

ANTIOXIDANT EFFECT OF MOUTHWASH CONTAINING ZINC, *ALOE VERA*, AND STABILIZED CHLORINE DIOXIDE FOR ORAL MANIFESTATION OF ACUTE MYELOBLASTIC LEUKEMIA (AML)

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ABSTRACT

Objective: This paper aims to report a study regarding the successful treatment using zinc, *Aloe vera*, and stabilized chlorine dioxide as an antioxidant mouthwash in a patient with AML.

Methods: A series of clinical examinations, including subjective and objective examinations, were done to establish the diagnosis.

Results: A 9 y old boy, who was already diagnosed with AML, referred to the oral medicine division because of the hemorrhagic crust of his lips. The extra-oral examination showed severe hemorrhagic crust and erosions on the upper and lower lips. The intra-oral examination could not be evaluated in detail, but the active bleeding was seen. A hematology investigation showed pancytopenia. Patients received packed red cell (PRC) and thrombocyte concentrate (TC) blood transfusions, as well as an antioxidant mouthwash containing zinc, *Aloe vera*, and stabilized chlorine dioxide, for compressing the lips every 1-2 h with a duration of 30 min. Significant improvement in lip lesions was gained in a short time after blood transfusions and regular use of the mouthwash compresses.

Conclusion: In this study, the mouthwash containing zinc, *Aloe vera*, and stabilized chlorine dioxide that can accelerate the healing process in our AML patient was estimated due to its antioxidant effects.

Keywords: Zinc, *Aloe vera*, Stabilized chlorine dioxide, Antioxidant, Oral manifestation, Acute Myeloblastic Leukemia

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INTRODUCTION

Acute Myeloblastic Leukemia (AML), which is a hematological malignancy commonly found in children, need an accurate and rapid diagnosis [1-3]. The etiology of AML is poorly defined. Exposure to carcinogenic chemicals have been identified as one of risk factors [3]. Pediatric AML is a relatively rare malignancy. The complete remission (CR) rate is around 80–90%, while the relapse incidence is 30–40%; overall survival (OS) and event-free survival (EFS) approach 70% and 50%, respectively [3]. Diagnoses of acute leukemia requires a bone marrow sample aspirate by morphology, showing $\geq 20\%$ blasts (immature cell population) [4]. Current treatment strategies for newly diagnosed AML typically consist of induction and post-remission consolidation with chemotherapy and/or followed by an allogenic hematopoietic stem cell transplant (HSCT) [5]. Its aim is to target the leukemic stem cell (LSC) compartment, to allow longer remission, and to provide the chance of further consolidation treatment [6]. The most front-line induction chemotherapy is a standard combination of an anthracycline (example doxorubicin) intravenous and continuous infusion cytarabine [4]. Uncontrolled development of AML or chemotherapy administration can cause complications.

Patients with AML generally present with symptoms related to complications of pancytopenia (anemia, neutropenia, and thrombocytopenia), including weakness and easy fatigue, infections of variable severity, and/or hemorrhagic findings such as gingival bleeding, ecchymoses, epistaxis or menorrhagia [7]. Pancytopenia also can result from aplastic anemia (reduction in hematopoietic stem cell production) or it may arise from infection, infiltration of bone marrow, immune-mediated damage or hypersplenism in which normal cells trapped in the hypertrophied and overactive reticuloendothelial system [8].

Compared to other types of leukemia, oral manifestations are ordinarily seen in AML [7]. The oral manifestation of AML is usually associated with bleeding due to pancytopenia [3,4]. Cheilitis with

bleeding followed by severe hemorrhagic crust formations on the lips is one of the manifestations that can sometimes be found and become secondary lesions of the cracked lips [1, 9-11]. Meanwhile, the side effects of chemotherapy are common and become life-threatening. The most common chemotherapy-induced side effects can altered the conditions and functions of the mouth, including nausea, vomiting, fatigue, decreased appetite, changes in taste, and dry mouth, as well as gastrointestinal system [12]. Moreover, it often associated with early mortality [13]. The efficacy of AML therapy can be improved by the management of these side effects [12].

