

DENTA JURNAL

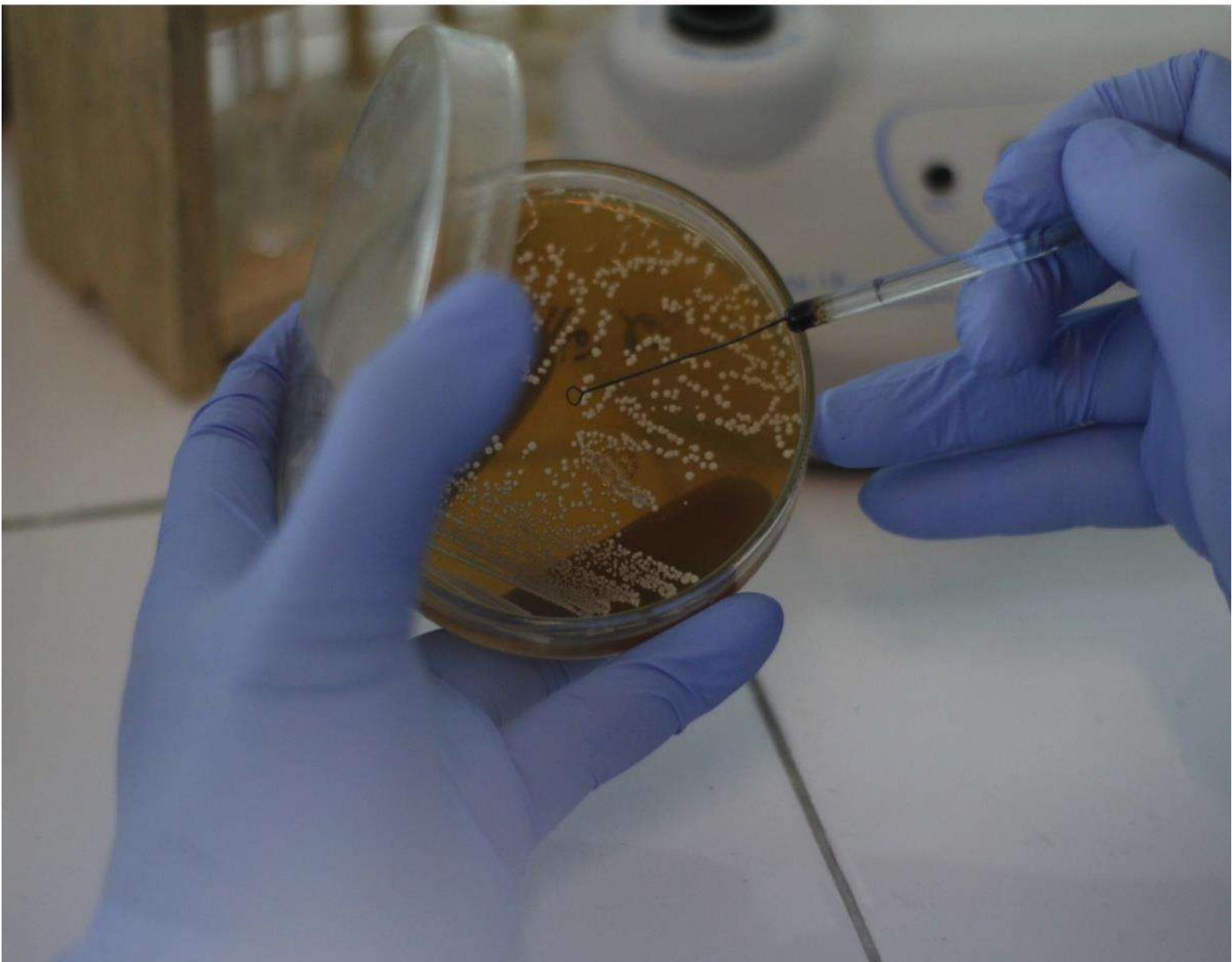
KEDOKTERAN GIGI



P-ISSN: 1907-5987

E-ISSN: 2615-1790

VOLUME 16 NO.1 FEBRUARI 2022



[HTTP://JOURNAL-DENTA.HANGTUAH.AC.ID](http://journal-denta.hangtuh.ac.id)

SUSUNAN REDAKSI

Editor in Chief

Widyasri Prananingrum

Editor

Dian Widya Damaiyanti, Anis Irmawati, Agni Febrina Pargaputri,
Recita Indraswary, Nunuk Purwanti, Fitria Rahmitasari

Peer Review

Laelia Dwi Anggraini, Mochamad Nur Ramadhani, Dian Mulawarmanti, Arya
Brahmanta, Kristanti Parisihni, Diana Soesilo, Dwi Andriani, Syamsulina
Revianti, Rima Parwati, Rizki Amalina, Noengki Prameswari, Endah
Wahjuningsih, Sularsih, Fanny M. Laihad, Arya Adiningrat

Editorial Staff and Administrator

Carissa Endianasari, Fitri Puji Rahayu, Arofatur Nur Ainiah

Jurnal Kedokteran Gigi diterbitkan setiap bulan Februari dan Agustus oleh
Fakultas Kedokteran Gigi Universitas Hang Tuah.

ALAMAT REDAKSI

Fakultas Kedokteran Gigi-Universitas Hang Tuah
Jl. Arief Rahman Hakim 150 Surabaya
Telp. 031-5945864, 5945894 psw 219/220 Fax. 031-5946261
E-mail: journal.denta@hangtuah.ac.id
<http://journal-denta.hangtuah.ac.id>

DAFTAR ISI

Susunan Redaksi	i
Daftar Isi	ii
Abnormality of Soft Tissue in the Oral Cavity of Youth with Normal Blood Pressure and Hypertension During Social Service Activities in Karang Pilang District <i>Kharinna Widowati, Isidora Karsini S, Aulia Dwi Maharani</i>	1-5
Dentist Role in Increasing Quality of Life in Mucositis Patient with Acute Lymphoblastic Leukemia <i>Theodora Adhisty Dwiarie, Nanan Nur'aeny, Nelly Nainggolan</i>	6-12
Parent's Oral and Dental Health Behavior as Predictors of Children's Oral and Dental Health Status <i>Dayu Annesti Viana, Sri Pandu Utami</i>	13-20
Prevalence of Patients with Oral Cavity Tumours at Hospital Abdoel Wahab Sjahranie Samarinda 2016-2020 <i>Rienda 'Afifah Khairunnisa, Sinar Yani, Cristiani Nadya Pramasari</i>	21-25
Risk Factor Analysis of Caries Through Saliva in Non-Syndromic Cleft Lips Children With or Without Cleft Palate <i>Yayun Siti Rochmah, Anindita Dyah Palupi, Aulia Noviana, Shofwatin Ni'mah</i>	26-31
Socket Preservation with Hydroxyapatite Gypsum Puger Scaffold and Aloe vera on Fibroblast and Type 1 Collagen Cells <i>Amiyatun Naini, Clarissa Astiasari, Muhammad Nurul Amin</i>	32-40
Steven Johnson Syndrome with Severe Oral Implications and Management <i>Fika Faradillah Drakel, Tenny Setiani Dewi</i>	41-46
The Effect of Kersen (<i>Muntingia calabura L.</i>) Leaf Extract Nanogel on Stomatitis <i>Ariyati Retno Pratiwi, Linda Risalatul Muyasaroh</i>	47-58

Abnormality of Soft Tissue in the Oral Cavity of Youth with Normal Blood Pressure and Hypertension During Social Service Activities in Karang Pilang District

Kharinna Widowati*, Isidora Karsini S*, Aulia Dwi Maharani**

*Department of Oral Medicine, Faculty of Dentistry, Universitas Hang Tuah

**Department of Dental Public Health, Faculty of Dentistry, Universitas Hang Tuah

Online submission : 05 November 2021

Accept Submission : 10 December 2021

ABSTRACT

Background: The oral mucosa soft tissue can develop white, red lesions, vesiculobullous lesions, and ulcerated lesions as a result of systemic disease. The age of patients with systemic diseases affects the profile of oral soft tissue abnormalities. In developed countries, roughly 60% of young people with systemic diseases have at least one oral lesion. Hypertension is one of the systemic diseases that can cause clinical manifestation in oral soft tissue mucosa. **Objective:** To discover the profile of soft tissue abnormalities of the oral cavity in youth with a normal blood pressure and hypertension in the Karangpilang district. **Methods:** The type of this research is analytical observational. The method is that blood pressure is measured in each sample, then grouped into 2 (normal blood pressure group and hypertension group). Furthermore, each group was examined with an intra-oral examination that will be carried out to determine the condition of the soft tissue of the oral cavity in each sample. Processing and analyzing the research data using the Spearman Correlation Test method. **Result:** There is a strong positive relationship between the systolic pressure and the number of soft tissue abnormalities in the oral cavity. **Conclusion:** The oral cavity's soft tissues are frequently obtained during examinations of patients with elevated blood pressure.

Keywords: Abnormalities, Hypertension, Oral cavity, Soft tissue.

Correspondence: Kharinna Widowati, Faculty of Dentistry, Universitas Hang Tuah. Jl. Arif Rahman Hakim 150, Surabaya, Indonesia. Phone +6287851266354. Email: kharinna.widowati@hangtuah.ac.id

INTRODUCTION

Soft tissue of the oral cavity consists of palate, tongue, gingiva, labial mucosa, buccal mucosa, and frenulum.¹ The healthy of the oral cavity soft tissue is part of a healthy body, come along play a role in determining somebody's health status. It can be seen from the presence or absence of abnormalities in oral soft tissue.² Disease or soft tissue abnormalities of the adult oral cavity become the most serious concern of experts, especially with the increasing number of deaths caused by a cancer of the oral cavity particularly in developed countries in Asia. Soft tissue abnormalities of the oral cavity progressively evolve and divided according to the cause such as hereditary, traumatic, stress, allergy, infection or an unknown cause (idiopathic), as well as manifestation from a systemic disease that has been affecting the by patient.³ Changes in the normal color of the oral mucosa are a symptom of a lesion in a disease or abnormalities.⁴ Clinical examination alone is not sufficient enough to determine the diagnosis of oral soft tissue lesions. Therefore, a proper anamnesis is required, and on some occasion a part of the diseased tissue (biopsy) is taken for histopathological anatomical examination, which allows us as dentists to establish the final diagnosis and provide an appropriate therapy.⁵

The age factor cannot be ignored. Along as a person gets older, will change in clinical and psychological aspects. Changes in the clinical aspects include providing various effects on oral tissues and the function of tissues.⁶ According to WHO, the age range is divided into 5, including minors, youth, middle-aged, old-adult, and elderly. The prevalence of hypertension in Indonesia reached 31.7% in 2013, starting from the population aged 18 years and over. That prevalence increases with age. The population range of youth to elderly in Indonesia in 2020 is predicted to increase by 11% of the current total population. The increase is concomitant with the increasing prevalence of systemic disease that can manifest in the oral cavity. Systemic disease can affect all age ranges, especially in the range

of youth to elderly.⁷ Systemic diseases that have the potential to cause clinical manifestations in the soft tissues of the oral mucosa are hypertension, diabetes mellitus, anemia, and others. Variety of lesions can be found in the soft tissue of the oral mucosa as a manifestation of systemic disease, including white red lesions, vesiculobullous lesions, and ulcerated lesions.⁴ The Profile at the soft tissue abnormalities of oral cavity in patients with systemic disease has variety dependent factors, such as age factor and medical treatment they used.⁷ In developed countries, approximately 60% of the youth population with systemic diseases has complaints of lesion in the oral cavity at least one case. This may be an oral manifestation due to the use of therapy related to their systemic disease.

Social service activities are held regularly four times a year in our community. There are 4 districts that we regularly visit in turn for the implementation of social services. Those are Karangpilang, Sukomanunggal, Wonokromo, and Tegalsari. Now it's the turn of the Karangpilang district that we visit to implement social services.

Therefore, on this occasion the researcher interested to conduct research on the profile of soft tissue abnormalities in the oral cavity in the youth age range (according to WHO) with a normal blood pressure and hypertension conditions in Karangpilang District.⁸

MATERIALS AND METHODS

This type of research is Analytical Observation. The design of this research is Analytical Observation with Cross Sectional approach. The populations in this study were patients (community) who attended Social Service activity in Karangpilang district, Surabaya. The experimental unit of this research is the patient's (community) who attends Social Service activities in Karangpilang district with a youth age range of 18-65 years. Determine the

sample size using the formula of Simple Random Sampling.

$$n = N/N(d)^2 + 1$$

Information :

n = big total sample
N = population
d = precision value (0.05)

Based on the estimated target population of patient's (communities) who participate in Social Service activities (N), which is 50 patients, the sample size (n) is 44 patients with a youth age range of 18-65 years. The sample size was divided into 2 groups, 22 patients with normal blood pressure of 86-120 mmHg (systolic) and 56-80 mmHg (diastolic), and 22 patients with high blood pressure which is above 120 mmHg (systolic) and 80 mmHg (diastolic). The soft tissue abnormality profile of the oral cavity examined was the condition of the soft tissue in the patient's oral cavity found through intra-oral clinical examination, which could be lichenoid lesions, xerostomia, angioedema, and/or gingival enlargement.

RESULTS AND DATA ANALYSIS

Based on the blood pressure examination and the condition of the soft tissue abnormalities of the oral cavity in each patient, the following results were attained:

Table 1. Patient examination results

Variable	N	%
Gender		
Male	11	23.40
Female	36	76.60
Blood Pressure		
Normal	26	55.32
Hypertension	21	44.68
Amount Of Intraoral (Soft Tissues) Cases Found In All Types Of Blood Pressure		
0 Case	10	21.28
1 Case	13	27.66
2 Cases	10	21.28

3 Cases	14	29.79
Amount Of Intraoral (Soft Tissues) Cases Found In Patients With Normal Blood Pressure		
0 Case	10	38.46
1 Case	13	50.00
2 Cases	3	11.54
3 Cases	0	0.00
Amount Of Intraoral (Soft Tissues) Cases Found In Patients With Hypertension		
0 Case	0	0.00
1 Case	0	0.00
2 Cases	7	33.33
3 Cases	14	66.67

Based on the examination of patient's systolic blood pressure at this social service, the number of the patients classified to the youth age range (18-65 years) was 47 patients, with a details of 26 patients having normal blood pressure, and 21 patients having a high systolic blood pressure (hypertension).

In this study, we only compared and processed data on the number of patients range 18-to 65 years old who had high systolic blood pressure and normal systolic blood pressure. We counted and compared the number of intraoral cases found on the oral mucosa (soft tissue abnormalities) of these patients (please see the dark blue column and light blue column).

The data obtained in the research does not require normality test because the scale of the data obtained is ordinal scale data. The data was tested for correlation using Spearman's test.

Table 2. Table of correlation between systolic pressure and soft tissue abnormalities case

Test	Blood Pressure			Oral Soft Tissue Cases		
	R	p	N	R	p	N
Spearman's rho	.768*	0.000	47	.768*	0.000	47

**Correlation is significant at the 0.01 level (2-tailed).

Based on the table, obtained a significant correlation (sig = 0.0000, Sig < 0.05). Furthermore, based on the correlation value (R

= 0.768) found a strong correlation with a positive direction between systolic pressure with the value of oral soft tissue abnormalities, in other words the higher the patient's systolic pressure, the larger or higher the value of oral soft tissue abnormalities discover in the patients.

DISCUSSION

Hypertension is a condition with an increased blood pressure above normal. Treatment of hypertension is proved to be very effective and widely available but some side effects inter alia in the oral cavity cannot be avoided.⁹ Based on data analyzed in this research, the higher a person's blood pressure (both systolic and diastolic), the taller or greater the number of soft tissue abnormalities found in the oral cavity. One possible reason is that the use of anti-hypertensive drugs triggers the appearance of lesions on the patient's oral mucosa.

Based on anamnesis, all patients with high blood pressure in this study sample, are taking anti-hypertensive drugs. Hypertension treatment which is proven to be very effective and widely available has succeeded in controlling hypertension patients thereby reducing morbidity and mortality due to hypertension.⁸ Consumption of anti-hypertensive drugs cannot be ignored by patients, but some side effects due to hypertension drugs cannot be avoided. Complaints about the soft tissues of the oral cavity are often obtained on examination of the patient's, namely in the form of conditions Xerostomia, Gingival enlargement, and Dysgeusia (taste disturbance).¹⁰

Kumar et al. examined complaints of antihypertensive drugs against the oral cavity and reported gingival bleeding with characteristic redness of the marginal gingiva (85.38%), hyposalivation (16.99%), lichenoid (4.5%), facial nerve paralysis (1.2%) , and gingival swelling (16.9%).⁶ Other complaints that arise are a gritty taste in the mouth, difficulty speaking, chewing, or swallowing due to a lack

of saliva production, which can cause xerostomia.¹¹

Anti-hypertensive drugs act on the autonomic nerves, namely through the parasympathetic nerves, which then have the same neurohumoral movement pattern as the sympathetic nerves which results in the emergence of salivary gland work interventions to drain saliva so that saliva is reduced.¹² Antihypertensive drugs indirectly affect the acid and base balance in saliva because they inhibit the entry of calcium ions into cells. The synergistic effect of using a combination of two or three types of anti-hypertensive drugs can increase the likelihood of xerostomia.¹³ Prolonged xerostomia condition causes a taste disorder known as dysgeusia. Taste disorders that often occur are a decrease in the ability to taste (*hypogeusia*). Taste disorders that occur continuously easily lead to the growth of bacteria and fungi in the oral cavity.¹⁴

In addition to xerostomia, clinical manifestations that are commonly found in the soft tissues of the oral cavity due to the use of anti-hypertensive drugs are in the form of gingival enlargement (gingival enlargement).¹⁵ These clinical manifestations are usually seen after 1 to 3 months of therapy. Gingival enlargement starts from the hyperplastic condition of the labial papillae of the anterior teeth and continues to the interdental papillae, which eventually extends to the surface of the tooth crown so that it can interfere with the masticatory process. Antihypertensive drugs that cause gingival enlargement work by triggering the process of collagen synthesis by gingival fibroblasts, reduction of collagen degradation due to the production of inactive collagenase enzymes and the addition of non-collagenous matrix, For example, glycosaminoglycans and proteoglycans in greater amounts than collagen matrix.¹⁶

CONCLUSION

The oral cavity's soft tissues are frequently obtained during examinations of

patients with elevated blood pressure. This is due to patients' increased reliance on antihypertensive medications. Soft tissue disorders such as xerostomia, dysgeusia, and gingival enlargement are frequently seen in patients with high blood pressure. This is due to the intensity of the use of anti-hypertensive drugs by patients. Cases of soft tissue disorders that are often found in patients with high blood pressure are in the form of xerostomia, dysgeusia, and gingival enlargement.

REFERENCES

- Setiadhi, Riani., Wihardja, Rosiliwati. Pengaruh Umur Terhadap Jaringan Lunak Mulut. *J Ked Gi Unpad*. Agustus 2019; 31(2): 76-81.
- Gopdianto R, Rattu AJM, Mariati NM. Status kebersihan mulut dan perilaku menyikat gigi. *J e-Gigi*. 2015; 3(1):130-8. DOI: [10.35790/eq.3.1.2015.6457](https://doi.org/10.35790/eq.3.1.2015.6457).
- Langlais RP, Miller CS, Gehrig JNS. Atlas berwarna lesi mulut yang sering ditemukan. Alih Bahasa. Edisi 4. Suta T. Jakarta: EGC; 2013 (pp 18,170-172).
- Scully. Oral and Maxillofacial medicine. The Basis of Diagnosis and Treatment. 3rd Edition. London Wright; 2012 (pp 326-339).
- Perry, A.G. & Potter, P.A. Buku Ajar Fundamental Keperawatan : Konsep, Proses, dan Praktik. Jakarta : EGC. 2012. pp 131-6
- Agarwal B. Chandra A, Singh SV, Agarwal S. Effect of age on oral tissues. *IJDSR*. 2017; 29(3):110– 2.
- Subiakto, Birgitta D.S., Endah, Adiasuti P. Prevalensi Kelainan Jaringan Lunak Rongga Mulut pada Lansia di Panti Surya dan Hargodedali Surabaya bulan Agustus - September 2014 [cited July 31st 2019]. Available from: <https://www.repository.unair.ac.id/id/eprint/19202/>
- Kenning I., Kerandi H., Luehr D., Margolis K., O'Connor P., Pereira C. et al. Hypertension diagnosis and treatment. Health care guideline. Institute for Clinical System Improvement; 2014.
- Tambuwun, G.J. Priscilia, Suling, L. Peter, Mintjelungan, N. Christy. Gambaran Keluhan di Rongga Mulut pada Pengguna Obat Antihipertensi di Poliklinik Penyakit Dalam RS Tingkat III Robert Monginsidi Manado. *Jurnal e-GiGi (eG)*. 2015;3(2): 1-5.
- Kumar P., Mastan KMK., Chowdhary R., Shanmugam K. Oral Manifestations in Hypertensive Patient : a Clinical Study. *Journal of Oral and Maxillofacial Pathology*. 2012; 16(2) May-Aug: 215-21.
- Pejcic, Ana. Drug-induced Oral Reactions. Emerging trends in oral Health Science and Dentistry. INTECH. 2015; (25): 567-80 [cited July 31st 2019]. Available from: <https://www.intechopen.com/chapters/47880>
- Villa A., Connel CL., Abati S. Diagnosis and Management of Xerostomia and Hyposalivation. Therapeutics and Clinical Risk Management. 11th ed; 2015 (pp 45-51).
- Allis TJ, Leopold DA. Smell and taste disorders. *Facial Plast Surg Clin North Am*. 2012 Feb; 20(1): 93-111. doi: 10.1016/j.fsc.2011.10.011. PMID: 22099622.
- Packirisamy S, Rajendiran D., Ganapathy B., Magdaline B.L. Drug Induced Oral Adverse Reactions : A Review Article. *International Journal of Current Advanced Research*. 2019 Oct; 8(10(B)): 20158-163.
- Pejcic, A. . Drug-Induced Oral Reactions. In: Virdi, M. S. , editor. Emerging Trends in Oral Health Sciences and Dentistry [Internet]. London: IntechOpen; 2015 [cited July 31st 2019]. Available from: <https://www.intechopen.com/chapters/47880> doi: 10.5772/59261.
- Nonzee V, Manopatanakul S, Khovidhunkit SO. Xerostomia, hyposalivation and oral microbiota in patients using antihypertensive medications. *J Med Assoc Thai*. 2012; 95(1):96-104.



