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Protective and Regenerative Effect of the Extract of Kombucha and the Fungus *Ganoderma sichuanense* on the Islets of Langerhans of Diabetic Rats

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Abstract

Objective: The present study consisted of challenging the extract of kombucha and the fungus Ganoderma reported as hypoglycemic and used as alternative treatments against diabetes on the number and morphology of islets of Langerhans. **Material and Methods:** 64 Wistar rats were used in 4 groups: one control, three experimental, streptozotocin, Kombucha y Ganoderma induced diabetes with streptozotocin. Divided into four post-induction stages at 2, 15, 30 and 45 days of treatment, sacrificing 4 rats at each stage, to perform the morphological analysis of the pancreas. **Results:** A decrease in the islets of Langerhans in size, volume and the number of cells within them was identified for the streptozotocin group from the second stage until almost disappearing due to diabetes, in the groups of Kombucha y Ganoderma the same was observed but they were recovered with the extract treatments and the average number of islets was similar in these groups, the group of Ganoderma. **Conclusion:** Under the conditions of this work, a protective and regenerative effect of both extracts is identified.

Keywords

Rats, Diabetes, Streptozotocin, Ganoderma, Kombucha, Pancreas

1. Introduction

Diabetes is a disease that worldwide wreaks havoc in the entire population regardless of age or sex, it is a chronic-degenerative condition that ends up damaging various organs of the body when it becomes complicated, and can cause death. Millions of dollars are spent on prevention campaigns, as well as for its treatment and control [1] [2]. In diabetes management and prevention, natural supplements are now supported by a growing body of scientific research [3].

Various scientific studies have reported, that kombucha has a hypoglycemic effect on mice after measuring the physiological, biochemical and histological characteristics changes and suggest that kombucha may be introduced as a new functional drink for T2DM prevention and treatment [4] [5]. Whereas Ganoderma regulating the expression of several key enzymes in the hepatic glucose metabolism pathway [6] [7]. Thus, the use of the extract of the fungus of kombucha and the extract of the fungus Ganoderma as alternative treatments to control diabetes mellitus with good results, for this reason, it was decided to challenge them in the present study to determine which of them had a greater hypoglycemic effect, as well as a protective and regenerative effect on the pancreas affected by diabetes mellitus [8] [9] [10].

The mushroom Ganoderma contains a considerable amount of metabolites, among which are: antioxidant alkaloids, sterols, polysaccharides, polyphenols, terpenoids, triterpenes, essential amino acids, B complex vitamins and minerals [11], whose therapeutic effects have very good results as antioxidant, anticancer, anti-inflammatory and hypoglycemic in addition to ergosterol and its derivatives that reduce lipid peroxidation [12] [13] [14] [15].

Various scientific publications have also demonstrated the curative effects of the fungus Ganoderma when used as an antimicrobial, anticancer, antifungal and hypoglycemic agent [16] [17]. This last effect is due to the presence of an active compound called ganoderan-B, since previous studies show that when administered increases insulin synthesis and improves glucose metabolism at the cellular level [10].

These studies suggest that the hypoglycemic mechanism called FYGL for its acronym in English (Fudan-Yueyang-G. lucidum) It occurs because the expression and activity of protein tyrosine phosphatase 1B (PTP1B) is blocked and as a consequence regulates tyrosine phosphorylation at the level of the IR13 subunit, thus regulating metabolic disorders of hyperglycemia [18].

Kombucha is a symbiotic mixture where bacteria, yeast, acetic, gluconic, glucuronic (GlcUA), citric, L-lactic, malic, tartaric, malonic, oxalic, and succinic acids are mixed, you can also find pyruvic, usnic, and vitamin B1, B6, B12, B2, C, and minerals copper, iron, manganese, nickel, and zinc [19].

Also, minerals, nutritional and therapeutic compounds were detected that have an important role in the body homeostasis of many biochemical processes, in addition to having anticancer, antioxidative, hepatoprotective and antihypertensive properties [20] [21] [22].

The polyphenols contained in kombucha at the intestinal level, they slow the

absorption of carbohydrates in such a way that they act as antidiabetics, in addition to protecting and regenerating the β cells of the islets of Langerhans of the pancreas [22] [23] [24] [25].

The acetic acid contained in the kombucha it also has antidiabetic activity by reducing the digestion and absorption of carbohydrates and inhibiting their conversion to more complex sugars by enzymatic activity, thereby preventing large amounts from reaching the bloodstream [9]. This paper is the first in evaluate the effects from Ganoderma and Kombucha extracts on regeneration of islets of Langerhans of the pancreas.

