroprotection of cordycepin in NMDA-induced excitotoxicity by modulating adenosine A1 receptors. Found that cordycepin remarkably alleviated LTP impairment and protected pyramidal cells of the hippocampal CA1 region against cerebral ischemia and excitotoxicity. Meanwhile, cordycepin prevented the reduction of the adenosine A1 receptor level caused by ischemia but did not alter the adenosine A2A receptor level in the hippocampal CA1 area. The improvement of LTP in the excitotoxic rats after cordycepin treatment could be blocked by DPCPX, a selective antagonist of adenosine A1 receptor. In summary, their findings provided new insights into the mechanisms of cordycepin neuroprotection in excitotoxic diseases, which is through regulating adenosine A1 receptors to improve LTP formation and neuronal survival. (Zhong-Si-Wei Dong et al., 2019).

A research study in 2019, Title: The Inhibitory Effect of Cordycepin on the Proliferation of MCF-7 Breast Cancer Cells, and Its Mechanism: An Investigation Using Network Pharmacology-Based Analysis. Found that the gene set enrichment analysis showed that the targets of cordycepin are mainly associated with the hedgehog signaling, apoptosis, p53 signaling, and estrogen signaling pathways. They further verified the predicted targets related to the apoptosis pathway using western blot analysis. The *C. militaris* concentrate and cordycepin exhibited the ability to induce apoptotic cell death by increasing the cleavage of caspase-7 -8, and -9, increasing the

Bcl-2-associated X protein/ B-cell lymphoma 2 (Bax/Bcl-2) protein expression ratio, and decreasing the protein expression of X-linked inhibitor of apoptosis protein (XIAP) in MCF-7 cells. Consequently, the *C. militaris* concentrate and cordycepin exhibited significant anticancer effects through their ability to induce apoptosis in breast cancer cells. (Lee D et al., 2019).

A research study in 2020, Title: thesis of cordycepin: Current scenario and future perspectives. Found that The current methods for cordycepin synthesis involve chemical synthesis, microbial fermentation, *in vitro* synthesis and biosynthesis; however, some defects are unavoidable and the production is still far from the demand of cordycepin. For the future study of cordycepin synthesis, based on the illumination of cordycepin biosynthesis pathway, genetical engineering of the *Cordyceps* strain or introducing microbes by virtue of synthetic biology will be the great potential strategies for cordycepin synthesis. This review will aid the future synthesis of the valuable cordycepin. (Liyang Yang et al., 2020).

A research study in 2020, Title: Cordycepin-loaded Nanoparticles from Cassava Starch Promote the Proliferation of Submandibular Gland Cells and Inhibit the Growth of Oral Squamous Carcinoma Cells. Found that Cordycepin-loaded cassava starch nanoparticles (CCSNPs) increased HSG proliferation, protein secretion, and the expression of salivary-specific genes, AMY and AQP5. Besides, CCSNPs also protected and scavenged of ROS via the stimulation of the antioxidant genes in HSGs, indicating the protective roles of CS to HSGs. On the other hand, CCSNPs inhibited the growth of HSC-4 cells by stimulating ROS generation and reducing protein secretion. This finding suggested that CCSNPs presented the dual actions against HSGs and human oral squamous carcinoma cells, and the encapsulation of CS with cassava nanoparticles enhanced the activity of CS. (Kaokaen, P et al., 2020).

A research study in 2020, Title: Neuroprotective effects of natural cordycepin on LPS-induced Parkinson's disease through suppressing TLR4/NF-KB/NLRP3-mediated pyroptosis. Found that cordycepin ameliorated LPS-induced PD symptoms and suppressed TLR4/NF-KB-mediated NLRP3 inflammasome activation and GSDMD-related pyroptosis. Additionally, cordycepin remarkably inhibited pore formation in the plasma membrane and reduced the release of proinflammatory mediators *in*

vitro, which is associated with the inhibition of NLRP3-dependent pyroptosis. Collectively, cordycepin exerts neuroprotective activity by regulating TLR4/NF-KB/NLRP3-dependent pyroptosis, which should be developed as healthcare food or natural medicine for the treatment of PD in the future. (Ying Sun et al., 2020).

A research study in 2020, Title: Cordycepin induces apoptosis in human tongue cancer cells *in vitro* and has antitumor effects *in vivo*. Found that Cordycepin was able to significantly suppress the proliferation of CAL-27 cells in a dose-dependent fashion (IC50 = 40 μg/mL at 24 h). Cordycepin further induced Bax, caspase-3, caspase-9, and caspase-12 upregulation at the mRNA and protein levels while simultaneously downregulating anti-apoptotic Bcl-2 expression. CAL-27 cells treated using cordycepin also exhibited elevated levels of intracellular ROS. Importantly, cordycepin was able to effectively suppress tongue cancer tumor growth in a murine xenograft model system and similar mRNA and protein levels were observed *in vivo*. Cordycepin can inhibit human tongue cancer cell growth and can drive their apoptotic death via the mitochondrial pathway. In addition, cordycepin can suppress tongue cancer growth *in vivo* in treated mice. (Qingwei Zheng et al., 2020).

A research study in 2020, Title: Cordycepin attenuates Salivary Hypofunction through the Prevention of Oxidative Stress in Human Submandibular Gland Cells. Found that after being exposed to H2O2, human submandibular gland (HSG) cells were treated with various concentrations of cordycepin (6.25-50 μM) for 24, 48, and 72h. To evaluate cell proliferation and reactive oxygen species (ROS) generation, 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide and 2, 7'-dichlorodihydrofluorescein diacetate assays were performed. The amylase activity was kinetically measured by 2-chloro-p-nitrophenol linked with maltotrioside. The expression of salivary, antioxidant and apoptotic markers at mRNA and protein levels were performed by reverse transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence analysis, respectively. They demonstrated that cordycepin (6.25-25 μM) contributed to significant increases in expression of the salivary marker genes, alpha-amylase 1 (AMY1A) and aquaporin-5 (AQP5), and in amylase secretion without changes in cell viability. Under oxidative stress, HSG cells showed remarkable

dysfunction. Cordycepin rescued the protective effects partially by decreasing ROS generation and restoring the expression of the salivary proteins, AMY and AQP5 via anti-oxidant and anti-apoptotic activity. In addition, the amount of amylase that was secreted from HSG cells cultured in cordycepin was increased. In conclusion, cordycepin demonstrated a protective effect on H2O2-induced HSG cells by decreasing ROS generation and upregulating the salivary function markers, AMY1A and AQP5, at both the transcriptional and translational levels. (Jaiboonma, A et al., 2020).

A research study in 2021, Title: Cordycepin attenuates high-fat diet-induced non-alcoholic fatty liver disease via down-regulation of lipid metabolism and inflammatory responses. Found that C57BL/6 J mice were randomly assigned into normal control group (NC), high fat diet group (HFD) and HFD + CRD group for 8 weeks. The body weights were recorded weekly, at the end of the experiments, the liver and serum samples were collected. They found that CRD administration reduced body weight and decreased the weight of adipose and liver, and CRD relieved liver injure through diminishing of histopathological changes and decreasing serum levels of AST, ALT, TG, TC, LDL-C and increased the level of HDL-C. Furthermore, treatment with CRD significantly alleviated expression of inflammatory factors (TNF-α, IL-6 and Il-1β) and macrophage markers (MCP1, MIP2, mKC and VCAM1). On the other hand, compared with HFD group, the CRD treated group markedly down-regulated relative proteins of lipid anabolism (SREBP1-c, ACC, SCD-1, LXRα and CD36) and up-regulated relative proteins of β-oxidation (p-AMPK, AMPK, CPT-1 and PPARα). They suggest that CRD can be a potential therapeutic agent in the prevention and treatment of NAFLD, which may be closely related to its effect on lipid metabolism and inflammatory responses. (Xiaobao Gong et al., 2021).

A research study in 2021, Title: The Acute and Sub-Chronic Oral Toxicity Testing of *Cordyceps militaris* in Wistar Rats. Found that adenosine, polysaccharides, cordycepin, and other compounds compensate for *Cordyceps militaris*. For many years, *C. militaris* was utilized as a component in dietary supplements in various nations, including Thailand. On the other hand, insufficient toxicological testing of *C. militaris* has been performed. Through acute and subchronic oral toxicological

studies on Wistar rats, the toxicity of *C. militaris* was evaluated in this study. According to OECD Guidelines for the Testing of Chemicals 423, Acute Oral Toxicity-Acute Toxic Class Method, *C. militaris* was evaluated for acute oral toxicity in Wistar rats at dosage levels of 300 and 2,000 mg/kg body weight. The results showed no evidence of toxicity, morbidity, or mortality in any of the animals. *Cordyceps militaris* was classified as GHS category 5 or unclassified, with the LD50 set at 5,000 mg/kg body weight to infinity. The OECD Guideline for Testing of Chemicals 408, Repeated Dose 90-Day Oral Toxicity Study in Rodents, was modified for the sub-chronic oral toxicity of *C. militaris*. The assessment and evaluation of toxic effects were performed using doses of 5, 20, and 80 mg/kg body weight of *C. militaris* in Wistar rats, and the results demonstrate that the no observed adverse effect level for *C. militaris* was 80 mg/kg body weight per day for Wistar rats. (Kittigan Suwannasaroj et al., 2021).

Related research on xerostomia

A research study in 1992, Title: Xerostomia in Diabetes Mellitus. Found that 43% of diabetic patients complained of xerostomia, of which 82% were women. The oral dryness was not related to age or the type and duration of diabetes. Symptoms of water loss and oropharyngeal, ocular, and vaginal dryness were much more common in the xerostomic than the nonxerostomic diabetic patients. The salivary flow rates of the diabetic subjects was consistently lower than those of healthy, nondiabetic control subjects. The mean, resting, and whole-saliva flow rate was abnormally low in the diabetic patients who complained of xerostomia; no significant differences were observed for the stimulated salivary and the lacrimal flow rates. Significant inverse relationships were shown between salivary flow and the level of HbA1; none were shown between flow and autonomic function. Conclusions: Dry mouth is a common complaint among ambulatory diabetic patients. It is strongly associated with objective measurements of poor salivary flow and with other oral and extraoral symptoms of desiccation. The oral dryness is not associated with cardiovagal autonomic system dysfunction but may be due to disturbances in glycemic control. (Sreebny, L. M. et al., 1992).

A research study in 2006, Title: Oral dryness examinations: use of an oral moisture checking device and the usefulness of an oral moisture checking device and a modified cotton method. Found that the objective of this study was to compare the modified cotton technique with an oral moisture checking device for measuring oral dryness. Methods: Thirteen healthy adults (HA) and thirteen patients with oral dryness had their oral moisture assessed at the lingual mucosa (LM) and buccal mucosa (BM) using an oral moisture checking device (OD). The same participants were subjected to the modified cotton technique, which involved placing cotton under and on the tongue for 30 seconds while weighing the amount of saliva that was absorbed by the cotton. The Mann-Whitney U-test was used to analyze group differences. Results: In the HA and OD groups, the moisture percentage at the LM was 30.0± 0.5% and 28.6± 1.1%, respectively; at the BM, this was 30.3± 0.2% and 29.6± 0.7%. The volume of salivary secretion on the surface of the tongue was 0.059± 0.023 g and 0.011± 0.007 g, respectively, whereas the amount on the hypoglossal level was 0.339± 0.172 g and 0.036± 0.033 g in the HA and OD groups, respectively. Between the HA and OD groups, there was a significant difference in oral moisture and resting saliva production ($p< 0.05$). Conclusion: For evaluating oral dryness, both the oral moisture checking device and the modified cotton method were effective. Oral dryness may be diagnosed by a salivary moisture content in the oral cavity of 30% or less, 0.1 g or less of saliva collected at the hypoglossus in 30 seconds, or 0.02 g of saliva collected from the surface of the tongue in 30 seconds. (Takahashi Fumi et al., 2006).

A research study in 2007, Title: Evaluation of Unstimulated Salivary Flow Rate and Oral Symptoms in Menopausal Women. Found that in males and females, the average unstimulated salivary flow rate was 0.214 ml/min (S.D.=0.105) and 0.127 ml/min (S.D.=0.057). Male and female subjects, respectively, observed a 50% prevalence of dry mouth, a 32% prevalence of difficulty eating dry foods, a 3% prevalence of oral mucosal burning, a 2% prevalence of taste reduction, a 4% prevalence of taste reduction, and an 8% prevalence of a 16% prevalence of a bitter or metallic taste. The prevalence of oral symptoms and the rate of salivary flow differed significantly between groups ($p<0.05$). The hormonal changes that occur at

this phase may explain why menopausal women have a decreased salivary flow rate and a high prevalence of oral problems. (Borhan Mojabi, K et al., 2007).

A research study in 2009, Title: A patient with dry mouth. Found that hyposalivation causes salivary proteins that prevent cariogenic bacteria and electrolytes that buffer oral acids to decrease. This has disastrous effects on teeth, leading to atypical dental caries such as caries along the cervical or incisal border of teeth, erosion, abrasion, and eventually tooth loss. In individuals with hyposalivation, new and recurrent dental caries rank as the second most common infection. In order to use a detachable prosthesis comfortably and with good retention, saliva is also necessary. Due to a lack of lubrication, denture sores can result from a lack of saliva at the denture-mucosa contact. If prostheses move while you're eating or speaking in front of others, it might be embarrassing. (Glore R.J. et al., 2009).

A research study in 2012, Title: Association of hyposalivation with oral function, nutrition and oral health in community-dwelling elderly Thai. Found that Among all subjects, 14.4 % were classified within the hyposalivation. Hyposalivation was associated with gender, systemic disease, medication, and smoking. Subjects within the hyposalivation group had a higher number of decayed teeth and a higher prevalence of periodontitis than the normal salivation group ($p<0.05$). The hyposalivation group also had a lower number of teeth present and a lower mean MNA score than the normal salivation group ($p<0.05$). Logistic regression analysis showed that hyposalivation in both dentate and edentulous subjects was significantly associated with tasting, speaking, swallowing and chewing. Conclusion: This study suggested that hyposalivation is a risk factor not only for dental caries and periodontal disease but also for taste disturbances, speaking problems, swallowing problems, poor chewing ability and malnutrition. Monitoring salivary flow is an important measure in the care of older people. (P. Samnieng et al., 2012).

A research study in 2012, Title: Xerostomia and salivary hypofunction in vulnerable elders: prevalence and etiology. Found that The goal of this article is to review existing research on the prevalence and etiology of dry mouth in the vulnerable elders and identify knowledge gaps. Study Design: Vulnerable elders (VE) are persons aged >65 years who have any or all of the following: limited mobility,

limited resources, or complex health status. A systematic search was conducted of PubMed sources from 1989 to May 2010. Evidence was evaluated on the prevalence and etiology of xerostomia and salivary gland hypofunction (SGH) in VE. The search identified 1,422 publications. The inclusion/exclusion criteria yielded 348 articles, 80 of which are cited herein. Research has showed a high prevalence of xerostomia and SGH in VE. Common etiologies include medications, poor general health, female gender, and age. Gaps still exist in the evaluation of dry mouth in VE. Nonetheless, oral dryness will remain an important health issue as life expectancy increases. (Bing Liu et al., 2012).

A research study in 2013, Title: Xerostomia is Associated With Old Age and Poor Appetite in Patients on Chronic Hemodialysis. The objective of this study was to assess variables associated with xerostomia in patients on chronic hemodialysis (HD). This was a cross-sectional study of 75 HD patients at an outpatient HD service. Demographic, clinical (renal disease, HD regimen/duration, Charlson comorbidity index, activities of daily living, instrumental activities of daily living [IADL], body mass index), and laboratory (hemoglobin, albumin, interleukin-6 [IL-6], and parathyroid hormone) parameters were recorded. They assessed the appetite through the Hemodialysis Study Appetite questionnaire and xerostomia through the Xerostomia Inventory (XI). A single question ("How often does your mouth feel dry?"; never = Class 1, almost never = Class 2, occasionally = Class 3, often = Class 4, very often = Class 5) was also included in the study questionnaire. They found that the median XI score was 18 (min-max = 11-33). Forty patients had an XI score of 18 or less (Group 1) and between 18 and 35 (Group 2). In Group 2, age, Charlson comorbidity index score, and number of patients with poor/very poor appetite were significantly higher. At the univariate analysis, the score of the XI was significantly associated with age, appetite, IADL, Charlson comorbidity index, and serum IL-6 levels. Multiple linear regression analysis showed that the XI was independently associated with age and appetite. Thirty-one patients were in Class 1 to 2, 23 were in Class 3, and 21 were in Class 4 to 5. In Classes 4 to 5, age and the number of patients with poor/very poor appetite were higher (p = .012 and .09, respectively). Xerostomia is associated with old age and poor appetite in patients on chronic HD (Maurizio Bossola et al., 2013).

A research study in 2014, Title: The Use of Xylitol for the Prevention of Xerostomia in Patients Receiving Intensity Modulated Radiation Therapy for Head and Neck Cancers. Found that in patients receiving Intensity modulated radiation therapy (IMRT) for head and neck cancers, xylitol increases salivary flow rates without causing noticeable adverse effects. When determining the mean dosage, the volume of parotid outside the parotid target volumes (PTV) should be taken into consideration. The submandibular gland should have an organs at risk (OAR) contour. Mucositis cannot be prevented by using xylitol. For evaluating the final result of xylitol in the prevention of xerostomia, long-term follow-up is recommended (V. Manoor Maiya et al., 2014).

A research study in 2016, Title: The Effect of Tobacco Smoking on Salivation. Found that there are no significant differences in secretion between smokers and non-smokers; nonetheless, saliva production considerably decreases with smoking duration and smokers' advancing age. The fact that smokers' saliva is thicker and nonsmokers' saliva is mostly serous was also demonstrated. Smokers also have worse oral hygiene than non-smokers, and studies have shown a relationship between oral hygiene standards and the duration of tobacco smoking. This study has demonstrated that smoking has a negative impact on salivation: continuous smoking decreases salivary production and alters its composition. (Petrušić N. et al., 2015).

A research study in 2016, Title: Xerostomia, Hyposalivation, and Salivary Flow in Diabetes Patients. They were perform systematic literature searches in biomedical databases from 1970 until January 18th, 2016. All studies showed higher prevalence of xerostomia in DM patients in relation to non-DM population, 12.5%-53.5% versus 0-30%. Studies that analyzed the quantity of saliva in DM population in relation to non-DM patients reported higher flow rates in non-DM than in DM patients. The variation flow rate among different studies in each group (DM/CG) is very large. Only one existing study showed higher hyposalivation prevalence in DM than non-DM patients (45% versus 2.5%). In addition, quality assessment showed the low quality of the existing studies.They recommend new studies that use more precise and current definitions concerning the determination and diagnosis of DM patients and salivary flow collection. (López-Pintor, R. M.et al., 2016).

A research study in 2016, Title: Prevalence of Xerostomia and its Related Factors in Patients Referred to Zahedan Dental School in Iran. Found that A total of 400 patients were included; 211 (52.8%) were female, 189 (47.2%) were male, and 143 (35.6%) had xerostomia. People older than 51 years had a higher prevalence of xerostomia (59.4%). Additionally, xerostomia was more common in women (39.8%), antihistamine (90.9%) and bronchodilator (83.3%) medication users, patients with neurological (78.3%) and psychotic (77.2%) disorders, smokers (52.2%), and hookah (61.3%) users. Conclusions: Females and elderly adults are more likely to suffer from xerostomia. The findings of this study suggest that xerostomia may be influenced by a number of variables, including systemic disease involvement, medication usage, age, and gender. (Shirzaiy, M. and Bagheri, F., 2016).

A research study in 2017, Title: Risk factors, hyposalivation and impact of xerostomia on oral health-related quality of life. Found that the study involved 566 patients assessed with xerostomia, based on a single standardized questionnaire. The severity and impact of xerostomia on OHRQoL was assessed using a visual analogue scale (VAS) and the short version of the Oral Health Impact Profile Questionnaire (OHIP-14sp), respectively. Stimulated and non-stimulated salivary flow rates were obtained from a sample of patients. Xerostomia was reported in 61 patients (10.8%), comprising 50 women (83.3%) and 11 men (16.7%) ($p < 0.013$). The prevalence was 13% among the women and 6.1% among the men. Gender, age and medication were found to be independent risk factors for the development of xerostomia. Hyposalivation was found in 10 of the 35 patients with xerostomia (28.6%) and in 2 patients without it ($p < 0.011$). Patients with xerostomia had a reduced OHRQoL, compared with patients without xerostomia, as shown by the total OHIP-14sp score ($p < 0.001$). Xerostomia was a common, potentially debilitating condition with a major impact on the OHRQoL of a patient population attending a university-based dental clinic. Hyposalivation was present in almost 30% of the patients who complained of xerostomia. It is important that general dentists be aware of this condition, so that they can provide patients with a good diagnosis, treatment and follow-up. (Niklander S et al., 2017).

A research study in 2018, Title: Medication-Induced Xerostomia and Hyposalivation in the Elderly: Culprits, Complications, and Management. Found that Medication-induced xerostomia and hyposalivation will increasingly become oral health issues for older and geriatric patients because of the likely high prevalence of medication intake and polypharmacy, with a complex negative impact on other symptoms such as dysphagia, caries incidence, malnutrition, and quality of life. All healthcare professionals are encouraged to investigate dry mouth symptoms among their patients, since diagnosis can easily be performed within daily clinical practice. This practical article also provides a review of available treatment options, which include medication changes towards products with fewer xerogenic side effects or dose reductions, if possible, as well as multidisciplinary, preventive care-oriented approaches that consider all influencing factors and treatment of the oral symptoms. In addition, several topical agents and saliva substitutes are discussed that may provide symptomatic relief but need to be carefully adapted to each patient's situation in terms of usability and practicability and in the knowledge that therapeutic success varies with each individual. Innovative methods such as intraoral electrostimulation or topical application of anticholinesterase on the oral mucosa are also discussed. The most commonly prescribed pharmaceutical treatment options for dry mouth are pilocarpine (a parasympathomimetic agent with potent muscarinic, cholinergic salivation-stimulating properties) and cevimeline (a quinuclidine analogue with therapeutic and side effects similar to those of pilocarpine). These pharmaceutic treatment options are described in the context of older patients, where the highly prevalent cholinergic side effects, which include nausea, emesis, bronchoconstriction, among others, need to be thoroughly supervised by the healthcare professionals involved. Providing these therapeutic options to patients with medication-induced dry mouth will help improve their oral health and therefore maintain a better quality of life, general health, and well-being. (Barbe AG et al., 2018).

A research study in 2020, Title: Accuracy of a questionnaire on xerostomia as a screening tool for hyposalivation. Found that Hyposalivation was identified in 162 participants (40.3%) and a total of 229 (57.0%) answered affirmatively to at least one question. The responses to each question revealed variable reproducibility (K =

0.450–0.785) and satisfactory internal consistency (Cronbach's α = 0.70). Individuals with a larger number of positive answers had lower salivary flow (Spearman's ρ = –0.193; $p < 0.001$). The mean number of positive answers was greater in the group with a clinical diagnosis of hyposalivation compared to those without low salivary flow. The sensitivity of the screening tool was 64.8%, with an area under the ROC curve of 0.60 (95% confidence interval: 0.547–0.645; $p < 0.001$). The questionnaire proved to be useful for the epidemiological screening of individuals with possible hyposalivation. (Handerson Nunes de Carvalho et al., 2020).

A research study in 2020, Title: Saliva electrolyte analysis and xerostomia-related quality of life in nasopharyngeal carcinoma patients following intensity-modulated radiation therapy. Found that Saliva and questionnaire were collected before Intensity-modulated radiation therapy (IMRT), 1 month, 3 months, 6 months and 12 months after IMRT. The concentration of saliva electrolytes was detected using inductively coupled plasma-optical emission spectroscopy (ICP-OES). Saliva flow rate significantly decreased after IMRT. Decrease in the mean value of pH was observed but the difference is not statistically significant. The concentrations of potassium, iodine, and calcium decreased and chloride concentration increased after IMRT, while the concentrations of sodium, magnesium, copper or zinc were kept at the same level before and after treatment. Xerostomia-related quality of life was adversely affected by IMRT, but partially recovered after 1 year. The change of saliva electrolytes and xerostomia-related quality of life in patients undergone IMRT for Nasopharyngeal carcinoma (NPC). (Xinmiao Lan et al., 2020).

A research study in 2020, Title: Association between symptoms of xerostomia and dry eye in older people. Found that Symptomatic dry eye was reported by 31% of participants, and xerostomia by 21%. A positive correlation was observed between dry eye symptoms and Summated Xerostomia Inventory–Dutch Version questionnaire (SXI-D) scores (Spearman's rho = +0.379, $p < 0.001$). Overall, participants with symptomatic dry eye had higher SXI-D scores than those without (10.6 ± 3.6 vs. 8.1 ± 2.8, $p < 0.001$), and were more likely to report xerostomia, with an odds ratio (95% CI) of 2.25 (1.52–3.35; $p < 0.001$). Symptoms of xerostomia and dry eye were relatively common in the cohort of older adult participants. The

potentially debilitating implications of – and positive association between – the two types of sicca symptoms support the routine evaluation of xerostomia symptoms as part of the assessment of dry eye patients, and vice versa. (Michael T.M. Wang et al., 2020).

A research study in 2020, Title: Type 2 diabetes-induced hyposalivation of the submandibular gland through PINK1/Parkin-mediated mitophagy. Found that high glucose induced mitochondrial dysfunction and PINK1/Parkin-mediated mitophagy in cultivated SMG-C6 cells. HG also increased reactive oxygen species (ROS) and lessened activation of antioxidants in SMG-C6 cells. In addition, HG lowered ERK1/2 phosphorylation and HG-induced mitophagy was decreased after ERK1/2 was activated by LM22B-10. Altogether, these data suggest that ROS played a crucial role in diabetes-induced mitochondrial dysfunction and PINK1/Parkin-mediated mitophagy and ERK1/2 was required in HG-induced mitophagy in SMG (Ruo-Lan Xiang et al., 2020).

A research study in 2021, Title: Association between xerostomia, oral and general health, and obesity in adults. A cross-sectional pilot study. Found that According to XI, overall, 30.7% of respondents reported having xerostomia. The "gold standard" XI question on dry mouth had diagnostic sensitivity and specificity of 70.37% and 83.27%, respectively (AUC=0.768, p <0.001). Individuals with poor self-perceived health had a higher xerostomia OR of 6.31 (CI 95% 2.89-13.80, p <0.001), according to logistic regression. The OR was 3.46 (CI 95% 1.47-8.18, p =0.005) in the model with adjustments for tooth mobility, bone or respiratory conditions, and use of anxiolytics and antidepressants. Conclusions: This cross-sectional pilot investigation revealed a high frequency of xerostomia, which was substantially more common in women and increased with advancing age. Numerous systemic illnesses, psychiatric issues, and oral functional abnormalities, including tooth mobility, have all been related to xerostomia (Pérez-González et al., 2021).

A research study in 2022, Title: Xerostomia as a key predictor of physical frailty among community-dwelling older adults in Japan: a five-year prospective cohort study from The Otassha Study. Found that 166 participants (27.3 %)

complained of xerostomia. During follow-up, 109 participants (17.9 %) developed physical frailty. After adjusting for confounding factors, such as sex, age, educational level, polypharmacy, comorbidities, and smoking habit, xerostomia was significantly associated with the incidence of physical frailty (adjusted HR 1.65; 95 % confidence interval [CI] 1.09-2.52). (Yuki Ohara et al., 2022).

Related research on randomized controlled trial

A research study in 2015, Title: Efficacy and safety of pilocarpine mouthwash in elderly patients with xerostomia. Found that forty elderly patients were randomly divided into a pilocarpine mouthwash or water rinse (control) group. Outcomes were assessed by visual analog scale (VAS) scores and stimulated salivary flow rate before and 1 month after treatment. Patients recorded all adverse effects. They found that In the pilocarpine group, they evaluated safety in 24 patients and efficacy in 19 patients. In the water rinse group, they evaluated safety and efficacy in 14 patients. VAS scores were significantly reduced after pilocarpine mouthwash treatment (70 ± 12.9 to 47.9 ± 13.1, $p < 0.05$). Overall improvement was observed in 47% of the pilocarpine group compared to 14% of the controls ($p < 0.05$). Stimulated salivary flow rate significantly increased (0.71 ± 0.14 to 0.83 ± 0.12 mL/minute, $p < 0.05$) after pilocarpine mouthwash treatment. Five of 24 patients reported side effects after pilocarpine mouthwash use, predominantly limited to oral discomfort. Pilocarpine mouthwash relieved dry mouth symptoms and improved saliva production with minor side effects. (Tohru Tanigawa et al., 2015).

A research study in 2016, Title: Evaluation of Efficacy of an Herbal Compound on Dry Mouth in Patients With Head and Neck Cancers: A Randomized Clinical Trial. Found that Dry mouth is a common complication of radiotherapy for head and neck cancers. This study compared the efficacy of an herbal compound containing Malva sylvestris and Alcea digitata (Boiss) with artificial saliva (Hypozalix) for improving the symptoms of dry mouth in head and neck cancer patients. The study examined a total of 62 subjects assigned to 2 groups. The herbal compound and Hypozalix were administered for 4 weeks. Efficacy was assessed using the visual analog scale and by grading the degree of dry mouth. Both groups showed a significant difference

between visual analog scale before and following intervention. There was also a significant difference in visual analog scale between groups at 4 weeks after onset of intervention. The herbal group showed a significant difference between the grade of dry mouth before and after intervention, but no change was observed for grade of dry mouth in the Hypozalix group. This study supports the efficacy of the herbal compound for controlling symptoms of dry mouth in head and neck cancer patients. (Ameri, A et al., 2016).

A research study in 2016, Title: Influence of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus. Found that Dry mouth is common in elderly patients. However, the use of saliva substitute has been limited due to its inedibility. This study investigated the efficacy of oral moisturizing jelly (OMJ), a novel edible saliva substitute. A pre-post design was conducted in 118 elderly patients diagnosed with hypertension and/or diabetes mellitus. After using OMJ, signs and symptoms of dry mouth were compared with baseline data. The properties of saliva were compared between the OMJ use and non-use periods. The use of OMJ for 2 weeks significantly reduced symptoms of dry mouth, while the use for 1 month reduced the signs of xerostomia, prevented the decline of salivary pH(s) and improved buffering capacities. OMJ was equally effective in patients taking 1 to 2 and 3 to 7 medications. Furthermore, 65% of patients preferred OMJ over a commercial product. OMJ could be new edible saliva substitute for elderly patients suffering from dry mouth. (Supranee Dalodom et al., 2016).

A research study in 2016, Title: A randomized, double-blind, placebo-controlled trial of a traditional herbal formula, Yukmijihwang-tang in elderly subjects with xerostomia. Found that This study was designed as a randomized, placebo-controlled, double-blinded, two center trial. Ninety-six subjects aged 60–80 years who had experienced xerostomia for at least 3 months and presented with score>40 on the visual analog scale (VAS) for subjective oral dryness were recruited and randomly allocated to YMJ and placebo groups. YMJ or placebo was administered to each group for 8 weeks (3 g of YMJ or placebo, three times per day). The primary outcome was change of VAS for xerostomia from 0 to 8 weeks. VAS for xerostomia

was decreased by 22.04±22.76 in the YMJ group and 23.58±23.04 in the placebo group. YMJ had no effect on xerostomia. However, participants with BMIs lower than 29.37 kg/m2 showed improvement of xerostomia after 8 weeks of treatment with YMJ compared to placebo. In addition, YMJ improved oral moisture, which is associated with subjective oral dryness in the YMJ group, and the relationship between VAS for xerostomia and YD was significant. A trend was observed in which YMJ improved oral moisture status and subjective oral dryness in elderly subjects with lower BMI and greater tendency toward YD. (Gajin Han et al., 2016).

A research study in 2017, Title: The effectiveness of thyme honey for the management of treatment-induced xerostomia in head and neck cancer patients: A feasibility randomized control trial. Found that Linear Mixed Models revealed the statistically significant effect of the intervention on xerostomia ($F = 8.474$, $p < 0.001$) and overall quality of life ($F = 13.158$, $p < 0.001$). Moreover, Generalised Estimating Equations revealed a statistically significant effect on strong and unbearable pain ($F = 10.524$, $p < 0.001$) and dysphagia ($F = 4.525$, $p = 0.033$).The study has demonstrated the safety and efficacy findings of Thyme honey in head and neck cancer patients for the management of treatment induced xerostomia. (Andreas Charalambous et al., 2017).

A research study in 2017, Title: Efficacy of a traditional Persian medicine preparation for radiation-induced xerostomia: a randomized, open-label, active-controlled trial. Found that They Synthesize the traditional use of Alcea digitata and Malva sylvestris with their known beneficial effects from recent studies, they evaluated the efficacy of the herbs in the quality of life (QOL) of HNC patients with radiation-induced xerostomia. This study is a randomized, double-arm, open-label active-controlled clinical trial. They evaluated the effect of A. digitata and M. sylvestris on QOL of HNC patients with radiation-induced xerostomia compared with Hypozalix (artificial saliva). Patients were enrolled from the Imam Hossein Hospital's oncology clinic in Shahid Beheshti University of Medical Sciences, Tehran, Iran. They found that between-group analysis showed that the intervention group patients obtained significantly lower (better) total EORTC QLQ-H&N 35 scores as compared to the control group at the end of the intervention period ($p= 0.007$). Mean scores of

dry mouth of EORTC QLQ-H&N 35 was also significantly lower (better) in the intervention group as compared to the control group (p = 0.017). Traditional Persian medicine preparation of hollyhocks and common mallow should be considered as a suitable treatment for xerostomia and improving QOL in HNC patients with radiation-induced xerostomia. (Ghazaleh Heydarirad et al., 2017).

