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RESEARCH ARTICLE
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HEPATOPROTECTIVE EFFECTS OF BROMOCRIPTINE ON LIVER MARKERS AND HISTOPATHOLOGICAL CHANGES IN DIABETES-INDUCED RATS

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ABSTRACT

Background: Globally, diabetes is a highly heritable disease that causes considerable damage to vital organs, compromising the liver's function. However, liver dysfunction, as indicated by abnormal liver function markers, poses a significant challenge nowadays.

Objectives: Bromocriptine has been found to enhance insulin sensitivity, reduce insulin resistance, and exhibit potential in treating type 2 diabetes mellitus. The purpose of this study is to assess its effect on liver. In this study, effects on hepatic markers were examined i.e. the levels of bilirubin, alkaline phosphatase, Gamma GT and SGPT.

Study Design: Experimental.

Place and Duration: The study was conducted at Karachi University, Department of Pharmacology, from November 2022 to April 2023.

Methods: The invivo testing was done by taking the blood samples of normal and diabetic male rat and assessed the liver function markers compared to control diabetic group. Moreover, diabetic induced group caused substantial damage to liver architecture, which was positively reversed by bromocriptine. In conclusion, demonstrates potential in treating diabetes and protecting the liver from diabetes-induced damage

Conclusion: The studied concluded that pandanus have marked good antidiabetic activity and protecting the liver from diabetes

Key words: Type 2 Diabetes, alkaline phosphatase, Gamma GT, SGPT, Bromocriptine.

INTRODUCTION

Diabetes possess significant threat to public health in Pakistan, resulting in various complications. The prevalence of diabetes mellitus (DM), a chronic condition, is escalating rapidly due to lifestyle modifications and environmental factors..[1] Diabetes can be found in newborns and the incidence is higher in females than males.[1,2,3] . patients with type 2 diabetes have an increased risk of chronic liver disease (CLD) such as non-alcoholic fatty liver disease and steatohepatitis and about one-third of cirrhotic patients have diabetes. [4]it also increases the risk of Acute liver failure. [5] However, the use of several antidiabetic agents may be a cause for concern in the case of hepatic impairment. Bromocriptine is a sympatholytic D2-dopamine agonist that has been approved for the treatment of type 2 diabetes [6,7]

Barra et al evaluated the improvement of insulin sensitivity and reversion of hepatic steatosis in an animal model of obese type 2 diabetes. [8]. In addition, bromocriptine exhibited activities that indicate it has the potential to ameliorate all major components of NAFLD [9]. It decreased hepatic steatosis, reduced adipose tissue, improved blood glucose levels. Millan MJ et al evaluate that the bromocriptine is indicated for the management of type 2 diabetes [10,11,12]. Luo S et al suggested that bromocriptine has the potential to reverse metabolic disruptions associated with insulin resistance and obesity by reorganizing the hypothalamic circadian system and monoamine neuronal function.[13] Additionally, dopamine agonist treatment exerts its effects by reducing the hypothalamic signals that regulate hepatic glucose production, lipid synthesis, and insulin resistance[14,15].Bromocriptine does not have a specific receptor that mediates its action on glucose and lipid metabolism. Rather, its effects are mediated via resetting of dopaminergic and sympathetic tone within the CNS [16].

This study explored the potential synergistic effects of bromocriptine, a dopamine D2 receptor agonist that effectively reduced postprandial plasma glucose levels. This study investigates the hepatoprotective activity of bromocriptine in a rat model of induced diabetes, evaluating the efficacy of different doses of dopamine agonist.

MATERIALS AND METHOD:

Invivo Study

Preparation sample: In this the study, male rats (200-250 g) were used, allocated into five groups of 10 animals each and maintained in a temperature- and humidity-controlled facility (n=50). first group is normal control group, other one was diabetic control group received streptozotocin, 55 mg/kg. next were treated group by drug bromocriptine *at low dose* 1.8mg/kg, *high dose* 4mg/kg and standard drug treated with 200mg/kg metformin. After the end of 3 months, cardiac puncture has done to collect blood samples from the rats for various biochemical analyses.

Biochemistry Analysis: Blood samples of normal and diabetic male rat was collected (Allain et al,1974) and taken for analysis by centrifugation for 20min. centrifugation was done at 4°C, and stored at−20°C. bilirubin, alkaline phosphatase, Gamma GT and SGPT level were analysed.

Histological Examination: For histopathological analysis, animal tissues were first rinsed with saline and preserved in 10% neutral buffered formalin. The fixed tissues were then embedded in paraffin wax using standard protocols. Sections (5 μm) were prepared from the paraffin blocks, mounted on coated glass slides, and stained with H&E. Light microscopy was used to evaluate the histological changes.

Ethical Approval: The project has approved by ASRB (Advance study and research board) with (ASRB/No./06788/PHARM) on 17 October 2022.

