Potential Effects Of Astaxanthin Gel On The Diameter Measurement Of Oral Cavity Ulcers In A Diabetic Rat Model

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ABSTRACT

Background: *Diabetes mellitus causes complications, prolongs the wound-healing phase, and manifests in the oral cavity as Recurrent Aphthous Stomatitis (SAR). Astaxanthin is a natural compound with antioxidant and anti-inflammatory properties that support ulcer healing in diabetes. This study aims to determine the effect of 1% astaxanthin gel, compared with commercial 0.2% hyaluronic acid gel, on the diameter of oral ulcers on days 3, 5, and 7 in rats with diabetes mellitus.*

Method: *The experimental animals were 18 Wistar Rattus norvegicus rats, randomly divided into 3 research groups, induced with STZ, followed by ulcer creation in the oral cavity. The treatment groups were K1 (gel base group), K2 (0.2% hyaluronic acid gel group), and P (1% astaxanthin gel group). Ulcers were measured with digital calipers. Data were analyzed on days 3 and 5 using the Kruskal-Wallis test followed by the Mann-Whitney test, and on day 7 using one-way ANOVA with the LSD post hoc test.*

Result: *The Kruskal-Wallis test showed a significant difference ($p<0.05$) in ulcer diameter on days 3 and 5. The One-Way ANOVA showed a significant difference ($p<0.05$) in ulcer diameter on day 7.*

Conclusion: *Both treatments with gel astaxanthin 1% and commercial hyaluronic acid 0,2% affected the diameter of oral ulcers in rats with diabetes mellitus on days 3, 5, and 7. Astaxanthin gel had the best effects compared to all groups.*

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that affects carbohydrates, fats, and proteins, caused by decreased insulin secretion and tissue sensitivity to insulin. Metabolic disturbances in DM are characterized by chronic hyperglycemia.[1] The results of RISKESDAS in 2018 showed that the prevalence of DM increased to 8.5%, compared to 6.9% in 2013.[2] In diabetic patients, issues may present themselves in the oral cavity.[3]

The high levels of glucose in the blood cause the wound healing process to be slower because it inhibits the immune response, resulting in poorly regulated blood plasma and prolonged inflammation.[4] The wound healing process consists of 4 dynamic stages. The stages are hemostasis, inflammation, proliferation, and remodeling.[5] The hemostasis phase, as the initial stage of wound healing, begins immediately after the injury with the constriction of blood vessels and the formation of fibrin.[6] The hemostasis phase is followed by the inflammatory response, which occurs on day 0 and ends on day 5 post-trauma. The next phase is the proliferation process, which involves granulation tissue consisting of new blood vessels, fibroblasts, collagen, macrophages, granulocytes, and endothelial cells that occurs from day 3 to 7 after the injury.[7,8] The final phase is remodeling, which begins from day 7 to day 14 after injury.[9]

Ulcers are lesions on the oral mucosa characterized by pain and a single lesion with varying shapes and sizes.[10] The size of these lesions usually ranges from 1 to 8 mm and can heal within 7–10 days.[11] A medication that can be chosen for the treatment of oral cavity ulcers is hyaluronic acid (HA) gel because it plays a role in the wound-healing stage, specifically in the inflammatory phase, which is the initial stage of wound repair by enhancing tissue synthesis. The drawback is that in patients with hypersensitivity to hyaluronic acid, it can cause local pain, a burning sensation, and redness.[12] An alternative treatment is needed using a medication containing natural ingredients, namely astaxanthin, for ulcer healing therapy in such cases.