Dentist Role in Increasing Quality of Life in Mucositis Patient with Acute Lymphoblastic Leukemia

Theodora Adhistry Dwiarie*, Nanan Nur'aeny**, Nelly Nainggolan*

*Oral Medicine Residency Program, Faculty of Dentistry, Universitas Padjadjaran,

**Department of Oral Medicine, Faculty of Dentistry, Universitas Padjadjaran

Online submission : 22 November 2021

Accept Submission : 12 January 2022

ABSTRACT

Background: Mucositis, a painful condition common in patients undergoing chemotherapy, can decrease the patient's quality of life. Treatment of mucositis by dentists supports the improvement of general health conditions and the patient's quality of life. **Objective:** This case report aims to discuss a case of a patient with mucositis after undergoing chemotherapy treatment for acute lymphoblastic leukemia. **Case:** 21 years old female diagnosed with acute lymphoblastic leukemia, referred to the oral medicine department from internal medicine, complained of pain in oral mucosa and lockjaw in the last three days after chemotherapy treatment with methotrexate. Internal medicine prescribes ceftriaxone intravenous (IV), dexamethasone IV, chlorhexidine gargle, and nystatin. Intraoral examination showed erosive lesions in the tongue, labial, and buccal mucosa and was diagnosed as oral mucositis grade 3 according to the World Health Organization scale. Her quality-of-life score is 46 according to The Functional Assessment of Cancer Therapy-General (FACT-G) and 58 according to Oropharyngeal Mucositis Quality of Life (OMQoL). **Case management:** She was treated with magic mouthwash containing diphenhydramine HCL, sucralfate, and aluminum hydroxide-magnesium hydroxide. Chlorhexidine and nystatin were advised to stop. The patient was instructed to keep her oral hygiene by gargling with sodium chloride and povidone-iodine after eating. Five days after the therapy, her condition improved (grade 1), and there was an increase in the FACT-G and OMQoL scores to 54 and 93. **Conclusion:** Mucositis can cause pain in the patient. A dentist can help diagnose and provide appropriate treatment to reduce the patient's complaints and improve the patient's quality of life.

Keywords: Acute Lymphoblastic Leukemia, Chemotherapy, Mucositis, Quality of Life

Correspondence: Theodora Adhistry Dwiarie, Oral Medicine Residency Program, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia. Email: Theodora14001@mail.unpad.ac.id



INTRODUCTION

Acute lymphoblastic leukemia (ALL), a leukocyte malignancy, has more than 6500 incidences every year in America.^{1,2} ALL is more common in children (80%) and diagnosed before the age of 20.² Chemotherapy is the most common therapy to stop the cancer cell from spreading.³ One of the adverse effects of chemotherapy is mucositis.^{4,5} Mucositis is found in 30 to 40% of chemotherapy patients.⁶ Chemotherapy agents, like 5-fluorouracil (5-FU), methotrexate, doxorubicin, paclitaxel, docetaxel, are more commonly causing mucositis.⁷

Chemotherapy drugs target the cells that have quick replication, including healthy cells in the oral mucosa.^{3,8} Reactive oxygen species (ROS) and inflammatory cytokines are released in the mucosa, activating NF- κ B, TNF, IL-6, and IL-1, thereby activating apoptosis.⁸ In addition, the loss of epithelial growth factor (keratinocyte growth factor) will interfere with normal epithelial growth.⁸ This will lead to mucosal layer damage, resulting in erosion or ulceration lesions.^{9,10} Mucositis is often found on the buccal mucosa, labial mucosa, lateral of the tongue, the floor of the mouth, and soft palate, with indistinct borders and sometimes covered by pseudomembranous.⁹ Mucositis appears three to seven days after the initiation of chemotherapy and persists for 7 to 14 days.^{3,11}

Mucositis can cause pain that makes the patients have difficulty in speaking, eating, drinking, and swallowing.^{9,11} This will reduce the patient's quality of life, affect the patient's nutritional status, and increase the risk of secondary infection.¹⁰ In severe mucositis, this condition can lead to the interruption of treatment.¹¹ Treatment of mucositis generally focuses on reducing symptoms and maintaining oral hygiene to prevent secondary infections.¹² In the treatment of oral mucositis, dentist play an important role and it will eventually leads to a better disease control.¹³ This case report discussed mucositis in ALL patients undergoing chemotherapy with methotrexate and the role of dentists in it.

CASE REPORT

A 21-year-old woman was referred to the oral medicine department from the internal medicine department for complaints of oral sores and evaluation of the use of 0.2% chlorhexidine gluconate and nystatin drugs. She was diagnosed with acute lymphoblastic leukemia six months ago and is currently undergoing the twelfth cycle of consolidation chemotherapy. The patient underwent chemotherapy with an OPAL regimen [oncovin (vincristine)], prednisolone, adriamycin (doxorubicin), and L-asparaginase, followed by chemotherapy with methotrexate, vincristine, dexamethasone, leucovorin, cyclophosphamide, daunorubicin, L-asparaginase, cytarabine, and Mercaptopurine (6-MP).



Figure 1. Mucositis at (a) upper mucosa labial, (b) lower mucosa labial, (c) right buccal mucosa, (d) left buccal mucosa, and (f) ventral tongue, with (e) limited mouth opening.

She complained of a burning sensation in her oral cavity that had appeared three days ago, and the patient had already received high-dose methotrexate therapy five days before the complaint appeared. She found it difficult to eat, drink, and open her mouth. The patient admitted that the complaint made it difficult for her to sleep but did not feel any bleeding in her oral cavity. The patient had repeated the same complaint for one month ago. When complaints arose, the patient was given 0.2% chlorhexidine gluconate mouthwash and nystatin, that used routinely four times a day. The patient had not used the two

drugs for several days because the complaints did not improve.

Intra-oral examination revealed an erosive lesion with a red base, shallow, diffuse border on the ventral tongue, buccal mucosa, and labial mucosa (Figure 1). The patient had difficulty opening her mouth. There was gingival covering half of teeth 38 and 48. Extraoral examination revealed dry and exfoliative lips. Based on the history and examination, the patient was diagnosed with mucositis grade 3 according to the World Health Organization (WHO), trismus, dental operculitis at 38 and 48, and exfoliative cheilitis. She was asked to fill out a questionnaire to assess the quality of life based on The Functional Assessment of Cancer Therapy - General (FACT-G) and Oropharyngeal Mucositis Quality of Life (OMQoL) with FACT-G scores 46 and OMQoL 58.

CASE MANAGEMENT

The drugs currently being used by the patient are chlorhexidine gluconate 0.2%, nystatin, intravenous (IV) ceftriaxone, IV dexamethasone, clinimix, fluoxetine, paracetamol, omeprazole, gabapentin, fluconazole, G-CSF, and KSR. The use of 0.2% chlorhexidine gluconate and nystatin is recommended to stop. Pharmacological management given to the patient is a mixture of diphenhydramine HCL, sucralfate, and aluminum hydroxide-magnesium hydroxide, that was used before meals. After meals, the patient was asked to gargle with sodium chloride (NaCl) and povidone-iodine 30 minutes after gargling with sodium chloride. The patient was also asked to apply a thin layer of Vaseline album to the lips. The non-pharmacological treatment given to the patient is to maintain the hygiene of the oral cavity by gargling after eating and trying to clean the teeth and oral cavity using gauze moistened with NaCl. If possible, the patient is recommended to brush teeth using a toothbrush with a small and soft bristles head with fluoride toothpaste.

Complaints in the patient's oral cavity began to decrease after three days of drugs administration, but she still felt sore on the buccal and labial mucosa. There were drug replacements by the internal medicine department, dexamethasone was stopped, and ceftriaxone and fluconazole were replaced with meropenem and micafungin. Erosion in the oral cavity was reduced. The patient routinely uses medication and cleans her oral cavity. However, the patient could not brush her teeth and could only clean the anterior of the oral cavity due to her limitations in opening her mouth.



Figure 2. Mucositis appears to be reduced after 5 days at (a) upper mucosa labial, (b) lower mucosa labial, (c) right buccal mucosa, (d) left buccal mucosa, and (f) ventral tongue, with hairy tongue at dorsal of the tongue(e)

The patient's condition has improved after five days. Painful complaints in the oral cavity have been significantly reduced. The patient felt more comfortable when eating and was able to open his mouth wider. Intra-oral examination showed the erosion has decreased, but on the dorsum of the tongue, a thin brownish plaque can be seen that can be scraped without leaving an erythematous area accompanied by hyperpapillation (Figure 2). There was a change in the patient's diagnosis to WHO scale 2 mucositis, dental operculitis 38 and 48, and hairy tongue. Patients are still advised to rinse their mouth using povidone-iodine and 0.9% NaCl up to a maximum of two weeks of use. In addition, the patient was asked to keep the oral hygiene and clean the tongue using gauze moistened with NaCl.



Figure 3. Improvement after one month (a) upper mucosa labial, (b) lower mucosa labial, (c) right buccal mucosa, (d) left buccal mucosa, (e) dorsal of the tongue, and (f) ventral tongue.

In the following month, the patient did not experience any pain in his oral cavity. There were no more erosions, and the patient's dorsal tongue condition had improved (Figure 3). She was asked to answer the FACT-G and OMQoL again to see if there was a change in her quality of life. The results showed an increase in the FACT-G value to 54 and the OMQoL value to 93. This shows an increase in the quality of life of patients before and after treatment. Improving the quality of life of patients indicates the success of treatment.

DISCUSSION

Mucositis is a side effect of chemotherapy, and patients with hematological malignancies are more likely to experience complications in the oral cavity than other types of cancer.¹⁴ Leukemic patients tend to experience mucositis during the consolidation phase of chemotherapy.¹⁰ Women are also more prone to mucositis than men.¹⁴ Several chemotherapy drugs can cause damage to the oral mucosa, including methotrexate, vincristine, and daunorubicin.¹⁵ Vincristine has been associated with ulceration, whereas methotrexate is a chemotherapeutic drug secreted in saliva, and it will increase its toxicity in the oral cavity.^{4,14} This condition is similar to our patient's condition, a female patient diagnosed with acute lymphoblastic leukemia with mucositis since consolidation therapy with

vincristine and methotrexate. Mucositis in our patient was found on the ventral tongue, buccal and labial mucosa, and this is still following the study, which stated that the prevalence of mucositis in acute leukemia was on the ventral tongue, followed by the buccal mucosa.¹⁶

The patient had been using 0.2% chlorhexidine gluconate and nystatin for approximately four weeks. Using both at the same time can interfere with the effectiveness of each drug.¹⁷ We recommended stopping chlorhexidine gluconate, although it can be used to maintain oral hygiene in patients with mucositis if brushing teeth is challenging to do.¹² We recommend it because chlorhexidine gluconate is only recommended for short-term use and is considered ineffective in reducing the severity of mucositis.^{4,18} In addition, using chlorhexidine for four weeks or more can stain the teeth and increase calculus formation if used for more than six months.¹⁹ Nystatin was also recommended to stop because there was no candida infection found in the patient's oral cavity, and the patient was already receiving an antifungal (fluconazole) IV. The use of nystatin also could not reduce the severity of mucositis.⁸

We can give patients with mucositis a magic mouthwash that may contain anesthetics, antacids, diphenhydramine, and steroids, while in this case, we gave the patients a magic mouthwash containing a mixture of diphenhydramine HCL, sucralfate, and aluminum hydroxide-magnesium hydroxide.⁶ Sucralfate was given to help reduce the severity of mucositis.⁴ NaCl and povidone-iodine for gargling after eating were also instructed to the patient. NaCl is considered more effective than chlorhexidine and has a microbicidal effect due to its high osmolality.^{8,9} Thirty minutes after gargling with NaCl, the patient was asked to gargle with povidone-iodine as an antiseptic to reduce the severity of mucositis.⁴

Maintaining oral hygiene is essential in patients with mucositis. There is a relationship between maintaining oral hygiene and the severity of mucositis.¹² Gently brushing, flossing, and using mouthwash can decrease the duration

and severity of mucositis.⁴ Using a toothbrush with soft bristles at least twice a day is also recommended.²⁰

Quality of life can be assessed physically, functionally, emotionally, and socially.¹¹ Oral health is important, not only physically but also enabling a person to interact socially and provide a sense of well-being.³ Mucositis can reduce the patient's quality of life due to the pain suffered by the patient.²¹ We can assess patient quality of life with FACT-G and OMQoL. FACT-G is a multidimensional instrument designed to evaluate the quality of life and pain severity in patients with chronic diseases such as cancer.²² FACT-G itself is often used to assess patients' quality of life.²³ OMQoL instrument can assess symptomatology, nutrition, social function, and symptomatology for swallowing in patients with mucositis due to cancer therapy.²² The patient was asked to answer FACT-G and OMQoL before being treated by a dentist, and the results showed FACT-G 46 and OMQoL 58. The FACT-G results were lower than the Jordanian study, with an average result of about 62.²⁴ After one month, the patient was asked to answer both of the instruments again. There was an increase in the FACT-G value to 54 and the OMQoL value to 93, which showed an improvement in the patient's quality of life. Improvement of the patient's quality of life can occur with treatment in the oral cavity.²⁵ The quality of life related to oral health in patients with mucositis is also lower than in patients without mucositis.²⁶

Dentists can play a role in the multidisciplinary care of haemato-oncology patients and play an essential role in the success of cancer treatment.²⁷ The treatment from dentists on patients before, during, and after chemotherapy is very important.⁹ Prior to chemotherapy, a thorough examination of oral health should be performed, and all invasive procedures, such as tooth extraction should be performed at least two weeks before chemotherapy.⁹ Dentists should encourage patients to keep their oral hygiene by brushing their teeth using a toothbrush with a small head

and soft bristles, using fluoride-containing toothpaste, recommending gargling with mouthwash, not after brushing teeth because it can reduce the benefits of toothpaste, and using dental floss.²⁸

CONCLUSION

Dentists have a role in treating cancer patients who will undergo chemotherapy, where one of the side effects of chemotherapy is mucositis. Dentists can help diagnose mucositis, provide appropriate treatment, and give the patient's oral hygiene instructions according to the patient's condition to maintain the cleanliness of their oral cavity better. Maintaining oral hygiene will help the patient prevent secondary infections that worsen their mucositis. Mucositis can cause a burning sensation in the patient's oral cavity, making it difficult to eat and decreasing the quality of life in patients. Treatment of mucositis by dentists can improve the patient's quality of life.

ACKNOWLEDGMENT

The authors would like to thank the patients who consent to be part of this case report.

REFERENCE

1. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J* 2017;7(6):e577.
2. Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. *Mayo Clin Proc* 2016;91(11):1645–66.
3. Pavithran S, Sreeleksmi M V., Sreelekshmi R. Oral-health related quality of life of patients on chemotherapy. *Biomed Pharmacol J* 2020;13(1):107–18.
4. Chaveli-López B, Bagán-Sebastián J V. Treatment of oral mucositis due to chemotherapy. *J Clin Exp Dent* 2016;8(2):e201–9.
5. Kirk LM, Brown SD, Luu Y, Ogle A, Huffman J, Lewis PO. Beyond-use dating of lidocaine alone and in two “magic mouthwash” preparations. *Am J Heal Pharm* 2017;74(9):e202–10.



6. Pulito C, Cristaudo A, Porta C La, Zapperi S, Blandino G, Morrone A, et al. Oral mucositis: The hidden side of cancer therapy. *J Exp Clin Cancer Res* 2020;39(1):1–15.
7. Kwon Y. Mechanism-based management for mucositis: Option for treating side effects without compromising the efficacy of cancer therapy. *Onco Targets Ther* 2016;9:2007–16.
8. Cidon EU. Chemotherapy induced oral mucositis: Prevention is possible. *Chinese Clin Oncol* 2018;7(1).
9. Pouloupoulos A, Papadopoulos P, Andreadis D. Chemotherapy: oral side effects and dental interventions. A review of the literature. *Stomatol Dis Sci* 2017;1(2):35–49.
10. Curra M, Soares Junior LAV, Martins MD, Santos PS da S. Chemotherapy protocols and incidence of oral mucositis. An integrative review. *Einstein (Sao Paulo)* 2018;16(1):eRW4007.
11. Al-rudayni AHM, Gopinath D, Maharajan MK, Menon RK. Impact of oral mucositis on quality of life in patients undergoing oncological treatment: a systematic review. 2020;9(4):3126–34.
12. Hurrell L, Burgoyne L, Logan R, Revesz T, Gue S. The Management of Pediatric Oncology Inpatients with Oral Mucositis. *J Pediatr Hematol Oncol* 2019;41(8):E510–6.
13. Ahmad P, Akhtar U, Chaudhry A, Rashid U, Saif S, Asif JA. Treatment and prevention of oral mucositis: A literature review. *Eur J Gen Dent* 2019;8(2):23–8.
14. Damascena LCL, de Lucena NNN, Ribeiro ILA, Pereira TL, Lima-Filho LMA, Valença AMG. Severe oral mucositis in pediatric cancer patients: Survival analysis and predictive factors. *Int J Environ Res Public Health* 2020;17(4).
15. European Oral Care in Cancer Group Oral Care Guidance and Support First Edition.
16. Lee YH, Hong J, Kim I, Choi Y, Park HK. Prospective evaluation of clinical symptoms of chemotherapy-induced oral mucositis in adult patients with acute leukemia: A preliminary study. *Clin Exp Dent Res* 2020;6(1):90–9.
17. Scheibler E, da Silva RM, Leite CE, Campos MM, Figueiredo MA, Salum FG, et al. Stability and efficacy of combined nystatin and chlorhexidine against suspensions and biofilms of *Candida albicans*. *Arch Oral Biol* 2018;89(February):70–6.
18. Haydari M, Bardakci AG, Koldslund OC, Aass AM, Sandvik L, Preus HR. Comparing the effect of 0.06% -, 0.12% and 0.2% Chlorhexidine on plaque, bleeding and side effects in an experimental gingivitis model: A parallel group, double masked randomized clinical trial. *BMC Oral Health* 2017;17(1):1–8.
19. James P, Worthington H V., Parnell C, Harding M, Lamont T, Cheung A, et al. Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. *Cochrane Database Syst Rev* 2017;2017(3).
20. Brown TJ, Gupta A. Management of cancer therapy-associated oral mucositis. *J Oncol Pract* 2020;16(3):103–9.
21. Kusiak A, Alicjajereczek-Fossa B, Cichońska D, Alterio D. Oncological-therapy related oral mucositis as an interdisciplinary problem—literature review. *Int J Environ Res Public Health* 2020;17(7).
22. Gutiérrez-Vargas R, Díaz-García ML, Villasís-Keever MÁ, Portilla-Robertson J, Zapata-Tárres M. Instruments to measure the quality of life in patients with oral mucositis undergoing oncological treatment: a systematic review of the literature. *Boletín Médico Del Hosp Infant México (English Ed)* 2016;73(6):457–66.
23. Berger K, Schopohl D, Bollig A, Strobach D, Rieger C, Rublee D, et al. Burden of Oral Mucositis: A Systematic Review and Implications for Future Research. *Oncol Res Treat* 2018;41(6):399–405.
24. Al Barmawi M, Al Hadid L, Alqudah H, Al Hadid W, Shamoun S. Measuring the Quality of Life among Head-and/or-Neck Cancer Patients with Oral Mucositis Using the Functional Assessment of Cancer Therapy-General in Jordan. *Asia-Pacific J Oncol Nurs* 2018;5(3):320–6.
25. Nunez-Aguilar J, Oliveros-Lopez LG, Fernandez-Olavarria A, Torres-Lagares D, Serrera-Figallo MA, Gutierrez-Corrales A, et al. Influence of dental treatment in place on quality of life in oral cancer patients undergoing chemoradiotherapy. *Med Oral Patol Oral Cir Bucal* 2018;23(4):e498–505.
26. Jung Y-S, Park E-Y, Sohn H-O. Oral Health Status and Oral Health-related Quality of Life According to Presence or Absence of Mucositis in Head and Neck Cancer Patients. *J Cancer Prev* 2019;24(1):43–7.
27. Zimmermann C, Meurer MI, Grando LJ, Gonzaga Del Moral JÂ, Da Silva Rath IB,



Schaefer Tavares S. Dental Treatment in Patients with Leukemia. J Oncol 2015;2015:1–14.

28. Kochhar AS, Bhasin R, Kochhar GK, Dadlani H. Provision of continuous dental care for oral oncology patients during & after COVID-19 pandemic. Oral Oncol 2020;106(January).

Parent's Oral and Dental Health Behavior as Predictors of Children's Oral and Dental Health Status

Dayu Annessi Viana*, Sri Pandu Utami**

*Undergraduate Faculty of Dentistry, Baiturrahmah University

**Department of Pediatric Dentistry, Faculty of Dentistry, Baiturrahmah University

Online submission : 05 November 2021

Accept Submission : 29 December 2021

ABSTRACT

Background: Knowledge Parents are considered to have the to teach their children basic things about maintaining a healthy body. The implantation of oral health behavior should start at an early age and start from the family environment. Childhood is the beginning of behavior formation, therefore parents are expected to be able to educate their children to behave properly to maintain healthy teeth and mouth. **Objective:** The purpose of this study was to determine the oral health behavior of parents to determine the oral health status of children in the pedodontics department of the Baiturrahmah University Dental Hospital. **Methods:** This research type is quantitative with analytic survey method with cross sectional research design. The population was pediatric patients who took care at the Paedodonti Department of the Baiturrahmah Hospital in July 2020. **Result:** The results showed that the educational status, tooth brushing behavior, eating sweet eating behavior, the habit of bringing children to the dentist and complaints in the oral cavity of the parents gave a picture. Predictions for their children about oral health. **Conclusion:** Parents' behavior will have an effect on their children because indirectly the habits of parents will be imitated and made an example for their children.

Keywords: Parental behavior, Predictors, Children's oral health.

Correspondence: Sri Pandu Utami, Department of Pediatric Dentistry, Faculty of Dentistry, Baiturrahmah University, Jl. Raya By Pass KM 14, Kuranji, Padang City, West Sumatra. Email: panduutamidrq@yahoo.co.id

INTRODUCTION

Dental health is an integral part of overall health which can affect the quality of life. Poor oral hygiene can continue to be a risk factor for the emergence of various diseases in the oral cavity such as caries and

periodontal tissue disease. The Household Health Survey Report (SKRT) of the Ministry of Health of the Republic of Indonesia¹ states, of the ten groups of diseases that the public complains about, dental and oral diseases rank first with a prevalence rate of 61% of the population.¹

Parents are considered to have the knowledge to teach their children basic things about maintaining a healthy body. The cultivation of oral health behavior should start at an early age and start in the family environment. Childhood is the beginning of behavior formation, therefore parents are expected to be able to educate their children to behave properly to maintain healthy teeth and mouth.

Parents' knowledge can be obtained naturally or in a planned manner, namely through the educational process. Parents with low knowledge of dental health are a predisposing factor for behavior that does not support children's dental health. Knowledge, attitudes and behavior of mothers towards dental health will determine the dental health status of children in the future. Knowledge is not enough, it needs to be followed by caring and acting. Starting to grow teeth is an important process of growing a child.¹

It is widely recognized that the behavior of parents, and especially mothers, affects the health of their children⁸. Also regarding oral health the role of parents is very important, because they are the main caregivers of oral health for their children during the first three years of life, even in preschool, parents are still the main supplier of children's oral health². Several factors such as mother's education, occupation, age, current knowledge, attitudes,

and behavior can indirectly provide insights to improve their health habits and the health of their children³. The relationship between maternal dental health and dental caries in their children can be explained by the influence of wrong diet and hygiene habits in infants as well as by infection of the child's mouth by mother's bacteria⁴⁹. Therefore, brushing habits in mothers, dietary habits, and dietary choices directly related to the habits of their children.⁸

Rogers (1974) states that before a person adopts a new behavior, a process occurs, namely: ¹¹

1. Awareness (awareness): a person is aware of the object stimulus
2. Interest: someone begins to be attracted to the object (stimulus)
3. Evaluation: respondent's attitude is better. Respondents began to consider whether or not the stimulus was good for themselves.
4. Trial: someone starts trying the new behavior
5. Adoption: someone has new behavior in accordance with the knowledge, awareness, and attitude towards the object (stimulus).

According to Holdsan, behavior change is essentially the same as the learning process. This behavior change describes the individual learning process.