Antioxidant mouthwashes can be given to help accelerate the healing of oral manifestations due to the side effects of the chemotherapy and the progression of AML itself [14, 15], in addition to the management of systemic conditions. Antioxidants are compounds that can inhibit or prevent the formation of free radicals. When antioxidants counteract free radicals by accepting or donating electrons, antioxidants do not turn into free radicals and remain stable [16].

There are two types of antioxidant mouthwash, herbal and chemical. Herbal mouthwash contains a natural ingredient called phytochemical that contains an antioxidant effect. Herbal mouthwashes are safe alternative, especially for children [17, 18]. One of the herbs that have antioxidant properties is *Aloe vera* [17]. It also has anti-inflammatory properties, so that as a mouthwash is quite effective to treat oral mucosal ulcer and infections.

There are three mechanism actions of *Aloe vera* as an antioxidant, including forming hydroperoxides, giving electrons to reactive oxidative stress (ROS), and increasing red blood cell glutathione levels. The examples of chemical antioxidants are gained from zinc and stabilized chlorine dioxide (SCD). The mechanism action of zinc and SCD as an antioxidant is by giving electrons to ROS [19]. This paper aims to report a study regarding the successful treatment using zinc, *Aloe vera*, and SCD as an antioxidant mouthwash for oral lesions in a patient with AML.

MATERIALS AND METHODS

This study has received approval and full consent from the patient’s mother for the publication of data and images. This study had complied with the Declaration of Helsinki. The institution has approved the publication of this study.

A series of clinical examinations have been carried out on patients, including exploring subjective information with anamnesis conducting objective examinations clinically, both physical, extra-oral, and intra-oral examinations. A 9-years-old boy have already diagnosed with AML. The nutritional status of the patient was overweight. AML were diagnosed based on the chief complaints of weakness and fever more than 39° C for more than a week; pale and reddish spots and bruises on the face, as well as found on hands and feet. Blood tests and bone marrow examinations were conducted to establish the diagnosis. Patient was referred from Department of Child Health to Oral Medicine Division of Dr. Hasan Sadikin Hospital because of the hemorrhagic crust of his lips with difficulty eating and opening his mouth.

The patient has been hospitalized and was already diagnosed with AML after bone marrow examination (fig. 1) 15 d ago. Patient was received PRC (packed red cell) and TC (thrombocyte concentrate) blood transfusions, ciprofloxacin (po), mefenamic acid (iv), tranexamic acid (iv), Kabiven (iv), and KA-EN Mg₃ (iv), from Department of Child Health. He also has already got chemotherapy cycle 1 for 5 d with Doxorubicin 50 mg and Cytarabine 126 mg intravenous 10 d ago. From Oral Medicine Divison, patient was received mouthwash containing zinc, *Aloe vera*, and SCD, for compressing the lips every 1-2 h with a duration of 30 min. The drug formula that we used in this study is the commercial preparation Oxyfresh® Lemon variant. The petroleum jelly was also given to moisturize the lips. We gave instructions to clean teeth and tongue if

possible, using gauze soaked in mouthwash containing zinc, *Aloe vera*, and SCD three times a day.

RESULTS

Bone marrow examination result

Bone marrow examination result revealed increased myeloblast (59%), with moderate to abundant cytoplasm, smooth nuclear chromatin, 2 to 4 nucleoli, and mature granulocytes (23%), as shown in (fig. 1).

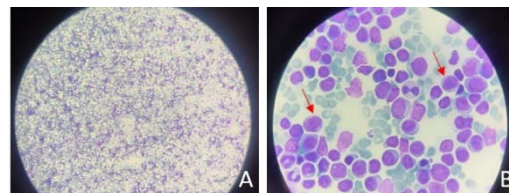


Fig. 1 : Bone marrow examination result (A) Magnification 100x; (B) Magnification 1000x (red arrow showed myeloblast; Source: documentation from Clinical Pathology of Hasan Sadikin Hospital)

Hematologic examination progress results

Hematology investigation showed pancytopenia with low erythrocyte levels and very low hemoglobin, hematocrit, leukocytes, and platelets. The patient’s mother provided informed consent to publish the patient’s study details and any accompanying images. Based on the history review, the clinical examination, and appropriate investigation, the patient was diagnosed with extensive cheilitis et causa pancytopenia AML on upper and lower lips.