A research study in 2019, Title: Comprehensive investigation of saliva replacement liquids for the treatment of xerostomia. Found that the aim of this study was to comprehensively investigate the most relevant physicochemical properties of three products frequently used in the clinics and compare them to unstimulated whole saliva (UWS). Sialin-Sigma®, Glandomed® and Xylitol CVS HealthTM Dry Mouth Spray were characterized regarding their pH, osmolality, electrical conductivity, buffer capacity, rheological behaviour, microstructure, surface tension and wettability and compared to UWS. The influence of residual saliva was examined under consideration of the conditions of xerostomia to assess whether the quantity given in the instruction for use is appropriate. All three products showed significant differences to UWS regarding the values received. Only Xylitol CVS HealthTM Dry Mouth Spray showed a comparable wettability. It could be further determined that the recommended doses were too low. These data can not only be used for an improved understanding of saliva, but also for the development of a replacement fluid to successfully alleviate xerostomia (C. Spirk et al., 2019).

A research study in 2019, Title: Radiotherapy-induced xerostomia: a randomised, double-blind, controlled trial of Visco-ease™ oral spray compared with placebo in patients with cancer of the head and neck. Found that Radiotherapy-induced xerostomia (RIX) is a common and untreatable side effect of radiotherapy to the head and neck. Visco-ease™ mouth spray (Lamellar Biomedical Ltd), a new product that is made from lamellar body mimetics, reduces the viscosity of saliva ex *vivo*. The purpose of this study was to evaluate its safety and effectiveness in the treatment of RIX in 43 patients with cancer of the head and neck. They were randomised into the Visco-ease™ or placebo groups, and asked to complete the Groningen radiotherapy-induced xerostomia (GRIX) questionnaire each week. The primary endpoint was a change in GRIX score from baseline to end of treatment.

There was no difference in scores between the two groups, and none of the patients had device-related serious adverse events. Visco-ease™ oral spray was safe and tolerable but no better than placebo in reducing RIX in this group of patients. (C. Paterson et al., 2019).

A research study in 2019, Title: Effect of True and Sham Acupuncture on Radiation-Induced Xerostomia Among Patients With Head and Neck Cancer: A Randomized Clinical Trial. They perform in 2-center, phase 3, randomized clinical trial compared a standard care control (SCC) with true acupuncture (TA) and sham acupuncture (SA) among patients with oropharyngeal or nasopharyngeal carcinoma who were undergoing radiation therapy in comprehensive cancer centers in the United States and China. Patients were enrolled between December 16, 2011, and July 7, 2015. Final follow-up was August 15, 2016. Analyses were conducted February 1 through 28, 2019. Either TA or SA using a validated acupuncture placebo device was performed 3 times per week during a 6- to 7-week course of radiation therapy. The primary end point was RIX, as determined by the Xerostomia Questionnaire in which a higher score indicates worse RIX, for combined institutions 1 year after radiation therapy ended. Secondary outcomes included incidence of clinically significant xerostomia (score >30), salivary flow, quality of life, salivary constituents, and role of baseline expectancy related to acupuncture on outcomes. Results: Of 399 patients randomized, 339 were included in the final analysis (mean [S.D.] age, 51.3 [11.7] years; age range, 21-79 years; 258 [77.6%] men), including 112 patients in the TA group, 115 patients in the SA group, and 112 patients in the SCC group. For the primary aim, the adjusted least square mean (S.D.) xerostomia score in the TA group (26.6 [17.7]) was significantly lower than in the SCC group (34.8 [18.7]) (p = .001; effect size = -0.44) and marginally lower but not statistically significant different from the SA group (31.3 [18.6]) (p = .06; effect size = -0.26). Incidence of clinically significant xerostomia 1 year after radiation therapy ended followed a similar pattern, with 38 patients in the TA group (34.6%), 54 patients in the SA group (47.8%), and 60 patients in the SCC group (55.1%) experiencing clinically significant xerostomia (p = .009). Post hoc comparisons revealed a significant difference between the TA and SCC groups at both institutions, but TA was significantly different from SA only at

Fudan University Cancer Center, Shanghai, China (estimated difference [SE]: TA vs SCC, -9.9 [2.5]; $p < .001$; SA vs SCC, -1.7 [2.5]; $p = .50$; TA vs SA, -8.2 [2.5]; $p = .001$), and SA was significantly different from SCC only at the University of Texas MD Anderson Cancer Center, Houston, Texas (estimated difference [SE]: TA vs SCC, -8.1 [3.4]; $p = .016$; SA vs SCC, -10.5 [3.3]; $p = .002$; TA vs SA, 2.4 [3.2]; $p = .45$). This randomized clinical trial found that TA resulted in significantly fewer and less severe RIX symptoms 1 year after treatment vs SCC. However, further studies are needed to confirm clinical relevance and generalizability of this finding and to evaluate inconsistencies in response to sham acupuncture between patients in the United States and China. (Garcia MK et al., 2019).

A research study in 2020, Title: Effect of photobiomodulation on salivary flow and composition, xerostomia and quality of life of patients during head and neck radiotherapy in short term follow-up: A randomized controlled clinical trial. Found that their study aimed to assess whether photobiomodulation (PBM) can minimize hyposalivation, xerostomia and qualitative changes on saliva and improve quality of life in patients undergoing radiotherapy in short-term follow-up. Twenty-one patients were randomly divided into two groups: sham group (SG) and laser group (LG). A diode laser was used for intra- (660 nm, 10 J/cm^2, 0.28 J per point, 40 mW) and extra-oral (810 nm, 25 J/cm2, 0.7 J per point, 40 mW) applications over the salivary glands, three times a week, during the entire radiotherapy period. In SG, the tip of the instrument was sealed with blue rubber to prevent the passage of light. Xerostomia and pH were evaluated and unstimulated and stimulated salivary flow was determined before the start of radiotherapy (T1), after the 15th session (T2), after the end of radiotherapy (T3) and 60 days after radiotherapy (T4). Concentrations of calcium, total proteins, chloride, sodium, potassium and amylase and catalase activities were evaluated in stimulated saliva samples. Quality of life was assessed at times T1 and T4. Generalized estimating equations were used to assess differences in the outcome between times and groups. All patients showed worsening in unstimulated ($p = .003$) and stimulated ($p < .001$) salivary flow, xerostomia ($p < .05$) and quality of life during radiotherapy ($p = .001$). An increase in chloride concentrations was observed at times T3 and T4 ($p < 0,05$), and a reduction in

amylase activity at T3 (p < .05). Unstimulated saliva pH was higher in LG than SG at T3 (p = .037). No difference between groups was noted in relation to salivary flow and composition, xerostomia or quality of life. The results suggest that PBM may help in preserving salivary pH during radiotherapy. (Gabriel Campos Louzeiro et al., 2020).

A research study in 2020, Title: Comparison of salivary nitric oxide and oral health in diabetic patients with and without xerostomia. Found that In this case control study, 70 patients with T2DM, which were matched according to age, sex, type of disease control, were enrolled conveniently. The subjects based on abeslang test were allocated to the two groups; 35 patients with xerostomia and 35 patients without xerostomia. Unstimulated whole saliva was collected by spitting method. nitric oxide (NO) levels was measured by ELISA method using Griess reaction. Data was analyzed using t-test, ANOVA and logistic regression analysis to examine the association of salivary NO and xerostomia. The mean and standard deviation of salivary NO in the diabetic subjects with xerostomia was significantly lower than diabetic subjects without xerostomia (138 ± 94.58 µmol/L vs. 356.61 ± 302.81 µmol/L (p-Value = 0.001). In logistic regression analysis, salivary NO level was associated with 0.994 fold decreased risk of xerostomia in diabetic subjects after adjustment for age, gender, FBS and HbA1c. The present study indicates salivary nitric oxide level was a predictor of xerostomia in diabetic patients. More longitudinal studies are necessary to understand the association of salivary NO level with diabetes-induced xerostomia. (Pegah Afsaneh Abadi et al., 2020).

A research study in 2020, Title: Xerostomia-related quality of life for patients with oropharyngeal carcinoma treated with proton therapy. Found that Patients receiving intensity-modulated proton therapy (IMPT) reported the greatest xerostomia-related QoL impairment at 6 weeks on treatment, with a 49% improvement by 10 weeks after treatment; however, Xerostomia-Related quality-of-life Scale (XeQoLS) scores remained above baseline after 2 years. As they aim to establish the value of IMPT in oropharyngeal tumors to de-intensify treatment over conventional therapy, these data help inform discussions about xerostomia-related

quality of life for patients with oropharyngeal cancer treated with IMPT. (Alexander F. Bagley et al., 2020).

A research study in 2020, Title: Effects of Phyllanthus emblica spray interventions on xerostomia after general anesthesia for gynecologic tracheal intubation: A randomised controlled trial. Found that 64 participants were enrolled, 6 were lost to follow-up, the remaining 58 were available for analysis. Mean age was 40.05 ± 10.35 and all were female. There were no statistically significant differences between the two groups in terms of age, body mass index, allergy history, surgical history, TCM diagnosis, grade, syndrome type, or duration of anesthesia and preoperative water fasting. After six hours of treatment, mean salivary flow rate scores at 3-h to 6-h significantly increased in the intervention group by 0.21 ± 0.14-0.29 ± 0.18 and by 0.14 ± 0.11-0.20 ± 0.12 in the controls (p = 0.028). Similar improvements were observed in the intervention group, compared to the control group, with respect to the grade of oral mucosa moisture at 1, 3, 4, 5 and 6 h (p = 0.034). Conclusions: The use of P. emblica spray appeared to be superior to warm water spray for treating postoperative xerostomia. (Haixia He et al., 2020).

A research study in 2021, Title: Duration of Effect of Biotène® Spray in Patients with Symptomatic Dry Mouth - A Pilot Study. Found that Study Design is double-blind randomized controlled cross-over trial compared the duration of effect of two agents on relieving xerostomia in adult subjects recruited through convenience sampling. Following a xerostomia questionnaire, qualifying subjects with an unstimulated whole saliva flow rate of ≤0.20 mL/min rated their baseline level of discomfort from oral dryness, and received a single dose (3 sprays) of Biotène® Spray or water (active-control). Subjects indicated their level of oral discomfort every 15 minutes, and the precise time when relief ceased. After a minimum 48-hour washout, subjects repeated the exercise with the alternative product. Results: The baseline severity of discomfort from oral dryness among qualifying subjects was significantly related to their level of hyposalivation (p=0.001). The mean duration of effect of Biotène® Spray was 27 ± 25 minutes, which was not significantly different from water (26 ± 25 minutes; p=0.88; n =25). Conclusion: Biotène® Spray and water spray had variable durations of effect averaging approximately 30 minutes. The results of this

pilot study provide guidance regarding anticipated usage and dispensing needs for patients with objective xerostomia. (Christine Bambi Lung et al., 2021).

2.8 Summary

Dry mouth, also known as xerostomia, is a condition caused by hypofunction of the salivary glands, which can be caused by a variety of systemic disorders, radiation to treat head and neck cancer, or age-related physical deterioration. Elderly people are more likely to suffer from dry mouth, also known as xerostomia . The report of the 8th National Oral Health Survey in Thailand, 2017, which found that elderly people suffer from xerostomia by 16.5%. When elderly people have a dry mouth, it feels like cotton wool in their mouth. Difficulties with eating or swallowing food, as well as speaking, have a detrimental influence on the quality of life.

According to literature reviews, the main risk factor for xerostomia is that it generally occurs in the elderly people and those with diabetes because these variables reduce the function of the salivary glands via neuropathic and microvascular abnormalities, including endothelial dysfunction and deterioration of microcirculation, that are associated with DM may play a role in disturbed salivary flow and composition. Persistent hyperglycemia caused by diabetes dysregulation may result in water loss, resulting in reduced salivation, hyposalivation, and finally xerostomia. Diabetic elderly patients are becoming more prevalent in Thailand. As a result, it should be decided for the diabetic elderly population to minimize xerostomia among diabetes patients. As a result, the elderly people with diabetes are at a significant risk of xerostomia. Typically, dentists can treat xerostomia with artificial saliva or chemical medications, rescuing the salivary gland function is still limited due to glandular damage. Therefore, choosing natural herbs with important substances to relieve xerostomia symptoms, such as *Cordyceps militaris* is a cordycepin with anti-aging, anti-inflammatory, or antioxidant properties. Cordycepin has also been demonstrated to decrease mitochondrial damage and boost immune responses by scavenging ROS. It may also be able to promote salivary gland function in diabetic individuals with xerostomia.

2.9 Conceptual framework

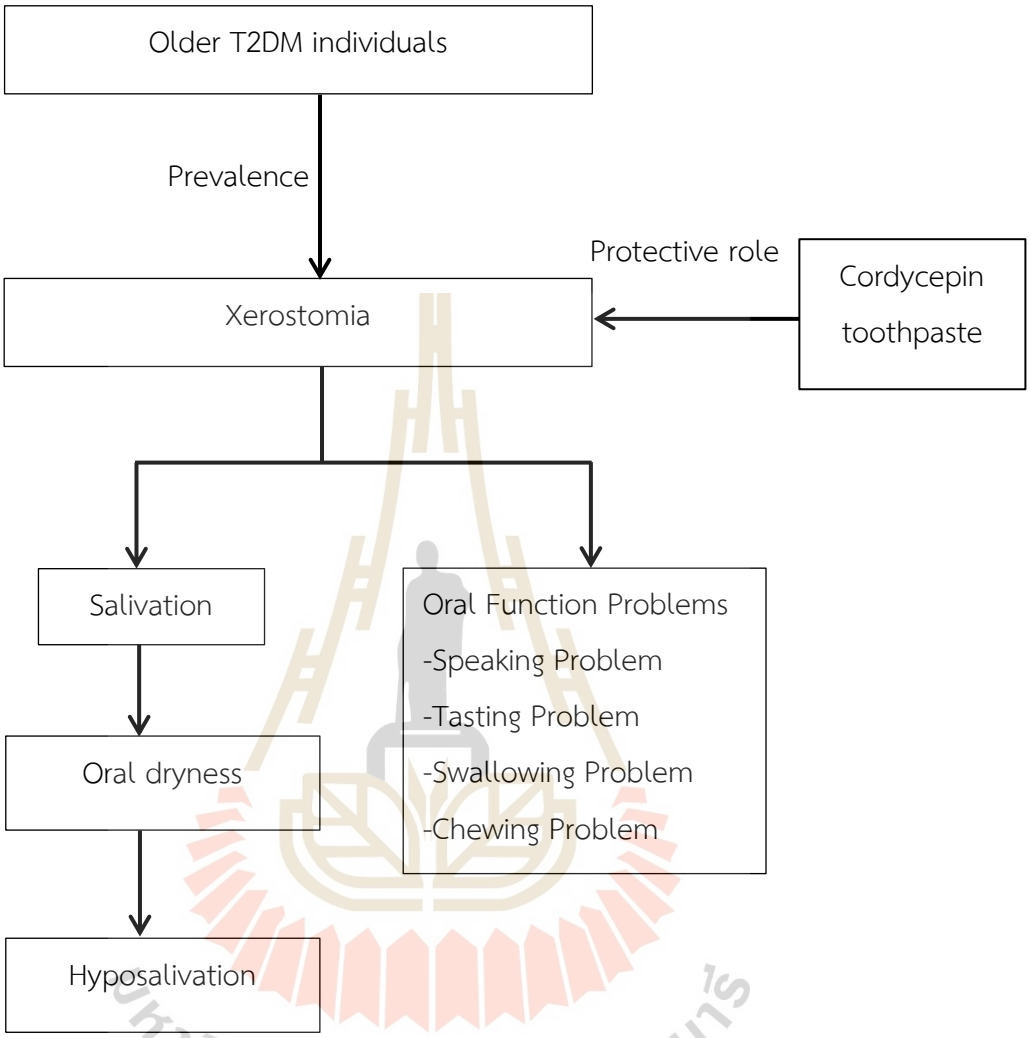


Figure 2.5 Conceptual framework of this study.

2.10 Study flowchart

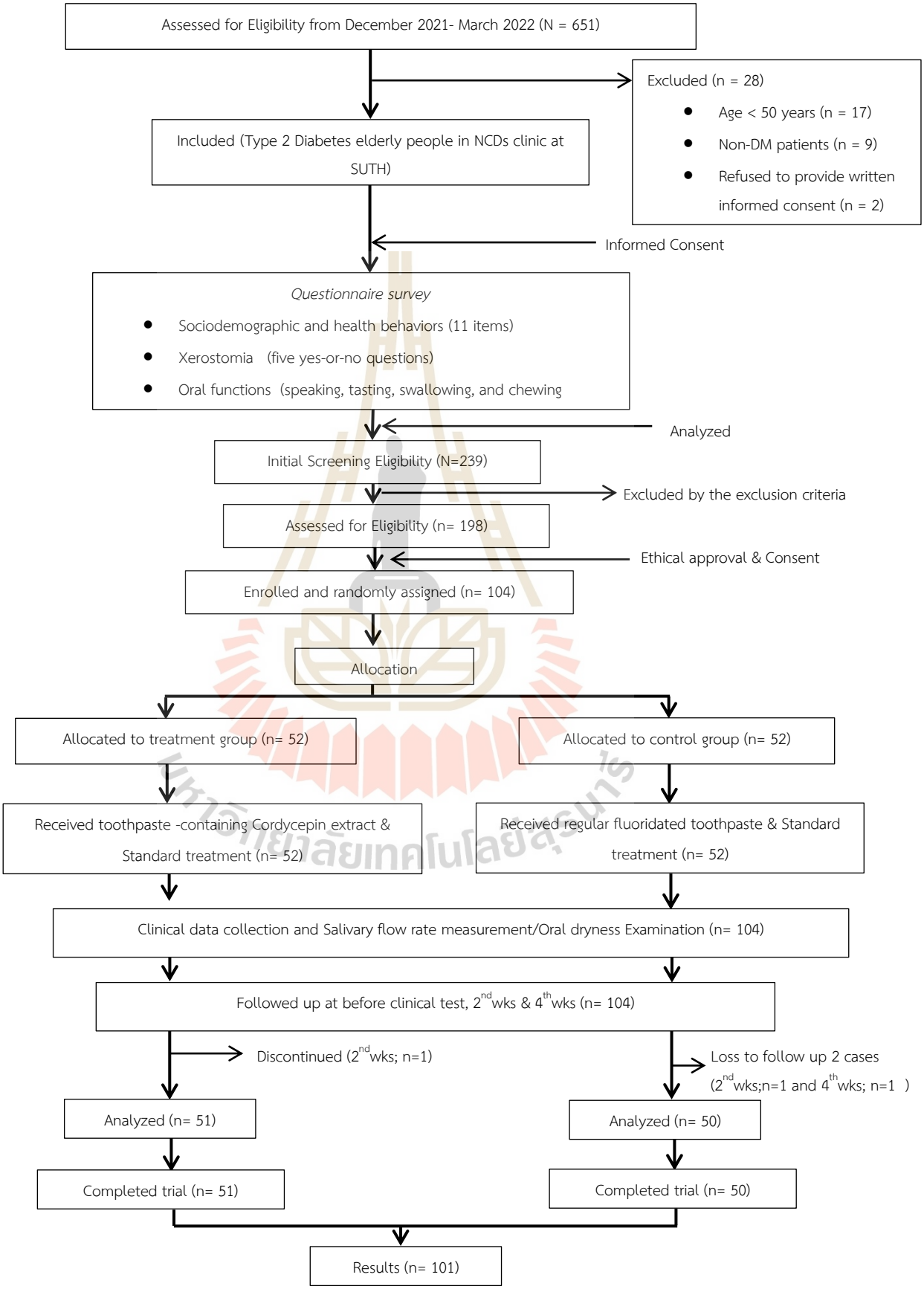


Figure 2.6 Study flowchart.

CHAPTER III

RESERCH METHODLOGY

In this study, titled "The Protective Role of Cordycepin in Oral Health Care of The Elderly Patients with Xerostomia" In this chapter, the research methodology is divided into various topics consisting of 3.1 Study design, 3.2 Study area, 3.3 Population and Sample size, 3.4 Sample sampling, 3.5 Material and method, 3.6 Instrumentation, 3.7 Construction and Efficiency of the instruments, 3.8 Data collection, 3.9 Data analysis, and 3.10 Ethical statement.

3.1 Study design

This study is a randomized clinical trial (RCT) type of clinical superiority trial to determine if the treatment group treated with toothpaste containing cordycepin extract combined with standard treatment was more effective than the control group that received normal fluoridated toothpaste combined with standard treatment. A double-blind study with allocation concealment, simple randomization was used. The study was divided into two parts:

1. Conduct a survey of the population composed of the elderly patients with diabetes who visit the noncommunicable diseases (NCDs) clinic at Suranaree University of Technology Hospital in four consecutive months (December 2021–March 2022). This study was conducted by giving a questionnaire about sociodemographic and health behavioral information and oral function, and then examining for association of the factors.

2. A clinical trial of cordycepin extract toothpaste for oral health care in diabetic elderly people with xerostomia was conducted. The toothpaste containing

cordycepin extract is a collaboration product of Lion Corporation (Thailand) Limited and Suranaree University of Technology, developed from laboratory research on the efficacy of cordycepin on human salivary gland cells and the expression of genes involved in salivation in human salivary gland cells. Previous studies examined the optimal concentration of cordycepin (Jaiboonma, A. et al., 2020), with the next step being a clinical trial based on the experiment on diabetic elderly people with xerostomia who received care at Suranaree University of Technology Hospital's non-communicable diseases (NCDs) clinic.

3.2 Study area

A survey population and clinical tests were performed on diabetic elderly people with xerostomia who received service at the non-communicable diseases (NCDs) clinic in Suranaree University of Technology Hospital.

3.3 Population and Sample size

3.3.1 Prevalence survey

A total of 651 older individuals who received ongoing care at 2 non-communicable disease clinics (NCDs) of Suranaree University Hospital, Thailand, were registered during the study period. Twenty-eight individuals were excluded, as shown in conceptual framework (Chapter 2). A total of 623 older T2DM individuals were included in this study. The sample size was calculated using the formula $n = Z^2 \times p(1 - p)/d^2$, where n = number of T2DM elderly patients, Z = 1.96 (standard normal variant at 95% CI), d = 5% (absolute error or precision), and p = 27.3% (Yuki Ohara et al., 2022)., the expected prevalence. According to the calculation formula below.

$$n = \frac{Z^2 \times p(1 - p)}{d^2}$$

$$= \frac{(1.96)^2(0.273)(1-0.273)}{0.05^2}$$

$$= 304.8 \approx 305 \text{ cases}$$

Thus, the calculated sample size was 305 elderly subjects but I collectively surveyed all the patients (N=623) over the course of four successive months (December 2021–March 2022).

3.3.2 Randomized clinical trial

The population is elderly people with diabetes who suffer from xerostomia. They received services in the NCDs clinic of Suranaree University of Technology Hospital from the prevalence survey. The samples in this study were randomly allocated by calculating the sample size of the two independent groups. Previous studies have shown that the standard deviation of oral hygiene products with xerostomia is 0.18 (Haixia He et al., 2020). I stipulated that if the difference between the average saliva flow rate between the treatment group and the control group is 0.1 ml, it will be considered clinically statistically significant. (Villa, A. et al., 2014) and (Farsi NM., 2007). According to the formula

$$n/gr = \frac{2\,(Z\alpha_{/2} + Z\beta)^2\,\sigma^2}{\delta^2}$$

Replace the value in the formula as follows:

$$n/gr = \frac{2\,(1.96 + 0.842)^2\;0.18^2}{0.1^2}$$

$$= \frac{2\,(7.85)\;0.03}{0.01}$$

= 47 samples per group.

Then, the dropout rate is calculated as 10 % = 51.7, or ≈ 52 samples per group. Therefore, the sample sizes used in this clinical test were 104 samples, divided into treatment and control groups, each of 52 samples.

3.4 Sample sampling

The population targeted by the general data survey is elderly people with diabetes who received services at the non-communicable disease (NCDs) clinic of the Suranaree University of Technology Hospital in 4 months. I performed sample sampling in simple randomization. Divided into two groups: treatment group and control group, each with 52 people.

3.5 Materials and methods

The population survey uses a questionnaires to measure both quantitative and qualitative aspects. I divided types of toothpastes used by participants into three groups according to the specific ingredients: toothpaste containing sodium lauryl sulfate (SLS) (Type 1), toothpaste containing spicy herbal extracts e.g. Eugenia Caryophyllus (Clove) Leaf Oil, Clove Oil, Peppermint Oil, Spearmint Oil, Olive Oil, Menthol, Eucalyptus Oil, Fennel Extract, Glycyrrhiza Extract, Cinnamon Bark Extract, Camphor (Type 2), and toothpaste containing artificial sweeteners e.g. Sorbital, Xylitol, Stevia, Aspartame, Sodium Saccharin, Sodium cyclamate, Acesulfame potassium, Sucralose (Type 3). The fluoride content of toothpastes in this study ranged between 1000 to 1500 ppm (parts per million).

The clinical test procedure of toothpaste containing cordycepin extract and standard treatment will be studied in the treatment group of the calculated sample size compared to the control group that received normal fluoridated toothpaste combined with standard treatment. For salivary flow rate measurement, I used the unstimulated saliva method because low salivary flow rate without stimulation is caused by xerostomia. (Sreebny, L. M., & Valdini, A., 1988). In this study, I measured salivary flow rate three times: before the clinical test (baseline data collections), 2 weeks, and 4 weeks (after the clinical test). (Ameri, A et al., 2016), (Thatreenaranon,S., 2018).

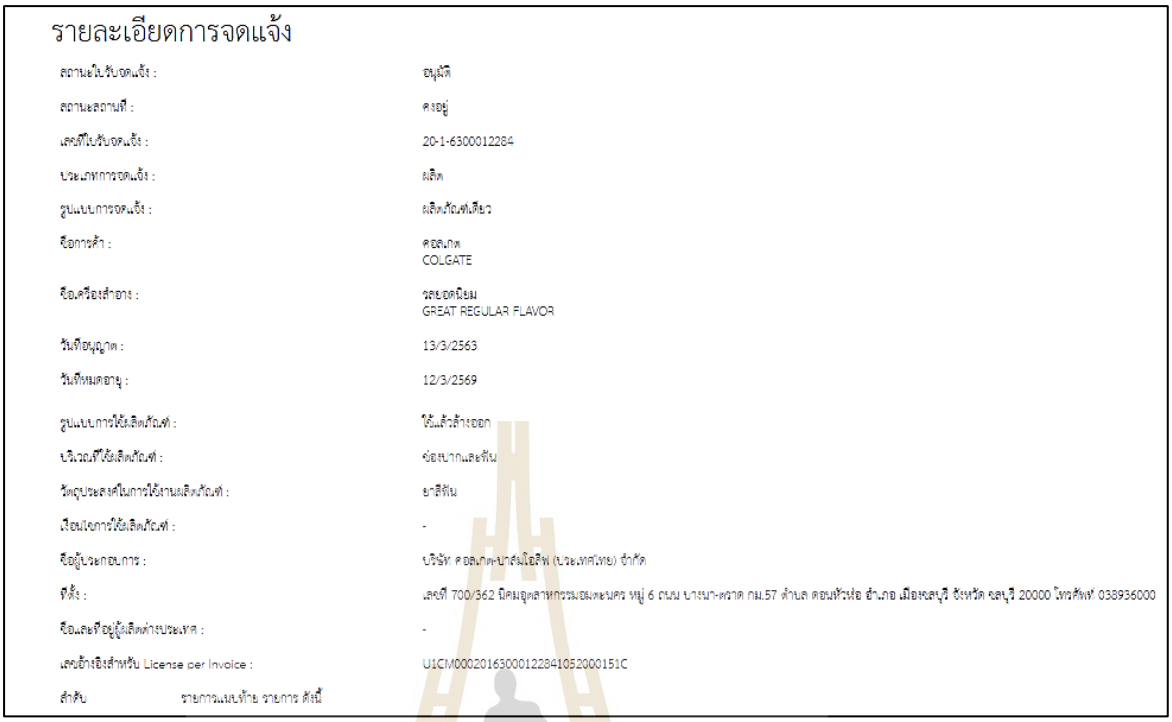
3.5.1 Safety assurance of the toothpaste products used in this study

1. Toothpaste products used in the control group

The product that I used in the control group was fluoride toothpaste, which contributes to the prevention of tooth decay. For cleanliness, brush for at least 2 minutes each time, at least twice a day, in the morning and before bedtime on a daily basis, as shown in Figure 3.1

Figure 3.1 Toothpaste containing fluoride used in the control group.

The popular flavor of fluoride toothpaste used in this control group has passed the approval review from the Food and Drug Administration (FDA), Ministry of Public Health (Thailand), Product Type: Cosmetics, Cosmetic name: COLGATE GREAT REGULAR FLAVOR TOOTHPASTE. Authorization date: 13 March 2020 to 12 March 2026. Notification number: 20-1-6300012284 was completed as detailed in Figure 3.2



รายละเอียดการจดแจ้ง

สถานะใบรับจดแจ้ง :	อนุมัติ
สถานะสถานที่ :	คงอยู่
เลขที่ใบรับจดแจ้ง :	20-1-6300012284
ประเภทการจดแจ้ง :	ผลิต
รูปแบบการจดแจ้ง :	ผลิตภัณฑ์เดียว
ชื่อการค้า :	คอลเกต COLGATE
ชื่อเครื่องสำอาง :	รสยอดนิยม GREAT REGULAR FLAVOR
วันที่อนุญาต :	13/3/2563
วันที่หมดอายุ :	12/3/2569
รูปแบบการใช้ผลิตภัณฑ์ :	ใช้แล้วล้างออก
บริเวณที่ใช้ผลิตภัณฑ์ :	ช่องปากและฟัน
วัตถุประสงค์ในการใช้งานผลิตภัณฑ์ :	ยาสีฟัน
เงื่อนไขการใช้ผลิตภัณฑ์ :	-
ชื่อผู้ประกอบการ :	บริษัท คอลเกต-ปาล์มโอลีฟ (ประเทศไทย) จำกัด
ที่ตั้ง :	เลขที่ 700/362 นิคมอุตสาหกรรมมหานคร หมู่ 6 ถนน บางนา-ตราด กม.57 ตำบล คอนหัวช้าง อำเภอ เมืองฉะเชิงเทรา จังหวัด ฉะเชิงเทรา 20000 โทรศัพท์ 038936000
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Figure 3.2 Approval information of toothpaste products in the control group from the Food and Drug Administration (FDA), Ministry of Public Health (Thailand).

2. Toothpaste products used in the treatment group

The toothpaste that I used in the treatment group is a toothpaste with *Cordyceps militaris* extract. It is a Hydration Plus toothpaste with a mixture of Cordycepin extract that has been developed into a concentrated formula found to be suitable and safe for the salivation process of salivary gland cells in the laboratory. This product was developed as the result of research collaborations between Lion Corporation (Thailand) Limited, the Institute of Dentistry, the Institute of Agricultural Technology Suranaree University of Technology.

Cordycepin extract toothpaste contains an appropriate concentration of cordycepin extract and is safe for salivary gland cells. The concentration of cordycepin extract in toothpaste was based on a research study titled "Cordycepin attenuates Salivary Hypofunction through the Prevention of Oxidative Stress in Human Submandibular Gland Cells," published in the International Journal of Medical Sciences (Jaiboonma, A. et al., 2020).

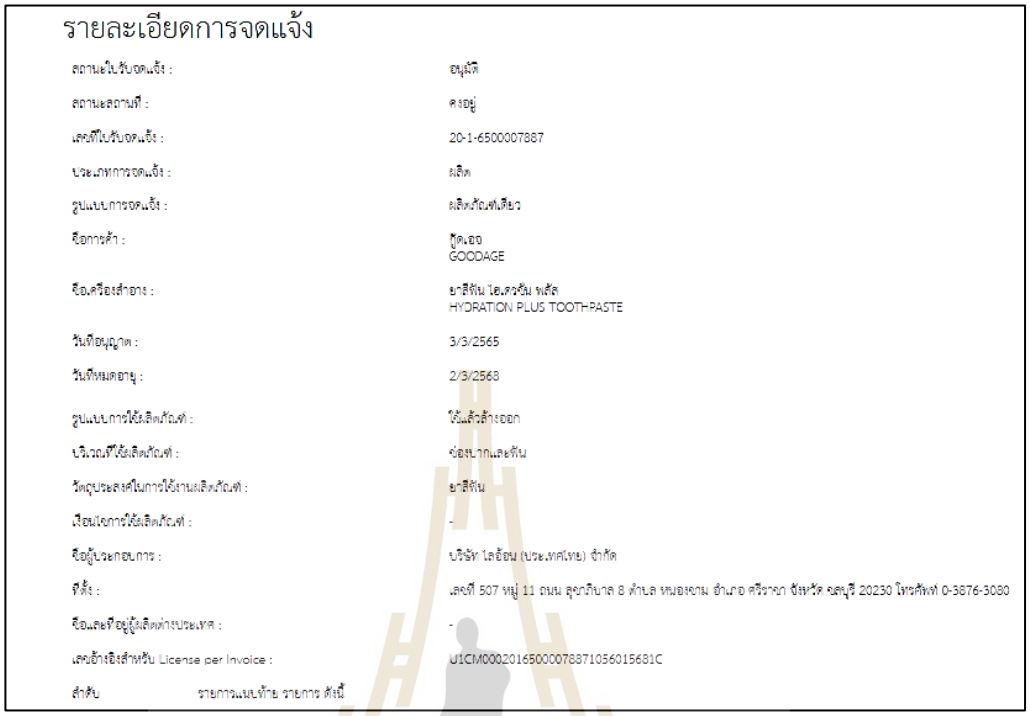
Furthermore, Lion Corporation (Thailand) Limited, which is the cooperative supporter in the production of this toothpaste containing cordycepin extract, has been certified for microbiological testing laboratories and analytical departments. Product Research and Development Department: It is an agency that has been certified for the ability of a public health/consumer protection testing laboratory according to ISO/IEC 17025 according to the Cosmetics Act, B.E. 2558, item 6 (toothpaste), as of May 20, 2021, to May 19, 2023 (registration number 1337/64), as shown in Figure 3.3

Figure 3.3 Laboratory ISO/IEC accreditation information, Lion Corporation (Thailand) Limited.