Mother's knowledge about dental health will greatly determine the dental health status of her child in the future. A mother plays an important role in a family, both as a wife and as a mother of her children. The first figure a child knows when he is born is his mother. Mother's behavior and habits can be imitated by children, but knowledge alone is not enough to be followed by the right attitudes and actions.

METHODS

This research type is quantitative with analytic survey method with cross sectional research design. The population was pediatric patients who took care at the Paedodonti



Department of the Baiturrahmah Hospital in July 2020. Sampling in this study used the total sampling method, which means that all members of the population were sampled.

Materials and tools used were questionnaire sheets, stationery and computers with statistical software.

Table 1. Operational Definition

No.	Variable	Operational definition	Measuring instrument	Measurement results	Scale
1.	Parental education	Parents' last education level	Questionnaire	1. SD 2. Junior High 3. High school 4. Bachelor	Ordinal
2.	Quantity brushing teeth	The behavior of parents in brushing their teeth every day.	Questionnaire	1. One time 2. Twice 3. > 2 times	Ordinal
3.	Eat sugary foods	Parents' behavior in consuming sweet foods	Questionnaire	1. Never 2. Sometimes 3. Always	Ordinal
4.	Dentist visit	Parents routinely come to the dentist to maintain healthy teeth and mouth	Questionnaire	1. Never 2. Once in 6 months 3. Once 1 year	Ordinal
5.	Complaints cavity of mouth	Oral health conditions of the parents	Questionnaire	1. There is 2. There is no	

Research variable

1. The dependent variable: The oral health behavior of the parents
2. Independent variable: dental and oral health status of children.

Data analysis

The data were analyzed using the chi square test to see the relationship between the level of patient satisfaction and the quality of service on the SPSS computer program with an error rate of 5% (0.05) and a confidence level of 95% (0.95).

RESULTS**Frequency Distribution of Father's Educational Characteristics****Table 1.** Frequency Distribution of Father's Educational Character as Predictors of Children's Oral and Dental Health Status in the Pedodonti Department of the Baiturrahmah University Dental Hospital

Father's Education	Frequency	Percentase
SD	3	4.0%
Junior High	6	8.0%
High school	17	22.7%
Bachelor	49	65.3%
Total	75	100.0%

Based on table 1 of the results of the research of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, the results of the father's education at the elementary level were 3 people (4.0%), junior high school level were 6 people (8.0%), high school level were 17 people (22.7%) and undergraduate level as many as 49 people (65.3%).

Frequency Distribution of Mother Education Characteristics**Table 2.** Frequency Distribution of Mother's Educational Character as Predictors of Children's Oral and Dental Health Status in the Pedodonti Department of the Baiturrahmah University Dental Hospital.

Father's Education	Frequency	Percentase
SD	6	8.0%
Junior High	7	9.3%
High school	26	34.7%
Bachelor	36	48.0%
Total	75	100.0%

Based on table 2 of the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah

University Hospital, the results of maternal education at the elementary level were 6 people (8.0%), junior high school level were 7 people (9.3%), high school level were 26 people (48.0%) and undergraduate level as many as 36 people (48.0%).

Frequency Distribution of Parents' Tooth Brushing Quantity**Table 3.** Frequency Distribution of Parents' Teeth Brushing Quantity as a Predictor of Children's Dental and Oral Health Status in the Pedodonti Department of the Dental Hospital of Baiturrahmah University

Brushing Teeth	Frequency	Percentase
Twice a day	49	65.3%
More than twice a day	20	26.7%
Once a day	6	8.0%
Total	75	100.0%

Based on table 3 of the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, it was found that the quantity of parents brushing their teeth twice a day was 49 people (65.3%), more than twice a day as many as 20 people (26.7%) and those who brushed their teeth once a day were 6 people (8.0%).

Frequency Distribution of Parents' Behavior Consuming Sweet Foods**Table 4.** Frequency Distribution of Parents Consuming Sweet Foods as a Predictor of Children's Oral and Dental Health Status in the Pedodonti Department of the Baiturrahmah University Dental Hospital

Consume Sweet Foods	Frequency	Percentase
Sometimes	55	73.3%
Always	10	13.3%
Never	10	13.3%
Total	75	100.0%

Based on table 4 of the results of the research of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, it is found that 55 people sometimes consume sweet foods (73.3%), always consume 10 people (13.3%).) and those who never consumed sweet foods were 10 people (13.3%).

Frequency Distribution of Parents' Behavior Visiting a Dentist

Table 5. Frequency Distribution of Parents Visiting a Dentist as a Predictor of Children's Oral and Dental Health Status in the Paedodonti Department of the Baiturrahmah University Dental Hospital

To the Dentist	Frequency	Percentase
1x 6 months	27	36.0%
1x a year	42	56.0%
not pern	6	8.0%
Total	75	100.0%

Based on table 5 of the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, the results of parents who routinely visit the dentist once in 6 months are 27 people (36.0%), 42 people routinely visit the dentist once a year. (56.0%), who never visited a dentist were 6 people (8.0%).

Frequency Distribution of Parents' Oral Cavity Complaints

Table 6. Distribution of Complaints Frequency of the Oral Cavity as a Predictor of Children's Oral and Dental Health Status in the Paedodonti Department of the Baiturrahmah University Hospital.

Complaints of the Oral Cavity	Frequency	Percentase
There is	29	38.7
There is no	46	61.3
Total	75	100.0%

Based on table 6 of the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, the results of the oral complaints were

29 people (38.7%), 46 people (61.3%) had no oral complaints.

DISCUSSION

Based on research from 75 respondents of children's parents in the Paedodonti Department of the Baiturrahmah University Dental Hospital, the results obtained from research on the behavior of parents' oral health as a predictor of children's oral health status, where the father's education is the highest at undergraduate level, namely 49 people and education. the highest level of mothers is the level of 36 people.

In line with the research conducted by Dwi Eni Purwati (2017) on the Effect of Parents 'Education and Occupation on the Number of Dental Caries in Primary School Children, it is stated that there is a significant effect on the level of parents' latest education on the number of dental caries in students. The results of the study showed that most of the respondents' parents had the last secondary level of education (SMA), namely 45 out of 60 people (75%), while the dental caries condition of the students indicated that most of the respondents had the criteria for low caries count (1,2-2,6) namely as many as 20 out of 60 students (33.3%).¹⁸

The alignment between the majority of respondents and parents with high school education and the criteria for a low number of caries is in accordance with the opinion (Christiano and Rama, 2015) which states that the higher the level of education, the easier it is to absorb new information and innovations including dental health. (Afati, et al., 2017) in their research also stated that when someone is at a higher level of knowledge, attention to dental health will be higher, and vice versa, when someone has less knowledge, dental attention and care are also low.¹⁸

Based on the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah University Dental Hospital, the highest number

of parents brushing their teeth was 49 people (65.3%).

Research conducted by Adhya Rizaldy, et al. Regarding the behavior of parents towards maintaining children's dental health at Mekarjaya State Elementary School, it was revealed that 74.55% of respondents' knowledge about the right time to brush their teeth was in the sufficient category. This result can occur because information about the time to brush your teeth is easy to obtain either through print or electronic media. The right time to brush your teeth is after breakfast and before bed, brushing your teeth before going to bed aims to reduce plaque, when at night the amount of saliva in the mouth decreases this can cause an increase in the process of cavity formation in the teeth. 14 Many respondents do not know (83.64%) about the use of good toothpaste.

This can occur due to the lack of information regarding the maintenance of dental health, causing many respondents to not know about the use of toothpaste. The use of a good toothpaste is the size of a pea seed, it is important in children because using too much toothpaste can increase the risk of fluorosis. The use of toothpaste in children that is not supervised by parents, especially for children under 7 years of age can cause health problems, because toothpaste contains detergent or sodium lauryl sulfate (SLS) which can produce foam or froth. The amount of foam or froth when brushing your teeth can cause canker sores. Most of the respondents (70.91%) knew that toothpaste that was good for teeth contained fluorine. 19

Based on the results of the research of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah Hospital, it was found that the parents who consumed the most sweet foods with the occasional category were as many as 55 people (73.3%).

In a study conducted by Ernawati revealed that the results of statistical tests showed that there was a relationship between sweet food consumption behavior and the

incidence of dental caries with $p\text{-value} = 0.007 \leq \alpha (0.05)$ and the correlation coefficient

(r) was 7.284 which means that it has a strong relationship. between the behavior of consuming sweet foods and the incidence of dental caries. 19

Based on the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah Hospital, it was found that 42 people (56.0%) routinely visit the dentist once a year.

This study is in line with the research of Nuri Yuniar, et al. (2019) regarding Parents' Perspectives on Early Childhood Dental Health which states in the results of their research that according to the American Dental Association and the American Academy of Pediatrics, every child should be taken to a dentist before the age of one year or at the time of eruption of the first primary tooth (Abbas et al. al., 2017). Oral disease in children is higher among poor and disadvantaged population groups (Mahmoud, Kowash, Hussein, Hassan, & Al Halabi, 2017). A number of factors associated with children, mothers or dentists can cause poor collaboration during dental treatment (Fazli & Reza, 2015). Determining children's oral health is heavily influenced by their mother; as the primary caregiver. A partial lack of knowledge combined with behaviors and beliefs that lead to poor feeding practices, poor oral hygiene maintenance, and failure to seek professional dental care appears to put certain children at higher risk of developing caries than other children with more care (Mahmoud et al., 2017).

23,24

Based on the results of the study of 75 respondents of parents of children in the Paedodonti Department of the Baiturrahmah Hospital, the results of the oral complaints were 29 people (38.7%), 46 people (61.3%) had no oral complaints. This means that many parents of children in the Pedodonti Department of the Baiturrahmah University Dental Hospital maintain their oral health so that this behavior becomes a role model for their children to always maintain oral health.

CONCLUSION

Based on the results of research on Parents' Oral and Dental Health Behavior as a Predictor of Children's Dental and Oral Health Status in the Paedodonti Department of the Baiturrahmah Hospital, it is concluded that educational status, tooth brushing behavior, sweet eating behavior, habit of bringing children to the dentist and complaints of the oral cavity in parents provide a predictive picture for their children about oral health.

Parents will always be role models for their children. Parents' education, habits, and behavior will have an effect on their children because indirectly the habits of parents will be imitated and used as an example for their children, so that ultimately people's behavior and attitudes can portray predictions of oral health for their children.

ACKNOWLEDGEMENT

Thank you to the Faculty of Dentistry, Baiturrahmah University, to the supervisory lecturers and all those who have helped to realize this task.

REFERENCE

- Adhya R., et al. Parents' Behavior Toward Maintenance of Children's Oral and Dental Health at Mekarjaya Public Elementary School. *J Ked Gi UNPAD*. 2017; 29(2):131-5
- Riyanti E. Introduction and Early Child Dental Health Care. June 2020.
- Sondang P., Hamada T. Towards Healthy Teeth and Mouth. Medan: USU Press. 2008; 4- 15.
- Fankari. The Effect of Counseling with Stimulation and Demonstration Methods on Behavior Changes in Maintaining Dental and Oral Health for Primary School Children. *DIV Scientific Papers. UGM Nurse Educator*. 2004:2
- Arikunto. Research Procedures A Practice Approach Revised Edition VI. Jakarta: PT Rineka Cipta. 2006.
- Azwar. Human Attitude, Theory and Its Measurement 2nd edition, fourth edition. Yogyakarta: Student Library. 2006.
- Berman. Child Health Science Edition 15. Jakarta: EGC. 1999.
- Candrawati. The Relationship Between Mother's Knowledge About Dental Health and the Incidence of Caries in Children Grade 1 - 3 SD Negeri 3 Sumber, Klaten Regency, Central Java *Thesis*. 2009. Available from: <http://stikes.wordpress.com>
- Dahlan M. S. Statistics for Medicine and Health. Jakarta: Salemba Medik. 2009.
- Made A. L. S., et al. Knowledge, Attitudes, and Parents' Behavior on Dental and Oral Health in Kindergarten Children in Yogyakarta and Banten Province in 2014. *Media Litbangkes*. 2014; 26(2): 119-26
- Gultom M. Knowledge, attitudes, and actions of housewives towards maintaining oral health of their toddlers in Balige District, Toba Samosir Regency, North Sumatra in 2009. [Research Report]. Medan: FKG-USU. 2010.
- Susanne B. R, Karin S., Lars M., and Gurilla K. Parental perspectives on preterm children's oral health behavior and experience of dental care during preschool and early school years, *International Journal of Pediatric Dentistry*. 2009; 19 (4): 243-50.
- Vahirarojpisan T., Shinada K., Kawaguchi Y., Laungwechkan P., Somkote T., Detsomboonrat P. Early childhood caries in children aged 6-19 Months. *Community Dent Oral Epidemiology*. 2004; 32 (2):133-42.
- Schroth R., Dahl P., Haque M., and Kliever E. Early childhood caries among hutterite preschool children in Manitoba, Canada. *Rural Remote Health*. 2010; 10 (4): 1535.
- Purwati D. E. The effect of education level and parents' occupation on the number of dental caries in elementary school students. *Journal of Dental Health*. 2017; 4(2)
- Ernawati et al. The Relationship Between Sweet Food Consumption Behavior And Tooth Brushing Behavior With The Incidence Of Dental Caries In Children Kindergarten Pertiwi 37 Gunung Pati. Fikkas. *Journal of Nursing*. 2011; 4 (2): 183 - 93
- Rizaldy A., et al. Parents' behavior towards maintaining children's dental health at Mekarjaya State Elementary School. *J Ked Gi Unpad*. 2017; 29 (2): 131- 37.
- Eternal N. Y. Parents' Perspectives on Early Childhood Dental Health. *Obsession Journal*. 2019; 3(1):161- 69



-
19. Mahmoud N., Kowash M., Hussein I., Hassan A., & Al Halabi M. Oral health knowledge, attitude, and practices of Sharjah Emirates. Journal of International Society of Preventive and Community Dentistry. 2017.

Prevalence of Patients with Oral Cavity Tumours at Hospital Abdoel Wahab Sjahranie Samarinda 2016-2020

Rienda 'Afifah Khairunnisa*, Sinar Yani**, Cristiani Nadya Pramasari***

*Undergraduate Medicine Study Program, Faculty of Medicine, Mulawarman University

**Oral Biology Laboratory, Faculty of Medicine, Mulawarman University

***Dentistry Profession Laboratory, Faculty of Medicine, Mulawarman University

Online submission : 26 January 2022

Accept Submission : 15 February 2022

ABSTRACT

Background: Tumour is an uncontrolled swelling of tissue. Tumour caused by uncontrolled proliferation abnormal tissue and cell. Based on the nature of the tumour, there are two types of tumours, that is benign tumour and malignant tumour. The malignant tumour can cause death while benign tumour only aggravate the surrounding tissue. The high incidence of tumors in various countries, including Indonesia, rarely finds research on the prevalence of oral tumors, especially in East Kalimantan, especially the capital city of Samarinda.

Objective: This research is to find out the incidence of oral cavity tumour at RSUD Abdoel Wahab Sjahranie periode 2016-2020. **Methods:** Used was a descriptive observational method retrieving secondary data in the form of medical records. The sampling method used in this research was the purposive sampling method.

Results: the profile of patients with oral cavity tumour at Regional General Hospital Abdoel Wahab Sjahranie 2016-2020 are as follows the age group with the highest incidence is 46-55 years: 32 patients (24,8%), The highest incidence by gender were women: 78 patients (60.5%) and man: 51 patients (39,5%). Most of the tumour were found in the mandible: 65 patients (50,4%). **Conclusion:** The prevalence of oral cavity tumour is higher in female patients than male patients.

Keywords: Oral Cavity, Benign Tumour, Malignant tumour

Correspondence: Sinar Yani, Oral Biology Laboratory, Faculty of Medicine, Mulawarman University, Jl. AW. Syahrani GG. 45 RT. 36 blok C no. 26 Samarinda, East Borneo; Phone : 081254537000; E-mail: sinaryani@yahoo.com

INTRODUCTION

Dental and oral health can be classified as good if it affects the quality of each individual who has a large enough role, such as preparing food substances as nutrients in the digestive tract, as well as aesthetic and speech functions.¹ However, there are still some people who do not care about maintaining oral health so it causes various types of diseases or systemic disorders and manifests in the body because the oral cavity is very vulnerable to trauma from exposure to intrinsic or extrinsic factors.² If people do not realize and detect this, it will become one of the problems of malignancy of dental and oral diseases, namely tumors in the oral cavity.¹

The tumor is abnormal tissue that grows continuously in excess and cannot be coordinated from normal tissue. Based on the nature of the tumor is divided into two, namely benign tumors and malignant tumors.³ Malignant tumors have the highest prevalence and can occur about 2% of all cases of malignancy in various countries and continue to increase with age up to over 50 years.^{3,4}

In a study in Nigeria, the prevalence of benign tumors in the oral cavity was around 36.3% with the most dominant cases in the mandibular region⁵ and occurring in both men and women.⁶ Patients with tumors are greater in men than women because oral cavity tumors have multifactorial causes, but the factors suspected of being the main cause are the use of alcohol and cigarettes dominated by men.⁷ Then, other factors occur due to intrinsic factors which are usually associated with heredity and growth factors, while extrinsic factors are about 50% in Asia, such as tobacco cigarettes and chewing betel nut^{8,9}.

The growth of benign tumors is different from malignant tumors which can cause death. The malignancy of oral cancer in America can cause one human to die within an hour because the cancer is easy to spread and the treatment is delayed due to a lack of public awareness of early cancer screening^{3,7}. Research on benign tumors rarely causes death, because of slow

growth and some are fast. However, indirectly some cases of benign tumors can interfere with the vital structures of the body around it.¹⁰

Benign tumors and malignant tumors are very important in determining the right type of treatment or therapy, one of which is to determine the malignancy of tumor cells through the degree of differentiation determined from microscopic assessment of tumor cell morphology that resembles normal cells.⁷ Based on this, researchers are interested in conducting research to determine the profile and distribution of patients with oral tumors at Abdoel Wahab Sjahranie Hospital Samarinda from 2016-2020 based on tumor classification, age, gender, tumor location, and the degree of tumor differentiation.

MATERIALS AND METHODS

This research method is descriptive observational research using secondary data from medical records. This research was conducted at the Medical Record Installation and Anatomical Pathology Laboratory of the Abdoel Wahab Sjahranie Hospital, Samarinda. The population of this study were all patients with a diagnosis of oral cavity tumors based on the results of Anatomical Pathology at the Abdoel Wahab Sjahranie Hospital in 2016-2020.

The sample in this study were patients with a diagnosis of oral cavity tumors based on the results of Anatomical Pathology at the Abdoel Wahab Sjahranie Hospital in 2016-2020 who met the inclusion criteria that had been set. The sampling technique in this study used a purposive sampling technique. The inclusion criteria in the study were all patients who were registered as inpatients, diagnosed patients who had undergone examinations in the histopathology laboratory, and patients who had medical record data at the Medical Record and Pathology Installation of RSUD Abdoel Wahab Sjahranie between 2016- 2020. The exclusion criteria were patients with incomplete medical record.

RESULTS

This research was carried out through medical record data and the conclusions of Anatomical Pathology at the Abdoel Wahab Sjahranie Hospital in 2016-2020 getting 129 samples with the following results:

From these data, it was found that patients with the highest oral cavity tumor were in the age category 46-55 years with 32 patients (24.8%), while the lowest was at the age of 12-16 years with 7 patients (5.4%). Both benign tumors and malignant tumors occupy the most age category is 46-65 years. Based on the classification of tumors in the 12-16 year age group, 7 patients had benign tumors and there were no patients with malignant tumors. The age group of 17-25 years consisted of 6 patients with benign tumors and 4 patients with malignant tumors. The age group of 26-35 years consisted of 10 patients with benign tumors and 5 patients with malignant tumors. The age group of 36-45 years consisted of 14 patients with benign tumors and 9 patients with malignant tumors. The 46-55 year age group consisted of 17 patients with benign tumors and 15 patients with malignant tumors. The 56-65 year age group consisted of 9 patients with benign tumors and 22 patients with malignant tumors. Age group >65 years as many as 1 patient with benign tumor and 10 patients with a malignant tumor.

Table 1. Characteristics of Patients with Oral Cavity Tumors by Age

Age	Benign Tumor	Malignant Tumor	Total	%
12-16	7	0	7	5,4
17-25	6	4	10	7,8
26-35	10	5	15	11,6
36-45	14	9	23	17,8
46-55	17	15	32	24,8
56-65	9	22	31	24
>65	1	10	11	8,5
Total	64	65	129	100

Table 2. Characteristics of Patients with Oral Cavity Tumors by Gender

Gender	Benign Tumor	Malignant Tumor	Total
Male	20	31	51
Female	44	34	78
Total	64	65	129

From these data, it was found that patients with the highest oral cavity tumors were women, 78 patients of whom 44 were benign oral tumors and 34 patients were oral malignant tumors, while 51 patients were male, of which 20 patients were benign oral tumors. and 31 patients were malignant tumors of the oral cavity.

Table 3. Characteristics of Patients with Oral Cavity Tumors Based on Location

Location Tumor	Benign	Malignant	Total	%
Maxilla	19	9	28	24,8
Mandible	29	36	65	50,4
Other locations (gingiva & labia)	8	12	20	15,5
No location information	8	4	12	9,3
Total	64	65	129	100

In table 3, it is found that oral cavity tumors with the highest location were the mandible as many as 65 patients (50.4%), maxilla as many as 28 patients (24.8%), other locations such as gingiva and labia as many as 20 patients (15.5%) and there is no location information in the medical records of 12 patients (9.3%).

DISCUSSION

Characteristics of Patients with Oral Cavity Tumors Based on Age

Table 1 shows that the age range of patients with oral cavity tumors is early teens 12-16 years to seniors >65 years. Previous research also found that the age range of patients with oral cavity tumors was >80 years. Then the age with the highest incidence in patients with oral cavity

tumors was in the early elderly group (46-55 years) as many as 32 patients (24.8%) and the late elderly (56-65 years) as many as 31 patients (24.0%). oral cavity tumors. Meanwhile, the lowest age of incidence was in the early adolescent age group 12-16 years as many as 7 patients (5.4%).