Table 1: Hematologic condition from initial visit to fourth visit

Parameter	Initial visit	Second visit (a day follow-up)	Third visit (2 d follow-up)	Fourth visit (9 d follow-up)
Haemoglobin	6,5 g/dl (LL)	6,5 g/dl (LL)	6,6 g/dl (LL)	9,8 g/dl (L)
Hematocrit	19,5% (LL)	19,5% (LL)	18,8% (LL)	28,9% (L)
Erythrocyte	2,46 million/ μ l (L)	2,46 million/ μ l (L)	2,31 million/ μ l (L)	3,47 million/ μ l (L)
Leucocyte	1,07 x 10 ³ / μ l (LL)	1,07 x 10 ³ / μ l (LL)	0,31 x 10 ³ / μ l (LL)	3,13 x 10 ³ / μ l (L)
Thombocyte	6000/ μ l (LL)	6000/ μ l (LL)	24000/ μ l (LL)	121000/ μ l (L)

Note: Normal range for Haemoglobin = 11,5-15,5 g/dl; Hematocrit = 35-45%; erythrocyte = 4,0-5,2 million/ μ l; leucocyte = 4,5-13 x 10³/ μ l; and thrombocyte = 24000/ μ l

Treatment progress result

The results of the extra-oral examination showed severe hemorrhagic crust and erythema erosions on the upper and lower lips (fig. 2). Lymph node examination revealed palpitation with painful on the right and left submandibular gland. The intra-oral examination could not be evaluated in detail, but the active bleeding was seen.



Fig. 2: Oral lesion of the lips in initial visit

From the initial visit to second visit, the patient hasn’t yet given blood transfusion, and there was no significant improvement in lip lesions (fig. 3). Patient has been given blood transfusion start from the second visit. Significant improvement in lip lesions was gained in a short time after blood transfusions and regular use of the mouthwash compresses, as shown in (fig. 4). It could be seen in third and fourth visit. The hematologic condition from the initial visit to fourth visit as shwn in (table 1).



Fig. 3: Oral lesion of the lips in the second visit. The patient hasn’t yet given blood transfusion from the initial to second visit. There was no significant improvement of the lesion



Fig. 4: Significant improvement in lips lesion after blood transfusion and regular use of the mouthwash compresses: (A) third visit (a day after initial blood transfusion), (B) fourth visit (eight days after initial blood transfusion)

DISCUSSION

The mouth may be the site of the first manifestation of AML symptoms. Lesions in the oral cavity in patients with leukaemia can be divided into primary (closely related to hematological disorders and blast infiltrates), secondary (microbial infection), and treatment-related [9]. The primary lesions in the oral cavity during AML include gingival hypertrophy, paresthesia and numbness of the lower lip, spontaneous bleeding, neutropenia-related ulcers, thrombocytopenia-related ecchymoses, pallor of the mucosa, exfoliative cheilitis, atrophic mucositis, ulcerative inflammation of the gums and oral mucosa, angular cheilitis, and bone and tooth pain with no radiological findings [9]. There may be bruising, ecchymosis on the soft and hard palate, and spontaneous bleeding from the gums [9]. This condition is likely a manifestation of thrombocytopenia symptoms which usually develop when the platelet count falls below 50,000 cells/mm³ [9]. The conditions found in this patient are primary and treatment-related oral lesions.

The patient in this study had received the first cycle of induction chemotherapy with doxorubicin and cytarabine. Doxorubicin, which has had wide use and is part of the anthracycline group of chemotherapeutic agents, is an antibiotic derived from the *Streptomyces peucetius* bacterium. It may be used to treat acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and small-cell lung cancer. The primary mechanism of action of doxorubicin involves the drug's ability to intercalate within DNA base pairs, causing breakage of DNA strands and inhibition of both DNA and RNA synthesis. Doxorubicin inhibits the enzyme topoisomerase II, causing DNA damage and induction of apoptosis. When combined with iron, doxorubicin also causes free radical-mediated oxidative damage to DNA, further limiting DNA synthesis. Iron chelators, such as dexrazoxane, may prevent free radical formation by limiting the binding of doxorubicin with iron. Adverse reactions are common after doxorubicin administration, including fatigue, alopecia, nausea and vomiting, and oral sores. Bone marrow suppression and an increased risk of secondary malignancy diagnoses may occur. Doxorubicin extravasation during intravenous administration can result in severe tissue ulceration and necrosis, which worsens over time [20].