2. Materials and Methods

2.1. Experimental Design

This work was carried out at the facilities of the Department of Veterinary Medicine of the University Center for Biological and Agricultural Sciences of the University of Guadalajara, Jalisco, Mexico. Sixty four young adult (two months old) male Wistar rats with an average weight of 150 ± 200 g were used for the study, which were housed in animal facility conditions with water and standard chow diet *ad libitum*, 12-hour light/dark cycles with climate and controlled ventilation. All the procedures used were approved according to Mexican regulations [26]. Rats were randomly divided into four groups (n = 12). One control and three diabetic experimental groups with streptozotocin: diabetic control without treatment, one experimental with the extract of Ganoderma mushroom at a daily dose of 250 mg/kg of body weight and another experimental group with the extract of kombucha orally, a daily dose of 324 mg/kg of body weight [27].

The study lasted 45 days, with four stages of sacrifice of 4 animals per date, which were at 2, 15, 30 and 45 days after the induction of diabetes with the intraperitoneal application of streptozotocin at a dose of 65 mg/kg of body weight, diluted in citrate buffer solution pH 4.5 for experimental animals as a single dose at the beginning of the study [28] [29] [30].

2.2. Morphological Analysis of the Pancreas

Four rats from each group were sacrificed on the scheduled dates to obtain the pancreas, fixed with 10% formalin, subjected to the histological process with increasing alcohols and xylol, to then be fixed in paraffin blocks and cut at 10 μm for later stain them with eosin-haematoxylin for analysis under a light microscope with the 40× objective in 10 randomly chosen visual fields per animal and with a total area of 1000 μm per section. The total islets of Langerhans were quantified and classified into small, medium and large in each of the stages and by treatment received.

2.3. Statistic Analysis

A two-way analysis of variance and a student's t were applied, at a significance

level of 0.05%, the SigmaStat 3.1 software was used.

3. Results

3.1. Average Islets of Langerhans

Figure 1 shows the average number of Islets of Langerhans in the first stage, that is, two days after the start of the study, no statistical differences were found, the range was from 13 to 15 islets. In the second stage (15 days) a statistical difference was found, the highest values were for the control and streptozotocin groups with an average of 20 and 23 islets, and the lowest values were for the groups kombucha and Ganoderma with average values of 7 islets. In the third stage, very different averages were identified between groups, however, due to the great dispersion of the values, no statistical differences were found, the averages were from 9 to 23 islets. In the fourth stage (45 days), significant differences were found, the highest values were for the groups control and Ganoderma with an average of 27 islets and the lowest values were for the streptozotocin and kombucha with an average of 14 and 16 islets.

3.2. Average of Large Islets

Figure 2 shows the averages of the large Islets of Langerhans variable. In the first, second, and third stages, no significant differences were found between the groups, the average values were from 0 to 3 islets. During the fourth stage, significant differences were identified ($p = 0.012$), the highest value was from the control group with an average of 8 islets, in the rest of the groups an average of 2 islets were identified.

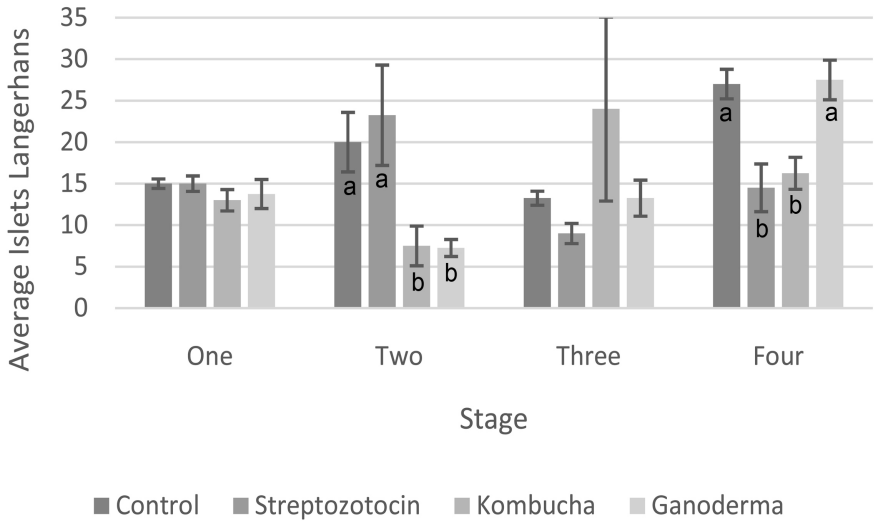

Figure 1. Average number of islets of Langerhans by groups and stages a, b literals indicate a statistical difference $p < 0.05$, between groups of the same experimental stage there is a significant difference on day 15 between the control, kombucha and Ganoderma, after day 45 there is a significant difference between the control, streptozotocin and kombucha.