This study found that the age group of patients with benign oral tumors in the 46-55 year group was 17 patients. The results of a study conducted by Kanaco in Manado with the highest prevalence of age group occurring in the age group that has reached 41-50 years.³ Cases of benign tumors in that age group were Ameloblastoma, a study conducted by Rusdiana et al., in 2011 obtained the results of Ameloblastoma occurring at the Jakarta Hospital in the age group of 31-50 years and was recognized by the analysis conducted by Small and Waldron (1955) and Mehlich, Dahlin and Masson (1972) from 1036 cases said cases of ameloblastoma often occur in patients aged 20-50 years.¹¹

The age group of patients with malignant tumors of the oral cavity was mostly in the group of 56-65 years as many as 22 patients. Other studies say that malignancy in tumors occurs in the 40-59 year age group, this is in line with research that has been done. The incidence of malignancy can occur due to the influence of behavioral factors, environmental factors, poor lifestyle, or exposure to carcinogenic substances at a young age that has been exposed for a long period, the longer the patient's immune system will weaken.⁴

Characteristics of Patients with Oral Cavity Tumors by Gender

Table 2 found that the sex of most patients with oral cavity tumors was female as many as 79 patients (60.3%), while the sex was male as many as 52 patients (39.7%). Benign tumors of the oral cavity by sex which have the highest incidence are women with 44 patients compared to men with 20 patients and malignant tumors of the cavity that have the highest incidence are women with 34 patients compared

to men with 31 patients. The higher incidence in women was due to the risk of tumor recurrence, which is dominated by women.¹² This is in contrast to other studies which state that tumors or cancer of the oral cavity are more common in men with the highest frequency in various countries, due to risk factors for smoking and alcohol.⁷

Characteristics of Patients with Oral Cavity Tumors Based on Location It was found in table 3 that there were 65 patients (50.4%), maxilla as many as 32 patients (24.8%), other locations such as the gingiva and labia as many as 20 patients (15.5%), and there was no location information as many as 12 patients. (9.3%). According to previous studies, the location of the tumor greatly influences the severity of the patient's status because it can cause death if nodule metastases occur through the severity of the tumor at each location.¹³

Tumor sites include the lip, anterior two thirds of the tongue, gingiva, mandible, maxilla, retromolar third and palate. The most common areas where malignant tumors occur are the tongue (40%) and the floor of the mouth (33%) with the highest incidence of squamous cell carcinoma.¹⁴ In the mandibular area about 80%, the most common benign tumor is ameloblastoma.¹⁵ The mandible has the highest incidence because the initial tumor is through invasion of the mandible on the floor of the mouth, the ventral surface of the tongue and through the gingivobuccal sulcus.¹⁶

CONCLUSION

Based on the results of research that has been carried out, the prevalence of oral cavity tumour is higher in female patients than male patients in the Abdoel Wahab Sjahranie Hospital. This hospital is a national referral hospital located in East Kalimantan so that it could represents a fairly high distribution for the incidence of tumors and oral cancer in East Kalimantan.

REFERENCES

- Agung IG, Siddhi M, & Setiawan IGB. Angka kejadian kanker rongga mulut pada pasien Di RSUP Sanglah dengan riwayat merokok dan minum minuman beralkohol dalam periode januari 2015 – juni 2016. E-Jurnal Medika. 2018; 7; 33–6. Available from: <https://ojs.unud.ac.id/index.php/eum/article/view/36534/22119>
- Agustina, D. Kanker Mulut (Kajian Pustaka). Majalah Kedokteran Gigi Indonesia, IX. 2008.
- Kanaco M, Pontoh V, & Sunaryo H. Pola tumor rongga mulut di Rsup Prof.Dr.R.D Kandou Manado periode 2014-2016. E-Clinic, 2016; 4(2). Available from <https://doi.org/10.35790/eci.4.2.2016.14474>
- Supriyanto N, Permana OR, & Cahyadi I. Karakteristik Pasien Keganasan Kepala Leher Di RSUD Waled Periode 2014-2018. Tunas Medika. 2019.
- Go B, Od O, & Ce A. Maxillofacial tumors and tumor-like lesions in a Nigerian teaching hospital : an eleven year retrospective analysis. 2014; 14(1); 56–63
- Rahardjo. Perawatan Ameloblastoma Rekuren Dengan Metode Dredging. Majalah Kedokteran Gigi. 2011; 160–2.
- To'bungan, N., A'liyah, S.H., Wijayanti, N., & Fachiroh, J.). Epidemiologi, Stadium, dan Derajat Diferensiasi Kanker Kepala dan Leher. Biogenesis: Jurnal Ilmiah Biologi. 2015; 3(1), 47–52. Available from <https://doi.org/10.24252/bio.v3i1.566>
- Nismal H, Syamsudin E, & Rizki KA. Karsinoma Sel Skuamosa dan Ameloblastoma yang Timbul Secara Bersamaan Pada Mandibula (Laporan Kasus). Majalah PABMI, Indonesian Journal of Oral and Maxillofacial Sugeons. 2012; 93–126.
- Syafriadi M. Patologi mulut: tumor neoplastik & non-neoplastik rongga mulut. CV. Andi Offset. 2008.
- Alrizzaqi MM, Mardi PRR, & Wardani NH. Implementasi Metode Dempster-Shafer untuk Mendiagnosis Jenis Tumor Jinak pada Manusia. Jurnal Pengembangan Teknologi Informasi Dan Ilmu Komputer (J-PTIIK) Universitas Brawijaya, 2018; 2(5); 2144–9. Available from <http://jptiik.ub.ac.id/index.php/jptiik/article/view/1494/52>
- Rusdiana, Sandini SU, Vitria EE, & Santoso TI. Profil Ameloblastoma dari Studi Retrospektif di Jakarta , Indonesia. Jurnal Kesehatan Gigi Indonesia. 2011; 18(2); 27–32.
- Kruse AL, Bredell M, & Grätz KW. Oral cancer in men and women: are there differences. 2011; 51–5. Available from <https://doi.org/10.1007/s10006-010-0253-6>
- Tripathi P, Mathur H, Goel S, & Khorate M. Adenoid Cystic Carcinoma: A Case Report Abstract. International Journal of Health Research, March 2012. 2010. <https://doi.org/10.4314/ijhr.v3i3.70304>
- Minic I., & Pejicic A. Oral Cancer : Incidence and Management. *Journal of Oral Cancer and Research*, March. 2018. Available from <https://doi.org/10.36959/915/573>
- Sandini SU, Vitria EE, & Santoso TI. Profile of Ameloblastoma from a Retrospective Study in Jakarta , Indonesia. Journal of Dentistry Indonesia. 2011; 18(2); 27–32
- Pablo HM, & Snehal GP. Cancer Of The Oral Cavity Pablo. Surg Oncol Clin. 2016; 24(3), 491–508. <https://doi.org/10.1016/j.soc.2015.03.006.Cancer>
- Medawati A. Karsinoma Sel Skuanmosa Sebagai Salah Satu Kanker Rongga Mulut Dan Permasalahannya. 2013; 1, 87–90.



Risk Factor Analysis of Caries Through Saliva in Non-Syndromic Cleft Lips Children With or Without Cleft Palate

Yayun Siti Rochmah, Anindita Dyah Palupi, Aulia Noviana, Shofwatin Ni'mah

Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University Islam Sultan Agung

Online submission : 05 August 2021

Accept Submission : 05 November 2021

ABSTRACT

Background: The number of cleft lips or palatal cases is still very high in Indonesia, the growth of cleft lips or palatal cases was 1: 700. This prevalence varies for each region in Indonesia. The condition and composition of saliva in children affect the condition of dental caries, including protein statherin, histatin -1, and calcium minerals. Statherin has the strongest interaction with calcium hydroxyapatite, Histatin-1 has an antimicrobe and antifungal effect and calcium is an imported mineral component. **Objectives:** The purpose of this study was to analyze the children's saliva of cleft lips with or without cleft palatal non- syndromic against the risk of caries. **Methods:** This study used an Observational Analytic method with a Post Test Only Control Group Design. Saliva samples were taken by the pipetting method, saliva samples were taken from 20 children with cleft lips with or without palate and 20 normal children, aged 3-17 years, with good general health. Analysis levels of Statherin, Histatin-1, and Calcium minerals used the ELISA Method. Statistical analysis used ANOVA. **Result:** The results showed that the average level of statherin for children with a cleft lip was 0.65 $\mu\text{g} / \text{ml}$, whereas for normal children was 1.1 $\mu\text{g} / \text{ml}$, the results of the analysis of histatin-1 salivary protein showed an average of 0.86 ± 0.50 at cleft children and 1.01 ± 0.71 for normal children, mean calcium levels in saliva for cleft children is $1.09 \pm 0.09 \text{ mmol} / \text{L}$ and normal children were $1.34 \pm 0.13 \text{ mmol} / \text{L}$. ANOVA analysis for the three salivary components were found to be $p = 0.001$, which means that there were significant differences between the average levels of statherin, histatin-1, and calcium in cleft lips children with or without cleft palate and normal children. **Conclusion:** The levels of statherin, histatin-1, and salivary calcium can be early diagnostic risk dental caries in children with cleft lips/palate nonsyndromic, to optimize management of preventing dental caries on clefts cases.

Keywords: Statherin, Histatin-1, Calcium, Non-syndromic lips/palate cleft, Caries risk

Correspondence: Yayun Siti Rochmah, Oral and Maxillofacial Surgery Department, Faculty of Dentistry, University Islam Sultan Agung, Jl. Kaligawe Raya No.Km.4, Terboyo Kulon, Genuk, Semarang, Indonesia. Email: yayun@unissula.ac.id

INTRODUCTION

Cleft lips with or without palate (CL/P) is the most common congenital craniofacial anomaly. The clefts can occur on the lip only (CL), alveolar (CA), involve both lip and alveolar, affect the palate (CP) or involve both lips and palate (CL/P). The congenital can syndromic (CL/P S) or non-syndromic (CL/P NS), it means related with another congenital or not. Prevalence cleft lip in Indonesia reaches 7.500 people. The highest prevalence in Indonesia reach 8,6% or 6-9 people of 1.000 population in East Nusa Tenggara. The multifactorial etiology of cleft lip was divided into genetic and environmental factors. Basic Health Research Data (Riskesdas) 2018, states that the prevalence of children aged 24-59 months suffering from congenital abnormalities reaches 0.53%, of which 0.08% is in the form of cleft lip disorders.¹ The cause of cleft lip or palate is generally divided into 22% genetic factors and 78% environmental factors or a combination of both.² So it is necessary to further explore the hereditary history and pregnancy history including the nutrition consumed by the mother during pregnancy. *Folic acid* intake during pregnancy has been shown to prevent cleft lip /palate.³

Dental caries in Indonesia is still a disease of the teeth and mouth with the highest prevalence in Indonesia, about 57.6% with the highest sufferer being infant.¹ Thus in cleft lip children with or without cleft palate. A study in England on 120 cases that children with cleft lip were twice risk than normal children both in deciduous and permanent teeth.⁴ While the study in Texas on 183 cases found that children with cleft lip/palate had a greater risk of experiencing enamel hypoplasia and caries.⁵ The causes of dental caries consist of the host, environment and agent.

Saliva contains a lot of proteins such as *IgA*, *IgG*, *Proline Rich Protein*, and *histatin* peptides which are biomolecules that can be used as biomarkers to predict the risk of dental caries.⁶ *Statherin* is the only salivary protein that

inhibits the precipitation of *calcium phosphate* salts.⁷ *Statherin* (StN43), a *phosphorylated* residual salivary protein similar to *osteopontin* and casein, binds to *calcium* and *hydroxyapatite* (HA). HA inhibits enamel demineralization. Demineralization causes loss of *calcium*, *phosphate* and *fluoride*. *Histatin-1* plays a role in defense of the pellicle on the tooth surface as an inhibitor of the colonization of caries-causing bacteria. *Calcium* reduction occurs in cases of dental caries.⁸ *Calcium* plays an important role in the remineralization process decreasing the amount of *calcium* in saliva.

The purpose of this study was to analyze the effect of the salivary components of *Statherin*, *Histatin* and *Calcium* on the risk of caries in children with CL/P NS.

MATERIALS AND METHODS

This study used the analytical observational method with the design of the Post Test Only Control Group Design. Samples were taken by consecutive sampling method with inclusion and exclusion criteria. Saliva samples were taken by pipetting method, saliva samples were taken from 20 children with cleft lip and 20 normal children, aged 3-12 years, in good general health. Analysis levels of *statherin*, *histatin-1*, and *calcium* minerals using the ELISA method and followed by the one-way ANOVA test. Ethical Clearance conducted at FKG UNISSULA No. 018 / B.1-KEPK / SA-FKG / II / 2019.

RESULTS

From a total of 20 samples CL/P NS, the following demographic data were obtained: patients who were male 35% (n = 7) and female 65% (n = 13). Based on the clinical patient, it was found that 53% unilateral lip clefts, 26% bilateral lip clefts, 21% palate clefts were found. Control group was normal children, male 55% (n=11) and female 45% (n=9).



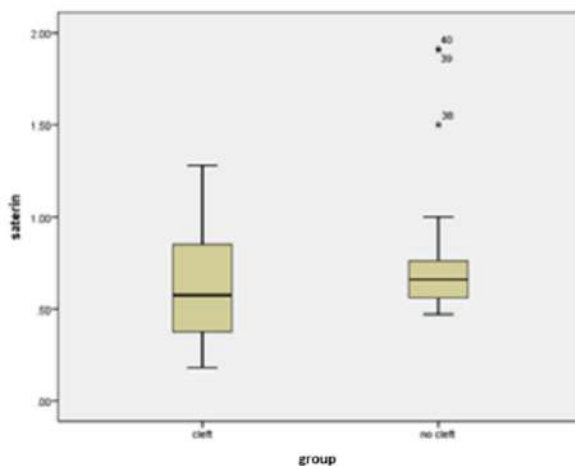
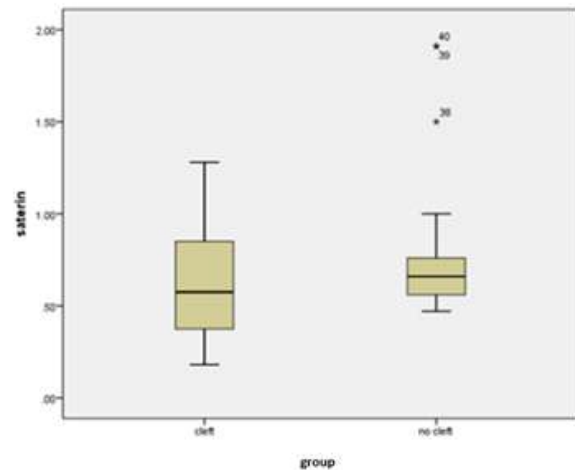
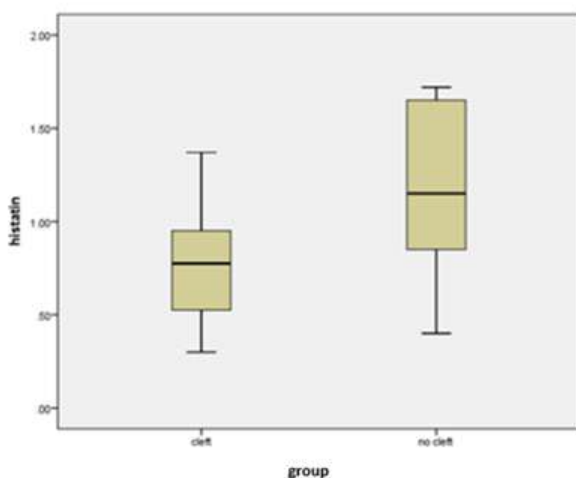
Table 1. The average value of the three salivary proteins, Statherin, Histatin and Calcium

Saliva Content	Groups	
	Cleft Lips (N : 20)	Normal (N : 20)
<i>Statherin</i> (µg/ml)±SD	0.65 ±0.32	1.10 ± 0.45
<i>Histatin</i> (µg/ml)±SD	0.86 ±0.50	1,01± 0.71
<i>Calcium</i> (µg/ml)±SD	1.09±0.09	1.34± 0.13

Table 2. The results of different tests with one way ANOVA, the three salivary proteins for normal children.

Saliva content	Group		Sig	Adj.
	Slit lips	Normal		
<i>Statherin</i>	N = 20	N = 20	0.148	Not significantly different
<i>Histatin</i>	N = 20	N = 20	0.002	Different meaning
<i>Calcium</i>	N = 20	N = 20	0.000	Different meaning

Based on the statistical test results, the statherin results were not significantly different compared to histatin and calcium.

**Figure 1.** Diagram Anova analysis

DISCUSSION

Saliva is one of the media to diagnose an abnormality or problem in the oral cavity. Many contents in saliva can be used as a marker of the abnormal conditions. Table 2 showed that salivary *statherin* in both CL/P NS and normal children are the same, unaffected by intraoral conditions. *Statherin* is secreted by the *acinar* cells of the submandibular and parotid salivary glands where the primary structure is the residual *tyrosine rich* and vicinal *phosphoserines* with a molecular weight of 5380 Daltons and a concentration of 10 - 40 µM in human saliva. *Statherin* levels are affected by calculus degree, not by irregular tooth structure as in CL/P NS patients.⁹ The CL/P NS samples did not show any significant calculus levels. Meanwhile,

histatin and *calcium* levels differed significantly between cases and controls. This shows that anatomical conditions affect the levels of *histatin* and *calcium* in saliva, while *statherin* has no effect. *Histatin* plays a very important role in the *hydroxyapatite* bonding process, so that *histatin* is often used as a material to prevent abrasion and enamel lysis.¹⁰ *Histatin* can also be used as prevention for infection due to implant failure because it has an antimicrobial effect as well as the main function of *histatin* in the peptidomic sphere. *Histatin* can also prevent gingivitis because of the effect of *histatin* which can reduce the entry of microorganisms.¹¹ *Histatin-1* is part of the salivary protein which has an antibacterial function to inhibit the occurrence of dental caries.¹² *Histatin-1* protein interacts with *mucin-7*; *mucin-5B*; and *cystatin-S* which will form the biological structure. The interactions between these salivary proteins provide antimicrobial functions and also form pellicles in the enamel to reduce microbial adhesion and reduce the demineralization process.¹³ The malfunction of salivary glands can lead the cariogenic and bacterial colonization which can increase the risk of caries. This situation will be exacerbated by abnormal anatomical conditions in the case of CL/P NS causing irregular tooth arrangement so that the risk of caries becomes greater.

In this study, it was found that calcium levels in children with CL/P NS were lower than in controls. This was consistent with *Whelton's* research that irregular tooth arrangement had an effect on salivary *calcium* levels, which is lower than that of regular (normal) teeth.¹⁴ Irregular tooth arrangement causes an imbalance of the demineralization and remineralization processes. Re mineralization causes the loss of *calcium*, *phosphate*, and *fluoride* ions and is replaced by *fluorapatite* crystals which are more resistant to acid dissolution and substantially larger than the original crystal, thereby providing a better (smaller) surface to volume ratio. Therefore the larger apatite crystals in remineralized enamel are more resistant to enamel demineralization by organic acids.

Otherwise, plaque concentrations and levels of Ca and P ions in saliva can affect the balance of demineralization and remineralization of enamel.¹⁵

The enamel crystals contain apatite carbonate which is demineralized by organic acids (lactic acid) which are produced by the cellular activity of plaque bacteria from the carbohydrate diet. Increasing the level of Ca in the remineralization solution can increase the rate of mineral deposition on tooth.¹⁶ Progress of dental caries is about the relationship between demineralization and remineralization is replaced by apatite crystals which are more resistant to acid solution and larger natural crystals. This processes caused the larger apatite crystals to be more resistant to enamel damage with residual organic acids and inhibit demineralized processes that induces caries. Crystalline enamel containing carbonate apatite that can be demineralized by organic acids produced by cellular plaque bacteria through consumption of carbohydrates.¹⁷

Besides, the composition of saliva also affects gingivitis and vice versa. In cases of gingivitis, it is usually accompanied by an increase in *statherin* levels and inhibits *calcium binding*. Gingivitis can prevent *statherin* from binding to *calcium* in saliva. All *statherin* molecule chains have a tendency to inhibit calcium and *phosphate* deposition.¹⁸ *Statherin* molecules bind strongly to HA in the form of *statherin-N terminals* which can inhibit secondary *calcium phosphate* deposition. *Statherin* inhibits the calcium deposition process with calcium-binding saliva so that it cannot survive in the plaque solution. *Statherin* also prevents the absorption of high molecular weight glycoproteins (HMWGP) on the tooth surface, then inhibits the attachment of HMWGP which binds to bacteria, including *Streptococcus mutans*. *Statherin*-rich layer on the tooth surface showed that high calcium zone facilitates mineralization of the tooth enamel, without further precipitation that actually resulted in the mineralization of tooth plaque.¹⁹ The interaction between *statherin* and *calcium* cause the

influence each other function. The condition low levels of *statherin* will be followed by abnormal conditions in salivary calcium levels which can affect the risk of caries which is supported by severe gingivitis conditions.²⁰

CONCLUSION

The levels of *statherin*, *histatin-1*, and salivary *calcium* could be early diagnostic risk dental caries on children with CB/P NS to optimize management of prevention dental caries on clefts cases.

REFERENCES

1. Riskesdas 2018, <https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/>
2. Loho, Jilly N., Prevalensi Labioschisis Di RSUP Prof. Dr. R. D. Kandou Manado Periode Januari 2011 – Oktober 2012, Jurnal E-Biomedik (Ebm), 2013; 1(1): 396–401.
3. Jahanbin A., Shadkam E., Miri H.H, Shirazi A.S, Abtahi M, Maternal Folic Acid Supplementation and the Risk of Oral Clefts in Offspring, J Craniofac Surg. 2018; 29(6):534-541. doi: 10.1097/SCS.00000000000004488. <https://www.ncbi.nlm.nih.gov/pubmed/29762322>
4. Worth V., Perry R., Ireland T, Wills A.K., Sandy J. A., Are people with an orofacial cleft at a higher risk of dental caries? A systematic review and meta-analysis, British Dental Journal, 2017: 223: 37–47
5. Sabrina S., Bhavini A.M, Catherine F., Brett C.M, Dental Caries Experience in Texan Children with Cleft Lip and Palate, Pediatric Dentistry, 2017; 39 (5): 397-402
6. Hemadi A.S, Huang R., Zhou Y., Zou J, Salivary proteins and microbiota as biomarkers for early childhood caries risk assessment, Int J Oral Sci. 2017; 9(11):1. doi: 10.1038/ijos.2017.35. <https://www.ncbi.nlm.nih.gov/pubmed/29125139>
7. Shah, Saleha, Statherin-Role in Biomimetic Early Caries Management. Acta Scientific Dental Sciences.2018; 2(6): 57–60.
8. Milaim S., Kastriot M., Nora B., Ekrem Ç., Nora A., Sokol K., and Sami S., The Effect of Ca and Mg Concentrations and Quantity and Their Correlation with Caries Intensity in School-Age Children, Int J Dent. 2018; 2759040. Published online 2018 May 8. doi: 10.1155/2018/2759040, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964478/>
9. Deepak G.S. P., Shilpa G., Swarna Y. M.D.G.M., and Sreejith M.N., Correlation of Salivary Statherin and Calcium Levels with Dental Calculus Formation: A Preliminary Study, International Journal of Dentistry, 2017; 29 (4). Doi: <https://doi.org/10.1155/2017/2857629>
10. Ulfah, R Zafar,MS, Oral and Dental delivery of Fluoride, A Review Fluoride, 2015; 48: 195-204
11. Yeo I, Kim H, Lim KS, Han J, , Implant Surface Factor and bacterial Adhesion, a Review of the literature Int, J. Artif.Organ, 2012; 35: 762-72
12. Hegde MN, Attavar SH, Shetty N, Hegde ND, Hegde NN. Saliva as a biomarker for dental caries: A systematic review. J Conserv Dent ,2019;22: 2-6
13. Hemadi, Abdullah S, Ruijie H., Yuan Zhou, and Jing Zou., Salivary Proteins and Microbiota as Biomarkers for Early Childhood Caries Risk Assessment. International Journal of Oral Science.2017; 9(11): 1-8.
14. Whelton, H., Introduction: The Anatomy and Phsyiology of Salivary Glands. London: Stephen Hancocks:2012. (pp. 11).
15. Carlos A. F, Paulo F. K., and Fabiana V.F., The Role of Diet and Oral Hygiene in Dental Caries. *Pediatric Restorative Dentistry Journal*, 2019: 31-55, DOI: 10.1007/978-3-319-93426-6_4
16. Ameta P., Yumi L., Irma E, Alteration of Salivary Calcium And Statherin Levels in Patients with Gingivitis And Periodontitis, IOSR Journal of Dental and Medical Sciences,2017; 16 (7): 17-19
17. Kun W., Xiuqing W., Haoran Li, Sainan Z., Qian Ren, Yufei W., A statherin-derived peptide promotes hydroxyapatite crystallization and in situ remineralization of artificial enamel caries, Royal Society of Chemistry Adv., 2018; 8: 1647–55
18. Deepak G. S. P.,Shilpa G.,Liew F. F , and Nur Sulwana M. H., Association of Salivary Statherin, Calcium, and Proline-Rich Proteins on Oral Hygiene: A Cross-Sectional Study, International Journal of Dentistry. 2021: 6. Doi: <https://doi.org/10.1155/2021/1982083>



-
- | | |
|--|--|
| 19. Tarigan A. The Role Of Statherin In Predicting Of Dental Enamel Plaque Calcification, Oral Biology, February 2018, DOI:10.13140/RG.2.2.33809.53609 | 20. Szabo, Gyula Tamas et al. Comparative Salivary Proteomics of Cleft Palate Patients. The Cleft Palate-Craniofacial Journal.;2012; 49(5): 519–523. |
|--|--|



Socket Preservation with Hydroxyapatite Gypsum Puger Scaffold and Aloe vera on Fibroblast and Type 1 Collagen Cells

Amiyatun Naini*, Clarissa Astiasari**, Muhammad Nurul Amin***

*Department of Prosthodontics, Faculty of Dentistry, Jember University

**Faculty of Dentistry, Jember University

***Department of Biomedicine, Faculty of Dentistry, Jember University

Online submission : 13 August 2021

Accept Submission : 05 November 2021

ABSTRACT

Background: The prevalence of tooth extraction was 7.29% according to RISKESDAS 2018. Post-tooth extraction will cause injury and bone resorption. Scaffold material combination of hydroxyapatite gypsum puger (HAGP) and aloe vera (AV) can be used for preservation of extraction socket. **Objective:** To analyze fibroblast and type 1 collagen cells in the extraction socket after being induction by a combination of hydroxyapatite gypsum puger scaffold and aloe vera. **Methods:** Making a combination of gypsum puger hydroxyapatite scaffold and aloe vera, divided into four groups, namely negative control, aloe vera scaffold, HAGP scaffold, and HAGP+AV scaffold. Extraction of the mandibular 1st molar in Wistar rats, the application on the extraction socket was waited for 3, 5, 7, and 14 days. Preparation of preparations using Hemaktocillin Eosin staining method. **Results:** LSD test on the HAGP+AV scaffold group between days 3 and 5, days 3 and 7, days 3 and 14, days 5 and 7, days 5 and 14, days 7, and 14 were obtained ($p=0.000$), this shows a significant difference between the treatment groups. The results of type 1 collagen in the HAGP+AV scaffold group between days 3 and 14 were obtained ($p=0.005$) showing a significant difference. Each group on day 14 showed the highest number of fibroblast and type 1 collagen cells. **Conclusion:** The combination of HAGP+AV+gelatin scaffold can increase fibroblast cells and type 1 collagen after tooth extraction. The socket healing process is getting faster on day 14.

