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Efficacy of *Stigma maydis* (Corn silk) in Reducing Blood Sugar Level and Subduing Periodontal Inflammation

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ABSTRACT

Diabetes is one of the most common non-communicable diseases in the world, according to the World Health Organization (WHO). Diabetes is a complex chronic disease with many side complications; one of them is periodontitis or periodontal tissue inflammation. The two are linked to each other by a high blood glucose level. The purpose of this research was to discern the efficacy of Stigma maydis extract as a topical medication to decrease hyperglycemia also subdues periodontal tissue inflammation. Fifteen Male Wistar rats were included in this study, and the periodontitis model was induced using ligatures tied in lower first incisors; also, alloxan was used to create a diabetes mellitus model in the study animals. The result showed that blood sugar level in Fa group was unsteady ($p > 0.05$), and there was an increase in the blood glucose level after a decrease, while both Fb and Fc groups showed stable blood glucose decrease ($p<0.05$). Fc managed to subdue the inflammation with mild inflammation results ($p<0.05$), while both Fa & Fb showed less effect with only moderate inflammation ($p>0.05$). From this study, it can be concluded that topically administered corn silk extract is efficient in reducing blood sugar levels and subduing periodontal tissue inflammation in diabetes-induced albino rats.

Keywords: Alloxan; Blood Glucose Level; Corn Silk (*Stigma maydis*) Extract; Diabetes Mellitus; Inflammation; Periodontal Tissue

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INTRODUCTION

Diabetes is one of the most common non-communicable diseases alongside heart disease, stroke, cancer, and chronic lung disease.[1] The number of people who have diabetes has nearly quadrupled since 1980, and its prevalence is increasing worldwide, particularly in low and middle-income countries. The causes of diabetes are complex, but mostly due to overweight/obesity and lack of physical activities.[2] Diabetes is a complex chronic disease with many side complications.[3] One of the complications diabetes has on the oral cavity is periodontitis.[4] Periodontitis is an inflammatory disease of the supporting tissue of the teeth caused by groups of specific microorganisms, resulting in the progressive destruction of the periodontal ligament and the alveolar bone, with pocket formation, recession, or both.[5] The risk of periodontitis become two or threefold higher in diabetic individuals compared to those without such condition, and the critical correlating factor in these two diseases is the level of blood glucose or glycemic control.[6] The chronic hyperglycemic state is associated with the formation of Advanced Glycation End Products (AGEs). AGEs are composites derived from the non-enzymatic, irreversible glycosylation of proteins and lipids that accumulate in plasma, walls of blood vessels, and tissues of diabetics patients.[7] The deposition of AGEs in diabetic patients is not only limited in plasma and blood vessels, but there is also an increase in the deposition of AGEs in periodontal tissues. Interactions between AGEs and its receptor (RAGE, the receptor for AGEs, found mainly on macrophages) lead to activation of local immune and inflammatory responses. These upregulated responses result in increased secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6, increased oxidative stress, and disruption of the receptor activator of NF-κB ligand/osteoprotegerin (RANKL/OPG) axis to promote bone resorption. All of these factors cause local tissue damage, increased breakdown of the periodontal connective tissues and resorption of alveolar bone, thus exacerbating the condition of periodontal inflammation.[6]

Diabetes treatment protocols require a life-long management approach. Treatment protocol for type 1 diabetes includes cautious planning of the diet and physical activities, also insulin injection. For type 2 diabetes, the treatments include weight loss, exercise, diet control, orally administered hypoglycemic drugs (e.g. metformin).[6] The treatment of periodontitis also involves professional care to reduce bacterial load with mechanical debridement such as scaling, root surface debridement, also oral hygiene instructions.[8] As mentioned before, patients with type 2 diabetes require orally administered drugs to regulate their blood sugar level, however along with the advancement of the disease, these medicines are not sufficient to control blood glucose levels; hence it is necessary to use insulin for sufficient blood sugar control.[9] On the other hand, the study shows that the use of insulin will worsen inflammation in periodontal tissue in patients with diabetes.[10] One of the substitute methods traditional medicine used to reduce blood glucose is by consuming tea or pills made of corn silk. Corn silk is made from stigmas, the yellowish thread-like strands from the female flower of maize.[11] Corn silk contains lots of secondary