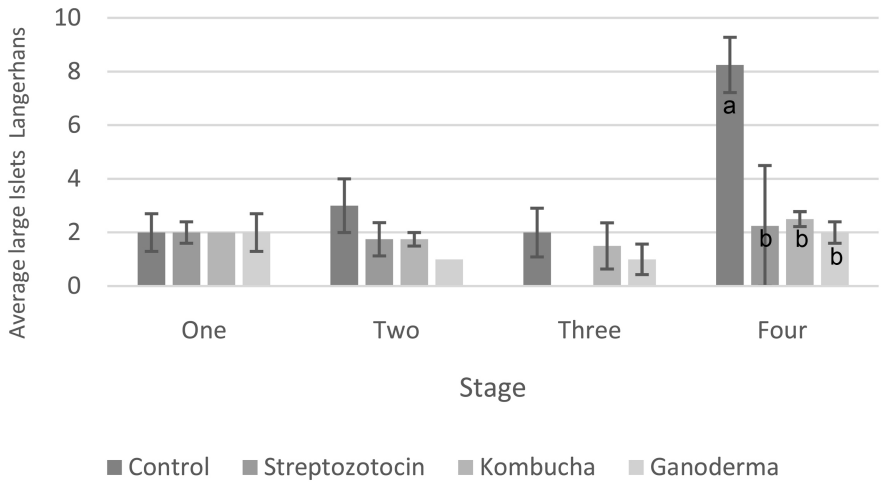

Figure 2. Average and large islets of Langerhans by group and experimental stage. a, b literals indicate statistical difference at $p < 0.05$, between groups of the same experimental stage.

3.3. Average of Medium Islets

Regarding the average number of islets of Langerhans of medium size as observed in **Figure 3**, no statistical difference was found between groups of the same stage. For the first stage (2 days post-treatment), the values ranged from 1 to 3 islets, with regard to stage two, the average number of islets ranged between 1 and 9, however, due to the variability of the data, no statistical difference was found. For the third stage, 0 to 3 islets were presented. Finally, for the final stage of the study (45 days), a statistical difference was found between the groups, the highest value was for the control group (4.75), followed by the group kombucha (3.75) the lowest value was for the streptozotocin group (1.5).

3.4. Average Small Islets

Regarding the average number of small Langerhans islets, as observed in **Figure 4**, no significant differences were found between groups in the first three stages. The values of the first stage (2 days) were from 8 to 12 islets. For the second stage, the range was wide from 3 to 14 islets; however, due to the variability of the data, no significant differences were found. In the third stage, the number of islets presented a range from 6 to 19 islets. For stage four, a significant difference was found, the highest value was for the group Ganoderma (22 islets), followed by the control group (14 islets), different from the kombucha and streptozotocin groups (10 islets).

3.5. Morphological Analysis of Pancreas

Figure 5 shows that in the islets of Langerhans, of all the groups on the second day after induction with streptozotocin, they presented a very similar cell morphology in terms of cell size and number.

In **Figure 6**, 15 days post-treatment, since the clinical signs of diabetes were

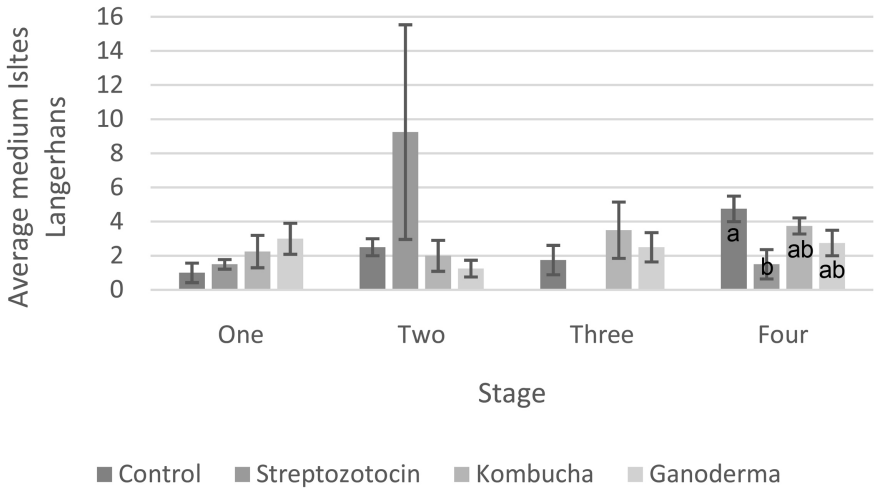

Figure 3. Means of median islets by group and experimental stage. a, b literals indicate statistical difference at $p < 0.05$, between groups of the same experimental stage.