Cytarabine, which belongs to the antimetabolic group of medications, is used in the management and treatment of leukemias and lymphomas. It is a pyrimidine analog and is also known as arabinosylcytosine (ARA-C). It is converted into the triphosphate form within the cell and competes with cytidine to incorporate itself into the DNA. It can cross the blood-brain barrier and hence has an off-label use in primary CNS lymphomas. Cytarabine metabolism primarily occurs in the liver. It has an active metabolite-azacytidine triphosphate; and an inactive metabolite-uracil arabinoside, which is cleared by the kidney. Myelosuppression is the most dreaded adverse effect of cytarabine and can present as acute and severe pancytopenia with striking megaloblastic changes. Less life-threatening symptoms include irritation at the site of administration, gastrointestinal disturbances, stomatitis, conjunctivitis, reversible hepatic enzyme elevation, and dermatitis [21].

In this study, patient was diagnosed with extensive cheilitis et causa pancytopenia AML. The patient suffered from hemorrhagic crust on upper and lower lips for about 5 d, accompanied with difficulty of eating and opening his mouth. Hemorrhagic crust is a secondary lesion of cracked lips [11]. These lesions need to be healed so that bleeding and crusting can stop.

Wound healing is an angiogenesis-dependent process reliant on blood vessels to deliver nutrients and oxygen to the regenerating tissue. Oxygen is a requirement for various processes in the healing of wounds, including collagen deposition, epithelialization, fibroplasia, angiogenesis, and resistance to infection. Oxygen is required for adenosine tri-phosphate synthesis within the mitochondria for oxidative metabolism; it is also essential for collagen synthesis and protein synthesis. Oxygen serves as a substrate for all NOX enzymes, which are a major source of ROS. The production of ROS during wound healing is critical for cell signaling, angiogenesis, and wound disinfection [22].

ROS play roles not only in disinfection during the inflammatory phase but also in other phases, including migration, proliferation, and angiogenesis by means of ROS signaling. The presence of excess levels of ROS causes oxidative stress, leading to apoptosis of cells in the surrounding tissues and/or the disruption of redox signaling. Redox homeostasis is established by controlling the balance between ROS generation systems and antioxidant systems. Redox homeostasis is defined as the balance between the levels of ROS and antioxidants in which antioxidative enzymes play central roles in scavenging ROS. Thus the, strict control of ROS levels is required to avoid their detrimental effects and to have beneficial roles [23].

In this study, the patient was received mouthwash containing zinc, *Aloe vera*, and SCD, for compressing the lips, every 1-2 h with a duration of 30 min. Zinc, which is a trace element, has an important role in the body's physiological processes, including immune system defense, cell membrane stability, and wound healing by increasing protein and nucleic acid synthesis, as well as increase oxygen transfer [24]. It has an antioxidant effect by giving electrons to ROS, neutralize the negative effects of ROS, and reducing oxidative stress, and the oxidation molecules [19]. It has an anti-inflammatory action through inhibiting the activity of cytokines, causing induction of apoptosis-enhancing macrophage and neutrophil functions, and by reducing the keratinocyte activation markers such as expression of intercellular adhesion molecule 1 and production of TNF, so it can inhibit the formation of ROS [25]. When myeloid cells were depleted of zinc by incubation in a zinc-deficient medium, basal and stimulation-induced ROS levels were increased. ROS as well as zinc are essential second messengers for the activation of various functions in neutrophils and other immune cells [26].

Aloe barbadensis miller is a botanical name of *Aloe vera* [27]. *Aloe vera* belongs to the Liliaceae family with mucilaginous tissue in its leaf's center [28]. The *Aloe vera* plant has anti-fungal, anti-inflammatory, antioxidant, immune-modulating, and anti-bacterial properties [17, 28]. Studies have reported the anti-inflammatory effect of *Aloe vera*, where the gel exerts its anti-inflammatory property through inhibition of COX2, prostaglandins, bradykinins, TNF- α , IL-1 β , and extracellular signal-regulated kinase pathway [28]. Based on study by Dapper *et al.*, *Aloe vera* gel could inhibit blood coagulation via a significant and dose-dependent increase in prothrombin time, clotting time, and decrease in plasma fibrinogen concentration in albino Wistar rats. *Aloe vera* has been reported to enhance pain management by inhibiting the production of bradykinin and thromboxane and to improve blood circulation via a vasodilator effect [29].