Astaxanthin is one of the strongest carotenoids with antioxidant activity obtained naturally or chemically. The main source of natural astaxanthin is Haematococcus pluvialis, a type of freshwater green microalgae with high intracellular potential.[14] Astaxanthin can accelerate the wound healing process by suppressing or speeding up the inflammatory phase.[15]

Research by Aras-Tosun et al. (2022) showed that astaxanthin therapy can increase cell proliferation and migration, thereby restoring delayed wound healing due to increased ROS.[16] Another study on the administration of astaxanthin (Haematococcus pluvialis) at a concentration of 1% by Aripin et al. (2022) found a reduction in ulcer diameter, with the most significant difference among three treatment groups in rats with traumatic ulcers.[11] Research by Andriani et al. (2025) reported the best antioxidant effects and safety tests on 1% astaxanthin gel.[17]

Based on the above explanation, the researchers aim to investigate the effect of topical 1% astaxanthin gel therapy on the diameter of oral cavity ulcers in rats (Rattus norvegicus strain Wistar) under diabetic conditions.

MATERIAL AND METHODS

The research conducted is a type of true experimental laboratory research, with a design known as a posttest-only control group design. The sample in this study consisted of 6 Wistar rats divided into 3 groups, resulting in a total sample of 18 Wistar rats. This research has been approved by the ethics committee of the Faculty of Dentistry,

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The tools and materials used in this research include: 3 cc syringe, 2 cc syringe, analytical balance, Wistar rat cage, feeding and drinking containers, sterile masks and gloves, anatomical tweezers, surgical tweezers, small scissors, glucometer, glucostrip, 2 x 0.5 mm punch biopsy, Vernier digital caliper, diabetogenic agent streptozotocin, citrate buffer, 10% dextrose monohydrate, 1% astaxanthin gel, 0.2% hyaluronic acid (Ricerfarma, Milan, Italy), sterile cotton buds, sterile cotton pellets, cotton, ketamine, sterile distilled water, xylazine, 3-10% povidone iodine.

The preparation of the test animals was carried out first by acclimatizing them for 7 days in cages with adequate air, room temperature, and lighting. The rats were fed and given water regularly. Before inducing diabetes, blood glucose levels were measured by cutting a small tip of the rat's tail and applying a Glucostrip to the blood. After that, the test animals were fasted for 8–12 hours before DM induction. The next step involved inducing DM in the test animals by administering streptozotocin (STZ) 50 mg/kg BW dissolved in citrate buffer and injected intraperitoneally, followed by administering 10% dextrose monohydrate overnight.[18] The rats' blood glucose levels were checked again 4 times over 24 hours after induction and were considered diabetic if the random blood glucose level was > 230 mg/dL.[19]

The next stage involved creating ulcers in the test animals after anesthesia with ketamine and xylazine administered intramuscularly. The creation of ulcers in the central area of the lower labial mucosa of rats was performed using a punch biopsy with a diameter of 2 mm and a depth of 0.5 mm. Observations were made when the ulcers formed, and therapy was administered 1 x 24 hours after the treatment. The therapy was given in the form of gel preparations: gel base (K1), 0.2% hyaluronic acid gel (K2), and 1% astaxanthin gel (P), with a dose of 0.1 mg applied to the oral cavity ulcers for 3, 5, and 7 days.

The clinical parameter for ulcer healing is the observation of ulcer diameter in rats with diabetes mellitus. The diameter of the ulcers in all groups of rats was measured using a digital caliper with the Morton method, which involved consistently measuring four ulcer diameters on days 3, 5, and 7, and then calculating the average diameter from each measurement in mm.[20]

The data from this study were analyzed using SPSS 27.0 software. The data were tested for normality using the Shapiro-Wilk test and for homogeneity using Levene's test. Normally distributed data were tested with the one-way ANOVA hypothesis test with Post Hoc Least Significant Difference (LSD), while non-normally distributed and non-homogeneous data were tested with the nonparametric Kruskal-Wallis hypothesis test with Post Hoc Mann-Whitney.