metabolite products, i.e., flavonoid, saponin, phenol, and many more. All these secondary metabolic products give corn silk an antihyperglycemic property as well as an anti-inflammation effect.[12] Corn silks also have therapeutic potentials for leukocyte adhesion and migration mediated by several pro-inflammatory substances i.e. TNF-α, IL-1β, VEGF-α, and IL-17A; it inhibits the inflammatory process as well.[13]

MATERIALS AND METHODS

Fifteen male albino rats (*Rattus novergicus*) were obtained from breeders. Afterwards, the experimental animals need to be adapted for seven days. The experimental animals were adapted in their new environment for seven days at room temperature under alternating natural light/dark photoperiod and were given standard feed two times a day with water available ad libitum. After being adapted for seven days, all experimental animals were weighed, and all animals weigh around 180-200 grams. Alloxan monohydrate from the Tokyo Chemical Industry was used to make a diabetic model on experimental animals. Alloxan is composed of allantoin and oxalic acid. Alloxan is toxic for beta cells in the pancreas, and this toxicity is induced by free radicals formed from redox reaction.[14,15] Alloxan is effective when given via intravenous, intraperitoneal, or subcutaneous routes.[16] For the positive control group, oral hypoglycemic agent Metformin of a generic brand was used.

Corn silks from 40 days old locally harvested corn were used in this study. Before being extracted, the corn silks were washed beforehand to cleanse the silks from other foreign objects, e.g., small insects. After being washed, corn silks were dried using direct sunlight for four days, and dried Simplicia was formed. The dried Simplicia was then macerated with 80% ethanol (200gr/5L) in a transparent glass jar with a closed lid for three days. After maceration, the ethanol-corn silks solution was put in a rotary evaporator to evaporate the alcohol solvent to obtain corn silk extract.

Three gel formulas were made in this study (Table 1). Carbomer 940 was dispersed for 24 hours in distilled water that has been mixed with methylparaben beforehand. Afterward, drops of triethanolamine (TEA) were added in the formulas while being mixed until a clear gel base was formed. Each formula was added corn silks extracts according to their respective concentration, 0.1,0.05, and 0.025 gram for Fa, b, and c, respectively. Before being added to the formulas, a small amount of distilled water was added to corn silk extracts to ease the procedure. After the extracts were added to the formulas, the formulas were then stirred until homogenous, and then glycerin also distilled water were added to finalize the formulas.[17]

After all of the formulas were made, each formula was evaluated. Homogeneity, pH level, viscosity, and gel dispersion were evaluated. Homogeneity was evaluated through visual inspection to observe if there's any existing mass within the gel. pH level was determined using a pH meter device (Sartorius®), viscosity was measured with viscometer using 100-rpm speed and spindle no 7. Gel dispersion was determined using two glass plates; each weighed 104.09 grams and 100-400 weights.

The diabetic model was made by fasting the experimental animals for 8 hours before injecting them with alloxan. After being fasted for 8 hours, the blood glucose levels were measured using a glucometer and blood from the tail vein. Afterward, each rats weight was measured to determine the dose of the alloxan. The dose is 150mg of alloxan per kilogram. Before being injected, the alloxan was first dissolved in saline before administered peritoneally. Silk ligatures (5-O) were used to imitate dental calculus as a plaque biofilm retention site. The ligatures were gently secured in the lower central incisor to avoid inflicting injury to the respective periodontal tissue. Seven days following the administration of alloxan, blood samples from the tail veins were drawn again to inspect if all experimental animals have fasting blood glucose level that exceed the normal value of 126mg/dl

