Original Article
DOI: https://doi.org/10.70749/ijbr.v3i6.1642

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Regeneration Potential of Aloe Vera Extract against Streptozotocin Induced Hepatic Damage

Mubeen Younas[1], Kinza Noor[2], Muhammad Ali Zahid[3], Muqaddas Iqbal[3], Noor-e-Saba Naz[4], Moha Akram Khan[5], Sana Javed Awan[6]

[1]Bajwa Hospital, Govt Teaching Hospital Shahdara, Lahore, Punjab, Pakistan.
[2]Tehran University of Medical Sciences, Tehran, Iran.
[3]FMH Institute of Allied Health Sciences, Lahore, Punjab, Pakistan.
[4]Institute of Microbiology and Molecular Genetics, University of the Punjab, Pakistan.
[5]Department of Public Health, University of Health Sciences, Lahore, Punjab, Pakistan.
[6]Institute of Molecular Biology & Biotechnology, University of the Lahore, Lahore, Punjab, Pakistan.

ARTICLE INFO

Keywords: STZ, Aloe Vera Extract, PCR, Antioxidant, Alpha Amylase Inhibition, Hypoglycemic Activity.

Correspondence to: Mubeen Younas
Bajwa Hospital, Govt Teaching Hospital Shahdara, Lahore, Punjab, Pakistan.
Email: mubeenrana78@gmail.com

Declaration
Authors' Contribution
All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 20-03-2025 Revised: 12-05-2025
Accepted: 28-05-2025 Published: 21-06-2025

ABSTRACT

Diabetes, a metabolic progressive disorder marked with high blood glucose due to resistance to insulin, insufficient secretion of insulin leading to malfunction of vital organs especially eyes, heart, kidneys, nerves and also blood vessels. The utilization of plants into practice of medicine represents one of the foremost human use of natural world. For the progress of novel pharmaceutical products, ethnomedical remedies propose striking templates which include compounds with pharmacological events, which could be altered into modern therapeutic agents as diabetic supplements, nutraceuticals and phytomedicines. The central purpose inside drug invention and upgrading is the production of safe and effective remedies. Streptozotocin have major contribution in the diabetes. STZ can cause different severity of diabetes according to selected dose and type of animal. Diabetes mellitus is growing to epidemic proportion, which cause complications if not treated properly. Although there are many anti diabetic medicines which have different mechanisms to control or treat diabetes. There are many natural substances which can be used for anti-diabetic effects. Therefore, the use of anti-diabetic agents is helpful in the therapeutic treatment of diabetes. The initiation of diabetes was used for 12 adult Wistar rats weighing between 150-250 grams (75-90 days old). The rats got doze after 16 hours of hunger. The rats were originally treated with nicotinamide (vitamin B3). On day 21 their biochemical parameters, pancreatic tissue and PCR Study of pancreas were determined. There is marked raised in different biochemical parameters. Diabetes Mellitus patients are seriously complicated by liver damage. Insulin resistance has grown into one of the main factors that contribute to liver damage, exacerbated by oxidative stress and aberrant inflammatory signals. Insulin resistance will then lead to chronic and possibly fatal conditions including cirrhosis or liver failure at the end of the cycle. Plant and natural products containing antioxidants with good antidiabetic, anti-inflammatory and anti-glycemic effects will be the treatment of the day. In summary, the loss of insulin in a rats from STZ induced injury leads to activation of cellular apoptotic pathway, increase in oxidative stress and decrease in proliferation thus disturbing the whole liver functions.

INTRODUCTION

Aloe vera (*Aloe barbadensis* Miller), belonging to the family *Xanthorrhoeaceae*, is a perennial succulent herbaceous plant characterized by its thick, fleshy leaves and distinctive bright yellow tubular inflorescences. The species predominantly thrives in arid and semi-arid climates of North Africa, the Western Mediterranean basin, and the Canary Islands. Over recent decades, *Aloe vera* has gained considerable scientific attention, with extensive investigations spanning *in vitro*, *in vivo*, and clinical domains, underscoring its pharmacological relevance in contemporary biomedical research. This renewed scientific inquiry stems from a growing global emphasis on phytotherapy as a pivotal component of complementary and alternative medicine (CAM), particularly in resource-constrained regions. Since antiquity, medicinal plants have provided a foundational framework for addressing human health challenges, serving both as primary therapeutic agents and as precursors to modern pharmaceutical innovation. The ethnobotanical utility of medicinal plants extends beyond cultural symbolism to tangible contributions in food security, clothing, shelter, and

therapeutic applications (Barboza et al., 2009). This long-standing integration of botanical remedies within traditional healthcare systems offers an indispensable resource for bioprospecting novel bioactive compounds with pharmacodynamic potential. Such bioactive agents serve as scaffolds for the development of phytotherapeutic products, nutraceuticals, and advanced pharmaceutical formulations. Within drug discovery pipelines, the extraction and characterization of plant-derived phytoconstituents remain crucial in fulfilling the critical objectives of generating therapeutically effective and toxicologically safe medications (Iwu, 2002). Medicinal flora continues to play a central role in the healthcare management of populations globally, with an estimated 70–80% of the African population relying on traditional medicine for primary healthcare needs (de Boer et al., 2005; Bekalo et al., 2009). The resilience of ethnomedicinal practices is particularly evident in managing chronic metabolic disorders, including diabetes mellitus, where botanical remedies are increasingly explored for their bioactive efficacy and minimal adverse profiles.