RESULTS

This study was performed by examining the variation in ulcer diameter between day 1 and day 3, day 1 and day 5, and day 1 and day 7. The findings from the examination of ulcer diameter measurements are presented in the table below:

Table 1. Mean and Standard Deviation of Ulcer Diameter Size Difference (mm)

	Groups	n	Mean Diameter Difference ± Standard Deviation
Day 1 and Day 3	K1	6	0.583 ± 0.944
	K2	6	0.317 ± 0.181

	P	6	0.204 ± 0.111
Day 1 and Day 5	K1	6	0.125 ± 0.105
	K2	6	0.679 ± 0.669
	P	6	0.979 ± 0.529
Day 1 and Day 7	K1	6	0.554 ± 0.334
	K2	6	0.992 ± 0.577
	P	6	1.300 ± 0.391

Note: n: replication

The statistical analysis presented in Table 1 reveals that on day 3, the K1 group exhibited the most significant increase in ulcer diameter, in contrast to the P group showed the least increase in diameter. On days 5 and 7, the P group exhibited the most significant reduction in diameter, whereas the K1 group showed the least reduction in diameter.

The results of the normality and homogeneity tests on the 3rd day, with a p-value < 0.05, indicate that the data are not normally and homogeneously distributed. On the 5th and 7th days, the normality test results showed a p-value > 0.05, indicating that the data are normally distributed. The homogeneity test results on the 5th day showed a p-value < 0.05, meaning the data were not homogeneous. On the 7th day, the data were homogeneous (p > 0.05).

Table 2. Results of the Kruskal-Wallis statistical test for Ulcer Diameter Difference

Variable	*Sig.*
Day 1 and Day 3	0,005*
Day 1 and Day 5	0,025*

Note: *significantly different

Based on Table 2, the significance values for both ulcer diameter differences were obtained with p < 0.05, indicating a significant difference in each treatment group. Afterward, the Mann-Whitney test was used as a post hoc test to determine significant differences between groups.

Table 3. Results of One-Way ANOVA Statistical Test on Ulcer Diameter Differences

Variable	*Sig.*
Day 1 and Day 7	0,035*

Note: *significantly different

Based on Table 3, the significance value of the diameter difference was obtained with a p-value < 0.05, indicating a significant difference between treatment groups. Next, post hoc LSD analysis was used to determine significant differences between groups.

Table 4. Results of the Mann-Whitney Test and Post Hoc LSD Test for Ulcer Diameter Differences

	Groups	K2	P
Day 1 and Day 3	K1	0,010*	0,001*
	K2		0,342
Day 1 and Day 5	K1	0,130	0,007*
	K2		0,234
Day 1 and Day 7	K1	0,238	0,028*
	K2		0,473

Note: *significantly different

Based on the results of the Mann-Whitney test analysis on days 3 and 5, a significance value of p < 0.05 was obtained, indicating a significant difference between group K1 and group K2 and group P on day 3, and between group K1 and group P on day 5. The results of the Post Hoc LSD test analysis on day 7 data showed a significance value of p < 0.05, indicating a significant difference between group K1 and group P.

DISCUSSION

In this study, ulcers formed 24 hours after the biopsy was performed. The clinical presentation shows an oval lesion with a yellowish-white center and a reddish edge. Ulcerative lesions in the oral cavity are marked by the appearance of painful yellowish-white ulcers.[21] Measurement of ulcer diameter is performed as an indicator of clinical ulcer healing.[22]

The use of male Wistar rats in this study was conducted due to their relatively rapid drug metabolism capability, providing more consistent research results as they are not influenced by pregnancy or hormones.[23] The condition of diabetes in rats is characterized by blood sugar levels > 200 mg/dl.[24] In this study, the blood sugar levels of the test animals after being induced with streptozotocin were 300 – 600 mg/dL.

The ulcer diameter increased from day 1 to day 3 in all groups. The increase in ulcer diameter is caused by the inflammatory process in the ulcer wound. In the inflammatory process, inflammatory cells and neutrophils will attack the inflamed area to destroy pathogens such as bacteria and debris.[7] The increase in ulcer diameter is consistent with the study by Aripin et al. (2018), which showed that all research groups experienced an increase in ulcer diameter from day 1 to day 3.[11]

Based on the research among the 3 treatment groups, the control group, which was only given the gel base (K1) had the highest average increase in diameter. The increasing size of the ulcer may occur because the control group was only given a gel base that does not contain active substances that can suppress the inflammatory process to accelerate ulcer healing.