Furthermore, the toothpaste containing cordycepin extract used in this experiment was approved by the Food and Drug Administration (FDA) of the Ministry of Public Health (Thailand), product type: cosmetics, Cosmetic name: GOODAGE HYDRATION PLUS TOOTHPASTE (as shown in Figure 3.4). Date of authorization: March 3, 2022. Notification number: 20-1-6500007887, valid until March 2, 2025, as shown in Figure 3.5. Directions for use: Brush thoroughly at least twice a day (in the morning

and before bedtime)or as directed by your dental professional. Do not swallow. Rinse with a small amount of water.

Figure 3.4 toothpaste containing cordycepin extract used in the treatment group.



รายละเอียดการจดแจ้ง

สถานะใบรับจดแจ้ง :	อนุมัติ
สถานะสถานที่ :	คงอยู่
เลขที่ใบรับจดแจ้ง :	20-1-6500007887
ประเภทการจดแจ้ง :	ผลิต
รูปแบบการจดแจ้ง :	ผลิตภัณฑ์เดียว
ชื่อการค้า :	กู๊ดเอจ GOODAGE
ชื่อเครื่องสำอาง :	ยาสีฟัน ไฮเดรชั่น พลัส HYDRATION PLUS TOOTHPASTE
วันที่อนุญาต :	3/3/2565
วันที่หมดอายุ :	2/3/2568
รูปแบบการใช้ผลิตภัณฑ์ :	ใช้แล้วล้างออก
บริเวณที่ใช้ผลิตภัณฑ์ :	ช่องปากและฟัน
วัตถุประสงค์ในการใช้งานผลิตภัณฑ์ :	ยาสีฟัน
เงื่อนไขการใช้ผลิตภัณฑ์ :	-
ชื่อผู้ประกอบการ :	บริษัท ไลอ้อน (ประเทศไทย) จำกัด
ที่ตั้ง :	เลขที่ 507 หมู่ 11 ถนน สุขาภิบาล 8 ตำบล หนองขาม อำเภอ ศรีราชา จังหวัด ชลบุรี 20230 โทรศัพท์ 0-3876-3080
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Figure 3.5 Approval information of toothpaste products in the treatment group from the Food and Drug Administration (FDA), Ministry of Public Health (Thailand).

Table 3.1 Comparison of toothpaste information between the control group and treatment group.

Toothpaste details	Groups	
	Control group (Normal fluoridated toothpaste)	**Treatment group (Toothpaste containing cordycepin extract)**
Brand	Colgate	GoodAge
Made by	Colgate-Palmolive (Thailand) Co Ltd.	Lion Corporation (Thailand) Limited.
Active ingredients	1.Sodium Monofluorophosphate (Active fluoride ion) 1,450 ppm	1.Sodium fluoride (Active fluoride ion) 1,500 ppm 2. cordycepin extract from *Cordyceps Militaris* 12.5 Micromolar (μM)
Containing SLS	Yes	No
Size	100 grams	90 grams
Approval by the Thai FDA	Approved	Approved

3.6 Instrumentation

Questionnaire surveys and clinical record forms were used as tools in the following four issues:

1.Sociodemographic and Health behavior is a questionnaire for 11 items consisting of Gender, Age, Education, Years of diabetes, Blood sugar level, Systemic disease, Medication, Smoking, Alcohol consumption, Toothpaste brands, and Denture wearing.

2.Oral function consists of 4 parts:

2.1 Speaking problems are rating scale questionnaires. The question is, Do you have speaking problems? If yes, what is your scale? the answer options have five scales, including

1 None

2 Very mild

3 Mild

4 Moderate

5 Severe

In interpreting the speaking problems questionnaire, this is done by adjusting the basic scores of all variables on average. Then divide the total score of each variable by the number of clauses of each variable. Calculate the score from the maximum point minus the minimum point, divided by grade level. In summary, the 3 levels are: Good, Moderate, and Poor as follows

$$\frac{\text{Maximum point - Minimum point}}{\text{Grade level}} = \frac{5 - 1}{3} = 1.33$$

Criteria for speaking ability level

The mean range of 3.68-5.00 indicated The ability to speak is poor

The mean range of 2.34 - 3.67 indicated The ability to speak is moderate

The mean range of 1.00–2.33 indicated The ability to speak is at a good

2.2 Tasting problems are rating scale questionnaires. The question is, Do you have taste problems? If yes, what scale are you in?. The answer options have five scales, including

1 None

2 Very mild

3 Mild

4 Moderate

5 Severe

In interpreting the taste problems questionnaire, this is done by adjusting the basic scores of all variables on average. Then divide the total score of each variable by the number of clauses of each variable. Calculate the score from the maximum point minus the minimum point, divided by grade level. In summary, the 3 levels are: Good, Moderate, and Poor as follows

$$\frac{\text{Maximum point - Minimum point}}{\text{Grade level}} = \frac{5 - 1}{3} = 1.33$$

Criteria for taste ability level

The mean range of 3.68 - 5.00 indicated	The ability to taste is poor
The mean range of 2.34 - 3.67 indicated	The ability to taste is moderate
The mean range of 1.00 - 2.33 indicated	The ability to taste is good

2.3 Swallowing problems is an evaluation of swallowing ability using a functional oral intake score (FOIS). It is used to assess the degree of swallowing according to the type of food that can be swallowed, classified into 7 levels (Crary MA et al., 2005) as follows:

Levels 1 through 3 relate to varying degrees of nonoral feeding; levels 4 through 7 relate to varying degrees of oral feeding without nonoral supplementation, whereas level 4 is taken by mouth with soft food as a single meat. Level 5 is taken orally, which must be ground or chopped first. Level 6 can be taken orally, but solid food should be avoided; level 7 is usually eaten orally.

The interpretation of the functional oral intake scale (FOIS) is divided into the following 7 levels (Crary MA et al., 2005)

TUBE DEPENDENT (levels 1-3)

1 No oral intake

2 Tube dependent with minimal/inconsistent oral intake

3 Tube supplements with consistent oral intake

TOTAL ORAL INTAKE (levels 4-7)

4 Total oral intake of a single consistency

5 Total oral intake of multiple consistencies requiring special preparation

6 Total oral intake with no special preparation, but must avoid specific foods or liquid items

7 Total oral intake with no restrictions

In interpreting the functional oral intake score, this is done by adjusting the basic scores of all variables on average. Then divide the total score of each variable by the number of clauses of each variable. Calculate the score from the maximum point minus the minimum point, divided by grade level. In summary, the 3 levels are: Good, Moderate, and Poor as follows

$$\frac{\text{Maximum point - Minimum point}}{\text{Grade level}} = \frac{7 - 1}{3} = 2.00$$

Criteria for swallowing ability level

The mean range of 5.02 - 7.00 indicated The ability to swallowing is good

The mean range of 3.01 - 5.01 indicated The ability to swallowing is moderate

The mean range of 1.00 - 3.00 indicated The ability to swallowing is poor

2.4 Chewing function: fill out the chewing function questionnaire. It is a question of patient ability in 14 kinds of chewing. This questionnaire was adapted from previous research by using the Likert scale with 3 levels. The scores are ranked from lowest to highest: "could not chew at all" is set to 0 point, "difficult to chew" is set to 1 point, and "could chew other" is set to 2 points, if "Never eaten or any other" is set to N/A. The assessment chewing function questionnaire has a total score of 28 points. Higher score values indicate better chewing ability. (Limpuangthip, N. & Arksornnukit, M., 2019), (Kunon, K., & Kaewplung, O., 2014).

These foods include 14 kinds of foods with different hardness and roughness. Including Rice soup or Porridge, Chinese Vegetable Stew, Clear Soup or Steamed vegetables, Cooked rice, Noodles, Omelette, Steamed fish, Sour curry, Banana, Fried fish, Orange, Guava, Fried pork and Stir-fried vegetables (Limpuangthip, N. & Arksornnukit, M., 2019) and (Kunon, K., & Kaewplung, O., 2014).

In interpreting the chewing function questionnaire, this is done by adjusting the basic scores of all variables on average. Then divide the total score of each variable by the number of clauses of each variable. Calculate the score from the maximum point minus the minimum point, divided by grade level. In summary, the 3 levels are: Good, Moderate, and Poor as follows.

$$\frac{\text{Maximum point - Minimum point}}{\text{Grade level}} = \frac{28 - 0}{3} = 9.33$$

Criteria for chewing ability level

The indicated points ranged from 18.68-28.00. The ability to chew is good

The indicated points ranged from 9.34-18.67. The ability to chew is moderate

The indicated points ranged from 0.00-9.33. The ability to chew is poor

3.Xerostomia assessment

Xerostomia assessment is a measure of diabetes elders' feelings related to dry mouth, which differs from hyposalivation assessment, which uses salivary flow rate criteria. The Xerostomia Questionnaire uses a questionnaire on xerostomia adapted from Handerson Nunes de Carvalho et al., 2020. It consists of five items. If a diabetic elderly person answers "Yes" to only 1 question, it is considered xerostomia.

4.Salivary flow rate in diabetes elders with xerostomia

For saliva flow rate measurement, unstimulated saliva should be measured. Only use the collection tubes. The results are recorded in the clinical record form.

By interpreting xerostomia problems on the basis of definition: A disorder characterized by reduced salivary flow in the oral region, divided into 4 levels: Grades 1 (Mild), 2 (Moderate), 3 (Severe), and 4 (Potentially Life-Threatening) (Melanoma Nursing Initiative, 2020) are as follows:

Grade 1 (Mild) mean Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min

Grade 2 (Moderate) mean Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min)

Grade 3 (Severe) mean Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva <0.1 mL/min

Grade 4 (Potentially Life-Threatening) mean Life-threatening consequences; urgent intervention indicated

3.7 Construction and Efficiency of the Instruments

I used the questionnaire from the previous research and a standardized survey to develop the questionnaire survey for this study. I consulted three dentists and a specialist in diabetes in the elderly patients with xerostomia for content validity to assess the effectiveness of the instruments. Determine the validity, reliability, objectivity, and practicality of the instrument before testing, and interpersonal reliability (Cronbach's alpha) = 0.832.

3.8 Data collection

In the data collection phase, I collects data manually, both the questionnaire survey data obtained from the population group and the salivary flow rate measurement and oral dryness examinations from the clinical test results of toothpaste containing cordycepin extract compared with normal fluoridated toothpaste.

The research data must be taken from the patient's photo, namely the straight face (lips), the corners of the mouth, and the protruding tongue, to assess the physical condition of xerostomia. Privacy and confidentiality must be respected. The research participants' names must be anonymous without seeing the patient's entire face, and does not provide information that would otherwise identify the subject without permission before taking pictures. Only the sample group that has signed the consent form should be taken.

Salivary flow rate measurement

Before measuring the saliva flow rate, all participants were not allowed to eat or drink for at least one hour. (Malicka, B..et al., 2014), (Hoseini, A.et al., 2017). Participants with removable partial dentures or complete dentures hold their dentures in place during saliva collection (Bergdahl, 2000).

The unstimulated whole saliva was collected between 7.30 and 11.00 a.m. I arranged the patient to sit comfortably in an upright position, with back support up to midscapular level but without a headrest, with their arms on their knees and their heads bent and slightly forward between their arms. Salivary samples were measured

at the same time under the same conditions on three separate visits within a 4-week interval (baseline data collections, second week, and fourth week) under quiet circumstances in a room and without stimulating saliva situations. The examiner asked the subjects to spit out the produced saliva into a 50-mL sterile plastic tube every 30 seconds (Maria Beatriz Duarte Gavião and Andries Van der Bilt., 2004) (Figure 3.7). The unstimulated whole saliva was collected with minimal effort for a period of 5 minutes by the spitting method. The samples were divided into two groups according to the salivary flow rate. Subjects whose unstimulated salivary flow rate was less than 0.1 ml/min were classified as hyposalivation (Villa, A. et al., 2014).

Saliva collection containers were reweighed on a precise balance. The weight of the saliva was calculated as the difference between the values before and after salivary collection. I have calculated the amount of saliva in the sample according to the formula below (Navazesh, M., et al., 2008). Since over 99% of saliva is composed of water, the flow rate was calculated in g/min, which is comparable to mL/min, by dividing the weight by the collecting period for 5 minutes (Alves, C. et al, 2010).

$$\text{Salivary Flow Rate} = \frac{\text{postweight measure - preweight measure}}{\text{Collection period}} = \ldots\ldots \text{ g/minute}$$

Oral Dryness Examinations

The oral mucosal moisture was measured by using the modified cotton method (placing sterile cotton rolls) in two areas: on the tongue and under the tongue (Figure 3.7). I then had the patients close their mouths for 30 seconds and measure the weight of the changed sterile cotton roll relative to the pretest dry cotton weight using the precision balance weighing method of the JOANLAB High Precision 3 Decimal Place Digital Laboratory Scale (Figure 3.6). Oral dryness is confirmed by a decrease in cotton weight of less than 0.02 g when measured on the tongue or less than 0.1 g when measured on the hypoglossus within 30 seconds. (Takahashi Fumi et al., 2006).

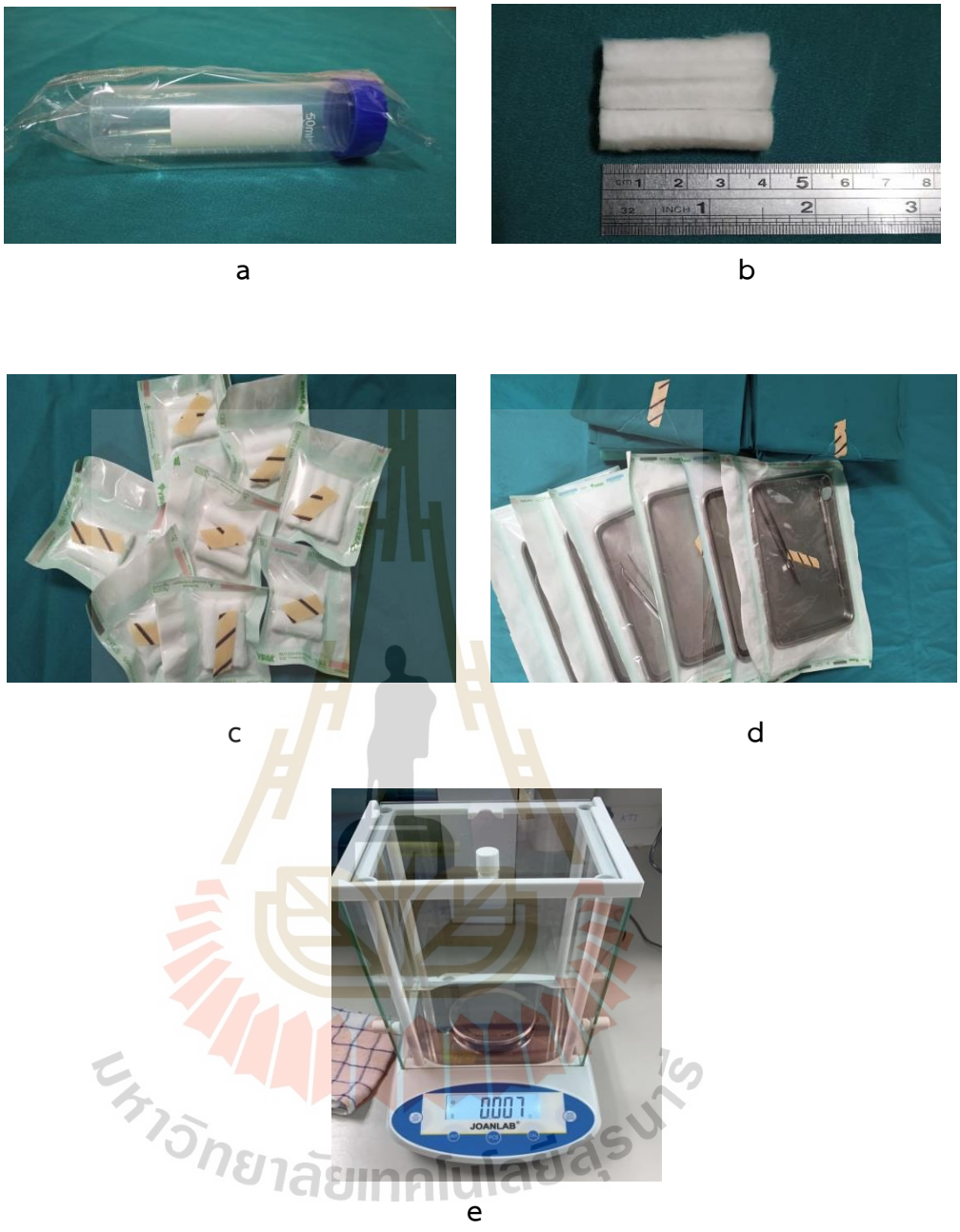
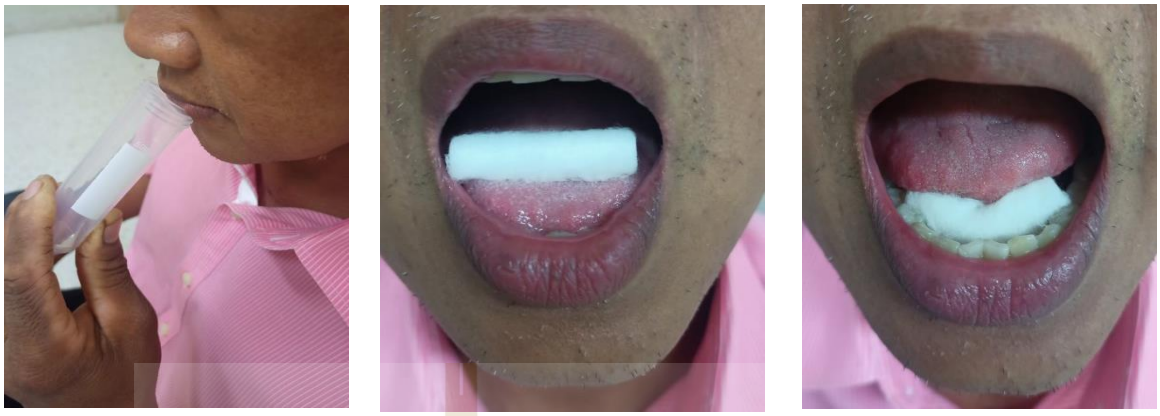


Figure 3.6 Examination sets of each measurement test (salivation and oral mucosal moisture); **(a)** 50 mL plastic sterile tube**, (b)** cotton rolls**, (c)** sterile cotton rolls**, (d)** Dental examination sets**, (e)** JOANLAB High Precision 3 Decimal Place Digital Laboratory Scale**.**



a b c

Figure 3.7 Outline of each measurement test.; **(a)** Unstimulated whole saliva volume using a conventional spitting method, **(b)** Measurement of oral mucosal moisture (on the tongue: tongue's surface), **(c)** Measurement of oral mucosal moisture (under the tongue: hypoglossus)

3.9 Data analysis

Statistical information was used to test the quality of the instrument to find reliability by analyzing the Cronbach's alpha coefficient for the questionnaire. The data obtained from the questionnaire survey using statistical analysis using SPSS software (IBM Corp., Armonk, NY) was considered statistically significant with a *p*-Value < 0.05. The Kolmogorov-Smirnov test, skewness, and kurtosis were used to analyze data distribution. For the Chi-square test, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare differences in frequency distribution and mean scores. Bivariable and multiple logistic regression analysis were used to predict and compute odds ratios (OR) of significant variables. In the relationship analysis, Chi-square and Pearson correlation coefficients were used.

For the clinical test, I interpreted the saliva amount and oral mucosal moisture of both the treatment group and control group into a mean score to compare the differences within the group, both before and after the experiment in the second and fourth weeks. For a normal distribution, use the repeated measures ANOVA, and for comparing the amount of salivation and oral mucosal moisture of both the treatment group and the control group between the groups before and after the experiment in every week (baseline data collections, second week, and fourth week), using the independent sample t-test.

The statistical analysis used in the study was classified according to the following variables, which are shown in Table 3.2 below.

Table 3.2 Statistical analysis in this study.

Research questions	Variables	Levels of measurement	Statistical Analysis
1. What is the prevalence of xerostomia in diabetic elderly patients and its related factors?	1.1 Xerostomia (Feeling of Dry mouth)	Nominal	Descriptive: frequency, percentage
	1.2 Sociodemographic and health behavior	-	-
	-Gender	Nominal	Descriptive: frequency, percentage
	- Systemic disease other than diabetes -Medication -Smoking -Toothpaste brands -Type of denture		
	- Education - Alcohol consumption	Ordinal	
	- Age - Duration of being a DM. - HbA1c	Ratio	Descriptive: frequency, percentage, mean, S.D., Min., Max.
	1.3 Oral functions - Speaking problems - Taste problems - Swallowing problems - Chewing ability	Interval	Descriptive: frequency, percentage, mean, S.D., Min., Max.

Table 3.2 (Continued).

Research questions	Variables	Levels of measurement	Statistical Analysis
1. What is the prevalence of xerostomia in diabetic elderly patients and its related factors? (continued)	1.4 Relationship between xerostomia , sociodemographic and health behavior, oral function in Diabetes elderly with xerostomia		1. Gender, Education, Systemic disease , Medication, Smoking , Alcohol consumption, Toothpaste brands, Type of denture with xerostomia use Chi-square test 2. Age, Blood sugar level, Duration of being a DM. ,Oral function with Salivation use Pearson correlation coefficient 3. Xerostomia, Sociodemographic and health behavior, Oral function with Salivation use ANOVA and ANCOVA (For ANCOVA are

Table 3.2 (Continued).

Research questions	Variables	Levels of measurement	Statistical Analysis
1. What is the prevalence of xerostomia in diabetic elderly patients and its related factors? (continued)	1.4 Relationship between xerostomia , sociodemographic and health behavior, oral function in Diabetes elderly with xerostomia (continued)		adjust by Gender, Systemic disease , Medication, Smoking Alcohol consumption, Toothpaste brands) 4. The common risk factors and Prognostic risk factors for xerostomia on demographic and health behaviour variables use bivariable logistic regression and Multiple logistic regression 5. Xerostomia, Sociodemographic and health behavior on Oral function use Odds ratios

Table 3.2 (Continued).

Research questions	Variables	Levels of measurement	Statistical Analysis
2. Can cordycepin extract containing toothpaste increase salivation in diabetic elderly patients with xerostomia?	-Salivation (mL/min.) -Oral Dryness (on the tongue & Hypoglossus)	Ratio	Descriptive: frequency, percentage, mean, S.D., Min., Max. Compare the differences within the group use Repeated measures ANOVA. And Compare between the groups use Independent sample t-test
	Reliability		Cronbach's Alpha Coefficient
	Data distribution		Kolmogorov–Smirnov test, Skewness and kurtosis

3.10 Ethical statement

All procedures performed in studies involving human participants are in accordance with the Ethical Standards of the Suranaree University of Technology. The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Researches Ethics Committee of Suranaree University of Technology (protocol code EC-64-92, date of approval: September 29, 2021).

Conflicts of Interest: I declare no conflict of interest.

Budget

The estimated budget for this study is 316,204 baht, as shown in Table 3.3 below.

Table 3.3 Budget details in this study

Items	Amount (Baht)
1. Research Equipment 1.1 Questionaire survey and clinical record form	2,944
2. Materials Supplies 2.1 Toothpaste containing cordycepin extract and normal fluoridated toothpaste 2.2 50-mL sterile plastic tube 2.3 Sterile cotton rolls 2.4 Disposable Gloves	187,560
3. Payment for research participation	61,200
Journal publication (*Geriatrics*)	64,500 (1,600 CHF)
Total cost	**316,204**

CHAPTER IV

RESULTS AND DISCUSSIONS

According to the research purposes, the results and discussions were divided into two parts: 4.1 Prevalence survey and 4.2 Randomized clinical trial. The results and discussions of the study are as follows:

4.1 Prevalence survey

4.1.1 Results

(**Research objectives I**: To investigate the prevalence of xerostomia and its impacts on oral functions, as well as determine potential risk factors for xerostomia in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital.)

A four-month demographic survey of Type 2 diabetes elderly patients at the Suranaree University of Technology Hospital's NCDs clinic (December 2021–March 2022). Patients received care in 623 cases. Females constituted 53.8 percent of the population, while males constituted 46.2 percent. The average age was 65.48 years (S.D.=7.73). The vast majority of patients were educated in high school, 45.3%, followed by bachelor's degrees at 26.0%, and elementary school at 23.8%, respectively. Most of these patients had type 2 diabetes diagnosed in the past 6–10 years. 38.7, followed by more than 10 years, 37.7 percent. The mean duration of illness was 10.13 years (S.D.= 5.57) with a hemoglobin A1c level (%), mean 8.38 (S.D.= 1.97). Of these, 21.7% had diabetes and no other diseases. Besides diabetes, the most common comorbidities were hypertension and dyslipidemia, which were 66.0% and 61.2%, respectively.

In terms of medications, it was found that most of the patients were on antihypertensive medication, followed by antidyslipidemic agents, antiplatelets, and

anticoagulant medication, at 64.8, 57.6, and 55.5 percent, respectively. In terms of smoking and alcohol consumption, the vast majority (96.6%) were nonsmokers, and 85.9% were alcohol non-drinkers. The Colgate brand was the most commonly used toothpaste, followed by SENDODYNE and Twin Lotus at 33.9 percent, 10.0 percent, and 9.6 percent, respectively. Most of the patients had no dentures (93.3%), had dentures with removable partial dentures (3.7%), or fixed partial dentures (2.1%). These results are shown in Table 4.1

Table 4.1 Descriptive Population data of Type 2 Diabetes elderly patients in NCDs clinic at the Suranaree University of Technology Hospital (N=623).

Variables	N	Percentage
Sex		
Male	288	46.2
Female	335	53.8
Total	623	100
Age (years)		
50-59	143	23.0
Over 59	480	77.0
Total	623	100
Mean= 65.48 , S.D.= 7.73, Min.= 50, Max.= 88		
Education		
None	12	1.9
Elementary School	148	23.8
High School	282	45.3
Bachelor's degree	162	26.0
Higher than the Bachelor's degree	19	3.0
Total	623	100
Years since diabetes diagnosis		
0-5	147	23.6
6-10	241	38.7
Over 10	235	37.7
Total	623	100
Mean= 10.13, S.D.= 5.57, Min.= 0.10, Max.= 32.00		
Hemoglobin A1c level (%)		
≤ 6.5	134	21.5
6.6-6.9	126	20.2
≥ 7	363	58.3
Total	623	100
Mean= 8.38, S.D.=1.97, Min.= 5.70, Max.=13.20		

Table 4.1 (continued).

Variables	N	Percentage
Systemic diseases other than diabetes		
None	135	21.7
Hypertension	411	66.0
Dyslipidemia	381	61.2
Cardiovascular disorders	9	1.4
Thyroid disorders	21	3.4
Hematologic disorder	11	1.8
Renal disorders	67	10.8
Respiratory disorders	55	8.8
Allergy	109	17.5
Gout	42	6.7
Medications		
None	137	22.0
Antihypertensive medication	404	64.8
Antidyslipidemic agents	359	57.6
Antiplatlets and Anticoagulant medication	346	55.5
Pain medication	199	31.9
Gastrointestinal agents	16	2.6
Cardiovascular medication	11	1.8
Antihistamine	79	12.7
Smoking (cigarettes per day)		
Never	602	96.6
1-5	21	3.4
5-10	0	0.0
Total	623	100
Mean= 0.09, S.D.= 0.54, Min.= 0, Max.=5		

Table 4.1 (continued).

Variables	N	Percentage
Alcohol consumption		
Never	535	85.9
Monthly or less	41	6.6
2-4 times a month	31	5.0
2 -3 times a week	11	1.7
4 or more times a week	5	0.8
Total	623	100
Toothpaste brands		
Colgate	211	33.9
SYSTEMA	35	5.6
DARLIE	47	7.5
Amway Glister	29	4.7
SALZ	44	7.1
SPARKLE	23	3.7
SENDODYNE	62	10.0
DENTISTE’	22	3.5
Parodontax	20	3.2
Twin Lotus	60	9.6
Tepthai	47	7.5
HI-HERB	22	3.5
Other (Salt)	1	0.2
Total	623	100
Denture		
None	581	93.3
Complete Dentures	6	0.9
Removable Partial Dentures	23	3.7
Fixed Partial Dentures	13	2.1
Total	623	100

I studied 623 cases of xerostomia, which were assessed on 5 subjective measures of xerostomia. The majority of patients felt the amount of saliva in their mouth was too little (33.7%), followed by often feeling dry mouth at night or in the morning (27.6%), and feeling dry mouth when eating meals 10.1%, swallowing their food is difficult for 9.3% of patients, and patients need to sip water all the time while swallowing food for 4.8% of patients, as shown in Table 4.2

Table 4.2 Data of Xerostomia assessment in Studied Population (N=623).

Subjective evaluation of xerostomia	Yes N (%)	No N (%)	Total N (%)
1. Do you feel the amount of saliva in your mouth is too little?	210 (33.7)	413 (66.3)	623 (100)
2. Do you feel dry mouth when you eat meals?	63 (10.1)	560 (89.9)	623 (100)
3. Do you often feel dry mouth at night or when you wake up in the morning?	172 (27.6)	451 (72.4)	623 (100)
4. Do you feel that swallowing your food is difficult?	58 (9.3)	565 (90.7)	623 (100)
5. Do you sip water all the time while swallowing food?	30 (4.8)	593 (95.2)	623 (100)

Based on the data in Table 4.2, the results of the diagnosis of Xerostomia in Type 2 Diabetes elderly patients are interpreted as 239 out of 623 cases as Xerostomia, (38.4%) as shown in Table 4.3

Table 4.3 Diagnosis of Xerostomia in Studied Population (N=623).

Diagnosis	N	Percentage
Xerostomia (Points 1 - 5)	239	38.4
Normal (Point 0)	384	61.6
Total	623	100

Statistical analysis was performed according to sociodemographic and health behaviours variables found that females had more xerostomia than males (43.3% and 32.6%, respectively), those age 60 and older had more xerostomia than the age group under 60 years old (41.7% and 27.3%, respectively), and xerostomia was more common in those who used SLS-containing toothpaste than in those who did not (38.38% and 38.23%, respectively). Likewise, those using toothpaste containing spicy herbal extracts had more xerostomia than those in the spicy herbal extracts-free group (39.47% and 35.46%, respectively).

In contrast, those using toothpastes containing artificial sweeteners had less xerostomia than the artificial sweeteners-free group (36.47% and 39.67%, respectively). Patients with diabetes for more than 10 years found xerostomia as high as 59.14%, a hemoglobin A1c level ≤ 6.5% as xerostomia as high as 59.14%, diabetic patients with the most common cardiovascular disorders were xerostomia (88.88%), and diabetic patients who took multiple drugs together had 90.47% more xerostomia than those who did not take any drugs. Likewise, alcohol drinkers were more likely to develop xerostomia than nondrinkers. It was found that xerostomia affected 100% of diabetic patients wearing complete dentures, as detailed in Table 4.4.

Table 4.4 Prevalence of xerostomia and differences in sociodemographic data and health behaviours of 623 patients with type 2 diabetes elderly.

Variables	Categories	No.of xerostomia cases (%)	*p*-Value
Sex	Male	94 (32.6)	0.006*
	Female	145 (43.3)	
Age (years)	50-59	39 (27.3)	0.002*
	Over 59	200 (41.7)	
Toothpaste (Type 1)	SLS-Free	26 (38.23)	0.982
	Containing SLS	213 (38.38)	
Toothpaste (Type 2)	Spicy herbal extracts-Free	61 (35.46)	0.358
	Containing spicy herbal extracts	178 (39.47)	
Toothpaste (Type 3)	Artificial sweeteners -Free	146 (39.67)	0.419
	Containing artificial sweeteners	93 (36.47)	
Education	None	4 (33.33)	0.468
	Elementary School	52 (35.13)	
	High School	115 (40.78)	
	Bachelor's degree	58 (35.80)	
	Higher than the Bachelor's degree	10 (52.63)	
Years since diabetes diagnosis	0-5	24 (16.32)	<0.001**
	6-10	76 (31.53)	
	Over 10	139 (59.14)	
Haemoglobin A1c level (%)	≤ 6.5	23 (59.14)	<0.001**
	6.6-6.9	32 (25.39)	
	≥ 7	184 (50.68)	

Table 4.4 (Continued).