All experimental subjects have more than 126 mg/dl blood glucose levels by the end of the induction period. Seven days after periodontitis model induction rats with erythematous gingiva, easily bleed, and appeared inflamed were acknowledged to have periodontitis and were included in the study. Fourteen hyperglycemic and periodontitis experimental animals were randomly selected into five different treatment groups; each group is composed of three rats apart for the negative control, which has two rats. The negative control group was given a clear gel base without any active compounds to play a role as a placebo. Metformin for the positive control group was given orally but was dissolved in water first before administered orally using an eyedropper. The other three groups are given Fa, Fb, and Fc respectively, each is given treatment once a day for one week. Blood glucose was monitored 3 and 7 days after treatment. On the 7th day of treatment, the last blood samples were drawn for monitoring, and periodontal tissues were collected to perform histopathology tests. Tissue samples that have been collected were then stained using hematoxylin and eosin. The histopathology test observed the number of infiltrating and the condition of inflammation in the periodontal tissue. All the data collected were analyzed using the Students' t-test in SPSS. The data presented represent means with 95% Confidence interval and value of p<0.05 considered significant.

RESULTS

Figure 1 shows the scheme of movement of the blood glucose level. From the graph, it can be observe that for the negative control, the blood glucose level has an increasing trend because the group has not received any treatment; they were only given clear gel with no active compound as a placebo. For positive control, Fb, and Fc groups, it can be seen that they have a decreasing trend. On the contrary, the Fa group seems to have a decrease in the first three days, but the blood glucose level increased again on the 7th day. Even though the final blood glucose level is still lowered then its blood glucose level after induction, statistical analysis shows no significant value (p=0.0583). It points out that Fa is unable to stabilize blood glucose levels and has no significant effect in lowering blood glucose levels. Metformin given to a positive group shows a decrease in blood glucose level, but after statistical analysis, the value showed no significance (p= 0.264). Whereas Fb and Fc both show efficacy in reducing blood

glucose level because both have shown that they have significant statistical value (Fb p=0.0086; Fc=0.035).

Due to some limitations in the extremely large number of leukocytes and PMN, the inflammation rates are shown in grades (1 for mild, 2 for moderate and 3 for severe). As observed from figure 2, the highest inflammatory score can be found on the negative control group, which is 3 for severe and along with cell necrosis (Fig 3A). Fc group showed the lowest inflammation, which is 1 for mild inflammation (p=0.001). The second highest inflammation degree is on Fb. But one thing to be observed is that in contrast to its blood glucose levels, the degree of inflammation is still high, and the formula shows no significant value (p=0.423). Fa also falls into a moderate category, but the same as Fb, it shows no significant value (p=0.225).

DISCUSSION

The orally administered hypoglycemic agent has been one of the standardized treatment regimens for diabetic patients. The orally administered drug is named Metformin.[6] Metformin worked as a hypoglycemic agent that has the property to lower basal and postprandial blood glucose levels also increase glucose tolerance in diabetic patients.[18] However, as diabetes progresses, metformin is no longer able to control blood glucose levels and keep it at a desirable level, hence over time, insulin usage will be necessary to control blood sugar at a desirable level. But, the use of insulin will increase the inflammation and aggravate periodontitis in diabetic patients.[10] From the results, it can be observed that Fb and Fc have better results in reducing blood glucose than metformin and further proved by statistical analysis that showed both formulas have significant values. The results are by studies conducted before, which show that corn silk (*Stigma maydis*) can lower blood glucose levels meaning it has an anti-hyperglycemic effect.[11,13,19,20] Due to secondary metabolites compounds such as alkaloids, saponins, flavonoids, and phenolic compounds, corn silk has the property to lower blood glucose levels and help repair the damaged pancreatic β cells. Flavonoids can inhibit the breakdown of complex carbohydrates to simple glucose; also, glucose absorption in small intestines, stimulate the secretion of insulin, and repair damaged β cells due to its antioxidant activity. Alkaloids can decrease blood glucose levels by increasing GLUT 4 translocation. Saponins can increase insulin secretion, and phenolic compounds with its antioxidant capacity can help improve the condition of damaged pancreatic β cells.[21] These traits and ability can allow corn silk to target the primary cause of diabetes, which is damaged β cells in the pancreas that produce insulin, and it acts differently from metformin.

