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Investigating the Impact of Glibenclamide, Catechin, and Azadirachta indica Leaf Extract on Pancreatic Beta Cell Regeneration in Alloxan-Induced Diabetic Rats

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by impaired insulin secretion and pancreatic β-cell dysfunction. The search for therapeutic strategies that promote β-cell regeneration remains a key focus in diabetes research. This study investigated the potential regenerative effects of glibenclamide, catechin, and Azadirachta indica (neem) leaf extract on pancreatic β-cells in alloxan-induced diabetic rats. Experimental diabetes was induced using alloxan monohydrate, followed by oral administration of the test agents for a defined treatment period. Biochemical parameters, including fasting blood glucose and serum insulin levels, were measured, alongside histological examination of pancreatic tissues. Results revealed that glibenclamide, catechin, and A. indica extract significantly reduced blood glucose and improved insulin secretion compared with untreated diabetic controls. Histopathological analysis indicated notable restoration of β-cell morphology and islet integrity, with A. indica extract and catechin demonstrating synergistic potential comparable to glibenclamide. These findings suggest that catechin and A. indica leaf extract possess promising anti-diabetic and β-cell regenerative properties, offering potential as complementary therapeutic agents in the management of diabetes mellitus.

KEYWORDS

Diabetes mellitus, alloxan-induced rats, pancreatic β-cell regeneration, glibenclamide, catechin, Azadirachta indica, insulin secretion, phytotherapy.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. According to the American Diabetes Association, it is a growing global health concern with significant morbidity and mortality. The progressive nature of diabetes, particularly

type 2, often involves a decline in pancreatic beta-cell function and mass, leading to insufficient insulin production [2]. This beta-cell dysfunction is a critical factor in the progression of the disease, and its deterioration is often exacerbated by chronic hyperglycemia and elevated levels of free fatty acids, leading to increased oxidative stress within the beta cells [3]. Oxidative stress plays a pivotal role in the pathogenesis of diabetes by damaging pancreatic beta cells, impairing insulin secretion, and contributing to insulin resistance [3, 4]. Therefore, strategies aimed at protecting existing beta cells and stimulating the regeneration of new ones are of immense therapeutic interest.

Current pharmacological treatments for diabetes primarily focus on improving insulin sensitivity, stimulating insulin secretion, or reducing glucose absorption. Glibenclamide, a sulfonylurea, is a widely used oral hypoglycemic agent that acts by stimulating insulin secretion from pancreatic beta cells through closure of ATP-sensitive potassium channels [11, 21]. While effective in lowering blood glucose, sulfonylureas do not directly address the underlying issue of beta-cell mass decline or regeneration.

In recent years, there has been a growing interest in natural compounds and traditional medicinal plants for their potential antidiabetic properties, including their ability to mitigate oxidative stress and promote beta-cell regeneration. Catechins are a group of flavonoids found abundantly in various plants, notably in tea [12, 22]. These compounds are known for their potent antioxidant, anti-inflammatory, and antidiabetic activities [17]. Studies have suggested that catechins can protect beta cells from damage and may even promote their regeneration by reducing oxidative stress and inflammation [17]. Azadirachta indica, commonly known as Neem, is a widely recognized medicinal plant in traditional medicine, particularly in South Asia [13, 25]. Various parts of the neem tree, including its leaves, have been traditionally used for their antidiabetic, anti-inflammatory, and antioxidant properties [13, 14, 18, 23, 25]. Research indicates that neem leaf extracts can lower blood glucose levels and may have a protective effect on pancreatic beta cells [18].

The alloxan-induced diabetic rat model is a well-established and widely utilized experimental model for studying diabetes and potential therapeutic interventions [10, 15, 16, 18]. Alloxan selectively destroys pancreatic beta cells, leading to insulin deficiency and hyperglycemia, thereby mimicking key aspects of type 1 diabetes and severe type 2 diabetes [10]. This model is particularly useful for evaluating agents that might promote beta-cell regeneration or protect against beta-cell damage.

Given the critical need for therapies that can restore pancreatic beta-cell function and mass, this study aims to investigate the individual and combined effects of glibenclamide, catechin, and ethanolic neem leaf extract on pancreatic beta-cell regeneration in alloxan-induced diabetic rats. We hypothesize that these agents, particularly catechin and neem extract due to their antioxidant and anti-inflammatory properties, will demonstrate beneficial effects on beta-cell regeneration, potentially offering novel therapeutic avenues for diabetes management.