The antioxidant effect of *Aloe vera* is obtained because it contains vitamin A (beta-carotene), C, and E. Among seventy-five potentially active constituents of *Aloe vera*, there are vitamins, asam amino, saponin, zinc, and enzymes (bradykinase). Vitamin A, C, E have an antioxidant effect by giving electrons to ROS, neutralize the negative effects of ROS, reducing oxidative stress and the oxidation molecules. Vitamin E induces a significant increase in red cell blood glutathione levels, a non-enzymatic antioxidant [19]. Saponin has an antioxidant effect by forming hydroperoxides as secondary antioxidants so as to inhibit the formation of lipid peroxides to cause cell injury and tissue damage [16]. Bradykinase can act as an antioxidant by reducing excessive inflammation that can induce ROS so as to inhibit formation of ROS [27]. *Aloe vera* mouthwash has anti-inflammatory effects equivalent to benzydamine in patients with radiotherapy-induced oral mucositis [30].

SCD is a powerful oxidant. It prevents tissue damage and causes denaturation of microbial proteins through irreversible oxidation [14]. SCD has antioxidant activity by giving electrons to ROS [19]. SCD releases oxygen to kill the anaerobic bacteria. It also has antiviral, anti-fungicidal, and antibacterial effects and maintains a normal pH in the oral cavity [13, 24]. The use of CD has made it possible to establish that 1) it is safe for local application without risk of systemic intoxication, 2) it does not intervene in the healing process, 3) it is effective even at low concentrations and 4) it does not generate antimicrobial resistance [14].

In this study, a patient was diagnosed AML with pancytopenia as the condition that most affects to the resistance of the oral mucosa. Pancytopenia is a hematologic condition characterized by a decrease

in all three peripheral blood cell lines. It is characterized by a hemoglobin value of less than 12 g/dl in women and 13 g/dl in men, platelets of less than 150,000 per mL, and leukocytes of less than 4000 per ml (or absolute neutrophil count of less than 1800 per ml). However, these thresholds mainly depend on age, sex, race, and varying clinical scenarios [32]. Pancytopenia is not a disease but a manifestation of other underlying conditions. The etiology of pancytopenia can be broadly categorized as a central type that involves production disorders or a peripheral type that involves disorders of increased destruction. These causes could contribute to pancytopenia independently or as a combination [32].

The clinical presentation can be variable, with mild pancytopenia being asymptomatic to life-threatening emergencies in severe pancytopenia. Anemia can present as shortness of breath, fatigue, and chest pain. Leukopenia is primarily seen as neutropenia since neutrophils constitute the majority of leukocytes. Leukopenia manifests as increased infections, while thrombocytopenia presents with bruising, petechiae, and a propensity for bleeding. Patients with severe neutropenia can present with severe infections [32]. Prompt initiation of broad-spectrum antibiotic therapy is recommended for patients with neutropenic fever or severe neutropenia with an absolute neutrophil count of less than 500 per ml due to the risk of death from sepsis [32]. This patient received ciprofloxacin as broad-spectrum antibiotic therapy.

The management of pancytopenia is an important component of successful therapy in this study. The things we have done are: improving nutritional conditions and giving blood transfusions of packed red cells (PRC) and thrombocyte concentrate (TC). These transfusions can improve homeostasis to normal, thus helping the rehabilitation process of damaged cells, including oral mucosal epithelium and blood cells [32-34].

Oral manifestations are often found in patients with bleeding disorders accompanying systemic diseases such as malignancy. Mucosal lesions can cause discomfort that prompts patients to visit a dentist. Therefore, a dentist may contribute to the early diagnosis of the disease. Good cooperation between dentists and haematology specialists plays a very important role in preparing the patient for the treatment of the underlying disease. A patient after oral cavity sanitation has a lower risk of dental complications even before starting oncological therapy [9].

CONCLUSION

In this study, the mouthwash containing zinc, Aloe vera, and stabilized chlorine dioxide that can accelerate the healing process in our AML patient was estimated due to its antioxidant effects.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest. The drug formula used in the study management that we wrote about is the commercial preparation Oxyfresh® Lemon variant, however, there is no conflict of interest.