Variables	Categories	No.of xerostomia cases (%)	*p*-Value
Systemic diseases other than diabetes	None	16 (11.85)	<0.001**
	Hypertension	206 (50.12)	<0.001**
	Dyslipidemia	191 (50.13)	<0.001**
	Cardiovascular disorders	8 (88.88)	0.002*
	Thyroid disorders	13 (61.90)	0.024*
	Hematologic disorders	8 (72.72)	0.018*
	Renal disorders	40 (59.70)	<0.001**
	Respiratory disorders	25 (45.45)	0.257
	Allergy	47 (43.12)	0.261
	Gout	28 (66.66)	<0.001**
Medications	None	22 (16.05)	<0.001**
	Antihypertensive medication	206 (60.00)	<0.001**
	Antidyslipidemic agents	186 (51.81)	<0.001**
	Antiplatlets and Anticoagulant medication	163 (47.10)	<0.001**
	Pain medication	77 (38.69)	0.907
	Gastrointestinal agents	7 (43.75)	0.653
	Cardiovascular medication	7 (63.63)	0.082
	Antihistamine	30 (37.97)	0.939
Smoking (cigarettes per day)	Never	220 (36.54)	<0.001**
	1-5	19 (90.47)	

Table 4.4 (Continued).

Variables	Categories	No.of xerostomia cases (%)	*p*-Value
Alcohol consumption	Never	172 (32.15)	<0.001**
	Monthly or less	31 (75.61)	
	2-4 times a month	22 (70.96)	
	2 -3 times a week	10 (90.90)	
	4 or more times a week	4 (80.00)	
Denture wearing	None	210 (36.14)	<0.001**
	Complete Dentures	6 (100)	
	Removable Partial Dentures	20 (86.95)	
	Fixed Partial Dentures	3 (23.07)	

Variables were identified by Chi Square Difference Testing, * *p*-Value were significant ($p < 0.05$), ** *p*-Value were significant ($p < 0.001$)

In addition to xerostomia, patients with oral function problems in the areas of speaking, tasting, swallowing problems, and chewing ability are also included (S.D. Tran et al., 2006), (P. Samnieng et al., 2012). I analyzed the problems from the questionnaire and found that in the speaking aspect, 96.5 percent of the patients had no problems, speaking problems were at a moderate level of 1.4% and a very mild level of 1.1%, where speaking problems have a mean of 1.07 and a S.D. of 0.41 are shown in Table 4.5

Table 4.5 Frequency of Speaking problems according to the severity in Studied Population (N=623).

Speaking problems	N	Percentage
None	601	96.5
Very mild	7	1.1
Mild	6	1.0
Moderate	9	1.4
Severe	0	0.0
Total	623	100
Mean= 1.07, S.D.=0.41, Min.=1.00, Max.=4.00		

When categorizing speaking problem levels by the mean of the patients, the majority were at a good level at 97.6 percent, followed by poor and moderate at 1.4 percent and 1.0 percent, respectively. These are shown in Table 4.6

Table 4.6 Frequency of Speaking problems according to the ability level in Studied Population (N=623).

Speaking problem level	N	Percentage
Good (Mean 1.00 - 2.33)	608	97.6
Moderate (Mean 2.34 - 3.67)	6	1.0
Poor (Mean 3.68 - 5.00)	9	1.4
Total	623	100

In terms of tasting problems, mean = 1.50 (S.D. = 0.93), the majority of patients had no problems at 73.4%, followed by mild at 11.6% and very mild at 9.3% (Table 4.6). As shown in Table 4.8, when categorizing patient mean, the majority was at a good level at 82.7%, followed by moderate and poor at 11.6% and 5.7%, respectively.

Table 4.7 Frequency of Tasting problems according to the severity in Studied Population (N=623).

Tasting problems	N	Percentage
None	457	73.4
Very mild	58	9.3
Mild	72	11.6
Moderate	32	5.1
Severe	4	0.6
Total	623	100
Mean=1.50, S.D.=0.93, Min.=1.00, Max.=5.00		

Table 4.8 Frequency of Tasting problems according to the ability level in Studied Population (N=623).

Tasting problem level	N	Percentage
Good (Mean 1.00 - 2.33)	515	82.7
Moderate (Mean 2.34 - 3.67)	72	11.6
Poor (Mean 3.68 - 5.00)	36	5.7
Total	623	100

In the swallowing aspect, most patients must avoid specific foods or liquid items 42.0%, followed by no restrictions (40.6%), and multiple consistencies requiring special preparation (17.2%). Swallowing problems have a mean of 6.23 and a standard deviation of 0.72 are shown in Table 4.9

Table 4.9 Frequency of Swallowing problems according to the severity in Studied Population (N=623).

Swallowing problem	N	Percentage
Nonoral feeding (TUBE DEPENDENT)	0	0.0
Single consistency	1	0.2
Multiple consistencies requiring special preparation	107	17.2
Must avoid specific foods or liquid items	262	42.0
No restrictions	253	40.6
Total	623	100
Mean=6.23, S.D.=0.72, Min.=4.00, Max.=7.00		

When categorizing swallowing problem levels according to the mean of patients, the majority were at the good level at 82.7%, followed by moderate at 17.3%, as shown in Table 4.10

Table 4.10 Frequency of Swallowing problems according to the ability level in Studied Population (N=623).

Swallowing ability level	N	Percentage
Good (Mean 5.02 - 7.00)	515	82.7
Moderate (Mean 3.01 - 5.01)	108	17.3
Poor (Mean 1.00 - 3.00)	0	0.00
Total	623	100

In terms of chewing ability, an analysis of 14 food list questionnaire results revealed that banana was the best food the patients could chew, followed by rice soup/porridge and steamed fish (99.5, 99.2, and 98.1, respectively). The food that patients had difficulty chewing and could not chew at all was fried pork, followed by guava and fried fish, 37.1%, 2.7, and 0.8, respectively are shown in Table 4.11

Table 4.11 Data of itemized food lists classified by Chewing ability in population (N=623).

Foods lists	Chewing ability N (%)				Interpretation
	Could chew well	Difficult to chew	Could not chew at all	Never eat or any other	
1. Rice soup/Porridge	618 (99.2)	5 (0.8)	0 (0.0)	0 (0.0)	Could chew well
2. Chinese Vegetable Stew	572 (91.8)	51 (8.2)	0 (0.0)	0 (0.0)	Could chew well
3. Clear Soup/Steamed vegetables	601 (96.5)	22 (3.5)	0 (0.0)	0 (0.0)	Could chew well
4. Cooked rice	595 (95.5)	28 (4.5)	0 (0.0)	0 (0.0)	Could chew well
5. Noodles	525 (84.3)	96 (15.4)	2 (0.3)	0 (0.0)	Could chew well
6. Omelette	604 (97.0)	19 (3.0)	0 (0.0)	0 (0.0)	Could chew well
7. Steamed fish	611 (98.1)	12 (1.9)	0 (0.0)	0 (0.0)	Could chew well
8. Sour curry	587 (94.2)	36 (5.8)	0 (0.0)	0 (0.0)	Could chew well
9. Banana	620 (99.5)	3 (0.5)	0 (0.0)	0 (0.0)	Could chew well
10. Fried fish	490 (78.7)	128 (20.5)	5 (0.8)	0 (0.0)	Could chew well
11. Orange	599 (96.1)	24 (3.9)	0 (0.0)	0 (0.0)	Could chew well

Table 4.11 (Continued).

Foods lists	Chewing ability N (%)				Interpretation
	Could chew well	Difficult to chew	Could not chew at all	Never eat or any other	
12. Guava	417 (67.0)	189 (30.3)	17 (2.7)	0 (0.0)	Could chew well
13. Fried pork	202 (32.4)	190 (30.5)	231 (37.1)	0 (0.0)	Could not chew at all
14. Stir-fried vegetables	528 (84.8)	93 (14.9)	2 (0.3)	0 (0.0)	Could chew well

When classifying chewing problems according to the patient's score, the majority were at the good level (99.4%), followed by moderate (0.6%). These are shown in Table 4.12

Table 4.12 Frequency of chewing problems according to the ability level in studied Population (N=623).

Chewing ability level	N	Percentage
Good (Points 18.68 - 28.00)	619	99.4
Moderate (Points 9.34 - 18.67)	4	0.6
Poor (Points 0.00 - 9.33)	0	0.00
Total	623	100
Mean=25.73, S.D.=1.87, Min.=14.00, Max.=28.00		

Using the one-way ANOVA statistic, I discovered that xerostomia was statistically different at the 0.05 level with age, years since diabetes diagnosis, hemoglobin A1c level, systemic diseases other than diabetes, medications, smoking, alcohol consumption, dentures, and oral functions (speaking, tasting, swallowing, and chewing problems) in Type 2 diabetic elderly patients. As shown in Table 4.13, there were no statistically significant differences between xerostomia and education or toothpaste brands at the 0.05 level.

Table 4.13 Differences between xerostomia and sociodemographic and health behavior variables in the population by One-way ANOVA.

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Age (years)					
50-59	143 (23.0)	0.56	1.06	0.18 -1.16	0.002*
Over 59	480 (77.0)	0.94	1.32		
Education					
None	12 (1.9)	0.91	1.56	0.07-1.91	0.769
Elementary School	148 (23.8)	0.77	1.19	0.57-0.96	
High School	282 (45.3)	0.86	1.23	0.71-1.00	
Bachelor's degree	162 (26.0)	0.88	1.38	0.66-1.09	
Higher than the Bachelor's degree	19 (3.0)	1.15	1.60	0.38-1.93	
Years since diabetes diagnosis					
0-5	147 (23.6)	0.38	1.02	0.22-0.55	<0.001**
6-10	241 (38.7)	0.63	1.11	0.49-0.78	
Over 10	235 (37.7)	1.37	1.40	1.18-1.55	

Table 4.13 (Continued).

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Hemoglobin A1c level (%)					
≤ 6.5	134 (21.5)	0.38	0.95	0.21-0.54	<0.001**
6.6-6.9	126 (20.2)	0.69	1.29	0.46-0.91	
≥ 7	363 (58.3)	1.08	1.32	0.95-1.22	
Systemic diseases other than diabetes					
None	135 (21.7)	0.21	0.70	0.15-1.98	<0.001**
Hypertension	411 (66.0)	1.03	1.34		
Dyslipidemia	381 (61.2)				
Cardiovascular disorders	9 (1.4)				
Thyroid disorders	21 (3.4)				
Hematologic disorders	11 (1.8)				
Renal disorders	67 (10.8)				
Respiratory disorders	55 (8.8)				
Allergy	109 (17.5)				
Gout	42 (6.7)				
Medications					
None	137 (22.0)	0.35	0.95	0.24-1.38	<0.001**
Antihypertensive medication	404 (64.8)	0.99	1.32		
Antidyslipidemic agents	359 (57.6)				

Table 4.13 (Continued).

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Antiplatlets and Anticoagulant medication	346 (55.5)				
Pain medication	199 (31.9)				
Gastrointestinal agents	16 (2.6)				
Cardiovascular med.	11 (1.8)				
Antihistamine	79 (12.7)				
Smoking					
Never	602 (96.6)	0.80	1.24	0.70-0.90	<0.001**
1 cigarette per day	3 (0.5)	1.00	1.00	0.48-3.48	
2 cigarettes per day	7 (1.1)	3.00	1.15	1.93-4.06	
3 cigarettes per day	6 (1.0)	2.00	1.41	0.51-3.48	
4 cigarettes per day	2 (0.3)	2.50	2.12	1.55-3.62	
5 cigarettes per day (Maximum)	3 (0.5)	2.00	1.73	1.30-4.37	
Alcohol consumption					
Never	535 (85.9)	0.68	1.16	0.58-0.78	<0.001**
Monthly or less	41 (6.6)	1.80	1.41	1.35-2.25	
2-4 times a month	31 (5.0)	1.93	1.54	1.36-2.50	
2 -3 times a week	11 (1.7)	2.18	1.66	1.06-3.29	
4 or more times a week	5 (0.8)	1.60	1.14	0.18-3.01	

Table 4.13 (Continued).

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Toothpaste brands					
Colgate	211 (33.9)	0.93	1.35	0.74-1.11	0.19
SYSTEMA	35 (5.6)	1.02	1.20	0.61-1.44	
DARLIE	47 (7.5)	1.12	1.52	0.67-1.57	
Amway Glister	29 (4.7)	0.93	1.09	0.51-1.34	
SALZ	44 (7.1)	0.84	1.31	0.44-1.23	
SPARKLE	23 (3.7)	0.60	1.15	0.10-1.10	
SENDODYNE	62 (10.0)	0.83	1.25	0.51-1.15	
DENTISTE'	22 (3.5)	0.77	1.02	0.32-1.22	
Parodontax	20 (3.2)	0.45	0.82	0.06-0.83	
Twin Lotus	60 (9.6)	0.66	1.17	0.36-0.97	
Tepthai	47 (7.5)	0.59	1.19	0.24-0.94	
HI-HERB	22 (3.5)	0.86	1.28	0.29-1.43	
Other (Salt)	1 (0.2)	4.00	0.00	0.00-4.00	
Denture					<0.001**
None	581 (93.3)	1.15		0.65-0.83	
Complete Dentures	6 (0.9)	0.40		4.40-5.26	
Removable Partial Dentures	23 (3.7)	2.82	1.26	2.27-3.37	
Fixed Partial Dentures	13 (2.1)	0.46	0.96	0.12-1.04	
Speaking problem					
Good	608 (97.6)	0.83	1.26	0.73-0.93	0.002*
Moderate	6 (1.0)	0.83	1.16	0.39-2.06	
Poor	9 (1.4)	2.33	1.80	0.94-3.71	

Table 4.13 (Continued).

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Tasting problem					
Good	515 (82.7)	0.70	1.20	0.60-0.80	<0.001**
Moderate	72 (11.6)	1.70	1.10	1.44-1.96	
Poor	36 (5.7)	1.30	1.83	0.68-1.92	
Swallowing problem					
Good	515 (82.7)	0.73	1.24	0.62-2.53	<0.001**
Moderate	108 (17.3)	1.40	1.29		
Poor	0 (0.0)	0.00	0.00		
Chewing problem					
Good	619 (99.4)	0.82	1.24	0.37-3.65	0.019*
Moderate	4 (0.6)	2.20	2.00		
Poor	0 (0.0)	0.00	0.00		

[a]Between Groups

[b]Within Groups

*The level of significance was $p < 0.05$, ** $p < 0.001$

**Results by T-Test

From Table 4.13, Differences between Xerostomia and Sociodemographic and Health Behavior Variables, it was found that with a statistically significant difference of 0.05 after testing with One-way ANOVA, I tested multiple comparisons between xerostomia and variables for years since diabetes diagnosis, hemoglobin A1c level, smoking, alcohol consumption, denture, and oral functions (speaking and tasting problems) by using Fisher's Least Significant Difference (LSD) test.

For years since diabetes diagnosis, three pairs were found to differ statistically at the 0.05 level: (1) 0–5 years and 6–10 years; (2) 0–5 years and Over 10 years; and (3) 6–10 years and over 10 years; with Type 2 diabetes elderly patients of 623 with different durations of diabetes; 147 cases in the 0–5 years group, mean xerostomia 0.38 (S.D. = 1.02, 95% CI = 0.22-0.55); 6-10 years group, 241 cases, mean xerostomia 0.63 (S.D. = 1.11, 95% CI = 0.49–0.78); and over a 10-year period, 235 cases, the mean of xerostomia was 1.37 (S.D. = 1.40, 95% CI = 1.18–1.55) (Table 14). The highest was in the over 10-year group, which was 0.98 more than the 0–5 years group and 0.73 more than the 6–10 years group, with a statistically significant difference at the 0.05 level. (Table 4.14)

Table 4.14 Multiple comparisons between xerostomia and years of diabetes by using Fisher's Least Significant Difference (LSD) test.

Years since diabetes diagnosis	xerostomia			
	Mean	(1)	(2)	(3)
		0.38	0.63	1.37
(1) 0-5 years	0.38		-	-
(2) 6-10 years	0.63	0.25*		-
(3) Over 10 years	1.37	0.98*	0.73*	

*The mean difference is significant at the 0.05 level.

Among of hemoglobin A1c levels, three pairs were found to differ statistically at the 0.05 level: (1) ≤ 6.5 % and 6.6-6.9%, (2) ≤ 6.5 % and ≥ 7%, and (3) 6.6-6.9%, and ≥ 7%, with Type 2 Diabetes elderly patients of 623 with a hemoglobin A1c level group ≤ 6.5%, 134 cases CI = 0.21-0.54). For the 6.6-6.9% group, 126 cases had a mean of xerostomia of 0.69 (S.D. =1.29, 95% CI = 0.46-0.91) and for the ≥ 7% group, 363 cases had a mean of xerostomia of 1.08 (S.D. =1.32, 95% CI = 0.95-1.22) (Table 4.15). The group with a hemoglobin A1c level ≥ 7% had the highest mean of xerostomia, 0.70 greater than the ≤ 6.5% group and 0.39 more than the 6.6-6.9% group, with a statistically significant difference at the 0.05 level, are shown in Table 4.15

Table 4.15 Multiple comparisons between xerostomia and Hemoglobin A1c level (%) by using Fisher's Least Significant Difference (LSD) test.

Hemoglobin A1c level	xerostomia			
	Mean	(1)	(2)	(3)
		0.38	0.69	1.08
(1) ≤ 6.5 %	0.38		-	-
(2) 6.6-6.9 %	0.69	0.30*		-
(3) ≥ 7 %	1.08	0.70*	0.39*	

*The mean difference is significant at the 0.05 level.

For smoking, there were three pairs with a statistically significant differences of 0.05: (1) never and 2 cigarettes per day; (2) never and 3 cigarettes per day; and (3) 1 cigarette per day; and 2 cigarettes per day. Of type 2 diabetic elderly patients there were 623 who smoked, and 602 cases that never smoked: the mean of xerostomia was 0.80 (S.D. =1.24, 95% CI = 0.70-0.90) in the 1 cigarette per day group, 3 cases had mean of xerostomia that was 1.00 (S.D. =1.00, 95% CI= 0.48-3.48) in the 2 cigarettes per day group of 7 cases the mean of xerostomia was 3.00 (S.D. =1.15, 95% CI=1.93-4.06), in the group 6 cases in the 3 cigarette per day group had a mean of xerostomia of 2.00 (S.D. =1.41, 95% CI = 0.51-3.48), 2 cases in the 4 cigarette per day group had a mean of xerostomia of 2.50 (S.D. = 2.12, 95% CI = 1.55-3.62), and 3 cases in the 5 cigarette per day group had a mean of xerostomia of 2.00 (S.D. = 1.73, 95% CI = 1.30-4.37) (Table 4.16).

With a statistically significant difference at 0.05, the smoking behavior group of 2 cigarettes per day had the greatest mean of xerostomia, 2.19 more than the non-smoking group and 2.00 higher than the 1 cigarette per day group. Table 4.16 shows that the group that smoked 3 cigarettes per day had 1.19 greater mean xerostomia than the group that did not smoke, with a statistically significant difference at the 0.05 level as well.

Table 4.16 Multiple comparisons between xerostomia and smoking by using Fisher's Least Significant Difference (LSD) test.

Smoking	xerostomia						
	Mean	(0)	(1)	(2)	(3)	(4)	(5)
		0.80	1.00	3.00	2.00	2.50	2.00
(0) Never	0.80		-	-	-	-	-
(1) 1 cigarette per day	1.00	0.19		-	-	-	-
(2) 2 cigarettes per day	3.00	2.19*	2.00*		-	-	-
(3) 3 cigarettes per day	2.00	1.19*	1.00	1.00		-	-
(4) 4 cigarettes per day	2.50	1.69	1.50	0.50	0.50		-
(5) 5 cigarettes per day	2.00	1.19	1.00	1.00	0.00	0.50	

*The mean difference is significant at the 0.05 level.

In terms of alcohol consumption, three pairs were statistically significantly different at 0.05: (1) Never and monthly or less; (2) Never and 2-4 times a month; and (3) Never and 2–3 times a week: There were 88 type 2 diabetic elderly patients with alcohol consumption, compared with 535 cases with no alcohol consumption; the mean of xerostomia was 0.68 (S.D. = 1.16, 95% CI = 0.58-0.78) and 41 cases in the monthly or less group, the mean of xerostomia 1.80 (S.D. =1.41, 95% CI=1.35-2.25), in the group 2-4 times a month, 31 cases mean of xerostomia 1.93 (S.D. =1.54, 95% CI=1.36-2.50) in Group 2 -3 times a week, 11 cases had a mean of xerostomia 2.18 (S.D. =1.66, 95% CI=1.06-3.29), and in Group 4 or more times a week, 5 cases had a mean of xerostomia 1.60 (S.D. =1.14, 95% CI=0.18-3.01)

The group with alcohol consumption 2–3 times a week had the highest mean of xerostomia, 1.49 more than the group without alcohol consumption, with a statistically significant difference of 0.05 and greater than the monthly or less group, 2-4 times a month, and group 4 or more times a week were 0.37, 0.24, and 0.58, respectively, with statistically insignificant differences at the 0.05 level are shown in Table 4.17

Table 4.17 Multiple comparisons between xerostomia and alcohol consumption by using Fisher's Least Significant Difference (LSD) test.

Alcohol consumption	xerostomia					
	Mean	(0)	(1)	(2)	(3)	(4)
		0.68	1.80	1.93	2.18	1.60
(0) Never	0.68		-	-	-	-
(1) Monthly or less	1.80	1.11*		-	-	-
(2) 2-4 times a month	1.93	1.24*	0.13		-	-
(3) 2 -3 times a week	2.18	1.49*	0.37	0.24		-
(4) 4 or more times a week	1.60	0.91	0.20	0.33	0.58	

*The mean difference is significant at the 0.05 level.

In terms of denture wearing, five pairs were found to differ statistically at the 0.05 level: (1) No dentures and complete dentures, (2) No dentures and removable partial dentures, (3) Complete dentures and removable partial dentures, (4) Complete dentures and fixed partial dentures, and (5) Removable partial dentures and fixed partial dentures. Besides, I discovered that the mean of xerostomia among type 2 diabetic elderly patients, 623 cases in the none-denture group of 581 cases, was 0.74 (S.D. = 1.15, 95% CI = 0.65-0.83)., six cases in the Complete Denture group had the mean of xerostomia 4.83 (S.D. =0.40, 95% CI= 4.40-5.26), the Removable Partial Dentures group 23 cases had the mean of xerostomia 2.82 (S.D. =1.26, 95% CI=2.27. -3.37), Fixed Partial Dentures group, 13 cases mean of xerostomia was 0.46 (S.D. =0.96, 95% CI=0.12-1.04).

The complete dentures group had the highest mean of xerostomia, which was 4.08 greater than the No denture group, 2.00, and 4.37 more than the Fixed Partial Dentures group, with a statistically significant difference at the 0.05 level, as shown in Table 4.18

Table 4.18 Multiple comparisons between xerostomia and denture by using Fisher's Least Significant Difference (LSD) test.

Denture	xerostomia				
	Mean	(0)	(1)	(2)	(3)
		0.74	4.83	2.82	0.46
(0) None	0.74		-	-	-
(1) Complete Dentures	4.83	4.08*		-	-
(2) Removable Partial Dentures	2.82	2.08*	2.00*		-
(3) Fixed Partial Dentures	0.46	0.28	4.37*	2.36*	

*The mean difference is significant at the 0.05 level.

There were two groups with statistically significant differences at the 0.05 level for the speaking problems: (1) good and poor, (2) moderate and poor, with 608 cases in the good group had a mean of xerostomia 0.83 (S.D. =1.26, 95%CI= 0.73-0.93), 6 cases had xerostomia with a mean of 0.83 (S.D. =1.16, 95%CI= 0.39-2.06), and 9 cases had xerostomia with a mean of 2.33 (S.D. =1.80, 95%CI= 0.94-3.71).

The poor group had the highest mean of xerostomia, 1.49 more than the good group and 1.50 more than the moderate group, with a statistically significant difference of 0.05, are shown in Table 4.19

Table 4.19 Multiple comparisons between xerostomia and speaking problem by using Fisher's Least Significant Difference (LSD) test.

Speaking problem	xerostomia			
	Mean	(1)	(2)	(3)
		0.83	0.83	2.33
(1) Good	0.83		-	-
(2) Moderate	0.83	0.00		-
(3) Poor	2.33	1.49*	1.50*	

*The mean difference is significant at the 0.05 level.

In tasting problems, there were two pairs with statistically significant differences at the 0.05 level: (1) good and moderate, (2) good and poor. The good group included 515 cases mean of xerostomia 0.70 (S.D. =1.20, 95% CI= 0.60-0.80), Moderate 72 cases mean of xerostomia 1.70 (S.D. =1.10, 95% CI= 1.44-1.96), In the poor group, 36 cases, the mean of xerostomia was 1.30 (S.D. =1.83, 95% CI=0.68-1.92).

The Moderate group had the highest mean of xerostomia; 1.00 greater than the Good group at 0.05, statistically significant, and 0.40 greater than the Poor group, with a statistically insignificant difference at 0.05 are shown in Table 4.20

Table 4.20 Multiple comparisons between xerostomia and tasting problem by using Fisher's Least Significant Difference (LSD) test.

Tasting problem	xerostomia			
	Mean	(1)	(2)	(3)
		0.70	1.70	1.30
(1) Good	0.70		-	-
(2) Moderate	1.70	1.00*		-
(3) Poor	1.30	0.60*	0.40	

*The mean difference is significant at the 0.05 level.

According to the differences between xerostomia and sociodemographic and health behavior variables in Type 2 diabetic elderly patients, using the One-way ANOVA statistics in Table 4.13, I wanted to analyze in detail the variables by adjusted xerostomia interaction test, adjusted by gender, systemic disease, medication, smoking, alcohol consumption, toothpaste brands, and dentures. Xerostomia was statistically significant at the 0.05 level for years of diabetes, hemoglobin A1c level, speaking and tasting problems with xerostomia, and education after adjusted variables that were not statistically significant at the 0.05 level are shown in Table 4.21

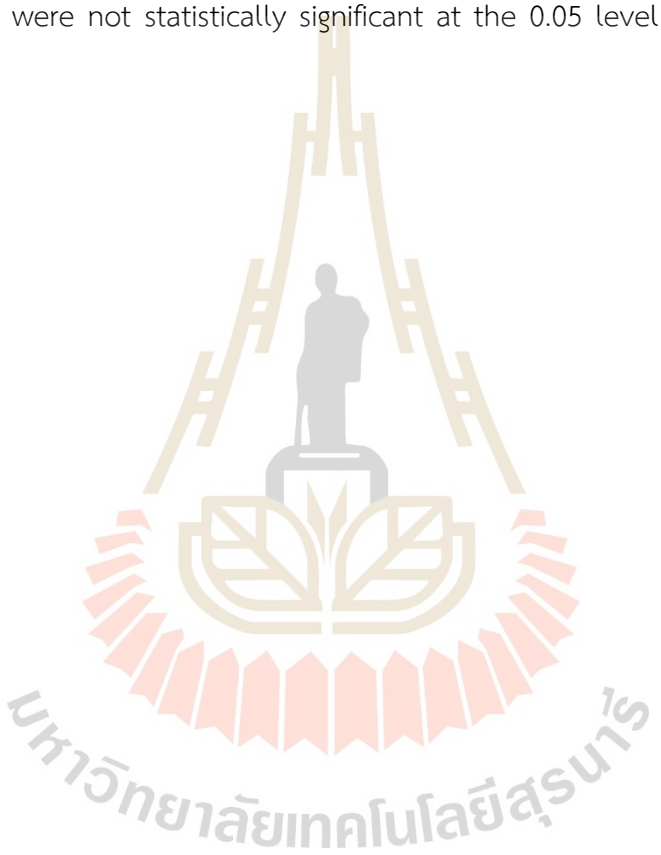


Table 4.21 Differences between xerostomia and sociodemographic and health behavior variables and oral funtions in the population by ANCOVA[a].

Variables	N (%)	Mean	S.D.	95% CI	*p*-Value
Education					
None	12 (1.9)	0.91	1.56	0.07-1.91	0.91[a]
Elementary School	148 (23.8)	0.77	1.19	0.57-0.96	(0.64[b])
High School	282 (45.3)	0.86	1.23	0.71-1.00	
Bachelor's degree	162 (26.0)	0.88	1.38	0.66-1.09	
Higher than the	19 (3.0)	1.15	1.60	0.38-1.93	
Bachelor's degree					
Years since diabetes					
diagnosis					
0-5	147 (23.6)	0.38	1.02	0.22-0.55	0.03[a] *
6-10	241 (38.7)	0.63	1.11	0.49-0.78	
Over 10	235 (37.7)	1.37	1.40	1.18-1.55	
Hemoglobin A1c					
level (%)					
≤ 6.5	134 (21.5)	0.38	0.95	0.21-0.54	0.22[a]
6.6-6.9	126 (20.2)	0.69	1.29	0.46-0.91	(<0.001[b]**)
≥ 7	363 (58.3)	1.08	1.32	0.95-1.22	
Speaking problem					
Good	608 (97.6)	0.83	1.26	0.73-0.93	0.79[a]
Moderate	6 (1.0)	0.83	1.16	0.39-2.06	(0.01[b]*)
Poor	9 (1.4)	2.33	1.80	0.94-3.71	
Tasting problem					
Good	515 (82.7)	0.70	1.20	0.60-0.80	0.23[a]
Moderate	72 (11.6)	1.70	1.10	1.44-1.96	(<0.001[b]**)
Poor	36 (5.7)	1.30	1.83	0.68-1.92	

[a] Interaction test: Adjusted by Gender, Systemic disease , Medication, Smoking ,Alcohol consumption, Toothpaste brands, and Denture

[b] Results from full factorial Model value

*The level of significance was $p < 0.05$

**Results by T-Test

From Table 4.21, Differences between xerostomia and sociodemographic and health behavior variables by ANCOVA, it was found that I tested multiple comparisons between xerostomia and variables for years of diabetes, hemoglobin A1c level, speaking and tasting problems by using Fisher's Least Significant Difference (LSD) test.

For years since diabetes diagnosis, three pairs were found to differ statistically at the 0.05 level: (1) 0-5 years and 6-10 years, (2) 0-5 years and over 10 years, and (3) 6-10 years and over 10 years; as well as the results of analysis using One-way ANOVA statistics in Table 13. In the over 10-year group, the mean of xerostomia was the highest, which was 0.98 more than the 0-5 years group and 0.73 more than the 6-10 years group, with a statistically significant difference at the 0.05 level as shown in Table 4.22

Table 4.22 Multiple comparisons between xerostomia and years of diabetes by using Fisher's Least Significant Difference (LSD) test (After ANCOVA analysis).

Years since diabetes diagnosis	xerostomia			
	Mean	(1)	(2)	(3)
		0.38	0.63	1.37
(1) 0-5 years	0.38		-	-
(2) 6-10 years	0.63	0.25*		-
(3) Over 10 years	1.37	0.98*	0.73*	

*The mean difference is significant at the 0.05 level.

At the hemoglobin A1c level, three pairs were found to differ statistically at the 0.05 level: (1) ≤ 6.5 % and 6.6-6.9%, (2) ≤ 6.5 % and ≥ 7%, and (3) 6.6-6.9%. and ≥ 7% as with the analysis results using One-way ANOVA statistics. The group with a hemoglobin A1c level ≥ 7% had the highest mean of xerostomia, 0.70 greater than the ≤ 6.5% group and 0.39 more than the 6.6-6.9% group, with a statistically significant difference at the 0.05 level are shown in Table 4.23

Table 4.23 Multiple comparisons between xerostomia and Hemoglobin A1c level (%) by using Fisher's Least Significant Difference (LSD) test (After ANCOVA analysis).

Hemoglobin A1c level	xerostomia			
	Mean	(1)	(2)	(3)
		0.38	0.69	1.08
(1) ≤ 6.5 %	0.38		-	-
(2) 6.6-6.9 %	0.69	0.30*		-
(3) ≥ 7 %	1.08	0.70*	0.39*	

*The mean difference is significant at the 0.05 level.

Regarding speaking problems, (1) Good and Poor, (2) Moderate and Poor, as well as the findings of the One-way ANOVA analysis, were two pairings with a statistically significant differences at the 0.05 level. As indicated in Table 23. The poor group had the highest mean of xerostomia, 1.49 more than the good group and 1.50 more than the moderate group, with a statistically significant difference of 0.05, are shown in Table 4.24

Table 4.24 Multiple comparisons between xerostomia and speaking problem by using Fisher's Least Significant Difference (LSD) test (After ANCOVA analysis).

Speaking problem	xerostomia			
	Mean	(1)	(2)	(3)
		0.83	0.83	2.33
(1) Good	0.83		-	-
(2) Moderate	0.83	0.00		-
(3) Poor	2.33	1.49*	1.50*	

*The mean difference is significant at the 0.05 level.

