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Potential of Aloe vera and Amaryl in amelioration of hyperglycemia correlated with Streptozotocin induced diabetes

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Abstract

Diabetes mellitus (DM) is multifarious group of disorders distinguished with hyperglycemia. Streptozotocin (STZ) induced diabetes frequently occurs animal model in the medical researches. Hence, amelioration of hyperglycemia associated with diabetes is a cardinal target for therapeutics. Therefore, this work aimed to assesses the possible ameliorative characteristic of Aloe vera and Amaryl in STZ-induced diabetes. In this study, forty male Wistar rats within average weight 130±20 gm and age 6-7 weeks were used. The animals were evenly divided; 10 rats of each as follow. Group 1 served as control. Group 2 only received STZ. Group 3 received STZ + Aloe vera extract. Group 4 received STZ + Amaryl. Venous blood samples collected for biochemical assay using colorimetric methods. Besides this, specimens from pancreas were excised for the histological findings. Biochemically, STZ induced diabetic rats led to significant elevation in mean levels of blood glucose, total bilirubin and malondialdehyde (MDA) when compared with control. Contrary, activity of superoxide dismutase (SOD) was significantly decreased in STZ induced group in comparison with control. In contrast, the administrations of Aloe vera and amaryl to STZ diabetic rats showed an improvement in the mean values of the altered parameters. Histopathology, diabetic group revealed vacuolation of the pancreatic B-cells, besides inflammatory edema. Aloe vera and amaryl treated groups exhibited apparently normal pancreatic tissues. Depending on theses evidence, we could say that Aloe vera followed by amaryl could have contributed for an improvement of the pathophysiological alterations promoted by STZ induced diabetes.

Keywords:
Aloe vera, Amaryl, Biochemically, Diabetes, Histopathology.

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Introduction

According to world health organization, diabetes mellitus constitutes one of the most prevalent metabolic disorders (Wild et al., 2004). At the same time, diabetes mellitus is defined as chronic plurimetabolic disease characterized by prolonged hyperglycemia (Gerstein, 2007) was attributed to alterations in the carbohydrate, fat and protein metabolisms accompanied by absolute or relative deficiencies in insulin secretion and/or its action. Moreover, basal hyperglycemia occurs irrespective of whether insulin deficiency or insulin resistance is the dominant defect (Rajasekaran et al., 2005a). Diabetic patients were suffered from an increased risk of diabetic nephropathy, retinopathy, neuropathy and cardiomyopathy and hyperglycemia (Oluleye, 2010).

Induction of diabetes in vivo is a convenient and beneficial strategy in the understanding and treatment of the disease. STZ function is a DNA alkylating agent in both bacterial and mammalian cells. It was frequently experimentally employed for induction of diabetes in the medical research via creation hyperglycemia in a large dose, as well as type 2diabetes or type 1diabetes with multiple low doses (Eleazu et al., 2013). An addition contributor to STZ that altered the pancreatic β-cells (Islam and du Loots, 2009) through a dose-response pattern, resulted in hyperinsulinemia, hyperglycemia, and a subsequently diabetes mellitus (Eleazu et al., 2013).

In the past two decades, scientific fulfillment explore that traditional medicinal plants play a significant importance in the treatment of diabetes in a wide-ranged scale (Schwab and Diem, 2009). Such traditional herbs exploited for diabetes treatment for attributed to several biological properties included effective, non-toxic, with less or no side effects and excellent candidates for oral therapy (Takamoto and Kadowaki, 2011). Many authors suggested that Aloe vera (L.) Burm f., Xanthorrhoeaceae is one of traditional herbaceous; well acknowledged in last few decades for diabetes management. Aloe vera utilized as valuable therapeutic which protectively act as a free radical scavenging, through its potent anti-oxidant property on diabetic patients (Tabolacci et al., 2010); by control elevated anions in an alloxan or STZ-induced diabetic animal models (Im et al., 2010).

