

**How to Cite:**

Hamza, A. M., Hassan, M. S., Mousa, R. F., Jahil, A. H., & Hassan, M. S. (2022). Effect of aloe vera on antioxidant in male rats exposed to high doses of dexamethasone therapy, and histological on liver and pancreas. *International Journal of Health Sciences*, 6(S6), 8050–8062. <https://doi.org/10.53730/ijhs.v6nS6.12201>

## **Effect of aloe vera on antioxidant in male rats exposed to high doses of dexamethasone therapy, and histological on liver and pancreas**

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**Abstract**---The present study was undertaken to observe the effect of the aqueous leaf extract of Aloe vera gel of the Antioxidant and histological on liver and pancreas. Twenty-four male rats were divided into four groups (6rats/group) and treated as follows for 28 days. G1 were intubated orally distal water serving as control while, G2 were administering of Dexamethason -induced diabetic 1 mg/kg/bw. Intraperitoneally, G3 were administering of diabetic rats given Dexamethason 1mg/kg/bw. + Aloe vera leaf gel extract (300 mg/kg) using an intragastric tube, G4 were administering of diabetic rats given Dexamethasone 1mg/kg/bw. intraperitoneally + Aloe vera leaf gel extract (500 mg/kg) using an intragastric tube, the following criteria were measured Antioxidant and histological on liver and pancreas. The findings show that Aloe Vera had a significant decrease influence in serum Antioxidant (MDA, ACE, and HSP70). In conclusion, this study mentioned a new evidence of the role of Aloe Vera on the decreasing of antioxidant.

**Keywords**---aloe vera gel, dexamethasone, antioxidant (MDA, ACE, HSP70), histological on liver, pancreas rats.

## Introduction

Aloe Vera Gel, (L.) Burm. f. (Liliaceae family) is the most extensively studied among the four other species of the genus Aloe, having diverse therapeutic potential as well as clinical effectiveness against a wide range of illnesses, including skin disorders (1,2). In ancient Egypt, this plant was considered as the “plant of immortality” and included in the traditional healthcare systems of various cultures, including the Arabs, the Egyptians, Greeks, Romans, Indians, Japanese, Koreans, and Chinese, to treat a variety of skin disorders such as burns and wounds, psoriasis and dermatitis (3,5,5) Historically, it has been used as a traditional medicine for the treatment of skin problems, infections, and other ailments in India, as well as as an antifungal, antidiabetic, and antihypertensive agent in Chinese, Mexican, and Trinidadian cultures (6,7,8). Dexamethasone (Dex), 16 $\alpha$ -methyl 9 $\alpha$ -fluoroprednisolone, is a synthetic glucocorticoid. Owing to its potency for anti-inflammation, Dex has been widely applied in clinic for decades as a treatment of diverse inflammatory and autoimmune diseases (e.g., rheumatic arthritis, asthma, allergy, and transplantation rejection) (9,10). Dex also has an influence on the physiologic process of metabolism of endogenous compounds, including lipids (11), glucose (12), and bile acids (13). Most of the physiologic effects of Dex are mediated through the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily of transcription factors (14)

## Materials and Method

### Animals of the Study

The experiment was carried at the laboratory animal's facilities Faculty of veterinary medicine karbala University. Twenty-four albino rats were used in this study with an arranged age range between 150-200g. These animals were kept in suitable environmental condition with a temperature of around 25-28 °C, relative humidity 40% - 60% conditions room with a 12:12 h/light / dark cycle (5). The animals were housed in a plastic cage with dimensions of 50×35×15cm. The feed given were pellets. The animals were kept for at least 15 days for acclimatization before experiment began.

### The Experimental Design

Twenty-four male rats were divided randomly into four groups:

- Group (G1) 6 rats will be administering normal saline and animals is euthanized after 28 day.
- Group (G2) 6 rats will be administering of *Dexamethason* -induced diabetic 1mg/kg/bw. intraperitoneally for 28 days (15).
- Group (G3) 6 rats will be administering of diabetic rats given *Dexamethason* 1mg/kg/bw. + *Aloe vera* leaf gel extract (300 mg/kg) in aqueous solution daily using an intragastric tube (16), for 21 days.

- Group (G4) 6 rats will be administering of diabetic rats given *Dexamethasone* 1mg/kg/bw.intraperitoneally + *Aloe vera* leaf gel extract (500 mg/kg) in aqueous solution daily using an intragastric tube (16), for 21 day

### **Preparation of Dexamethasone**

Dexamethasone was obtained from Sigma Aldrich Company (USA).