Diabetes mellitus (DM) represents a global non-communicable disease burden, characterized by chronic hyperglycemia due to defective insulin secretion, impaired insulin action, or a combination of both. This metabolic derangement underpins progressive multi-organ dysfunction, notably affecting the cardiovascular system, kidneys, retina, peripheral nerves, and microvascular structures (American Diabetes Association, 2014). The pathophysiology of DM involves intricate mechanisms, including autoimmune-mediated β-cell destruction in Type 1 DM and peripheral insulin resistance in Type 2 DM. Gestational diabetes mellitus (GDM), conversely, is defined by glucose intolerance first recognized during pregnancy, with implications for both maternal and fetal health (Triplitt et al., 2000). Despite the pharmacological advancements in oral hypoglycemic agents and insulin analogs, the search for alternative, cost-effective, and well-tolerated therapeutic options remains imperative, particularly in regions with limited healthcare access. Previous studies have indicated that medicinal plants, including *Aloe vera*, harbor promising antihyperglycemic properties. Several phytoconstituents present in *Aloe vera*, such as anthraquinones, polysaccharides (notably acemannan and glucomannans), chromones, lectins, and various polyphenolic compounds, have demonstrated hypoglycemic, anti-inflammatory, and antioxidative effects (al-Awadi et al., 1991; Yagi et al., 2009; Sharrif Moghaddasi & Res, 2011). Notably, experimental data revealed enhanced glycoprotein synthesis following administration of *Aloe vera* leaf gel extract in diabetic animal models (Rajasekaran et al., 2007). *Aloe vera* has shown potential hepatoprotective properties, attributed to its modulation of oxidative stress markers and hepatic enzyme activity (Can et al., 2004; Parihar et al., 2004). Nevertheless, while preliminary *in vivo* and *in vitro* studies substantiate the hepatoprotective and hypoglycemic effects of *Aloe vera*, robust clinical trials remain sparse, often marred by methodological inconsistencies (Bunyapraphatsara et al., 1996; Devaraj et al., 2013; Fallah et al., 2012). Oxidative stress and inflammation serve as pivotal mediators in both the pathogenesis of diabetes and its associated hepatic dysfunction. The liver, central to metabolic regulation, is particularly susceptible to oxidative insults resulting from hyperglycemia-induced reactive oxygen species (ROS) production, dysregulated lipid metabolism, and chronic inflammatory processes (Loguercio et al., 2001; Parola & Robino, 2001). These oxidative perturbations contribute to hepatocellular apoptosis, fibrosis, and eventually cirrhosis, representing significant morbidity risks in diabetic populations. Further compounding these risks, diabetes-associated oxidative stress perturbs the pharmacokinetics of therapeutics by altering hepatic enzyme function and drug clearance (Chávez-Piña et al., 2009). The hepatotoxic potential of conventional pharmaceuticals underscores the need for comprehensive preclinical toxicological assessments, with *HepG2* cell lines frequently employed as *in vitro* models for elucidating cytotoxicity profiles during drug development (O'Brien et al., 2006; Xu et al., 2008). Additionally, emerging research highlights the role of bile acids in cholesterol homeostasis, hepatic metabolism, and glucose regulation. By facilitating the emulsification and absorption of dietary fats and fat-soluble vitamins, bile acids also play ancillary roles in modulating lipid profiles and hepatic lipid deposition, further emphasizing their relevance in metabolic disorders (Li Sha et al., 2016; Elhardallou, 1992; Ramaswamy et al., 1994).

Chronic liver diseases, culminating in fibrosis and hepatocellular carcinoma, remain pressing global health concerns. The pathogenesis involves multifaceted molecular interactions, prominently featuring ROS-mediated hepatocellular damage, pro-inflammatory cytokine release (e.g., tumor necrosis factor-alpha, transforming growth factor-beta), and hepatic stellate cell (HSC) activation, culminating in extracellular matrix deposition and fibrogenesis (Tilg & Diehl, 2000; Friedman et al., 1993; Kawada et al., 1998; Ramadori, 1992). The modulation of these cellular and molecular events by bioactive phytochemicals represents a frontier in hepatoprotective therapeutics. Given these considerations, the present study was designed to investigate the dose-dependent effects of ethanolic *Aloe vera* extract on hepatic apoptosis and cellular proliferation in a diabetic rodent model, with particular emphasis on liver functional parameters and oxidative stress modulation post-diabetes induction.

Objectives of the Study

- ✓ To induce diabetes in experimental rats using Streptozotocin (STZ).
- ✓ To extract and prepare standardized ethanolic extracts of *Aloe vera* gel.
- ✓ To evaluate the impact of STZ-induced diabetes on hepatic morphology, oxidative stress, and cellular apoptosis in experimental models treated with *Aloe vera* extract.

METHODOLOGY

This experimental study was conducted to evaluate the antidiabetic potential of ethanolic extracts of *Aloe vera* in streptozotocin (STZ)-induced diabetic rats, alongside

comprehensive biochemical, histopathological, and molecular assessments.

Chemicals and Induction of Diabetes

Streptozotocin (STZ), a cytotoxic antibiotic with established antineoplastic properties, was procured in sterile, lyophilized form (1 g vials, Pharmacia Corporation). For diabetes induction, 12 adult Wistar rats (150–250 g, aged 75–90 days) were fasted for 16 hours prior to experimentation. To mitigate the cytotoxic effect of STZ, a protective dose of nicotinamide (120 mg/kg) was first administered intraperitoneally, followed by intravenous injection of STZ (60 mg/kg) after 30 minutes. To prevent hypoglycemia, glucose supplementation was provided post-injection. Diabetic status was confirmed through elevated blood glucose levels within 72 hours.