In tasting problems, there were two pairs with a statistically significant difference at the 0.05 level: (1) Good and Moderate, (2) Good and Poor, as well as the results of the One-way ANOVA analysis. The Moderate group had the highest mean of xerostomia; 1.00 greater than the Good group at 0.05, statistically significant, and 0.40 greater than the Poor group, with a statistically insignificant difference at 0.05, are shown in Table 4.25

Table 4.25 Multiple comparisons between xerostomia and tasting problem by using Fisher's Least Significant Difference (LSD) test (After ANCOVA analysis).

Tasting problem	xerostomia			
	Mean	(1)	(2)	(3)
		0.70	1.70	1.30
(1) Good	0.70		-	-
(2) Moderate	1.70	1.00*		-
(3) Poor	1.30	0.60*	0.40	

*The mean difference is significant at the 0.05 level.

Based on the aforementioned variable analysis of Type 2 diabetic elderly patients in the NCDs clinic at the Suranaree University of Technology Hospital, I wanted to analyze the relationship between sociodemographic and health behavior data with xerostomia of the population in order to explore data-driven associations of the patient population. In this regard, I have analyzed the relationship by analyzing the types of variables. If it's continuous variables, choose the Pearson correlation coefficient statistic; if it's categorical variables, choose the test with the Chi-square statistic.

Analysis of the relationship between continuous variables including age, years of diabetes, hemoglobin A1c level and Xerostomia found that years of diabetes and hemoglobin A1c level variables were significantly associated with Xerostomia at a 0.05 level (p-Value <0.001 (both) by years of diabetes (r = 0.296) and hemoglobin A1c level (r = 0.219). For the age variable, no association with xerostomia (p-Value = 0.097) are shown in Table 4.26

Table 4.26 Relationship between Sociodemographic and Health behavior data with xerostomia of population by Pearson correlation coefficient (N=623).

Variables	**Xerostomia** (N=623, Mean=0.85, S.D.=1.27)				
	N	**Mean**	**S.D.**	**r**	***p*-Value**
Age	623	65.48	7.73	0.067	0.097
Years of diabetes	623	10.13	5.57	0.296	<0.001**
Hemoglobin A1c level	623	8.38	1.97	0.219	<0.001**

**The level of significance was $p < 0.001$

I then analyzed the relationship between categorical variables, including gender, age, education, systemic diseases other than diabetes, medications, smoking, alcohol consumption, toothpaste brands, dentures, and xerostomia. At the 0.05 level, systemic diseases other than diabetes, medications, smoking, alcohol consumption, and dentures were significantly associated with the occurrence of Xerostomia. By gender (Cramer's V=0.109), age (Cramer's V=0.124), systemic diseases other than diabetes (Cramer's V=0.287), medications (Cramer's V=0.244), smoking (Cramer's V=0.200), alcohol consumption (Cramer's V. =0.315) and wearing denture (Cramer's V=0.170). The variables of education and toothpaste brand were not associated with xerostomia (*p*-Value = 0.718 and 0.982, respectively) and there is no multicollinearity, as shown in Table 4.27

Table 4.27 Relationship between Sociodemographic and Health behavior data with xerostomia of population by Chi-square test (N=623).

Variables	Groups (N (%))		N (%)	X^2	*p*-Value
	Xerostomia	Normal			
Gender					
Male	94 (32.6)	194 (67.4)	288 (46.2)	7.421	0.006*
Female	145 (43.3)	190 (56.7)	335 (53.8)		(Cramer's
Total	239 (38.4)	384 (61.6)	623 (100)		V=0.109)
Age					
50-59 years	39 (27.3)	104 (72.7)	143 (23.0)	9.654	0.002*
60 years and older	200 (41.7)	280 (58.3)	480 (77.0)		(Cramer's
Total	239 (38.4)	384 (61.6)	623 (100)		V=0.124)
Education					
None	4 (33.3)	8 (66.7)	12 (1.9)	0.131**	0.718
Elementary School	52 (35.1)	96 (64.9)	148 (23.8)		
High School	115 (40.8)	167 (59.2)	282 (45.3)		
Bachelor's degree	58 (35.8)	104 (64.2)	162 (26.0)		
Higher than the Bachelor's degree	10 (52.6)	9 (47.4)	19 (3.0)		
Total	239 (38.4)	384 (61.6)	623 (100)		
Systemic diseases other than diabetes					
None	16 (11.8)	119 (88.2)	135 (21.7)	51.227**	<0.001**
Hypertension	206 (50.1)	205 (49.9)	411 (66.0)		(Cramer's
Dyslipidemia	191 (50.1)	190 (49.9)	381 (61.2)		V=0.287)
Cardiovascular disorders	8 (88.8)	1 (11.2)	9 (1.4)		
Thyroid disorders	13 (62.0)	8 (38.0)	21 (3.4)		
Hematologic disorders	8 (72.7)	3 (27.3)	11 (1.8)		
Renal disorders	40 (59.7)	27 (40.3)	67 (10.8)		

Table 4.27 (Continued).

Variables	Groups (N (%))		N (%)	X^2	*p*-Value
	Xerostomia	Normal			
Systemic diseases other than diabetes (cont.)					
Respiratory disorders	25 (45.4)	30 (54.6)	55 (8.8)		
Allergy	47 (43.1)	62 (56.9)	109 (17.5)		
Gout	28 (66.6)	14 (33.4)	42 (6.7)		
Medications					
None	22 (16.0)	115 (84.0)	137 (22.0)	36.949**	<0.001**
Antihypertensive medication	206 (51.0)	198 (49.0)	404 (64.8)		(Cramer's V=0.244)
Antidyslipidemic agents	186 (51.8)	173 (48.2)	359 (57.6)		
Antiplatlets and Anticoagulant-medication	163 (47.1)	183 (52.9)	346 (55.5)		
Pain medication	77 (38.7)	122 (61.3)	199 (31.9)		
Gastrointestinal agents	7 (43.7)	9 (56.3)	16 (2.6)		
Cardiovascular medication	7 (63.6)	4 (36.4)	11 (1.8)		
Antihistamine	30 (38.0)	49 (62.0)	79 (12.7)		
Smoking (cigarettes per day)					
Never	220 (36.5)	382 (63.5)	602 (96.6)	24.961**	<0.001**
1-5	19 (90.5)	2 (9.5)	21 (3.4)		(Cramer's V=0.200)
5-10	0 (0.0)	0 (0.0)	0 (0.0)		
Over 10	0 (0.0)	0 (0.0)	0 (0.0)		
Total	239 (38.4)	384 (61.6)	623 (100)		

Table 4.27 (Continued).

Variables	Groups (N (%))		N (%)	X^2	*p*-Value
	Xerostomia	Normal			
Alcohol consumption					
Never	172 (32.1)	363 (67.9)	535 (85.9)	61.836**	<0.001**
Monthly or less	31 (75.6)	10 (24.4)	41 (6.6)		(Cramer's
2-4 times a month	22 (71.0)	9 (29.0)	31 (5.0)		V=0.315)
2 -3 times a week	10 (91.0)	1 (9.0)	11 (1.7)		
4 or more times a week	4 (80.0)	1 (20.0)	5 (0.8)		
Total	239 (38.4)	384 (61.6)	623 (100)		
Toothpaste brands					
Colgate	87 (41.2)	124 (58.8)	211 (33.9)	0.001*	0.982
SYSTEMA	18 (51.4)	17 (48.6)	35 (5.6)		
DARLIE	21 (44.7)	26 (55.3)	47 (7.5)		
Amway Glister	13 (44.8)	16 (55.2)	29 (4.7)		
SALZ	16 (36.4)	28 (63.6)	44 (7.1)		
SPARKLE	7 (30.4)	16 (69.6)	23 (3.7)		
SENDODYNE	24 (38.7)	38 (61.3)	62 (10.0)		
DENTISTE’	10 (45.4)	12 (54.6)	22 (3.5)		
Parodontax	6 (30.0)	14 (70.0)	20 (3.2)		
Twin Lotus	17 (28.3)	43 (71.7)	60 (9.6)		
Tepthai	11 (23.4)	36 (76.6)	47 (7.5)		
HI-HERB	8 (36.4)	14 (63.6)	22 (3.5)		
Other (Salt)	1 (100)	0 (0.0)	1 (0.2)		
Total	239 (38.4)	384 (61.6)	623 (100)		

Table 4.27 (Continued).

Variables	Groups (N (%))		N (%)	X^2	*p*-Value
	Xerostomia	Normal			
Denture					
None	210 (36.1)	371 (63.9)	581 (93.3)	17.933**	<0.001**
Complete Dentures	6 (100)	0 (0.0)	6 (0.9)		(Cramer's
Removable Partial	20 (87.0)	3 (13.0)	23 (3.7)		V=0.170)
Dentures					
Fixed Partial Dentures	3 (23.0)	10 (77.0)	13 (2.1)		
Total	239 (38.4)	384 (61.6)	623 (100)		

*The level of significance was $p < 0.05$, **$p < 0.001$

**In X^2, results by computed for a 2x2 table

From the perspective of the relationship between the above factors and xerostomia, I wanted to analyze the causation of xerostomia on demographic and health behavior variables to determine the true cause of xerostomia by using logistic regression. Xerostomia was significantly associated with gender (OR=1.57, 95% CI= 1.13 to 2.18), age. (OR=1.90, 95% CI= 1.26 to 2.87), years of diabetes (OR=4.50, 95% CI= 3.19 to 6.36), hemoglobin A1c level (OR=3.81, 95% CI= 2.35 to 6.19), systemic diseases other than diabetes(OR=6.25, 95% CI= 3.60 to 10.86), medications (OR=4.21, 95% CI= 2.58 to 6.88), smoking (OR=16.49, 95% CI= 13.80 to 17.48), alcohol consumption (OR=6.73, 95% CI= 3.99 to 11.35), wearing denture (OR=3.94, 95% CI= 2.00 to 7.74).

No relationship of xerostomia was found in patients regarding education and toothpaste brand variables (*p*-Values 0.718 and 0.982, respectively), with education (OR=0.80, 95%CI=0.23 to 2.68), and toothpaste containing SLS (OR=1.00, 95%CI= 0.59 to 1.68). It is interesting that the type of toothpaste affects the occurrence of xerostomia in both wellcontrolled (HbA1c ≤ 6.5%) and uncontrolled T2DM patients (HbA1c > 6.5%). Significantly, the prevalence of xerostomia in uncontrolled T2DM patients using toothpaste containing spicy ingredients was found to be 4.34 times higher than was the case for well-controlled patients are shown in Table 4.28

Table 4.28 The common risk factors for xerostomia on demographic and health behaviour variables by using logistic regression.

Independent factors	N	Percentage	Odds Ratio	95% CI		*p*-Value
				Lower bounds	Upper bounds	
Sex						
Male (reference)	288	46.2	1.57	1.13	2.18	0.007*
Female	335	53.8				
Total	623	100				
Age (years)						
50-59 (reference)	143	23.0	1.90	1.26	2.87	0.002*
Over 59	480	77.0				
Total	623	100				
Toothpaste (Type 1)						
SLS-Free (reference)	68	11.0	1.00	0.59	1.68	0.082
Containing SLS	555	89.0				
Toothpaste (Type 2)						
Spicy herbal extracts-Free (reference)	172	27.6	1.86	0.82	1.90	0.039*
Containing spicy herbal extracts	451	72.4				
Toothpaste (Type 3)						
Artificial sweeteners – Free (ref.)	368	59.0	0.87	0.62	1.21	0.041*
Containing artificial sweeteners	255	41.0				

*The level of significance was $p < 0.05$, ** $p < 0.001$

Table 4.28 (Continued).

Independent factors	N	Percentage	Odds Ratio	95% CI		*p*-Value
				Lower bounds	Upper bounds	
Having Education						
Educated (reference)	611	98.1	0.80	0.23	2.68	0.718
None	12	1.9				
Total	623	100				
Education						
None (reference)	12	1.9	-	-	-	-
Elementary School	148	23.8	0.45	0.10	2.01	0.297
High School	282	45.3	0.48	0.18	1.27	0.143
Bachelor's degree	162	26.0	0.62	0.24	1.57	0.314
Higher than the Bachelor's degree	19	3.0	0.50	0.19	1.30	0.158
Total	623	100				
Years since diabetes diagnosis						
0-5 (reference)	147	23.6	-	-	-	-
6-10	241	38.7	2.36	1.41	3.95	0.001*
Over 10	235	37.7	7.42	4.46	12.34	<0.001**
Hemoglobin A1c level (%)						
≤ 6.5 (reference)	134	21.5	-	-	-	-
6.6-6.9	126	20.2	1.64	0.90	3.00	0.106
≥ 7	363	58.3	4.96	3.02	8.13	<0.001**
Total	623	100				

*The level of significance was $p < 0.05$, ** $p < 0.001$

Table 4.28 (Continued).

Independent factors	N	Percentage	Odds Ratio	95% CI		*p*-Value
				Lower bounds	Upper bounds	
Having systemic diseases other than diabetes						
No (reference)	135	21.7	6.25	3.60	10.86	<0.001**
Yes	488	78.3				
Total	623	100				
Systemic diseases other than diabetes						
None (reference)	135	21.7	-	-	-	-
Hypertension	411	66.0	5.45	3.58	8.28	<0.001**
Dyslipidemia	381	61.2	4.06	2.79	5.90	<0.001**
Cardiovascular disorders	9	1.4	13.26	1.64	26.73	0.015*
Thyroid disorders	21	3.4	2.70	1.10	6.62	0.030*
Hematologic disorders	11	1.8	4.39	1.15	16.74	0.030*
Renal disorders	67	10.8	2.65	1.58	4.46	<0.001**
Respiratory disorders	55	8.8	1.37	0.79	2.40	0.259
Allergy	109	17.5	1.27	0.83	1.93	0.262
Gout	42	6.7	3.50	1.80	6.80	<0.001**
Having medications						
No (reference)	137	23.0	4.21	2.58	6.88	<0.001**
Yes	486	77.0				
Total	623	100				

*The level of significance was $p < 0.05$, ** $p < 0.001$

Table 4.28 (Continued).

Independent factors	N	Percentage	Odds Ratio	95% CI		*p*-Value
				Lower bounds	Upper bounds	
Medications						
None (reference)	137	22.0	-	-	-	-
Antihypertensive medication	404	64.8	5.86	3.85	8.91	<0.001**
Antidyslipidemic agents	359	57.6	4.28	2.97	6.16	<0.001**
Antiplatlets and Anticoagulant medication	346	55.5	2.35	1.68	3.30	<0.001**
Pain medication	199	31.9	1.02	0.72	1.44	0.907
Gastrointestinal agents	16	2.6	1.25	0.46	3.42	0.654
Cardiovascular medication	11	1.8	2.86	0.83	9.89	0.096
Antihistamine	79	12.7	0.98	0.60	1.59	0.939
Smoking						
Never (reference)	602	96.6				
Current smoker	21	3.4	16.49	13.80	17.48	<0.001**
Total	623	100				
Having alcohol consumption						
No (reference)	535	85.9	6.73	3.99	11.35	<0.001**
Yes	88	14.1				
Total	623	100				

*The level of significance was $p < 0.05$, ** $p < 0.001$

Table 4.28 (Continued).

Independent factors	N	Percentage	Odds Ratio	95% CI		*p*-Value
				Lower bounds	Upper bounds	
Alcohol consumption						
Never (reference)			-	-	-	-
Monthly or less			6.54	3.13	13.65	<0.001**
2-4 times a month			5.15	2.32	11.44	<0.001**
2 -3 times a week			21.10	2.68	26.18	0.004*
4 or more times a wk.			8.44	0.93	16.09	0.057
Denture wearing						
No (reference)	581	93.3	3.94	2.00	7.74	<0.001**
Yes	42	6.7				
Total	623	100				
Type of denture						
None (reference)	581	93.3	-	-	-	-
Complete Dentures	6	0.9	7.88	2.01	8.93	0.039*
Removable Partial Dentures	23	3.7	9.41	6.01	12.01	0.009*
Fixed Partial Dentures	13	2.1	2.22	1.78	6.62	0.001*
Total	623	100				
Types of toothpastes	**Subcategories**					
Toothpaste containing SLS (type 1: n = 555)	HbA1c ≤ 6.5% (n = 122) (reference)		0.24	0.14	1.40	0.071
	HbA1c ≥ 6.6% (n = 433)					

*The level of significance was $p < 0.05$, ** $p < 0.001$

Table 4.28 (Continued).

Types of toothpastes	Subcategories	Odds Ratio	95% CI		*p*-Value
			Lower bounds	Upper bounds	
Toothpaste containing spicy herbal extracts (type 2: n = 451)	HbA1c ≤ 6.5% (n = 97) (reference)	4.34	1.94	5.76	<0.001**
	HbA1c ≥ 6.6% (n = 354)				
Toothpaste containing artificial sweeteners (type 3: n = 255)	HbA1c ≤ 6.5% (n = 55) (reference)	0.36	0.17	0.73	0.005*
	HbA1c ≥ 6.6% (n = 200)				

*The level of significance was $p < 0.05$, ** $p < 0.001$

Because xerostomia also causes issues with oral function, I utilized logistic regression to investigate the causal relationship between oral function and demographic and health behavior variables (speaking problem, tasting problem, swallowing problem, and chewing problem). A study of causes of oral function problems and demographic and health behavior variables found that years since diabetes diagnosis were statistically significant test results (*p*-Value<0.05) for tasting problems (OR = 1.74, 95% CI = 1.15 to 2.65), and chewing problems (OR = 3.73, 95% CI = 1.17 to 4.84).

Systemic diseases other than diabetes showed statistically significant test result (*p*-Value<0.05) associated with tasting problems (OR=2.26, 95% CI= 1.12 to 4.19), and swallowing problems (OR=3.56, 95% CI= 1.74 to 7.25).

Medications had statistically significant test results (*p*-Value<0.05) associated with tasting problems (OR=3.20, 95% CI= 1.62 to 6.33), and swallowing problems (OR=2.31, 95% CI= 1.25 to 4.28).

Smoking had statistically significant test results (*p*-Value<0.05) associated with tasting problems (OR=3.81, 95% CI= 1.56 to 9.28)

Alcohol consumption had statistically significant test results (*p*-Value<0.05) associated with tasting problems (OR=2.31, 95% CI= 1.38 to 3.87), swallowing problems (OR=2.31, 95% CI= 1.38 to 3.87), and chewing problems (OR=3.16, 95% CI= 1.05 to 9.48).

Wearing denture had statistically significant test results (*p*-Value<0.05) associated with chewing problems (OR=5.45, 95% CI= 1.65 to 7.93), and

Xerostomia had statistically significant test results (*p*-Value<0.05) associated with all oral functions, speaking problems (OR=3.31, 95% CI= 1.11 to 9.80), tasting problems (OR=5.12, 95% CI. = 3.26 to 8.06), swallowing problems (OR=3.59, 95% CI= 2.32 to 5.53), and chewing problems (OR=3.34, 95% CI= 1.15 to 5.82) as shown in Table 4.29

Table 4.29 The common risk factors[a] for oral function problems on demographic and health behaviour variables by using logistic regression.

Independent factors	Categories	Speaking Problem	Tasting problem	Swallowing problem	Chewing problem
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Xerostomia	No (reference)	3.31*	5.12**	3.59**	3.34*
	Yes	(1.11-9.80)	(3.26-8.06)	(2.32-5.53)	(1.15-5.82)
Toothpaste (Type 1)	SLS-Free (reference)	1.73	0.87	0.87	0.47
	Containing SLS	(0.22-13.39)	(0.45-1.66)	(0.45-1.66)	(0.13-1.74)
Toothpaste (Type 2)	Spicy herbal extracts-Free(ref.)	1.54	1.10	1.24	1.05
	Containing spicy herbal extracts	(0.42-5.52)	(0.69-1.77)	(0.77-2.01)	(0.33-3.34)
Toothpaste (Type 3)	Artificial sweeteners –Free (ref.)	0.51	0.86	0.94	2.20
	Containing artificial sweeteners	(0.16-1.64)	(0.56-1.31)	(0.61-1.44)	(0.77-6.28)
Sex	Male (reference)	1.29	0.79	0.99	0.98
	Female	(0.45-3.69)	(0.52-1.20)	(0.65-1.51)	(0.35-2.74)
Age (years)	50-59 (reference)	1.19	0.98	1.05	0.81
	Over 59	(0.33-4.30)	(0.60-1.61)	(0.63-1.73)	(0.25-2.60)
Education	None (reference)	-	-	-	-
	Elementary School	0.05 (0.02-1.12)	4.25 (0.63-8.24)	2.83 (0.39-8.17)	0.08 (0.01-4.65)
	High School	0.24 (0.02-2.85)	2.25 (0.49-4.27)	1.98 (0.43-9.08)	0.37 (0.17-3.77)
	Bachelor's degree	0.25 (0.02-2.43)	1.36 (0.30-6.13)	1.83 (0.41-8.18)	0.32 (0.16-2.93)
	Higher than the Bachelor's degree	0.93 (0.11-7.91)	2.09 (0.46-9.52)	1.55 (0.33-7.13)	0.69 (0.07-6.07)

Table 4.29 (Continued).

Independent factors	Categories	Speaking Problem	Tasting problem	Swallowing problem	Chewing problem
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Years since diabetes diagnosis	0-5 (reference)	-	-	-	-
	6-10	0.81 (0.17-3.67)	2.00* (1.05-3.81)	1.69 (0.93-3.04)	1.84 (0.19-7.85)
	Over 10	1.69 (0.44-6.48)	2.69* (1.43-5.07)	1.65 (0.91-2.98)	7.17 (0.91-8.12)
Haemoglobin A1c level (%)	≤ 6.5 (reference)	-	-	-	-
	6.6-6.9	3.30 (0.65-16.66)	1.55 (0.82-2.94)	1.65 (0.86-3.14)	0.52 (0.04-5.89)
	≥ 7	1.29 (0.26-6.32)	1.15 (0.66-1.99)	1.24 (0.71-2.17)	2.25 (0.49-10.21)
Having Systemic diseases other than diabetes	No (reference)				
	Yes	3.95 (0.51-5.37)	2.26* (1.22-4.19)	3.56** (1.74-7.25)	1.82 (0.40-8.16)
Systemic diseases other than diabetes	None (reference)	-	-	-	-
	Hypertension	2.09 (0.58-7.50)	3.26** (1.88-5.64)	2.61** (1.55-4.38)	2.09 (0.58-7.50)
	Dyslipidemia	2.59 (0.72-9.27)	2.27* (1.41-3.66)	1.92* (1.21-3.04)	1.76 (0.55-5.62)
	Cardiovascular disorders	1.00 (0.02-2.22)	3.92* (1.03-14.85)	2.42 (0.59-9.84)	13.20* (2.50-19.80)
	Thyroid disorders	0.09 (0.01-2.32)	1.51 (0.54-4.22)	1.12 (0.37-3.41)	0.05 (0.01-2.14)

* *p*-Value were significant ($p < 0.05$) , ** *p*-Value were significant ($p < 0.001$)

Table 4.29 (Continued).

Independent factors	Categories	Speaking Problem	Tasting problem	Swallowing problem	Chewing problem
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Systemic diseases other than diabetes (cont.)	Hematologic disorders	4.27 (0.51-9.68)	1.81 (0.47-6.93)	2.79 (0.80-9.70)	0.90 (0.10-3.28)
	Renal disorders	0.08 (0.02-3.44)	1.90* (1.05-3.41)	2.07* (1.16-3.70)	4.40* (1.45-13.29)
	Respiratory disorders	1.61 (0.35-7.33)	1.21 (0.60-2.43)	1.06 (0.51-2.18)	0.73 (0.09-5.68)
	Allergy	1.18 (0.32-4.26)	1.08 (0.63-1.86)	1.35 (0.80-2.26)	2.42 (0.81-7.23)
Having Medications	No (reference)	-	-	-	-
	Yes	3.85 (1.54-6.71)	3.20* (1.62-6.33)	2.31* (1.25-4.28)	4.03 (1.52-6.95)
Medications	None (reference)	-	-	-	-
	Antihypertensive medication	2.20 (0.61-7.89)	3.45** (1.99-5.97)	2.58** (1.55-1.30)	2.20 (0.61-7.89)
	Antidyslipidemic agents	3.00 (0.84-10.77)	2.71** (1.68-4.35)	1.94* (1.24-3.04)	2.05 (0.64-6.52)
	Antiplatlets and Anticoagulant medication	2.24 (0.70-7.17)	1.84* (1.19-2.86)	1.38 (0.90-2.11)	3.28 (0.91-11.74)
	Pain medication	3.30* (1.15-9.40)	1.08 (0.69-1.67)	1.08 (0.69-1.67)	1.89 (0.67-5.30)
	Gastrointestinal agents	2.82 (0.34-22.88)	0.67 (0.15-3.01)	2.97* (1.05-8.35)	2.82 (0.34-22.88)
	Cardiovascular medication	2.10 (0.02-3.54)	2.79 (0.80-9.70)	1.81 (0.47-6.93)	10.23* (2.01-52.14)

* *p*-Value were significant ($p < 0.05$) , ** *p*-Value were significant ($p < 0.001$)

Table 4.29 (Continued).

Independent factors	Categories	Speaking Problem	Tasting problem	Swallowing problem	Chewing problem
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Antihistamine	1.06 (0.23-4.79)	0.83 (0.43-1.60)	1.48 (0.84-2.63)	1.75 (0.48-6.34)
Smoking (cigarettes per day)	Never (reference)	-	-	-	-
	1-5	2.10 (0.26-3.76)	3.81* (1.56-9.28)	2.48 (0.97-6.30)	3.52 (1.07-4.78)
Having Alcohol consumption	No (reference)	-	-	-	-
	Yes	2.26 (0.70-7.28)	2.31* (1.38-3.87)	2.31* (1.38-3.87)	3.16* (1.05-9.48)
Alcohol consumption	Never (reference)	-	-	-	-
	Monthly or less	2.44 (0.53-11.41)	2.86* (1.44-5.69)	2.02 (0.97-4.20)	4.14* (1.09-15.69)
	2-4 times a month	3.28 (0.69-15.51)	1.92 (0.83-4.44)	2.63* (1.19-5.70)	1.75 (0.21-14.12)
	2 -3 times a week	1.00 (0.50-3.25)	1.22 (0.26-5.78)	3.15 (0.90-11.02)	5.25 (0.61-15.01)
	4 or more times a week	2.00 (1.20-4.54)	3.68 (0.60-22.38)	1.38 (0.15-12.51)	2.50 (1.60-5.23)
Denture wearing	No (reference)	-	-	-	-
	Yes	0.98 (0.12-7.69)	1.77 (0.86-3.64)	1.54 (0.73-3.23)	5.45* (1.65-7.93)

* *p*-Value were significant ($p < 0.05$) , ** *p*-Value were significant ($p < 0.001$)

Table 4.29 (Continued).

Independent factors	Categories	Speaking Problem	Tasting problem	Swallowing problem	Chewing problem
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Type of denture	None (reference)	-	-	-	-
	Complete Dentures	8.10* (2.88-13.95)	4.99 (0.99-25.09)	2.00 (1.50-5.22)	25.90** (4.28-56.61)
	Removable Partial Dentures	2.00 (0.30-4.52)	2.18 (0.87-5.44)	2.62* (1.08-6.37)	2.35 (0.29-19.06)
	Fixed Partial Dentures	1.00 (0.42-8.23)	0.41 (0.05-3.23)	0.89 (0.19-4.10)	4.31 (0.51-36.17)

[a]The common risk factors were identified by bivariable logistic regression, OR = Odds Ratio, 95% CI = 95% confidence interval, * *p*-Value were significant ($p < 0.05$), ** *p*-Value were significant ($p < 0.001$)

Multivariate logistic regression analysis (Table 4.30) showed prognostic risk factors for xerostomia (In multiple logistic regression, with *p*-Value < 0.05 in the bivariable analysis or in combination with 95% confidence interval consideration) after adjusting for potential confounding factors (systemic diseases other than diabetes, medications, smoking, and alcohol consumption). Eight variables were identified as the significant prognostic risk factors (Table 4.30). Prognostic risk factors were female (OR = 1.36, 95% CI = 1.21 to 2.61), age ≥60 years (OR = 3.46, 95% CI = 2.24 to 6.87), toothpaste containing spicy herbal extracts (OR = 9.32, 95% CI = 3.46 to 15.25), more than 10 years since diabetes diagnosis (OR = 2.40, 95% CI = 0.23 to 4.68), haemoglobin A1c level ≥7 % (OR = 8.17, 95% CI = 2.08 to 12.34), and removable partial dentures wearing (OR = 8.59, 95% CI = 1.60 to 12.55). However, I found that toothpaste containing artificial sweeteners was a protective factor for xerostomia (OR = 0.35, 95% CI = 0.02 to 4.82).

Table 4.30 Prognostic risk factors[a] for xerostomia on demographic and health behaviour variables.

Independent factors	Categories	OR	95% CI	*p*-Value
Sex	Male (reference)	-	-	-
	Female	1.36	1.21-2.61	<0.001**
Age (years)	50-59 (reference)	-	-	-
	Over 59	3.46	2.24-6.87	0.018*
Toothpaste (Type 1)	SLS-Free (reference)	-	-	-
	Containing SLS	1.40	0.13-1.67	0.096
Toothpaste (Type 2)	Spicy herbal extracts-Free (ref.)	-	-	-
	Containing spicy herbal extracts	9.32	3.46-15.25	0.032*
Toothpaste (Type 3)	Artificial sweeteners –Free (ref.)	-	-	-
	Containing artificial sweeteners	0.35	0.02-4.82	0.013*
Years since diabetes diagnosis	0-5 (reference)	-	-	-
	6-10	1.08	0.03-1.18	<0.001**
	Over 10	2.40	0.23-4.68	0.001*
Haemoglobin A1c level (%)	≤ 6.5 (reference)	-	-	-
	6.6-6.9	5.10	1.05-9.21	<0.001**
	≥ 7	8.17	2.08-12.34	<0.001**
Type of denture	None (reference)	-	-	-
	Complete Dentures	3.66	1.51-5.96	0.003*
	Removable Partial Dentures	8.59	1.60-12.55	0.001*
	Fixed Partial Dentures	1.97	1.00-19.95	0.004*

* *p*-Value were significant ($p < 0.05$) , ** *p*-Value were significant ($p < 0.001$)

[a]Prognostic risk factors were identified by multiple logistic regression analysis (Estimates from multivariate logistic regression analysis including terms for education, systemic diseases other than diabetes, medications, smoking, and alcohol consumption), OR = Odds Ratio, 95% CI = 95% confidence interval, * *p*-Value were significant ($p < 0.05$), ** *p*-Value were significant ($p < 0.001$)

4.1.2 Discussions

As for the prevalence survey, I divided the discussion into four issues: 4.1.2.1 Xerostomia; 4.1.2.2 Type of toothpaste; 4.1.2.3 Oral function problems; 4.1.2.4 The association between diabetes, xerostomia, type of toothpaste, and oral function problems; and conclusions. Details are as follows:

4.1.2.1 Xerostomia

The prevalence of xerostomia in the studied population was 38.4%, which is greater than in previous research that was studied in Asia and Europe (27.3% and 30.7%, respectively) (Yuki Ohara et al., 2022), (Pérez-González et al., 2021). This was owing to a prevalence survey conducted in this study among older people with DM. Our result is corresponding to the study that found xerostomia was present in roughly 43% of diabetics (Sreebny, L. M. et al., 1992), and dry mouth was common in the elderly people (Dalodom et al., 2016).

Moreover, the present study demonstrated that xerostomia is more common in females (43.3%), which agrees with the findings of (Shirzaiy, M. and Bagheri, F., 2016). Consistent with other studies (Mojabi, K et al., 2007), menopause and hormonal changes are seen as potential xerostomia risk factors, and menopausal women frequently complain of oral dryness. Additionally, they discovered that menopausal women had significantly lower mean unstimulated salivary flow rates than male controls. The hormonal changes associated with menopause in women may increase the risk of developing xerostomia.

4.1.2.2 Type of toothpaste

Nearly 90% of elderly patients diabetics use toothpaste that contains Sodium Lauryl Sulfate (SLS). This study revealed that the majority of toothpaste ingredients utilized SLS synthetic compounds (9 out of 13 toothpaste brands from this study). SLS was contained in the majority of toothpaste ingredients (Paul, T. et al., 2019). There were patients who chose toothpaste containing spicy herbal extracts (451 cases), probably because Thai food culture and most Thai people have a preference for spicy food (Trachootham, D. et al., 2017). This study's investigation of toothpaste revealed that the majority of toothpaste available on the Thai market frequently contains both hot and cold spice ingredients. Consistent with the results of this study, 72.40% of diabetic patients from this study chose toothpaste containing spicy herbal extracts that may irritate oral tissues causing mucosal desquamation.

In this study, I found that each brand of toothpaste in diabetic patients used artificial sweeteners such as Sodium Saccharin, Sorbital, and Xylitol, and 41.0% of these 623 cases used toothpaste containing artificial sweeteners. This is consistent with the current toothpaste industry that often adds artificial sweeteners to flavors for the purpose of breath freshening users (van Loveren, C., 2013). In addition, sugar-free and artificially sweetened products were found in various supermarkets as well (Priyanka Sharma et al., 2019).