### **Preparation of aloe vera gel**

The outer part of the aloe vera leaf was peeled off to obtain aloe vera gel directly, and using a small spoon, the entire gel was extracted, and then the gel was transferred to a blender to obtain a mixture and foam ready to be dosed to the animals under study.

### **Blood sample collection**

At the end of experiment, the animals anesthetized, this done by putting the rats in closed jar containingsoaked by chloroform. Then the blood collected by heat puncture. the blood gelled tube and centrifuged for 15minutes ( 300 RPM ) . The supernatant serum was drawnand kept by eppendorf tubes and store at ( -4 C°) until analyzed .

### **Statistical Analysis**

The data were analyzed by using one-way analysis of variance (ANOVA) and significant difference between groups was of the level ( $P \leq 0,05$ ) according to least significant difference (LSD)(version 29,SPSS,in UAS 2010).

### **Biochemical tests**

- Determination of Serum Malondialdehyde (MDA)concentration ( $\mu$  mol /L): Malondialdehyhe was estimated by Thiobarbituric acid (TBA) assay method of (Buege and Aust, 1978) on spectrophotometer(17).
- Determination of Serum Heat shock protein 70 (HSP70 ng/ml). The kit is a sandwich enzyme immunoassay for in vitro quantitative measurement of HSP70 in rat serum, plasma,tissue homogenates, cell lysates, cell culture supernates and other biological fluids (18).
- Determination of Serum Angiotensin Converting Enzyme (ACEng/ml). Principle: The kit uses a double-antibody sandwich enzyme-linked immunosorbent onestep process to assay Angiotensin Converting Enzyme (ACE) in human serum(19)

## Result

### Antioxidant Level

#### Effect of Alovera gel 300mg/kg and 500mg/kg on some antioxidant status in adult male rats

A significant decreased ( $P < 0.05$ ) was noticed in the concentration of (MDA), (ACE) and (HSP70) in the (G1), (G3), and (G4) groups respectively compared with the (G2) group (Figure1).

Table 1  
Comparison of Antioxidant levels for all groups under study

| Groups<br>parameters | Control<br>(G1)    | Dexamethzone<br>(G2) | Dexamethzone<br>+Alovera 300<br>(G3) | Dexamethzone<br>+Alovera 500<br>(G4) |
|----------------------|--------------------|----------------------|--------------------------------------|--------------------------------------|
| MDA nmole/mL         | 205.33 ± 3.25<br>D | 280.46 ± 7.69 A      | 245.71 ± 7.27 B                      | 221.7 ± 5.51 C                       |
| ACE ng/ml            | 1.53 ± 0.15 D      | 8.08 ± 0.63 A        | 5.61 ± 0.77 B                        | 3.74 ± 0.96 C                        |
| HSP70 ng/ml          | 10.10 ± 1.03<br>D  | 16.25 ± 0.45 A       | 14.29 ± 0.62 B                       | 12.46 ± 0.41 C                       |

Different letters in the same column represent a significant different at ( $P < 0.05$ )