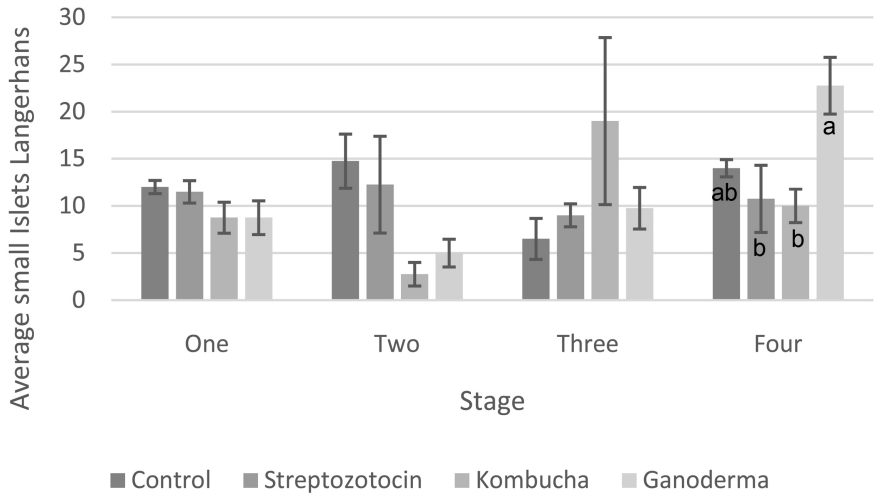

Figure 4. Means of small islets by group and experimental stage. a, b literals indicate a statistical difference at $p < 0.05$, between groups of the same experimental stage, significant differences are observed in the fourth stage between groups and between treatments with a greater number of small islets in the group of Ganoderma.

well present in all the induced animals, polyuria, polydipsia and hyperphagia were identified in the islets and the cell morphology in size and number of the islets of Langerhans had changed in the groups, the most affected being that of streptozotocin that did not receive any treatment.

In Figure 7, it can be seen in the third post-induction stage that the number of islets and their morphology did not recover, since the streptozotocin group continued to be highly affected, unlike the other groups, in some counts of the 10 random fields. There were no islets and/or they were very small. At this stage, the group treated with Kombucha presented a number of islets similar to those of the control group.

In Figure 8, as the group treated with Ganoderma is observed with a number

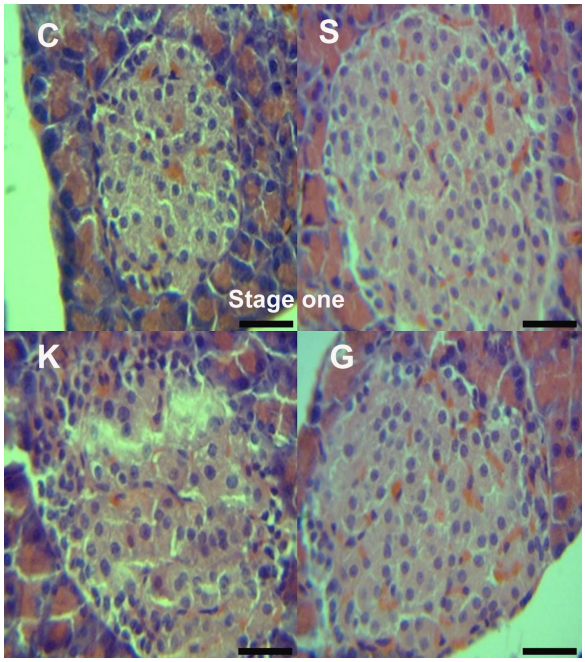

Figure 5. Images of the islets of Langerhans taken with the 40× objective are observed in the second post-induction stage of the groups. (C = Control), (S = Streptozotocin), (K = Kombucha) and (G = Ganoderma). The islets of the experimental groups with inflammatory processes and with morphological changes in their cellular architecture are observed, unlike the control group (20 μm bar).