4.1.2.3 Oral function problems

More than half of the population had problems with swallowing. The results were consistent with the chewing problems. Patients complained that the most difficult foods to chew were fried pork, guava, and fried fish, which are relatively dry and hard foods. These problems can cause difficulty with consuming food in these patients, resulting in a lack of good nutrients for their health. In the long term, this will increase the chance of developing health problems. Therefore, the types of food should be considered as one important variable provided for these patients.

4.1.2.4 The association between diabetes, xerostomia, type of toothpaste, and oral function problems

The study also found that higher haemoglobin A1c levels and longer duration of diabetes were associated with xerostomia. Recently, studies have shown that xerostomia and hyposalivation may not always be concomitant (Solgun Folke et al,. 2009). Xerostomia may be present even though salivary secretion is normal. In fact, there may be hyposalivation even though the patient does not complain of xerostomia. One possible explanation is that because the process is slow, they get used to reduced saliva secretion. Therefore, the term "symptomatic xerostomia" or "pseudo xerostomia" may also be used in this study (Kapourani, A. et al., 2022). The diagnosis of xerostomia requires a thorough history of the patient's reported symptoms of oral dryness, medication use, and past medical history (Villa, A. et al., 2014). Several questionnaires have been proposed to identify patients with xerostomia. However, it was found to have high sensitivity but low specificity for hyposalivation. Interestingly, xerostomia patients frequently do not show any objective signs of hyposalivation. A diagnosis of hyposalivation is made when the stimulated salivary flow rate is ≤ 0.5–0.7 mL/min and the unstimulated salivary flow rate is ≤ 0.1 mL/min. Patients' subjective symptoms or self-reported feeling of dry mouth alone are not always parallel to the real signs of xerostomia and/or hyposalivation (Pedersen, A.M. et al., 2002). Therefore, the diagnosis of xerostomia and true hyposalivation is dependent upon a careful and detailed history and objective diagnostic tests such as salivary flow rates and oral moisture tests.

It is noted that I assessed solely subjective symptoms of xerostomia and I discovered that the longer the diabetes has existed, the higher the prevalence of xerostomia, especially in women. Although the findings is consistent with several previous studies (López-Pintor, R. M. et al., 2016.; Khovidhunkit, S. O. et al., 2009.; Borahan MO. et al., 2012.; Gholami, N. et al., 2017.; Nadig, S. D. et al., 2017.; Pinelopi-Theopisti Memtsa et al., 2017.; Hoseini, A. et al., 2017) which reported that the subjective symptom of xerostomia paralleled in salivary flow rates and that there was a statistically significant correlation between hyposalivation (reduction in the quantity of saliva) and xerostomia. It is however to confirm that the patient had true

xerostomia as a result of impaired salivary gland function, the measurement of salivary flow rate in combination with the Xerostomia Questionnaire should be performed in a further modest study.

Hyperglycemia in diabetes usually causes functional damage to many organ systems. In addition, mitochondrial dysfunction can be generated. Mitochondria play an important role in regulating salivary secretion. Once it functions improperly, salivary gland dysfunction can occur in diabetic patients (Ruo-Lan Xiang et al., 2020). A previous study of Shetty, S. R.,et al in 2012, suggested that a medical condition other than diabetes should be concerned in aged patients. For instance, polymedications such as anticholinergics, and antidepressants drugs may result in xerostomia. These medications were shown to be significantly linked to xerostomia caused by their xerogenic effects.

The study found that smoking, alcohol consumption, and denture wearing were also responsible for xerostomia since salivary macromolecules, enzymes, and proteins that serve as defense mechanisms are destroyed by tobacco smoke. The salivary glands are adversely affected by smoking tobacco, which also decreases the quality and flow of the saliva (Petrušić N. et al., 2015). Furthermore, alcohol consumption has a diuretic impact, which can cause dehydration and enhance xerostomia (M. Grace Eggleton., 1942). In addition (Glore R.J. et al., 2009) reported that denture wearing could cause xerostomia due to a possibility of denture stomatitis from the increased dental tissues-denture contact. Besides, wearing an ill-fitting denture may result in decreased saliva secretion.

I found that 39.47% of diabetic patients who used toothpaste containing spicy herbal extracts had xerostomia and also found that in these types of toothpaste there were spicy or cold ingredients such as menthol, clove, etc. Long-term usage of this type of toothpaste may increase the risk of xerostomia (Table 4.4, Table 4.28, Table 4.30) since it is often found that people with xerostomia already have altered tastes or intolerances to spicy or sour tastes (Thomson, W., 2015).

On the other hand, in this study's research, I discovered that the risk of xerostomia among diabetes individuals was decreased by toothpaste containing artificial sweeteners. In a similar previous studies, they discovered that artificial

sweeteners like xylitol can improve salivary flow rates in patients receiving intensity modulated radiation therapy for head and neck cancers without causing significant side effects (V. Manoor Maiya. et al., 2014)., and were effective in alleviating the manifestations of dry mouth (J. A. SHIP et al., 2007). Additionally, they reported that products containing olive oil, betaine, and xylitol that were structured like toothpaste, gel, and spray considerably reduced the majority of symptoms and the constraints on quality of life caused by dry mouth in patients receiving radiation. In particular, xylitol plays an important role in salivary stimulation activity (Martín, M. et al., 2017).

The results confirm that xerostomia caused problems with all aspects of oral function (Table 4.29) and other oral diseases since saliva serves a variety of crucial functions. I also observed an association between sex and the number of years since developing diabetes with xerostomia which is intriguing. Because the numbers were comparable in each group (Table 4.4), this could have had an impact on xerostomia. Notwithstanding, I discovered in this study that the type of toothpaste was related to xerostomia (Table 4.30). In order to reduce the symptoms of xerostomia, choosing the appropriate toothpaste for diabetic patients is a consideration that should not be disregarded. Although smoking, drinking alcohol, and denture wearing are all associated with xerostomia, the number of patients in each category varies greatly. Further studies should be focused on a smaller proportion of the population and should be studied in the healthy elderly group or other patient groups to investigate xerostomia trends and their prevalence in diverse populations. The limitation of present study was that I did not exclude diabetic patients having other diseases and included them in calculating the prevalence of xerostomia because I wanted the study population to be broadly representative of the general population to increase generalisability of the findings. Additionally, a further study should be conducted to investigate the salivary flow rate combined with xerostomia questionnaire to reflect the functional and physical salivary gland status. Furthermore, data of the fluoride content of toothpaste and the length of time patients brush their teeth should be considered because these issues might contribute to xerostomia.

Regarding the most commonly used toothpaste products, findings from a survey of older adults with Type 2 diabetes are mentioned above. The majority (89.0%) of them were found to use toothpaste that contains SLS (89.0%). Followed by toothpaste containing spicy herbal extracts (72.4%). Nevertheless, none of the diabetic patients who used hydrating toothpaste were reported. Although some patients have been reported to use herbal toothpastes such as menthol, peppermint, Eugenia caryophyllus (Clove) leaf, olive oil, eucalyptus oil, chamomile extract, fennel extract, cinnamon bark extract, guava extract, and spearmint oil, These herbs, as therapeutic agents and flavoring agents, do not contribute to oral moisturizing issues or increase the flow of saliva. The use of hydrating toothpaste may contribute to the resolution of xerostomia. In my perspective, herbal remedies are safer for type 2 diabetes patients than chemical or medication therapy. One of the herbs that is notable for increasing oral moisture is *Cordyceps militaris*, which contains cordycepin as an active ingredient and was found to increase the expression of salivary marker genes (alpha-amylase 1 (AMY1A) and aquaporin-5 (AQP5)) in human submandibular gland (HSG) cells in the laboratory.

This is consistent with the prevalence survey above. No patient was found to have used cordycepin extract before either. Therefore, based on this gap in research, I devised a plan to test the efficacy of toothpaste containing cordycepin extract on the relief of xerostomia status and on increasing the secretion of saliva in T2DM older people compared with normal fluoridated toothpaste.

From the aforementioned prevalence survey's analysis of xerostomia-related variables, the prevalence of xerostomia, the common risk factors and prognostic risk factors for xerostomia, as well as the risk factors for oral function problems in elderly diabetes patients were studied. In addition, additional experiments were conducted in this study. In a randomized clinical trial (RCT), the effectiveness of cordycepin extract toothpaste in reducing xerostomia was compared with that of normal fluoridated toothpaste. This is research to determine the efficacy of toothpaste for applying the research findings further to address or alleviate the xerostomia problem in older diabetes patients, details are as follows:

4.2 Randomized clinical trial

(**Research objectives II**: To clinically test the effects of toothpaste containing cordycepin extract for oral health care in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital)

4.2.1 Results

Based on a prevalence study of xerostomia in type 2 diabetic elderly patients in the non-communicable diseases (NCDs) clinic at the Suranaree University of Technology Hospital in four successive months (December 2021–March 2022). There were type 2 diabetic elderly patients in 623 cases, of which 239 cases (38.4%) had xerostomia (Table 4.3).

The efficacy of normal fluoridated toothpaste and toothpaste containing cordycepin extract was tested to compare the effect of the toothpastes on xerostomia relief. The patients with xerostomia were recruited and divided into two groups: a control group (normal fluoridated toothpaste) and a treatment group (toothpaste containing cordycepin extract). Patients were given toothpaste according to their assigned group, by registered nurses. Randomized double-blind control studies (The researcher and patients) were randomized. Before the baseline experiment, all elderly diabetic patients had to consent to participate in the research and complete a consent form (week 0: baseline data collections).

One hundred and four (104) cases of diabetic elderly patients were randomly allocated, and they were divided into two groups, each with 52 cases. The group was

given toothpaste to brush their teeth regularly at home, at least twice a day, in the morning and before bedtime. There is a compliance form on which to take daily notes. At baseline, prior to the experiment, the unstimulated whole saliva volume and oral mucosal moisture measurement (surface of the tongue and hypoglossus) were measured at the same time under the same conditions on three separate visits within a 2 weeks interval (baseline data collections, second week, and fourth week).

Diabetic elderly patients were all enrolled in the trial. Two follow-up visits were required with the investigator after the use of toothpaste in their respective groups at second week and fourth week, I measured salivary flow rate and oral dryness, same examinations as baseline, including assessment of xerostomia and monitoring for side effects after toothpaste use, and assessed their satisfaction with toothpaste after use as well. I presented the effect of toothpaste on xerostomia among diabetic elderly patients divided into three phases: before the clinical test (baseline), the second week, and the fourth week, details as follows:

Baseline data collections

An analysis of differences in demographic data between the control and treatment groups at baseline found that, comparing the differences between groups before the experiment, 10 of the 11 variables were not different statistically significant at the 0.05 level, consisting of, Sex (*p*-Value=0.556), Age (*p*-Value=0.923), Toothpaste (*p*-Value=0.104), Years since diabetes diagnosis (*p*-Value=0.810), Haemoglobin A1c level (*p*-Value=0.131), Having systemic diseases other than diabetes (*p*-Value=0.727), Having Medications (*p*-Value=1.00), Smoking (*p*-Value=0.141), Alcohol consumption (*p*-Value=0.908), and Type of denture (*p*-Value=0.212). As for education, it was found that between the control and treatment groups were different, statistically significant (*p*-Value=0.001). As shown in Table 4.31.

Table 4.31 Differences in diabetic elderly demographic data between the control and treatment groups in the baseline (before the experiment) by Chi-square test (n = 104).

Variables	Categories	Groups n (%)		n (%)	*p*-Value
		Control group (n=52)	Treatment group (n=52)		
Sex	Male	27 (52.94)	24 (47.06)	51 (49.04)	0.556
	Female	25 (47.17)	28 (52.83)	53 (50.96)	
Age (years)	50-59	0 (0.00)	0 (0.00)	0 (0.00)	0.923
	Over 59	52 (100)	52 (100)	104 (100)	
Toothpaste (Type 1)	SLS-Free	9	13	22 (21.15)	0.515
	Containing SLS	43	39	82 (78.85)	
Toothpaste (Type 2)	Spicy herbal extracts-Free	7	5	12 (11.54)	0.241
	Containing spicy herbal extracts	45	47	92 (88.46)	
Toothpaste (Type 3)	Artificial sweeteners - Free	41	44	85 (81.73)	0.352
	Containing artificial sweeteners	11	8	19 (18.27)	
Education	None	0 (0.00)	4 (100)	4 (3.85)	0.001*
	Elementary School	7 (29.16)	17 (70.84)	24 (23.07)	
	High School	17 (43.59)	22 (56.41)	39 (37.50)	
	Bachelor's degree	24 (80.00)	6 (20.00)	30 (28.85)	
	Higher than the Bachelor's degree	4 (57.14)	3 (42.86)	7 (6.73)	

* *p*-Value were significant ($p < 0.05$)

Table 4.31 (Continued).

Variables	Categories	Groups n (%)		n (%)	*p*-Value
		Control group (n=52)	Treatment group (n=52)		
Years since diabetes diagnosis	0-5	7 (50.00)	7 (50.00)	14 (13.46)	0.810
	6-10	16 (45.71)	19 (54.29)	35 (33.66)	
	Over 10	29 (52.72)	26 (47.28)	55 (52.88)	
Haemoglobin A1c level (%)	≤ 6.5	9 (42.86)	12 (57.14)	21 (20.19)	0.131
	6.6-6.9	18 (66.67)	9 (33.33)	27 (25.96)	
	≥ 7	25 (44.64)	31 (55.36)	56 (53.85)	
Having systemic diseases other than diabetes	No	4 (44.44)	5 (55.56)	9 (8.65)	0.727
	Yes	48 (50.53)	47 (49.47)	95 (91.35)	
Having Medications	No	4 (50.00)	4 (50.00)	8 (7.69)	1.00
	Yes	48 (50.00)	48 (50.00)	96 (92.31)	
Smoking (cigarettes per day)	Never	46 (47.92)	50 (52.08)	96 (92.30)	0.141
	1-5	6 (75.00)	2 (25.00)	8 (7.70)	
	Never	41 (50.62)	40 (49.38)	81 (77.89)	
Alcohol consumption frequency	Monthly or less	6 (54.54)	5 (45.46)	11 (10.58)	0.908
	2-4 times a month	4 (44.44)	5 (55.56)	9 (8.65)	
	2 -3 times a week	1 (33.33)	2 (66.67)	3 (2.88)	

* *p*-Value were significant ($p < 0.05$)

Table 4.31 (Continued).

Variables	Categories	Groups n (%)		n (%)	*p*-Value
		Control group (n=52)	Treatment group (n=52)		
Type of denture	None	44 (48.35)	47 (51.65)	91 (87.50)	0.212
	Complete Denture	3 (100)	0 (0.00)	3 (2.88)	
	Removable Partial Denture	5 (50.00)	5 (50.00)	10 (9.62)	
	Fixed Partial Denture	0 (0.00)	0 (0.00)	0 (0.00)	

* *p*-Value were significant ($p < 0.05$)

At baseline, there were 104 diabetic elderly patients in both the control group (normal fluoridated toothpaste) and the treatment group (toothpaste containing cordycepin extract), 52 patients each, and all (100%) had xerostomia in both groups. The means of xerostomia in the control group and treatment group were 2.44 and 2.12, respectively, with no statistically significant difference. (*p*-Value=0.128) (Table 4.32).

Salivary flow rate measurements showed that both the control group and treatment group had means of salivary flow rate (mL/min) of 0.085 and 0.083, respectively, with no statistically significant difference. (*p*-Value=0.533). Oral dryness examinations (surface of the tongue) showed that the mean of the saliva weight (g) in the control group and treatment group was 0.0165 and 0.0160, respectively, with no statistically significant difference. (*p*-Value=0.646) and oral moisture under the tongue (hypoglossus) showed that the means of saliva weight (g) were 0.096 and 0.092, respectively, with no statistically significant difference. (*p*-Value=0.485) as well (Table 4.32).

Table 4.32 Comparison of the differences of xerostomia, salivary flow rate, and oral dryness in type 2 diabetic elderly patients with xerostomia between the groups by independent sample t-test before clinical testing (baseline).

Variables	n	Mean	S.D.	$\bar{d}$	95% CI	t	*p*-Value
Xerostomia							
Control group	52	2.44	1.25	0.32	-0.09	1.53	0.128
Treatment group	52	2.12	0.87		to 0.74		
Salivary flow rate (mL/min.)					-0.003		
Control group	52	0.085	0.011	0.001	to	0.62	0.533
Treatment group	52	0.083	0.012		0.006		
Oral moisture (surface of the tongue) (g)					-0.001		
Control group	52	0.0165	0.004	0.0004	to	0.46	0.646
Treatment group	52	0.0160	0.005		0.002		
Oral moisture (hypoglossus) (g)					-0.008		
Control group	52	0.096	0.034	0.004	to	0.70	0.485
Treatment group	52	0.092	0.032		0.017		

$\bar{d}$ = mean difference, 95% CI = 95% confidence interval, t = The test statistic for an Independent Samples t Test, * The level of significance was $p < 0.05$, ** *p*-Value < 0.001

Second week

In the second week, there were 102 cases of diabetic elderly patients, both in the control group (normal fluoridated toothpaste) and the treatment group (toothpaste containing cordycepin extract), with 51 cases each, and the mean of xerostomia in the treatment group (1.16) was lower than that in the control group (2.43), which has a statistically significant difference (*p*-Value < 0.001) (Table 4.33).

Salivary flow rate measurements showed that the treatment group had higher salivary flow rates than the control group. The means of the salivary flow rates (mL/min) of the treatment group and the control group were 0.129 and 0.089, respectively. with a statistically significant difference (*p*-Value < 0.001). Oral dryness examinations (surface of the tongue) found that the control group and treatment group had no statistically significant difference. (*p*-Value=0.807), with the means of saliva weight (g) being 0.020 and 0.021, respectively. It was found that oral moisture in the treatment group had a higher mean of saliva weight (g) than the control group (0.186 and 0.102, respectively), with a statistically significant difference (*p*-Value < 0.001) (Table 4.33).

Table 4.33 Comparison of the differences of xerostomia, salivary flow rate, and oral dryness in type 2 diabetic elderly patients with xerostomia between the groups by independent sample t-test in the second week.

Variables	n	Mean	S.D.	$\bar{d}$	95% CI	t	*p*-Value
Xerostomia							
Control group	51	2.43	1.41	1.275	0.763 to	4.94	<0.001**
Treatment group	51	1.16	1.17		1.786		
Salivary flow rate							
(mL/min.)					-0.055		
Control group	51	0.089	0.010	-0.03	to	-5.23	<0.001**
Treatment group	51	0.129	0.053		-0.024		
Oral moisture (surface of							
the tongue) (g)							
Control group	51	0.020	0.033	-0.001	-0.010	-0.24	0.807
Treatment group	51	0.021	0.006		to 0.008		
Oral moisture							
(hypoglossus) (g)					-0.104		
Control group	51	0.102	0.038	-0.083	to	-7.68	<0.001**
Treatment group	51	0.186	0.067		-0.061		

$\bar{d}$ = mean difference, 95% CI = 95% confidence interval, t = The test statistic for an Independent Samples t Test, * The level of significance was $p < 0.05$, ** *p*-Value < 0.001

Fourth week

In the fourth week, there were 102 diabetic elderly patients, a control group (normal fluoridated toothpaste), 50 cases, and a treatment group (toothpaste containing cordycepin extract), 52 cases. The mean of xerostomia in the treatment group (0.17) was lower than that in the control group (2.48), which was significantly different (*p*-Value <0.001) (Table 4.34).

Salivary flow rate measurements showed that the treatment group had higher salivary flow rates than the control group. The means of the salivary flow rates (mL/min) of the treatment group and the control group were 0.336 and 0.086, respectively, with a statistically significant difference (*p*-Value < 0.001).

Oral dryness examinations (surface of the tongue) showed that the treatment group had a higher mean of saliva weight (g) than the control group and that the means were 0.036 and 0.017, respectively, with a statistically significant difference. (*p*-Value=0.004), and oral moisture under the tongue (hypoglossus). It was found that the mean of the saliva weight (g) in treatment group was greater than the control group, 0.266 and 0.097, respectively, with statistically significant differences. (*p*-Value <0.001) (Table 4.34).

Table 4.34 Comparison of the differences of xerostomia, salivary flow rate, and oral dryness in type 2 diabetic elderly patients with xerostomia between the groups by independent sample t-test in the fourth week.

Variables	n	Mean	S.D.	$\bar{d}$	95% CI	t	*p*-Value
Xerostomia							
Control group	50	2.48	1.34	2.30	1.90 to	11.42	<0.001**
Treatment group	52	0.17	0.55		2.70		
Salivary flow rate (mL/min.)							
Control group	50	0.086	0.013	-0.24	-0.27 to	-17.87	<0.001**
Treatment group	52	0.336	0.098		-0.22		
Oral moisture (surface of the tongue) (g)							
Control group	50	0.017	0.010	-0.01	-0.03 to	-2.95	0.004*
Treatment group	52	0.036	0.043		-0.006		
Oral moisture (hypoglossus) (g)					-0.188		
Control group	50	0.097	0.038	-0.16	to	-17.36	<0.001**
Treatment group	52	0.266	0.057		-0.149		

$\bar{d}$ = mean difference, 95% CI = 95% confidence interval, t = The test statistic for an Independent Samples t Test, * The level of significance was $p < 0.05$, ** *p*-Value < 0.001

On xerostomia, there was no statistically significant difference between diabetic elderly patients in the control group (normal fluoridated toothpaste) over 4 weeks (baseline, second week, and fourth week). The means of xerostomia in the control group at baseline, the second week, and the fourth week were 2.44, 2.43, and 2.48, respectively. (Table 4.35 and Figure 4.1).

The treatment group (toothpaste containing cordycepin extract) found that over the four weeks, xerostomia among diabetic elderly patients was statistically different (*p*-Value <0.001) at all stages, with a tendency to decrease in mean xerostomia in both the baseline, second week, and fourth week of 2.12, 1.16, and 0.17, respectively. (Table 4.36 and Figure 4.1). The results of the comparative analysis of xerostomia in both the control group and treatment group are shown in Figure 4.1.

Table 4.35 Comparison of xerostomia in type 2 diabetic elderly patients with xerostomia in the control group (normal fluoridated toothpaste) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Xerostomia	n	Mean	S.D.	*p*-Value 1	*p*-Value *2*
Before clinical test (baseline)	52	2.44	1.25	-	-
After 2nd week	51	2.43	1.41	0.850	-
After 4th week	50	2.48	1.34	0.766	0.735

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

Table 4.36 Comparison of xerostomia in type 2 diabetic elderly patients with xerostomia in the treatment group (toothpaste containing cordycepin extract) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Xerostomia	n	Mean	S.D.	*p*-Value 1	*p*-Value *2*
Before clinical test (baseline)	52	2.12	0.87	-	-
After 2nd week	51	1.16	1.17	<0.001**	-
After 4th week	52	0.17	0.55	<0.001**	<0.001**

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

**The level of significance was $p < 0.001$

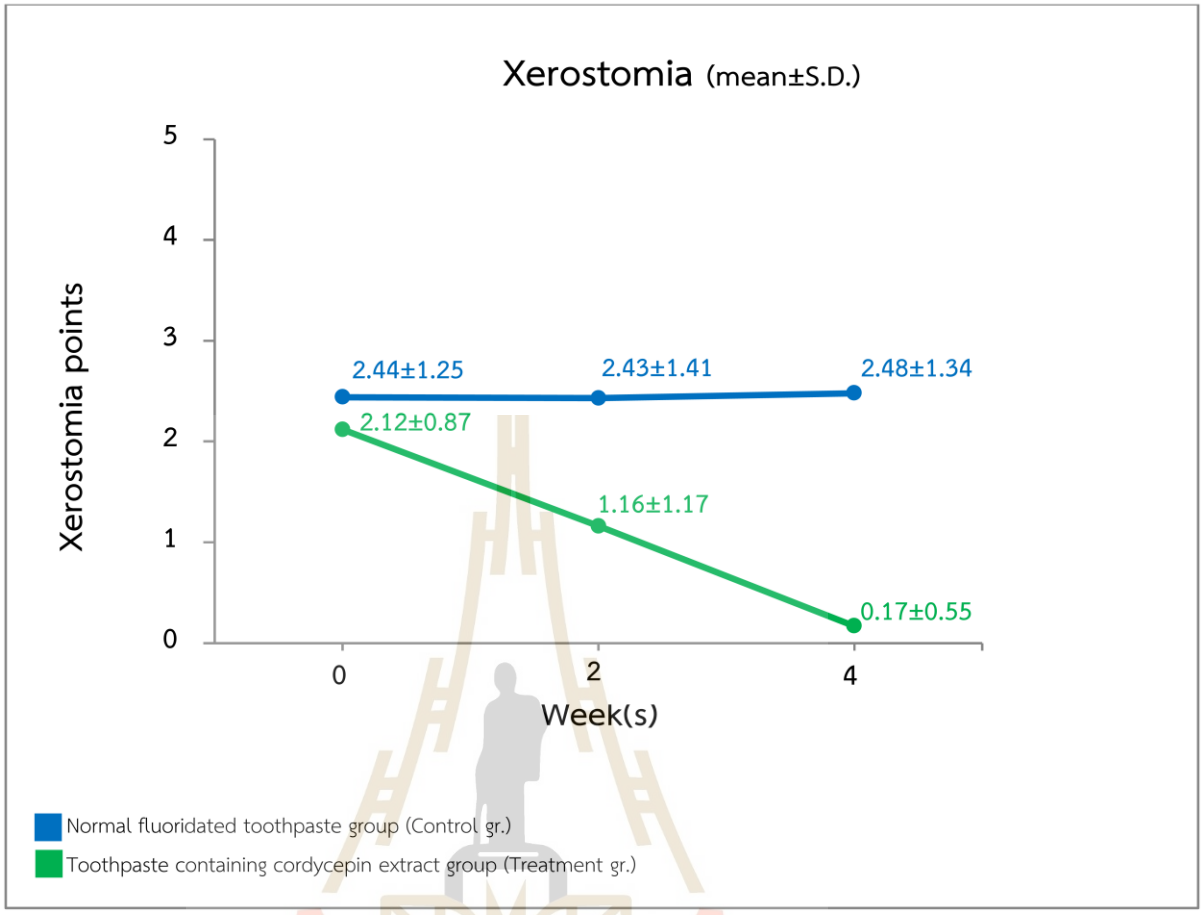


Figure 4.1 Comparison of xerostomia in the control group and treatment group.

In terms of salivary flow rate, the results were analyzed after all three phases (baseline, second week, and fourth week). In the control group (normal fluoridated toothpaste) over 4 weeks, there was no statistically different xerostomia among diabetic elderly patients; the means of the salivary flow rate (mL/min) at baseline, the second week, and the fourth week were 0.085, 0.089, and 0.086, respectively. (Table 4.37).

The treatment group (toothpaste containing cordycepin extract) found that over 4 weeks the salivation of diabetic elderly patients was statistically different (*p*-Value <0.001) at all stages, with a tendency to increase the mean of the salivary flow rate for both the baseline, second week, and fourth week, which were 0.083, 0.129, and 0.336, respectively. (Table 4.38). The results of the comparative analysis of salivary flow rate in both the control group and the treatment group are shown in Figure 4.2.

Table 4.37 Comparison of salivary flow rate in type 2 diabetic elderly patients with xerostomia in the control group (normal fluoridated toothpaste) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Salivary flow rate (mL/min.)	**n**	**Mean**	**S.D.**	***p*-Value 1**	***p*-Value *2***
Before clinical test (baseline)	52	0.085	0.011	-	-
After 2nd week	51	0.089	0.010	0.050	-
After 4th week	50	0.086	0.013	0.674	0.088

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

Table 4.38 Comparison of salivary flow rate in type 2 diabetic elderly patients with xerostomia in the treatment group (toothpaste containing cordycepin extract) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Salivary flow rate (mL/min.)	n	Mean	S.D.	*p*-Value 1	*p*-Value *2*
Before clinical test (baseline)	52	0.083	0.012	-	-
After 2nd week	51	0.129	0.053	<0.001**	-
After 4th week	52	0.336	0.098	<0.001**	<0.001**

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

**The level of significance was p < 0.001

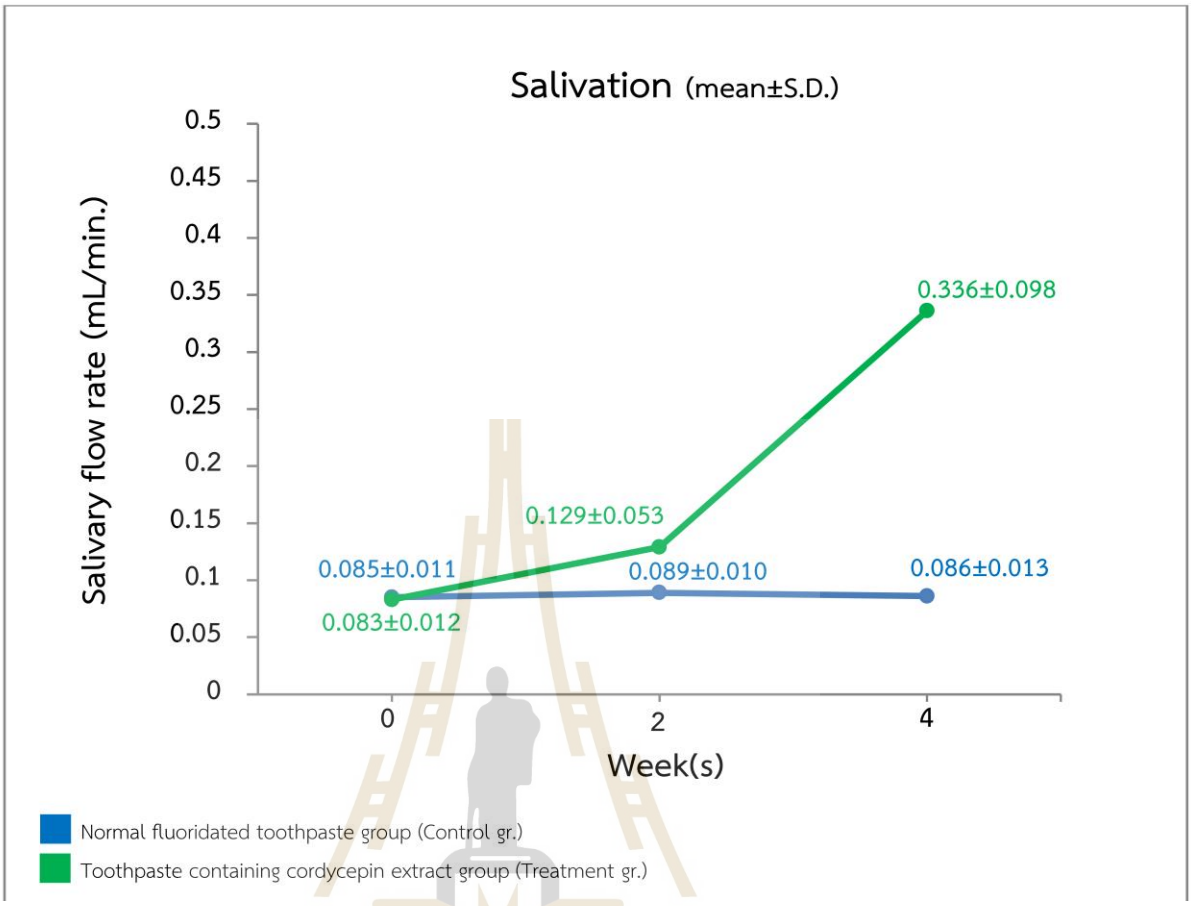


Figure 4.2 Comparison of salivary flow rate in the control group and treatment group.

In oral dryness examinations (surface of the tongue), the results after all three phases (baseline, second week, and fourth week) were analyzed in the control group (normal fluoridated toothpaste) over four weeks for oral moisture in diabetics. Elderly patients were not statistically different; the means of saliva weight (g) at baseline, the second week, and the fourth week were 0.016, 0.020, and 0.017, respectively (Table 4.39).

The treatment group (toothpaste containing cordycepin extract) found that over 4 weeks, the oral moisture of diabetic elderly patients was statistically different at all stages, which showed an increase in the mean of saliva weight (g) at baseline, the second week, and the fourth week of 0.016, 0.021, and 0.036, respectively. (Table 4.40). The results of the comparative analysis of differences in oral dryness examinations (surface of the tongue) in both the control group and treatment group are shown in Figure 4.3.