Collection and Extraction of Plant Material

Whole *Aloe vera* plants were collected from agricultural fields in Qasur, Punjab, Pakistan (January–February 2018) and authenticated by the Department of Botany, Government College University Lahore (Voucher No. GC Herb Bot.3465). After shade-drying at ambient temperature (25°C) for 21 days, the material was ground into a fine powder. Maceration extraction was performed using 500 g of powder soaked in 1.5 liters of ethanol for seven days at room temperature, with intermittent agitation. Filtration was followed by solvent removal via rotary evaporation. The final concentrated extract was stored in sterile vials at 4°C for further use.

Experimental Design and Treatment Groups

Rats were randomly divided into seven groups (n=5 per group):

- Group I: Normal control
- Group II: Diabetic control (STZ only)
- Group III: Diabetic + Metformin (120 mg/kg/day)
- Group IV: Normal + *Aloe vera* extract (0.5 mL/day)
- Group V: Diabetic + *Aloe vera* extract (0.5 mL/day)
- Group VI: Normal + *Aloe vera* extract (1 mL/day)
- Group VII: Diabetic + *Aloe vera* extract (1 mL/day)

Treatment continued for 21 consecutive days. Metformin served as the standard antidiabetic control.

Biochemical Analyses

On day 21, blood was collected via cardiac puncture using EDTA vacutainers, and serum was separated. Glucose, urea, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were analyzed at the University of Lahore Diagnostic Laboratory. Liver function tests, including bilirubin, alkaline phosphatase (ALP), and albumin, were performed using commercially available kits (Bioneed Diagnostic GmbH; Diazyme Europe GmbH) following manufacturer protocols.

Histopathology and Gene Expression Analysis

Liver tissues were fixed in paraformaldehyde, embedded in paraffin, sectioned, and subjected to histological staining. For molecular profiling, RNA was extracted from liver tissues using the Trizol method, followed by cDNA synthesis utilizing M-MLV reverse transcriptase. Real-time PCR (CFX Connect, Bio-Rad) was conducted to assess expression levels of hepatic genes involved in glucose metabolism, apoptosis, and proliferation, using specific primers with GAPDH as the reference gene.

Statistical Analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons among groups were performed using one-way ANOVA followed by appropriate post hoc tests. Graphical representations were constructed using GraphPad Prism, while image analyses were conducted with specialized image software. Reference management was handled using EndNote.

RESULTS & FINDINGS

Hypoglycemic potential of EEAL

Results exhibited significant hypoglycemic activity of Aleovera in streptozotocinnicotinamide
induced diabetic rats. The results were analysed by one-way ANOVA. which showed statistical significant difference (P<0.05) in contrast with normal control.

Table 1

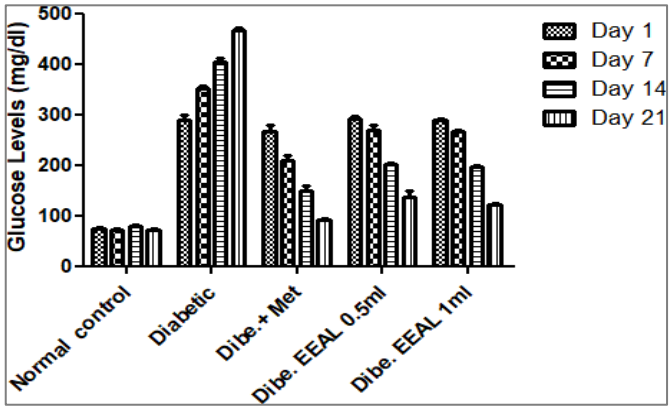
Hypoglycemic effect of Aleovera in STZ induced diabetic rats

Day	Negative control	Diabetic	Dibe. +Met	Dibe. EEAL 0.5ml	Dibe. EEAL 1ml
1st	77 ± 4.06	299.4±3.04**	278.2±3.42**	296.6±2.07**	291.2±1.78**
7	74.6±5.02	346 ± 4.47**	220 ± 3.39**	279.6±2.30**	269.6±2.70**
14	81.8±4.20	396.4±4.03**	160.8±3.42*	205.6±4.82**	191 ± 3.67**
21	70.6±2.79	460.4±4.03**	90.6 ± 4.03*	149.4±3.04**	125.4±2.88**

The data are presented as mean +S.D (n=5) *indicates that results are statistically significant (P< 0.05) in comparison with normal control ** indicate that results are statistically significant (P< 0.01) in comparison with normal control .

Figure 1

Graphical presentation of antihyperlycemic effect of ethanol extract of Aleovera at different concentrations in STZ induced diabetic rats.



*indicates that results are statistically significant (P< 0.05) . ** indicate that results are statistically significant (P< 0.01).