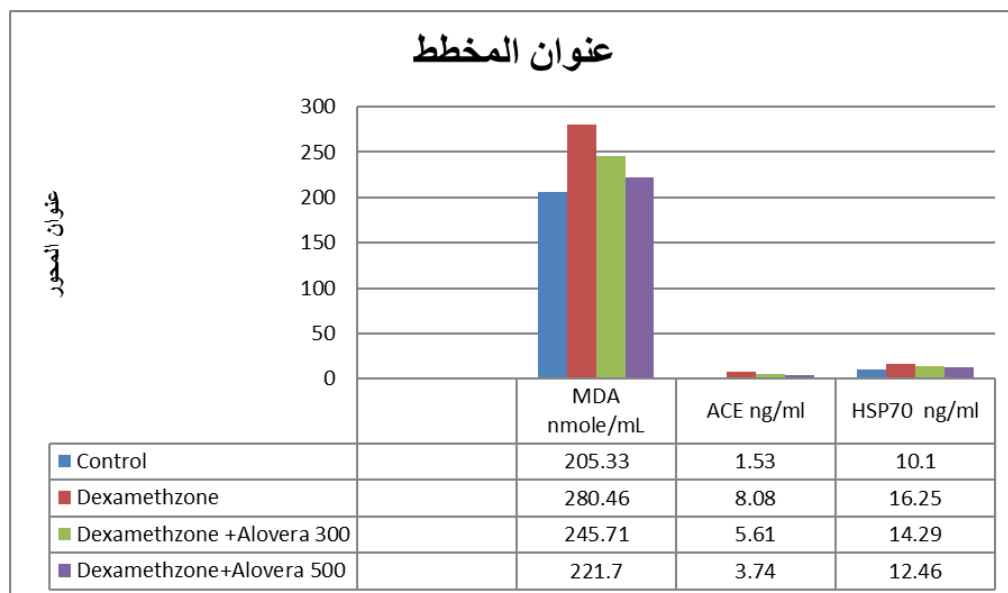


Figure1. Effect of Alovera gel in the alleviating the deleterious effect of Dexamethzone on Antioxidant levels in adult male rats

## The Histological Examinations

### Liver

The results of the histopathologic examination of the liver are shown in Figures (2) & (5). There was no visible lesion observed in livers of rats in control group and slight lesion in Aleo Vera 500mg treated group. Livers from rats treated with the Aleo Vera 300mg showed slight to moderate vascular congestion, significant necrosis and depletion in hepatocytes with cellular vacuolation (Figure 4). While the liver of rats that had been dosed with dexamethasone showed lesions such as significant degenerative changes of hepatocytes, severe dilation and congestion of portal vein and arteriole and inflammatory cells infiltration (Figure 3).

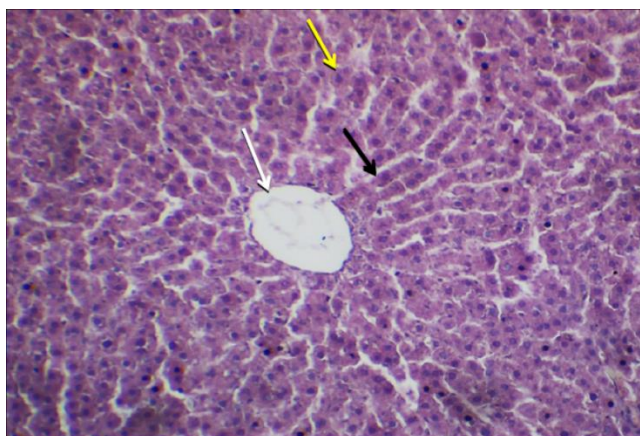


Figure 2. Photomicrograph of liver tissue section of a control group animal, showed the normal hepatic architecture (cords) (black arrow), around central vein (white arrow), hepatocytes with significant rounded large nuclei (yellow arrow). (H and E, 10X)

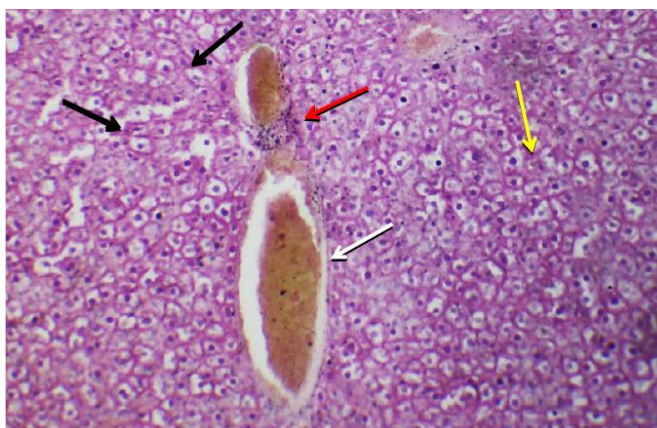


Figure 3. Photomicrograph of liver tissue section from *Dexamethazone* group animal, showed the significant degenerative changes of hepatocytes (ballooning) (black arrow), severe dilation and congestion of portal vein and arteriole (white arrow) with inflammatory cells infiltration (red arrow) and remarkable hepatocyte pyknotic nuclei (yellow arrow). (H and E, 10X)