Keywords: Aloe vera, Gelatin, Gypsum Puger Hydroxyapatite (HAGP), Scaffold, Tooth Extraction

Correspondence: Amiyatun Naini, Faculty of Dentistry, Jember University, Jl. Kalimantan Tegalboto No.37, Krajan Timur, Summersari, Jember, East Java Indonesia. Email: amiyatunnaini.fkg@unej.ac.id

INTRODUCTION

The act of tooth extraction occupies the second-highest position after drug consumption. The prevalence of tooth extraction shows a figure of 7.29% according to RISKESDAS 2018. Post-tooth extraction will cause injury and the occurrence of alveolar bone resorption which can affect the readiness of the dental tissue in the installation of dentures or implants.¹ In this case, it is necessary to preserve the extraction socket with bone graft material to accelerate the wound healing process and prevent bone resorption.

Bone graft material that can be used as an alternative for extraction socket preservation is a combination of gypsum puger hydroxyapatite scaffold and Aloe vera. Hydroxyapatite (HA) is a biomaterial which has the chemical formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, HA has good biocompatibility and bioactivity properties. Crystallographically and chemically, HA is close to the structure of bones and teeth, and HA functions can be bound directly to tissue and can stimulate tissue growth. Based on the research conducted by Naini (2014), it was found that Puger gypsum material in the Jember area was successfully synthesized into hydroxyapatite called Hydroxyapatite Gypsum Puger (HAGP). The characterization of HAGP by XRD and FTIR tests had the same results with HA 200 from Japan as the standard for comparison.^{2,3} According to Salim (2015), the activity of new bone formation or tissue regeneration will occur optimally with the addition of bone graft material in the form of a scaffold.⁴

Aloe vera is a natural ingredient that is combined with gypsum puger hydroxyapatite to maximize the healing process. Aloe vera contains tannins, flavonoids, saponins, steroids, terpenoids, anthraquinone glycosides, and glucomannan compounds.⁵ Glucomannan compounds include polysaccharides (β 1,4)-mannosylation) which can accelerate the wound healing process. Glucomannan compounds are able to stimulate the activity and proliferation of fibroblast cells and can increase collagen production.⁶ Cells that

play an important role in the wound healing process are fibroblast cells, these cells play a role in the formation of connective tissue and support the formation of new bone after tooth extraction.⁷

In the process of tooth extraction, there will be mechanical trauma to the alveolar bone and an extraction socket will be formed, if there is an injury then hydroxyapatite is applied, it will cause inflammation in the tissue. In the inflammatory process, it will activate macrophages that secrete cytokines such as IL-1, IL-6, TNF- α .⁸ TNF- α as a homing stem cell chemoattractant, secretes cytokines and attracts endogenous mesenchymal stem cells so that attachment occurs and then proliferation and differentiation stimulate osteoprogenitors to become preosteoblasts, then differentiates preosteoblasts into osteoblasts. Osteoblasts secrete osteocalcin, alkaline phosphatase and type 1 collagen.^{3,9} Type 1 collagen is the most abundant collagen fiber found in adult connective tissue, bones, and teeth. This hydroxyapatite material can function as an osteoconductive.¹⁰

The difference is on this research author used gelatin as a gelling agent. Gelatin has a quality of biocompatibility that effectively increases support cell adhesion, also doesn't result in dangerous products at the time of enzyme degradation. Gelatin that is added for the manufacture of scaffolds can be biodegradable and has good porosity. If the gelatin is combined with another natural polymer or even the synthetic, the gelatin will show an increasing mechanical behavior and affinity on the scaffold.¹¹ The goal of this research is to analyze the fibroblast cell and collagen type 1 on extraction socket after induced by the combination of gypsum puger hydroxyapatite scaffold, aloe vera, and gelatin.

MATERIALS AND METHODS

This research was an experimental laboratory research with post test only control group design. This research has been approved by the Health Research Ethics Commission

(KEPK) No. 1070/UN25.8/KEPK/DL/2020 Faculty of Dentistry, University of Jember.

The combination of HAGP scaffold, Aloe vera, and gelatin (from cow skin, Pro Analysis, Merck, catalog number 104078, Malincord, JT. Baker) was made with a ratio of 1:1. HAGP material was a hydroxyapatite material that was successfully synthesized from gypsum from Mount Gamping Jember based on previous research according to Naini (2019) in the following way. Preparation of HAGP hydroxyapatite samples, weighing 0.5 grams of gypsum, 0.5 grams of DHP, 500 ml of distilled water, mixed into a tube, then placed in an oven at 100°C for 30 minutes. The solution was washed, filtered, and dried in a microwave at 50°C.¹² To form the aloe vera gel, we blended the aloe vera ingredients until smooth. Then mix 5 grams of HAGP powder with aloe vera gel in a ratio of 1:1 (w/v), after that add 10 ml of gelatin solution and mixed until homogeneous. Then the material is put in a scaffold mold and cooled in a freezer at -60°C for 24 hours and then freeze-drying was carried out at a temperature of -84°C for 24 hours.

This study used 32 males *Rattus norvegicus* rats which were divided into 16 study groups (4 control groups and 12 treatment groups). The sample size in each treatment group was two rats according to the Federer formula.¹² The control group was a negative control in the form of extraction of the mandibular first molar teeth of rats without being given scaffold material. The treatment group consisted of extraction of the mandibular first molar teeth of rats and induction of scaffold material (PI group: Aloe vera (AV) scaffold, PII group: Gypsum Puger hydroxyapatite scaffold (HAGP), and PIII group: HAGP+AV scaffold.

Experimental animals were anesthetized using ketamine injection at a dose of 0.04 - 0.08 ml/200kg body weight rats.³ The extraction of the rat's teeth was carried out by a simple extraction method using a Half moon sonde and an excavator. After the tooth was extracted completely, the socket was irrigated using sterile distilled water and given scaffold material until it

was completely filled. The experimental animals were then reared and euthanized on the 3rd day, 5th day, 7th day, and 14th day. Tissue decapitation in the left lower jaw of rats. Then decalcification using 3% nitric acid, then processing the tissue into histological preparations using Hematoxylin Eosin staining.

The calculation of the number of fibroblasts and the density of type 1 collagen were observed using a binocular microscope (EC1152 Euromex Ecoblue, Holland) with a magnification of 400x. Calculations were carried out in 3 fields of view and then tabulated the average number of fibroblast cells and type 1 collagen density.¹³ The average number of fibroblasts and type 1 collagen density was analyzed using One Way Anova and the Least Significant Different (LSD) test with a significance value of $p < 0.05$.

RESULTS

The preservation of extraction sockets by induction of a combination of Hydroxyapatite Gypsum Puger scaffold, Aloe vera, and gelatin (HAGP+AV+Gelatin) on the number of fibroblast cells and the density of type 1 collagen in the socket was carried out by histological observation of the rat sample preparations using a light microscope. Microscopic appearance of fibroblast cells in each group can be seen in Figure 1, while the microscopic image of the density of type 1 collagen in each group can be seen in figure 2.

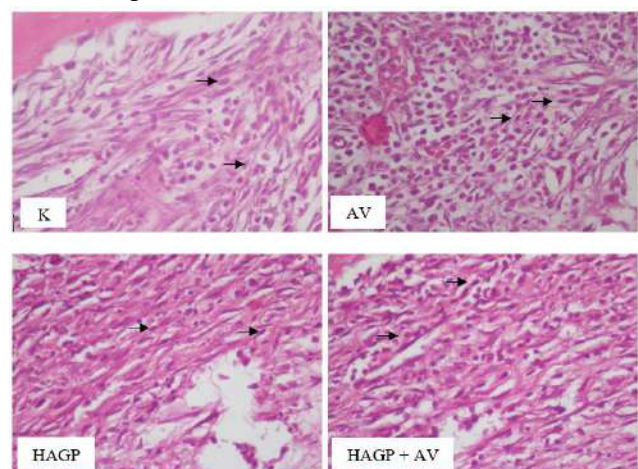


Figure 1. Microscopic image of fibroblast cells in control group (K), Aloe vera + gelatin (AV) scaffold

treatment group, HAGP + gelatin (HAGP) scaffold treatment group, and HAGP+AV+gelatin (HAGP+AV) scaffold treatment group (HE stains, light microscopy, 400x). Calculated cells are marked with arrows.

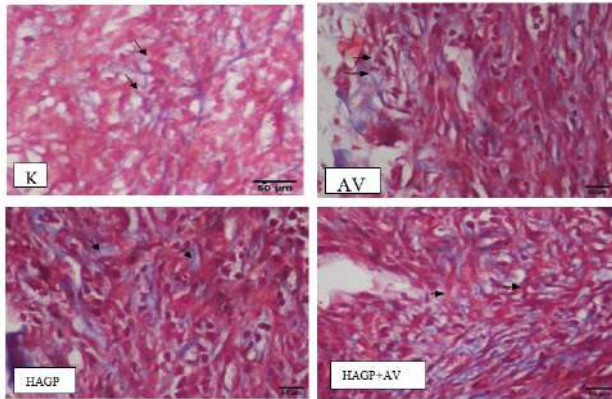


Figure 2. Microscopic image of Collagen density type 1 Control group (K), Aloe vera + gelatin (AV) scaffold treatment group, HAGP + gelatin (HAGP) scaffold treatment group, and HAGP+AV+gelatin (HAGP+AV) scaffold treatment group (HE stains, light microscopy, 400x). Calculated cells are marked with arrows.

Figures 1 and 2 showed an overview of fibroblast cells and type 1 collagen density taken in one field of view of each research group after tooth extraction. The calculation of the number of fibroblast cells, the density of type 1 collagen, and the *Least significant Different* (LSD) test results can be seen in table 1.

Table 1. The calculation of the number of fibroblast cells, the density of type 1 collagen, and LSD test results

Group	The number of fibroblast cells ($X \pm SD$) and LSD				The density of type 1 collagen ($X \pm SD$) and LSD			
	Day 3	Day 5	Day 7	Day 14	Day 3	Day 5	Day 7	Day 14
Control	8,38 $\pm$ 0,54	11,83 $\pm$ 0,72	16,17 $\pm$ 0,39	18,24 $\pm$ 1,08	15,86 $\pm$ 2,1	31,14 $\pm$ 6,3	34,73 $\pm$ 13,7	80,41 $\pm$ 10,9
	(5,7,14) (PI,PII,PIII)	(3,7,14) (PI,PII,PIII)	(3,5,14) (PI,PII,PIII)	(3,5,7) (PI,PII,PIII)	(4) (PI,PII,PIII)	(-) (PI,PII,PIII)	(-) (PI,PII,PIII)	(-) (PI,PII,PIII)
Scaffold Aloe vera + gelatin (PI)	13,33 $\pm$ 0,47	16,67 $\pm$ 1,41	17,72 $\pm$ 1,33	21,65 $\pm$ 0,49	34,05 $\pm$ 12,8	43,07 $\pm$ 4,7	72,85 $\pm$ 24,4	80,41 $\pm$ 22,2
	(5,7,14) (K,PII,PII)	(3,14) (K,PIII)	(3,14) (K,PII,PIII)	(3,5,7) (K,PII,PIII)	(3,4) (K,PII,PIII)	(4) (K,PII,PIII)	(1) (K,PII,PIII)	(1,2) (K,PII,PIII)
Scaffold HAGP + gelatin (PII)	17,16 $\pm$ 1,64	18,16 $\pm$ 1,64	19,89 $\pm$ 0,94	23,5 $\pm$ 0,24	36,58 $\pm$ 24,5	42,17 $\pm$ 19	76,07 $\pm$ 28,1	79,65 $\pm$ 19,9
	(7,14) (K,PI,PIII)	(7,14) (K,PIII)	(3,5,14) (K,PI,PIII)	(3,5,7) (K,PI,PIII)	(3,4) (K,PI,PIII)	(4) (K,PI,PIII)	(1) (K,PI,PIII)	(1,2) (K,PI,PIII)
Scaffold HAGP + AV+gelatin (PIII)	23,83 $\pm$ 1,18	28,16 $\pm$ 1,18	31,5 $\pm$ 2,58	34,83 $\pm$ 1,18	36,67 $\pm$ 9,3	58,4 $\pm$ 20,8	68,53 $\pm$ 18,3	93,01 $\pm$ 7,5
	(5,7,14) (K,PI,PII)	(3,7,14) (K,PI,PII)	(3,5,14) (K,PI,PII)	(3,5,7) (K,PI,PII)	(4) (K,PI,PII)	(-) (K,PI,PII)	(-) (K,PI,PII)	(1) (K,PI,PII)

Description:

$X \pm SD$: Mean fibroblast cell count $\pm$ Standard Deviation

(3,5,7,14) : significantly different based on the day of treatment in one group of treatment materials
(³) significantly different from the 3rd day, (⁵) significantly different from the 5th day, (⁷) significantly different from the 7th day, (¹⁴) significantly different from the 14th day)

(K,PI,PII,PIII) : significantly different based on the treatment material group in one treatment day group (^K) significantly different from group K, (^{PI}) significantly different from group PI, (^{PII}) significantly different from group PII, (^{PIII}) significantly different from group PIII).

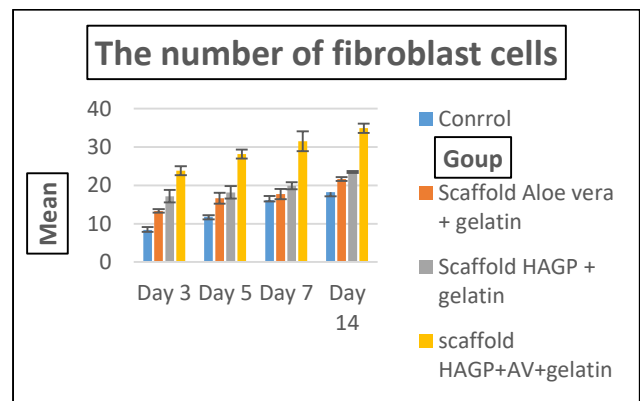


Figure 3. Histogram of the calculation results of the average number of fibroblast cells, (PI) The group given the scaffold Aloe vera+gelatin, (PII) the group giving the scaffold HAGP+gelatin, and (PIII) the group giving the scaffold HAGP+AV+gelatin.

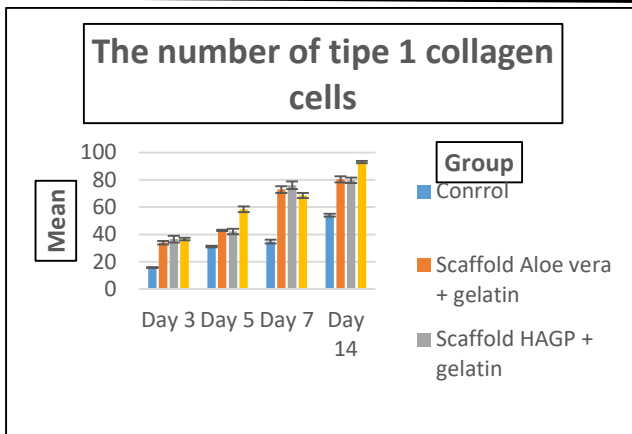


Figure 4. Histogram of the calculation results of the average number of type 1 collagen, the group control, (PI) The group given the scaffold Aloe vera+gelatin, (PII) the group giving the scaffold HAGP+gelatin, and (PIII) the group giving the scaffold HAGP+AV+gelatin.

Figures 3 and 4 are the average number of fibroblasts and type 1 collagen cells in the control and treatment groups. The fibroblast cell data showed that the largest increase was in the PIII group, that is the scaffold group with a combination of HAGP, gelatin, and Aloe vera. While the control group had the lowest fibroblast cell count value, although it experienced a significant increase in value from day 3 to day 14. In addition, the trendline also shows that the Aloe vera and gelatin (AV) scaffold group showed an insignificant increase in the number of fibroblasts from day 5 to day 7. Meanwhile, in the Hydroxyapatite Gypsum Puger and gelatin (HAGP) scaffold group, there was an insignificant increase in the number of cells on the 3rd to 5th day.

Analysis of the data on the number of fibroblasts was tested for normality using the Shapiro-Wilk test with the results of the data being normally distributed with $p > 0.05$. Then the homogeneity test was carried out using Levene's test and showed that the data were homogeneously distributed with a P-value of 0.374 so that the data had a p value > 0.05 . Furthermore, the One-way Anova parametric statistical test was carried out with the results of a P-value of 0.000 which meant that there was a significant difference in the average number of fibroblasts between the study groups due to the

$p < 0.05$. Furthermore, the LSD test was carried out with results showing that most of the data between groups had significantly different values ($p < 0.05$) both based on the length of treatment day group and the treatment material group (table 1).

Based on the results of this study, the average density of type 1 collagen was found to be the highest on day 14 in all groups, the denser the collagen density increased (figure 3). Data analysis was carried out by normality test using the Shapiro Wilk test which obtained results that were normally distributed, carried out by homogeneity test with the Levene test to obtain homogeneous data, then the One-way Anova test was carried out showing a P-value of 0.000 which means there is a significant difference between the research groups because of the p -value < 0.05 . Furthermore, an LSD test showed that most of the data between groups had significantly different values ($p < 0.05$) both based on the treatment day group and the treatment group (table 1).

DISCUSSION

Socket preservation is still often used to accelerate wound healing and the occurrence of alveolar bone resorption after tooth extraction. In this study, a combination of hydroxyapatite gypsum puger scaffold, aloe vera, and gelatin was used for fibroblast cells and type 1 collagen.

The use of scaffolds in tooth extraction sockets has important benefits in the treatment group. Scaffold is a porous structure that acts as a substrate for cells to migrate, adhere, grow, proliferate and differentiate. In addition, the scaffold can accelerate the bone healing process by acting as a delivery vehicle for cells, providing space for vascularization, new tissue formation, and bone remodeling. With biocompatible and biodegradable scaffold properties to support cell growth such as fibroblasts and type 1 collagen.¹¹

Aloe vera and gelatin scaffold treatment group showed a higher average number of fibroblast cells than the control group based on the results of the research that had been done.

Aloe vera is a natural polymer gel that has excellent biocompatibility and is non-toxic. Active components of Aloe vera such as acemannan can bind special ligands to mannose receptors found on the surface of fibroblasts and macrophages so this will trigger cell proliferation and growth factors.¹⁴ In addition to acemannan, there is another polysaccharide component, namely glucomannan which has healing properties by influencing the secretion of fibroblast growth factors, stimulating cell proliferation, and increasing the production of type 1 collagen through increasing the transformation of growth factor TGF- β in the wound area.¹⁵

Aloe vera will activate macrophage cells that are present in the inflammatory phase of the wound healing process. So along with the increased activation of macrophage cells, it increases the stimulation of the release of growth factors such as Fibroblast Growth Factor (FGF) and Transforming Growth Factor (TGF- β) as well as other important cytokines in accelerating wound healing by increasing the proliferation of fibroblast cells and collagen type 1.⁷ This is why the results of the study on the Aloe vera scaffold group showed no significant difference between the 5th and 7th-day groups. Macrophages that increase their cell activation in the inflammatory phase will increase the migration of fibroblast cells to the wound area at the beginning of the proliferative phase so that the number of fibroblast cells increases significantly on day 3 and day 5. While on day 5 to day 7 the number of fibroblasts will tend to be stable.

The provision of HAGP scaffold and gelatin showed an increase in the number of fibroblast cells when compared to the control group. Hydroxyapatite (HA) has been widely used as a tooth and bone repair material because it can chemically interact and blend with bone due to its non-toxic, non-allergenic, non-mutagenic, osteoconductive, and weak osteoinductive properties. So that the use of HAGP scaffold can increase the number of

fibroblast cells and type 1 collagen in the post-extraction socket.

The main property of the HAGP scaffold is its osteoconductivity which can support bone growth above the surface and direct new bone formation through the matrix support, acting as a scaffold that can be absorbed and replaced by bone tissue. HAGP has a major role as an interconnected porous structure. Its osteoconductive properties can attract healing cells to be able to adhere to the porous space. So, it can be seen from the results of the study that between day 3 and day 5 there was no significant difference in the number of fibroblast cells due to the main ability of HAGP only as a framework to facilitate cells adhesion. Thus, the proliferation of fibroblasts was not seen to increase in the early phase of wound healing.