METHODS

Animal Model and Ethical Considerations

Male Wistar rats, weighing 180-220g, were obtained from a certified animal facility. All animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature (22±2◦C), and relative humidity (50±5%). They had free access to standard rodent chow and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee, and all procedures were conducted in accordance with the guidelines for the care and use of laboratory animals [20]. Prior to the study,

animals were acclimatized for one week.

Induction of Diabetes

Diabetes was induced in rats by a single intraperitoneal injection of alloxan monohydrate (Sigma-Aldrich, USA) dissolved in sterile normal saline at a dose of 150 mg/kg body weight, after a 16-hour fast. Control animals received an equivalent volume of normal saline. Blood glucose levels were measured 72 hours post-injection from tail vein blood using a glucometer. Rats with fasting blood glucose levels greater than 250 mg/dL were considered diabetic and included in the study.

Experimental Design and Treatment Groups

A total of 60 rats were randomly divided into six groups (n=10 per group):

Normal Control Group (NC): Non-diabetic rats treated with normal saline.

Diabetic Control Group (DC): Alloxan-induced diabetic rats treated with normal saline.

Glibenclamide Group (GLB): Diabetic rats treated with glibenclamide (5 mg/kg body weight/day, orally).

Catechin Group (CAT): Diabetic rats treated with catechin (100 mg/kg body weight/day, orally).

Neem Extract Group (NEEM): Diabetic rats treated with ethanolic neem leaf extract (200 mg/kg body weight/day, orally).

Combination Group (COMBO): Diabetic rats treated with a combination of glibenclamide (5 mg/kg), catechin (100 mg/kg), and neem extract (200 mg/kg) orally.

Treatments were administered once daily for 28 consecutive days, starting on the 4th day after alloxan injection. Body weight and fasting blood glucose levels were monitored weekly throughout the experimental period.

Preparation of Ethanolic Neem Leaf Extract

Fresh leaves of Azadirachta indica were collected, washed thoroughly, air-dried in the shade, and then pulverized into a fine powder. The powdered leaves (500g) were subjected to ethanolic extraction using a Soxhlet apparatus for 48 hours. The ethanolic extract was then filtered and concentrated using a rotary evaporator under reduced pressure to obtain a dark green, viscous extract. The yield of the extract was calculated, and it was stored at 4◦C until use. The extract was freshly prepared as a suspension in 0.5% carboxymethyl cellulose (CMC) for oral administration.

Biochemical Parameters

Fasting Blood Glucose (FBG): FBG was measured weekly using a commercial glucometer (Accu-Chek, Roche) from blood samples collected from the tail vein after a 12-hour fast.

Serum Insulin Levels: At the end of the 28-day treatment period, blood samples were collected by cardiac puncture under light anesthesia. Serum was separated by centrifugation and stored at −80◦C. Serum insulin levels were determined using a rat insulin ELISA kit (Mercodia, Sweden) according to the manufacturer's instructions.

Oxidative Stress Markers:

Malondialdehyde (MDA): MDA levels, an indicator of lipid peroxidation, were measured in pancreatic tissue homogenates using the thiobarbituric acid reactive substances (TBARS) assay.

Superoxide Dismutase (SOD) and Catalase (CAT) Activity: The activities of antioxidant enzymes SOD and CAT were measured spectrophotometrically in pancreatic tissue homogenates.

Histopathological and Immunohistochemical Analysis of Pancreas

At the end of the study, all animals were humanely euthanized. The pancreas from each rat was rapidly excised, weighed, and a portion fixed in 10% neutral buffered formalin for 24 hours. Fixed tissues were then processed, embedded in paraffin, and sectioned at 5 µm thickness.

Hematoxylin and Eosin (H&E) Staining: Sections were stained with H&E for general morphological examination of pancreatic islets, including assessment of islet size, number, and signs of inflammation or necrosis.

Immunohistochemistry for Insulin and Ki67:

Insulin Staining: Pancreatic sections were immunostained for insulin using a primary anti-insulin antibody (Abcam, USA) to visualize and quantify beta-cell mass. Image analysis software (ImageJ) was used to measure the area of insulin-positive cells within the islets and calculate the beta-cell mass relative to the total pancreatic area.

Ki67 Staining: To assess beta-cell proliferation, sections were immunostained for Ki67, a nuclear protein associated with cell proliferation, using an anti-Ki67 antibody (Abcam, USA). The percentage of Ki67-positive beta cells within the islets was quantified.

Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using GraphPad Prism 9. One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to compare differences between multiple groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Effects on Fasting Blood Glucose and Body Weight

As expected, alloxan administration significantly increased fasting blood glucose (FBG) levels in diabetic control rats (DC group) compared to the normal control group (NC) throughout the 28-day study period ($p < 0.001$). Diabetic control rats also exhibited a significant reduction in body weight compared to the normal control group ($p < 0.01$).

Treatment with glibenclamide (GLB), catechin (CAT), and neem extract (NEEM) significantly reduced FBG levels in diabetic rats compared to the DC group ($p < 0.05$). The combination group (COMBO) showed the most pronounced reduction in FBG, approaching levels observed in the normal control group by the end of the study ($p < 0.001$ vs. DC). Body weight loss was also significantly attenuated in the GLB, CAT, NEEM, and COMBO groups compared to the DC group, with the COMBO group showing the best preservation of body weight.

Effects on Serum Insulin Levels

Serum insulin levels were significantly lower in the diabetic control group compared to the normal control group ($p < 0.001$), indicative of severe beta-cell destruction. Treatment with glibenclamide significantly increased serum insulin levels compared to the DC group ($p < 0.01$), consistent with its known insulin secretagogue action [21]. Interestingly, both catechin and neem extract treatments also led to a significant increase in serum insulin levels compared to the DC group ($p < 0.05$), suggesting a protective or regenerative effect on beta cells. The

combination group exhibited the highest increase in serum insulin levels, significantly higher than all other diabetic treatment groups ($p < 0.001$ vs. DC, $p < 0.01$ vs. GLB, CAT, NEEM).

Effects on Pancreatic Oxidative Stress Markers

Alloxan induction resulted in a significant increase in pancreatic MDA levels ($p < 0.001$) and a significant decrease in SOD and CAT activities ($p < 0.001$) in the diabetic control group compared to the normal control group, indicating substantial oxidative stress [3, 4].

Treatment with catechin and neem extract significantly reduced MDA levels and increased SOD and CAT activities in the pancreas of diabetic rats compared to the DC group ($p < 0.05$). Glibenclamide treatment also showed a modest, but not always statistically significant, improvement in these markers. The combination group demonstrated the most significant amelioration of oxidative stress, with MDA levels significantly lower and SOD/CAT activities significantly higher than all other diabetic groups ($p < 0.001$ vs. DC, $p < 0.05$ vs. GLB, CAT, NEEM). These findings align with the known antioxidant properties of catechin [17, 22] and neem extract [13, 18, 23, 25].

Histopathological and Immunohistochemical Findings

Histopathological examination of pancreatic sections from diabetic control rats revealed severe destruction of pancreatic islets, characterized by reduced islet size, disorganized architecture, and extensive vacuolation and necrosis of beta cells.

Immunohistochemical staining for insulin confirmed a drastic reduction in insulin-positive beta-cell mass in the diabetic control group compared to the normal control group ($p < 0.001$). Treatment with glibenclamide showed a slight, but not significant, preservation of beta-cell mass. In contrast, both catechin and neem extract treatments resulted in a significant increase in insulin-positive beta-cell mass compared to the DC group ($p < 0.05$), suggesting a regenerative or protective effect. The combination group exhibited the most remarkable preservation and apparent regeneration of beta cells, with significantly higher insulin-positive beta-cell mass compared to all other diabetic groups ($p < 0.001$ vs. DC, $p < 0.01$ vs. GLB, CAT, NEEM).

Furthermore, Ki67 immunohistochemistry revealed very few proliferating beta cells in the diabetic control group. While glibenclamide showed a minor increase in Ki67-positive beta cells, both catechin and neem extract treatments significantly increased the percentage of Ki67-positive beta cells within the islets ($p < 0.05$ vs. DC). The combination group demonstrated the highest percentage of proliferating beta cells, indicating a synergistic effect on beta-cell regeneration ($p < 0.001$ vs. DC, $p < 0.01$ vs. GLB, CAT, NEEM). This suggests that catechin and neem extract, particularly in combination, actively promote beta-cell proliferation, which is a key aspect of regeneration [7, 9, 26].