Determination of biochemical parameters:

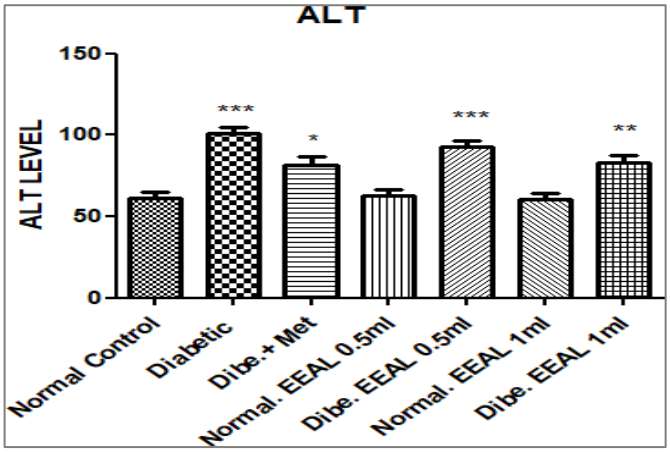
ALT:

After completion of 21 days, blood samples were collected

for ALT and AST and different doses of ethanolic extract of Aleovera showed significant reduction (P<0.05) in elevated levels of enzymes in STZ induced diabetic rats. The results were estimated by using one- way ANOVA. The data are presented as mean + S.D (n=5) *indicates that results are statistically significant (P< 0.05) in comparison with normal control.** indicate that results are statistically significant (P< 0.01) in comparison with normal control.

Figure 2

Effect of Aleovera on ALT at different concentrations in STZ induced diabetic rats.



*indicates that results are statistically significant (P< 0.05) ** indicate that results are statistically significant (P< 0.01)

Renal Function Test:

A significant decline was observed (P<0.05) in elevated levels of urea and creatinine with different doses of extract of Aleovera. The results were examined by using one-way ANOVA. The data are presented as mean±S.D (n=5)

*indicates that results are statistically significant (P< 0.05) in comparison with normal control ** indicate that results are statistically significant (P< 0.01) in comparison with normal control.

Figure 3

Creatinine levels in diseased and treated rats with selected doses of ethanolic extract and standard metformin in comparison to normal group of rats.

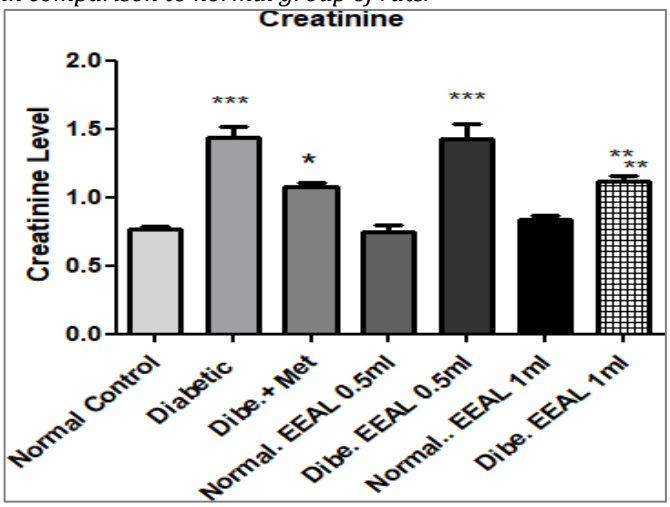
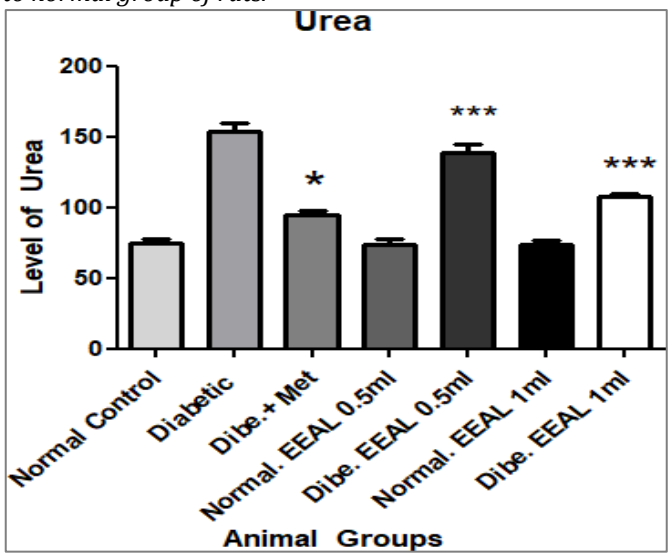


Figure 4

Urea levels in diseased and treated rats with selected doses of ethanolic extract and standard metformin in comparison to normal group of rats.



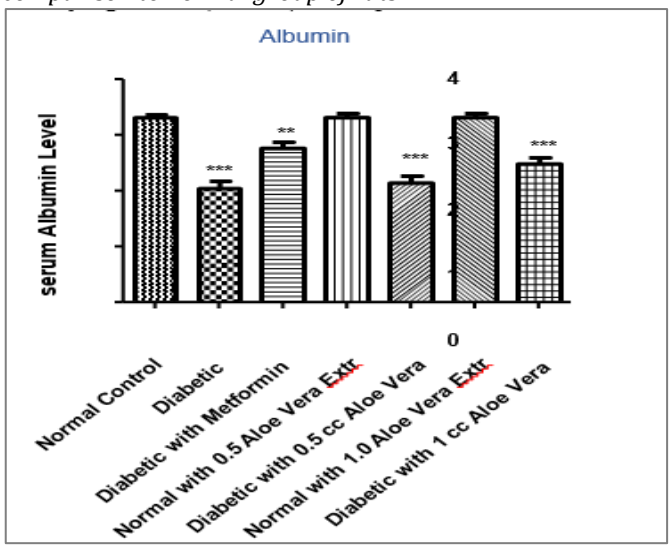
*indicates that results are statistically significant (P< 0.05). ** indicate that results are statistically significant (P< 0.01)

Albumin and ALP

After 21 days, albumin and ALP levels were evaluated using samples of streptozotocin induced diabetic rats. The improvement in lipid profile was showed by ethanolic extract of Aleovera in comparison with normal group and results were estimated by applying one way ANOVA with a statistical significance (P<0.05). The data are presented as mean±S.D (n=5). *indicates that results are statistically significant (P< 0.05) in comparison with normal control. ** indicate that results are statistically significant (P< 0.01) in comparison with normal control.