As for chemical remedies, a variety of drugs have been devoted to the development of optimal therapeutic regimens for the management of type 2 diabetes. Various pharmacologic agents are available for the management of type 2 diabetes, including first-and second generation sulfonylureas (Khadre et al., 2011). Glimepiride (Amaryl®), a third-generation sulfonylurea administered once daily, has been confirmed to supply therapeutic advantages over other sulfonylureas in terms of glucose level-dependent insulinotropic action, insulin-sparing effects, and hypoglycemic risk (Qi et al., 1995). Glimepiride afforded many advantages over other sulfonylureas including lower dosage, rapid onset, prolonged duration of action and lower insulin C-peptide levels (Mohamed et al., 2012). Besides this, it stimulates pancreatic β cells to secrete insulin. Furthermore, it has been known to work by means of several extra pancreatic mechanisms (Basit et al., 2012).

Therefore, the present study has been planned to evaluate the possible ameliorative effect of Aloe vera and Amaryl on STZ-induced diabetic rats.

Materials and methods

Materials:

a) Experimental animals:

This study was established on forty adult male Wister albino rats within average

body weight 130±20 gm. It was brought from Laboratory Animal House, Giza, Egypt. Animals were housed in the Laboratory Animal House of the Faculty of Science, South Valley University, Qena, Egypt. Animals were placed under good environmental conditions during the maintained experiment. Moreover, adequate standard *ad libitum* and water were offered along over the exposure.

b) Drugs:

1- Streptozotocin:

Streptozotocin (STZ, 1) (2-deoxy-2-(3-methyl-3- nitrosourea)-1-D-glucopyranose) is a naturally occurring alkylating agent that is specific toxic to the insulin-producing β-cell of the pancreas in mammals. STZ was purchased from Sigma Company for Pharmaceutical Drugs, (St. Louis, MO., USA).

2- Aloe vera:

Aloe vera (L.) Burm.f., Xanthorrhoeaceae was obtained from Plant Farm concerning to the Faculty of Agriculture, South Valley University, Qena, Egypt. Aloe vera gel was freshly prepared through washing its leaves with water and swap followed by alcohol.

3- Glimepiride (Amaryl®):

Amaryl (Glimepiride tablet) was obtained from local Pharmacies belonging to Qena, Egypt and undergone grinding using a mortar. The powder was dissolved in distilled water and orally administrated.

Methods:

1- Induction of experimental diabetes:

After fasting of the animals, diabetes was induced by intraperitoneal injection of single dose STZ freshly dissolved in 0.1 M cold sodium citrate buffer, (pH 4.5) at a dose of 45 mg/kg b.wt. After injection, they had given abundant food and water, and 5% glucose solution to drink overnight to counter hypoglycemic shock. The blood glucose levels were calculated by Accu Chek glucometer (Manufacture: Johnson and Johnson). The animals were considered as diabetic, if their blood glucose exceeded 180 mg/dl on the 4th day after STZ injection.

2- Experimental design:

The protocol was performed on forty (40) adult male albino rats weighing 130±20 gm. Rats were evenly divided into four groups of ten animals in each group as follows:

Group 1: Control rats, rats were administered only saline solution (Nacl 0.9%).

Group 2: Diabetic rats; where rats once ip injected with 45 mg/kg body weight of STZ.

Group 3: Diabetic (45 mg/kg body weight of STZ) + Aloe vera extract (5 mg/kg body weight in ethanol solution once orally daily for 30 days).

Group 4: Diabetic (45 mg/kg body weight of STZ) + Amaryl (1 mg/kg body weight in ethanol solution orally daily for 30 days).

Time of the experimentation extended for 30 days. Then animals were sacrificed after 24 hrs of the last treatment via cervical decapitation. Blood samples collected for biochemical evaluation. Furthermore, pancreas tissues were dissected and divided into two parts. Whereas, one part was processed for histological results, while, other part is thoroughly washed with ice-cold saline, and immediately stored in deep freeze at -80C for lipid peroxidant and antioxidant parameters.