Hydroxyapatite content in the HAGP scaffold has an important role related to the ideal properties of the scaffold. Despite having only osteoconductive properties, hydroxyapatite can provide a microenvironment that resembles the physiological environment so that stem cells can interpret biomaterial instructions and change according to their fate. The topographical and chemical properties of HAGP are almost the same as hydroxyapatite in human bone, so HAGP is able to send special signals to cells that will translate the code into biochemical signals.¹⁶ So in wound healing, especially seen from the increase in the number of fibroblast cells and type 1 collagen, the HAGP scaffold has a higher average cell count compared to the Aloe vera scaffold as seen in the research results.

The scaffold group with the combination of HAGP, gelatin and Aloe vera increased the number of fibroblasts and type 1 collagen in the tooth extraction socket compared to the treatment group without the combination and the control group. This is because the combination of properties of the two materials gives a synergistic effect as a scaffolding material. Hydroxyapatite is a complex inorganic material with weak osteoinductive properties and does not have sufficient ability to stimulate vascularization thus limiting its application.

Therefore, hydroxyapatite must be combined with other materials that can optimize the potency of the material.¹⁷ The osteoinduction properties of Aloe vera will be able to optimize the properties of the hydroxyapatite material when combined in a scaffold.¹⁸ So that the combination of HAGP and Aloe vera into a scaffold can accelerate the healing process in bone by enabling osteoblast cell proliferation, cell differentiation, as well as inorganic apatite deposition.

Aloe vera combined with HAGP to become a scaffold material will be able to increase the biocompatibility of the scaffold. Aloe vera is not only able to increase the number of cells attached to the scaffold but also able to increase the growth and proliferation of cells.¹⁸ Based on research conducted by Prabakaran et al. (2020), the substitution of mineral HA with natural ingredients Aloe vera can increase collagen protein deposition in the first week and second week after extraction so that this scaffold can induce connective tissue in the damaged bone area.

In this research, it can be seen an increase in the number of fibroblast cells between the treatment group and the control group on the 3rd, 5th, 7th, and 14th days. The 3rd day after tooth extraction was the day group that had the lowest number of fibroblast cells in the control group and the treatment group, this was because the 3rd post-extraction day was the beginning of the proliferation phase which overlapped with the end of the inflammatory phase so that Fibroblasts begin to migrate and are seen to secrete their extracellular matrix proteins.¹⁹ Migration of fibroblasts to the wound area reaches its peak until the 5th day after extraction to prepare for the synthesis and maturation of the matrix so that it will replace the blood clot with the formation of granulation tissue.²⁰

Granulation tissue will completely replace the blood clot on the 7th day after tooth extraction.¹⁹ When the fibroblasts have filled the wound area, the fibroblast cells will proliferate and make the matrix of the injured area rich in

collagen by secreting extracellular matrix proteins.^{18,20} However, in the results of this study, the number of fibroblast cells in the tooth extraction socket was more visible on the 14th day of the treatment group than on the 7th day of treatment. This is because the 14th day after extraction is the peak of the proliferation phase and the highest amount of connective tissue accumulation. So at this time fibroblast cells will appear to be formed a lot because they have fully migrated and are active.²¹

In this research also seen an increase in the density of type 1 collagen between the treatment group and the control group on the 3rd, 5th, 7th and 14th days. These ingredients contain glucomannan and hydroxyapatite compounds that can activate growth factors to accelerate fibroblast cell proliferation, angiogenesis, and re-epithelialization. TGF β -1 and FGF can increase mitosis from fibroblast cells thereby stimulating the formation of extracellular matrices such as fibronectin, proteoglycans, and collagen.

The socket healing process after tooth extraction consists of three phases, the first one is the inflammatory phase, after that the proliferative phase, and the maturation phase. In the proliferative phase, fibroblasts play an important role in forming granulation tissue and secrete collagen to form the extracellular matrix.²² So that if fibroblasts have increased cell proliferation, it can indicate a gradual wound healing process.

The use of a combination of HAGP, Aloe vera, and gelatin will form a signaling complex that can stimulate macrophages to release important growth factors in bone healing such as VEGF, FGF, TGF- β . Increased expression of growth factors will also stimulate an increase in fibroblast cell proliferation. So that it can be seen in the combined scaffold group which has the highest mean number of fibroblast cells on the 14th day after tooth extraction and significantly increases the number of fibroblast cells from the 3rd day to the 14th day. This result is different from the scaffold group without the combination, namely the group treated with Aloe vera plus

gelatin scaffold and HAGP+gelatin scaffold. The mean number of fibroblast cells was found to be not significantly different between the HAGP+gelatin scaffold group and the Aloe vera+gelatin scaffold group on day 5. This is because the scaffold made from a single material is not able to meet the ideal scaffold requirements, so it provides a less than optimal function.

CONCLUSION

The combination of gypsum puger hydroxyapatite scaffold, aloe vera, and gelatin can increase fibroblast cells and type 1 collagen cells after tooth extraction. With the combination of this scaffold, the socket healing was faster until it entered the 14th day when the mean number of fibroblasts was 34.83 and type 1 collagen was 93.01.

REFERENCES

1. Riskesdas K. Hasil Utama Riset Kesehata Dasar (RISKESDAS). J Phys A Math Theor [Internet]. 2018;44(8):1–200. Available from: <http://arxiv.org/abs/1011.1669v0Ahttp://dx.doi.org/10.1088/1751-8113/44/8/085201v0Ahttp://stacks.iop.org/1751-8121/44/i=8/a=085201?key=crossref.abc74c979a75846b3de48a5587bf708f>
2. Naini A, Ardhianto HB, Yustisia Y. Proses sintesis dan karakterisasi hydroxyapatite menggunakan analisis XRD FTIR dari gypsum puger Kabupaten Jember sebagai material augmentasi ridge alveolar. Stomatognathic (JKG Unej). 2014;11(2):32–7.
3. Naini A, Sudiana IK, Rubianto M, Kresnadi U, Latief FDE. Effects of hydroxyapatite gypsum puger scaffold applied to rat alveolar bone sockets on osteoclasts, osteoblasts and the trabecular bone area. Dent J (Majalah Kedokt Gigi). 2019;52(1):13.
4. Sherman Salim, Mefina Kuntjoro. Efek Kombinasi Spirulina Kitosan Untuk Preservasi Soket Terhadap Osteoblas, Osteoklas Dan Kepadatan Kolagen. Dentika Dent J. 2015;18(3):225–31.
5. Levina Priscilla. Perbandingan Efektivitas Aplikasi Topikal Lidah Buaya (Aloe vera), Madu (Apis mellifera), dan Kombinasi Keduanya Terhadap Penyembuhan Luka Sayat Pada Mencit (Mus musculus). 2017;17. Available from: [http://repository.unhas.ac.id/bitstream/handle/123456789/15556/TINGKAT PENGETAHUAN DAN KESADARAN PELAJAR TERHADAP KANKER RONGGA MULUT.pdf?sequence=1](http://repository.unhas.ac.id/bitstream/handle/123456789/15556/TINGKAT%20PENGETAHUAN%20DAN%20KESADARAN%20PELAJAR%20TERHADAP%20KANKER%20RONGGA%20MULUT.pdf?sequence=1)
6. Novyana RM, Susanti. Lidah Buaya (Aloe vera) untuk Penyembuhan Luka. J Kedokt Univ Lampung. 2016;5:149–53.
7. Sularsih S, Rahmitasari F. Penggunaan Scaffold Kitosan-Aloe Vera Terhadap Proliferasi Sel Fibroblas pada Penyembuhan Luka Pasca Pencabutan Gigi Cavia Cobaya. J Mater Kedokt Gigi. 2018;7(2):24.
8. Ramadhani T, Sari RP, W W. Efektivitas Kombinasi Pemberian Minyak Ikan Lemuru (Sardinella longiceps) dan Aplikasi Hidroksiapatit terhadap Ekspresi FGF-2 pada Proses Bone Healing. Denta. 2016;10(1):20.
9. Kumar S, Kumar Gupta K, Bhowmick D, Singh A. Concepts of Healing in Periodontal Therapy -Part I. IOSR J Dent Med Sci [Internet]. 2015;14(10):2279–861. Available from: www.iosrjournals.org
10. Turhani D, Weißenböck M, Watzinger E, Yorit K, Cviki B, Ewers R, et al. In vitro study of adherent mandibular osteoblast-like cells on carrier materials. Int J Oral Maxillofac Surg. 2005;34(5):543–50.
11. Fitriyana N. Scaffold adalah biomaterial tiga dimensi (3D) yang memfasilitasi sel untuk regenerasi jaringan dan organ. Struktur scaffold harus memiliki porositas tinggi dan saling terhubung sehingga memungkinkan perlekatan sel. Scaffold yang ideal harus memiliki sifat. [Thesis]. 2020;
12. Hanafiah KA. Rancangan Percobaan Teori dan Aplikasi Edisi Ketiga. Jakarta: Rajawali Post; 2014.
13. Rahman AO, Humaryanto. Terhadap Level Fibroblast Dan Kolagen Pada Proses Penyembuhan Luka. JAMBI Med J “Jurnal Kedokt dan Kesehatan.” 2019;7:19–25.
14. Takzaree, NasrinAbbas, Gholamreza Hassanzadeh, Hadjiakhondi, Mohammad Reza Rouini, Azadeh Manayi MMZ. TGF- β Expression in Aloe Vera Treated Wounds Transforming Growth Factor- β (TGF- β) Activation in Cutaneous Wounds after Topical Application of Aloe Vera Gel Abstract : Can J



- Physiol Pharmacol [Internet]. 2016;1–22. Available from: www.nrcresearchpress.com
15. Dadashzadeh A, Imani R, Moghassemi S, Omidfar K, Abolfathi N. Study of hybrid alginate/gelatin hydrogel-incorporated niosomal Aloe vera capable of sustained release of Aloe vera as potential skin wound dressing. Polym Bull [Internet]. 2020;77(1):387–403. Available from: <https://doi.org/10.1007/s00289-019-02753-8>
 16. Herda E, Puspitasari D. Tinjauan peran dan sifat material yang digunakan sebagai scaffold dalam rekayasa jaringan. J Mater Kedokt gigi. 2016;1(5):56–63.
 17. Luo Y, Li D, Zhao J, Yang Z, De Kang P. In vivo evaluation of porous lithium-doped hydroxyapatite scaffolds for the treatment of bone defect. Biomed Mater Eng. 2018;29(6):699–721.
 18. Tahmasebi A, Shapouri Moghadam A, Enderami SE, Islami M, Kaabi M, Saburi E, et al. Aloe Vera-Derived Gel-Blended PHBV Nanofibrous Scaffold for Bone Tissue Engineering. ASAIO J. 2020;66(8):966–73.
 19. Zulfah Al-Fa'izah, Yani Corvianindya Rahayu NH. Peran Fibroblas pada Proses Penyembuhan Luka Pasca Pencabutan Gigi (Role of Fibroblast Cells in the Wound Healing Process after Tooth Extraction). 2017;3(3):69–70.
 20. Christine Theoret D, MV, PhD DA. Physiology of Wound Healing. Vol. 99, Praktische Tierarzt. 2018. 792–793 p.
 21. Ashrin MN, Prananingrum W, Yonatasya FD. Pengaruh Bone Graft Senyawa Kalsium Hasil Sintesis Cangkang Kerang Darah (Anadara granosa) dengan Variasi Waktu Sintering terhadap Proliferasi Sel Fibroblas pada Proses Socket Healing. Denta. 2019;13(1):34–43.
 22. Desjardins-Park HE, Foster DS, Longaker MT. Fibroblasts and wound healing: An update. Regen Med. 2018;13(5):491–5.



Steven Johnson Syndrome with Severe Oral Implications and Management

Fika Faradillah Drakel*, Tenny Setiani Dewi**

*Department of Dental Public Health, Faculty of Dentistry, Padjadjaran University

**Department of Oral Medicine, Faculty of Dentistry, Padjadjaran University

Online submission : 20 November 2021

Accept Submission : 06 December 2021

ABSTRACT

Background: Steven Johnson Syndrome (SJS) is an acute mucocutaneous syndrome that predominantly involve the skin and mucous membranes. SJS is an immune-mediated disease that have been associated with erythema multiforme (EM). The most common triggers are viruses, food allergies, autoimmune reactions and medicine. The medicines that most commonly cause SJS are non-steroidal anti-inflammatory drugs, antibiotics, antifungals, and anticonvulsants. **Objective:** This case report aims to describe the appropriate management for oral lesions of SJS. **Case:** A 32-year-old man was consulted from the Dermatology Department with a diagnosis of drug induce SJS and was given cetirizine and dexamethasone. The patient presented to the Oral Medicine Department complaining of mouth pain, dysphagia, ulcers, oedema and haemorrhagic of the lips, difficult eating, drinking and speaking. Extra-oral examination found that the surface of the lips was covered with a white layer, bloody and crusted, and erythematous rash on his neck, arm, abdomen, palms and feet, with a diameter of 2-6 mm. Intra-oral examination found multiple ulcers and erosive lesions that spread on the tongue, palate, buccal and labial mucosa. This condition established as an oral lesion related to SJS. **Case Management:** The management of the oral lesion was given corticosteroid mouthwash, 0.12% chlorhexidine digluconate, lip compress with 0.9% NaCl and 1% hydrocortisone ointment. **Conclusion:** Steroid mouthwash to suppress inflammation as well as a combination of 0.12% chlorhexidine digluconate antiseptic drug suppresses the infection process and complications that continue in the oral cavity and 0.9% NaCl solution as a moist wound healing. This therapy plays an important role in the healing process of oral lesions in patients with SJS.

Keywords: Drugs induced, Oral lesion, Treatment, SJS

Correspondence: Oral Health and Dental Specialist Education Program, Faculty of Dentistry, Padjadjaran University, Bandung. Email: drqdrakel@gmail.com

INTRODUCTION

Steven Johnson Syndrome (SJS) is an acute hypersensitivity reaction characterized by cutaneous necrosis.¹ This disease is rare but life-threatening diseases. SJS was first recognized in 1922 by two clinicians, dr.Stevens and dr.Johnson, whose cause was still unknown.² Immune complex-mediated hypersensitivity reactions are an ongoing condition of erythema multiforme.³ SJS is a disorder that occurs with features of erythema, vesicles, bullae, purpura on the skin of the body as well as the mucosa of the eyelids and oral mucosa.⁴ The exact cause of SJS is currently unknown, however there are predisposing factors such as viruses, food allergies, autoimmune reactions and drug reactions.^{4,5}

The mechanism of the syndrome in SJS is a hypersensitivity reaction, usually not long after the drug is injected or taken and this event is not dose related.⁵ Clinically seen, it is widespread, especially in the body, peeling of the epidermis occurs approximately 10-30% of the body surface area and usually involves the mucous membranes of two or more organs.^{6,7} A more in-depth history is needed regarding previous medical history. Predilection generally occurs in children and young adults, especially men. The oral signs of SJS are the same as those of erythema multiforme, the difference being that it involves more skin and mucous membranes, with more severe general symptoms, including fever, malaise, headache, cough, chest pain, diarrhea, vomiting and arthralgia.⁸⁻¹⁰

Incidence and epidemiology were seen from observational studies on the epidemiology of SJS using validated clinical data in various European countries. In 1995-2013 the incidence rate was 5.76 at 1,000,000 cases per year, occurring in patients aged 1-10 years to 80 years. Mortality rates in childhood were found to be lower than in old age. [11] Indonesia does not have definitive data on the morbidity of SJS. Based on data from Dermatology and Venereology 5th edition of the Faculty of

Medicine, University of Indonesia in 2007.¹² Drugs that often cause SJS in Indonesia are analgesic/antipyretic drugs (45%), carbamazepine (20%), herbal medicine (13.3%) and the rest are other drug classes such as amoxicillin, cotrimoxazole, dilantin, chloroquine and ceftriaxone.^{11,12}

This case report aims to describe the appropriate management for oral lesions of SJS, the patient gets a nutritional balance and help the healing process of the lesion.

CASE

A 32-year-old man was consulted from the Department of Dermatology and Venereology with a diagnosis of drugs induce Steven Johnson Syndrome. The patient presented to the Oral Medicine Department complaining of pain in the mouth, dysphagia, ulcers, oedema of the lips, haemorrhagic crusts of the lips, difficult to eat, drink and speak. Extra-oral examination found that the surface of the lips was covered with a white layer, bloody and crusted, and erythematous rash on his neck, arm, abdomen, palms and feet, with a diameter of 2-6 mm. Intra-oral examination revealed multiple ulcers and erosive lesions on the tongue, palate, buccal mucosa and labial mucosa.



Figures 1. a and b. dry lips, edema, erythema and serosanguinolent crusting; c. White plaque on the tongue;

d, e and f. Erosive, erythematous, irregular lesions on the palate, right and left buccal mucosa; g, h, i and j. Blackish red vesicles on the palms, feet as well as the abdomen and neck.

Intra-oral examination of the lips showed clinical signs of dry, exfoliative lips, oedema of the upper and lower lips accompanied by erythema and serosanguinolent crusts, easy bleeding and pain (Figures 1. a and b). Upper and lower lips have multiple superficial erosive lesions, erythematous base of irregular shape, and very painful. White plaques were seen on the dorsum of the tongue, and on the right and left lateral sides of the tongue (Figures 1. c), on the palate and right and left buccal mucosa, shallow, and multiple erosive lesions were found with an erythematous base and irregular edges (Figures 1. d, e and f). The palm and feet as well as the abdomen and neck have blackish red papules and vesicles (Figures 1. g, h, i and j).

CASE MANAGEMENT

Based on the history and clinical examination, the patient's history was taking ciprofloxacin due to cough and fever. Medicines are given by the health clinic where the patient is treated. The drug is taken 2 days later then symptoms appear in the body. the diagnosis was made as an oral lesion associated with Steven Johnson Syndrome. The management in Dermatology department are the administration of cetirizine and dexamethasone as well as the results of laboratory tests including anti-HSV 1 and HSV 2 with non-reactive IgG IgM results, TPHA TITER@ and VDRL with non-reactive results, PCT@ with High ratio (0, 36%), SGOT (AST) with a low value ratio (8 U/L), AP Thoracic examination with no visible bronchopneumonia and cardiomegaly and a negative PCR test for COVID.

The management treatment are prednisone 5 mg mixed with 10 ml of distilled water to be gargled 1-3 minutes and then discarded, 3 times a day, and after 1 hour gargling with prednisone 5 mg followed by, chlorhexidine digluconate 0.12% mouthwash 3 times a day, compress the lips using 0.9% NaCl

dripped on sterile gauze 3-5 times a day with a long compress

for 30 minutes and 1% hydrocortisone ointment is applied to the lips 3 times a day. The dentist is educated the patients and their families about the use of drugs accordance with the rules of drug administration and to always maintain dental and oral hygiene.

The patient's symptoms began to improve on day 5, marked by improving conditions on the lips. The patient is able to speak, eat, drink well and rinse his mouth and brush his teeth slowly. Intra-oral examination showed erythematous and hyperkeratotic areas in almost the entire oral cavity, right and left buccal mucosa, upper and lower labial, and palatal areas. The dermatology department continuing the management of the skin of the patients.

After 3 weeks, the symptoms in the oral cavity showed a very significant improvement. Intraoral examination showed erythema and hyperkeratotic conditions with healing occurs in almost the entire oral cavity. Patients are allowed to consume soft foods orally. Therapy from dermatology department was continued and the oral disease section was chlorhexidine digluconate 0.12% mouthwash and the patient was still asked to maintain his oral health.

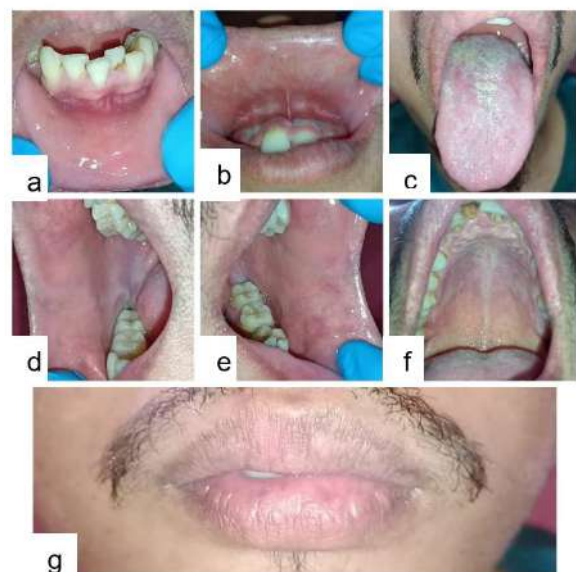


Figure 2. a, b, c, d, e, f and g Clinical features of healing at visit 3

DISCUSSION

The case of Stevens Johnson Syndrome in this patient was found with features of oedema of the lips, crust and easy bleeding, so an examination of HSV 1 HSV 2 IgG IgM was carried out with non-reactive results, then the suspicion of SJS related to the role of the virus could be denied with the results of a non-reactive HSV titer. The definitive diagnosis in this patient was an oral lesion associated with Steven Johnson syndrome caused by a drug reaction.

Drug reactions are described through 4 pathophysiological processes, which are drug-specific CD8+ cytotoxic lymphocytes, apoptotic processes, Fas-Fas ligand (FasL), granule-mediated exocytosis and *tumor-alfa* necrosis factor (TNF- α).¹⁴ SJS can involve the interaction and binding of certain drug-associated antigens or metabolites with type 1 major histocompatibility complexes (MHCs) or cellular peptides to form immunogenic compounds.¹⁵

Reactions that occur usually start from day 2 to day 30 after taking certain drugs. In this patient, vesicles appeared on the body on the 2nd day after taking ciprofloxacin and mefenamic acid, previously the patient had no history of excessive drug allergic reactions. Hypersensitivity reactions are thought to be caused by drug reactions after being consumed by the patient. Several theories can explain the condition of patients with drug-related hypersensitivity reactions, including apoptotic process found in cytotoxic granules, is the main cause of keratinocyte apoptosis, the second process is Fas-fas ligand (FasL) expressed on activated cytotoxic T cells can also destroy keratinocytes through the production of intracellular caspases, the third process is Cytotoxic lymphocytes secrete perforin and Granzyme B which create channels in the target cell membrane activating Caspases. The fourth process by which TNF- α can cause apoptosis and induce Nitrous oxide (NO) which is also induced by TNF- α and interferon

(IFN)- α that stimulated Caspases enzymes.¹³

Ciprofloxacin normally in the body works with the help of CYP1A2 and CYP3A4 enzyme metabolism, but in SJS patients the process is inhibited.^{16,17} Some literature describes the SJS process associated with ciprofloxacin being activated by CD8+ cells and cytotoxicity to keratinocytes occurs through activation of the enzymes Granzyme B and granzysin in the Fas-Fas ligand (FasL) pathway. Epidermal cell apoptosis, which can be mediated through keratinocyte Fas-FasL interactions or through the release of cytotoxic T cells from perforin and Granzyme B, is also associated with tissue damage to skin and mucosal tissues.¹⁴⁻²⁰ It can be seen that the apoptotic process, Fas-fas ligand (FasL), Cytotoxic lymphocytes, TNF- α , that damage or inflammation of tissue in the skin and oral cavity is closely related to drug-related hypersensitivity reactions.