Figure 5

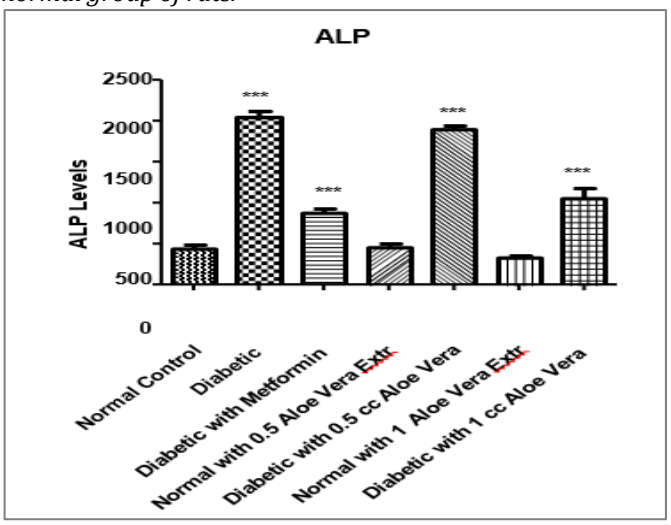
Albumin levels in diseased and treated rats with selected doses of ethanolic extract and standard metformin in comparison to normal group of rats.



*indicates that results are statistically significant (P< 0.05). ** indicate that results are statistically significant (P< 0.01)

Figure 6

ALP levels in diseased and treated rats with selected doses of ethanolic extract and standard metformin in comparison to normal group of rats.



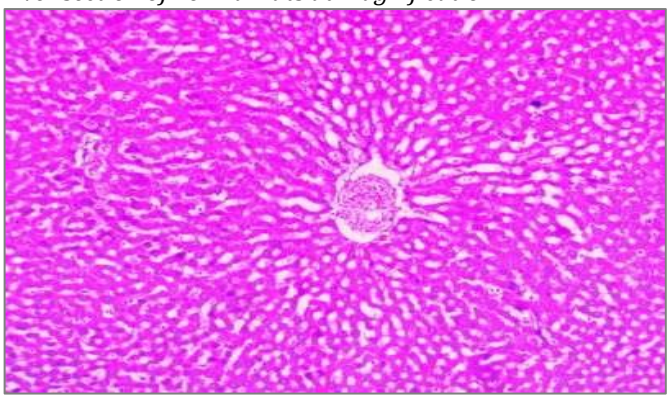
*indicates that results are statistically significant (P< 0.05).
** indicate that results are statistically significant (P< 0.01)

Histopathological Report

LIVER (Normal group)

Figure 6

Liver section of normal rats at magnification 40X

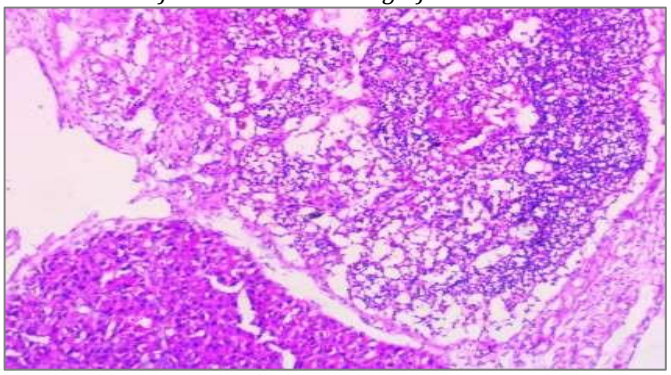


Histological examination of the submitted liver tissue revealed normal looking endo-and exocrine elements of liver. The liver tissue contained normal looking cells concentration. The acinar cells also appeared normal. No evidence of any degeneration, inflammation, calcification, granuloma or malignancy was observed.

LIVER (Injury group)

Figure 7

Liver section of diabetic rats at magnification 40X

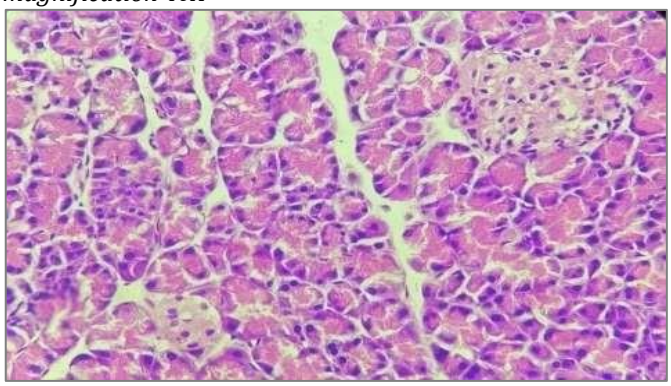


Histological examination of the submitted injury liver tissue revealed normal looking exocrine elements of Liver. Chronic inflammation of liver cells seen.