3- Sampling:

a- Blood samples:

Animals of all groups were sacrificed, and then blood samples were collected for biochemical examination. Serum was obtained via the subsequent centrifugation at 3000 rpm for 10 minutes. The resultant sera were preserved at -20° C till a forthcoming biochemical assay.

b- Tissue sampling:

As soon as the animals were sacrificed, pancreas from all groups were dissected and

immediately checked for macroscopic findings then divided into two parts from each animal within each group. One part was fixed in 10% neutral buffered formalin for histopathology. Whilst other part was homogenized with phosphate buffer saline (PBS) solution pH=7.4 for oxidative stress and antioxidant parameters.

c- Biochemical analysis:

Standard biochemical kits purchased from Biodiagnostic Company (Biodiagnostic Company, Giza, Egypt) were utilized for determination of the serum glucose, total bilirubin and Immunoglobulin M (IgM) as described by Trinder (1969), Walter and Gerade (1970) and Miyazawa et al. (1988), respectively.

Enzymatic colorimetric method of Ohkawa et al. (1979) and Nishikimi et al. (1972) was utilized for assessment of the activity level of the pancreatic MDA and SOD, respectively.

3- Histopathological examination:

Pancreas biopsies were consecutively processed through the convential paraffin embedding techniques according to Bacha and Bacha (2000) and stained with Harries hematoxylin and eosin (H&E.) for microscopic findings as mentioned by Larson et al. (2011).

4 - Statistical analysis:

The data were statistically analyzed using One-way Analysis of Variance (ANOVA) using Statistical Package for Social Sciences (SPSS) according to Borenstein et al. (1997). The resultant data were expressive in Mean ± Standard Deviation. Significant difference was statistically when P<0.05.

Results

1- Biochemical analysis:

Glucose level was significantly increased (P<0.05) in groups 2, 3 and 4 when compared with control. Groups 3 and 4 showed significant reduction (P<0.05) in glucose level when compared with group 2. As for the mean values of total bilirubin, it exhibited significant elevation (P<0.05) only in group 2 in comparison with control. Groups 3 and 4 displayed significant decreases (P<0.05) in level of total bilirubin in comparison with group 2. Regarding to the mean level of IgM, there was significant decrease (P<0.05) in group 4 when compared with control and group 2 as shown in Table 1, Fig. 1, Fig. 2 & Fig. 3.

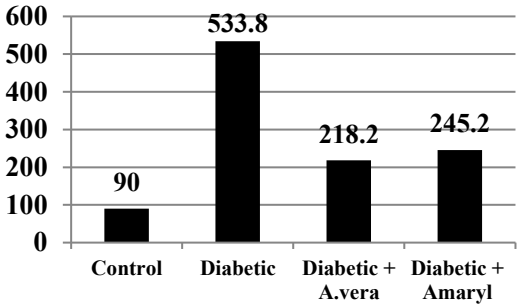

Fig. 1. The effect of Aloe vera and Amaryl on glucose level (IU/l) on Streptozotocin (STZ) induced diabetic rats.

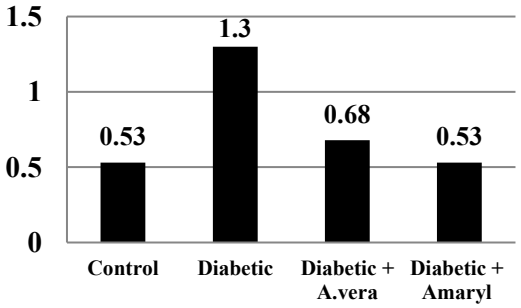

Fig. 2. The effect of Aloe vera and Amaryl on total bilirubin (IU/l) on Streptozotocin (STZ) induced diabetic rats.