Mucosal conditions mostly involving the oral mucosa can cause erythema, edema, peeling, ulceration, crusting and necrosis. Seen in the oral mucosa, abnormalities can be in the form of ulcers on the lips, tongue, palate and buccal mucosa.^{15,16} Based on U.K guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016 in the treatment of SJS, especially in the oral cavity, requires topical analgesics, topical antiseptics, corticosteroid ointments and corticosteroid mouthwashes. in this case we use prednisone 5 mg as anti-inflammatory drugs is considered only to reduce the severity of ulcers in the oral cavity.¹⁷ Prednisone gargling can relieve complaints and reduce symptoms in the oral cavity because there is an inflammatory reaction by suppressing the inflammatory process, hydrocortisone ointment 1% is used to treat redness, swelling and itching. Hydrocortisone belongs to a class of drugs called corticosteroids that act as anti-inflammatory and suppress the inflammatory process. Considered very effective for complaints in the oral cavity function generally suppresses cytokine and chemokine responses



related to inflammation and inflammation in the oral cavity.¹⁸

Topical hydrocortisone is used to treat redness, swelling and itching. Hydrocortisone belongs to a class of drugs called corticosteroids that act as anti-inflammatory and suppress the inflammatory process

Treatment of ulcers in the oral cavity can use hydrocortisone ointment 1% and prednisone 5 mg mixed with 10 ml of saline water or 10 ml of distilled water, prescribed for 7-10 days with 2-4 times daily use.¹⁷ The topical therapy used in this case involves several methods of transporting topical drugs across the oral mucosa, namely passive diffusion (passing and entering mucosal cells, and passing between mucosal cells), carrier mediated transport (paths mediated by membrane proteins) and endocytosis (macromolecular pathways and drug material into mucosal cells and mucoadhesion occurs).¹⁹

The mechanism of 0.9% NaCl solution in the treatment of lesions on the lips of SJS patients as a moist wound healing that has a moisturizing principle.²⁰ The goal is to maintain moisture in the lesion to facilitate cell movement in the wound, and accelerate the granulation process which reaches 40% compared to the dry state, keep the surface of the lesion moist so that the development and migration of epithelial tissue increases.^{21,22} This condition will optimize the activity of neutrophils, macrophages, and fibroblasts. The basic theory in the process of healing lesions with the moist principle includes accelerating fibrinolysis, accelerating angiogenesis, reducing the risk of infection, accelerating the process of formation of growth factors, and accelerating the formation of active cells.^{22,23}

CONCLUSION

Steroid mouthwash to suppress inflammation as well as a combination of 0.12% chlorhexidine digluconate antiseptic drug suppresses the infection process and complications that continue in the oral cavity and

0.9% NaCl solution as a moist wound healing. This therapy plays an important role in the healing process of oral lesions in patients with SJS.

REFERENCES

1. Banik B, Bhar D, Sil A. Terbinafine-induced Steven-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) overlap. *Postgrad Med J* 2020;1(D):1–2.
2. Ward KE, Archambault R, Mersfelder TL. Severe adverse skin reactions to nonsteroidal antiinflammatory drugs: A review of the literature. *Am J Heal Pharm* 2010;67(3):206–13.
3. Shah SN, Chauhan GR, Manjunatha BS, Dagrur K. Drug induced erythema multiforme: Two case series with review of literature. *J Clin Diagnostic Res* 2014;8(9):ZH01–4.
4. Hall JC, Hall BJ. Cutaneous drug eruptions: Diagnosis, histopathology and therapy. *Cutan Drug Eruptions Diagnosis, Histopathol Ther* 2015;1–444.
5. Miya R, Malpani AK, Keri S, Panagaon R. Drug Induced Steven- Johnson Syndrome (SJS). *Indian J Pharm Pract* 2019;12(2):133–5.
6. Xu L, Zhu Y, Yu J, Deng M, Zhu X. Nursing care of a boy seriously infected with Steven-Johnson syndrome after treatment with azithromycin. *Med (United States)* 2018;97(1):9–12.
7. Rajput R, Sagari S, Durgavanshi A, Kanwar A. Paracetamol induced Steven-Johnson syndrome: A rare case report. *Contemp Clin Dent* 2015;6(Suppl 1):S278–81.
8. Asif SM, Shamsudeen SM, Assiri KI, Muburak HM Al, Kaleem SM, Khan AA, et al. Drug induced oral erythema multiforme: Case report. *Medicine (Baltimore)* 2021;100(17):e22387.
9. Aschalew S, Hailu L. Drug Induced-Stevens Johnson Syndrome. 2020;(January):0–4.
10. Isaac Joseph T, Vargheese G, George D, Sathyan P. Drug induced oral erythema multiforme: A rare and less recognized variant of erythema multiforme. *J Oral Maxillofac Pathol* 2012;16(1):145–8.
11. Fitriana A, Endaryanto A, Hidayati AN, Kedokteran F, Airlangga U. Gambaran Klinis Steven Johnson Syndrome dan Toxic Epidermal Necrolysis pada Pasien Anak (Clinical Presentation of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in



- Pediatric Patient). *Period Dermatology Venereol* 2018;30(2):102–10.
12. Dr. dr. Ago Harlim, MARS SK. *ILMU KESEHATAN KULIT DAN KELAMIN DASAR DIAGNOSIS DERMATOLOGI*. 2017.
 13. Davis RL, Gallagher MA, Asgari MM, Eide MJ, David J, Macy E, et al. *HHS Public Access*. 2020;24(7):684–92.
 14. Cravens MG, Sherman N, Sawaya J. Ciprofloxacin-induced Stevens-Johnson Syndrome with Grapefruit Juice Consumption: A Case Report. *Cureus* 2019;11(1):1–4.
 15. Charlton OA, Harris V, Phan K, Mewton E, Jackson C, Cooper A. Toxic Epidermal Necrolysis and Steven-Johnson Syndrome: A Comprehensive Review. *Adv Wound Care* 2020;9(7):426–39.
 16. Raffaele RM. Treatment Using Low Level Laser Therapy in The Oral Manifestations of Steven Johnson Syndrome. *J Intern Med Emerg Res* 2020;1(3).
 17. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JKG, et al. U.K. guidelines for the management of Stevens–Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016;174(6):1194–227.
 18. Rafika M, Sufiawati I. Efficacy of corticosteroids in oral lesion treatment associated with Steven-Johnson syndrome and toxic epidermal necrolysis in HIV patient (A Case Report). *J Int Dent Med Res* 2019;12(2):709–15.
 19. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Adv Drug Deliv Rev* 2012;64(1):16–28.
 20. Varga MA. Moist Wound Healing: Past and Present. *Wound Care Canada* 2012;10(2):12–9.
 21. Nagakeerthana S, Rangaraj M, Karthikeyan K. One drug-two similar reactions. Report of cases of ciprofloxacin induced stevens-johnson syndrome and bullous fixed drug eruption. *J Young Pharm* 2016;8(2):161–3.
 22. Rostini, Intang A, Darwis. Pengaruh penggunaan larutan nacl 0,9% terhadap lama hari rawat pada pasien vulnus laceratum di rumah sakit umum daerah h. andi sulthan daeng radja kabupaten bulukumba. *Ilm Kesehat diagnosis* 2013;2(4):1–6.
 23. Handayani LT. Studi Meta Analisis Perawatan Luka Kaki Diabetes Dengan Modern Dressing. *Indones J Heal Sci* 2016;6(2):149–59.



The Effect of Kersen (*Muntingia calabura L.*) Leaf Extract Nanogel on Stomatitis

Ariyati Retno Pratiwi*, Linda Risalatul Muyasaroh**

*Department of Oral Biology, Faculty of Dentistry, Brawijaya University

**Student Faculty of Dentistry, Brawijaya University

Online submission : 15 February 2022

Accept Submission : 23 February 2022

ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is common painful mucosal condition affecting the 5%-60% world's population and become the third largest oral disease in Indonesia. Despite their high prevalence, RAS treatment is currently still dominated by the use of chemicals that scientifically have adverse side effects. Therefore, it is necessary to develop new approach using herbal product with no side effects. This literature review summarizes the potential of kersen leaf extract (*Muntingia calabura L.*), its dosage forms, and the possibility using nanotechnology that can speed up the drug delivery process. **Objective:** to determine the possibility effect of nanoparticle cherry leaf extract in gel form on decreasing number of macrophages and stimulating collagen in stomatitis. **Methods:** literature search using the PRISMA method with Science Direct, PubMed, Scielo, NCBI, Research gate, and Google Scholar databases of 1107 articles with keywords "Muntingia calabura L. leaves extract", "nanogel", "flavonoid", "quercetin", "fisetin", "macrophage", "collagen", "soft tissue healing process" and "recurrent aphthous stomatitis". The results of the literature selection found 22 articles. **Results:** flavonoids in cherry leaf extract can reduce the number of macrophages and increase collagen stimulation. The mechanism of action begins by inhibiting the production of pro-inflammatory cytokines, inhibiting macrophage migration and adhesion, stimulating the production of growth factors by macrophages for collagen synthesis, and decreasing collagenase. Nano gel form may increase retention time and drug penetration. **Conclusion:** Nanogel based cherry leaf extract may reduce the number of macrophages and stimulating collagen in minor RAS.

Keywords: Kersen leaf, Nanoparticle, Collagen, Macrophage, RAS

Correspondence: Ariyati Retno Pratiwi, M.Kes, Department of Oral Biology, Faculty of Dentistry, Brawijaya University, Malang, East Java, Indonesia Email: ariyatiretnop@ub.ac.id

INTRODUCTION

Dental and oral health is a very important aspect of a person's life. However, Indonesian people's awareness of the importance of maintaining dental and oral health is still low. This is consistent with the fact that there has been an increase in the prevalence of dental and oral diseases in Indonesia from 2013 to 2018 by 25.9% to 57.6%.^{1,2} Recurrent aphthous stomatitis (RAS) is the third largest oral disease in Indonesia with a prevalence of 8%, reaching 5%-60% of the world's population.³ The prevalence of RAS is very high in developing countries and 80% of people experience RAS before the age of 30 years.⁴

Recurrent aphthous stomatitis (RAS) is the most common ulcerated condition of the oral mucosa with characteristic round, painful ulcers, surrounded by a reddish area, and covered by a pseudomembrane.⁵ The etiology of RAS is unknown, but it is associated with various predisposing factors such as a family history of RAS, mechanical trauma, hormonal imbalance, stress, food allergies, bacterial and viral infections, immunological factors, iron deficiency, nutrition, and smoking.^{6,7} Management of RAS aims to reduce pain, speed healing, reduce the number and size of ulcers, and increase the disease-free period^[8].

Drugs used for the treatment of RAS include topical anti-inflammatory steroids (Hydrocortisone hemisuccinate, Triamcinolone acetonide, and Betamethasone valerate), topical antiseptics (Chlorhexidine, Triclosan), topical non-steroidal anti-inflammatory drugs (Benzydamine Hydrochloride, Diclofenac) and systemic drugs (Tetracycline, Colchicine, Dapsone, thalidomide). Generally, RAS treatment uses topical steroids.⁹ However, long-term and/or repeated use of steroid drugs have side effects such as adrenal suppression, candidiasis, and burning sensation, bad taste in the mouth, mucosal atrophy, nausea, sore throat, and xerostomia.^{10,11} Currently, the use of herbal medicines is more widely developed because it has no side effects and 85% comes

from plant extracts.^{12,13} Therefore, the author wants to know the effect of herbal ingredients, namely cherry plants, on the healing of RAS.

Cherry plant is a flowering plant from the Elaeocarpaceae family which is widely found in tropical areas such as Malaysia, India, South America, Central America, and Indonesia.¹⁴ Several studies have proven that the content in cherry leaves has anti-inflammatory and antioxidant activity^[13,14,16]. Cherry leaves contain flavonoid compounds, tannins, triterpenes, saponins, and polyphenols with the highest flavonoid concentration of 70%^[17]. The types of flavonoids found in cherry leaves include flavones, flavonols, flavans, and biflavans^[18]. Flavonoids themselves are known as anti-inflammatory and antioxidant bioactive substances that can accelerate the healing of RAS.¹⁹

Flavonoids are compounds with low solubility in water, very hydrophobic, and chemically unstable under physiological conditions. Flavonoids are very sensitive to environmental factors such as temperature, pH, and light. The low solubility causes limitations on the use of flavonoids and the acceptance of flavonoids as herbal medicines.²⁰ The most effective way of drug delivery for poorly soluble bioactive molecules such as flavonoids is to use nanoparticles. Nanoparticles have the highest drug loading efficiency and can protect flavonoids from degradation due to physiological conditions (especially due to endogenous enzyme activity).^{20,21} Flavonoids in cherry leaf extract can work optimally in treating recurrent aphthous stomatitis (RAS) if it is in the form of nanogels. Based on the problems above, the authors wanted to know the effect of cherry leaf extract (*Muntingia calabura* L.) on the reduction of the number of macrophages and stimulation of collagen as an alternative treatment for stomatitis based on nanogels.

PURPOSE

To determine the effect of cherry leaf extract nanogel on decreasing the number of

macrophages and collagen stimulation in stomatitis.

METHODS

The research design used is a systematic literature review (SLR) by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. Systematic literature review is a research method to identify, evaluate and interpret all relevant research results related to certain research questions and topics.²²

The journals used in the literature review were obtained through a database of international journal providers, namely Science Direct, PubMed, Scielo, NCBI, Research Gate, and Google Scholar. The relevant sources are then stored as a reference for selection. The keywords used for the journal search were "Muntingia calabura L. leaves extract", "nanogel", "flavonoid", "quercetin", "fisetin", "macrophage", "collagen", "soft tissue healing process" and "recurrent aphthous stomatitis". The data search was taken based on the inclusion criteria. The inclusion criteria in this literature review include literature that is included in the category of journal articles (original article), published in English, fully accessible, belongs to the health sciences group, published from 2011-2021, and must contain research data related to keywords

RESULTS

As shown in the image below (Figure 1), based on online search of the database, 1,107 articles were found. Furthermore, they were selected using the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) method. The final results of the selection were 22 literatures.

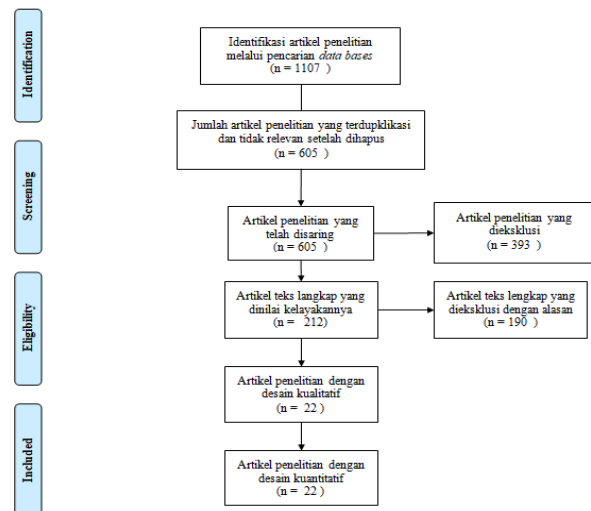


Figure 1. PRISMA Diagram

DISCUSSION

This literature review discusses the effect of cherry leaf extract (*Muntingia calabura* L.) as a nanogel-based topical drug on the treatment of Recurrent Aphthous Stomatitis (SAR) with variable number of macrophages and collagen stimulation. Recurrent aphthous stomatitis (RAS) is a common oral lesion with unclear etiology, but has predisposing factors such as stress and nutritional deficiency. In RAS patients there is an excessive inflammatory process. SAR treatment itself aims to reduce pain and speed up the healing process. Research Pandya et al. in 2017 showed that flavonoid compounds from herbal ingredients were able to provide analgesic, antibacterial, anti-inflammatory effects, and without side effects in patients with minor RAS.²⁴

Cherry leaves through a maceration process with 70% and 96% ethanol solvents produced the highest amount of flavonoids. Types of flavonoid compounds in cherry leave include rutin, quercetin, and fisetin. However, the type of flavonoid compound that has the highest concentration is quercetin. The concentration of quercetin in cherry leaves reached 10.255%.

25,18,26,27,28,29

Cherry leaf extract (*Muntingia calabura* L.) was then developed into nanoparticles and processed into a gel-based topical preparation.

The application of nanotechnology in drug delivery aims to protect flavonoids from degradation due to oxidative and enzymatic environments. The gel preparation was chosen because it has advantages such as stabilizing the application of nanoparticles, prolonging drug contact time with the mucosa, increasing bioavailability, and providing a protective layer on the lesion from mechanical irritation and bacterial contamination.^{30,31,24} Research by Karavana et al. in 2012 also proved that nanogel preparations increase retention time and penetration of bioactive ingredients to the mucosal surface thereby accelerating the healing process of RAS.³²

The mechanism of action of flavonoids in suppressing excessive inflammation in RAS is by reducing the number of inflammatory cells such as macrophages, neutrophils, and lymphocytes, suppressing the production of pro-inflammatory cytokines (IL-6, IL-1, TNF-, NF-B), and reducing pro-inflammatory cytokines and

release of reactive oxidative stress (ROS) by macrophages.^{28,33,34,35,36,37,38} The research of Cui et al. in 2019 also explained the effect of flavonoids on macrophage activity including by inhibiting Nitric Oxide (NO) production, migration, and macrophage adhesion.³⁹ The mechanism of action of flavonoids in the wound healing process (ulcer) in RAS includes stimulating macrophages to produce growth factors (TGF- β , FGF-2, and VEGF) and reducing collagenase (MMP-9 and MMP-13). Increased TGF- will induce fibroblast cell proliferation and increase collagen synthesis, deposition, and maturation. Increased fibroblast growth factor (FGF-2) will increase the synthesis and formation of collagen. Increased vascular endothelial growth factor (VEGF) will stimulate angiogenesis so that it can induce the process of migration, proliferation, and differentiation of endothelial cells. Proliferation of capillary blood vessels is needed as an oxygen and nutrient pathway for tissue growth.^{35,40,41,31,42,43,44}

Table 1. Literature review

No	Name	Year	Title	Objective	Research Methods	Research Results	Conclusion
1.	Nguyen and Thao	2020	Wound Healing Activity of <i>Crassocephalum crepidioides</i> (Benth.) S. Moore. Leaf Hydroethanolic Extract	Histological observation using H&E staining	Observation of TNF- α , NF-B, TGF- β , and VEGF numbers using Quantitative Real-Time PCR.	The quercetin-type flavonoid increases TGF- β and VEGF. Elevated TGF- induces fibroblast proliferation and increases collagen synthesis, deposition, and maturation. Quercetin can also decrease the number of inflammatory cells such as macrophages and pro-inflammatory cytokines (TNF- α , NF- κ B).	Quercetin-type flavonoids can reduce the number of inflammatory cells such as macrophages and increase the synthesis, deposition, and maturation of collagen.
2.	Pertiwi, R. D., Suwaldi, Martien, R., & Setyowati, E. P.	2020	Radical Scavenging Activity and Quercetin Content of <i>Muntingia calabura</i> L. Leaves Extracted by Various Ethanol Concentration	Determination of the amount of flavonoids	Determination of flavonoids using colorimetric and the amount of quercetin using thin layer chromatography (TLC)	Cherry leaf ethanol extract contains flavonoids, tannins, saponins, and phenols. The highest number of flavonoids was obtained with 96% ethanol solvent. The highest amount of quercetin was obtained by using 50% ethanol as solvent.	Cherry leaf ethanol extract contains flavonoids, tannins, saponins, and phenols.

3	Prayitno and Rahim	2020	Comparison of Extracts (Ethanol and Aqueous Solvents) <i>Muntingia calabura</i> Leaves on Total Phenol, Flavonoid, and Antioxidant (Ic ₅₀) Properties	Determination of the number of flavonoids and analysis of the antioxidant activity of cherry leaves.	Extraction using the maceration method was then carried out by the DPPH method.	The number of flavonoids using 96% ethanol and aqueous solvents, respectively, was 42.46 mg of QE/g and 16.22 mg of QE/g.	The highest number of flavonoids was obtained from cherry leaf extraction using 96% ethanol.
4	Sari, A. S., Melly, E., Nasir, M. M., Muhammad, R. A. R.	2020	Identification of Active Compounds on <i>Muntingia calabura</i> L. Leaves Using Different Polarity Solvents	To identify the content of cherry leaf extract with polar solvents (ethanol, ethyl acetate, and n-hexane).	.Mayer- Dragendorff test (alkaloids), Shinoda test (flavonoids), saponin (H ₂ O) test, iron chloride test (tannins and phenols), and Salkowski test (terpenoids)	The content of cherry leaves is higher in polar solvents such as ethanol than in non-polar solvents. Cherry leaf ethanol extract contains high flavonoids, tannins, saponins, alkaloids, and terpenoids.	Cherry leaf content was higher in polar solvents such as ethanol than non-polar. Cherry leaf ethanol extract contains high flavonoids, tannins, saponins, alkaloids, and terpenoids.
5	Setyadewi, C. M., Suzery, M., Agustina, L. N. A., & Bambang, C.	2020	The Comparison of Spectrophotometric and TLC-Densitometric for DPPH Radical Scavenging Activity Analysis of Three Medicinal Plant Extract.	To identify flavonoid compounds and antioxidant activities.	DPPH and TLC.	Cherry leaf extract contains high levels of flavonoids. The highest type of flavonoid is quercetin with a concentration of 10.255%.	Cherry leaf extract contains high levels of quercetin-type flavonoids.
6	Cui, S., Wu, Q., Wang, J., Li, M., Qian, J., & Li, S	2019	Quercetin Inhibits LPS-induced Macrophage Migration by Suppressing the iNOS/FAK/Paxillin Pathway and Modulating The Cytoskeleton	To determine the effect of quercetin on migration, adhesion, and production of NO in macrophages.	Histological testing with crystal violet staining, method of Transwell cell culture chambers.	Quercetin inhibits NO production, migration and adhesion of macrophages.	Quercetin type flavonoids can inhibit macrophage production.
7	Permatasari, D. A., Karliana, D., Iskandarsyah, I., Arsianti, A., & Bahtiar, A.	2019	Quercetin Prevent Proteoglycan Destruction by Inhibits Matrix Metalloproteinase-9, Matrix Metalloproteinase-13, A Disintegrin and Metalloproteinase with	To find out the number of MMP.	The in vivo test was then carried out histological test.	Quercetin nanogels were able to reduce the number of MMP-9 and MMP-13 so that they could reduce ECM (collagen) degradation.	The quercetin type flavonoid nanogel can reduce ECM (collagen) degradation.