Place and Duration: Study was conducted at Karachi University, Department of Pharmacology, from November 2022 to April 2023.

Statistical Analysis: Statistical analysis was performed using SPSS 20.0 software (IBM SPSS, USA). A significance level of $p < 0.05$ was adopted for all two-tailed tests. Normally distributed continuous variables with homogeneous variance are presented as mean ± standard deviation (SD) and were compared using one-way analysis of variance (ANOVA).

RESULTS

Effect On Liver Function

Bilirubin level: The total bilirubin level of control nondiabetic rat was 0.05 ± 0.01 mg/dl and of control diabetic was 0.13 ± 0.03 mg/dl, which after bromocriptine became 0.35 ± 0.21 mg/dl (low dose) 0.29± 0.10 mg/dl (high dose). the bilirubin level after standard drug treatment became 0.3± 0.25 mg/dl.

Alkaline phosphatase: The SGPT level of control non-diabetic rat was 61 ± 1.91 U/L dl and of control diabetic was 89 ± 0.03 U/L, which after bromocriptine became 68± 0.21 U/L (low dose) 61 ± 0.01 U/L (high dose). the bilirubin level after standard drug treatment became 61U/L.

Gamma GT: The SGPT level of control non-diabetic rat was7 ± 1.91 U/L dl and of control diabetic was 13 ± 0.03 U/L, which after bromocriptine became13 ± 1.3U/L (low dose) 12 ± 0.41U/L (high dose). the bilirubin level after standard drug treatment became 9± 0.35U/L.

SGPT(ALT) level: The SGPT level of control non-diabetic rat was 61 ± 1.91 U/L dl and of control diabetic was 89 ± 0.53, which after bromocriptine became 68± 0.53U/L (low dose) 61 ± 1.23U/L (high dose). the bilirubin level after standard drug treatment became 61 ± O.21U/L.

SGOT (AST)level: The SGPT level of control non-diabetic rat was182 ± 0.91 U/L dl and of control diabetic was 208± 1.93, which after bromocriptine became 137 ± 1.23 U/L (low dose) 112± 0.31 U/L(high dose).the bilirubin level after standard drug treatment became150± 2.31 U/L .

Table: Hepatic markers of control and treated groups of rats

LIVER MARKERS	Control non diabetic	Control diabetic	Control diabetic + bromocriptine (low dose)	Control diabetic + bromocriptine (high dose)	Control diabetic+ Standard treated
Total Bilirubin level	0.05mg/dl	0.35mg/dl	0.35mg/dl	0.29mg/dl	0.3 mg/dl
Alkaline phosphatase	79U/L	148U/L	140U/L	108U/L	88U/L
Gamma GT	7U/L	13U/L	13U/L	12U/L	9U/L
SGPT(ALT) level	61U/L	89U/L	68U/L	61 U/L	61U/L
SGOT(AST) level	182U/L	208U/L	137U/L	112U/L	150U/L

Values are given in mean standard deviation is equal to signifiacant at p <0.05.
values shown with * are compared with control non diabetic group as significant .
values shown with ^ are compared with control diabetic group as significant .

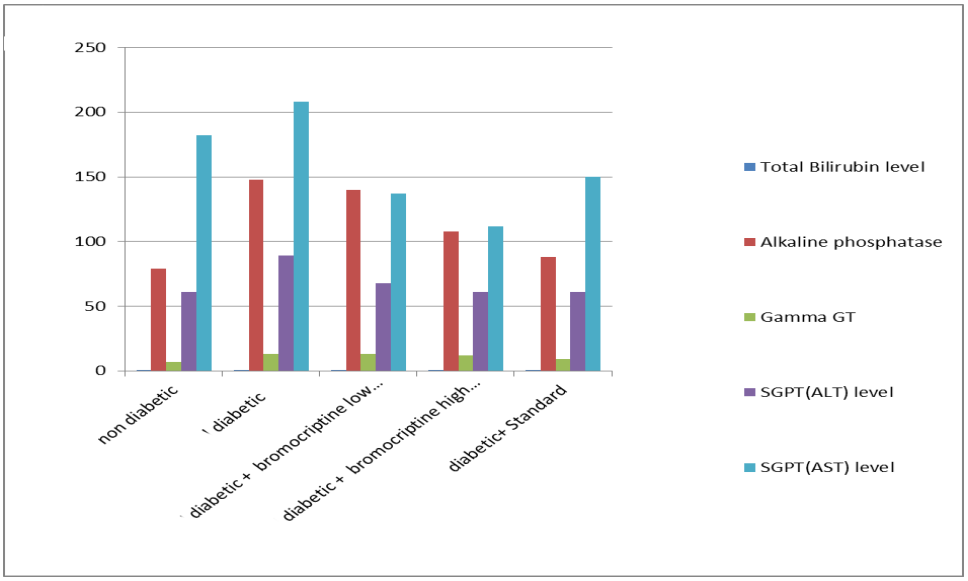

Figure 1: Graph showed the effect of bromocriptine and standard drug on liver enzymes

Histopathological Results of Liver

Control Non diabetic Group: Microscopic studies showed that the liver architecture was generally preserved with uniformly arranged, polygonal cells with distinct cell borders, central nuclei and intact lobular architecture as shown in Fig 2.