REFERENCES

1. Inayah Y, Sumintarti, Horax S, Fajriani, Marhamah. Early detection and manifestation of leukemia in the oral cavity of the child. MDJ 2021;10(3):283-7. doi: 10.35856/mdj.v10i3.466.
2. Rosa BPP, Ito FA, Trigo FC, Mizuno LT, Junior AT. Oral manifestation as the main sign of advanced-stage acute

- promyelocytic leukemia. Acta Stomatol Croat. 2018;52(4):358-62. doi: 10.15644/asc52/4/10, PMID 30666067.
3. Cammarata Scalisi F, Girardi K, Strocchio L, Merli P, Garret Bernardin AG, Galeotti A. Oral manifestations and complications in childhood acute myeloid leukemia. Cancers (Basel). 2020;12(6):1-11. doi: 10.3390/cancers12061634, PMID 32575613.
4. Stubbins RJ, Francis A, Kuchenbauer F, Sanford D. Management of acute myeloid leukemia: a review for general practitioners in oncology. Curr Oncol. 2022;29(9):6245-59. doi: 10.3390/curroncol29090491, PMID 36135060.
5. Lin TL, Pagano L. The important role of intensive induction chemotherapy in the treatment of acute myeloid leukemia. Expert Rev Hematol. 2021;14(3):303-14. doi: 10.1080/17474086.2021.1886920, PMID 33593202.
6. Fleischmann M, Schnetzke U, Hochhaus A, Scholl S. Management of acute myeloid leukemia: current treatment options and future perspectives. Cancers (Basel). 2021;13(22). doi: 10.3390/cancers13225722, PMID 34830877.
7. Francisconi CF, Caldas RJ, Oliveira Martins LJ, Fischer Rubira CM, da Silva Santos PS. Leukemic oral manifestations and their management. Asian Pac J Cancer Prev. 2016;17(3):911-5. doi: 10.7314/APJCP.2016.17.3.911, PMID 27039811.
8. Jalaeikhoo H, Kashfi SMH, Azimzadeh P, Narimani A, Gouhari Moghadam K, Rajaienejad M. Acute myeloid leukemia as the main cause of pancytopenia in Iranian population. Iran J Pathol. 2017;12(3):265-71. doi: 10.30699/ijp.2017.25647, PMID 29531552.
9. Michalak E, Dudzik A, Sreba J, Kesek B, Darczuk D. Oral manifestations of leukaemia: cooperation between dentist and haematologist. Hematologia. 2022. doi: 10.5603/HCP.a2022.0009.
10. Lugovic Mihic L, Pilipovic K, Crnaric I, Situm M, Duvancic T. Differential diagnosis of cheilitis-how to classify cheilitis? Acta Clin Croat. 2018;57(2):342-51. doi: 10.20471/acc.2018.57.02.16, PMID 30431729.
11. Behnaz M, Mortazavi H, Baharvand M, Dalaie K, Faraji M, Khalighi H. Oral lesion description: a mini-review. Int J Med Rev. 2019;6(3):81-7. doi: 10.29252/IJMR-060303.
12. Altun I, Sonkaya A. The most common side effects experienced by patients were receiving first cycle of chemotherapy. Iran J Public Health. 2018;47(8):1218-9. PMID 30186799.
13. Ezekwudo D, Lupak O, Vaddepally R, Gbadamosi B, Kuriakose P. Unexplained pancytopenia in acute myeloid leukemia treatment. Clin Case Rep. 2018;6(8):1504-6. doi: 10.1002/ccr3.1570, PMID 30147892.
14. Aparicio alonso M. Infection prevention and tissue repair in skin lesions using treatments based on a chlorine dioxide solution: case studies; 2022. p. 1-8.
15. Mani S, Mani A, Saini R. Clinical and microbiological evaluation of chlorine dioxide based mouthwash and toothpaste in periodontitis patients along with the combination of nutritional dietary supplement of CoQ10. International Journal of Experimental Dental Science. 2013;2(2):98-103. doi: 10.5005/jp-journals-10029-1049.
16. Kartika L, Ardana M, Rusli R. Aktivitas antioksidan tanaman Artocarpus. Proceeding Mulawarman Pharm Conf. 2020;12:237-44. doi: 10.25026/mpc.v12i1.432.
17. Selvakumar R, Np M. Comparison in benefits of herbal mouthwashes with chlorhexidine mouthwash: a review. Asian J Pharm Clin Res. 2017;10(2). doi: 10.22159/ajpcr.2017.v10i2.13304.
18. Prasad KA, John S, Deepika V, Dwijendra KS, Ram Reddy B, Chincholi S, Ravi Varma. Efficacy of herbal and 0.2% chlorhexidine gluconate mouthwash: a comparative study. J Int Oral Heal. 2015;7:98-102.
19. Martemucci G, Costagliola C, Mariano M, D'andrea L, Napolitano P, D'Alessandro AG. Free radical properties, source and targets, antioxidant consumption and health. Oxygen. 2022;2(2):48-78. doi: 10.3390/oxygen2020006.
20. Johnson Arbor K, Dubey R. Doxorubicin-StatPearls-NCBI bookshelf. Treasure. Islands: StatPearls Publishing LLC.; 2021.
21. Faruqi A, Tadi P. Cytarabine-StatPearls-NCBI bookshelf. Treasure. Islands: StatPearls Publishing; 2023.