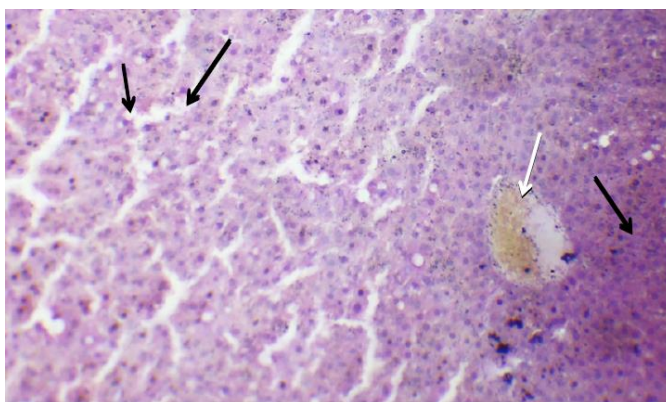


Figure 4. Photomicrograph of hepatic tissue section of Aleo Vera 300mg treated group animal, revealed the significant necrosis and depletion in hepatocytes with cellular vacuolation (black arrow), and slight to moderate vascular congestion (white arrow), areas showed histological structure resembling normal tissue with mild degenerative changes (right side). (H and E, 10X)

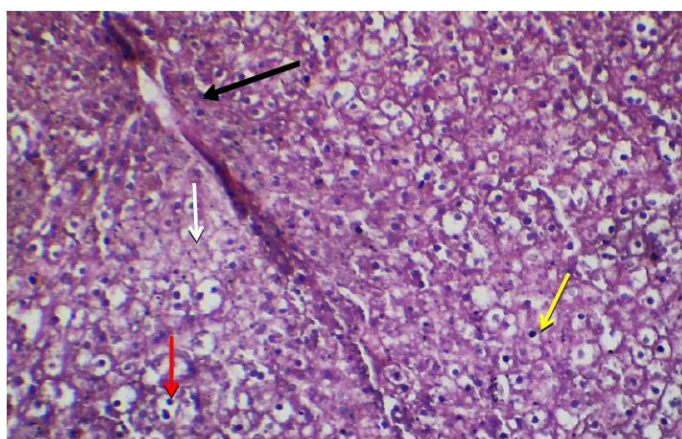


Figure 5. Photomicrograph of liver tissue section of Aleo Vera 500mg treated group animal, revealed the normal morphological structure of portal area components (black arrow), mild hepatocytes degeneration and vacuolation (red arrow) with nuclear pyknosis in some areas (yellow arrow), and slight leukocytic infiltration (white arrow). (H and E, 10X)

## Pancreas

The results of the histopathologic examination of the pancreas are shown in Figures (6) & (9). There was no visible lesion observed in pancreas of the rats in control group and slight lesion in Aleo Vera 500mg treated group. Pancreas from rats treated with the Aleo Vera 300mg showed moderate vascular congestion, acinar necrosis and perivascular inflammatory cells infiltration (Figure 8). While the pancreas of rats that had been dosed with dexamethasone showed lesions such as significant structural changes and damage, severe acinar necrosis with vascular congestion and shrinkage of islets of Langerhans (Figure 7).

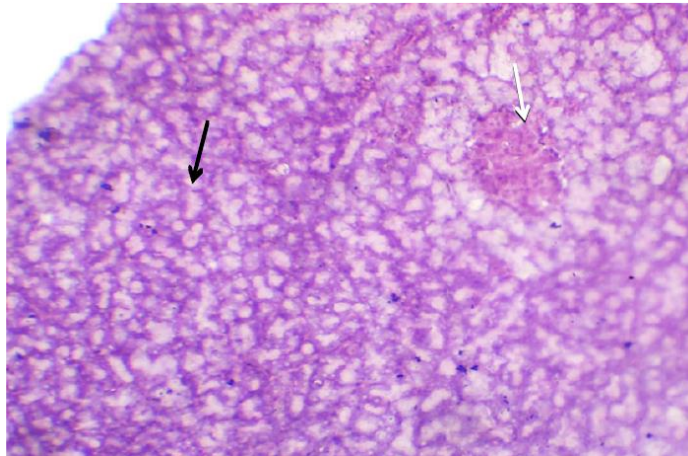


Figure 6. Photomicrograph of pancreatic tissue section of a control group animal , revealed the normal architecture of tissue , normal exocrine acini (black arrow) , and normal Islets of Langerhans embedded in exocrine pancreatic acini (white arrow). (H and E ,10X)