LIVER (Treated with metformin 100mg/kg)

Figure 8

Liver section of rats treated with metformin at magnification 40X

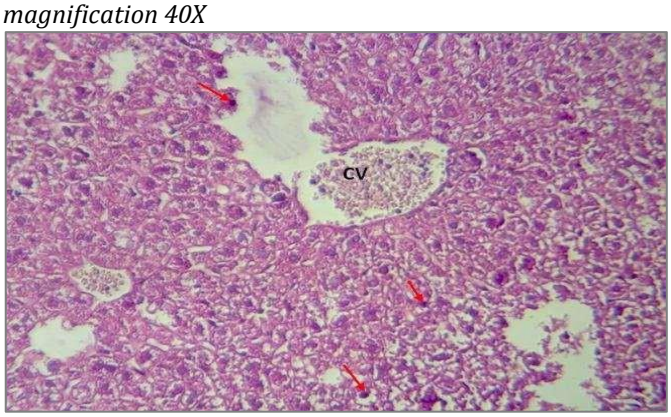


Histological study of metformin treated liver tissue has demonstrated natural features. There has been no suggestion of swelling, calcification, granuloma or malignancy.

LIVER (Treated with EEAL 0.5ml)

Figure 9

Liver of diabetic rats treated with EEAL 0.5ml at magnification 40X

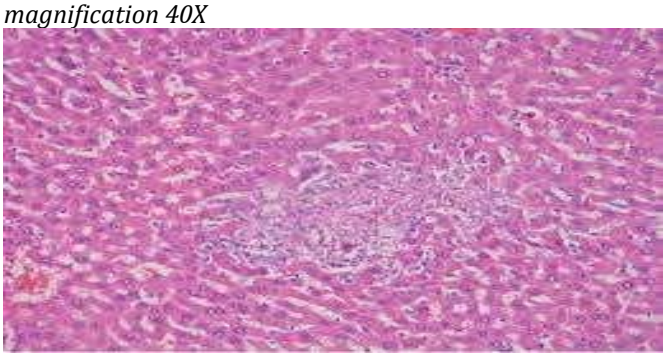


Histological examination of the submitted Liver tissue revealed normal looking exocrine elements of Liver. The acinar cells also appeared lesser in number. Sparsely present Liver cells degeneration is evident. No evidence of any inflammation, calcification, granuloma or malignancy was seen.

LIVER (Treated with EEAL 1.0ml)

Figure 10

Liver of diabetic rats treated with EEAL 1ml at magnification 40X



Histological examination of the submitted Liver tissue revealed normal looking exocrine elements of Liver. The acinar cells also appeared lesser in number. Sparsely present Liver cells degeneration is evident. No evidence of any inflammation, calcification, granuloma or malignancy was seen.

PCR results

Evaluation of apoptosis and effect of Aleovera

BAX

The upregulation of Bax was observed in the diseased group in comparison to normal group. A very slight decline in saline treated group was noted as compared with injury group. Likewise, the gene expression level of Bax was significantly (P< 0.05) downregulated in ethanolic extract group and positive control in contrast to injury group.

P53

Graphical representation showed an increased expression of P53 in the diseased group in contrast to normal group.An insignificant decrease in (saline group) was noted as compared with injury group. Likewise, the gene expression level of P53 showed significant downregulation in ethanolic extract group and positive control group in comparison to injury group.

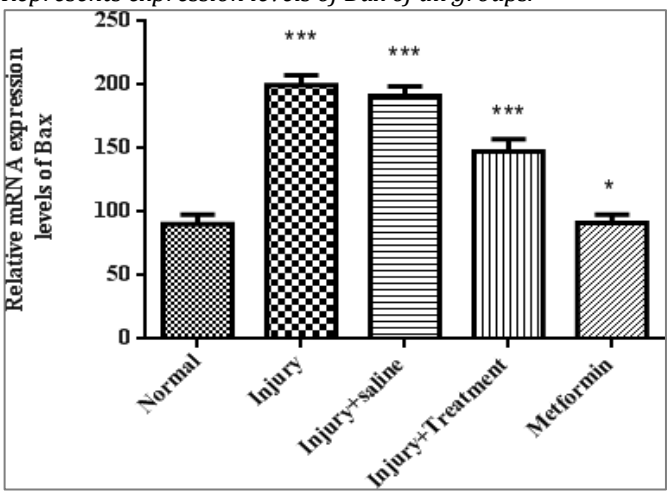
GAPDH

The gene expression level of GAPDH (internal control) of all groups remained non- significant.

Data represented relative gene expression of Bax, P53 and GAPDH in liver tissue of normal, diabetic and treated rats. Values are expressed as mean ± SEM of three replicates. *E. helioscopia* decreased the expression of apoptosis while GAPDH expression was remained non-significant.

Figure 11

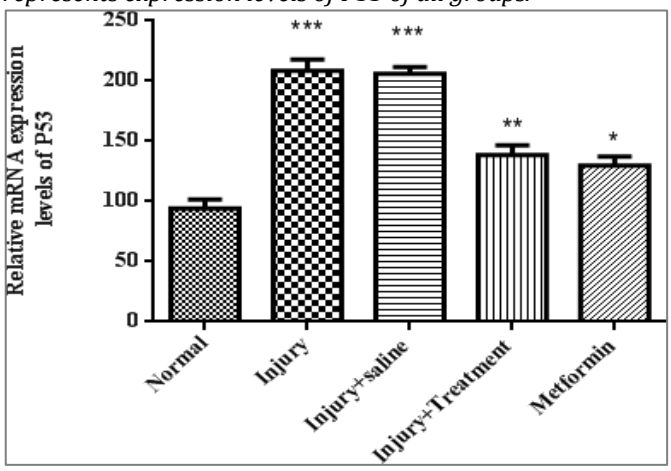
Represents expression levels of Bax of all groups.