Table 1. The effect of Aloe vera and Amaryl on glucose, total bilirubin (IU/l), and IgM (mg/dl) on STZ induced diabetic rats:

Parameters / Groups	Glucose (IU/l)	T. bilirubin (IU/l)	IgM (mg/dl)
Control	90.0±17.7	0.538±0.12	41.2±2.0
Diabetic	533.8±94.4[a]	1.3±0.57[a]	39.2±9.6
Diabetic + A.vera	218.2±61.0[b]	0.684±0.18[b]	35.6±5.1
Diabetic+ Amaryl	245.2±84.2[ab]	0.538±0.26[b]	24.2±5.6 [ab]

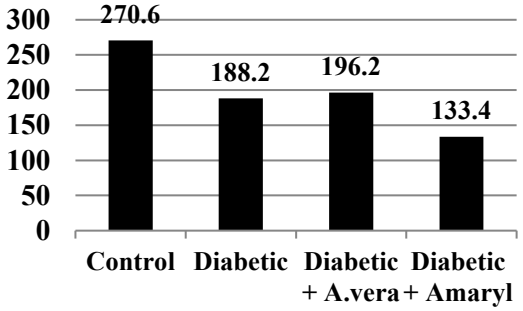

Fig. 3. The effect of Aloe vera and Amaryl on IgG (mg/dl) on Streptozotocin (STZ) induced diabetic rats.

Activity of MDA showed significant increase ($P<0.05$) in groups 2 and 3 when compared with control. However, group 3 showed significant increase ($P<0.05$) in MDA activity when compared with group 2. While, a significant decrease ($P<0.05$) observed in group 4 in comparison with group 2. Subsequently, there was significant increase ($P<0.05$) in activity of SOD in groups 2, 3 and 4 when compared with control. Group 4 showed significant increase ($P<0.05$) in activity of SOD when compared with group 2. While, there was significant decrease ($P<0.05$) detected among group 3 when compared with group 2 as shown in Table 2, Fig. 4 & Fig. 5.

Table 2. Effect of Aloe vera and Amaryl on lipid peroxidation and antioxidant parameters (MDA nmol/mg and SOD U/mg) on STZ induced diabetic rats.

Parameters / Groups	MDA (nmol/mg)	SOD (U/mg)
Control	0.42±0.02	177.7±11.5
Diabetic	1.5±0.56 [a]	126.0±8.2 [a]
Diabetic + A.vera	2.6±0.76 [ab]	116.6±16.9 [ab]
Diabetic+ Amaryl	0.75±0.20 [b]	171.5±9.5 [b]

a: The mean difference is significant when compared with control at 0.05.

b: The mean difference is significant when compared with diabetic group at 0.05.

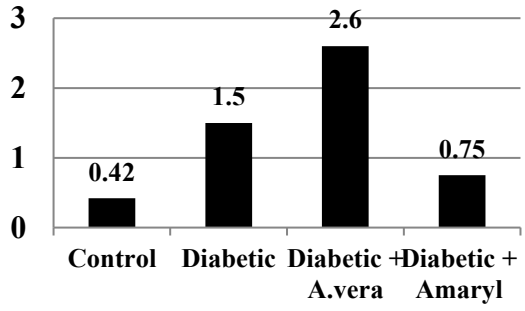

Fig. 4. The effect of Aloe vera and Amaryl on MDA (nmol/mg) on Streptozotocin (STZ) induced diabetic rats.

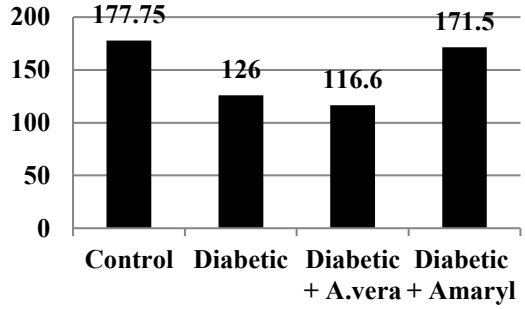

Fig. 5. The effect of Aloe vera and Amaryl on SOD (u/mg) on Streptozotocin (STZ) induced diabetic rats.