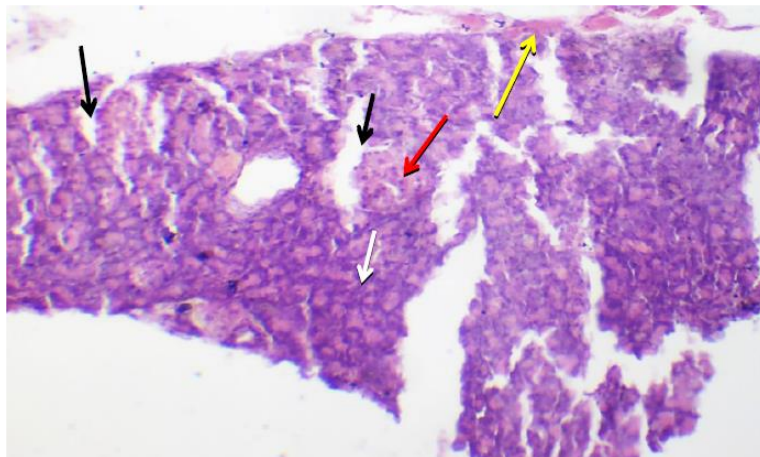


Figure 7. Photomicrograph of Pancreas histological section from *Dexamethazone* group animal , showed significant structural changes and damage , remarkable pancreatic ductals widening (black arrow) , acinar necrosis (white arrow) with vascular congestion (yellow arrow) and marked shrinkage islets of Langerhans due to degeneration of cellular components (red arrow) . (H and E ,10X)

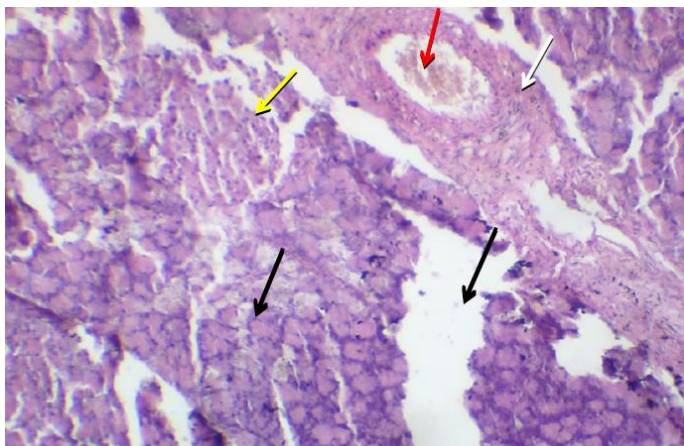


Figure 8. Photomicrograph of Pancreatic tissue section of Aleo Vera 300mg treated group animal , revealed depletion of Pancreas tissue with acinar necrosis (black arrow) , moderate vascular congestion (red arrow) with perivascular inflammatory cells infiltration (white arrow) and significant reversible changes to normal cellular components of islets of Langerhans (yellow arrow). (H and E ,10X)

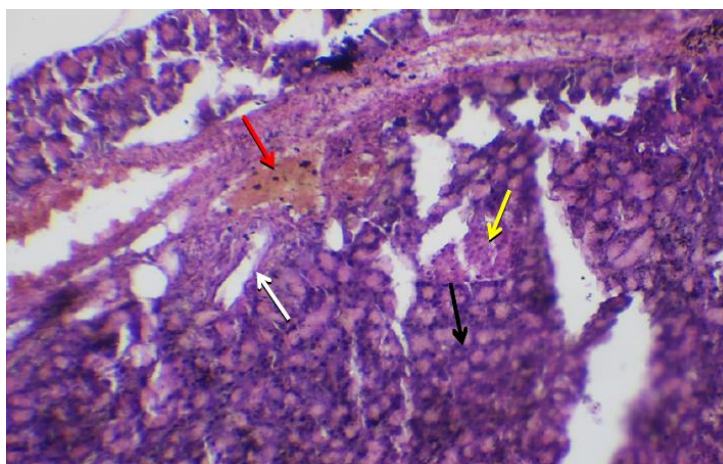


Figure 9. Photomicrograph of Pancreatic tissue section of Aleo Vera 500mg treated group animal, revealed reversion of Pancreatic tissue to their normal structure (black arrow), vascular congestion (red arrow) with periductal inflammatory cells infiltration (white arrow) islets of Langerhans resembling normal (yellow arrow). (H and E ,10X)