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Data analysis of the research shows that the difference in the increase in diameter on day 3 between the group given 0.2% hyaluronic acid gel (K2) and the group receiving 1% astaxanthin gel therapy (P) did not show a significant difference. These results indicate that both 0.2% HA gel and 1% astaxanthin gel can suppress inflammation on day 3. The results of this study are consistent with the research by Andriani et al. (2025), which showed the same increase in diameter between the 1% astaxanthin gel and the 0.2% non-commercial high molecular weight hyaluronic acid gel. [25]

The research data show that there is a difference in ulcer diameter between day 1 and day 5. The ulcer diameter on day 5 decreased in all groups. On the 5th day, the wound healing process occurs between the inflammatory phase and the proliferative phase. This stage is consistent with the research conducted by Sofyanita and Iswara (2021), which showed that the wound expansion in diabetic patients began to decrease on the 4th day because the formation of new blood vessels could provide the necessary nutrients for skin formation during wound closure.[26]

The results of the data analysis, the average difference in diameter size on the 5th day and the 1st day, showed a decrease in the diameter size difference, indicating no significant difference between the group given the gel base (K1) and the group given 0.2% hyaluronic acid gel (K2), but a significant difference with the therapy using 1% astaxanthin gel. These results differ from the study by Andriani et al. (2025), which showed the same diameter reduction between the control, 1% astaxanthin gel, and 0.2% high molecular weight non-commercial hyaluronic acid gel.[25] This may be due to the different conditions of each test animal and the different types of hyaluronic acid administered, affecting the reduction in ulcer diameter size difference. Based on the research conducted by Trilaksani et al. (2019), the results of the antioxidant activity test showed that hyaluronic acid has weak antioxidant activity. In contrast, the 1% astaxanthin gel has high antioxidant effects. The antioxidant effects of astaxanthin influence the

ulcer healing process by inhibiting pro-inflammatory agents (TNF-α, IL-1, IL-6) through the PDGF pathway and NF-κB.[27]

The research data show that there is a difference in ulcer diameter between day 1 and day 7. The ulcer diameter on day 7 in all groups decreased, but none showed complete wound closure. This may be caused by diabetes conditions that lead to a decrease in fibroblast proliferation, which is a key factor in the active tissue formation phase during the late stages of wound healing.[25] Wound closure in diabetic rats takes longer compared to normal wounds, up to more than 21 days.[26]

The results of the data analysis indicate that the average difference in diameter size on day 7 and day 1 shows a significant difference between the group given the gel base (K1) and the group given 1% astaxanthin gel (P). This occurs because the active substance in astaxanthin can aid the wound healing process during inflammation and proliferation. The mechanism of action of astaxanthin during the inflammatory phase of wound healing is to suppress inflammation by inhibiting the production of inflammatory mediators through the NF-κB inhibition pathway.[18] During the proliferative phase, astaxanthin increases bFGF, which has significant potential to reduce wound size.[28]

Based on data analysis, the research results show that the average difference in diameter between the 7th day and the 1st day indicates a significant difference between the group given 0.2% hyaluronic acid gel (K2) and the group given 1% astaxanthin gel (P). These research results differ from the study by Andriani et al. (2025), which showed a similar reduction in diameter difference between the 1% astaxanthin gel and the 0.2% non-commercial high molecular weight hyaluronic acid gel on the 7th day.[25] This occurs because astaxanthin contains active ingredients involved in all wound healing processes. Hyaluronic acid is also known to play an active role in all stages of wound healing, such as early inflammation, granulation tissue formation, re-epithelialization, as well as keratinocyte proliferation and migration.[29] Research by Marin et al. (2020) showed that 0.8% hyaluronic acid applied to wounds after tooth extraction in uncontrolled diabetes mellitus can enhance wound healing.[30]

CONCLUSION

The administration of 1% astaxanthin gel and 0.2% commercial hyaluronic acid gel affects the size of oral cavity ulcers in diabetic rats, as indicated by the reduction in the difference in ulcer diameter. The administration of 1% astaxanthin gel provides a better reduction effect compared to the other groups.

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