2- Histopathological results:

a- Macroscopic findings:

Grossly, normal appearance of pancreas observed in control group. Contrary, diabetic group suffered from mixture areas of paleness and congestion. While, diabetic treated groups with aloe vera and amaryl appeared within normal criteria.

b- Microscopic results:

Pancreas:

Table 3, Fig. 6 elucidated normal arrangement of pancreatic acini and islets of Langerhans of the control group (Fig. 6a). Conversely, pancreas of diabetic animals was severely necrosed with vacuolation of B-cells of Langerhans, and extensive dilatation and congestion with inflammatory edema (Fig. 6b). Pancreatic tissues of group 3 were apparently normal with slight degenerative changes of the pancreatic acini (Fig. 6c). Ultimately, group 4 clarified slight vacuolation of B-cells of Langerhans (Fig. 6d).

Table 3. Histopathological score of control and experimental groups stained with Haematoxylene and eosin were classified depending on severity of the lesions according to Elaidy et al. (2018).

Groups Lesions	Control	Diabetic	Diab + A. vera	Diab + Amaryl
Necrosis and vacuolation of the B-cells and pancreatic acini	-	+++	++	++
Congestion and dilatation of the blood vessels	-	+++	++	+
Thickening of the wall of the blood vessels	-	+++	+	+
Hemorrhage with RBCs infiltration	+	+	+	+
Inflammatory cells infiltration	-	++	+	+

Absent, (-), mild (+), moderate (++), and severe (+++).