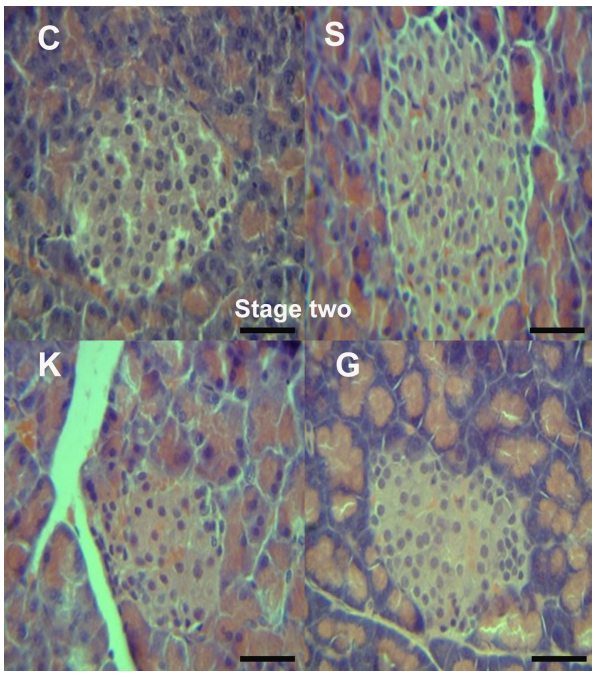

Figure 6. Images of the islets of Langerhans taken with the 40× objective are observed in the second post-induction stage of the groups. (C = Control), (S = Streptozotocin), (K = Kombucha) and (G = Ganoderma) It is observed that the islets treated with the extracts recover their normality with a morphology similar to that of the control group, however the one treated only with streptozotocin continues with the inflammatory process and with severe damage in its morphology of the islets.(bar 20 μm).

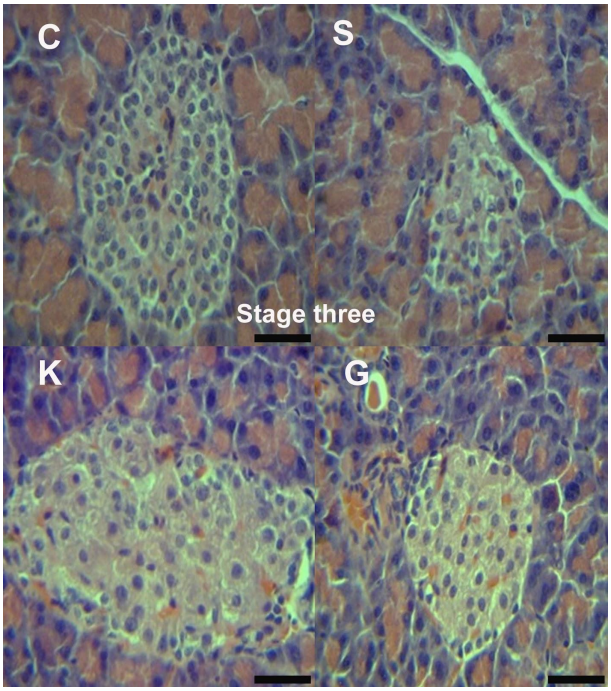

Figure 7. Images of the islets of Langerhans taken with the 40× objective are observed in the third stage of the groups. (C = Control), (S = Streptozotocin), (K = Kombucha) and (G = Ganoderma), the streptozotocin group drastically decreases the size and number of islets (20 μm bar).