22. Castilla DM, Liu ZJ, Velazquez OC. Oxygen: implications for wound healing. *Adv Wound Care (New Rochelle)*. 2012;1(6):225-30. doi: 10.1089/wound.2011.0319, PMID 24527310.
23. Kurahashi T, Fujii J. Roles of antioxidative enzymes in wound healing. *J Dev Biol*. 2015;3(2):57-70. doi: 10.3390/jdb3020057.
24. Hasanah NT, Dewi TS. Holistic approach of a leukemic child suffering from oral mucositis with coinfections: a case report. *Int Med Case Rep J*. 2023;16:363-9. doi: 10.2147/IMCRJ.S400497, PMID 37333035.
25. Chaitanya NCSK, Chintada S, Kandi P, Kanikella S, Kammari A, Waghmare RS. Zinc therapy in the treatment of symptomatic oral Lichen Planus. *Indian Dermatol Online J*. 2019;10(2):174-7. doi: 10.4103/idoj.IDOJ_230_18, PMID 30984596.
26. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. *Nutrients*. 2017;9(12):9-12. doi: 10.3390/nu9121286, PMID 29186856.
27. Surjushe A, Vasani R, Saple DG. Aloe vera: a short review. *Indian J Dermatol*. 2008;53(4):163-6. doi: 10.4103/0019-5154.44785, PMID 19882025.
28. Poorkazemi D, Malekzadeh Shafaroudi A, Nasiri P, Aarabi M, Mehrani Sabet J. Evaluation of aloe vera as a natural pharmaceutical in mouthwashes: a narrative review. *Jundishapur J Nat Pharm Prod*. 2022;17(4). doi: 10.5812/jjnpp-122155.
29. Dapper DV, Achinike PN, Gwotmut MD. The effects of Aloe vera [gel] on clotting time, prothrombin time and plasma fibrinogen concentration in albino wistar rats. *Port Harcourt Med J*. 2007;2(1). doi: 10.4314/phmedj.v2i1.38894.
30. Chandra VC, Nuraeny N, Wahyuni IS. Anti-inflammatory potential of aloe vera in oral mucositis therapy: systematic review. *Int J App Pharm* 2022;14:22-7. doi: 10.22159/ijap.2022.v14ti.21.
31. Keremi B, Marta K, Farkas K, Czumbel LM, Toth B, Szakacs Z. Effects of chlorine dioxide on oral hygiene-a systematic review and meta-analysis. *Curr Pharm Des*. 2020;26(25):3015-25. doi: 10.2174/1381612826666200515134450, PMID 32410557.
32. Chiravuri S, De JO. Pancytopenia. *Treasure Islands: StatPearls Publishing LLC*; 2023.
33. Müller MM, Geisen C, Zacharowski K, Tonn T, Seifried E. Transfusion of packed red cells: Indications, Triggers and Adverse Events. *Dtsch Arztebl Int*. 2015;112(29-30):507-18. doi: 10.3238/arztebl.2015.0507, PMID 26249256.
34. Khan A, Anwer F. Platelet transfusion-StatPearls-NCBI bookshelf, treasure. *Islands: StatPearls Publishing LLC*; 2023.