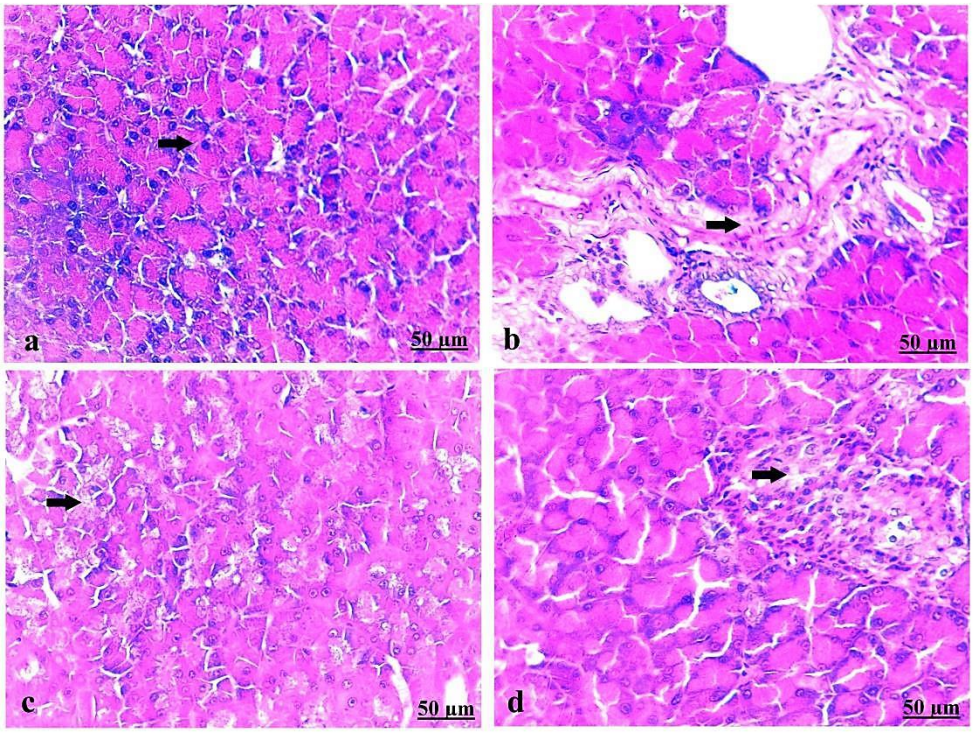

Fig. 6 (a-d). Light photomicrograph of pancreas of control and experimental groups sectioned stained with H&E: **(a)** control showed normal architecture of the pancreas. **(b)** group 2 showing extensive dilatation and congestion with inflammatory edema. **(c)** group 3 showing slight degenerative changes of the pancreatic acini. While, **(d)** group 4 showing slight vacuolation of the pancreatic B-cells of Langerhans.

Discussion

Streptozotocin induced diabetes is accompanied by significant elevation in level of glucose, total bilirubin and MDA with significant reduction in SOD level. On other hand, results of the present investigation intensely suggest an antidiabetic potential for Aloe vera and Amaryl in improvement of the altered parameters. STZ is naturally occurring alkylating anticarcinogenic substance used in scientific researches as an animal model for induction of diabetes, as well as hyperglycemia (Eleazu et al., 2013). Streptozotocin is not used as the first line of treatment due to β-cell-specific pancreatic cytotoxicity (Islam and du Loots, 2009). It exerts toxic effects on pancreatic islet beta cells and could interfere with cellular

metabolic oxidative mechanisms (Papaccio et al., 2000). 40 mg/kg of STZ along with a high-fat diet can manifest a metabolicsyndrome model (Suman et al., 2016; Ameer and Salman, 2021). GLUT-2 is a plasma membrane glucose transporter through which can allow to STZ enters and accumulates in pancreatic β-cell (Damasceno et al., 2014). STZ induced DNA fragmentation and damage through DNA-alkylating properties of its methyl nitrosourea (Murata et al., 1999). Fragmented DNA causes the depletion in cellular NAD+ and ATP. In this pathway, much substrate for xanthine oxidase formed through dephosphorylation, resulted in elevation in hydrogen peroxide/hydroxyl radicals leading to oxidative stress and ATP synthesis suppression (Szkudelski, 2001).

Since millennia, herbal medicines are frequently used in the field of diseases treatment (Hardy, 2021). Notably, Aloe vera could been used as an alternative medicine due to its abundant bioactivity, such as alkaloids, anthraquinones, saponins, and salicylic acid derivatives, inter alia, with significant therapeutic characteristics as antioxidant, anti-inflammatory, neuro-protective, and anti-diabetic natural agents (Langmead et al., 2004; Lanka, 2018). Furthermore, sub-chronic oral administration of Aloe vera is characterized by safety with lack of side effects (Hęś et al., 2019). Aloe vera gel extract could improve biochemical alterations in STZ-induced diabetic rats (Rajasekaran et al., 2004; Ramachandraiahgari et al., 2012; Arora et al., 2019). Bioactive anthraquinones isolated from A. vera own multiple characters included anti-diabetic, anti-cancer, anti-microbial, hepatoprotective, and vasodilator effectiveness (El-Shemy et al., 2010; Salah et al., 2017; Kahramanoğlu et al., 2019). Oral administration of A. vera extract could favor hepatic function in STZ induced diabetes (Rajasekaran et al., 2007). Anthraquinone seems to promote the glucose tolerance and insulin sensibility via upregulation of insulin receptor substrates-1 (IRS-1) and phosphoinositide-3-kinase (PI3Ks) and modulation of metabolic-related genes (Mohammed et al., 2020). Aloe vera possesses another bioactive compound rather than anthraquinones termed melatonin (Chen et al., 2003). Melatonin control insulin secretion via activation the melatonin receptors (MT1 and MT2). Also, it stimulates phospholipase-C/IP3 pathway, consequently mobilizes calcium from organelles and expansion the secretion of insulin. Likewise, melatonin can stimulate production of insulin growth factor and enhance tyrosine phosphorylation of insulin receptors in pancreatic β-cells, which results in more insulin secretion (Sharma et al., 2015). In addition, melatonin improves hyperglycemia through increase liver glycogen (Li et al., 2018). Antioxidant activity of A. vera secondary metabolites has been well assured (Rajasekaran et al., 2005b). Aloe vera has beneficial role in a dose-dependent manner in treatment of many diseases due to having antioxidant agents such as α-tocopherol, carotenoids, and ascorbic acid (Aburjai and Natsheh, 2003; Eshun and He, 2004; Radha and Laxmipriya, 2015). Owing to, antioxidant activity and total phenolic contents of A. vera extract are peak (Moniruzzaman et al., 2012); A. vera could diminish the harmful impact resulted from the oxidative damage of STZ in diabetic rats (Ozsoy et al., 2008). Whereas, aloe vera at the doses between 150 and 300 mg/kg offered decreased lipid peroxidation through increase superoxide dismutase and glutathione levels (Mohapatra et al., 2013).