Data represents relative gene expression of Bax in liver tissue of diabetic rats. Values are expressed as mean ± SEM of three replicates. P < 0.05 was considered a significant difference between diabetic control and treated groups. *signifies that results are statistically significant at (P<0.05) in comparison with normal control group.**shows (p < 0.01) and indicates significant difference compared to normal control group ***shows (p < 0.001) and indicates significant difference compared to normal control group.

Figure 12

represents expression levels of P53 of all groups.

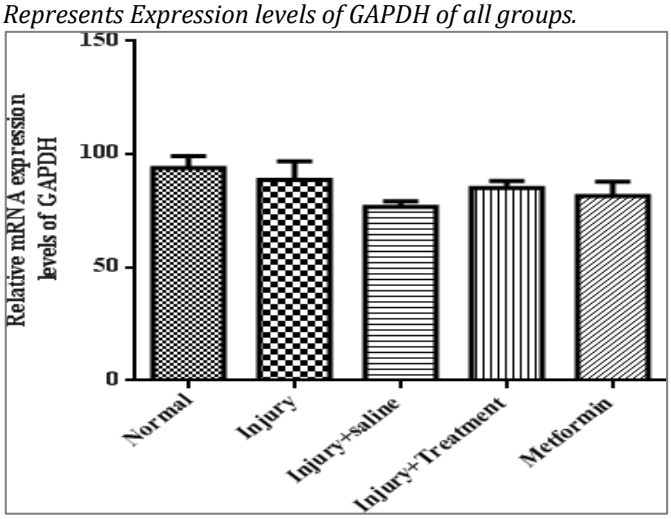


Data represents relative gene expression of P53 in the liver tissue of diabetic rats. Values are expressed as the mean ± SEM of three replicates. P < 0.05 was considered a significant difference between diabetic control and treated groups. *signifies that results are statistically significant at (P<0.05) in comparison with normal control group.

**shows (p < 0.01) and indicates significant difference compared to normal control group ***shows (p < 0.001) and indicates significant difference compared to normal control group.

Figure 13

Represents Expression levels of GAPDH of all groups.



Data represents relative gene expression of GAPDH in the liver tissue of diabetic rats. Values are expressed as the mean ± SEM of three replicates. P < 0.05 was considered a significant difference between diabetic control and treated groups.

DISCUSSION

Diabetes Mellitus patients are seriously complicated by liver damage. Insulin resistance has grown into one of the main factors that contribute to liver damage, exacerbated by oxidative stress and aberrant inflammatory signals. Insulin resistance will then lead to chronic and possibly fatal conditions including cirrhosis or liver failure at the end of the cycle. Plant and natural products containing antioxidants with good antidiabetic, anti-inflammatory and anti-glycemic effects will be the treatment of the day.

Antioxidants can be an effective, efficient way of preventing and treating this endemic infection, as opposed to traditional drugs. STZ destroys the β-cells that cause hypoinsulinemia and high blood glucose (Lenzen 2008). The distribution of β cells in β cells and the chemical structural similarities with glucose cause STZ to bind to the present receptor based on dosage. STZ can induce a diabetic disease in 2 cases, mismatch GLUT2 glucose transporter receptor. STZ targets ß cells, usually individually given, at high doses by their alkylating properties that approximate cytotoxic nitrosourea compounds (Dufrane et al. 2006).

Liver fibrosis might generally be a condition due to chronic liver injury, often leading to liver disease and ultimate liver failure (Li D. and Friedman 1999). Liver fibrosis is simply an injury healing response that reinforces an acceptable balance between injury and liver repair (Lee U. E. and Friedman 2011). Excessive matrix proteins buildup in the liver parenchyma (importantly collagen type 1) results in liver fibrosis (Tsukada et al. 2006). Different types of drugs like NSAIDs and nitrosourea compounds (STZ) damage liver brutally. At a high dose of drug affected cyt-P450, decreased mono-oxygenase system and also tends to have multiple effects on hepatic enzymes. In-vivo studies also showed reduced other mono-oxygenase systems in liver. The decrease in liver cytochrome is due to endotoxins and other factors resulting in liver damage (Falzon et al. 1985). As STZ cause damage by reducing the activity of cyt p450, b5 and AD, as well as reducing the microsomal enzyme activity in the liver. The endotoxins that causes liver damage is due to clostridium bacteria that produces toxins in the intestine and results to enter in enterohepatic circle through blood thus targeting liver damage (Fracasso et al. 1987). Keeping in view this background this study evaluate the damage of liver via STZ. This research investigate the insulin role for: 1) critical regulation of stress related signaling pathway in hepatic cells, 2) modulation of cell death and proliferation pathways.