Table 4.39 Comparison of oral mucosal moisture (surface of the tongue) in type 2 diabetic elderly patients with xerostomia in the control group (normal fluoridated toothpaste) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Oral mucosal moisture (surface of the tongue)	**n**	**Mean**	**S.D.**	***p*-Value 1**	***p*-Value *2***
Before clinical test (baseline)	52	0.016	0.004	-	-
After 2nd week	51	0.020	0.033	0.414	-
After 4th week	50	0.017	0.010	0.360	0.619

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

Table 4.40 Comparison of oral mucosal moisture (surface of the tongue) in type 2 diabetic elderly patients with xerostomia in the treatment group (toothpaste containing cordycepin extract) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Oral mucosal moisture (surface of the tongue)	**n**	**Mean**	**S.D.**	***p*-Value 1**	***p*-Value *2***
Before clinical test (baseline)	52	0.016	0.005	-	-
After 2nd week	51	0.021	0.006	<0.001**	-
After 4th week	52	0.036	0.043	0.001*	0.017*

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

*The level of significance was $p < 0.05$

**The level of significance was $p < 0.001$

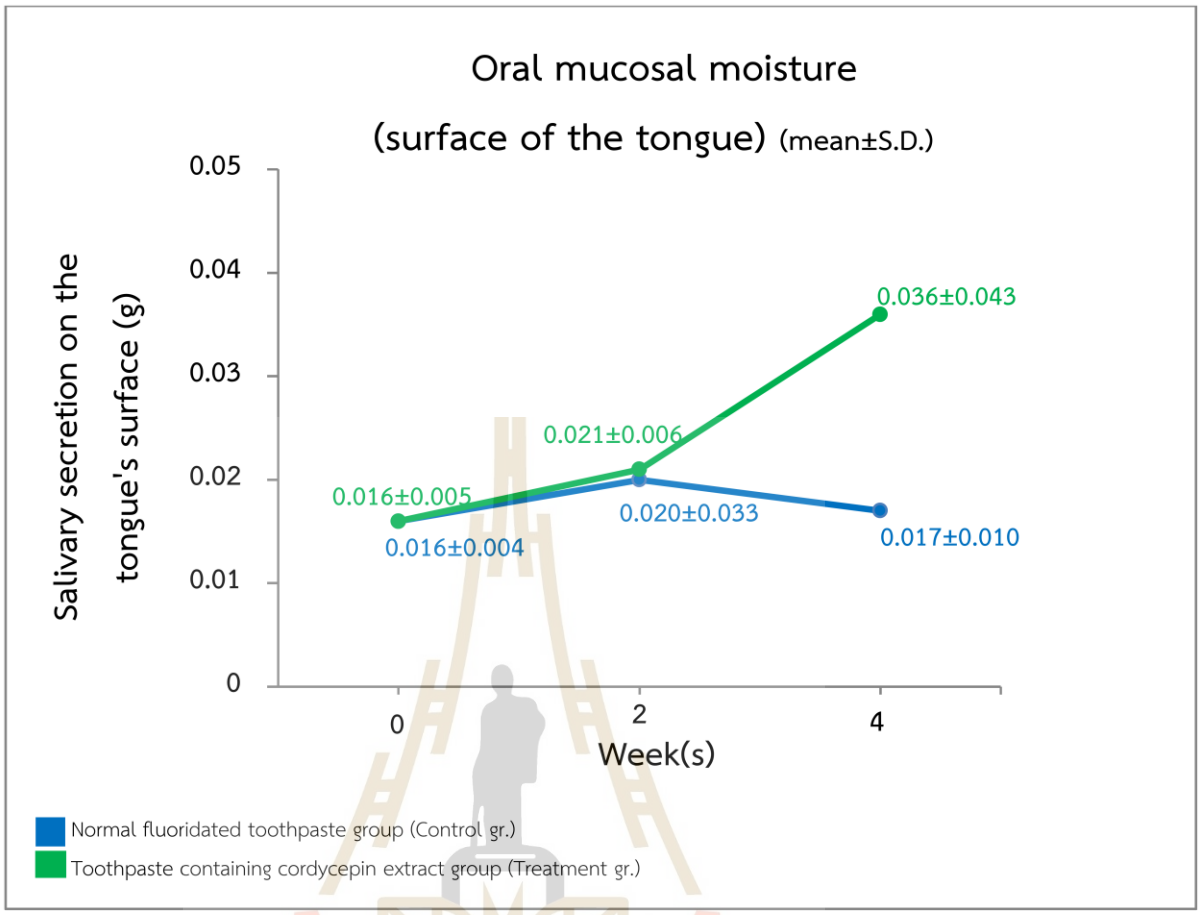


Figure 4.3 Comparison of Oral mucosal moisture (surface of the tongue) in the control group and treatment group.

In oral dryness examinations (hypoglossus), after all three phases (baseline, second week, and fourth week) were analyzed in the control group (normal fluoridated toothpaste) over four weeks, oral moisture was found in diabetic elderly patients. There was no statistical difference; the means of the saliva weight (g) at baseline, the second week, and the fourth week were 0.096, 0.102, and 0.097, respectively (Table 4.41).

The treatment group (toothpaste containing cordycepin extract) found that over 4 weeks, the oral moisture of diabetic elderly patients was statistically different (*p*-Value <0.001) at all stages, showing an increase in mean saliva weight. (g) in the baseline, second week, and fourth week are 0.092, 0.186, and 0.266, respectively. (Table 4.42). The results of the comparative analysis of the differences in oral dryness examinations (hypoglossus) in both the control group and treatment group are shown in Figure 4.4.

Table 4.41 Comparison of oral mucosal moisture (hypoglossus) in type 2 diabetic elderly patients with xerostomia in the control group (normal fluoridated toothpaste) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Oral mucosal moisture (hypoglossus)	n	Mean	S.D.	*p*-Value 1	*p*-Value *2*
Before clinical test (baseline)	52	0.096	0.034	-	-
After 2nd week	51	0.102	0.038	0.193	-
After 4th week	50	0.097	0.038	0.919	0.179

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

Table 4.42 Comparison of oral mucosal moisture (hypoglossus) in type 2 diabetic elderly patients with xerostomia in the treatment group (toothpaste containing cordycepin extract) by repeated measures ANOVA at baseline, the 2nd week, and the 4th week.

Oral mucosal moisture (hypoglossus)	n	Mean	S.D.	*p*-Value 1	*p*-Value *2*
Before clinical test (baseline)	52	0.092	0.032	-	-
After 2nd week	51	0.186	0.067	<0.001**	-
After 4th week	52	0.266	0.057	<0.001**	<0.001**

p-Value 1 is the *p*-Value of comparing after treatment (2nd and 4th week) with before treatment.

p-Value 2 is the *p*-Value of comparing after 2nd week with after 4th week

**The level of significance was $p < 0.001$

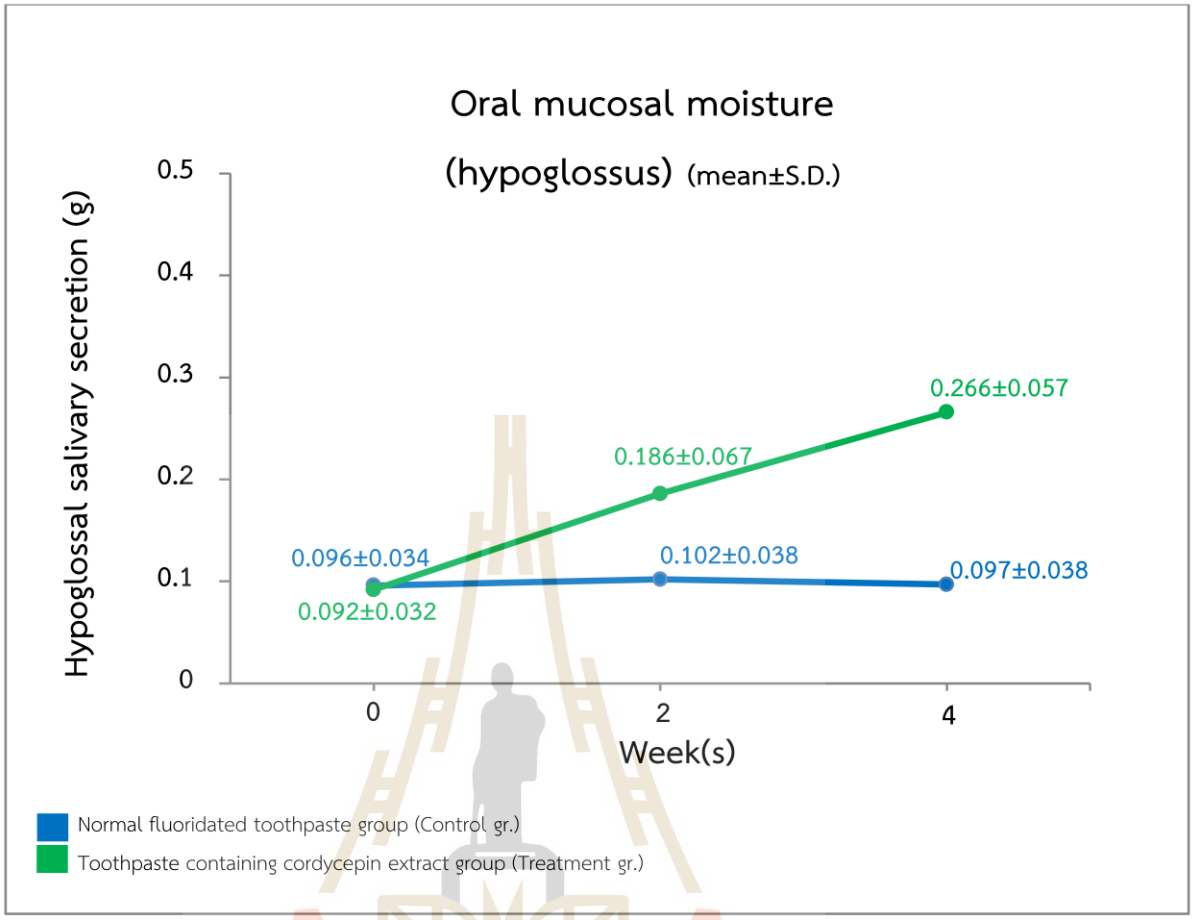


Figure 4.4 Comparison of Oral mucosal moisture (hypoglossus) in the control group and treatment group.

The analysis of inter-group comparison in type 2 diabetic elderly patients with xerostomia in three phases showed that the xerostomia in the treatment group tended to decrease in mean; there was a statistically significant difference compared to the control group at the second and fourth weeks (*p*-Value<0.001), The salivary flow rate in the treatment group had a mean tendency to increase with a statistically significant difference compared to the control group at the second and fourth weeks (*p*-Value<0.001), The oral moisture (surface of the tongue) in the treatment group variable tended to mean an increase with a statistically significant difference compared to the control group at the fourth week (*p*-Value=0.004). The oral moisture (hypoglossus) in the treatment group variable showed a mean tendency to increase with a statistically significant difference compared to the control group at the second and fourth weeks (*p*-Value<0.001) (Table 4.43).

Table 4.43 The Inter-group comparison of the differences of xerostomia, salivary flow rate, and oral dryness in type 2 diabetic elderly patients with xerostomia between the groups by independent sample t-test on three separate visits.

Variables	Mean± S.D.		
	baseline	2nd week	4th week
Xerostomia		**	**
Control group	2.44±1.25	2.43±1.41	2.48±1.34
Treatment group	2.12±0.87	1.16±1.17	0.17±0.55
Salivary flow rate (mL/min.)		**	**
Control group	0.085±0.011	0.089±0.010	0.086±0.013
Treatment group	0.083±0.012	0.129±0.053	0.336±0.098
Oral moisture (surface of the tongue) (g)			*
Control group	0.0165±0.004	0.020±0.033	0.017±0.010
Treatment group	0.0160±0.005	0.021±0.006	0.036±0.043
Oral moisture (hypoglossus) (g)		**	**
Control group	0.096±0.034	0.102±0.038	0.097±0.038
Treatment group	0.092±0.032	0.186±0.067	0.266±0.057

* The level of significance was $p < 0.05$, ** p-Value < 0.001

The efficacy results of normal fluoridated toothpaste in the control group and toothpaste containing cordycepin extract in the treatment group for all 4 weeks showed that in diabetic elderly patients using toothpaste containing cordycepin extract, there was a decrease in the number of xerostomia patients compared to the normal fluoridated toothpaste group. At week 4, the treatment group still had six cases of xerostomia remaining, while the control group had 47 xerostomia patients remaining, as shown in Table 4.44 and Figure 4.5.

Table 4.44 Number and percentage of xerostomia cases in type 2 diabetic elderly patients after 4 weeks of clinical testing, both a control group (normal fluoridated toothpaste) and treatment group (toothpaste containing cordycepin extract).

Group	Baseline (week 0)		2nd week		4th week	
	n	No.of xerostomia cases (%)	n	No.of xerostomia cases (%)	n	No.of xerostomia cases (%)
Control group	52	52 (100.0)	51	45 (88.2)	50	47 (94.0)
Treatment group	52	52 (100.0)	51	28 (54.9)	52	6 (11.5)

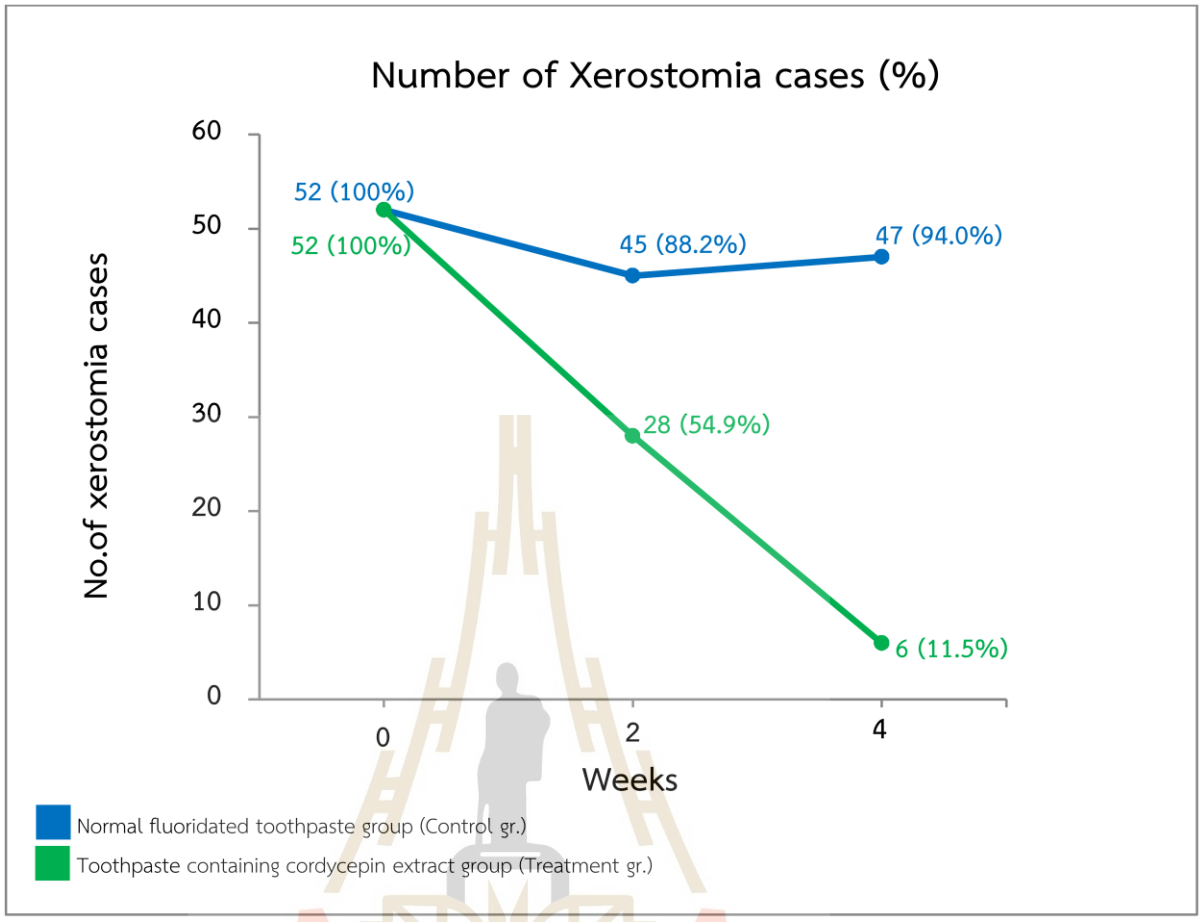


Figure 4.5 Comparison of number and percentage of xerostomia cases in the control group and treatment group.

Evaluation of the adverse events of using normal fluoridated toothpaste and toothpaste containing cordycepin extract in the sample

At weekly follow-up visits (second week and fourth week), I evaluated the risk of adverse events for both toothpaste groups following the trial of regular fluoridated toothpaste in the control group and toothpaste containing cordycepin extract in the treatment group. All patients (100%) in the control group and the treatment group were evaluated using the follow-up record. There were no adverse events attributable to the study treatments in either group, as shown in Table 4.45

Table 4.45 Assessment of adverse events from toothpaste usage in the treatment and control group.

Adverse events	Control group				treatment group			
	2nd wk. (n=51)		4th wk. (n=50)		2nd wk. (n=51)		4th wk. (n=52)	
	Yes	No	Yes	No	Yes	No	Yes	No
1. Do you have an allergic reaction, irritation, or burning sensation in your mouth after using this toothpaste?	0	51	0	50	0	51	0	52
2. Do you have an allergic reaction or irritation to other areas outside your mouth, such as your face, skin, or throat after using this toothpaste?	0	51	0	50	0	51	0	52
3. Do you feel uncomfortable in your mouth after using this toothpaste?	0	51	0	50	0	51	0	52
4. Do you experience sensitive teeth or other mouth and tooth problems after using this toothpaste?	0	51	0	50	0	51	0	52
5. Do you have nausea, vomiting, or any other discomfort after using this toothpaste?	0	51	0	50	0	51	0	52
6. Do you have an adverse reaction related to an additional complication of your underlying disease after using this toothpaste?	0	51	0	50	0	51	0	52
7. Have you been examined or treated in a medical facility regarding adverse reactions caused by the use of this toothpaste?	0	51	0	50	0	51	0	52
8. Your personal physician determined that using this toothpaste worsened your underlying disease condition?	0	51	0	50	0	51	0	52

4.2.2 Discussions

As for the randomized clinical trial, I divided the discussion into five issues: 4.2.2.1 Safety of Cordycepin extract from *Cordyceps Militaris*, 4.2.2.2 Safety of toothpaste containing cordycepin extract in the treatment group., 4.2.2.3 Differences in diabetic elderly demographic data between the control and treatment groups in the baseline (before the experiment), 4.2.2.4 The method used for this study, 4.2.2.5 Efficacy of a trial of Cordycepin Extract Toothpaste in Type 2 Diabetes Mellitus (T2DM) Elderly Patients with Xerostomia. Details are as follows:

4.2.2.1 Safety of Cordycepin extract from *Cordyceps militaris*

One of the herbs used in traditional Chinese medicine (TCM) is *Cordyceps,* which has a wide range of beneficial pharmacological effects and is thought to be safe. According to certain findings that have been published, it is typically advised to avoid using it in individuals with autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis (Wong KL. et al., 2007). According to Mizuno (1999), humans can generally safely and effectively take 3-4.5 g of *cordyceps* per day, with the exception of people with severe liver disease.

The potential for cordycepin as a safe anti-diabetic drug is quite great. For instance, Dong, Y. et al. (2014) published a research paper with the title "Studies on the antidiabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic Sprague-Dawley rats." They discovered that *Cordyceps militaris* extracts protected against diabetic nephropathy as evidenced by their inhibitory effects on blood urea nitrogen, creatinine, uric acid, and protein, which were supported by a pathological morphological reversal. As a safe pharmacological agent with good antidiabetic and antinephropathic properties, *Cordyceps militaris* extract has a significant amount of potential as a novel source for treating diabetes. *Cordyceps militaris* was confirmed as a pharmacological safe agent (Dong, Y. et al., 2014).

A well-known traditional Chinese medication known as *cordyceps* is also known as the "miracle mushroom" due to its extraordinary health advantages. It is regarded as pharmacologically safe for human consumption due to its natural occurrence (Syed Amir Ashraf et al., 2020). Additionally, it was discovered that *cordyceps* and other diseases, such as cancer, could be used to estimate the optimal

dose for their safety and effectiveness. (Mehra A. et al., 2017). One of the most effective and safest medicinal fungi is *cordyceps,* which is renowned for its broad range of beneficial pharmacological effects. For human consumption, *cordyceps* continues to be primarily regarded as safe and non-toxic (Tuli, H. S. et al., 2014).

Considering the research on *Cordyceps militaris* reviewed above, I am confident that Cordycepin extract from *Cordyceps militaris* is very safe for elderly patients with type 2 diabetes mellitus (T2DM) in this study.

4.2.2.2 Safety of toothpaste containing cordycepin extract in the treatment group.

The cordycepin toothpaste that I used in the treatment group was safe in terms of quality and standards. This toothpaste is a collaboration between Lion Corporation (Thailand) Limited, the Institute of Dentistry, and the Institute of Agricultural Technology, Suranaree University of Technology.

The Lion Corporation (Thailand) Limited laboratory that produces this toothpaste has been certified ISO/IEC 17025 according to the Cosmetics Act, B.E. 2015, and its products, including cordycepin toothpaste, have been approved by the Food and Drug Administration (FDA), Ministry of Public Health (Thailand) (date of authorization: March 3, 2022). Notification number: 20-1-6500007887, valid until March 2, 2025 (as shown in Figures 3.3 and 3.5 in Chapter 3).

The concentration of the cordycepin extract model used as active ingredients in cordycepin toothpaste was derived from a study conducted by the Institute of Dentistry and Institute of Agricultural Technology at Suranaree University of Technology on the benefits of cordycepin in human submandibular gland (HSG) cells, which were found to reduce Reactive oxygen species (ROS) production through antioxidant and anti-apoptotic capabilities. And they discovered that cordycepin could effectively protect against HSG cell death caused by H2O2-induced toxicity. The expression of salivary marker genes, alpha-amylase 1 (AMY1A) and aquaporin-5 (AQP5) are both enhanced by cordycepin, which also has a preventive effect.

For cordycepin, 12.5 μM was chosen as the optimal concentration. (Jaiboonma, A. et al., 2020). They discovered that the concentration of cordycepin at 12.5 μM of cordycepin was chosen for further study since I expected the most

effective result with the lower concentration of cordycepin. 12.5 μM of cordycepcin significantly increased AMY1A expression and 12.5 μM of cordycepin treated HSG cells showed the highest level of amylase secretion at 8 hours. This concentration showed an increasing effect in AMY1A and AQP5 for both gene and protein levels. This is promising since the previous study showed that AQP5 is one of key proteins to cause xerostoma. In addition, a study has previously reported that Aquaporin-5 protein expression was abnormally low in the salivary glands of diabetic rats, which increased hyposalivation and led to salivary dysfunction. (Bhattarai, K. R. et al., 2017).

The main reason that I selected a cordycepin toothpaste from *Cordyceps* was to treat elderly patients with type 2 diabetes mellitus (T2DM) with xerostomia because *Cordyceps* is a plant used in traditional Chinese medicine (TCM) that has many positive pharmacological effects and is considered safe. (Wong KL. et al., 2007). Consistent with Mizuha et al. (2007), they found that a water extract of *Cordyceps sinensis* was found to be non-toxic to the proliferation of the macrophage cell line RAW264.7 and was effective against type 2 diabetes mellitus (T2DM) in elderly patients. This study is consistent with previous research that found that *Cordyceps militaris* extract can significantly lower blood sugar levels. It is based on increased glucose metabolism and prevention of diabetic nephropathy (Dong, Y et al., 2014).

In the same direction as the 2009 study, they found that cordycepin prevents the production of NO and pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 in LPS stimulated by macrophages. By inhibiting the protein expression of pro-inflammatory mediators, the expression of type 2 diabetes regulatory genes (11β-HSD1 and PPARλ) is reduced. The expression of co-stimulatory molecules such as ICAM-1 and B7-1/ -2 also decreased as cordycepin concentration increased (Shin, S. et al., 2009), and found a significant improvement in the effectiveness of the glucose tolerance test after cordycepin administration (Ma, L. et al. , 2015). This is consistent with research from 2014 that discovered that *Cordyceps militaris* extract, a safe pharmaceutical agent, presents excellent antidiabetic and antinephropathic activities and thus has great potential as a new source for diabetes treatment (Dong, Y et al., 2014) and cordycepin may be a useful tool as an anti-hyperglycemic agent in the

control of blood glucose levels in diabetes without defects of immune responses and other side effects. (Yun, Y.H. et al., 2003).

Therefore, I am confident in the safety of toothpaste containing cordycepin extract in type 2 diabetic mellitus (T2DM) elderly patients being tested from the aforementioned study that there were no harms or adverse effects from this trial. This is in accordance with the findings of the post-trial cordycepin toothpaste risk assessment in this study, which showed that no serious adverse events were reported (Table 4.45).

4.2.2.3 Differences in diabetic elderly patients demographic data between the control and treatment groups in the baseline (before the experiment)

At baseline (before the experiment) demographic data heterogeneity analysis was performed of type 2 diabetes mellitus (T2DM) in elderly patients with xerostomia before the toothpaste trial between the control and treatment groups.

This research revealed that there was no significant difference in most patients' demographic data between the two groups (Table 4.31). This is in accordance with the findings of a study published in 2020, which showed that neither the baseline generalizations of the pre-experimental sample nor the differences between the two groups (control and treatment groups) were statistically different (Haixia He et al., 2020). This is owing to the fact that both groups of study subjects were over 60 and had comparable age ranges, with 100% of them also suffering xerostomia, which may have contributed to the demographic characteristics of the participants. There were no differences between the two sample groups. These results indicate that the trial toothpaste was effective and that the results of these trial were reliable.

The only variable that differed significantly between the treatment and control groups (p = 0.001) was education. Even though the control and treatment groups' education characteristics differed, the population's xerostomia was not associated with education, according to an analysis of sociodemographic and health behavior data using the Chi-square test (Table 4.27). The results of the above analysis show that the sociodemographic and health behavior data of the two groups were

largely similar, with this data strongly supporting the efficacy results of the toothpaste trial.

4.2.2.4 The methods used for this study.

When considering the study methods used in this study, looking at the effect of using two types of toothpaste, normal fluoridated toothpaste (control group) and a toothpaste containing cordycepin extract (treatment group), for a period of 4 weeks to test and follow up, this study monitored the patients at 2 and 4 weeks after usage, which is consistent with previous research from a randomized clinical trial study on the Herbal Compound on Dry Mouth in Patients With Head and Neck Cancers that was conducted in 2016. The four-week trial was completed, and the statistical significance of the results were confirmed. (Ameri, A et al., 2016). According to Tohru Tanigawa et al. (2015) pilocarpine mouthwash relieved dry mouth symptoms and improved saliva production within 1 month. This was similar to Gajin Han et al. (2016), a randomized, double-blind, placebo-controlled trial of a traditional herbal formula, Yukmijihwang-tang, in elderly subjects with xerostomia which was found to improve oral moisture status and subjective oral dryness in elderly subjects at 8 weeks.

A short-term study of Haixia He et al. (2020) that studies the effects of Phyllanthus emblica spray appeared to be superior to warm water spray for treating postoperative xerostomia within 6 hours. Also, the study of Supranee Dalodom et al. (2016) that studies the effects of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus found that as 2 weeks it significantly reduced symptoms of dry mouth. However, because I aims to test the efficacy of toothpaste for a longer period of time this study lasted 4 weeks since it is a reasonable period of time to evaluate the outcomes in order to identify trends in salivation and adverse events related to toothpaste usage. This ensures that the subjects in the study are not inconvenienced for any longer than necessary.

Concerning the technique for measuring salivary flow, in this study I used the unstimulated whole saliva method, which is consistent with the Christine Bambi Lung et al. (2021) study that studied the effect of Biotène® Spray in patients with

symptomatic dry mouth in a double-blind, randomized, controlled cross-over to evaluate the relief of xerostomia in adult subjects.

This study is comparable to a previous one by Pegah Afsaneh Abadi et al. (2020), in which xerostomia and diabetes were studied in participants who spit out unstimulated whole saliva. They used the unstimulated salivary flow rate technique, which was also performed in the 2007 study, to evaluate oral symptoms in menopausal women. (Borhan Mojabi, K et al., 2007). In the same direction as the previous research, unstimulated whole saliva (UWS) was chosen to assess xerostomia. (C. Spirk et al., 2019). Unstimulated whole saliva obtained by the spitting method was chosen for this study due to the salivary flow without any stimulation caused by xerostomia (Sreebny, L. M., & Valdini, A., 1988) and the flow rate of unstimulated whole saliva (this more closely correlates with symptoms of hyposalivation than do stimulated flow rates) (R.Felten et al., 2016).

The unstimulated whole saliva was collected in the morning between 7.30 and 11.00 a.m. because it is related to the issue of circadian rhythms in the human salivary flow rate that saliva flow is weak in the morning and increases in the afternoon (Nishide, S. et al., 2019). To obtain results that match the conditions literally secreted by the patient's saliva.

The reference study was created for a toothpaste containing cordycepin extract, which was used in this treatment group. They studied the effects of cordycepin extract from *Cordyceps militaris* on human submandibular gland (HSG) cells (Jaiboonma, A et al., 2020). In relation to the study in 2009, they discovered in the resting (unstimulated) state, approximately two-thirds of the total volume of the whole saliva is produced by submandibular glands (Iorgulescu G., 2009).

4.2.2.5 Efficacy of a trial of cordycepin extract toothpaste in type 2 diabetes mellitus (T2DM) elderly patients with xerostomia

Efficacy outcomes in the reduction of Xerostomia and increased salivary flow rate in Type 2 Diabetes Mellitus (T2DM) elderly patients with Xerostomia after using cordycepin extract toothpaste. Before the experiment, the xerostomia factors of the control and treatment groups (mean±S.D.) were 2.44±1.25 and 2.12±0.87 respectively, which can be interpreted as xerostomia in both groups. The volumes of

salivary flow rate (mean±S.D.) were 0.085±0.011 and 0.083±0.012 respectively, which can be interpreted as having less salivary secretion and is considered hyposalivation due to the unstimulated salivary flow rate for both groups was less than 0.1 ml/min (Villa, A. et al., 2014).

Oral moisture (surface of the tongue) measurements of the control and treatment groups (mean±S.D.) were 0.0165±0.004 and 0.0160±0.005 respectively. When saliva weight was less than 0.02 grams within 30 seconds in the patient groups, this was classified as oral dryness (Takahashi Fumi et al., 2006). Oral moisture (hypoglossus) of the control and treatment groups (mean±S.D.) were 0.096±0.034 and 0.092±0.032 respectively**.** This was interpreted as oral dryness in both groups of patients due secreted saliva weight of less than 0.1 gram within 30 seconds. (Takahashi Fumi et al., 2006).

There was also no statistically significant difference between all the initial studied factors among the control and treatment groups. (p>0.05) (Table 4.32). This showed that there was no significant difference between the two groups' initial levels for the xerostomia-related variables. Therefore, the outcomes of the toothpaste trial containing cordycepin extract were able to demonstrate that there was an increase in efficacy compared to the control group. I am quite certain that, according to this initial analysis, the outcomes of these studies accurately represent the effectiveness of toothpaste containing cordycepin extract.

At the end of the second week of the trial, elderly patients with type 2 diabetes mellitus (T2DM) in the treatment group treated with cordycepin extract toothpaste had a mean xerostomia reduction of 1.16 (from baseline = 2.12) and this was statistically significant compared to the baseline. (p <0.001) (Table 4.36). The mean xerostomia in the control group was 2.43, not different from the baseline. (p= 0.850) (Table 4.35). Despite a mean decrease in xerostomia in the treatment group that used toothpaste containing cordycepin extract, xerostomia was nevertheless persistent since the mean was greater than 0 (Handerson Nunes de Carvalho et al., 2020).

Regarding salivary flow rate, I discovered that, compared to the baseline, the control group observed a slight increase in the second week (mean±S.D.=

0.089±0.010 and 0.085±0.011), However, there was no statistically significant difference compared to the baseline (p =0.050) (Table 4.37). I observed that the treatment group's salivary flow rate increased from the baseline (mean±S.D.= 0.129± 0.053 and 0.083±0.012). The increase was significantly different from the baseline (p <0.001) (Table 4.38). In the second week, there was a significant increase in the group of toothpaste containing cordycepin extract, which was nearly outside the criteria for diagnosing hyposalivation.

In terms of oral moisture (surface of the tongue), in the control group the amount of saliva was not significantly different from baseline (mean±S.D.) 0.020±0.033 (baseline=0.016±0.004) (p =0.414) (Table 4.39). The treatment group had an increase in saliva volume compared to baseline (mean±S.D.) at 0.021±0.006 (baseline=0.016±0.005) and this was a statistically significant difference. (p <0.001) (Table 4.40).

The amount of saliva in the control group was not statistically significant difference from baseline in terms of oral moisture (hypoglossus) (mean±S.D.) at 0.102±0.038 (baseline=0.096±0.034) (p =0.193) (Table 4.41), However, compared to the baseline, the treatment group had an increase in salivary volume (mean±S.D.) at 0.186±0.067 (baseline=0.092±0.032) and this was a statistically significant difference (p <0.001) (Table 4.42).

When the efficiency of a toothpaste containing cordycepin extract was evaluated at the second week, I found that there was a statistically significant trend for improvements in xerostomia, increased salivary secretion, and oral moisture (hypoglossus). However, there was no change in oral moisture (the surface of the tongue) from baseline (Table 4.33).

In the fourth week of the trial, I observed that elderly patients with type 2 diabetes mellitus (T2DM) who used toothpaste containing cordycepin extract had a mean xerostomia reduction of 0.17 (from baseline = 2.12 and second week = 1.16). and there was a statistically significant difference compared to the baseline and the second week (p <0.001) in both phases (Table 4.36). The mean xerostomia in the control group was 2.48, not different from the baseline or the second week (p= 0.850 and 0.76, respectively) (Table 4.35).