Corn silk (*Stigma maydis*) possesses anti-inflammatory effect, also has therapeutic potentials for cytokine mediated leukocyte adhesion and migration, it also inhibits the inflammatory process.[12,13] This effect can be observed in Fc that shows mild inflammation by the end of the experiment period. This is also in accordance with a previous study, which showed that corn silk has the capability to subdue periodontal inflammation.[20]

As mentioned beforehand in figure 2, it can be observed the inflammatory degree in Fb is still high despite its low blood glucose levels. Theoretically speaking the degree of inflammation should have been lowered because the hyperglycemia is well-controlled, but such a thing was not evident. It could be caused by stress because our experimental animal showed signs of stress. All the rats in the Fb groups showed clinical signs of distress, always hunching or cowering in the corner of the cage, lying on one's side, a higher volume of urine and feces, frequent vocalizations, and decrease of appetite also water intake.[22] Stress can harm periodontal tissue because it can change how the immune system responds to a biological challenge, delay wound healing process, and change hormonal level also one's behavior hence it can alleviate the degree of inflammation in periodontal tissue.[23–25] Nonetheless, the Fc treatment group shows mild inflammation. It shows a statistically significant value, which indicates that corn silk extract has the efficacy to subdue inflammation in periodontal tissue.

CONCLUSION

From this study, it can be concluded that topically administered corn silk extract is efficient in reducing blood sugar level also subduing periodontal tissue inflammation in diabetes-induced albino rats.

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Table 1. Formulas for three different corn silk gels

Formula	Materials					
	Corn silk extract (g)	Carbomer 940	TEA	Glycerin	Methyl paraben	Distilled Water
Fa	0.1	1	2	5	0.15	Till 100 gram
Fb	0.05	1	2	5	0.15	
Fc	0.025	1	2	5	0.15	