Control diabetic Group: Microscopic studies showed hepatocytes with the prominent cytoplasmic vacuoles, indicating fatty change, accumulation of lipid droplets within hepatocytes and presence of inflammatory cells, such as lymphocytes and macrophages, within the liver parenchyma as shown in Figure 3.

Diabetic treated Group (bromocriptine)

Microscopic studies showed that the liver architecture was generally preserved with few cytoplasmic vacuoles and lipid droplets .Polygonal cells were showed with distinct cell borders ,central nuclei and intact lobular architecture as shown in Fig 4.

Diabetic treated Group (standard group)

The pancreatic section of the diabetic treated Group with standard drug exhibited structure with intact lobular architecture, polygonal cells and uniformly arranged, cells with central nuclei and distinct cell borders in Fig 5.

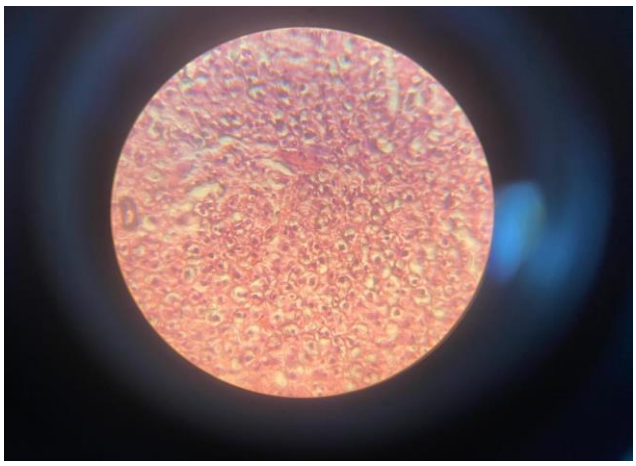

Fig. 2: 40X Photomicrograph of liver showing normal hepatic cells, polygonal cells and uniformly arranged, cells with central nuclei and distinct cell borders No significant change in control non-diabetic rat

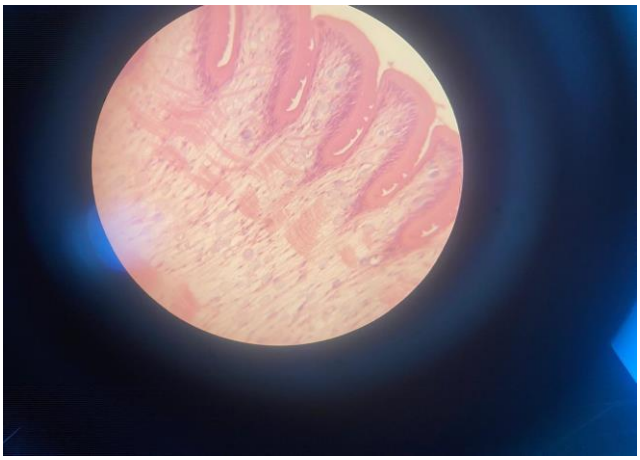

Fig. 3: 40X Photomicrograph of liver showing significant change in hepatic cells and presence of inflammatory cells, such as lymphocytes and macrophages within the liver parenchyma in control diabetic rat

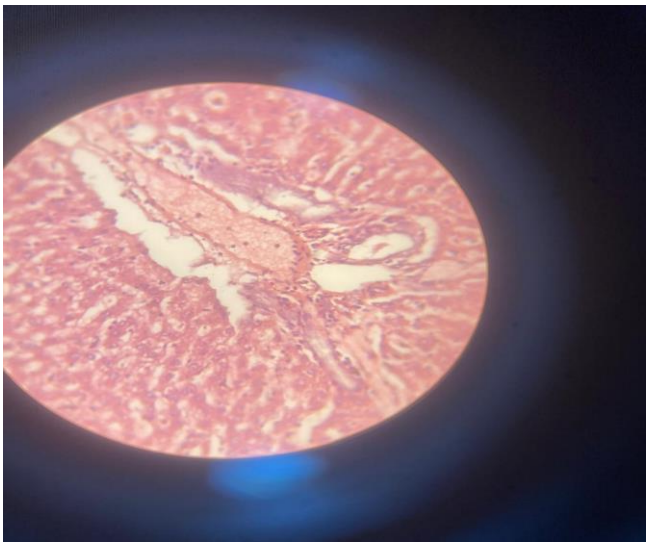

Fig. 4: 40X Photomicrograph of liver of STZ treated group with bromocriptine showed liver architecture was generally preserved with few cytoplasmic vacuoles and lipid droplets