In terms of salivary flow rate, I observed that the control group's flow rate had slightly decreased after the fourth week compared to the second week (mean±S.D.= 0.086±0.013 and 0.089 ±0.010), and there was no statistically significant difference compared to the baseline and the second week (*p* =0.050 and 0.674, respectively) (Table 4.37). I observed that the salivary flow rate in the treatment group increased from baseline to the second week by mean±S.D.= 0.336±0.098 (baseline=0.083±0.012 and second week= 0.129±0.053). In comparison to the baseline and the second week, the increase was significantly different (*p* <0.001) in both phases (Table 4.38). The presence of hyposalivation in the cordycepin extract toothpaste group was not observed in the fourth week because the amount of saliva increased by more than 0.1 g in 1 minute (Villa, A. et al., 2014).

In terms of oral moisture (surface of the tongue), in the control group, the amount of saliva was not significantly different from baseline or the second week (mean±S.D.) at 0.017±0.010 (baseline=0.016±0.004 and second week=0.020±0.033) and (p =0.414 and 0.360, respectively) (Table 4.39). However, the treatment group had an increase in saliva volume compared to the baseline and the second week. (mean±S.D.) at 0.036±0.043 (baseline=0.016±0.005 and second week=0.021±0.006) and this was a statistically significant difference (baseline *p* <0.001 and second week *p* =0.001) (Table 4.40). When measured at the surface of the tongue in the fourth week, I observed that the treatment group did not have an oral moisture problem since there was more than 0.02 gram of saliva within 30 seconds (Takahashi Fumi et al., 2006).

Saliva quantity in the control group was not statistically different from baseline or during the second week of the fourth week of oral moisture (hypoglossus) (mean±S.D.) at 0.097±0.038 (baseline=0.096±0.034 and second week=0.102±0.038) (baseline p =0.193 and second week *p* =0.919) (Table 4.41). Nonetheless, the amount of saliva in the treatment group continued to rise when compared to the baseline and second week (mean±S.D.) at 0.266±0.057 (baseline=0.092±0.032 and second week= 0.186±0.067) and this was a statistically significant difference (*p* <0.001) in both phases (Table 4.42). When oral moisture was evaluated at the hypoglossus in the fourth week, it was found that the treatment

group had no problems with oral moisture because the saliva volume was higher than 0.1 gram in 30 seconds (Takahashi Fumi et al., 2006). At the end of the fourth week, I observed that the cordycepin extract toothpaste group was able to restore oral moisture problems, either on the surface of the tongue or the hypoglossus, to normal levels.

The results of the fourth week efficacy trial of cordycepin extract compared with normal fluoridated toothpaste showed that the cordycepin extract toothpaste group had a significant reduction in the mean of xerostomia compared to baseline and the control group, as well as a significant reduction in xerostomia cases. Six cases remained out of a total of 52, while xerostomia cases in the control group left 50 out of 52 cases (Table 4.43). The number of cases of xerostomia reported at 4 weeks was in accordance with positive trends in salivary flow rate, oral moisture (surface of the tongue and hypoglossus), and xerostomia in the cordycepin extract toothpaste group. In contrast to the baseline in the cordycepin group and control groups, the potential for restoring oral dryness, salivary secretion, and xerostomia in the cordycepin extract toothpaste group returns to accepted criteria for the diagnosis of xerostomia. This is due to the difference in active ingredients between the control group's (normal fluoridated toothpaste) and treatment group's toothpaste. The control group (normal fluoridated toothpaste) contained Sodium Monofluorophosphate (Active fluoride ion) 1,450 ppm, and the treatment group (toothpaste containing cordycepin extract) contained Sodium fluoride (Active fluoride ion) 1,500 ppm and cordycepin extract from *Cordyceps Militaris* 12.5 μM.

As observed, both the control group and the treatment group use toothpaste containing fluoride. This chemical serves as a therapeutic agent for a caries-prevention role (Wright, J. T. et al., 2014). The fluoride did not affect the increase in oral cavity moisture, but the toothpaste used in the treatment group contained cordycepin extract from *Cordyceps militaris*. In the previous study in 2009, they found that when comparing the amount of cordycepin and adenosine synthesis between the two species (*C. militaris* and *C. sinensis*). Both species were reported to have considerably different amounts of adenosine synthesis, and the concentration

of cordycepin and adenosine in the fruiting bodies of *C. militaris* were higher than that in natural *C. sinensis* (Huang, L. et al., 2009).

Furthermore, cordycepin extract from *Cordyceps militaris* increased salivary secretion in the treatment group's oral cavity, which is consistent with previous research showing that cordycepin can increase HSG proliferation, protein secretion, and the expression of salivary-specific genes, AMY and AQP5 (TacGhee Yi, et al., 2016), as well as previous studies that found Cordycepin rescued the protective effects partially by decreasing ROS generation and restoring the expression of the salivary proteins, AMY and AQP5 via anti-oxidant and anti-apoptotic activity. In addition, the amount of amylase that was secreted from HSG cells cultured in cordycepin was increased (Jaiboonma, A et al., 2020).

Moreover, cordycepin extract from *Cordyceps militaris* increased oral moisture in the treatment group, both on the surface of the tongue and in the hypoglossus. This is consistent with previous studies that found that *Cordyceps* species have moisture 7.18%, *Cordyceps* fruiting bodies contain 5.7% moisture, and mycelial biomass contains 13.1% moisture (Syed Amir Ashraf et al., 2020). The concentration of cordycepin extract from *Cordyceps militaris* contained in the toothpaste is safe for elderly patients with type 2 diabetes mellitus (T2DM) with xerostomia.

4.3 T-Phases of Translational Research in this thesis

4.3.1 Results

This thesis includes both a cross-sectional study and a randomized clinical trial. Overall, in this thesis, I found that this research is comprehensive from T0 to T3 (from T4 Research classifications: Translation to Communities) and can be indicative at the level of clinical outcomes research, dissemination, and implementation research.

4.3.2 Discussions

Phases T1 through T4 translational research. Some examples are as follows (Zarbin, M., 2020).

T1: Development and validation of animal models, preclinical drug studies, development of clinically relevant technologies, and phase 1 and 2 clinical studies ("bench to bedside" research).

T2: Phase 3 clinical trials (including comparative effectiveness trials), phase 4 clinical research, and development of clinical guidelines ("bedside to practice" research).

T3: Research focused on implementation and dissemination of phase 3 and 4 clinical research results (dissemination and implementation research).

T4: Research focused on outcomes and effectiveness in populations, including assessment of benefit to communities through public health policies and programs, as well as adoption of proven interventions' best practices in communities (diffusion research), and cost-benefit analyses.

From the definition of Phases T1 through T4 translational research, compared to the results in this thesis, I found that this thesis can be done up to T3 phases. This is because this study has both a cross-sectional study and a randomized clinical trial, which is at T3 Research: Translation to Practice, including comparative effectiveness research and clinical outcomes research. However, this thesis can be progressed to T4 Outcomes Research (which includes many disciplines): population monitoring of morbidity, mortality, benefits, and risk studies. If the study results are expanded to practice, population health impact and cost-benefit analyses that study a larger population and look at the long-term effectiveness of clinically testing the effects of

toothpaste containing cordycepin extract for oral health care in diabetic elderly patients with xerostomia could increase the T4 stage as well.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

According to the research purposes, the conclusions and recommendations were divided into three parts: 5.1 Prevalence survey; 5.2 Randomized clinical trial; and 5.3 Recommendations and possible future studies. The discussion and conclusion that the study showed are as follows:

5.1 Prevalence survey

(**Research objectives I**: To investigate the prevalence of xerostomia and its impacts on oral functions, as well as determine potential risk factors for xerostomia in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital.)

Conclusions

The prevalence of xerostomia in older Thai individuals with T2DM in this study is 38.4%. The findings from this study indicate that the diabetic elderly population is more prone to have xerostomia. Dental health personnel should monitor and emphasize that patients be aware of the high-risk behaviors that can result in this problem, and consult a doctor for appropriate care to help reduce or alleviate the severity of xerostomia to the greatest feasible extent.

The occurrence of xerostomia is associated with the elderly group, particularly in those with Type II diabetes using toothpaste containing spicy herbal extracts and denture wearing, which could ultimately lead to oral function problems. Therefore, the dental public health movement should focus more on the xerostomia problem in this population.

5.2 Randomized clinical trial

(**Research objectives II**: To clinically test the effects of toothpaste containing cordycepin extract for oral health care in diabetic elderly patients with xerostomia at Suranaree University of Technology Hospital)

Conclusions

Toothpaste containing cordycepin extract can reduce xerostomia and improve salivary flow rate and oral moisture in type 2 diabetes mellitus (T2DM) elderly patients compared with the normal fluoridated toothpaste group at 2 weeks and showed improvement at 4 weeks, and there were no adverse events in the patients.

5.3 Recommendations and Possible future studies

A number of findings in the present study revealed my recommendations and opportunities for further research and this could be addressed in future studies.

1. The scope of this study was elderly patients with type 2 diabetes mellitus (T2DM) receiving services only at Suranaree University of Technology Hospital (SUTH). In order to determine the trend and distribution of xerostomia, studies should be done over a larger area or in provincial hospitals, center hospitals, or sub-district health-promoting hospitals to study different patient contexts.

2. Future studies should be done on healthy individuals or patients other than those with diabetes mellitus or other age groups other than the elderly group to investigate the prevalence and tendency of xerostomia in order to discover solutions for providing oral health care that address all age groups and other disease groups and not only one group.

3. In the next study, Other oral health problems should also be studied, such as the evaluation of tooth decay, gingivitis, periodontitis, or other oral lesions in addition to assessing salivary secretion or xerostomia to study the prevalence of such diseases and the relationship between the disease and the occurrence of xerostomia.

4. In future studies Randomized clinical trial (RCT) may be conducted to compare the efficacy of toothpaste containing cordycepin extract between people with diabetes and those with other conditions. To determine whether cordycepin extract is as effective as a trial in treating type 2 diabetes mellitus (T2DM) in elderly

patients by increasing salivation. Especially in patients with head and neck cancer who have been treated with radiation therapy, which directly affects the salivary glands.

5. In this study, the quantitative method of measuring salivary secretion using unstimulated whole saliva was chosen, and future studies should use other methods of salivary quantification. To compare unstimulated whole saliva and stimulated whole saliva (gum-stimulated (masticatory) whole saliva and candy-stimulated (gustatory and masticatory) whole saliva) or saliva collection from individual glands, such as a modified Carlson-Crittenden device for collecting parotid gland saliva or a custom-made Wolff saliva collector for submandibular and sublingual gland saliva collection. This will allow evaluation of whether or how the quantities of saliva measured using different methods differ and to further study the most appropriate method for measuring the participants' volumes of saliva secretion.

6. In this study, the scope was to study xerostomia. Therefore, further studies in the future should study the issue of hyposalivation in the sample group as well as the relationship between xerostomia and hyposalivation. However, to confirm that all patients have true hyposalivation, the measurement of salivary flow rate in combination with the xerostomia questionnaire should be performed for all subjects in a further modest study.

7. Randomized clinical trial (RCT) were conducted throughout the study to evaluate the efficacy of using both toothpastes for a total of four weeks. The assessment and monitoring of trends in salivary secretion and oral moisture, as well as the evaluation of potential adverse effects from patients using toothpaste continuously for a long period of time, may require additional long-term studies that last at least three months in the future. Researchers should make use of this information to help the cordycepin extract toothpaste become more reliable and accepted in the future.

8. In the future, cordycepin extract research and products should be further developed into other products; for example, cordycepin extract-containing sugar-free candy or gum or artificial saliva spray can be used as another option for patients or those with xerostomia.

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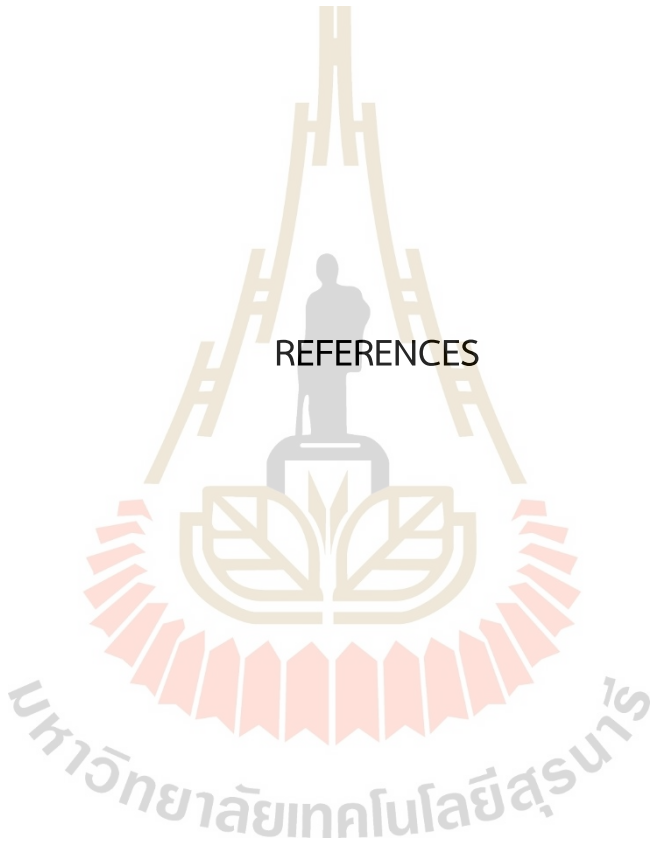

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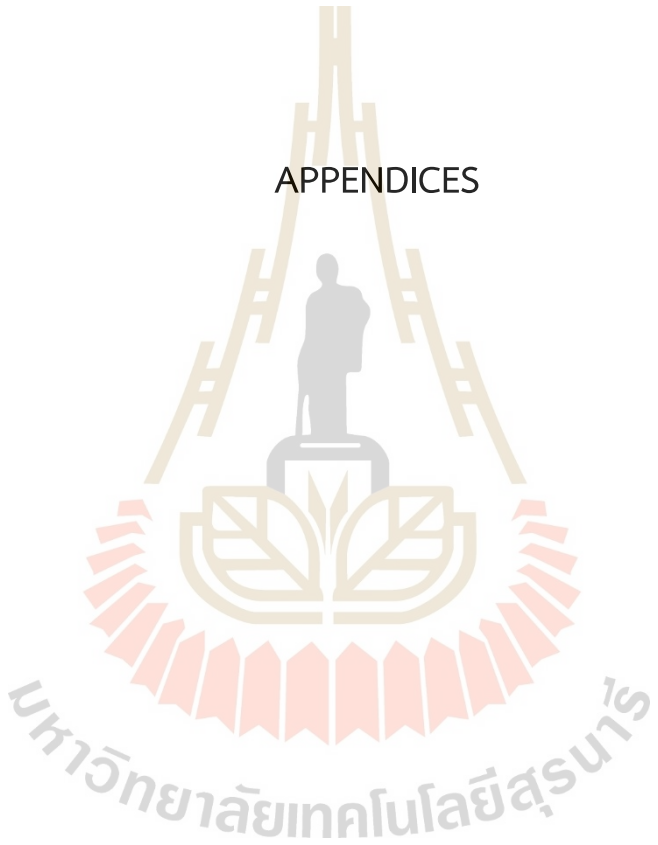
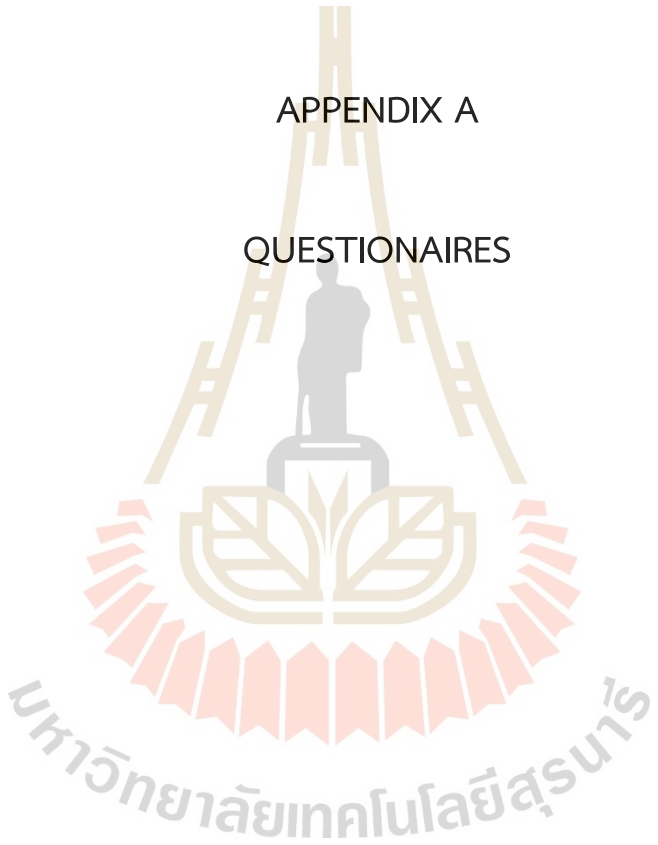
APPENDICES



APPENDIX A

QUESTIONAIRES



ID ☐☐☐
Date...../...../.....
Recorder.....

Questionaires

Questionaire survey is part of the Ph.D. Thesis in title: *The Role of Cordycepin extract In Oral Health Care of Type 2 Diabetes Mellitus Elderly Patients with Xerostomia*

Directions: Please respond to the following questions by provide your information as truthful as possible and place an "✓" mark in the box of your answer or providing the requested information.

Part 1 Sociodemographic and Health behavior

1. What is your gender ?
☐ Male ☐ Female

2. Age.....years old

3. Education
☐ None
☐ **Elementary School**
☐ **High School**
☐ **Bachelor's degree**
☐ **Higher than the Bachelor's degree**

4. You were diagnosed with DM by a medical doctor for.....year(s)....month(s)

5.Your blood sugar level in last time
When...../...../.....
FBS..... mg /dL or/and HbA1c.....%

6. Do you have a systemic diseases other than diabetes ?
☐ No
☐ Yes, (please specify).....

7. Do you have the medication ?
☐ No
☐ Yes, (please specify).....
.....

8. Do you smoke ?
☐ No
☐ Yes, (How many cigarettes per day).....
cigarettes

9.How often do you have a drink containing alcohol ?
☐ Never
☐ Monthly or less
☐ 2-4 times a month
☐ 2 -3 times a week
☐ 4 or more times a week

10. Toothpaste brands that you are using at present
☐ Colgate
☐ SYSTEMA
☐ DARLIE
☐ Amway Glister
☐ SALZ
☐ SPARKLE
☐ SENDODYNE
☐ DENTISTE'
☐ Parodontax
☐ Twin Lotus
☐ Tepthai
☐ HI-HERB
☐ Other, (please specify).....

11. Denture wearing
☐ None
☐ Complete Dentures
☐ Removable Partial Dentures
☐ Fixed Partial Dentures

Part 2 Oral function consists of 4 parts:

Issues	None	Very mild	Mild	Moderate	Severe
1. Speaking problems					
Do you have speaking problems?					
2.Taste problems					
Do you have taste problems?					
3.Swallowing problems (Use Functional oral intake score (FOIS) adapted from Crary MA et al., 2005).					
☐ Tube dependent , (please specify)..... ☐ Total oral intake of a single consistency ☐ Total oral intake of multiple consistencies requiring special preparation ☐ Total oral intake with no special preparation, but must avoid specific foods or liquid items ☐ Total oral intake with no restrictions					

Directions: Please respond to the following questions by checking *Could chew well, Difficult to chew, Could not chew at all, Never eat or any other* (Place an "✓" mark in the box of your answer) or providing the requested information.

4.Chewing ability

(Use Chewing function questionnaire adapted from Limpuangthip, N. & Arksornnukit, M., 2019), (Kunon, K., & Kaewplung, O., 2014).

Foods list	Could chew well	Difficult to chew	Could not chew at all	Never eat or any other
1. Rice soup/Porridge (ข้าวต้ม/โจ๊ก)				
2. Chinese Vegetable Stew (จับฉ่าย)				
3. Clear Soup/Steamed vegetables (แกงจืด/ผักนึ่ง)				
4. Cooked rice (ข้าวสวย)				
5. Noodles (บะหมี่,ก๋วยเตี๋ยว)				
6. Omelette (ไข่เจียว)				
7. Steamed fish (ปลานิล/ปลาทับทิมนึ่ง)				
8. Sour curry (แกงส้ม)				
9. Banana (กล้วย)				
10. Fried fish (ปลานิล/ปลาทับทิมทอด)				
11. Orange (ส้ม)				
12. Guava (ฝรั่ง)				
13. Fried pork (หมูทอด)				
14. Stir-fried vegetables (ผัดผักรวม)				

Part 3 Xerostomia assessment

(Use questionnaire on xerostomia adapted from Handerson Nunes de Carvalho et al., 2020).

Directions: Please respond to the following questions by checking YES or NO (Place an "✓" mark in the box of your answer) or providing the requested information.

Questions	Yes	No
1. Do you feel the amount of saliva in your mouth is too little?		
2. Do you feel dry mouth when you eat meals?		
3. Do you often feel dry mouth at night or when you wake up in the morning?		
4. Do you feel that swallowing your food is difficult?		
5. Do you sip water all the time while swallowing food?		

Compliance form

Directions: Please check ✓ in the ☐ for using toothpaste from SUTH. of was actually used (Brush your teeth for two minutes twice a day for 30 days)

D/M/Y	Time			Note
	Morning	Before bed	other	
1...../...../.....				
2...../...../.....				
3...../...../.....				
4...../...../.....				
5...../...../.....				
6...../...../.....				
7...../...../.....				
8...../...../.....				
9...../...../.....				
10...../...../.....				
11...../...../.....				
12...../...../.....				
13...../...../.....				
14...../...../.....				
15...../...../.....				

Creeth JE et al., 2009.

Compliance form (continued)

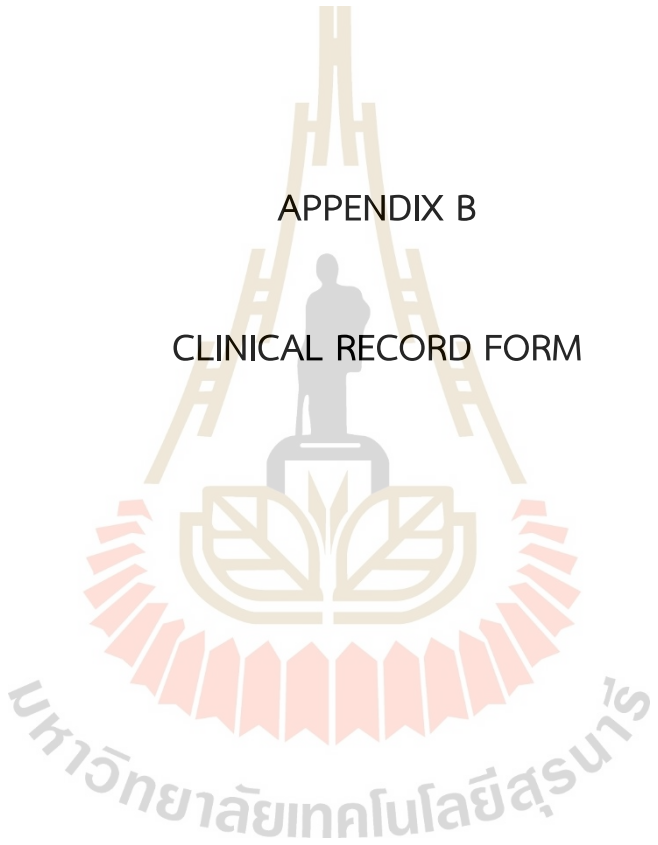
Directions: Please check ✓ in the ☐ for using toothpaste from SUTH. of was actually used (Brush your teeth for two minutes twice a day for 30 days)

D/M/Y	Time			Note
	Morning	Before bed	other	
16...../...../.....				
17...../...../.....				
18...../...../.....				
19...../...../.....				
20...../...../.....				
21...../...../.....				
22...../...../.....				
23...../...../.....				
24...../...../.....				
25...../...../.....				
26...../...../.....				
27...../...../.....				
28...../...../.....				
29...../...../.....				
30...../...../.....				

Creeth JE et al., 2009.

APPENDIX B

CLINICAL RECORD FORM



ID□□□

Clinical Record Form

Salivary flow rate (Unstimulated saliva for 5 minutes) and Oral moisture tests

Weeks	D/M/Y	Time (Saliva collection)	Volume (ml.)	Oral moisture tests (g)
0 (Before clinical test)	...../...../.....	.....to.....	.....	surface of the tongue =.....g in 30 s
				Hypoglossus =.....g in 30 s
2nd	...../...../.....	.....to.....	.....	surface of the tongue =.....g in 30 s
				Hypoglossus =.....g in 30 s
4th	...../...../.....	.....to.....	.....	surface of the tongue =.....g in 30 s
				Hypoglossus =.....g in 30 s

Note:.....

.....

.....

.....

.....

Recorder:.....

ID□□□

Assessment of adverse events from toothpaste usage

Adverse events	Week			
	2nd wk.		4th wk.	
	Yes	No	Yes	No
1. Do you have an allergic reaction, irritation, or burning sensation in your mouth after using this toothpaste?				
2. Do you have an allergic reaction or irritation to other areas outside your mouth, such as your face, skin, or throat after using this toothpaste?				
3. Do you feel uncomfortable in your mouth after using this toothpaste?				
4. Do you experience sensitive teeth or other mouth and tooth problems after using this toothpaste?				
5. Do you have nausea, vomiting, or any other discomfort after using this toothpaste?				
6. Do you have an adverse reaction related to an additional complication of your underlying disease after using this toothpaste?				
7. Have you been examined or treated in a medical facility regarding adverse reactions caused by the use of this toothpaste?				
8. Your personal physician determined that using this toothpaste worsened your underlying disease condition?				

APPENDIX C

CONTENT VALIDITY RESULTS BY EXPERT DENTISTS

แบบรับรองการตรวจสอบคุณภาพเครื่องมือที่ใช้ในการเก็บข้อมูลวิจัยโดยผู้เชี่ยวชาญ

ชื่อเรื่องวิจัย THE ROLE OF CORDYCEPIN EXTRACT IN ORAL HEALTH CARE OF TYPE 2 DIABETES MELLITUS ELDERLY PATIENTS WITH XEROSTOMIA

ชื่อนักศึกษา นายปณิธาน สนพะเนา ระดับ ปริญญาเอก สาขา Translational Medicine (International Program) สำนักวิชา แพทยศาสตร์ สถาบัน มหาวิทยาลัยเทคโนโลยีสุรนารี

ชื่ออาจารย์ที่ปรึกษาหลัก ผศ.ทพ.ดร.ไพบูลย์ จิตประเสริฐวงศ์ สำนักวิชา ทันตแพทยศาสตร์ สถาบัน มหาวิทยาลัยเทคโนโลยีสุรนารี

ทั้งนี้โครงร่างงานวิจัยนี้ได้รับการอนุมัติจากคณะกรรมการจริยธรรมวิจัยในมนุษย์ของมหาวิทยาลัยเทคโนโลยีสุรนารี เลขที่ 85/2564 รหัสโครงการ EC-64-92 เรียบร้อยแล้ว

ข้าพเจ้า (นาย/นาง/นางสาว) หริรัตน์ หล้าเขาทุ่ง ตำแหน่ง ทันตแพทย์

หน่วยงาน ร.พ. มหาราชนครราชสีมา ขอรับรองว่า นายปณิธาน สนพะเนา ได้นำเครื่องมือการเก็บข้อมูลวิจัยมาให้ข้าพเจ้าตรวจสอบความตรงเชิงเนื้อหาและโครงสร้างจริง เมื่อวันที่ 26/10/64

ผลการตรวจสอบพบว่า

....

ข้อควรปรับปรุง - เพิ่มเติม ในส่วน สภาวะทางจิตใจที่เกี่ยวกับภาวะปากแห้ง

- ในส่วนที่ 3 แบบประเมินสภาวะปากแห้ง

ข้อเสนอแนะ - เพิ่ม - ท่านมีความวิตกกังวล เรื่องปัญหาการดำเนินชีวิต ในสภาวะที่รู้สึกว่าปากแห้ง หรือ ไม่?

เหตุผล : ความวิตกกังวล อาจมีผลต่อปัจจัยหนึ่ง ให้ ภาวะน้ำลายน้อย รู้สึก ปากที่เกิดขึ้นจริง

ลงชื่อ [signature] ผู้ตรวจสอบ

(หริรัตน์ หล้าเขาทุ่ง)

ตำแหน่ง ทันตแพทย์

วันที่ 27/10/64

แบบรับรองการตรวจสอบคุณภาพเครื่องมือที่ใช้ในการเก็บข้อมูลวิจัยโดยผู้เชี่ยวชาญ

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ชื่อนักศึกษา นายปณิธาน สนพะเนา ระดับ ปริญญาเอก สาขา Translational Medicine (International Program) สำนักวิชา แพทยศาสตร์ สถาบัน มหาวิทยาลัยเทคโนโลยีสุรนารี

ชื่ออาจารย์ที่ปรึกษาหลัก ผศ.ทพ.ดร.ไพบูลย์ จิตประเสริฐวงศ์ สำนักวิชา ทันตแพทยศาสตร์ สถาบัน มหาวิทยาลัยเทคโนโลยีสุรนารี

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ข้าพเจ้า (นาย/นาง/นางสาว) ชิงคณา วิสุทธางกูร ตำแหน่ง ทันตแพทย์ชำนาญการพิเศษ หน่วยงาน โรงพยาบาลมหาราชนครราชสีมา ขอรับรองว่า นายปณิธาน สนพะเนา ได้นำเครื่องมือการเก็บข้อมูลวิจัยมาให้ข้าพเจ้าตรวจสอบความตรงเชิงเนื้อหาและโครงสร้างจริง เมื่อวันที่ 26 พ.ย. 64

ผลการตรวจสอบพบว่า

เครื่องมือที่ใช้เก็บข้อมูลมีความครอบคลุมในการประเมินภาวะปากแห้งได้ดีมาก โดยมีข้อการประเมินสมรรถภาพการทำงานของต่อมน้ำลายร่วมกับความสามารถด้านการบดเคี้ยวทำมาประกอบด้วย

ข้อควรปรับปรุง

-

ข้อเสนอแนะ

ในส่วนพฤติกรรมด้านทันตสุขภาพ เช่น จำนวนครั้งในการทำความสะอาดช่องปาก ปริมาณขาสีฟันที่ใช้ในแต่ละบุคคล อาจจะมีผลต่อภาวะปากแห้งได้

ลงชื่อ ชิงคณา วิสุทธางกูร ผู้ตรวจสอบ

(นางสาว ชิงคณา วิสุทธางกูร)

ตำแหน่ง ทันตแพทย์ชำนาญการพิเศษ

วันที่ 27 พ.ย. 64

แบบรับรองการตรวจสอบคุณภาพเครื่องมือที่ใช้ในการเก็บข้อมูลวิจัยโดยผู้เชี่ยวชาญ

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ข้าพเจ้า (นาย/นาง/นางสาว) ไพศาล วิไลจิตเลิศ ตำแหน่ง ทันตแพทย์ชำนาญการพิเศษ หน่วยงาน ศูนย์ทันตกรรม สรจ. นม ขอรับรองว่า นายปณิธาน สนพะเนา ได้นำเครื่องมือการเก็บข้อมูลวิจัยมาให้ข้าพเจ้าตรวจสอบความตรงเชิงเนื้อหาและโครงสร้างจริง เมื่อวันที่ 26 พย 2564

ผลการตรวจสอบพบว่า

-

ข้อควรปรับปรุง

-

ข้อเสนอแนะ

- ควรมีการเพิ่มเรื่อง ของ ทันตกรรมประดิษฐ์ ในแบบสอบถามด้วย

ลงชื่อ .... ผู้ตรวจสอบ

(ไพศาล วิไลจิตเลิศ)

ตำแหน่ง ทันตแพทย์ชำนาญการพิเศษ

วันที่ 27 พย. 2564

CURRICULUM VITAE

NAME: Mr.Panitan Sonpanao

DATE OF BIRTH: December 28, 1994.

PLACE OF BIRTH: Nakhon Ratchasima Province, Thailand.

EDUCATION

DEGREE	INSTITUTION AND LOCATION	YEAR	FIELD OF STUDY
High Vocational Certificate	Sirindhorn College of Public Health Khon kaen , Thailand	2014	Dental Public Health
B.P.H.	Mahasarakham University, Thailand	2016	Public Health
M.P.H.	Mahasarakham University, Thailand	2018	Public Health (Health promotion and health behavior development)
Ph.D.	Suranaree University of Technology, Thailand	2023	Translational Medicine (International Program)

POSITIONS AND EMPLOYMENTS:

2014 - present Dental Public Health officer, Operational Level at Poansung health promoting hospital, Muenwai sub-district, Muang district, Nakhon Ratchasima Province

SCHOLARSHIPS:

1. Ph.D. Scholarship from Institute of Dentistry, Suranaree University of Technology (SUT), One Research One Grant (OROG) Scholarship.

2. Graduate Development Scholarship 2022 from the National Research Council of Thailand (NRCT) and Suranaree University of Technology (SUT), grant number D6200381-5/2565.

Ph.D. THESIS PUBLICATION:

The title of “The Prevalence of Xerostomia in Older Thai Individuals with Type II Diabetes Mellitus and Its Association with Type of Toothpaste and Oral Functions: A Cross-Sectional Study Using Questionnaires”. In *Geriatrics* 2023, *8*, 76.