Therapeutic administration of glimepiride (amaryl) at 0.03 mg/g b.wt. led to a significant reduction of the serum glucose level in alloxan induced diabetic rats. Similarly, amaryl had reduced the serum glucose level in case of STZ diabetic rats. The primary mechanism of action of

glimepiride in lowering the blood glucose is though stimulation the release of insulin from functioning pancreatic beta-cells (Rabbani et al., 2009). Also, main effect of the sulfonylureas is to enhance secretion of insulin and improvement of metabolism both by pancreatic and extra-pancreatic mechanisms. It was shown that Amaryl stimulate the serum levels of antioxidant enzymes (CAT, SOD and GPx) and reduced the LPO and hyperglycemia (Kecskemeti et al., 2002; Yassin and Mwafy, 2007). The antioxidant role of amaryl on streptozotocin-induced hyperglycemic rats was characterized by increased plasma levels of SOD, GPx besides decreased levels of H_2O_2 and malondialdehyde in association with decrease the ROS mediated damage in the host cells (Krauss et al., 2003).

Histopathology, STZ -induced diabetic group revealed vacuolation of the pancreatic B-cells, besides inflammatory condition and edema. Whiles, Aloe vera and amaryl treated groups could restore normal histological architecture of pancreas. STZ could alter β-cells of the pancreas depending on a dose-response pattern developing hyperinsulinemia and hyperglycemia (Eleazu et al., 2013). Owing to the disrupted β-cells and hyperglycemia, the inflammation of pancreatic islets was promoted (Böni-Schnetzler and Meier, 2019). Mechanism of STZ cytotoxicity on β-cell of the pancreas is partially attributed to apoptotic and necrotic cell deaths. Besides this, the reactive oxygen species (ROS) and the reactive nitric oxide species (NO/RNS) production, otherwise, induction of inflammatory responses, are supposed to play validation in STZ cytotoxicity (Van Dyke et al., 2008; Raza and John, 2012).

Aloe vera gel extract could improve histological alterations in association with diminished oxidative stress in STZ-induced diabetic rats (Bolkent et al., 2004; Rajasekaran et al., 2004; Arora et al., 2019). It was through regulation of the carbohydrate-metabolizing enzymes (Rajasekaran et al., 2004). Since, A. vera has been claimed for has a role in an inhibition the absorption of glucose in the jejunum leading to protection of pancreatic β-cells. Moreover, A. vera possess compounds that avoid destruction of Langerhans islets resulted from methyl radical derived from STZ (Beppu et al., 2006). Concerning to amaryl, it possesses antioxidant activity on streptozotocin-induced diabetes with reduction in the reactive oxygen species (ROS) mediated damage in the target cells (Krauss et al., 2003).

Conclusion

Depending on our findings, we could say that Aloe vera followed by Amaryl was afforded an antidiabetic activity against pathophysiological alterations enhanced by STZ induced diabetes.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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