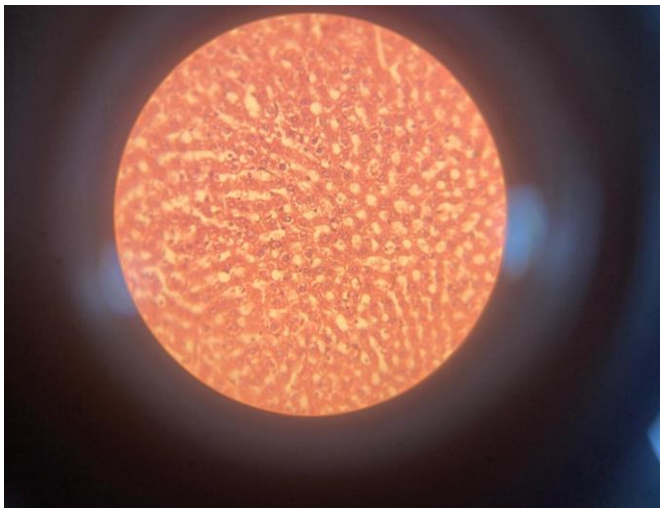

Fig. 5: 40X Photomicrograph of liver of STZ treated with standard drug showed intact lobular architecture,polygonal cells with central nuclei and distinct cell borders.

DISCUSSION

The incidence of diabetes mellitus is rising rapidly worldwide, frequently giving rise to severe metabolic disturbances and life-threatening complications [17]. Fletcher et al stated that Insulin resistance is a critical risk factor for the development of impaired glucose tolerance and type 2 diabetes. Individuals with insulin resistance often exhibit a cluster of risk factors, including hyperinsulinemia, atherogenic dyslipidemia and glucose intolerance, which are also commonly observed in people with type 2 diabetes. [18] The secondary outcomes of this study will examine the impact on cardiovascular disease and its associated risk factors, as well as changes in glycemic control, insulin dynamics, obesity, physical activity, nutrient intake, quality of life and the incidence of adverse events [19,20]. G M Reaven supported the view that the concurrent presence of insulin resistance and hyperinsulinemia sets the stage for the emergence of a constellation of metabolic abnormalities, characterized by impaired glucose tolerance, elevated plasma triglycerides, reduced high-density lipoprotein cholesterol, and hypertension [21].

Chen et al stated that bromocriptine has been shown to reduce liver fibrosis, a common complication of chronic liver disease [22]. Additionally, research by S Lous et al revealed that bromocriptine significantly improved insulin's ability to suppress hepatic glucose production during hyperinsulinemic-euglycemic clamp conditions [23]. Vicchi et al studied that the discovery of dopamine receptors' role in glucose regulation paved the way for the FDA's approval of

bromocriptine as a treatment for adults with type 2 diabetes, aiming to enhance glycemic control [24]. Ellen Bakke et al stated that bromocriptine is a robust diabetic treatment and resilient to genetically induced obesity, diabetes, and circadian disruption[25]. Dopamine have a therapeutic role in increasing hepatic perfusion and minimizing the loss in liver function [26] Rajeshwara evaluated that dopamine agonist reduce hypoperfusion and hence reduce the complications. [27] El-Sayed et al stated that bromocriptine has been shown to decrease levels of liver enzymes, such as alanine transaminase (ALT) and aspartate transaminase (AST), indicating reduced liver damage [28] According to the findings of the study, administration of dopamine agonist bromocriptine for 12 weeks significantly reduced SGPT and SGOT as shown in table 1. The study's findings revealed a significant hepatoprotective effect and decrease in bilirubin and alkaline phosphatase levels, with (0.29±0.10 p^ Mean±SEM) and (61±0.01, p^ Mean±SEM) showing substantial reductions in the diabetic treated group. . p-value (0.0001) gives significant difference in treated group as compared to diabetic group. As per results,no significant change in Gamma GT after bromocriptine treatment in diabetic group near to standard treated. Histopathological examination of liver tissue revealed that hepatocytes with the prominent cytoplasmic vacuoles, indicating fatty change,accumulation of lipid droplets within hepatocytes. (Fig.2) Notably, these changes were significantly mitigated in the bromocriptine treated groups. (Fig.3,4)

CONCLUSION

This study revealed that bromocriptine exhibits substantial antidiabetic as well as hepatoprotective effects. Our findings proposed a promising, natural therapeutic strategy for diabetes management, potentially serving as a complementary or alternative approach to conventional treatments.

Conflict of Interest

No conflict of interest associated with this work.

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