## Discussion

### Histopathological Effect of Aloe Vera on Antioxidant levels

Generation within the membrane and lipoprotein of peroxy and alkoxyl radicals, aldehyde and other products of lipid oxidation affects the liver to a great extent, causing the formation of high molecular mass protein aggregate within the membrane. Hence increased level of MDA and associated products viz. conjugated dienes is a factual indicator of lipid peroxidation<sup>26</sup> which highlight

the toxic effect of AOM in liver. Thiols are thought to play a vital role in protecting cells against lipid oxidation(20). AGE feeding was found to be effective in increasing the GSH content rendering the protection against AOM-induced hepatic and colonic lipid peroxidation (21). have outlined the potential of uric acid as a biological antioxidant in mitigating cellular damage caused by oxygen free radical(21). Hence, it is relevant to note the increase in uric acid by the treatment of AOM. Possible reason for raise in bilirubin and uric acid levels by AGE warrants further investigation.HSP70

Among the HSPs, HSP70 is considered to be one of the most conserved and important protein families. In fact, HSP70 refers to a family of 70 kDa chaperone proteins participating in house-keeping functions. These ATP-dependent chaperones are key elements of the cellular protein surveillance network involved in a large variety of protein-folding processes (22).It is well appreciated that under various stress conditions, adaptive synthesis of stress inducible HSP70 enhances the ability of stressed cells to maintain proteostasis by dealing with increased concentrations of unfolded or denatured proteins (for recent reviews, see References (23,24,25,26)).

### **Histopathological Study**

The influence of aloe vera on liver and pancreas was investigated in the present study.

### **Histopathological Effect of Aloe Vera on liver**

Given that many millions of people take Aloe vera every day around the world with no ill effect, hepatotoxicity appears to be a very rare problem, particularly with the decolorized gel, which is purely made from the plant pulp and does not contain any skin of the leaf (27). It is worth noting though that the skin of the plant is not digestible and can cause liver toxicity; it has therefore not been recommended for human oral consumption by EFSA(28).Therefore, Aloe vera should only be consumed from a trusted source, using the fresh inner flesh of the plant, or a decolorised derivative (28). The previous reports of liver toxicity are, barring one case, suspected rather than proven.(29,30). It is sometimes difficult to assess the effects of herbal and health food compounds as hepatotoxic agents in the populations of the developed world, given that 25-30% of the western European population have increased liver enzymes from multiple causes such as obesity, diabetes, high cholesterol levels, consumption of alcohol to excess and the use of a variety of medications which have known liver effects. As there are usually multiple potential reasons for abnormal liver enzymes on blood testing, picking out a single cause does require expert interpretation and in this increasingly obese world, being overweight is becoming the commonest reason.

### **Histopathological Effect of Aloe Vera on pancreas**

In recent years, various plant extracts have been claimed to be useful for the cure of diabetes mellitus (31, 32, 33, 34,35) but few of them have been tested for their effects on tissues of diabetic animals (36, 37,38): parsley extracts did not cause any morphological changes in pancreatic  $\beta$ -cells (39). Acute treatment with Aloe

leaf pulp resulted in 30 and 34% decreases in blood sugar levels of n0-STZ-diabetic rats, after 2 and 3 hr of administration of the extract respectively (40), and 11 and 14% reductions in blood glucose levels 3 and 4 hr after administration of Aloe leaf-gel extract.

However these effects could not be repeated with the same extracts in chronic treatment (41). There were no significant differences in blood glucose levels between the groups given Aloe leaf-pulp and gel extracts compared to the control group given PBS, and there were no significant differences in blood sugar levels between Aloe extracts compared with the group given glibenclamide. Alongside claims of hypoglycaemic activity for Aloe extracts, (42,43,44,45,46,40), there are also reports of negative effects (47,48,49,41). These may be due to variation in the content and quality of natural drugs as well as to differences in the animals studied. Further studies with well-defined preparations or pure compounds are needed to eliminate the confusion which still exists about Aloe preparations. In the present study, the fact that neither glibenclamide nor Aloe extracts showed any stimulation of the pancreatic  $\beta$ - cells in type-II diabetic rats suggests that any decreases in blood glucose levels caused by Aloe extracts is not mediated by insulin release from  $\beta$ -cells, but by extra-pancreatic usage of glucose. Thus we conclude that, contrary to reports in the literature (50,51), treatment of diabetic rats with Aloe vera (gel and pulp) extracts or glibenclamide has no beneficial influence on the pancreas and thus may not be appropriate for the treatment of type-II diabetes in alternative medicine.

## Conclusion

It was concluded that aloe vera gel had an important role in reducing the level of antioxidants (MDA, ACE, HSP70)

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