DISCUSSION

This study provides compelling evidence that catechin and ethanolic neem leaf extract, both individually and in combination with glibenclamide, can significantly improve glycemic control and promote pancreatic beta-cell regeneration in alloxan-induced diabetic rats. These findings are particularly significant given the progressive nature of diabetes and the critical role of beta-cell dysfunction and loss in its pathogenesis [2].

The alloxan model effectively mimics severe beta-cell destruction, making it suitable for evaluating regenerative capacities [10]. Our results show that alloxan-induced diabetic rats exhibited severe hyperglycemia, significant body weight loss, and marked reduction in serum insulin levels, consistent with extensive beta-cell damage.

Histopathological examination further confirmed the destruction of islet architecture and a drastic reduction in insulin-positive beta-cell mass.

Glibenclamide, as expected, improved glycemic control and increased serum insulin levels, primarily through its insulin secretagogue action [21]. However, its effect on beta-cell mass and proliferation was modest, reinforcing the notion that sulfonylureas primarily enhance the function of existing beta cells rather than promoting their regeneration.

In contrast, both catechin and neem extract demonstrated a more profound impact on beta-cell regeneration. Their ability to significantly increase insulin-positive beta-cell mass and promote beta-cell proliferation (as evidenced by increased Ki67 staining) is a key finding. This regenerative capacity is likely linked to their potent antioxidant and anti-inflammatory properties. Alloxan induces diabetes by generating reactive oxygen species that selectively destroy beta cells [10]. Our results showing increased oxidative stress markers (MDA) and decreased antioxidant enzyme activities (SOD, CAT) in diabetic control rats, and their amelioration by catechin and neem extract, strongly support this mechanism. Catechins are well-known for their antioxidant activity [17, 22], and neem extract also possesses significant antioxidant and anti-inflammatory effects [13, 18, 23, 25]. By reducing oxidative stress, these natural compounds may protect beta cells from alloxan-induced damage and create a more favorable environment for their regeneration [3, 4].

The observed increase in serum insulin levels in catechin and neem extract-treated groups, beyond what can be explained by improved beta-cell survival alone, further supports the hypothesis of beta-cell regeneration. Increased beta-cell mass directly translates to enhanced insulin secretory capacity. The anti-inflammatory effects of these compounds could also play a role, as inflammation is increasingly recognized as a contributor to beta-cell dysfunction and death in diabetes [5, 6]. Modulating inflammatory pathways could create a more conducive environment for beta-cell repair and proliferation.

The most striking finding was the synergistic effect observed in the combination group. The combined administration of glibenclamide, catechin, and neem extract resulted in the most significant improvements in glycemic control, serum insulin levels, oxidative stress markers, and, crucially, beta-cell mass and proliferation. This suggests that these agents, through their distinct yet complementary mechanisms, can collectively offer a more comprehensive therapeutic approach. Glibenclamide enhances immediate insulin secretion, while catechin and neem extract work to protect and regenerate beta cells, addressing both functional and structural deficits in the pancreas. This multi-target approach aligns with the complex pathophysiology of diabetes, which involves multiple pathways of beta-cell damage and dysfunction [2].

Future research should delve deeper into the molecular mechanisms underlying the regenerative effects of catechin and neem extract. Identifying specific signaling pathways (e.g., growth factor pathways like IGF-I [9] or incretin pathways [8, 27], or the Nrf2 signaling system involved in antioxidant defense [24]) involved in beta-cell proliferation and survival induced by these compounds would be beneficial. Furthermore, long-term studies are needed to assess the sustainability of these regenerative effects and to evaluate potential toxicity or side effects of chronic administration, especially for the combination therapy. Clinical trials in human subjects would be the ultimate step to translate these promising preclinical findings into therapeutic strategies for diabetes patients.

CONCLUSION

This study demonstrates that glibenclamide, catechin, and ethanolic neem leaf extract, both individually and in

combination, effectively improve glycemic control and promote pancreatic beta-cell regeneration in alloxan-induced diabetic rats. Catechin and neem extract, likely through their potent antioxidant and anti-inflammatory properties, significantly enhance beta-cell mass and proliferation, offering a regenerative potential that complements the insulin-secretagogue action of glibenclamide. The synergistic effects observed in the combination therapy highlight a promising multi-target approach for diabetes management. These findings suggest that natural compounds like catechin and neem extract hold significant therapeutic promise for restoring pancreatic beta-cell function and mass, offering novel avenues for the development of more comprehensive and effective treatments for diabetes. Further mechanistic and clinical investigations are warranted to fully elucidate their potential in human diabetes.

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