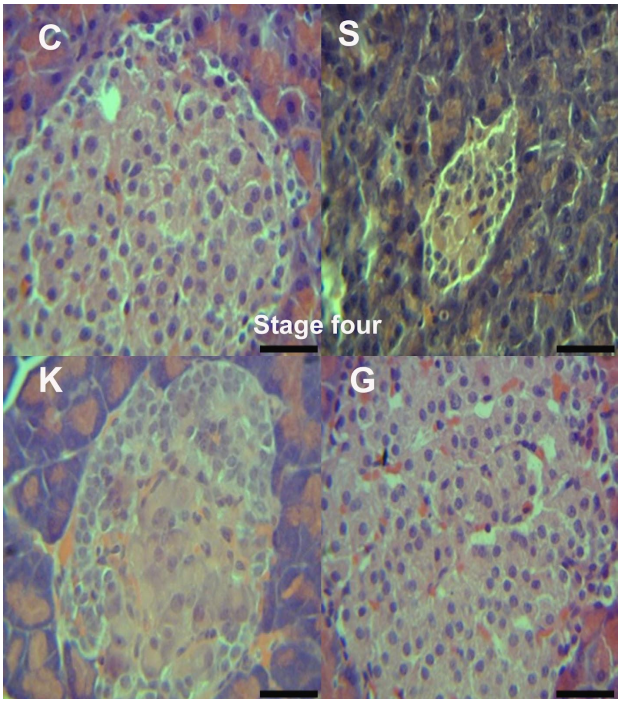

Figure 8. Images of the islets of Langerhans taken with the 40× objective are observed in the fourth post-induction stage of the groups.(C = Control), (S = Streptozotocin), (K = Kombucha) and (G = Ganoderma), the islets of the groups treated with the extracts are observed already recovered with a morphology and a cellular architecture similar to that of the control group (20 μm bar).

of islets and a cellular architecture similar to the control, the streptozotocin group without treatment remained highly affected throughout the study.

4. Discussion

The average number of islets in the early stages was very similar between the treated and control groups with no significant differences (**Figure 1**), only on day 15 were there significant differences when comparing the control group with that of the groups control, kombucha and Ganoderma that present a lower average number of islets, but as we can see on day 30, the groups treated with the extracts begin with a recovery, raising the average number of islets, which is maintained until day 45, being the group of Ganoderma followed by the of kombucha that end up with a greater number of islets than the other groups, thus demonstrating the protective and/or regenerative effect of the pancreas and its islets [23] [24] [31].

As can be seen in (**Figure 2**) in the first stage all the groups presented an average number of large islets, but at the beginning of the second stage these large islets decreased to the extent that in the third stage the streptozotocin group had no islets. large or very few and in the fourth stage the statistical differences were very evident when comparing the control group with the experimental groups and there was a marked pancreatitis attributed to the effect of the drug in the streptozotocin group without treatment [32], unlike those who were treated with the extracts of kombucha [27] and Ganoderma [31].

In (**Figure 3**) the effect of streptozotocin is observed from the first stage because the average number of medium islets begins to increase and in the second stage in the streptozotocin group without treatment they are triggered exaggeratedly by acute pancreatitis that tries to counteract the effects of streptozotocin. effects of diabetes to then drop drastically in the third stage where the islets in the pancreas of these animals that were not protected with the extracts were very scarce, as happened with the groups that were treated and protected with kombucha and Ganoderma [33].

The histological findings of the pancreas in the first stage, as observed in (**Figure 4**), show that the groups presented small islets with the same morphological characteristics and on average, however, in the second stage the treated groups decreased their small islets re-drastically structuring and increasing its average in the third and fourth stages, this is attributable to the treatment with the extracts, which did not happen with the diabetic group of streptozotocin without treatment, which maintained a high number of small islets that are not functional like the large ones, this is attributable to acute pancreatitis presented by all the animals in this group [34] [35].

In **Figures 6-8**, the groups treated with the extracts modify the cell architecture and cell morphology of the islets, decreasing the inflammatory process of the pancreatic tissue during the different stages of the study; however, the same does not happen with the groups. pancreas and the islets of the animals of the

streptozotocin group that did not receive treatment with the extracts, since, as seen in **Figure 1** and **Figure 2**, the averages of the large and medium islets, which are the functional ones, drastically decrease to the degree that they almost completely disappear from the tissue. Pancreatic and hardly any islets are seen in the visual fields that were reviewed [24] [27].

5. Conclusions

Definitely the treatment with the extracts of kombucha and Ganoderma, they actually act as protectors of the pancreas by decreasing the damage due to diabetes caused by streptozotocin induction.

Both extracts presented a regenerative effect according to the morphology and architecture of the pancreatic islets found in each of the stages of the study, since the groups treated with the extracts had a greater number of large and medium islets than the untreated group.

The animals treated with the extracts of the two extracts the Ganoderma presented better protective and regenerative effect according to the data obtained and followed after the extract of kombucha

The animals that were treated with the extracts did not present acute pancreatitis and severe destruction of the pancreatitis, like the animals in the streptozotocin group, attributable to the anti-inflammatory effect of the components of the extracts.

Authors' Contribution

PHG, JRCP, SFG and LGD, contributed to the data collection and execution. EAR, and VBC, contributed to the data interpretation. EAR, GNR, MRC and JRCP, contributed to the study design, data interpretation, and manuscript preparation. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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