			Thrombospondin Motifs-5 Expression on Osteoarthritis Model Rats				
8	Rhimi, W., Hlel, R., Ben Salem, I., Boulila, A., Rejeb, A., & Saidi, M.	2019	<i>Dirtrichia viscosa</i> L. Ethanol Extract Based Ointment with Antiradical, Antioxidant, and Healing Wound Activities	To determine the number of inflammatory cells and collagen fibers.	In vivo test. Histological observations using H&E staining	Flavonoids (quercetin) can reduce the number of inflammatory cells and increase collagen fiber proliferation.	Flavonoids (quercetin) can increase collagen fiber proliferation.
9	Roodbordei, F., Afshar, M., Haji Abas Tabrizi, F., Chooapani, S., Torkaman, G., Moayer, F., & Salimi, M.	2019	Topical Hydrogel Containing <i>Fumaria vaillantii</i> Loisel. Extract Enhances Wound Healing in Rats.	To determine the amount of quercetin type flavonoid and its use in the wound healing process	Determination of quercetin using HPLC. Histopathological observation of collagen with H&E staining.	Quercetin-type flavonoid hydrogel has anti-inflammatory activity and increases collagen synthesis. Hydrogel preparations are suitable for promoting wound healing.	The preparation of quercetin type flavonoid in gel form is suitable for promoting wound healing.
10	Desrini, S., Mashita, A. I., Rosary, A. N., Hidayah, U. N., & Farm, S.	2018	Antibacterial Activity Screening of <i>Muntingia Calabura</i> L. Leaves Methanol Extract on Three Bacterial Pathogens	To determine the content of cherry and its antibacterial activity.	A phytochemical test of cherry leaf extract using TLC, then an in vitro test was carried out.	Cherry leaf extract contains flavonoid, tannin and saponin compounds. These compounds possess antibacterial activity.	Cherry leaf extract contains flavonoid, tannin and saponin compounds.
11	Ernawati and Ade	2018	Expression of Vascular Endothelial Growth Factor and Matrix Metalloproteinase-9 in <i>Apis mellifera</i> Lawang Propolis Extract Gel-Treated Traumatic Ulcers in Diabetic Rats	To determine the effect of flavonoids in propolis gel on the amount of VEGF and MMP-9 chronic traumatic ulcers in the oral cavity.	In vivo test, then immunohistochemical imaging was also performed using monoclonal antibody combined with antigen reaction.	Flavonoids stimulate macrophages to produce VEGF and FGF-2 thereby inducing angiogenesis, and can increase the synthesis of ECM (collagen). Flavonoids also decrease MMP-9 expression.	Flavonoids can increase ECM (collagen) synthesis.

12	Jin, Y., Lin, X., Song, L., Liu, M., Zhang, Y., Qi, X., & Zhao, D.	2017	The Effect of Puding Anti-Inflammatory Oral Liquid on the Treatment of Mild Recurrent Aphthous Ulcers	To determine the effect of flavonoids on RAS.	Experimental.	Flavonoids can inhibit the production of pro-inflammatory mediators (NO, PGE2, TNF- α , and IL-6) macrophages.	Flavonoids can inhibit macrophage production.
13	Pandya, M., Kalappanavar, A. N., Annigeri, R. G., & Rao, D. S.	2017	Relative Efficacy of Quercetin Compared with Benzydamine Hydrochloride in Minor Aphthae: A Prospective, Double-Blind, Active Control, Preliminary Study	To prove that flavonoid gel (quercetin) is effective, safe, and faster in curing minor RAS compared to Benzydamine Hydrochloride.	Randomized, prospective, parallel-group, and active-controlled.	The flavonoid gel (quercetin) cured minor SAR faster than Benzydamine HCL 0.15% in 7 days. Quercetin is able to provide analgesic, antibacterial, and anti-inflammatory effects on the patient. Giving quercetin has no side effects.	Flavonoid gel (quercetin) heals minor RAS more quickly.
14	Quagliarillo, V., Iaffaioli, R. V., Armenia, E., Clemente, O., Barbarisi, M., Nasti, G., Berretta, M., Ottaiano, A., & Barbarisi, A.	2017	Hyaluronic Acid Nanohydrogel Loaded with Quercetin Alone or in Combination to a Macrolide Derivative of Rampamycin RAD001 (Everolimus) as A New Treatment for Hormone-Responsive Human Breast Cancer.	To determine the effectiveness of quercetin nano hydrogel.	Nanotechnology	Nano technology as a drug delivery flavonoid type quercetin was developed as a drug protector from oxidative and enzymatic environments.	The nanogel formulation improves drug delivery.
15	Zaccaria, V., Curti, V., Di Lorenzo, A., Baldi, A., Maccario, C., Sommatì, S., Mocchi, R., & Daglia, M.	2017	Effect of Green and Brown Propolis Extracts on the Expression Levels of microRNAs, mRNAs and Proteins, Related to Oxidative Stress and Inflammation	To determine the effect of flavonoids on the inflammatory process.	Real-Time PCR Test.	Flavonoids can inhibit the production of pro-inflammatory cytokines (TNF- α) by macrophages.	Flavonoids as an anti-inflammatory compounds.
16	Krishnappa, P., Venkatarangaiah, K., Venkatesh, Shimoga	2016	Wound Healing Activity of <i>Delonix elata</i> Stem Bark and Its	To determine the effect of quercetin-type flavonoids on the amount of collagen in the	In Vivo test was then carried out histopathological observation of collagen with	The flavonoid gel (quercetin) increases collagen synthesis through up-regulation of Col 1.	Flavonoid gel (quercetin) can increase collagen synthesis.

	Rajanna, S. K., & Kayattukan dy Balan, R.		Isolated Constituent Quercetin-3-rhamnopyranosyl-(1-6) Glucopyranoside in Rats	wound healing process.	H&E staining. The amount of collagen was calculated using the Neuman and Logan method.		
17	Albaayit, S. F. A., Abba, Y., Rasedee, A., & Abdullah, N.	2015	Effect of <i>Clausena excavata</i> Burm. F. (Rutaceae) Leaf Extract on Wound Healing and Antioxidant Activity in Rats	To find out the role of quercetin in the wound healing process.	In vivo test. Histopathological observations using H&E staining and Masson trichome.	Flavonoids (quercetin) reduce the inflammatory response, increase collagen synthesis and maturation, increase angiogenesis.	Flavonoid (quercetin) has anti-inflammatory activity and can increase collagen synthesis.
18	Kim, J. H., Kim, M.-Y., Kim, J.-H., & Cho, J. Y.	2015	Fisetin Suppresses Macrophage-Mediated Inflammatory Responses by Blockade of Src and Syk	To determine the effect of fisetin on macrophages.	In Vitro test.	Fisetin is a type of flavonoid compound that functions as a suppressor of the macrophage cell inflammatory response.	Flavonoids (Fisetin) have anti-inflammatory activity.
19	Gavanji, S., Larki, B., & Bakhtari, A.	2014	The Effect of Extract of <i>Punica granatum</i> var. Pleniflora for Treatment of Minor Recurrent Aphthous Stomatitis	To determine the effect of Punica granatum alcohol extract flavonoids on minor RAS	Double-blind.	Flavonoids can inhibit pro-inflammatory cytokines (IL-1 and IL-6) and oxidative stress produced by macrophages.	Flavonoids have anti-inflammatory activity.
20	Zakaria, Z. A., Sani, M. H. M., Cheema, M. S., Kader, A. A., Kek, T. L., & Salleh, M. Z.	2014	Ant nociceptive Activity of Methanolic Extract of <i>Muntingia calabura</i> Leaves: Further Elucidation of The Possible Mechanism	Determination of cherry content and types of flavonoids.	Phytochemical screening using HPLC analysis then performed ant nociceptive assays.	Cherry leaf ethanol extract contains flavonoids, triterpenes, saponins, and tannins. The types of flavonoids found in cherry leaves are routine, quercetin, and fisetin. Quercetin can inhibit pro-inflammatory cytokines.	Cherry leaf ethanol extract contains the flavonoids of rutin, quercetin, and fisetin.
21	Karavana, S. Y., Gökçe, E. H., Rençber, S., Özbal, S., Pekçetin, Ç., Güneri, P., & Ertan, G.	2012	A New Approach to The Treatment of Recurrent Aphthous Stomatitis with Bio adhesive Gels Containing Cyclosporine A Solid Lipid Nanoparticles : in vivo/in	To determine the effectiveness of gel formulations with Nano technology for SAR treatment.	In Vivo test and In Vitro test.	Nano gel preparations increase retention time and penetration of bioactive ingredients to the mucosal surface thereby accelerating the healing process of RAS.	Nanogel preparations are suitable for RAS treatment

			vitro Examinations				
22	Machado, J. L., Assunção, A. K. M., da Silva, M. C. P., Dos Reis, A. S., Costa, G. C., Arruda, D. de S., Rocha, B. A., Vaz, M. M. de O. L., Paes, A. M. de A., Guerra, R. N. M., Berretta, A. A., & do Nascimento, F. R. F.	2012	Brazilian Green Propolis: Anti-Inflammatory Property by Immunomodulatory Activity	To determine the effect of flavonoids in propolis on the inflammatory response.	In Vivo test	Flavonoids can reduce the number of inflammatory cells (macrophages, neutrophils, and lymphocytes).	Flavonoids can reduce the number of macrophages.

CONCLUSION

Based on a literature review study that has been carried out by the authors of 22 journals, it can be concluded that the cherry leaf extract (*Muntingia calabura L.*) may have effect on healing minor type of recurrent aphthous stomatitis (RAS). This is because the content of flavonoids in cherry leaves as an anti-inflammatory can reduce the number of macrophages and increase collagen synthesis. Further research in the laboratory is needed to determine the effectiveness of cherry leaf (*Muntingia calabura L.*) as a nanogel-based herbal medicine for recurrent aphthous stomatitis (RAS).

REFERENCES

- Kementerian Kesehatan RI. Riset Kesehatan Dasar. Jakarta; 2014.
- Kementerian Kesehatan RI. Riset Kesehatan Dasar. Jakarta; 2018.
- Abdullah M. Prevalence of Recurrent Aphthous Ulceration Experience in Patients Attending Piramird Dental Speciality in Sulaimani City. Journal of Clinical and Experimental Dentistry. 2013; 89-94. Available from: <https://doi.org/10.4317/jced.51042>.
- Ranganath SP, Pai A. Is Optimal Management of Recurrent Aphthous Stomatitis Possible? A Reality Check. Journal of Clinical and Diagnostic Research : JCDR. 2016; 10(10): 8-13. Available from: <https://doi.org/10.7860/JCDR/2016/19519.8643>
- Bahramian A, Falsafi P, Abbasi T, Ghanizadeh M, Abedini M, Kavoosi F, et al. Comparing Serum and Salivary Levels of Vitamin D in Patients with Recurrent Aphthous Stomatitis and Healthy Individuals. Journal of Dentistry. 2018; 19(4): 295–300.
- Chiang CP, Yu-Fong CJ, Wang YP, Wu YH, Wu YC, Sun A. Recurrent Aphthous Stomatitis – Etiology, Serum Autoantibodies, Anemia, Hematinic Deficiencies, and Management. Journal of the Formosan Medical Association. 2019; 118(9):1279–89. Available from: <https://doi.org/10.1016/j.jfma.2018.10.023>.
- Ajmal M, Ibrahim L, Mohammed N, Al-Qarni H. Prevalence and Psychological Stress in Recurrent Aphthous Stomatitis among Female Dental Students in Saudi Arabia. Clujul Medical. 2018; 91(2): 216–21. Available from: <https://doi.org/10.15386/cjmed-840>.



8. Mehdipour M, Taghavi ZA., Sohrabi A, Gholizadeh N, Bahramian A, Jamali Z. A Comparison of the Effect of Triamcinolone Ointment and Mouthwash with or without Zinc on the Healing Process of Aphthous Stomatitis Lesions. *Journal of Dental Research, Dental Clinics, Dental Prospects*. 2016; 10(2): 87–91. Available from: <https://doi.org/10.15171/joddd.2016.014>.
9. Susanto H, Kendarwati P, Imanusti, K, Widyanigsih L, Budiarti S, Supriatno A. Decreased Salivary Cortisol in Recurrent Aphthous Stomatitis Treated with Topical Steroids. *Journal of Islamic Dental Association of IRAN*. 2019; 31(1): 26–32. Available from : <https://doi.org/10.30699/jidai.31.1.5>.
10. Wahba A, Farid M, Adawy H. A Comparative Study between the Combined Effect of Frankincense and Myrrh versus the Effect of Triamcinolone Acetonide on Healing of Induced Labial Mucosal Ulcer in Albino Rats. *Al-Azhar Dental Journal for Girls*. 2017; 4(4): 339–45. Available from: <https://doi.org/10.21608/adjg.2017.5281>.
11. Bakhshi M, Gholami S, Mahboubi, A, Jaafari MR, Namdari M. Combination Therapy with 1% Nanocurcumin Gel and 0.1% Triamcinolone Acetonide Mouth Rinse for Oral Lichen Planus: A Randomized Double-Blind Placebo Controlled Clinical Trial. *Dermatology Research and Practice*. 2020; 1–7. Available from: <https://doi.org/10.1155/2020/4298193>.
12. Rafieian N, Abdolsamadi H, Moghadamnia A, Jazayeri M, Seif-Rabiee M, Salmanzadeh M, et al. Efficacy of Alum for Treatment of Recurrent Aphthous Stomatitis. *Caspian Journal of Internal Medicine*. 2016; 7(3): 201–5.
13. Mahmood N, Nasir NLM, Rofiee MS, Tohid SFM, Ching SM, et al. *Muntingiacalabura L*: a Review on Its Traditional Uses, Chemical Properties and Pharmacological Observations. *Pharm Biol.* . 2014; 52: 1598–1623.
14. Niwele F, Sitepu PS, Simamora A, Timotius KH, Santoso AW. Nutritional Enzymes Inhibitory Activities of Fruit Juice and Fruit Pulp Extract of *Muntingia Calabura L*. *Current Research in Nutrition and Food Science Journal*. 2020; 8(3). Available from : <https://www.foodandnutritionjournal.org/volume8number3/nutritional-enzymes-inhibitory-activities-of-fruit-juice-and-fruit-pulp-extract-of-muntingia-calabura-l-2/>
15. Zakaria ZA, Balan T, Suppaiah V, Ahmad S, Jamaludin F. Mechanism(s) of Action Involved in the Gastroprotective Activity of *Muntingia calabura*. *J Ethnopharmacol*. 2014; 151:1184-93.
16. Rofiee MS, Yusof MIM, Abdul HEE, Bannur Z., Zakaria ZA, Somchit MN, The LK, Salleh MZ. Isolating the Metabolic Pathways Involved in the Hepatoprotective Effect of *Muntingia calabura* against CCl₄-induced Liver Injury using LCMS Q-TOF. *J Ethnopharmacol*. 2015; 106: 109–18.
17. More S, Mohini U, Archana L, Sneha J. Comparative Quantification of Flavonoid Content and Antioxidant Potential of Indigenous Medicinal Plants. *Journal of Pharmacognosy and Phytochemistry*. 2018; 7(1): 343-45. Available from : <http://www.phytojournal.com/archives/2018/vol7issue1/PartE/6-6-296-434.pdf>.
18. Prayitno SA, Rahim AR. Comparison of Extracts (Ethanol And Aquos Solvents) *Muntingia calabura* Leaves on Total Phenol, Flavonid and Antioxidant (Ic50) Properties. *Kontribusi (Research Dissemination for Community Development)*. 2020;3(2):319–25. Available from: <https://doi.org/10.30587/kontribusi.v3i2.1451>.
19. Halim SZ, Zakaria ZA, Omar MH, Mohtarrudin N, Wahab IRA, Abdullah MNH. Synergistic Gastroprotective Activity of Methanolic Extract of a Mixture of *Melastoma malabathricum* and *Muntingia calabura* Leaves in Rats. *BMC Complementary and Alternative Medicine*. 2017;17. Available from: <https://doi.org/10.1186/s12906-017-1992-9>.
20. Mandić L, Sadžak A, Strasser V, Baranović G, Domazet JD, Dutour SM, Šegota S. Enhanced Protection of Biological Membranes during Lipid Peroxidation: Study of the Interactions between Flavonoid Loaded Mesoporous Silica Nanoparticles and Model Cell Membranes. *International Journal of Molecular Sciences*. 2019; 20(11): 2709. Available from: <https://doi.org/10.3390/ijms20112709>.
21. Sims KR, He B, Koo H, Benoit DS W. Electrostatic Interactions Enable Nanoparticle Delivery of the Flavonoid Myricetin. *ACS Omega*. 2020; 5(22): 12649–59. Available from: <https://doi.org/10.1021/acsomega.9b04101>.



22. Kitchenham B. Procedures for Performing Systematic Reviews. Eversleigh: Keele University; 2004.
23. Boren SA, David M. Systematically Reviewing the Literature: Building the Evidence for Health Care Quality. Science of Medicine (Health Management and Informatics) . 2015; 112(1): 58-62.
24. Pandya M, Kalappanavar AN, Annigeri RG, Rao DS. Relative Efficacy of Quercetin Compared with Benzydamine Hydrochloride in Minor Aphthae: A Prospective, Parallel, Double Blind, Active Control, Preliminary Study. International Journal of Dentistry. 2017: 1-6. Available from: <https://doi.org/10.1155/2017/7034390>.
25. Pertiwi RD, Suwaldi, Martien R, Setyowati EP. Radical Scavenging Activity and Quercetin Content of *Muntingia calabura* L. Leaves Extracted by Various Ethanol Concentration. Journal of Food and Pharmaceutical Sciences. 2020; 8(1): 174-84. Available from: <https://doi.org/10.22146/jfps.581>.
26. Sari AS, Melly E, Nasir MM, Muhammad RAR. Identification of Active Compounds on *Muntingia calabura* L. Leaves Using Different Polarity Solvents. Indonesian Journal of Chemical Science and Technology. 2020; 3(1): 1-7.
27. Desrini S, Mashita AI, Rosary AN, Hidayah UN, Farm S. Antibacterial Activity Screening of *Muntingia Calabura* L. Leaves Methanol Extract on Three Bacterial Pathogens. Pharmacologyonline. 2018; 11(2): 1-10. Available from: https://www.researchgate.net/publication/327570126_Antibacterial_activity_screening_of_Muntingia_Calabura_L_leaves_methano_extract_on_three_bacterial_pathogens.
28. Zakaria ZA, Sani MHM, Cheema MS, Kader AA, Kek TL, Salleh MZ. Antinociceptive Activity of Methanolic Extract of *Muntingia calabura* Leaves: Further Elucidation of The Possible Mechanisms. BMC Complementary and Alternative Medicine. 2014; 14: 63. Available from: <https://doi.org/10.1186/1472-6882-14-63>.
29. Setyadewi CM, Suzery M, Agustina LNA, Bambang C. The Comparison of Spectrophotometric and TLC-Densitometric for DPPH Radical Scavenging Activity Analysis of Three Medicinal Plant Extracts. Jurnal Kimia dan Pendidikan Kimia. 2020; 5(2): 110-122.
30. Quagliariello V, Iaffaioli RV, Armenia E, Clemente O, Barbarisi, M, Nasti G, et al. Hyaluronic Acid Nanohydrogel Loaded With Quercetin Alone or in Combination to a Macrolide Derivative of Rapamycin RAD001 (Everolimus) as a New Treatment for Hormone-Responsive Human Breast Cancer. Journal of Cellular Physiology. 2017; 232(8): 2063–74. Available from: <https://doi.org/10.1002/jcp.25587>
31. Roodbordeii F, Afshar M, Haji ATF, Choopani S, Torkaman G, Moayer F, Salimi M. Topical Hydrogel Containing *Fumaria vaillantii* Loisel. Extract Enhances Wound Healing in Rats. BMC Complementary and Alternative Medicine. 2019; 19(254): 1-9. Available from: <https://doi.org/10.1186/s12906-019-2645-y>.
32. Karavana SY, Gökçe EH, Rençber S, Özbal S, Pekçetin Ç, Güneri P, et al. A New Approach to The Treatment of Recurrent Aphthous Stomatitis with Bioadhesive Gels Containing Cyclosporine A Solid Lipid Nanoparticles: In Vivo/In Vitro Examinations. International Journal of Nanomedicine. 2012; 7: 5693–704. Available from: <https://doi.org/10.2147/IJN.S36883>.
33. Gavanji S, Larki B, Bakhtari A. The effect of extract of *Punica granatum* var. *Pleniflora* for Treatment of Minor Recurrent Aphthous Stomatitis. Integrative Medicine Research. 2014; 3(2): 83–90. Available from: <https://doi.org/10.1016/j.imr.2014.03.001>.
34. Zaccaria V, Curti V, Di Lorenzo A, Baldi A, Maccario C, Sommati S, et al. Effect of Green and Brown Propolis Extracts on the Expression Levels of microRNAs, mRNAs and Proteins, Related to Oxidative Stress and Inflammation. Nutrients. 2017;9(10). Available from: <https://doi.org/10.3390/nu9101090>.
35. Nguyen C, Thao D. Wound Healing Activity of *Crassocephalum crepidioides* (Benth.) S. Moore. Leaf Hydroethanolic Extract. Oxidative Medicine and Cellular Longevity, 2020. 2020; 1–10. Available from: <https://doi.org/10.1155/2020/2483187>.
36. Kim JH, Kim MY, Kim JH, Cho JY. Fisetin Suppresses Macrophage-Mediated Inflammatory Responses by Blockade of Src and Syk. Biomolecules & Therapeutics. 2015; 23(5): 414–20. Available from: <https://doi.org/10.4062/biomolther.2015.036>.
37. Jin Y, Lin X, Song L, Liu M, Zhang Y, Qi X, Zhao D. The Effect of Pudilan Anti-Inflammatory Oral Liquid on the Treatment of Mild Recurrent Aphthous Ulcers. Evidence-Based



- Complementary and Alternative Medicine : ECAM. 2017: 1-6. Available from: <https://doi.org/10.1155/2017/6250892>.
38. Machado JL, Assunção AKM, da Silva MCP, Dos RAS, Costa GC, Arruda D, et al. Brazilian Green Propolis: Anti-Inflammatory Property by An Immunomodulatory Activity. Evidence-Based Complementary and Alternative Medicine: ECAM. 2012: 157652. Available from: <https://doi.org/10.1155/2012/157652>.
39. Cui S, Wu Q, Wang J, Li M, Qian J, Li S. Quercetin Inhibits LPS-Induced Macrophage Migration by Suppressing The iNOS/FAK/paxillin Pathway and Modulating The Cytoskeleton. Cell Adhesion & Migration. 2018; 13(1): 1–12. Available from: <https://doi.org/10.1080/19336918.2018.1486142>.
40. Permatasari DA, Karlina D, Iskandarsyah I, Arsianti A, Bahtiar, A. Quercetin Prevent Proteoglycan Destruction by Inhibits Matrix Metalloproteinase-9, Matrix Metalloproteinase-13, A Disintegrin and Metalloproteinase with Thrombospondin Motifs-5 Expressions on Osteoarthritis Model Rats. Journal of Advanced Pharmaceutical Technology & Research. 2019; 10(1): 2–8. Available from: https://doi.org/10.4103/japtr.JAPTR_331_18.
41. Rhimi W, Hlel R, Ben SI, Boulila A, Rejeb A, Saidi M. *Dittrichia viscosa* L. Ethanolic Extract Based Ointment with Antiradical, Antioxidant, and Healing Wound Activities. BioMed Research International. 2019: 1-10. Available from: <https://doi.org/10.1155/2019/4081253>.
42. Ernawati DS, Puspa A. Expression of Vascular Endothelial Growth Factor and Matrix Metalloproteinase-9 in *Apis mellifera* Lawang Propolis Extract Gel-Treated Traumatic Ulcers in Diabetic Rats. Veterinary World. 2018 11(3): 304–9. Available from: <https://doi.org/10.14202/vetworld.2018.304-309>.
43. Krishnappa P, Venkatarangaiah K, Venkatesh, Shimoga RSK, Kayattukandy BR. Wound healing activity of *Delonix elata* Stem Bark Extract and Its Isolated Constituent Quercetin-3-rhamnopyranosyl-(1-6) Glucopyranoside in Rats. Journal of Pharmaceutical Analysis. 2016; 6(6): 389–95. Available from: <https://doi.org/10.1016/j.jpha.2016.05.001>.
44. Albaayit SFA, Abba Y, Rasedee A, Abdullah N. Effect of *Clausena excavata* Burm. F. (Rutaceae) Leaf Extract on Wound Healing and Antioxidant Activity in Rats. Drug Design, Development and Therapy. 2105; 9: 3507–351.