For investigating this point, first the liver biochemical markers were checked in post treated animals. They include injury markers LDH and liver function tests. A study demonstrate that stellate cells are involved in the development of different extracellular components of liver fibrogenesis (Friedman Scott L. 1993, Kawada N. et al. 1998a, Ramadori 1992). when the stellate cells improve their proliferation and production of collagen with oxidative stress (Lee K. S. et al. 1995). This shows that oxidative stress mediators and cytokines play a key role in hepatic injury progression. Diabetic rats treated with STZ have shown a significant increase in ALT and ALP serum while insulin and albumin serum levels have significantly decreased (Ghanbari et al. 2016). Serum ALT concentrations have been shown to interact with hepatic insulin resistance and to decrease later in hepatic insulin sensitivity in contrast with AST and GGT rates, which have shown little association with hepatic insulin. While serum albumin and bilirubin may be high, ALP and GGT may not be high. Hepatocytes are also a marker of severe or mild hepatic dysfunctions of synthesis of serum albumin (Mohamed et al. 2016). Similar results were found in this study as the level of all injury biomarkers is higher in treated group as compared to normal ones.

Oxidative stress is characterized as the difference between reactive oxygen species production and the biologics ' ability to easily detoxify reactive intermediate substances (Fridovich 1978). Reactive forms of oxygen include hydrogen peroxide (H2O2), radical hydroxyle hydraul (OH-), peroxynitrites (ONOO), and superoxide hydroxyl hydrides (O2-) (Block et al. 2007, Block et al. 2010, Wickramasinghe 1975). The association between hypertension, oxidative stress, and oxidative DNA damage is shown in studies. While many experiments have been undertaken to explain the diabetes- induced congenital malformation, more research is needed to identify new markers for the control of fetal development and the incidence of congenital malformations. DNA trigger factors in diabetes must be understood in order to reduce gene expression disorder, prevent fetal congenital malformations and help normal organ development during organogenesis. In this study a critical biomarker for ROS, Gpx is been investigated and show that it is highly downregulated after treatment with STZ. These results are in accordance with the previous studies.

Further the genes for proliferation and apoptosis are also investigated in post treated animals. They again are in favour of liver damage caused by the STZ. Cell death overlap, metabolic and proliferative signals reveal that the underlying metabolic changes including resistance to insulin and obesity influence the apoptosis in hepatocytes. The pathole pathways that facilitate liver cell damage are mostly unexplored and the processes of disease initiation and development are poorly defined in the sense of these risk factors. An exact orchestrated anti- and proapoptotic balance is associated with homeostasis of the hepatic tissue, and mild disorder could lead to serious injuries in the organ (Kohl et al. 2013, Schattenberg et al. 2011). In summary, the loss of insulin in a rats from STZ induced injury leads to activation of cellular apoptotic pathway, increase in oxidative stress and decrease in proliferation thus disturbing the whole liver functions.

CONCLUSION AND FUTURE RECOMMENDATIONS

The findings of the present study provide compelling evidence that *Aloe vera* extract possesses significant hepatoregenerative potential in the context of streptozotocin (STZ)-induced diabetes mellitus in albino rats. The experimental outcomes demonstrated that administration of *Aloe vera* extract resulted in marked improvements in hepatic histoarchitecture and restoration of liver function parameters. Specifically, the extract effectively ameliorated the elevated levels of key biochemical enzymes commonly associated with hepatic injury and metabolic dysfunction, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). These enzymes are well-established biomarkers of hepatic integrity, and their normalization following *Aloe vera* administration strongly suggests the extract's protective and regenerative influence on hepatocytes subjected to oxidative stress and glycotoxic damage induced by hyperglycemia. The phytochemical constituents of *Aloe vera*, particularly its

rich profile of bioactive compounds such as polysaccharides, flavonoids, vitamins, and phenolic compounds, are believed to be primarily responsible for its antioxidant, anti-inflammatory, and cytoprotective properties. These bioactives likely function synergistically to counteract oxidative stress-mediated cellular damage, thereby facilitating hepatocyte regeneration and enhancing the overall functional capacity of hepatic tissues. The current findings are consistent with previous reports in the literature highlighting the therapeutic applications of *Aloe vera* in managing metabolic disorders and oxidative stress-related complications.

While the present study successfully establishes a foundational understanding of *Aloe vera*'s hepatoprotective role in diabetic models, it also highlights the need for further comprehensive research to strengthen the evidence base. One major limitation of this study is its confinement to a small-scale animal model, which restricts the generalizability of the findings to human populations. Moreover, the precise molecular mechanisms underpinning the regenerative potential of *Aloe vera* remain inadequately explored in this context. Future investigations should incorporate advanced biochemical and molecular techniques, such as proteomic and genomic analyses, to elucidate the specific signaling pathways, gene expression modulations, and enzymatic activities influenced by *Aloe vera* treatment. It is also recommended that future studies employ larger sample sizes with extended treatment durations to assess the long-term safety and efficacy of *Aloe vera* in diabetic hepatopathy. Dose-response studies are particularly warranted to determine the optimal therapeutic dosage with maximal regenerative potential while minimizing any possible toxicological effects. Additionally, clinical trials involving human subjects will be essential to validate these preclinical findings and to facilitate the translation of *Aloe vera*-based therapies into routine clinical practice for the management of diabetic liver complications. The present study substantiates the therapeutic potential of *Aloe vera* extract as a natural hepatoprotective agent capable of restoring biochemical and histological integrity of the liver in STZ-induced diabetic models. With further validation through rigorous experimental and clinical research, *Aloe vera* may emerge as a promising adjunct or alternative therapeutic intervention in the management of diabetes-associated hepatic dysfunction.

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