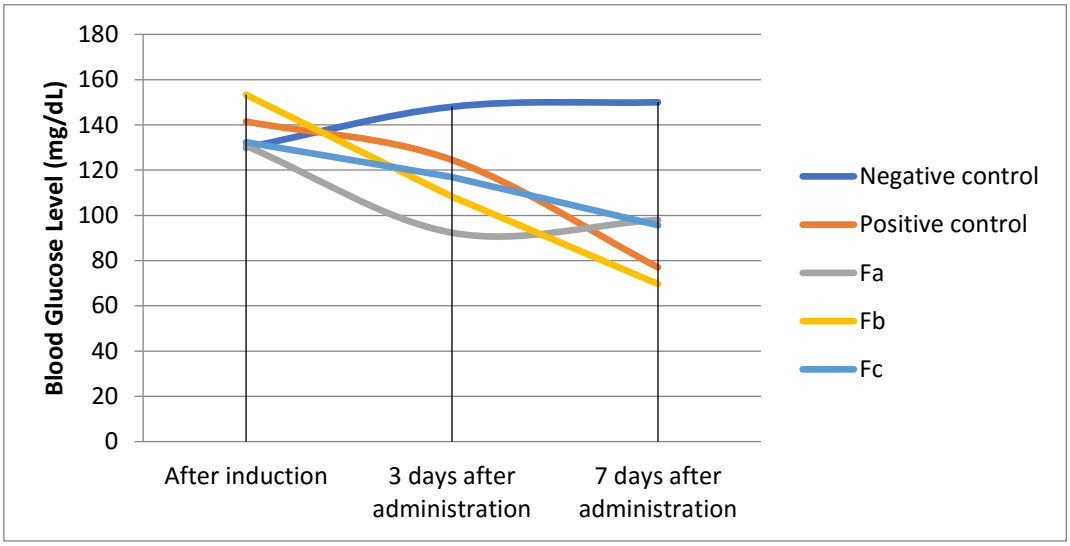

Figure 1. Blood sugar level for each treatment group

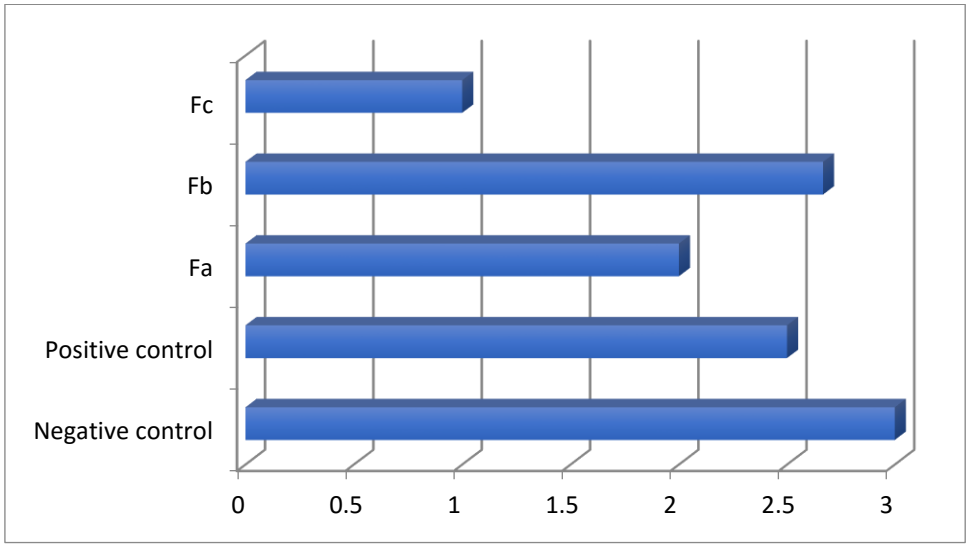

Figure 2. Inflammatory scores in each group

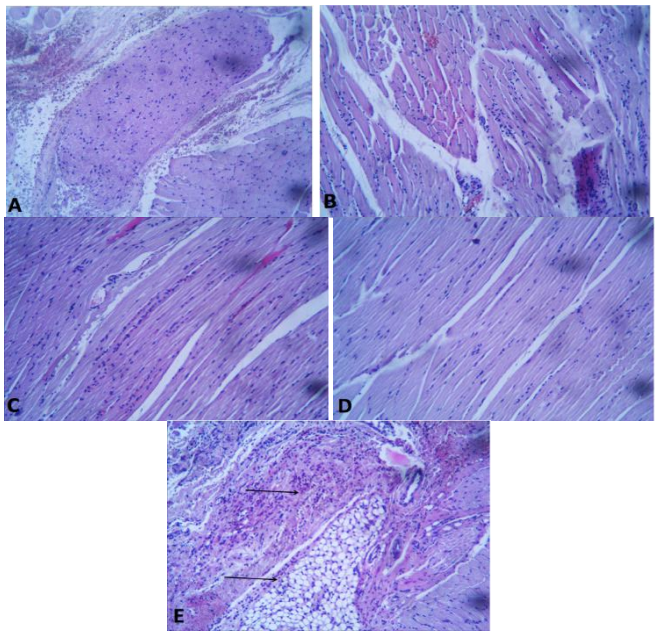

Figure 3: Histopathologic view of the periodontal tissues after HE is staining. (A) Negative control group exhibited numerous inflammatory cell (severe inflammation) along with cell death (B) Fa and Fb (C) both showed moderate inflammatory responses (C) but for Fb histopathology test shows new connective tissue formation (D) Mild inflammation observed in Fc test groups (E) Positive control group showed severe inflammation